Institut für Organische Chemie der Justus-Liebig-Universität Gießen

Hydrogen-Bonding (Thio)urea Organocatalysts in Organic Synthesis: State of the Art and Practical Methods for Acetalization, Tetrahydropyranylation, and Cooperative Epoxide Alcoholysis

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Hydrogen-Bonding (Thio)urea Organocatalysts in Organic Synthesis: State of the Art and Practical Methods for Acetalization, Tetrahydropyranylation, and Cooperative Epoxide Alcoholysis

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Wasserstoffbrücken-bildende (Thio)Harnstoff-Organokatalysatoren in der Organischen Synthese: Stand der Forschung und praktische Methoden zur Acetalisierung, Tetrahydropyranylierung und Kooperativen Epoxidalkoholyse

Bewertung dieser Dissertation

„Summa cum laude"
(ausgezeichnet)

Erstgutachter	Univ.-Prof. Dr. Peter R. Schreiner, Ph.D.
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	Univ.-Prof. Dr. Peter R. Schreiner, Ph.D. (OC)
	Univ.-Prof. Dr. Bruno K. Meyer (Physik)

Die in dieser Dissertation dokumentierten Forschungsergebnisse entstanden in der Zeit von Juli 2002 bis Oktober 2008 am Institut für Organische Chemie der Justus-Liebig-Universität Gießen, Heinrich-Buff-Ring 58, D-35392 Gießen, unter der wissenschaftlichen Betreuung des Arbeitsgruppenleiters Herrn Prof. Dr. Peter R. Schreiner, Ph.D.

The research results documented in this PhD thesis have been achieved in the research period between July 2002 and October 2008 at the Institute of Organic Chemistry, Justus-Liebig University Giessen, Heinrich-Buff-Ring 58, 35392 Giessen, Germany, under the scientific supervision of the group leader Prof. Dr. Peter R. Schreiner, Ph.D.

Ich danke sehr meinem wissenschaftlichen Betreuer Herrn Prof. Dr. P. R. Schreiner, Ph.D für die Themenstellung aus einem aktuellen Forschungsgebiet der Organischen Chemie, die konstruktiven Diskussionen, sein stetes Interesse am Fortgang der Arbeit, die mehrjährige vertrauensvolle Zusammenarbeit sowie für die erwiesene Unterstützung und zugestandene forscherische Freiheit.

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Diese Dissertation ist in englischer Sprache verfasst, da sie nahezu vollständig als englischsprachige Fachliteratur publiziert ist oder publiziert werden wird (vgl. Publikationsliste/ ”List of Publications“). Dem englischen Hauptteil sind ein deutsches Vorwort und eine deutsche Zusammenfassung vorangestellt.

Diese Dissertation ist meiner
lieben Mutter *Eva Kotke*
gewidmet,
die mich nicht nur während der Jahre dieser Arbeit
auf vielfältige Weise immer unterstützte.

- in unbeschreiblicher Dankbarkeit, Hochachtung und Liebe -

Meinem
lieben Vater *Eugen Kotke*
danke ich schon hier ganz herzlich
für seine Unterstützung.

In Erinnerung
an meine lieben Omas

Eva Semmel
(*22.12.1920 – †04.04.2005)

Lydia Kotke
(*27.09.1911 – †23.01.1999)

The present PhD thesis is a contribution to catalysis research.
Die vorliegende Dissertationsarbeit ist ein Beitrag zur Katalyseforschung.

"Chemistry without catalysis is like a sword without a hilt,
a candle without light or a bell without sound."

„Chemie ohne Katalyse ist wie ein Schwert ohne Griff,
eine Kerze ohne Licht oder eine Glocke ohne Klang."

Alwin Mittasch (*27.12.1869; †04.06.1953)

German chemist, founder of BASF's Catalysis Research
Deutscher Chemiker, Begründer der BASF-Katalyseforschung

List of Publications

This PhD thesis represents a chronological and conceptual composition of the following publications that evidence own successful research activities and projects, respectively, predominantly towards hydrogen-bonding (thio)urea organocatalysts. The journal articles and the book chapter are published by the leading publishers in chemistry: ACS (American Chemical Society), Elsevier, Georg Thieme Verlag, and Wiley-VCH. Herein, the original articles are presented with reprint permission of the respective publisher and are available from there. The Journal Impact Factor JIF of each journal is given in parentheses.

Journal Articles and Book Chapter

1. **Mike Kotke**, R. R. Schreiner, "(Thio)urea Organocatalysts". Book chapter in "Hydrogen Bonding in Organic Synthesis", *204 pages*, Wiley-VCH Weinheim/Germany, Editor: P. M. Pihko, **2009**. ISBN 978-3-527-31895-7, *published.* 1st edition available Oct. 2009.

2. E. Lamy, C. Crößmann, A. Saeed, P. R. Schreiner, **Mike Kotke**, V. Mersch-Sundermann, "Three Structurally Homologous Isothiocyanates Exert ''Janus'' Characteristics in Human HepG2 Cells". *Environ. Mol. Mutagen.* **2009**, *50*, 164–170. (JIF 2.361, year 2007)

3. T. Weil, **Mike Kotke**, C. M. Kleiner, P. R. Schreiner, "Cooperative Brønsted Acid-Type Organocatalysis: Alcoholysis of Styrene Oxides". *Org. Lett.* **2008**, *10*, 1513–1516.
Highlights in Current Synthetic Organic Chemistry: "Cooperative Brønsted Acid Catalysis". *Synfacts* **2008**, *6*, 644. (*Org. Lett.*: JIF 5.128, year 2008)

4. **Mike Kotke**, P. R. Schreiner, "Generally Applicable Organocatalytic Tetrahydropyranylation of Hydroxy Functionalities with Very Low Catalyst Loading". Feature article, *Synthesis* **2007**, *5*, 779–790. (JIF 2.257, year 2007)

5. **Mike Kotke**, P. R. Schreiner, "Acid-free, Organocatalytic Acetalization". *Tetrahedron* **2006**, *62,* 434–439. (JIF 2.897, year 2009)

6. P. R. Schreiner, A. A. Fokin, **Mike Kotke**, T. Weil, "Non-covalent Organocatalysis". *Ann. Polish Chem. Soc.* **2004**, *3*, 21–24.

7. C. M. Kleiner, **Mike Kotke**, T. Weil, P. R. Schreiner, "Organocatalytic 1,3-Dioxolane Formation from Styrene Oxides". **2009**, *manuscript in preparation*.

Poster Presentations

1. **Mike Kotke**, P. R. Schreiner, "Non-covalent Organocatalysis: Novel Application of the Thiourea Motif". ORCHEM, Vortragstagung der Liebig-Vereinigung für Organische Chemie, Bad Nauheim, Germany, **2006**.

2. **Mike Kotke**, P. R. Schreiner, "Acid-free, Organocatalytic Acetalization". GDCh Jahrestagung, Düsseldorf, Germany, **2005**.

3. **Mike Kotke**, P. R. Schreiner, "Metal-Free, Non-covalent Enantioselective Organocatalysis by Hydrogen-Bonding Chiral Thiourea Derivatives". BASF Transfer-Workshop, Ludwigshafen, Germany, **2003**.

4. **Mike Kotke**, P. R. Schreiner, "Metal-Free Non-covalent Enantioselective Organocatalysis of Diels-Alder Reactions by Hydrogen-Bonding Chiral Thiourea Derivatives". WISOR XII (Postgraduate Winter School on Organic Reactivity), Bressanone, Italy, **2003**.

Table of Contents

I. Preface and Motivation

Catalysis describes the significant acceleration of a chemical reaction through the substrate-specific action of a “reaction mediator“ termed catalyst that - in contrast to the substrate - is not consumed itself in course of this reaction. Ideally, the catalyst should be inexpensive, readily accessible, highly efficient even in substoichiometric amounts to initiate numerous product-forming catalytic cycles; moreover, it should be recoverable (e.g., heterogeneous catalysis with polymer-bound catalysts) after completion of the reaction, reusable without loss of catalytic activity (recyclable catalyst), and additionally environmentally benign.

The individual mode of action of a catalyst depends on the complex interplay of various factors such as its structure, the substrate(s), and reaction parameters (e.g., solvent, p*H* value, temperature, stoichiometry) that have to be optimized in course of method developments. A detailed mechanistic picture that elucidates the origin of the catalyst’s efficiency requires a systematic combination of experimental and theoretical approaches. However, the accelerating effect (catalytic effect) typically results from specific covalent and/or non-covalent interactions between the catalyst and the substrate(s) such that the initially formed catalyst-substrate(s) complex (substrate coordination and activation) leads to a preferential relative stabilization of the transition state of the rate-determining reaction step along the product-forming reaction pathway. Consequently, the catalyst lowers the energy barrier of the desired conversion of the substrate(s) (starting material) into the target product(s) in comparison to the uncatalyzed reaction (rate enhancement).

In case of chiral catalysts the specific substrate coordination and transition state stabilization additionally induces a chirality transfer (stereoinduction) to the converting substrate giving preferably one enantiomer (stereodifferentiation). Thus, enantioselective catalysts accelerate and also stereochemically alter a chemical reaction providing synthetically valuable enantiomerically enriched or even enantiopure building-blocks or target products, respectively (asymmetric catalysis).

The rationale application of well-designed catalysts allows to conduct chemical transformations within a reasonable timeframe under mild conditions, increases the product yield, provides straightforward access to enantiopure products, extends the substrate scope, minimizes or even avoids side-product formation and thus waste production, simplifies work-up, and reduces energy costs owing to often drastically shortened reaction times and lower reaction temperatures.

Owing to this economical and ecological impact of catalysis on the progress and the outcome of a chemical reaction the syntheses of nearly 90 percent of all chemical products rely on the efficiency of a catalyst in one or more of their synthetic steps. Catalysis has become a key technology in the development of profitable and sustainable modern synthetic methodologies providing routinely access to high-quality chemical products both in laboratory and industry. Thus, catalysis research including, e.g., tailor-made catalyst design, method optimization, mechanistic studies, and the evaluation of novel concepts as well as the application of catalysts will remain one of the crucial challenges of chemistry. This PhD thesis is a contribution to catalysis research.

Nucleophile-electrophile reactions (e.g., acetalizations, esterifications, Mannich, Henry, Michael reactions) are broadly utilized in synthetic organic chemistry. The activation of the electrophilic component is often crucial for the success of these reactions. In the last decades electrophile activation predominantly have been achieved with metal(-ion) centered Lewis-acids due to intensive research on these catalyst type. Lewis-acid catalysis is highly efficient and undoubtedly has led to numerous milestone achievements, but

suffer from potential limitations and drawbacks owing to the metal(-ion) unit, e.g., overstoichiometric loading (product inhibition), waste production, high costs due to noble metals, toxicity of the heavy metal(-ion) component makes it often unsuitable for, e.g, the pharmaceutical and nutrition chemistry. Moreover, strong oxophilicity leads to oxygen- and water-incompatibility, and water-free reaction conditions including an inert atmosphere as well as often drastic reaction conditions are required. Brønsted-acid catalysis in fact is metal-free, but operates under often strong acidic conditions leading to unwanted side-reactions of acid-labile substrates such as polymerizations, epimerizations, eliminations, and decompositions.

Therefore, an environmentally benign, powerful, and metal-free catalysis strategy operating under mild and (nearly) neutral conditions is highly desirable. Organocatalysis ("organic catalysis"), that is, an old, but neglected discipline employing as catalysts small, purely organic compounds ("organic catalysts") circumvents the drawbacks mentioned above. Thio(urea) organocatalysts as representatives of non-covalent organocatalysis utilize explicit double hydrogen-bonding interactions for substrate coordination and activation. They show no apparent product inhibition, are readily accessible and electronically as well as sterically modular (tailoring), inexpensive, metal-free, weakly acidic or even neutral, they operate under mild conditions, are stable towards oxygen, and are water-compatible. These key advantages make them appear ideal catalysts. The Schreiner group have studied these catalysts since 1996; between 2000 and 2004 the same group reported seminal findings on this catalyst type and identified *N*,*N'*-bis[3,5-(trifluoromethyl)phenyl]thiourea as efficient hydrogen-bonding catalyst acting akin to weak Lewis-acids.

The research focus on hydrogen-bonding (thio)urea organocatalysts and the objective of this PhD thesis results from the motivation to continue and utilize these seminal findings (for details see Chapter 1, section 1.1). It aims at the development of straightforward, mild, high-yielding, routinely applicable, and of course metal-free synthetic methodologies operating in the presence of very low catalyst loadings of the *N*,*N'*-bis[3,5-(trifluoromethyl)phenyl]thiourea catalyst and selected derivatives under (nearly) neutral conditions. Thus, this PhD thesis marks the departure from the proof-of-concept phase to demonstrate the catalytic potential of hydrogen-bonding thio(urea) organocatalysts in organic synthesis.

The following chapters document the research strategies, projects, and novel methods on this ambitious research objective: The preface and summary prepared in English and German open this PhD thesis. They are followed by **Chapter 1** *"Hydrogen Bonding in Organic Synthesis – (Thio)urea Organocatalysts"* that comprehensively reviews the *"state of the art"* of these non-covalent organocatalysts including the introduction and background *(also the introduction of the entire PhD thesis)* as well as all non-stereoselective and stereoselective methodologies of one decade (1998–2008). **Chapter 2** chronologically presents novel practical methods resulting in own *"Journal Publications on Organocatalysis"*: The *"Acid-free, Organocatalytic Acetalization"* (Chapter 2.1), the *"Generally Applicable Organocatalytic Tetrahydropyranylation of Hydroxy Functionalities with Very Low Catalyst Loading"* (Chapter 2.2), and the *"Cooperative Brønsted Acid-Type Organocatalysis: Alcoholysis of Styrene Oxides"* (Chapter 2.3). The *"Design and Synthesis of Oxazoline-Thiourea Derivatives"* and the *"1,3-Dioxolane Formation from Styrene Oxides"* are described in **Chapter 3**, while **Chapter 4** is attributed to an interdisciplinary research project and publication entitled *"Three Structurally Homologous Isothiocyanates Exert ''Janus'' Characteristics in Human HepG2 Cells"*. **Chapter 5** *"Outlook – Research Perspectives"*, **Chapter 6** *"Appendix"* providing important supporting information, and the *"Acknowledgement"* complete the present PhD thesis.

II. Summary

Hydrogen-Bonding (Thio)urea Organocatalysts in Organic Synthesis: State of the Art and Practical Methods for Acetalization, Tetrahydropyranylation, and Cooperative Epoxide Alcoholysis

The research focus and the results documented in this PhD thesis are guided by the motivation to increase the popularity and the routine applicability of hydrogen-bonding (thio)urea organocatalysts in organic synthesis. Intensive literature and laboratory research have led to a critical, highly informative overview on this research field (Chapter 1) and to the development of five straightforward, metal-free experimental procedures. The organocatalytic acetalization (Chapter 2.1), tetrahydropyranylation (Chapter 2.2), and MOP protection (Chapter 2.2) represent acid-free contributions to the protective group chemistry of carbonyl- and hydroxy-functionalized substrates; the cooperative Brønsted acid-type organocatalysis (Chapter 2.3) and the 1,3-dioxolane formation (Chapter 3.2) employ styrene epoxides, alcohols, and carbonyl compounds as the substrates. All these non-stereoselective methodologies are characterized through mild, (nearly) neutral reaction conditions, reasonable reaction times, a broad substrate scope, high product yields after ready work-up, and their high efficiency expressed in TOF values even in preparative-scale experiments. The application of the privileged explicit double hydrogen-bonding *N*,*N*′-bis[3,5-(trifluoromethyl)phenyl]thiourea catalyst and its polymer-bound analogue in very low loadings allows the access to numerous synthetically useful acyclic and cyclic acetals (1,3-dioxolanes), THP and MOP ethers as well as *β*-alkoxy alcohols. Remarkably, the uncatalyzed reference experiments show in all cases no conversion. The beneficial features of these powerful organocatalytic procedures make them competitive alternatives or at least complements to procedures using Brønsted- or Lewis-acid catalysis often suffering, e.g., from toxicity, drastic reaction conditions (high reaction temperature, inert atmosphere), overstoichiometric loading (product inhibition), acidic conditions and substrate limitations. Thus, a broad routine utilization and establishment of these novel metal-free and environmentally benign procedures in synthetic organic chemistry appear to be practicable.

Additional research results reported herein aim at the development of novel potentially enantioselective thiourea derivatives (Chapter 3.1 and 5) such as oxazoline-thioureas and also at the synthesis of chemopreventive isothiocyanates as part of an interdisciplinary project (Chapter 4). The crystal structure of the *N*,*N*′-bis[3,5-(trifluoromethyl)phenyl]thiourea catalyst have been solved, refined, and visualized (Chapter 6.1)

– Chapter 1 –
Hydrogen Bonding in Organic Synthesis – (Thio)urea Organocatalysts

(Published: Book chapter in "Hydrogen Bonding in Organic Synthesis", 204 pages, *Wiley-VCH Weinheim/Germany*, Editor: P. M. Pihko, **2009**. ISBN 978-3-527-31895-7.)

This meticulously prepared manuscript critically reviews the success story and synthetic applications of hydrogen-bonding (thio)urea organocatalysts in organic synthesis and represents the key contribution to the seminal Wiley-VCH book "Hydrogen Bonding in Organic Synthesis". Based on intensive, comparative literature research an in-depth overview on the field of (thio)urea organocatalysis is provided covering historical and conceptual roots in enzyme catalysis, molecular (anion) recognition, crystal structure analysis, as well as milestone achievements leading to guidelines and principles for the catalyst development and optimization. One research decade (1998–2008) on (thio)urea organocatalysts is comprehensively elucidated and discussed (~150 original articles). The synthetic applications and limitations of both stereoselective as well as for the first time non-stereoselective (thio)urea catalysts are presented. Additionally, the key role of the privileged *N*,*N*′-bis[3,5-(trifluoromethyl)phenyl]thiourea catalyst for the development of stereoselective (thio)urea organocatalysts incorporating the 3,5-bis(trifluoromethyl)phenyl thiourea moiety is emphasized. Stereoselective mono- and bifunctional (thio)urea organocatalysts are classified according to their respective chiral scaffold, which is the leitmotif of the chronologically organized chapter. Catalyst design concepts, experimental details such as structure optimization studies, screening conditions, reaction conditions, typical substrate and product scopes together with yields and stereochemical data of each experimental procedure as well as mechanistic scenarios and analytical findings are thoroughly given for *each* published methodology (184 Schemes; 64 Figures). The critical "Summary and Outlook" and the detailed "Reference and Notes" section complete this chapter. In conclusion, this comprehensive picture on this rapidly growing research field aims on both newcomers and experts to find useful aspects, a deep insight, and encouraging impulses for own research efforts and applications of (thio)urea organocatalysts for "Hydrogen Bonding in Organic Synthesis".

– Chapter 2.1 –
Acid-free, Organocatalytic Acetalization

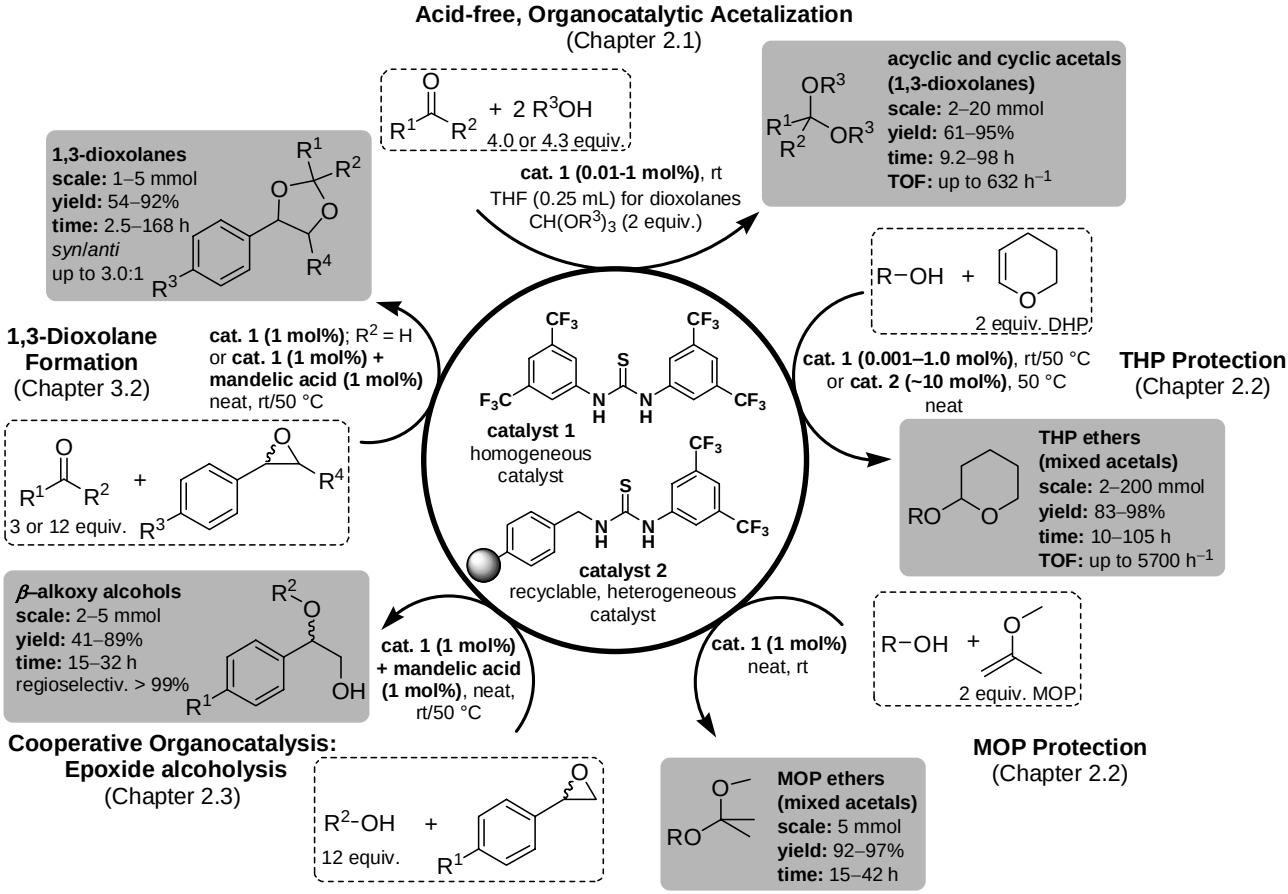
(Published: *Tetrahedron* **2006**, *62,* 434–439)

The acid-free, organocatalytic acetalization of various aliphatic and aromatic aldehydes and ketones with *N*,*N*′-bis[3,5-(trifluoromethyl)phenyl]thiourea is reported (see Scheme). This neutral, double hydrogen-bonding thiourea catalyst **1** can be employed routinely at very low loadings of 0.01–1 mol% at room temperature affording the respective acyclic dimethyl, diethyl, dipropyl, diisopropyl as well as cyclic (1,3-dioxolanes) acetals in good to excellent yields (61%–99%; 9.2 h–98 h) Scheme). Acid-labile TBDMS-protected as well as unsaturated aldehydes can be

efficiently acetalized utilizing this very mild and highly practical method that operates in the presence of orthoester and the respective alcohol component as the solvent. Scale-up in preparative (20 mmol) experiments works also well and underline further the synthetic utility of this organocatalytic approach. Turnover frequencies (TOF) up to 632 h^{-1} (TON = 9800) are found, while the uncatalyzed reference experiments showed no conversion.

Under the acetalization reaction conditions (0.1–1 mol% catalyst **1**) aliphatic *α*,*β*-unsaturated enones and enals undergo a domino *oxy*-Michael addition followed by acetalization (1,1,3-trialkoxylation) to give highly oxygenated products (71%–85 yield; ~15 h) (Chapter 2.2). Various experimental results on the acetalization support a thiourea-assisted heterolysis of the orthoester as entry into the product-forming mechanistic scenario depicted as catalytic cycle. The orthoester is suggested to serve as alcoholate source.

Additionally, this publication provides a straightforward multi-gram synthesis (100 mmol scale) of the *N*,*N*′-bis[3,5-(trifluoromethyl)phenyl]thiourea catalyst in reproducible high analytical grade and in 84% yield (36.1 g).



Scheme. The *five* experimental methodologies developed in course of this PhD thesis. Acetals, THP and MOP ethers as well *β*-alkoxy alcohols are readily accessible utilizing catalyst **1** and **2** under mild, metal-free conditions. Cooperative organocatalysis marks a seminal concept that appears to be very useful for the development of further efficient synthetic procedures.

– Chapter 2.2 –
Generally Applicable Organocatalytic Tetrahydropyranylation of Hydroxy Functionalities with Very Low Catalyst Loading

(Published: *Synthesis* **2007**, *5*, 779–790)

This chapter presents the first acid-free, organocatalytic tetrahydropyran (THP) and 2-methoxypropene (MOP) protection of alcohols, phenols, and other ROH derivatives utilizing privileged *N*,*N*′-bis[3,5-(trifluoromethyl)phenyl]thiourea catalyst and a novel polystyrene-bound analogue (catalyst **2**). This protocol is optimized to be broadly applicable also on preparative scale up to 200 mmol, in particular, to sterically hindered and acid-sensitive substrates such as tertiary alcohols, aldol products, hydroxy esters, acetals, silyl-protected alcohols, oximes, epoxides, and cyanohydrins without apparent polymerization, elimination, or any decomposition (see Scheme).

The respective THP and MOP ether (mixed acetals) are formed in 10 h–105 h reaction time and can be readily isolated in high yields ranging from 83% to 98% (Scheme). The catalytic efficiency is truly remarkably with TON values of 100,000 and TOF values of up to 5700 h^{-1} at catalyst loadings down to 0.001 mol%. *This is the most efficient organocatalytic reaction reported to date.*

The polymer-bound analogue (~10 mol% loading) improves the practicability further owing to its ready recovery and reusability (4 catalytic cycles) without loss of catalytic activity. Catalyst **2** efficiently accelerates the THP protection of various hydroxy-functionalized substrates under heterogeneous conditions giving the desired THP ethers in excellent yields (92%–98%; 21 h–53 h).

The computationally supported mechanistic interpretation emphasizes the hydrogen-bond assisted heterolysis of the alcohol and concomitant preferential stabilization of the oxyanion hole in the transition state resulting in the observed high catalytic effect. This rationalization is a *new concept* in non-covalent organocatalysis and marks the departure from the often-implied functionality group activation through explicit hydrogen-bonding catalysts.

In addition to the development and synthetic application of the THP and MOP protection this chapter presents a straightforward multi-gram preparation of 3,5-bis(trifluoromethyl)phenyl isothiocyanate (scale: 40 mmol; yield: 8.0 g; 74%) from inexpensive starting materials. This commercially available, but expensive isothiocyanate represents a key building block in the synthetic accessibility of thiourea derivatives; it allows facile incorporation of the privileged 3,5-bis(trifluoromethyl)phenyl thiourea moiety into (chiral) primary amine functionalized scaffolds giving a broad variety of highly efficient thiourea organocatalysts both non-stereoselective and stereoselective (Chapter 1).

– Chapter 2.3 –
Cooperative Brønsted Acid-Type Organocatalysis: Alcoholysis of Styrene Oxides

(Published: Org. *Lett.* **2008**, *10*, 1513–1516 and highlighted in *Synfacts* **2008**, *6*, 644–644)

This chapter introduces the innovative catalysis concept termed *"cooperative organocatalysis"* offering promising research perspectives and novel useful applications in (thio)urea organocatalysis (see Chapter 5). Cooperative catalysis is defined as a catalytic effect resulting from the cooperation of two components being individually inefficient in accelerating the respective reaction.

The first implementation of this conceptual approach have led to the development of a mild and efficient method for the completely regioselective alcoholysis of styrene oxides utilizing a cooperative Brønsted acid-type organocatalytic system; it comprises of the individual components mandelic acid (1 mol %) and *N*,*N*′-bis[3,5-(trifluoromethyl)phenyl]thiourea (1 mol %). Under neat conditions at rt or 50 °C, respectively, representative styrene oxides are readily transformed into their corresponding *β*-alkoxy alcohols in good yields (41%–89%; 15 h–32 h) and in excellent regioselectivity (>99%) at full conversion. The substrate spectrum includes simple aliphatic and sterically demanding, as well as unsaturated and acid-sensitive alcohols underlining the mildness of this methodology (see Scheme).

Experimental and computational findings elucidate the interactions between the cooperating components (binary complex between mandelic acid and thiourea catalyst) and the epoxide substrate (ternary complex formation) supporting a hydrogen-bonding-mediated cooperative Brønsted-acid catalysis mechanism visualized as catalysis cycle.

– Chapter 3.1–
Design and Synthesis of Novel Oxazoline-Thiourea Derivatives: Potential Organocatalysts

This chapter provides the conceptual background, design principles, and structure key units of chiral oxazoline-thiourea derivatives envisioned to serve as bifunctional hydrogen-bonding organocatalysts. The newly developed and optimized experimental procedure presented herein offers access to a series of these novel catalysts canditates. Various proof-of-principle experiments, however, indicate these derivatives to be catalytically inactive. This unexpected result is ascribed to a strong intramolecular hydrogen bond, which inhibits the formation of a substrate activating intermolecular double hydrogen-bonding interaction. To circumvent this catalytic inactivity alternative oxazoline-thiourea derivatives presumably capable of providing clamp-like double hydrogen-bonds are suggested and discussed.

– Chapter 3.2 –
Organocatalytic 1,3-Dioxolane Formation from Styrene Oxides
(Manuscript under preparation)

Herein, a novel and mild experimental procedure for the direct formation of 1,3-dioxolanes from carbonyl compounds and styrene oxides is presented. This useful, solvent-free organocatalytic approach operates in the absence of any water scavenger under cooperative catalysis conditions utilizing mandelic acid (1 mol %) and *N*,*N*′-bis[3,5-(trifluoromethyl)phenyl]thiourea (1 mol %) (see also Chapter 2.3) for the addition of acetylacetone (54%–62 yield; 18 h–68 h; rt or 50 °C); the acetal-forming addition of various aldehyde substrates to styrene oxide, however, was found to proceed under acid-free conditions in the presence of *N*,*N*′-bis[3,5-(trifluoromethyl)phenyl]thiourea (1–5 mol% loading). The desired 1,3-dioxolanes are readily isolated in yields ranging from 80%–92% (2.5 h–168 h; 40 °C) (see Scheme). A mechanistic picture is discussed and illustrated.

– Chapter 4 –
Three Structurally Homologous Isothiocyanates Exert ‘‘Janus’’ Characteristics in Human HepG2 Cells
(Published: *Environ. Mol. Mutagen.* **2009**, *50*, 164–170)

Interdisciplinary Research Project on Medical Chemistry

Isothiocyanates (ITCs) including terminal methylthioalkyl isothiocyanates such as the homologous 4-(methylthio)butyl isothiocyanate (MTBITC) and 5-(methylthio)pentyl isothiocyanate (MTPeITC) are potent chemopreventive agents. These commercially available, very expensive ITCs can be isolated through extraction methods from, e.g., rocket plant. A straightforward synthetic protocol have been desirable to provide these naturally occurring compounds in reproducible and high grade suitable for reliable human cell culture experiments and studies towards the origin of their chemopreventive potency.

Herein, an optimized four-step experimental procedure is introduced affording MTBITC (1.3 g) and MTPeITC (1.5 g), respectively, in high grade (>99.9%) from inexpensive starting materials. Various successful cell culture studies, performed by Lamy, Mersch-Sundermann et al. rely on the quality of both MTBITC and MTPeITC prepared by Kotke utilizing this protocol. The medical studies in human HepG2 cells test systems performed by the Lamy group identified MTBITC and MTPeITC to be “Janus” compounds: They exert an ambivalent character (“Janus” characteristic) both significant genotoxicity and antigenotoxicity, depending on their concentration. The ITC syntheses, the abstract as well as the introduction of the interdisciplinary research publication are given in this chapter.

– Chapter 5 –
Outlook – Research Perspectives

The outlook chapter contributes aspects, inspirations, and practicable perspectives that could lead to novel research projects on explicit hydrogen-bonding (thio)urea organocatalysts both in non-stereoselective and stereoselective organic transformations, applications, and methodologies. The potential research objectives described herein predominantly originates from the research focus and the results reported in chapter 1 and the chapters 2.1 – 2.3. They have paved the avenue for the systematic development of novel powerful hydrogen-bonding (thio)urea organocatalysts and synthetically useful methodologies such as cooperatively catalyzed epoxide openings with variable nucleophiles as well as organocatalytic variants of both the Neber and the Favorskii rearrangement offering access to numerous achiral and chiral building blocks and compound classes, respectively.

III. Vorwort und Motivation
(Preface and Motivation**)**

Katalyse beschreibt die in Relation zur unkatalysierten Referenzreaktion signifikante Beschleunigung einer chemischen Reaktion durch die vor allem substrat-spezifische Einwirkung eines „Reaktionsvermittlers“ mit der Bezeichnung Katalysator, der im Verlaufe dieser Reaktion – im Gegensatz zum Substrat – selbst nicht verbraucht wird. Im Idealfall ist ein Katalysator günstig, leicht verfügbar und sogar in deutlich unterstöchiometrischen Mengen hochwirksam, um eine Vielzahl produktbildender Katalysezyklen einzuleiten; er läßt sich nach Ablauf der Reaktion einfach zurückgewinnen (z. B. heterogene Katalyse mit einem polymer-gebundenen Katalysator), was die Aufarbeitung erleichtert, er ist möglichst ohne Verlust an Katalyseaktivität wiederverwendbar (recycelbarer Katalysator) und umweltverträglich.

Der individuelle Wirkmechanismus eines Katalysators hängt von einem komplexen Zusammenspiel verschiedener Faktoren wie z. B. der Katalysator- und Substratstruktur sowie den Reaktionsparametern (z. B. Lösungsmittel, pH-Wert, Reaktionstemperatur, Stöchiometrie) ab, die es bei der Methodenentwicklung zu optimieren gilt. Ein detailliertes mechanistisches Bild, das den Ursprung der Katalysatorwirksamkeit aufklärt, erfordert eine systematische Kombination experimenteller und theoretischer Methoden. Ohne diese umfangreichen Untersuchungen kann nur eine allgemeine Aussage getroffen werden. Typischerweise resultiert der Beschleunigunseffekt (Katalyseeffekt) aus spezifischen kovalenten und/oder nicht-kovalenten Wechselwirkungen zwischen dem Katalysator und dem/den Substrat(en). Diese Interaktion führt zunächst zu einem Katalysator-Substrat-Komplex (Substrat-Koordination und -Aktivierung), wodurch eine bevorzugte relative Stabilisierung des geschwindigkeitsbestimmenden Übergangszustandes entlang des produktbildenden Reaktionspfades erfolgt. Der Katalysator verringert dadurch deutlich die Energiebarriere (Aktivierungsenergie) für die Umwandlung zwischen dem/den Substrat(en) (Edukt(e)) und dem/n Zielprodukt(en) im Vergleich zur unkatalysierten Reaktion, so dass pro Zeiteinheit mehr Zielprodukt(e) gebildet wird/werden (erhöhte Umsatzrate); die Reaktion verläuft insgesamt schneller.
Im Falle chiraler Katalysatoren induziert die spezifische Substrat-Koordination und die Stabilisierung des Übergangszustandes einen Chiralitätstransfer (Stereoinduktion) auf das sich umwandelnde Substrat, so dass bevorzugt ein Enantiomer ensteht (Stereodifferenzierung). Enantioselektive Katalysatoren beschleunigen eine chemische Reaktion also nicht nur, sie sind auch in der Lage, diese stereochemisch zu beinflussen. Durch diese Katalysestrategie werden synthetisch wertvolle enantiomerenreine Synthese-bausteine oder gar direkt die Zielprodukte erhalten (Asymmetrische Katalyse).

Die gezielte Anwendung gut-konzipierter Katalysatoren ermöglicht, chemische Reaktionen innerhalb eines vernünftigen Zeitrahmens unter milderen Reaktionsbedingungen auszuführen, die Produktausbeute zu steigern, enantiomerenreine Produkte einfach herzustellen, das Substratspektrum zu erweitern, die Nebenproduktbildung und damit die Abfallproduktion zu minimieren oder gar zu vermeiden, den Aufarbeitungsprozess zu vereinfachen und die Energiekosten infolge oft drastisch verkürzter Reaktionszeiten und niedriger Reaktionstemperaturen zu senken.
Infolge dieses ökonomischen und ökologischen Einflusses der Katalyse auf den Ablauf und das Ergebnis einer chemischen Reaktion werden Katalysatoren inzwischen bei der Synthese von nahezu 90 Prozent aller chemischen Produkte verwendet. Katalyse hat längst die Bedeutung einer Schlüsseltechnologie bei der Entwicklung profitabler und nachhaltiger moderner Synthesemethoden erlangt, so dass routinemäßig

qualitativ hochwertige Chemieprodukte sowohl im Labor- als auch im Industriemaßstab zugänglich werden. Demzufolge wird die Katalyseforschung eine der zentralen Herausforderungen der Chemie bleiben und vor allem die anwendungsspezifische Katalysatorentwicklung, die Methodenoptimierung, mechanistische Studien sowie die Evaluierung neuer Konzepte und Katalysatortypen umfassen, wobei der Umweltschutzaspekt („Grüne Chemie“) eine immer wichtigere Rolle spielen wird.
Diese Dissertation ist ein Beitrag zur Katalyseforschung und trägt zeitgemäßen Forschungszielen Rechnung.

Metall(-ionen)haltige Lewis-Säure- und Brønsted-Säure-Katalysatoren sind hoch wirksam in der Aktivierung von Elektrophilen und sind in der Synthesechemie längst etabliert, doch sie zeigen auch einige Nachteile und Einschränkungen: Metall(-ionen) sind oft giftig, was die Aufarbeitung erschwert und eine Anwendung dieser Katalysatoren z.B. in der Pharma- oder Lebensmittelindustrie ausschließt oder zumindest erschwert; sie sind oft teuer, sauerstoff- und wasserempfindlich, zeigen Produktinhibition und erfordern deshalb eine hohe Beladung, was wiederum kostenintensiv und umweltschädlich ist. Die alternativen Brønsted-Säure-Katalysatoren sind zwar metallfrei, aber die stark sauren Bedingungen tolerieren nur säurestabile Substrate.

Aus den genannten Gründen ist eine umweltfreundliche, hoch wirksame, metallfreie Katalysestrategie, die unter milden (nahezu) neutralen Bedingungen wirksam ist, unbedingt erforderlich. Die Organokatalyse scheint dazu ideal geeignet zu sein, denn sie umgeht die oben genannten Nachteile und Einschränkungen. Wasserstoffbrücken-bildende (Thio)Harnstoff-Organokatalysatoren, nicht-kovalente Katalysatoren, wie sie von der Arbeitsgruppe um Schreiner seit 1996 systematisch untersucht werden, zeigen genau die geforderten Eigenschaften (vgl. Details dazu im Kapitel 1, Abschnitt 1.1) und können eine sinnvolle Ergänzung oder sogar eine Alternative zur etablierten Lewis- und Brønsted-Säure-Katalyse sein.

Dieses ambitionierte Ziel verfolgt diese Dissertation, indem der von der Arbeitsgruppe Schreiner eingeführte nicht-stereoselektive *N,N'*-Bis[3,5-(trifluormethyl)phenyl]-Thioharnstoff-Katalysator und einige neue Derivate eingehend auf ihr katalytisches Potenzial in der organischen Synthesechemie hin untersucht werden. Die hierfür notwendigen Forschungsstrategien, die Einzelprojekte und die neu entwickelten metallfreien Synthesemethoden werden in den nachfolgenden Kapiteln dieser Arbeit vollständig dokumentiert:
Diese Dissertation beginnt mit dem jeweils englischen und deutschen Vorwort sowie der Zusammenfassung. **Kapitel 1** *„Wasserstoffbrückenbildung in der Organischen Synthese – (Thio)Harnstoff-Organokatalysatoren“* vermittelt einen vollständigen Überblick über den *„Stand der Forschung“* bei diesen nicht-kovalenten Organokatalysatoren. Inbegriffen sind dabei die *„Einleitung und der Hintergrund“* dieses Forschungsgebietes *(dies ist gleichzeitig die Einleitung der gesamten Dissertation)* ebenso wie alle nicht-stereoselektiven und stereoselektiven Methoden einer Forschungsdekade (1998-2008). **Kapitel 2** präsentiert chronologisch neu entwickelte, praktische Methoden, die zu eigenen *„Journal-Publikationen zur Organokatalyse“* führten: Die *„Säurefreie, Organokatalytische Acetalisierung“* (Kapitel 2.1), die *„Allgemein Anwendbare Organokatalytische Tetrahydropyranylierung von Hydroxyfunktionalitäten bei sehr niedriger Katalysatorbeladung“* (Kapitel 2.2) und die *„Kooperative Brønsted-Säure-artige Organokatalyse: Alkoholyse von Styroloxiden”* (Kapitel 2.3). *„Design und Synthese neuer Oxazolin-Thioharnstoffderivate: Potenzielle Organokatalysatoren“ und die „Organokatalytische Synthese von 1,3-Dioxolanen aus Styroloxiden“* sind in **Kapitel 3** beschrieben, während sich **Kapitel 4** einem interdisziplinären Forschungsprojekt aus der medizinischen Chemie widmet. **Kapitel 5** *„Ausblick – Forschungsperspektiven“*, **Kapitel 6** *„Anhang“*, das wichtige Zusatzinformationen liefert, und die *„Danksagung“* komplettieren diese Dissertation.

IV. Zusammenfassung
(Summary)

Wasserstoffbrücken-bildende (Thio)Harnstoff-Organokatalysatoren in der Organischen Synthese: Stand der Forschung und praktische Methoden zur Acetalisierung, Tetrahydropyranylierung und Kooperativen Epoxidalkoholyse

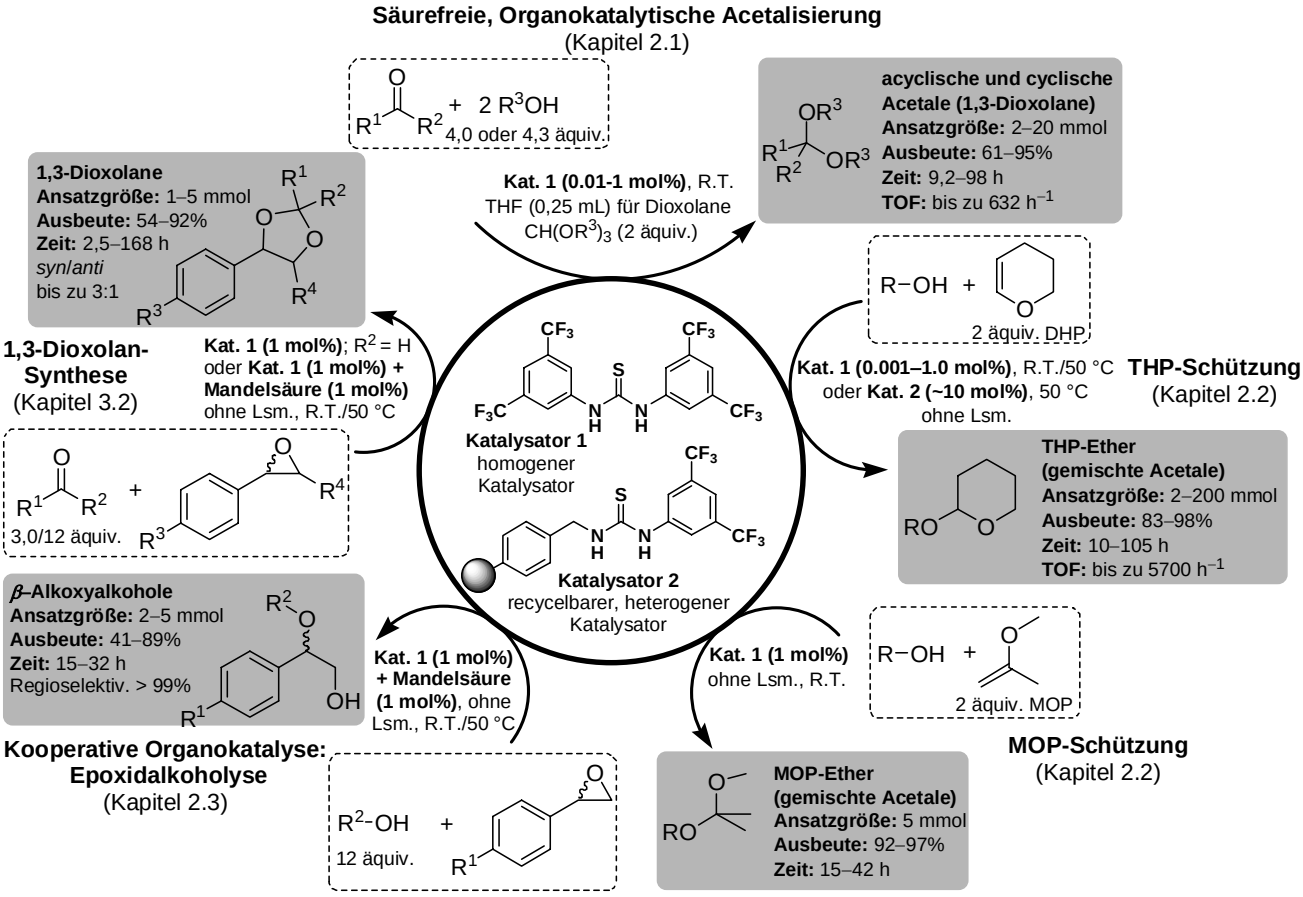
Der Forschungsschwerpunkt dieser Dissertation und die hier dokumentierten Ergebnisse folgen aus der Motivation heraus, durch neu entwickelte Synthesemethoden und Konzepte die Bekanntheit und Zweckmäßigkeit wasserstoffbrücken-bildender (Thio)Harnstoff-Organokatalysatoren zu steigern, so dass diese eine sinnvolle Anwendung in der organischen Synthesechemie finden. Intensive Literaturrecherche und Laborforschung führten zu einem kritischen, sehr informativen Übersichtskapitel über dieses Forschungsgebiet (Kapitel 1) und zu fünf einfach anwendbaren, metallfreien Synthesemethoden. Die organokatalytische Acetalisierung (Kapitel 2.1), die Tetrahydropyranylierung (Kapitel 2.2) und die MOP-Schützung sind säurefreie Beiträge zur Schutzgruppenchemie von Carbonyl- und Hydroxy-Substraten; die kooperative Brønsted-Säure-artige Organokatalyse (Kapitel 2.3) und die 1,3-Dioxolan-Synthese (Kapitel 3.2) verwenden Styroloxide, Alkohole und Carbonylverbindungen als Substrate. Alle diese nicht-stereoselektiven Methoden zeichnen sich aus durch milde Reaktionsbedingungen, vernünftige Reaktionszeiten, ein jeweils breites Substratspektrum, hohe Produktausbeuten nach einfacher Aufarbeitung und nicht zuletzt durch ihre unvermindert wirkungsvolle Anwendbarkeit auch für Synthesen im präparativen Maßstab. Die Anwendung des *N*,*N*′-Bis[3,5-(trifluormethyl)phenyl]-Thioharnstoff-Katalysators und eines polymer-gebundenen Strukturanalgons in sehr niedrigen Beladungen erlaubt die Darstellung acyclischer und cyclischer Acetale (1,3-Dioxolane), THP- und MOP-Ether und von β-Akoxy-alkoholen. Ausbleibender Substratumsatz bei allen unkatalysierten Referenzexperimenten unterstreicht die synthetische Notwendigkeit dieser neu entwickelten und optimierten Methoden. Die vorteilhaften Eigenschaften dieser praktischen organokatalytischen Prozeduren machen sie zu konkurrenzfähigen Alternativen oder wenigstens Ergänzungen zu den Prozeduren, die Brønsted- oder Lewis-Säurekatalyse verwenden und oft Nachteile wie z. B. eine stark eingeschränkte Substrattoleranz sowie drastische Reaktionsbedingungen aufweisen. Somit erscheint die Routineanwendung der vorgestellten Prozeduren in der organischen Synthesechemie zweckmäßig. Zusätzliche Forschungsergebnisse dieser Arbeit konzentrieren sich auf die Entwicklung neuer, enantioselektiver Thioharnstoff-Katalysatoren wie z. B. Oxazolin-Thioharnstoffe (Kapitel 3.1 und 5) sowie als Teil eines interdisziplinären Projektes auf die Synthese chemopräventiver Isothiocyanate (Kapitel 4). Die Kristallstruktur des *N*,*N*′-Bis[3,5-(trifluormethyl)phenyl]-Thioharnstoff-Katalysators wurde gelöst, verfeinert und bildlich dargestellt (Kapitel 6.1).

– Kapitel 1 –
Wasserstoffbrückenbindung in der Organischen Synthese – (Thio)Harnstoff-Organokatalysatoren

(Publiziert: 204 Seiten umfassendes Buchkapitel in "Hydrogen Bonding in Organic Synthesis", *Wiley-VCH Weinheim/Germany*, Editor: P. M. Pihko, **2009**. ISBN 978-3-527-31895-7.)

Dieses sorgfältig ausgearbeitete Manuskript bietet einen kritischen Überblick über die Erfolgsgeschichte und das synthetische Potenzial wasserstoffbrücken-bildender (Thio)Harnstoff-Organokatalysatoren und repräsentiert den zentralen Beitrag zum wegweisenden Wiley-VCH-Buch "Wasserstoffbrückenbindung in der Organischen Synthese". Basierend auf intensiver, vergleichender Literaturrecherche deckt dieses Kapitel das Forschungsgebiet der (Thio)Harnstoff-Organokatalyse vollständig und tiefgehend ab. Die historischen und konzeptionellen Wurzeln in der Enzymkatalyse, der molekularen (Anionen-)Erkennung und der Kristallstrukturanalyse werden ebenso berücksichtigt wie bahnbrechende Erkenntnisse, die zu bedeutenden Richtlinien und Prinzipien für die Katalysatorentwicklung und Strukturoptimierung führten. Eine gesamte Forschungsdekade (1998–2008) mit nahezu 150 Originalartikeln ausschließlich über (Thio)Harnstoff-Organokatalysatoren ist übersichtlich und informativ aufbereitet und diskutiert. Die Syntheseanwendungen und Einschränkungen aller stereoselektiven und erstmals auch nicht-stereoselektiven Katalysatoren werden in übersichtlicher Form präsentiert. Dabei wird auch erstmals die Schlüsselrolle des privilegierten *N*,*N*′-Bis[3,5-(trifluormethyl)phenyl]-Thioharnstoff-Katalysators für die Entwicklung vor allem stereoselektiver Organokatalysatoren, die die 3,5-Bis(trifluormethyl)phenyl-Thioharnstoffgruppe als Strukturelement enthalten, herausgearbeitet. Stereoselektive mono- und bifunktionale (Thio)Harnstoffkatalysatoren sind nach ihrer jeweiligen chiralen Struktureinheit klassifiziert, die das Leitmotiv dieses chronologisch organisierten Kapitels darstellt. Katalysatordesign- und Strukturkonzepte wie z. B. Bifunktionalität, experimentelle Details wie Strukturoptimierungsstudien, Bedingungen für die Katalysatorauswahl, Reaktionsbedingungen, typische Substrat- und Produktpaletten jeder Syntheseprozedur, stereochemische Kenndaten genauso wie vorgeschlagene mechanistische Szenarien zusammen mit analytischen Befunden sind vollständig für *jede* in dieser Dekade publizierte Methode angegeben (184 Schemata; 64 Abbildungen).

Der Abschnitt "Zusammenfassung und Ausblick" und die detaillierten "Referenzen und Anmerkungen" vervollständigen dieses Kapitel. Folglich wird hier ein umfassendes Bild von diesem schnell wachsenden und zeitgemäßen Forschungsgebiet vermittelt, so dass Neueinsteiger wie Experten hilfreiche Aspekte, tiefe Einblicke und ermutigende Impulse für eigene Forschungsbemühungen und Anwendungen von (Thio)Harnstoff-Organokatalysatoren in der organischen Synthesechemie finden mögen.



Schema. Die *fünf* experimentellen Methoden, die im Rahmen dieser Dissertation entwickelt wurden. Acetale, THP und MOP Ether sowie *β*-Alkoxyalkohole sind einfach synthetisch zugänglich, wenn Katalysator **1** oder **2** unter milden Reaktionsbedingungen verwendet wird. Die *kooperative Organokatalyse* stellt ein zukunftsträchtiges Konzept mit einem breiten Anwendungspotenzial dar.

– Kapitel 2.1 –
Säurefreie, Organokatalytische Acetalisierung

(Publiziert: *Tetrahedron* **2006**, *62,* 434–439)

In diesem Kapitel wird die säurefreie, organokatalytische Acetalisierung verschiedener aliphatischer und aromatischer Aldehyde und Ketone in Gegenwart des *N*,*N*′-Bis[3,5-(trifluormethyl)phenyl]-Thioharnstoff-Katalysator vorgestellt (vgl. Schema) Der neutrale, eine doppelte Wasserstoffbrücke bildende Katalysator **1** kann routinemäßig bei sehr niedrigen Katalysatorbeladungen von 0,01–1 mol% eingesetzt werden. Bereits bei Raumtemperatur werden die entsprechenden acyclischen Dimethyl-, Diethyl-, Dipropyl-, Diisopropylacetale und ebenso cyclische Acetale (1,3-Dioxolane) in guten bis ausgezeichneten Ausbeuten und akzeptablen Reaktionszeiten erhalten (61%–99%; 9,2 h–98 h) (siehe Schema). Säurelabile TBDMS-geschützte ebenso wie ungesättigte Aldehyde können durch diese sehr milde und sehr praktische Methode wirkungsvoll acetalisiert werden. Die Acetalisierungen laufen in Gegenwart von Orthoester ab, ein Lösungsmittelzusatz ist

allerdings nicht erforderlich, denn die Alkoholkomponente wird auch als Lösungsmittel verwendet. Unverändert hohe Produktausbeuten und Reaktionszeiten selbst bei präparativen Experimenten im 20 mmol-Maßstab sowie TOF-Werte bis zu 632 h^{-1} (TON-Wert = 9800) unterstreichen die synthetische Zweckmäßigkeit dieser organokatalytischen Methode.

Aliphatische *α*,*β*-ungesättigte Enone und Enale durchlaufen unter den Reaktionsbedingungen der Acetalisierung (0,1–1 mol% Katalysator **1**) eine Dominoreaktion bestehend aus einer *Oxy*-Michael-Addition und einer sich anschließenden Acetalisierung der Carbonylfunktion. Durch diese insgesamt 1,1,3-Trialkoxylierung entstehen stark mit Sauerstoff angereicherte Produkte (Ausbeute: 71%–85; ~15 h) (siehe Kapitel 2.2), die bisher nur unter drastischen Bedingungen erhältlich waren.

Experimentelle Befunde favorisieren einen Acetalisierungsmechanismus, bei dem der Thioharnstoffkatalysator über eine doppelte explizite Wasserstoffbrückenbindung die Heterolyse des Orthoesters einleitet, so dass Alkoholat freigesetzt wird und der produktbildende Katalysezyklus beginnt. Der Orthoester wirkt demnach als Alkoholatquelle.

Der *N*,*N*′-Bis[3,5-(trifluormethyl)phenyl]-Thioharnstoff hat als privilegierter Katalysator eine große Bedeutung in der nicht-kovalenten Organokatalyse erlangt (vgl. Kapitel 1), indem seine Struktur und Wirksamkeit als Maßstab für die Methoden- und Katalysatorentwicklung gilt. Erstmals wird hier eine einfach durchzuführende Synthesevorschrift für diesen Organokatalysator beschrieben. Sie ist für Ansatzgrößen bis zu 100 mmol optimiert und liefert den Katalysator reproduzierbar in hoher analytischer Reinheit und mit 84% Ausbeute (36,1 g).

– Kapitel 2.2 –
Allgemein Anwendbare Organokatalytische Tetrahydropyranylierung von Hydroxyfunktionalitäten bei sehr niedriger Katalysatorbeladung

(Publiziert: *Synthesis* **2007**, *5*, 779–790)

Dieses Kapitel beschreibt die erste säurefreie, organokatalytische Tetrahydropyran- (THP) und 2-Methoxypropen- (MOP) Schützung von Alkoholen, Phenolen und anderen ROH-Derivaten. Die ausgearbeitete und optimierte Methodik verwendet als Organokatalysatoren *N*,*N*′-Bis[3,5-(trifluormethyl)phenyl]-thioharnstoff und ein neu entwickeltes, an Polystyrol gebundenes Analogon (Katalysator **2**) (vgl. Schema). Die Synthesevorschrift ist für eine breite Anwendbarkeit bis zu 200 mmol Ansatzgrößen optimiert. Aus dem umfangreichen Substratspektrum sind vor allem sterisch anspruchsvolle und säurelabile hydroxyfunktionalisierte Substrate wie z. B. tertiäre Alkohole, Aldole, Hydroxyester, Acetale, silyl-geschützte Alkohole, Oxime, Epoxide und

Cyanhydrine hervorzuheben. Die Einführung der jeweiligen Schutzgruppe erfolgt ohne Polymerisationen, Eliminierungen oder Zersetzungsreaktionen. Die jeweiligen THP- und MOP-Ether (gemischte Acetale) entstehen innerhalb von 10 h–105 h und können einfach in hohen Ausbeuten (83%–98%) isoliert werden (vgl. Schema). Die katalytische Wirksamkeit von Katalysator **1** ist hier beachtlich hoch und liefert bei sehr niedrigen Beladungen von nur 0,001 mol% TON-Werte von 100000 und TOF-Werte bis 5700 h^{-1}.
Mit diesen hohen Reaktionskennzahlen ist die hier vorgestellte organokatalytische Tetrahydropyranylierung die bisher wirksamste aller dokumentierten Organokatalysereaktionen.

Die Anwendung des polymergebundenen Katalysators **2** (~10 mol% Beladung) bedeutet dank seiner unkomplizierten Rückgewinnung aus der Reaktionsmischung und Wiederverwendbarkeit (4 Katalysezyklen) eine zusätzliche Verbesserung der Praktikabilität, zumal der recycelte Katalysator unverändert aktiv bleibt (vgl. Schema). Katalysator **2** beschleunigt unter heterogenen Reaktionsbedingungen wirkungsvoll die THP-Schützung unterschiedlicher hydroxy-funktionalisierter Substrate, so dass die geforderten THP-Ether innerhalb von 21 h–53 h Reaktionszeit und nach einfacher Aufarbeitung in ausgezeichneten Ausbeuten (92%–98%) anfallen.

Die mechanistische Interpretation der organokatalytischen Tetrahydropyranylierung stützt sich vor allem auf quantenmechanische Berechnungen und betont die entscheidende Rolle von Wasserstoffbrückenbindungen bei der Alkoholheterolyse ebenso wie bei der gleichzeitigen Vorzugsstabilisierung des entstehenden Oxyanion-Lochs im Übergangszustand; hieraus resultiert der beobachtete große Katalyseeffekt. Dieses Erklärungsmodell für die Katalysatorwirkung bedeutet ein *neues Konzept* in der nicht-kovalenten Organokatalyse und kennzeichnet ein Abweichen von der oft implizierten Aktivierung funktioneller Gruppen durch explizite Wasserstoffbrückenbindungen.

Dieses Kapitel bietet neben der THP- und MOP-Schützung eine kostengünstige, einfach durchzuführende Darstellung von 3,5-Bis(trifluoromethyl)phenyl-isothiocyanat (Ansatzgröße: 40 mmol; Ausbeute: 8,0 g; 74%). Dieses käufliche, aber teure Isothiocyanat ist ein Schlüsselbaustein bei der Synthese von Thioharnstoffderivaten, durch den die privilegierte 3,5-Bis(trifluoromethyl)phenyl-Thioharnstoff-Einheit synthetisch mühelos in (chirale) Strukturgerüste mit primärer Aminfunktion eingeführt werden kann. Dadurch erst wird eine große Vielfalt (nicht-)stereoselektiver Thioharnstoff-Organokatalysatoren zugänglich (vgl. Kapitel 1).

– Kapitel 2.3 –
Kooperative Brønsted-Säure-artige Organokatalyse: Alkoholyse von Styroloxiden

(Publiziert: Org. *Lett.* **2008**, *10*, 1513–1516; in *Synfacts "Highlight"* **2008**, *6*, 644–644)

In diesem Kapitel wird das innovative Katalysekonzept *"Kooperative Organokatalyse*" vorgestellt. Dieses Konzept bietet vielversprechende Forschungsperspektiven und wird die nicht-kovalente Organokatalyse um neue, nützliche Syntheseanwendungen bereichern (vgl. Kapitel 5). Die kooperative Katalyse ist definiert als ein katalytischer Effekt, der sich aus der Kooperation zweier Komponenten bzw. Substanzen ergibt, die jedoch als Einzelkomponenten katalytisch unwirksam sind und die jeweilige Reaktion nicht zu beschleunigen vermögen.

Dieses neue Konzept wurde an der Alkoholyse von Styroloxiden entwickelt und erforscht, die damit gleichzeitig die erste synthetische Anwendung darstellt. Die vollständig regioselektive Alkoholyse dieser terminalen Epoxide nutzt ein Brønsted-Säure-artiges Organokatalysesystem bestehend aus den Einzelkomponenten Mandelsäure (1 mol%) und *N*,*N*′-Bis[3,5-(trifluormethyl)phenyl]-Thioharnstoff (1 mol%). Repräsentative Styroloxide lassen sich ohne Lösungsmittelzusatz bei Raumtemperatur oder 50 °C einfach in die entsprechenden *β*-Alkoxyalkohole umwandeln, die in guten Ausbeuten (41%–89%; 15 h–32 h) isoliert werden können; die Epoxidöffnungen verlaufen vollständig regioselektiv (>99%). Das breite Substratspektrum umfasst einfache aliphatische und sterisch gehinderte ebenso wie ungesättigte und säurelabile Alkohole, was den milden Charakter und die praktische Bedeutung dieser Methode unterstreicht (vgl. Schema).

Experimentelle und theoretische Befunde aus Berechnungen werden herangezogen, um die Wechselwirkungen zwischen den kooperierenden Komponenten Mandelsäure und Katalysator **1** (binärer Komplex) und zusätzlich zum Epoxidsubstrat (ternärer Komplex) aufzuklären; darauf basierend wir ein durch Wasserstoffbrückenbindung vermittelter kooperativer Brønsted-Säure-artiger Katalysemechanismus favorisiert, der als Katalysezyklus formuliert ist.

– Kapitel 3.1–
Design und Synthese neuer Oxazolin-Thioharnstoffderivate: Potenzielle Organokatalysatoren

Dieses Kapitel bietet den konzeptionellen Hintergrund, Designprinzipien und wichtige Struktureinheiten chiraler Oxazolin-Thioharnstoffe, die als mögliche bifunktionale wasserstoffbrücken-bildende Organokatalysatoren in Betracht gezogen werden. Die neu entwickelte Synthesestrategie und die optimierte Synthesevorschrift, die in diesem Kapitel beschrieben werden,

ermöglichen den Zugang zu einer Serie dieser neuartigen Katalysatorkandidaten. In verschiedenen Testreaktionen zeigen diese neuen Thioharnstoffderivate allerdings keinen Katalyseeffekt. Dieses unerwartete Resultat wird einer starken intramolekularen Wasserstoffbrücke zugeschrieben, die die Ausbildung einer aktivierenden, doppelten Wasserstoffbrückenbindung zum Substrat unterbindet. Deshalb werden Strukturmodifikationen dieser Oxazolin-Thioharnstoffe vorgeschlagen und diskutiert, die eine vermeintlich schwächere intramolekulare, dafür aber deutlich ausgeprägte doppelte intermolekulare Wasserstoffbrücken-Wechselwirkung zulassen und dadurch katalytisch wirken sollten.

– Kapitel 3.2 –
Organokatalytische Synthese von 1,3-Dioxolanen aus Styroloxiden

(Publizierbares Manuskript in der Fertigstellung)

Hier wird eine neuartige, milde Prozedur zur direkten Synthese von 1,3-Dioxolanen aus Carbonylverbindungen und Styroloxiden präsentiert. Diese nützliche, organokatalytische Methode kommt ohne Wasserfänger und Lösungsmittel aus. Mit Mandelsäure (1 mol%) und *N*,*N*′-Bis[3,5-(trifluormethyl)phenyl]thioharnstoff (1 mol%) unter Bedingungen der kooperativen Organokatalyse (vgl. auch Kapitel 2.3) kann Acetylaceton in moderaten Ausbeuten (54%–62%; 18 h–68 h; 25 oder 50 °C) an ausgewählte Styroloxide addiert werden. Im Gegensatz dazu verläuft die acetalbildende Addition verschiedener Aldehyde unter säurefreien Bedingungen nur in Gegenwart von Katalysator **1** (1–5 mol% Beladung). Die gewünschten 1,3-Dioxolane lassen sich nach 2,5 h–168 h Reaktionszeit bei 40 °C einfach in guten bis sehr guten Ausbeuten von 80%–92% gewinnen (vgl. Schema). Um die experimentellen Ergebnisse zu erklären, wird ein vorläufiger Mechanismus dargestellt und diskutiert.

– Kapitel 4 –
Drei Strukturhomologe Isothiocyanate zeigen “Janus”-Eigenschaften in menschlichen HepG2 Zellen

(Publiziert: *Environ. Mol. Mutagen.* **2009**, *50*, 164–170)

Interdisziplinäres Forschungsprojekt

Isothiocyanate (ITC) wie z. B. die strukturhomologen terminalen Methylthioalkyl-isothiocyanate 4-(Methylthio)butyl-isothiocyanat (MTBITC) und 5-(Methylthio)pentyl-isothiocyanat (MTPeITC) sind als stark chemopräventive Wirkstoffe bekannt. Diese kommerziell erhältlichen, in hoher Reinheit sehr teuren ITC können durch aufwendige Extraktionsverfahren aus kohlartigen Gemüsesorten wie Brokkoli oder Blumenkohl, aber auch aus Senf isoliert werden. Das chemopräventive Potenzial dieser ITC und dessen Ursprung werden an menschlichen Zellkulturen erforscht. Eine hohe und reproduzierbare Reinheit der ITC ist dabei entscheidend für verlässliche Resultate und damit für den Forschungserfolg. Mit dem hier vorgestellten vierstufigen

Syntheseprotokoll lassen sich MTBITC (1.3 g) und MTPeITC (1.5 g) in moderaten Gesamtausbeuten und hoher Reinheit (>99,9%) herstellen. Die einfache, vierstufige Synthese verwendet günstige Chemikalien und ist auch für die Synthese höherer ITC-Homologe anwendbar.

Verschiedene erfolgreiche Zellkulturstudien, die von den Arbeitsgruppen um Lamy und Mersch-Sundermann durchgeführt wurden, beruhen auf der Qualität der von Kotke nach diesem Protokoll hergestellten Isothiocyanate MTBITC und MTPeITC. Diese medizinischen Studien identifizieren MTBITC und MTPeITC als „Janus"-Verbindungen, weil beide in Abhängigkeit von ihrer Konzentration deutliche Gentoxizität und auch Antigentoxizität zeigen. In diesem Kapitel sind die ITC-Synthesen sowie die Kurzfassung und die Einleitung der interdisziplinären Forschungspublikation enthalten.

– Kapitel 5 –
Ausblick – Forschungsperspektiven

Dieses Kapitel bietet Aspekte, Inspirationen und praktikable Perspektiven für mögliche neue Forschungsprojekte über explizit wasserstoffbrücken-bildende (Thio)Harnstoff-Organokatalysatoren in (nicht-)stereoselektiven organischen Reaktionen, Anwendungen und Methoden. Die hier skizzierten Forschungsziele entstammen vorwiegend dem Forschungsschwerpunkt und den Resultaten in Kapitel 1 sowie den Kapiteln 2.2–2.3. Sie ebnen den Weg für die systematische Entwicklung neuer, hochwirksamer (Thio)Harnstoff-Organokatalysatoren und nützlicher, innovativer Synthesemethoden. Kooperativ katalysierte Epoxidöffnungen mit variablen Nucleophilen, Kaskadenreaktionen sowie organokatalytische Varianten der Neber- und der Favorskii-Umlagerung werden vorgeschlagen, schematisch dargestellt und hinsichtlich ihrer Realisierbarkeit erörtert. Diese Reaktionen ermöglichen die Darstellung unterschiedlichster Synthesebausteine sowie Verbindungsklassen und versprechen dadurch eine breite Anwendbarkeit in der organischen Synthesechemie.

– CHAPTER 1 –

– Hydrogen Bonding in Organic Synthesis –

(Thio)urea Organocatalysts

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This book chapter is dedicated to my mother Eva Kotke for her untiring support

Preface

The entire chapter 1 represents the core contribution to the seminal Wiley-VCH book "Hydrogen Bonding in Organic Synthesis".
The section 1.1 (*"Introduction and Background"*) of this chapter additionally serves as the introduction of the present PhD thesis.

This chapter for the first time provides the entire success story of explicit double hydrogen-bonding (thio)urea organocatalysts. All mono- and bifunctional stereoselective and also non-stereoselective (with a special focus on *N*,*N'*-bis[3,5-(trifluoromethyl)phenyl]thiourea) representatives of this rapidly growing and timely class of non-covalent organocatalysts are presented and discussed; *all 150 original articles of one research decade* (1998–2008) exclusively involved in this field are reviewed and adequately cited to demonstrate the correlations among the various catalysts and methods, respectively.

The topics of this critical and comprehensive overview range from the initial investigations and roots in enzyme catalysis, co-crystal structure analysis, and supramolecular chemistry to the development, optimization, and modern synthetic applications of highly efficient enantioselective (thio)urea organocatalysts even in multistep syntheses. This highly informative picture given herein employs *184 schemes* and *64 figures* (e.g., typical substrate and product ranges, reaction parameters, mechanistic proposals, catalyst structure design aspects) to document and evaluate the potential of *each* (thio)urea organocatalyst and methodology, respectively, in synthetic organic chemistry.

– CHAPTER 1 –

– Hydrogen Bonding in Organic Synthesis –

(Thio)urea Organocatalysts

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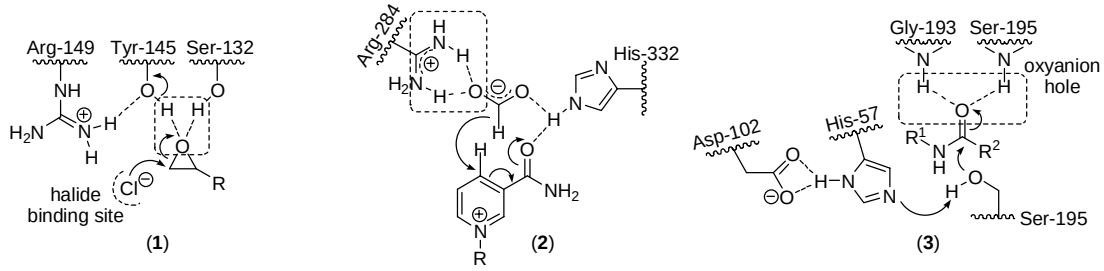
This book chapter is dedicated to my mother Eva Kotke for her untiring support.

1.1 Introduction and Background

The concept of non-covalent organocatalysis[1-8] utilizing explicit hydrogen-bonding (thio)urea derivatives originates from natural catalytic systems such as ribonucleases, antibodies, and enzymes that can be considered as archetypes of organocatalysts.[9] Crystal structure analyses, spectroscopic investigations[10, 11], and computational studies[12, 13] revealed that enzymes, for instance, typically do not contain strong Lewis acids for the binding (recognition) of the substrate resulting in catalytic activity and stereoselectivity owing to weak enthalpic binding and small Gibbs energy changes.[14] In metal-free enzymes the recognition process is dominated by hydrogen-bonding ("partial protonation")[15-20] and hydrophobic interactions[21-23] in an often complex interplay with other weak non-covalent interactions such as aromatic π-stacking,[24] van der Waals,[25, 26] and dipole-dipole interactions[27, 28] making the details of enzyme catalysis difficult to rationalize.[14, 29-31] These interactions are provided by the enzyme's active site, that is, an ensemble of various functionalities, e.g., hydrogen-bond donors properly arranged in the enzyme binding pocket capable to coordinate selectively and to activate the embedded substrate(s) for highly specific biochemical transformations via host-guest complexes. Scheme 1 exemplarily visualizes the active sites of enzymes employing double hydrogen-bonding interactions to the hydrogen bond accepting basic site of various substrates leading to substrate activation and acceleration of the respective reactions. Haloalcohol dehalogenase (**1**) activates an epoxide for reversible epoxide ring opening by chloride[32] akin to enzymatic epoxide hydrolysis catalyzed by epoxide hydrolase (Scheme 8),[33-35] formate dehydrogenase (**2**) promotes the oxidation of formate,[29] and serine protease (**3**) accelerates amide hydrolysis by double hydrogen-bonding, multiple non-covalent catalyst-substrate interactions, and bifunctional catalysis (Scheme 1).[36]



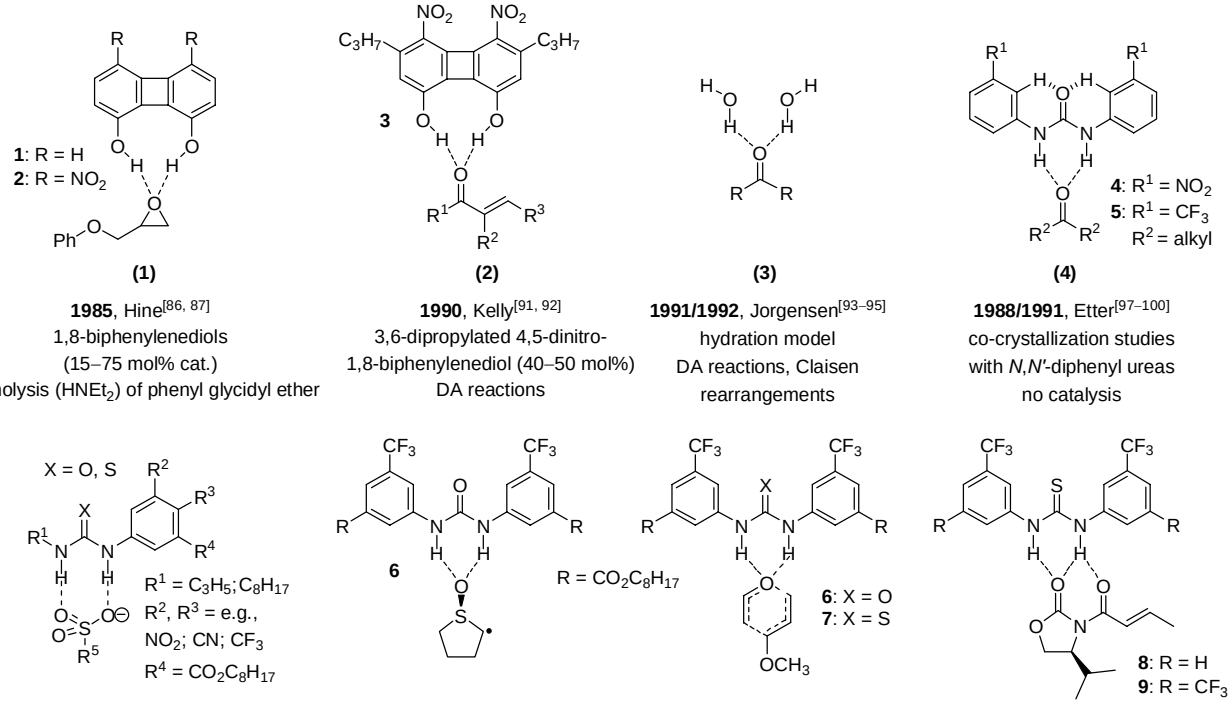
Scheme 1. Active sites of enzymes employing a double hydrogen-bonding motif for substrate coordination and activation in various biochemical transformations: Haloalcohol dehalogenase (**1**), formate dehydrogenase (**2**), and serine protease (**3**).

Metal-free catalysis as performed by hydrogen-bonding enzymes show no apparent product inhibition[37] resulting in high TOF values while proceeding in the natural medium water under aerobic conditions.[38, 39] These characteristics offer attractive perspectives for the development of artificial metal-free catalytic systems as supplementation and/or alternatives to traditional metal(-ion)-containing, often toxic,

water-incompatible, and air-sensitive catalysts. Artificial enzymes or enzyme mimetics[40-42] designed according to the Pauling paradigm[43, 44] or related paradigms[45, 46] aim at the imitation of the entire enzyme architecture including the active sites(s) and also the structurally complex proteine backbone.[47] This design strategy leads to "synzymes" presumably employing mechanisms akin to the natural counterparts obeying general acid catalysis[48, 49] and Michaelis-Menten kinetics[50] to provide high catalytic efficiencies comparable to natural systems.[29, 51] The structure design of non-covalent and covalent organocatalysts,[52-83] however, limits itself to the mimicry of the suggested active site of the natural catalyst thus resulting in readily accessible, small, purely organic compounds operating in an enzyme-like fashion aiming at high catalytic activities and stereoselectivities at minimal structural complexity such as *explicit double hydrogen-bonding (thio)urea organocatalysts* closely described in this book chapter.

The success story of explicit double hydrogen-bonding (thio)urea organocatalysts was initiated by seminal studies performed by Hine and co-workers,[84] when identifying the clamp-like double hydrogen-bonding motif in co-crystals[85] between conformationally rigid 1,8-biphenylenediol **1** and Lewis basic substrates such as hexamethyl phosphoramide 1,2,6-trimethyl-4-pyridone, and 2,6-dimethyl-γ-pyrone. X-ray crystal structure analyses showed 1,8-biphenylenediol **1** capable of providing simultaneously two identical strong hydrogen bonds to the same oxygen atom of the respective substrate.[84] The same group, in 1985, reported diol **1** (15–70 mol% loading) to efficiently catalyze the aminolysis of the epoxide phenyl glycidyl ether with diethyl amine in butanone at 30 °C (**(1)**; Figure 1). A Brønsted plot based on catalysis of this model reaction by a range of substituted phenols suggested that diol catalyst **1** promoted this epoxide opening with an efficiency per OH group that would expected from a phenol 600-fold as acidic, and that both hydroxy groups are involved in the epoxide activation as depicted in complex **(1)** (Figure 1).[33, 86, 87] Further investigations on the ionization constants (pK_a values) and the double hydrogen-bonding ability of various 1,8-biphenylenediols bearing electron-rich or electron-deficient substituents, respectively,[87, 88] indicated a close correlation between acidity and improved hydrogen-bonding properties in the formation of co-crystals; acidic 4,5-dinitro-1,8-biphenylenediol **2** was found to be the strongest double hydrogen-bond donor (**(1)**; Figure 1).[89, 90] Based on these results Kelly et al., in 1990, synthesized 3,6-dipropyl-4,5-dinitro-1,8-biphenylenediol **3** more soluble than **2** in the reaction solvent CD_2Cl_2 for catalysis (40–50 mol% loading **3**) of Diels-Alder reactions between various α,β-unsaturated aldehydes as well as ketones and predominantly cyclopentadiene at 55 °C. The observed up to 30-fold rate enhancements determined by ^{1}H NMR were interpreted by the activation of the dienophile through double hydrogen-bonding of **3** to the carbonyl group giving substrate-catalyst complex **(2)** depicted in Figure 1.[91, 92] This catalyst-substrate association motif was supported by computational studies on the accelerating solvent effect of water relative to aprotic solvents in Diels-Alder reactions[93, 94] and Claisen rearrangements.[95] The resulting hydration model suggested by Jorgensen et al., in 1991/1992, explained the observed rate enhancements in water not with *cooperative* hydrogen bonding effects, but with a significant aqueous solvent effect described as clamp-like *explicit* hydrogen-bonding interaction of two water molecules to the carbonyl group leading to a preferential stabilization of the transitions states (**(3)**; Figure 1). The pioneering work by Hine and Kelly demonstrated that structural rigidity of a double hydrogen-bonding organocatalyst such as 1,8-biphenylenediols and general acid catalysis[48, 49] ("partial *de*protonation") instead of specific acid catalysis ("full *de*protonation") typical for Brønsted-acid catalysis[6, 47] are important aspects upon which to base (thio)urea organocatalyst design. From 1988 to 1991 the Etter group published seminal X-ray structural studies on hydrogen-bond directed co-crystallization of imides and *N*,*N*′-diphenyl ureas with Lewis basic compounds such as triphenylphospine oxide,[96] nitroaromatics, ethers, ketones, and sulfoxides. For the first time urea derivatives were identified to be also capable of explicit double hydrogen-bonding interactions affording stable host-guest complexes such as **(4)** formed by *N*,*N*′-bis(3-nitrophenyl)urea **4** (Figure 1).[97, 98] Further intensive investigations on various hydrogen-bond patterns in co-crystal structures of organic compounds[99] and on hydrogen-bonding mediated molecular recognition[100] suggested that urea derivative **4** readily formed stable highly qualitative 1:1 co-crystals with cyclohexanone due to the electron-withdrawing substituent at the *meta* position. This substituent pattern allows structure stabilizing intramolecular hydrogen bonds between the carbonyl group and the adjacent hydrogen atoms at the *ortho* position and inhibits self-association through intermolecular hydrogen bonds to the carbonyl group; replacing the nitro group, however, with electron-donating substituents (CH_3, OCH_3) or the nitro group at the *para* position led to decreased hydrogen-bonding properties, complexation, and co-crystals of reduced quality, while electron-deficient *N*,*N*′-bis[(3-trifluoromethyl)phenyl]urea **5** was found to be a good complexing agent.[98] Hydrogen-bonding interactions between a ligand and a substrate have long been known to be responsible - among other non-covalent interactions - for the formation of supramolecular structures called supra- or supermolecules ("Übermolekül") a term coined by Wolf et al., in 1937.[101] In often-overlooked experimental and theoretical investigations reported by Wilcox and co-workers, in 1992, a series of electron-rich and electron deficient *N*-allyl[102]- and

N-octyl-*N*′-phenyl (thio)ureas[103] were evaluated in solution ($CHCl_3$) for hydrogen-bond based molecular recognition of sulfonates, phosphates, carboxylates, and zwitterionic 4-tributylammonium-1-butanesulfonate as well as for their potential in supramolecular chemistry in dependence on their substituent pattern.[103, 104] The formation of the complex and the host-guest association, respectively, were estimated in titration experiments by ^{1}H NMR shift data (downfield shifts of the N-H signal) and the shift of the UV/Vis absorptions relative to the substrate-free (thio)urea solutions.[102] In these studies again electron-deficient *meta*- or *para*-substituted thiourea derivatives turned out to be stronger double hydrogen-bond donors than the respective ureas and (thio)ureas, and acidity could be confirmed as a useful parameter for the prediction of the hydrogen bond ability and thus improved molecular recognition (**(5)**; Figure 1). Curran and Kuo, in 1994, introduced *N*,*N*′-diphenylurea **6** as first double hydrogen-bonding urea organocatalyst accelerating the allylation of α-sulfinyl radicals with allytributylstannane (**(6)**; Figure 1). Urea **6** incorporates *meta*-CF_3 groups as electron-withdrawing substituents more compatible with the radical reaction than NO_2 groups and also lipophilic ester substituents to improve the solubility in common organic solvents. In the presence of substoichiometric amounts of **6** (20–100 mol%) small rate accelerations and increased *cis*/*trans* selectivities were observed.[105] The same group, in 1995, utilized urea catalyst **6** (10–50 mol%) in Claisen rearrangements in C_6D_6 at 80–100 °C resulting in



(1)

1985, Hine[86, 87]
1,8-biphenylenediols
(15–75 mol% cat.)
aminolysis ($HNEt_2$) of phenyl glycidyl ether

(2)

1990, Kelly[91, 92]
3,6-dipropylated 4,5-dinitro-
1,8-biphenylenediol (40–50 mol%)
DA reactions

(3)

1991/1992, Jorgensen[93–95]
hydration model
DA reactions, Claisen
rearrangements

(4)

1988/1991, Etter[97–100]
co-crystallization studies
with *N*,*N*′-diphenyl ureas
no catalysis

(5)

1992/1995, Wilcox[102–104]
N,*N*′-disubstituted (thio)urea derivatives;
studies on substituent effects in anion
recognition and supramolecular chemistry

(6)

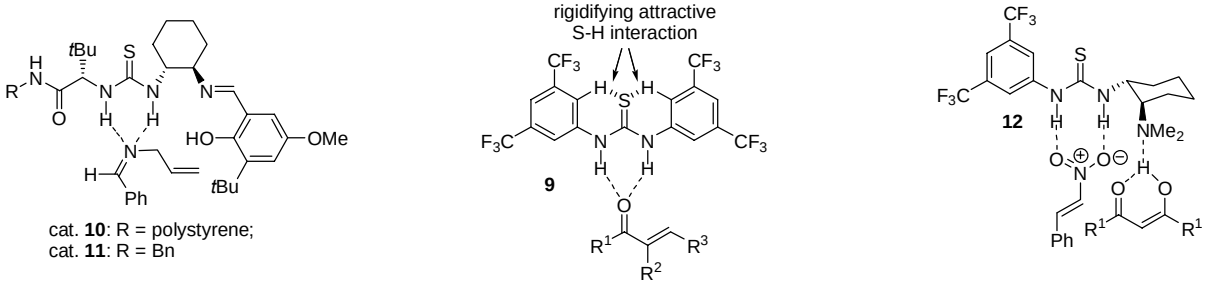
1994, Curran[105]
N,*N*′-diaryl urea (20–100 mol%)
allylation of sulfinyl radicals

(7)

1995, Curran[106]
N,*N*′-diphenyl (thio)urea
(10–100 mol%); first thiourea cat. **7**
Claisen rearrangements

(8)

1997/2000/2002, Schreiner[107, 112, 114, 116]
electron-deficient *N*,*N*′-diphenyl
thioureas (1 mol%; 25 mol% cat.),
DA reactions



(9)

1998/2002, Jacobsen[123]
Schiff base thiourea catalysts (2 mol%)
first enantioselective (polymer-bound) thioureas,
Strecker reactions (92% yl.; 91% *ee*)

(10)

2003, Schreiner[1, 114, 125]
guidelines for (thio)urea catalyst
structure design, DA reactions and 1,3-dipolar
cycloadditions ("catalytic amount": 1 mol% **9**)

(11)

2003/2005, Takemoto[131]
first bifunctional thiourea catalyst
asym. addition of malonates to
nitrostyrenes (up to 99% yl.; 94% *ee*)

Figure 1. Chronological order of milestone achievements towards catalytically active (thio)urea organocatalysts utilizing explicit double hydrogen-bonding interactions for substrate activation.

1.7- to 5.0-fold rate accelerations; at 100 mol% **6** up to 22-fold relative rate enhancements were reported.[106] A derivative of **6** lacking both NH protons due to dimethylation (k_{rel} = 1.0) and a corresponding benzanilide (k_{rel} = 1.6) capable of providing only a single hydrogen bond proved to be catalytically inactive in the model Claisen rearrangement under identical conditions. This finding is in line with the aforementioned results on hydrogen-bonded substrate-catalyst complexes and emphasizes the importance of the double hydrogen-bonding motif on the catalytic activity of (thio)urea organocatalysts. It is notable that thiourea derivative **7** was also examined in the model Claisen rearrangement of 1-methoxy-3-vinyloxy-propene. Although **7** turned out to slowly decompose under the reaction conditions a small rate accelerating effect could be estimated (at <10% decomp.: k_{rel} = 3–4); however, this experiment by Curran and Kuo marks the first application of a hydrogen-bonding thiourea derivative as organocatalyst.[106] Incomprehensibly, these promising findings had not been continued and their potential for catalyst development had remained unrecognized until the Schreiner group, in 1997, started research efforts towards explicit hydrogen-bonding thiourea organocatalysts.[107] Thiourea instead of urea derivatives were chosen for proof-of-principle studies since thiourea derivatives a) are more soluble in a variety of organic solvent, b) easier to prepare (liquid thiophosgene is much easier to handle than phosgene), c) the thiocarbonyl group is a much weaker hydrogen-bond acceptor leading to less catalyst self-association and to a higher concentration of free catalyst, and d) show a higher acidity (urea: pK_a = 26.9; thiourea: pK_a = 21.0)[108] possibly leading to more stable hydrogen-bonded catalyst-substrate complexes consistent with Hine's, Kelly's, Etter's and Wilcox's results mentioned above. Furthermore, encouraging clues for the strong hydrogen-bonding ability of thiourea derivatives have been provided from different research fields and applications, respectively, e.g., supramolecular chemistry, molecular (anion) recognition,[109-111] crystal engineering, herbicides, and inclusion compounds. In 2000, Schreiner and Wittkopp published their first results on thiourea organocatalysis.[112] The modification of Curran's thiourea derivative **7** by removal of the coordinating ester groups led to electron-deficient hydrogen-bonding *N,N'*-bis[(3-fluoromethyl)phenyl]thiourea **8** that was found to accelerate the Diels-Alder reaction of methyl vinyl ketone with cyclopentadiene employing a substoichiometric "catalytic amount"[113] of 1 mol% in cyclohexane (no cat: 18% conv.; **8**: 30% conv./1 h), chloroform (no cat.: 31% conv.; 8: 52% conv./1 h), and even in the hydrogen-bonding environment of water (no cat.: 74% conv.; **8**: 85% conv.).[112] Based on computations for the DA reaction between MVK and Cp catalyst **8** was found to compete effectively with water and it stabilizes MVK by 6.4 kcal mol^{-1} (two water molecules by only 3.7 kcal mol^{-1}) and the polarized DA transition state through explicit double hydrogen-bonding interactions complementary to hydrophobic interactions through water.[112, 114] Subsequent binding studies on the interaction of **8** with a bidentate *N*-acyloxazolidinone dienophile were performed to verify the working hypothesis that a hydrogen-bonding thiourea organocatalyst such as **8** behave like a Lewis acid (e.g., Et_2AlCl_2)[115] such that the 1,3-diketone is activated through bidentate coordination to both carbonyl groups accelerating Diels-Alder reactions.[116] Utilizing a combination of NMR methods, low-temperature IR spectroscopy, and computations on reduced model systems various double hydrogen-bonded model complexes (1:1 ratio) between **8** and the *N*-acyloxazolidinone were analyzed assuming that the thiourea moiety in catalyst **8** adopts the required *syn* orientation (*trans*/*trans* rotamer);[117] this was suggested from the crystal structure data of urea **4**[97, 98] and in particular of structurally related thiourea **9**.[1, 118, 119] The analyses of the temperature-dependent NH signal situation (^{1}H NMR) revealed that **8** exhibits a large dimerization entropy (ΔS = –35.6 cal mol K^{-1}) leading to efficient self-association only at low temperature (193 K) thus making at room temperature (291 K) free catalyst **8** available for favored complexation of the 1,3-diketone dienophile (ΔS = –9.6 cal mol K^{-1}). A comparison of computed and measured (at 77 K) IR-active carbonyl absorptions employed as indicator for intermolecular hydrogen-bonding interactions upon binding implies that **8** interacts with both the ring carbonyl ($\Delta\nu$ = +24 cm^{-1}) and the side chain carbonyl group ($\Delta\nu$ = +7.2 cm^{-1}) in a mode of the bidentate complex **(8)** leading to stabilization of the selective, but disfavored 1,3-diketone *syn* conformation (Figure 1). This catalyst-substrate interaction is supported by the observed diastereoselectivity (*dr*) of Diels-Alder reactions between cyclopentadiene and *N*-acyloxazolidinone in the presence of 25 mol% **8**, **9**, or $AlCl_3$, respectively. **8** gave 74 % conv. (48 h, 23 °C) and (*dr* 77:23) and $AlCl_3$ 95% conv. (*dr* 92:8 at –78 °C; 1 h). An even increased efficiency at 25 mol% loading in the same model reaction was found for more acidic *N,N'*-bis[3,5-(trifluoromethyl)phenyl]thiourea **9** (78% conv.; *dr* 81:19; 48 h, 23 °C) that, later on, was established by Schreiner and co-workers as highly active non-stereoselective privileged[120] organocatalyst for various organic reactions (section 1.2.1.1). These results demonstrated that small hydrogen-bond donors and metal-containing Lewis-acids lead to isostructural complexes with 1,3-diketones despite large differences in the interaction energies, and that double hydrogen-bonding thiourea organocatalysts such as **8** and **9** act like weak Lewis acids by lowering the LUMO of the dienophile through electron-deficient complexation affording the observed rate accelerations.[116, 121, 122] Moreover, hydrogen-bonding (thio)urea organocatalysis for the first time had been specifically identified as the desired metal-free approach for catalysis of a organic transformation traditionally dominated by metal-containing catalysts. In parallel developments, the Jacobsen group,

however, originally involved in the development of organometallic catalytic systems searched for a novel tridentate chiral ligand for the efficient chirality transfer in asymmetric Strecker reactions of *N*-allyl-protected aldimines. In 1998, high-throughput screening (HTS) of polystyrene-bound tridentate Schiff bases provided the first enantioselective (92% yield.; 91% *ee*) thiourea organocatalysts **10** and **11** (Figure 1);[123] the high efficiencies of these Schiff base catalysts[124] were ascribed, in 2002, to activating double hydrogen-bonding interactions between the imine and the thiourea catalyst (**(9)**; Figure 1) consistent with Schreiner's findings[112, 116, 125] on thiourea catalyst activity (section 1.2.2.1).[126] Schreiner and Wittkopp, in 2003, elucidated the thiourea structure-activity relationship in a series of Diels-Alder reactions between cyclopentadiene and five different dienophiles such as MVK and (aza)chalcones in the presence of various symmetrically *N*,*N*′-dialkyl- and diphenyl- substituted thiourea derivatives (1 mol% loading) as potential catalysts.[114] Kinetic data determined with ^{1}H NMR revealed thiourea derivatives incorporating rigid electron-withdrawing aromatic substituents such as **8** (k_{rel} = 2.5–5.9) and **9** (k_{rel} = 4.8–8.2) to be the most efficient in accelerating model DA reactions, while dialkyl- and electron-rich *N*-phenyl thioureas bearing *ortho* substituents proved to be poor catalysts (e.g., *N*,*N*′-diphenyl thiourea: k_{rel} = 1.1–1.5). Product inhibition turned out to be low since the catalytic activity was still present after 80% conversion. This is in line with the weak enthalpic binding of the thiourea catalyst to carbonyl groups (~7 kcal mol^{-1} at rt)[116] and emphasizes the entropy term in the formation of the catalyst-substrate complex. The more rigid the free thiourea catalyst, the more stable is the complex, minimizing the entropy loss upon complexation. Thiourea catalysts bearing flexible substituents such as octyl or the phenyl groups have low rotational barriers (e.g., *N*,*N*′-diphenyl thiourea: 1.5 kcal mol^{-1}), while thiourea derivative **9** appears to be conformationally stable, forms more stable complexes, and gives increased rate enhancements due to a higher barrier (3.4 kcal mol^{-1}), an approach already applied by Hine and Kelly.[86, 91] The rigidity of **9** and comparable thioureas bearing electron-deficient *meta*- or *para*-substituted phenyl substituents is suggested to root in intermolecular hydrogen-bonding interactions between the positively polarized *ortho* hydrogen atom and the Lewis-basic thiocarbonyl sulfur visualized in complex **(10)** (Figure 1). This attractive interaction hinders the rotation of the thiourea moiety and favors complexation entropically, while substituents at the *ortho* position lead to repulsive interactions with the thiocarbonyl group decreasing the rotational barrier. In addition to this structural effect, **9** possesses due to CF_3 substitution acidified NH protons capable of providing strong hydrogen bonds. In 2003, Schreiner highlighted these experimental and theoretical findings in the first review[1] on (thio)urea organocatalysts utilizing explicit double hydrogen-bonding interactions and provided rough guidelines and concepts for (thio)urea catalyst design: a) If the catalyst is able to interact with the starting material, the transition state (TS), and the products, it is necessary that the relative stabilization of the TS is the largest, b) the bi- or multidentate mode of catalyst-substrate binding increases catalytic efficiency and restricts degrees of freedom, c) the catalyst structure should be an adequate compromise between rigidity and flexibility, d) to avoid self-association the catalyst should not incorporate strong hydrogen bond acceptors such as ester groups; the non-coordinating acidifying CF_3 group as in the 3,5-(trifluoromethyl)phenyl moiety of **9** appeared to be ideal, e) weak interactions reduce product inhibition allowing "catalytic amounts" of the catalyst, and also from an environmental point of view[38, 39, 127, 128] f) the catalyst should be water-compatible or even catalytically active in water.[129, 130] These guidelines are not limited to the development of non-stereoselective (thio)urea organocatalysts (section 1.2.1), but also or in particular are applicable to stereoselective derivatives of benchmark thiourea catalyst **9** (section 1.2.2) as for the first time demonstrated by Takemoto and co-workers, in 2003, when introducing the first bifunctional hydrogen-bonding thiourea organocatalyst **12** depicted in **(11)** (Figure 1) (section 1.2.2.1).[131]

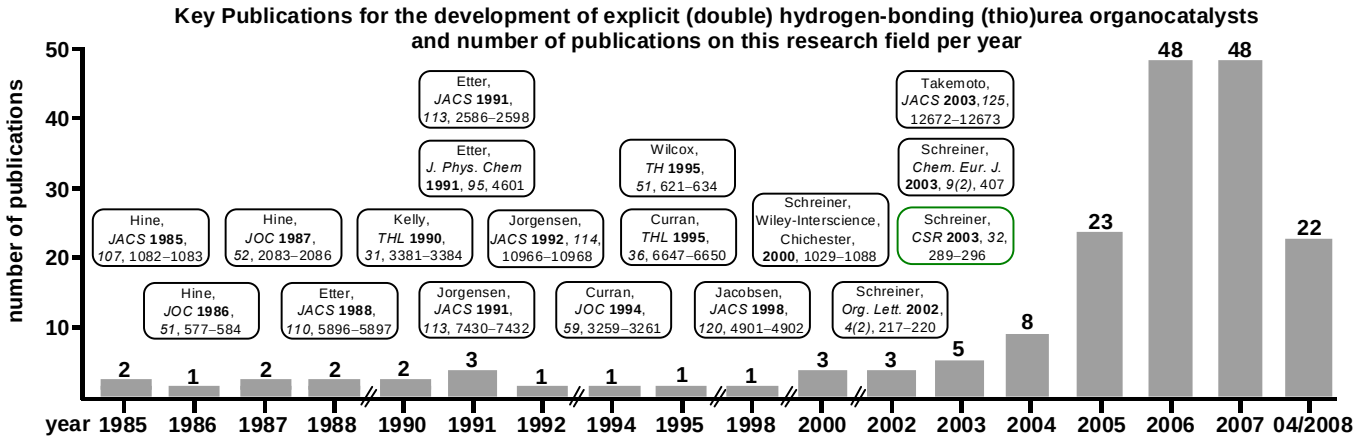


Figure 2. Key publications on hydrogen-bonding (thio)urea organocatalysts and number of publications per year in this research field.

The number of publications per year on (thio)urea organocatalysis illustrated in the bar chart (Figure 2) mirror that not only the resurrection of the term "organocatalysis", in 2000,[132] a translation of the old and neglected concept "organic catalysis" coined by Langenbeck with the first authoritative review on "organic catalysts",[133-138] but also the early publications in 1997 to 2003 provided inspiring and encouraging impulses on the scientific community to refocus on this research field. The steep increase of publications also arises from the often easy and inexpensive preparation of tailor-made (thio)urea organocatalysts in a fashion akin to a unit construction system employing primary amine functionalized chiral compounds, e.g., chiral pool compounds, as (privileged) chiral scaffolds[120] and isocyanates or isothiocyanates as building blocks, respectively, to obtain the respective chiral (thio)urea derivatives. Notably, these chiral scaffolds such as *trans*-1,2-diaminocyclohexane and related amines,[139] cinchona alkaloids,[140, 141] 2,2′-binaphthol derivatives,[142] amino alcohols,[140] oxazolines[143, 144] and (thio)urea derivatives[145, 146] are incorporated in chiral ligands of highly efficient organometallic catalytic systems that represent a benchmark for the catalytic performance of (thio)urea organocatalysts. Owing to the strong hydrogen-bond donor ability the 3,5-bis(trifluoromethyl)phenyl thiourea moiety derived from thiourea **9** has gained importance as "substrate anchor" and is incorporated in various highly active and (non)-stereoselective double hydrogen-bonding thiourea derivatives (Figure 3). The corresponding achiral 3,5-bis(trifluoromethyl)phenyl isothiocyanate is readily accessible by a one-step procedure developed by Kotke and Schreiner.[119, 147]

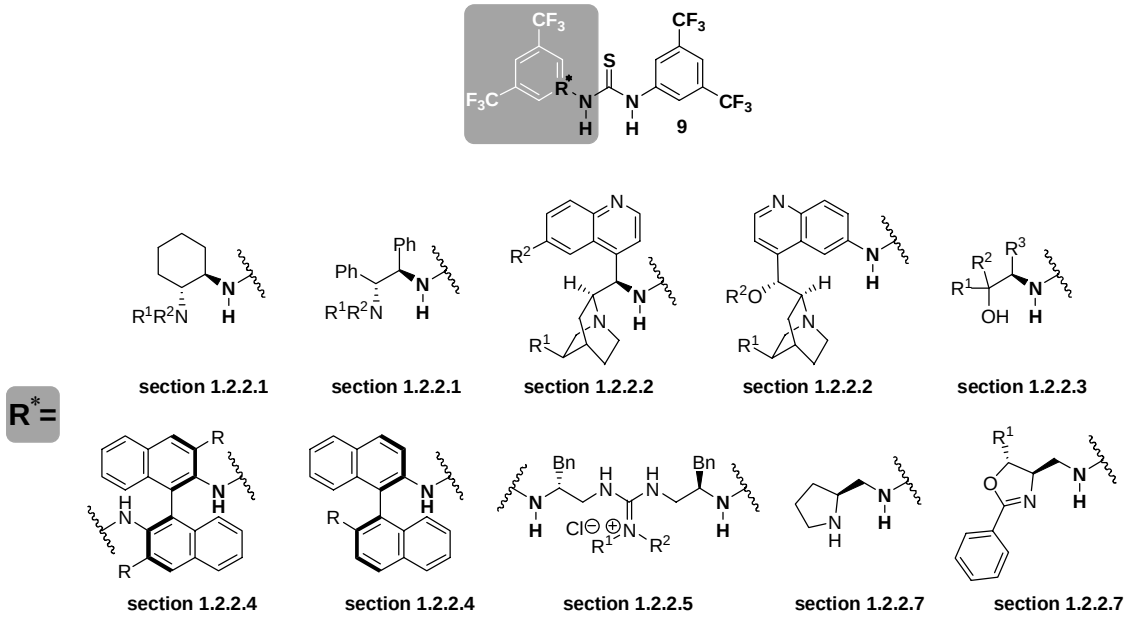


Figure 3. Stereoselective, chiral thiourea derivatives of achiral benchmark thiourea organocatalyst *N,N′*-bis[3,5-(trifluoromethyl)phenyl]thiourea **9**; stereoselective hydrogen-bonding thiourea organocatalysts incorporating the privileged 3,5-bis(trifluoromethylphenyl)thiourea moiety. The (thio)urea catalyst structure is the leitmotif for the chapter organization.

In the following book chapter[119] the last 10 years of research on (thio)urea organocatalysis are extensively summarized considering catalyst design concepts, experimental details such as structure optimization studies, screening conditions, reaction conditions, the typical substrate and product spectrum of each procedure as well as proposed mechanistic scenarios for each published methodology (~150 articles). The reader may obtain an impression on the variety of this relatively young research field, may find helpful aspects for own research efforts and synthetic applications, or become simply "generally" informed on (thio)urea organocatalysts for *"Hydrogen Bonding in Organic Synthesis"*.

1.2 Synthetic Applications of Hydrogen-bonding (Thio)urea Organocatalysts

1.2.1 Non-stereoselective (Thio)urea Organocatalysts

1.2.1.1 Privileged Hydrogen-bonding *N*,*N*′-bis[3,5-(trifluoromethyl)phenyl]thiourea

Wittkopp and Schreiner introduced the simple electron-deficient *N*,*N*′-bis[3,5-(trifluoromethyl)phenyl]thiourea **9** as an efficient double hydrogen-bonding organocatalyst in a series of Diels-Alder reactions and 1,3-dipolar cycloadditions of nitrones.[1, 114, 116] These proof-of-principle studies were also accompanied by computational investigations and soon thereafter were taken up by several groups for the development of metal-free, non-stereoselective synthetic applications, which are summarized and presented in the following section. Thiourea catalyst **9** is readily accessible in over 80% yield from inexpensive thiophosgene and 3,5-bis(trifluoromethyl) aniline by a straightforward large-scale (100 mmol) procedure developed by Kotke and Schreiner.[119, 148]

As demonstrated in a series of kinetic experiments by Wittkopp and Schreiner nitrone *N*-benzylideneaniline *N*-oxide can be activated for 1,3-dipolar cycloadditions through double-hydrogen-bonding **9**.[1] Takemoto and co-workers, in 2003, published the nucleophilic addition of TMSCN and ketene silyl acetals to nitrones and aldehydes proceeding in the presence of thiourea organocatalyst **9** (Figure 4).[149]

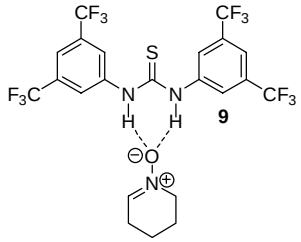
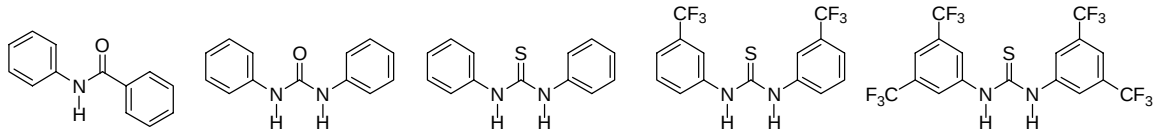


Figure 4. Proposed double hydrogen-bonding activation of nitrones through thiourea derivative **9**.

The initial screening reaction of 6-methyl-2,3,4,5-tetrahydropyridine *N*-oxide and TMSCN (5 equiv.) in the presence of 50 mol% of amide **13**, diphenyl urea **14**, and thiourea derivatives **15**, **8**, and **9**, respectively, in CH_2Cl_2 at −78 °C verified the correlation between N-H acidity and the strength of hydrogen bonds. These studies emphasized the necessity of double hydrogen-bonding coordination for effective substrate activation and rate acceleration (Figure 5).



13
83% yield/180 min

14
77% yield/90 min

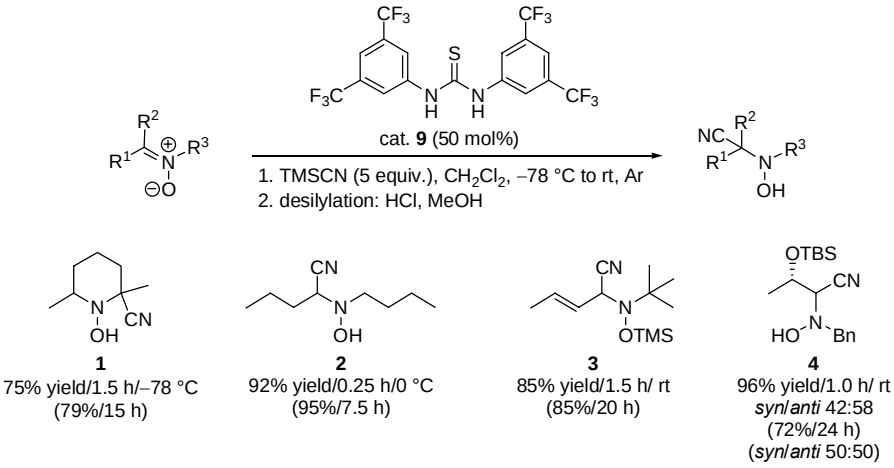
15
81% yield/45 min

8
75% yield/15 min

9
81% yield/15 min

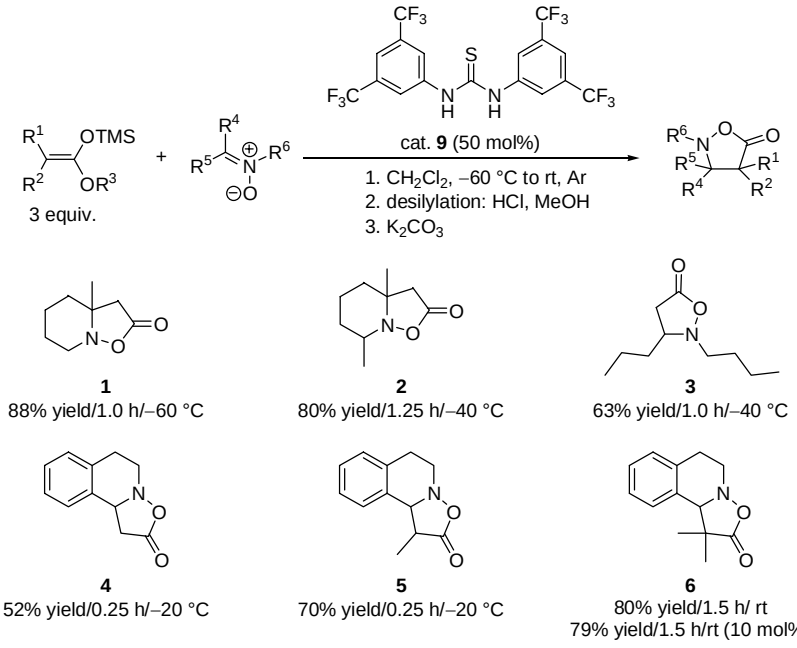
Figure 5. Hydrogen-bond donors (50 mol% loading) screened for the reaction of nitrone 6-methyl-2,3,4,5-tetrahydropyridine *N*-oxide and TMSCN at −78 °C. The yields and reaction times are given for the resulting adducts.

The scope of this cyanation was demonstrated by the reaction of acyclic, cyclic, and chiral nitrones with TMSCN affording the respective desilylated adducts **1**–**4** in yields ranging from 75–96% when utilizing 50 mol% of thiourea catalyst **9** (Scheme 2). The uncatalyzed reference experiments gave comparable yields but required longer reaction times (Scheme 2). In case of a conjugated nitrone the 1,2-adduct **3** instead of the 1,4-adduct was isolated and only a marginal effect of catalyst **9** on the diastereoselectivity (*syn*/*anti* 42:58) was observed for the formation of adduct **4** from a chiral nitrone (Scheme 2).



Scheme 2. Cyanation of nitrones utilizing TMSCN as cyanide source and catalyst **9**; yields in parentheses refer to uncatalyzed reactions.

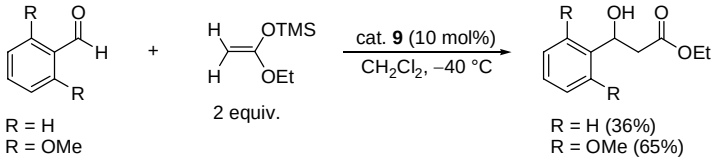
The authors also reported addition reactions of ketene silyl acetals to various **9**-activated nitrones followed by a desilylation and subsequent base-induced cyclization resulting in the products **1**–**6** in moderate to good yields (52%–88%) shown in Scheme 3. Without **9** for all examples no product formation occurred under otherwise identical conditions. Performing the reaction at reduced catalyst loading (10 mol%) did not affect reaction time nor product yield **(**adduct **6**; Scheme 3). For the screening reaction the quantitative recovery of catalyst **9** through column chromatography as well as catalyst reusability without loss of catalytic activity (1. cycle: 76% yield; 20 min; 2. cycle: 86%; 20 min) were demonstrated.



Scheme 3. Product range of the addition reactions of ketene silyl acetals to various nitrones activated by thiourea catalyst **9**.

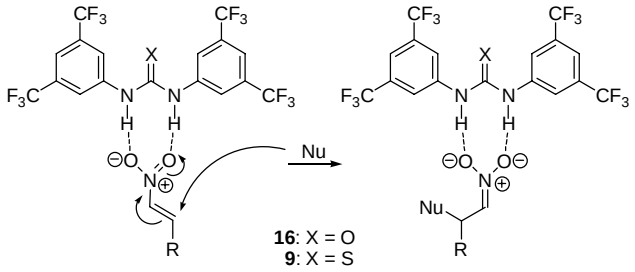
The **9**-catalyzed Mukaiyama-aldol reaction[74] of benzaldehyde and 1,2-dimethoxy benzaldehyde, respectively, with a ketene silyl acetal in the presence of 10 mol% thiourea **9** furnished the target product in low yield (36%), while the same reaction of an aldehyde bearing the methoxy groups at the *ortho* position of the aromatic ring proceeded smoothly giving 65% yield (Scheme 4).[149] The reason for the higher

reactivity of the electron-rich benzaldehyde could derive from a potential bidentate coordination of **9** at the oxygens of the carbonyl group and the contiguous methoxy group, respectively, affording a more activated catalyst-substrate intermediate.



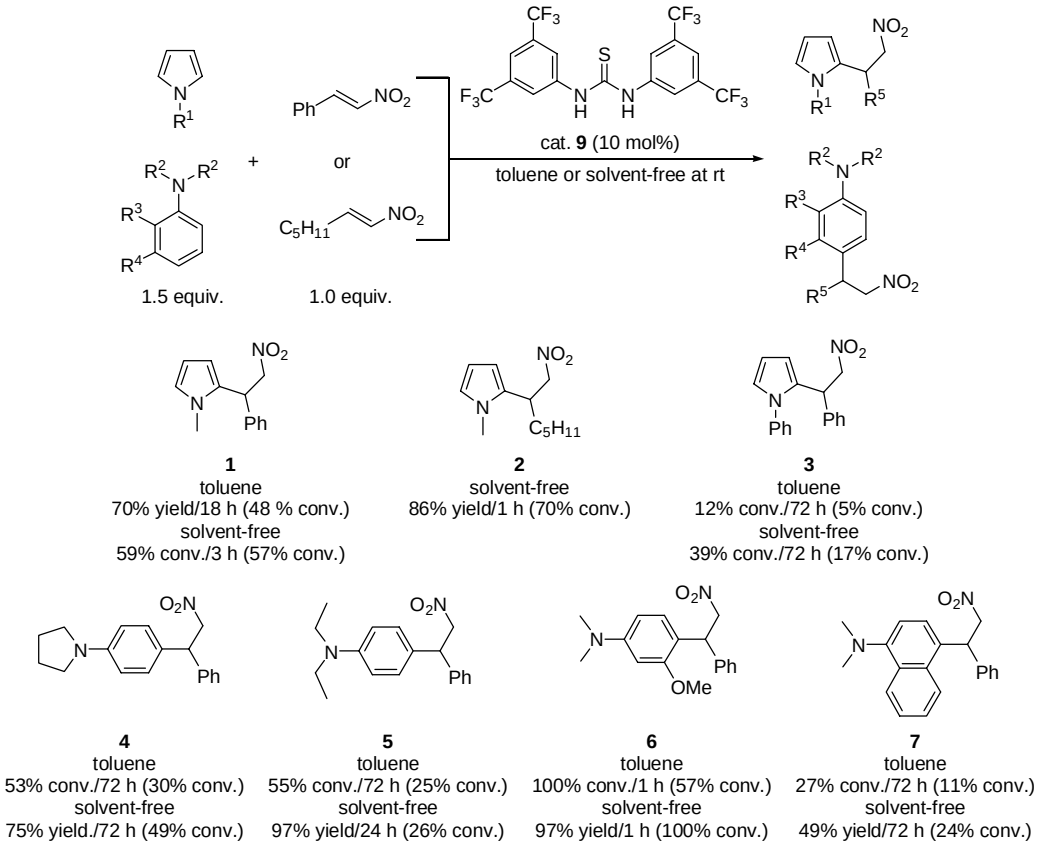
Scheme 4. Mukaiyama-aldol reaction of benzaldehydes with a ketene silyl acetal catalyzed by thiourea **9**.

Ricci et al. applied thiourea derivative **9** and its oxygen analogue urea **16** in a comparative catalysis study to the syntheses of alkylated aromatic and heteroaromatic *N*-containing compounds through Friedel-Crafts alkylation.[150] In analogy to the outlined working hypothesis (Scheme 5) the alkylating nitroalkenes may be activated through double hydrogen-bonding to facilitate the product-forming Michael-type nucleophilic attack on the *β*-position of *β*-nitrostyrene and (2-nitroethenyl) cyclohexane.

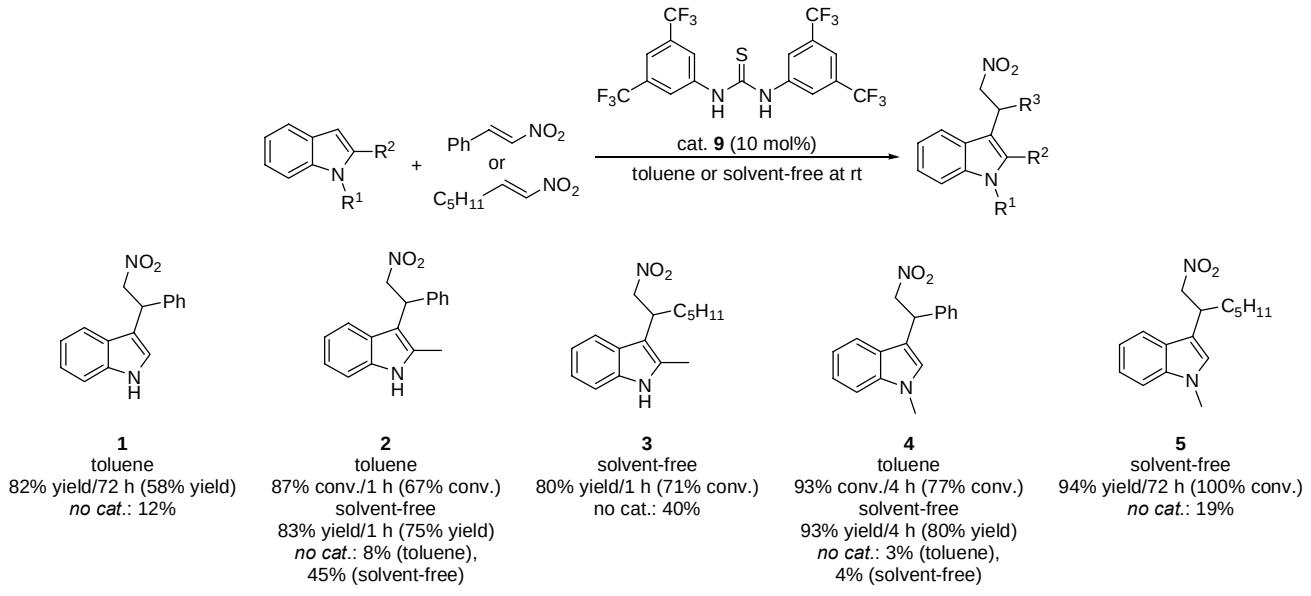


Scheme 5. Nitroalkene activation via double hydrogen-bonding enhances electrophilicity at *β*-position and facilitates Michael-type attack of the (hetero)aromatic nucleophile resulting in Friedel-Crafts adducts.

To demonstrate the catalytic efficiency of thiourea **9** and urea **16** (each 10 mol% loading) Friedel-Crafts alkylation of various aromatic and heteroaromatic substrates were performed at room temperature in toluene as well as under solvent-free conditions. The results for the products **1**–**7** shown in Scheme 6 revealed that in all cases the **9**-catalyzed reactions gave higher yields. In toluene *N*-methylpyrrole reacted smoothly to give the 2-substituted Friedel-Crafts adduct **1**, while the adducts **3**–**5** and **7** formed slowly and required longer reaction times (72 h). The presence of an electron-releasing function in the aryl moiety, as in the case of *m*-OMe-*N,N'*-dimethylaniline increased the reactivity and led to quantitative yields of adduct **6** within 1 h reaction time (Scheme 6). Solvent-free conditions remarkably improved the catalytic activity resulting in moderate to excellent yields of the Friedel-Crafts adducts (Scheme 6). Notably, catalyst-free control experiments failed in all cases. The same group extended this organocatalytic Friedel-Crafts alkylation to indole and various methyl-indoles serving as nucleophiles towards Michael acceptor *β*-nitroalkenes.[150] The formation of the products **1–5** proceeded with good conversions (82–93%) in toluene and provided good (83%) to very good yields (94%) under solvent-free conditions (Scheme 7). Under these conditions and MW irridiation (100 W) at 10 mol% loading of **9** even the challenging 2-position of 3-methyl indole was alkylated (49% yield/20 min). Since the **9**-promoted Friedel-Crafts alkylation and Michael addition,[151-154] respectively, worked under acid-free and mild conditions no polymerization side products were detected.

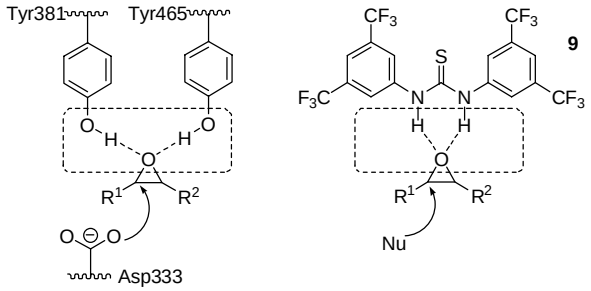


Scheme 6. Products resulting from **9**-catalyzed Friedel-Crafts alkylation of aromatic and heteroaromatic *N*-containing substrates performed in toluene and without solvent.



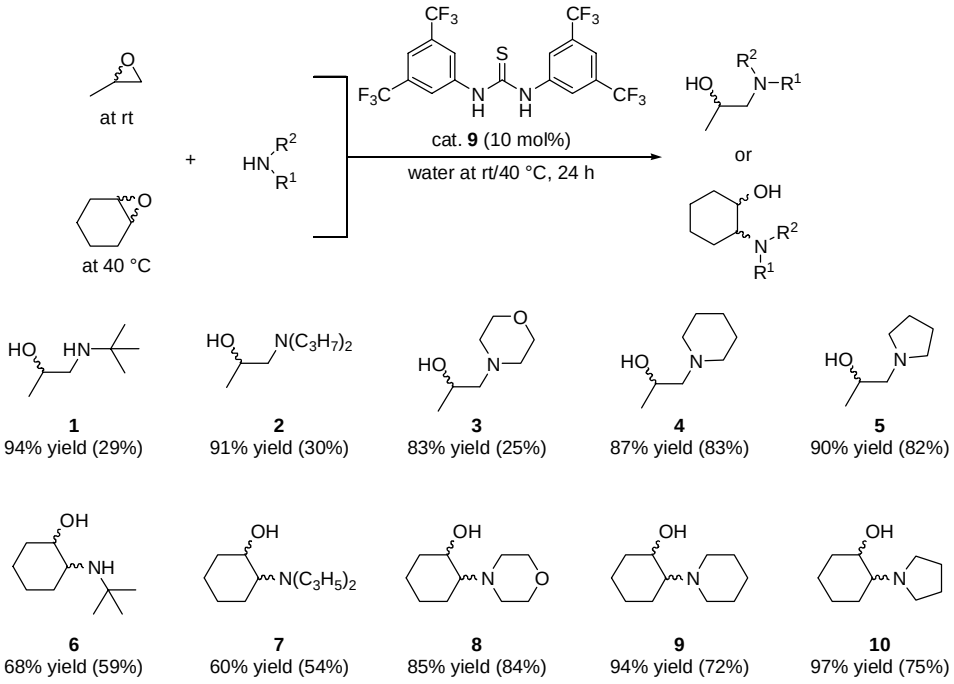
Scheme 7. Product range of **9**- and urea **16**-catalyzed Friedel-Crafts alkylations of indole and methyl indoles.

In 2006, the Schreiner group published an environmentally benign protocol towards *β*-amino alcohol synthesis utilizing the effects of hydrogen-bonding thiourea **9** and the hydrogen-bonding environment of water for the acceleration of nucleophilic epoxide aminolysis with various primary and secondary amines.[155] Water served not only as the solvent but also promoted the reaction through "hydrophobic hydration"[156, 157] akin to Nature's enzyme catalysis in water. The simple rationale behind the development of this concept is that water avoids mixing with organic solutes, because this would lead to increased structuring and thus a loss of entropy of the water molecules around the solutes. Catalysis in water depends on the ability of the catalysts to tolerate water on the one hand and to remain active on the other. As already shown by Wittkopp and Schreiner in Diels-Alder reactions hydrogen-bonding thiourea derivatives such as **9** displayed catalytic efficiency at substoichiometric loadings even in water,[1] that is, thiourea **9** remained capable of forming explicit double hydrogen-bond patterns in an enzyme-like fashion (Scheme 1; Figure 1) to the basic epoxide oxygen and thus facilitated nucleophilic ring-opening (Scheme 8). Hence, instead of being mutually exclusive, hydrogen-bonding catalysts and water complement each other.



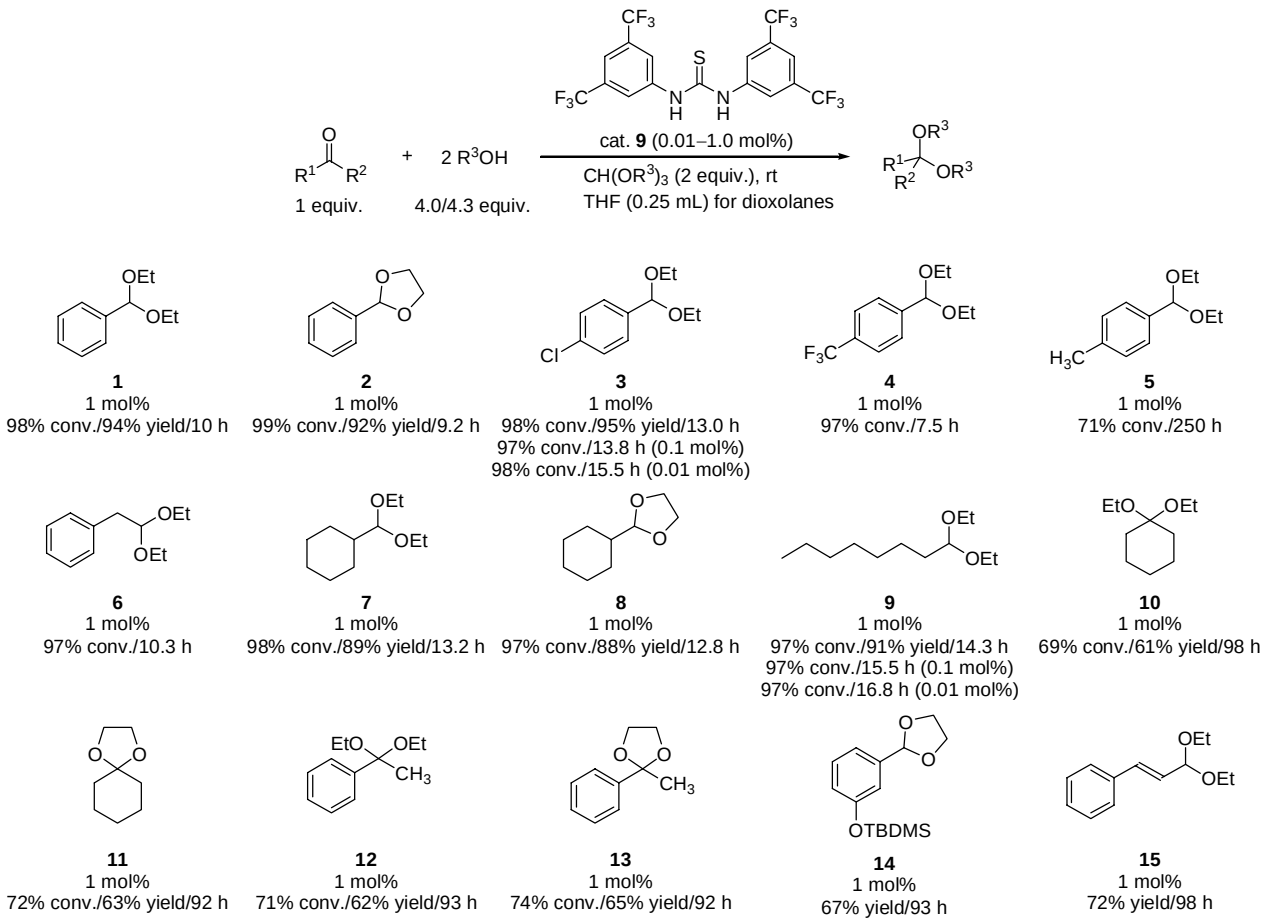
Scheme 8. Epoxide recognition for epoxide hydrolase that detoxify living cells by catalyzing alcoholysis to water soluble diols. The working model involves the phenolic H-atoms of two tyrosines activating the epoxide for nucleophilic attack. This principle is realized analogously by double hydrogen-bonding thiourea catalyst **9** in the natural medium water.

Running a series of aminolysis reactions of propene oxide (at rt) and cyclohexene oxide (at 40 °C) in a heterogeneous water mixture (emulsion or suspension, respectively) and in the non-hydrophobic solvent dichloromethane (solution) under otherwise identical conditions at 10 mol% loading of **9** revealed that the reactions proceeded best in water. The catalytic activity of hydrogen-bonding catalyst **9** was amplified in comparison to dichloromethane to give the corresponding *β*-amino alcohols **1**–**10** in good (60%) to excellent (97%) yields within 24 h reaction time as shown in Scheme 9. These findings of relative accelerations as large as 200-fold supported the assumed catalytic amplification owing to hydrophobic interactions and this eventually led to the term "hydrophobic amplification", a key element in enzyme catalysis that for the first time was implied in organocatalytic reactions with neutral molecules. The amplifying effect also occurred in the **9**-catalyzed (10 mol%) opening of styrene oxide with thiophenol (DCM: 32%; 76% yield; 24 h; rt) and phenol (DCM: 30%; 74% yield; 24 h; rt). With propene oxide only the sterically less hindered regioisomer was formed, while the opposite was found for styrene oxide. The latter result is likely due to benzyl conjugation that outweighed the steric effect. DFT computations performed on the hydrogen bonded complexes and transition structures (TS) for the opening of ethylene oxide with NH_3 with and without thiourea in the gas phase, CH_2Cl_2, and water as model clusters identified a polar TS that was favorably stabilized by water molecules resulting in the lowest overall barrier and an additional rate enhancement due to the TS inclusion into the hydrophobic hydration cavity. Further evidence for "hydrophobic amplification" was provided by the 20–40% decrease in the yields when the aminolysis was carried out, e.g., with morpholine in D_2O (62% yield; 36 h) instead of H_2O (83% yield; 36 h). D_2O has an approx. 20% higher viscosity that makes mixing more difficult and reduces the hydrophobic effect.



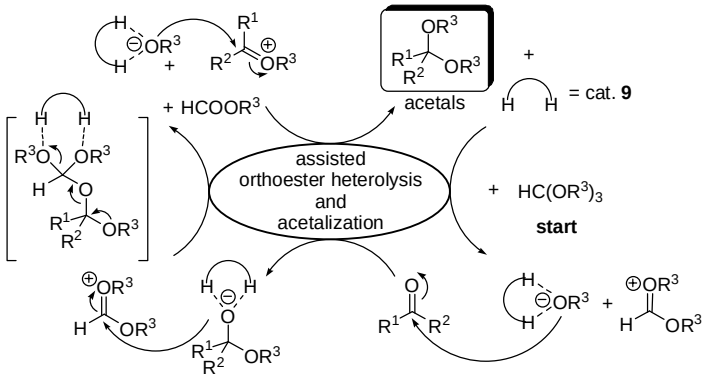
Scheme 9. Thiourea **9**-catalyzed aminolysis of propene oxide and cyclohexene oxide conducted in water to utilize "hydrophobic amplification". The yields of uncatalyzed control experiments in water are given in parentheses.

Kotke and Schreiner applied the principle of double hydrogen-bonding organocatalysts to high-yielding acid-free acetalizations.[119, 148] This approach was reported to include various aromatic, aliphatic, unsaturated and acid-labile aldehydes and ketones that could be cleanly acetalized in the presence of ethanol, methanol, 1-propanol, 2-propanol, and 1,2-ethanediol as the alcohol components and as solvents to the respective acetals **1**–**15** in good to excellent yields (61%–95%) at low catalyst loadings of only 0.01 mol%–1 mol% at room temperature (Scheme 10). The **9**-catalyzed acetalization of aromatic aldehydes and simple aliphatic aldehydes worked equally well resulting in the respective acetals in excellent yields (Scheme 10). Considerably less reactive ketones such as cyclohexanone and acetophenone can also be acetalized to the corresponding products (61%–65% yield) but, as expected, at considerably longer reaction times (92–98 h) (Scheme 10). Scale-up in preparative (20 mmol) experiments (Scheme 10) worked also well and underlined the synthetic utility of this organocatalytic protocol; the catalyst loading could be reduced routinely to 0.01 mol%, which still gave high yields at marginally extended reaction times (Scheme 10). Turnover revealed significant enough to be expressed in terms of turnover number (TON) and, better, turnover frequency (TOF). The authors found for the diethyl acetalization of *p*-chlorobenzaldehyde (product **3**) and octanal (product **9**) TOFs of 632 h^{-1} (TON = 9800) and 577 h^{-1} (TON = 9700), respectively. A limitation of this protocol concerned the acetalization of electron-rich substrates such as *p*-tolylbenzaldehyde because these required reaction longer reaction times (250 h) owing to their lower electrophilicities. The significant difference in reaction times of aldehydes and ketones translated into the observed chemoselectivity as evident from a competition experiment between benzaldehyde and acetophenone to prepare the respective diethyl acetals. After 8 h an acetal product mixture of 6.1:1 in favor of the acetal of diethyl benzaldehyde acetal was detected (^{1}H NMR). The practicality of this acid-free acetalization was further exemplified (Scheme 10) with the acetalization of acid-labile TBDMS-protected *m*-hydroxy benzaldehyde to give the desired acetal in 67% yield (93 h) that was reported to react rather sluggishly under Brønsted or Lewis-acid catalysis. The clean conversion of *trans*-cinnamic aldehyde to its diethyl acetal also emphasized the synthetic usefulness of this acid-free conversion (Scheme 10). All uncatalyzed reactions run in parallel under otherwise identical conditions gave no product within the time required for completion of the catalyzed transformation. Even after one week, the uncatalyzed reactions generally gave <1% of the respective acetals.[148]



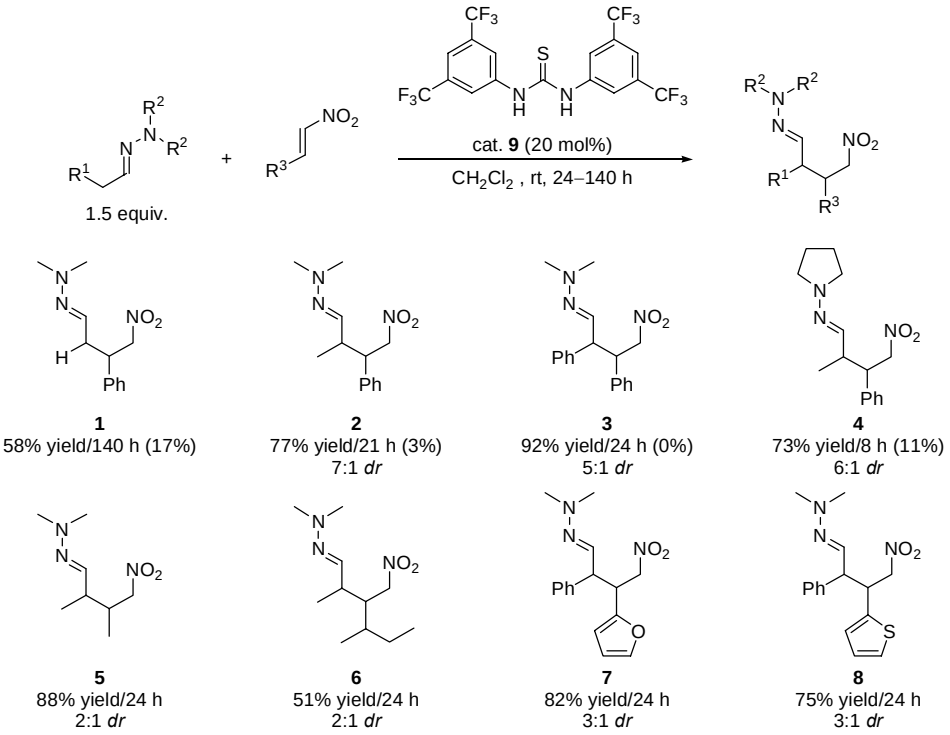
Scheme 10. Range of representative acetals prepared from the **9**-catalyzed acid-free acetalization of various aldehydes and ketones. The yields refer to preparative experiments (20 mmol scale).

Mechanistically, the authors favored a thiourea **9**-assisted heterolysis of the orthoester through hydrogen-bonding as the entry into the catalysis cycle of the organocatalytic acetalization. The orthoester was suggested to serve as the source of the alcoholate, which rapidly attacks the carbonyl compound to form a hydrogen-bonded hemiacetal anion as visualized in Scheme 11. Subsequent nucleophilic attack furnished the acetal and released the catalyst **9** without product inhibition to start a new cycle. Experimental evidence for this mechanistic proposal resulted from the attempts to perform thioacetalization reactions, which were found to be also accelerated in the presence of **9** in the absence of $HC(OEt)_3$. Addition of the orthoester only gave the normal diethyl acetal although the thiols are much better nucleophiles.[148]

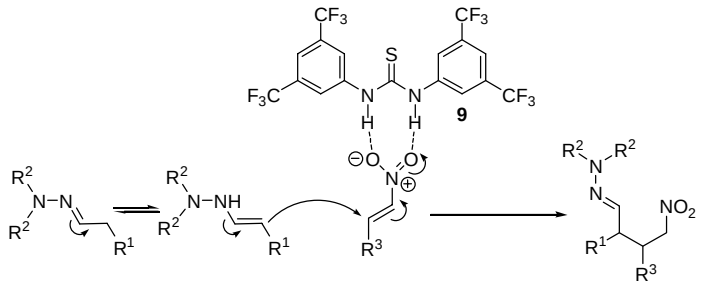


Scheme 11. Proposal for the catalytic cycle of the acid-free, organocatalytic acetalization induced by **9**-assisted orthoester heterolysis.

Ricci and co-workers utilized thiourea **9** for the activation of *β*-nitrostyrene for the conjugate addition of (hetero)aromatic *N*-containing compounds such as indoles resulting in the Friedel-Crafts alkylated adducts (Scheme 6 and 7).[150] The same group employed various **9**-activated nitroalkenes as Michael acceptors for the conjugate addition of hydrazones derived from formaldehyde and enolizable aldehydes.[158] In the initial **9**-catalyzed Michael reaction[151-154] (20 mol% catalyst loading) *N,N'*-dimethyl formaldehyde hydrazone showed the expected reactivity and added via the azomethine carbon to *β*-nitrostyrene to form the Michael adduct in 90% yield after 18 h at room temperature, while the uncatalyzed reaction remained incomplete under otherwise identical conditions. Enolizable hydrazones were identified to react as ene-hydrazine nucleophiles not from the azomethine carbon but from the *β*-position to afford the resulting *γ*-nitrohydrazones **1**–**8** in yields ranging from 58% to 92% (Scheme 12). The observed product formation was explained by a mechanistic proposal based on the equilibrium between the enolizable hydrazone and its ene-hydrazine structure, which attacked the **9**-activated nitroalkene on the electrophilic *β*-position as shown in Scheme 13.



Scheme 12. Product range of the **9**-catalyzed Michael addition between nucleophilic hydrazones and various nitroalkenes.

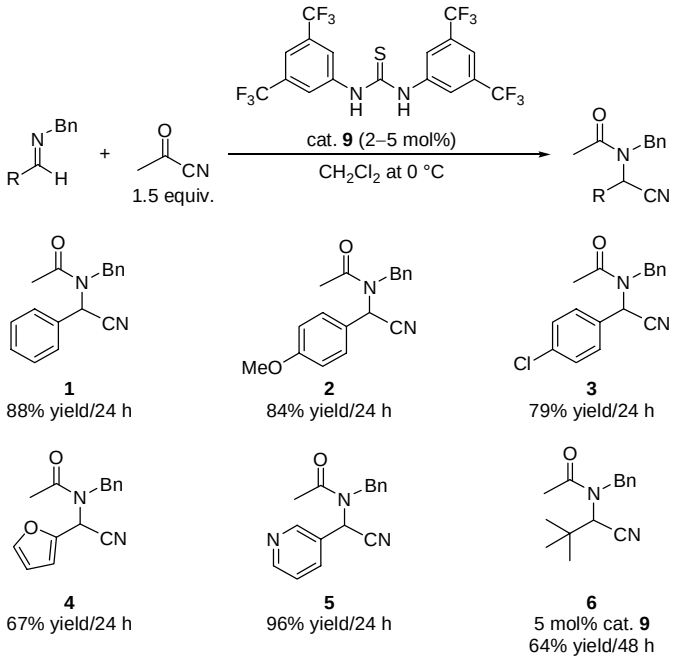


Scheme 13. Mechanistic proposal for the catalytic effect of hydrogen-bonding thiourea **9** and the product formation resulting from an equilibrium between the hydrazone and its nucleophilic ene-hydrazine form.

Products containing two adjacent stereogenic centers were obtained as mixtures of diastereoisomers that could be separated by column chromatography (*dr* values, Scheme 12). The *N,N*'-dimethyl acetaldehyde hydrazone appeared remarkably less reactive and provided the resulting adduct **1** in 140 h, while the adducts **2** and **3** were formed smoothly after approx. 24 h (Scheme 12). These results could be

rationalized by considering the different stabilities of the ene-hydrazine moieties of the hydrazones; the less substituted acetaldehyde derived ene-hydrazine was rather unstable as compared to the more substituted or conjugated ene-hydrazines, which afforded product **2** and **3**, respectively. The hydrazone originated from isobutyraldehyde turned out to be unreactive due to steric hindrance of the bulky isopropyl group at the reacting center in the corresponding ene-hydrazine. The Michael reaction of the *N,N'*-dimethyl hydrazone of benzaldehyde or pivalaldehyde with *β*-nitrostyrene as Michael acceptor failed because no ene-hydrazine could form. Ionic liquids ($BMImBF_4$ or $BMImPF_6$: 1-butyl-3-methylimidazolium tetra- or hexafluoroborate) accelerated the uncatalyzed formation of product **2** compared to other solvents (THF, MeOH, DCM) and showed full disappearance of *β*-nitrostyrene after 24 h, but gave poorer yields after work-up (30%–50%). The self-evident combination of an ionic liquid with catalyst **9** proved to be unsuccessful. The synthetic utility of this mild organocatalytic approach was underlined when applying Lewis-acid catalysis (e.g., catalytic amounts of $Sc(OTf)_3$, $In(OTf)_3$, InF_3, or $Cu(OTf)_2$) to the formation of adduct **2**; in all cases the starting material underwent acid-induced decomposition resulting in just traces of the desired product.[158]

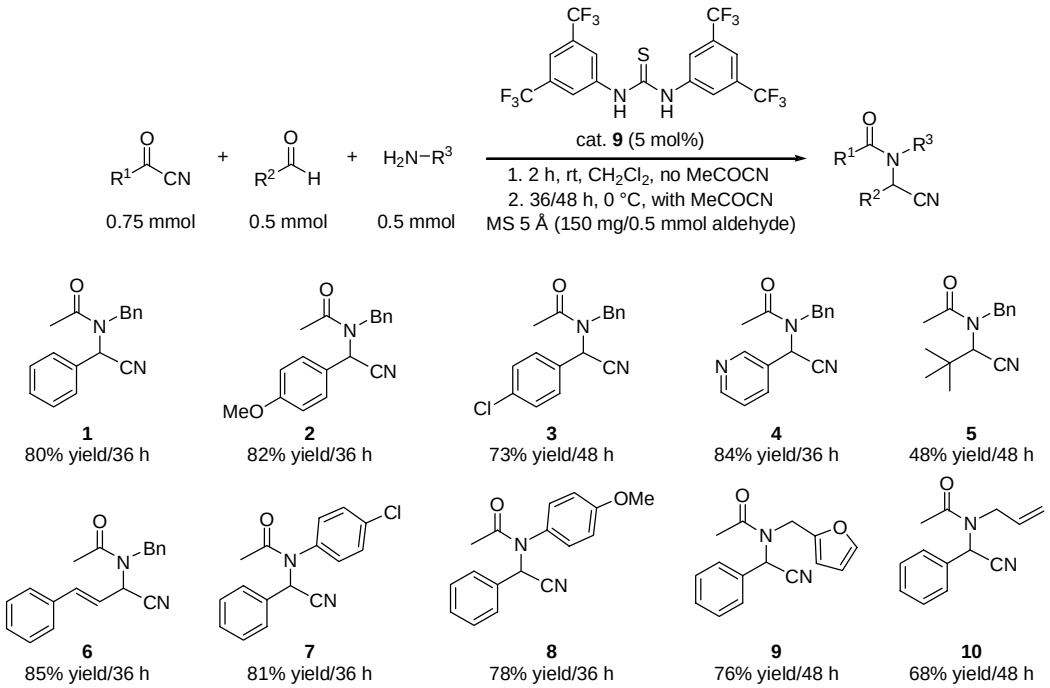
In 2006, List et al. presented a thiourea **9**-catalyzed procedure for the synthesis of *N*-acetylated Strecker adducts,[159] which are useful intermediates in the synthesis of *α*-amino acids.[160] This novel approach introduced acetyl cyanide as practical and readily available aldimine cyanation reagent that was first studied by Dornow et al., in 1958.[161, 162] Utilizing thiourea **9** (2–5 mol% loading) and dichloromethane as solvent at 0 °C a variety of aldimine substrates were transformed to their corresponding *N*-acetyl Strecker adducts **1**–**8** in yields ranging from 64–96% (Scheme 14). Both aromatic aldimines with electron-donating or -withdrawing substituents (adducts **1**–**3**), as well as (hetero)aromatic aldimines (adducts **4** and **5**), could be transformed with similar efficiencies. Aliphatic *α*-branched adducts such as **6** were also accessible (Scheme 14). Mechanistically, the authors suggested the reaction proceeded via an initial reaction of the aldimine with acetyl cyanide to form an acyl iminium-cyanide ion pair, which recombines in a final **9**-catalyzed product forming step.



Scheme 14. Product range of the **9**-catalyzed acetyl cyanation reaction of aldimines with acetyl cyanide as the cyanide source.

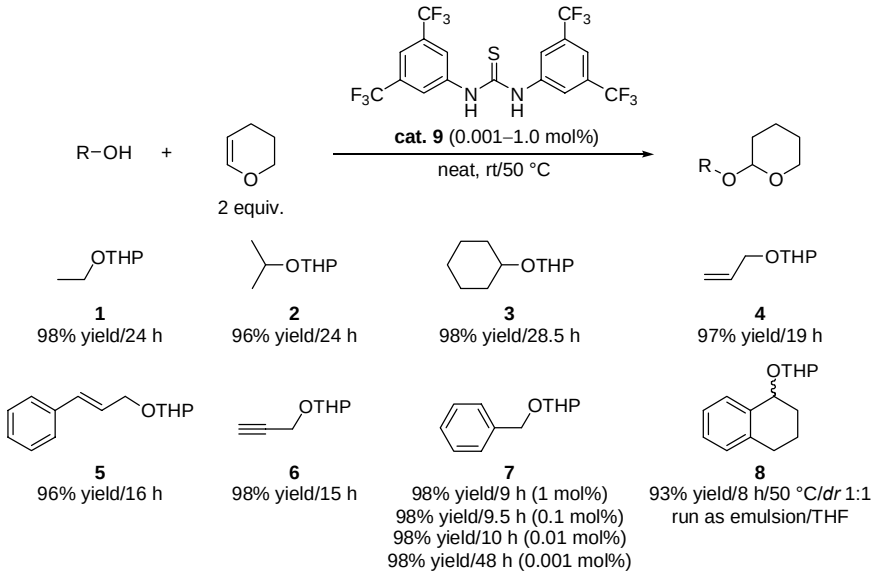
An asymmetric version of the aldimine acylcyanation utilizing Jacobsen's Schiff base catalyst **47** (section 1.2.2.1; Scheme 47)[163] and a one-pot, three-component **9**-catalyzed modification of the acylcyanation described above were developed quickly.[164] This three-component acyl-Strecker reaction[159] was performed with various aliphatic and (hetero)aromatic aldehydes, amines, and acetyl cyanide for the in situ aldimine formation and hydrogen cyanide generation, respectively. The **9**-promoted reaction required the presence of a drying agent to scavenge the water formed during the aldimine synthesis in the absence of an HCN source. The best results in the initial screening reaction of benzaldehyde, benzyl amine, and acetyl cyanide in dichloromethane were observed with molecular sieve (MS) 5 Å (99% conv.; 24 h)

instead of $MgSO_4$ (86% conv.; 24 h) and when the aldimine formation proceeded under stirring of the mixture of aldehyde, amine, MS, and thiourea **9** (5 mol% loading) for 2 h at room temperature before the acetylcyanation step was initiated by the addition of acetyl cyanide at 0 °C. The uncatalyzed screening reaction showed 42% conversion after 24 h. Under optimized conditions this method afforded the *N*-acetyl-Strecker adducts **1**–**10** of various aldehydes and amines in moderate to good yields (48%–85%) at practical reaction times (36 or 48 h) as visualized in Scheme 15.

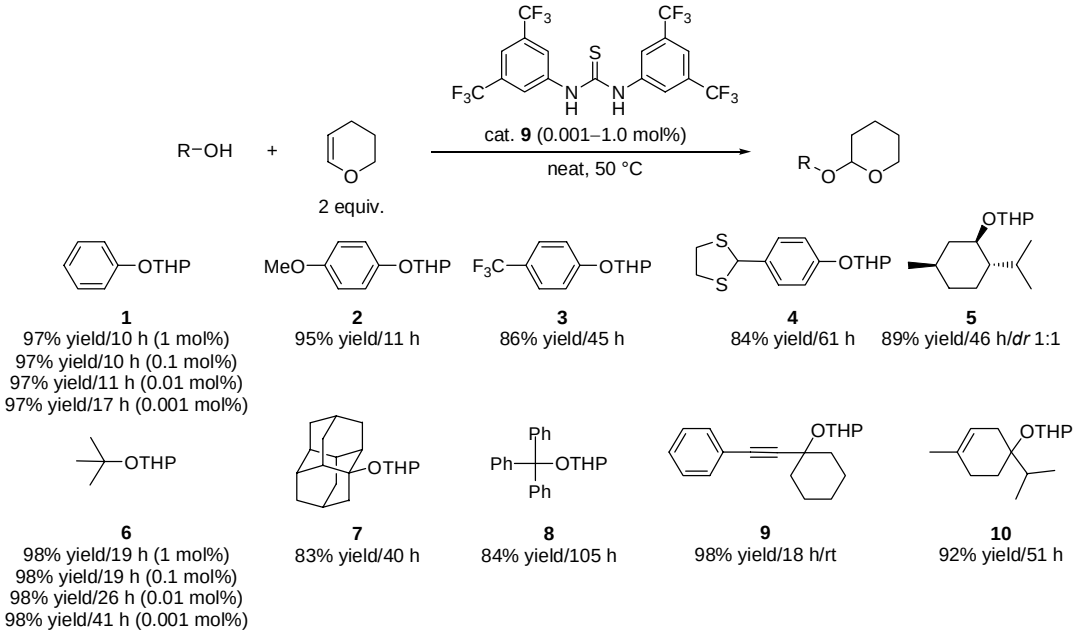


Scheme 15. Representative *N*-acetyl-Strecker products resulting from the **9**-catalyzed three-component acylcyanation reaction.

In 2007, another departure from carbonyl-type activation was marked by Kotke and Schreiner in the organocatalytic tetrahydropyran and 2-methoxypropene protection of alcohols, phenols, and other ROH substrates.[119, 147] These derivatives offered a further synthetically useful acid-free contribution to protective group chemistry.[148] The **9**-catalyzed tetrahydropyranylation with 3,4-dihydro-2*H*-pyran (DHP) as reactant and solvent was described to be applicable to a broad spectrum of hydroxy functionalities and furnished the corresponding tetrahydropyranyl-substituted ethers, that is, mixed acetals, at mild conditions and with good to excellent yields. Primary and secondary alcohols can be THP-protected to afford **1**–**8** at room temperature and at loadings ranging from 0.001–1.0 mol% thiourea **9** (Scheme 16). The effective THP protection of benzyl alcohol at very low catalyst loadings down to 0.001 mol% emphasized the catalytic power of **9** (Scheme 16) and revealed a calculated maximum turnover number (TON) close to 100,000 and a turnover frequency (TOF) of around 2,000 h^{-1}. Tertiary alcohols, which normally are difficult to protect as THP ethers owing to steric hindrance and elimination as a side reaction, could also be THP protected under this conditions affording the THP ether **1**–**10** (Scheme 17). Particularly remarkable is the tolerance of even the most sterically hindered substrates diamantan-1-ol and triphenylmethanol resulting in the THP ethers **7** and **8**, respectively. Phenol derivatives were also readily converted into their corresponding THP ethers at 50 °C (Scheme 17). As shown for phenol, THP protection to its THP ether could be achieved with catalyst loadings down to 0.001 mol%, resulting in a TOF of 5700 h^{-1}, which marks the most efficient organocatalytic reaction to date. Selected scale-up experiments (50 mmol scale), e.g., in the case of phenol, demonstrated that also loadings of only 0.01–0.1 mol% are sufficient and practical for routine preparative THP protection (Scheme 17). Phenol derivatives also provided the important experimental clue that the hydroxy-group acidity was not a factor for the mechanistic interpretation of these reactions because phenols are more acidic than alkanols and electron-deficient phenols such as 4-(trifluoromethyl)phenol (product **3**: 86% yield/45 h) were found to react more slowly than electron-rich 4-methoxyphenol (product **2**: 95%; 11 h) (Scheme 17).



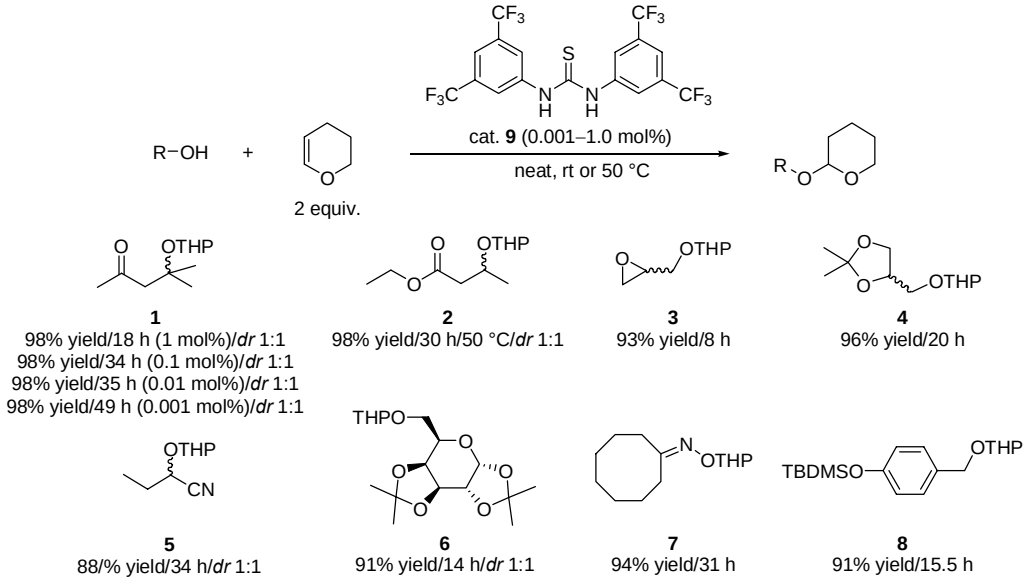
Scheme 16. Product range of the **9**-catalyzed tetrahydropyranylation of primary and secondary alcohol substrates.



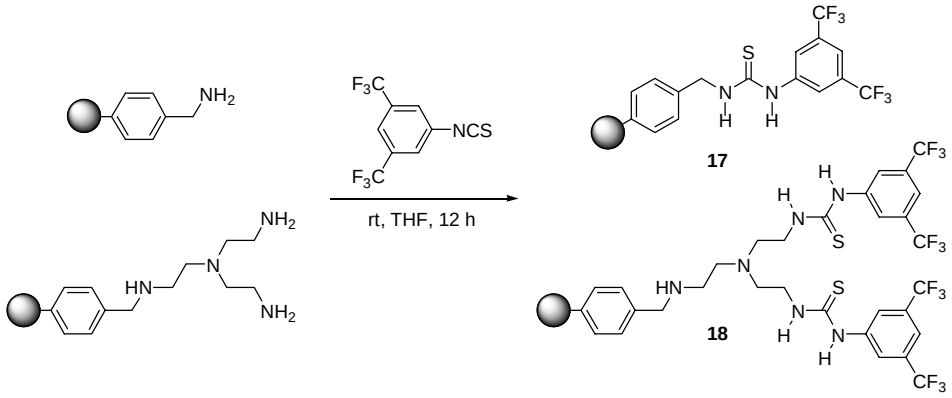
Scheme 17. Product range of the **9**-catalyzed tetrahydropyranylation of sterically hindered and phenolic substrates.

Owing to the mild and acid-free conditions the protocol tolerated also acid-labile hydroxy-functionalized substrates as typical aldol products (product **1**; TOF = 2000 h^{-1}), β-hydroxy esters, epoxides, acetonides, cyanhydrines, oximes as well as highly acid-sensitive TBDMS-protected benzyl alcohol without detectable side reactions in excellent yields (88%–98%) as depicted in Scheme 18.[119, 147] To improve the practicality of this reaction further, the authors utilized readily prepared 3,5-bis(trifluoromethyl)phenyl isothiocyanate[147] to attach the bis(trifluoromethyl)phenyl thiourea moiety of the catalytic motif in a straightforward protocol to simple amino-terminated polystyrene beads resulting in thiourea derivatives **17** and **18**, respectively (Scheme 19). **9**-analogue polymer-bound **17** (~10 mol% loading) was found to efficiently catalyzed the THP protection of various hydroxy-functionalized substrates under heterogeneous conditions affording the desired THP ethers **1**–**7** in excellent yields (92%–98%) (Scheme 20); additionally, catalyst **17** was demonstrated to be readily recoverable by simple filtration and reusable (4 cycles) for THP protection after washing with dichloromethane without loss of catalytic activity.[61, 62] Polymer-bound bisthiourea **18** bearing a secondary and tertiary amine group, however, turned out to be catalytically inactive in the examined THP

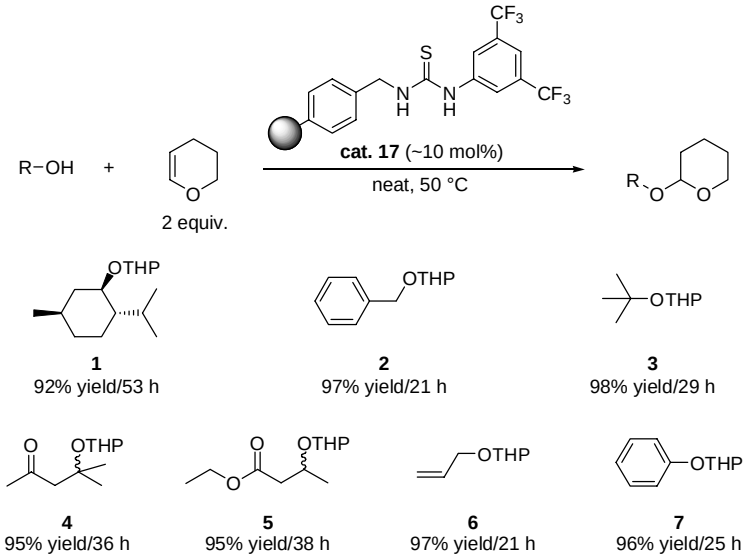
protections. This was consistent with the finding that hydroxy substrates such as amino alcohols incorporating an amine functionality could not be THP protected with the reported protocol.



Scheme 18. Product range of the tetrahydropyranylation of acid-sensitive substrates catalyzed by thiourea derivative **9**.

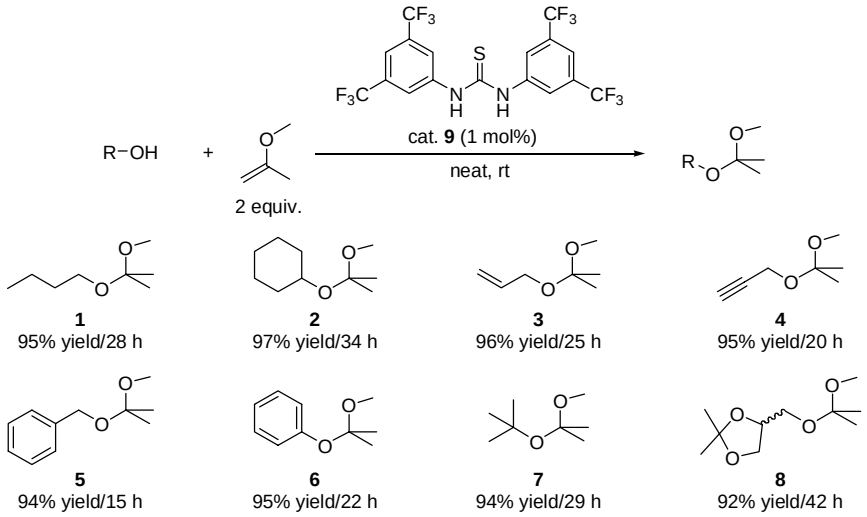


Scheme 19. Synthesis of polystyrene-bound thiourea derivatives **17** and **18** screened in the THP protection of hydroxy substrates.



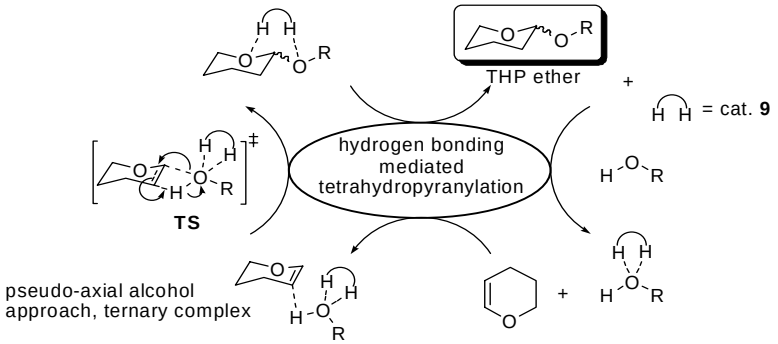
Scheme 20. THP ethers obtained from the THP protection of various hydroxy substrates utilizing polymer-bound catalyst **17**.

The authors successfully applied their protocol to the alternative enol ether 2-methoxypropene (MOP) to prepare the MOP ether **1**–**8** from a subset of the various alcohol substrates as depicted in Scheme 21. This high-yielding (92%–97%) MOP protection occurred smoothly at room temperature; MOP turned out to be so reactive that the uncatalyzed reaction also proceeded albeit at lower rates.[119, 147]



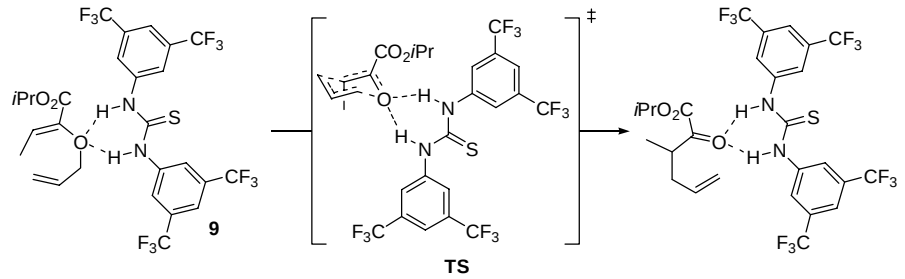
Scheme 21. Product range of the **9**-catalyzed MOP protection of hydroxy functionalities.

A reasonable mechanistic entry into this reaction may start with the complexation of catalyst **9** with the alcohol substrate. This double hydrogen-bonding mediated coordination increases the alcohol's acidity as well as polarizability and hence its ability to form a subsequent ternary complex with the enol ether DHP via a pseudo-axial approach and interaction, respectively. The catalyst remains attached during the polar addition through a highly polarized transition structure and is finally released from the product complex to initiate a new catalytic cycle (Scheme 22). This mechanistic proposal clearly indicates the departure from the often-implied concept of carbonyl (or related functionalities) activation through hydrogen bonding with (thio)urea derivatives and other hydrogen-bonding organocatalysts.[165] Hence, this mechanistic alternative suggested either the hydrogen-bond assisted generation of the free nucleophile (e.g., RO^-, CN^-) or the stabilization of the active form of the nucleophile through hydrogen bonding and polar interactions to the respective precursor (e.g. ROH, $HC(OR)_3$, HCN, TMSCN). Density functional theory (DFT) and high-level coupled cluster computations, demonstrated that the catalyst preferentially stabilized the developing oxyanion hole[166] in the transition state through double hydrogen bonding without formation of the charged alkoxide nucleophile. This conclusion was reached on the basis of a comparative computational analysis of the uncatalyzed versus catalyzed model reaction of methanol with DHP.[119, 147] The stabilizing effect of **9** on the key transition structure amounted to ca. 23 kcal mol^{-1} resulting in a minimized barrier of only 17.7 kcal mol^{-1} (uncatalyzed: 45.2 kcal mol^{-1}), which was in line with the experimentally found efficacy of **9** already at room temperature in contrast to the uncatalyzed THP protection, which showed no product formation under otherwise identical conditions. Closer inspection of the transition structure with **9** revealed that the catalyst helps pre-organize the reactants and the overall geometric changes in going from the complexes to the transition structures (least motion principle); **9** is placed sideways and points away from the R group of the substrate making steric hindrance not a critical factor, as found experimentally (Scheme 17).



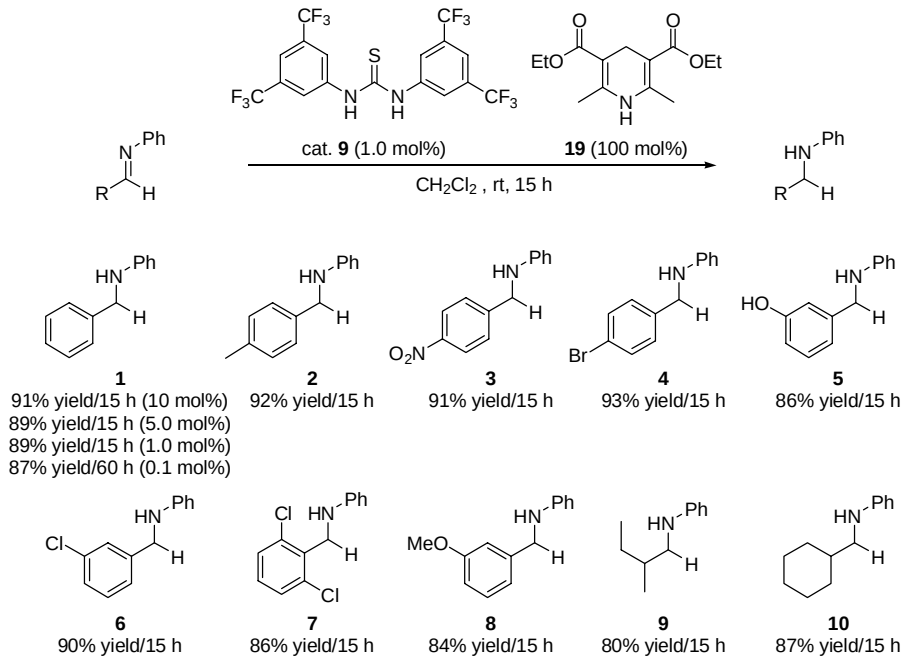
Scheme 22. Proposed tetrahydropyranylation cycle catalyzed by hydrogen-bonding thiourea derivative **9**.

Hiersemann, Strassner, and co-workers, in 2007, reported a combined computational (DFT) and experimental study on the Claisen rearrangement of a 2-alkoxycarbonyl substituted allyl vinyl ether[106] in the presence of thiourea derivative **9** (20 mol% and 100 mol%) as potential hydrogen-bonding organocatalyst (Scheme 23).[167] Proof-of-principle experiments on this Claisen rearrangement performed in a sealed tube at 25 °C and 45 °C using 1,2-dichloroethane, chloroform, and trifluoroethanol, respectively, as the solvents revealed that the conversion in the presence of thiourea **9** was nearly identical to the control experiment without **9** under otherwise unchanged conditions (e.g., in trifluoroethanol with 20 mol% **9**: 44% conv.; 45 °C; 6 d; without **9**: 41% conv; 6 d). Employing stoichiometric amounts (100 mol%) loading of thiourea **9** at 45 °C indicated only a poor accelerating effect in the model reaction resulting in 87% conversion (without **9**: 74% conv.) after 7 d reaction time in chloroform. These experimental results identified **9** to be catalytically ineffective in the observed Claisen rearrangement and were supported by computations that suggested the transition state stabilization was not significant enough to overcome the energetic costs of conformational changes and complexation required for the formation of the reactive complex. Since the corresponding TS was found to be characterized by a concerted but asynchronous bond reorganization process that led to TS polarization the authors suggested that the design of a non-covalent (thio)urea organocatalysts for the Claisen rearrangement must focus on significant polarization of the TS by strong hydrogen-bonding to the ether oxygen atom of the 2-alkoxycarbonyl substituted allyl vinyl ether.



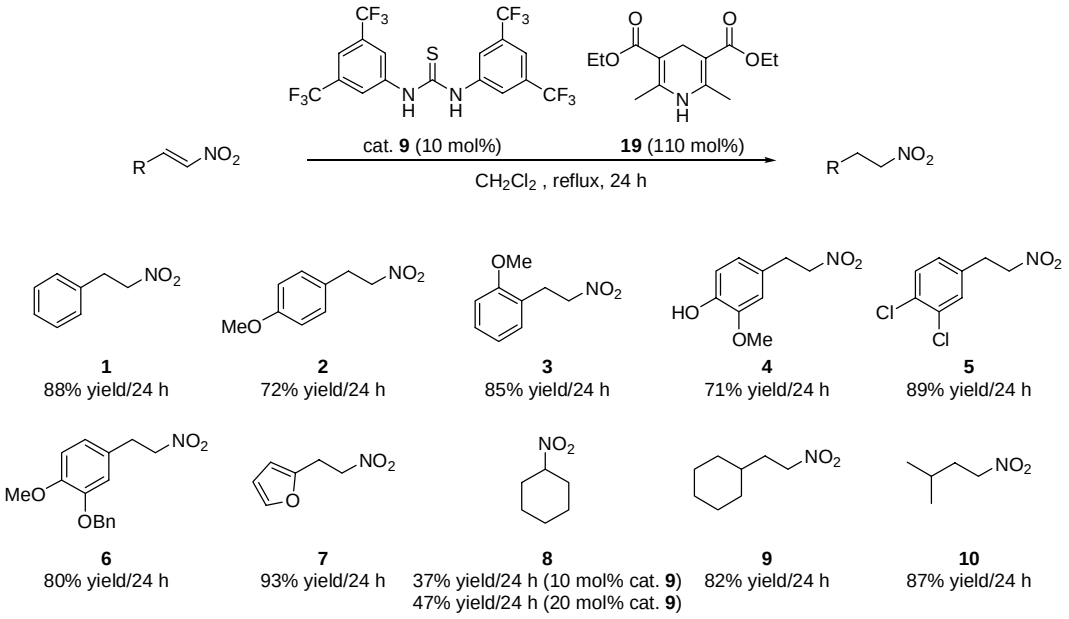
Scheme 23. Claisen rearrangement of a 2-alkoxycarbonyl substituted allyl vinyl ether in the presence of thiourea derivative **9**.

In 2007, the Schreiner group published a **9**-catalyzed transfer hydrogenation of aldimines through hydrogen-bonding activation utilizing Hantzsch 1,4-dihydropyridine **19** "Hantzsch ester"[168] as the hydrogen source.[169] While the ketimine derived from acetophenone only gave traces of product, the benzaldehyde imine produced the corresponding amine product **1** even at 0.1 mol% loading of **9**, but at a longer reaction time (Scheme 24). Employing dichloromethane as solvent, thiourea **9** (1 mol% loading) as catalyst, and Hantzsch ester as reductant the scope of this acid- and metal-free transfer hydrogenation was explored. In general, a variety of aromatic aldimines underwent this reductive amination, including electron-rich, electron-deficient, as well as *ortho*-, *meta*-, and *para*-substituted aryl aldehydes, and provided the corresponding secondary amines **1**–**8** in yield ranging from 80%–93% within 15 h; in addition, aliphatic aldimines could also be reduced to give the respective amines **9** and **10** with good yields (80% and 87%) as depicted in Scheme 24.



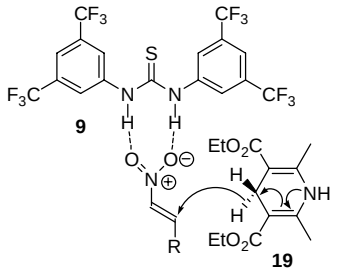
Scheme 24. Amines obtained from the transfer hydrogenation of aldimines in the presence of catalyst **9** and Hantzsch ester **19**.

A systematic study on enzymatic catalysis has revealed that isolated enzymes from baker's yeast or Old Yellow Enzyme (OYE) termed nitroalkene reductase, can efficiently catalyze the NADPH-linked reduction of nitroalkenes. For the OYE-catalyzed reduction of nitrocyclohexene a catalytic mechanism was proposed in which the nitrocyclohexene is activated by nitro-oxygen hydrogen bonds to the enzymes His-191 and Asn-194.[170, 171] Inspired by this study Schreiner et al. mimicked this natural procedure in preparative chemistry with hydrogen-bonding organocatalyst **9** functioning as the "reductase" and Hantzsch ester[168] as NADPH analogue to develop a mild, efficient, and selective method for the synthesis of nitroalkanes from *α,β*-unsaturated nitroalkenes.[172] This biomimetic reduction is not only practical, but may also provide insights into the mechanisms of redox transformations in biological systems. In the initial experiments *trans*-*β*-nitrostyrene as the model substrate was reduced in the presence of 10 mol% catalyst **9** and 1.1 equiv. Hantzsch ester to give the respective nitroalkene in 87% yield after 48 h in toluene (50 °C), while the uncatalyzed reaction running under otherwise identical conditions showed no product formation. Using only 5 mol% catalyst **9** under the same conditions decreased the product yield (75%/48 h). Reductions of nitrostyrene (10 mol% **9**; 1.1 equiv. Hantzsch ester **19**) in non-polar media such as benzene (84 yield/24 h) and toluene (78% yield/24), as well as halogenated solvents such as chloroform (76% yield/24 h) and dichloromethane (88%/24 h) proceeded smoothly. Performing the reaction in more polar media led to sluggish reactions and considerably diminished yields. A moderate yield was also obtained in the protic solvent methanol (52%/24 h), but a conversion was also detected without catalyst **9** affording the desired nitroalkane **1** (45% yield/24 h) and the corresponding Michael adduct. Under optimized conditions with dichloromethane as solvent, 10 mol% **9**, and 1.1 equiv. Hantzsch ester **19** various aromatic nitroalkenes were smoothly reduced to the corresponding nitoalkanes **1**–**10** in yield ranging from 72%–93% after 24 h (Scheme 25). The electronic effect of the substituents and the substituent pattern turned out to have no marked effect on the outcome of this reaction (Scheme 25). The reductions of electron-rich nitrostyrenes took longer and afforded the product in lower yield. Aliphatic nitroalkenes were reduced to the corresponding nitroalkenes in good yields (82% and 87%) as shown in Scheme 25. Only the reduction of nitrocyclohexene gave the corresponding nitroalkane **8** in poor yield (10 mol% loading: 37%) even at 20 mol% loading of catalyst **9** (47% yield). Reduction of the nitro group and polymerization of the alkenes did not occur in any case and underlined the mild conditions of this organocatalytic methodology.



Scheme 25. Product range of the biomimetic reduction of *α*,*β*-unsaturated nitroalkenes catalyzed by **9** in the presence of **19**.

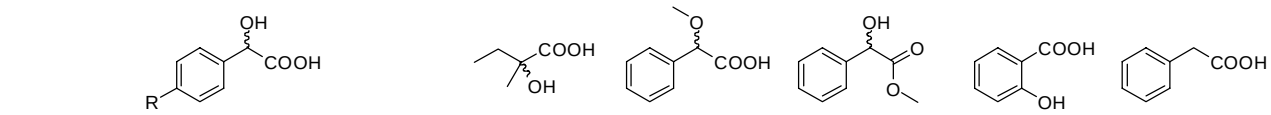
In analogy to the enzymatic mode of substrate binding, activation and reduction[170, 171] the authors proposed enzyme-like hydrogen-bonding interactions between the nitro-group and thiourea **9** to effectively lower the LUMO of the conjugated double bond; this facilitated the reducing hydride transfer from the Hantzsch ester and led to the observed accelerating effect in the nitroalkane formation (Scheme 26).



Scheme 26. Proposed model of the biomimetic reduction of conjugated nitroalkenes in the presence of thiourea catalyst **9** and **19**.

In Nature epoxide ring-opening is catalyzed by enzymes employing the (double) hydrogen-bonding motif (Scheme 1) for epoxide activation towards hydrolysis resulting in the removal of unsaturated toxic organic compounds (epoxidation-hydrolyis sequence).[34, 173] Based on the result found by the Schreiner group that the effects of hydrogen-bonding organocatalysis and water operate cooperatively ("hydrophobic amplification") in the epoxide aminolysis[155] (Scheme 8) Kotke, Weil, and Schreiner developed a cooperative[18, 174, 175] Brønsted acid-type organocatalytic system for epoxide alcoholysis,[176] highlighted by List, in 2008.[177] Initial experiments performed for the ethanolysis of styrene oxide utilizing privileged thiourea catalyst **9** (1 mol%) in combination with mandelic acid **20** (1 mol%) (pK_a = 3.37) showed 99% conversion (GC/MS) after 22 h reaction time at room temperature and with ethanol (12 equiv. to avoid byproduct formation by nucleophilic attack of the product) as the solvent and the nucleophile. Further Brønsted acid screening in the model alcoholysis under otherwise identical conditions revealed that only aromatic acids incorporating a second coordination center in the *α*-position (hydroxy or carbonyl) induced appreciable conversions as shown for representative acids **20**–**27** in Figure 6. The removal or blocking of the *α*-coordination center (**24**; **27**) or removal of the aromatic system (**23**) drastically reduced the conversion rates. Aqueous acidity (pK_a) proved to be not suitable to predict

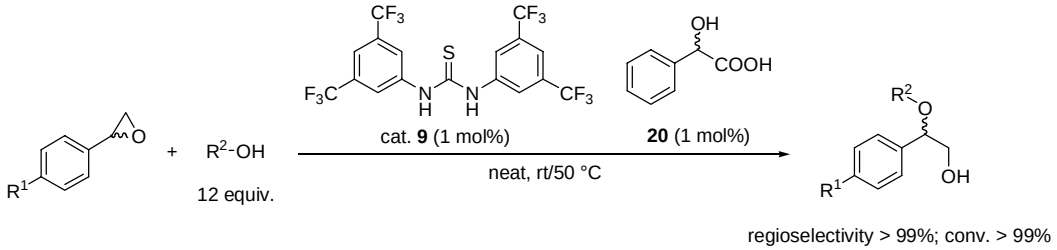
the catalytic activity (**22**; **26**). Performing the model alcoholysis in various solvents revealed a remarkable solvent effect; reactions in ethanol (99% conv./22 h/rt) were found to be two times faster than reactions in nonpolar or aprotic solvents (e.g., *n*-hexane: 99% conv./48 h/rt; THF: 99% conv./48 h/rt; CH_3CN: no conv./48 h/rt).

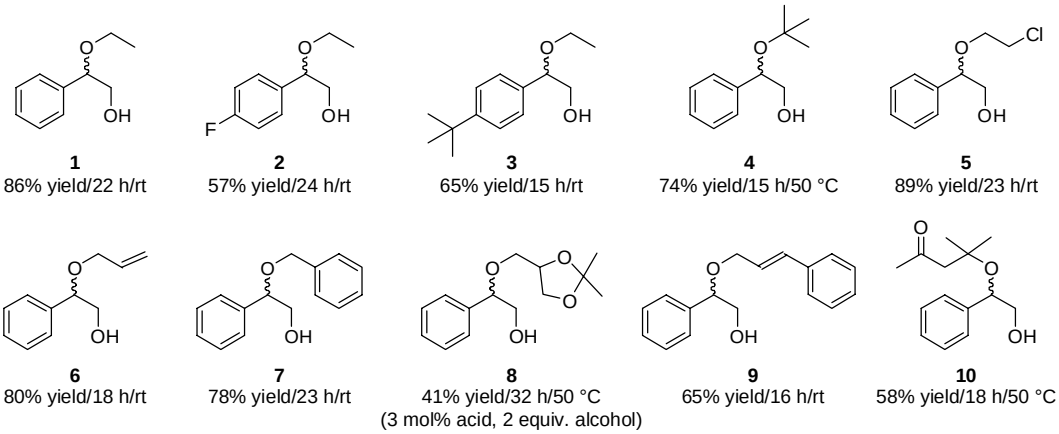


20 R = H >99% conv./22 h (pK_a 3.37) | **21** R = OMe >99% conv./19 h (pK_a 3.43) | **22** R = CF_3 >99% conv./16 h (pK_a 3.01) | **23** ~5% conv./24 h (pK_a 4.05) | **24** no conv./26 h (pK_a 3.10) | **25** no conv./26 h (pK_a not available) | **26** ~12% conv./12 h (pK_a 3.00) | **27** no conv./26 h (pK_a 4.28)

Figure 6. Structurally diverse Brønsted acids (1 mol% loading) screened in the cooperative Brønsted acid-type organocatalytic system (1 mol% thiourea **9**) utilizing the ethanolysis (12 equiv. EtOH) of styrene oxide as model reaction.

Under optimized conditions regarding the choice of Brønsted acid (mandelic acid **20**), stoichiometry (1:1 ratio **9** and mandelic acid **20**), solvent (the respective alcohol; neat conditions), temperature (rt or 50 °C), and catalyst loading (1 mol% **9** and 1 mol% mandelic acid **20**) electron-rich and electron-deficient styrene oxides underwent alcoholysis with simple aliphatic, sterically demanding as well as unsaturated and acid-labile alcohols. The completely regioselective (> 99%) alcoholysis was reported to afford the corresponding *β*-alkoxy alcohols **1**–**10** in moderate (41%) to good (89%) yields without detectable decomposition or polymerization reactions of acid-labile substrates (Scheme 27). Notably, all uncatalyzed reference experiments showed no conversion even after two weeks under otherwise identical conditions.



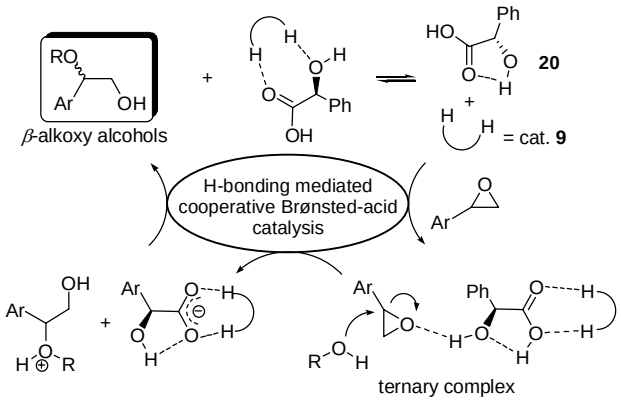


1 86% yield/22 h/rt | **2** 57% yield/24 h/rt | **3** 65% yield/15 h/rt | **4** 74% yield/15 h/50 °C | **5** 89% yield/23 h/rt

6 80% yield/18 h/rt | **7** 78% yield/23 h/rt | **8** 41% yield/32 h/50 °C (3 mol% acid, 2 equiv. alcohol) | **9** 65% yield/16 h/rt | **10** 58% yield/18 h/50 °C

Scheme 27. Typical *β*-alkoxy alcohols obtained from the highly regioselective alcoholysis of styrene oxides catalyzed by thiourea **9** and mandelic acid **20** in a cooperative organocatalytic system.

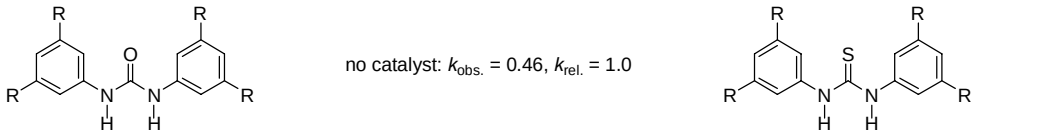
These experimental results suggested a hydrogen-bonding mediated cooperative Brønsted acid catalysis mechanism (Scheme 28). Thiourea cocatalyst **9** is viewed to coordinate to mandelic acid **20** through double hydrogen-bonding, stabilizes the acid in the chelate-like *cis*-hydroxy conformation, and acidifies the α-OH proton via an additional intramolecular hydrogen bond. The epoxide was suggested to be activated by a single-point hydrogen bond that facilitates regioselective nucleophilic attack of the alcohol at the benzylic position akin to the monodentate binding reported for diol catalysts.[178] The incipient oxonium ion reprotonates the mandelate and provides the observed β-alkoxy alcohol products (Scheme 28). This mechanistic proposal originating from the concept of cooperativity of two catalysts was supported by DFT computations indicating that the ternary complex between styrene oxide, **9**, and mandelic acid **20** has an overall binding energy of 20.0 kcal/mol, while the possible binary complexes are less stable and disfavored (styrene oxide and **9**: 9.2 kcal mol^{-1}; mandelic acid **20** and **9**: 11.9 kcal mol^{-1}; styrene oxide and mandelic acid **20**: 5.7 kcal mol^{-1}).



Scheme 28. Mechanistic proposal for the regioselective alcoholysis of styrene oxides utilizing a cooperative Brønsted acid-type organocatalytic system comprised of thiourea **9** and mandelic acid **20**.

1.2.1.2 Miscellaneous Non-stereoselective (Thio)urea Organocatalysts

Connon and Maher identified, in 2004, simple symmetrically substituted achiral *N,N'*-bisphenyl (thio)urea derivatives as efficient, stable and recyclable DABCO-compatible hydrogen-bonding promoters for the Morita-Baylis–Hillman (MBH) reaction[179, 180] for a range of aromatic aldehydes and methyl acrylate.[181] For catalyst screening the pseudo-first-order rate constants of the reaction between methyl acrylate (10 equiv.) and benzaldehyde catalyzed by both DABCO (100 mol%) and (thio)ureas **9**, **15**, **16**, **26**, and **27** (each 20 mol%) were determined by ^{1}H NMR kinetic experiments. This revealed that urea analogue **16** of catalyst **9** was the most efficient in accelerating this MBH reaction under solvent-free conditions at room temperature (Figure 7).

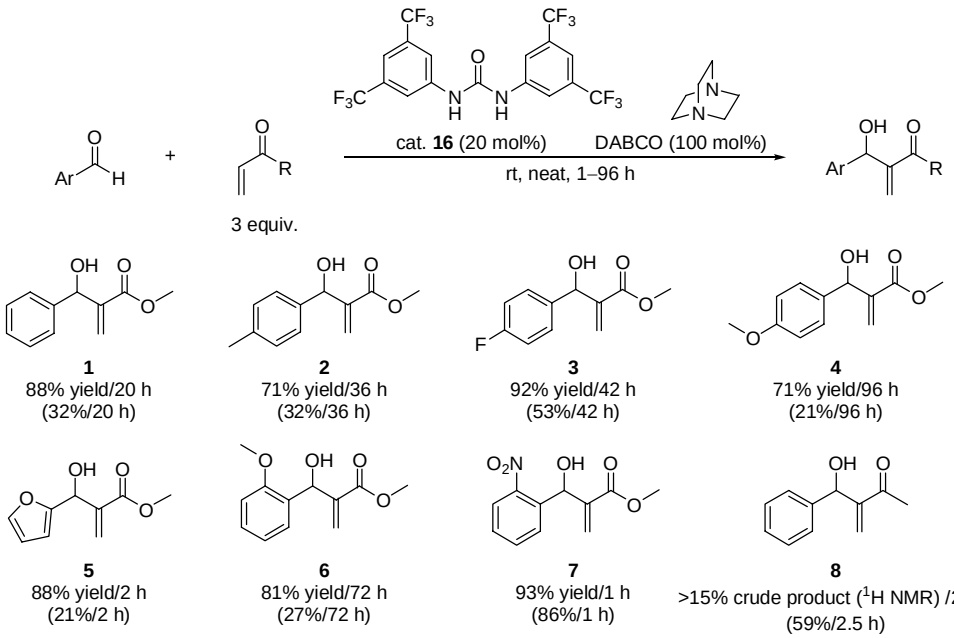


28: R = F; k_{obs} = 2.50; k_{rel} = 5.4 (20 mol%)
16: R = CF_3; k_{obs} = 3.06; k_{rel} = 6.7 (20 mol%)

15: R = H; k_{obs} = 0.76; k_{rel} = 1.7 (20 mol%)
29: R = F; k_{obs} = 2.63; k_{rel} = 5.7 (20 mol%)
9: R = CF_3; k_{obs} = 1.73; k_{rel} = 3.7 (20 mol%)

Figure 7. Hydrogen-bonding (thio)ureas screened in the DABCO-promoted MBH reaction between benzaldehyde and methyl acrylate; the pseudo-first order rate constants relative to the uncatalyzed reaction are given in h^{-1}.

This result represented an uncommon example for the inferiority of thioureas as compared to ureas.[1] Under optimized conditions the DABCO (100 mol%)-promoted MBH reaction of various electron-deficient and electron-rich aromatic aldehydes (1 equiv.) with methyl acrylate (3 equiv.) was accelerated in the presence of urea catalysts **16** (20 mol%) and furnished the respective adducts **1**–**8** in moderate to very good yields (71–93%) within 2 h–42 h reaction time. Only the challenging deactivated anisaldehydes proved to require longer reaction times affording the MBH adducts **4** (96 h) and **6** (72 h), respectively (Scheme 29). The catalytic effect of urea catalyst **16** was illustrated by the poor product yields obtained in the urea-free control reactions involving deactivated substrates over the same time period (Scheme 29).



Scheme 29. Range of products for the DABCO-promoted MBH reaction utilizing urea derivative **16** as hydrogen-bonding organocatalyst. The results of the uncatalyzed reference reactions are given in parentheses.

In all cases urea catalyst **16** could be recovered unchanged after the reaction by column chromatography in good to excellent yield (82–95%) and be reused without loss of activity. This protocol turned out to be not applicable to MBH reactions involving acrolein or methyl vinyl ketone, because catalyst **16** promoted the rapid decomposition of the Michael acceptor resulting in poor yields (e.g., MBH adduct **8** in Scheme 29: 15% yield/2.5 h). The screening reaction was also accelerated when replacing the (thio)ureas shown in Figure **7** with 40 mol% of the strong hydrogen bond donors methanol (k_{obs} = 1.15 h^{-1}) or water (k_{obs} = 0.72 h^{-1}) under otherwise identical conditions, but the accelerating effect was reduced in comparison to the use of catalyst **16**. The authors suggested that **16** preferably coordinates through explicit hydrogen-bonding to the more basic zwitterionic MBH key intermediate (**(1)**; Figure 8) or possibly initiated and stabilized a Zimmerman-Traxler type transition state (**(2)**; Figure 8) for the addition of the zwitterion to benzaldehyde. This mechanistic proposal was supported by the experimental finding that **16** was completely deactivated in the presence of an equimolar amount of the strong hydrogen bond acceptor tetrabutylammonium acetate (TBAA), which competed with the zwitterion for the urea N-H bonds.[181]

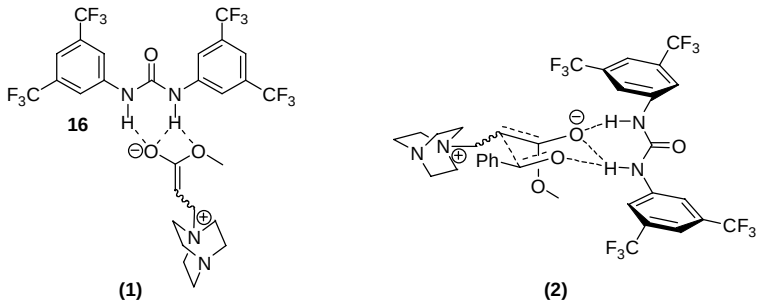


Figure 8. Proposed modes of action of hydrogen bonding catalyst **16**: Bidentate hydrogen bonding coordination of the zwitterion derived from Michael-type DABCO attack to methyl acrylate **(1)** and Zimmerman-Traxler transition state for the reaction of methyl acrylate with benzaldehyde **(2)**.

To fuse the efficiency of hydrogen-bonding (thio)urea and nucleophilic tertiary amine into one structure the hybride compounds **30** and **31** were prepared by analogy to the known efficient catalyst 3-hydroxyquinuclidine. These were evaluated in the MBH reaction between methyl acrylate and *o*-chlorobenzaldehyde (Figure 9). 3-Amino quinuclidine derivatives **30** and **31** (10 mol%) proved to be poor bifunctional organocatalysts (**30**: 31% yield/20 h; **31**: 23% yield/20 h) and these were less efficient than DABCO (86% yield/20 h). This result correlated with the findings by Aggarwal et al. that in quinuclidine derivative-catalyzed Baylis–Hillman reactions the protonated amine pK_a was the governing factor in determining catalyst efficiency, thus making quinuclidine itself a better catalyst than 3-heteroatom substituted analogues, which are of reduced basicity/nucleophilicity and give consequently lower reaction rates.

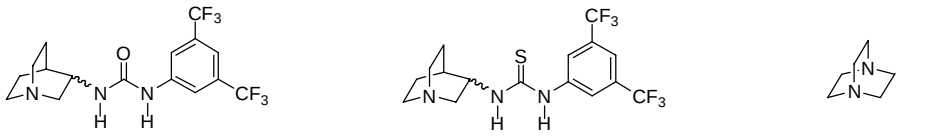
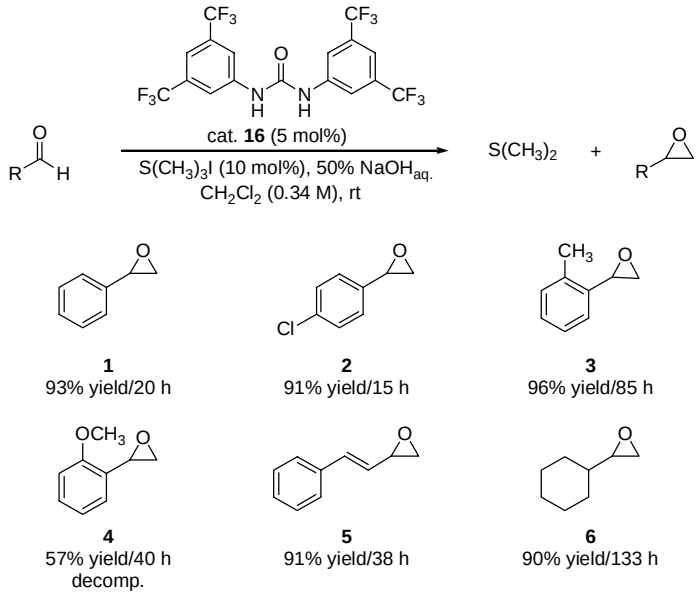


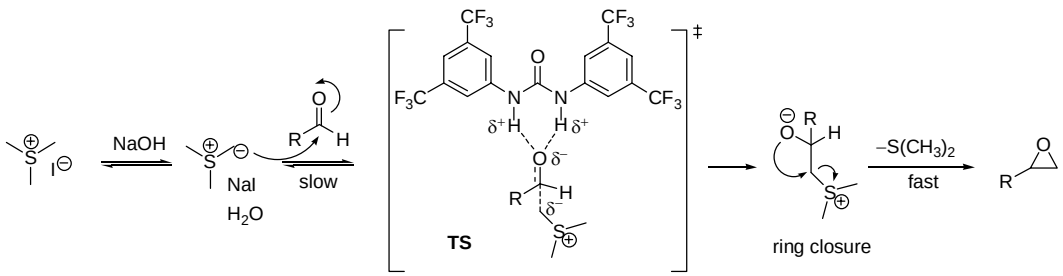
Figure 9. Bifunctional 3-amino quinuclidine derivatives **30** and **31** and DABCO probed in the MBH reaction between methyl acrylate and *o*-chlorobenzaldehyde.

In 2008, the Connon group published a protocol for the organocatalyzed Corey-Chaykovsky epoxidation utilizing electron-deficient *N*,*N*'-3,5-bis(trifluoromethyl)phenyl substituted urea **16** as hydrogen-bonding catalyst (5 mol% loading) and trimethylsulfonium iodide (1.0 equiv.) as precursor of sulfonium methylide generated in situ under biphasic conditions through deprotonation with aqueous NaOH.[182] The established reaction parameters (CH_2Cl_2, 50% $NaOH_{aq}$, rt) tolerated a broad substrate scope including electron-rich and electron-deficient aromatic aldehydes as well as cyclohexane carbaldehyde that were converted to the corresponding epoxides **1**–**6** in yields ranging from 57%–96% (Scheme 30). Aldehydes bearing an α-proton proved to be incompatible with the chosen basic conditions and showed

competitive aldol reactions. Thiourea derivatives such as **9** proved to be catalytically less effective than the urea counterparts presumably due to the higher N-H acidity of thioureas relative to the sulfonium methylide (pK_a in DMSO: *N*,*N*′-diphenyl urea: 19.55; *N*,*N*′-diphenyl thiourea: 13.4; $S(CH_3)_3I$: 18.2). Mechanistically, the epoxide formation is initiated with a nucleophilic attack of the in situ formed ylide to the aldehyde; this rate-determining addition step was suggested to be accelerated through hydrogen-bond mediated stabilization of the developing negative charge on the carbonyl oxygen in the proposed transition state resulting in a zwitterionic intermediate; fast ring closure afforded the observed epoxide product (Scheme 31). Based on the epoxidation protocol the authors developed a tandem organocatalytic epoxidation-transition metal catalyzed ring opening process employing the Cu(II) ion-catalyzed (25 mol% $Cu(BF_3)_2$) Meinwald rearrangement[183] to reach a homologation of aldehydes via the respective epoxide. This straightforward procedure was exemplified for 2-methyl benzaldehyde that was epoxidized in the presence of **16** and subsequently chain extended to 2-methyl phenyl acetaldehyde in 69% overall yield.



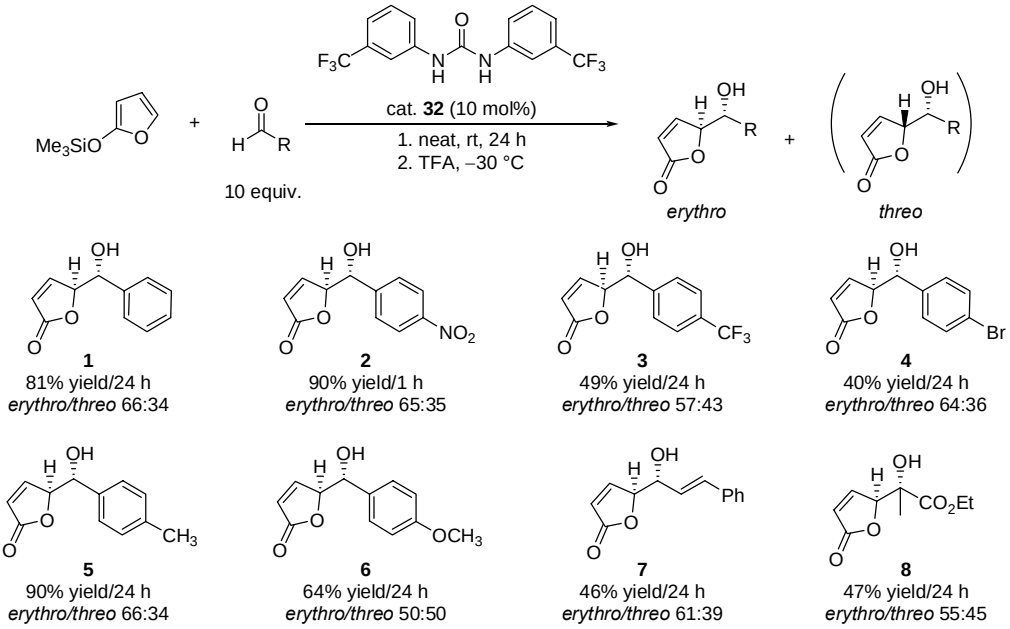
Scheme 30. Typical epoxides obtained from the Corey-Chaykovsky epoxidation of aldehydes catalyzed by urea **16**.



Scheme 31. Proposed mechanism for the Corey-Chaykovsky epoxidation of aldehydes catalyzed by urea **16**.

Urea **32**, the bis-(mono-trifluoromethyl)phenyl derivative of urea catalyst **16**,[181] was reported to operate as double hydrogen-bonding organocatalyst in the diastereoselective synthesis of γ-butenolide products substituted at the γ-position by a hydroxy functionalized alkyl chain.[184] This structural moiety is an important subunit in diverse natural products and biologically active compounds. Soriente and co-workers, in 2006, realized the catalyzing efficiency of urea derivative **32** (10 mol% loading) in the exploratory addition experiment of

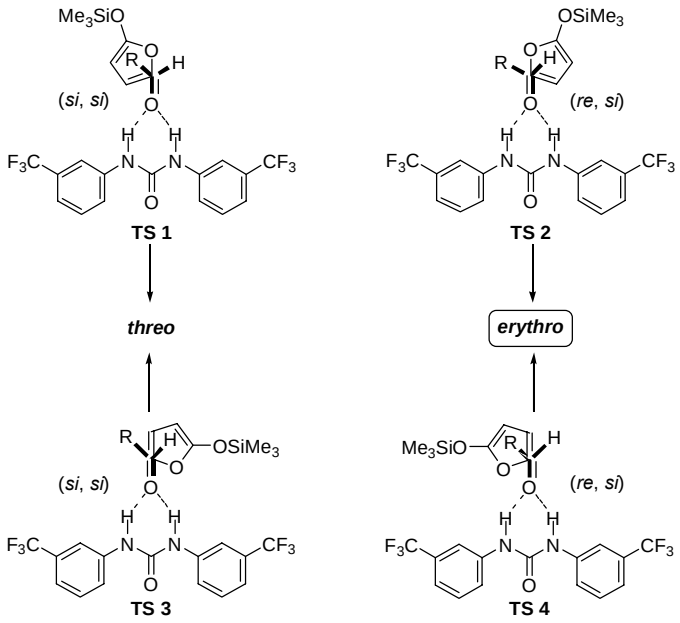
commercially available 2-trimethylsilyloxyfuran (TMSOF) to benzaldehyde (5 equiv.) at variable conditions.[184] The corresponding model γ-butenolide **1** was obtained after 24 h at room temperature in 81% yield with a *dr* 66:34 (Scheme 32). Using only 1 equiv. benzaldehyde at room temperature or performing the reaction with 5 equiv. at –20 °C affected only the yield of product **1** and gave 67% (24 h) and 73% (72 h), respectively; the diastereoselectivity remained constant at the lower temperature (*dr* 66:34) or decreased marginally (*dr* 61:39). Under optimized conditions the urea derivative **32** (10 mol%) catalyzed the addition of electron-rich and -deficient benzaldehydes to TMSOF followed by a TFA mediated desilylation step giving the desired γ-butenolide adducts **1**–**7** in moderate to good yields (40–90%) in 1–24 h reaction time and with *dr* values up to 66:34 in favor of the *erythro* isomer (Scheme 32). The addition to a ketone was exemplified with the formation of product **8** (47% yield/24 h) from the addition of TMSOF to the activated ketone group of ethyl 2-oxo propanoate (Scheme 32).



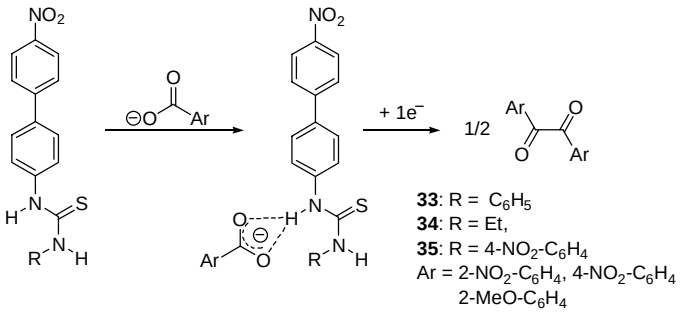
Scheme 32. γ-Butenolides obtained from diastereoselective aldol addition of 2-trimethylsilyloxyfuran to aldehydes catalyzed by urea **32**.

The authors interpreted the observed stereochemical preference of the *anti* isomer in this addition with the synclinal arrangement of the reagents in the open-chain transition state (**TS2**) depicted in Scheme 33. The *anti* diastereoselectivity was ascribed to the unfavorable steric interaction between the R group of the aldehyde and the furan ring of TMSOF (**TS1**). An antiperiplanar arrangement of the reagents demonstrated steric congestion in both conformers (**TS3** and **TS4**). In particular transition state **TS4**, which also furnished the *erythro* aldol adduct via **TS2**, possessed the same steric crowding as **TS1**. The examination of **TS3** also revealed steric repulsion between the bulky trimethylsilyl group and the trifluoromethyl-phenyl ring of the catalyst. Hence, the **32**-catalyzed reaction may proceed via the proposed transition state **TS2** and produces the observed *erythro* adduct (Scheme 33).

In 2007, Costero at al. reported on the basis of voltametric studies the cathodic reduction of aromatic carboxylates to give the corresponding dicarbonyl compounds (Scheme 34).[185] This transformation was catalyzed by hydrogen-bonding biphenylthiourea derivatives **33**, **34**, and **35**, which coordinate the carboxylate ion and facilitate the single electron transfer reducing step. The catalyst can be recovered unchanged after the reduction. Surprisingly, the authors assumed an activating hydrogen-bonding interaction of the anion with the thiourea derivative via a single amide proton as depicted in Scheme 34.

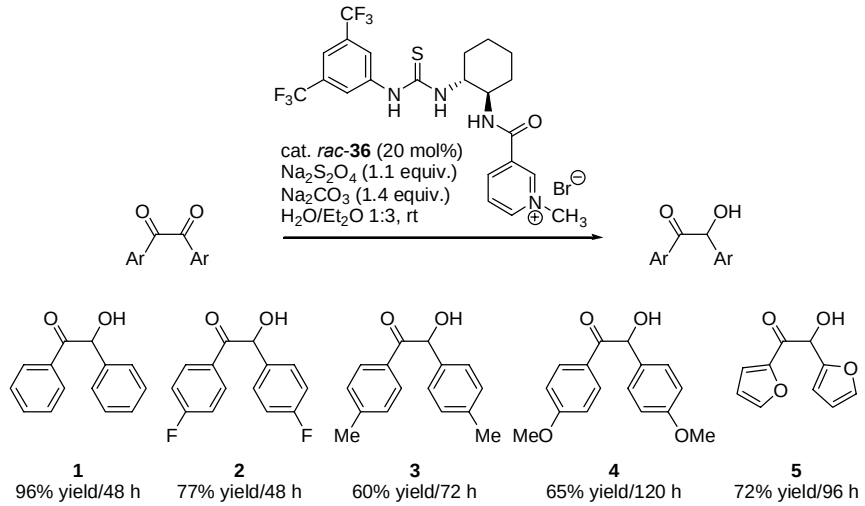


Scheme 33. Transitions states to explain the diastereoselectivity of the *γ*-butenolide formation from TMSOF and aldehydes in the presence of urea catalyst **32**.



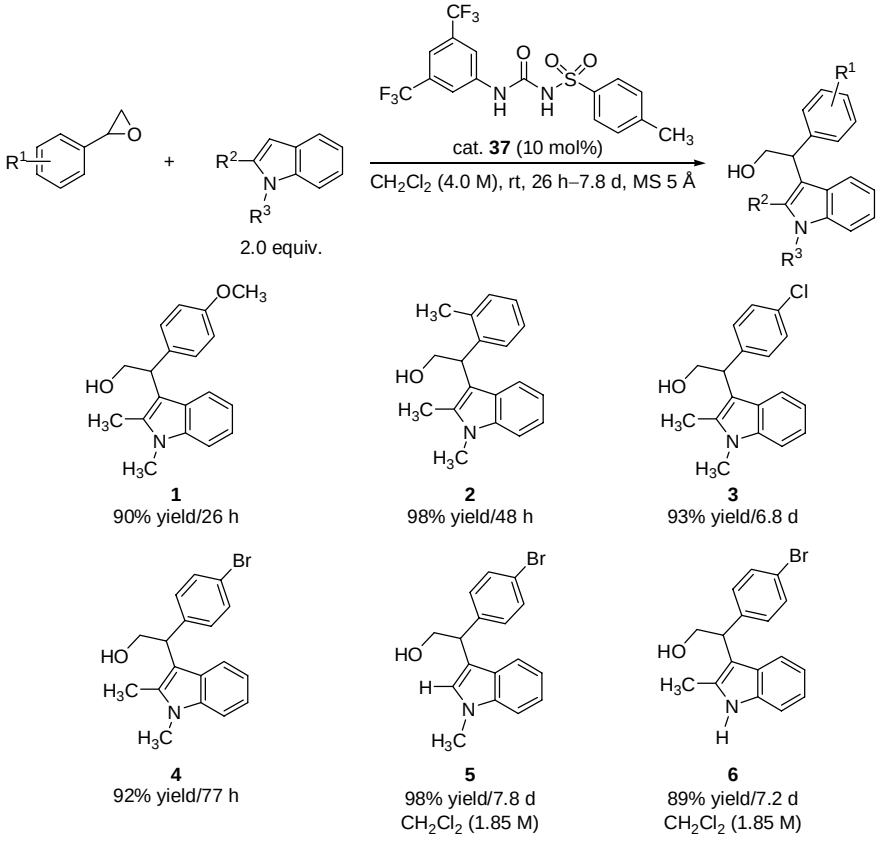
Scheme 34. Electrochemical reduction of aromatic carboxylates to benzils in the presence of thiourea catalyst **33**, **34**, or **35**.

Connon and Procuranti, in 2008, introduced new bifunctional organocatalysts classified as reductase-mimicking (thio)urea catalysts incorporating both a substrate-activating hydrogen-bonding (thio)urea moiety and a covalently bound NADH analogue moiety as hydride donor.[186] Thiourea derivative *rac*-**36** turned out to catalyze the chemoselective reduction of benzil to benzoin in a biphasic aqueous/organic solvent (Et_2O). In contrast to a binary catalytic system employing Hantzsch ester or a stoichiometric Lewis-acidic additive such as Mg^{2+} in combination with an organocatalyst this methodology was reported to operate under acid-free conditions and required only inexpensive sodium dithionate (1.1 equiv.) as co-reductant that generated and recycled in situ the catalytically active hydropyridine species. To interpret the experimental findings the authors suggested a bifunctional reduction mechanism in which an intramolecular hydride donation from the in situ generated hydropyridine moiety to the hydrogen-bonded and activated 1,2-diketone occurred and not the thiourea-catalyzed reduction of the diketone by dithionate. Under optimized conditions electron-rich and electron-poor benzils were transformed to the target benzoins (2-hydroxyketones) **1**–**5** in good to excellent yields (60%–96%) as shown in Scheme 35. The protocol was also applicable in the synthesis of unsymmetrical benzoins difficult to access in useful yields from the benzoin condensation of the corresponding aldehydes.



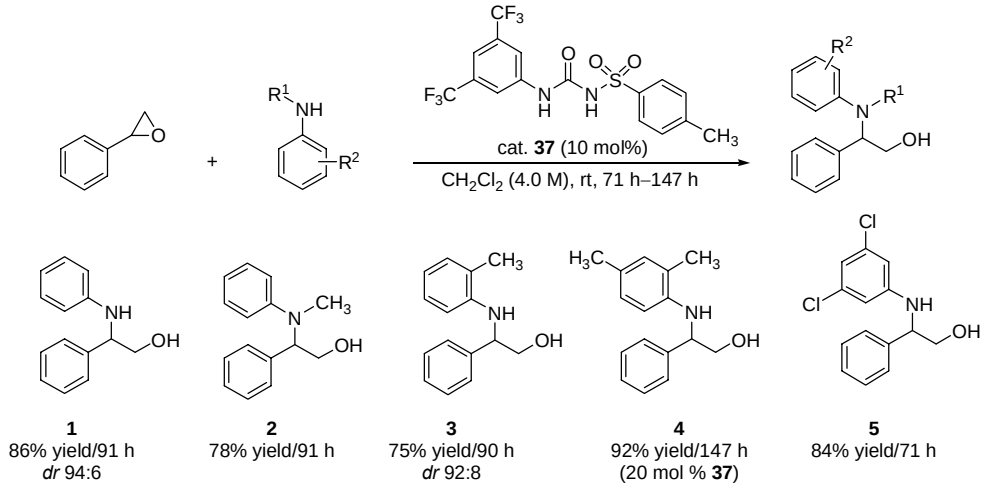
Scheme 35. Benzoins obtained from the reduction of benzils in the presence of thiourea derivative *rac*-**36** and sodium dithionate.

Rozas, Connon, and co-workers, in 2008, published a computational study-guided catalyst design strategy (DFT computations) applied in combination with experimental structure-efficiency studies that led to the identification of acidic *N*-tosyl urea derivative **37**.[187] This novel thiourea catalyst turned out to be capable of accelerating the highly regioselective opening of styrene oxides with predominantly 1,2-dimethylindols as well as with anilines. Under optimized reaction conditions (CH_2Cl_2; MS 5 Å; rt) catalyst **37** (10 mol% loading) promoted the addition of various methylindols to electron-rich and electron-deficient styrene oxides resulting in desired adducts **1**–**6** in consistently high yields (89%–98%) after 26 h–7.8 d as depicted in Scheme 36.



Scheme 36. Products obtained from the addition of indols to various styrene oxides in the presence of *N*-tosyl urea catalyst **37**.

The addition of anilines to styrene oxide was reported to proceed also in the presence of 10 mol% **37** affording the corresponding *β*-amino alcohols **1**–**5** in yields ranging from 75% to 92% (Scheme 37). Additionally, urea derivative **37** (20 mol% loading) was found to catalyze the addition of aniline (2.0 equiv.) to (*E*)-stilbene oxide (92% yield; 5.9 d; 30 °C), the addition of thiophenol (2.0 equiv.) to 2-methoxy styrene oxide (85%; 20 h; rt), and the alcoholysis of 4-methoxy styrene oxide with benzyl alcohol (2.0 equiv.) affording the respective *β*-alkoxy alcohol (82%; 20 h; rt).



Scheme 37. Product range of the styrene oxide opening with anilines promoted by *N*-tosyl urea catalyst **37**.

Ema, Sakai, and co-workers, in 2008, introduced trifunctional (thio)urea derivatives **38** and **39** mimicking the active site of serine hydrolases[188] in the biomimetic organocatalysis of the acetyl-transfer reaction (transesterification)[189, 190] from vinyl trifluoroacetate as reactive acetyl donor to methanol and 2-propanol, respectively.[191] In analogy to the active site of serine hydrolases such as lipases, esterases, and serine proteases the designed trifunctional catalysts **38** and **39** incorporated a hydroxy functionality expected to operate as a nucleophile, a pyridine moiety as a base, and a (thio)urea unit as an oxyanion hole[166] stabilizing the carbonyl oxyanion in the transition state (Figure 10); the privileged 3,5-bis(trifluoromethyl)phenyl moiety introduced by the Schreiner group[1, 116] was utilized to enhance the hydrogen-bond donor ability and thus the substrate binding of the (thio)urea unit. Proof-of-principle studies employing ^{19}F NMR kinetic experiments (100 mM vinyl trifluoroacetate; 500 mM MeOH) revealed urea catalyst **37** to be catalytically more active (100% conv.; 30 min; rt) than the thiourea counterpart **38** (100% conv.; 1 h; rt) at 1 mol% catalyst loading in $CDCl_3$ as the solvent. In the presence of 0.1 mol% catalyst the acetylation were completed after 16 h (**38**) and 4 h (**39**), respectively. Control compounds lacking either the hydroxy, pyridine, or the (thio)urea moiety displayed little or no conversions under otherwise identical conditions indicating that the three functional groups operate cooperatively to effectively catalyze the model acetylation reactions with up to 3 700 000-fold accelerations (for the acetylation of 2-propanol) and with high turnover. The OH group of the catalyst was suggested to be acetylated in a fast step to an acetyl-catalyst intermediate that was deacetylated in the rate-determining step resutling in the acetylation of the respective alcohol (Figure 10).

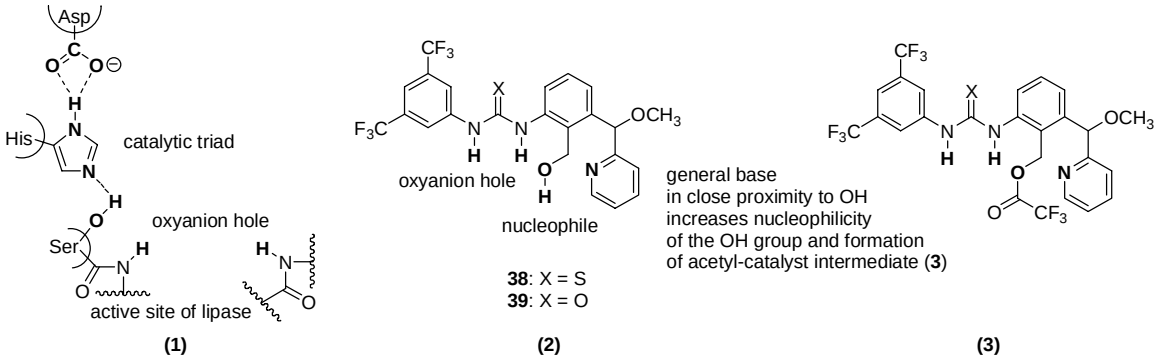
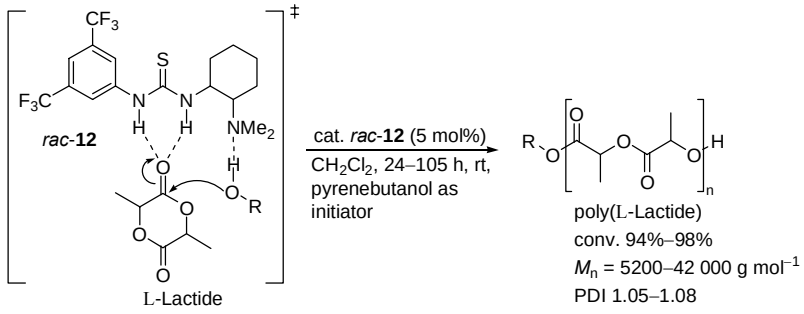


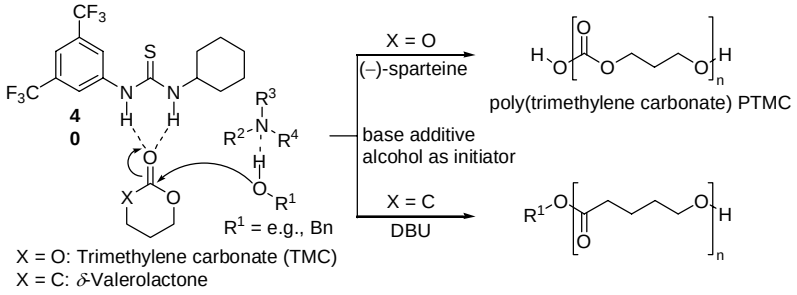
Figure 10. Active sites of lipase **(1)**, trifunctional (thio)urea derivatives (**38**; **39**) mimicking the acive site of serine hydrolases **(2)**, and acetyl-catalyst intermediate of the biomimetic transesterification between vinyl trifluoroacetate methanol and 2-propanol, respectively **(3)**.

In 2005, Hedrick, Waymouth, and co-workers reported racemic tertiary-amine functionalized thiourea derivative *rac*-**12** (5 mol% loading) to be catalytically active in supramolecular recognition for the living polymerization (evidenced by the linear correlation between ^{1}H NMR detected M_n and monomer conversion; PDI < 1.07) of L-lactide affording desired poly(L-Lactide) (Scheme 38).[192] Employing pyrenebutanol as initiator this ring-opening polymerization (ROP) proceeded in high conversions (94%–98%; 24 h–105 h) at room temperature with minimal transesterification of the polymer chain owing to the higher binding affinity of the thiourea catalyst to the cyclic ester monomer than to the linear ester polymer (examined by ^{1}H NMR titrations). As illustrated in Scheme 38 this specific bifunctional activation of the monomer favored the ROP instead of the competing transesterification.[75, 193]



Scheme 38. Ring-opening polymerization of L-lactide catalyzed by tertiary amine functionalized thiourea *rac*-**12**.

Hedrick, Waymouth, and co-workers modified the ROP methodology applied to the L-lactide monomer such that monofunctional electron-deficient *N*-bis(trifluoromethyl)phenyl *N'*-phenyl thiourea **40** was utilized in combination with a strong base [(–)-sparteine; DBU].[194, 195] Under these conditions the ROP of trimethylene carbonate (TMC) and, e.g., the cyclic ester δ-valerolactone proceeded to give the target polymers as depicted in Scheme 39. The authors assumed dual catalysis in which the base activated the alcohol that initiated the ROP by nucleophilic attack to the double hydrogen-bonded carbonyl monomer. The growing research field of organocatalytic ROP including catalysis through hydrogen-bonding thiourea derivatives was reviewed by Hedrick, Waymouth, and co-workers, in 2007.[75]



Scheme 39. Ring-opening polymerization of trimethylene carbonate and δ-valerolactone, respectively, catalyzed by a thiourea derivative **40** in the presence of a base.

1.2.2 Stereoselective (Thio)urea Organocatalysts

1.2.2.1 (Thio)ureas Derived from *trans*-1,2-Diaminocyclohexane and Related Chiral Primary Diamines

Trans-1,2-diaminocyclohexane, the most popular representative of the primary diamines and its derivatives have been widely utilized in the field of stereoselective organometallic catalysis as chiral reagents, scaffolds, and ligands.[139] This C_2 symmetrical chiral diamine first reported in 1926 by Wieland and co-workers[196] is commercially available, since it is a component in a byproduct amine stream generated during the purification of 1,6-hexanediamine that is used in the industrial Nylon 66 production. The racemic mixture of this diamine can be easily resolved with D- or L-tartaric acid to provide the enantiopure (*R*,*R*)- or (*S*,*S*)-isomer, respectively.[197] Owing to this cost-efficient availability of enantiopure *trans*-1,2-diaminocyclohexane and the multiple options of derivatization of the primary amine functionality, in particular the straightforward symmetrical or unsymmetrical incorporation of the urea or thiourea moiety via addition to (a)chiral isocyanates or isothiocyanates, respectively, this diamine has gained importance as an attractive chiral building block for the design and synthesis of a broad spectrum of structurally diverse (thio)urea derivatives operating as stereoselective (bifunctional) hydrogen-bonding organocatalysts. This section is dedicated to the conceptually important class of diamine-derived (thio)ureas ranging from monofunctional Schiff base catalysts that were actually the first enantioselective (thio)urea catalysts, to bifunctional tertiary, secondary, and primary amine functionalized as well as pyrrole and bisthiourea catalysts. The few catalysts structures based on related chiral diamines such as 1,2-diphenylethylene diamine and their applications are also considered herein.

In 1998, Sigman and Jacobsen identified and optimized the first enantioselective (thio)urea organocatalysts from synthetic libraries of polystyrene-bound tridentate Schiff bases and their high-throughput screening[56, 71, 198] (HTS) in the asymmetric Strecker reaction[159] of *N*-allyl benzaldimine with TBSCN as the cyanide source.[123] The basic catalyst design concept resulted from the original research goal to develop a novel tridentate chiral ligand for the efficient chirality transfer in an organometallic catalytic system as well as from the methodical necessity for solid-phase synthesis and systematic structure-optimizing variations to obtain high diversity of potential catalysts. Considering these aspects the typical core structure of tridentate ligands (chiral amino alcohol, salicylaldehyde derivative, metal-ion) was modified such that the amino alcohol was replaced with a chiral 1,2-diamine ((*R*,*R*)-1,2-diaminocyclohexane or (*R*,*R*)-diphenyl-1,2-ethylenediamine) that could be attached with a linker to the solid support; additionally, an amino acid was incorporated as a chiral diversity element located between the caproic acid and the (thio)urea linker (Figure 11).

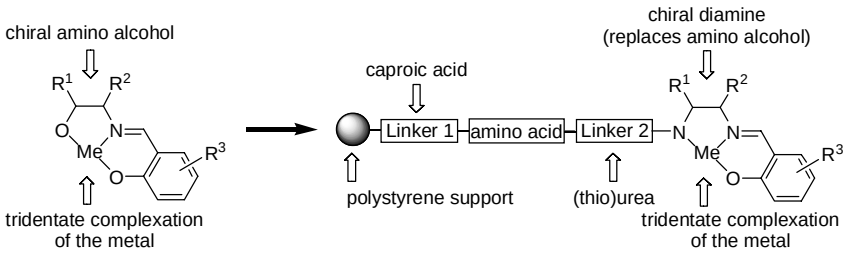
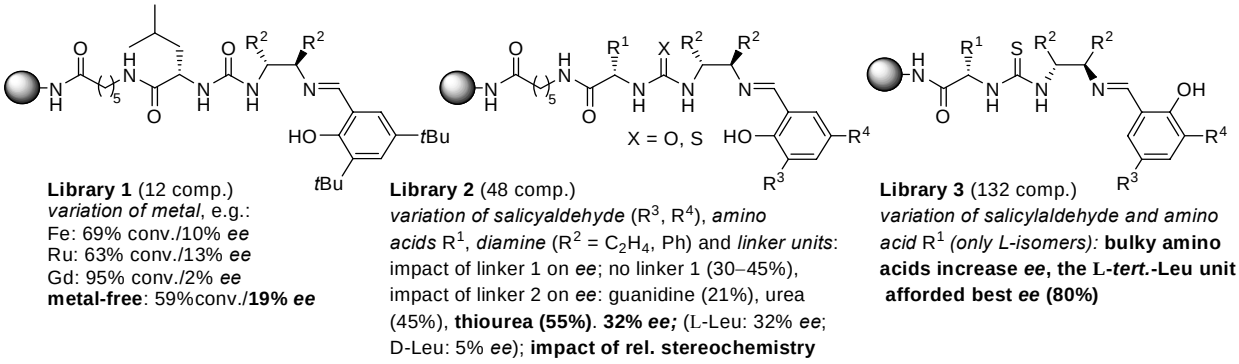


Figure 11. Typical tridentate ligand structure incorporating an chiral amino alcohol and modified diamine-based tridentate ligand structure attached to the solid support for parallel catalyst library strategy.

On the basis of this initial ligand target structure iterative HTS-optimization of the Strecker reaction enantioselectivity (GC analysis) was performed in parallel with an autosampler in three stages with three libraries consisting of 12 (library 1), 48 (library 2), and 132 (library 3) polymer-bound catalyst candidates (Figure 12), respectively. For the screening hydrocyanation reaction of *N*-allyl benzaldimine followed by trifluoroacetylation of the Strecker adduct library 1 (variation of the metal-ion) demonstrated in this first screening stage that the metal-free, organocatalytic system, was more enantioselective (19% *ee*) than the 11 metal-ion containing alternatives (e.g., 13% *ee* with Ru) examined under the same conditions. Library 2 revealed that the amino acid unit, the relative stereochemistry of the diamine versus the amino acid and the salicylaldehyde derivative had a detectable impact on the stereoinduction; linker 1 (caproic acid) was found to be responsible for

background side reactions and was removed for improved enantioselectivity, while the amino acid group of the catalyst was directly attached to the polystyrene support. Linker 2, however, turned out to be crucial for stereoinduction: thiourea derivatives (55% *ee*) turned out to be superior to both urea (45% *ee*) and guanidine (21% *ee*) based systems. The more focused library 3 consisting of 132 thiourea derivatives incorporating exclusively nonpolar L-amino acids and 3-*tert*-butyl-substituted salicylaldehydes supported the stereodifferentiating influence of the amino acid unit: the bulkiest thiourea derivatives bearing L-*tert*-Leu, cyclohexylglycine, and isoleucine, respectively, afforded the best *ee* values (up to 80%) (Figure 12).[56, 71]



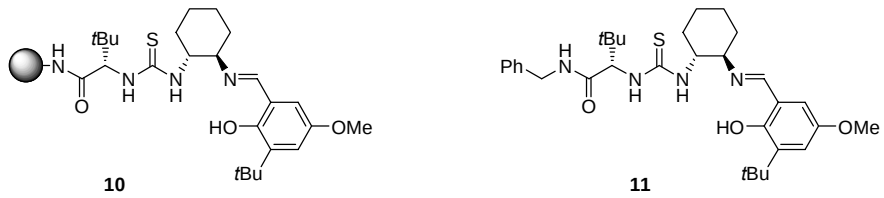
Library 1 (12 comp.)
variation of metal, e.g.:
Fe: 69% conv./10% *ee*
Ru: 63% conv./13% *ee*
Gd: 95% conv./2% *ee*
metal-free: 59%conv./**19% *ee***

Library 2 (48 comp.)
variation of salicylaldehyde (R^3, R^4), *amino acids* R^1, *diamine* (R^2 = C_2H_4, Ph) and *linker units*: impact of linker 1 on *ee*; no linker 1 (30–45%), impact of linker 2 on *ee*: guanidine (21%), urea (45%), **thiourea (55%)**. **32% *ee*;** (L-Leu: 32% *ee*; D-Leu: 5% *ee*); **impact of rel. stereochemistry**

Library 3 (132 comp.)
variation of salicylaldehyde and amino acid R^1 *(only L-isomers):* **bulky amino acids increase *ee*, the L-*tert.*-Leu unit afforded best *ee* (80%)**

Figure 12. Polystyrene-bound Schiff base (thio)urea catalysts HTS-optimized in the asymmetric Strecker reaction between *N*-allyl-protected benzaldimine and TBSCN; key results obtained from the different libraries.

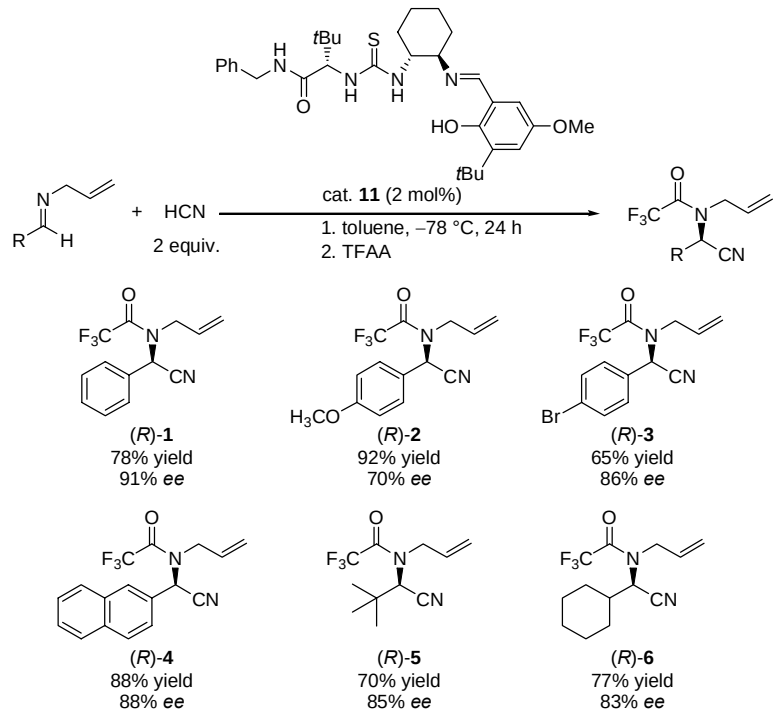
Schiff base thiourea[124] derivative **11** incorporating the (1*R*,2*R*)-diaminocyclohexane unit as chiral backbone was synthesized independently in solution on the basis of the structural features of polystyrene-bound **10** that was identified by parallel screening to be the most efficient in terms of enantioselectivity (Figure 13).



10 **11**

Figure 13. Diaminocyclohexane-derived Schiff base catalyst **10** representing the optimized structure identified from parallel catalyst screening and its polymer-free (solution-phase) counterpart **11** prepared for application in asymmetric Strecker reactions.

In the presence of Schiff base catalyst[124] **11** (2 mol%) and HCN as the cyanide source at −78 °C in toluene the respective chiral trifluoroacetylated Strecker adducts **1**–**6** of aromatic and also aliphatic *N*-allyl aldimines were formed in yields ranging from 65%–92% and *ee* values ranging from 70%–91% as shown in Scheme 40. On the basis of the core structure illustrated in Figure 14 various slightly modified Schiff base (thio)urea derivatives have been developed and efficiently applied predominantly to the asymmetric Strecker reaction[159] of *N*-protected aldimines and ketimines as described in detail below. Although this new type of organocatalyst displayed high catalytic activity, stereoselectivity, and synthetic utility the authors had not made a proposal for the mode of action of the Schiff base catalysts until 2002, when they suggested that double-hydrogen-bonding interactions between the (thio)urea amid protons and the imine lone pair activated the carbonyl analogue electrophile for the product-forming nucleophilic attack by the cyanide ion.[126] This mechanistic proposal is supported by the theoretical and experimental findings towards double hydrogen-bonding activation of carbonyl-dienophiles through thiourea derivatives reported earlier by Schreiner and Wittkopp, in 2000[112] and 2002,[116] and ascribes the catalytically essential function of substrate binding and activation to the (thio)urea moiety originally incorporated as simple linker unit in the Schiff base structure.



Scheme 40. Product range of the **11**-catalyzed asymmetric Strecker reaction of aromatic and aliphatic *N*-allyl-protected aldimines.

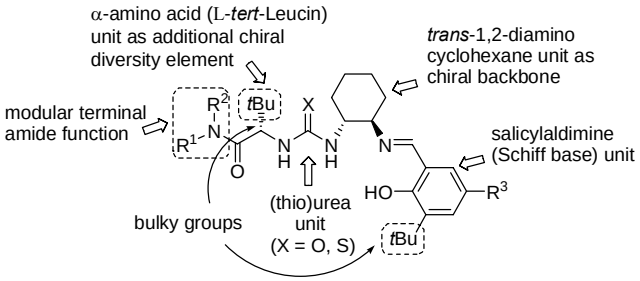


Figure 14. The key units of Jacobsen's Schiff base (thio)urea organocatalysts offering access to various structural modifications.

On the basis of the core structure of catalyst **11** (Figure 14) the Jacobsen group constructed a new optimization parallel library of 70 Schiff base compounds incorporating seven amino acids with bulky α-substituents and ten new salicylaldehyde derivatives.[199] Each library member was evaluated for enantioselectivity in the HCN[200] addition to the *N*-allyl imine of 2,2-dimethyl-propionaldehyde at 23 °C revealing polymer-bound 5-pivaloyl-substituted Schiff base **41** to be the most efficient catalyst. For further intensive studies with respect to scope and limitations the soluble non-immobilized urea-analogue **42** was employed for the asymmetric Strecker reaction of aldimines (Figure 15); the urea moiety was preferred due to an easier preparation at comparable catalyst efficiency.

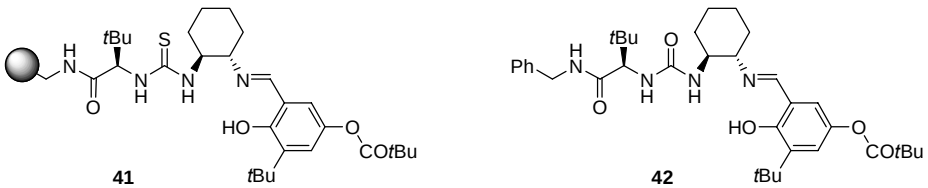
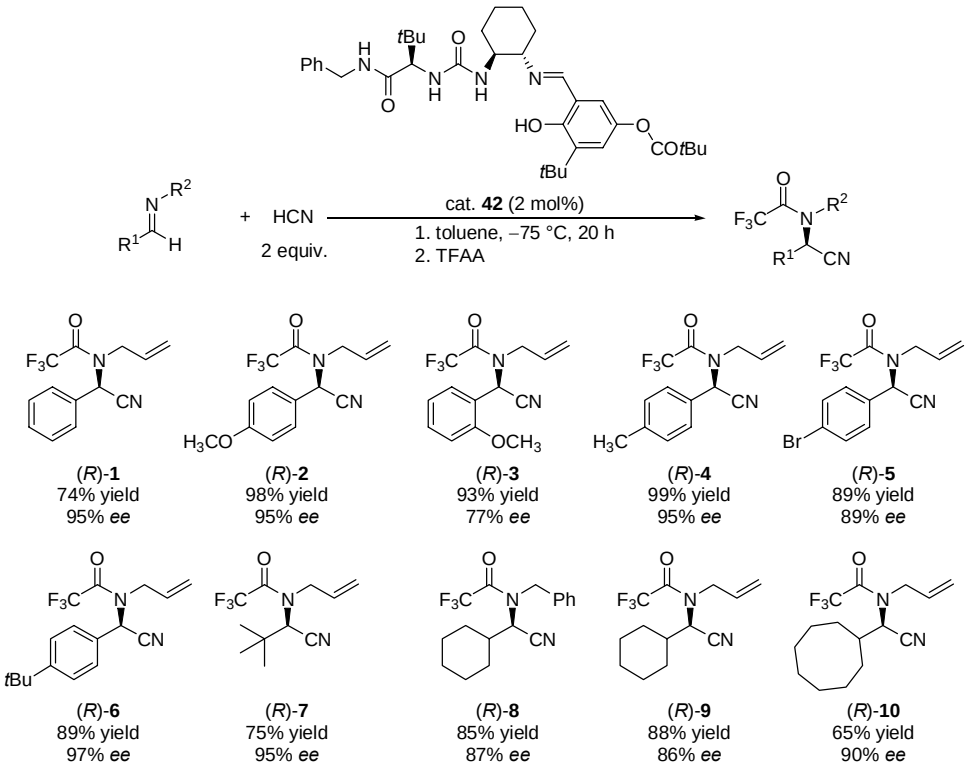


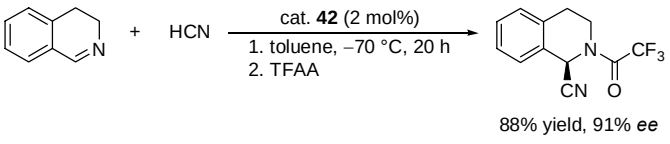
Figure 15. Polymer-bound Schiff base thiourea catalyst **41** bearing 5-pivaloyl-substitution and its nonimmobilized urea analogue **42** optimized for the asymmetric Strecker reaction of aromatic and aliphatic aldimines.

In the presence of **42** (2 mol% loading) aliphatic and aromatic *N*-allyl as well as *N*-benzyl aldimines were efficiently converted after 20 h at –70 °C in toluene to the respective Strecker adducts and subsequently trifluoroacetylated to obtain the products **1**–**10** in good to excellent yields (65%–99%) and *ee* values (77%–97%) (Scheme 41). It turned out that *N*-benzyl imines could be used as substrates without significant difference in comparison to analogous *N*-allyl imines (e.g., *N*-benzyl adduct **8**: 85% yield, 87% *ee*; *N*-allyl adduct **9**: 88% yield, 86% *ee*; Scheme 41).



Scheme 41. Typical products obtained from the asymmetric Strecker reaction of aliphatic and aromatic aldimines catalyzed by urea **42**.

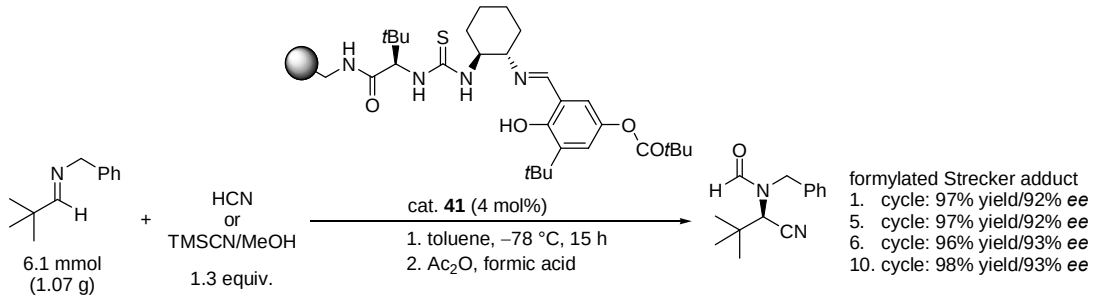
While all of the aryl imine substrates examined for this Strecker methodology existed predominantly or exclusively as the *E*-isomers, this did not appear to be a requirement for high enantioselectivity as demonstrated in the asymmetric **42**-catalyzed (2 mol% loading) hydrocyanation of the cyclic *Z*-imine 3,4-dihydroisoquinoline that was converted to the corresponding adduct (88% yield, 91% *ee*) with the same sense of stereoinduction with respect to the benzylic stereogenic center as the examined acyclic *E*-imines (Scheme 41 and 42).[199]



Scheme 42. In the presence of **42** the asymmetric Strecker reaction of the cyclic *Z*-imine 3,4-dihydroisoquinoline afforded the (*R*)-adduct.

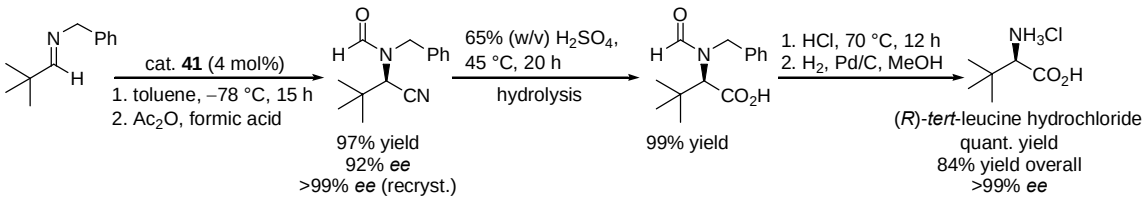
To reveal the practical potential of polymer-bound Schiff base thiourea catalyst **41** the Jacobsen group presented a recycling study using this catalyst in 4 mol% loading at –78 °C for the hydrocyanation of *N*-benzyl pivalaldimine under preparative conditions (6.1 mmol scale) (Scheme 43). Clean hydrocyanation of the model imine was observed and the target Strecker adduct was obtained with only a slight reduction in enantioselectivity (**42**: 96% *ee*; **41** 93% *ee*). The product was isolated in nearly quantitative yield after removal of the catalyst from the reaction mixture by simple filtration and no loss of catalyst activity or product enantioselectivity was detected after ten reaction cycles (Scheme 43).[61, 62] This simple work-up procedure, the easy catalysts recovery, and the reusability made **41** a practical alternative to

its soluble analogue **42** that gave 2%–4% higher *ee* values (loading 2 mol%) for the respective Strecker products, but reduced yields (e.g., for *N*-benzyl pivalaldimine: 88%) due to the required chromatographic product purification and catalyst separation.



Scheme 43. Recycling study: Polymer-bound Schiff-base thiourea **41** catalyzed the Strecker reaction of pivalaldimine without loss of activity or enantioselectivity, respectively, even after 10 catalytic cycles.

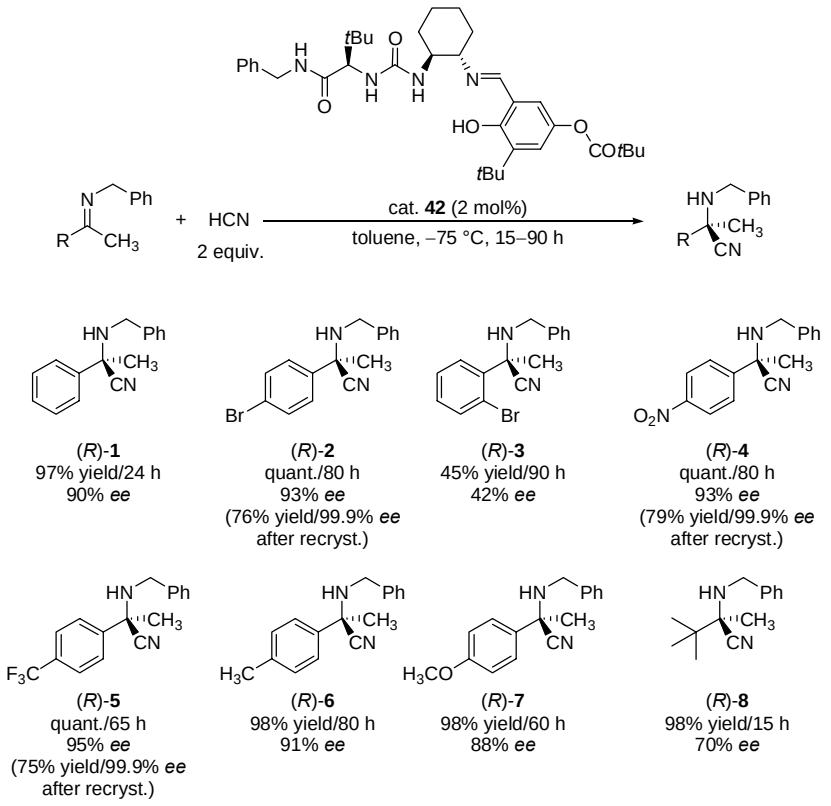
The synthetic utility and importance of the obtained Strecker adducts as precursors for access to enantiomerically pure α-amino acids was examplified for the synthesis of (*R*)-*tert*-leucine hydrochloride starting from *N*-benzyl pivalaldimine that was enantioselectively converted in the presence 4 mol% **41** to the corresponding α-amino nitrile. Since direct acidic hydrolysis of the (*R*)-amino nitrile failed and led to considerable decomposition due to harsh reaction conditions, the amino nitrile was first *N*-formylated (97% yield, 92% *ee*; 99% *ee* after recrystalization) before the racemization-free hydrolysis to the respective *N*-protected (*R*)-amino acid proceeded in 99% yield. The final steps included deformylation and removal of the *N*-benzyl group using H_2/Pd/C yielding the desired enantiopure (*R*)-*tert*-leucine hydrochloride (quant. yield, >99% *ee*) in high overall yield of 84% based on pivalaldimine (Scheme 44).



Scheme 44. Reaction sequence for the synthesis of enantiopure (*R*)-*tert*-leucine hydrochloride starting from the pivalaldimine Strecker adduct obtained under catalysis with polymer-bound thiourea **41**.

In addition to aldimines (Scheme 41), the Jacobsen group applied urea catalyst **42** to the asymmetric Strecker reaction[159] of *N*-allyl and, in particular, *N*-benzyl ketimines resulting in α-amino nitriles bearing a (*R*)-configured stereogenic quaternary carbon center.[201] (*R*)-amino nitriles are suitable precursors for the synthesis of enantiopure α-quaternary α-amino acids that are key intermediates for the synthesis of a broad variety of pharmaceutically important compounds. Although the resin-bound Schiff base catalyst **41**, which proved efficient in the hydrocyanation of aldimines (Scheme 44) also turned out to promote the model Strecker reaction of *N*-allyl acetophenone imine, long reaction times (180 h) were required to give the desired Strecker adduct (**41**: 95% yield; 85% *ee* at 4 mol% loading; –75 °C in toluene). Catalyst **42** (2 mol% loading), however, displayed higher catalytic activity under unchanged conditions (97% yield/30 h; 85% *ee*) and was therefore utilized for the enantioselective hydrocyanation of various *N*-benzyl-protected ketimines that were found to be the substrates of choice due to higher stability of their Strecker adducts under either acidic or basic conditions (no retro-Strecker decomposition) and due to slightly increased *ee* values (e.g., *N*-allyl acetophenone imine: 85% *ee*; *N*-benzyl: 90% *ee*; at –75 °C in toluene) compared to *N*-allyl-protected ketimines. Under optimized reaction conditions (–75 °C; 2 equiv. HCN, toluene) **42** (2 mol%) converted a variety of *N*-benzyl-protected ketimins bearing both electron-withdrawing and electron-donating aromatic substituents to their α-amino nitriles **1**–**8** in mostly

excellent yields (45%, 97%–100%) and *ee* values ranging from 42%–95% (Scheme 45). Some of the Strecker adducts (**2**, **4**, and **5**; Scheme 45) were isolated as crystalline compounds affording enantiomerically pure products (99.9% *ee*; 75–79% overall yield) after recrystallization from hexanes. Since catalysts **42** was soluble in hexanes, no chromatographic product purification was necessary as the catalysts remained in the mother liquors and could be recovered, purified, and reused in the Strecker reaction with results identical to those reached with freshly prepared catalyst. Employing the typical Strecker adducts of *N*-benzyl and *N*-4-bromobenzyl acetophenone imine (prepared in 40 h: 95% yield; 92% *ee*/75% yield, 99.9% *ee* after recryst.), respectively, the authors presented a three-step reaction sequence that furnished the desired enantiopure α-methyl phenylglycine in 92% overall yield (91% *ee*) for the *N*-benzyl and 93% overall yield (99.9% *ee*) for the *N*-4-bromobenzyl Strecker adduct (see also Scheme 44).[201]



Scheme 45. Typical products of the asymmetric Strecker reaction of ketimines catalyzed by urea **42**.

In 2002, Vachal and Jacobsen utilized a number of approaches such as systematic structural modifications, NMR methods, kinetic, and computational studies to investigate and elucidate in detail the mode of action of Schiff-base type urea catalyst **42**[199, 201, 202] in the mechanism of the highly enantioselective Strecker reaction[159] between the model substrate *N*-allyl-4-methoxybenzaldimine and HCN as the cyanide source.[126] It was found through NOE and ROESY NMR experiments that **42** adopted a well-defined secondary structure in solution despite its relatively small size (fw = 621 g mol^{-1}). The hydrocyanation reaction of the model imine obeyed an enzyme-like Michaelis-Menten kinetic model with a first-order dependence on catalyst **42** and HCN, and saturation kinetics with respect to the imine substrate implicating reversible formation of a hydrogen-bonded imine-catalyst complex. To identify and locate, respectively, the relevant proton(s) involved in these hydrogen-bond interactions, a series of analogues of **42** were prepared and evaluated as catalysts for catalytic activity and enantioselectivity in the model Strecker reaction. Deletion of the secondary amide proton, the phenolic proton, and the imine functionality did not suppress catalytic activity; in contrast, alkylation of either of the urea nitrogens or replacement with a carbamate group led to dramatic loss of activity and enantioselectivity. These findings suggested that exclusively the two urea amide protons interacted with the imine substrate resulting in the observed catalytic efficiency. NMR titrations of a solution of representative ketoimine *N*-*p*-methoxybenzyl acetophenone imine (*E*:*Z* = 20:1) with **42** resulted in a downfield shift of the *Z*-imine methyl resonance exclusively revealing the preferred binding of **42** to the *Z*-isomer instead to the *E*-isomer. This reaction occurred in quantitative yield and in 89% *ee*, while cyclic imines

restricted to *E*-configurations such as 6-phenyl-2,3,4,5-tetrahydropyridine underwent no reaction under the same conditions even under extended reaction times, in contrast to the cyclic *Z*-imine 3,4-dihydroisoquinoline (Scheme 42). A detailed 3-D structure model of the imine-catalyst complex based on molecular modelling studies and experimentally on multiple NOE interactions between **42** and various *Z*-imines mirrored the complex geometry resulting from the relative orientation of the imine substrate relative to the catalyst **42**. The imine substrate was placed in bridging mode in the sense of an explicit double hydrogen-bonding interaction between the two urea amide protons of **42**, while the Strecker product-catalyst complex showed only single hydrogen-bonding. This provided the probable origin of the catalyst turnover number (TON) and turnover frequency (TOF), respectively, since gas-phase calculations for a model (thio)urea and imine showed that the double hydrogen-bonding interaction (8.5 kcal mol^{-1} urea; 10.0 kcal mol^{-1} thiourea) was stronger than the single hydrogen-bonding interaction (5.0 kcal mol^{-1} urea; 6.3 kcal mol^{-1} thiourea). The model of the imine substrate-catalyst complex gave important rationalizations for the observed scope and stereoselectivity of the **42**-catalyzed Strecker reaction[199, 201, 202] and clues for further catalyst structure optimization: (1) The large group on the imine carbon was directed away from the catalyst into the solvent allowing **42**-catalyzed hydrocyanation of most aldimines with high *ee*, regardless of the steric and electronic properties of the substrate. (2) The small group (H for aldimines, Me for methylketoimines) was directed towards catalyst; ketoimines bearing larger substituents turned out to poor substrates for the reaction, presumably because they could not be accommodated within the less hindered optimal geometry. (3) The *N*-substituent was also directed away from the catalyst. However, its size was restricted as a result of the requirement to access the *Z*-isomer of the imine. (4) On the basis of the observed stereoinduction trend, the addition of HCN took place over the diaminocyclohexane portion of the catalyst and away from the amino acid and amide unit. The last hypothesis led to the prediction that a more sterically demanding amino acid or amide unit (Figure 14), respectively, could additionally favor the cyanide attack over the comparably less bulky diaminocyclohexane unit and thus made the Schiff base catalyst more enantioselective in Strecker reactions of aldimines as well as of ketimines. To evaluate this perspective the authors performed a model-(mechanism-) driven systematic structure optimizations by stepwise modification of the amide, the amino acid, and the (thio)urea unit of catalyst **42** and examined these derivatives of **42**(1 mol% loading) in the model Strecker reaction (toluene; –78 °C; HCN) of *N*-benzyl-protected 2-methylpropionaldehyde imine (Figure 16). It was found that the both the replacement of the secondary amide unit with a bulkier tertiary amide and the incorporation of a thiourea moiety instead of the urea unit afforded a measureable improvement in stereoinduction (from initial 80% *ee* obtained with **42** to 97% *ee*) and led to the identification of hydrogen-bonding Schiff base thiourea catalyst **47**, while the urea derivatives **43**–**46** gave lower *ee* values (Figure 16).

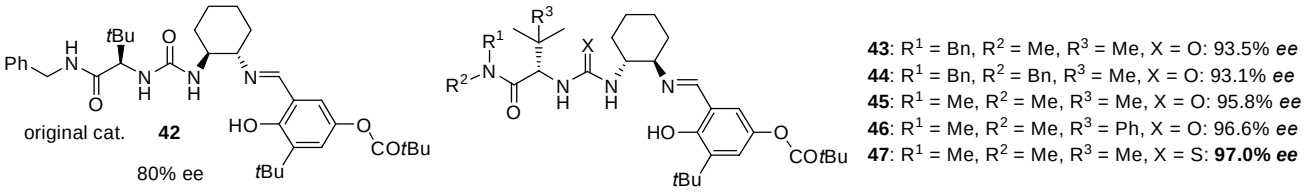
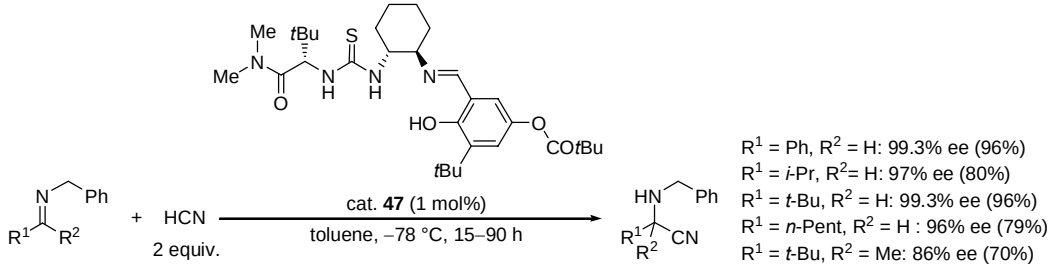


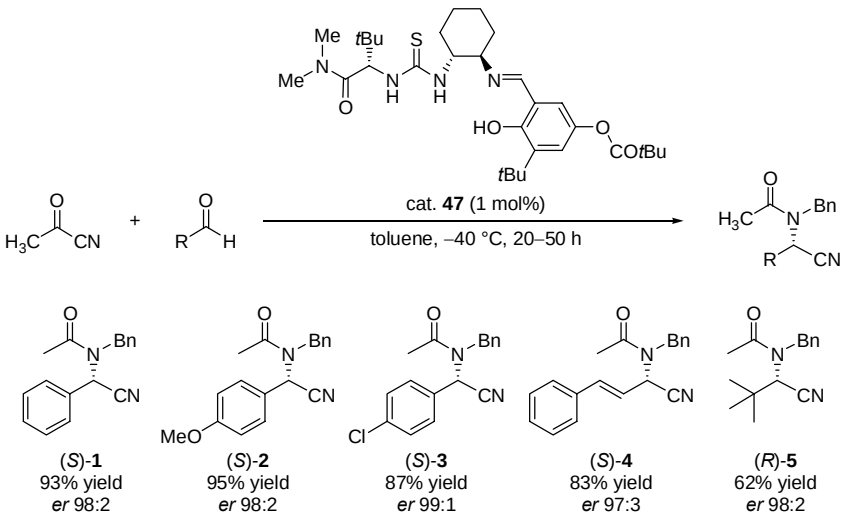
Figure 16. Structure optimization of **42** in the asymmetric Strecker reaction of *N*-benzyl-protected 2-methylpropionaldehyde imine identified tertiary amide functionalized Schiff base thiourea **47** as the most enantioselective catalyst structure.

This tertiary amide functionalized Schiff base thiourea was found to efficiently catalyze the asymmetric Strecker reaction[159] of *N*-benzyl-protected aldimines and also one ketimine in high enantioselectivities (86%–99% *ee*) and proved superior to **42** examined under the same conditions (1 mol% loading, toluene, –78 °C, HCN) (Scheme 46).[201]



Scheme 46. Products of the **47**-catalyzed asymmetric Strecker reaction; ***ee*** values obtained with urea **42** are given in parentheses.

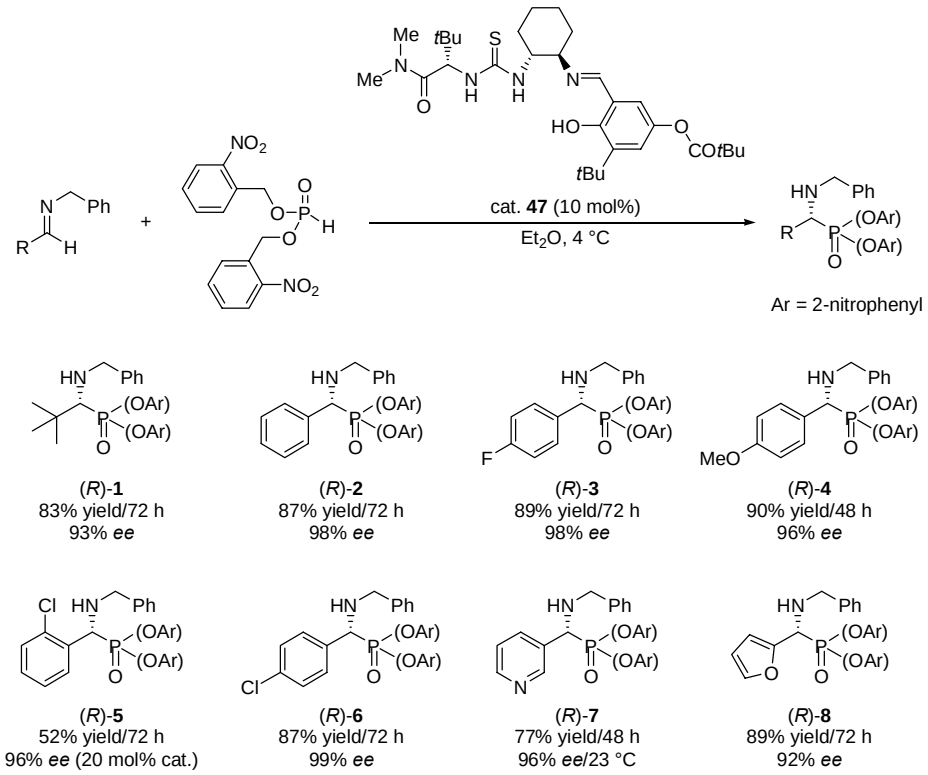
List and co-workers reported the **47**-catalyzed (1 mol% loading) asymmetric acetylcyanation of *N*-benzyl-protected aliphatic and aromatic aldimines using commercially available liquid acetyl cyanide as the cyanide source instead of HCN.[163] Under optimized reaction parameters (toluene, –40 °C) the procedure afforded the desired *N*-protected α-amino nitriles **1**–**5** in yield ranging from 62% to 95% and in high enantiomeric ratios (*er* up to 99:1) as shown for some typical products in Scheme 47.



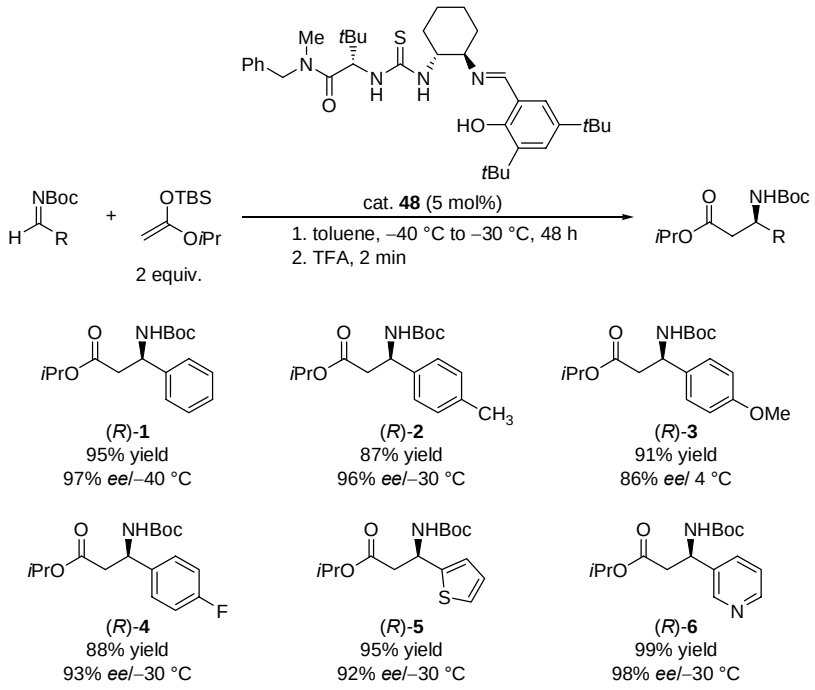
Scheme 47. Strecker products obtained from the **47**-catalyzed asymmetric acetylcyanation using acetyl cyanide as cyanide source.

Hydrogen-bonding Schiff base thiourea **47** originally developed for the asymmetric HCN addition to *N*-protected imines[126] (Strecker reaction)[159] (Figure 16) was identified by Joly and Jacobsen to promote also the asymmetric addition of di(2-nitrobenzyl)phosphate to aliphatic and (hetero)aromatic *N*-benzyl-protected aldimines.[203] This **47**-catalyzed (10 mol% loading) enantioselective hydrophosphonylation generated the respective (*R*)-α-amino phosphonates **1**–**8** in yields in the range of 52%–90% and in excellent *ee* values (92%–99%) (Scheme 48). It is notable that the absolute configuration of the isolated adducts was found to be consistent with the sense of stereoinduction observed for the asymmetric Strecker[123, 126, 199, 201] and Mannich reactions.[72, 204] For selected examples of the obtained (*R*)-α-amino phosphonates the authors demonstrated the synthesis of the corresponding α-amino phosphonic acids via a selective hydrogenolysis strategy (87%–93% yield; 96%–98% *ee*).

Wenzel and Jacobsen, in 2002, identified Schiff base thiourea derivative **48** as catalyst for the asymmetric Mannich addition[72] of *tert*-butyldimethylsilyl ketene acetals to *N*-Boc-protected (hetero)aromatic aldimines (Scheme 49).[204] The optimized structure of **48** was found through the construction of a small, parallel library of 22 catalyst candidates with systematic variation of the salicylaldimine, diamine, amino acid, and amide unit (Figure 14). Since the *para* substituent turned out to be without impact on the stereoinduction of the initially explored Mannich test reaction commercially available di-*tert*-butylsalicylaldehyde was used for the synthesis of subsequent catalyst candidates. As already shown in the case of catalyst **47** (Figure 16) the presence of a tertiary amide unit improved the stereoinduction and, additionally, prevented undesired formation of thiohydantoin byproducts during the preparation of the respective Schiff base catalyst. Under optimized conditions concerning the choice of catalyst (5 mol% **48**), the silyl ketene acetal (TBS-group, *iso*-propyloxy substituent), reaction temperature (at –40 °C/–30 °C the racemic background reaction was suppressed), and toluene as the solvent the Mannich reaction proceeded highly enantioselectively (86%–98% *ee*) and gave the target (*R*)-configured Mannich adducts **1**–**6** in high yields (87%–99%) in a practical reaction time (48 h) (Scheme 49). The *N*-Boc-protected β-amino acid derivatives were readily deprotected under mild acidic conditions to yield enantiopure β-aryl-β-amino acids suitable for peptide synthesis.



Scheme 48. Product range of the asymmetric hydrophosphonylation of *N*-benzylated aldimines promoted by thiourea derivative **47**.



Scheme 49. Typical Boc-protected *β*-amino acid derivatives obtained from **48**-catalyzed Mannich reactions of *N*-Boc-protected aldimines with silyl ketene acetal.

In 2004, Taylor and Jacobsen published a procedure for the enantioselective acetyl-Pictet-Spengler reaction, that is the cyclization of electron-rich aryl or heteroaryl groups onto *N*-acyliminium ion affording access to substituted tetrahydro-β-carbolines and tetrahydroisoquinolines that are core structure elements in natural and synthetic organic compounds.[205, 206] Screening various thiourea catalyst candidates such as **47** in the formation of model product N_{β}-acetyl-tetrahydro-β-carboline **1** (Scheme 50) from the corresponding tryptamine-derived imine starting material failed and showed no conversion even at high temperatures (Pictet-Spengler conditions). Performing the same test reaction, however, in the presence of acetyl chloride (1.0 equiv.) serving as acetylating reagent, that activated the imine function through formation of the corresponding *N*-acetyliminim ion, the desired product-forming intramolecular Friedel-Crafts cyclization occurred and the target tetrahydro-β-carboline was isolated in 65% yield and 59% *ee* (**47**: 10 mol%; 2,6-lutidine, Et_2O; at –30 °C).[204] The authors modulated the Schiff base structure of **47** such that the salicylaldimine moiety was replaced with the bulky *N*-pivaloyl amide unit resulting in catalytically more efficient novel thiourea derivatives **49**–**52** (Figure 17). Variation of the pyrrole substituents and fine-tuning of the amide unit demonstrated that 2-methyl-5-phenylpyrrole thiourea **52** bearing the *N*,*N*-diisobutyl amide group was the best catalyst in terms of activity (70% yield) and enantioselectivity (93% *ee*) (Figure 17).

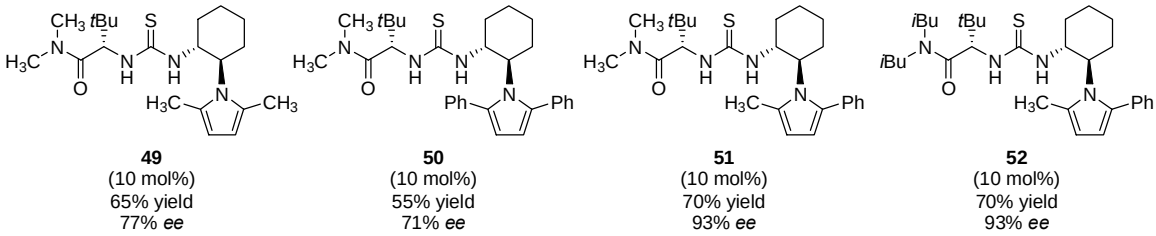
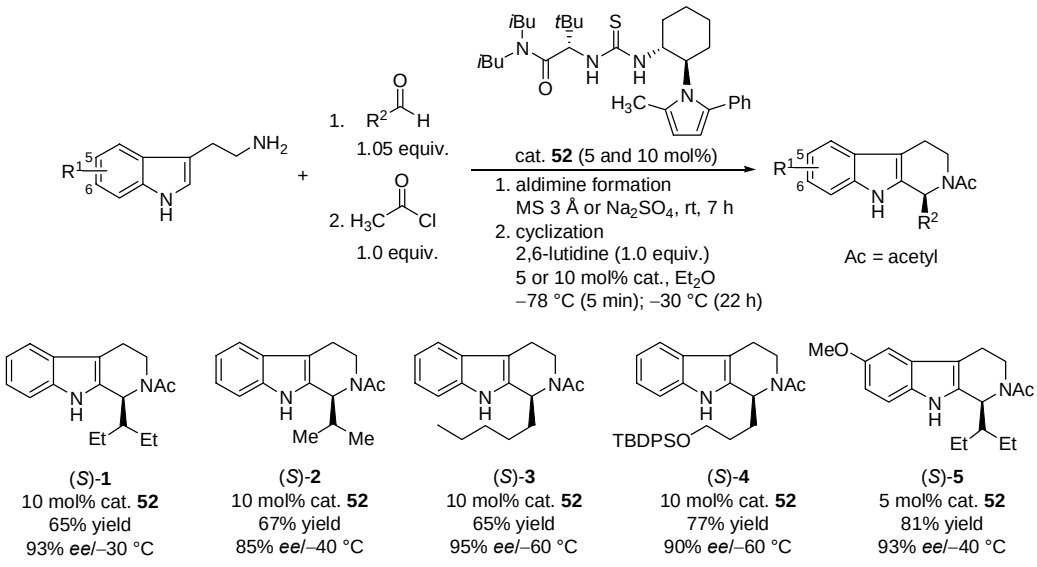


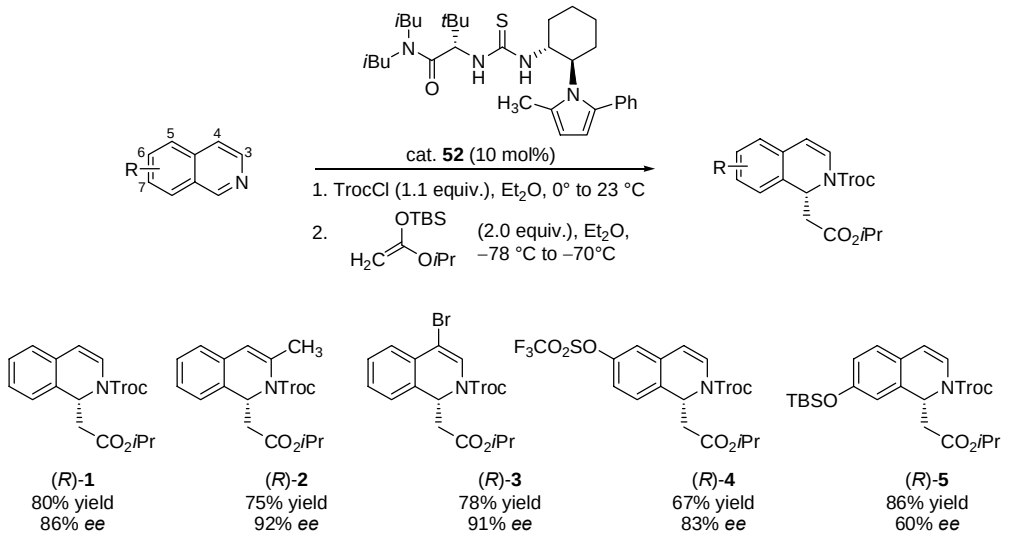
Figure 17. Pyrrole thiourea derivatives evaluated for catalytic activity and selectivity in the asymmetric acetyl-Pictet-Spengler reaction.

With thiourea **52** as the catalyst (5–10 mol%) a range of substituted *S*-configured tetrahydro-β-carbolines **1**–**5** were accessible in good yields (65%–81%) and high enantioselectivities (85%–95%) as shown in Scheme 50. The imine substrates of this two-step procedure were generated in situ by condensation of the tryptamine with the respective aldehyde (1.05 equiv.) and were directly used without further purification (Scheme 50). Recovered (by chromatography) pyrrole thiourea catalyst **52** could be reused without loss of activity or selectivity.



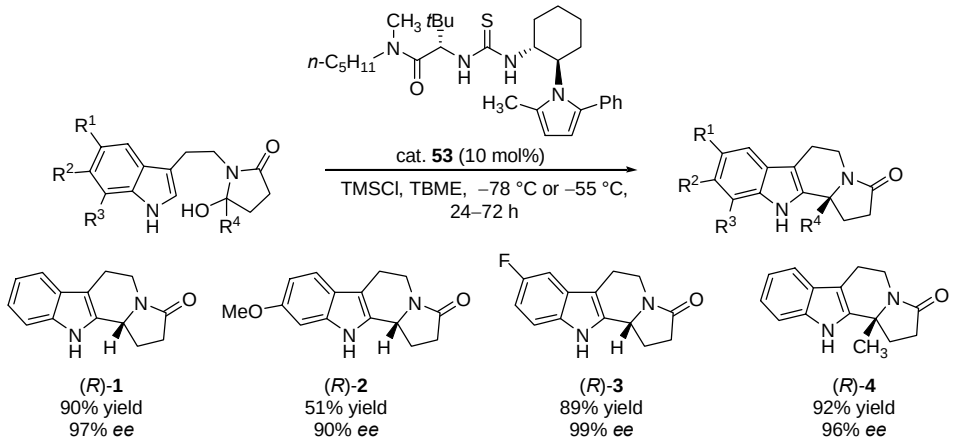
Scheme 50. Typical tetrahydro-β-carbolines prepared with the **52**-catalyzed enantioselective acetyl-Pictet-Spengler reaction.

Hydrogen-bonding pyrrole thiourea **52** proved capable of activating weakly Lewis-acid *N*-acetyliminium ions towards an enantioselective cyclization step in the acetyl-Pictet-Spengler reaction as reported by the Jacobsen group.[204] On the basis of this novel hydrogen-bonding activation the same group applied catalyst **52** (10 mol%) to acyl-Mannich reactions[72] of substituted isoquinoline substrates offering access to a number of dihydroisoquinolines **1**–**5** in good yields (67%–86%) and *ee* values (60%–92%) (Scheme 51).[207] The reaction afforded the best results in terms of product yield and stereoinduction, when using *tert*-butyldimethylsilyl ketene acetal (2.0 equiv.) derived from isopropyl acetate as nucleophilic enolate equivalent and 2,2,2-trichloroethyl chloroformate (TrocCl) as the acylating reagent (1.1 equiv.). Akin to the acyl-Pictet-Spengler reaction (Scheme 50) the **52**-catalyzed acyl-Mannich reaction exhibited a strong dependence on the substitution pattern of the pyrrole moiety (e.g., 2,5-dimethyl-pyrrole: 60% yield; 30% *ee*; 2,5-diphenyl-pyrrole: 55% yield; 78% *ee* in then acyl-Mannich reaction of isoquinoline). The crystal structure geometry of catalyst **52** suggested an explanation of this observation. The 2-methyl-5-phenylpyrrole structural motif located the phenyl group in a position to interact closely with any incoming substrate that unterwent hydrogen-bonding interactions with the thiourea amide protons.[207] To underline the synthetic importance of the obtained dihydroisoquinolines the authors developed a two-step conversion to the corresponding 1-substituted tetrahydroisoquinoline derivatives (e.g., 83% yield; 86% *ee*) that are important chiral building blocks for, e.g., alkaloid synthesis.

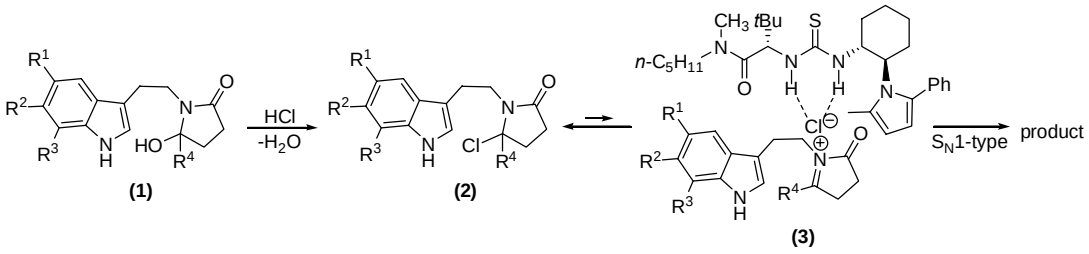


Scheme 51. Dihydroisoquinolines obtained form asymmetric acyl-Mannich reaction of substituted isoquinolines promoted by **52**.

In 2007, Jacobsen and co-workers reported the enantioselective Pictet-Spengler-type cyclization of *β*-indolyl ethyl hydroxylactams affording highly enantioenriched indolizidinones and quinolizidinones with fully substituted stereogenic centers.[208] The hydroxylactam substrates prepared either by imide reduction using $NaBH_4$ or by imide alkylation with organolithium reagents underwent conversion to the desired cyclization products **1**–**4** in yields ranging from 51% to 92% and in excellent *ee* values (90%–99%) (Scheme 52). This methodology utilized pyrrole 2-methyl-5-phenylpyrrole catalyst **53** (10 mol%), the *N*-methylpentyl amide derivative of **52** (Scheme 50 and 51), in the presence of TMSCl (2 equiv.) that served as dehydrating agent to generate the mechanistically essential *N*-acyliminium ion[76] from the hydroxylactam (Scheme 53). Based on substituent, counterion, solvent effect, and variable temperature ^{1}H NMR) studies the mechanistic proposal started with the TMSCl-induced irreversible and rapid formation of a chlorolactam. Catalysis and enantioinduction resulted from the **53**-promoted initial abstraction of a chloride counterion (S_N1-type rate-determining step) affording a chiral *N*-acyliminium chloride-thiourea complex that subsequently unterwent product-forming cyclization mediated by anion-bound thiourea pyrrole catalyst **53** (Scheme 53). This methodology and the mechanistic proposal, respectively, are of conceptual importance as for the first time a hydrogen-bonding organocatalyst is suggested to bind an anion (recognition) in an enantioselective reaction. An important parallel, e.g., represents the **9**-assisted orthoester heterolysis and subsequent non-stereoselective acetalization reported by Kotke and Schreiner (Scheme 11).[119, 148]

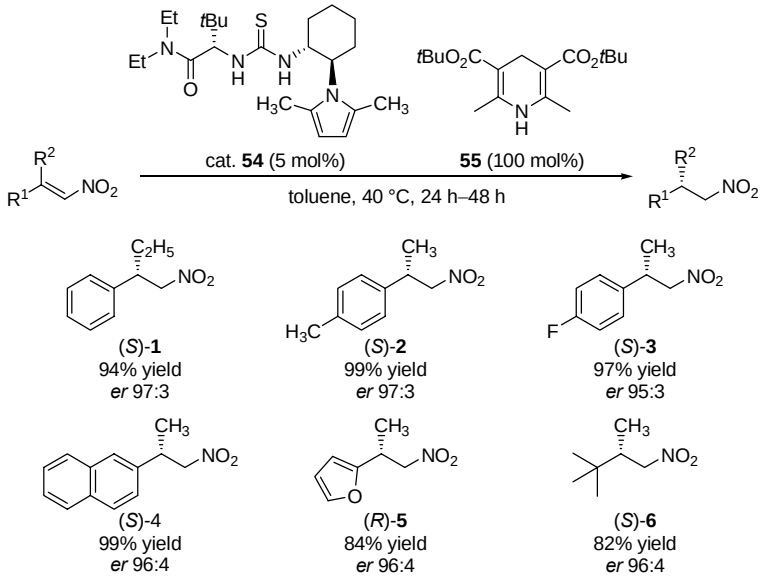


Scheme 52. Products of the asymmetric Pictet-Spengler-type cyclization of *β*-indolyl ethyl hydroxylactams catalyzed by **53**.



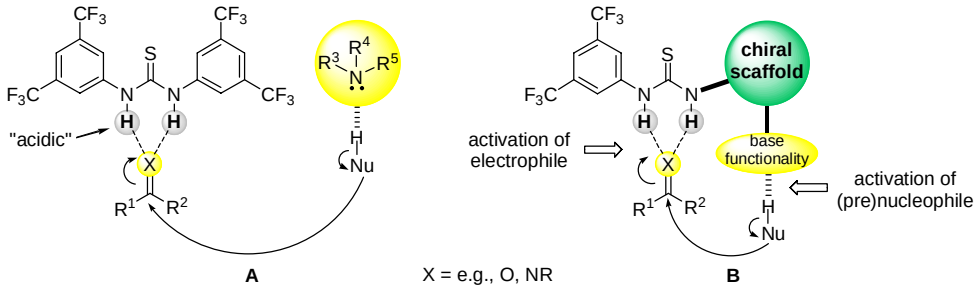
Scheme 53. Proposed mechanism for the **53**-catalyzed asymmetric Pictet-Spengler-type cyclization of *β*-indolyl ethyl hydroxylactams: Hydroxylactam **(1)** forms chlorolactam **(2)** followed by chiral *N*-acyliminium chloride-thiourea complex **(3)** and the observed product generated by intramolecular cyclization; catalysis and enantioinduction result from chloride abstraction and anion binding.

Pyrrole-containing thiourea derivatives **52** and **53** were developed and optimized for hydrogen-bonding activation of *N*-acyliminium ions[76] in the acyl-Pictet-Spengler[205, 208] (Scheme 50 and 52) and acyl-Mannich reaction[207] (Scheme 51). List et al. extended the applicability of this thiourea type to the asymmetric transfer hydrogenation of nitroalkenes and prepared a range of (*S*)-configured nitroalkanes such as **1**–**6** utilizing catalyst **54** (5 mol%) in the presence of Hantzsch ester[168] **55** (1.1 equiv.).[209] The protocol was reported to be high-yielding (82%–99%) and enantioselective (up to *er* 97:3) for various nitroalkene substrates as shown in Scheme 54.



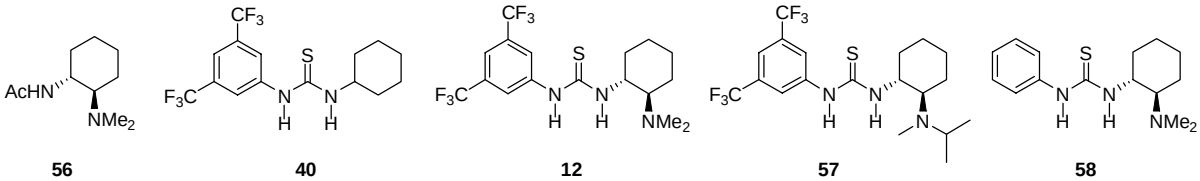
Scheme 54. Chiral nitroalkanes provided from the **54**-catalyzed asymmetric transfer hydrogenation of nitroalkenes in the presence of **55**.

In 2003, Takemoto and co-workers introduced the first tertiary amine-functionalized thiourea catalyst.[131] This new type of stereoselective thiourea catalyst incorporating both (*R*,*R*)-1,2-diaminocyclohexane as the chiral scaffold and the privileged 3,5-bis(trifluoromethyl)phenyl thiourea motif for strong hydrogen-bonding substrate binding, marked the introduction of the concept of bifunctionality in synthetic (thio)urea catalysis systems. Bifunctionality is a structural principle orginating from highly efficient natural catalytic systems such as enzymes (Scheme 1) and has been mimicked by various synthetic catalytic systems to enable a catalyst to employ its Lewis/Brønsted acidic and Lewis/Brønsted basic functionality synergistically for activation of both the nucleophilic and electrophilic reaction components simultaneously (Scheme 55). This bifunctional activation often results in much higher rate enhancements and strereoinductions than achieved with comparable monofunctional synthetic catalysts.[210]



Scheme 55. Design principle of amine-functionalized bifunctional thiourea organocatalysts derived from privileged monofunctional thiourea **9** cooperating with an amine base additive (**A**) and basic bifunctional mode of action of chiral amine thioureas (**B**), simultaneous activation of both the electrophile and (pre)nucleophile (triple-collision scenario) through partial protonation (H-bonding) and (partial) deprotonation, respectively.

The Takemoto group synthesized a series of diaminocyclohexane-based thiourea derivatives (e.g., **12**, **40**, **57**, and **58**) for catalysis of the Michael addition[151-154] of malonates to *trans*-*β*-nitrostyrenes (Figure 18).[131, 211] In the model Michael addition of diethyl malonate to *trans*-*β*-nitrostyrene at room temperature and in toluene as the solvent tertiary amine-functionalized thiourea **12** (10 mol% loading) was identified to be the most efficient catalyst in terms of catalytic activity (86% yield/24 h) and enantioinduction (93% *ee*/rt). Performing the same reaction under otherwise identical conditions in the presence of 10 mol% of chiral amine **56** lacking the thiourea moiety the desired Michael adduct in only 14% yield (24 h) and 35% *ee*; with triethylamine (TEA) as base additive (10 mol%) and achiral thiourea **40** (10 mol%) lacking the tertiary amine group the target Michael adduct was provided in only 57% yield after 24 h (Figure 18). These experimental findings indicated that for this type of reaction high yields and enantioselectivities required a bifunctional catalyst structure such that the catalyst incorporated both a thiourea moiety and a tertiary amine functionality in a suitable relative arrangement to each other (Scheme 55).



56
14% yield/24 h
35% *ee*/rt

40
TEA as additive
57% yield/24 h/rt

12
86% yield/24 h
93% *ee*/rt

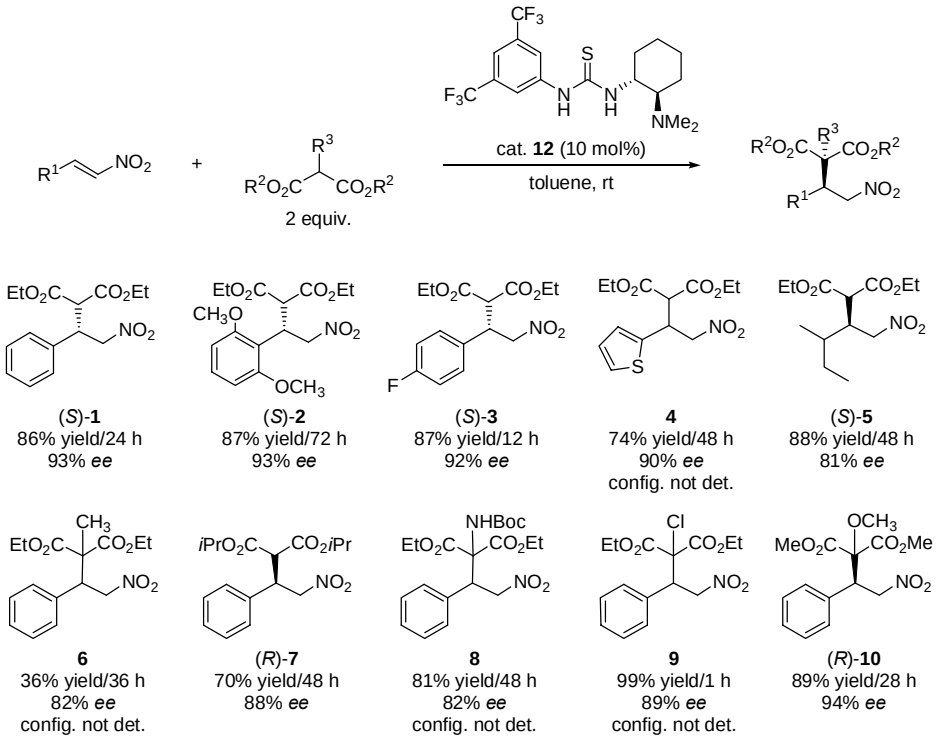
57
76% yield/48 h
87% *ee*/rt

58
58% yield/48 h
80% *ee*/rt

Figure 18. Chiral amine **56** and thiourea derivatives (10 mol% loading) screened in the asymmetric Michael addition of diethyl malonate to *trans*-*β*-nitrostyrene in toluene.

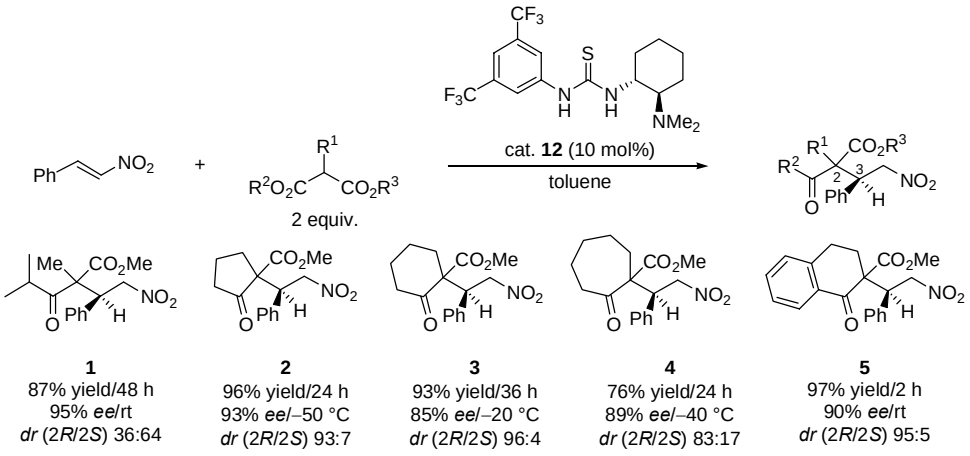
Apart from the increased catalytic efficiency this structure design afforded two positive side effects. In contrast to monofunctional (thio)ureas that exhibit low solubility in nonpolar solvents due to intermolecular hydrogen-bonding association tertiary amine thioureas of type **12** revealed intramolecular hydrogen-bonding between the amine group and the amide protons making these (thio)ureas soluble in a nonpolar reaction medium such as toluene. The analysis of the X-ray crystallographic structure of *rac*-**12** supported this intramolecular hydrogen-bonding interaction.[211] Furthermore, the efficient application of bifunctional amine thiourea catalyst **12** without the practical

necessity of a base additive such as TEA, DBU, or DABCO led to milder reaction procedures tolerating base-sensitive substrates (e.g., *trans*-*β*-nitrostyrene decomposes with DBU)[211] as well as acid-labile products due to a more facile, acid-free work-up. Under optimized reaction conditions (rt, toluene) bifunctional thiourea **12** (10 mol%) catalyzes the asymmetric Michael addition of various dimethyl-, diisopropyl-, and predominantly diethyl malonates to *trans*-*β*-nitrostyrene Michael acceptors. The protocol was reported to furnish the desired adducts**1**–**10** in yields ranging from 36%–99% and in *ee* values ranging from 81%–94% as depicted in Scheme 56.[131, 211]



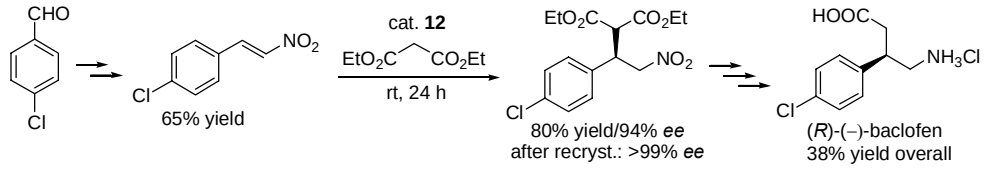
Scheme 56. Typical products of the asymmetric Michael addition of dialkyl malonates to *trans*-*β*-nitrostyrenes in the presence of **12**.

At reduced reaction temperatures (–50 °C to rt) bifunctional thiourea **12** (10 mol% loading) catalyzes the stereoselective Michael addition[151-154] of prochiral *α*-substituted *β*-ketoesters to *trans*-*β*-nitrostyrene affording the respective adducts **1**–**5** in yields ranging from 76%–97%, in high enantioselectivities (85%–95%), and diastereoselectivities (up to *dr* 93:7) (Scheme 57).[211] The absolute configuration of the constructed stereogenic center at the C3 position was determined to be (*R*) suggesting that the addition of symmetric (dialkyl malonates) and unsymmetrical (*α*-substituted *β*-ketoesters) 1,3-dicarbonyl compounds followed the same mechanism (Scheme 57).



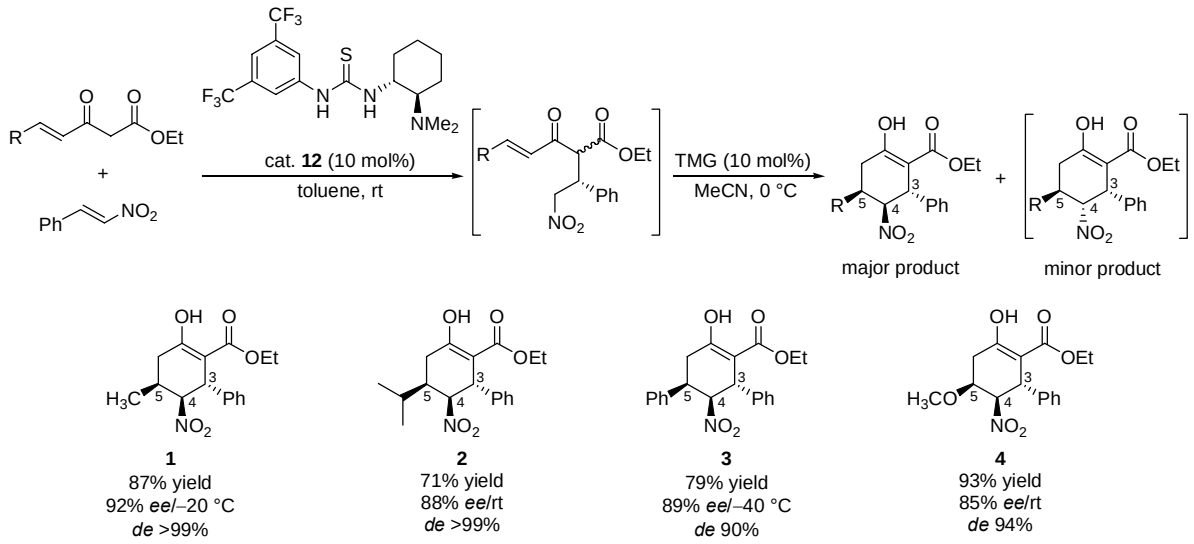
Scheme 57. Representative products of the **12**-catalyzed enantio- and diastereoselective Michael addition of *α*-substituted *β*-ketoesters to *trans*-*β*-nitrostyrene.

The authors demonstrated the synthetic utility of the **12**-catalyzed enantioselective Michael reaction in the total synthesis of (*R*)-(–)-baclofen, an antispastic agent and lipophilic analogue of GABA (*γ*-amino butyric acid) playing an important role as an inhibitory neurotransmitter in the central nervous system of mammals. Starting from 4-chlorobenzaldehyde and nitromethane (Henry reaction) the obtained alcohol underwent dehydration to give 4-chloro nitrostyrene that served as Michael acceptor for the **12**-catalyzed asymmetric addition of diethyl malonate affording the desired adduct in 80% yield and 94% *ee* in 24 h at rt. A single recrystallization of the adduct from *n*-hexane/ethyl acetate increased the *ee* value to 99%. Subsequent reduction of the nitro group, imide formation, hydrolysis of the remaining ester group, decarboxylation and final hydrolysis of the imide in the presence of hydrochloric acid provided the target *γ*-amino acid product (*R*)-(–)-baclofen as ammonium salt in 38% yield overall (Scheme 58).[211]

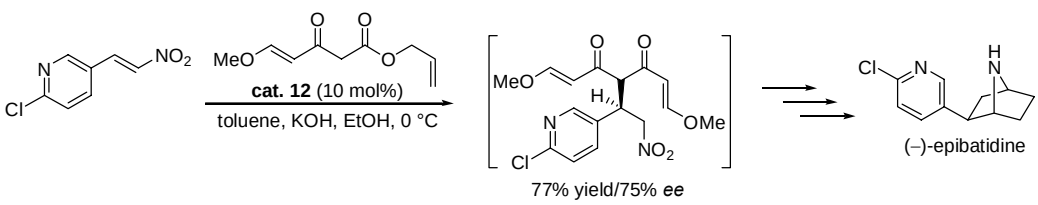


Scheme 58. Total synthesis of (*R*)-(–)-baclofen including an asymmetric Michael addition step promoted by bifunctional thiourea **12**.

In the presence of 10 mol% of bifunctional thiourea **12** the intermolecular Michael addition[151-154] of *γ*,*δ*-unsaturated *β*-ketoesters as CH-acidic 1,3-dicarbonyl substrates to *trans*-*β*-nitrostyrene was catalyzed and after subsequent 1,1,3,3-tetramethylguanidine (TMG)-mediated intramolecular Michael cyclization 4-nitrocyclohexanone derivatives such as **1**–**4** were obtained (Scheme 59).[212] This thiourea **12**/TMG-catalyzed double Michael reaction constructed three contiguous stereogenic centers and gave yields ranging from 71%–93%, good enantioselectivities (85%–92%), and diastereoselectivities (up to *de* 99%). The **12**-catalyzed asymmetric addition of a *γ*,*δ*-unsaturated *β*-ketoester to *trans*-*β*-nitrostyrene was successfully applied to the total synthesis of the alkaloid (–)-epibatidine as illustrated in Scheme 60.[212, 213]

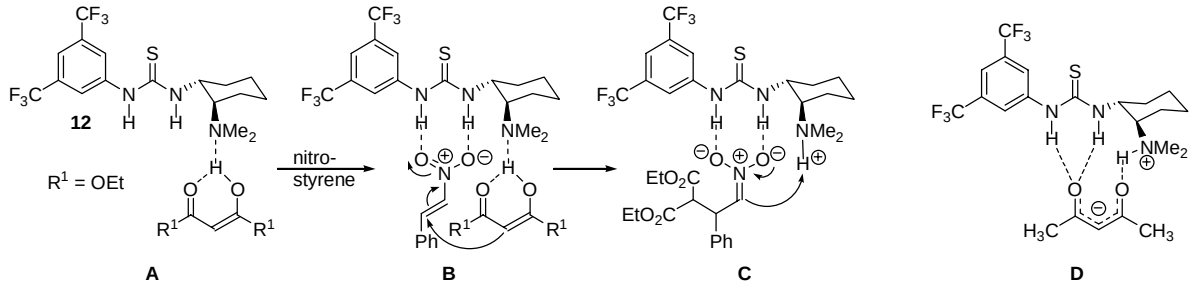


Scheme 59. Typical 4-nitrocyclohexanone derivatives prepared from the thiourea **12**/TMG-catalyzed enantio- and diastereoselective double Michael addition of *γ*,*δ*-unsaturated *β*-ketoesters to *trans*-*β*-nitrostyrene.



Scheme 60. Total synthesis of (–)-epibatidine including a **12**-catalyzed Michael addition as enantioselective key step.

The Takemoto group interpreted the catalytic activity and the observed stereochemical outcome of the Michael addition of CH-acidic 1,3-dicarbonyl compounds such as dialkyl malonates to *trans*-β-nitrostyrene on the basis of experimental data derived from the investigation of solvent effects and variable catalyst loadings as well as from NMR kinetic studies and NMR titrations.[211] As visualized by the reaction cascade **A**, **B**, and **C** in Scheme 61 diethyl malonate was enolized and adopted the six-membered enol form stabilized through interaction with the tertiary amine group of catalyst **12** that facilitated the enolization (**A**). The incoming Michael acceptor *trans*-β-nitrostyrene was coordinated through hydrogen-bonding interaction with the thiourea moiety resutling in ternary complex **B** that allowed proper steric organization and relative orientation of the reaction partners such that the nucleophilic addition step could occur in a (*R*)-favored mode to give complex **C**; final protonation of the nitronate provided the desired Michael adduct.[211] DFT computations performed by Liu and co-workers suggested that the enantioselectivity of thiourea **12**-catalyzed Michael reaction was controlled by the C–C bond-formation step (**B**), while the rate determining step was identified to be the proton transfer from the amine group of the catalyst to the α-carbon of the nitronate (**C**).[214] In contrast to the mechanistic picture shown in **A**, **B**, and **C** Soós, Pápai and co-workers favored an alternative mechanism based on theoretical investigations for the asymmetric Michael addition of acetylacetone to *trans*-β-nitrostyrene.[215] The amine thiourea catalyst **12** deprotonated the 1,3-dicarbonyl compound to form the corresponding enolate that was triple hydrogen-bonded and stabilized through both the thiourea moiety (double hydrogen-bonding) and the generated ammonium group (single hydrogen-bonding) as visualized in **D** (Scheme 61). The Michael acceptor *trans*-β-nitrostyrene was found to be preferentially coordinated and activated through single hydrogen-bonding interaction with the ammonium hydrogen-bond donor, while the enolate was proposed to be hydrogen-bonded via each oxygen atoms to one amide proton of the thiourea moiety. The enantioinduction was expected to originate from the extensive hydrogen-bond network provided by the three acidic N–H groups of protonated catalyst **12** that determined the preferential relative orientation of the approaching substrates.



Scheme 61. Mechanistic proposals of the **12**-catalyzed asymmetric Michael addition of diethyl malonate to *trans*-β-nitrostyrene proposed by the Takemoto group (**A**, **B**, and **C**) and initial enolate complex (**D**) with the ammonium group as additional hydrogen-bond donor initiating an alternative mechanism suggested by Soós, Pápai and co-workers.

In 2006, Takemoto and co-workers reported case studies towards the immobilization of bifunctional thiourea **12** on polymer support using an ester moiety as the linker group.[216] While soluble ester-functionalized thiourea derivative **59** (10 mol% loading) turned out to catalyze the model Michael addition of diethyl malonate to *trans*-β-nitrostyrene in 88% yield and in 91% enantioselectivity after 48 h in toluene, the insoluble cross-linked polystyrene-bound thiourea derivatives **60** and **61** exhibited a drastically reduced catalytic activity and gave the desired (*S*)-configured Michael adduct after 6 d at room temperature in 37% (87% *ee*) and 4% yield (88% *ee*), respectively, (Figure 19). In contrast, soluble poly(ethylene glycol) (PEG)-bound thiourea **62** could be used in dichloromethane under homogeneous conditions and at increased catalytic activity affording the model Michael adduct in 71% yield and in 86% *ee* (rt) after 6 d reaction time (Figure 19). The catalyst was readily recovered by filtration after addition of diethyl ether to the reaction mixture and could be reused without further purification to give the same adduct in comparable yield (74%) and *ee* value (90%) in a second run. As shown in Scheme 62 PEG-bound thiourea **62** also catalyzed the enantioselective double Michael addition of a γ,δ-unsaturated β-ketoester to *trans*-β-nitrostyrene resulting in the desired 4-nitrocyclohexanone derivative (63% yield; 76% *ee*; rt, 6 d). The recovery and reusability of the catalyst[61, 62] turned out to have no impact on catalytic activity and enantioselectivity (second run: 64% yield; 76% *ee* third run: 63% yield; 79% *ee*) in this test reaction.

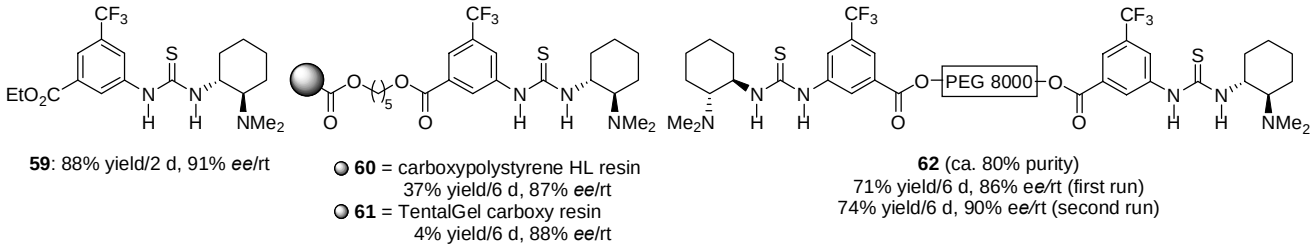
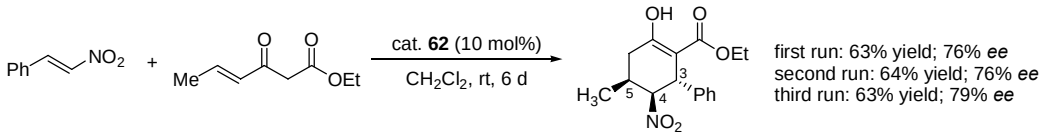
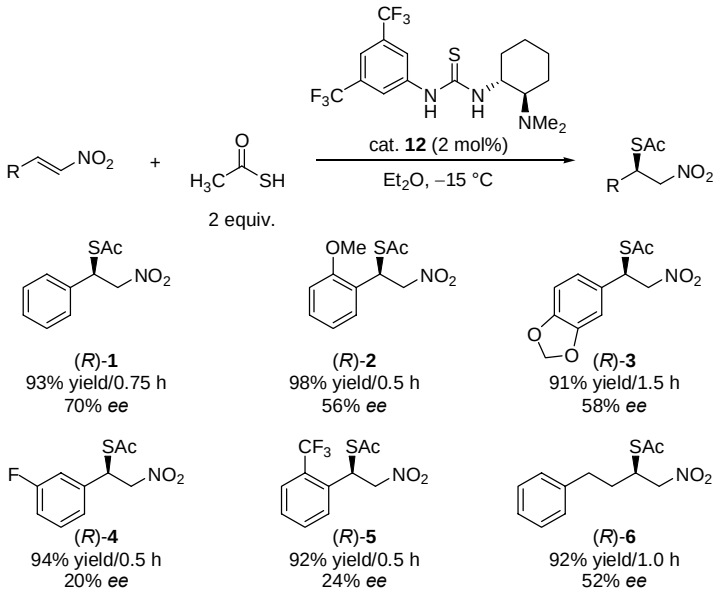


Figure 19. Ester functionalized thiourea **59**, insoluble cross-linked polymer-bound thioureas (**60**; **61**) and soluble PEG-bound thiourea **62** screened in the asymmetric Michael addition of diethyl malonate to *trans*-*β*-nitrostyrene at rt in toluene (**59**, **60**, and **61**) and dichloromethane (**62**).



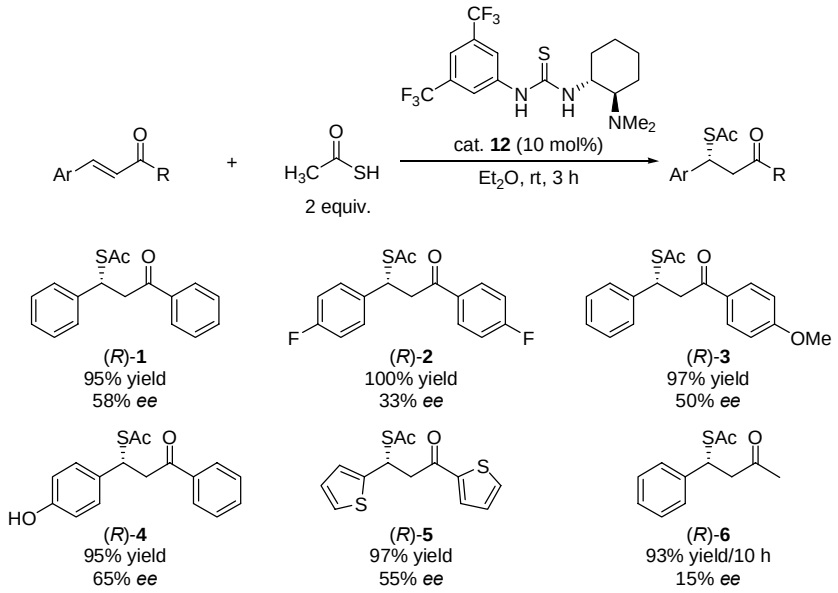
Scheme 62. Double Michael addition of a *γ*,*δ*-unsaturated *β*-ketoester to *trans*-*β*-nitrostyrene catalyzed by PEG-bound thiourea **62**.

Wang et al. identified bifunctional thiourea **12** to catalyze the enantioselective Michael addition[151-154] of thioacetic acid to a range of *ortho*-, *meta*-, and *para*-substituted *trans*-*β*-nitrostyrenes.[217] In the presence of 2 mol% **12** in diethyl ether as the solvent and at –15 °C reaction temperature the transformations required short reaction times (0.5 h–1.5 h) to furnish the corresponding (*R*)-configured adducts **1**–**6**, precursors of synthetically useful thiols, in high yields (91%–95%), but low (20% *ee*) to moderate (70% *ee*) enantioselectivities (Scheme 63). Nitrostyrenes bearing electron-donating substituents at the phenyl ring were found to provide Michael adducts with higher enantioselectivities (e.g., 56% and 58% *ee*) than nitrostyrene Michael acceptors bearing electron-withdrawing substituents (e.g., 20% and 24% *ee*) (Scheme 63). Mechanistically, bifunctional catalyst **12** deprotonated thioacetic acid generating nucleophilic thioacetate that selectively attacked the hydrogen-bonded nitroalkene. Final protonation of the primary adduct gave the observed target product and regenerated catalyst **12** as shown in Scheme 65.

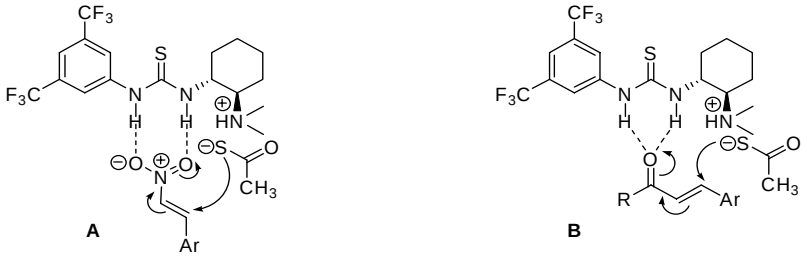


Scheme 63. Typical products obtained from the **12**-catalyzed asymmetric Michael addition of thioacetic acid to nitroalkenes.

The same group utilized thiourea **12** (10 mol% loading) for the catalysis of the enantioselective Michael addition of thioacetic acid to various chalcones.[218] At room temperature and otherwise unchanged conditions in comparison to the protocol described in Scheme 63 electron-rich and electron-deficient chalcones served as Michael acceptors affording the desired adducts **1**–**6** in high yields (93%–100%) and low (15% *ee*) to moderate (65% *ee*) enantioselectivities (Scheme 64). The mechanistic picture of this reaction was described to be akin to that proposed for the Michael addition of thioacetic acid to nitroalkenes (Scheme 65).[217] Catalyst **12** coordinated and activated the Michael acceptor chalcone through explicit double hydrogen-bonding interaction and facilitated the selective nucleophilic attack of the in situ generated thioacetate resulting in the observed products (Scheme 65).



Scheme 64. Michael adducts provided from the **12**-catalyzed asymmetric addition of thioacetic acid to various chalcones.

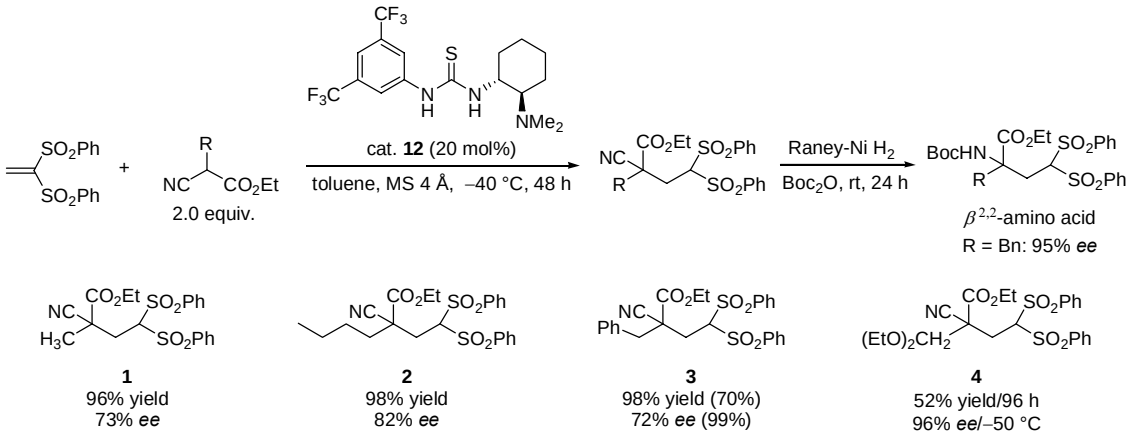


Scheme 65. Mechanistic proposals for the bifunctional mode of action of catalyst **12** in the Michael addition of thioacetic acid to nitroalkenes (**A**) and to chalcones (**B**).

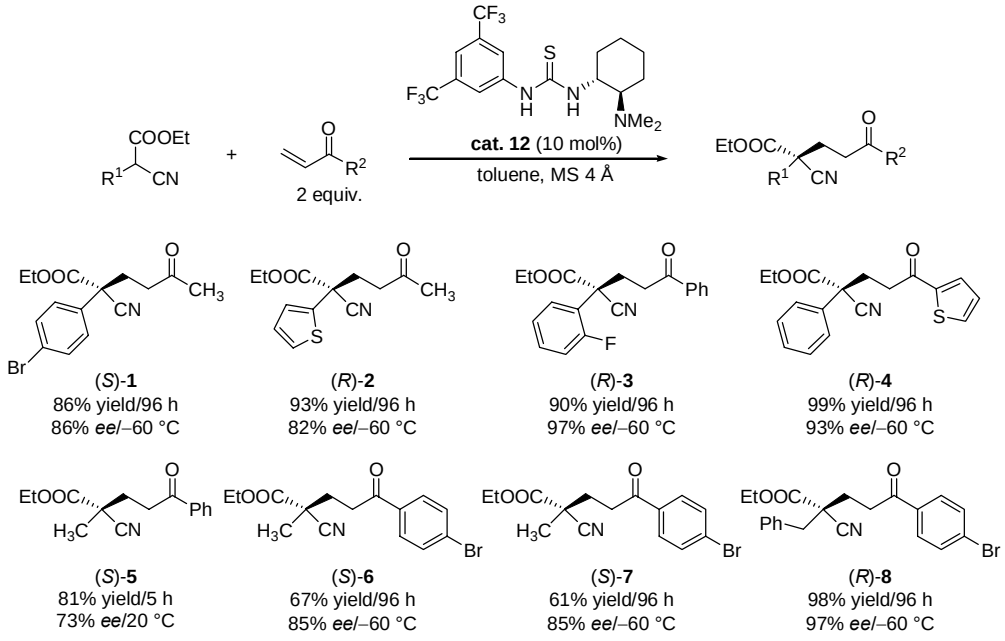
Chen and co-workers described the **12**-catalyzed asymmetric Michael addition[151-154] of α-alkyl cyanoacetates to vinyl sulfone resulting in the respective adducts **1**–**4** in 52%–98% yield and in *ee* values ranging from 72%–99% after 48 h reaction time at –40 °C in toluene as the solvent (Scheme 66).[219] After single recrystallization from 2-propanol/*n*-hexane one adduct example (R = Bn) could be purified to increase the *ee* value from 72% (98% yield) to 99% (72% yield). An one-pot strategy employing Raney-Nickel hydrogenation at 50 psi H_2 pressure in the presence of Boc_2O exemplarily converted this adduct o the corresponding *N*-Boc-protected $\beta^{2,2}$-amino acid derivative (95% *ee*) as shown in Scheme 66.

The same group reported that bifunctional thiourea **12** catalyzed the enantioselective Michael addition[151-154] of α-alkyl and also α-aryl cyanoacetates to alkyl vinyl ketones and aryl vinyl ketones, respectively, to give the desired multifunctional adducts **1**–**8** in yields ranging from 61%–99% and in enantioselectivities in the range of 73%–97% (Scheme 67).[220] The protocol was described to have broad substrate

scope, when utilizing catalyst **12** (10 mol% loading) at –60 °C reaction temperature in toluene as the solvent and in the presence of molecular sieve 4 Å. Notably, the addition of α-alkyl cyanoacetates was found to be limited to aryl vinyl ketone Michael acceptors such as phenyl vinyl ketone. The authors demonstrated the synthetic versatility of the products in the conversion to various *N*-Boc-protected $\beta^{2,2}$-amino acid ethylesters (91%–96% *ee*) using Raney-Ni-catalyzed hydrogenation in the presence of Boc_2O. Semi-empirical computations indicated multiple hydrogen-bonding interactions between catalyst **12**, the enolized cyanoacetate nucleophile, and the vinyl ketone electrophile, although this theoretical approach is generally not suitable to describe hydrogen bonding. Apart from a single hydrogen-bond between the hydroxy group of the ester enol and the tertiary amine group of catalyst **12** the computations located an additional weak hydrogen-bonding interaction between the ethoxy group of the enol and one amide proton of the thiourea moiety, which was proposed to be crucial to adjust the enol in a more rigid conformation resulting in improved enantiocontrol. The vinyl ketone was simultaneously activated and sterically orientated through typical double hydrogen-bonding via the thiourea moiety facilitating the *re*-face attack of the *Z*-enolate to give the observed (*S*)-configured Michael adduct. In contrast, the *si*-face attack of the *E*-enolate would be sterically disfavored resulting in the (*R*)-configured product.[220]

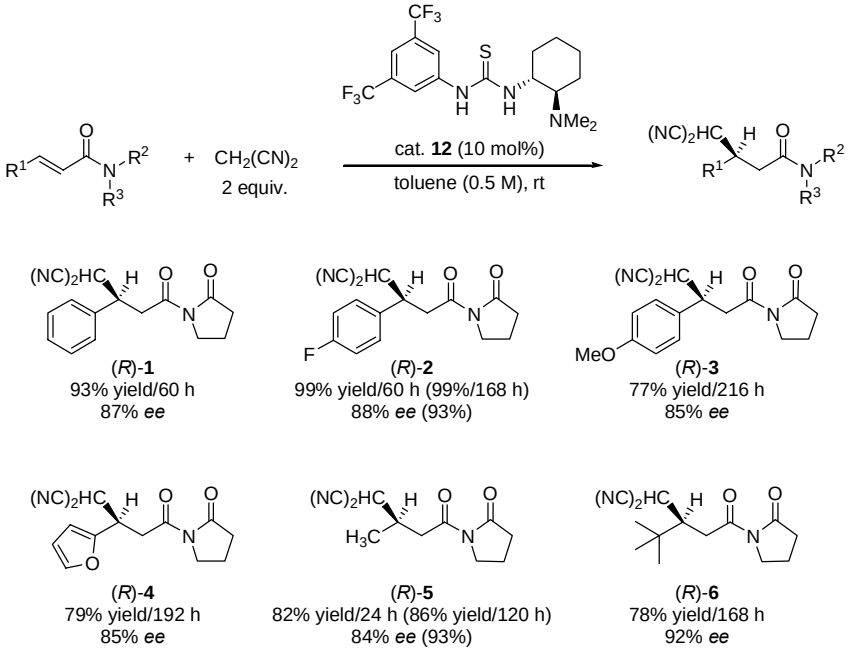


Scheme 66. Products of the **12**-catalyzed asymmetric Michael-addition of α-alkyl cyanoacetates to vinyl sulfone and exemplary conversion of one adduct to the respective $\beta^{2,2}$-amino acid. The values in parentheses were obtained after single recrystallization; the absolute configurations of the products were not determined.



Scheme 67. Products of the **12**-catalyzed enantioselective Michael addition of α-alkyl and α-aryl cyanoacetates to alkyl vinyl ketones and aryl vinyl ketones.

To extend the applicability of bifunctional thiourea catalyst **12** Takemoto et al. performed substrate screening experiments to evaluate the potenial of α,β-unsaturated imides to react as suitable acceptors in the Michael addition[151-154] of malononitrile.[221] In the presence of **12** (10 mol% loading) at room temperature and in toluene as the solvent 1-(3-phenyl-acryloyl)-pyrrolidin-2-one was found to give the highest yield (93%/60 h) and *ee* value (87%) for the desired malononitrile adduct, e.g., in comparison to the Michael acceptors 3-(3-phenyl-acryloyl)-oxazolidin-2-one (89 yield/96 h; 83% *ee*) and 1-(3-phenyl-acryloyl)-piperidin-2-one (42% yield/140 h, 59% *ee*) respectively. Under optimized reactions conditions (toluene 0.5 M, rt) thiourea **12** (10 mol% loading) enantioselectively catalyzed the Michael addition of CH-acidic malononitrile to various β-aryl and alkyl substituted *N*-acyl pyrrolidinones resulting in yields ranging from 77%–99% and in good *ee* values (84%–92%) for the desired products **1**–**6** (Scheme 68).

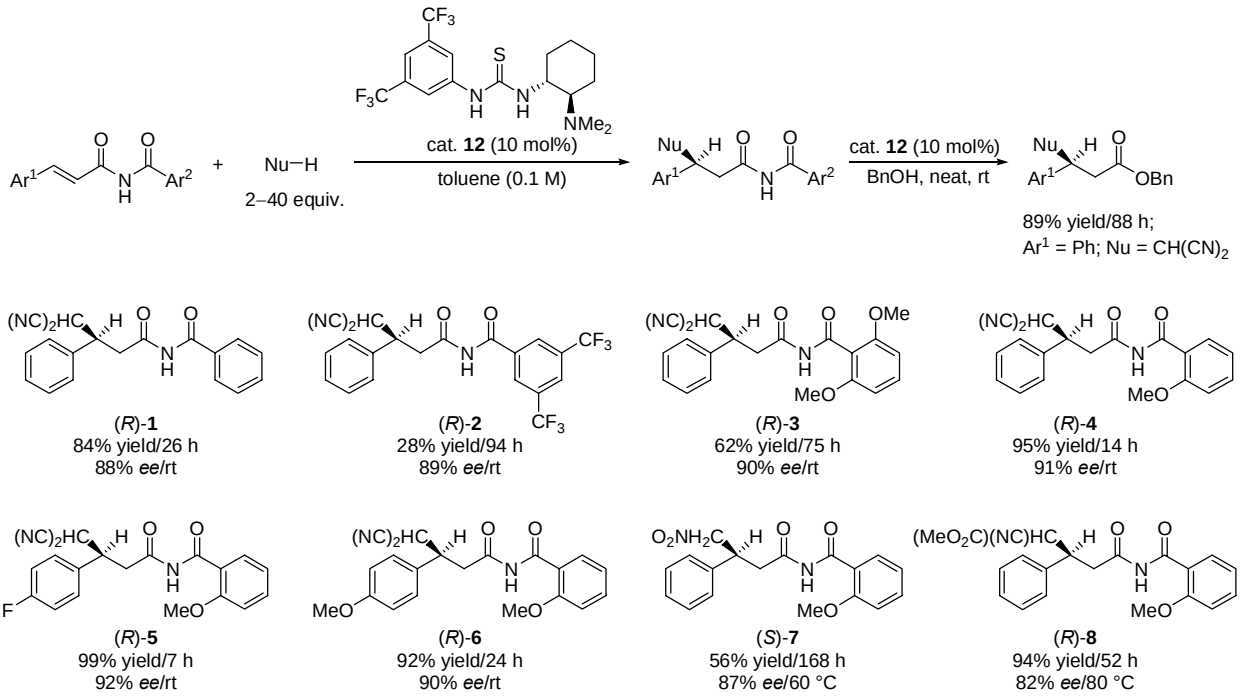


Scheme 68. Typical adducts obtained from the **12**-catalyzed asymmetric Michael reaction between malononitrile and α,β-unsaturated *N*-acyl pyrrolidinones (cyclic imides); the values in parentheses refer to reactions at lower concentration (0.1 M).

As visualized in Scheme 70 a ternary complex (**A**) among bifunctional catalyst **12**, the imide, and malononitrile was suggested as transition state to explain the predominant formation of the (*R*)-configured adducts. After deprotonation of malononitrile the corresponding nucleophilic anion is hydrogen-bonded and sterically positioned through the tertiary ammonium group, while the 1,3-dicarbonyl groups of the imide are coordinated and are activated in a bidentate mode through hydrogen-bonds provided by the thiourea moiety. This proposal based on ^{1}H NMR spectroscopic chemical shift experiments aiming at the imide-catalyst complex (1:1 mixture of imide and catalyst **12** in toluene-d_8) were supported by DFT computations performed for the addition of malononitrile to 1-but-2-enoyl-pyrrolidin-2-one published by Zhang and co-workers, in 2008.[222] The computed data obtained for the (*R*)- and (*S*)-reaction channel affording the (*R*)- and (*S*)-adduct, respectively, revealed that this Michael addition underwent three elementary steps , that is, the protonation of catalyst **12** at the tertiary amine group, the C–C bond formation, and the final deprotonation of the catalyst. The (*R*)-channel turned out to be energetically more favorable than the competing (*S*)-channel through each elementary step and led to the preferred formation of the observed (*R*)-configured adduct.[222] Again, further computations are desirable because current DFT implementations neglect dispersion forces.[223-225]

Further investigations performed by the Takemoto group focussed on various *N*-cinnamoylbenzamide derivatives as Michael acceptors and demonstrated that the protocol developed for the **12**-catalyzed enantioselective Michael addition of malononitrile to α,β-unsaturated cyclic imides (Scheme 68) could be also successfully applied to acyclic imides.[226] Since *N*-cinnamoyl-2-methoxy benzamide exhibited the highest reactivity (95% yield/14 h) towards the Michael addition of malononitrile and gave the best *ee* value of the corresponding adduct (91%; rt) in comparison with *N*-cinnamoylbenzamide derivatives lacking a single 2-methoxy group (e.g., adducts **1**, **2**, and **3**; Scheme 69) the optimized

protocol utilized α,β-unsaturated *N*-aryl substituted 2-methoxybenzamides ("2-methoxybenzimides") as preferred substrates. In the presence of 10 mol% loading of thiourea **12** the respective (*R*)-configured adducts **4**, **5**, and **6** could be isolated in excellent yields (92%–99%) and very good enantioselectivities (90%–92%) as shown in Scheme 69. The addition of nitromethane (56% yield/168 h; 87% *ee*) or methyl α-cyanoacetate (94% yield/52 h; 82% *ee*) as alternative CH-acidic methylene compounds required increased reaction temperatures (60 °C to 80 °C) to furnish the adducts **7** and **8**. As exemplarily depicted in Scheme 69 for benzylic alcohol thiourea **12** catalyzes the transformation of the obtained malononitrile Michael products to the respective carboxylic acid derivatives (89% yield/88 h). This method of derivatization also described for methanol (87% yield/24 h; rt), benzyl amine (77% yield/3 h; rt), and *N*,*O*-dimethylhydroxyamine (75% yield/20 h; 60 °C) as nucleophiles was reported to be feasible as an one-pot strategy without isolation of the initially formed Michael adduct.[226]



Scheme 69. Products obtained from the **12**-catalyzed asymmetric Michael addition of malononitrile, nitromethane, and methyl α-cyanoacetate to *N*-cinnamoylbenzamide derivatives (acylic imides) and **12**-catalyzed derivatization of the Michael adduct.

IR and ^{1}H NMR experiments indicated that the observed higher reactivity of *N*-aryl substituted 2-methoxybenzamides in comparison to *N*-cinnamoylbenzamide probably originated from an intramolecular hydrogen-bonding interaction between the NH imide moiety and the 2-methoxy group increasing the electrophilicity of the α,β-unsaturated carbonyl moiety and thus the reactivity towards a Michael-type nucleophilic attack. Additionally, this interaction was proposed to be responsible for a coplanar orientation of the 2-methoxybenzamide moiety facilitating efficient bidentate hydrogen-bonding interactions with catalyst **12** as suggested by NMR titrations between *N*-cinnamoyl-2-methoxybenzamide (Figure 20). With an increase of in the ratio of catalyst **12** to the imide substrate the chemical shift of the imide N-H was gradually shifted downfield to obtain the maximum shift for a 1:1 mixture (from 10.22 ppm to 10.24 ppm). The spectroscopic data and ^{1}H NMR kinetic studies under pseudo-first-order conditions supported a mechanistic picture consistent with the proposal for the Michael reaction between malononitile and cyclic imides (Scheme 70). The bifunctional catalyst **12** simultaneously activated malononitrile through deprotonation and the bidendate imide through explicit hydrogen-bonding forming a ternary complex with hydrogen-bonded reaction partners. The predominant formation of the (*R*)-configured adducts resulted from the nucleophilic attack of the in situ generated anion at the β-position of the imide (Scheme 70).[222]

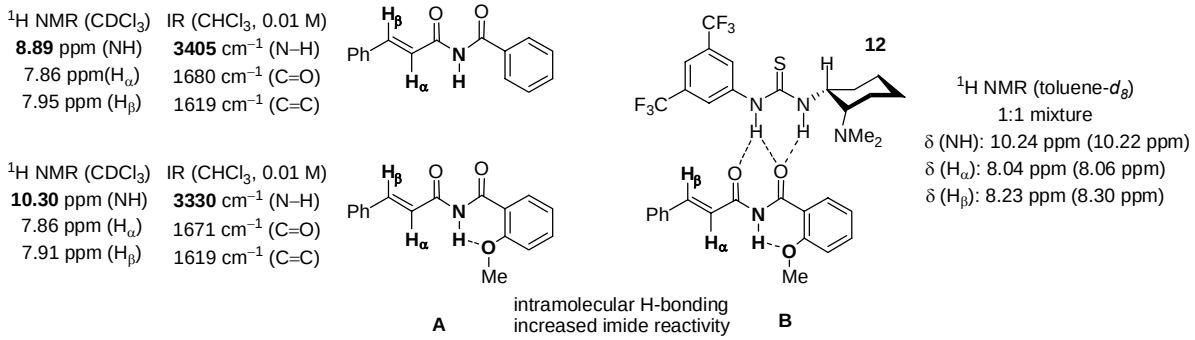
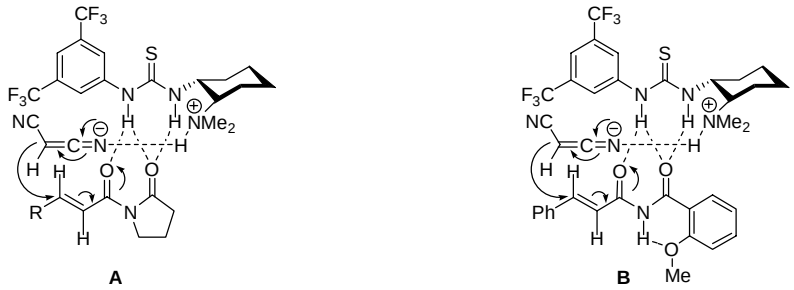
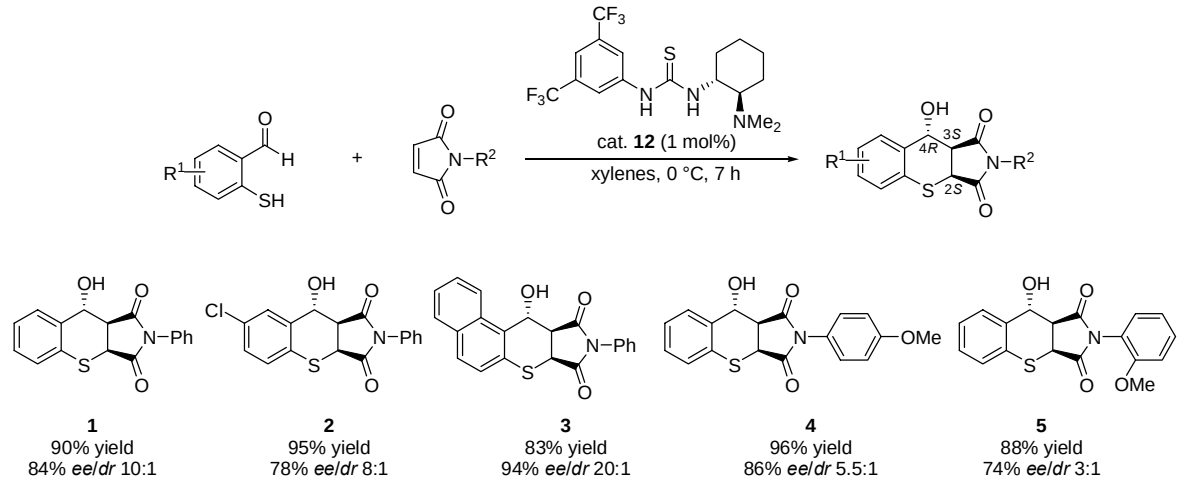


Figure 20. IR and ^{1}H NMR spectroscopic data suggesting intramolecular hydrogen-bonding responsible for increased reactivity of 2-methoxybenzimides (**A**) and proposed hydrogen-bonding pattern of the catalyst-imide complex supported by NMR titration (**B**); the chemical shift values in parentheses refer to the imide in the absence of **12**.



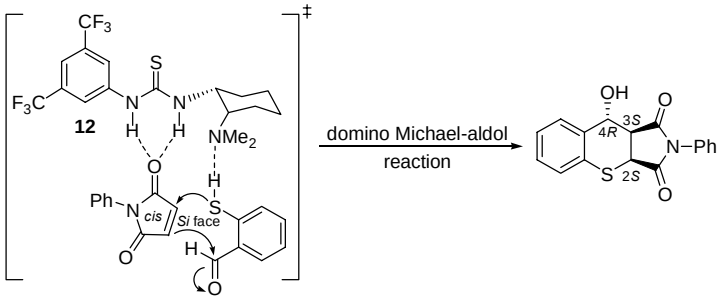
Scheme 70. Mechanistic proposal for the **12**-catalyzed asymmetric Michael addition of malononitrile to *β*-aryl and alkyl substituted *N*-acyl pyrrolidinones (cyclic imide) (**A**) and to *α*,*β*-unsaturated *N*-aryl substituted 2-methoxybenzamides such as *N*-cinnamoyl-2-methoxybenzamide (acyclic imide) (**B**).

In 2007, Wang and co-workers published a protocol for an enantio- and diastereoselective domino Michael-aldol reaction using electron-rich and electron-deficient 2-mercaptobenzaldehydes and maleimides as substrates.[227] The conversion was described to proceed smoothly in the presence of bifunctional catalyst **12** (1 mol% loading) in xylenes at 0 °C reaction temperature affording the desired chiral succinimide-containing substituted thiochromanes **1**–**5** in high yields (83%–96%), in synthetically useful *ee* values (74%–94%), and diastereoselectivities (up to *dr* 20:1) in 7 h reaction time (Scheme 71).



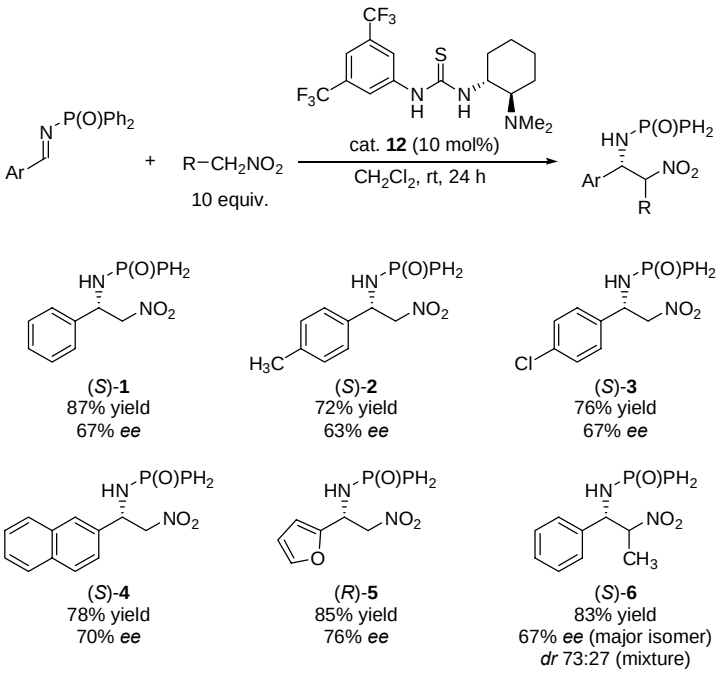
Scheme 71. Succinimide-containing substituted thiochromanes obtained from the **12**-catalyzed enantio- and diastereoselective domino Michael-aldol reaction between 2-mercaptobenzaldehydes and maleimides.

The stereoconfigurations of the thiochromane products were determined by crystal structure analysis to be (2*S*, 3*S*) corresponding to *cis* stereochemistry. This stereochemical outcome was interpreted with a transition state in which the *cis*-cyclic maleimide was double hydrogen-bonded through the thiourea moiety of bifunctional catalyst **12** and thus properly activated and sterically organized for the initial Michael-addition step of the activated thiol group of 2-mercaptobenzaldehyde (Scheme 72). This *Si* face attack gave the (2*S*)-configured stereogenic center and was followed by the ring-forming aldol reaction resulting in the construction of the (3*S*)- and (4*R*)-configured stereogenic centers of the product. An alternative mechanism employing the Diels-Alder reaction between maleimide (dienophile) and enolized 2-mercaptobenzaldehyde (diene) would provide (2*R*, 3*R*, 4*S*)-configured products being not consistent with the detected stereochemistry (2*S*, 3*S*, 4*R*).



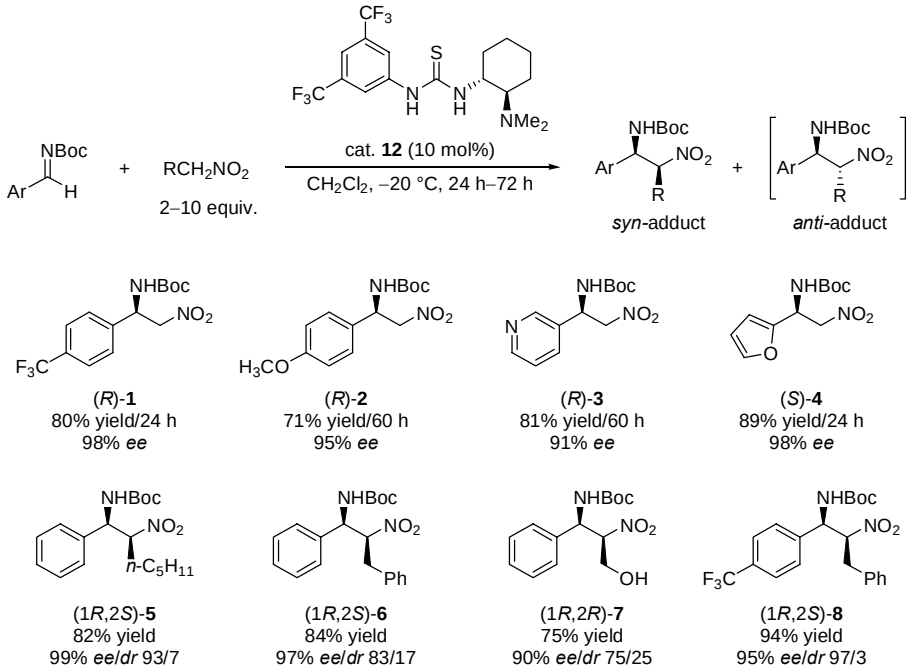
Scheme 72. Mechanistic proposal for the **12**-catalyzed enantio- and diastereoselective domino Michael-aldol reaction between *N*-phenyl maleimides and 2-mercaptobenzaldehyde; bifunctional mode of action of **12**.

Takemoto et al. discovered *N*-phosphinoyl-protected aldimines as suitable electrophilic substrates for the enantioselective aza-Henry[228] (nitro-Mannich) reaction[72] with nitromethane, when utilizing thiourea **12** (10 mol%) as the catalyst in dichloromethane at room temperature.[229] The (*S*)-favored 1,2-addition of nitromethane to the electron-deficient C=N double bond allowed access to various *β*-aryl substituted *N*-phosphinoyl-protected adducts **1**–**5** in consistently moderate to good yields (72%–87%) and moderate enantioselectivities (63%–76%) as depicted in Scheme 73. Employing nitroethane under unchanged reaction conditions gave adduct **6** as a mixture of diastereomers (*dr* 73:27) at an *ee* value of 67% (83% yield) of the major isomer (Scheme 73)



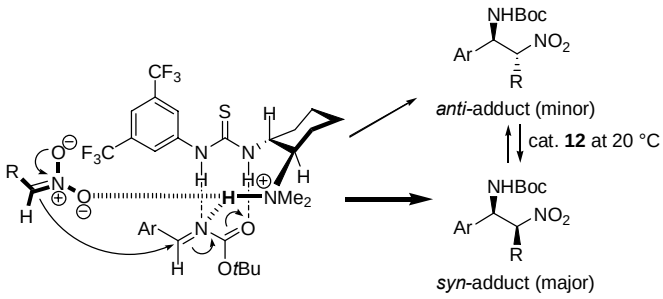
Scheme 73. Typical products of the enantioselective aza-Henry (Nitro-Mannich) reaction between nitroalkanes and *N*-phosphinoylimines proceeding in the presence of catalyst **12**.

N-Boc-protected (hetero)aromatic aldimines bearing both electron-donating or electron-withdrawing substituents were reported by the Takemoto group to undergo a **12**-catalyzed enantio- and diastereoselective aza-Henry (nitro-Mannich) reaction with various aliphatic nitroalkanes including nitromethane, nitroethane, and also nitroalcohols such as 2-nitroethanol.[230] Performing the conversion under optimized reaction parameters in the presence of 10 mol% of catalyst **12** afforded the respective aza-Henry adducts **1**–**8** in consistently high enantioselectivities (90%–99% *ee* at –20 °C in CH_2Cl_2) and in a broad range of yields (71%–94%; 24 h–72 h) (Scheme 74). In contrast to the aza-Henry reaction of *N*-phosphinoyl-protected aldimines[229] (Scheme 73) *N*-Boc-protected aldimines were found to give the (*R*)-configured adducts in preferred *syn*-diastereoselectivity (up to *dr* 97:3). Mechanistically, this outcome was explained through the ternary model complex visualized in Scheme 75.



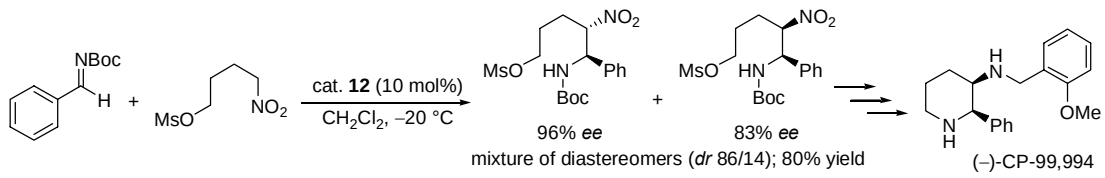
Scheme 74. Typical *N*-Boc protected *syn*-*β*-nitroamines obtained from the enantio- and diastereoselective aza-Henry (nitro-Mannich) reaction between *N*-Boc-protected (hetero)aromatic aldimines and nitroalkanes in the presence of bifunctional thiourea catalyst **12**.

The nucleophilic nitronate generated in situ by deprotonation of the corresponding nitroalkane was singly hydrogen-bonded through the tertiary ammonium group and properly sterically arranged to attack the hydrogen-bonded and activated electrophilic *N*-Boc-protected aldimine such that the *syn*-adduct was observed as the major diastereomer. Increasing the reaction temperature from –20 °C to 20 °C for 48 h in the presence of 10 mol% catalyst **12** decreased the diastereoselectivity indicating that **12** catalyzed the epimerization of the *syn*-adduct in favor of the thermodynamically nor stable *anti*-adduct; the retro aza-Henry reaction, however, seemed not to occur keeping the *ee* value of the adduct unchanged at 20 °C (Scheme 75).



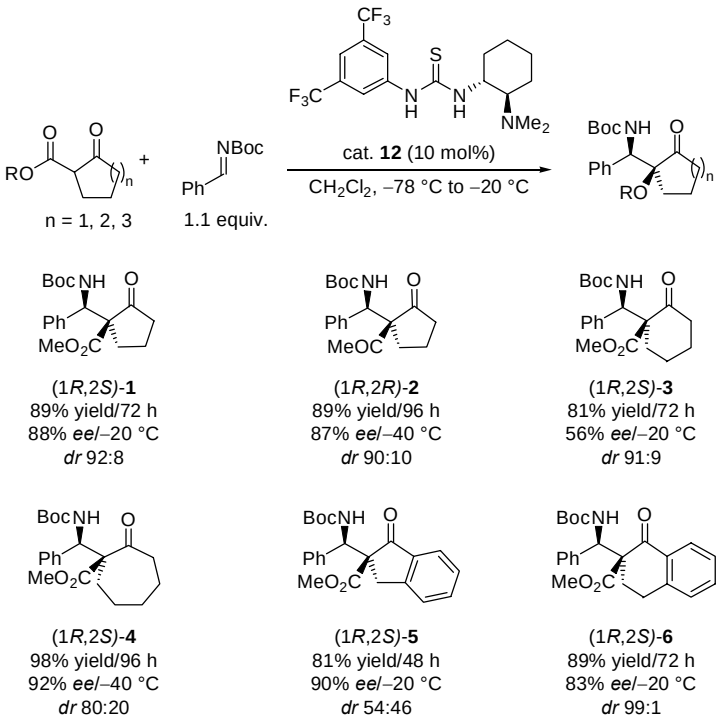
Scheme 75. Proposed mechanism of the enantio- and diastereoselective aza-Henry reaction between *N*-Boc-protected aldimines and nitroalkanes in the presence of bifunctional catalyst **12** and catalyzed epimerization of the *syn*-adduct at increased temperature.

This stereoselective aza-Henry methodology allowed access to physiologically important 2,3,6-trisubstituted and 2,3-disubstituted piperidines such as neurokinin-1 (NK-1) receptor antagonist (–)-CP-99,994 as shown for the key-steps of the total synthesis in Scheme 76.[231] Starting from *N*-Boc-protected benzaldimine the enantio- and diastereoselective aza-Henry addition[228] of mesylated 4-nitrobutanol was catalyzed by **12** (at –20 °C in CH_2Cl_2) affording a mixture of diastereomers (*dr* 86/14; 96% *ee* and 83% *ee*, 80% yield) that could be directly used for the subsequent steps including the removal of the Boc group, cyclization, epimerization, reduction, imine formation with 2-anisaldehyde, and final reduction to yield the target compound spectroscopically consistent with the literature data.[232]



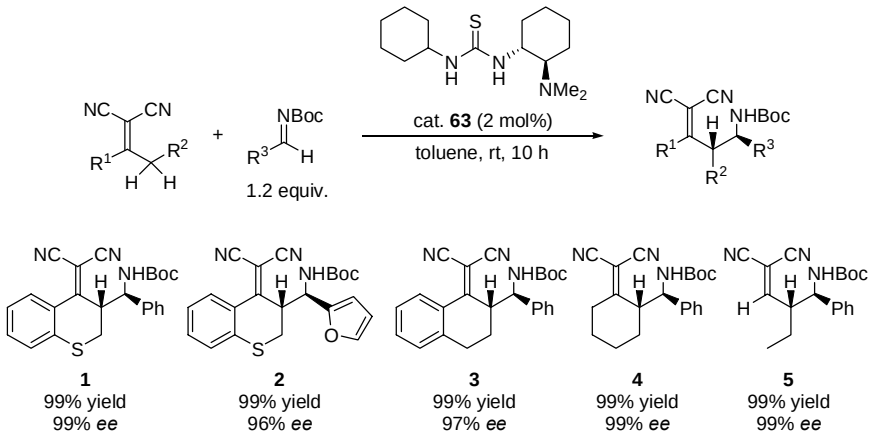
Scheme 76. Total synthesis of NK-1 receptor antagonist (–)-CP-99,994 utilizing the **12**-catalyzed enantio- and diastereoselective aza-Henry methodology.

Takemoto and co-workers could identify *N*-Boc-protected benzaldimine to react with prochiral cyclic 1,3-dicarbonyl compounds such as *β*-keto methylesters.[233] These stereoselective Mannich reactions[72] proceed in the presence of 10 mol% thiourea **12** in dichloromethane as the solvent at –78 °C to –20 °C giving the desired adducts **1**–**6** in good (81%) to excellent yields (98%), *ee* values ranging from 56%–92%, and diastereoselectivities up to 99:1 (Scheme 77). The necessity and potential of bifunctional catalysis became evident from results obtained in the model Mannich reaction (formation of adduct **1**; Scheme 77) using DBU (86% yield/8 h; *dr* 66:34), TEA (93% yield/8 h; *dr* 60:40), and bifunctional catalyst **12** (98% yield/9 h; *dr* 91:9; 82% *ee*) under identical conditions (10 mol% loading at rt in CH_2Cl_2).

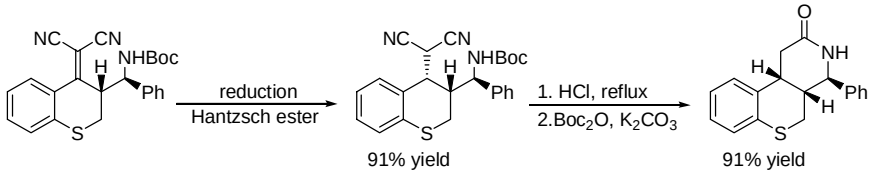


Scheme 77. Product range of the **12**-catalyzed enantio- and diastereoselective Mannich addition of prochiral cyclic 1,3-dicarbonyl compounds to *N*-Boc-protected benzaldimine.

The stereoselective direct vinylogous Mannich reaction (γ-aminoalkylation of α,β-unsaturated carbonyl compounds) is a variant of the traditional Mannich reaction[72] and offers facile access to highly functionalized δ-amino compounds. In 2007, Chen and co-workers described the development of a bifunctional thiourea catalyzed protocol for the regio- and enantioselective vinylogous Mannich reaction between C–H acidic α,α-dicyanoalkenes using the addition of 2-thiochroman-4-ylidene-malononitrile to *N*-Boc-benzaldimine as a model reaction resulting in Mannich adduct **1** (Scheme 78).[234] At room temperature, in toluene, and at 10 mol% loading thiourea **12** (adduct **1**: 99% yield/6 h; 89% *ee*) proved to be less catalytically efficient than its *N*-cyclohexyl-substituted derivative **63** (adduct **1**: 99% yield/6 h; 99% *ee*) introduced earlier by the Berkessel group for the DKR of azlactones[235, 236] and the KR of oxazinones.[237] While this bifunctional aliphatic thiourea catalyst revealed excellent catalytic activity and enantioinduction even at 0.5 mol% (adduct **1**: 99% yield/16 h; 99% *ee*) and 0.1 mol% loading (adduct **1**: 98% yield/24 h; 98% *ee*) the authors decided to evaluate the scope of the optimized protocol at the more practical 2 mol% catalyst loading. Various aliphatic and aromatic α,α-dicyanoalkenes reacted with *N*-Boc-protected aldimines to give the respective vinylogous Mannich adducts such as **1**–**5** in consistently nearly quantitative yields (99%) and in excellent enantioselectivities (96%–99%) (Scheme 78). Adduct **1** in Scheme 78 was exemplarily converted to the corresponding chiral δ-lactam utilizing a high-yielding reduction-hydrolysis-cyclization sequence as outlined in Scheme 79.



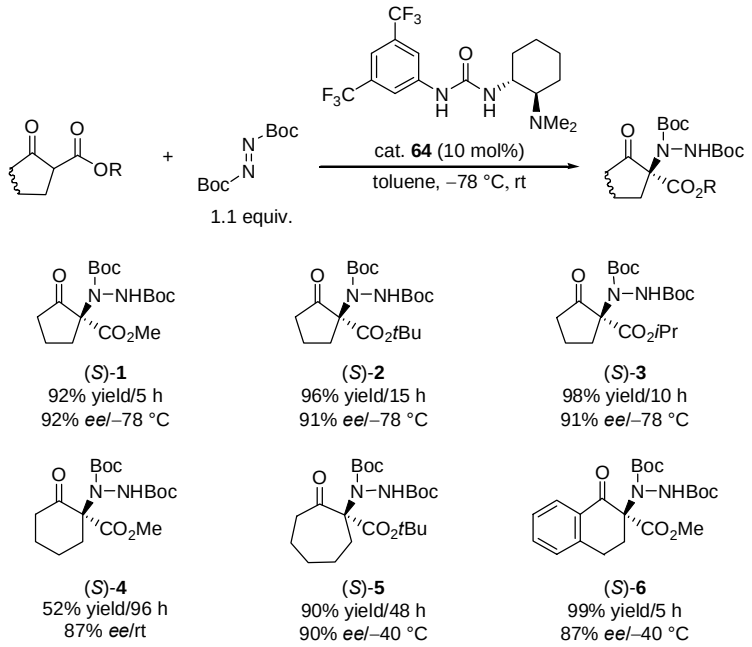
Scheme 78. Typical products of the vinylogous Mannich addition of α,α-dicyanoalkenes to *N*-Boc-protected aldimines catalyzed by **63**.



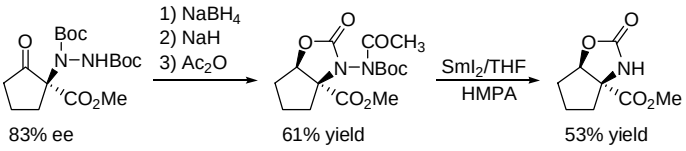
Scheme 79. Conversion of one vinylogous Mannich adduct obtained from the **63**-catalyzed Mannich addition of α,α-dicyanoalkenes to *N*-Boc-protected aldimines to the corresponding chiral δ-lactam.

The enantioselective addition of CH acidic α-substituted β-keto esters to N=N bonds incorporated in electrophilic azodicarboxylates such as di-*tert*-butyl azodicarboxylate was reported by the Takemoto group, in 2006.[238] This α-hydrazination of cyclic 1,3-dicarbonyl compounds (Diels amination)[239, 240] offered access to highly functionalized precursors of non-natural cyclic α,α-disubstituted α-amino acid derivatives that represented valuable chiral building blocks for, e.g., peptide synthesis[241] or the development of neuroactive glutamate analogues.[242] Initial experiments revealed that thiourea catalyst **12** exhibited catalytic activity (91% yield/1 h) and enantioselectivity (75% *ee*/rt) in the formation of model adduct **1** (Scheme 80), but turned out to be instable under the hydrazination conditions (10 mol% loading, toluene, rt) at longer reaction times; the urea analogue **64** of thiourea **12**, however, was identified to be compatible to the reaction conditions and catalyzed the formation of model adduct **1** in 84% yield and in 60% *ee* after 0.5 h at room temperature. In the presence of **64** (10 mol%) representative five-, six-, and seven-membered monocyclic and in one example bicyclic β-keto methyl-, *iso*-propyl-, and *tert*-butyl esters underwent the

enantioselective addition to di-*tert*-butyl azodicarboxylate providing the (*S*)-configured adducts **1**–**6** in predominantly high yields (52%; 90%–99%) and *ee* values (87%–91%) as shown in Scheme 80. For one adduct the authors demonstrated the straightforward three-step transformation to the corresponding oxazolidinone amino acid derivative (32% yield overall) (Scheme 81).



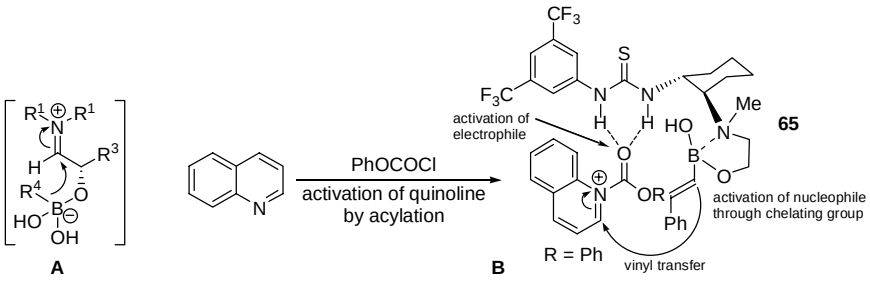
Scheme 80. Typical products obtained from the **64**-catalyzed enantioselective addition of α-substituted β-keto esters to di-*tert*-butyl azodicarboxylate (α-hydrazination).



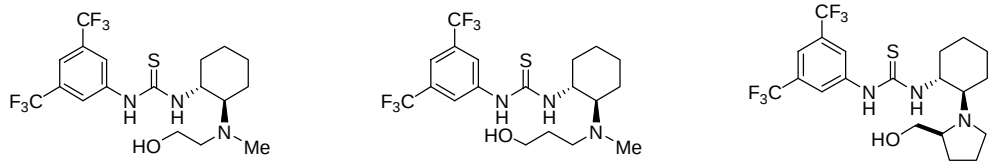
Scheme 81. Transformation of one adduct prepared from the **64**-catalyzed asymmetric addition of α-substituted β-keto esters to di-*tert*-butyl azodicarboxylate (α-hydrazination) into the corresponding oxazolidinone amino acid derivative.

The catalytic efficiency of bifunctional thiourea **12** turned out to be mainly limited to (pre)nucleophiles such as CH-acidic 1,3-dicarbonyl compounds and nitroalkanes that could be deprotonated by the tertiary amine functionality to be activated for the product-forming nucleophilic attack to the hydrogen-bonded electrophile. On the basis of the suggested key complex (**A**) of the Petasis reaction (Petasis boronic acid-Mannich reaction) utilizing α-hydroxy aldehydes, amines, and organic boronic acids for the vinylation of in situ generated iminium ions[76] (Scheme 82), the Takemoto group modified thiourea catalyst **12** through formal mono-hydroxy alkylation of the tertiary amine group resulting in thiourea derivatives **65**, **66**, and **67** (Figure 21).[243] These newly designed thiourea derivatives were proposed to operate bifunctionally in an enantioselective Petasis-type 2-vinylation of *N*-acetylated quinolinium ions such that the chelating hydroxy group activated the vinylboronic acid inducing the nucleophilic addition of the alkyl vinyl unit to the iminium moiety of the hydrogen-bonded electrophile as visualized in complex (**B**) (Scheme 82). The catalyst screening (10 mol% loading) was performed in the reaction among quinoline, phenylvinyl boronic acid, and phenyl chloroformate (2 equiv.) at –65 °C in dichloromethane. After 24 h reaction time thiourea derivative **65** (70% yield; 90% *ee*) bearing a 1,2-amino alcohol functionality proved to be more efficient in both catalytic activity and enantioselectivity than the derivative **66** (47% yield; 27% *ee*) bearing a 1,3-amino alcohol group and thiourea **67** incorporating the hydroxy methyl pyrrolidine moiety, respectively (Figure 21). Under identical conditions tertiary amine catalyst **12** gave only 34% yield of the model adduct and exhibited no stereoinduction affording a racemic product mixture. The addition of water (56 equiv.) as proton source

decreased the catalytic activity (27% yield) but slightly increased the enantioselectivity (93% *ee*) of thiourea **65** in the model Petasis-type reaction, while the combination of the additives water and $NaHCO_3$ (2 equiv.) improved the yield and led to optimized results (65% yield; 94% *ee*) (Figure 21). The remarkable impact of water and $NaHCO_3$ on the this reaction was ascribed to the promoted regeneration of the active catalyst structure through the proton source and the removal of the resulting boronic acid sideproduct through the base.



Scheme 82. Proposed reactive complex of the Petasis reaction utilizing α-hydroxy aldehydes, amines, and organic boronic acids (**A**) and bifunctional mode of action of chelating thiourea catalyst **65** in the enantioselective Petasis-type 2-vinylation of *N*-acetylated quinolinium ions (**B**).



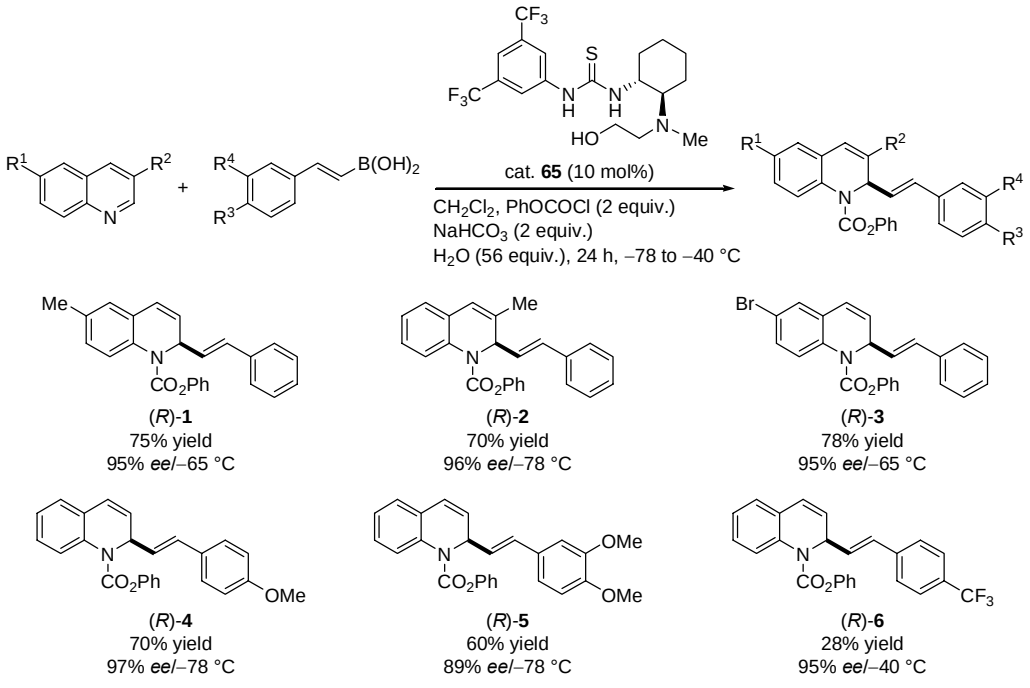
65
70% yield, 90% *ee* (no additive)
27% yield, 93% *ee* (with H_2O)
65% yield, 94% *ee* (with H_2O, $NaHCO_3$)

66
47% yield, 27% *ee*

67
60% yield, 68% *ee*

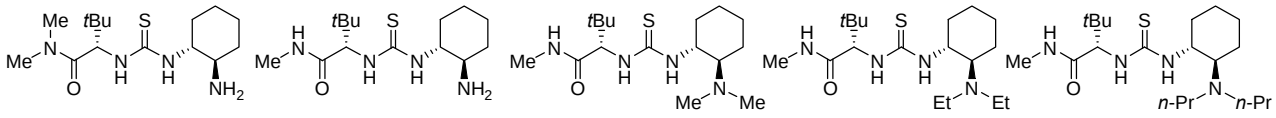
Figure 21. Chelating thiourea derivatives screened in the Petasis-type 2-vinylation of the *N*-acetylated quinolinium ion at –65 °C.

Employing chelating thiourea catalyst **65** (10 mol% loading) along with variable boronic acids, phenyl chloroformate and water/$NaHCO_3$ as additives in dichloromethane as the reaction medium numerous *N*-phenoxycarbonyl quinolinium salts were regioselectively (no 1,4-addition) and enantioselectively converted to the corresponding Petasis-type (*R*)-configured 1,2-adducts such as **1**–**6** (Scheme 83). The yields of this reaction ranged from 28%–78% and the adducts were isolated with high *ee* values (89%–97%).[243]



Scheme 83. Product range of the **65**-catalyzed asymmetric Petasis-type 2-vinylation of *N*-phenoxycarbonyl quinolinium salts.

The Jacobsen group, in 2005, described the systematic structure optimization and identification of a bifunctional tertiary amine-functionalized thiourea derivative operating as a bifunctional catalyst in the enantioselective cyanosilylation of ketones.[244] While the established Schiff base thiourea catalyst **47** (Figure 16; Scheme 46, 47, and 48) displayed no detectable catalytic activity in the model cyanosilylation (with TMSCN) of acetophenone primary amine **68** (10 mol%), the immediate synthetic precursor of **47**, was found to be highly active (100% conv./3 h). Further structure modulation revealed that less bulky amide derivatives such as secondary methyl amide catalyst **69** afforded the best *ee* values (55%/–40 °C). *N*,*N*-Dimethylation of the primary amine function in **69** led to catalytically inactive *N*,*N*-dimethyl tertiary amine thiourea **70**; the addition the trifluoroethanol for in situ generation of HCN as the active nucleophile, however, restored catalytic activity (80% conv./24 h) and enantioselectivity (90% *ee*). The crucial role of the amine substituent on both catalyst activity and selectivity became evident upon comparison of *N*,*N*′-dimethyl (**70**), *N*,*N*′-diethyl (**71**), and *N*,*N*′-di-*n*-propyl (**72**) thiourea derivatives, when the most sterically demanding catalyst **72** was identified to be the most efficient in the cyanosilylation of acetophenone (Figure 22).



68
(10 mol%); toluene
100% conv./3 h
25% *ee*/–40 °C

69
(10 mol%); toluene
100% conv./3 h
55% *ee*/–40 °C

70
(10 mol%); toluene
0% conv./24 h
no *ee*/–40 °C

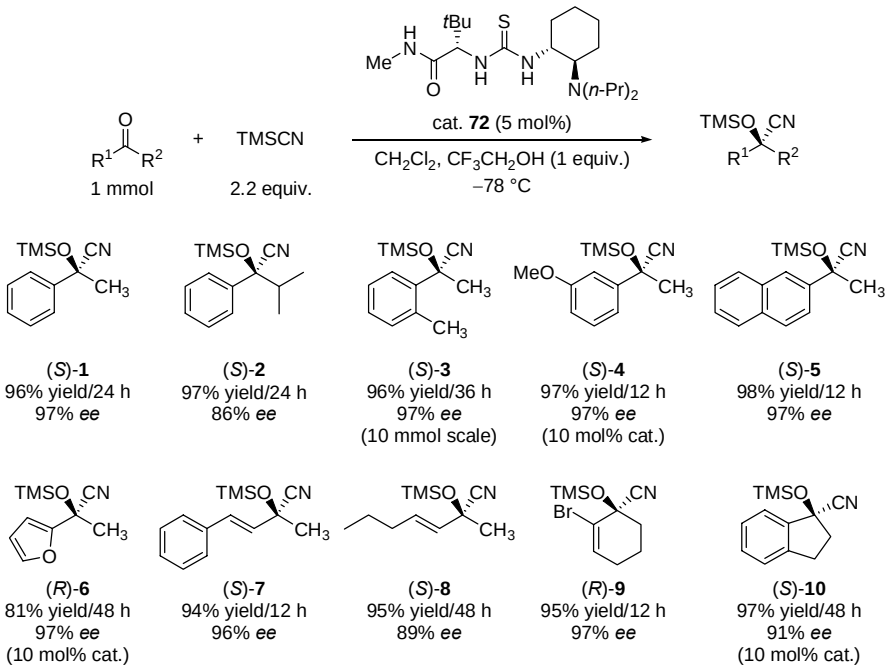
70
(10 mol%); toluene
80% conv./24 h
90% *ee*/–40 °C
CF_3CH_2OH

71
(10 mol%); CH_2Cl_2
100% conv./12 h
94% *ee*/–78 °C
CF_3CH_2OH

72
(10 mol%); CH_2Cl_2
100% conv./12 h
97% *ee*/–78 °C
CF_3CH_2OH

Figure 22. Primary and tertiary amine thioureas evaluated for catalytic efficiency in the cyanosilylation of acetophenone.

The optimized protocol utilizing thiourea derivative **72** as the catalysts (5 mol%), trifluoroethanol (1 equiv.) as the additive, and dichloromethane as the solvent was applied to the asymmetric cyanosilylation of a broad spectrum of ketone substrates (e.g., **1**–**10**) including various alkyl aryl ketones, heteroaromatic ketones, α,β-unsaturated ketones, and also to the aldehydes benzaldehyde (96% *ee*/2 h; 0.05 mol% **72**) and *trans*-cinnamaldehyde (93% *ee*/2 h; 0.05 mol% **72**). The silylated cyanohydrins, important precursors of α-hydroxy acids, β-amino alcohols, and other valuable chiral building blocks,[245] were isolated in high yields (81%–98%) and *ee* values (86%–97%) (Scheme 84). A combination of experimental (e.g., kinetic analysis, structure-efficiency studies) and theoretical methods (DFT computations) utilized for the elucidation of the **72**-catalyzed cyanosilylation of ketones suggested that this 1,2-carbonyl addition obeyed a cooperative mechanism in which both the thiourea and the tertiary amine of the catalyst were involved productively in the rate-limiting addition step.[246] DFT transition state analyses distinguished between two mechanistic pathways and thus two transition states (**TS 1** and **TS 2**, Figure 23) involving thiourea hydrogen-bonding activation of the ketone (**TS 1**) or of cyanide (**TS 2**). Computed transition state energies and the strong correlation between the experimentally observed sense and degree of enantioinduction for a variety of catalysts and ketone substrates favored **TS 1**, in which the tertiary amine group activated the nucleophile HNC (isonitrile-form of HCN) generated from tautomerization of HCN and the thiourea moiety the ketone through explicit double hydrogen-bonding interaction with both ketone lone pairs, respectively.[246]



Scheme 84. Typical silylated cyanohydrins prepared from various ketones under asymmetric **72**-catalysis (cyanosilylation).

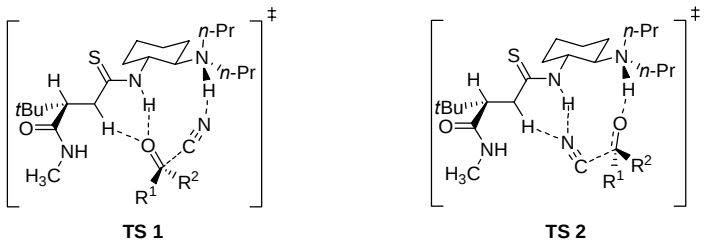
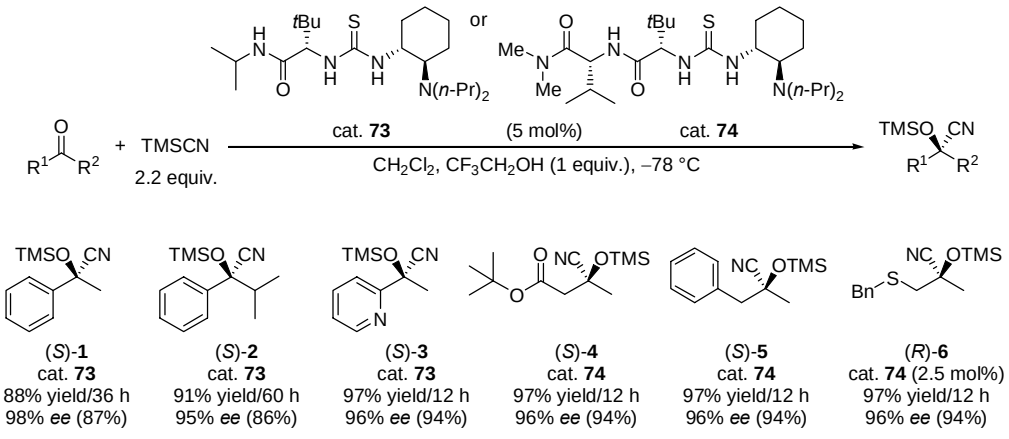


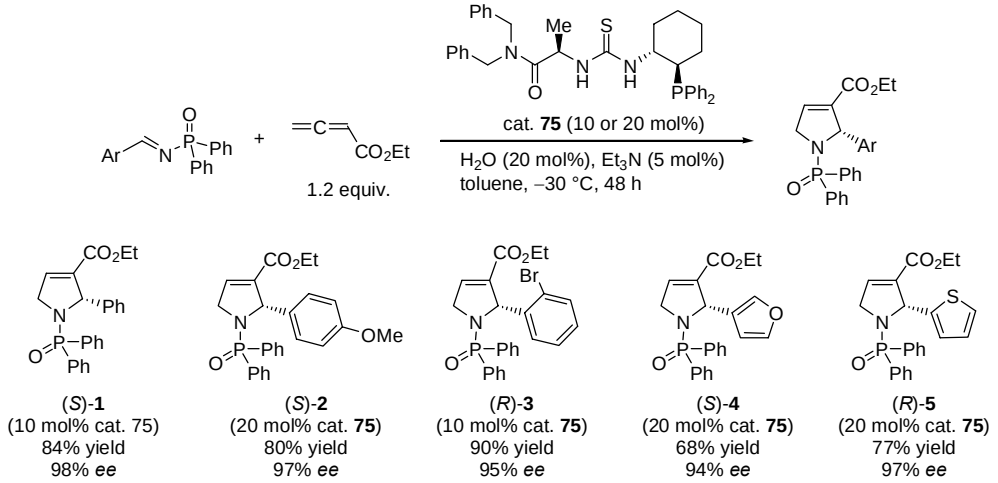
Figure 23. Proposed transition states of the asymmetric **72**-catalyzed cyanosilylation of ketones describe two alternative mechanistic pathways for cooperative catalysis: Addition via thiourea-bound ketone (**TS 1**, preferred) and addition via thiourea bound cyanide (**TS 2**).

The computations suggested that the enantioselectivity of the cyanosilylation arose from direct interactions between the ketone substrate and the amino-acid derived unit of the catalyst type represented by thiourea **72**. On the basis of this insight the Jacobsen group designed thiourea catalysts **73** and dipepetide thiourea catalyst **74**.[67] These optimized catalysts gave access to a broader spectrum of silylated cyanohydrins (e.g., **1**–**6)** and proved to be more active (88%–97% yield) and more enantioselective (98%–98% *ee*) than **72** (Scheme 85).[246]



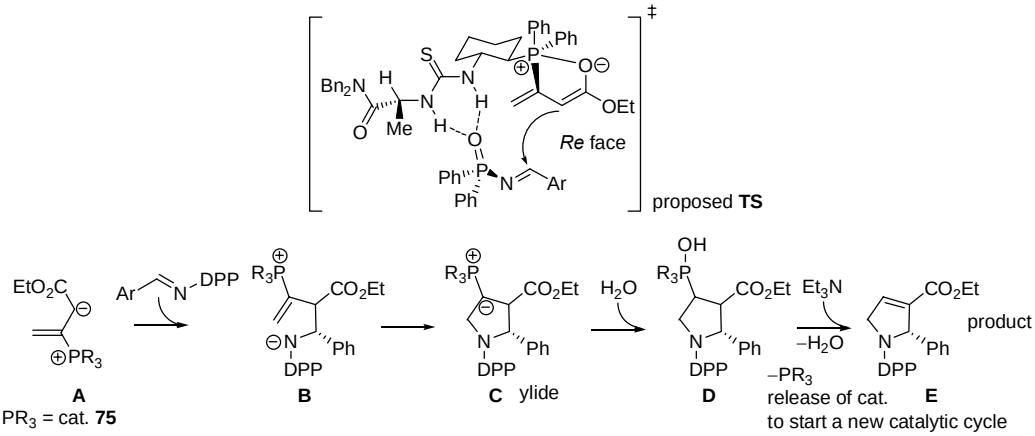
Scheme 85. Product range of the **73**- and **74**-catalyzed asymmetric cyanosilylation of ketones.

Based on the structure of highly efficient enantioselective *tert*-leucine derived thiourea catalysts bearing a tertiary amine functionality such as **72**, **73**, and **74** (Scheme 84 and 85) Jacobsen and Fang developed a new class of chiral bifunctional phosphinothioureas derived from readily accessible *trans*-2-amino-1-(diphenylphosphino)cyclohexane.[247, 248] Structure optimization studies including the variation of the amide group and the amino acid unit demonstrated alanine-derived phosphinothiourea **75** to be the most efficient in the asymmetric model [3+2] cycloaddition reaction between diphenylphosphinoyl-(DPP) protected benzaldehyde imine and buta-2,3-dienoic acid ethyl ester as the allene component (adduct **1**; Scheme 86). In the presence of Et_3N (5 mol%) and H_2O (20 mol%) this thiourea catalyst (10 or 20 mol% loading) exhibited an increased accelerating effect and promoted the enantioselective [3+2] cycloaddition between the model allene and various DPP-protected (hetero)aromatic imines in 48 h reaction time resulting in the target 2-aryl-2,5-dihydropyrrole derivatives **1**–**5** in good yields ranging from 68%–90% and with excellent *ee* values (94%–98%) (Scheme 86).



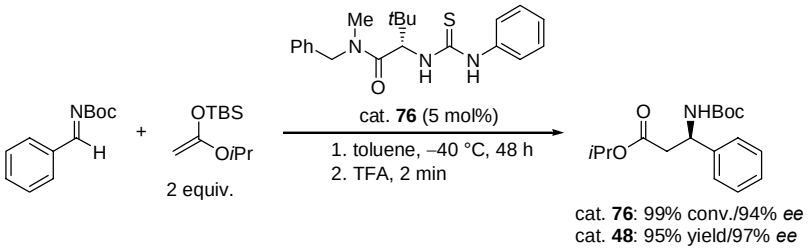
Scheme 86. Typical 2-aryl-2,5-dihydropyrrole derivatives prepared with the asymmetric [3+2] cycloaddition between buta-2,3-dienoic acid ethyl ester and various DPP-protected (hetero)aromatic imines catalyzed by phosphinothiourea **75**.

In the mechanistic scenario visualized in Scheme 87 the allene is activated through the nucleophilic attack of the phosphino group providing zwitterion (**A**) that takes part in the proposed transition state for asymmetric addition on the hydrogen-bonded DPP-protected imine (**B**). The beneficial effect of Et_3N and H_2O on the reaction rate without impact on the enantioinduction suggests that these additives are not involved in the rate-determining step(s). Most likely H_2O effects the formation of (**D**) through deprotonation of (**C**) and Et_3N promotes the elimination and the release of catalyst **75** via either E_2 or E_1cb mechanisms affording the product (**E**). Secondary interactions (π–π stacking or C=O···Ar) between the amide portion of the catalyst and the diphenyl portion of the imine were suggested to additionally stabilize the lowest energy **TS** leading to the observed high enantioselectivities.



Scheme 87. Mechanistic proposal for the asymmetric [3+2] cycloaddition between buta-2,3-dienoic acid ethyl ester and various DPP-protected imines catalyzed by phosphinothiourea **75**.

Systematic investigations of the catalyst structure-enantioselectivity profile in the Mannich reaction[72] led to significantly simplified thiourea catalyst **76** lacking both the Schiff base unit and the chiral diaminocyclohexane backbone (Figure 14; Scheme 88). Yet, catalyst **76** displayed comparable catalytic activity (99% conv.) and enantioselectivity (94% *ee*) to the Schiff base catalyst **48** in the asymmetric Mannich reaction of *N*-Boc-protected aldimines (Scheme 49 and 88).[249] This confirmed the enantioinductive function of the amino acid-thiourea side chain unit, which also appeared responsible for high enantioselectivities obtained with catalysts **72**, **73**, and **74**, respectively, in the cyanosilylation of ketones (Scheme 84 and 85).[244, 246]



Scheme 88. Asymmetric Mannich reaction of *N*-Boc-protected aldimines catalyzed by simplified thiourea **76**.

Berkessel and co-workers synthesized a library of structurally diverse tertiary amine functionalized catalyst candidates incorporating a chiral 1,2- or 1,4-diamine chiral backbone, respectively.[235, 236, 250] Structure-efficiency studies through sequential modification of the diamine backbone, the tertiary amine functionality, the (thio)urea *N*-substituents as well as of the amide substituent pattern, exemplarily illustrated for a Jacobsen-type 1,2-diamine-based structure (Figure 24), identified dimethylated amine (*R*,*R*)-diaminocyclohexane-(thio)ureas **64**, **77**, and **78** (5 mol% loading) to be the most active and stereoselective catalysts in the model asymmetric alcoholytic dynamic kinetic resolution (DKR)[251, 252] of phenylalanine- (R = Bn; Scheme 90) and *tert*-leucine-derived (R = *t*Bu; Scheme 90) racemic oxazol-5(4*H*)-ones ("azlactones") with allyl alcohol, respectively (Figure 25). Azlactones are readily accessible α-amino acid derivatives prepared by the Erlenmeyer azlactone synthesis or from *N*-acylated (e.g., with benzoyl chloride) racemic α-amino acids through cyclodehydration in the presence of a condensation agent (e.g., acetic anhydride).[253] Owing to the acidic hydrogen atom (pK_a = 8.9) azlactones are configurationally labile substrates that undergo base-catalyzed or autocatalytic racemization through enol formation.

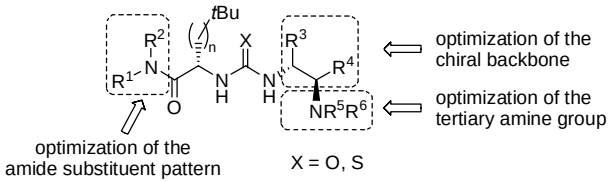


Figure 24. Systematic structure modification led to "second generation" catalyst **78** optimized for the asymmetric DKR of azlactones.

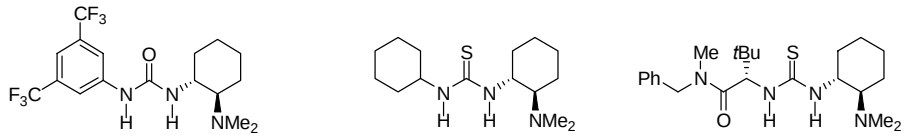
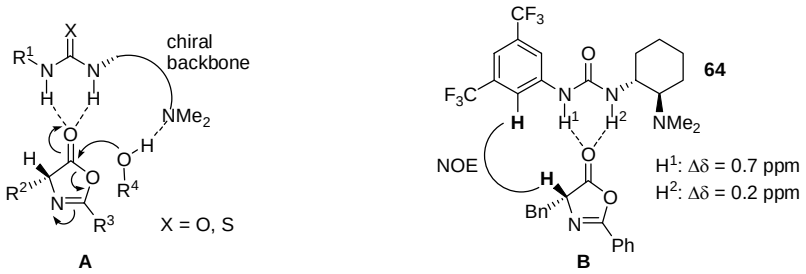


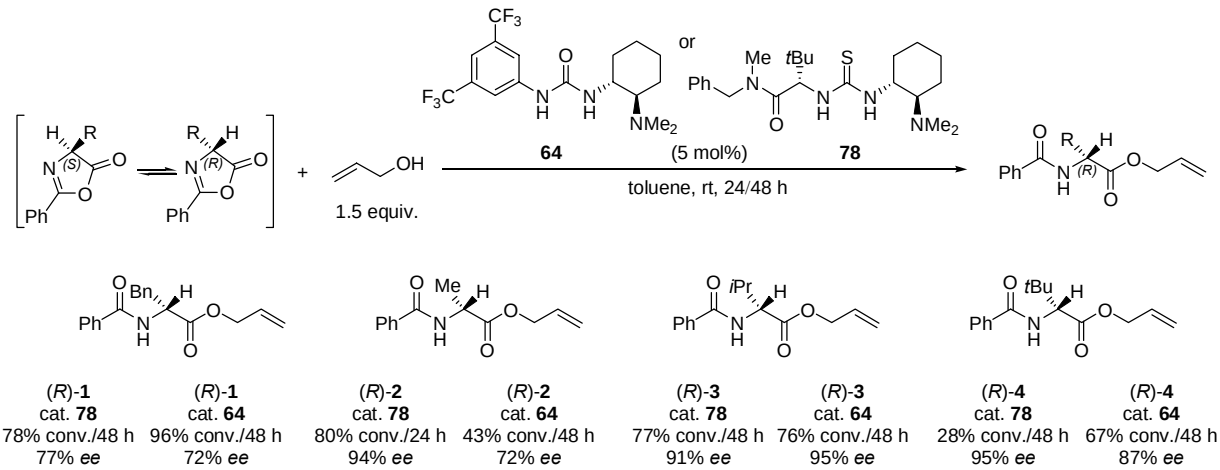
Figure 25. The most efficient (thio)urea derivatives in the asymmetric DKR of phenylalanine-derived azlactone (R = Bn; Scheme 90).

The authors assumed that **64**, **77**, and also "second generation" catalyst **78** structurally closely related to **72** (Figure 22) operated in a bifunctional mode such that the azlactone carbonyl was activated through double hydrogen-bonding interaction with the (thio)urea moiety, while the tertiary amine group increased the nucleophilicity of the attacking alcohol (Scheme 89). This proposal for the hydrogen-bonded azlactone-catalyst complex was supported by NMR spectroscopic experiments using **64** as the catalyst. Upon addition of the racemic azlactone substrate to a solution of catalyst **64** in d_8-toluene (NMR titration), downfield shifts of $\Delta\delta$ = 0.2 ppm and $\Delta\delta$ = 0.7 ppm were observed for the urea N–H hydrogen atoms of the catalyst (Scheme 89). Furthermore, an intermolecular NOE of the azlactone 4-H resonance was observed upon irradiation at the resonance frequency of the aromatic hydrogen atoms at the 2- and 6-positions of the catalyst. The ^{1}H and ^{13}C NMR spectra of this azlactone-**64** complex consisted of only one set of signals indicating the preferential formation of one of the two possible diastereomers of the catalyst–azlactone complex due to rapid interconversion of the azlactone enantiomers.[250]



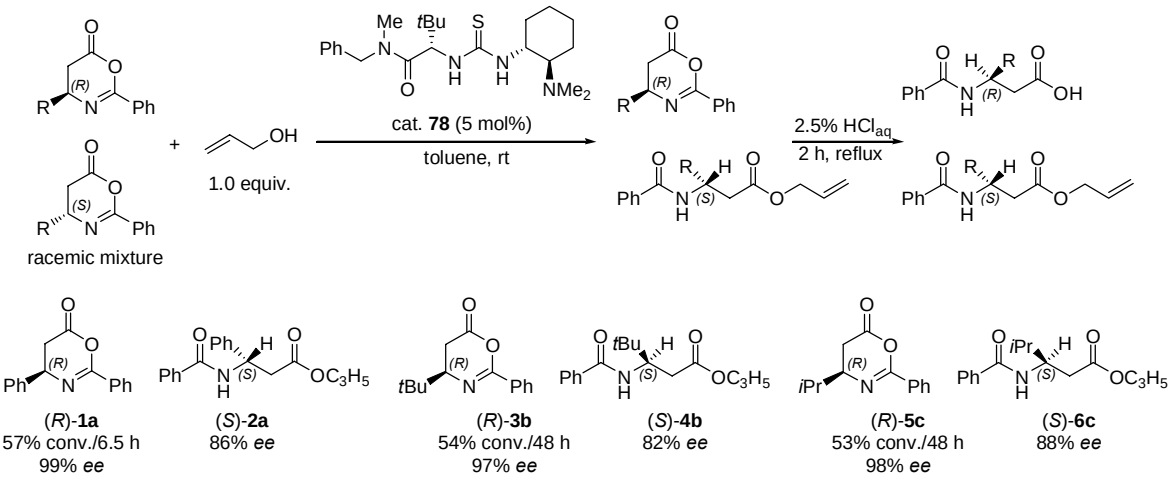
Scheme 89. Proposed mechanistic picture for the asymmetric alcoholytic DKR of racemic azlactones promoted by bifunctional (thio)urea catalysts **64**, **77**, and **78**, respectively (**A**); hydrogen-bonded azlactone-**64** complex supported by NMR methods (**B**).

The chiral information of the *tert*-leucine amide motif introduced by the Jacobsen group (Figure 22),[244] was found to enhance the stereodifferentiation predominantly induced by the diaminocyclohexane moiety.[235] Employing catalyst **64** (5 mol%) or **78** (5 mol%) under optimized conditions (toluene, rt; 1.5 equiv. allyl alcohol) to the alcoholytic ring opening of selected racemic azlactones exhibited conversions of 28%–96% (24 h–48 h) and enantioselectivities of 72%–95% (at rt) for the formation of the desired enantiomerically enriched *N*-benzoyl-protected α-amino acid allyl esters **1**–**4** (Scheme 90),[235, 250] that could be readily converted to synthetically useful enantiopure α-amino acids. Additionally, this organocatalytic DKR methodology was utilized for clean stereoinversion of enantiopure natural or non-natural L- (or D-) α-amino acids resulting in the corresponding *N*-benzoyl-D- (or L-) α-amino acids allyl esters.[235]



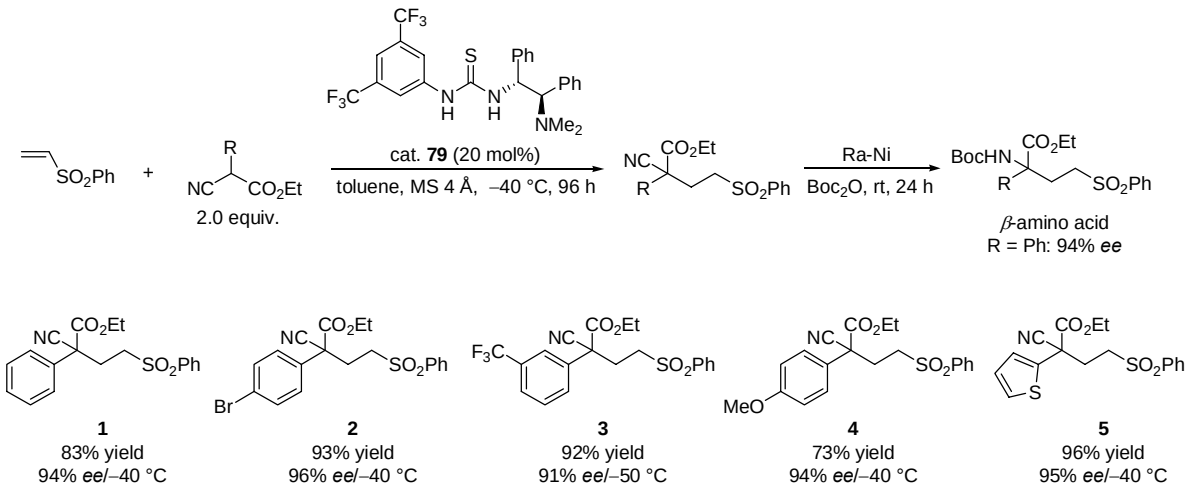
Scheme 90. Chiral *N*-benzoyl-protected α-amino acid allyl esters obtained from **64**- and **78**-catalyzed asymmetric DKR of racemic azlactones derived from racemic natural non-natural α-amino acids.

Berkessel and co-workers extended the synthetic applicability of hydrogen-bonding thiourea catalyst **78** in the DKR of azlactones to the kinetic resolution (KR) of structurally related, but configurationally stable 4,5-dihydro-1,3-oxazine-6-ones ("oxazinones").[237] Oxazinones are six-membered cyclic derivatives of *β*-amino acids and can be synthesized similar to azlactones by cyclodehydration of the corresponding *N*-benzoyl-protected amino acids or, alternatively, by the one-step protocol reported by Tan and Weaver for the synthesis of racemic *β*-amino acids using aldehydes, malonic acid, and ammonium acetate as inexpensive starting materials.[254] The KR of racemic oxazinone mixtures based on the (*S*)-favored hydrogen-bonding activation through **78** and thus preferred alcoholytic (1.0 equiv. allyl alcohol) ring opening of the (*S*)-configured oxazinone in comparison to its (*R*)-counterpart resulting in both the formation of the corresponding enantiomerically enriched (*S*)-configured *N*-benzoyl-protected *β*-amino acid allyl ester and the remaining(*R*)-oxazinone (Scheme 91). Due to the difficulty in the accurate determination of the selectivity factor *S* the authors used the conversion and *ee* values of the substrates and products, respectively, to describe the quality of the KR.[255] After practical reaction times (6.5 h–48 h at rt) and with 5 mol% loading of **78** the unreacted (*R*)-oxazinones **1a, 3b**, and **5c** were obtained in high enantioselectivities (97%–99%) and the (*S*)-configured *N*-benzoyl-protected *β*-amino acid allyl ester **2a**, **4b**, and **6c** in *ee* values ranging from 82%–88% (Scheme 91). Performing the KR for oxazinone R = Ph in the presence of only 1 mol% catalyst **78** afforded 61% conversion after 10 h, 98% *ee* for the (*R*)-**1a**, and 85% *ee* for the protected allyl ester (*S*)-**2a** (Scheme 91). Simple hydrolytic work-up of the product mixture with aqueous HCl converted the remaining (*R*)-oxazinone to the corresponding insoluble *N*-benzoyl-protected *β*-amino acid that was separable from the desired (*S*)-configured *N*-benzoyl-protected *β*-amino acid allyl ester through filtration (Scheme 91).[237]



Scheme 91. Typical enantioenriched (*R*)-oxazinones and (*S*)-configured *N*-benzoyl-protected *β*-amino acid allyl esters obtained from the **78**-catalyzed kinetic resolution of racemic oxazinone mixtures; subsequent isolation of the ester through (*R*)-oxazinone hydrolysis.

Chen et al. identified (*R*,*R*)-1,2-diphenylethylenediamine-derived tertiary amine-functionalized thiourea **79** (20 mol% loading), an analogue of Takemoto's bifunctional thiourea catalyst **12** (Figure 18),[131] as enantioselective catalyst for the Michael addition[151-154] of *α*-aryl cyanoacetates to phenyl vinyl sulfone affording the desired adducts **1**–**5** in good (73%) to excellent (96%) yields (after 96 h) and in very good enantioselectivities (91%–96% at –50 °C to –40 °C) (Scheme 92).[219] The protocol using **79** was limited to aromatic cyanoacetates (R = aryl), while thiourea **12** catalyzed the addition of aliphatic (R = alkyl) *α*-alkyl cyanoacetates to phenyl vinyl sulfone and gave the adducts in yield ranging from 52%–96% and *ee* values of 72%–96% after 48 h at –40 °C.[219] The authors presented a one-pot protocol to convert the obtained Michael adducts efficiently into synthetically important protected *β*-amino acid precursors as shown for one example (R = Ph: 94% *ee*) in Scheme 92.[219] In analogy to catalyst **12**, thiourea derivative **79** was classified as bifunctional catalyst activating both the phenyl vinyl sulfone through hydrogen-bonding to the sulfone functionality and also the respective cyanoacetates through tertiary-amine mediated deprotonation resulting in the formation of the active nucleophile.



Scheme 92. Product range of the **79**-catalyzed Michael addition of α-aryl cyanoacetates to phenyl vinyl sulfone and conversion of one exemplary adduct (R = Ph) to the corresponding protected β-amino acid. The absolute configurations of the adducts were not determined.

In 2008, Wu and co-workers introduced a small series of novel multiple hydrogen-bonding tertiary amine functionalized thiourea derivatives **80**, **81**, **82**, and **83** for catalysis of the asymmetric Michael addition[151-154] of acetylacetone to aliphatic and aromatic nitroalkenes (Figure 26).[256] The new catalyst design concept based on the working hypothesis that amine thioureas bearing multiple hydrogen-bonding donors could form more activating hydrogen-bonds to the substrates and thus could display higher catalytic efficiency (at reduced catalyst loadings) than a thiourea catalyst bearing only one thiourea group capable of only one double hydrogen-bonding interaction. This strategy was already known from bis-thiourea catalysts **106** and **114** (Scheme 107 and 110) but was for the first time realized in chiral amine thioureas. Additionally, these thiourea derivatives incorporated both the 1,2-diphenylethylenediamine as well as the 1,2-diaminocyclohexane backbone closely connected via a bridging thiourea functionality to create an efficient chiral environment. In the model Michael reaction between *trans*-β-nitrostyrene and acetylacetone at room temperature, with diethyl ether as the solvent, and in the presence of **80**, **81**, **82**, or **83** (10 mol% loading), respectively, all catalyst candidates exhibited enantioinduction and consistently high catalytic activity (Figure 26). Thiourea **80**, however, that combining the (*R*,*R*)-diaminocyclohexane with the (*S*,*S*)-diphenylethylenediamine unit furnished only a moderate *ee* value (76%), while the (*R*,*R*)-configuration in both diamine units proved to be the matched combination and gave increased enantioinduction (e.g., with **81**: 93% *ee* at rt). Replacing the tosyl (Ts) group of **81** with the less bulky mesyl (Ms) group led to sterically more flexible, but less enantioselective (89% *ee*) thiourea derivative **82**. The best results in terms of catalytic activity (97% yield/1 h) and enantioselectivity (97% *ee*/rt/Et_2O) were reached with electron-deficient thiourea derivative **83** again incorporating the 3,5-bis(trifluoromethyl)phenyl moiety. The **83**-catalyzed (10 mol%) model reaction demonstrated that polar protic and strongly were incompatible and drastically reduce both catalytic activity and enantioselectivity (e.g., MeOH: 69% yield/17 h, 18% *ee*/rt; DMSO: 72% yield/16 h; 0% *ee*), while aprotic nonpolar or less polar solvents such as DCM (97% yield/0.5 h/89% *ee*/rt) or MeCN (90% yield/10 h/86% *ee*/rt) gave better results. Diethyl ether was identified as the solvent of choice (97% yield, 1 h; 97% *ee* at rt). Reducing the reaction temperature to 0 °C and –20 °C did not affect the *ee* values. Lowering the catalyst loading from initial 10 mol% to 1 mol% catalyst **83** gave an unchanged yield (97%/1 h) and *ee* value (97% *ee*/rt) for the model Michael adduct, while 0.1 mol% loading resulted in 81% yield and 95% *ee* after 10 h at room temperature.

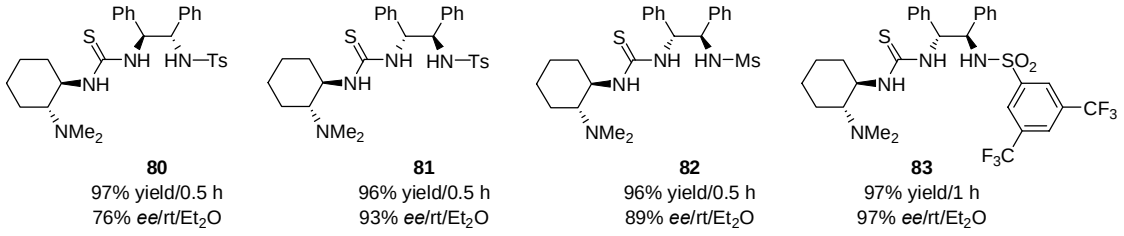
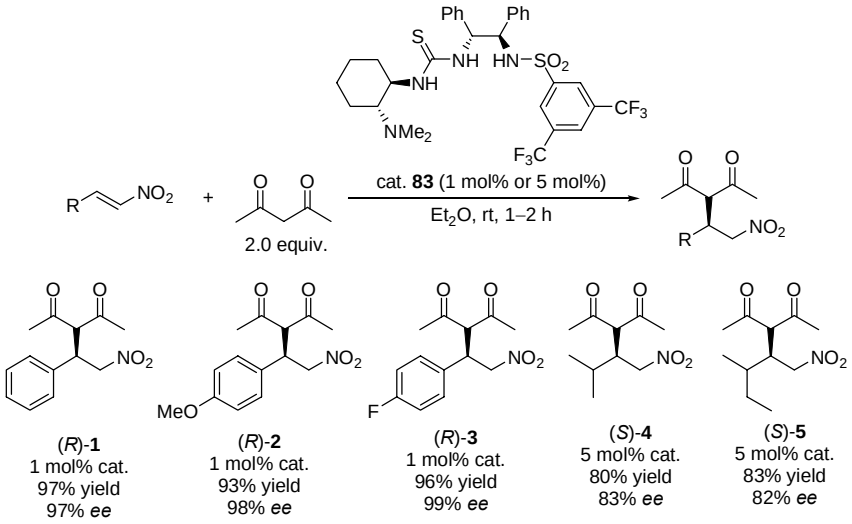


Figure 26. Multiple hydrogen-bonding tertiary amine-functionalized thioureas screened in the asymmetric Michael reaction between *trans*-β-nitrostyrene and acetylacetone at 10 mol% loading.

Under optimized conditions the **83**-catalyzed (1 mol% loading) Michael addition of acetylacetone to various aryl nitroalkenes as well as alkyl nitroalkenes proceeded in good to excellent yields (80%–97%) and enantioselectivities (82%–99%) of the desired adducts **1**–**5** (Scheme 93). The authors also reported the successful enantioselective Michael addition of 1,3-diphenylpropane-1,3-dione (adduct in 95% yield/12 h; 85% *ee*/rt) and 2-acetylcyclopentanone (adduct in 92% yield/10 h; 96% *ee*/*dr* :85:15; rt) to *trans*-*β*-nitrostyrene. A derivative of **81** lacking the third amide proton due to methylation of the sulfonamide proved less effective in the model Michael reaction (80% yield/16 h; 68% *ee*); this observation indicated that the NH of the sulfonamide on the 1,2-diphenylethylenediamine moiety played a significant role in this Michael reaction.[256]



Scheme 93. Typical products of the asymmetric Michael addition of acetylacetone to various nitroalkenes catalyzed by **83**.

Dixon and Richardson developed (*R*,*R*)-1,2-diaminocyclohexane-derived hydrogen-bonding thiourea derivatives incorporating the phthalimide (Phthal) and tetraphenylphthalimide (TPhP) unit, respectively, for enantioselective catalysis of the conjugate addition[151-154] of aryl methyl ketone derived morpholine enamines to various aromatic nitroalkenes.[257] The catalyst evaluation performed for the Michael reaction between acetophenone-derived morpholine enamine and *trans*-*β*-nitrostyrene (10 mol% catalyst loading; in toluene at –10 °C) afforded the desired (*S*)-adduct after acidic hydrolytic work-up in very low *ee* values for thioureas bearing the phthalimide moiety such as **84** (8% *ee*) and **85** (12% *ee*) (Figure 27). In contrast, the tetraphenylphthalimide-containing counterparts showed under the same screening conditions enhanced and reversal enantioinduction resulting in 38% (with **86**) and 25% (with **87**) enantioselectivity, respectively, for the (*R*)-configured Michael adduct (Figure 27). Thiourea derivative **86**, which was prepared in two-steps (20% yield) from (*R*,*R*)-1,2-diaminocyclohexane and tetraphenylphthalic anhydride, turned out to be the most efficient catalyst and was utilized for the synthesis (10 mol% loading) of a broad range of Michael adducts.

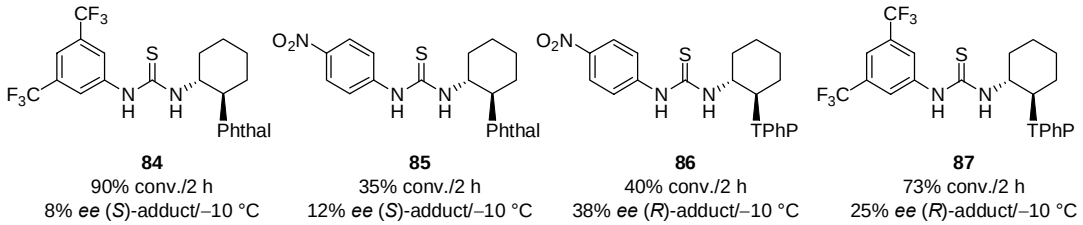
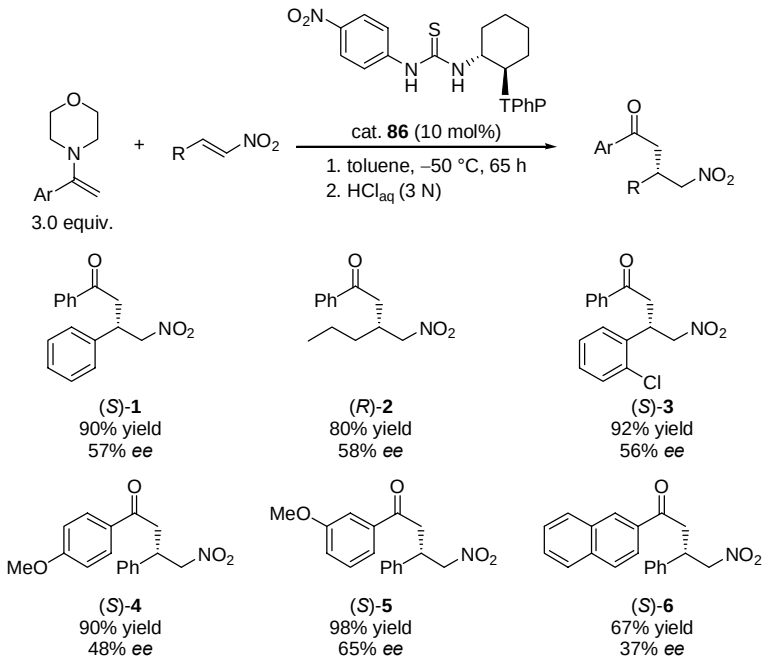


Figure 27. Representative (*R*,*R*)-1,2-diaminocyclohexane-derived thiourea derivatives incorporating a phthalimide (Phthal) and tetraphenylphthalimide (TPhP) moiety, respectively; catalyst screening was performed in the Michael addition of acetophenone-derived morpholine enamine to *trans*-*β*-nitrostyrene in toluene as the solvent.

The optimized protocol reached yields ranging from 67%–98% and moderate *ee* values (37%–65%) of the typical adducts **1**–**6** (Scheme 94). The enantioenriched products represented useful synthetic intermediates serving, e.g, as precursors of 1,4-dicarbonyl compounds and γ-amino acids.[258]



Scheme 94. Typical products obtained from the **86**-catalyzed Michael addition of aryl methyl ketone derived morpholine enamines to various aromatic nitroalkenes and subsequent acidic hydrolysis.

The Roussel group introduced new atropoisomeric thiourea derivatives bearing the (*R,R*)-1,2-diaminocyclohexane backbone and an tertiary amine functionality to bifunctionally catalyze the enantioselective addition of TMSCN (cyanosilylation) to aromatic and aliphatic aldehydes.[259] Thiourea catalyst (*aR/aR*)-(*R,R*)-**88**, which was a inseparable mixture of the two diastereomers (*aR*)-(*R,R*)-**88** and the (*aS*)-(*R,R*) isomer, was prepared from the racemic mixture (*aR/aS*) of atropoisomeric *N*-(2-aminophenyl)-4-methyl-thiazoline-2-thione (ΔG_{rot} > 145 kJ/mol) through isothiocyanation (1. CS_2, Et_3N, 1 h; 2. DCC, MeCN, 24 h) and subsequent coupling with enantiopure (*R,R*)-*N,N*-dimethyl-1,2-diaminocyclohexane. The single diastereomeric thioureas (*aR*)-(*R,R*)-**88** and (*aR*)-(*S,S*)-**88** were accessible, when the pure (*aR*)-atropoisomeric of the 2-amino-thiozoline-2-thione (obtained by semi-preparative HPLC) was transformed to the corresponding atropoisomeric (*aR*)-isothiocyante followed by addition of enantiopure (*R,R*)- or (*S,S*)- *N,N*-dimethyl-1,2-diaminocyclohexane, respectively (Figure 28). The cyanosilylation of the model substrate benzaldehyde at 10 mol% loading of the prepared thiourea derivatives demonstrated that the mixture of diastereomers (*aR/aR*)-(*R,R*)-**88** showed higher catalytic activity (100% yield/27 h) and enantioselectivity (66% *ee*/–20 °C) of the acetylated adduct than the single diastereomers (Figure 28). The authors proposed this observation could originate from the involvement of more than one thiourea molecule in the transition state of this cyanosilylation so that the diastereomers could self-associate ("preorganization") to stabilize a catalytically more active thiourea conformation than a single diastereomer could adopt. Thiourea **58** lacking the atropoisomeric unit turned out to be less active (15% yield/27 h) and enantioselective (32% *ee* at –20 °C).

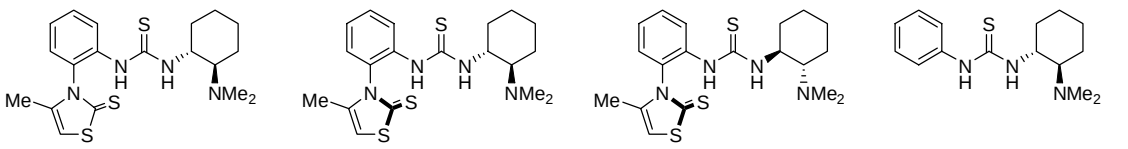
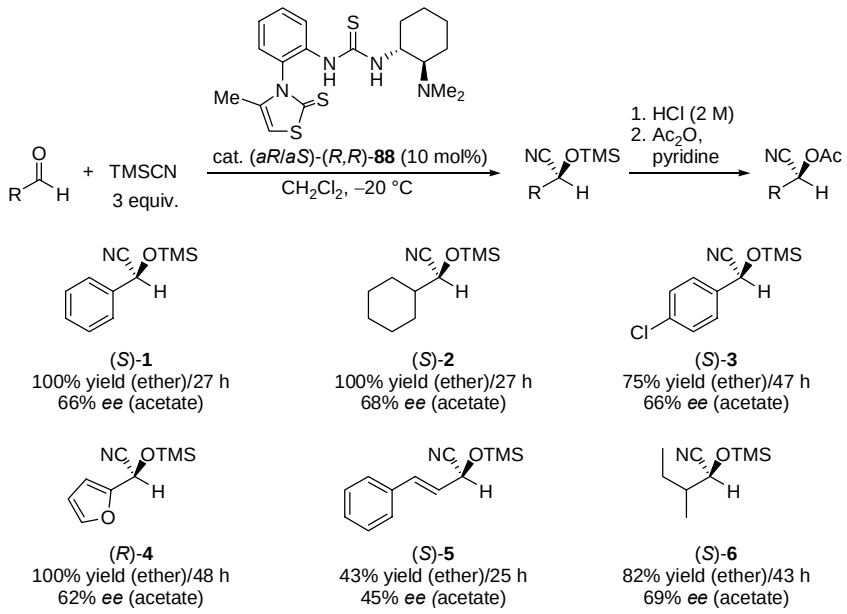


Figure 28. Bifunctional atropoisomeric thioureas and **58** lacking axial chirality screened in the cyanosilylation of benzaldehyde.

Utilizing the readily accessible diastereomeric atropoisomeric thioureas (*aR/aR*)-(*R,R*)-**88** as the catalyst (10 mol%) various (hetero)aromatic and aliphatic aldehydes could be cyanosilylated to the corresponding TMS-protected cyanohydrins **1**–**6** and desilylated as well as acetylated to the respective acetates (Scheme 95). The yields of the TMSCN-adducts ranged from 43%–100% and the *ee* values of the obtained acetates were moderate (45%–69%).



Scheme 95. TMS-protected cyanohydrins prepared from the cyanosilylation of aldehydes in the presence of atropoisomeric thiourea catalyst (*aR/aR*)-(*R,R*)-**88**. Desilylation and acetylation to the respective more stable acetates are given in the subsequent reaction step.

Based on the modular structure of Schiff base catalysts such as "first-generation" Strecker urea catalyst **42**[199, 201] (Figure 15; Scheme 41 and 45) Yoon and Jacobsen developed acetamide (thio)urea derivatives **89** and **90** for enantio- and diastereoselective catalysis of the Nitro-Mannich reaction[72] between *N*-Boc-protected aldimines and nitroethane as well as nitropropane (Figure 29).[260] Thiourea **90** (10 mol% loading) was found to accelerate the model Mannich reaction between *N*-Boc-protected benzaldimine and nitroethane (in toluene at 0 °C) more efficiently (95% conv./18 h) than the urea analogue **89** (36% conv./24 h); the stereoinduction, however, turned out to be nearly identical (**89**: 91% *ee*; **90**: 92% *ee*). A screen of additives revealed that the addition of molecular sieve (MS) 4 Å improved both the reproducibility and the diastereoselectivity of the reaction, while the use of MS 5 Å and MS 3 Å had a detrimental effect on the reaction rate and on the enantioselectivity. This suggested a direct function of the MS in the reaction mechanism. Replacing initially used triethyl amine with diisopropylethylamine ("Hünig's base") as base additive increased the diastereoselectivity of the reaction.

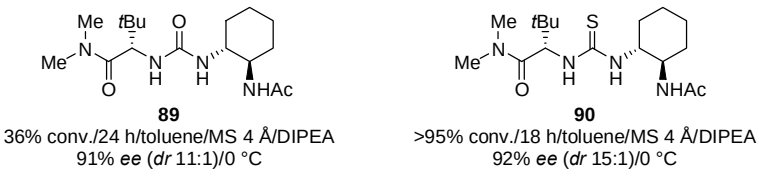
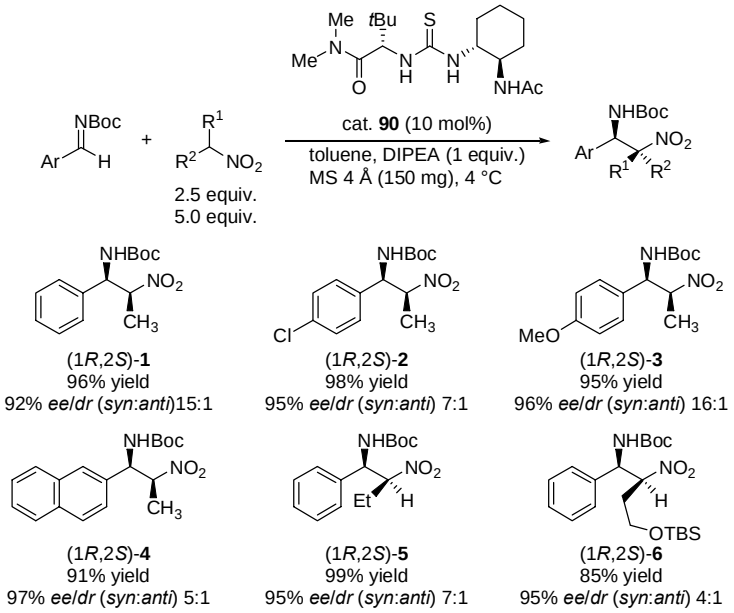


Figure 29. Acetamide (thio)urea derivatives evaluated for catalytic efficiency in the Nitro-Mannich reaction between *N*-Boc-protected benzaldimine and nitroethane.

In the presence of 10 mol% loading of **90** the optimized reaction conditions allowed the high-yielding (85%–99%) addition of nitroethane and nitropropane to a range of *N*-protected aromatic aldimines and furnished the respective Nitro-Mannich adducts **1**–**6** in high enantioselectivities (92%–97% *ee*) and *syn*-favored diastereoselectivities (up to *dr* 16:1) (Scheme 96). The acid labile TBS-group (adduct **6**;

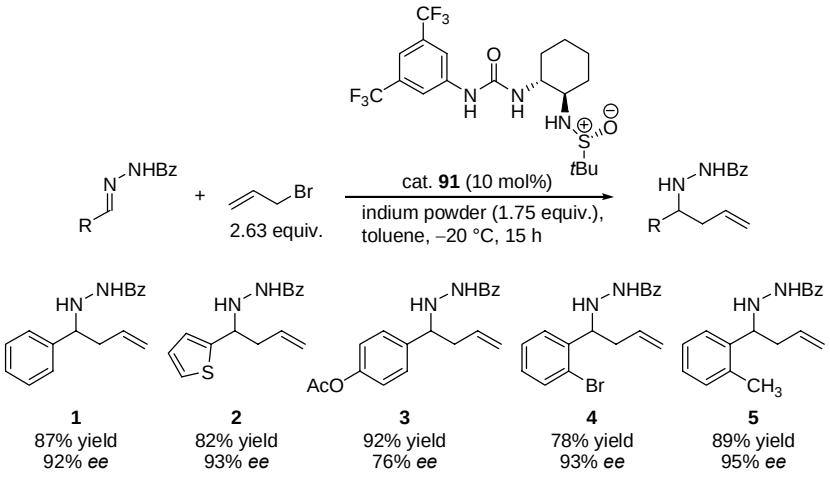
Scheme 96) underwent neither desilylation nor elimination and remained stable under the mild reaction conditions. Since thioureas are known to bind and modulate the reactivity of nitronate anions the catalytic function of thiourea **90** could be the activation of the nitroalkane component through hydrogen-bonding or dual activation of both the aldimine and the nitroalkane. The sense of enantiofacial selectivity in this reaction was observed to be identical to that reported for the thiourea-catalyzed Strecker,[123, 126, 199, 201] Mannich,[204] and hydrophosphonylation reactions[203] suggesting a commonality in the mode of substrate activation and comparable mechanisms.



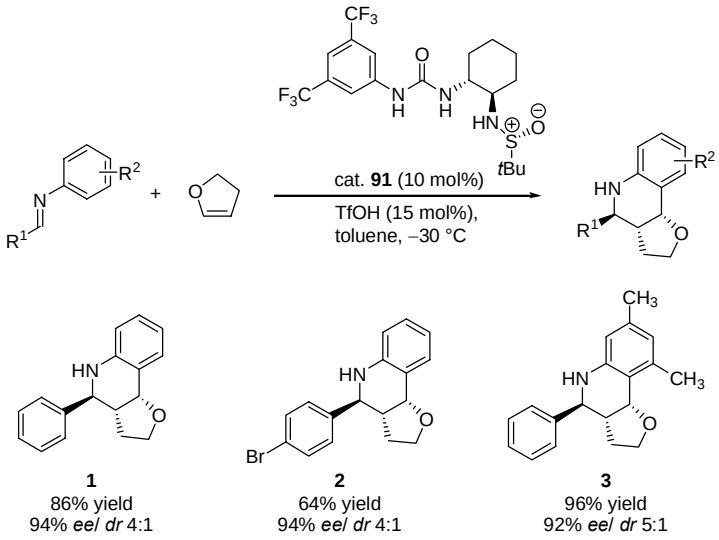
Scheme 96. Product range of the **90**-catalyzed Nitro-Mannich reaction between *N*-Boc-protected aromatic aldimines and nitroalkanes.

Tan and Jacobsen discovered urea derivative **91** to catalyze the enantioselective addition of in situ generated allylindium *N*-benzoyl-protected hydrazones derived from aromatic aldehydes.[261] The catalyst incorporated both a hydrogen-bonding urea group and a Lewis basic *tert*-butyl sulfinamide functionality properly positioned and in close proximity to enable a bifunctional mode of action. Crystallographic analysis of the catalyst solid structure revealed an interaction between these groups through an intramolecular hydrogen bond between the NH group of the sulfinamide unit and the oxygen of the urea carbonyl group. This interaction could serve to increase the hydrogen-bonding ability of the urea group and/or the rigidity of the catalyst structure to attain high catalytic activity and enantioselectivity. The **91**-catalyzed (10 mol%) allylation of *N*-benzoyl-protected hydrazones occurred in toluene at –40 °C in the presence of indium (0) powder (1.75 equiv.) and furnished the corresponding adducts **1**–**5** (Scheme 97) in yield ranging from 78%–92% and in good (76%) to high (95%) *ee* values. *N*-benzoyl-protected hydrazones derived from aliphatic aldehydes were allylated with substantially lower *ee* values (>50%). During the studies the authors observed that the batch of indium and the stirring rate effected the in situ generation of the organometallic allylindium species; a high stirring rate led to a rapid formation of allylindium and entire consumption of the indium powder resulting in increased yields, but slightly lowered *ee* values (e.g., adduct **4**; Scheme 97: high stirring rate gave 89% yield, 90% *ee*).

Woll and Jacobsen found that sulfinamide-functionalized thiourea **91** (10 mol%) catalyzed the asymmetric Povarov reaction between *N*-aryl imines and 2,3-dihydrofuran. At –30 °C in toluene the resulting cyclic products **1**–**3** were obtained in yields ranging from 64%–96% and in high enantioselectivities (92%–94%) (Scheme 98).[7] Mechanistically, a anion-binding model analogous to that proposed for the **53**-catalyzed acyl-Pictet-Spengler reaction was suggested (Scheme 53).[208] In the case of the **91**-catalyzed Povarov reaction the urea/strong acid (TfOH) system was proposed to generate an active electrophilic species consisting of a protioiminium[76] electrophile with a catalyst-bound sulfonate counterion.

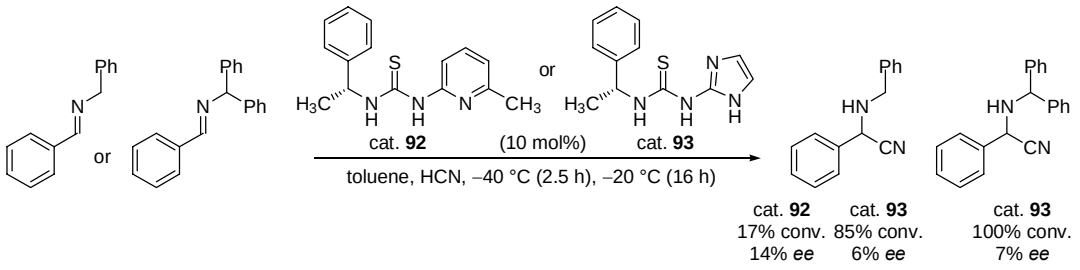


Scheme 97. Typical products obtained from the **91**-catalyzed asymmetric allylation of *N*-benzoyl-protected aromatic hydrazones. The product configurations were not determined.



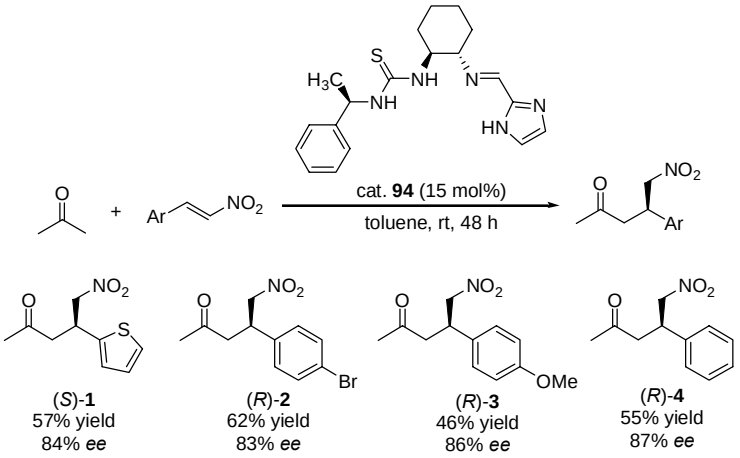
Scheme 98. Products of the enantioselective Povarov reaction of *N*-aryl imines with 2,3-dihydrofuran promoted by thiourea catalyst **91**.

Tsogoeva and co-workers explored the catalytic potential of pyridyl- and imidazoyl-containing thiourea derivatives (e.g., thiourea **92** and **93**) in the asymmetric model Strecker reactions[159] of *N*-benzyl- and benzhydryl-protected benzaldimine with HCN.[262] The observed enantioselectivities were consistently very low (4%–14% *ee*) for all catalyst candidates and were far below synthetically useful levels, while imidazoyl-thiourea **93** was reported to be highly active and displayed 100% conversion (at 7% *ee*) of the *N*-benzhydryl-protected benzaldimine (Scheme 99). X-structure analysis of a pyridyl-thiourea revealed an intramolecular hydrogen-bond between the basic ring nitrogen and one amide proton. This could make this type of thiourea incapable of providing double hydrogen-bonding to the imine resulting in low enantioinduction.



Scheme 99. Typical pyridyl- and imidazoyl-thioureas evaluated for bifunctional catalysis in the asymmetric Strecker reaction of aldimines.

The modification of thiourea catalyst **93** through incorporation of the (*S*,*S*)-diaminocyclohexane backbone as additional chirality element and a Schiff base imidazoyl-moiety led to bifunctional catalyst **94** that, in contrast to **93** in the Strecker reaction (Scheme 99), exhibited enantioinduction (83%–87% *ee*) in the nitro-Michael addition of acetone to *trans*-*β*-nitrostyrenes. The desired adducts were isolated in moderate yields (46%–62%) as depicted in Scheme 100).[263]



Scheme 100. Products of the asymmetric nitro-Michael addition of acetone to *trans*-*β*-nitrostyrenes catalyzed by thiourea **94**.

The Tsogoeva group, in 2006, reported the introduction of newly designed bifunctional secondary amine-functionalized proline-based thioureas (**95** and **96**) and the primary amine-functionalized thioureas (**97**, **98**, and **99**) for catalysis of the asymmetric addition of ketones to *trans*-*β*-nitrostyrenes (Figure 30).[264, 265] Using the Michael reaction[151-154] between acetone and *trans*-*β*-nitrostyrene for catalyst screening (15 mol% loading; toluene; rt) and optimization of the reaction conditions demonstrated that primary amine-thioureas were superior to the proline-based canditates in both catalytic activity and enantioselectivity. The thioureas **97** (85% yield/16 h; 86% *ee*) and **99** (98% yield/48 h; 91% *ee*) turned out to be the most efficient when the reaction was performed in the presence of water (2.0 equiv.) and acetic acid (0.15 equiv.) as additives that facilitated the reversible formation of an enamine intermediate. In the absence of these additives the catalytic activity as well as the enantioinduction of the catalysts decreased as exemplarily shown for **99** (75% yield/72 h; 87% *ee*) in Figure 30.

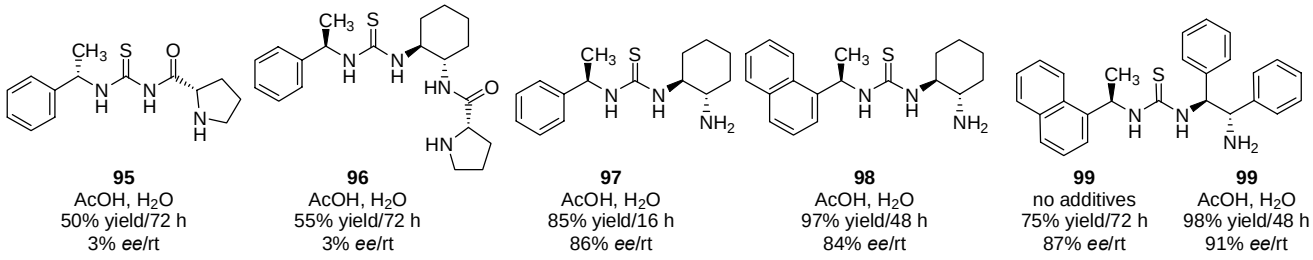
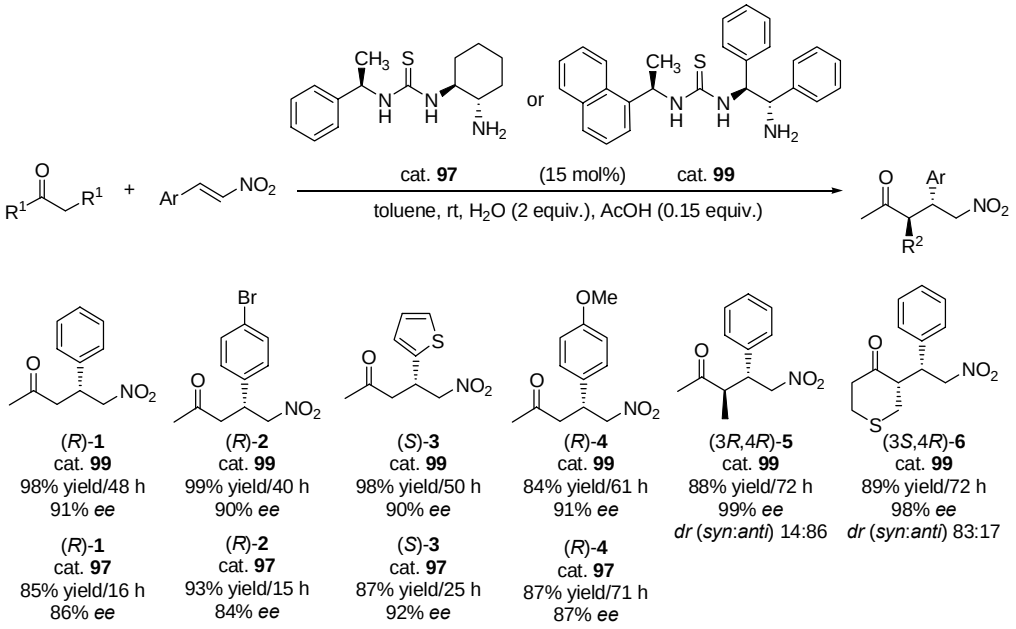


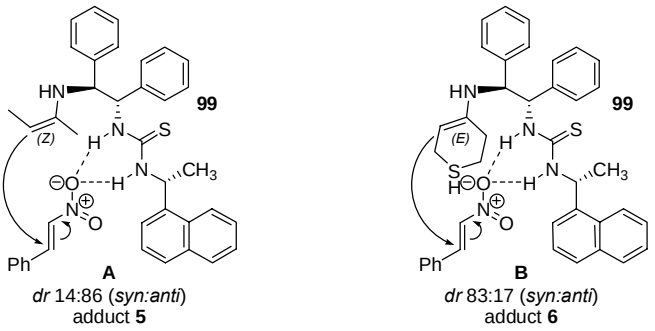
Figure 30. Secondary amine- and primary amine-functionalized bifunctional thiourea derivatives (15 mol% loading) screened in the model Michael addition of acetone to *trans*-*β*-nitrostyrene in toluene at rt.

Catalyst **97** derived from (*S*,*S*)-diaminocyclohexane and **99** derived from (*S*,*S*)-diphenylethylenediamine, respectively, promoted the enantioselective Michael addition of various ketones to electron-rich and electron-deficient *trans*-*β*-nitrostyrenes to afford predominantly the respective (*R*)-adducts **1**–**6** in good to excellent yields (84%–99%) and *ee* values (84%–99%) (Scheme 101). Notably, the addition of methyl ethyl ketone occurred *anti*-diastereoselectively (adduct **5**: *dr syn*:*anti* 14:86), while the addition of tetrahydrothiopyran-4-one favored the formation of the opposite diastereomer (adduct **6**: *dr syn*:*anti* 83:17). This stereochemical outcome was interpreted on the basis of the proposed transition states **A** and **B** visualized in Scheme 102. An acyclic ketone formed a *Z*-configured enamine intermediate[55, 58, 77] with the primary amine group and attacked the hydrogen-bonded nitrostyrene in a mode that the *anti*-adduct was preferred; a cyclic ketone,

however, reacted from the *E*-configured enamine to give the *syn*-diastereomer. Computational studies performed for catalyst **97** suggested an activation through double hydrogen-bonding to only a single oxygen of the nitro group (Scheme 102).[264]

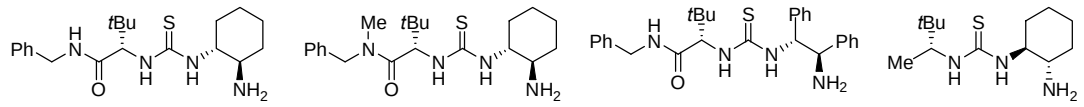


Scheme 101. Typical Michael products obtained from the **97**- and **99**-catalyzed addition of ketones to *trans*-*β*-nitrostyrenes.



Scheme 102. Bifunctional catalysis with primary amine thiourea **99**: Proposed transition states to explain the *anti*-diastereoselectivity (**A**) and the *syn*- diastereoselectivity (**B**) of the Michael addition of both acylic and cyclic ketones to *trans*-*β*-nitrostyrene.

The Jacobsen group independently focussed on the development of primary amine-functionalized thiourea derivatives and published, in 2006, the thioureas **100**, **101**, **102**, and **103** incorporating the established *tert*-leucine (amide) motif (Figure 14) and the diaminocyclohexane or diphenylethylenediamine chiral backbone, respectively (Figure 31).[266] The catalyst screening was carried out in the asymmetric Michael addition[151-154] of 2-phenylpropionaldehyde, an *α*,*α*-disubstituted aldehyde, to 1-nitrohex-1-ene (at 20 mol% loading, DCM, rt, variable equiv. of H_2O) and identified primary amine thioureas **100** (64% yield/24 h; 96% *ee*) and **102** (100% yield/24 h; 99% *ee*) bearing a secondary amide functionality to be the most catalytically active and stereoselective catalysts (Figure 31). In the presence of 5.0 equiv. water the more applicable diaminocyclohexane-derived thiourea **100** was utilized instead of **102** to catalyze the enantio- and diastereoselective Michael addition of various *α*,*α*-disubstituted aldehydes to aliphatic and aromatic nitroalkenes. The protocol tolerates a broad substrate scope and provides the corresponding Michael adducts such as **1**–**6** in yields ranging from 54%–94%, in excellent enantioselectivities (96%–99%), and in *syn*-favored diastereoselectivity (up to *dr* 28:1) (Scheme 103).



100
no H_2O
34% yield/24 h
96% *ee*
dr (*syn*:*anti*) 10:1

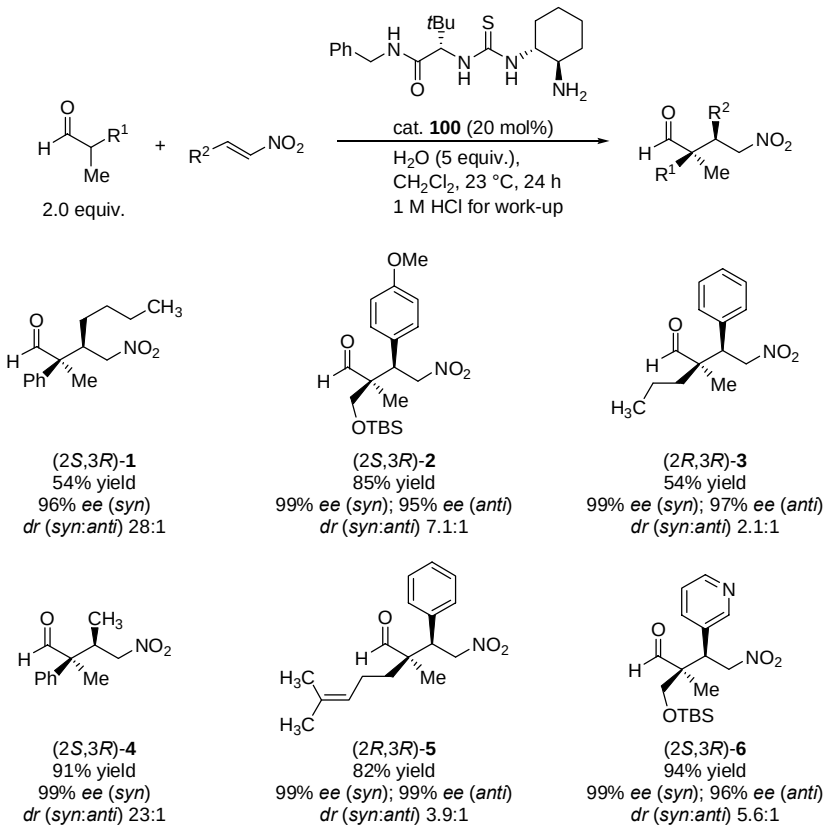
100
H_2O (5 equiv.)
64% yield/24 h
96% *ee*
dr (*syn*:*anti*) 10:1

101
H_2O (5 equiv.)
31% yield/24
96% *ee*
dr (*syn*:*anti*) 10:1

102
H_2O (5 equiv.)
100% yield/24 h
99% *ee*
dr (*syn*:*anti*) 10:1

103
H_2O (5 equiv.)
<5% yield/24 h

Figure 31. Primary amine-functionalized thioureas screened in the asymmetric Michael addition of 2-phenylpropionaldehyde to 1-nitrohex-1-ene using DCM as the solvent.



(2*S*,3*R*)-**1**
54% yield
96% *ee* (*syn*)
dr (*syn*:*anti*) 28:1

(2*S*,3*R*)-**2**
85% yield
99% *ee* (*syn*); 95% *ee* (*anti*)
dr (*syn*:*anti*) 7.1:1

(2*R*,3*R*)-**3**
54% yield
99% *ee* (*syn*); 97% *ee* (*anti*)
dr (*syn*:*anti*) 2.1:1

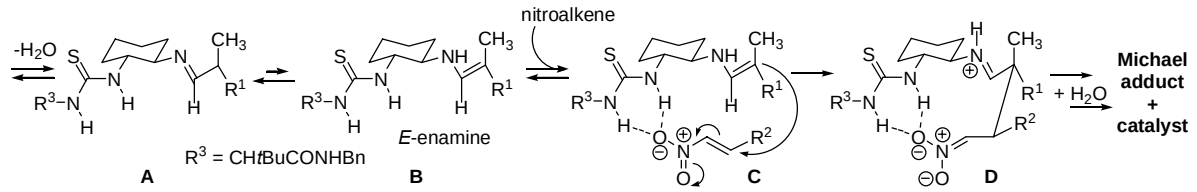
(2*S*,3*R*)-**4**
91% yield
99% *ee* (*syn*)
dr (*syn*:*anti*) 23:1

(2*R*,3*R*)-**5**
82% yield
99% *ee* (*syn*); 99% *ee* (*anti*)
dr (*syn*:*anti*) 3.9:1

(2*S*,3*R*)-**6**
94% yield
99% *ee* (*syn*); 96% *ee* (*anti*)
dr (*syn*:*anti*) 5.6:1

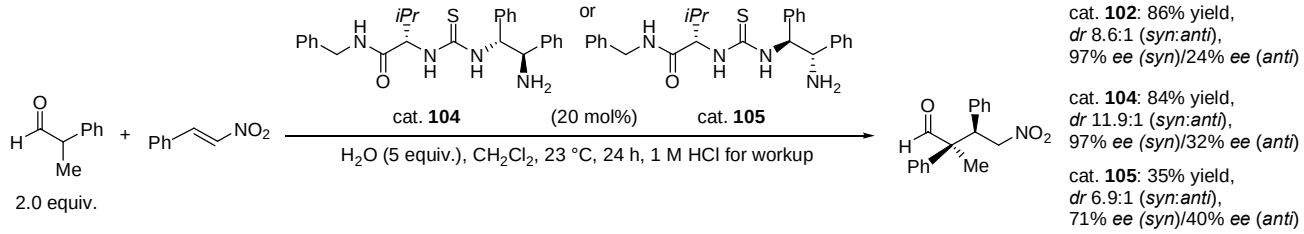
Scheme 103. Representative products provided from the **100**-catalyzed asymmetric Michael addition of α,α-disubstituted aldehydes to aliphatic and aromatic nitroalkenes.

To explain the mode of action of bifunctional thiourea catalyst **100** in the studied Michael reactions the authors proposed a catalytic cycle in which **100** initially formed an imine (**A**) through condensation with the aldehyde substrate. (Scheme 104) Tautomerization of the imine led to the preferred formation of the thermodynamically favored *E*-enamine (**B**) that was proposed to be responsible for the observed *syn*-diastereoselectivities. The double hydrogen-bonding activation of the nitroalkene via only one oxygen atom[264] allowed the enamine to attain sufficiently close proximity for the carbon-carbon bond forming nucleophilic attack (**C**) resulting in zwitterionic intermediate (**D**) typical for the conjugate addition of enamines to nitroalkenes. Intramolecular proton transfer followed by imine hydrolysis yields the desired Michael adduct and regenerates catalyst **100** to start a new cyclus (Scheme 104). The beneficial impact of water on catalyst turnover and yield, respectively, was especially ascribed to the acceleration of this final imine hydrolysis as well as to the initial imine formation (**A**) effecting the subsequent imine-enamine equilibrium. Too much water reduced the enamine formation and thus the product-forming steps as shown in the model Michael reaction(10 equiv. H_2O: 54% yield); in contrast, too less water hampered the release of the product and the catalyst (2.0 equiv. H_2O: 54% yield), while the ideal amount of H_2O (5 equiv.) gave 64% yield. The enantioselectivity (96% *ee*) and the diastereoselectivity (*dr* 10 :1 *syn*/*anti*) of this reaction appeared to be independent of the water amount.[266]



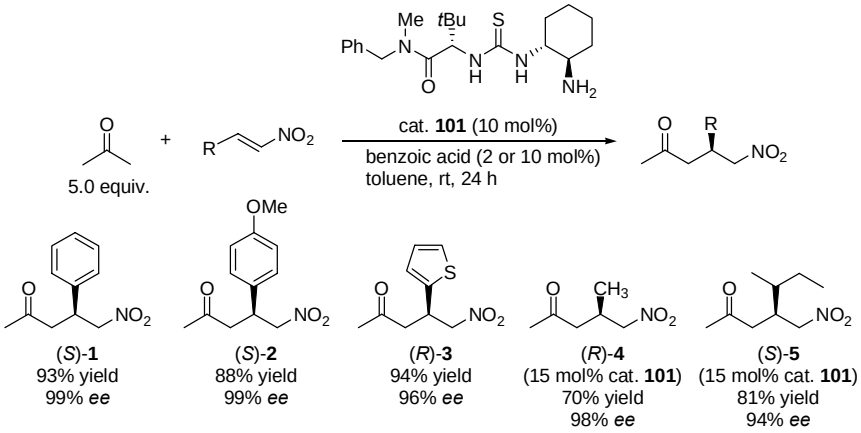
Scheme 104. Key intermediates of the proposed catalytic cycle for the **100**-catalyzed Michael addition of α,α-disubstituted aldehydes to aliphatic and aromatic nitroalkenes: Formation of imine (**A**) and *E*-enamine (**B**), double hydrogen-bonding activation of the nitroalkene and nucleophilic enamine attack (**C**), zwitterionic structure (**D**), product-forming proton-transfer, and hydrolysis.

The same group reported primary amine-functionalized diphenylethylene-thiourea derivatives **104** and **105** to catalyze the enantioselective and diastereoselective Michael addition of phenylpropionaldehyde to *trans*-β-nitrostyrene (Scheme 105).



Scheme 105. Asymmetric Michael addition of phenylpropionaldehyde to *trans*-β-nitrostyrene catalyzed by primary amine thioureas **102**, **104**, and **105**.

Primary amine thiourea derivative **101** bearing a tertiary amide functionality was found by Huang and Jacobsen to catalyze the enantio- and diastereoselective Michael addition of ketones to *trans*-β-nitrostyrenes at 10 mol% standard catalyst loading and in the presence of benzoic acid (2 to 10 mol%) in toluene.[267] As shown in Scheme 106 for the addition of acetone to various nitroalkenes this protocol reached synthetically useful yields (70%–94%) and excellent *ee* values (94%–99%) of the corresponding adducts **1**–**5**. Catalyst **101** was identified to show a strong bias for activation of ethyl ketones allowing highly regio-(up to *rr* 30:1) and *anti*-diastereoselective (up to *dr* 20.1) addition reactions of dialkyl ketones to β-alkyl and β-aryl nitroalkenes affording the respective Michael adducts in high enantioselectivities (86%–99%).[267]



Scheme 106. Typical product obtained from the Michael addition of acetone to *trans*-β-nitrostyrenes in the presence of catalyst **101**.

A bifunctional mechanism involving enamine catalysis[55, 58, 77] was clearly indicated in the Michael reactions promoted by catalyst **101**. The observed *anti*-diastereoselectivity suggested the participation of a *Z*-enamine intermediate (Figure 32) that provided the complementary diastereoselectivity obtained in analogous reactions involving *E*-enamines such as in **100**-catalyzed Michael reactions affording *syn*-adducts (Scheme 103).[266]

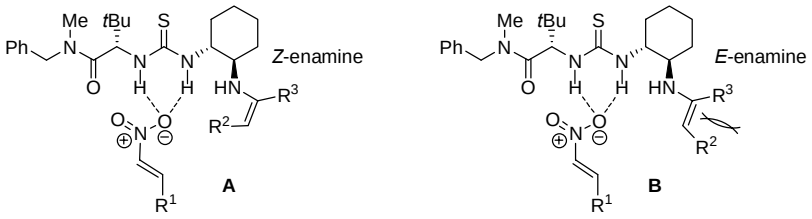
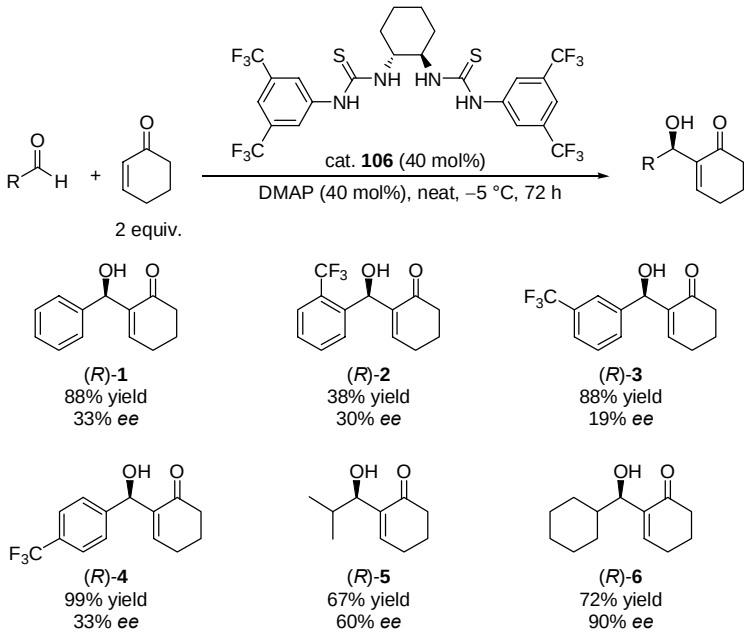
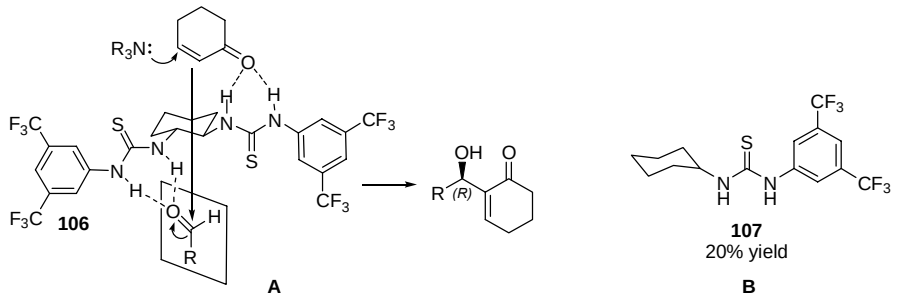


Figure 32. Proposed intermediates in the **100**-catalyzed Michael addition of ketones to nitroalkenes: Favored *Z*-enamine (**A**) and disfavored *E*-enamine (**B**).

Nagasawa and co-worker, in 2004, introduced the first bis-thiourea-type catalyst **106** to accelerate the DMAP-catalyzed asymmetric MBH reaction[179, 180] between cyclohexenone and selected aliphatic and aromatic aldehydes.[268] The catalyst was reported to be readily accessible as a crystalline solid from (*R*,*R*)-diaminocyclohexane and 3,5-bis(trifluoromethyl)phenyl isothiocyanate (2 equiv.) in a high-yielding (94%) one-step procedure. At –5 °C reaction temperature and in the presence of 40 mol% DMAP as base additive bis-thiourea **106** (40 mol%) converted predominantly CF_3-substituted benzaldehydes as well as cyclic and acyclic aliphatic aldehydes with 2-cyclohexen-1-one into the corresponding (*R*)-configured MBH allyl alcohols **1**–**6** (Scheme 107). The obtained yields (38%–99%/72 h) and enantioselectivities (19%–90% *ee*) varied strongly in dependence on the aldehyde substrate. Owing to the incorporation of two electron-deficient thiourea functionalities catalyst **106** was capable of providing twice double hydrogen-bonding interactions resulting in simultaneous activation of both electrophilic components the aldehyde and the enone as depicted in Scheme 108. Since the aldehyde and the enone were coordinated in mode such that the organic residue R of the aldehyde was located on the opposite side of the thiourea group interacting with the enone the carbon-carbon bond forming nucleophilc attack of the base-activated enone preferably afforded the (*R*)-MBH adduct (Scheme 108). The importance of bifunctionality in this tranformations was demonstrated by the use monofunctional thiourea **107** that displayed low catalytic activity (**107**: 20% yield; **106**: 88%) in the MBH reaction between benzaldehyde and 2-cyclohexen-1-one (Scheme 108).[268]

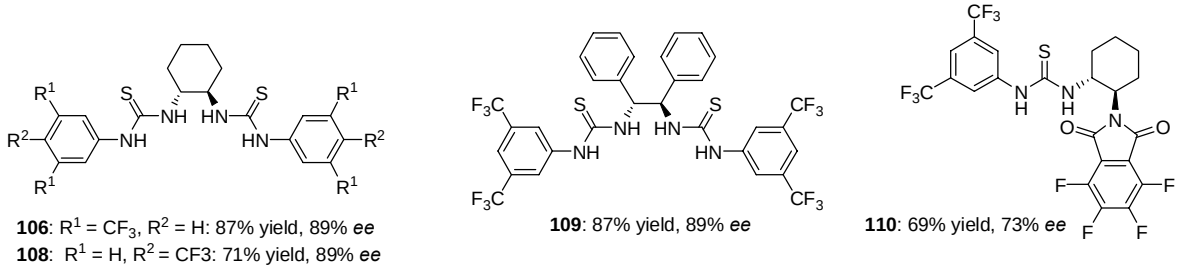


Scheme 107. Product range of the **106**-catalyzed asymmetric MBH reaction between aldehydes and 2-cyclohexen-1-one.



Scheme 108. Proposed mechanistic picture for the **106**-catalyzed MBH reaction affording (*R*)-adducts (**A**) and monofunctional thiourea **107** displaying low catalytic activity (**B**).

β-Amino carbonyl compounds containing an *α*-alkylidene group are densely functionalized materials, which are widely applied in the synthesis of medicinal reagents and natural products.[269] These products are usually prepared through the classic aza-Morita-Baylis-Hillman reaction[179, 180] of activated imines and electron-deficient alkenes catalyzed by tertiary amines or phosphines. Chen and co-workers, in 2008, identified bis-thiourea **106** as suitable catalyst for the asymmetric Mannich addition reaction[72] of stabilized phosphorus ylides to activated *N*-Boc-protected aliphatic and (hetero)aromatic aldimines.[270] Alternative thiourea catalysts such as bis-thioureas **108** and **109** as well as the imide-functionalized thiourea **110** turned out to be less efficient in the screening Mannich reaction with *N*-Boc-protected benzaldimine (Figure 33). Under optimized conditions (*m*-xylene, MS 4 Å; –20 °C; rt) bis-thiourea **106** promoted the nucleophilc P-ylide attack to various *N*-Boc-protected aldimines (Mannich reaction). The subsequent treatment of the Mannich adducts with formaldehyde at rt (Wittig reaction) gave access to the corresponding *N*-Boc-protected *β*-amino-*α*-methylene ethyl esters **1**–**6** in yield ranging from 37%–85% and in *ee* values ranging from 57%–96% (Scheme 109).

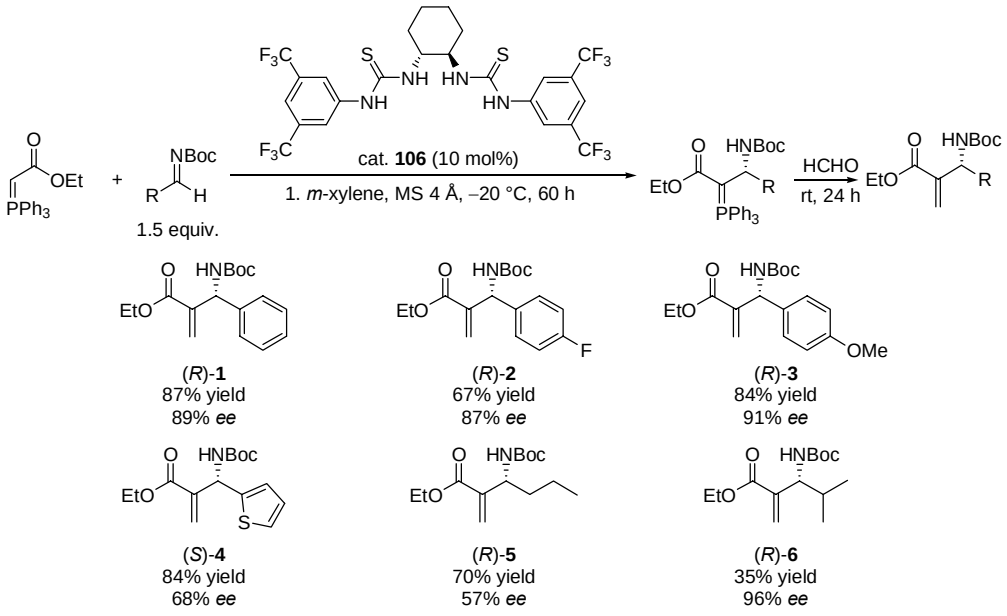


106: R^1 = CF_3, R^2 = H: 87% yield, 89% *ee*
108: R^1 = H, R^2 = CF3: 71% yield, 89% *ee*

109: 87% yield, 89% *ee*

110: 69% yield, 73% *ee*

Figure 33. Thiourea derivatives evaluated for catalytic efficiency in the Mannich addition of P-ylides to *N*-Boc-protected benzaldimine.



Scheme 109. Typical *N*-Boc-protected *β*-amino-*α*-methylene ethyl esters obtained from the **106**-catalyzed asymmetric Mannich reaction and subsequent Wittig reaction with formaldehyde.

The Berkessel group, in 2006, introduced novel bis-(thio)urea catalysts **111**, **112**, **113**, and **114** derived from isophosphoronediamine [3-(aminomethyl)-3,5,5-trimethyl cyclohexylamine, IPDA] for the enantioselective catalysis of the Morita-Baylis-Hillman reaction[179, 180] between aldehydes and 2-cyclohexen-1-one as well as 2-cylopenten-1-one.[271] IPDA is a readily available 1,4-diamine produced industrially on a multiton scale. IPDA and its derivative isophoronediisocyanate [5-isocyanato-1-(isocyanatomethyl)-1,3,3-trimethylcyclohexane, IPDI] are used as monomers for urethane and epoxy resins.[272] **111**–**114** were prepared in yields ranging from 60% and 85% (ureas) to 100% (thioureas) from IPDA and the respective iso(thio)cyanates in a straightforward one-step procedure. Catalyst evaluation (20 mol% loading) in the model MHB reaction between cyclohexanecarbaldehyde and 2-cyclohexen-1-one in the presence of DABCO as the nucleophilic promoter revealed bis-thiourea **114** bearing the privileged 3,5-bis(trifluoromethyl)phenyl thiourea moiety to be the most active (81% yield/ 72 h) and enantioselective (90% *ee*/10 °C) catalyst (Figure 34).

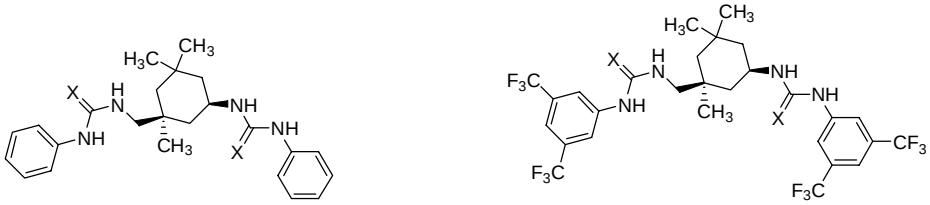
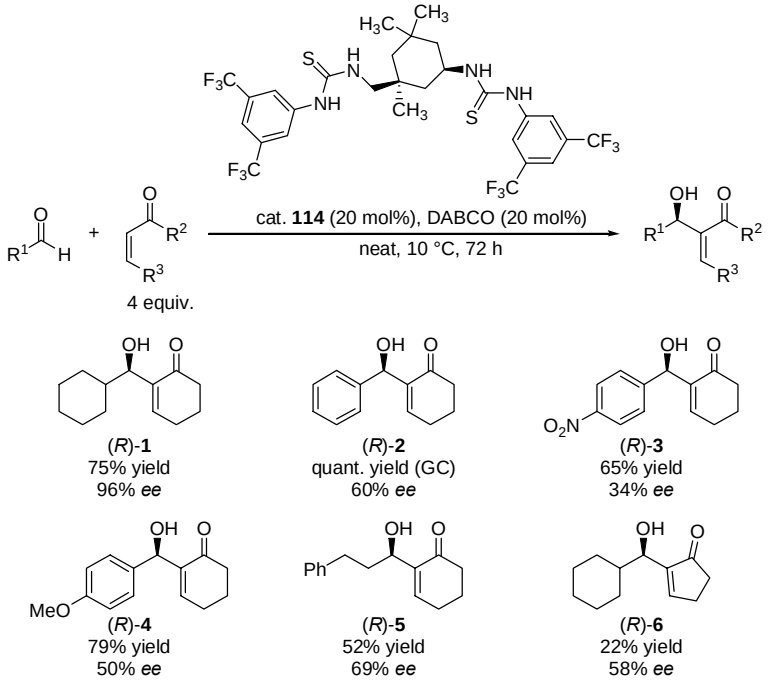


Figure 34. Bis-(thio)ureas **111**–**114** derived from IPDA and results of the screening in the DABCO-promoted MBH reaction between cyclohexanecarbaldehyde and 2-cyclohexen-1-one under neat conditions at 10 °C.

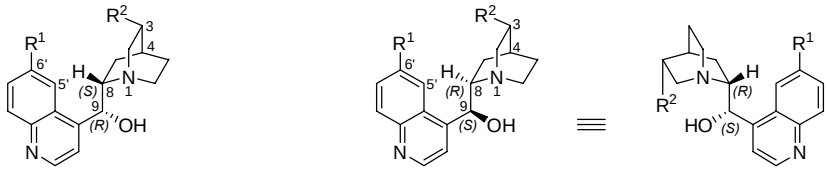
At 20 mol% loading of **114**, with DABCO (20 mol%), and under solvent-free conditions the desired MBH adducts **1**–**6** were obtained in very different yields (22%–100%) and enantioselectivities (34%–96%) (Scheme 110). Generally, aliphatic aldehydes gave higher *ee* values than aromatic aldehydes independent of the enone.



Scheme 110. Typical products of the **114**-catalyzed MBH reaction between various aldehydes and 2-cyclohexen-1-one as well as 2-cylopenten-1-one.

1.2.2.2 (Thio)ureas Derived from Cinchona Alkaloids

Naturally occurring cinchona alkaloids and numerous analogues have been widely utilized in a broad spectrum of organic transformations as chiral auxiliaries, as ligands for transition-metal catalysis, as phase-transfer catalysts, and as organocatalysts (Figure 35).[141, 273] Bredig and Fiske, in 1913, reported the first asymmetric organocatalytic reaction utilizing pseudoenantiomeric alkaloids quinine and quinidine as catalysts for the addition of HCN to benzaldehyde affording mandelonitrile in less than 10% *ee*.[274]



C3-(*R*), C4-(*S*) and **C8-(*S*)**, **C9-(*R*)**

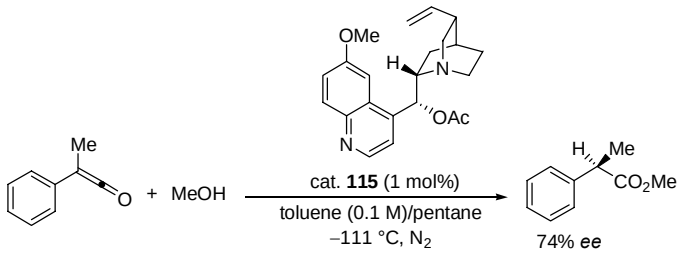
quinine (**QN**): R^1 = OMe, R^2 = vinyl
dihydroquinine (**DHQ**): R^1 = OMe, R^2 = Et
cinchonidine (**CD**): R^1 = H, R^2 = vinyl
cupreine (**CPN**): R^1 = OH, R^2 = vinyl

C3-(*R*), C4-(*S*) and **C8-(*R*)**, **C9-(*S*)**

quinidine (**QD**): R^1 = OMe, R^2 = vinyl
dihydroquinidine (**DHQD**): R^1 = OMe, R^2 = Et
cinchonine (**CN**): R^1 = H, R^2 = vinyl
cupreidine (**CPD**): R^1 = OH, R^2 = vinyl

Figure 35. Starting materials for the synthesis of (thio)urea functionalized cinchona alkaloids: The main cinchona alkaloids **QN**, **CD**, and their *pseudo*-enantiomers **QD** and **CN**, respectively, with opposite absolute configuration at the key stereogenic centers (N1, C8, C9) and identical absolute configuration in the quinuclidine fragment (C3, C4), the dihydrogenated derivatives **DHQ** and **DHQD** as well as the 6′-OH derivatives **CPN** and **CPD**.

The first synthetically useful levels of stereoinduction can be dated to 1960, when Pracejus systematically studied the addition of various alcohols such as methanol to phenyl ketene. In the presence of *O*-acetylquinine **115** as catalyst the respective (–)-α-phenyl methylpropionate was isolated in 74% *ee* in nearly quantitative yield (Scheme 111).[275]



Scheme 111. Synthesis of (–)-α-phenyl methylpropionate in the presence of *O*-acetylquinine as catalyst.

Wynberg and Hiemstra, in 1981, published pioneering research results on cinchona alkaloids as chiral nucleophilic catalysts for the enantioselective 1,2- and 1,4-addition reactions to cycloalkenones.[276] Unmodified natural quinine, quinidine, cinchonine, and cinchonidine were found to promote the Michael addition reactions of aromatic thiols to, e.g., cyclohexenone in higher rates and enantioselectivities (up to 75% *ee*) than their derivatives acylated at the C9-OH group. These results led to the proposal that cinchona alkaloids are bifunctional catalysts operating through a mechanism in which the cyclic enone and the attacking thiol nucleophile are simultaneously activated through hydrogen-bonding (OH group) and deprotonation (quinuclidine nitrogen), respectively, as visualized in Figure 36.[64]

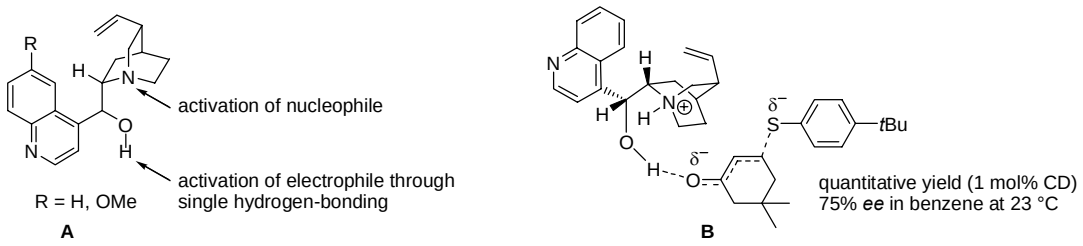


Figure 36. Bifunctionality of cinchona alkaloids (**A**) and Wynberg's proposal for the transition state of the cinchonidine-catalyzed Michael addition of 4-*tert*-butylthiophenol to 5,5-dimethyl-2-cyclohexenone (**B**).

In 2005, various groups independently realized the potential of the easily available cinchona alkaloids as chiral templates for the synthesis of the new class bifunctional hydrogen-bonding (thio)urea organocatalysts utilizing cinchona alkaloids (Figure 35). The cinchona alkaloid backbone incorporates both a basic quinuclidine moiety and a secondary alcohol function in a well-defined chiral environment and offers easy modulation for an improvement of the bifunctional character. The basic catalyst design results from Wynberg's original proposal[276] that the C9-OH group of cinchonine and cinchonidine participate in electrophile activation hydrogen-bond donation and also from Takemoto's bifunctional hydrogen-bonding amine-thiourea catalyst **12** (see also section 1.2.2.1),[131] which demonstrated the compatibility of the (thio)urea moiety with a Lewis basic site incorporated in one catalyst structure. Replacing the C9-OH group with a stronger hydrogen-bond donor moiety such as the privileged 3,5-bis(trifluoromethyl)phenyl-thiourea group furnishes cinchona alkaloid-derived (thio)ureas exhibiting in the most cases higher activities as well as selectivities than the unmodified cinchona alkaloids (Figure 37). This section presents the catalytically efficient bifunctional hydrogen-bonding (thio)urea-alkaloids in the chronological order of their literature appearance and separates principally into C9-(thio)ureas derived from cinchonidine, cinchonine, quinine, and quinidine; a few examples of alkaloids bearing the thiourea moiety at C6′-position are also considered (Figure 37).

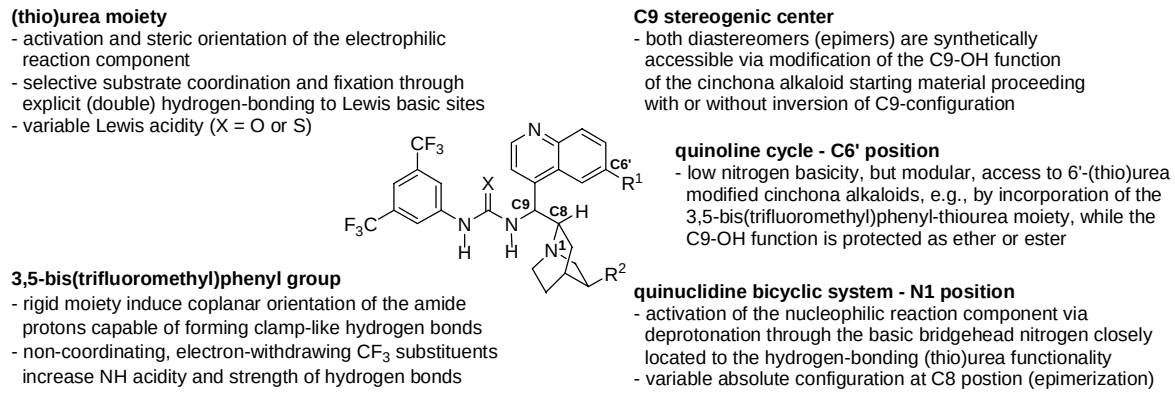
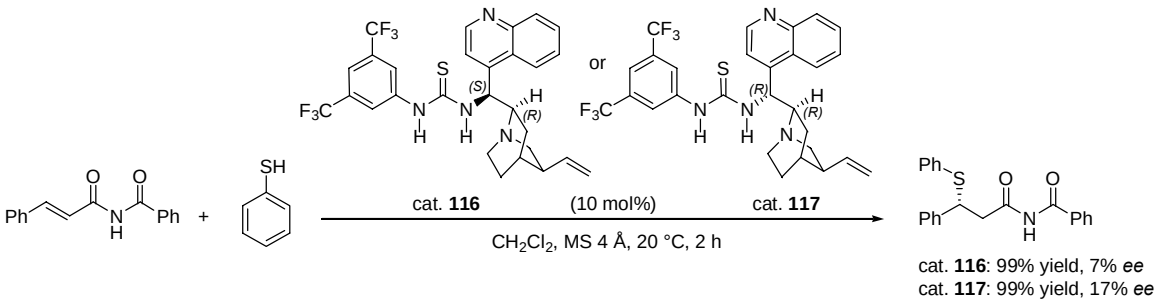


Figure 37. Design principles, functionalities, and characteristics of bifunctional H-bonding (thio)ureas derived from cinchona alkaloids.

The Chen group early in 2005 constituted the novel class of thiourea-functionalized cinchona alkaloids with the first reported synthesis and application of thioureas **116** (8*R*, 9*S*) and **117** (8*R*, 9*R*) prepared from cinchonidine and cinchonine in over 60% yield, respectively (Scheme 112).[277] In the Michael addition of thiophenol to an α,β-unsaturated imide the thioureas **116** and **117** displayed only poor stereoinduction (at rt **116**: 7% *ee*; **117**: 17% *ee*), but high catalytic activity (99% yield/2 h) (Scheme 112).



Scheme 112. Michael addition of thiophenol to an α,β-unsaturated imide catalyzed by cinchonidine-derived thiourea **116** and cinchonine-derived thiourea **117**, the first representatives of this class of bifunctional hydrogen-bonding cinchona alkaloid-thioureas.

Dixon et al. screened cinchonine-derived thioureas **117**, **118**, **119**, and **120** for their performance in the dimethyl malonate Michael addition to *trans*-β-nitrostyrene in dichloromethane at room temperature and at –20 °C.[278] As shown in Figure 38 all candidates revealed comparable activity, but monodentate hydrogen-bond donor **118** exhibited very low asymmetric induction affording the desired Michael adduct in only 8% *ee*. Derivative **117** was identified to be the most active (98% conv./40 h) and most selective (94% *ee*/–20 °C) catalyst.

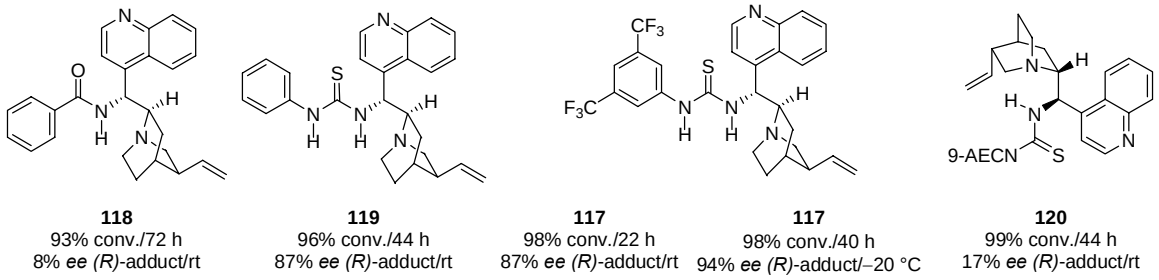
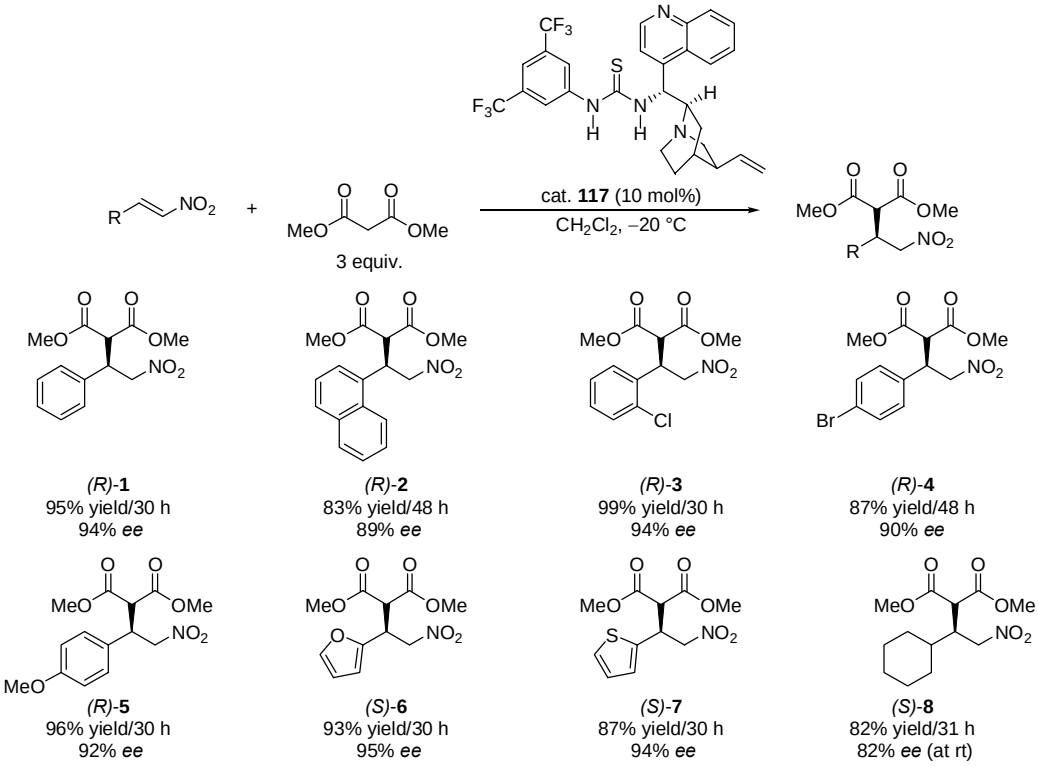
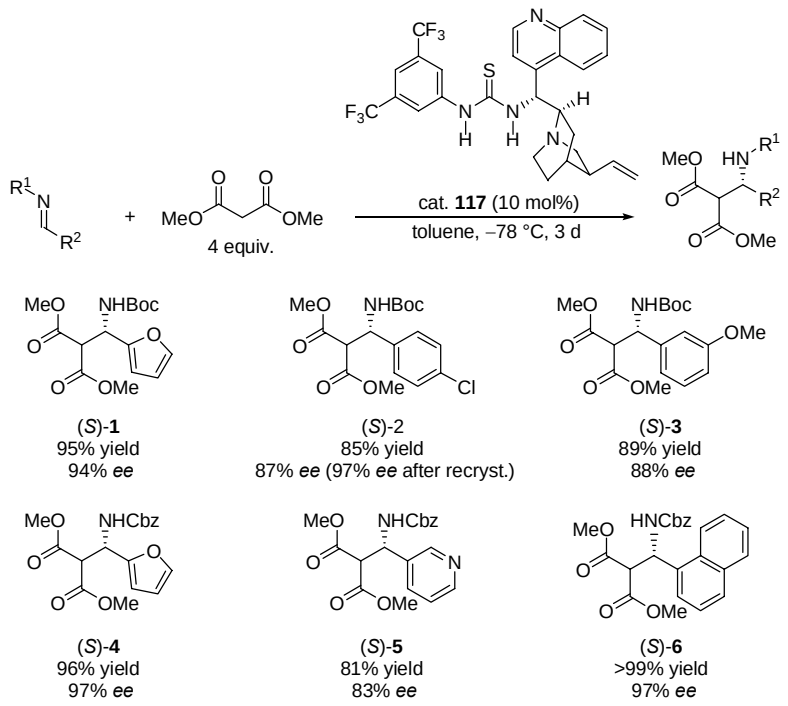


Figure 38. Cinchonine-derived thioureas (10 mol% loading) screened in the Michael reaction of dimethyl malonate to trans-β-nitrostyrene.



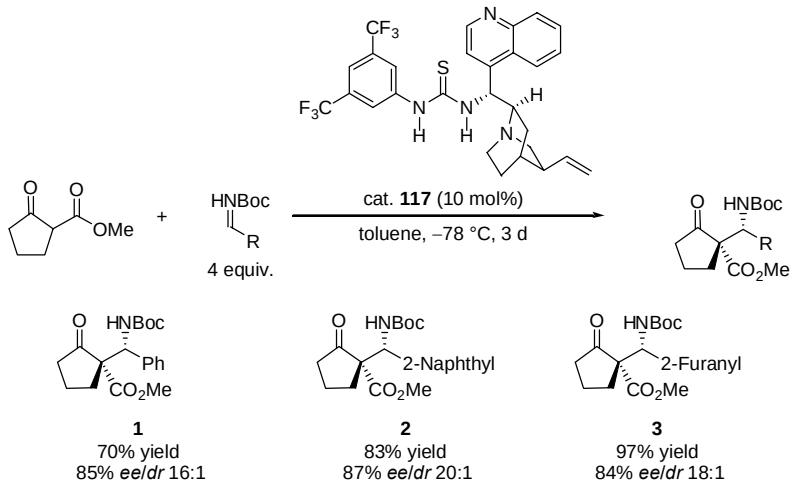
Scheme 113. Product range for the **117**-catalyzed Michael reaction of dimethyl malonate to various *trans*-β-nitrostyrenes.

The model reaction turned out to be independent of the choice of solvent, but due to solubilizing properties for substrates and products, the authors decided to study the Michael addition[151-154] of methyl malonates to various *trans*-β-nitroalkenes in dichloromethane. In the presence of 10 mol% of catalyst **117** at –20 °C aromatic and heteroaromatic substrates were converted to the corresponding Michael adducts **1**–**8** in good to excellent yields (83%–99%) and very good enantioselectivities ranging from 89%–95% after practical reaction times (30 h–48 h) as shown in Scheme 113. Aliphatic nitroalkenes as exemplified by the formation of adduct **8** reacted more slowly and gave lower *ee* values; in the case of R = *t*Bu no conversion was detected (Scheme 113). The Dixon group extended the application of *epi*-cinchonine-thiourea **117** to the direct enantio- and diastereoselective Mannich reaction[72] of dialkylmalonates and β-ketoesters with *N*-Boc- and *N*-Cbz-protected aldimines.[279] The optimizing experiments were performed for the addition of acetylacetone to *N*-Boc benzaldimine using toluene as the solvent. With 10 mol% **117** at room temperature the Mannich adduct was isolated in quantitative yield with 37% *ee*. Reducing the reaction temperature to –78 °C for 72 h gave the same adduct in 82% *ee*. *N*-Cbz-protected benzaldimine as model substrate was converted with acetylacetone to give the adduct in 73% yield and 86% *ee*. A range of malonates was investigated to determine potential nucleophiles; dimethyl malonate turned out to be the most reactive and afforded 99% yield and 89% *ee* in the reaction with *N*-Boc-protected benzaldimine in toluene at –78 °C. In dichloromethane under otherwise identical conditions the yield dropped to 76% (87% *ee*). The optimized protocol was applicable to a series of *N*-Boc- and *N*-Cbz-protected aromatic and heteroaromatic aldimines independent on the substituent pattern. Scheme 114 shows typical Mannich adducts **1**–**6** obtained after 3 d reaction time at –78 °C in the presence of catalyst **117** (10 mol%).



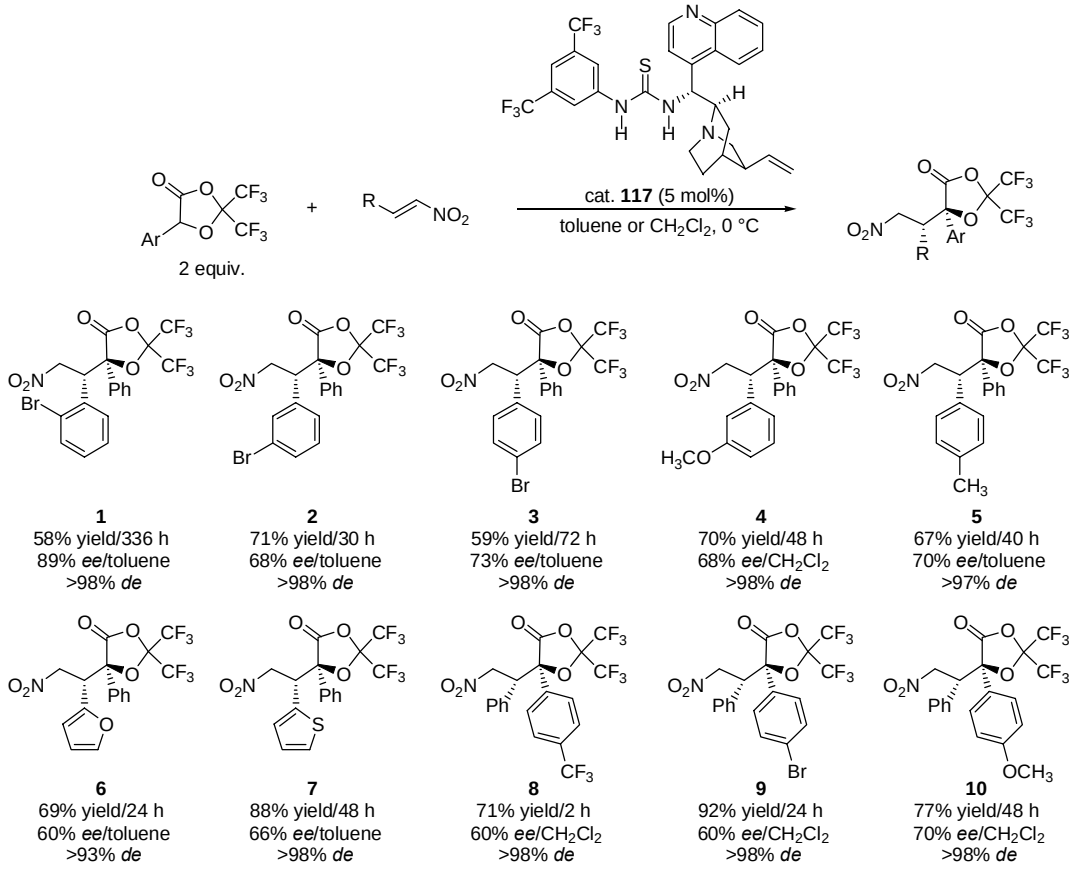
Scheme 114. Chiral Mannich adducts of the **117**-promoted reaction between dimethyl malonate and *N*-Boc as well as *N*-Cbz aldimines.

The construction of a quaternary α-stereocenters was demonstrated in the **117**-catalyzed Mannich addition[72] of methylcyclo-pentanone-2-carboxylate to *N*-Boc protected aromatic aldimines and furnished the adducts **1–3** in 70%–97% yield, with good *ee* values (85%–87%) and diastereoselectivities (Scheme 115). The authors exemplified the synthetic utility of the protocol by a simple racemization-free decarboxylation of the Mannich adduct of *N*-Boc benzaldimine and dimethyl malonate to obtain the respective *N*-Boc-protected β-amino ester (68% yield/89% *ee*/12 h at 160 °C), which are precursors of β-amino acids. Bifunctional hydrogen-bonding **117** also revealed catalytic efficiency in the enantio- and diastereoselective Michael addition reaction between 2,2-bis(trifluoromethyl)-substituted 5-aryl-1,3-dioxolan-4-ones, which are easily accessible from mandelic acid derivatives and hexafluoreacetone, and electron-rich as well as electron-deficient aromatic and heteroaromatic nitroalkenes.[280] The Dixon group identified this type of dioxolan-4-ones as new and efficient



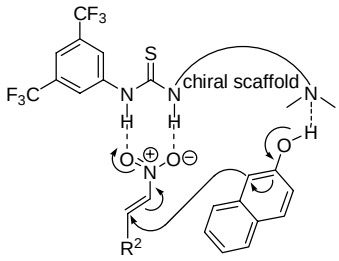
Scheme 115. Products of the **117**-catalyzed Mannich addition of methylcyclo-pentanone-2-carboxylate to *N*-Boc-protected aldimines.

prenucleophiles that were deprotonated by the basic quinuclidine nitrogen at the acidic benzylic α-position and gave the enolate attacking the *trans*-β-nitroalkene in the product-forming step. The optimized protocol allowed the Michael addition[151-154] of various enolizable dioxolan-4-ones to *trans*-β-nitroalkenes at 0 °C and 5 mol% loading of **117** affording the Michael products **1–10** in moderate (58%) to very good yields (92%), with moderate to good enantioselectivities (60%–89% *ee*), and very good diastereoselectivities (>93% *de*) (Scheme 116). The preferred (*R*)-configuration of the Michael adducts, already observed for the malonate addition (Scheme 113),[278] was confirmed by an efficient multi-step transformation of one example to its (*R*,*R*,*R*)-α-hydroxy acid derivative and subsequent X-ray analysis of the hydroxy acid crystals. This result supported the addition of the dioxolan-4-one nucleophile to the *re*-face of the *trans*-β-nitroalkene.



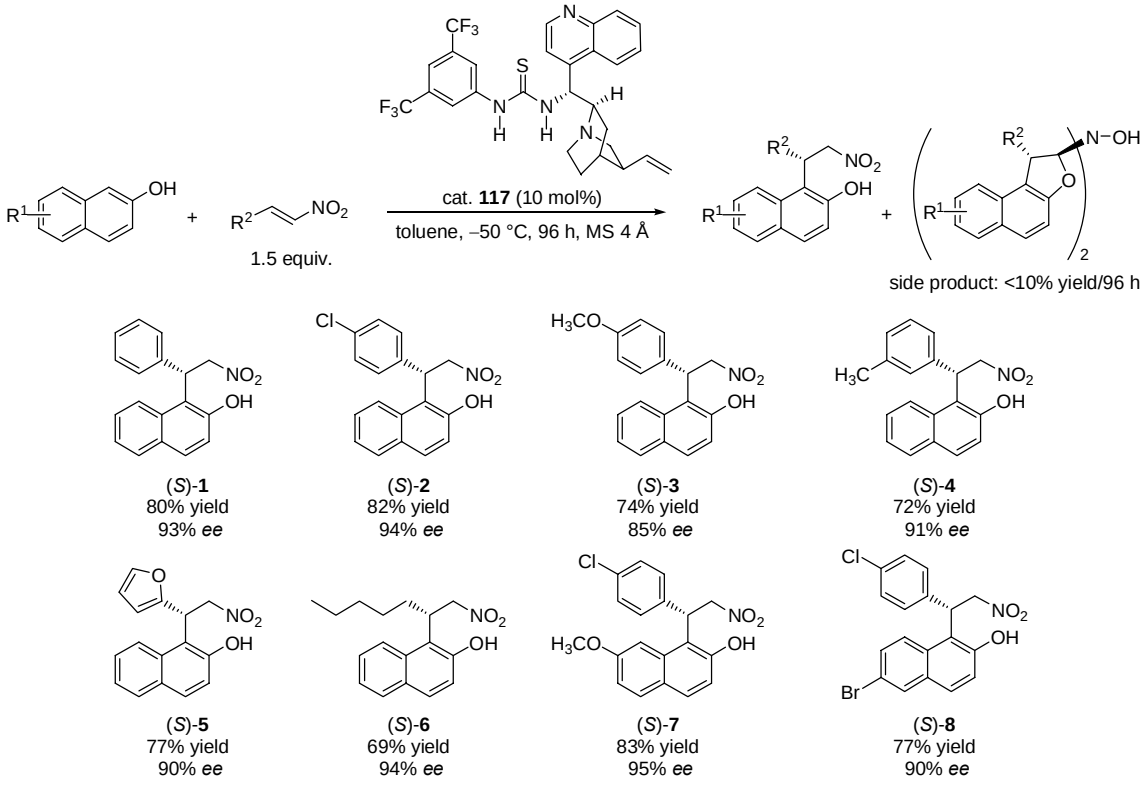
Scheme 116. Adducts of the **117**-catalyzed Michael reaction between 5-aryl-1,3-dioxolan-4-ones and various *trans*-β-nitroalkenes.

Chen and co-workers presented, in 2007, a Michael-type Friedel-Crafts reaction of 2-naphthols and *trans*-β-nitroalkenes utilizing the bifunctional activating mode of cinchonine-derived catalyst **117**.[281] The nitroalkene substrate was activated and sterically orientated by double hydrogen-bonding, while the tertiary amino group interacts with the naphthol hydroxy group to activate the naphthol for the nucleophilic β-attack at the Michael acceptor nitroalkene (Scheme 117).



Scheme 117. Proposed bifunctional activation of the reactants through catalyst **117** in the asymmetric Michael-type Friedel-Crafts alkylation of 2-naphthols.

Employing 10 mol% loading of **117** at –50 °C in toluene this Friedel-Crafts protocol allowed the synthesis of the products **1**–**8** in yields ranging from 69%–83% with good to very good *ee* values (85%–95%) (Scheme 118). The authors identified a dimeric tricyclic hydroxyl amine derivative as side product (yield <10%), when conducting the reaction at optimized conditions (96 h reaction time). Performing the Friedel-Crafts alkylation at longer reaction time (144 h) under otherwise unchanged conditions the side product became the major product in moderate yields (52%–67%) and with excellent stereochemical induction (99.5% *ee*; 99.5% *dr*).



Scheme 118. Products resulting from the **117**-catalyzed Michael-type Friedel-Crafts alkylation of 2-naphthols and observed side products.

The Soós group, in 2005, prepared the first thiourea derivatives from the cinchona alkaloids quinine **QN** (8*S*,9*R*-**121**), dihydroquinidine **DHQD** (8*S*, 9*S*-**122**), C9-*epi*-**QN** (8*S*, 9*R*-**123**), and quinidine **QD** (8*R*, 9*R*-**124**) via an experimentally simple one-step protocol with epimerization at the C9-position of the alkaloid starting material (Figure 39).[282] The catalytic efficiency of these new thiourea derivatives and also of unmodified **QN** and C9-*epi*-**QN** was evaluated in the enantioselective Michael addition[151-154] of nitromethane to the simple model chalcone 1,3-diphenyl-propenone resulting in adduct **1** in Scheme 119. After 99 h reaction time at 25 °C in toluene and at 10 mol% catalyst loading **QN** turned out to be a poor catalyst (4% yield/42% *ee*; (*S*)-adduct) and C9-*epi*-**QN** even failed to accelerate the screening reaction. In contrast, the C9-modified cinchona alkaloid thiourea **121** (8*S*, 9*S*) and its pseudoenantiomer **124** (8*R*, 9*R*) revealed catalytic activity (**121**: 71% yield; **124**: 59% yield) and selectivity (**121**: 95% *ee,* (*R*)-adduct **1**; **124**: 86% *ee,* (*S*)-adduct **1**). **DHQ**-derived thiourea **122** (8*S*, 9*S*) was identified to be the most active (93% yield) and selective (96% *ee*, (*R*)-adduct **1**) candidate (Figure 39). It is remarkable that C9-*epi*-**QN** derived thiourea **123** bearing the natural (8*S*, 9*R*)-configuration of the alkaloid turned out to be inactive in this reaction, while the C9-modified candidates **121**, **122**, and **124** with the unnatural C9-stereochemistry (C9-epimerized) exhibited conversion as well as stereoinduction.[283]

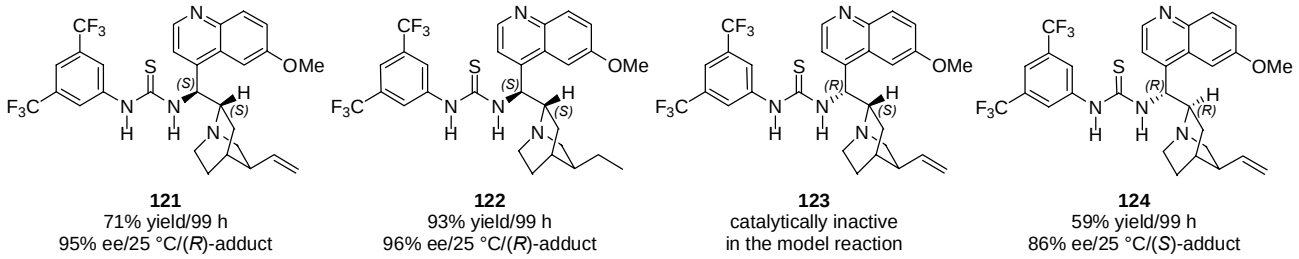
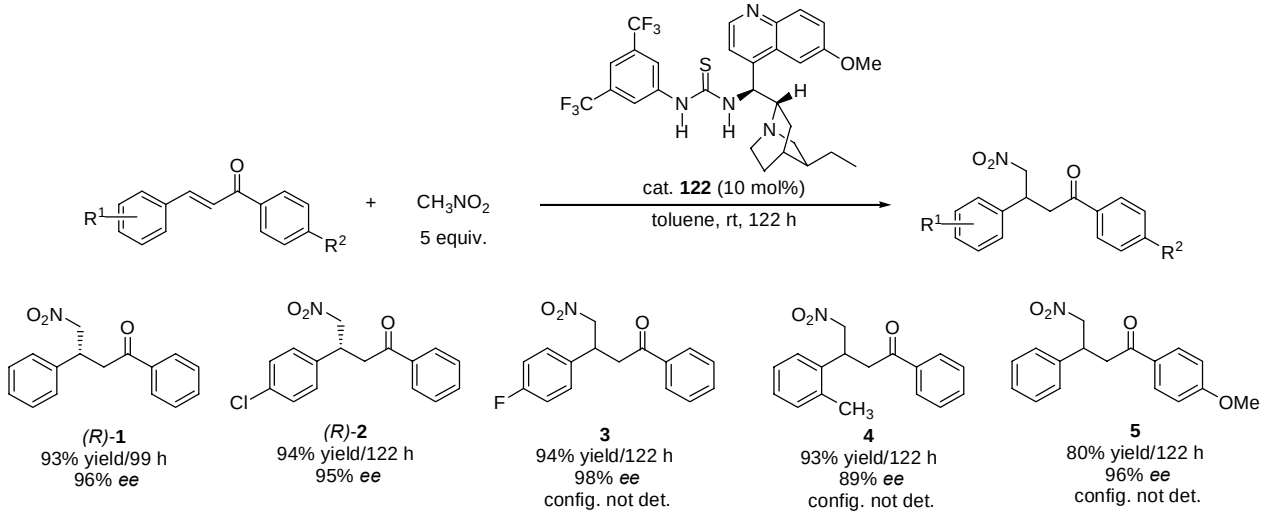


Figure 39. Cinchona alkaloid-thioureas prepared from quinine (**121**), dihydroquinine (**122**), C9-*epi*-quinine (**123**), and quinidine (**124**); catalytic efficiency evaluated in the Michael addition of nitromethane to *trans*-chalcone 1,3-diphenyl-propenone at 10 mol% loading and rt.

These findings strongly indicated that a well-defined relative stereochemical arrangement of the hydrogen-bonding thiourea moiety and the basic sites in cinchona alkaloid derived thioureas was an essential structural prerequisite to enable synergetic operation of these functionalities and thus for stereodifferentiating bifunctional catalysis. Additionally, it became evident from these results that the quinuclidine subunit of the cinchona alkaloids themselves was not able to facilitate the model reaction and that incorporation of the thiourea moiety drastically improved catalytic activity and selectivity. Under optimized reaction conditions (10 mol% loading; in toluene at 25 °C) thiourea **122** catalyzed the Michael additions of some electron-rich and electron-deficient chalcones providing the respective products **1**–**5** in synthetically useful yields (80%–94%) and very good *ee* values (95%–96%) as depicted in Scheme 119.



Scheme 119. Michael adducts from the asymmetric addition of nitromethane to *trans*-chalcones catalyzed by **122**.

Connon and McCooey shortly after the report published by the Soós laboratory[282] presented their independently performed investigations, which focussed on the catalytic efficiency of (thio)urea derivatives prepared from the dihydrogenated cinchona alkaloids dihydroquinine and dihydroquinidine (Figure 40).[283] The catalyst evaluation in the Michael addition[151-154] of dimethyl malonate to *trans*-*β*-nitrostyrene demonstrated the effect of the relative stereochemistry at the C8- and C9-position of these materials on the catalyst performance. Neither epimerization of dihydroquinine (C9-*epi*-**DHQ**: 46% conv./144 h/18 % *ee* at 5 mol% loading) nor substitution with an *N*-arylurea moiety (**125**: 26% conv./25% *ee*/24 h at 5 mol% loading) increased catalyst activity which dropped from 98% conv. to 26% conv. with a small increase of the stereoinduction from 12% *ee* to 25% *ee* in comparison to unmodified **DHQ** (Figure 40). The combination of both cinchona alkaloid modifications, however, resulted in more active and selective catalysts; urea C9-*epi*-**126** showed 98% conv. (88% *ee*) after 24 h and thiourea C9-*epi*-**122** 98% conv. (99% *ee*) after 30 h, respectively (Figure 40). This structure-efficiency relationship supported the results already published by the Soós group for quinine- and quinidine-derived thioureas (Figure 39).[282] C9-epimeric catalysts were found to be remarkably more efficient in terms of rate acceleration and stereoinduction than analogues of natural cinchona alkaloid stereochemistry. This trend was also observed for the corresponding (thio)ureas derived from **DHQD** as shown by the experimental results in Figure 40.[283]

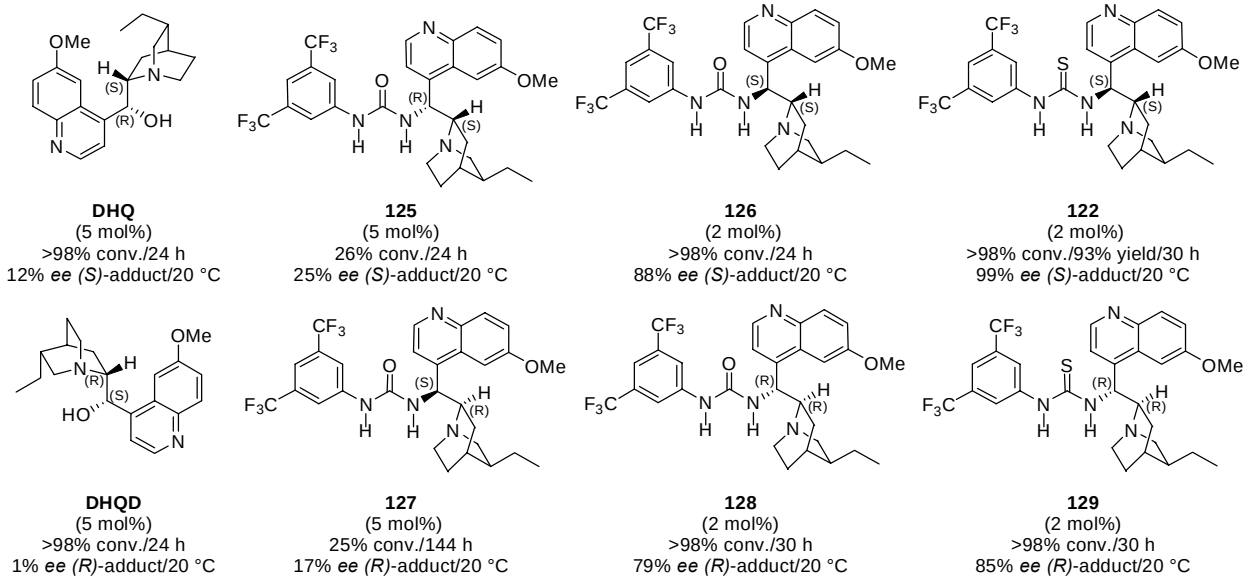
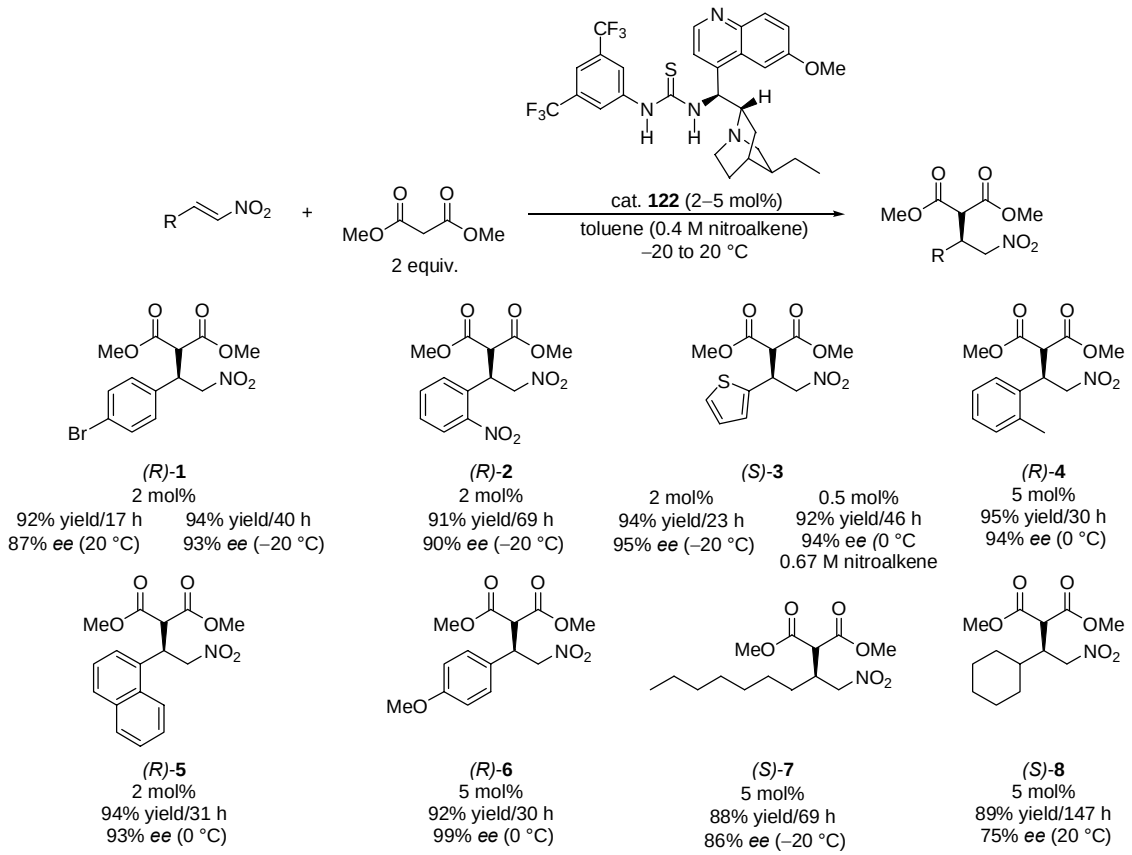


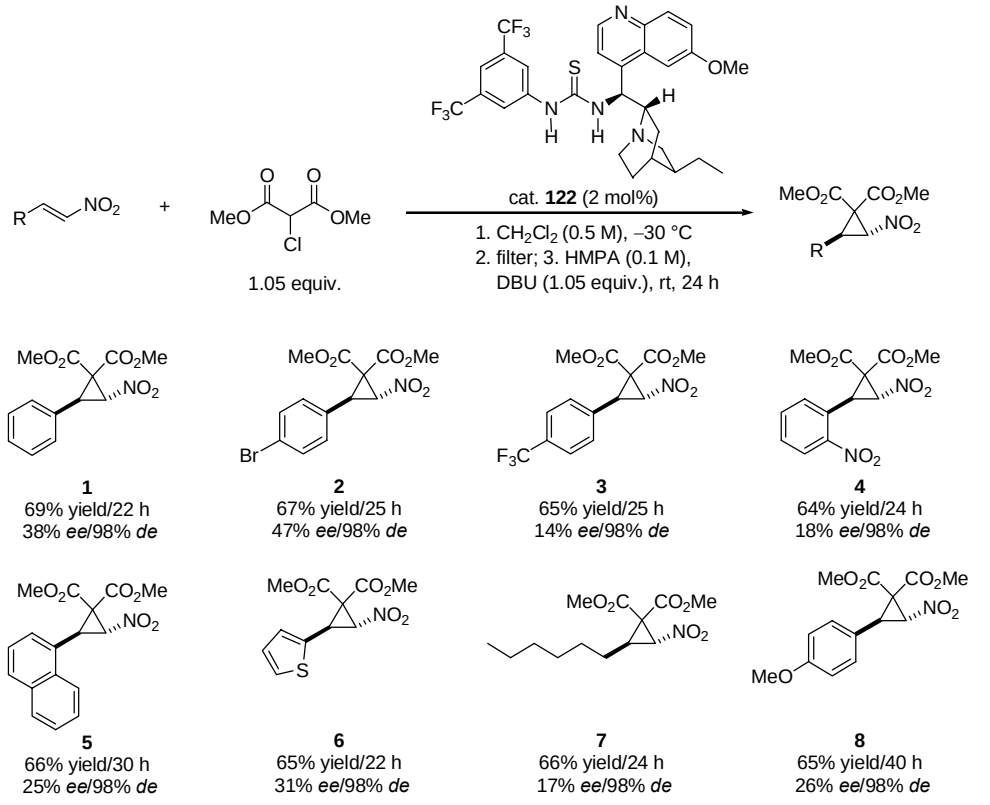
Figure 40. (Thio)urea catalysts derived from dihydroquinine and dihydroquinidine; screening results obtained from the asymmetric Michael addition of dimethyl malonate to *trans*-*β*-nitrostyrene.

In the presence of thiourea catalyst **122** the authors converted various (hetero)aromatic and aliphatic *trans*-*β*-nitroalkenes with dimethyl malonate to the desired (*S*)-configured Michael adducts **1**–**8**. The reaction occurred at low **122**-loading (2 mol%–5 mol%) in toluene at –20 to 20 °C and furnished very good yields (88%–95%) and *ee* values (75%–99%) for the respective products (Scheme 120). The dependency of the catalytic efficiency and selectivity on both the presence of the (thio)urea functionality and the relative stereochemistry at the key stereogenic centers C8/C9 suggested bifunctional catalysis, that is, a quinuclidine-moiety-assisted generation of the deprotonated malonate nucleophile and its asymmetric addition to the (thio)urea-bound nitroalkene Michael acceptor.[283]

In 2006, the Connon group reported a one-pot methodology for the stereoselective synthesis of highly functionalized nitrocyclopropanes.[284] This protocol utilized **DHQ**-derived thiourea **122**, which was introduced by Soós at al. (Figure 39),[282] to catalyze the initial Michael addition[151-154] of dimethyl chloromalonate to various *trans*-*β*-nitroalkenes followed by a DBU-mediated cyclization in the presence of HMPA as the solvent. At –30 °C and 2 mol% loading of **122** the reaction sequence proceeded highly diastereoselectively (98% *de*) and gave moderate to good yields (64%–69%) of the corresponding nitrocyclopropanes **1**–**8**; the *ee* values were low and ranged from 14%–47% as depicted in Scheme 121.

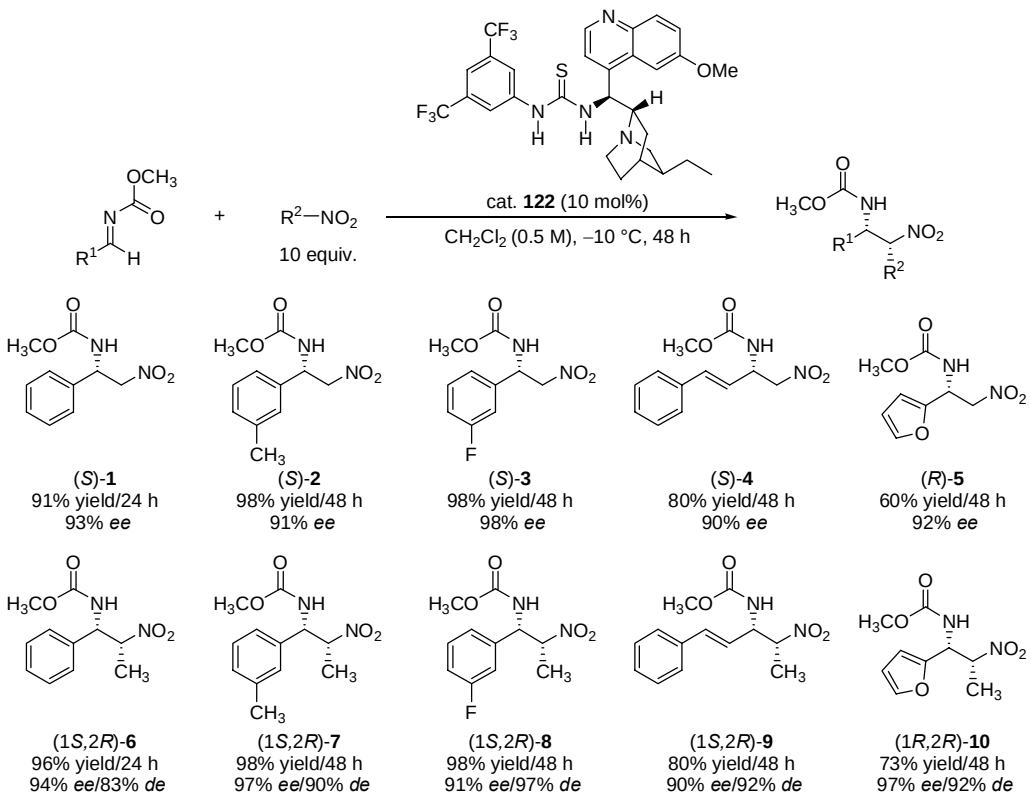


Scheme 120. Michael adducts prepared from the **122**-catalyzed asymmetric addition of dimethyl malonate to *trans*-β-nitroalkenes.

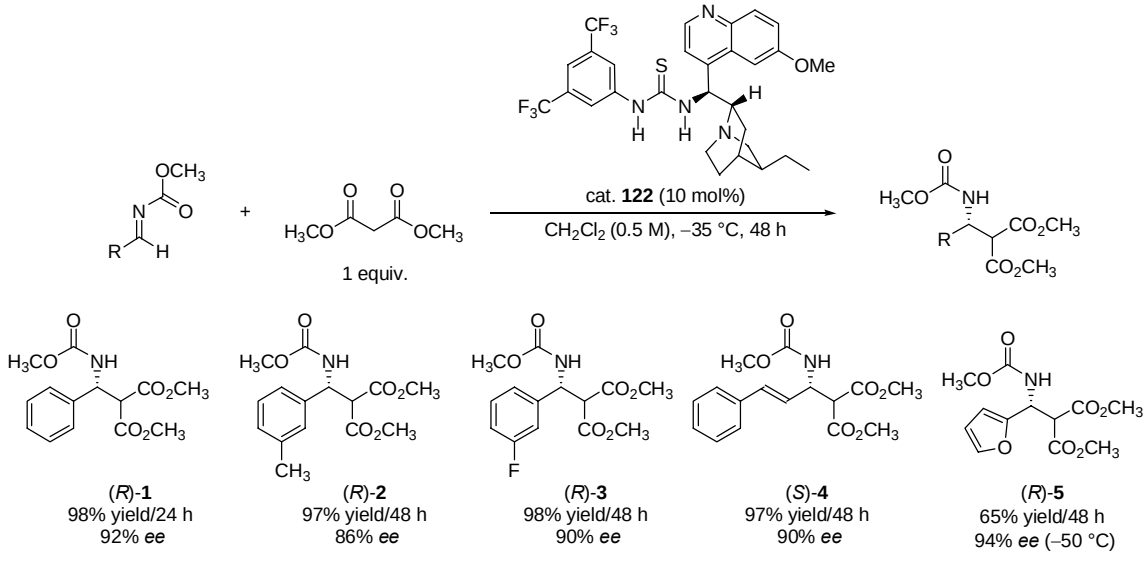


Scheme 121. Nitrocyclopropanes obtained from **122**-catalyzed Michael addition of dimethyl chloromalonate to *trans*-β-nitroalkenes and subsequent DBU-promoted cyclization.

In 2006, Schaus et al. identified acetyl-protected (hetero)aromatic aldimines as suitable substrates for the **122**-catalyzed asymmetric aza-Henry[228] (nitro-Mannich) additions[72] of nitromethane and nitroethane affording the corresponding *β*-nitroamines **1**–**10** in yields ranging from 60%–98% with enantioselectivities of 90%–98% and diastereoselectivities of 83%–97% (Scheme 122).[285] Replacing the nitroalkane with dimethyl malonate as alternative nucleophile a range of acylated (hetero)aromatic aldimines were enantioselectively (86%–94% *ee*) converted to the respective Mannich adducts **1**–**5** (65%–98% yield) under thiourea **122**-catalysis (Scheme 123). The authors also developed a new method for transforming the obtained Mannich adducts to the respective *β*-amino esters; as exemplified for adduct **1** in Scheme 123 microwave irradiation at 160 °C gave the corresponding ester in 80% yield and 85% *ee* after only 10 min reaction time.



Scheme 122. Products of the **122**-catalyzed aza-Henry (nitro-Mannich) addition of nitromethane and nitroethane to acylated aldimines.



Scheme 123. Spectrum of adducts of the **122**-catalyzed asymmetric Mannich addition of dimethyl malonate to acylated aldimines.

The utility of C9-*epi*-**DHQ** thiourea **122** for the catalysis of asymmetric Michael reactions[151-154] were further demonstrated, in 2006, by the Wang group.[286] The presented protocol tolerated a spectrum of enolizable species including dialkyl malonates, 1,3-diketone, ketoester, 1,3-dinitriles, and nitroesters to be added to the model *trans*-chalcone 1,3-diphenyl-propenone affording the desired Michael adducts in good to excellent yields (67%–99%) and with attractive *ee* values (88%–93%). Figure 41 shows some selected results of the nucleophile evaluation.

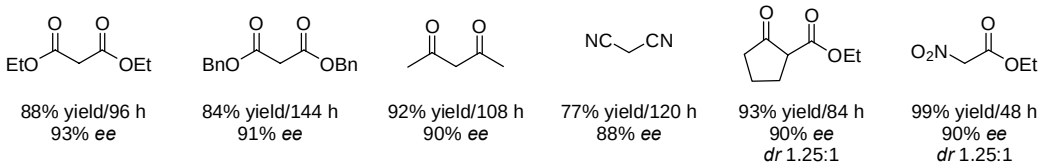
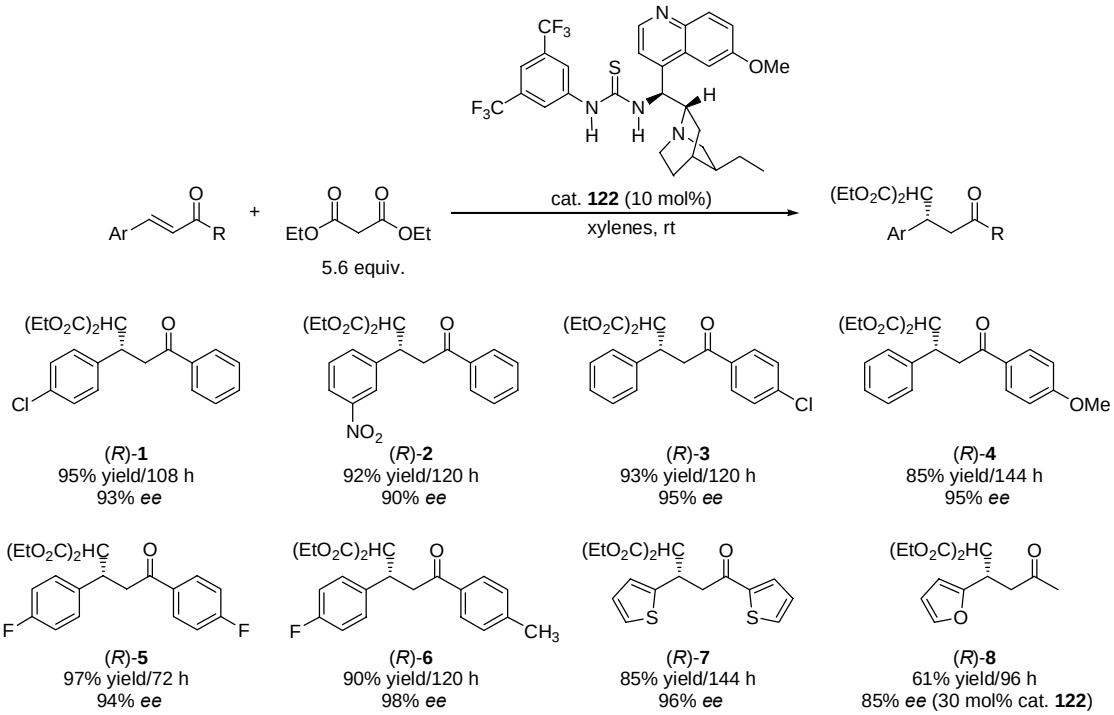


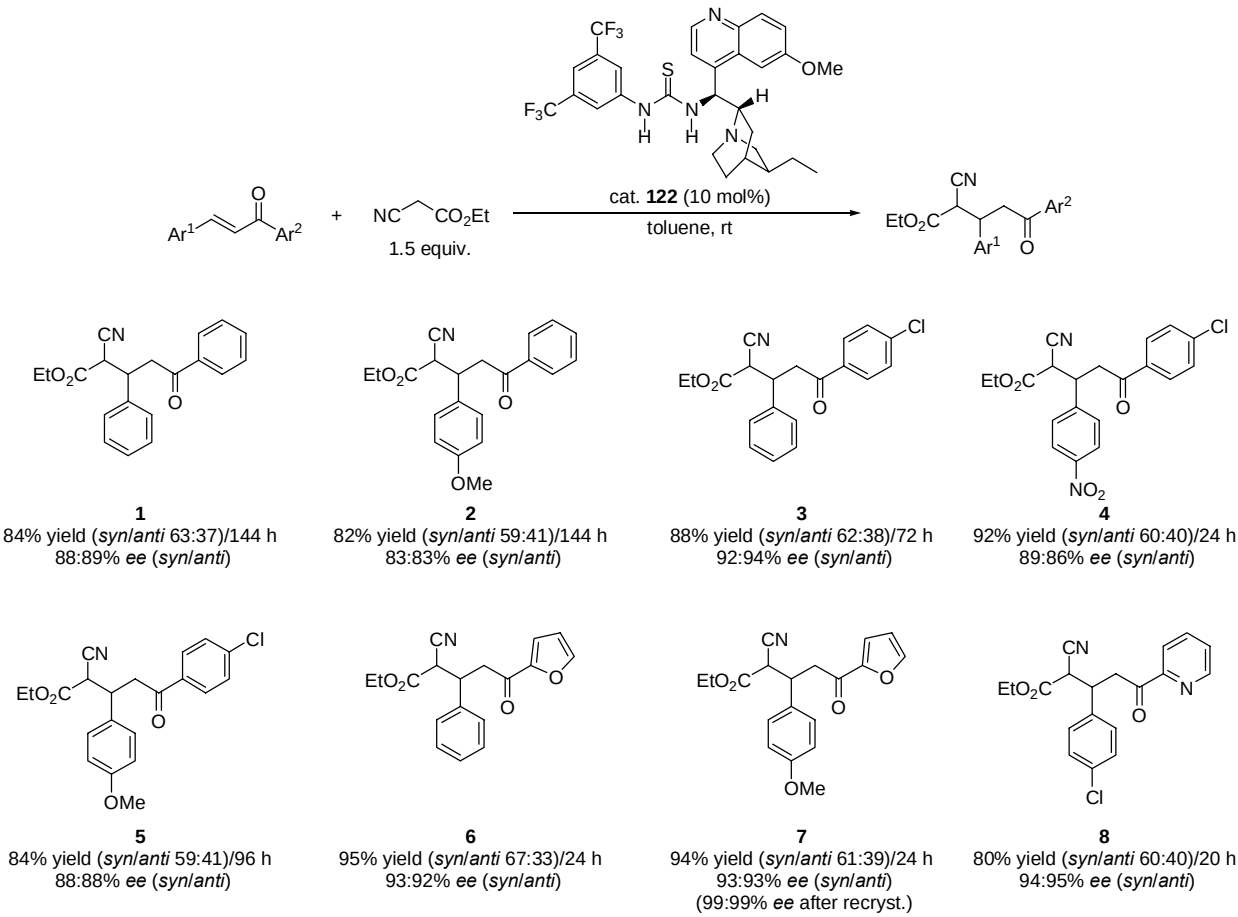
Figure 41. Enolizable compounds screened for the **122**-catalyzed asymmetric Michael addition to 1,3-diphenyl-propenone.

Diethyl malonate was found to be the most suitable nucleophile and was used to probe the scope and limitations of the catalyzed addition to various electron-rich and electron-deficient *trans*-chalcones. With optimized reaction parameters including the choice of bifunctional thiourea catalyst **122**, xylenes as reaction medium (e.g., THF: 40% yield; 81% *ee*; Et_2O: 35% yield; 53% *ee*; toluene: 86% yield; 90% *ee*), catalyst loading (10 mol%), and reaction temperature (rt) the reaction furnished the target adducts **1**–**8** in yield of 61%–97% and *ee* values ranging from 85%–98% (Scheme 124). Chalcones bearing a methyl group on the carbonyl unit proved to be less reactive and desired 30 mol% loading under otherwise unchanged conditions to be converted to the respective Michael adduct in reasonable reaction times.



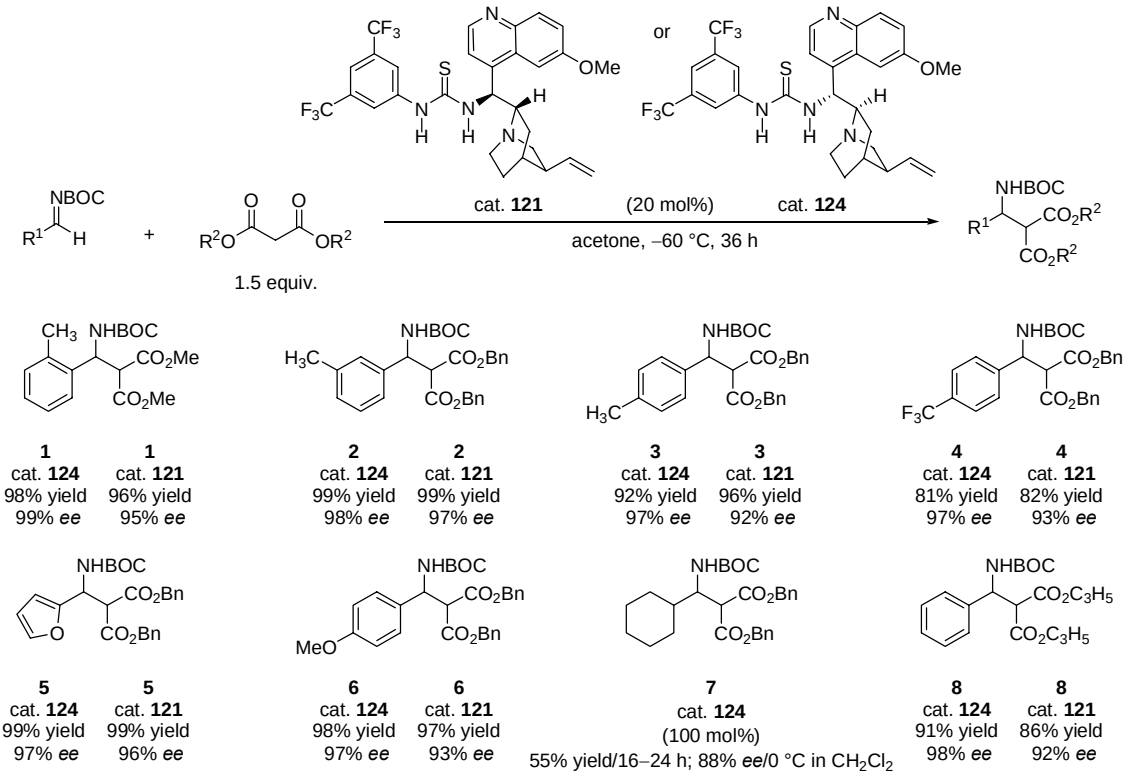
Scheme 124. Product range of the asymmetric Michael addition of diethyl malonate to various *trans*-chalcones promoted by **122**.

In 2007, Chen and co-workers reported the **122**-catalyzed (10 mol% loading) enantioselective Michael addition[151-154] of ethyl α-cyanoacetate to various electron-rich and electron deficient *trans*-chalcones.[287] The reaction was performed for a broad spectrum of chalcones and gave the corresponding adducts in yields of 80%–95% and in *ee* values of 83%–95%, but at low *syn*/*anti*-diastereoselectivities as shown for representative products **1**–**8** in Scheme 125.



Scheme 125. Typical products of the **122**-catalyzed enantioselective Michael addition of ethyl α-cyanoacetate to various chalcones. The product configurations were not determined.

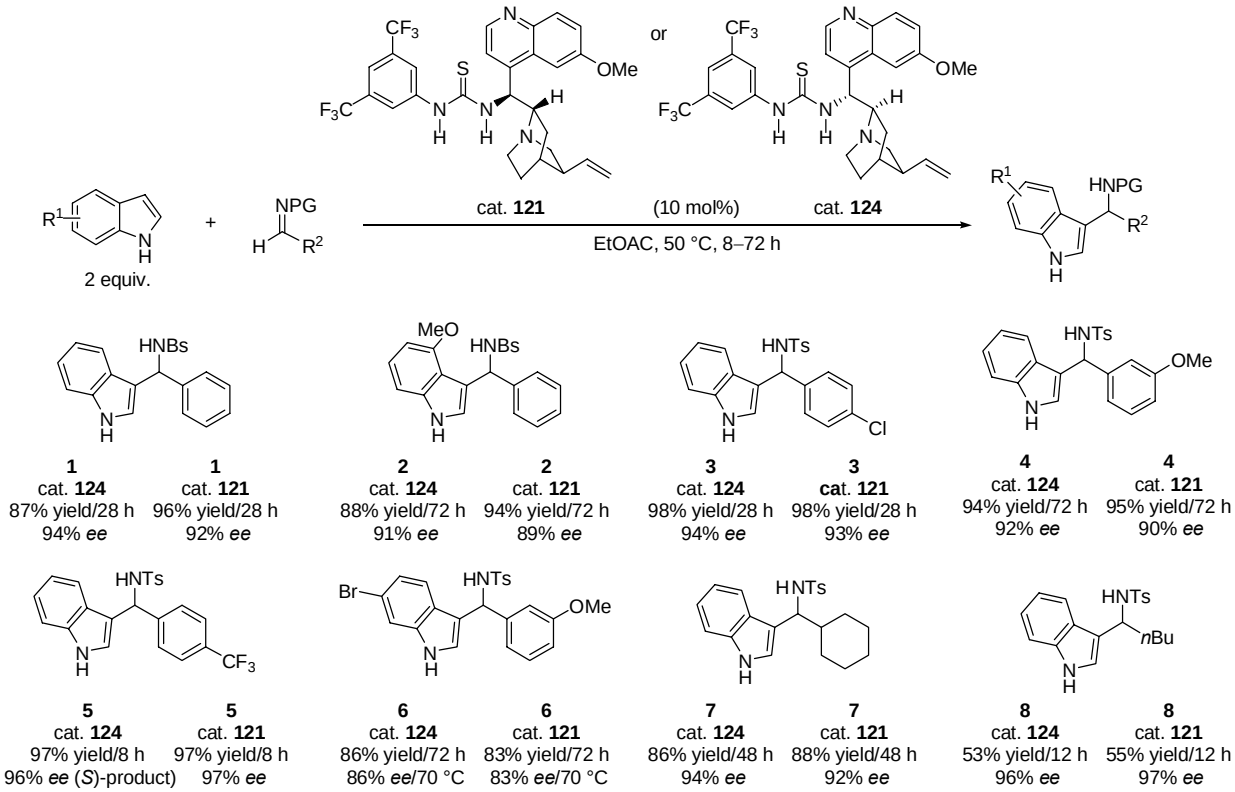
In 2006, Deng and co-workers identified **QN**-derived thiourea **121** and **QD**-derived thiourea **124**, which were already introduced by the Soós group for the Michael addition[151-154] of nitromethane to *trans*-chalcones (Figure 39),[282] to efficiently catalyze the enantioselective Mannich reaction[72] of *N*-Boc-protected (hetero)aromatic and aliphatic aldimines.[288] The choice of acetone as solvent at –60 °C reaction temperature resulted from the initial addition reaction of dimethyl malonate to the *N*-Boc-protected aldimine of 4-methyl-benzaldehyde. The optimized protocol utilizing thioureas **121** and **125** at 10 mol% loading was reported to be high-yielding (81%–99%, 36 h) and highly enantioselective (92%–99%) in the case of (hetero)aromatic substrates affording the respective Mannich adducts **1**–**8** depicted in Scheme 126. To sustain a useful level of enantioselectivity for α-branched *N*-Boc-protected aldimine substrates, e.g., the *N*-Boc-protected aldimine of cyclohexane carbaldehyde, the catalyst loading of **124** was increased to 100 mol%, however, **124** could be recycled in more than 95% yield after the reaction (Scheme 126). Since both catalysts **121** and **124** tolerated malonates of different bulk (Scheme 126) and also various β-ketoester as nucleophiles for the asymmetric Mannich addition to *N*-Boc-protected aldimines this protocol provided access to a wide variety of optically activeβ-amino ketones and β-amino acids, respectively.[288]



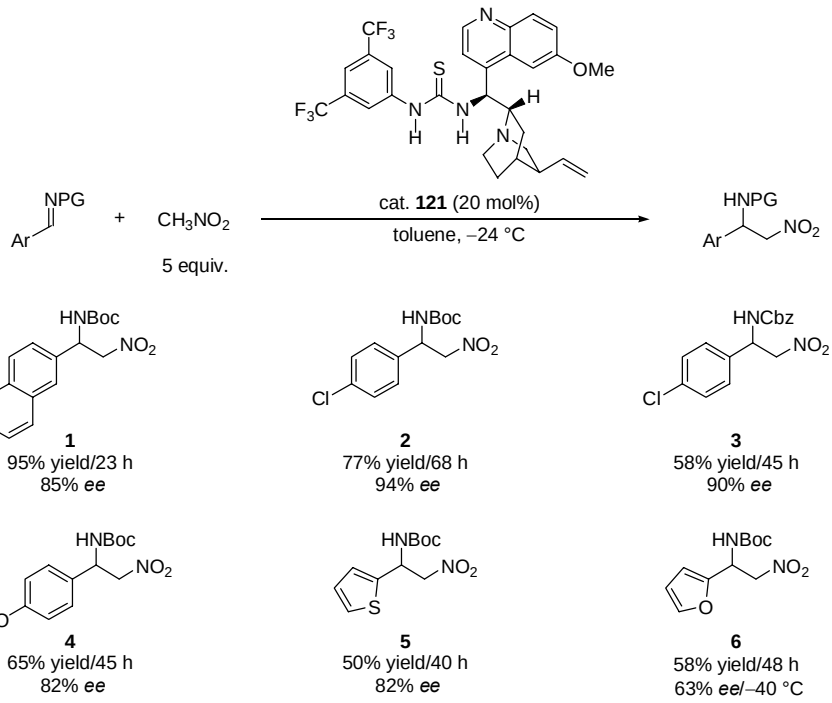
Scheme 126. Mannich adducts obtained from the **121**- and **124**-catalyzed asymmetric addition of dialkyl malonates to *N*-Boc aldimines. The product configurations were not determined.

The same group developed a methodology for the enantioselective Friedel-Crafts reaction between indols and *N*-protected aldimines to construct the 3-indolyl methanamine structural motif.[289] In the presence of 10 mol% of thiourea **121** or **124**, respectively, various indols reacted with brosyl(Bs)- and tosyl(Ts)-*N*-protected aromatic as well as aliphatic aldimines to give the corresponding Friedel-Crafts adducts **1**–**8** (Scheme 127) in yields ranging from 53%–98% and with high *ee* values (83%–97%), although the standard reaction temperature was remarkably high (50 °C). The stereoinduction was found to be insensitive to the electronic properties of the indole ring and to the *N*-protective group of the alkylating aldimines. Owing to the efficient selectivity of **121** and **124** even at increased temperature electron-deficient 6-bromo-1*H*-indole could be alkylated with an electron-rich *N*-tosyl aldimine giving the desired Friedel-Crafts adduct **6** in good yields (83%; 86%) and *ee* values (83%; 86%) (Scheme 127).

Ricci and co-workers published a protocol for the enantioselective aza-Henry reaction[228] of *N*-protected aldimines with nitromethane in the presence of C9-*epi*-quinine thiourea **121**.[8] The reaction was optimized for 20 mol% loading of **121** at –24 °C in toluene and converted preferably *N*-Boc-protected (hetero)aromatic aldimines to the desired *N*-protected *β*-nitroamine adducts **1**–**6** in moderate to very good yields ranging from 50%–95% and with synthetically useful levels of enantioselectivity (63%–94%). 2-Naphthaldehyde-derived imine (adduct **1**; Scheme 127) and benzaldimine derivatives bearing both electron donating and electron withdrawing substituents proved to be suitable substrates and the tolerance of the Cbz-group was exemplified by the formation of adduct **3** (58% yield; 90% *ee*; 48 h). Among the aromatic heterocyclic aldimines, the 2-thiophenecarboxyaldehyde derived imine (adduct **5**: 50% yield; 82% *ee*; 40 h) gave better results than its oxygenated analogue (adduct **6**: 58% yield; 53% *ee*; 48 h) (Scheme 128).

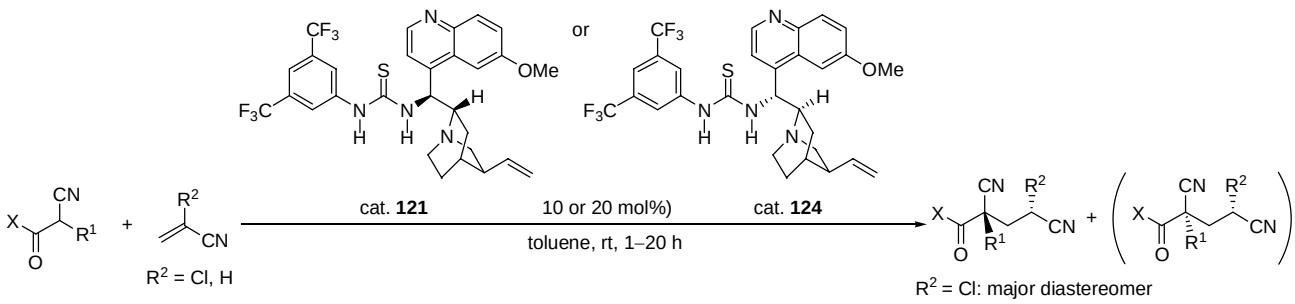


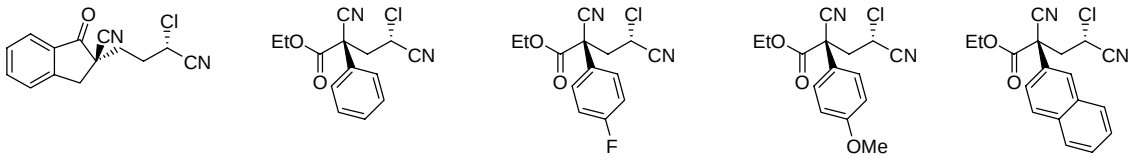
Scheme 127. Typical Friedel-Crafts adducts resulted from the **121**- and **124**-catalyzed alkylation of indols with *N*-protected aldimines. The configurations of the products were not determined.



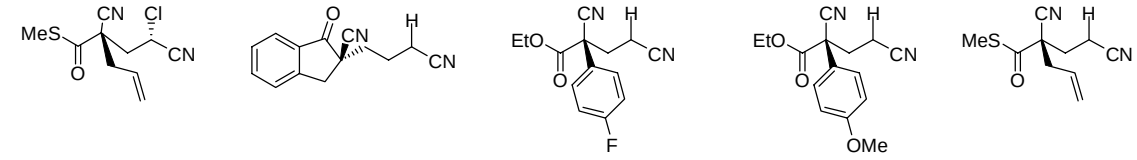
Scheme 128. Product range of **121**-catalyzed asymmetric aza-Henry reactions between *N*-protected aldimines and nitromethane. The configurations of the products were not determined.

QN-derived **121** and **QD**-derived **124** also proved catalytic efficiency as bifunctional hydrogen-bonding organocatalyst in the diastereoselective and enantioselective conjugate addition[151-154] of α-chloroacrylonitrile and acrylonitrile to a variety to cyclic α-cyanoketones and acyclic α-substituted cyanoesters as reported by Deng and co-workers, in 2007.[290] The reaction occurred at room temperature in toluene and gave the Michael adducts **1–10** in high diastereoselectivities (9–25:1 *dr*), enantioselectivities (88%–97% *ee*), and good (82%) to excellent (100%) yields (Scheme 129). This asymmetric tandem conjugate addition-protonation sequence allowed the stereoselective construction of 1,3-tertiary-quaternary stereocenters.





1 cat. **121** 99% yield 97% *ee* *dr* 10:1 — **1** cat. **124** 99% yield 97% *ee* *dr* 9:1 — **2** cat. **121** 98% yield 95% *ee* *dr* 15:1 — **2** cat. **124** 99% yield 95% *ee* *dr* 16:1 — **3** cat. **121** 98% yield 95% *ee* *dr* 13:1 — **3** cat. **124** 98% yield 95% *ee* *dr* 12:1 — **4** cat. **121** 99% yield 95% *ee* *dr* 13:1 — **4** cat. **124** 99% yield 95% *ee* *dr* 15:1 — **5** cat. **121** 100% yield 95% *ee* *dr* 14:1



6 cat. **121** 99% yield 95% *ee* *dr* 9:1 — **6** cat. **124** 98% yield 95% *ee* *dr* 10:1 — **7** cat. **121** 100% yield 93% *ee* — **8** cat. **121** 84% yield 88% *ee* — **8** cat. **124** 87% yield 90% *ee* — **9** cat. **121** 85% yield 90% *ee* — **10** cat. **121** 82% yield 91% *ee*

Scheme 129. Products prepared from the **121**- and **124**-catalyzed stereoselective Michael additions of α-chloroacrylonitrile and acrylonitrile to a variety to cyclic α-cyanoketones and acyclic α-substituted cyanoesters.

To interpret the stereochemical outcome of this tandem reaction the authors suggested a transition-state model, in which the bifunctional catalyst **121** interacted with the Michael donor and acceptor in a mode that the enolic Michael donor approached the acceptor from its *Si* face providing the observed adduct (Figure 42).

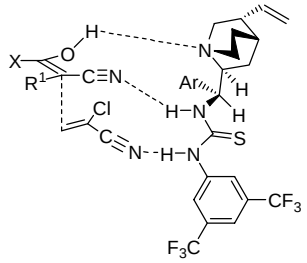
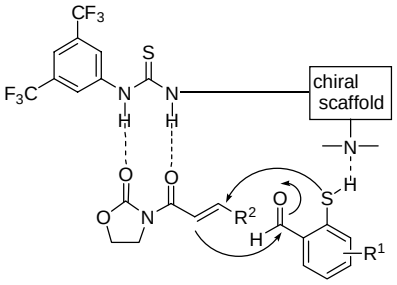


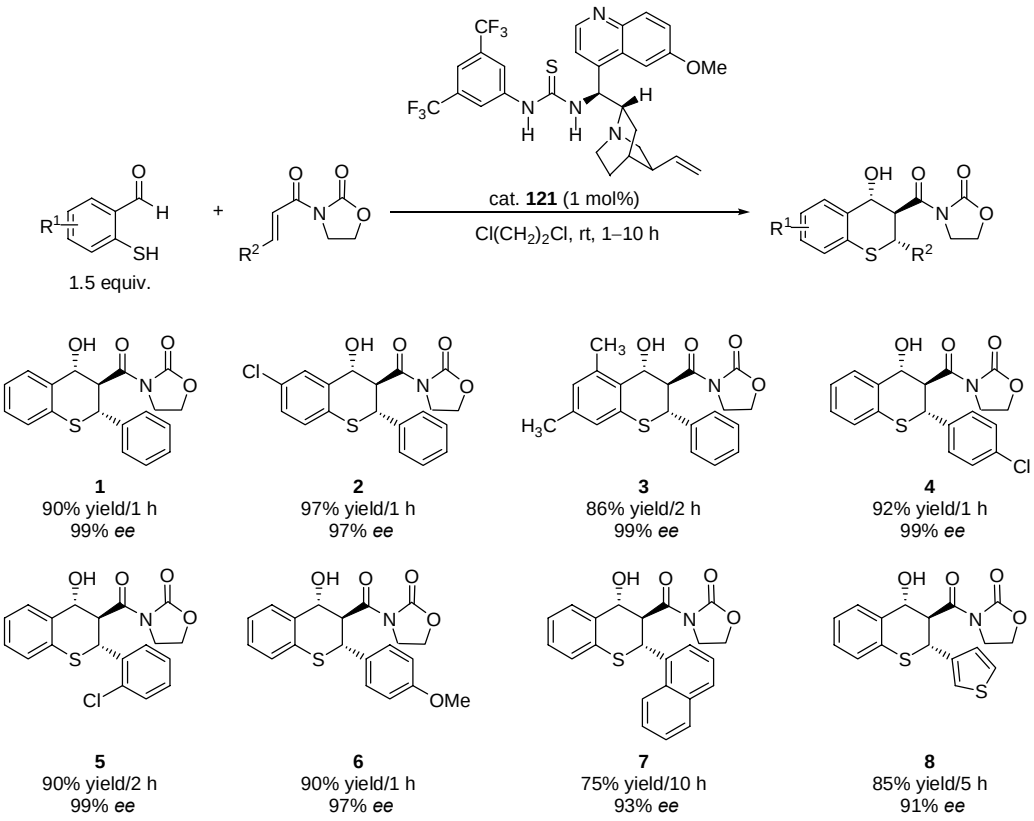
Figure 42. Transition-state model for the Michael addition of α-chloroacrylonitrile to cyclic α-cyanoketones or acyclic α-substituted cyanoesters; activation mode of quinine-derived thiourea **121**.

Chiral benzothiopyrans (thiochromanes) were prepared from 2-mercaptobenzaldehydes and α,β-unsaturated oxazolidinones via a one-pot method developed by the Wang group.[291] This asymmetric tandem thio-Michael-aldol process[151-154] utilized thiourea **121** as highly efficient catalyst (1 mol% loading) that bifunctionally activated both the oxazolidinone Michael acceptor through hydrogen-bonding and the 2-mercaptobenzaldehyde through deprotonation to induce the initial thio-Michael addition and the ring-forming aldol reaction (Scheme 130). It is noteworthy, that the proposed hydrogen-bonding interactions with bidentate oxazolidinones are not in line with the theoretical and experimental findings published by Schreiner and Wittkopp.[116]



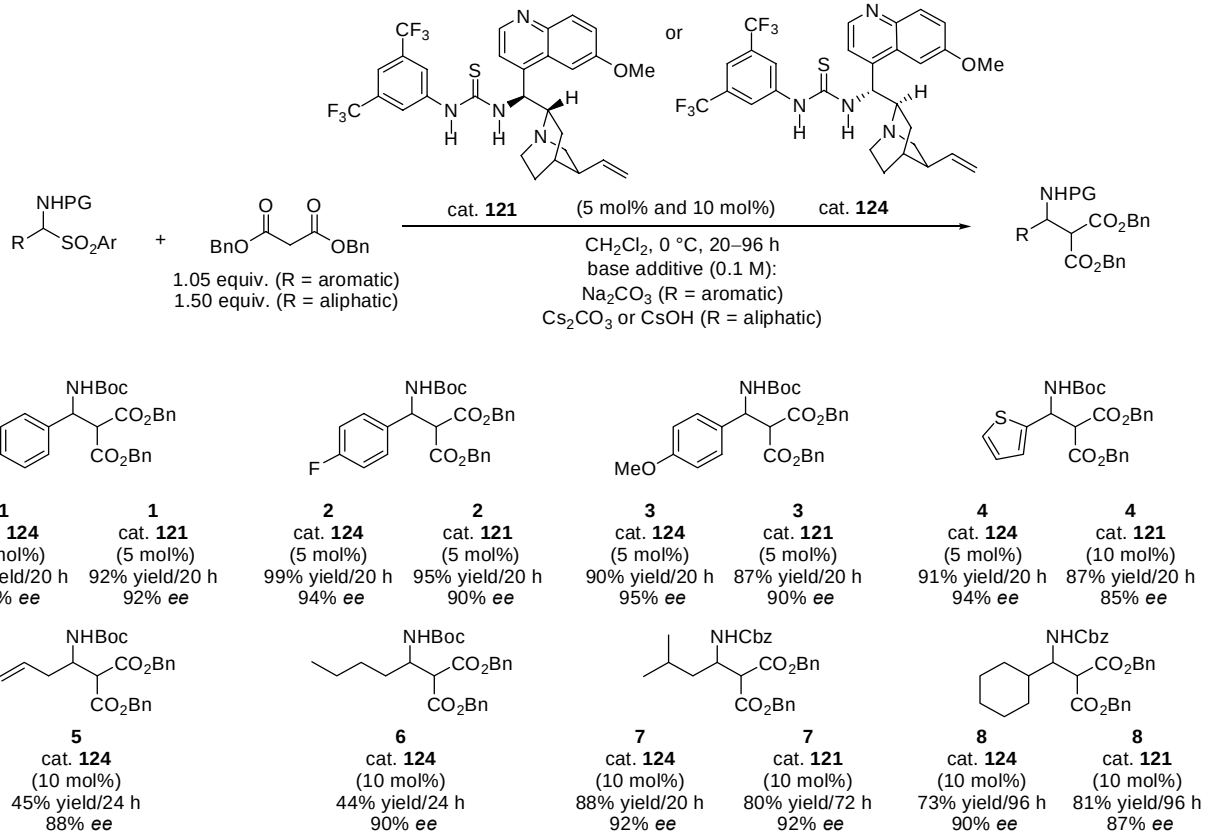
Scheme 130. Proposed mechanism of the **121**-catalyzed enantioselective thio-Michael-aldol tandem reaction of 2-mercaptobenzaldehydes with α,β-unsaturated oxazolidinones; bifunctional activation through thiourea **121**.

With established reaction parameters this tandem-process offered the facile synthesis of a range of substituted thiochromanes bearing three stereogenic centers. The reaction was reported to be high-yielding (75%–97%) and afforded the respective products **1**–**8** in excellent *ee* values (91%–99%) as well as in very good diastereoselectivities (20:1 *dr*) after short reaction times (1 h–10 h) in 1,2-dichloroethane; the electronic properties of the 2-mercaptobenzaldehydes and the steric nature of the α,β-unsaturated oxazolidinones had only minimal impact on the yields and the stereoinduction of this **121**-catalyzed transformation (Scheme 131).



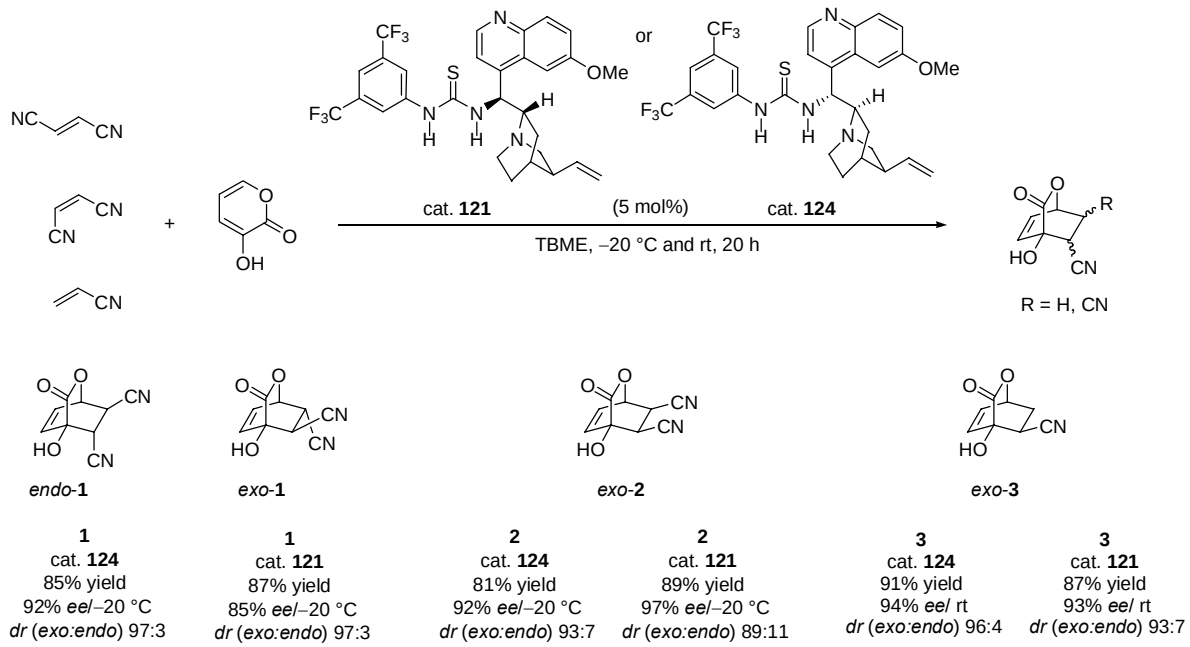
Scheme 131. Typical thiochromanes obtained from the **121**-catalyzed asymmetric thio-Michael-aldol tandem reaction between various 2-mercaptobenzaldehydes and α,β-unsaturated oxazolidinones.

On the basis of the **121**- and **124**-catalyzed enantioselective direct Mannich additions[72] of dialkyl malonates to *N*-Boc-protected (hetero)aromatic and aliphatic aldimines[288] (Scheme 126) Deng and co-workers developed a modified Mannich protocol starting from readily accessible and stable *N*-Boc- and *N*-Cbz-protected α-amido sulfones instead of using often unstable *N*-protected aldimines.[292] In the presence of an inorganic base additive (0.1 M aqueous solution: Na_2CO_3 for aromatic, Cs_2CO_3 or CsOH for aliphatic aldimines) *N*-Boc- and *N*-Cbz-protected α-amido sulfones derived from (hetero)aromatic and aliphatic aldehydes **121** and **124** (5 mol% and 10 mol%) catalyzed the asymmetric Mannich addition to the in situ generated *N*-Boc and *N*-Cbz aldimines. This one-pot strategy avoided the handling of Cbz-protected aldimines as unstable starting materials and furnished the desired Mannich adducts **1**–**8**, which are precursors for optically acive β-amino acids, in yields of 45%–99% and *ee* values ranging from 85%–96% (Scheme 132). The stereoinduction of the catalysts **121** and **124** proved to be complementary to each other and afforded the respective opposite enantiomer.[292]

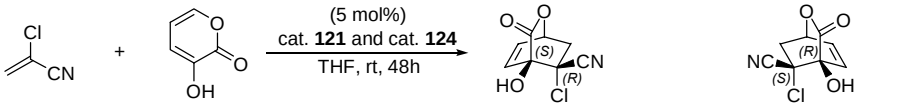


Scheme 132. Representative Mannich adducts obtained from the base-catalyzed in situ generation of *N*-protected aldimines from *N*-Boc- and *N*-Cbz-protected α-amido sulfones and subsequent **121**- and **124**-catalyzed addition of dibenzyl malonate. The product configurations were not determined.

The Deng group identified **QN**-derived thiourea **121** and **QD**-derived thiourea **124** to be also efficient promoters of enantio- and diastereoselective Diels-Alder reactions between the 2-pyrone diene 3-hydroxypyran-2-one and the dienophiles fumaronitrile, maleonitrile as well as acrylonitrile, while various C9-hydroxy acylated and alkylated (dihydro)cupreines and (dihydro)cupreidines failed for the same reactions under identical conditions (e.g., 97% yield, 15% *ee*, 64:36 *endo*:*exo*).[293] Catalysts **121** and **124** (5 mol% loading), however, afforded the corresponding Diels-Alder adducts **1**–**3** with synthetically useful enantioselectivities (85%–97%), diastereoselectivities (up to 96:4 *exo*:*endo*), and yields (87%–91%), when performing the transformation at –20 °C in TBME (Scheme 133). The tolerance of dienophiles bearing either *E*- or *Z*-double bonds was illustrated by the successful conversion of fumaronitrile and maleonitrile, respectively. The *exo*-stereoselectivity of both C9-thiourea functionalized alkaloids **121** and **124** became evident from the Diels-Alder reaction between α-chloroacrylonitrile and 3-hydroxypyran-2-one, which afforded the adducts in high yields (91%; 93%) and stereoselectivities (89% *ee*; *dr* 93:7 and 85% *ee*; *dr* 91:9) as depicted in Scheme 134. In contrast, various C9-modified **CPN** and **CPD** (5 mol% in Et_2O), respectively, were found to be complementary to the thiourea catalysts (**121**; **124**) and provided the respective *endo*-diastereomers in up to 90% yield, 85% *ee*, and *dr* 87:13.



Scheme 133. Adducts of the **121**- and **124**-catalyzed stereoselective Diels-Alder reactions between the 3-hydroxypyran-2-one and the dienophiles fumaronitrile, maleonitrile, and acrylonitrile.

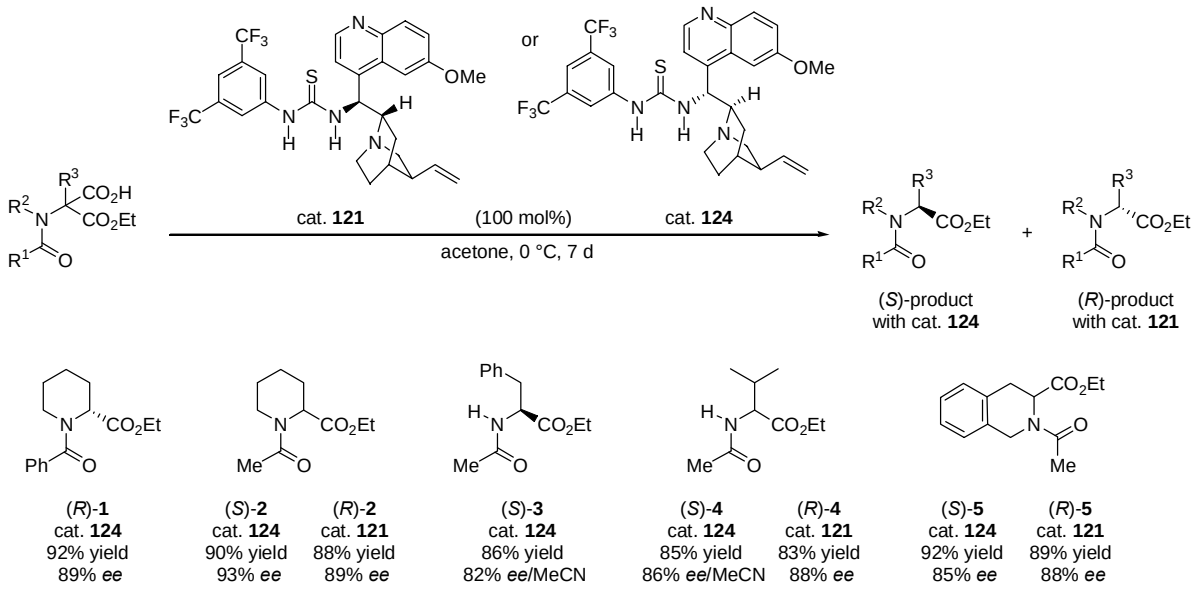


Scheme 134. *Exo*-selective **121**- and **124**-catalyzed Diels-Alder reaction between α-chloroacrylonitrile and 3-hydroxypyran-2-one.

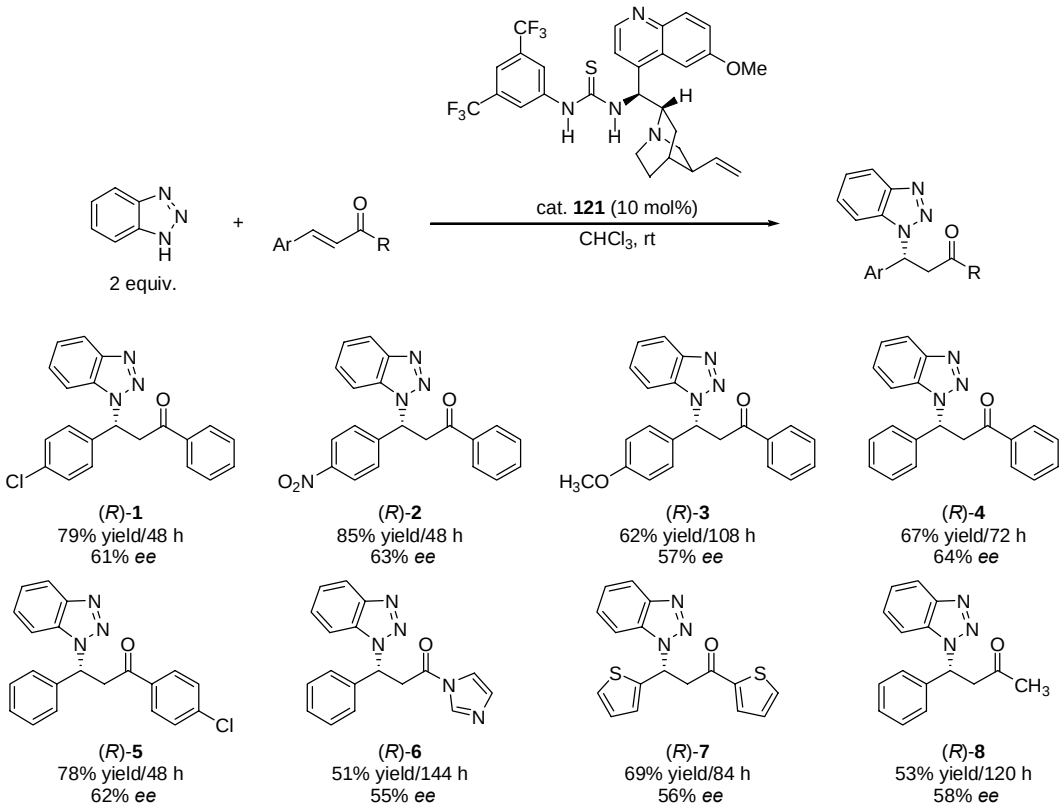
The Rouden group utilized **121** and **124** as "organic bases" for the asymmetric decarboxylative protonation of cyclic, acyclic, and bicyclic *N*-acylated α-amino hemimalonates.[294] The introduced protocol suffered from high catalyst-loading (100 mol%; catalysts were recycled by acid-base work-up) and long reactions times (7 d), but it furnished the protected α-amino esters **1**–**5**, which represent precursors of α-amino acids, in good yields (83%–92%) and *ee* values (82%–93%) at low temperature (0 °C). The catalyst activity and selectivity turned out to be highly dependent on the reaction temperature (e.g., product **1** in Scheme 135: 85% yield/70% *ee* at 25 °C after 2 d; 25% yield/83% *ee* at –15 °C after 7 d), but appeared nearly insensitive to the choice of solvent; a wide range oft polar aprotic (CH_3CN, acetone) and apolar aprotic (toluene, Et_2O, THF) was tolerated. The pseudoenantiomeric catalysts **121** and **124** afforded access to both enantiomers of the desired *N*-acylated α-amino esters. (Scheme 135)

Wang and co-workers developed a **121**-catalyzed enantioselective Michael addition[151-154] of 1*H*-benzotriazole to a variety of α,β-unsaturated ketones such as the model substrate 3-(4-Chloro-phenyl)-1-phenyl-propenone affording the N-1 product **1** (Scheme 136).[295] The evaluation of the reaction medium revealed, that in polar and/or protic solvents (e.g., isopropyl alcohol, DMSO) no reaction occurred possibly due to competitive hydrogen-bonding interactions disturbing those between catalyst **121** and the substrate. Nonpolar and aprotic solvents, however, such as diethyl ether (70% yield; 43% *ee*), acetonitrile (77% yield, 46% *ee*), toluene (74% yield, 44% *ee*), and dichloromethane (81% yield; 52% *ee*) gave conversion as well as stereoinduction; the best result was obtained with chloroform (79% yield, 61% *ee*). With optimized reaction parameters including the choice of solvent ($CHCl_3$), catalyst loading (10 mol% **121**), and reaction temperature (rt) electron-rich and electron-deficient α,β-unsaturated ketones turned out to be suitable Michael acceptors for the addition of

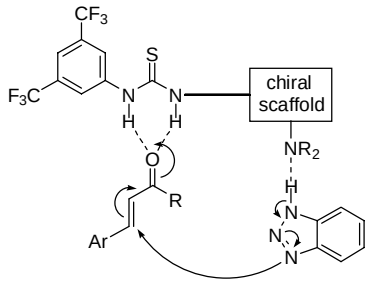
1*H*-benzotriazole. After 48 h–144 h reaction time the desired products **1**–**8** were isolated in moderate to good yields (51%–85%) and moderate *ee* values (55%–64%) (Scheme 136). The authors proposed a synergistic activation of the substrates based on double hydrogen-bonding activation of the enone and on amine-group mediated deprotonation of 1*H*-benzotriazole facilitating the product-forming Michael addition step (Scheme 137).



Scheme 135. Typical products obtained from the **121**- and **124**-catalyzed asymmetric decarboxylative protonation of *N*-acylated α-amino hemimalonates.

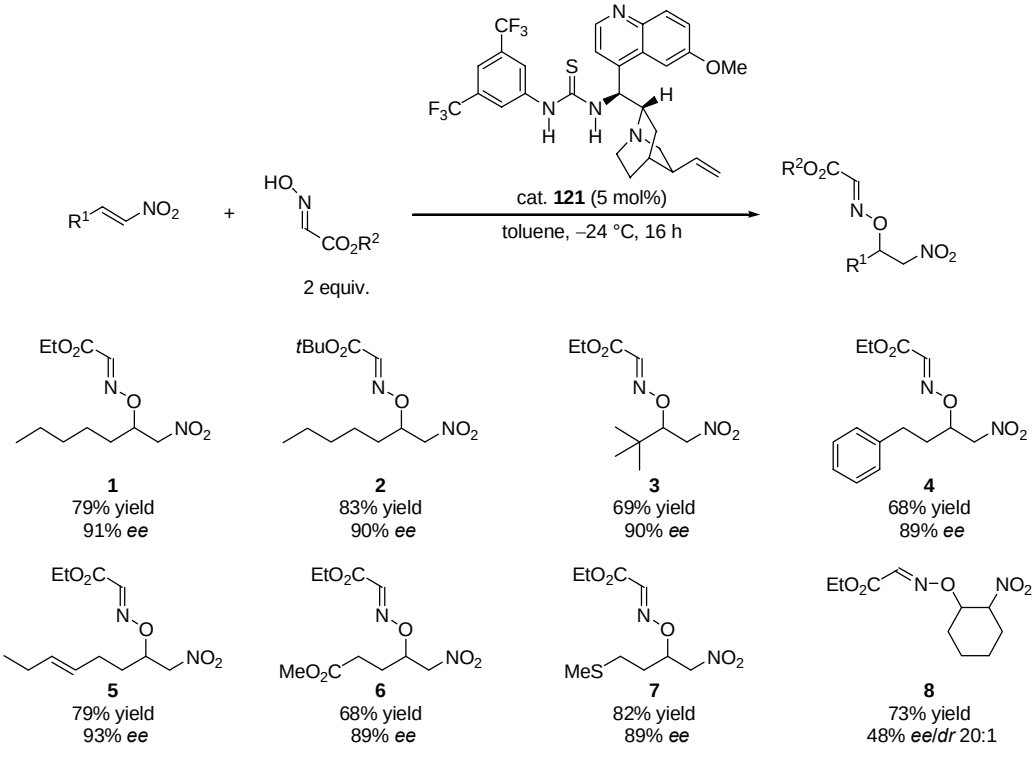


Scheme 136. Products of **121**-catalyzed asymmetric Michael additions of 1*H*-benzotriazole to a variety of α,β-unsaturated ketones.



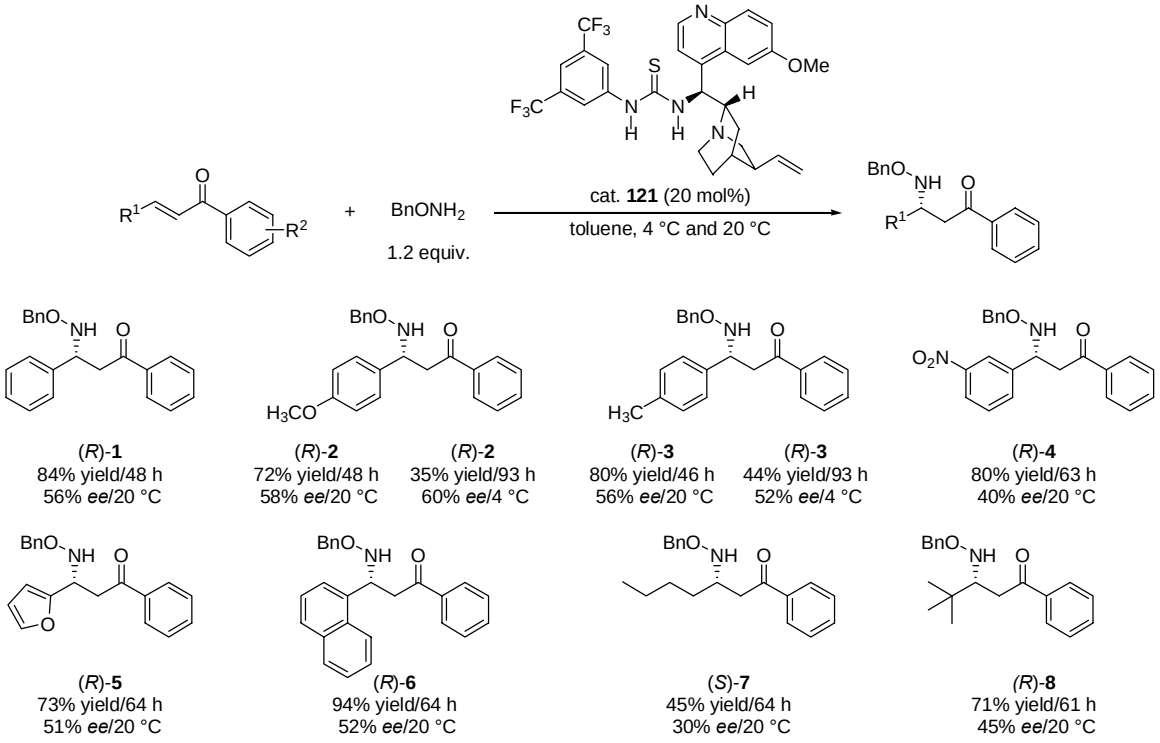
Scheme 137. Mechanistic proposal for **121**-catalyzed asymmetric Michael additions of 1*H*-benzotriazole to α,β-unsaturated enones.

The Jørgensen group extended the application of **QN**-derived thiourea catalyst **121** to the enantioselective β-hydroxylation of functionalized aliphatic nitroalkenes using predominantly ethyl glyoxylate oxime as oxygen source.[296] **CN**, **CD**, **QD**, and **QN** revealed poor selectivities (5%–10% *ee*/–24 °C/73–82% conv. after 16 h/toluene) in the catalyst-screening Michael reaction between (*E*)-1-nitrohept-1-ene and ethyl glyoxylate oxime (adduct **1**; Scheme 138), while **121** was found to be more efficient (95% conv./91% *ee*) even at 5 mol% loading at otherwise identical conditions. These experimental results represented a further example of improved bifunctional catalysis through incorporation of the privileged 3,5-bis(trifluoromethyl)phenyl-thiourea motif into the cinchona alkaloid backbone; catalyst **121** was suggested to activate both the oxime by single hydrogen-bonding to the basic quinuclidine nitrogen atom and by double hydrogen-bonding of the C9-thiourea moiety to the nitroalkene Michael acceptor. Employing the optimized protocol (5 mol% **121**; toluene; –24 °C; 16 h) to the enantioselective Michael additions of oximes to various aliphatic nitroalkenes furnished the desired adducts **1**–**8** in 68%–83% yield and 48%–93% *ee* (Scheme 138*)*. This β-hydroxylation tolerated variable functionalizations of the nitroalkane substrates such as a phenyl-substitution, the presence of an isolated double bond, an ester group, and a thioether group as outlined in Scheme 138. To demonstrate the synthetic utility of the protocol and the prepared adducts, respectively, the authors presented selective reductions to transform the adduct of ethyl glyoxylate oxime to (2-nitro-vinyl)-cyclohexane (prepared in 82% yield/90% *ee*) either to its corresponding optically active *N*-Boc-protected amino alcohol (via hydrogenation: 1. H_2/Pd/C 2. $(Boc)_2O$) or to its (*R*)-configured β-hydroxy nitroalcohol ($ZrCl_4$, $NaBH_4$/THF).[296]

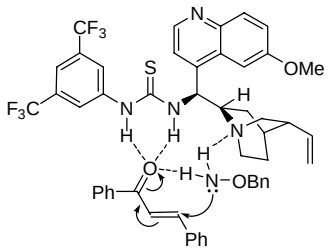


Scheme 138. Product range of the **121**-catalyzed asymmetric β-hydroxylating Michael addition of oximes to aliphatic nitroalkenes. The product configurations were not determined.

In the presence of thiourea **121** (20 mol% in toluene at 4 °C/20 °C) the aza-Michael addition[151-154] of *O*-benzylhyroxylamine to numerous *trans*-chalcones bearing electron-rich and electron-deficient (hetero)aromatic substituents as well as aliphatic side chains provided the respective *β*-keto hydroxylamines **1**–**8** in moderate to very good yields (35%–94%) and low to moderate (30%–60%) *ee* values (Scheme 139).[297] Ricci and co-workers explained the outcome of their aza-Michael reaction with the mechanistic picture visualized in Scheme 140; C9-*epi*-**QN**-derived thiourea **121** displayed a bifunctional mode of catalysis, which simultaneously activated both the chalcone Michael acceptor and the donor *O*-benzylhydroxylamine through explicit hydrogen-bonding.



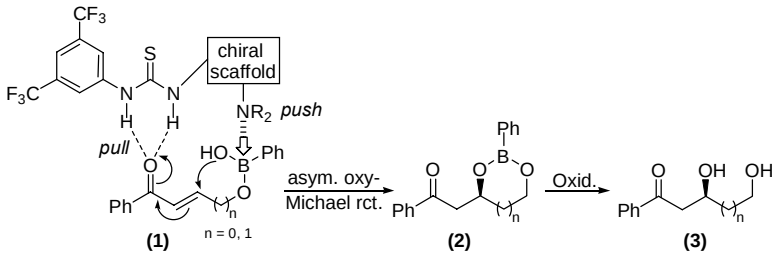
Scheme 139. Typical products of the aza-Michael addition of *O*-benzylhydroxylamine to *trans*-chalcones under bifunctional **121**-catalysis.



Scheme 140. Proposal for the role of catalyst **121** in the Michael reaction between *O*-benzylhydroxylamine and 1,3-Diphenyl-propenone.

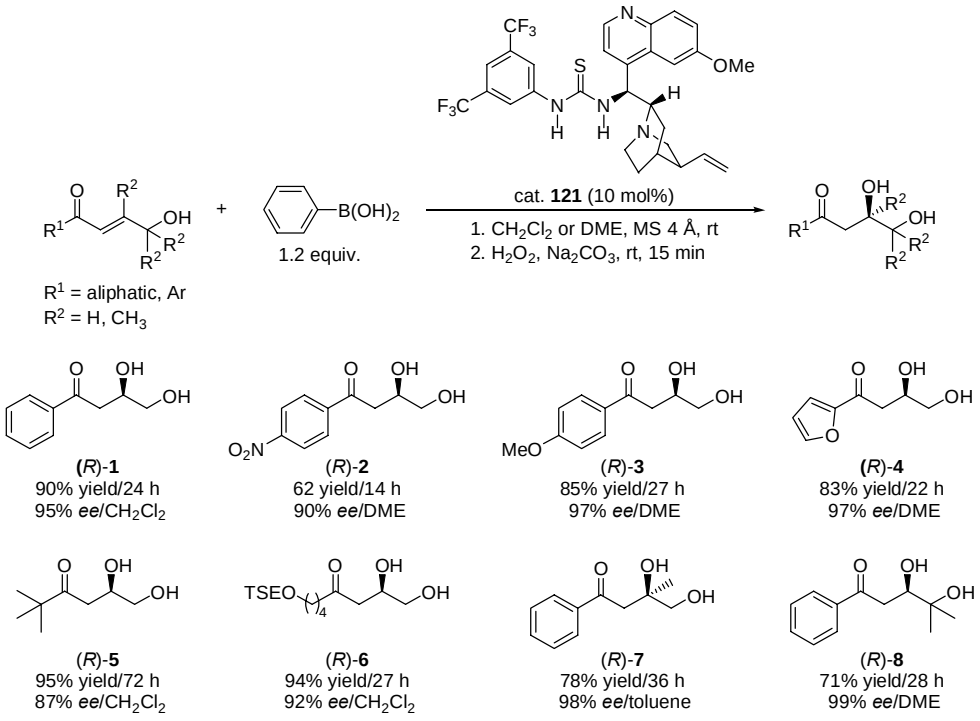
In 2008, Falck et al. reported the **121**-catalyzed enantioselective intramolecular oxy-Michael addition[151-154] of *γ*-hydroxy-*α,β*-enones and *δ*-hydroxy-*α,β*-enones in the presence of phenylboronic acid resulting in the respective *β,γ*-dihydroxy-enones and *β,δ*-dihydroxy-enones, respectively.[298] The *β*-hydroxylation of the hydroxy-enone substrates was described as asymmetric intramolecular conjugate addition of an in situ generated boronic acid hemiester to the enone *β*-position forming dioxaborolane (n = 0) or dioxaborinane (n = 1) intermediates, respectively, which afforded the chiral target diol after mild oxidative work-up (H_2O_2/Na_2CO_3) (Scheme 141). The authors suggested that **121** operated as a push/pull-type bifunctional hydrogen-bonding organocatalyst. As shown in Scheme 141 hydrogen-bonding coordination of the carbonyl group by the thiourea moiety (the pull) and complexation of the tertiary nitrogen to boron (the push) were expected to

enhance simultaneously the nucleophilicity of the boronate oxygen as well as envelope the enone in a chiral environment giving rise to stereoinduction. In this mechanistic picture the intermediate amine-boronate complex served as a chiral hydroxide surrogate or synthon. Notably, organic bases such as triethylamine (42% yield/48 h), diisopropylamine (86% yield/16 h), and DABCO (70%/48 h) in dichloromethane also catalyzed the intramolecular Michael addition of the model substrate (*E*)-4-hydroxy-1-phenyl-2-buten-1-one, while inorganic bases Na_2CO_3 and $NaHCO_3$ incapable of forming an activating push-type boron complexation remained catalytically inactive under otherwise identical conditions.



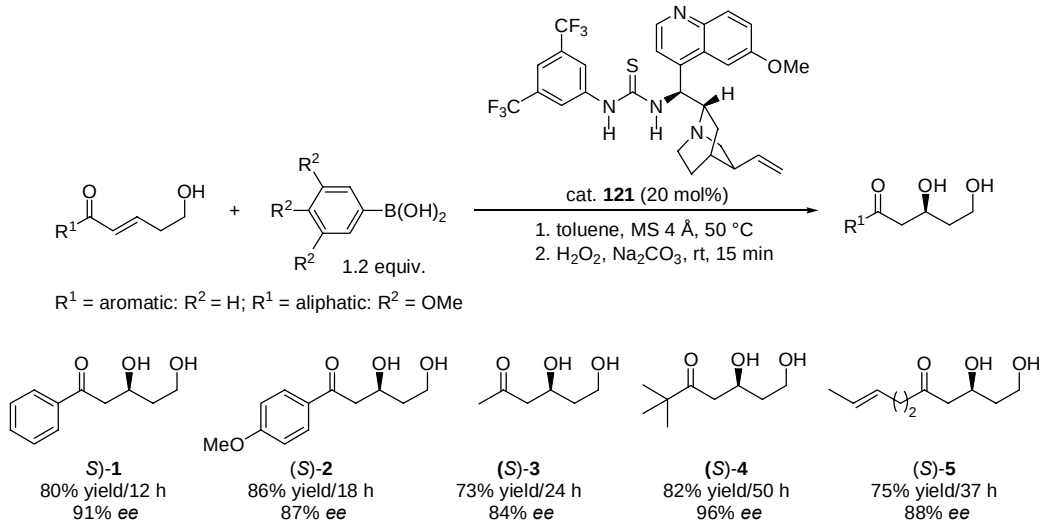
Scheme 141. Mechanistic proposal for the **121**-catalyzed asymmetric intramolecular Michael addition exemplified for the model substrates (*E*)-4-hydroxy-1-phenyl-2-buten-1-one (n = 0) and (*E*)-5-hydroxy-1-phenyl-2-buten-1-one (n = 1); **121** functions as push/pull-type bifunctional catalyst inducing the cyclization of boronic acid hemiester (**1**) to form intermediate (**2**); release of diol product (**3**) by oxidation.

Under optimized conditions the substrate scope of the **121**-catalyzed (10 mol% loading) intramolecular oxy-Michael addition was reported to cover various γ-hydroxy-α,β-enones that could be converted at room temperature in dichloromethane or 1,2-dimethoxyethane to the desired (*R*)-configured adducts **1**–**8** in good to excellent yields (62%–95%) and *ee* values (87%–99%) (Scheme 142). Arylketones bearing strong electron-withdrawing substituents reacted faster than electron-rich systems, although the *ee* values of the latter were better. Aliphatic ketones regardless of steric congestion adjacent to the carbonyl, had longer reaction times, yet still afforded excellent overall yields. The tolerance of the labile triethylsilyl (TES) ether, the additional substitution at the double bond, and the carbinol group testified the mildness of the reaction conditions and the level of structural substrate complexity, respectively (Scheme 142).[298]



Scheme 142. Product range of the catalyzed asymmetric intramolecular Michael addition of γ-hydroxy-α,β-enones catalyzed by **121**.

The transformations of δ-hydroxy-α,β-enones to the corresponding internal Michael adducts were performed at 20 mol% loading of C9-*epi*-quinine-thiourea **121** in toluene at increased reaction temperature (50 °C) using 3,4,5-trimethoxyphenylboronic acid for aliphatic and phenylboronic acid for aromatic enones. Under these conditions this protocol furnished the desired (*R*)-configured adducts **1**–**5** in yields ranging from 73%–86% and *ee* values of 84%–96% (Scheme 143).[298] Product **5** in Scheme 143 was identical in all respects with (+)-(*S*)-streptenol A, one of four known streptenols produced by *Streptomyces luteogriseus* that has attracted attention as an immunostimulant as well as an inhibitor of cholesterol biosynthesis and tumor cells.[299]

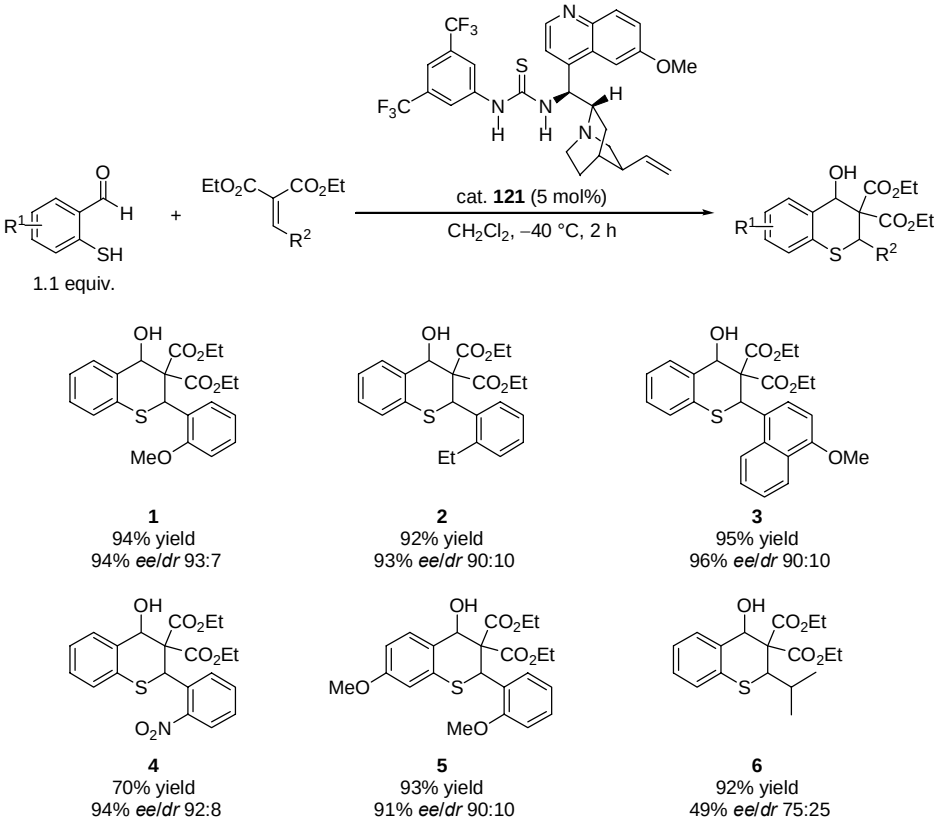


Scheme 143. Product range of the **121**-catalyzed asymmetric intramolecular Michael addition of δ-hydroxy-α,β-enones.

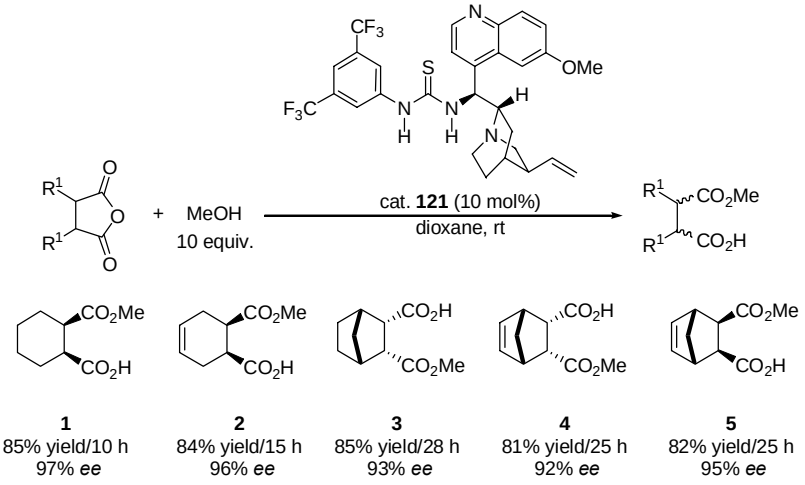
The **121**-catalyzed synthesis of thiochromanes starting from 2-mercaptobenzaldehydes and α,β-unsaturated oxazolidinones was developed by the Wang group and proceeded via a tandem Michael process[151-154] (Scheme 131).[291] Zhao and co-workers, however, reported a tandem Michael-Knoevenagel approach towards tetrasubstituted thiochromanes replacing the oxazolidinone component with benzylidenemalonates that were readily accessible through Knoevenagel condensation of malonates and aldeyhdes.[300] Utilizing catalyst **121** (5 mol% loading) in dichloromethane at –40 °C various 2-mercaptobenzaldehydes and diethyl malonates were converted to the corresponding thiochromanes **1**–**6** in yields of 70%–95% (after 2 h), *ee* values of 49%–96%, and *dr* values up to 93:7 (Scheme 144). Steric and electronic effects turned out to have a strong impact on the stereochemical outcome of this reaction. Diastereoselectivity proved sensitive mainly towards steric factors at the 2-position of the malonate phenyl ring, while enantioselectivity was influenced by the electronic effects of the substituent on the aromatic ring (= R^2). Substituents (= R^1) on the 2-mercaptobenzaldehyde ring had minimal impact on the reaction.

Chin, Song, and co-workers experimentally identified quinine-derived thiourea **121** (10 mol%) as efficient bifunctional organocatalyst for the methanolic desymmetrization of bicyclic *meso*-anhydrides resulting in the respective chiral hemiesters **1**–**5** in excellent yields (92%–96%) and good enantioselectivities ranging from 81%–85% (Scheme 145).[301] The evaluation of the reaction conditions performed for the **121**-catalyzed (10 mol%) asymmetric methanolysis of *cis*-1,2-cyclohexane dicarboxylic anhydride in THF (product **1**; Scheme 145) demonstrated the influence of concentration, temperature, and solvent effects on the level of stereoinduction. Dilution of the reaction mixture increased the *ee* value of the model hemiester **1** from 82% *ee* (2.5 mL THF) to 96% *ee* (80 mL THF) and a higher reaction temperature afforded also an improved stereoinduction (77% *ee* at –20 °C; 82% *ee* at 25 °C in 2.5 mL THF) under otherwise unchanged conditions. Employing polar protic solvents such as methanol that accept and donate hydrogen-bonds weakened the explicit hydrogen-bonding between catalysts **121** and the anhydride resulting in reduced stereoinduction (31% *ee*), while aprotic, hydrogen-bonding accepting solvents such as dioxane (97% *ee*) or THF (95% *ee*) appeared compatible with this approach. This observations suggested, that catalyst **121** existed mainly in the dimeric (or higher order) form by hydrogen-bonded self-association at high concentrations, at low temperature and with non-coordinating solvents. On the other hand, at reduced concentration of the reaction mixture, at ambient temperature, and in the presence

of coordinating solvents **121** existed mainly in the monomeric form that was responsible for high enantioselectivity. To confirm the hypothesis, ^{1}H NMR dilution experiments of **121** were carried out in d_8-toluene and concentration dependencies were detected for the chemical shift of the –C(=S)N(**H**)–Ar proton; the chemical shift of this proton was downfield-shifted from 9.3 ppm to 11.1 ppm upon concentration from 10 mM to 212 mM. This concentration dependency was consistent with the hydrogen-bonded self-association of **121**. The authors assumed that the efficiency of **121** originated from the simultaneous activation of the nucleophile (methanol) by the basic quinuclidine that functioned as general base and the electrophile (the *meso*-anhydride) through double hydrogen-bonding interactions with the thiourea moiety. The rate-determining step for the methanolysis reaction was assumed to be a general base catalyzed addition of methanol to the anhydride rather than the ring opening step since carboxylate was a better leaving group than methoxide.[301]



Scheme 144. Thiochromanes prepared from the **121**-catalyzed enantioselective tandem Michael-Knoevenagel reaction between 2-mercaptobenzaldehydes and diethyl methylenemalonates. The product configurations were not determined.



Scheme 145. Chiral hemiesters obtained from the **121**-catalyzed methanolic desymmetrization of cyclic *meso*-anhydrides.

The novel class of C6′-thiourea functionalized cinchona alkaloids was constituted by Hiemstra and co-workers, in 2005, when introducing cupreidine-derived **131** and its cupreine-derived[64] pseudoenantiomer **132** as bifunctional hydrogen-bonding organocatalysts for the asymmetric Henry (nitroaldol) reaction[228] between nitromethane and various (hetero)aromatic aldehydes (Figure 43).[302] Thiourea **131**, a bench-stable crystalline solid, was synthesized on a multi-gram scale from C9-hydroxy-benzylated **CPD** via a high-yielding reaction sequence.[302] Bifunctional cinchona alkaloid **130** designed by Deng et al.,[303-305] was previously utilized by the Hiemstra group to catalyze the asymmetric Henry addition of nitromethane to benzaldehydes affording yields of 70%–92% and low *ee* values (6%–35%),[306] while **131** revealed drastically improved catalytic activity and selectivity for an extended substrate spectrum.

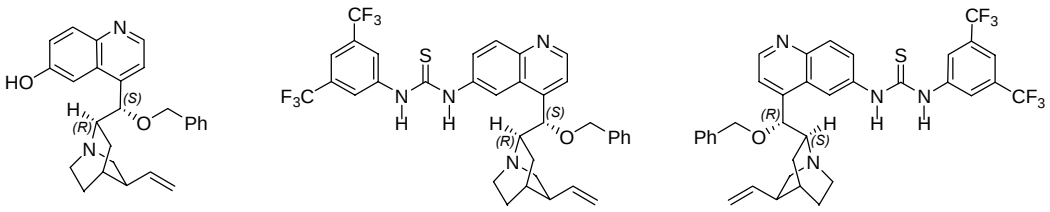
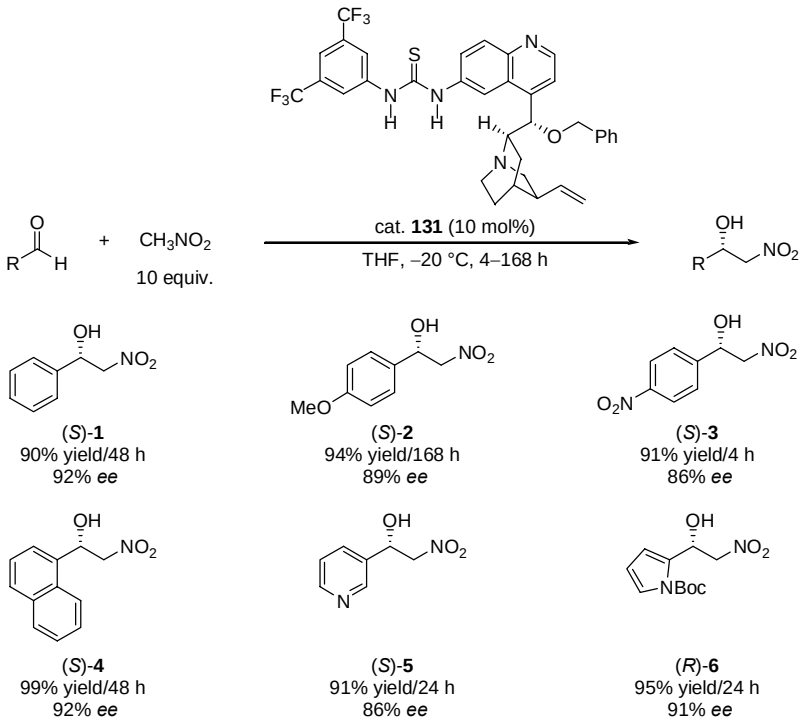


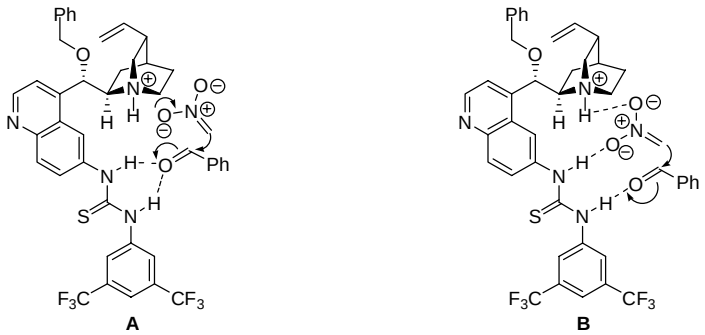
Figure 43. C9-OH protected cinchona alkaloid **130**, C6′-thiourea derivative **131** and its pseudoenantiomer **132**.

For the model Henry reaction between benzaldehyde and nitromethane a solvent dependency of the enantioselectivity was detected (e.g., CH_2Cl_2: 6% *ee*; MeOH: 49% *ee*; THF: 62% *ee*; all at rt). Under optimized reaction conditions concerning catalyst loading (10 mol% of **131**), solvent (THF), and reaction temperature (–20 °C) a variety of (hetero)aromatic aldehydes were transformed into nitroalcohols **1**–**6** in consistently high yields (90%–99%) and *ee* values (86%–92%) as shown in Scheme 146. The protocol failed for aliphatic aldehydes such as cyclohexanecarboxaldehyde and isobutyraldehyde that displayed incomplete conversion to the respective nitroalcohols even after 1 week reaction time and gave low *ee* values (<20%) of the adducts. Catalyst **132**, the pseudoenantiomer of **131**, gave access to nitroalcohols with the opposite configuration and comparable enantiomeric excess, as exemplified for three aldehydes (e.g., (*R*)-adduct **3**: 87% yield; 93% *ee*).



Scheme 146. Representative adducts obtained from the asymmetric Henry reaction between nitromethane and (hetero)aromatic aldehydes under bifunctional catalysis of C6′-thiourea functionalized cinchona alkaloid **131**.

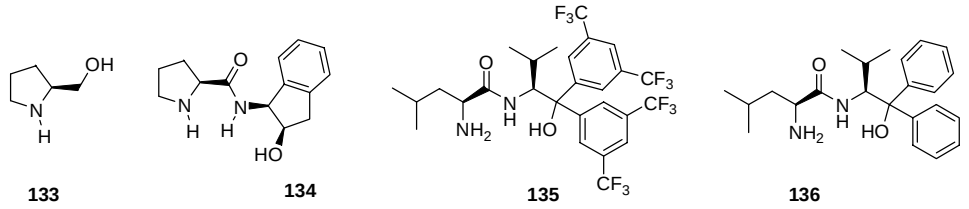
Scheme 147 visualizes two proposals for the mechanism of the **131**-catalyzed Henry addition of nitromethane to benzaldehyde. In (**A**) benzaldehyde is activated by the thiourea moiety through double hydrogen-bonding to the carbonyl function, while the nitromethane is deprotonated and activated by the basic quinuclidine nitrogen;[302] proposal (**B**), however, based on detailed DFT computations favors single hydrogen-bonding to the nitronate and the carbonyl group facilitating C-C-bond formation through nucleophilc attack resulting in the preferred (*S*)-configured adduct.[307]



Scheme 147. Mechanistic proposals for the **131**-catalyzed asymmetric Henry addition of nitromethane to benzaldehyde. Preliminary model (**A**) involving double hydrogen bonding and DFT-based model (**B**) supporting single hydrogen-bonding to benzaldehyde and nitronate, respectively.

1.2.2.3 (Thio)urea Catalysts Derived from Chiral Amino Alcohols

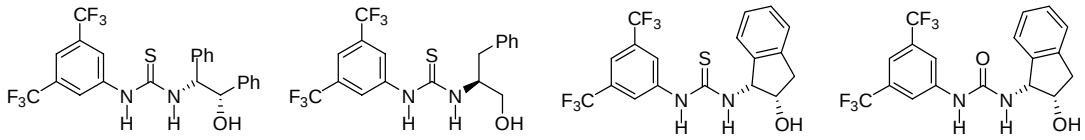
Chiral amino alcohols have been utilized as auxiliaries, ligands, and as important building blocks in organic synthesis.[140] Recently the chiral amino alcohols D- and L-prolinol **133** were utilized as organocatalysts for the asymmetric fluoroaldol reaction of aldehydes with fluoroacetone;[308] β-amino alcohols served as starting material for the synthesis of a series of bifunctional hydrogen-bonding L-prolinamides such as *(1S,2R)-cis*-1-amino-2-indanol derived catalyst **134** applicable to asymmetric nitro-Michael additions,[309] and for the synthesis of compounds **135** and **136** that catalyze enantioselective direct *syn*-aldol reactions of various aldeyhdes with ketones (Figure 44).[310]



133 **134** **135** **136**

Figure 44. Stereoselective organocatalysts derived from amino alcohols

Ricci and co-workers introduced a new class of amino alcohol based thiourea derivatives, which were easily accessible in a one-step coupling reaction in nearly quanitative yield from the commercially available chiral amino alcohols and 3,5-bis(trifluoromethyl)phenyl isothiocyanate or isocyanate, respectively (Figure 45).[311] The screening of (thio)urea derivatives **137**, **138**, **139**, and **140** in the enantioselective Friedel-Crafts reaction of indole with *trans*-β-nitrostyrene at 20 °C in toluene demonstrated (1*R*,2*S*)-*cis*-1-amino-2-indanol derived thiourea **139** to be the most active catalyst regarding conversion (95% conv./60 h) as well as stereoinduction (35% *ee*), while the canditates **137**, **138**, and the urea derivative **140** displayed a lower accelerating effect and poorer asymmetric induction (Figure 45). The uncatalyzed reference reaction performed under otherwise identical conditions showed 17% conversion in 65 h reaction time.



137
86% conv./ 64 h
13% *ee*

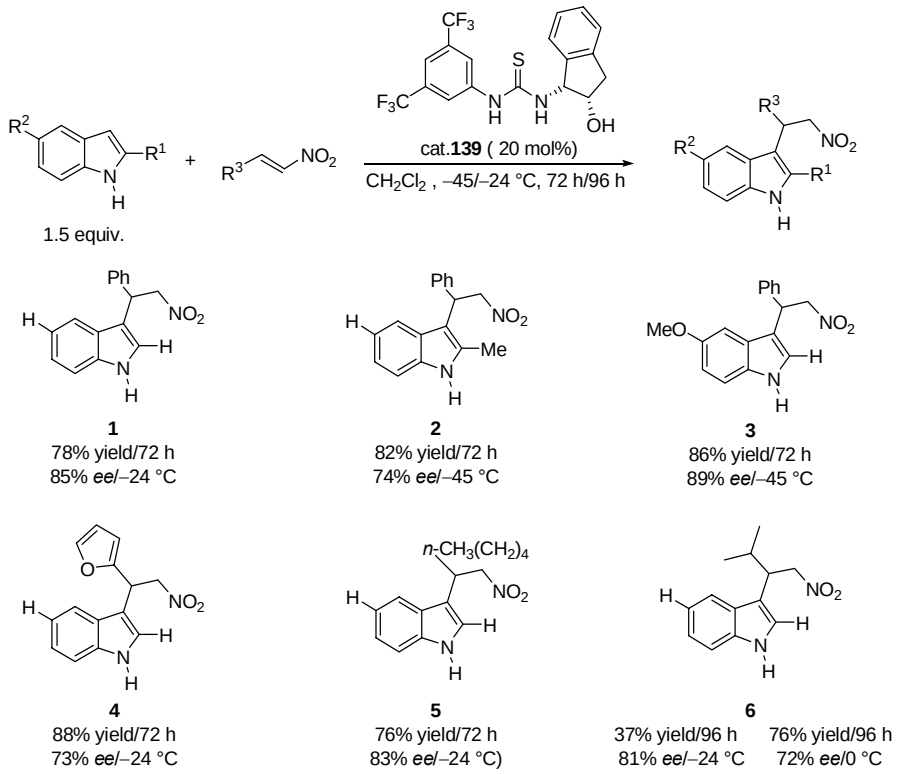
138
41% conv./45 h
13% *ee*

139
>95% conv./60 h
35% *ee*

140
23% conv./118 h
25% *ee*

Figure 45. Hydroxy-functionalized thiourea derivatives (20 mol% loading) screened in the enantioselective Friedel-Crafts reaction of indole with *trans*-β-nitrostyrene at 20 °C in toluene.

To examine the scope and limitations of this protocol Friedel-Crafts reactions of various nitroalkenes and indole were carried out under optimized conditions utilizing thiourea catalyst **139** in dichloromethane at 20 mol% loading (Scheme 148). The transformations of indole and electron-rich indole derivatives such as 5-methoxyindole with aliphatic and aromatic nitroalkenes to the corresponding 2-indyl-1-nitro compounds proceeded in good enantioselectivities (71%–89%) and in moderate to good yields (35%–88%). Electron-poor 5-chloro indole substrate gave 71% yield at longer reaction time (142 h), but provided a significantly lower *ee* value (35%) similar to the *ee* value reported for the isopropyl-substituted nitroalkene substrate resulting in adduct **6** (37% *ee*) shown in Scheme 148. The yield of adduct **6** could be considerably increased without remarkable loss of enantioselectivity when performing the reaction at 0 °C (76% yield/96 h; 72% *ee*) instead of –24 °C (37% yield/96 h; 81% *ee*) (Scheme 148).



Scheme 148. Product range of the enantioselective **139**-catalyzed Friedel-Crafts alkylations of various indols. The product configurations were not determined.

To elucidate the substrate-catalyst interactions the authors prepared derivatives of structure **139** and probed their efficiencies in the reactions of indole with *trans*-*β*-nitrostyrene. TMS-protected **141** and **142** lacking the hydroxyl functionality and the use of *N*-methylated indole (75% yield/6% *ee*) as a substrate gave lower conversions and enantioselectivities, indicating the presence of a weak single hydrogen-bonding interaction between the indole proton and the hydroxy oxygen in addition to the double hydrogen-bonding activation of the nitroalkene by the thiourea amide protons. This assumed bifunctional catalysis induced the nucleophilic attack of the incoming indole on the *Si face* of the nitroalkene (Figure 46). The Ricci group demonstrated the synthetic versatility of the optically active Friedel-Crafts adducts through a two-step conversion of product **1** in Scheme 148 to tryptamine (74% yield; 85% *ee*) and 1,2,3,4,-tetrahydro-*β*-carboline (76% yield; 85% *ee*).[311]

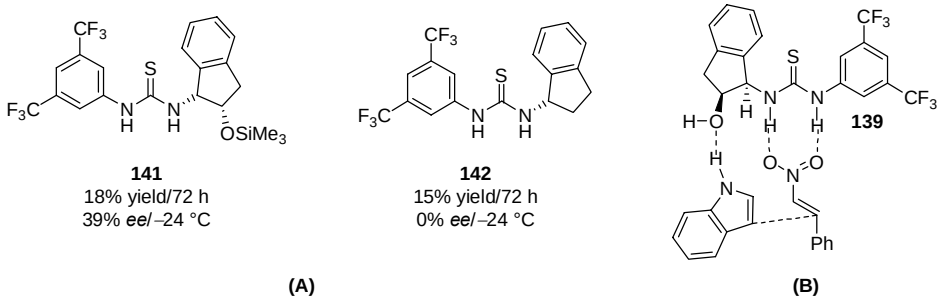


Figure 46. **(A)** Hydroxy-protected thiourea **141** and **142** lacking the hydroxy function and their catalytic efficiency in the Friedel-Crafts alkylation of indole with *trans*-*β*-nitrostyrene (**139**: 78% yield; 85% *ee* under identical conditions). **(B)** Proposal for the key hydrogen-bonding interactions between **139** and the model substrates.

To develop a metal-free synthetic access to precursors of *β*-amino acids Sibi and Itoh studied the thiourea-mediated conjugate addition[151-154] of various amines to pyrazole derived enoates.[312] The addition products are synthetically useful owing to their simple conversion to *β*-amino acids.[313] The authors evaluated the optimal reaction conditions using a stoichiometric amount of **139** to catalyze the model conjugate addition of *O*-benzylhydroxylamine to 2,4-dimethyl pyrazole crotonate. The best results concerning product yield and asymmetric induction for model product **1** (Scheme 149) were obtained when the reaction proceeded in the nonhydrogen- bonding solvent trifluorotoluene at 0 °C reaction temperature and in the presence of powdered activated molecular sieve (MS) 4 Å (500 mg/1 mmol *α,β*-unsaturated amide). The MS was found to improve the yield (no MS: 76%/48 h; with MS: 75%/24 h; at rt), but had no impact on the *ee* value (unchanged 71% *ee* at rt); the function of this additive was not examined and remained ambiguous. The screening of amino alcohol derived (thio)ureas such as **137**, **140**, and **142**–**146** in their role as "chiral activators" (Figure 45, 46 and 47) in the formation of model product **1** at room temperature revealed bifunctionality, rigidity, and the incorporation of the 3,5-bis(trifluoromethyl)phenyl thiourea functionality as catalyst structure key features (Figure 47).[312]

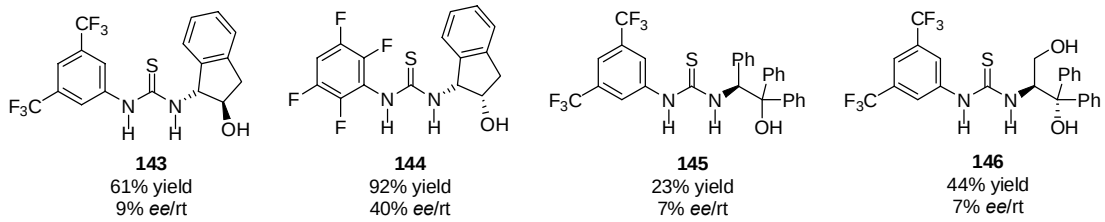
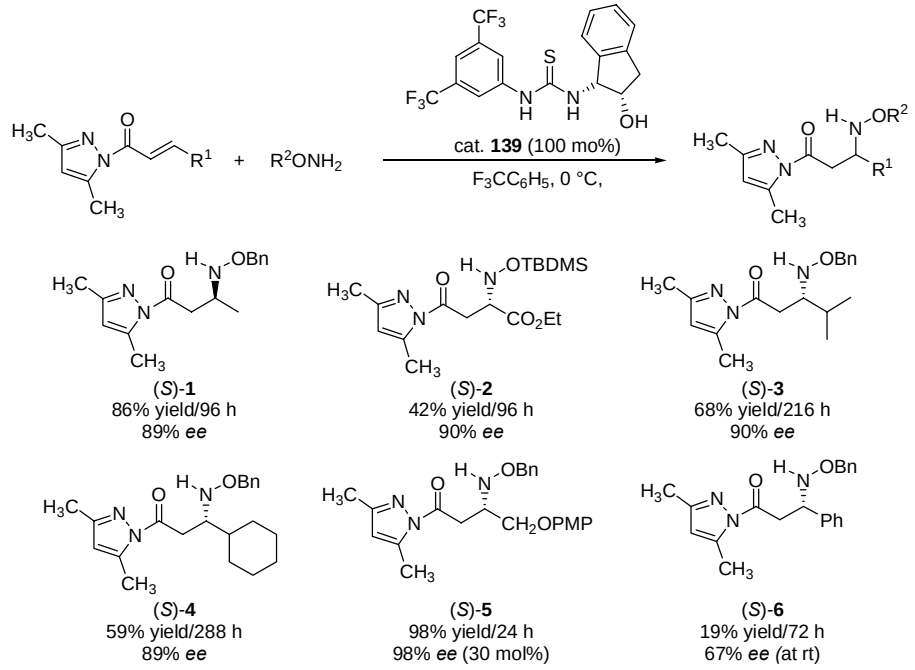


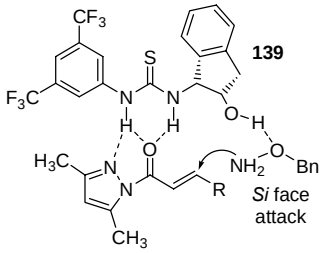
Figure 47. Various thiourea catalysts screened in the Michael addition of *O*-benzylhydroxylamine to 2,4-dimethyl pyrazole crotonate.

Lowering the catalyst loading from 100 mol% to 30 mol% led to longer reaction times (up to 168 h at rt), while the *ee* value of model product **1** remained unchanged. Employing the optimized protocol (100 mol% loading of thiourea **139**; $F_3CC_6H_5$ as the solvent at 0 °C) and 2,4-dimethyl pyrazole substituted *α,β*-unsaturated substrates bearing an aliphatic substituent at the *β*-carbon the respective Michael adducts **1**–**5** were obtained in moderate to excellent product yields (42%–98%; 1 d to >10 d reaction time) and in high *ee* values (89%–98%) (Scheme 149). In contrast, *β*-phenyl substituted adduct **6** was isolated in only 19% yield (72 h) and 67% enantioselectivity (Scheme 149).



Scheme 149. Typical products obtained from the **139**-catalyzed asymmetric Michael addition of protected hydroxyl amines to *α,β*-unsaturated 2,4-dimethyl pyrazole substituted substrates.

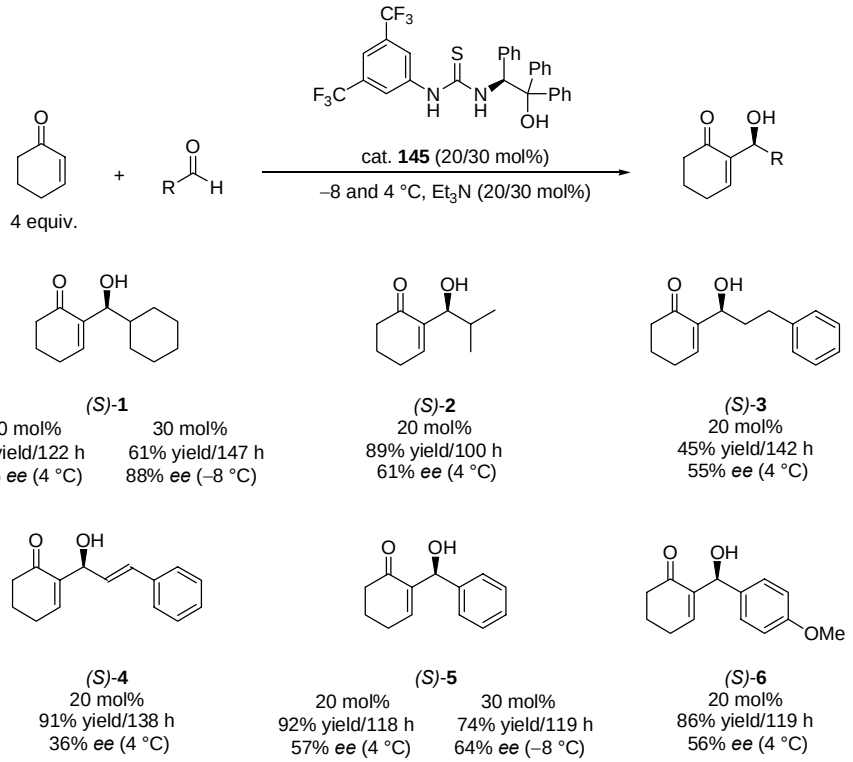
The authors suggested a double hydrogen-bonding coordination of the bidentate α,β-unsaturated 2,4-dimethyl pyrazole substituted substrates resulting in a hydrogen bond pattern examined by Schreiner and Wittkopp[1, 116]. This additional fixation of *O*-benzylhydroxylamine in favor of a *Si face* nucleophilic Michael addition was led to the observed stereochemical outcome of *(S)*-configured adducts (Scheme 150).



Scheme 150. Proposed mechanistic picture for (*S*)-favored enantioselective Michael addition of *O*-benzylhydroxylamine to 2,4-dimethyl pyrazole substituted α,β-unsaturated substrates in the presence of hydrogen-bonding thiourea catalyst **139**.

Thiourea catalyst **139** was also screened in the asymmetric Friedel-Crafts reaction between 2-naphthol *trans*-nitrostyrene (73% yield; 0% *ee*; 18 h in toluene at –20 °C and 10 mol%),[281] in the asymmetric aza-Michael reaction of *O*-benzylhydroxylamine to chalcone (72% conv.; 19% *ee*; 72 h in toluene at 20 °C and 20 mol% catalyst loading),[297] and in the asymmetric Morita-Baylis-Hillman[179, 180] reaction between cyclohexenecarbaldehyde and 2-cyclohexene-1-one (20% yield; 31% *ee*; 46 h at rt and 20 mol% DABCO and **139**).[314] In all these transformations thiourea **139** proved to be not competitive to the organocatalysts probed for these transformations under identical screening conditions and thus was not employed in the optimized protocols.

Lattanzi screened various amino alcolhol derived thioureas in the enantioselective Morita-Baylis-Hillman model reaction[179, 180] between cyclohexenecarbaldehyde and 2-cyclohexene-1-one (MBH adduct **1**; Scheme 151) under solvent-free conditions and indentified readily accessible thiourea **145** as the most effective catalyst.[314] Notably, thiourea **145** exhibited poor activity and enantioinduction in the Michael addition of *O*-benzylhydroxlyamine to α,β-unsaturated 2,4-dimethyl pyrazole substituted substrates (Figure 47).



Scheme 151. Range of allylic alcohols prepared from **145**-catalyzed MBH reactions of 2-cyclohexene-1-one with various aldehydes.

To evaluate the scope and limitations of this protocol various aldehydes were utilized as substrates to react with 2-cyclohexene-1-one under optimized conditions in the presence catalyst **145** (20 and 30 mol% loading) and triethylamine (20/30 mol%) as base additive at 4 °C as standard reaction temperature. After an average reaction time of approx. 120 h the corresponding (*S*)-configured allylic alcohols **1**–**6** were provided in enantioselectivities ranging from 36 to 88% *ee* and yields ranging from 45 to 92%.(Scheme 151) The asymmetric induction decreased significantly when using aliphatic sterically unhindered aldehydes such as 2-methyl-propionaldehyde forming product (*S*)-**2** (Scheme 151). Running the reaction with benzaldehyde at –8 °C but at 30 mol% loading of **145** and triethylamine (instead of 20 mol% standard amount) increased the *ee* value of MBH adduct *(S)*-**5** from 57 to 64% (Scheme 151). The author suggested that bifunctional hydrogen-bonding thiourea catalyst **145** stabilized the zwitterionic intermediate and accelerated the product-forming proton transfer by the closely located catalyst hydroxyl group followed by the catalyst regeneration after base elimination (Figure 48).

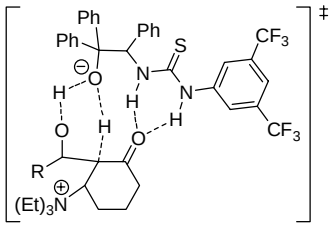
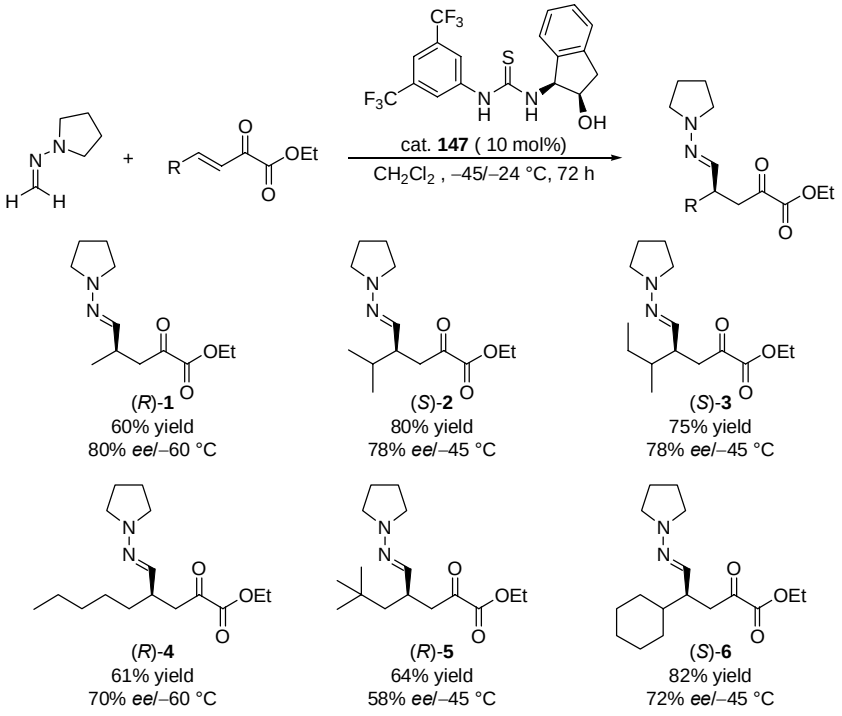


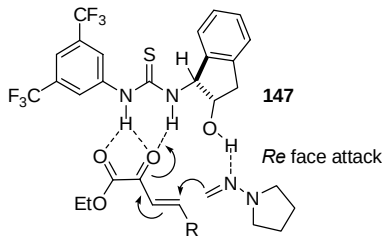
Figure 48. Proposed transition state for the proton-transfer step promoted by amino alcohol derived hydrogen-bonding thiourea **145**.

In 2007, Fernández, Lassaletta, and co-workers reported an approach for the enantioselective conjugate addition[151-154] of formaldehyde hydrazone 1-methyleneaminopyrrolidine to aliphatic γ,β-unsaturated α-keto ethylesters as enoate surrogates providing the 1,4-dicarbonyl compounds **1**–**6** in moderate (60%) to good yields (82%) and *ee* values (58%–80%) as depicted in Scheme 132.[315] The reaction occurred in the presence of (1*S*,2*R*)-1-aminoindan-2-ol-derived thiourea catalyst **147** (10 mol% loading), the enantiomer of thiourea catalyst **139** introduced by the Ricci group (Scheme 152). In contrast to the umpolung strategies applied in the catalytic Stetter reaction that failed in the formaldehyde case due to oligomerizations[316] in this mild protocol 1-methyleneaminopyrrolidine turned out to be a suitable formyl anion equivalent (umpoled formaldehyde) that underwent the symmetric nucleophilic addition to γ,β-unsaturated α-keto ethylesters without side reactions.



Scheme 152. Products of the asymmetric addition of 1-methyleneaminopyrrolidine to aliphatic γ,β-unsaturated α-keto ethylesters in the presence of catalyst **147**.

Mechanistically, the authors proposed a stereochemical model in which the hydroxy functionality of bifunctional catalyst **147** controlled the approach of the hydrazone through single hydrogen-bonding such that the triple hydrogen-bonded unsaturated ketoester was preferably attacked from the *Re* face resulting in observed (*R*)-configured adducts (Scheme 153). The synthetic utility of the prepared adducts was demonstrated by straightforward transformations using magnesium monoperoxyphthalate hexahydrate (MMPP·$6H_2O$) for the racemization-free oxidative cleavage of the hydrazone moiety into the corresponding 4-cyano α-keto ethylesters; the ozonolytic cleavage, subsequent oxidation with HCO_2/H_2O, and treatment with $SOCl_2$/MeOH allowed access to the respective succinate derivatives resulting from deoxidative decarboxylation.[315]



Scheme 153. Proposed stereochemical model for the asymmetric addition of 1-methyleneaminopyrrolidine to aliphatic γ,β-unsaturated α-keto ethylesters in the presence of catalyst **147**.

1.2.2.4 Binaphthyl-based (Thio)urea Derivatives

In 2005, Wang and co-workers utilized the catalytically "privileged"[120] axially chiral binaphthyl framework to design a new class of bifunctional hydrogen-bonding thiourea derivatives **148**, **149**, and **150** readily prepared from commercially available *(R)*-binaphthyl diamine (Figure 49).[317] This bifunctional catalyst design rationale has been already successfully realized in Takemoto's tertiary amine functionalized thiourea catalyst **12** derived from (*R*,*R*)-1,2-diaminocyclohexane.[131] Screening studies regarding catalyst, solvent, and temperature effects on the enantioselective MBH reaction[179, 180] of 2-cyclohexen-1-one with 3-phenylpropionaldehyde identified thiourea **148** as the most active binaphthyl organocatalyst in terms of reaction yield (83%) and enantioselectivity (71% *ee*). While **149** was found to show similar asymmetric induction (73% *ee*) the yield of the model MBH product was lower (**149**: 56% yield; **150**: 18 % yield) after 48 h at rt (Figure 49).

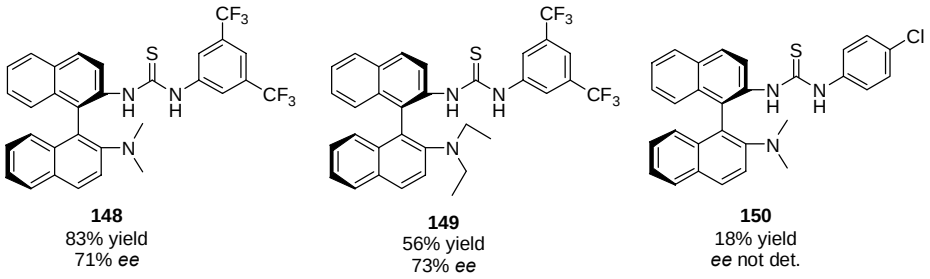
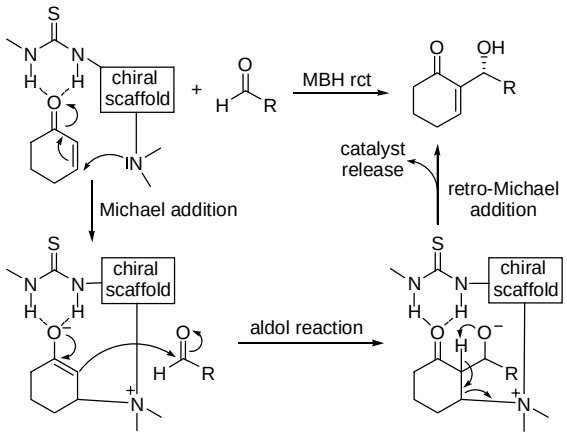
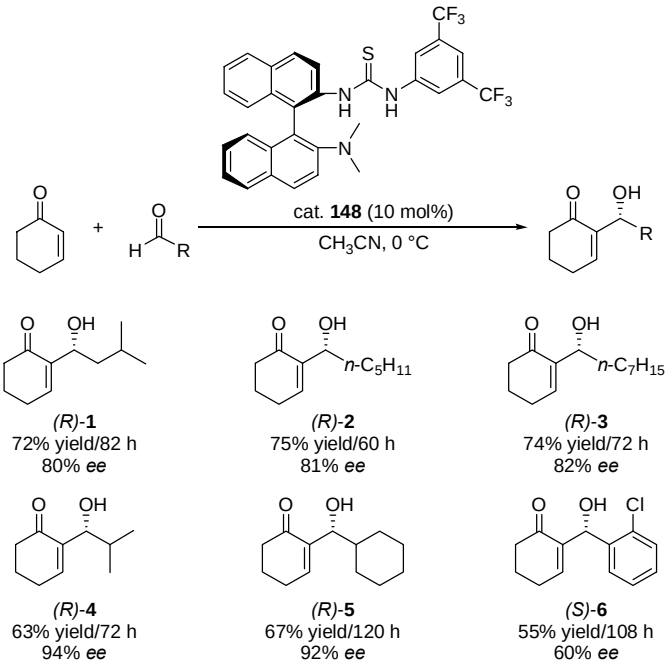


Figure 49. Binaphthyl-derived tertiary amine functionalized bifunctional thiourea derivatives screened in the MBH reaction between 2-cyclohexen-1-one and 3-phenylpropionaldehyde at rt in dichloromethane.

The significant difference in catalyst activity was in line with the known effect of the electron-withdrawing 3,5-bis(trifluoromethyl) phenyl functionality on the hydrogen-bonding strength of (thio)urea catalysts[1, 116] that led to a stronger binding of 2-cyclohexene-1-one and activation through double hydrogen-bonding. This interaction facilitated the initial Michael addition of the tertiary amine to the β-position and initiated the proposed catalytic cycle (Scheme 154). A sequence of aldol/retro-Michael reactions afforded synthetically valuable chiral allylic alcohols **1**–**6** in moderate to good yields (55%–75%) and enantioselectivities (60%–94% *ee*). The optimized protocol was reported to operate under mild conditions at rather low catalyst loadings and practical reaction times for aliphatic, aromatic, and sterically demanding aldehydes (Scheme 155).[317]

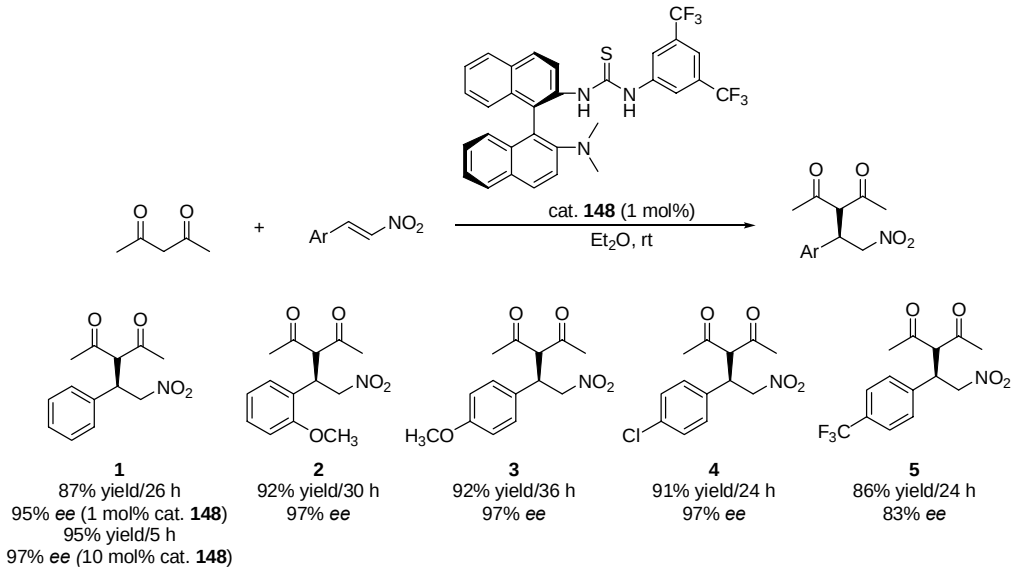


Scheme 154. Proposed catalytic cycle for the binaphthyl amine thiourea-promoted MBH reaction of aldehydes with 2-cyclohexen-1-one revealing the bifunctional mode of action of catalyst **148**, **149**, and **150**.



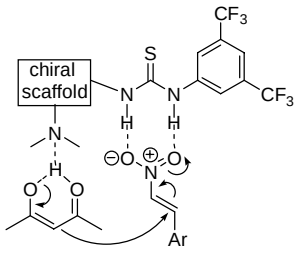
Scheme 155. Representative products resulting from enantioselective MBH reactions catalyzed by binaphthyl thiourea **148**.

Almost simultaneously the Wang group published an additional application of binaphthyl thiourea catalyst **148**.[318] Asymmetric Michael reactions[151-154] of 2,4-pentandione with a series of *trans*-β-nitrostyrenes bearing electron-withdrawing and electron-donating substituents were performed at room temperature in the presence of **148** (1 mol% loading) affording the desired Michael adducts **1**–**5** in high yields (86%–92%) and *ee* values (83%–97%) in reasonable reaction times (Scheme 156).



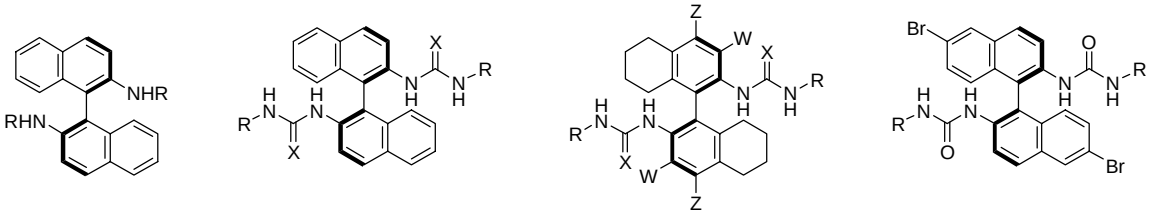
Scheme 156. Product range for the **148**-catalyzed asymmetric Michael addition of 2,4-pentandione to *trans*-β-nitrostyrenes.

Thiourea derivative **148** was expected to coordinate and stabilize the enolized 2,4-pentandione through the basic amine function to facilitate the nucleophilic attack of at the activated β-position of the hydrogen-bonded *trans*-nitroalkene resulting in the observed products (Scheme 157). Using Michael adduct **1** depicted in Scheme 156 as the starting material the authors developed a synthetically useful method for the synthesis of the corresponding α-substituted-β-amino building block (38% yield).[318]



Scheme 157. Mechanistic proposal for the bifunctional coordination and simultaneous activation of 2,4-pentandione and *trans*-*β*-nitrostyrene through thiourea catalyst **148** leading to chiral Michael adducts.

Connon and co-workers synthesized a small library of novel axially chiral binaphthyl-derived bis(thio)ureas **152**–**165** and elucidated the influence of the steric and electronic characteristics of both the chiral backbone and the achiral *N*-aryl(alkyl) substituents on catalyst efficiency and stereodifferentiation in the FC type additions of indole and *N*-methylindole to nitroalkenes (Figure 50).[319]



151: R = SO_2-4-Me-C_6H_4

152: X = O, R = SO_2-4-Me-C_6H_4
153: X = O, R = cyclohexyl
154: X = O, R = C_6H_5
155: X = O, R = 2,6-$(Me)_2$-C_6H_3
156: X = O, R = 4-OMe-C_6H_4
157: X = O, R = 3,5-$(CF_3)_2$-C_6H_3
158: X = S, R = 3,5-$(CF_3)_2$-C_6H_3
159: X = O, R = C_6F_5

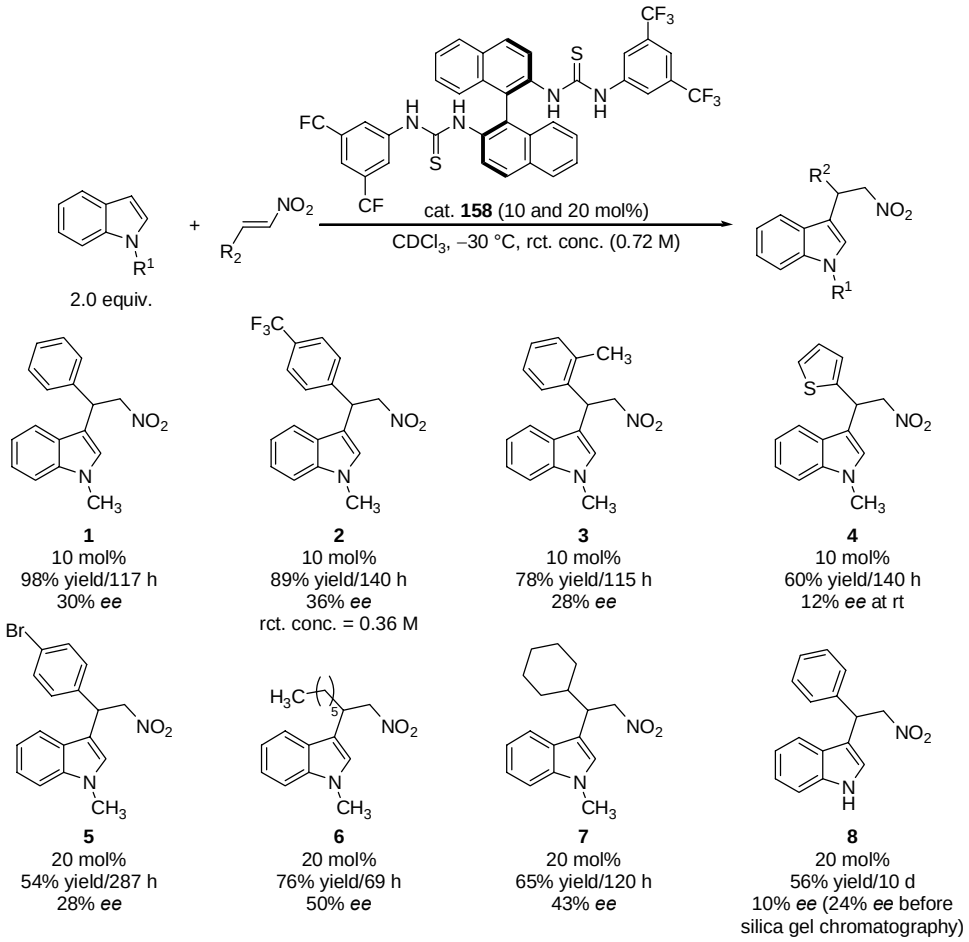
160: X = O, W = H, Z = H, R = C_6F_5
161: X = O, W = Br, Z = H, R = C_6F_5
162: X = O, W = Br, Z = Br, R = C_6F_5
163: X = S, .W = H, Z = H,
R = 3,5-$(CF_3)_2$-C_6H_3

164: R = 3,5-$(CF_3)_2$-C_6H_3
165: R = C_6F_5

Figure 50. (*R*)-bis-*N*-tosyl-BINAM-derivative **151** and axially chiral bis(thio)ureas **152**–**165** screened for catalytic efficiency in the asymmetric addition of indole and *N*-methylindole to nitroalkenes.

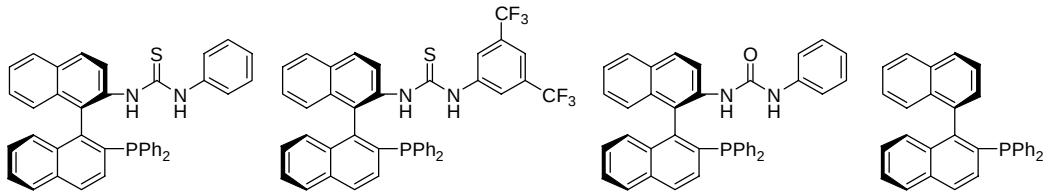
A screening of (*R*)-bis-*N*-tosyl-BINAM **151** and axially chiral (thio)urea derivatives **152**–**162** (10 mol% loading; 0.36 M catalyst concentration incorporating the *N*-aryl(alkyl) structural motif was performed at various reaction temperatures in d_1-chloroform using the asymmetric FC addition of *N*-methylindole to *trans*-*β*-nitrostyrene as model reaction (product **1**; Scheme 158**).** The structure of bis(3,5-bistrifluoromethyl) phenyl functionalized binaphthyl bisthiourea **158** was identified to represent the best practical compromise of both catalytic activity and stereoinduction. For (*R*)-bis-*N*-tosyl-BINAM **151** no catalytic effect was detected (adduct **1**: <2% conv.; no *ee* after 72 h at rt) comparable to the uncatalyzed reference experiment affording only trace levels of FC adduct **1** after the same reaction time. The importance of the (thio)urea motif for catalytic efficiency became evident from the screening results obtained for BINAM-derivative **151** in comparison with the accelerating effect of tosyl-urea **152** (adduct **1**: 80% conv./20 h; 100% conv./166 h, no *ee*). Urea derivative structures **153**–**156** bearing either aliphatic (cyclohexyl) or electron-rich/sterically hindered aromatic substituents afforded model FC adduct **1** in very low enantioselectivities (7%–10%) and exhibited low conversions (2–14%) even after 113 h reaction time. In contrast, the structural analogues **157**, **158**, and **159** incorporating electron-deficient aromatic substituents displayed a higher catalytic efficiencies ranging from 100% conv. (113 h) and 11% *ee* for urea structure **157** and 100% conv. after 160 h (12% *ee*) for thiourea counterpart **158** to 93% conv. (166 h) to 15% *ee* for decafluoro urea **159**. At –20 °C thiourea **159** revealed a loss of catalytic activity, but an increase of stereoinduction (adduct **1**: 42% conv./167 h; 34% *ee*), while catalyst **158** showed at –30 °C an increase of the *ee* value (30%) without a remarkable decrease of catalytic activity (88%/64 h). A higher catalyst concentration enhanced the conversion (e.g., **159** at –20 °C: 80% conv.; 28% *ee* after 70 h at 0.76 M conc.). The comparability and interpretation of the experimental screening data, however, suffered from different reaction times and conditions chosen by the authors. The modification of the axially chiral backbone represented by the (thio)ureas **160**–**163** led to no

appreciable improvements in both rate enhancement and stereoinduction (no *ee* to < 30% *ee*) . The octahydro-analogues of **158** and **159** (**160** and **163**, respectively) were significantly less efficient in the formation of model adduct **1** (**160**: 23% conv./65 h; 20% *ee*/rt; **163**: 15% conv./113 h; 28% *ee*/–30 °C). Mono- and di-bromo derivatives of **160** (**161** and **162**, respectively) gave the racemic product. The catalytic activity of urea-based catalyst **157** could be substantially increased through the incorporation of bromo substituents at C-6 and C-6' position (urea **164**: 100% conv.; 22 h; 5 % *ee* at rt). Under optimized reaction conditions thiourea **158** (10 and 20 mol%) catalyzed the asymmetric addition of indole and *N*-methylindole to aliphatic and predominantly electron-rich as well as electron-poor aromatic *trans*-*β*-nitroalkenes. The respective FC adducts **1**–**8** were obtained in moderate to excellent yields (54–98%) and in low enantioselectivities (12–50% *ee*) in long reactions times (69 h–287 h) as shown in Scheme 158. For understanding the mode of action of catalysts **158** and the origin of stereoinduction the authors performed a crystal structure analysis of catalyst **158**, which revealed the *s*-*trans*, *cis* conformation of the thiourea moiety instead of the expected *s*-*cis*, *cis* alternative[1, 116] and a long distance of the most suitably oriented thiourea amide hydrogen atoms of 3.53 Å (O–O distance in nitroolefin was considerably shorter: approx. 2.15 Å). Assuming that the conformation of the crystalline thiourea catalyst **158** represented the catalytically active conformation the authors suggested a nitroalkene activation through single hydrogen-bonding of the nitro functionality akin to primary amine functionalized thiourea catalysts **99** (Scheme 102) and **100** (Scheme 104), respectively.



Scheme 158. Product spectrum of the **158**-catalyzed asymmetric FC addition of indole and *N*-methylindole to various nitroakenes. The product configurations were not determined.

M. Shi and Y.-L. Shi reported the synthesis and application of new bifunctional axially chiral (thio)urea-phosphine organocatalysts in the asymmetric aza-Morita-Baylis-Hillman (MBH) reaction[179, 180] of *N*-sulfonated imines with methyl vinyl ketone (MVK), phenyl vinyl ketone (PVK), ethyl vinyl ketone (EVK) or acrolein, respectively.[320] The design of the catalyst structure is based on axially chiral BINOL-derived phosphines[321, 322] that have already been successfully utilized as bifunctional catalysts in asymmetric aza-MBH reactions. The formal replacement of the hydrogen-bonding phenol group with a (thio)urea functionality led to catalysts **166**, **167**, and **168** (Figure 51).



166 (70% yield)
97% yield/10 h
91% *ee* at rt

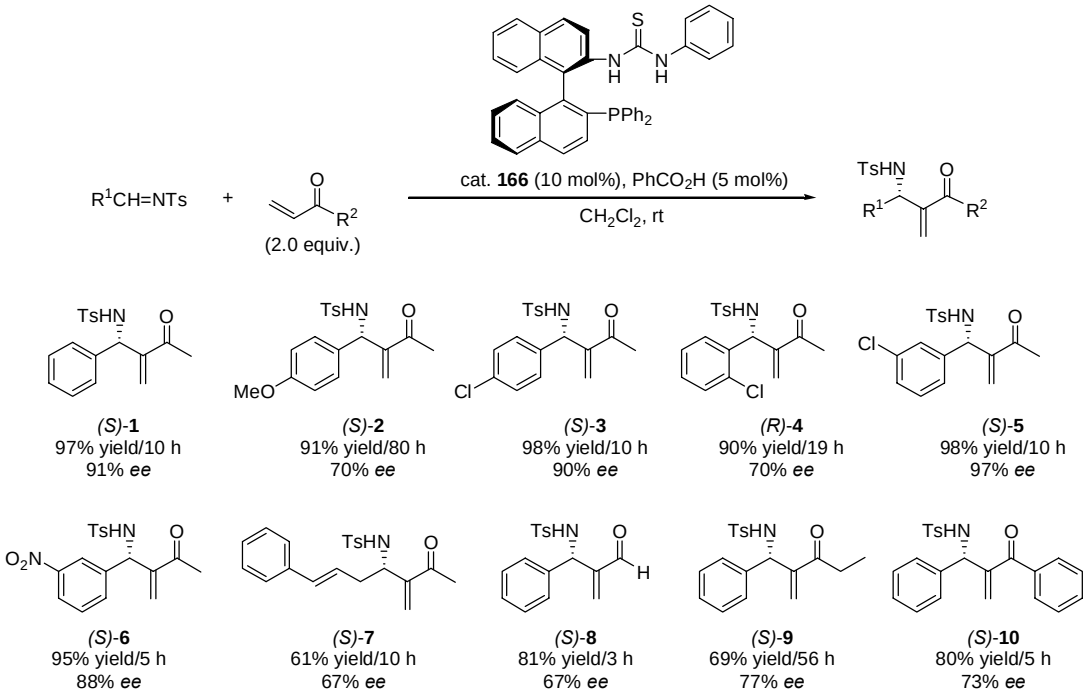
167 (94% yield)
50% yield/10 h
70% *ee* at rt

168 (78% yield)
63% yield/10 h
64% *ee* at rt

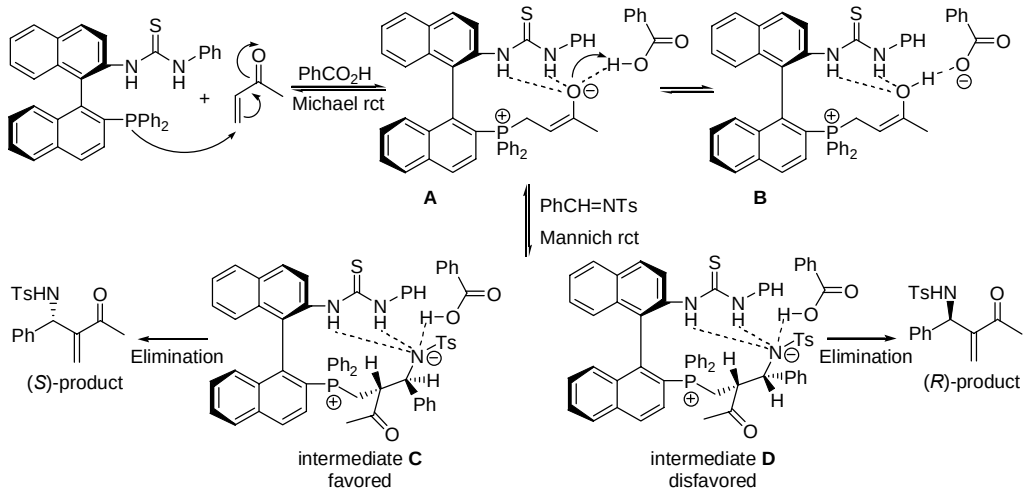
169
62% yield/17 h
13% *ee* at rt

Figure 51. Bifunctional (thio)urea-phoshine catalysts **166**–**168** prepared from (*R*)-2′-diphenylphosphanyl-[1,1′]binaphthalenyl-2-ylamine and the corresponding iso(thio)cyanate; the yield of the catalysts is given in parentheses. Catalyst screening results of the model product (*S*)-**1** (Scheme 159) formation in the presence of 5 mol% benzoic acid are given below and identifies **166** as the most active catalyst. **169** lacking the thiourea group was significantly less active.

The aza-MBH model reaction of *N*-benzylidene-4-methylbenzenesulfonamide and methyl vinyl ketone in the presence of catalyst **166** (10 mol%) furnished different yields and *ee* values of the resulting adduct (*S*)-**1** (Scheme 159), when using long-stored (adduct **1**: 78% yield; 70% *ee*) or freshly prepared (adduct **1**: 12% yield; 16% *ee*) sulfonamide starting material under otherwise identical conditions. ^{1}H NMR analysis of the long-stored *N*-benzylidene-4-methylbenzenesulfonamide showed 4-methylbenzenesulfonamide and benzoic acid as impurities formed by decomposition of the starting material. The addition of benzoic acid (10 mol%) to the model MBH reaction of freshly prepared *N*-benzylidene-4-methylbenzenesulfonamide with MVK indicated that this additive accelerated the conversion (96% yield/10 h) and increased the *ee* value (87%/rt/CH_2Cl_2) of adduct **1**, while the addition of 4-methylbenzenesulfonamide turned out to be without impact on the progress and outcome of this aza-MBH reaction. The optimization of the reactions conditions including benzoic acid loading, acidic additives, solvent, temperature, and the catalytic efficiency of **166**–**168** were carried out in the formation of model product **1** (Scheme 159). Variable loadings of benzoic acid in the range of 2.0 mol% (adduct **1**: 81% yield/10 h; 87% *ee*/rt) to 50 mol% (adduct **1**: 11% yield/10 h; 74% *ee*/rt) to demonstrate 5 mol% (adduct **1**: 97%, 91% *ee*/rt) loading to be the best. Various acidic additives with different steric hindrances and acididities were explored; these experiments revealed that additives with weaker (e.g., *p*-nitrophenol, pK_a = 7.15: yield 32%/ 10 h; 17 % *ee*) or stronger (e.g., *o*-iodobenzoic acid, pK_a = 2.86, 41% yield/10 h 76% *ee*/rt) acidity resulted in lower yields and *ee* values of adduct **1**. Only those additives with similar acidity to benzoic acid (pK_a = 4.20) gave satisfactory results (e.g., naphthalene-2-carboxylic acid, pK_a 4.16, 95% yield/10 h, 88% *ee*/rt); benzoic acid afforded the highest *ee* value (91%) and yield (97%) of the aza-MBH adduct **1** in 10 h reaction time. A longer reaction time and a lower reaction temperature (0 °C) had no significant effect on yield or enantioselectivity (adduct **1**: 95% yield; 92% *ee* after 72 h; 10 mol% **166**, 5 mol% benzoic acid). Thiourea **166** proved to be the most active thiourea catalyst (Figure 51) and was utilized at 10 mol% loading under optimized conditions to organocatalyze aza-MBH reactions of various *o*-, *m*-, and *p*- substituted aromatic *N*-sulfonated imines with simple *α,β*-unsaturated carbonyl compounds affording the adducts **1**–**10** in moderate to excellent yields (61–98%) and enantioselectivities (67–97% *ee*) (Scheme 159). The thiourea functionality appeared to be essential for the accelerating effect as well for the stereoinduction as shown by the application of **159** under optimized conditions and longer reaction time (Figure 51). The mechanism proposed for the **166**-catalyzed aza-MBH reaction and the function of benzoic acid based upon ^{31}P NMR spectroscopic investigations (Scheme 160). Thiourea **166** was suggested to operate as a bifunctional organocatalyst such that the phosphine group serves as the nucleophile to initiate the transformation by a Michael addition step, while the thiourea group served as a hydrogen-bonding donor to stabilize the in situ generated enolate intermediate **A**. A subsequent Mannich reaction furnishes the sterically favored intermediate **C** instead of disfavored **D,** and elimination give the observed (*S*)-configured product **1** in Scheme 159. Benzoic acid serves as a proton source leading to rate enhancement and improved asymmetric induction. The protonation of **A** gives intermediate **B** that is additionally stabilized through benzoate acting as a hydrogen-bond acceptor; benzoic acid, however, protonated the negatively charged nitrogen in **C** to give (*S*)-configured adduct **1** and suppressed reversible steps that could led to decreased enantioselectivities. Too much benzoic acid or addition of stronger acids, however, disfavored the formation of intermediate **A** in its rapid equilibrium with intermediate **B** (Scheme 160). In contrast, weaker acids proved to be less efficient as proton sources to generate the enol intermediate and to accelerate the reaction rate**.** This methodology represents a rare example for dual catalysis between a Brønsted acid and a hydrogen-bonding thiourea derivative akin to the cooperative Brønsted-acid type organocatalysis of the styrene oxides alkoholysis developed by the Schreiner group (Scheme 28).[176]

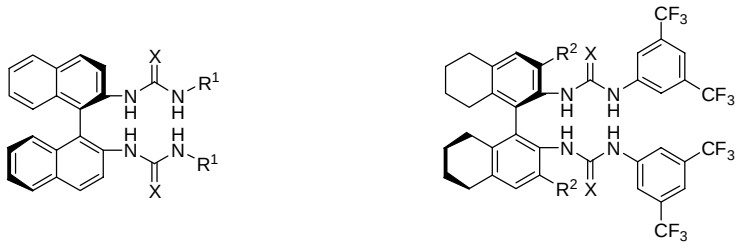


Scheme 159. Representative products obtained from the **166**-catalyzed asymmetric aza-MBH reaction between *N*-sulfonated imines α,β-unsaturated ketones and acrolein.



Scheme 160. Mechanistic proposal for the **166**-catalyzed aza-MBH reaction using benzoic acid as additive.

M. Shi and co-workers utilized axially chiral bis(arylurea)- and bis(arylthiourea)-based organocatalysts already introduced by Connon et al.[319] (Figure 50) in the enantioselective Henry addition[228] of nitromethane to arylaldehydes.[323] The synthesis of these thiourea organocatalysts is based on axially chiral (*R*)-(+)-binaphthalenediamine (BINAM) as the starting material to obtain successively the hydrogenated and the 3,3′-disubstituted BINAM-derivatives that were subsequently condendsed with 3,5-bis(trifluoromethyl) phenyl iso(thio)cyanate providing binaphthyl (thio)ureas **157**, **158**, **163**, and **170**–**175** in yields ranging from 58% (**170**) to 99% (**172**) (Figure 52).



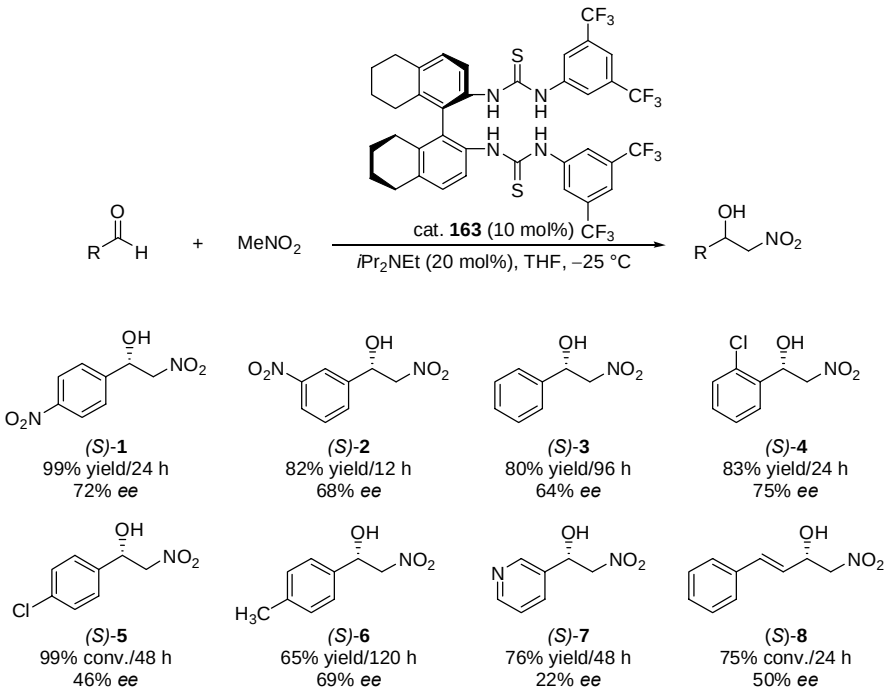
170: X = S, R^1 = Ph
157: X = O, R^1 = 3,5-$(CF_3)_2C_6H_3$
158: X = S, R^1 = 3,5-$(CF_3)_2C_6H_3$

171: X = O, R^2 = H
163: X = S, R^2 = H
172: X = O, R^2 = Ph

173: X = S, R^2 = Ph
174: X = S, R^2 = 4-MeC_6H_4
175: X = S, R^2 = 3,5-$Me_2C_6H_3$

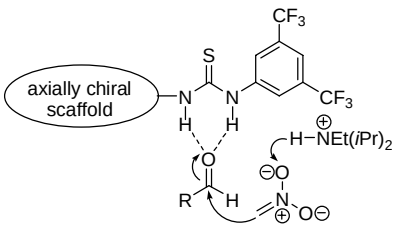
Figure 52. Axially chiral Bis(thio)ureas prepared from BINAM (**157**, **158**, and **170**), (*R*)-(+)5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl-2,2′-diamine **(163** and **171**), and (*R*)-(+)3,3′-disubstituted-5,6,7,8,5′,6′,7′,8′-octahydro-[1,1′]binaphthalenyl-2,2′-diamines (**172**–**175**), respectively, for organocatalysis of Henry reactions between aromatic aldehydes and nitromethane.

The catalyst screening experiments were performed in the asymmetric Henry addition of nitromethane (10 equiv.) to 4-nitrobenzaldehyde in the presence of DABCO (20 mol%) as the base and (thio)ureas **157**, **158**, **163**, and **170**–**175** (each 10 mol% loading), respectively. After 12 h in reaction time at room temperature and in THF as the solvent the corresponding Henry adduct was obtained in excellent yields (99%) but very low *ee* values (7%–17%) nearly independently of the sterical hindrance of the axially chiral backbone skeleton (e.g., **172**: and **174**: each 99% yield; 11% *ee*). Thioureas appeared slightly more enantioselective (e.g., **163**: 83% yield, 33% *ee*; **171**: 99% yield, 15% *ee*) than their urea counterparts probably owing to more efficient substrate complexation through stronger hydrogen-bonding interactions. Thiourea **163** derived from (*R*)-(+) 5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl-2,2′-diamine was identified to be the most active catalyst and was employed for the Henry reactions of electron-rich and electron-poor aromatic aldehydes with nitromethane under solvent-, temperature-, and base additive optimized conditions. The protocol worked under mild conditions to furnish the corresponding nitroalcohols **1–8** in good to excellent yields (75%–99%) and moderate to good enantioselectivities (50–75% *ee*) as depicted in Scheme 161.



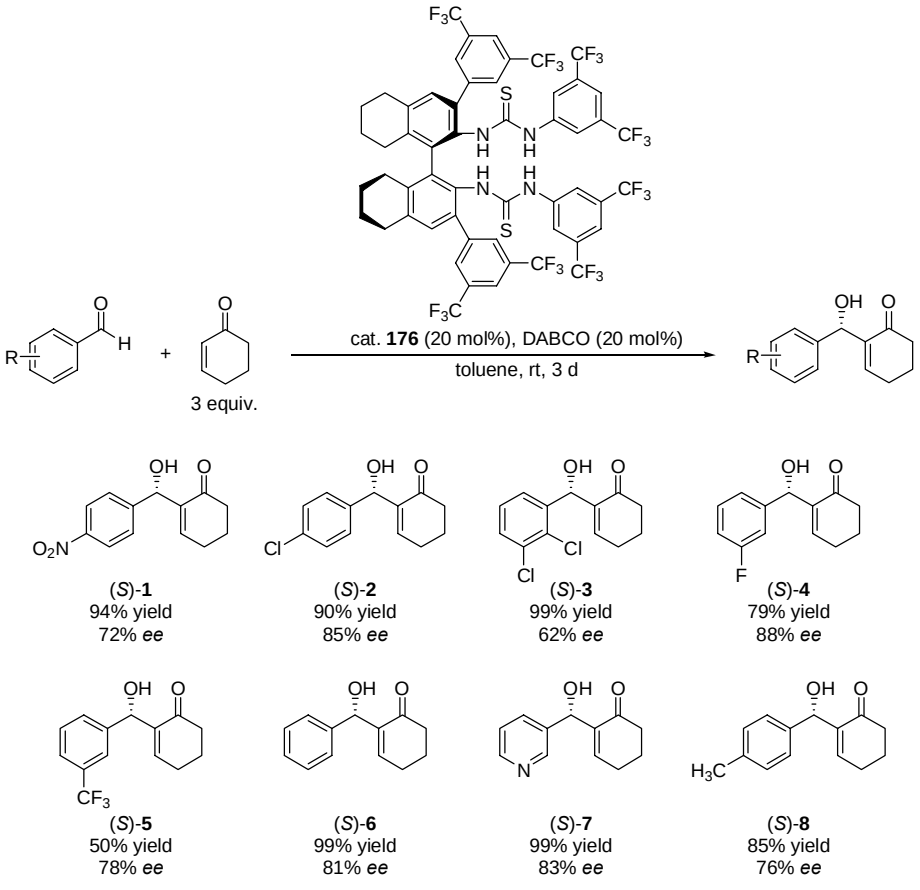
Scheme 161. Product range for the **163**-catalyzed enantioselective Henry reaction of arylaldehydes with nitromethane.

The authors interpreted the outcome of these Henry reactions with an activation of the aldehyde component through double hydrogen-bonding interactions with the thiourea moiety facilitating the product-forming nucleophilic attack of the in situ generated nitronate (Scheme 162).[323]



Scheme 162. Mechanistic proposal for the Henry reaction catalyzed by bifunctional double hydrogen-bonding thiourea derivative **163**.

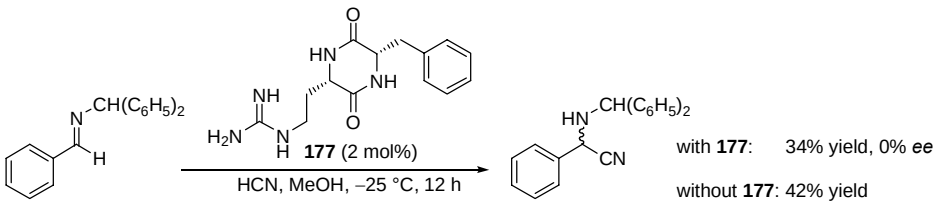
In 2008, M. Shi and Liu reported the synthesis of novel axially chiral bis(thio)ureas from the (*R*)-(–)5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl-2,2′-diamine (H_8-BINAM) building block and the application of these (thio)ureas as hydrogen-bonding catalysts in the enantioselective Morita-Baylis-Hillman reaction[179, 180] between predominantly 2-cyclohexen-1-one and a wide range of electron-deficient and electron-rich benzaldehydes in the presence of DABCO (20 mol%).[324] Employing the optimized reaction parameters (toluene, rt, 3 d reaction time) the most efficient axially chiral bisthiourea **176** (20 mol%) incorporating the 3,5-bis(trifluoromethyl)phenyl moiety at the 3,3′-position furnished the desired MBH adducts **1**–**8** in moderate (50%) to excellent yields (99%) and in good enantioselectivities (62%–88%) as shown in Scheme 163. The MBH reaction between 2-cyclopenten-1-one and 4-nitrobenzaldehyde was described to proceed under standard conditions affording the corresponding adduct in 43% yield and 60% *ee*. Notably, this protocol turned out to favor the formation of the (*S*)-configured MBH adducts.



Scheme 163. Product range of the asymmetric MBH reaction catalyzed by bisthiourea **176** in the presence of DABCO.

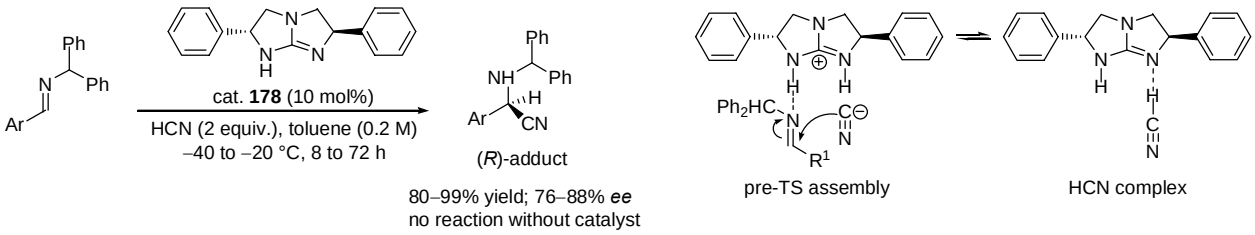
1.2.2.5 Guanidine-based Thiourea Derivatives

Guanidines and guanidinium salts have been widely used in organic synthesis[325] and due to their hydrogen-bond donor ability they are utilized for anion recognition.[111] 1996 guanidine-functionalized diketopiperazine **177** was introduced and suggested to be an efficient catalyst for the asymmetric Strecker reaction[159] of various aldimines (80–97% yield/up to 99% *ee*).[326] In the following decade of growing interest in organocatalysis this publication has been cited frequently as the first example of an organocatalyzed enantioselective Strecker reaction. During their investigations towards the development of a metal-free protocol for the Strecker reaction the Kunz group could not, however, reproduce the reported synthesis of guanidine-diketopiperazine **177** nor the reported catalytic effect.[327] Structure **177** was prepared by a different procedure and structurally confirmed by X-ray analysis; this compound has proven not to be an enantioselective organocatalyst for the Strecker reaction at 0°, –25 °C, or –70 °C, neither as the hydroacetate nor as the hydronitrate, and without **177** the Strecker reaction was found to proceed even slightly faster (Scheme 164).[327]



Scheme 164. Strecker reaction for examination of the catalytic efficiency of guanidine functionalized diketopiperazine **177**.

The first organocatalyzed enantioselective Strecker reaction[159] thus has been reported by Corey and Grogan in 1999.[328] The C_2-symmetric chiral bicyclic guanidine **178** was described to operate as a bifunctional single hydrogen-bonding organocatalyst, which activated the aldimine substrate and formed the corresponding Strecker adducts in good to excellent yields (80–99%) and good enantioselectivities (76%–88%) (Scheme 165). This guanidine catalyst was found to be recoverable (80–90%) and reusable in these asymmetric Strecker reactions.



Scheme 165. Enantioselective Strecker reactions catalyzed by bifunctional hydrogen-bonding guanidine organocatalyst **178**. Catalytic action of **178**: HCN hydrogen-bonds to **178** and generates a guanidinium cyanide complex after protonation, which activates the aldimine through single hydrogen-bonding and facilitates stereoselective cyanide attack and product formation.

In 2005, Nagasawa and co-workers developed a new catalyst design concept leading to novel hydrogen-bonding bifunctional organocatalysts, which incorporate both a guanidinium alkyl chain moiety and two electron-poor thiourea functional groups linked by a modular chiral spacer (Figure 53).[329-331] Based on this concept a series of C_2-symmetric guanidine-thiourea derivatives **179**–**189** bearing various substituents were prepared via multistep synthesis starting from enantiomerically pure amino acids (Figure 54). These were screened for their catalytic efficiency in the enantioselective Henry (nitroaldol) reaction[228] between cyclohexane carboxaldehyde and nitromethane under toluene/aqueous potassium hydroxide biphasic conditions at 0 °C and 5 mol% catalyst loading.[329]

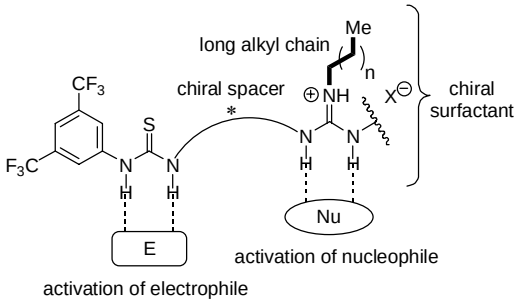
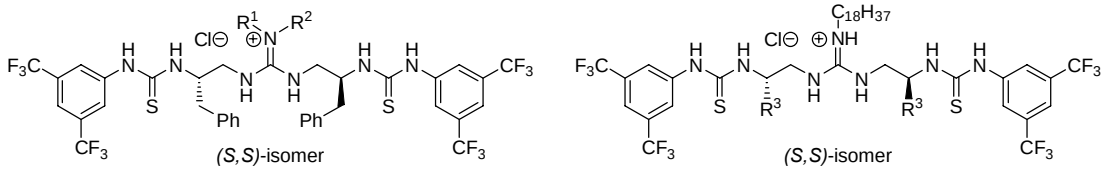


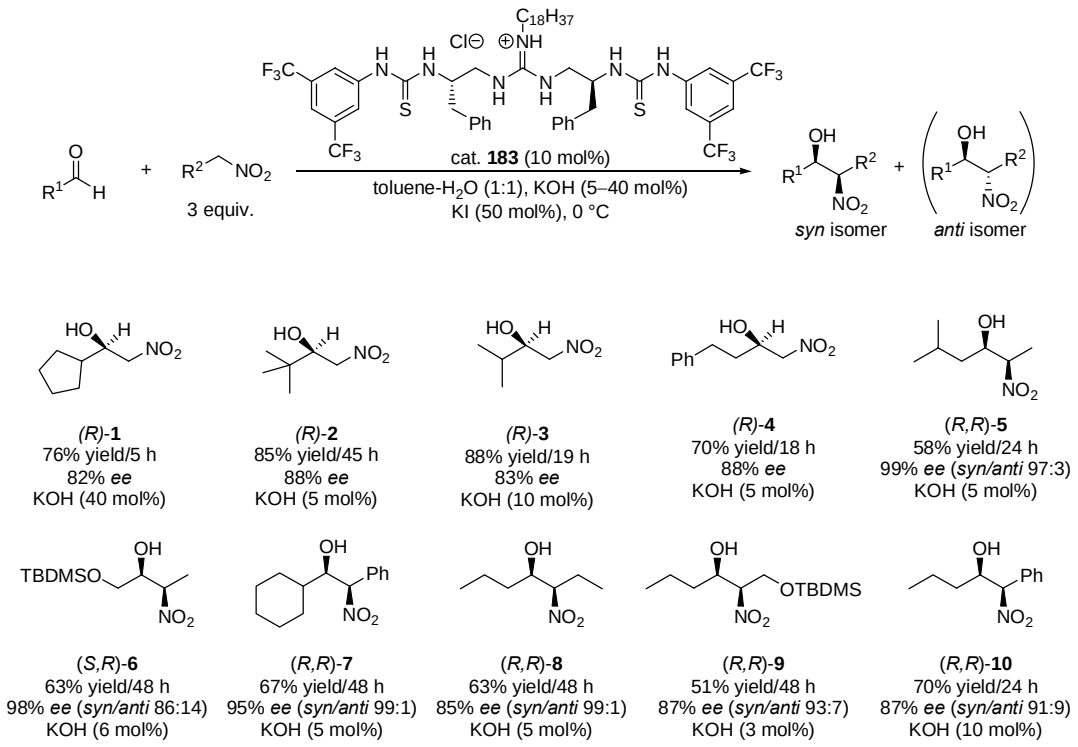
Figure 53. Structural concept for the design of guanidine-based bifunctional thiourea organocatalysts **179**–**189** and mode of bifunctional substrate activation.



179: $R^1 = C_4H_9$, R^2 = H
180: $R^1 = R^2 = C_4H_9$
181: $R^1 = R^2 = (CH_2)_4$
182: $R^1 = C_8H_{17}$, R^2 = H
183: $R^1 = C_{18}H_{37}$, R^2 = H
184: R^1 = 3,5-$(CF_3)_2$-C_6H_4 , R^2 = H
185: R^1 = 3,5-$(OMe)_2$-C_6H_4 , R^2 = H
186: R^1 = *(R,R)*-isomer of **183**
187: R^3 = Me
188: R^3 = *i*Pr
189: R^3 = *t*Bu

Figure 54. Structures of guanidine-based thiourea derivatives screened in the Henry reaction of nitromethane with cyclohexane carboxaldehyde under phase-transfer conditions.

Guanidine-thiourea **183** incorporating an octadecyl substituent (R^1) at the guanidine moiety and benzyl groups as chiral spacers (R^3) revealed the highest efficiency in the formation of the model Henry adduct considering both reaction rate (91% yield/24 h) and asymmetric induction (43% *ee*) while catalyst candidates **179**–**182**, **184**–**185**, and **187**–**189** gave poorer yields (24–89%) and *ee* values (8–36%).[329] Time course studies with catalyst **183** for the above screening reaction indicated that the retro-nitroaldol reaction occurred under the chosen biphasic reaction conditions resulting in the (*R*)-configured adduct and gradual decrease of enantioselectivity (after 1 h: 52% yield/52% *ee*; 12 h: 90% yield/47% *ee*; 24 h: 91% yield/43% *ee*).[331] Since counter anions of not only ammonium salts, but also guanidinium salts have been reported to influence catalytic activity and stereoinduction the authors examined various alkali bromides, iodides, and tetrafluoroborates as additives (50 mol%) in the standard screening reaction. A hard counter anion furnished no improvement of the *ee* value (KBF_4: 77% yield; 47% *ee*/24 h) while soft KI was identified to serve as an effective inhibitor of the retro-mode reaction (KI: 88% yield; 74% *ee*/24 h). Utilizing catalyst **183** with iodide instead of chloride Henry adduct (*R*)-1-cyclohexyl-2-nitro-ethanol was formed with 85% yield and 72% *ee.* This result suggested that under these biphasic conditions the chloride counter anion of **183** was replaced with iodide in situ. Under optimized reactions conditions concerning the choice of the organic solvent, ratio of organic solvent and water, the amount of base, and the additive the enantioselective and *syn*-diastereoselective Henry reactions of nitromethane[329] and prochiral nitroalkanes[330] with aliphatic cyclic and α-branched aldehydes were performed (Scheme 166). The resulting nitroalcohol products (**1**–**10**) were isolated in moderate to good yields (51%–88%) with moderate to excellent enantioselectivities (51%–99% *ee*) (Scheme 166). In all cases the addition reactions proceeded with high *syn*-diastereoselectivity (up to 99:1 *dr*).[329-331] The derivatives of catalyst **183** without a guanidine moiety (**190**) or without a thiourea functionality (**191**) revealed no or only a very poor catalytic efficiency under optimized reaction conditions (Figure 55).[331]



Scheme 166. Product range of the asymmetric Henry (nitroaldol) reaction of aldehydes with various nitroalkanes in the presence of (*S,S*)-configured catalyst **183**.

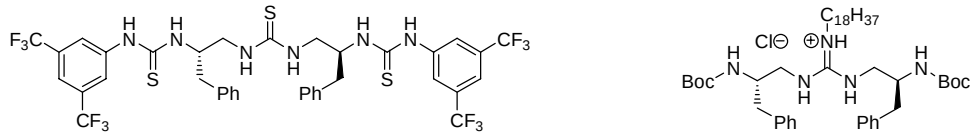
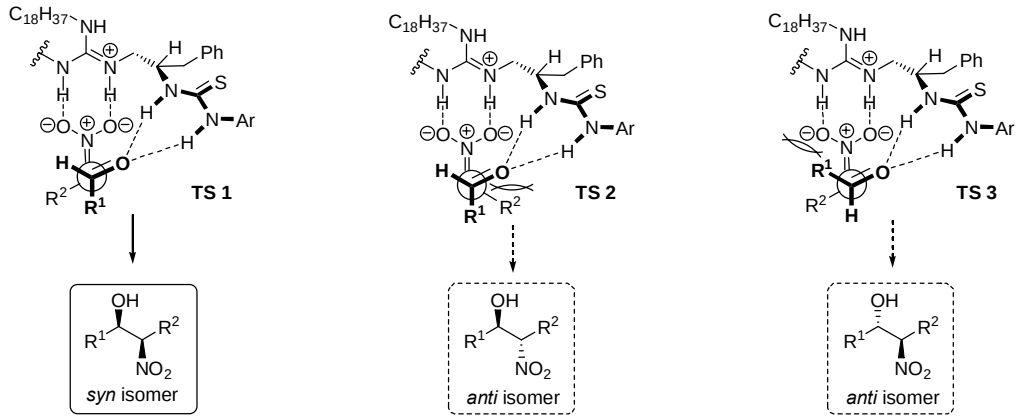


Figure 55. Uncharged tris-thiourea **190** without guanidinium moiety and charged guanidinium structure **191** without a thiourea group appeared catalytically inactive in the Henry reaction of cyclohexane carboxaldehyde with nitromethane, while guanidine-thiourea **183** gave 99% yield and 95% *ee* under identical (optimized) conditions.

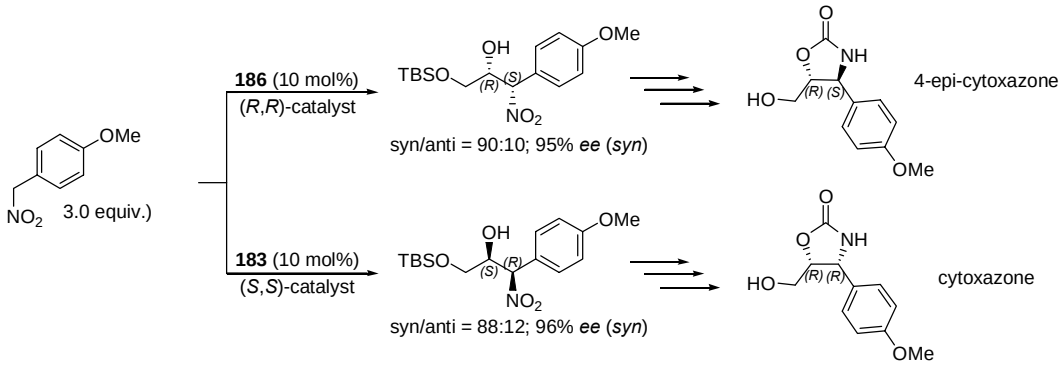
To gain insight into the structure-activity relationships various substituent patterns of (*S,S*)-catalyst **183** were studied utilizing the standard screening reaction. The substituent on the guanidinium moiety influenced the catalytic efficiency resulting in a poor yield when using an alkyl chain shorter than 12 carbon atoms (e.g., **182** C_8H_{17}: 8% yield/86% *ee*, but **183** $C_{18}H_{37}$: 91% yield/92% *ee*, in 24 h; Figure 54). The introduction of an aromatic group at the terminal position of a short alkyl chain (e.g., catalysts **184** and **185**; Figure 54) also enhanced the reaction rate and the asymmetric induction (e.g., **184**: 88% yield/82% *ee*; **185**: 82% yield/97% *ee* in 24 h) in comparison to an unsubstituted short alkyl chain (e.g., **179**: 8% yield/87% *ee* in 24 h; Figure 54). The substituent R^3 at the chiral spacer was found to be critical for both the reaction rate and the selectivity. Thee *ee* values decreased as the bulk of the R^3 group was increased (structure **187**: R^3 = Me: 3% yield/76% *ee*; **189**: R^3 = *t*Bu: 65 yield/6% *ee* after 24 h; Figure 54). Anionic (SDS, AOT) and non-ionic (Triton® X-100)[332] surfactants (20 mol%) completely inhibited the catalytic activity of **183** in the nitroaldol screening reaction, while the cationic surfactant CTAB at 20 mol% loading lowered the catalytic activity to obtain 53% yield and 80% *ee*, but suppressed the reaction entirely at 50 mol% loading. The authors assumed, that the cationic surfactant properties under biphasic conditions were important for the reactivity as well as for the selectivity, which were controlled through self-aggregation. The alkyl chain of the guanidinium moiety was suggested to contribute to the reactivity by

controlling the proximity of the substrates owing to hydrophobic interactions, and the benzyl group (= R^3) linked to the chiral spacer fix the high-order asymmetric structure through intramolecular π–π stacking interactions.[331] On the basis of these experimental findings the authors explained the observed selectivities with cooperative effects of the guanidinium moiety and the thiourea functionality for a chemoselective coordination and dual activation of the substrates through ionic as well as through hydrogen-bonding interactions as demonstrated in the transition state model visualized in Scheme 167.[329-331]



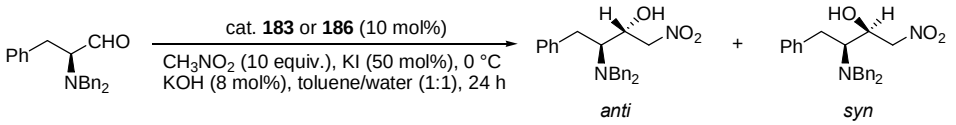
Scheme 167. Proposed transition-state models for the enantioselective Henry (nitroaldol) reaction in the presence of (*S,S*)-configured catalyst **183**: **TS 1**: *anti*,*anti* conformation; **TS 2**: gauche-*anti* conformation; **TS 3**: gauche-*anti* conformation.

The guanidinium cation and the thiourea group were suggested to coordinate selectively to the in situ formed nitronate and the carbonyl oxygen of the aldehyde, respectively, and substituents in both aldehyde (R^1) and nitronate (R^2) favor an *anti* relationship to minimize steric repulsion (Scheme 167: **TS 1**: *anti*, a*nti* conformation). This geometry induced the observed high *ee* and *dr* values of the nitroaldol products. The enantiodifferentiation in the case of prochiral ($R^2 \neq H$) was found to be higher than those with nitromethane ($R^2 = H$); this finding was in line with the model, because the less sterically hindered **TS 1** conformation was more favorable than the gauche, anti conformations of **TS 2** and **TS 3**, respectively (Scheme 167). The synthetic utility of this *syn*-selective enantioselective nitroaldol reaction was demonstrated by the multi-step synthesis of 4-*epi*-cytoxazone and cytoxazone.[331] (*S,S*)-configured catalyst **183** and its (*R,R*)-enantiomer **186** catalyzed the initial asymmetric key steps of these syntheses, in which two stereogenic centers were constructed (Scheme 168).[330, 331]



Scheme 168. Syntheses of 4-*epi*-cytoxazone and cytoxazone utilizing guanidine-thioureas **183** and **186** for the initial asymmetric Henry reaction step.

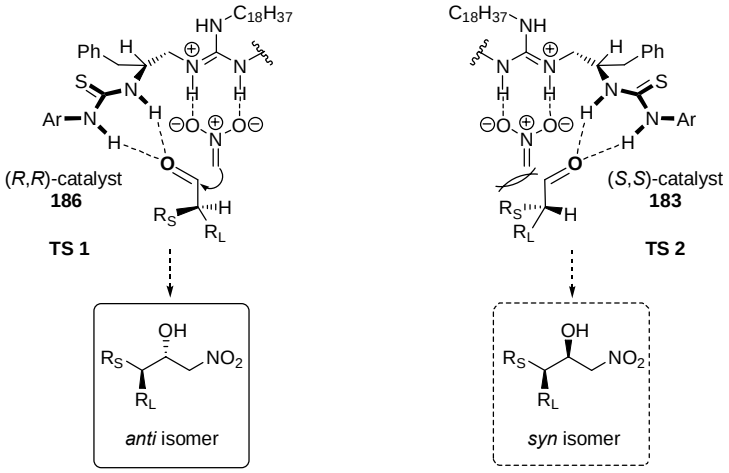
Since α-branched aldehydes gave rather higher asymmetric induction (Scheme 166) Nagasawa et al. extended the biphasic strategy to the diastereoselective Henry reaction of nitromethane with enantiomerically pure (*S*)-configured *N*,*N*′-dibenzyl protected α-amino aldehydes and α-hydroxy aldehydes protected as silyl ethers. The screening reaction (Scheme 169) demonstrated a match/mismatch relationship between the guanidine catalysts **183** and **186**, respectively, and (*S*)-α-amino aldehyde substrate.



(*S*,*S*)-catalyst **183**: 8% yield, *anti*/*syn* 64:36, 80% *ee* (*anti*), 62% *ee* (*syn*)
(*R*,*R*)-catalyst **186**: 75% yield, *anti*/*syn* 95:5, 99% *ee* (*anti*), 85% *ee* (*syn*)

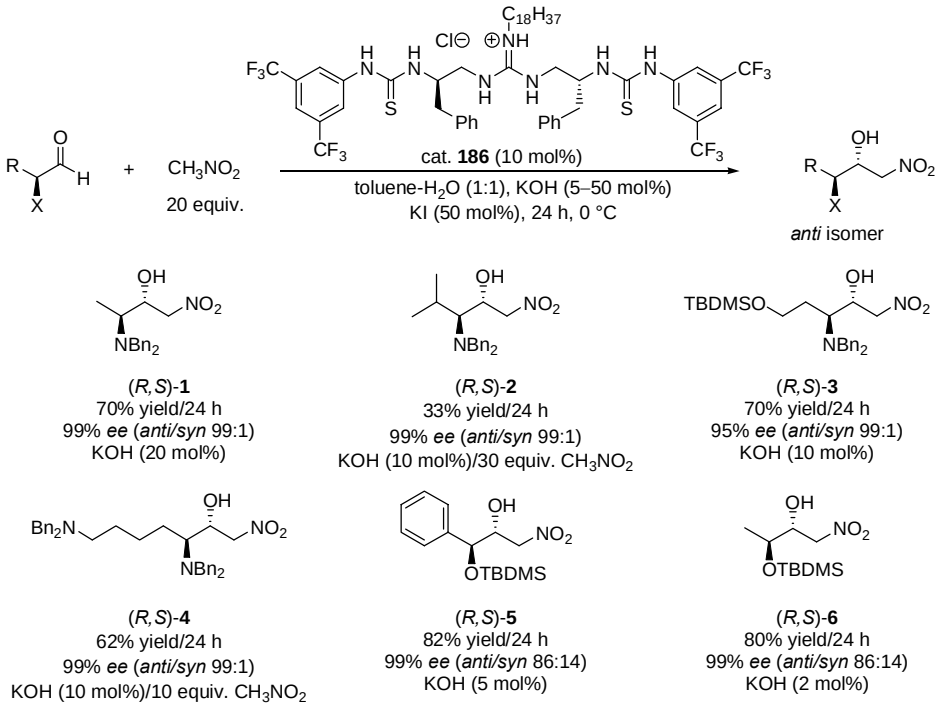
Scheme 169. Screening reaction to identify (*R*,*R*)-configured guanidine-thiourea **186** as matching catalyst for the *anti*-diastereoselective and enantioselective Henry reaction of (*S*)-α-amino aldehydes with nitromethane.

High *anti*-diastereoselectivity (95:5 *dr*) and enantioselectivity of the major isomer (99% *ee*) were obtained when utilizing the combination (*R*,*R*)-catalyst and (*S*)-aldehyde. This stereochemical outcome (Scheme 169) was explained in terms of the Cram rule proposed transition-state model. The substituent on the aldehyde would be located in an *anti*-relationship to the nitronate. As the largest substituent (R_L) should be in an *anti* position to the carbonyl group of the carbonyl substrate, the combination of (*R*,*R*)-catalyst **186** and (*S*)-substrate (**TS 1**) was favored rather than that of (*S*,*S*)-catalyst **183** and (*S*)-substrate (**TS 2**) owing to the steric repulsion between R_S (smallest substituent) and nitronate (Scheme 170).



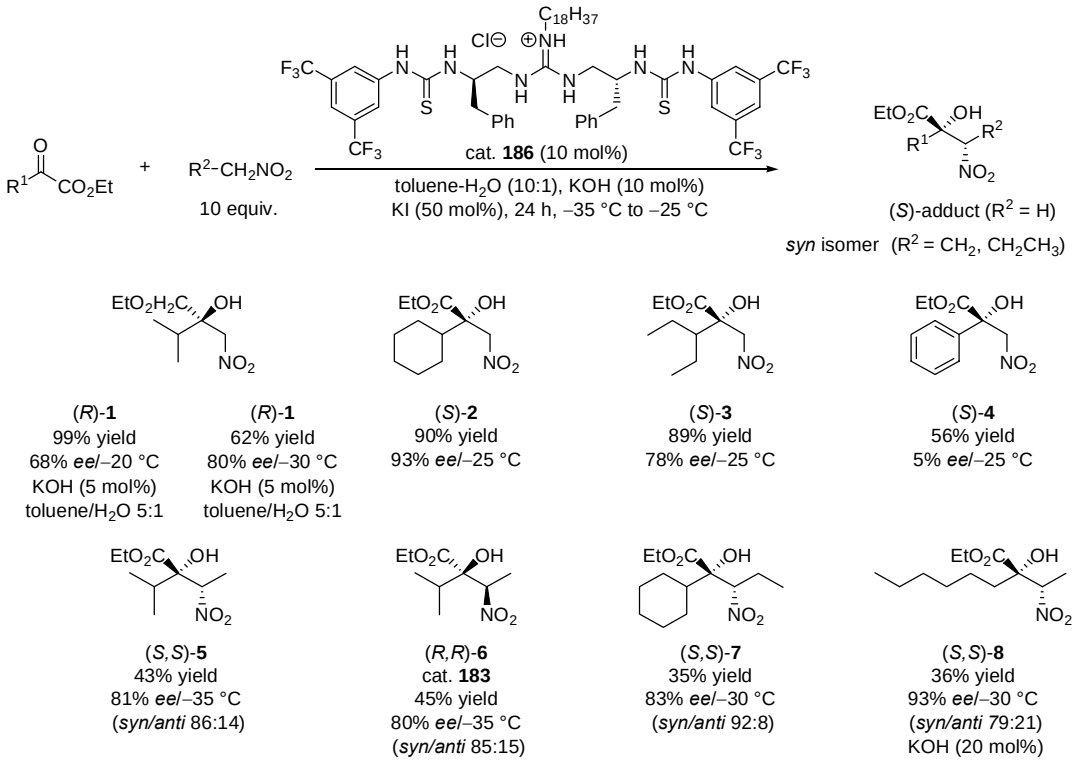
Scheme 170. Suggested transitions states for the *anti*-diastereoselective Henry (nitroaldol) reaction promoted by (*R*,*R*)-catalyst **186** (**TS 1**) and its (*S*,*S*)-isomer **183** (**TS 2**) to demonstrate the match/mismatch relationship between guanidine-thiourea catalyst and (*S*)-α-aldehyde.

Utilizing 10 mol% of (*R*,*R*)-guanidine-thiourea catalyst **186** under optimized biphasic conditions for the Henry reaction[228] of (*S*)-α-amino aldehydes with nitromethane furnished the corresponding nitroalcohols **1**–**6** in yields ranging from 33% to 82% and with excellent diastereoselectivities (up to 99:1 *anti*/*syn*) and enantioselectivities of the major isomer (95–99% *ee*) (Scheme 171).[333] Boc and Cbz protective groups turned out to be not tolerable in this protocol as indicated by epimerization of Boc or Cbz protected α-amino aldehydes substrates (e.g., *N*-Boc-protected 2-amino-3-phenyl-propionaldehyde: 70% yield/24 h, *anti*/*syn* ratio 50:50, 20% *ee* with **186**).

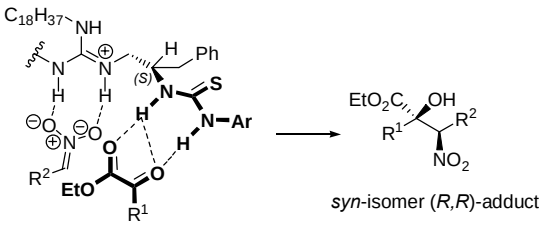


Scheme 171. Product range of the **186**-catalyzed *anti*-diastereoselective Henry (nitroaldol) reaction of α-chiral aldehydes with nitromethane.

The Nagasawa group modified the guanidine-thiourea catalyzed nitroaldol reaction[228] of nitroalkanes to aldehydes[329, 330, 333] proceeding under biphasic conditions and at 0 °C and published, in 2008, a new protocol working at subzero temperatures (–20 to –35 °C) for α-ketoesters reacting with chiral tertiary nitroalcohols.[334] The optimized protocol utilized organocatalysts **183** and **186** (10 mol%) under biphasic conditions in the presence of KOH (10 mol%) as base additive, and KI (50 mol%) to reduce the retro-mode of the reaction at a minimized toluene–water ratio (10:1 and 5:1); employing cyclic, branched-type, and linear α-ketoesters as well as nitroalkanes as substrates the protocol afforded the desired *tert*-nitroaldol alcohol adducts **1**–**8** in moderate to excellent yields (35–99%) with moderate to very good *ee* values (35–93%) as depicted in Scheme 172. An exemplified aromatic α-ketoester (R^1 = Ph) gave only a moderate yield (56%) and a very low *ee* value (5%) (adduct **4;** Scheme 172). The addition of nitroethane and 1-nitropropane was reported to proceed under *syn*-diastereoselectivity (e.g., adduct **7**, Scheme 172: syn/anti 92:8) und afforded the (*S*,*S*)-adducts when using (*R*,*R*)-catalysts **186** and the enantiomeric (*R*,*R*)-adducts in the presence (10 mol%) of the (*S*,*S*)-catalyst **183**. Performing the **183**-catalyzed (10 mol%) formation of nitroaldol adduct **1** (Scheme 172) under water-free conditions in pure toluene (–20 °C, 5 mol% KOH, 50 mol% KI) the respected adduct was obtained in only 8% yield and 15% *ee*, while the aqueous protocol (toluene/water 5:1) under otherwise identical conditions gave the same adduct in 99% yield and 68% *ee* (Scheme 172); this underlined the key role of water on both the accelerating effect and the asymmetric induction through guanidine-thiourea derivatives such as **183** and **186**, respectively. The stereochemical outcome of this nitroaldol reaction was ascribed to a transition state comparable to that proposed for aldehyde substrates (Scheme 167 and 170) and was based on the hydrogen-bonding mediated chemoselective dual activation of the reactants. To minimize steric repulsion the larger substituent of the R^1 group of the α-ketoester and the R^2 group of the nitroalkane was considered to favor the relative *anti* geometry with respect to the nitroalkane and the ketone affording the (*R*,*R*)-configured *syn*-isomeric adduct **6** under catalysis with (*S*,*S*)-configured catalyst **183** (Scheme 172 and 173).[334]



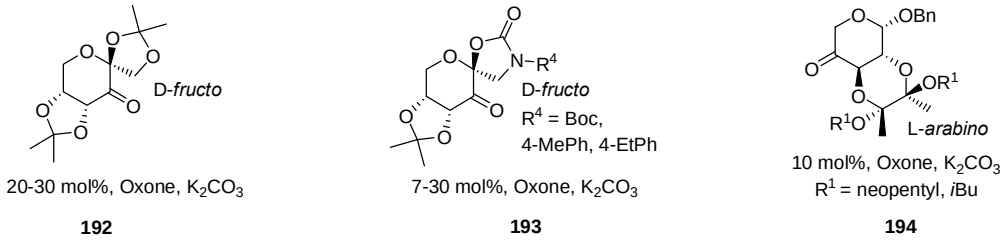
Scheme 172. Typical chiral adducts obtained from the **186**-catalyzed nitroaldol reaction between α-ketoesters and nitroalkanes.



Scheme 173. Proposed transitions state geometry for the nitroaldol reaction of nitroalkanes with α-ketoesters in the presence of (*S*,*S*)-configured guanidine thiourea **183**.

1.2.2.6 Saccharide-based (Thio)urea Derivatives

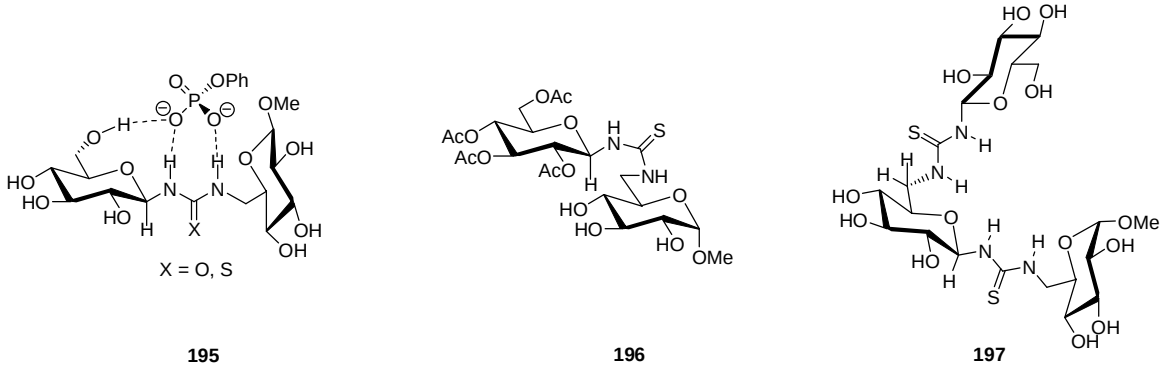
Carbohydrates are configurationally stable, easily available in enantiopure quality from the chiral pool, and they show a high density of chiral information per molecular unit. Their polyfunctionality and structural diversity facilitate their tailor-made modification, derivatization, and structural optimization for a broad spectrum of synthetic applications. While derivatives of various saccharides have already been utilized as versatile starting materials and building blocks for chiral auxiliaries, ligands, and reagents[335] their obvious role as precursors for the synthesis of organocatalysts is underdeveloped. Shi and co-workers introduced D-fructose based ketone **192** and its L-enantiomer as epoxidizing organocatalysts (Figure 56). In combination with oxone®[336] a wide range of unsaturated compounds such as hydroxy alkenes,[337] enynes,[338] and esters[339] were highly stereoselectively epoxidized to the corresponding oxiranes. Replacing the spiroketal functionality of **192** with a spiro oxazolidinone moiety to obtain organocatalyst **193** supplemented the substrate scope of **192** to terminal and 1,2-*cis*-configured alkenes as well as styrenes;[340] Catalysts **192** and **193** has also been successfully applied to the oxidation of disulfides to chiral thiosulfinates.[341, 342] The Shing group prepared ketone derivatives of L-arabinose such as catalyst **194** to achieve good to excellent results for the epoxidation of aromatic *trans*- and tri-substituted alkenes (Figure 56).[343]



192 **193** **194**

Figure 56. Saccharide-based epoxidizing organocatalysts derived from D-fructose (**192** and **193**) and L-arabinose (**194**).

Series of various mono,- bi-, and poly-(thio)urea functionalized (poly)saccharides have already been synthesized and studied for molecular recognition of, e.g., dimethyl and phenylphosphate as model compounds for monoanionic and polyanionic phosphate esters, respectively.[111] Thiourea derivatives such as **195**, **196**, and **197** were analytically identified to provide double hydrogen-bonding mediated host-guest complexes of well-defined dimension and orientations and were also reported to serve as phosphate binders even in the hydrogen bonding environment of water (Figure 57).[111]

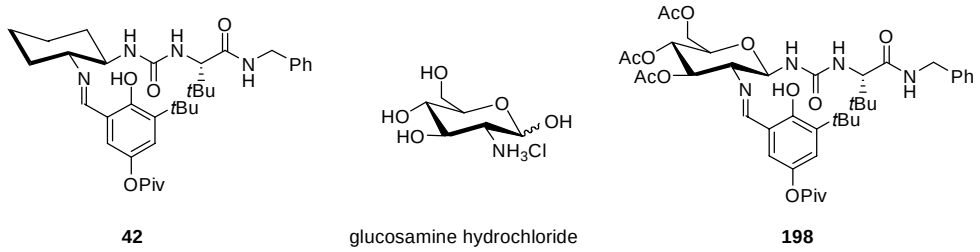


195 **196** **197**

Figure 57. Saccharide-based (thio)ureas that coordinate phosphate anions through hydrogen-bonding even in water.

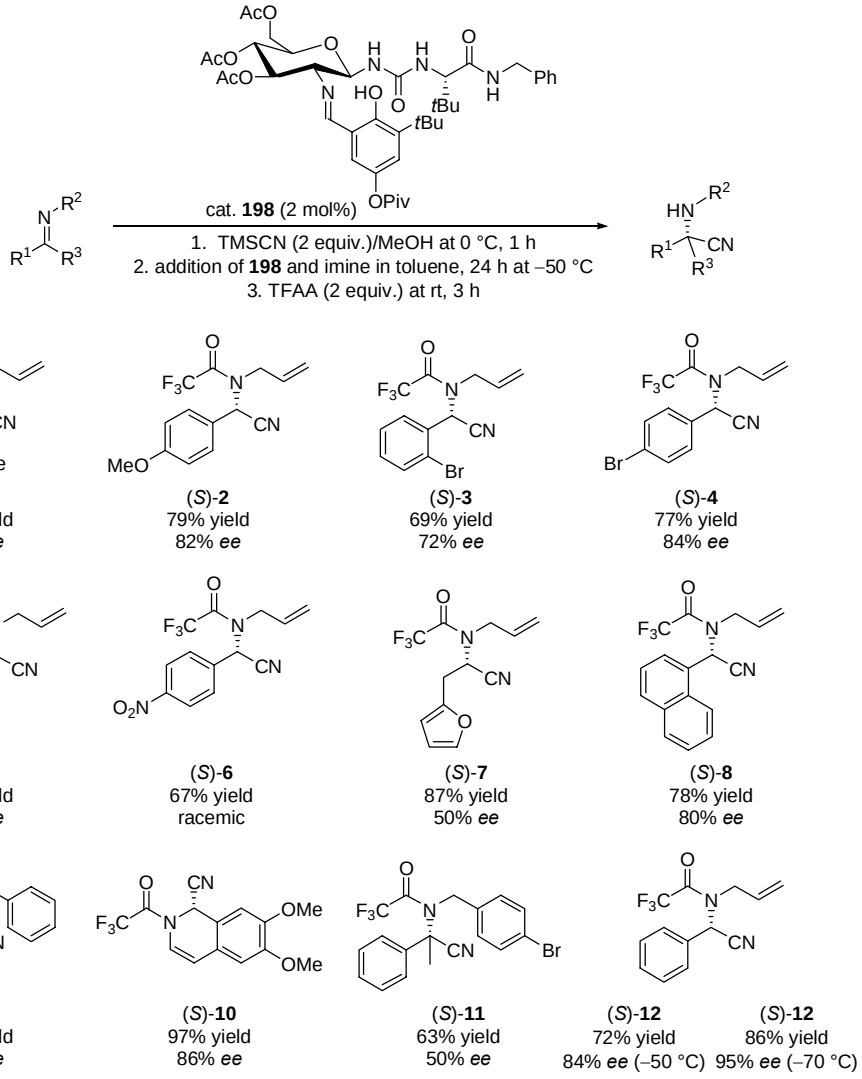
Kunz and co-workers for the first time realized the potential of saccharides to facilitate synthetic access to a novel class of hydrogen-bonding organocatalysts such as urea derivative **198**.[344] The rational design of these urea-functionalized monosaccharide is based on the structure of Jacobsen's *trans*-1,2-diaminocyclohexane derived urea Schiff base catalysts **42** (Figure 14) that had been described as being highly efficient

(up to 99% yield and *ee*) in the enantioselective hydrocyanation of a broad spectrum of aldimines (Strecker reaction)[159] (Scheme 41; 45).[123, 199] Urea **198** was prepared from enantiomerically pure polyfunctional glucoseamine hydrochloride which is readily accessible from chitin as a component of the natural chiral pool; it appeared to be an alternative backbone structure supplanting the *trans*-1,2-diamocyclohexane of Schiff base catalyst **42** (Figure 58).



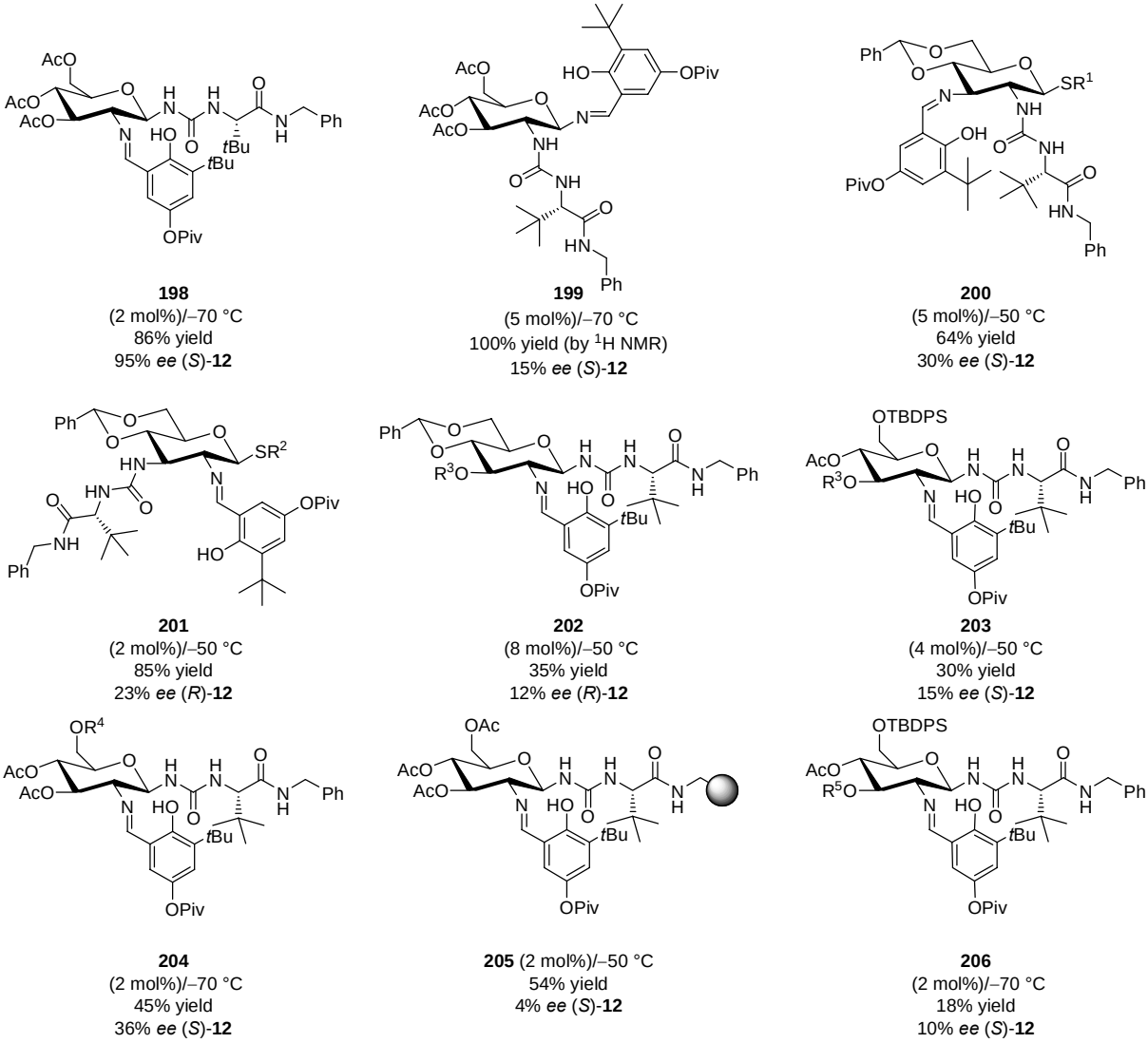
42 glucosamine hydrochloride **198**

Figure 58. Schiff base catalyst **42** and glucosamine hydrochloride as starting material for the synthesis of saccharide-based catalyst **198**.



Scheme 174. Product range obtained from asymmetric Strecker reactions catalyzed by saccharide urea **198**.

Glucosaminylurea derivative **198** proved to be an efficient catalyst for the asymmetric hydrocyanation of a broad range of aromatic aldimines (Scheme 174) affording the respective Strecker adducts (*S*)-**1**–(*S*)-**12** in high yields (up to 98%) and *ee* values (up to 84%) at –50 °C, while the protocol developed by the Jacobsen group was reported to operate at –70 °C providing 74% yield (95% *ee*). Performing the urea **198**-catalyzed Strecker reaction of benzaldimine at –70 °C under otherwise identical conditions increased the yield (86%) and enantioselectivity (95%) of Strecker adduct (*S*)-**12** (Scheme 174). Aliphatic aldimines or ketimines furnished only products with moderate yields and enantioselectivities (adducts (*S*)-**9** and (*S*)-**11**) and nitrophenylglycinonitrile (adduct (*S*)-**6**) underwent racemization during the Strecker reaction (Scheme 174). In the case of the 2-furfuryl derivatived aldimine the non-catalyzed transformation took place to a perceptible extent resulting in a moderate *ee* value of only 50% (adduct (*S*)-**7**).

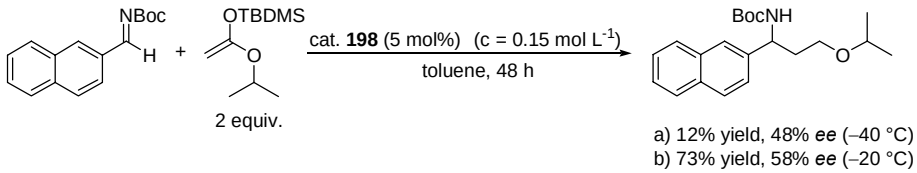


R^1 = Et; R^2 = -$(CH_2)_4$COOEt; R^3 = -(CO)$(CH_2)_2$(CO)O$(CH_2)_8$O(CO)Ps; R^4 = -(CO)$(CH_2)_2$(CO)O$(CH_2)_8$OTBDS; R^5 = -(CO)$(CH_2)_9$OTBDS

Figure 59. Structural modifications of glucosamine-derived urea catalysts; screening in the formation of Strecker adduct **12** (Scheme 174).

Structural modifications of catalyst **198** concerned the positions of the urea and Schiff base side-chains (**199**, **200**, and **201**; Figure 59), the alterations of the protective group pattern of the D-glucosamine scaffold (**202**, **203**, **204**, and **205**; Figure 59) as well as immobilization of the catalyst on polystyrene (**202**, **203**, and **205**) were prepared to perform structure-efficiency relationships for the asymmetric model Strecker reaction of benzaldimine providing adduct **12** at –50/–70 °C and 2–8 mol% catalyst loadings. The experimental results visualized in Figure 59 suggested that the saccharide backbone was not just a surrogate of the cyclohexane ring incorporated in catalyst **42**, but decreased drastically the yields and enantioselectivities (4–36% *ee*). While the *exo*-anomeric effect, that is, the π-electron delocalization of the nitrogen

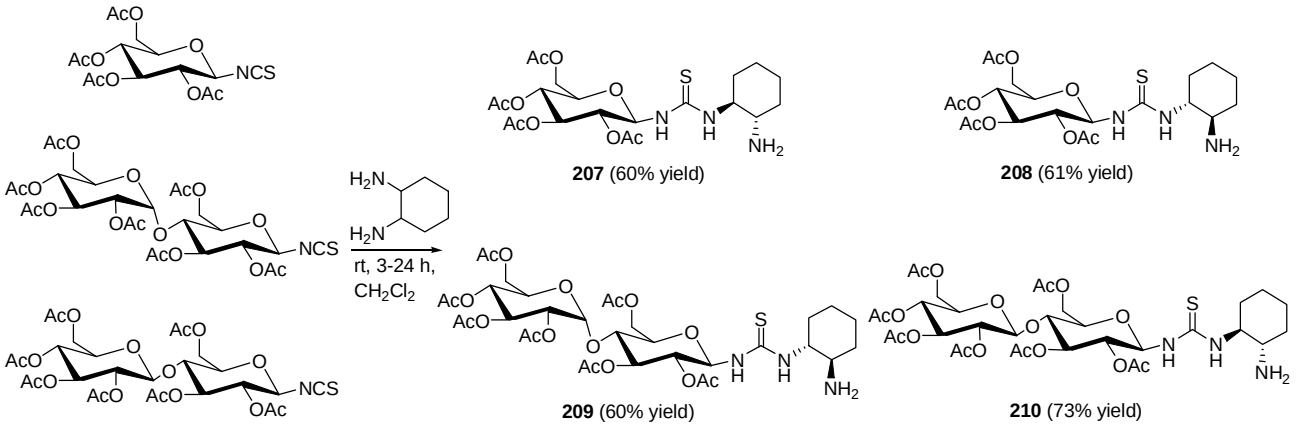
substituent in the anomeric position, enhanced the NH-acidity in catalyst **198** and made it a better hydrogen-bond donor; in catalyst **199**, however**,** the electron density of the imine nitrogen was reduced and thus also its ability to form a intramolecular hydrogen-bond to the phenol hydroxy group stabilizing the salen structure. Catalysts **200** and **201** are 4,6-*O*-benzylidene acetal protected and contain reversed positions of the urea and the salen side-chain, but gave low selectivities potentially due to the rigid heterodecaline framework. The result of the Strecker reactions catalyzed by **202**–**206** illustrate the influence of substituents in the carbohydrate moiety even of those quite remote from the catalytic center on the enantiodifferentiating potency of the respective catalyst (Figure 59). The use of catalysts with larger protecting groups and the introduction of linkers (catalyst **204** and **206**) instead of the *O*-acetyl groups resulted in a decrease of enantioinduction. Immobilization on polystyrene either via the carbohydrate (ureas **202** and **203**) or via the amino acid amide (urea **205**) afforded catalysts that also displayed low enantioselectivities (Figure 59). The authors suggested that the modifications in the protecting group pattern forced the carbohydrate scaffold to adopt a less favorable conformation. None of the examined catalysts (**199**–**206**) appeared to be competitive to Schiff base catalyst **42**. Only urea catalyst **198** showed an attractive catalytic efficiency obviously due to the enhanced hydrogen-bonding donor capacity, which may compensate the reduced conformational flexibility compared to diaminocyclohexane-derived urea-catalyst **42**. Additionally, the high density of polar functions within the saccharide-backbone offers too many basic centers for interaction with HCN and decreases enantiodifferentiation, while in the structure of the more effective Jacobson-type catalysts **42** such an interaction is located close to the catalytic center.[344]



Scheme 175. Mannich reaction catalyzed by glucosaminylurea derivative **198**.

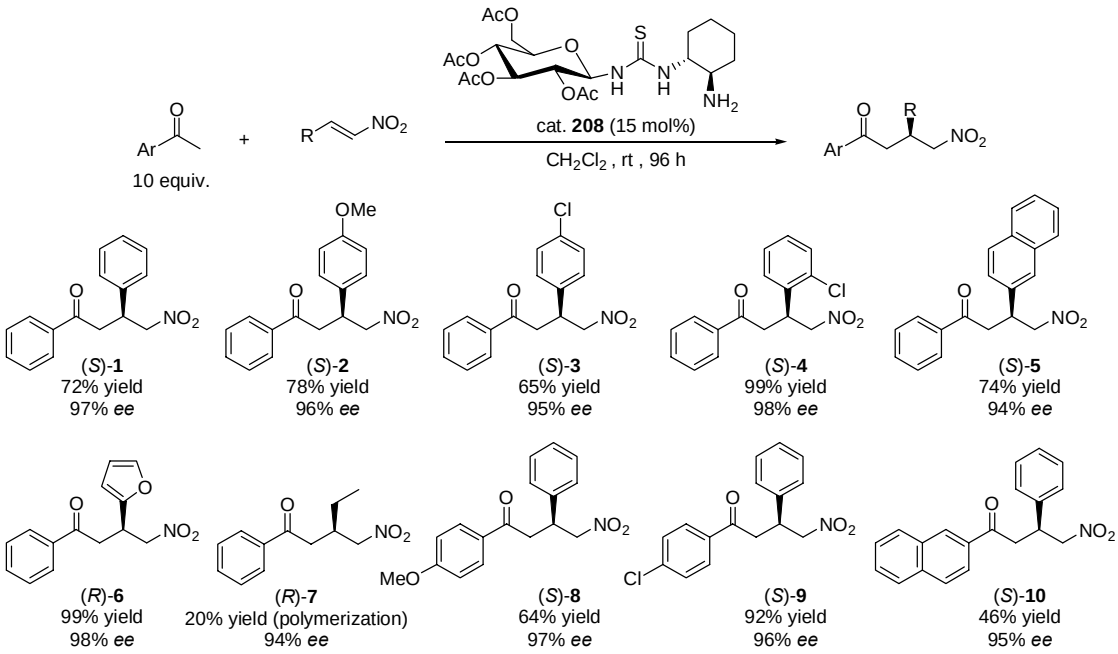
Glucosaminylurea derivative **198** was also applied to catalyze the enantioselective Mannich addition[72] of a silyl ketene acetal to the *N*-Boc-protected imine naphthalene-2-carbaldehyde resulting in the desired *β*-amino acid ester (Scheme 175). Under optimized reaction conditions with regard to temperature, solvent, equivalents of the ketene acetal, and concentration of the reaction solution good yields (up to 76%) and moderate *ee* values (about 50%) were reached (Scheme 175). In contrast to the results obtained by Jacobsen et al. when utilizing Schiff base catalyst **42** (the decrease of reaction temperature to –40 °C reduced the yield as well as enantioselectivity of the resulting Mannich adduct (Scheme 175).[204] Catalyst **198** turned out to be less effective in the Mannich reaction in terms of yield and enantiomeric induction due to reduced basicity of the *N*-acylamine and weaker hydrogen-bonding interactions compared to the more basic Strecker substrates (Scheme 174).

The Ma group introduced bifunctional primary amine-thiourea organocatalysts incorporating the *trans*-diaminocyclohexane as well as a saccharide backbone for enantioselective Michael addition reactions[151-154] of aromatic ketones to a range of nitroalkenes.[345] The saccharide-based catalysts **207**, **208**, **209**, and **210** were prepared in moderate to good yields from the simple addition reaction of racemic *trans*-diaminocyclohexane to the corresponding saccharide-derived isothiocyanates (Scheme 176); **207**–**210** were screened at 15 mol% loading under various conditions in the addition reactions of acetophenones to nitroalkenes. In dichloromethane at room temperature (*S*,*S*)-configured catalyst **207** furnished adduct (*R*)-**3** (Scheme 176) with good enantioselectivity (87% *ee*) and 46% yield, while (*S,S*)-configured catalyst **208** inducing the opposite sense of asymmetric induction affording product (*S*)-**3** with 97% *ee* in a moderate 60% yield; maltose-(**209**) and lactose-based (**210**) catalyst also bearing the *trans*-1,2-diaminocyclohexane moiety gave product (*S*)-**3a** in very low yields, but high enantioselectivities (**209**: <10% yield, 93% *ee*; **210**: 17% yield, 96% *ee*). These results indicated that the (*R*,*R*)-configuration of *trans*-1,2-diaminocyclohexane matched the *β*-D-glucopyranose scaffold and thus enhanced the stereochemical control. The choice of solvent showed no significant effect on the asymmetric reduction but reduced the yield of Michael adduct (*S*)-**3** (catalyst **208**, e.g., 62% yield, 96% *ee* in $CHCl_3$; 23% yield, 95% *ee* in diethyl ether).



Scheme 176. Synthesis of bifunctional saccharide-based amine thioureas **207**–**210** from the corresponding glucose-, maltose, and lactose-isothiocyanates, respectively.

Asymmetric Michael additions[151-154] of various aromatic and aliphatic nitroalkenes and acetophenones utilizing catalyst **208** revealed that aromatic- and heteroaromatic-substituted nitroalkenes and afforded excellent yields (65–99%) and high enantioselectivities (94–98% *ee*) of the corresponding Michael adducts **1**–**6** and **8**–**10**, while the ethyl-substituted nitroalkene substrate polymerized resulting in a poor yield (20%) with a high *ee* value (94%) of adduct **7** (Scheme 177). **208**-catalyzed conjugate addition processes were also applicable to various aromatic methyl ketones in moderate to high yields (42%–92%) and excellent enantioselectivities (95%–97% *ee*) as visualized in Scheme 177. This method was described to operate under mild conditions and tolerated a broad range of substituents, independent of the substituent pattern or the electronic properties of these substituents and without loss of stereocontrol. The authors suggested a bifunctional catalytic mechanism in which the thiourea moiety interacted through hydrogen-bonding with the nitro functionality of the nitroalkenes to increase electrophilicity while the neighboring primary amine group activated the ketone through formation of an enamine intermediate.[55, 58, 77] The primary amine seemed to play a key role, since dimethylation of catalyst **208** to the tertiary amine saccharide-thiourea **211** (Figure 60), an analogue of Takemoto's bifunctional thiourea catalyst **12**,[131] eliminated any catalytic efficiency. The absolute configuration (*S*) of the conjugate adduct was explained by the proposed transition state assembly in which the *si*-face of the nitroalkene was predominantly approached by the enamine intermediate generated from the ketone and the primary amine group of the bifunctional catalyst. The attack of the enamine to the *re*-face of the nitroalkene was restricted by the bulky cyclohexyl scaffold of the catalyst (Figure 60).[345]



Scheme 177. Typical products obtained from the **208**-catalyzed asymmetric Michael addition of ketones to nitroalkenes.

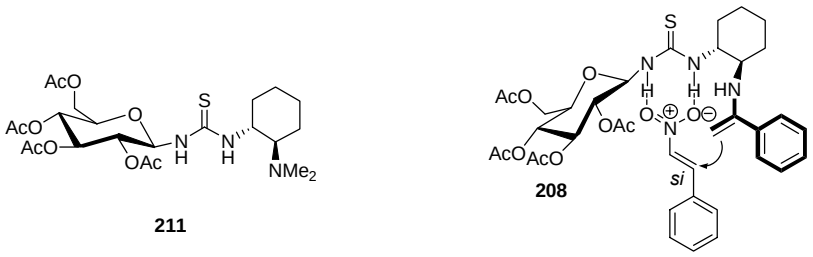
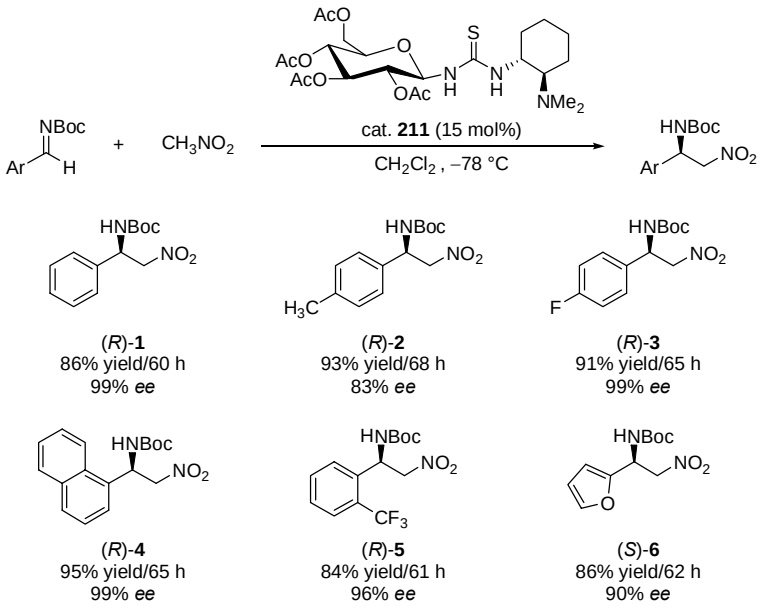


Figure 60. Tertiary amine saccharide-thiourea **211** and proposed transition state model to explain the stereodifferentiation induced by **208**.

In 2008, Tang and co-workers reported the utilization of tertiary-amine functionalized saccharide-thiourea **211** as bifunctional hydrogen-bonding catalyst for the enantioselective aza-Henry[228] (nitro-Mannich) addition[72] of nitromethane to electron-rich and electron-deficient (hetero)aromatic *N*-Boc-protected aldimines.[346] The optimized protocol (15 mol% loading of **211**; CH_2Cl_2 as the solvent; –78 °C) furnished predominantly (*R*)-configured aza-Henry adducts such as **1**–**6** in synthetically useful yields (84%–95%) and enantioselectivities (83%–99%) as shown in Scheme 178.



Scheme 178. Typical products provided from the asymmetric aza-Henry addition of nitromethane to *N*-Boc-protected aldimines in the presence of saccharide thiourea **211** as bifunctional hydrogen-bonding catalyst.

1.2.2.7 Miscellaneous Stereoselective (Thio)urea Derivatives

This section considers the applications of bifunctional hydrogen-bonding (thio)urea derivatives that have been designed and utilized for asymmetric organocatalysis, but can not clearly be assigned to one of the structural classification mentioned above or are the catalysts of choice in only one publication that may mark the basis of further research efforts.

Inspired by the excellent catalytic efficiency of the bifunctional organocatalyst proline and its derivatives in enantioselective organic transformations[55, 63, 80, 81, 347] the Tang group in 2006 introduced new (thio)urea derivatives **212** and **213** incorporating a pyrrolidine ring as chiral scaffold and evaluated their potential as bifunctional organocatalysts in the Michael reaction[151-154] between cyclohexanone and *trans*-nitrostyrene (Figure 61).[152, 348]

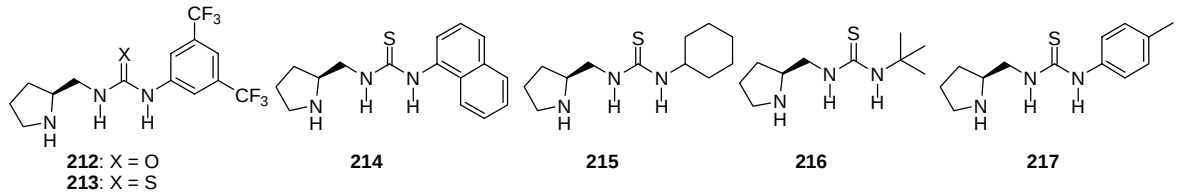
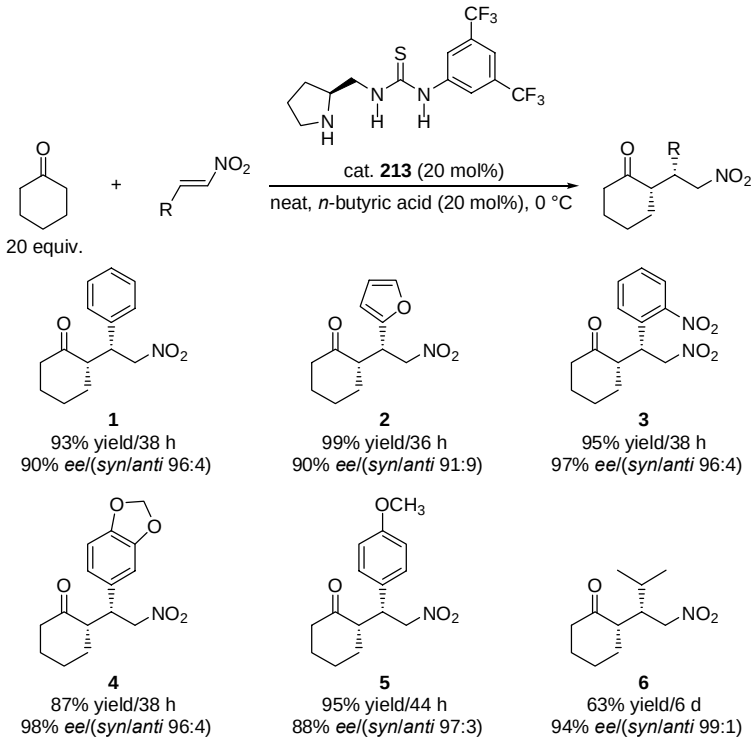


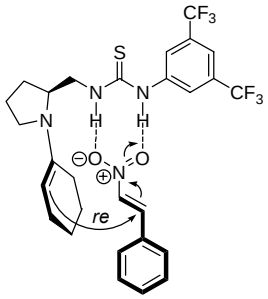
Figure 61. Bifunctional hydrogen-bonding pyrrolidine-(thio)ureas utilized for Michael reactions of ketones with nitroalkenes.

At room temperature and 20 mol% (thio)urea loading polar solvents such as MeOH or THF gave only trace amounts of the model adduct **1** (Scheme 179), while aprotic, nonpolar solvents such as *n*-hexane (73% conv.; 80% *ee* in 4 d) and benzene (68% conv.; 67% *ee* in 2 d) turned out to be much more suitable. The addition of an organic acid (10 mol%) increased the reaction rate without loss of stereoinduction (e.g., *n*-butyric acid: 100% conv., 80% *ee* in 12 h). Under solvent-free conditions and at 0 °C the *ee* value was improved to 87% and, additionally, when using thiourea **213** instead of **212** the *ee* value of adduct **1** reached 90% at 100% conversion in 1.5 h. This result indicated that thiourea **213** was slightly more efficient than its urea analogue **212**.



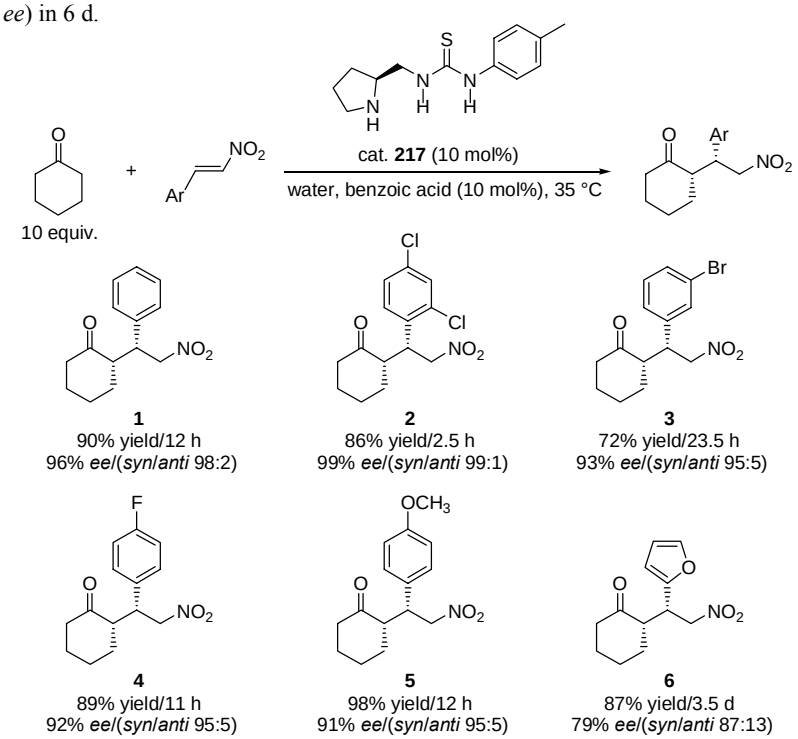
Scheme 179. Product range of the **213**-catalyzed Michael reaction of cyclohexanone with various nitroalkenes.

Scheme 179 visualizes the typical product range of the **213**-catalyzed Michael reactions of cyclohexanone with various aromatic *trans*-nitroalkenes, when running the reaction under optimized conditions. The adducts **1**–**6** were formed in yields ranging from 87% to 99%, *ee* values from 88 to 98%, and in *dr* up to 97:3. As exemplified for the synthesis of product **6** (63% yield; 94% *ee*) an aliphatic nitroalkene was also successfully converted, but required a longer reaction time (6 d). Pyrrolidine-thiourea **213** (20 mol%) could also organocatalyze the Michael reaction between *trans*-nitrostyrene and other ketones; with acetone the corresponding adduct was formed in 80% yield and 48% *ee*, while cyclohexanone gave its adduct in only 27% yield and 71% *ee*. The catalytic efficiency of catalyst **213** was proposed to be similar to a proline-like substrate activation mode,[55, 63, 349] whereby the pyrrolidine moiety activated the ketone through formation of a nucleophilic enamine,[55, 58, 77] which attacked the hydrogen-bonded nitroalkene from the *re*-face affording the desired adduct. The organic acid additive may facilitate the generation of the enamine intermediate and thus lead to an additional accelerating effect (Scheme 180).



Scheme 180. Mechanistic proposal for the Michael reaction of cyclohexanone with *trans*-nitrostyrene catalyzed by **213**.

The Michael reactions[151-154] between cyclohexanone and *trans*-nitroalkenes were also explored by Xiao and co-workers utilizing bifunctional pyrrolidine-thiourea **213** and the pyrrolidine-thioureas **214**, **215**, **216**, and **217** (Figure 61).[350] The model Michael reaction between cyclohexanone and *trans*-nitrostyrene identified water as the best solvent and **217** to be the most efficient catalysts concerning activity and asymmetric induction (90% yield; 96% *ee*; *dr* 98:2 in 12 h at 35 °C) in the presence of benzoic acid (10 mol%) as additive. The optimized catalytic system allowed the formation of a broad spectrum of Michael adducts such as **1**–**6** resulting from nitroalkenes with both electron-donating and electron-withdrawing substituents at the aryl group; the adducts were obtained in yields ranging from 79%–98%, in *ee* values between 79% and 99%, and *dr* values up to 99:1 (Scheme 181). The Michael adduct of acetone and *trans*-nitrostyrene was prepared in 65% yield (57% *ee*) in 6 d.



Scheme 181. Typical products of the **217**-catalyzed Michael reaction between cyclohexanone and various nitroalkenes.

Chang et al., in 2007, presented a novel class of thiourea organocatalysts incorporating a chiral oxazoline-ring,[351] which is widely utilized for enantiocontrolling ligands in asymmetric organometallic catalysis.[143] Oxazoline-thioureas **218**–**222** (Figure 62) were obtained from the high-yielding (78%–92%) addition of the aminomethylene-functionalized phenyl-oxazoline to the corresponding isothiocyante and were screened for their efficiency in the enantioselective formation of aza-Henry adduct **1** in Scheme 182.

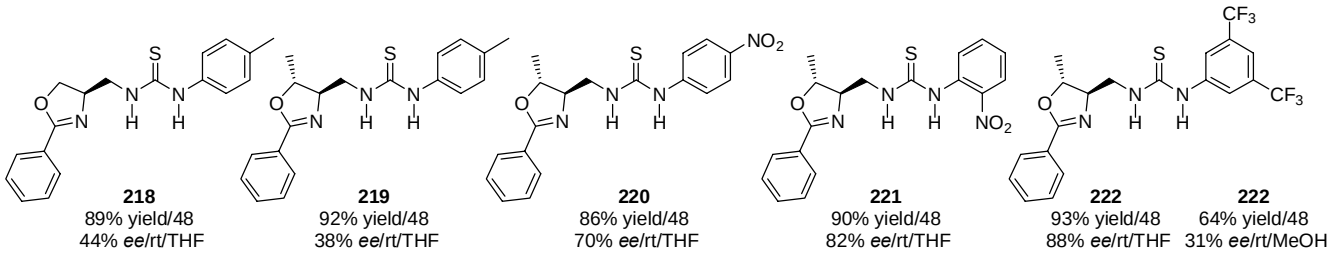
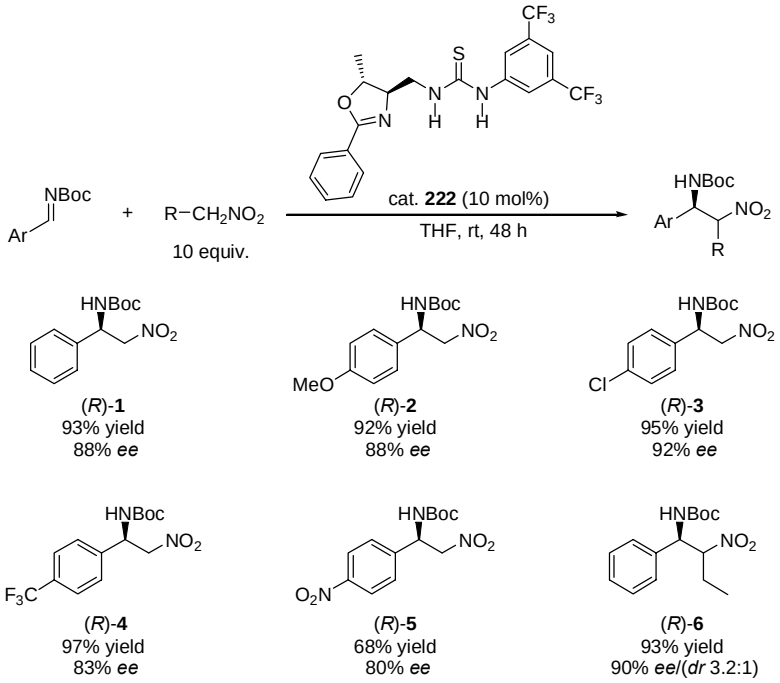


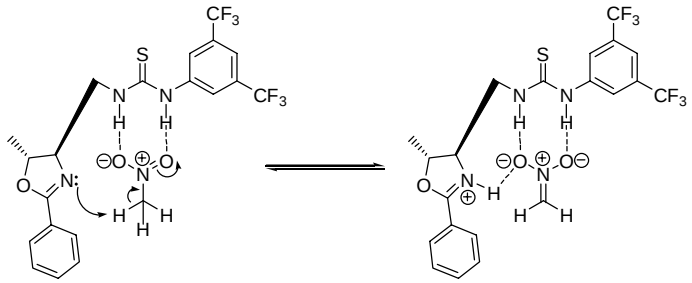
Figure 62. Oxazoline-thioureas screened in the aza-Henry reaction of *N*-Boc-protected benzaldimine with nitromethane.

Electron-deficient oxazoline thiourea **222** turned out to be the most effective catalyst concerning activity (93% yield/48 h/THF) and asymmetric induction (88% *ee*/rt) in contrast to **218**–**221**, which gave poor results (Figure 62). The solvent-screening revealed aprotic THF to be the solvent of choice, while polar protic solvents such as methanol reduce the yield (64%/48 h) and the *ee* value (31% at rt) potentially owing to the destruction of explicit hydrogen-bonding interactions between catalyst and reactants. Lowering the reaction temperature from rt to 0 °C did not provide a higher *ee* value for the model adduct **1** (72% yield; 89% *ee*/48 h/THF). Under optimized reaction conditions oxazoline-thiourea **222** (10 mol%) promoted the asymmetric aza-Henry reaction[228] of nitromethane and in one example of nitropropane with various *N*-protected phenyl imines to furnish the desired adducts **1**–**6** in 48 h at room temperature in good to excellent yields (68%–97%) and enantioselectivities (80%–92%) as depicted in Scheme 182.



Scheme 182. Representative products obtained from the **222**-catalyzed aza-Henry reaction of *N*-Boc-protected aromatic imines with nitromethane and nitroethane.

The authors suggested that **222** operates in a bifunctional mode by hydrogen-bonding activation of the nitroalkane and subsequent α-deprotonation through the basic oxazoline nitrogen providing a nucleophilic nitronate, which attacks the imine and give the observed aza-Henry adduct (Scheme 183).[351]



Scheme 183. Proposed bifunctional activation mode of oxazoline-thiourea catalyst **222**.

The most popular classes of (thio)urea-based hydrogen-bonding organocatalysts either incorporate an acidifying group such as the privileged 3,5-bis(trifluoromethyl)phenyl moiety directly adjacent to an amide nitrogen, or a chiral directing group first developed by Jacobsen (Figure 14).[123, 199] Ellman and co-workers, in 2007, constituted a novel class of hydrogen-bonding organocatalysts, which are characterized by the *N*-sulfinyl substituent combining both the amide-proton acidification (2–3 pK_a units more acidifying than the 3,5-bis(trifluoromethyl)phenyl group) and the chiral directing function due to its directly contiguous stereogenic center (Figure 63).[352]

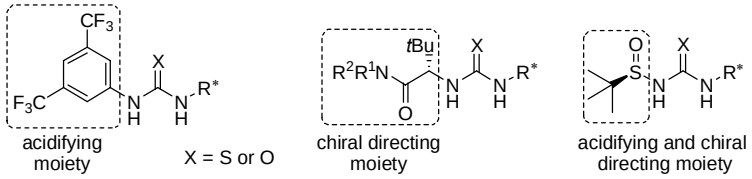
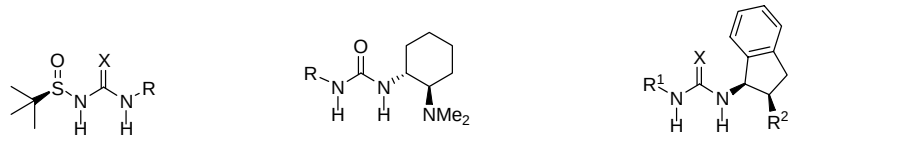


Figure 63. Design concept for the development of bifunctional *N*-sulfinyl (thio)urea derivatives.

The *N*-sulfinyl (thio)ureas are modular and easily accessible in one step by condensing *tert*-butanesulfinamide with the appropriate isocyanate or isothiocyanate, respectively. Figure 64 shows a representative selection of the prepared *N*-sulfinyl (thio)ureas evaluated for their catalytic activity in the aza-Henry[228] (nitro-Mannich) reaction[72] of *N*-Boc-protected benzaldimine and nitroethane affording adduct **1**.



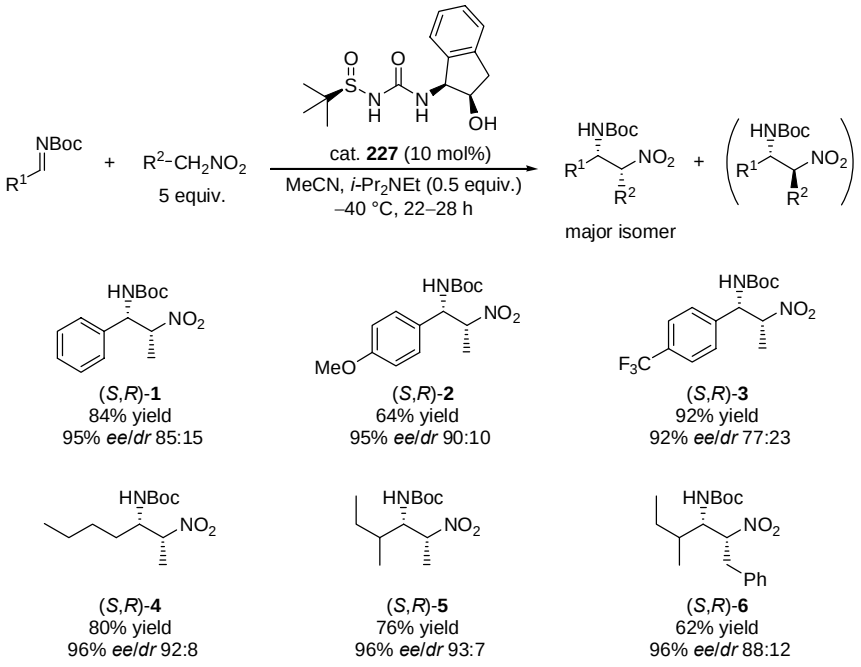
223: X = O, R = C_6H_5
224: X = S, R = C_6H_5

225: R = (*R*)-S(O)*t*Bu
226: R = (*S*)-S(O)*t*Bu

227: X = O, R^1 = (*R*)-S(O)*t*Bu, R^2 = OH
228: X = S, R^1 = (*S*)-S(O)*t*Bu, R^2 = OH
229: X = O, R^1 = (*R*)-S(O)*t*Bu, R^2 = OTBS
230: X = O, R^1 = SO_2*t*Bu, R^2 = H
231: X = O, R^1 = 3,5-$(CF_3)_2C_6H_3$, R^2 = OH

Figure 64. Representative *N*-sulfinyl (thio)ureas evaluated for catalytic activity in the asymmetric aza-Henry reaction of *N*-Boc-protected benzaldimine with nitroethane affording model product **1**.

The catalyst screening was performed in dichloromethane at –40 °C and revealed for urea **223** 59% conv. and 30% *ee*, while the sulfur analogue **224** gave only 17% conv. and a racemic product mixture. Diaminocyclohexane derivative **225** and *cis*-amino indanol derivative **227** bearing additional chirality and functionality were identified to be the most effective catalysts for the investigated screening reaction (**225**: 85% conv.; 89% *ee*; **227**: 82% conv.; 90% *ee*). Optimization of the reaction conditions including solvent and stoichiometry revealed high selectivity in acetonitrile with 0.5 equiv. of *i*Pr_2NEt. Since thiourea derivative **228** (42% conv.; 58% *ee*) and the more acidic sulfonyl derivative **230** (35% conv.; 16% *ee*) turned out to be less efficient than **227**, acidity seems not to be the leading factor responsible for the reaction rate; a catalyst too acidic may be deactivated by deprotonation through the base additive. For high asymmetric induction the OH-group of **227** is essential as demonstrated by the results obtained with silyl-protected **229** (73% conv.; 7% *ee*) and the derivative of **227** (99% conv.; racemic) lacking the coordinating OH-functionality.[311] Replacing the chiral sulfinyl-group with the benchmark 3,5-bis(trifluoromethyl)phenyl moiety resulted in urea **231**, which exhibited reduced stereoinduction (80% *ee*) and conversion (82%) for the screening reaction. The protocol utilizing *N*-sulfinyl urea derivative **227** was found to be applicable not only to electron-rich and electron-deficient aromatic *N*-Boc protected imines, but also to aliphatic imines and furnished the corresponding products **1**–**6** in yields ranging from 62%–92%, in very good enantioselectivities (92%–96%), and good diastereoselectivities (up to *dr* 93:7) as depicted in Scheme 184.[352]



Scheme 184. Product range of the aza-Henry reaction of *N*-Boc-protected aliphatic and aromatic imines catalyzed by *N*-sulfinyl urea **227**.

1.3 Summary and Outlook

This book chapter reviews the last decade (1998–2008) of intensive research towards explicit double hydrogen-bonding (thio)urea organocatalysts, summarizes the development and synthetic applications of non-stereoselective and stereoselective (thio)urea derivatives in this period, describes catalyst design principles (e.g., bifunctional catalysts, impact of various chiral backbones), and presents mechanistic proposals to explain the observed (stereochemical) outcome of each catalytic procedure. Nearly 150 journal articles including four review articles exclusively revolving around (thio)urea organocatalysts (118 publications from 2005 to date) impressively confirm the success story of these catalysts, and emphasize that the scientific community - after initial ignorance and scepticism in the early years - has recognized the potential and importance of (thio)urea derivatives for catalysis. The growing interest in this research fields in the end has not been surprising, since the milestone achievements and seminal guidelines for (thio)urea catalyst design given in the introduction of this chapter have paved the avenue for further research efforts in this new field and underline the evident advantages of (thio)urea organocatalysts in comparison to traditional Brønsted acid and metal(-ion) containing Lewis acid catalysis. Hydrogen-bonding (thio)urea derivatives are readily synthesized from inexpensive starting materials, are easy to handle, water-compatible, air-stable, non- or low-toxic and thus environmentally benign, easily modulated from both electronic and steric standpoints, can be immobilized on solid-support (polymer-bound catalysts), show no product inhibition owing to weak enthalpic binding, operate under (nearly) neutral conditions tolerating acid-labile substrates, and are highly catalytically efficient. These features have been utilized for the development of various structurally diverse hydrogen-bonding mono- and bifunctional (thio)urea organocatalysts to catalyze and stereochemically alter predominantly addition reactions such as Michael, (aza)-Henry, and Mannich reactions that have been preferably used for catalyst evaluation and model reactions in many examples. With a critical and constructive look on the achievements and research results of the last decade some important conceptual and practical points have to be emphasized: a) Several reactions that require the activation of strong bonds, e.g., in Heck, Suzuki, Stille reactions are still only feasible with metal catalysts; b) uncatalyzed reference reactions should always be reported and catalyzed reactions should be expressed in terms of TON or better TOF values; both would make the catalyst performance more transparent; c) procedures utilizing (thio)urea organocatalysts are typically performed on very small 0.1 to 0.2 mmol scale model experiments. Up-scaled (5–10 mmol) experiments should be reported as well. Up-scaled experiments are also crucial to leave the "proof-of-concept" phase towards the challenging phase in which research should focus on broader, even large-scale applications. d) Bifunctional (thio)urea organocatalysts are able to activate simultaneously the electrophile and the nucleophile resulting in high catalytic efficiencies. However, the key principle of bifunctional catalysis is usually interpreted in terms of a triple-collision scenario, although this mechanistic model appears to be entropically disfavored; refined models have to be developed on the basis of experimental as well as computational techniques. The research on hydrogen-bonding (thio)urea organocatalysts can help in enzyme profiling and provides closer insights to enzyme catalysis and biochemical processes on a molecular level. The advantages of (thio)urea organocatalysts mentioned above have not been entirely realized and utilized to date. For instance, methods in water , which are attractive for pharmaceutical applications, polymer-bound (thio)urea catalysts that are easily separable from reaction mixtures and are reusable, tandem reactions, multi-step syntheses, the activation of new (not the standard small molecule) starting-materials including acid-labile substrates, and further reduction of the catalyst loading still offer, along with novel analytical as well as computational methods, numerous perspectives and challenges, both experimentally and theoretically.

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1.5 References and Notes

[1] P. R. Schreiner, *Chem. Soc. Rev.* **2003**, *32*, 289–296.
[2] P. M. Pihko, *Angew. Chem. Int. Ed.* **2004**, *43*, 2062–2064.
[3] Y. Takemoto, *Org. Biomol. Chem.* **2005**, *3*, 4299–4306.
[4] S. J. Connon, *Chem. Eur. J.* **2006**, *12*, 5418–5427.
[5] M. S. Taylor, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2006**, *45*, 1520–1543.
[6] T. Akiyama, J. Itoh, K. Fuchibe, *Adv. Synth. Catal.* **2006**, *348*, 999–1010.
[7] A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713–5743.
[8] L. Bernardi, F. Fini, R. P. Herrera, A. Ricci, V. Sgarzani, *Tetrahedron* **2007**, *62*, 375–380.
[9] Special issue on enzyme catalysis: V. L. Schramm, Ed., *Chem. Rev.*, *"Princpiles of Enzymatic Catalysis"* **2006**, *106*, 3029–3496.
[10] P. R. Carey, *Chem. Rev.* **2006**, *106*, 3043–3054.
[11] D. D. Boehr, H. J. Dyson, P. E. Wright, *Chem. Rev.* **2006**, *106*, 3055–3079.
[12] D. Antoniou, J. Basner, S. Núñez, S. D. Schwartz, *Chem. Rev.* **2006**, *106*, 3170–3187.
[13] T. C. Bruice, *Chem. Rev.* **2006**, *106*, 3119–3139.
[14] J. Goa, S. Ma, D. T. Major, K. Nam, J. Pu, D. G. Truhlar, *Chem. Rev.* **2006**, *106*, 3188–3209.
[15] L. Pauling, *"The Nature of the Chemical Bond"*, 3rd ed., Cornell University Press, Ithaca, **1968**.
[16] G. C. Pimentel, A. L. McClellan, *"The Hydrogen Bond"*, Freeman, San Francisco, **1960**.
[17] G. A. Jeffrey, *"An Introduction to Hydrogen Bonding"*, Oxford University Press, New York, **1997**.
[18] L. J. Prins, D. N. Reinhoudt, P. Timmerman, *Angew. Chem. Int. Ed.* **2001**, *40*, 2382–2426.
[19] T. Steiner, *Angew. Chem. Int. Ed.* **2002**, *41*, 48–76.
[20] C. A. Hunter, *Angew. Chem. Int. Ed.* **2004**, *43*, 5310–5324.
[21] S. P. Kim, A. G. Leach, K. N. Houk, *J. Org. Chem.* **2002**, *67*, 4250–4260.
[22] R. Breslow, *Acc. Chem. Res.* **1991**, *24*, 159–163.
[23] L. R. Pratt, A. Pohorille, *Chem. Soc. Rev.* **2002**, *102*, 2671–2692.
[24] E. A. Meyer, R. K. Castellano, F. Diederich, *Angew. Chem. Int. Ed.* **2003**, *42*, 1210–1250.
[25] C. E. H. Dessent, K. Müller-Dethlefs, *Chem. Rev.* **2000**, *100*, 3999–4021.
[26] M. A. Wear, D. Kan, A. Rabu, M. D. Walkinshaw, *Angew. Chem. Int. Ed.* **2000**, *46*, 6453–6456.
[27] D. A. Kraut, P. A. Sigala, B. Pybus, C. W. Liu, D. Ringe, G. A. Petsko, D. Herschlag, *PLoS Biology* **2006**, *4*, 501–519.
[28] A. Warshel, P. K. Sharma, M. Kato, Y. Xiang, H. Liu, M. H. M. Olsson, *Chem. Rev.* **2006**, *106*, 3210–3235.
[29] T. C. Bruice, S. J. J. Benkovic, *Biochemistry* **2000**, *39*, 6267–6274.
[30] D. H. Williams, E. Stephens, D. P. O'Brien, M. Zhou, *Angew. Chem. Int. Ed.* **2004**, *43*, 6596–6616.
[31] M. J. Evans, B. F. Cravatt, *Chem. Rev.* **2006**, *106*, 3279–3301.
[32] E. J. de Vries, D. B. Janssen, *Curr. Opin. Biotechnol.* **2003**, *14,* 414–420.
[33] E. Y. Lau, Z. E. Newby, T. C. Bruice, *J. Am. Chem. Soc.* **2001**, *123*, 3350–3357.
[34] K. H. Hopmann, F. Himo, *J. Phys. Chem. B* **2006**, *110*, 21299–21310.
[35] K. H. Hopmann, H. Fahmi, *Chem. Eur. J.* **2006**, *12*, 6898–6909.
[36] C. W. Wharton, *"Comprehensive Biological Catalysis", Vol. 1*, Academic Press, London, **1998**.
[37] Product inhibition and substrate inhibition are effects also known in enzyme catalysis that can reduce catalytic efficiency. Generally, catalytic systems (natural or artificial) based on covalent interactions are more sensitive towards inhibitions than non-covalent systems utilizing weak interactions: E. Garcia-Junceda, *"Multi-Step Enzyme Catalysis"*, Wiley-VCH, Weinheim, Germany, **2008**.
[38] D. G. Blackmond, A. Armstrong, V. Coombe, A. Wells, *Angew. Chem. Int. Ed.* **2007**, *46*, 3798–3800.
[39] R. A. Sheldon, *Chem. Commun.* **2008**, 3352–3365.
[40] R. Breslow, *Science* **1982**, *218*, 532–537.
[41] R. Breslow, *"Artificial Enzymes"*, Wiley-VCH, Weinheim, Germany, **2005**.
[42] R. Pascal, *Eur. J. Org. Chem.* **2003**, 1813–1824.
[43] L. Pauling, *Chem. Eng. News* **1946**, *24*, 1375–1377.
[44] L. Pauling, *Nature* **1948**, *161*, 707–709.
[45] X. Zhang, K. N. Houk, *Acc. Chem. Res.* **2005**, *38*, 379–385.
[46] A. Kohen, J. P. Klinman, *Acc. Chem. Res.* **1998**, *31*, 397–404.
[47] T. Akiyama, *Chem. Rev.* **2007**, *107*, 5744–5758.
[48] W. P. Jencks, *Acc. Chem. Res.* **1976**, *9*, 425–432.
[49] W. P. Jencks, *Acc. Chem. Res.* **1980**, *13*, 161–169.
[50] L. Michaelis, M. L. Menten, *Biochem. Z.* **1913**, *49*, 333–369.
[51] T. C. Bruice, *Acc. Chem. Res.* **2002**, *35*, 139–148.
[52] P. I. Dalko, L. Moisan, *Angew. Chem. Int. Ed.* **2001**, *40*, 3726–3748.
[53] E. R. Jarvo, S. J. Miller, *Tetrahedron* **2002**, *58*, 2481–2495.
[54] P. I. Dalko, L. Moisan, *Angew. Chem. Int. Ed.* **2004**, *43*, 5138–5175.
[55] B. List, *Acc. Chem. Res.* **2004**, *37*, 548–557.
[56] M. H. Fonseca, B. List, *Curr. Opin. Chem. Biol.* **2004**, *8*, 319–326.
[57] P. R. Schreiner, A. A. Fokin, *Chem. Rec.* **2004**, *3*, 247–257.
[58] W. Notz, F. Tanaka, C. F. Barbas, III., *Acc. Chem. Res.* **2004**, *37*, 580–591.
[59] A. Berkessel, H. Gröger, "*Asymmetric Organocatalysis"*, Wiley-VCH, Weinheim, Germany, **2005**.
[60] M. J. Gaunt, C. C. C. Johansson, A. McNally, N. T. Vo, *Drug Discov. Today* **2006**, *12*, 8–27.
[61] F. Cozzi, *Adv. Synth. Catal.* **2006**, *348*, 1367–1390.
[62] M. Benaglia, *New J. Chem.* **2006**, *30*, 1525–1533.
[63] B. List, *Chem. Commun.* **2006**, 819–824.
[64] T. Marcelli, J. H. van Maarseveen, H. Hiemstra, *Angew. Chem. Int. Ed.* **2006**, *45*, 7496–7504.

[65] H. Pellissier, *Tetrahedron* **2007**, *63*, 9267–9331.
[66] P. I. Dalko, "*Enantioselective Organocatalysis – Reactions and Experimental Procedures"*, Wiley-VCH, Weinheim, Germany, **2007**.
[67] E. A. C. Davie, S. M. Mennen, Y. Xu, S. J. Miller, *Chem. Rev.* **2007**, *107*, 5759–5812.
[68] D. Enders, O. Niemeier, A. Henseler, *Chem. Rev.* **2007**, *107*, 5606–5655.
[69] R. M. de Figueiredo, M. Christmann, *Eur. J. Org. Chem.* **2007**, 2575–2600.
[70] D. Enders, C. Grondal, M. R. M. Hüttl, *Angew. Chem. Int. Ed.* **2007**, *46*, 1570–1581.
[71] J. D. Revell, H. Wennemers, *Curr. Opin. Chem. Biol.* **2007**, *11*, 269–278.
[72] A. Ting, S. E. Schaus, *Eur. J. Org. Chem.* **2007**, 5797–5815.
[73] P. J. Walsh, H. Li, C. A. de Parrodi, *Chem. Rev.* **2007**, *107*, 2503–2545.
[74] G. Guillena, C. Nájera, D. J. Ramón, *Tetrahedron: Asymmetry* **2007**, *18*, 2249–2293.
[75] N. E. Kamber, W. Jeong, R. M. Waymouth, R. C. Pratt, B. G. G. Lohmeijer, J. L. Hedrick, *Chem. Rev.* **2007**, *107*, 5817–5840.
[76] A. Erkkilä, I. Majander, P. M. Pihko, *Chem. Rev.* **2007**, *107*, 5416–5470.
[77] S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *12*, 5471–5569.
[78] J. M. M. Verkade, L. J. C. van Hemert, P. J. L. M. Quaedflieg, F. P. J. T. Rutjes, *Chem. Soc. Rev.* **2008**, *37*, 29–41.
[79] X. Yua, W. Wang, *Org. Biomol. Chem.* **2008**, *6*, 2021–2216.
[80] L.-W. Xua, Y. Lu, *Org. Biomol. Chem.* **2008**, *6*, 2047–2053.
[81] A. Dondoni, A. Massi, *Angew. Chem. Int. Ed.* **2008**, *47*, 4638–4660.
[82] D. W. C. MacMillan, *Nature* **2008**, *455*, 304–308.
[83] Special journal issues on organocatalysis: a) K. N. Houk, B. List, Eds., *Acc. Chem. Res.*, *"Asymmetric Organocatalysis"* **2004**, *37(8)* 487–631; (b) *Adv. Synth. Catal.*, *"Organic Catalysis"* **2004**, *346(9–10)*, 1007–1249; c) P. Kočovský, A. V. Malkov, Eds., *Tetrahedron*, *Symposia-in-Print "Organocatalysis in Organic Synthesis"* **2006**, *62(2–3)*, 243–250; d) B. List, Ed., *Chem. Rev.*, *"Organocatalysis"* **2007**, *107(12)*, 5413–5883; e) A. Alexakis, Ed., *Chimia*, *"Organocatalysis"* **2007**, *61(5)*, 212–281.
[84] J. Hine, K. Ahn, J. C. Gallucci, S.-M. Linden, *J. Am. Chem. Soc.* **1984**, *106*, 7980–7981.
[85] A crystal structure of an unstable *N*,*N'*-[bis-(*α*-tosylbenzyl)urea-acetone hydrogen-bonded adduct had been reported earlier: R. M. Tel, J. B. F. N. Engberts, *J. Chem. Soc. Perkin Trans.* 2 **1976**, 483–488.
[86] J. Hine, S. M. Linden, V. M. Kanagasabapathy, *J. Am. Chem. Soc.* **1985**, *107*, 1082–1083.
[87] J. Hine, S. Hahn, D. E. Miles, K. Ahn, *J. Org. Chem.* **1985**, *50*, 5092–5096.
[88] J. Hine, S. Hahn, D. E. Miles, *J. Org. Chem.* **1986**, *51*, 577–584.
[89] J. Hine, K. Ahn, *J. Org. Chem.* **1987**, *52*, 2089–2091.
[90] J. Hine, K. Ahn, *J. Org. Chem.* **1987**, *52*, 2083–2086.
[91] T. R. Kelly, P. Meghani, V. S. Ekkundi, *Tetrahedron Lett.* **1990**, *31*, 3381–3384.
[92] T. R. Kelly, M. H. Kim, *J. Am. Chem. Soc.* **1994**, *116*, 7072–7080.
[93] J. F. Blake, W. L. Jorgensen, *J. Am. Chem. Soc.* **1991**, *113*, 7430–7432.
[94] J. F. Blake, D. Lim, W. L. Jorgensen, *J. Org. Chem.* **1994**, *59*, 803–805.
[95] D. L. Severance, W. L. Jorgensen, *J. Am. Chem. Soc.* **1992**, *114*, 10966–10968.
[96] M. C. Etter, P. W. Baures, *J. Am. Chem. Soc.* **1988**, *110*, 639–640.
[97] M. C. Etter, P. T. W., *J. Am. Chem. Soc.* **1988**, *110*, 5896–5897.
[98] M. C. Etter, *J. Phys. Chem.* **1991**, *95*, 4601–4610.
[99] M. C. Etter, *Acc. Chem. Res.* **1990**, *23*, 120–126.
[100] M. C. Etter, S. M. Reutzel, *J. Am. Chem. Soc.* **1991**, *113*, 2586–2589.
[101] K. L. Wolf, H. Frahm, H. Harms, *Z. Phys. Chem. Abt. B* **1937**, *36*, 17.
[102] P. J. Smith, M. V. Reddington, C. S. Wilcox, *Tetrahedron Lett.* **1992**, *33*, 6085–6088.
[103] C. S. Wilcox, J. James C. Adrian, T. H. Webb, F. J. Zawacki, *J. Am. Chem. Soc* **1992**, *114*, 10189–10197.
[104] C. S. Wilcox, E. Kim, D. Romano, L. H. Kuo, A. L. Burt, D. P. Curran, *Tetrahedron Lett.* **1995**, *51*, 621–634.
[105] D. P. Curran, L. H. Kuo, *J. Org. Chem.* **1994**, *59*, 3259–3261.
[106] D. P. Curran, L. H. Kuo, *Tetrahedron Lett.* **1995**, *36*, 6647–6650.
[107] A. Wittkopp, *Diploma Thesis*, University Göttingen, Germany, **1997**.
[108] E. Fan, S. A. V. Arman, S. Kincaid, A. D. Hamilton, *J. Am. Chem. Soc.* **1993**, *115*, 369–370.
[109] D. E. Gómez, L. Fabbrizzi, M. Licchelli, E. Monzani, *Org. Biomol. Chem.* **2005**, *3*, 1495–1500.
[110] M. Bonizzoni, L. Fabbrizzi, A. Taglietti, F. Tiengo, *Eur. J. Org. Chem.* **2006**, 3567–3574.
[111] J. L. J. Blanco, P. Bootello, J. M. Benito, C. O. Mellet, J. M. G. Fernández, *J. Org. Chem.* **2006**, *71*, 5136–5143.
[112] A. Wittkopp, P. R. Schreiner, "*The Chemistry of Dienes and Polyenes", Vol. 2* (Ed.: Z. Rappoport), John Wiley & Sons Ltd, Chichester, **2000**, pp. 1029–1088.
[113] W. Ostwald, *Chemiker Zeitung* **1910**, *34*, 397–399.
[114] A. Wittkopp, P. R. Schreiner, *Chem. Eur. J.* **2003**, *9*, 407–414.
[115] D. A. Evans, K. T. Chapman, J. Bisaha, *J. Am. Chem. Soc.* **1984**, *106*, 4261.
[116] P. R. Schreiner, A. Wittkopp, *Org. Lett.* **2002**, *4*, 217–220.
[117] R. Custelcean, M. G. Gorbunova, P. V. Bonnesen, *Chem. Eur. J.* **2005**, *11*, 1459–1466.
[118] The structure of thiourea catalyst **9** was deposited in the Cambridge Crystallographic Data Center (CCDC 206506) and can be retrieved free of charge from there. Key data: 1,3-bis-(3,5-bis-trifluoromethyl-phenyl)-thiourea; Formula: C_{17} H_8 F_{12} N_2 S_1; unit cell parameters: *a* 15.178(2) *b* 8.2203(8) *c* 17.399(2) *β* 112.495(14); space group $P2_1/c$.
[119] Mike Kotke, *PhD Thesis*, University Giessen, Germany, **2009**; online access via the Electronic Library, University Giessen.
[120] T. P. Yoon, E. N. Jacobsen, *Science* **2003**, *299*, 1691–1693.
[121] T. Schuster, M. Kurtz, M. W. Göbel, *J. Org. Chem.* **2000**, *65*, 1697–1701.
[122] T. Schuster, M. Bauch, G. Dürner, M. W. Göbel, *Org. Lett.* **2000**, *2*, 179–181.
[123] M. S. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 4901–4902.

[124] The Jacobsen group introduced the term "Schiff base catalyst"[123] to demonstrate that the structure of this novel catalyst class originates from Schiff base ligands and incorporates a Schiff base moiety; notably, this term does not indicate that these catalysts operate as bases, but their high catalytic efficiencies result from explicit double hydrogen-bonding as shown in section 1.2.2.1. In the following the scientifically established term "Schiff base (thio)urea" is used to describe this class of organocatalysts.
[125] A. Wittkopp, *PhD Thesis*, University Göttingen, Germany, **2001**, published online.
[126] P. Vachal, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 10012–10014.
[127] P. T. Anastas, J. C. Warner, *"Green Chemistry: Theory and Practice"*, Oxford University Press, Oxford, UK, **1998**.
[128] "Green Chemistry": P. T. Anastas, J. B. Zimmerman, "*Environmental Science & Technology"* **2003**, 95A–101A.
[129] U. M. Lindström, *Chem. Rev.* **2002**, *102*, 2751–2772.
[130] K. Manabe, S. Kobayashi, *Chem. Eur. J.* **2002**, *8*, 4094–4101.
[131] T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673.
[132] K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243–4244.
[133] J. v. Liebig, *Liebigs Ann.* **1860**, *113*, 246.
[134] J. v. Liebig, *Liebigs Ann.* **1870**, *153*, 9.
[135] W. Ostwald, *Z. physik. Chem.* **1900**, *34*, 510.
[136] W. Langenbeck, *Ber. Dtsch. Chem. Ges.* **1927**, 60, 930; W. Langenbeck, *Angew. Chem.* **1928**, *41*, 740–745.
[137] W. Langenbeck, *Angew. Chem.* **1932**, *45*, 97–99.
[138] W. Langenbeck, "*Die organischen Katalysatoren und ihre Beziehungen zu den Fermenten" ("Organic Catalysts and their Relation to the Enzymes")*, 2 ed., Springer, Berlin, **1949**; W. Langenbeck, *Tetrahedron* **1958**, *3*, 185–196.
[139] Y. L. Bennani, S. Hanessian, *Chem. Rev.* **1997**, *97*, 3161–3195.
[140] F. Fache, E. Schulz, M. L. Tommasino, M. Lemaire, *Chem. Rev.* **2000**, *100*, 2159–2231.
[141] H. M. R. Hoffmann, J. Frackenpohl, *Eur. J. Org. Chem.* **2004**, 4293–4312.
[142] Y. Chen, S. Yekta, A. K. Yudin, *Chem. Rev.* **2003**, *103*, 3155–3211.
[143] H. A. McManus, P. J. Guiry, *Chem. Rev.* **2004**, *104*, 4151–4202.
[144] G. Desimoni, G. Faita, K. A. Jørgensen, *Chem. Rev.* **2006**, *106*, 3561–3651.
[145] M. Mellah, A. Voituriez, E. Schulz, *Chem. Rev.* **2007**, *107*, 5133–5209.
[146] H. Pellissier, *Tetrahedron* **2007**, *63*, 1297–1330.
[147] M. Kotke, P. R. Schreiner, *Synthesis* **2007**, 779–790.
[148] M. Kotke, P. R. Schreiner, *Tetrahedron* **2006**, *62*, 434–439.
[149] T. Okino, Y. Hoashi, Y. Takemoto, *Tetrahedron Lett.* **2003**, *44*, 2817–2821.
[150] G. Dessole, R. P. Herrera, A. Ricci, *Synlett* **2004**, 2374–2378.
[151] D. Enders, K. Lüttgen, A. A. Narine, *Synthesis* **2007**, 959–980.
[152] S. Sulzer-Mossé, A. Alexakis, *Chem. Commun.* **2007**, 3123–3135.
[153] J. L. Vicario, D. Badía, L. Carrillo, *Synthesis* **2007**, *14*, 2065–2092.
[154] S. B. Tsogoeva, *Eur. J. Org. Chem.* **2007**, 1701–1716.
[155] C. M. Kleiner, P. R. Schreiner, *Chem. Commun.* **2006**, 4315–4317.
[156] F. Franks, "*Water–A Matrix of Life"*, 2 ed., Royal Society of Chemistry, Cambridge, UK, **2000**.
[157] J. B. F. N. Engberts, *Pure Appl. Chem.* **1995**, *67*, 823–828.
[158] D. Pettersen, R. P. Herrera, L. Bernardi, F. Fini, V. Sgarzani, R. Fernandez, J. M. Lassaletta, A. Ricci, *Synlett* **2006**, 239–242.
[159] H. Gröger, *Chem. Rev.* **2003**, *103*, 2795–2827.
[160] S. C. Pan, J. Zhou, B. List, *Synlett* **2006**, *19*, 3275–3276.
[161] A. Dornow, S. Lüpfert, *Chem. Ber.* **1956**, *89*, 2718.
[162] A. Dornow, S. Lüpfert, *Chem. Ber.* **1957**, *90*, 1780.
[163] S. C. Pan, J. Zhou, B. List, *Angew. Chem. Int. Ed.* **2007**, *46*, 2971–2971.
[164] S. C. Pan, B. List, *Synlett* **2007**, 318–320.
[165] Mechanistically, in these reactions the catalytic effect of hydrogen-bonding thiourea **9** results from the stabilization of the oxyanion hole in the TS and not from the activation of the substrate through hydrogen-bonding. This marks a new concept.
[166] F. M. Muñiz, V. A. Montero, A. L. F. de Arriba, L. Simón, C. Raposo, J. R. Morán, *Tetrahedron Lett.* **2008**, *49*, 5050–5052.
[167] M. Kirsten, J. Rehbein, M. Hiersemann, T. Strassner, *J. Org. Chem.* **2007**, *72*, 4001–4011.
[168] Y. Huang, *Synlett* **2007**, *14*, 2304–2305.
[169] Z. Zhang, P. R. Schreiner, *Synlett* **2007**, 1455–1457.
[170] Y. Kawai, Y. Inaba, M. Hayash, N. Tokitoh, *Tetrahedron Lett.* **2001**, *42*, 3367–3368.
[171] Y. Kawai, Y. Inaba, N. Tokitoh, *Tetrahedron: Asymmetry* **2001**, *12*, 309–318.
[172] Z. Zhang, P. R. Schreiner, *Synthesis* **2007**, *16*, 2559–2564.
[173] M. Korn, R. Wodarz, W. Schoknecht, H. Weichardt, E. Bayer, *Arch. Toxicol.* **1984**, *55*, 59–63.
[174] M. Kanai, N. Kato, E. Ichikawa, M. Shibasaki, *Synlett* **2005**, *10*, 1491–1508.
[175] Y. J. Park, J.-W. Park, J.-H. Jun, *Acc. Chem. Res.* **2008**, *41*, 222–234.
[176] T. Weil, M. Kotke, C. M. Kleiner, P. R. Schreiner, *Org. Lett.* **2008**, *10*, 1513–1516.
[177] B. List, C. Reisinger, *Synfacts* **2008**, *6*, 644.
[178] J. D. McGilvra, A. K. Unni, Modi, K., V. H. Rawal, *Angew. Chem. Int. Ed.* **2006**, *45*, 6130–6133.
[179] Y.-L. Shi, M. Shi, *Eur. J. Org. Chem.* **2007**, 2905–2916.
[180] V. Singh, S. Batra, *Tetrahedron* **2008**, *64*, 4511–4574.
[181] D. J. Maher, S. J. Connon, *Tetrahedron Lett.* **2004**, *45*, 1301–1305.
[182] S. A. Kavanagh, A. Piccinini, E. M. Fleming, S. J. Connon, *Org. Biomol. Chem.* **2008**, *6*, 1339–1343.
[183] J. Meinwald, S. S. Labana, S. S. Chadha, *J. Am. Chem. Soc.* **1963**, *85*, 582.
[184] M. De Rosa, L. Citro, A. Soriente, *Tetrahedron Lett.* **2006**, *47*, 8507–8510.
[185] A. M. Costero, G. M. Rodríguez-Muñiz, P. Gaviña, S. Gil, A. Domenech, *Tetrahedron Lett.* **2007**, *48*, 6992–6995.
[186] B. Procuranti, S. J. Connon, *Chem. Commun.* **2007**, 1421–1423.
[187] E. M. Fleming, C. Quigley, I. Rozas, S. J. Connon, *J. Org. Chem.* **2008**, *73*, 948–956.

[188] T. Ema, T. Fujii, M. Ozaki, T. Korenaga, T. Sakai, *Chem. Commun.* **2005**, 4650–4651.
[189] J. Otera, *Chem. Rev.* **1993**, *93*, 1449–1470.
[190] K. Ishihara, Y. Kosugi, M. Akakura, *J. Am. Chem. Soc.* **2004**, *126*, 12212–12213.
[191] T. Ema, D. Tanida, T. Matsukawa, T. Sakai, *Chem. Commun.* **2008**, 957–959.
[192] A. P. Dove, R. C. Pratt, B. G. G. Lohmeijer, R. M. Waymouth, J. L. Hedrick, *J. Am. Chem. Soc.* **2005**, *127*, 13798–13799.
[193] R. C. Pratt, B. G. G. Lohmeijer, D. A. Long, P. N. P. Lundberg, A. P. Dove, H. B. Li, C. G. Wade, R. M. Waymouth, J. L. Hedrick, *Macromolecules* **2006**, *39*, 7863–7871.
[194] B. G. G. Lohmeijer, R. C. Pratt, F. Leibfarth, J. W. Logan, D. A. Long, A. P. Dove, F. Nederberg, J. Choi, C. Wade, R. M. Waymouth, J. L. Hedrick, *Macromolecules* **2006**, *39*, 8574–8583.
[195] F. Nederberg, B. G. G. Lohmeijer, F. Leibfarth, R. C. Pratt, J. Choi, A. P. Dove, R. M. Waymouth, J. L. Hedrick, *Biomacromolecules* **2007**, *8*, 153–160.
[196] H. Wieland, O. Schlichtung, W. V. Langsdorf, *Z. Phys. Chem.* **1926**, *161*, 74.
[197] F. Glasbol, P. Steenbol, S. B. Sorenson, *Acta Chem. Scand.* **1980**, *26*, 3605.
[198] C. Gennari, U. Piarulli, *Chem. Rev.* **2003**, *103,* 3071–3100.
[199] M. S. Sigman, P. Vachal, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2000**, *39*, 1279–1281.
[200] HCN was generated by the method of Ziegler. Alternatively, the generation of HCN in situ by reaction of TMSCN and MeOH afforded identical results. K. Ziegler in Organic Synth. Coll. Vol. 1 (Eds.: H. Gilman, A. H. Blatt), Wiley, New York, **1932**, p. 314.
[201] P. Vachal, E. N. Jacobsen, *Org. Lett.* **2000**, *2*, 867–870.
[202] D. J. Harriman, G. F. Deleavey, A. Lambropoulos, G. Deslongchamps, *Tetrahedron* **2007**, *63*, 13032–13038.
[203] G. D. Joly, E. N. Jacobsen, *J. Am. Chem. Soc.* **2004**, *126*, 4102–4103.
[204] A. G. Wenzel, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 12964–12965.
[205] M. S. Taylor, E. N. Jacobsen, *J. Am. Chem. Soc.* **2004**, *126*, 10558–10559.
[206] K. W. Bentley, *Nat. Prod. Rep.* **2004**, *21*, 395–424.
[207] M. S. Taylor, T. Tokunaga, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2005**, *44*, 6700–6704.
[208] I. T. Raheem, P. S. Thiara, E. A. Peterson, E. N. Jacobsen, *J. Am. Chem. Soc.* **2007**, *129*, 13404–13405.
[209] N. J. A. Martin, L. Ozores, B. List, *J. Am. Chem. Soc.* **2007**, *129*, 8976–8977.
[210] In contrast to monofunctional (thio)urea organocatalysts bifunctional catalyst structures enable simultaneous coordination, activation, and suitable relative orientation of both reaction components the electrophile and the nucleophile resulting in high catalytic efficiencies. Notably, the key principle of bifunctional catalysis is usually interpreted in terms of a triple-collision scenario, although this mechanistic model appears to be entropically disfavored. Refined models have to be developed.
[211] T. Okino, Y. Hoashi, T. Furukawa, X. Xu, Y. Takemoto, *J. Am. Chem. Soc.* **2005**, *127*, 119–125.
[212] Y. Hoashi, T. Yabuta, Y. Takemoto, *Tetrahedron Lett.* **2004**, *45*, 9185–9188.
[213] Y. Hoashi, T. Yabuta, P. Yuan, H. Miyabe, Y. Takemoto, *Tetrahedron* **2006**, *62*, 365–374.
[214] R. X. Zhu, D. J. Zhang, J. Wu, C. B. Liu, *Tetrahedron: Asymmetry* **2006**, *17*, 1611–1616.
[215] A. Hamza, G. Schubert, T. Soos, I. Papai, *J. Am. Chem. Soc.* **2006**, *128*, 13151–13160.
[216] H. Miyabe, S. Tuchida, M. Yamauchi, Y. Takemoto, *Synthesis* **2006**, 3295–3300.
[217] H. Li, J. Wang, L. Zu, W. Wang, *Tetrahedron Lett.* **2006**, *47*, 2585–2589.
[218] H. Li, H. Wang, L. S. Zu, W. Wang, *Tetrahedron Lett.* **2006**, *47*, 3145–3148.
[219] T. Y. Liu, J. Long, B. J. Li, L. Jiang, R. Li, Y. Wu, L. S. Ding, Y. C. Chen, *Org. Biomol. Chem.* **2006**, *4*, 2097–2099.
[220] T. Y. Liu, R. Li, Q. Chai, J. Long, B. J. Li, Y. Wu, L. S. Ding, Y. C. Chen, *Chem. Eur. J.* **2007**, *13*, 319–327.
[221] Y. Hoashi, T. Okino, Y. Takemoto, *Angew. Chem. Int. Ed.* **2005**, *44*, 4032–4035.
[222] D. Zhang, G. Wang, R. X. Zhu, *Tetrahedron: Asymmetry* **2008**, *19*, 568–576.
[223] M. D. Wodrich, C. Corminboeuf, P. R. Schreiner, A. A. Fokin, P. v. R. Schleyer, *Org. Lett.* **2007**, *9*, 1851–1854.
[224] D. A. Jose, A. Singh, A. Das, B. Ganguly, *Tetrahedron Lett.* **2007**, *48*, 3695–3698.
[225] A. Fu, W. Thiel, *J. Mol. Struct.* **2006**, *765*, 45–52.
[226] T. Inokuma, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2006**, *128*, 9413–9419.
[227] L. Zu, H. Xie, H. Li, J. Wang, W. Jiang, W. Wang, *Adv. Synth. Catal.* **2007**, *349*, 1882–1886.
[228] C. Palomo, M. Oiarbide, A. Laso, *Eur. J. Org. Chem.* **2007**, 2561–2574.
[229] T. Okino, S. Nakamura, T. Furukawa, Y. Takemoto, *Org. Lett.* **2004**, *6*, 625–627.
[230] X. Xu, T. Furukawa, T. Okino, H. Miyabe, Y. Takemoto, *Chem. Eur. J.* **2006**, *12*, 466–476.
[231] M. G. P. Buffat, *Tetrahedron* **2004**, *60*, 1701–1729.
[232] M. Atobe, N. Yamazaki, C. Kibayashi, *J. Org. Chem.* **2004**, *69*, 5595–5607.
[233] Y. Yamaoka, H. Miyabe, Y. Yasui, Y. Takemoto, *Synthesis* **2007**, *16*, 2571–2575.
[234] T. Y. Liu, H. L. Cui, J. Long, B. J. Li, Y. Wu, L. S. Ding, Y. C. Chen, *J. Am. Chem. Soc.* **2007**, *129*, 1878–1879.
[235] A. Berkessel, S. Mukherjee, F. Cleemann, T. N. Müller, J. Lex, *Chem. Commun.* **2005**, 1898–1900.
[236] A. Berkessel, S. Mukherjee, T. N. Müller, F. Cleemann, K. Roland, M. Brandenburg, J. M. Neudörfl, J. Lex, *Org. Biomol. Chem.* **2006**, *4*, 4319–4330.
[237] A. Berkessel, F. Cleemann, S. Mukherjee, *Angew. Chem. Int. Ed.* **2005**, *44*, 7466–7469.
[238] X. N. Xu, T. Yabuta, P. Yuan, Y. Takemoto, *Synlett* **2006**, 137–140.
[239] P. M. Pihko, A. Pohjakallio, *Synlett* **2004**, 2115–2118.
[240] S. Saaby, M. Bella, K. A. Jørgensen, *J. Am. Chem. Soc.* **2004**, *126*, 8120–8121.
[241] C. Cativiela, M. D. Diaz-de-Villegas, *Tetrahedron: Asymmetry* **2000**, *11*, 645–732.
[242] J. Watts, A. Benn, N. Flinn, T. Monk, M. Ramjee, P. Ray, Y. Wang, M. Quibell, *Bioorg. Med. Chem.* **2004**, *12*, 2903–2925.
[243] Y. Yamaoka, H. Miyabe, Y. Takemoto, *J. Am. Chem. Soc.* **2007**, *129*, 6686–6687.
[244] D. E. Fuerst, E. N. Jacobsen, *J. Am. Chem. Soc.* **2005**, *127*, 8964–8965.
[245] R. J. Gregory, *Chem. Rev.* **1999**, *99*, 3649–3682.
[246] S. J. Zuend, E. N. Jacobsen, *J. Am. Chem. Soc.* **2007**, *129*, 15872–15883.
[247] Y.-Q. Fang, E. N. Jacobsen, *J. Am. Chem. Soc.* **2008**, *130*, 5660–5661.

[248] Both enantiomers of *trans*-1,2-aminocyclohexanephosphine were readily accessed on a multi-gram scale using a modification of the literature procedure: A. Caiazzo, S. Dalili, A. K. Yudin, *Org. Lett.* **2002**, *4*, 2597–2600.
[249] A. G. Wenzel, M. P. Lalonde, J. E. N., *Synlett* **2003**, *12*, 1919–1922.
[250] A. Berkessel, F. Cleemann, S. Mukherjee, T. N. Müller, J. Lex, *Angew. Chem. Int. Ed.* **2005**, *44*, 807–811.
[251] F. Faigl, E. Fogassy, M. Nógrádi, E. Pálovics, J. Schindler, *Tetrahedron: Asymmetry* **2008**, *19*, 515–536.
[252] H. Pellissier, *Tetrahedron* **2008**, *64*, 1563–1601.
[253] H. E. Carter, *Org. React.* **1946**, *3*, 198–239.
[254] C. Y. K. Tan, D. F. Weaver, *Tetrahedron* **2002**, *58*, 7449–7461.
[255] C. S. Chen, Y. Fujimoto, G. Girdaukas, C. J. Sih, *J. Am. Chem. Soc.* **1982**, *104*, 7294–7299.
[256] C.-J. Wang, Z.-H. Zhang, X.-Q. Dong, X.-J. Wu, *Chem. Commun.* **2008**, 1431–1433.
[257] D. J. Dixon, R. D. Richardson, *Synlett* **2006**, 81–85.
[258] R. Ballini, G. Bosica, D. Fiorini, A. Palmieri, M. Petrini, *Chem. Rev.* **2005**, *105*, 933–971.
[259] R. Steele, C. Monti, C. Gennari, U. Piarulli, F. Andreoli, N. Vanthuyne, C. Roussel, *Tetrahedron: Asymmetry* **2006**, *17*, 999–1006.
[260] T. P. Yoon, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2005**, *44*, 466–468.
[261] K. L. Tan, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2007**, *46*, 1315–1317.
[262] S. B. Tsogoeva, M. J. Hateley, D. A. Yalalov, K. Meindl, C. Weckbecker, K. Huthmacher, *Bioorg. Med. Chem.* **2005**, *13*, 5680–5685.
[263] S. B. Tsogoeva, D. A. Yalalov, M. J. Hateley, C. Weckbecker, K. Huthmacher, *Eur. J. Org. Chem.* **2005**, 4995–5000.
[264] D. A. Yalalov, S. B. Tsogoeva, S. Schmatz, *Adv. Synth. Catal.* **2006**, *348*, 826–832.
[265] S. B. Tsogoeva, S. W. Wei, *Chem. Commun.* **2006**, 1451–1453.
[266] M. P. Lalonde, Y. G. Chen, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2006**, *45*, 6366–6370.
[267] H. B. Huang, E. N. Jacobsen, *J. Am. Chem. Soc.* **2006**, *128*, 7170–7171.
[268] Y. Sohtome, A. Tanatani, Y. Hashimoto, K. Nagasawa, *Tetrahedron Lett.* **2004**, *45*, 5589–5592.
[269] T. Nemoto, T. Fukuyama, E. Yamamoto, S. Tamura, T. Fukuda, T. Matsumoto, Y. Akimoto, Y. Hamada, *Org. Lett.* **2007**, *9*, 927.
[270] Y. Zhang, Y.-K. Liu, T.-R. Kang, Z.-K. Hu, Y.-C. Chen, *J. Am. Chem. Soc.* **2008**, *130*, 2456–2457.
[271] A. Berkessel, K. Roland, J. M. Neudörfl, *Org. Lett.* **2006**, *8*, 4195–4198.
[272] J. Tillack, L. Schmalstieg, W. Puetz, G. Ruttmann, German patent DE 19935329 A1, **2001**.
[273] Y.-C. Chen, *Synlett* **2008**, *13*, 1919–1930.
[274] G. Bredig, P. S. Fiske, *Biochemische Z.* **1913**, *46*, 7–23.
[275] H. Pracejus, *Liebigs Ann.* **1960**, *634*, 9–22.
[276] H. Hiemstra, H. Wynberg, *J. Am. Chem. Soc.* **1981**, *103*, 417–430.
[277] B. J. Li, L. Jiang, M. Liu, Y. C. Chen, L. S. Ding, Y. Wu, *Synlett* **2005**, 603–606.
[278] J. X. Ye, D. J. Dixon, P. S. Hynes, *Chem. Commun.* **2005**, 4481–4483.
[279] A. L. Tillman, J. X. Ye, D. J. Dixon, *Chem. Commun.* **2006**, 1191–1193.
[280] P. S. Hynes, D. Stranges, P. A. Stupple, A. Guarna, D. J. Dixon, *Org. Lett.* **2007**, *9*, 2107–2110.
[281] T.-Y. Liu, H.-L. Cui, Q. Chai, J. Long, B.-J. Li, Y. Wu, L.-S. Ding, Y.-C. Chen, *Chem. Commun.* **2007**, 2228–2230.
[282] B. Vakulya, S. Varga, A. Csampai, T. Soos, *Org. Lett.* **2005**, *7*, 1967–1969.
[283] S. H. McCooey, S. J. Connon, *Angew. Chem. Int. Ed.* **2005**, *44*, 6367–6370.
[284] S. H. McCooey, T. McCabe, S. J. Connon, *J. Org. Chem.* **2006**, *71*, 7494–7497.
[285] C. A. Bode, A. Ting, S. E. Schaus, *Tetrahedron* **2006**, *62*, 11499–11505.
[286] J. Wang, H. Li, L. S. Zu, W. Jiang, H. X. Xie, W. H. Duan, W. Wang, *J. Am. Chem. Soc.* **2006**, *128*, 12652–12653.
[287] C. L. Gu, L. Liu, Y. Sui, J. L. Zhao, D. Wang, Y. J. Chen, *Tetrahedron: Asymmetry* **2007**, *18*, 455–463.
[288] J. Song, Y. Wang, L. Deng, *J. Am. Chem. Soc.* **2006**, *128*, 6048–6049.
[289] Y. Q. Wang, J. Song, R. Hong, H. M. Li, L. Deng, *J. Am. Chem. Soc.* **2006**, *128*, 8156–8157.
[290] B. M. Wang, F. H. Wu, Y. Wang, X. F. Liu, L. Deng, *J. Am. Chem. Soc.* **2007**, *129*, 768–769.
[291] L. Zu, J. Wang, H. Li, H. Xie, W. Jiang, W. Wang, *J. Am. Chem. Soc.* **2007**, *129*, 1036–1037.
[292] J. Song, H. W. Shih, L. Deng, *Org. Lett.* **2007**, *9*, 603–606.
[293] Y. Wang, H. Li, Y.-Q. Wang, Y. Liu, B. M. Foxman, L. Deng, *J. Am. Chem. Soc.* **2007**, *129*, 6364–6365.
[294] M. Amere, M.-C. Lasne, J. Rouden, *Org. Lett.* **2007**, *9*, 2621–2624.
[295] L. Zu, H. Li, H. Xie, W. Wang, *Synthesis* **2007**, *16*, 2576–2580.
[296] P. Dinér, M. Nielsen, S. Bertelsen, B. Niess, K. A. Jørgensen, *Chem. Commun.* **2007**, 3646–3648.
[297] D. Pettersen, F. Piana, L. Bernardi, F. Fini, M. Fochi, V. Sgarzani, A. Ricci, *Tetrahedron Lett.* **2007**, *48*, 7805–7808.
[298] D. R. Li, A. Murugan, J. R. Falck, *J. Am. Chem. Soc.* **2008**, *130*, 46–48.
[299] H. Dollt, P. Hammann, S. Blechert, *Helv. Chim. Acta* **1999**, *82*, 1111–1122 and references cited therein.
[300] R. Dodda, T. Mandal, C.-G. Zhao, *Tetrahedron Lett.* **2008**, *49*, 1899–1902.
[301] H. S. Rho, S. H. Oh, J. W. Lee, J. Y. Lee, J. Chin, C. E. Song, *Chem. Commun.* **2008**, 1208–1210.
[302] T. Marcelli, R. N. S. van der Haas, J. H. van Maarseveen, H. Hiemstra, *Angew. Chem. Int. Ed.* **2006**, *45*, 929–931.
[303] S.-K. Tian, Y. Chen, J. Hang, L. Tang, P. McDaid, L. Deng, *Acc. Chem. Res.* **2004**, *37*, 621–631.
[304] X. Liu, H. Li, L. Deng, *Org. Lett.* **2005**, *7*, 167–169.
[305] H. Li, J. Song, X. Liu, L. Deng, *J. Am. Chem. Soc.* **2005**, *127*, 13774–13775.
[306] T. Marcelli, R. N. S. van der Haas, J. H. van Maarseveen, H. Hiemstra, *Synlett* **2005**, *18*, 2817–2819.
[307] P. Hammar, T. Marcelli, H. Hiemstra, F. Himo, *Adv. Synth. Catal.* **2007**, *349*, 2537–2548.
[308] G. F. Zhong, J. Fana, C. F. Barbas, III, *Tetrahedron Lett.* **2004**, *45*, 5681–5684.
[309] D. Almasi, D. A. Alonso, C. Nájera, *Tetrahedron: Asymmetry* **2006**, *17*, 2064–2068.
[310] X.-Y. Xu, Y.-Z. Wang, L.-Z. Gong, *Org. Lett.* **2007**, *9*, 4247–4249.
[311] R. P. Herrera, V. Sgarzani, L. Bernardi, A. Ricci, *Angew. Chem. Int. Ed.* **2005**, *44*, 6576–6579.
[312] M. P. Sibi, K. Itoh, *J. Am. Chem. Soc.* **2007**, *129*, 8064–8065.
[313] M. P. Sibi, J. J. Shay, M. Liu, C. P. Jasperse, *J. Am. Chem. Soc.* **1998**, *120*, 6615–6616.
[314] A. Lattanzi, *Synlett* **2007**, 2106–2110.
[315] R. P. Herrera, D. Monge, E. Martín-Zamora, R. Fernández, J. M. Lassaletta, *Org. Lett.* **2007**, *9*, 3303–3306.

[316] T. Matsumoto, H. Yamamoto, S. Inoue, *J. Am. Chem. Soc.* **1984**, *106*, 4829–4832.
[317] J. Wang, H. Li, X. H. Yu, L. S. Zu, W. Wang, *Org. Lett.* **2005**, *7*, 4293–4296.
[318] J. Wang, H. Li, W. H. Duan, L. S. Zu, W. Wang, *Org. Lett.* **2005**, *7*, 4713–4716.
[319] E. M. Fleming, T. McCabe, S. J. Connon, *Tetrahedron Lett.* **2006**, *47*, 7037–7042.
[320] Y.-L. Shi, M. Shi, *Adv. Synth. Catal.* **2007**, *349*, 2129–2135.
[321] M. Shi, L. H. L. H. Chen, *Chem. Commun.* **2003**, 1310–1311.
[322] M.-J. Qi, T. Ai, M. Shi, G. Li, *Tetrahedron* **2008**, *64*, 1181–1186.
[323] X.-G. Liu, J.-J. Jianga, M. Shi, *Tetrahedron: Asymmetry* **2007**, *18*, 2773–2781.
[324] M. Shi, X.-G. Liu, *Org. Lett.* **2008**, *10*, 1043–1046.
[325] T. Ishikawa, T. Kumamoto, *Synthesis* **2006**, *5*, 737–752.
[326] M. S. Iyer, K. M. Gigstad, N. D. Namdev, M. Lipton, *J. Am. Chem. Soc.* **1996**, *118*, 4910–4911.
[327] C. Becker, C. Hoben, D. Schollmeyer, G. Scherr, H. Kunz, *Eur. J. Org. Chem.* **2005**, 1497–1499.
[328] E. J. Corey, M. J. Grogan, *Org. Lett.* **1999**, *1*, 157–160.
[329] Y. Sohtome, Y. Hashimoto, K. Nagasawa, *Adv. Synth. Catal.* **2005**, *347*, 1643–1648.
[330] Y. Sohtome, Y. Hashimoto, K. Nagasawa, *Eur. J. Org. Chem.* **2006**, 2894–2897.
[331] Y. Sohtome, N. Takemura, K. Takada, R. Takagi, T. Iguchi, K. Nagasawa, *Chem. Asian J.* **2007**, *2*, 1150–1160.
[332] Triton X-100 (octyl phenol ethoxylate) is a registered trademark of Union Carbide and is commonly used as a detergent in biochemistry laboratories; formula $C_{14}H_{22}O(C_2H_4O)_n$ (n = 9, 10), [CAS-RN 9002-93-1].
[333] Y. Sohtome, N. Takemura, T. Iguchi, Y. Hashimoto, K. Nagasawa, *Synlett* **2006**, 144–146.
[334] K. Takada, N. Takemura, K. Cho, Y. Sohtome, K. Nagasawa, *Tetrahedron Lett.* **2008**, *49*, 1623–1626.
[335] M. M. K. Boysen, *Chem. Eur. J.* **2007**, *13*, 8648–8659.
[336] Oxone is a registered trademark of DuPont with potassium peroxymonosulfate $KHSO_5$ (potassium monopersulfate) as oxidizing ingredient of a triple salt with the formula $2KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$ (potassium hydrogen peroxymonosulfate sulfate), [CAS-RN 70693-62-8].
[337] Wang, Z.-X., Y. Shi, *J. Org. Chem.* **1998**, *63*, 3099–3104.
[338] Z.-X. Wang, G.-A. Cao, Y. Shi, *J. Org. Chem.* **1999**, *64*, 7646–7650.
[339] Y. Zhu, Y. Tu, H. Yu, Y. Shi, *Tetrahedron* **1998**, *39*, 7819–7822.
[340] H. Tian, X. She, H. Yu, L. Shu, Y. Shi, *J. Org. Chem.* **2002**, *67*, 2435–2446.
[341] S. Colonna, V. Pironti, J. Drabowicz, F. Brebion, L. Fensterbank, M. Malacria, *Eur. J. Org. Chem.* **2005**, 1727–1730.
[342] N. Khiar, S. Mallouk, V. Valdivia, K. Bougrin, M. Soufiaoui, I. Fernandez, *Org. Lett.* **2007**, *9*, 1255–1258.
[343] T. K. M. Shing, G. Y. C. Leung, T. Luk, *J. Org. Chem.* **2005**, *70*, 7279–7289.
[344] C. Becker, C. Hoben, H. Kunz, *Adv. Synth. Catal.* **2007**, *349*, 417–424.
[345] K. Liu, H. F. Cui, J. Nie, K. Y. Dong, X. J. Li, J. A. Ma, *Org. Lett.* **2007**, *9*, 923–925.
[346] C. Wang, Z. Zhou, C. Tang, *Org. Lett.* **2008**, *10*, 1707–1710.
[347] M. Klussmann, H. Iwamura, S. P. Mathew, D. H. Wells Jr., U. Pandya, A. Armstrong, D. G. Blackmond, *Nature* **2006**, *441*.
[348] C. L. Cao, M. C. Ye, X. L. Sun, Y. Tang, *Org. Lett.* **2006**, *8*, 2901–2904.
[349] C. Allemann, R. Gordillo, F. R. Clemente, P. H.-Y. Cheong, K. N. Houk, *Acc. Chem. Res.* **2004**, *37*, 558–569.
[350] Y. J. Cao, Y. Y. Lai, X. Wang, Y. H. Li, W. J. Xiao, *Tetrahedron Lett.* **2007**, *48*, 21–24.
[351] Y.-W. Chang, J.-J. Yang, J.-N. Dang, Y.-X. Xue, *Synlett* **2007**, *14*, 2283–2285.
[352] M. T. Robak, M. Trincado, J. A. Ellman, *J. Am. Chem. Soc.* **2007**, *129*, 15110–15111.

– CHAPTER 2 –

Journal Publications on Organocatalysis

Preface

Systematic investigations by Kotke and Schreiner on diverse (potential) thiourea catalysts, substrates, and reaction parameters have identified *N*,*N'*-bis[3,5-(trifluoromethyl)phenyl]thiourea as the catalyst of choice for the organocatalytic acetalization (Chapter 2.1), tetrahydropyranylation and MOP protection (Chapter 2.2), and the cooperatively catalyzed epoxide alcoholysis (Chapter 2.3 and 2.3.1; see also Chapter 3.2). These procedures and the mechanistic backgrounds demonstrate that the catalytic efficiency of this hydrogen-bonding thiourea derivative is not limited to the activation of carbonyl compounds. Thus, the "privileged character" of this organocatalyst is disclosed and confirmed; for the first time the application of this thiourea catalyst have left the "proof-of-concept" phase (see Chapter 1.2.1.1). Efficient accelerations of even preparative-scale experiments in combination with very low catalyst loadings, broad substrate scopes, straightforward work-up, and high product yields make these mild, metal-free procedures useful alternatives or complements to their counterparts utilizing Brønsted- or Lewis-acid catalysis.

Inspired by a publication on the deprotection of aromatic acetals in the presence of β-cyclodextrin as the catalyst (*JOC Note*, **2003**, *68*, 2018–2019) the research on acetals was started in February 2003. Since initial experiments on the hydrolysis of *p*-chlorobenzaldehyde diethyl acetal failed the diethyl acetalization of *p*-chlorobenzaldehyde, however, turned out be feasible in the presence of ≥100 mol% of *N*,*N'*-bis[3,5-(trifluoromethyl)phenyl]thiourea. This procedure suffering from (over-)stoichiometric catalyst amounts and long reaction times (3–7 days) operated without stirring of the homogeneous reaction mixture. A drastic improvement of the organocatalytic acetalization, however, could be achieved through permanent stirring of the reaction mixture: The reaction times and the catalyst loading could be reduced, while the substrate scope could be extended. GC analysis was found to be a reliable method for reaction monitoring. The experimental and analytical know-how acquired in this three-year project has proved to be very useful for the development of subsequent projects such as the tetrahydropyranylation and the epoxide alcoholysis. The experimental studies on the organocatalytic THP protection started in April 2006. Initial computations on the THP protection suggested that the nucleophilicity of the alcohol is increased due to a hydrogen-bonding mediated (partial) deprotonation. In August 2006, this role of the hydrogen-bonding thiourea catalyst and the organocatalytic aminolysis of epoxides (see Chapter 1.2.1.1; page 12) led Kotke to the hypothesis that not only amines, but also even less nucleophilic components such as alcohols could be added on epoxides resulting in an organocatalytic epoxide alcoholysis. The first experimental studies towards this project were performed in December 2006 by Kotke employing styrene oxide and ethanol as the components giving the desired β-alkoxy alcohol in 16 h. A side-product was identified and the reactions conditions were subsequently optimized to reduce side-product formation. These promising results initiated the epoxide-alcoholysis project. Further investigations in close collaboration with Weil and Schreiner finally succeeded in the introduction of the novel concept termed *"cooperative organocatalysis*" (for supporting information see Chapter 6.2). In the following the original articles are presented in chronological order to demonstrate the conceptual research progress that have led to these highly efficient and practical methods operating in the presence of hydrogen-bonding *N*,*N'*-bis[3,5-(trifluoromethyl)phenyl]thiourea organocatalyst.

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Acid-free, organocatalytic acetalization

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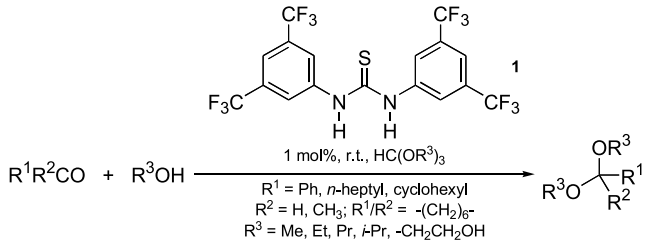
Abstract—The acid-free, organocatalytic acetalization of various aldehydes and ketones with *N*,*N*′-bis[3,5-bis(trifluoromethyl)phenyl] thiourea is presented. The neutral, double hydrogen bonding thiourea catalyst can be used at very low loadings of 0.01–1 mol% at room temperature to furnish the respective acetals in 65–99% yield at turnover frequencies around 600 h^{-1}. Acid-labile TBDMS-protected as well as unsaturated aldehydes can be converted efficiently into their acetals utilizing this very mild and highly practical method.

1. Introduction

Acetals are masked carbonyl derivatives that are important intermediates in synthetic as well as carbohydrate chemistry. They often are the synthetic targets themselves; acetals are one of the most frequently used protecting groups[1] for aldehydes and ketones against the attack of nucleophiles, organometallic reagents, oxidants, and basic reagents, for example, in synthetic carbohydrate,[2] steroid,[3] and pharmaceutical chemistry.[4] As the reaction of an alcohol with a carbonyl compound is thermodynamically disfavored and reversible, catalytic activation is practically always required; this is traditionally the domain of Lewis- and Brønsted acids. The only exceptions are acetalizations in the presence of $LiBF_4$,[5] ionic liquids (only aldehydes),[6] and NBS[7,8] as well as tetrabutylammonium tribromide (TBATB),[9] which, however, also generate acids (in case of NBS and TBATB) or suffer from a lack of generality. It would be highly desirable to develop a general acid-free method so that acid-labile substrates (e.g., carrying silyl groups or unsaturation) can also be acetalized. Since such a method apparently does not exist, we set out to develop an acid-free route to acetalization utilizing neutral, double hydrogen-bonding organocatalysis.[10,11]

The selective activation of carbonyl groups by Brønsted and Lewis acids is a milestone achievement of modern chemistry that relies on the principle that coordination lowers the orbital energies, thereby activating the functional group towards nucleophilic attack. However, these types of reactions often require overstoichiometric amounts of the 'catalyst' because the product still contains a basic moiety that binds the Lewis acid.[12] Hence, catalytic turnover may be hampered by product inhibition that derives from the fact that many of the highly electron-deficient Lewis acids bind basic sites too strongly. Much progress has been made by using weaker Lewis acids[13] such as the lanthanides that retain activity even in water.[14] On the other hand, the simplest catalyst, the proton, which often works best, is not tolerated in many interesting C–-X-bond forming reactions, as the required nucleophiles may be rapidly deactivated under acidic conditions. It is therefore attractive to design catalysts that are capable of 'partial protonation' by means of hydrogen-bonding for the activation of compounds with Lewis basic sites. This is generally feasible when a reaction proceeds under general acid catalysis where the catalyst stabilizes the transition state (TS) by hydrogen bonding. As nucleophilic additions to carbonyl compounds are often accompanied by a substantial increase in negative charge on the carbonyl atom in the TS, it can be preferentially stabilized. As we were able to show recently the similarities between the double-hydrogen bonding ability of a series of electron-deficient thiourea derivatives such as *N*,*N*′-bis[3,5-bis(trifluoro-methyl)phenyl]thiourea (**1**) and traditional Lewis acid catalysis,[10] we hoped that **1** would also catalyze the acetalization of a variety of aldehydes and ketones (Scheme 1).



Scheme 1.

Keywords: Acetalization; Organocatalysis; Protective groups; Turnover.
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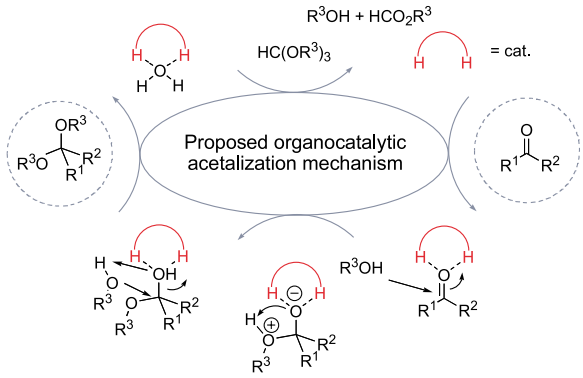
The reasoning behind this idea is that during the acetalization there will also be an increase of negative charge on the carbonyl oxygen that can then be stabilized by double hydrogen-bonding (Scheme 2).



Scheme 2.

2. Results and discussion

Our experiments with benzaldehyde (**2**) and ethanol as well as 1,2-ethanediol as the alcohol components cleanly gave the respective acetals in excellent yields at a catalyst loading of only 1 mol% (Table 1) at room temperature. Considering that typical acetalizations with strong acids are carried out in, for instance, refluxing toluene for azeotropic water removal (see below, Section 4.6), we were very pleased with the high activity of catalysts **1** in this reaction. The application of this protocol to other aromatic (e.g., **4**–**8**) but also simple aliphatic aldehydes (**9** and **10**) worked equally well and resulted in the respective acetals in excellent yields. The considerably less reactive ketones (e.g., **11**–**13**) can also be acetalized in good yields but, as expected, at considerably longer reaction times. All uncatalyzed reactions run in parallel under otherwise identical conditions gave no product within the time required for completion of the catalyzed transformation. Even after 1 week, the uncatalyzed reactions generally gave $<1\%$ of the respective acetals. The scale-up in preparative (20 mmol) experiments (noted in parentheses in Table 1) is also excellent and makes this reaction synthetically useful; the catalyst loading can be reduced routinely to 0.01 mol%, which still gives high yields at marginally extended reaction times.

The current reaction operates, to the best of our knowledge, at the lowest catalyst loadings for an organocatalytic reaction reported to date (0.01 mol%). Hence, turnover is significant enough to express it in terms of turnover number (TON) and, better, turnover frequency (TOF). For the acetalization of **4** and **10** we find TOFs of 632 h^{-1} (TON = 9800) and 577 h^{-1} (TON = 9700), respectively.

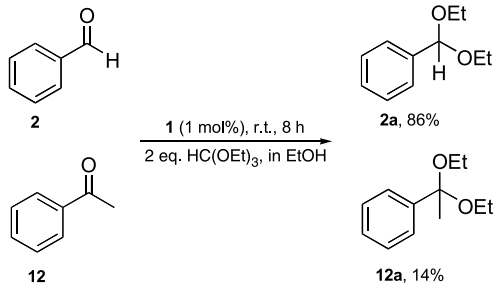
Thus far, the only limitation of our protocol concerns the acetalization of electron-rich *p*-tolylbenzaldehyde (**8**), which required very long reaction times owing to the low

Table 1. Organocatalytic acetalization of aryl as well as alkyl aldehydes and ketones with **1** at room temperature

Carbonyl compound	Mol% **1**	Alcohol[a,b]	*t* (h)[c]	Acetal (%)[d,e]
Benzaldehyde (**2**)	1	A	10	98 (94)
2	1	B	9.2	99 (92)
p-Fluorobenzaldehyde (**3**)	1	A	11.3	97
p-Chlorobenzaldehyde (**4**)	1	A	13 (3)	98 (95)
4	1	B	11.5 (2.5)	98 (87)
4	0.1	A	13.8	97
4	0.01	A	15.5	98
4	0.001	A	—	—
4	1	C	13.5	98
4	1	D	11	98
4	1	E	16	98
p-Bromobenzaldehyde (**5**)	1	A	21.5	98
p–CF_3-benzaldehyde (**6**)	1	A	7.5	97
Phenylacetaldehyde (**7**)	1	A	10.3	97
p-Tolylaldehyde (**8**)	1	A	250	71
8	1	B	250	76
Cyclohexanecarbaldehyde (**9**)	1	A	13.2	98 (89)
9	1	B	12.8	97 (88)
Octanal (**10**)	1	A	14.3 (4.3)	97 (91)
10	0.1	A	15.5	97
10	0.01	A	16.8	97
10	0.001	A	—	—
10	1	B	11.8 (3.8)	98 (89)
Cyclohexanone (**11**)	1	A	98	69 (61)
11	1	B	92	72 (63)
Acetophenone (**12**)	1	A	93	71 (62)
12	1	B	92	74 (65)
p-Chloroacetophenone (**13**)	1	A	94	71
13	1	B	91	65

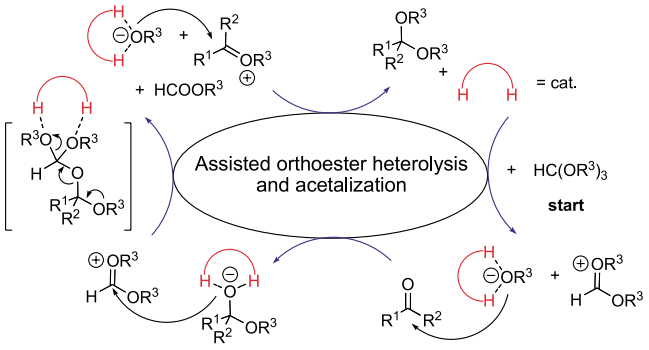
[a] Using alcohol A (ethanol), B (1,2-ethanediol), C (methanol), D (propanol), E (2-propanol, with dry THF as co-solvent).
[b] For each experiment alkyl orthoformate $HC(OR^3)_3$ (Schemes 2 and 4) was used, R depends on the alcohol (see Section 4).
[c] Reaction times of comparative experiments using 1 mol% *p*-toluenesulfonic acid monohydrate as catalyst under otherwise indentical conditions given in parentheses.
[d] Yield (GC).
[e] Preparative experiment (20 mmol scale, in parentheses), isolated yield of NMR-pure product.

reactivity of **8**; this high sensitivity to electronic effects is also apparent in the series of *p*-halogen-substituted benzaldehydes (**3**–**5**). The significant difference in reaction times of aldehydes and ketones translates approximately into the observed chemoselectivity in a competition experiment between benzaldehyde (**2**) and acetophenone (**12**): after 8 h we detect an acetal product mixture of 6.1:1 (NMR) in favor of the acetal of **2** with ethanol; a shorter reaction times (and non-quantitative conversion) gave higher chemoselectivity (Scheme 3).



Scheme 3.

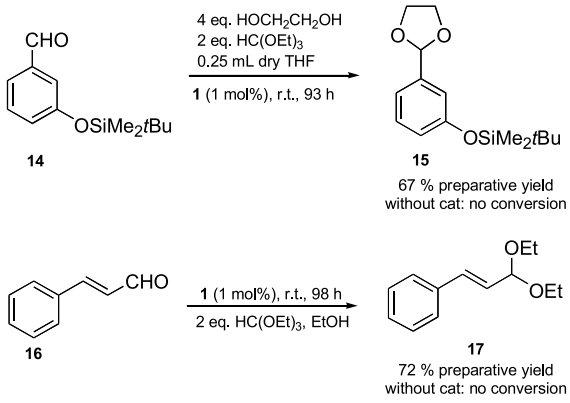
Our current mechanistic proposal for the organocatalytic acetalization of aldehydes and ketones (Scheme 2) begins with the coordination of **1** to the carbonyl group (binding and activation), followed by the nucleophilic attack of the first mole of alcohol. Increased binding to the incipient zwitterion emphasizes the notion of preferential stabilization through partial protonation by means of double hydrogen bonding (general acid catalysis). The catalyst also aids in activating the hydroxide as a formally rather poor leaving group by assisting proton transfer from the second mole of catalyst during nucleophilic attack onto the hemiacetal. This step is remarkable as it emphasizes the role of **1** as a partial proton donor because the key step in acid-catalyzed acetalizations is the protonation of the hydroxy function to produce water in the final S_N1 displacement with a second mole of alcohol.[15] Finally, **1** is released from the cycle by water removal with orthoformate. One problem of this proposal (Scheme 2) is the formal S_N2-like substitution of the OH group (with concomittant proton transfer) of the hemiacetal. A mechanistic alternative would be the thiourea-assisted heterolysis of the orthoester followed by the rapid attack of the alcoholate onto the carbonyl compound as outlined in Scheme 4.



Scheme 4.

Evidence for this mechanistic proposal comes from our attempts to perform thioacetalization reactions, which are also accelerated in the presence of our catalysts **1** in the absence of $HC(OEt)_3$. Addition of the orthoester only gave the normal diethyl acetal although the thiols are much better nucleophiles. Clearly, the full mechanistic elucidation of this reaction requires more elaborate studies that are under way in our laboratories and will be reported in full in due course.

The practicality of our acid-free acetalization is further exemplified (Scheme 5) with the acetalization of TBDMS-protected aldehyde **14**, which is acid-sensitive and reacts rather sluggish under alternative conditions (e.g., in the presence of 2 mol% NBS[8] or in refluxing cyclohexane (80 °C) with higher catalyst ($InCl_3$) loading[16] of 5 mol%): acetal **15** is formed in 67% preparative yield; there is no reaction without catalyst over the same period of time. The clean conversion of *trans*-cinnamic aldehyde to the acetal **17** also emphasizes the synthetic usefulness of this acid-free conversion.



Scheme 5.

3. Conclusions

In summary, we have successfully extended the principle of double-hydrogen bonding organocatalysis as provided by hydrogen-bonding thiourea derivative **1** to the acetalization of various aliphatic and aromatic carbonyl compounds. The scope of our high-yielding acid-free acetalization includes saturated, aromatic as well as unsaturated aldehydes and ketones, and proceeds at the highest turnover frequencies (around 600 h^{-1}) reported for an organocatalytic reaction to date (catalyst loadings down to 0.01 mol%). Comparative experiments using *p*-toluenesulfonic acid monohydrate as a traditional catalyst still are faster by a factor of 4–5 for some representative carbonyl substrates under otherwise identical conditions but this protocol is obviously not applicable to acid-sensitive substrates for which our approach works well. We currently focus on the elucidation of the reaction mechanism, the acetalization of unsaturated ketones, and enantioselective acetalizations.

4. Experimental

4.1. General information

All chemicals were purchased from Aldrich, Acros Organics, and Lancaster in the highest purity available;

for all syntheses and experiments dry chemicals were used; methanol and ethanol were dried according to the usual literature procedures using magnesium and sodium/diethyl phthalate, respectively; propanol, isopropanol, and 1,2-ethandiol were distilled once over a 20 cm Vigreux column; alkyl orthoformates were distilled twice over a 20 cm column filled with Raschig rings; THF and triethylamine were freshly distilled from Na/benzophenone; all dry chemicals were stored until use under argon atmosphere over new molecular sieve 3 Å (alcohols), 4 Å (alkyl orthoformates), and sodium (THF, triethylamine). Solid aldehydes were dried over Sicapent™ in a desiccator and were used without further purification; to remove traces of benzoic acid all liquid aldehydes were purified by vacuum destillation over a 10 cm Vigreux column directly before use. Column chromatography was performed on activated basic Al_2O_3 (50–200 microns; Acros Organics). All experiments were carried out in oven-dried and flame-dried glassware (Schott DURAN), all equipment was dry, including syringes, pipettes, and cannulas.

For progress monitoring of acetalizations GC-analysis was performed with Carlo Erba instruments 5300 equipped with a 10 m OV 101 column using N_2 as carrier gas; *T*-program standard 100–250 °C, heating rate 15 °C/min, injector and detector (FID) 250 °C; time-dependent conversion in percent was determined from integral ratio of educt and product signals; retention times of the products were detected by analyzing the pure acetals (reference compounds); ^1H and ^{13}C NMR spectra were recorded with a Bruker AM 400 spectrometer using TMS as the internal standard; chemical shift values are given in ppm. IR spectra were measured with a Bruker IFS 25 spectrometer; HRMS was performed with a Sectorfield-MS: Finnigan MAT 95, CHN-Analysis were obtained from a Carlo Erba 1106 (balance: Mettler Toledo UMX-2); the melting point (corrected) of **1** was determined with a BÜCHI SMP-20; pH-value of a representative organocatalyzed reaction was measured with a portable HANNA HI 8314 pH meter.

4.1.1. Synthesis of organocatalyst *N,N′*-bis[3,5-bis(trifluoromethyl)phenyl]thiourea. For large-scale preparation the synthesis of **1** followed a modified literature protocol.[17] In an oven-dried 1000 mL three-necked flask equipped with thermometer, addition funnel, gas inlet, and magnetic stirring bar a mixture of 3,5-bis(trifluoromethyl)aniline (23.39 g, 100 mmol) and triethylamine (16.57 mL, 119 mmol) in THF (720 mL) was prepared. Under argon atmosphere a mixture of thiophosgene (3.29 mL, 43 mmol) in THF (70 mL) was added dropwise to the stirred solution at −5–0 °C. After addition, the yellow suspension (a white solid precipitated) was allowed to stir at room temperature After 24 h the bulk of solvent was removed in a rotary evaporator under reduced pressure, the concentrated brown-colored residue was added to water (450 mL), and the aqueous layer was extracted with diethyl ether (2× 150 mL). The combined organic layers were washed with brine (1×80 mL) and dried over sodium sulfate. After filtration and evaporation of the solvent the red-brown solid crude product was purified by recrystallization from chloroform once, and the resulting slightly yellow solid, was dissolved in a minimum amount of diethyl ether to be re-precipitated by addition of *n*-hexane as a nearly colorless solid that was dried over Sicapent™ in a desiccator to obtain spectroscopically pure thiourea derivative **1** (36.1 g, 72 mmol, 84%). Concentrating the mother liquor to a minimum volume and cooling in an ice box afforded an additional amount (2.9 g, 5.8 mmol) of **1**. Mp 172–173 °C; X-ray data,[18] IR (KBr): 3207, 3050, 2987, 1555, 1467, 1376, 1326, 1289, 1181, 1133, 930, 891, 714, 701, 684; ^1H NMR (400 MHz, [d_4] methanol): δ=7.33–7.27 (m, 6H), 7.68 (s, 2H), ^{13}C NMR (100 MHz, [d_4] methanol): δ= 120.47 (CH), 123.17 (C_q), 125.87 (CH), 132.67 (C_q), 142.51 (C_q), 182.20 (C=S); HRMS calcd $C_{17}H_8N_2SF_{12}$: 500.0216; found: 500.0210; CHN-analysis: calcd C 40.81, H 1.61, N 5.60; found C 40.69, H 1.65, N 5.68.

4.2. Organocatalytic synthesis of acyclic acetals from aldehydes and ketones

In a flame-dried 10 mL one-necked flask tightly sealed with a plastic plug a mixture of 2 mmol freshly distilled carbonyl compound, 0.5 mL (8.6 mmol) dry ethanol, 0.66 mL (4 mmol) dry triethyl orthoformate, and 10 mg (1 mol%) organocatalyst **1** was magnetically stirred (~900 rpm, stirring bar: 1 cm) at room temperature. The progress of the homogenous reaction was monitored by GC analysis. After completion of the reaction a saturated aqueous solution of $NaHCO_3$ (5 mL) was added, the resulting mixture was extracted with CH_2Cl_2 (3×5 mL), the collected organic layers were washed with water (1× 5 mL) and finally dried over anhydrous Na_2SO_4. Evaporation of solvent in a rotary evaporator under reduced pressure furnished almost pure products. Further purification was achieved by column chromatography through a column of basic Al_2O_3 (20 cm×1.5 cm, ~35 g) with *n*-hexane/ethyl acetate (5/1) as eluent to afford the corresponding diethyl acetal spectroscopically pure in good to excellent yields.

4.3. Organocatalytic synthesis of cyclic acetals from aldehydes and ketones

In a flame-dried 10 mL one-necked flask tightly sealed with a plastic plug a mixture of 2 mmol freshly distilled carbonyl compound, 0.45 mL (8 mmol) dry 1,2-ethandiol, 0.66 mL (4 mmol) dry triethyl orthoformate, 0.25 mL dry THF, and 10 mg (1 mol%) organocatalyst **1** was magnetically stirred (~900 rpm) until completion of the reaction (GC-analysis), the reaction mixture was worked up according to the procedure described for acyclic acetals to gave pure 1,3-dioxolanes in good to excellent yields.

Acyclic and cyclic acetals were identified by comparison of their NMR, IR, and GC co-injection of authentic samples (reference compounds) synthesized by established procedures.

4.4. Synthesis of reference compounds

4.4.1. Synthesis of dimethyl and diethyl acetals. A mixture of freshly distilled carbonyl compound (0.06 mol), dry methanol (20 mL) or ethanol, trimethyl orthoformate, and triethyl orthoformate (0.09 mol), respectively, and

p-toluenesulfonic acid monohydrate (150 mg) was stirred in an argon atmosphere at room temperature for 24 h (ketones were refluxed for 12 h). The acid was neutralized by dropwise addition of a saturated aqueous solution of sodium carbonate, the organic layer was separated und washed with an aqueous solution of sodium hydrogen sulfite (5 mL, 20%), and dried over sodium sulfate. After evaporation of the solvent the crude product was distilled over a 10 cm Vigreux column (in case of benzaldehyde **2** a 20 cm column was used) under reduced pressure to furnish the pure acetals in yields ranging from 64–81%.

4.5. Synthesis of dipropyl and diisopropyl acetal of 4

Dipropyl and diisopropyl acetals of *p*-chlorobenzaldehyde **4** were synthesized by refluxing a solution of the aldehyde (4.21 g, 30 mmol), *p*-toluenesulfonic acid monohydrate (200 mg), tripropyl orthoformate (8.56 g, 45 mmol) and triisopropyl orthoformate (8.56 g, 45 mmol), respectively, in the corresponding dry alcohol (6 mL) for 12 h in an argon atmosphere. The reaction mixture was neutralized with an aqueous solution of sodium carbonate, the aqueous layer was extracted with diethyl ether (once 5 mL), and after drying with sodium carbonate, the solvent was removed. Vacuum destillation over a 10 cm Vigreux column afforded at 131–133 °C (~10 mbar) pure *p*-chlorobenzaldehyde dipropyl acetal (4.6 g, 19.0 mmol, 63%) and at 120–122 °C (~10 mbar) *p*-chlorobenzaldehyde diisopropyl acetal (4.8 g, 19.8 mmol, 66%), respectively.

4.5.1. *p*-Chlorobenzaldehyde dipropyl acetal. Colorless liquid, IR (neat): ν=2964, 2937, 2877, 1490, 1339, 1205, 1090, 1067, 1042, 1016, 809; ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.95 (t, 3H, J=7.5 Hz), 1.58–1.67 (m, 2H, J=7.4 Hz), 3.38–3.36 (m, 2H), 5.5 (s, 1H), 7.27–7.34 (m, 2H), 7.37–7.42 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=10.7 (CH_3), 22.9 (CH_2), 66.9 (CH_2), 100.7 (CH), 128.1 (CH), 128.2 (CH), 133.9 (C_q), 137.7 (C_q); HRMS calcd $C_{13}H_{19}ClO_2$ 242.1074; found: 242.1091; CHN-analysis: calcd C 64.32, H 7.89; found C 64.54, H 8.16.

4.5.2. *p*-Chlorobenzaldehyde diisopropyl acetal. Colorless liquid, IR (neat): ν=2973, 2931, 1599, 1491, 1466, 1381, 1324, 1295, 1204, 1180, 1126, 1089, 1075, 1035, 1015, 943, 833, 815 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 1.13–1.19 (m, 6H), 3.85–3.94 (m, 1H, J=6 Hz), 5.03 (s, 1H), 7.27–7.34 (m, 2H), 7.37–7.42 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=22.4 (CH_3), 23.0 (CH_3), 67.9 (CH), 98.5 (CH), 128.1 (CH), 128.2 (CH), 133.8 (C_q), 139.0 (C_q); HRMS calcd $C_{13}H_{19}ClO_2$ 242.1074; found: 242.1086; CHN-analysis: calcd C 64.32, H 7.89; found C 64.47, H 8.09.

4.6. Synthesis of 1,3-dioxolanes as reference compounds

In a oven-dried 50 mL one-necked flask equipped with a water separator and a reflux condenser a mixture of 0.1 mol of the corresponding freshly distilled carbonyl compound, 7.45 g (0.12 mol) 1,2-ethandiol, 30 mL toluene, and 150 mg *p*-toluenesulfonic acid monohydrate were magnetically stirred and refluxed until no more water separated. For work-up the reaction mixture was poured into an aqueous saturated solution of $NaHCO_3$ (20 mL), the organic layer was washed with water (2×15 mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvent in a rotary evaporator under reduced pressure the crude products were purified by vacuum destillation over a 10 cm Vigreux column to afford colorless liquids; the yields ranged from 67 to 85%. Spectral data were identical to those reported in the literature.

The acid-labile aldehyde **14** incorporating the TBDMS-group was prepared by a straightforward literature procedure (yield:79%).[19]

4.7. Analytical methodology

All analytical reaction mixtures of the acetalizations were prepared in clean (for cleaning glass flasks were stored for 8 h in a KOH/*iso*-propanol bath, washed intensively with water, demineralized water, and acetone, successively), oven-dried (5 h) and flame-dried 10 mL (for 2 mmol scale; 25 and 250 mL flasks for larger scale) one-necked glass flasks were tightly sealed with a plastic plug. Two millimoles of the respective carbonyl compound (for catalyst loading of 0.1 and 0.01 mol% a 20 mmol scale was used, for 0.001 mol% 200 mmol scale) and organocatalysts **1** (various loadings: 1.0 [10 mg/2 mmol], 0.1 [10 mg/20 mmol], 0.01 [1 mg/20 mmol], and 0.001 mol% [1 mg/200 mmol scale] relative to the carbonyl compound) were weighted out directly into the flasks and were dissolved in 2 equiv of the corresponding alkyl orthoformate and alcohol (methanol, ethanol, propanol, and isopropanol, respectively) by intensive stirring (900 rpm) with a new magnetic stirring bar wrapped with plastics (size: 0.8 cm for 2 mmol, 1.4 cm for larger scale experiment); stirring was continued until completion of the reaction. The volume of the alcohol was adjusted relative the volume of alkyl orthoformate, to keep total volume constant (1.16 mL) making all experiments comparable to each other (Table 2). For the formation of cyclic acetals 2 mmol of carbonyl compound, 4 equiv 1,2-ethandiol, 2 equiv triethyl orthoformate, and 0.25 mL THF as cosolvent were mixed; all reactions were carried out at room temperature (25 °C); the reaction time measurements started with the addition of the alcohol, that served as reagent as well as solvent; the volumes were measured with 1 and 2 mL pipettes. Every mixture containing catalyst was prepared twice, and for detection of catalytic efficiency all experiments were accompanied by a parallel control experiment under same conditions, but without catalyst. Samples (0.8–1.2 μL; volume depended on progress of reaction) were taken directly from the stirred homogenous reaction mixture by a Hamilton syringe (10 μL) and were injected immediately to record the GC chromatogram. The course of each acetalization was monitored by integrating the educt/product ratio. Signals were assigned by injecting

Table 2. Volumes of orthoformates (2 equiv/4 mmol) and alcohols for 2 mmol scale experiments

Orthoformate	Volume (mL)	Alcohol	Volume (mL)
Trimethyl	0.44	Methanol	0.72
Triethyl	0.66	Ethanol	0.50
Tri-*n*-propyl	0.87	1-Propanol	0.29
Triisopropyl	0.87	2-Propanol	0.29

the starting material and reference compound; in case of the acetalization of **14** and **16** reference compounds **15** and **17** were not prepared, so completion of the reaction was indicated by disappearance of starting material, yield was obtained by preparative work-up, product identification by NMR and IR. Comparative experiments using 1 mol% (4 mg) *p*-toluenesulfonic acid monohydrate were accomplished in 2 mmol scale and ran under the same conditions (alcohol, orthoformate, room temperature) as described in the details given in Table 1).

Acknowledgements

This work was supported by the Deutsche Forschungsgemeinschaft (SPP1179). This article is dedicated to Eva Kotke on the occasion of her 60th birthday.

References and notes

1. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Thieme: New York, 1999. Kocienski, P. J. *Protecting Groups*; Thieme: New York, 1994.
2. Clode, D. M. *Chem. Rev.* **1979**, *79*, 491–513.
3. Bull, J. R.; Floor, J.; Kruger, J. G. *J. Chem. Res.* **1979**, *7*, 224–225.
4. Salimbeni, A.; Manghisi, E.; Fregnan, G. B. *Eur. J. Med. Chem.* **1977**, *5*, 413–420.
5. Hamada, N.; Kazahaya, K.; Shimizu, H.; Sato, T. *Synlett* **2004**, 1074–1076.
6. Li, D. M.; Shi, F.; Peng, J. J.; Guo, S.; Deng, Y. Q. *J. Org. Chem.* **2004**, *69*, 3582–3585.
7. Karimi, B.; Ebrahimian, G. R.; Seradj, H. *Org. Lett.* **1999**, *1*, 1737–1739. Karimi, B.; Seradj, H.; Ebrahimian, G. R. *Synlett* **1999**, 1456–1458.
8. Karimi, B.; Hazarkhani, H.; Maleki, J. *Synthesis* **2005**, 279–285.
9. Gopinath, R.; Haque, S. J.; Patel, B. K. *J. Org. Chem.* **2002**, *67*, 5842–5845.
10. Wittkopp, A.; Schreiner, P. R. *Chem. Eur. J.* **2003**, *9*, 407–414. Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289–296. Schreiner, P. R.; Wittkopp, A. *Org. Lett.* **2002**, *4*, 217–220. Wittkopp, A.; Schreiner, P. R. In Rappoport, Z., Ed.; *The Chemistry of Dienes and Polyenes*; Wiley: Chichester, 2000; Vol. 2, pp 1029–1088.
11. Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 10012–10014. Vachal, P.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 867–870. Su, J. T.; Vachal, P.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 197–200. Sigman, M. S.; Vachal, P.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2000**, *39*, 1279–1281. Pihko, P. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2062–2064. Okino, T.; Nakamura, S.; Furukawa, T.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 625–627. Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673. Okino, T.; Hoashi, Y.; Takemoto, Y. *Tetrahedron Lett.* **2003**, *44*, 2817–2821. Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X. N.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119–125. Berkessel, A.; Cleemann, F.; Mukherjee, S.; Muller, T. N.; Lex, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 807–811. Berkessel, A.; Mukherjee, S.; Cleemann, F.; Muller, T. N.; Lex, J. *Chem. Commun.* **2005**, 1898–1900.
12. Oppolzer, W.; Rodriguez, I.; Blagg, J.; Bernadinelli, G. *Helv. Chim. Acta* **1989**, *72*, 123.
13. Otto, S.; Bertoncin, F.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1996**, *118*, 7702–7707.
14. Kobayashi, S. *Eur. J. Org. Chem.* **1999**, 15–27.
15. The pH of our reactions remains constant at around 6.7.
16. Ranu, B. C.; Jana, R.; Samanta, S. *Adv. Synth. Catal.* **2004**, *346*, 446–450.
17. (a) Trifluormethyl thiourea derivatives: Wittkopp, A. Diplomarbeit, University of Göttingen, 1998. (b) General synthesis of thioureas and molecular recognition of a zwitterion: Wilcox, C. S.; Kim, E.; Romano, D.; Kuo, L. H.; Burt, A. L.; Curran, D. P. *Tetrahedron* **1995**, *51*, 621–634.
18. The structure of **1** was deposited in the Cambridge Crystallographic Data Center (CCDC 206506) and can be retrieved free of charge from there. Key data: formula C17 H8 F12 N2 S1; unit cell parameters: *a* 15.178(2) *b* 8.2203(8) *c* 17.399(2) 112.495(14); space group *P*21/*c*.
19. Tremblay, M. R.; Luu-The, V.; Leblanc, G.; Noël, P.; Breton, E.; Labrie, F.; Poirier Bioorg, D. *Bioorg. Med. Chem.* **1999**, *7*, 1013–1023.

Generally Applicable Organocatalytic Tetrahydropyranylation of Hydroxy Functionalities with Very Low Catalyst Loading

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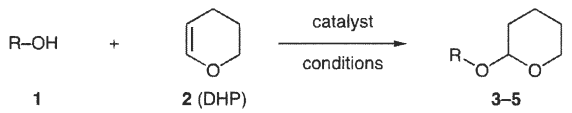
Abstract: This paper presents the first acid-free, organocatalytic tetrahydropyran and 2-methoxypropene protection of alcohols, phenols, and other ROH derivatives utilizing privileged *N,N'*-bis[3,5-bis(trifluoromethyl)phenyl]thiourea and a polystyrene-bound analogue. The reactions are broadly applicably (also on preparative scale), in particular, to acid-sensitive substrates such as aldol products, hydroxy esters, acetals, silyl-protected alcohols, and cyanohydrins. The catalytic efficiency is truly remarkably with turnover numbers of 100,000 and turnover frequencies of up to 5700 h^{-1} at catalyst loadings down to 0.001 mol%. The computationally supported mechanistic interpretation emphasizes the hydrogen bond assisted heterolysis of the alcohol and concomitant preferential stabilization of the oxyanion hole in the transition state.

Key words: acetals, alcohols, catalysis, protecting groups, supported catalysis

Introduction

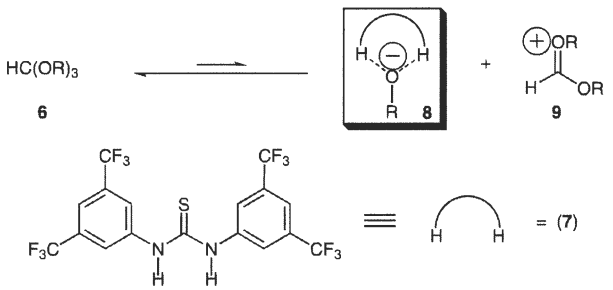
The acid-catalyzed reaction of alcohols and phenols **1** with 3,4-dihydro-2*H*-pyran (DHP, **2**) to give tetrahydropyranyl-substituted ethers **3** is a classic, and one of the most common, strategies for the protection of hydroxy functions (tetrahydropyranylation, Scheme 1).[1] The utility and popularity of this reaction lies in the ease of introducing and removing the tetrahydropyranyl (THP) group and the fact that pyrans of type **3** are remarkably stable under basic conditions.



Scheme 1 General tetrahydropyran protection (tetrahydropyranylation). The product numbering refers to different types of THP-protected alcohols, as depicted in Tables 1–3.

There are many ways to catalyze this important reaction. Various Brønsted acids, including acidic polymers and ionic liquids,[2] and also a large variety of Lewis acids, including zeolites,[3] acidic alumina,[4] and clays,[5] have been utilized. There have been a few attempts to find 'acid-free' variants of this reaction, e.g., with benzyltriphenylphosphonium tribromide or tetrabutylammonium tribromide salts,[6] but these generate HBr in situ;[7] cerium(III) chloride[8] also catalyzes this reaction but is ineffective for sterically hindered alcohols (e.g., adamantan-1-ol). There is no single catalyst that can be applied to the entire spectrum of alcohols, in particular, to sterically hindered tertiary alcohols (elimination is a major side reaction) and deactivated phenols. We do not know of any general approach to the THP protection of highly acid-labile substrates; such a method would, indeed, be highly desirable.

Based on our excellent experience on the catalysis of acetalization reactions[9] we contemplated that tetrahydropyranylations would also be feasible. The reasoning for this is based on the observation that in the acetalization reactions the thiourea catalyst (**7**, *N,N'*-bis[3,5-bis(trifluoromethyl)phenyl]thiourea) assists the heterolysis of the ortho ester **6** in the initial stages of the reaction by stabilizing the incipient alcoholate (**8**, Scheme 2). This rationalization is in line with well-established concepts in a multitude of enzymatic reactions that are characterized through 'oxyanion stabilization' through explicit hydrogen bonds to partially negatively charged oxygen atoms.[10]



Scheme 2 Initiation step in thiourea-catalyzed acetalizations and the structure of catalyst **7**.

A second clue was provided by the reactions of α,β-unsaturated carbonyl compounds **10** that underwent a domino Michael addition followed by acetalization to give highly oxygenated products **11** under the acetalization reactions conditions (Scheme 3).[9]

These mechanistic insights clearly mark the departure from the often-implied concept of carbonyl[11,12] (or imino[13,14]) group activation through hydrogen bonding with (thio)urea and other hydrogen-bonding catalysts. Hence, this mechanistic alternative suggests either the hydrogen bond assisted generation of the free nucleophile (e.g., RO^-, CN^-) or the stabilization of the active form of

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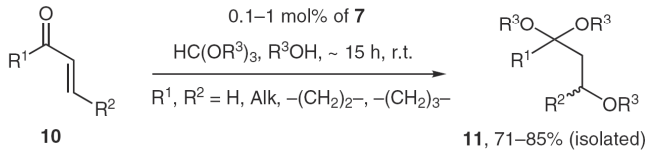


Scheme 3 Domino Michael addition of R^3OH to α,β-unsaturated carbonyl compounds followed by acetalization.

the nucleophile through hydrogen bonding and polar interactions to the respective precursor [ROH, $HC(OR)_3$, HCN, TMSCN, etc.].

We envisioned that the intrinsic reactivity (not necessarily acidity) of simple alcohols should be increased through hydrogen bonding so that the polar reactions with, e.g., enol ethers such as **2** should be significantly accelerated. As we will demonstrate in the following, this concept works extremely well for the tetrahydropyranylation of a wide variety of alcohols including phenols and sterically hindered alcohols. Furthermore, the generality of this method is demonstrated through the reactions of alcohols with 2-methoxypropene (MOP), the protection of oximes as well as aldols and several other highly acid-sensitive substrates. The application of polystyrene-bound thiourea catalysts and computations underscoring our mechanistic hypothesis are also included.

Results and Discussion

We used 3,4-dihydro-2*H*-pyran (DHP) as reactant and solvent and conducted most of our reactions using two equivalents of DHP; in cases where the alcohol was insoluble in DHP, a small amount of tetrahydrofuran was added as a co-solvent (see the experimental section for details). We conducted control experiments in parallel and found no conversion of the respective substrates in the given time required for full conversion of the starting materials in the catalyzed reactions. The catalyst loadings of **7** were 1 mol% or less. Organocatalysts incorporating a thiourea motif are generally highly effective and allow practically low catalyst loadings.[9] In combination with the 3,5-bis(trifluoromethyl)phenyl moiety, which was introduced by us,[11,15] these catalysts enjoy the status of being 'privileged'[16] because their success rate in a manifold of reactions[9,14,17,18] is exceptionally high. Our current results are summarized in Tables 1– 4 and emphasize the broad applicability of **7** in the THP protection of a very broad variety of alcohols and other hydroxy-functionalized compounds.

Primary and secondary alcohols can be THP protected at room temperature in excellent yields and reasonable reaction times (Table 1). Benzyl alcohol stands out as being

Biographical Sketches

Mike Kotke was born in Hanau, a city near Frankfurt/Main, Germany, in 1969. He joined the Degussa company (Hanau-Wolfgang, Germany) in 1989 on an apprenticeship as a chemical laboratory technicien. After two and a half years, Mike took his examination early in 1992 and continued working for six months as an assistant instructor in the training department of Degussa with responsibilities for the education of chemical laboratory workers. In October 1992 he began his chemistry studies at the Justus-Liebig University, Gießen, Germany, and he completed his coursework within eight semesters. After a period of working in various occupations, he returned to the university in 2001 to prepare his diploma thesis in organic chemistry in the group of Prof. R. Askani. Mike received his diploma degree on the 'Synthesis of potential precursors of a homoaromatic semibullvallene' in the spring of 2002 and then began his Ph.D. studies on thiourea-based organocatalysis under the supervision of Prof. Peter R. Schreiner.

Peter R. Schreiner is professor of organic chemistry at the Justus-Liebig-University Gießen. He studied chemistry in his native city at the University Erlangen-Nürnberg, Germany, where he received his Dr. rer. nat. (1994) in organic chemistry with P. v. R. Schleyer. Simultaneously, he received a Ph.D. (1995) with Henry F. Schaefer III in computational chemistry from the University of Georgia. He completed his Habilitation at the University of Göttingen (1999) in the group of A. de Meijere. Before becoming head of the Organic Institute in Gießen in 2002, he was associate professor of chemistry at the University of Georgia (1999–2002). P. R. Schreiner is the 2003 recipient of the Dirac Medal of the World Association of Theoretically Oriented Chemists. Amongst other awards, he also received the ADUC Prize for Habilitanden (assistant professors) in 1999, was a Liebig Fellow (1997–1999) of the Fonds der Chemischen Industrie, and held a Habilitandenstipendium of the Deutsche Forschungsgemeinschaft (1999). He currently serves as the assistant editor for the Journal of Computational Chemistry and as an international advisory board member of the European Journal of Organic Chemistry.

the most reactive in this group. Its effective THP protection at very low catalyst loadings down to 0.001 mol% to give **3j** emphasizes the catalytic power of **7**. For the reaction with the lowest catalyst loading we calculate maximum turnover numbers (TONs) close to 100,000 and turnover frequencies (TOFs), a much more sensible measure of practicality, of around 2,000 h^{-1}.

While ethylene glycol is diprotected to give **3m**, the difference in the relative rates of reaction of primary vs. secondary hydroxy groups results in the formation of the di-THP-substituted glycerol **3n**. Our acid-free protocol also allows the protection of *tert*-butyldimethylsilyl-substituted substrates leading to orthogonal hydroxy protection as shown for **3k**. For the same reason, tertiary alcohols, which normally are difficult to protect as THP ethers owing to steric hindrance and elimination as a side reaction, can also be THP protected under our conditions (Table 2). Particularly striking is the tolerance of even the most sterically hindered adamantan-1-ol (**4k**),[8] diamantan-1-ol (**4l**), and triphenylmethanol (**4m**) that can not be THP protected by established methods (see above).

Phenol derivatives are also readily converted into their corresponding THP ethers (Table 2); only the reaction temperature must be raised to 50 °C in order to maintain comparable reaction times as for the substrates in Table 1. As shown for phenol, THP protection to **4a** can be achieved with catalyst loadings down to 0.001 mol%, resulting in a TOF of 5700 h^{-1}! This is in the range of excellent metal-catalyzed reactions and, to the best of our knowledge, the most efficient organocatalytic reaction to date.[9,19] Indeed, although we mostly report reactions run at 1 mol% catalyst loading used for our substrate screening, selected scale-up experiments show that a loadings of only 0.01–0.1 mol% are sufficient and practical for preparative THP protection; we routinely ran these reactions on a 50 mmol scale.

The phenol derivatives also provide the important clue that acidity is not a factor for the mechanistic interpretation of these reactions because (a) phenols are more acidic than alkanols and (b) electron-deficient phenols such as 4-chlorophenol, 4-(trifluoromethyl)phenol, and 4-hydroxybenzonitrile react more slowly than electron-rich 4-methylphenol or 4-methoxyphenol (products **4c**, **4e**, and **4f** vs. **4b** and **4d**, respectively).

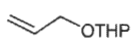
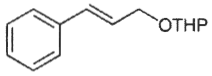
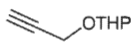
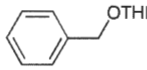
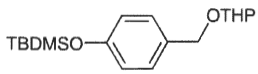
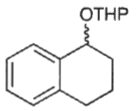
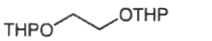
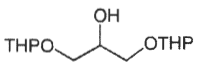
α-Hydroxy ketones can also be THP protected (Table 3, products **5a** and **5b**) at 50 °C in good yields. More remarkable is the possibility of protecting typical aldol products (**5c**, TOF = 2000 h^{-1}) as well as other highly acid-sensitive substrates (at r.t.) such as β-hydroxy ester **5d**, epoxide **5e**, and acetonides **5f** and **5g** without side reactions in excellent yields. Although there are methods for the THP protection of aldol products,[20] the present method is by far the most efficient and practical.

Cyanohydrins are also effectively THP protected at room temperature (**5h** and **5i**). As thiourea catalysts also affect the addition of HCN to carbonyl as well as imino functionalities,[18,21,22] this opens up possibilities for organocatalytic domino reactions.

Oximes can also be THP protected at longer reaction times in good preparative yields (**5j** and **5k**). Protected oximes are valuable building blocks in a variety of transformations.[23]

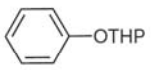
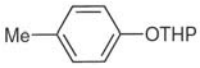
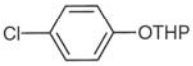
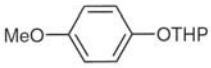
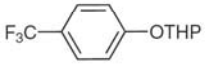
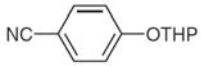
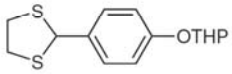
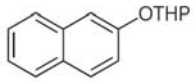
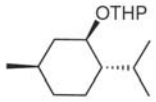
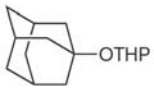
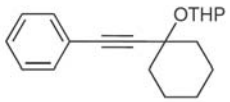
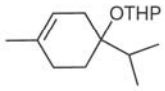
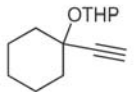
To improve the practicality of this reaction further, we attached the bis(trifluoromethyl)phenyl part of our catalytic motif to simple amino-terminated polystyrene beads (**P1** and **P3**, Scheme 4);[21] the coupling of the isothiocyanate **12** is highly efficient and generates polymers that can be handled easily. Commercially available, expensive com-

Table 1 THP Protection of Simple Primary and Secondary Substrates[a]

Product		Time (h)	Yield (%)
THP–O–THP (from H_2O)	**3a**[b]	19	94
EtOTHP	**3b**	24	98
PrOTHP	**3c**	24.5	98
BuOTHP	**3d**	23	96
i-PrOTHP	**3e**	24	96
CyOTHP	**3f**	28.5	98
	**3g**	19	97
	**3h**	16	96
	**3i**	15	98
	**3j**	9 9.5 10 48	98 98 (0.1 mol%)[c] 98 (0.01 mol%)[c] 98 (0.001 mol%)[c]
	**3k**	15.5	91
	**3l**[d,e]	31	93
	**3m**[d]	18	89
	**3n**[d]	24	63

[a] Preparative yields of products given from the respective alcohols (5 mmol scale). Catalyst loading = 1 mol%, unless noted otherwise; all reactions were carried out at r.t. No reactions occurred for reference experiments run in parallel even after one week.
[b] Reaction run as emulsion.
[c] Reaction scale increased (see experimental section).
[d] Run as emulsion with THF (0.1 mL) added as co-solvent.
[e] Reaction run at 50 °C, d.r. (GC) ~1:1.

Table 2 THP Protection of Sterically Hindered and Phenolic Substrates[a]

Product		Time (h)	Yield (%)
	**4a**	10 10 11 17	97 97 (0.1 mol%)[b] 97 (0.01 mol%)[b] 97 (0.001 mol%)[b]
	**4b**	10	95
	**4c**	13	93
	**4d**	11	95
	**4e**	45	86
	**4f**	57	96
	**4g**[c]	61	84
	**4h**	48	83
	**4i**[c]	46	89
t-BuOTHP	**4j**	19 19 26 41	98 98 (0.1 mol%)[b] 98 (0.01 mol%)[b] 98 (0.001 mol%)[b]
	**4k**[d]	18.5	97
	**4l**[d,e]	40	83
Ph_3COTHP	**4m**	105	84
	**4n**[f]	18	98
	**4o**	51	92
	**4p**	16	98

[a] Scale: 5 mmol. Preparative yields of products given from the respective alcohols. Catalyst loading = 1 mol%, T = 50 °C. No reactions occurred for control experiments run in parallel, even after one week.
[b] Reaction scales increased (see experimental section).
[c] d.r. (GC) ~1:1.
[d] Carried out on a 2 mmol scale.
[e] DHP (1 mL) and THF (2 mL) were added as co-solvent.
[f] Run at r.t.

pound **12** can be prepared in a straightforward manner (see experimental section). We selected a variety of substrates for polymer-catalyzed THP protection and found these transformations generally to be quite effective (Table 4); this is in marked contrast to earlier attempts with some other simple polystyrene-bound thiourea derivatives.[24]

All reactions with polymer-bound catalysts were conducted on a 2 mmol scale with 50 mg of catalyst; the approximate thiourea concentration was 4 mmol per 1 g of polymer. The catalyst loading on the polymer was determined through determining the residual amounts of **12**. The change in the polymer texture is visually apparent; while the amino-terminated white polystyrene beads lump together and are difficult to handle, the thiourea-functionalized off-white beads are well defined and do not aggregate (Figure 1). The polymer-bound catalyst are handled and recovered easily (see below).

Figure 1 Untreated amino-terminated polystyrene beads (left) and polymer-bound thiourea **P2** (cf. Scheme 4).

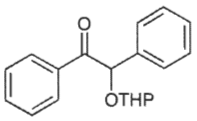
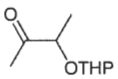
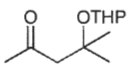
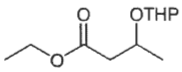
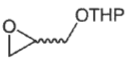
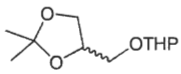
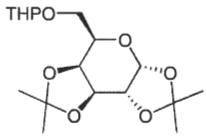
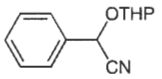
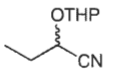
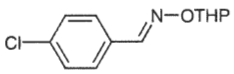
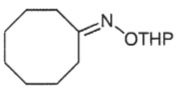
The catalyst loading is calculated to be ca. 10 mol% in the reactions summarized in Table 4. Only **P2** proved to be effective in the THP protection of a selection of alcohols and phenols because the N/NH moieties present in **P4** apparently suppress the catalytic process. This is consistent with our finding that, in general, the presence of an NR_2 moiety is incompatible with the catalytic process presented here. As a consequence, amino alcohols cannot be THP protected with the current protocol.

The polymer-supported catalytic reactions essentially run to completion at the expense of longer reaction times (Table 4). It is encouraging to see that a large variety of different substrates can be protected with this very convenient method. The polymer catalyst can be readily separated by simple filtration, washed with dichloromethane and be reused several times without loss of activity; we checked this for the repeated preparation of **3j** (4 cycles).

Protection with Alternative Enol Ethers

Other enol ethers such as benzofuran, dihydrofuran, and 2-methoxypropene (MOP)[25] can also be used utilizing virtually the same experimental protocol (see below). MOP protection is particularly attractive because it does not

Table 3 THP Protection of Acid-Sensitive Substrates[a]

Product		Temp (°C)	Time (h)	Yield (%)
	**5a**[b,c]	50	26	59
	**5b**	50	19	87
	**5c**	r.t.	18 34 35 49	98 98 (0.1 mol%)[d] 98 (0.01 mol%)[d] 98 (0.001 mol%)[d]
	**5d**	50	30	98
	**5e**	r.t.	8	93
	**5f**	r.t.	20	96
	**5g**[c]	r.t.	14	91
	**5h**[c]	r.t.	36	89
	**5i**[c]	r.t.	34	88
	**5j**	r.t.	30	68
	**5k**	r.t.	31	94

[a] Preparative yields of products given from the respective alcohols (5 mmol scale). Catalyst loading = 1 mol%. No reactions occurred for reference experiments run in parallel even after one week.
[b] Reaction from suspension, THF (2 mL) and DHP (4.5 mL) added as co-solvents.
[c] d.r. (GC) ~1:1.
[d] Reaction scales increased (see experimental section).

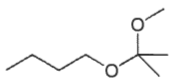
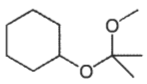
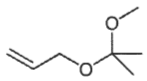
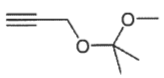
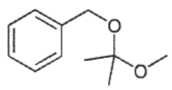
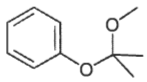
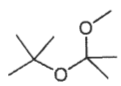
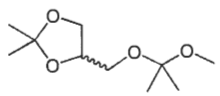
generate a stereogenic center that can sometimes unnecessarily clutter the NMR spectra of THP as well as other adducts. A second advantage is the low boiling point of MOP (34–36 °C) easing its removal after the reaction. As this normally limits the reaction temperature we were pleased to see that the catalyzed reactions run smoothly at room temperature for the examined subset of the substrates presented above (products **13**, Table 5). It must be noted, however, that MOP is so reactive that the uncatalyzed reaction also proceeds, albeit at lower rates.

Table 4 THP Protection of Selected Substrates Utilizing Polymer-Bound Thiourea **P2**[a]

Product	Time (h)	Yield (%)
4i	53	92
3j	21	97
4j	29	98
5c	36	95
5d	38	95
3g	21	97
4a	25	96

[a] Products given from the respective alcohols (suspension, 2 mmol scale). Catalyst loading approximately 10 mol%, T = 50 °C. Reference reactions without **P2** revealed no conversion under otherwise identical conditions.

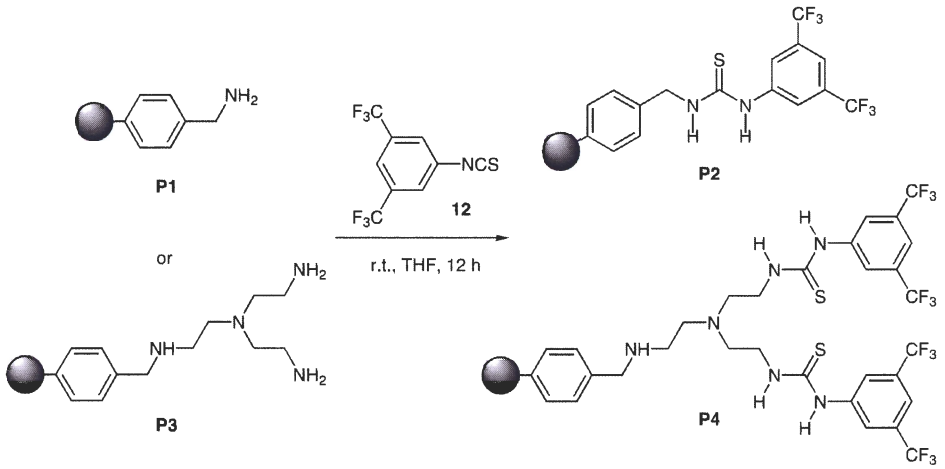
Table 5 MOP Protection of Selected Substrates[a]

Product		Time (h)	Yield (%)
	**13a**	28	95
	**13b**	34	97
	**13c**	25	96
	**13d**	20	95
	**13e**	15	94
	**13f**	22	95
	**13g**	29	94
	**13h**	42	92

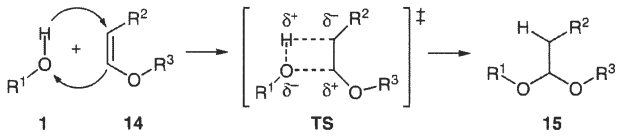
[a] Products given from the respective alcohols. Scale: 5 mmol; catalyst loading = 1 mol%, r.t.

Mechanism

From a mechanistic viewpoint, the addition of an alcohol **1** to the double bond of an enol **14** is formally a forbidden thermal [2+2] cycloaddition (Scheme 5). As a conse-



Scheme 4 Simple preparation of polymer-bound thiourea derivatives.



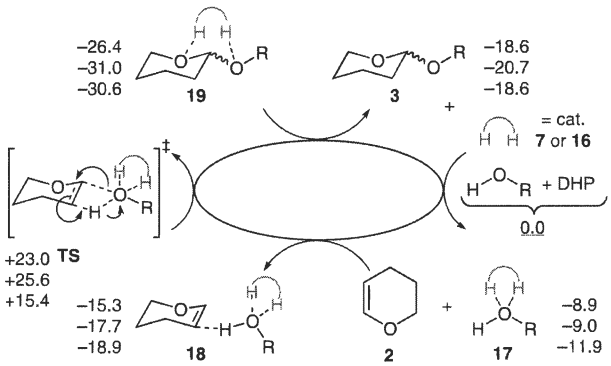
Scheme 5 Generalized mechanism for the uncatalyzed formally forbidden [2+2] cycloaddition of an alcohol to an enol ether, and importance of strong polarization in the transition structure.

quence, the transition structure (**TS**) must be highly polar and the overall addition highly asynchronous.

A reasonable mechanistic entry into this reaction may begin with the complexation of the thiourea catalyst **7**, or thiourea **16** itself, with the alcohol to give **17** (Scheme 6). This coordination increases the alcohol's acidity as well as polarizability and hence its ability to form a subsequent complex **18** with **2**; the catalyst remains attached during the polar addition through transition structure **TS** and in the product complex **19**. Dissociation delivers the free product **3** and returns the catalyst **7** or **16** for the next cycle.

In order to elucidate this mechanistic proposal we undertook density functional theory [DFT, B3LYP/6-31G(d,p)] and high-level coupled cluster computations (CCSD(T)/cc-pVDZ, see below for details); details are revealed in Figures 2 and 3 with energies given in Scheme 6. To the best of our knowledge, these are the first mechanistic computations on an addition reaction of ROH to enol derivatives and specifically for a tetrahydropyranylation.

A comparison of the DFT relative energies with the high level coupled cluster energy results (on the DFT optimized structures) in Scheme 6 reveals that although DFT methods do not include weak van der Waals interactions, the results are qualitatively rather similar for a model reaction of methanol with DHP catalyzed with thiourea **16**. In particular, the first complexation to give **17** is also quantitatively reproduced at the DFT level, which provides further evidence that this association and the steps



Scheme 6 Proposed thiourea-catalyzed tetrahydropyranylation cycle. First entry: ΔH_0 at B3LYP/6-31G(d,p) for MeOH and thiourea as models; second entry: ΔH_0 at CCSD(T)/cc-pVDZ//B3LYP/6-31G(d,p)+ZPVE for MeOH and thiourea **16** as models; third entry: ΔH_0 at B3LYP/6-31G(d,p) for MeOH and our thiourea catalyst **7** (all entries in kcal mol^{-1}).

thereafter are dominated by polar interactions (which are described well). The DFT approach is the only one feasible for our 'real' system utilizing **7** as the catalyst; these results are given as the third entries in Scheme 6.

The structural changes upon complexation of methanol with thiourea and **7** (Figure 2) are quite remarkable and much stronger for the latter. Generally, while the O–H bond of methanol is lengthened only very slightly, the C–O bond distance increases significantly (by 0.02 Å for **7**). This is the result of increased polarization of the alcohol because the increased negative charge on oxygen repels the C–H bonds of the methyl group. The interaction can also be analyzed based on the changes in the thiourea moiety in which the N–H and C=S bonds are significantly lengthened. The complexation energies are remarkably large (and would be significantly less in solution). Particularly striking is the fact that this complexation energy is even larger than that of thiourea with simple diketones (ca. 6.5 kcal mol^{-1}).[12]

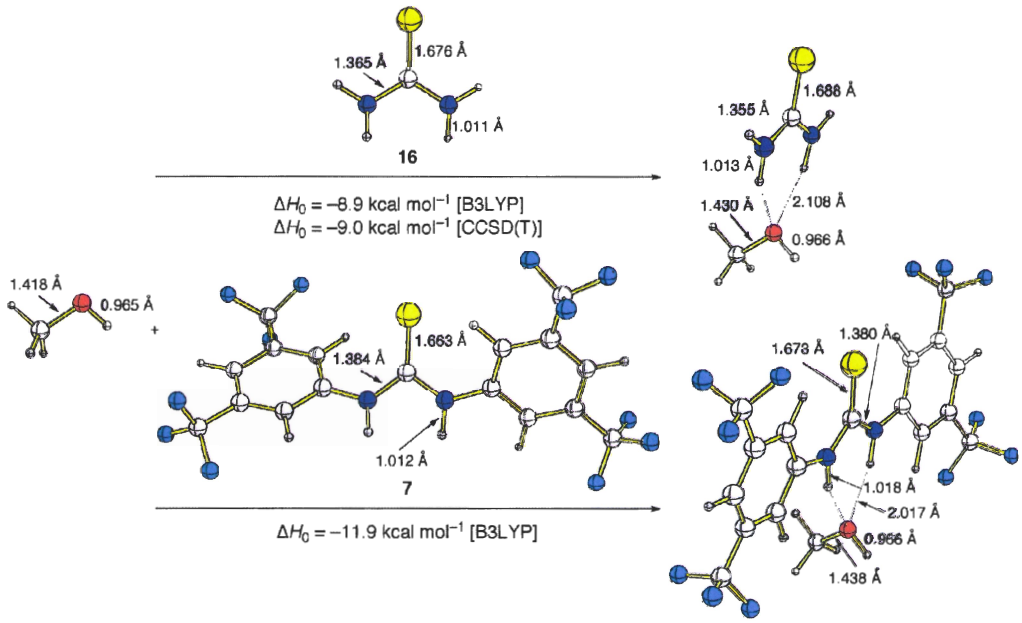


Figure 2 Computed structures [at B3LYP/6-31G(d,p) and CCSD(T)/-cc-pVDZ+ZPVE(B3LYP/6-31G(d,p)] and dissociation energies of the complexes of methanol as a model alcohol with thiourea **16** and our actual catalyst **7**.

The ternary complex **18** is stabilized relative to the complex without the catalyst or **7** by about 70% (Figure 3, top structures from left to right). The association is tightened upon complexation as evident from the geometrical features of the complexes. We also examined complexes to the oxygen atom of DHP but they were all considerably less favorably than those with the β-carbon atom that eventually accepts the proton. Hence, the catalyst helps pre-organize the reactants and the overall geometric changes in going from the complexes to the transition structures (**TS**s, Figure 3 bottom row) are small and evidently follow the least motion principle. The computed absolute barrier for the addition of methanol to DHP is prohibitively high (45.2 kcal mol^{-1} at CCSD(T)) and no reaction occurs, in agreement with experimentation. Complexation with thiourea **16** already lowers the absolute barrier by a remarkable 20 kcal mol^{-1}! Electron-deficient **7** maximizes this stabilization to yield a barrier of 'only' 17.7 kcal mol^{-1}. As a consequence, the catalytic effect is truly remarkable, as demonstrated by the experimental results discussed.

The transition structures follow all the expected geometrical parameters: the methanol O–H bond is lengthened (1.384 Å to 1.675 Å) and this is concomitant with H–C bond lengthening of the newly formed bond (1.251 Å to 1.161 Å); the other structural parameters follow this trend very closely. The only bond that is lengthened in going from the uncatalyzed to the reaction catalyzed with **7** is the newly forming C–O bond (2.187 Å to 2.578 Å), which perfectly agrees with the oxyanion stabilization concept that is particularly effective for **7**. A closer inspection of the transition structure with **7** reveals that the catalyst is placed sideways and points away from the R group on the alcohol. Hence, steric hindrance is not a critical factor, as found experimentally (Table 2).

A comparison of the differential stabilization energies of starting materials, transition structure, and product (Scheme 6) reveals that while the starting materials and product receive about 2–3 kcal mol^{-1} differential stabilization, the transition structure benefits by about 5–6 kcal mol^{-1} from complexation with the catalyst. Of course, this is a precondition in order to observe catalysis, but it is comforting to see that it is shown by the computations as well. Finally, the dissociation energies of the products associated with catalyst are in the same range (7.8, 10.3, and 12.0 kcal mol^{-1}, respectively, at the levels of theory given in Scheme 6) as those of the catalyst with the alcohol reactant (8.9, 9.0, and 11.9 kcal mol^{-1}). Within the expected level of accuracy of our qualitative computations, the comparable complexation energies suppress product inhibition and, as a consequence, this reaction displays very high turnover.

Conclusions and Outlook

Thiourea organocatalyst **7** allows the highly efficient THP protection of a large variety of hydroxy functionalities. While virtually all reported non-organocatalytic methods can protect either primary and secondary alcohols or tertiary as well as phenolic substrates, **7** operates effectively on all classes of hydroxy functionalities. This also includes acid-sensitive substrates such as α- and β-hydroxy carbonyl compounds (including aldol products), cyanohydrins, acetals, and oximes.

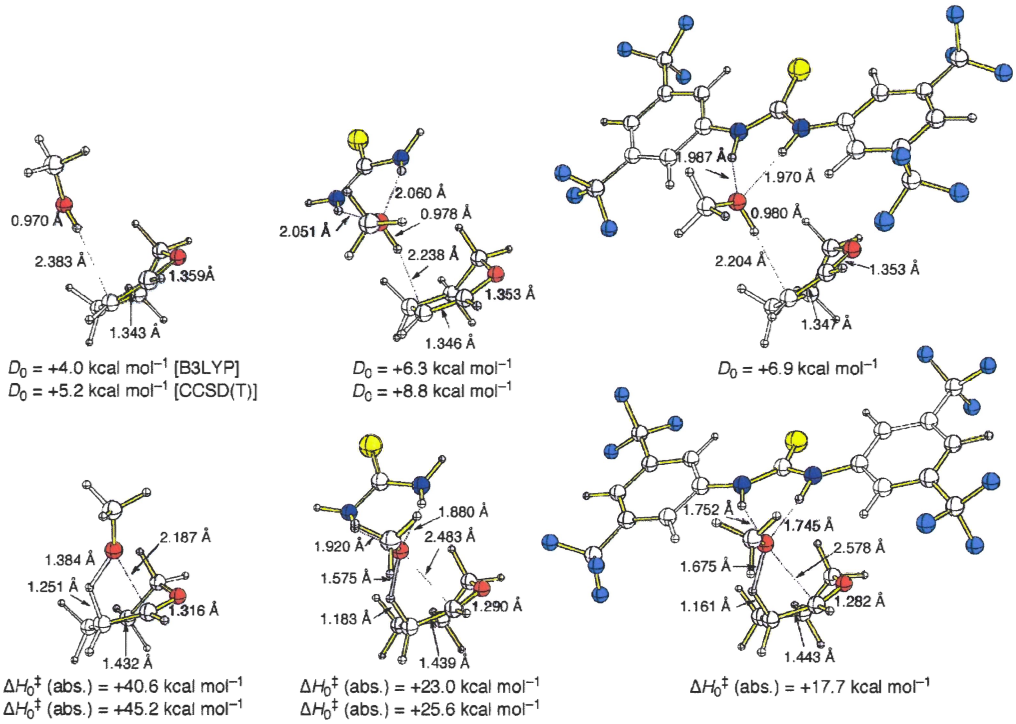


Figure 3 Optimized complexes (top) between methanol and DHP without and with thiourea **16** as well as catalyst **7**; transition structures (bottom) for the addition of methanol to DHP without and with thiourea as well as with **7** as catalyst. Level of theory for optimization: first entry = B3LYP/6-31G(d,p), energy evaluations: second entry = CCSD(T)/cc-pVDZ, including ZPVE corrections at B3LYP/6-31G(d,p).

The catalyst is remarkably active for THP protection reactions. Catalyst loadings can be as low as 0.001 mol%, giving a maximum turnover number of about 100,000 and turnover frequencies of up to 5700 h^{-1}. To the best of our knowledge, this is the most efficient organocatalytic reaction reported to date, and this emphasizes the power of noncovalent catalysis and the remarkable role the thiourea motif plays in organocatalysis.

From a mechanistic viewpoint, the reactions presented here also mark the deviation from carbonyl (and related functionalities) activation through double hydrogen bonding.[26] Instead, the catalyst preferentially stabilizes the developing oxyanion hole in the transition state through double hydrogen bonding. This conclusion was reached on the basis of a comparative computational analysis of the uncatalyzed vs. catalyzed reactions. The stabilizing effect of **7** on the key transition structures amounts to ca. 23 kcal mol^{-1}, which is in line with the experimentally found efficacy of **7**.

An analogue of **7** bound to polystyrene beads also effectively catalyzes THP protection reactions although the formal catalyst loading is significantly higher and the reaction times are longer.

All chemicals were purchased from Aldrich, Acros Organics, Alfa Aesar, Merck, and Lancaster in the highest purity available and were used without further purification unless otherwise noted. 3,4-Dihydro-2*H*-pyran (DHP) and 2-methoxypropene (MOP) (both 97% grade, Aldrich) were used as purchased; MOP was stored at −18 °C until required. Except for (–)-menthol and (–)-terpinen-4-ol all chiral substrates were used as racemates. Aminomethylated polystyrene **P1** (200–400 mesh, loading 2.00–3.00 mmol/g resin) and tris-(2-aminoethyl)amine polystyrene **P3** (200–400 mesh, loading 2.20 mmol/g resin) were ordered from Merck Novabiochem and were stored under an argon atmosphere at −18 °C. 4-*tert*-Butyldimethylsilyloxybenzyl alcohol was synthesized by reduction of TBDMS protected 4-hydroxybenzaldehyde with $NaBH_4$ following a literature protocol.[27] Hydroxy(phenyl)acetonitrile (technical grade) was distilled once over a 10 cm Vigreux column prior to use; all solvents used for extractions or filtrations were distilled once with a rotary evaporator. Drying followed established literature procedures: THF and Et_3N (both freshly distilled from Na/benzophenone ketyl); CH_2Cl_2 (P_2O_5, reflux, 3 h, then distilled once before storage); EtOH (Na/diethyl phthalate, reflux); PrOH, *i*-PrOH, BuOH, ethane-1,2-diol, and propane-1,3-diol (distilled once, 20 cm Vigreux column). All dry chemicals were stored under an argon atmosphere and over activated 3 Å molecular sieve (MS) (alcohols) and Na wire (Et_3N, THF), respectively: *t*-BuOH, allyl alcohol, BnOH, and propargyl alcohol were stored over MS 3 Å without prior distillation; $CDCl_3$ (99.8%, purchased from Deutero GmbH) was stored over MS 4 Å. Filtrations for product purification were performed on activated basic alumina (50–200 microns; Acros Organics). TLC was carried out on pre-coated Macherey-Nagel plastic sheets Polygram ALOX N/UV_{254} (40–80 mm) using UV light or molybdatophosphoric acid (5% in EtOH) for visualization. The progress of reactions was monitored by GC-MS analyses with a Quadrupol-MS HP MSD 5971(EI) and HP 5890A GC equipped with a J & W Scientific fused silica GC column (30 m × 0.250 mm, 0.25 micron DB–5MS stationary phase: 5% phenyl and 95% methyl silicone) using He (4.6 grade) as carrier gas; T-program standard 60–250 °C (15 °C/min heating rate), injector and transfer line 250 °C; ^1H and ^{13}C NMR spectra were recorded with Bruker spectrometer Avance II 200 MHz (AV 200) and Avance II 400 MHz

WB (AV 400) using as the internal standard: TMS $\delta(^1H) = 0.00$, $\delta(^{13}C) = 0.0$; $CHCl_3$ [$\delta(^1H) = 7.26$], $CHCl_3$ [$\delta(^{13}C) = 77.0$]; ^{13}C signals were assigned with DEPT or APT (attached proton test) experiments. IR spectra were measured with Bruker IFS25 and IFS48 spectrophotometers [for **P2** and **P4** using attenuated total reflection (ATR)]; HRMS were recorded with a Sectorfield-MS: Finnigan MAT 95, CHN analyses were obtained with a Carlo Erba 1106 (balance: Mettler Toledo UMX-2) analyzer. To keep reaction temperatures constant a standard mercury contact thermometer controlled by an IKAMAG RET-GS hot plate-stirrer was used.

All analytical reaction mixtures were prepared in clean oven-dried one-necked 10 mL (2 and 5 mmol scale experiments) and 25 mL (50 and 100 mmol scale experiments) standard glass flasks (Schott DURAN) tightly sealed with a plastic plug. For experiments at 50 °C, reaction flasks were sealed with a clamped glass plug and were placed in a tempered oil bath (50 °C). For homogeneous catalysis organocatalyst **7** and solid hydroxy substrate **3–5** were directly weighed out into the reaction flasks, liquid substrates were added via syringe and were dissolved in DHP (2 equiv, 0.91 mL/5 mmol substrate, for larger scales the volume was adjusted proportionally) or MOP (2 equiv, 0.96 mol/5 mmol substrate), respectively. The quantity of catalyst refers to the substrate quantity that determines the scale of the experiment. To reveal catalyst efficiency various catalyst loadings (mol%) of **7** were employed: 1.0 [25 mg/5 mmol], 0.1 [12.5 mg/25 mmol], 0.01 [2.5 mg/50 mmol], and 0.001 mol% [1 mg/200 mmol scale]. If not otherwise noted all experiments utilizing **7** were run in homogeneous solns. In each experiment utilizing heterogeneous catalysis **P2** or **P4** (each 50 mg: ~10 mol% based on ~4 mmol thiourea motif per gram polymer) were weighed into the reaction flask, the respective hydroxy substrate **3–5** (2 mmol), and DHP (0.36 mL) was added. In general, all volumes for the preparation of analytical reactions were measured with new 1 mL plastic syringes using dry cannulas. The reaction time measurements started with stirring of the freshly prepared reaction mixture after addition of DHP or MOP, respectively, serving as reagent as well as solvent; in some cases THF was used as co-solvent (see Table footnotes). For stirring, standard Teflon-coated magnetic stirring bars (1 to 1.5 cm) were used. Reaction temperature (25 or 50 °C) for each substrate is given in Tables 1– 5. To determine the catalytic efficiency, all experiments were accompanied by a parallel control experiment under same conditions, but without catalyst. In the case of heterogeneous organocatalysis, reference experiments were performed with aminomethylated polystyrene resin **P1** or **P3**, respectively. Sample volumes (~0.5 μL) were taken directly from the stirred reaction mixture via 10 μL Hamilton syringe (in heterogeneous experiments given in Table 4 stirring was stopped prior to sampling to allow the catalyst to precipitate) and were injected immediately to record the GC-MS chromatogram. The course of each hydroxy-protection reaction was monitored by integrating the starting material and product signal; time-dependent conversion as a percentage was determined from the integral ratio of starting material and product signal. After completion of the reaction as confirmed by GC-MS, work-up followed according to the procedures described below. More details concerning the various substrates and potential exceptions to these general procedures are mentioned in the footnotes to Tables 1– 5.

All THP and MOP ethers were isolated and characterized by ^1H and ^{13}C NMR, IR, and MS; **3a–n**, **4a–k**, **4n–p**, **5a–i**, **13a–e**, and **13h** are known compounds and their spectral data were consistent with literature data.

1,3-Bis(trifluoromethyl)phenyl Isothiocyanate (12)

In an oven-dried, three-necked, 1 L flask equipped with argon-inlet, thermometer, septum, and magnetic stirring bar, a homogeneous mixture of 1,3-bis(trifluoromethyl)aniline (9.16 g, 40 mmol) and anhydrous Et_3N (16.9 mL) in anhydrous THF (400 mL) was prepared and subsequently cooled with an ice/salt bath at approx. –5 °C. Thiophosgene (7.85 mL, 100 mmol, 97% grade) was placed in a second oven-dried three-necked flask serving as reaction vessel, equipped with argon inlet, addition funnel with septum, thermometer, and magnetic stirring bar; it was cooled (–5 to –10 °C) with an ice/salt bath and vigorously stirred. The amine mixture was slowly added to the cooled thiophosgene through an addition funnel to initiate the exothermic reaction; to minimize warming of the amine mixture only small portions (20–30 mL) were transferred with a 50 mL plastic syringe into the addition funnel. The resulting orange mixture was stirred at –10 °C for 15 min and the mixture was allowed to warm to r.t. (~45 min) and stirred at r.t. for 12 h. The brown mixture was poured into demineralized H_2O (850 mL) in a separation funnel and NaCl was added to facilitate separation of layers. The aqueous layer was extracted with Et_2O (3 × 250 mL) and the organic layers were collected and dried (anhydrous Na_2SO_4/Na_2CO_3). The drying agent was separated by filtration and washed intensively with Et_2O (~300 mL) to reduce loss of product. Evaporation of the solvent from the combined organic layers afforded a red-brown oily residue. Fractionated distillation (10 cm Vigreux column) in vacuo gave analytically pure **12** as a yellowish transparent liquid that could be stored for several weeks under an argon atmosphere at 4 °C; yield: 8.03 g (74%); bp 103 °C/~20 mbar; n_{20}^D +1.4336.

IR (film): 2034 (NCS), 1992, 1620, 1465, 1378, 1279, 1235, 1181 1137, 1107, 1004, 892, 849, 785, 712, 698, 683 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.65 (s, 2 H), 7.78 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 118.5, 120.5, 123.9 ($^1J_{CF}$ = 273 Hz), 125.8, 133.3 ($^2J_{CF}$ = 32 Hz), 141.1.

HRMS: *m/z* calcd for $C_9H_3F_6NS$: 270.9890; found: 270.9891.

Anal. Calcd for $C_9H_3F_6NS$: C, 39.86; H, 1.12; N, 5.17. Found: C, 39.50; H, 1.08; N, 5.16.

Polystyrene-Bound Thiourea Organocatalysts P2 and P4

In an oven-dried, two-necked, 10 mL flask equipped with argon-inlet and septum, aminomethylated polystyrene **P1** (0.8 g) was suspended in anhydrous THF (5 mL) with low stirring with a magnetic stirring bar. Pure 1,3-bis(trifluoromethyl)phenyl isothiocyanate (**12**, 1.95 g, 7.2 mmol) was added over 5 min. The resulting mixture was stirred at r.t. under an argon atmosphere for 12 h, after which the resin was separated by suction filtration through a round filter paper. Excessive washing with anhydrous CH_2Cl_2 (5 × 10 mL) and subsequent removal of CH_2Cl_2 in vacuo furnished yellowish thiourea functionalized **P2**; this was stored until use in a Schlenk tube at –18 °C under argon. The unreacted excess of isothiocyanate **12** was recovered from the filtrate by evaporation of CH_2Cl_2. The catalyst loading (thiourea moiety per gram **P2**) was determined via consumption of isothiocyanate and amounted to about 4 mmol per 1 g polymer-bound organocatalyst.

P4 was synthesized analogously from tris(2-aminoethyl)amine polystyrene **P3** (0.8 g) suspended in anhydrous THF (5 mL) and isothiocyanate **12** (2.86 g, 10.56 mmol, 3 equiv per NH_2 group). Catalyst loading was identical to **P2**. Thiourea functionalization of **P2** and **P4**, respectively, was analytically detected via IR measurement revealing a strong thiocarbonyl band that is typical for thiourea derivatives; no residual isothiocyanate bands were detected.

P2

Yellowish, crystalline, free-floating particles.

IR (ATR): 3257, 2923, 1582 (C=S), 1470, 1381, 1274 (CF_3), 1170, 1125, 948, 883, 698, 680 cm^{-1}.

P4

Yellow, crystalline, free-floating particles.

IR (ATR): 3267, 3025, 2922, 1668 (C=S), 1376, 1331, 1274 (CF_3), 1170, 1126, 883, 846, 735, 697, 680 cm^{-1}.

2-(Benzyloxy)tetrahydro-2*H*-pyran (3j); Typical Procedure for Homogeneous Organocatalysis Using Catalyst 7

Organocatalyst **7** (25 mg, 0.05 mmol, 1 mol% loading) was weighed into an oven-dried, one-necked, 10 mL flask equipped with a magnetic stirring bar (1.5 cm). After addition of BnOH (0.52 mL, 5 mmol) and DHP (0.91 mL, 10 mmol) via a 1 mL syringe, the reaction flask was sealed with a plastic plug and the mixture was vigorously stirred at r.t. until the reaction was complete (9 h, temperatures and times are given in Table 1). DHP was mostly evaporated in vacuo, the resulting yellowish crude product was dissolved in *n*-pentane (~ 8 mL) and slowly passed through a short column of basic alumina (2.5 × 4.5 cm). Evaporation of *n*-pentane and residual DHP with a rotary evaporator under reduced pressure (~30 mbar) at 50 °C bath temperature afforded analytically pure THP ether **3j**; yield: 0.94 g (98%); physical data were identical to those reported in literature.

2-(Phenoxy)tetrahydro-2*H*-pyran (4a); Typical Procedure on a Preparative Scale

In an oven-dried, one-necked, 25 mL flask, organocatalyst **7** (2.5 mg, 0.005 mmol, 0.01 mol% loading), phenol (4.71 g, 50 mmol), and DHP (9.1 mL, 100 mmol) were added and the mixture was magnetically stirred for 11 h (Table 2) at 50 °C. The scaled-up workup was performed according to the procedure for the 5 mmol experiment (alumina column, 2.5 × 8 cm) to give **4a**; yield: 8.64 g (97%); physical data were consistent with those reported in literature.

3-(1-Methoxy-1-methylethoxy)prop-1-ene (13c); Typical Procedure for Organocatalytic MOP Protection Using Catalyst 7

MOP protection of allyl alcohol (0.34 mL, 5 mmol) followed the procedure described for THP protection of benzyl alcohol with the modification that THP is replaced by MOP (0.96 mL, 10 mmol); excess MOP was evaporated without warming. Analytical grade MOP ether **13c** was obtained at r.t. in 25 h (Table 5); yield: 0.62 g (96%); physical data were consistent with those reported in literature.

2-(Phenoxy)tetrahydro-2*H*-pyran (4a); Typical Procedure for Heterogeneous Organocatalysis Using Polymer Catalyst P2

For heterogeneously catalyzed THP protection a suspension of phenol (0.19 g, 2 mmol), polystyrene-bound thiourea **P2** (50 mg, ~10 mol%), and DHP (0.36 mL, 4 mmol) was prepared in an oven-dried, one-necked, 10 mL flask sealed with a plastic plug. Under gentle stirring with a magnetic stirring bar (1 cm) at 50 °C the reaction was complete within 25 h (Table 4). The catalyst was removed from product by simple suction filtration, washed with CH_2Cl_2 (5 × 10 mL), and dried in vacuo to evaporate residual CH_2Cl_2. Recovered **P2** was directly reused for new THP protection reactions of phenol (4 use/recovery cycles were examined) only with minor weight loss (approx. 6% per recovery), but no detectable loss of catalytic activity. Evaporation of solvent with a rotary evaporator in vacuo (50 °C bath temperature/~30 mbar) afforded a yellowish crude THP ether that was diluted in *n*-pentane (5 mL) and slowly passed through a basic alumina column (2.5 × 3 cm) to give analytically pure **4a**; yield: 0.34 g (96%); spectroscopic data were consistent with those reported in literature.

2-(Diamantan-1-yloxy)tetrahydro-2*H*-pyran (4l)

Yellowish crude product, purification: basic alumina column (2.5 × 4.5 cm, *n*-pentane, ~6 mL, then Et_2O, ~10 mL); the solvent was evaporated in vacuo at 50 °C bath temperature.

Colorless oil, aromatic smell; yield: 83%.

IR (film): 2905, 2849, 1460, 1439, 1379, 1127, 1112, 1091, 1076, 1023, 982, 869 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.3–2.37 (m, 25 H), 3.48 (m, 1 H), 3.97 (m, 1 H), 4.82 (t, ^3J = 3.3 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.8, 25.3, 25.9, 30.2, 32.3, 32.5, 32.6, 32.7, 32.9, 37.1, 37.4, 37.5, 38.2, 39.8, 42.2, 42.7, 63.4, 68.8, 92.2.

HRMS: *m/z* calcd for $C_{19}H_{28}O_2$: 288.2089; found: 288.2083.

Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 11.09. Found: C, 78.34; H, 10.10.

2-(Trityloxy)tetrahydro-2*H*-pyran (4m)

Yellowish crude product, purification: basic alumina column (2.5 × 8 cm, *n*-pentane, ~ 10 mL, then Et_2O ~15 mL); the solvent was evaporated in vacuo at 50 °C bath temperature.

Colorless solid; yield: 84%.

IR (film): 3061, 3033, 2942, 2851, 1959, 1665, 1598, 1490, 1445, 1331, 1277, 1203, 1180, 1156, 1077, 1032, 1010, 970, 891, 759, 698, 639, 584, 510, 449 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.54–1.89 (m, 6 H), 3.52–3.59 (m, 1 H), 3.85–3.92 (m, 1 H), 4.96 (t, ^3J = 3.3 Hz, 1 H), 7.19–7.78 (m, 15 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.4, 25.4, 31.5, 64.2, 82.1, 102.1, 126.4, 128.6, 130.1.

HRMS: *m/z* calcd for $C_{24}H_{24}O_2$: 344.1776; found: 344.1761.

Anal. Calcd for $C_{24}H_{24}O_2$: C, 83.69; H, 7.02. Found: C, 84.01; H, 7.18.

4-Chlorobenzaldehyde *O*-(Tetrahydro-2*H*-pyran-2-yl)oxime (5j)

Yellowish crude product, purification: basic alumina column (2.5 × 3 cm, *n*-pentane, ~ 6 mL, then Et_2O, ~10 mL); the solvent was evaporated in vacuo without warming.

Colorless oil, aromatic smell; yield: 68%.

IR (film): 2944, 2870, 1648, 1596, 1492, 1203, 1113, 1090, 1079, 1041, 1015, 981, 948, 825, 514 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.62–1.93 (m, 6 H), 3.66–3.70 (m, 1 H), 3.89–3.95 (m, 1 H), 5.38 (t, ^3J = 3.3 Hz, 1 H), 7.42 (d, ^3J = 8.8 Hz, 2 H), 7.56 (d, ^3J = 8.8 Hz, 2 H), 8.16 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.3, 23.8, 30.2, 62.9, 101.2, 128.2, 128.8, 128.9, 141.4, 149.2.

HRMS: *m/z* calcd for $C_{12}H_{14}ClNO_2$: 239.0713; found: 239.0705.

Anal. Calcd for $C_{12}H_{14}ClNO_2$: C, 60.13; H, 5.89; N, 5.84. Found: C, 60.00; H, 6.18; N, 5.67.

Cyclooctanone *O*-(Tetrahydro-2*H*-pyran-2-yl)oxime (5k)

Yellowish crude product, purification: basic alumina layer (2.5 × 4.5 cm, *n*-pentane, ~8 mL, then Et_2O, ~10 mL); the solvent was evaporated in vacuo at 50 °C bath temperature.

Colorless semi-solid; yield: 94%.

IR (film): 3102, 2926, 2855, 2688, 1659, 1466, 1445, 1424, 1449, 1340, 1277, 1228, 1103, 1025, 954, 923, 904, 856, 825, 767, 748, 738, 614, 575, 514 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.40–2.50 (m, 20 H), 3.48–3.51 (m, 1 H), 3.93–3.96 (m, 1 H), 4.68 (t, ^3J = 3.3 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.5, 22.8, 24.3, 24.5, 24.6, 25.5, 25.7, 26.6, 27.2, 27.3, 65.8, 100.8, 164.2.

HRMS: *m/z* calcd for $C_{13}H_{23}NO_2$: 225.1728; found: 225.1782.

Anal. Calcd for $C_{13}H_{23}NO_2$: C, 69.29; H, 10.29; N, 6.22. Found: C, 69.09; H, 9.93, N, 6.38.

(1-Methyl-1-methylethoxy)benzene (13f)

Yellowish crude product, purification: basic alumina column (2.5 × 5 cm, *n*-pentane, ~8 mL then Et_2O, ~15 mL); the solvent was evaporated in vacuo at 50 °C (bath temperature).

Colorless oil, aromatic smell; yield: 95%.

IR (film): 2994, 2942, 2831, 1596, 1586, 1493, 1382, 1372, 1278, 1257, 1231, 1209, 1181, 1131, 1066, 1026, 946, 875, 803, 766, 730, 694, 630, 511 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.47 (s, 6 H), 3.40 (s, 3 H), 7.05 (t, 1 H), 7.10 (d, 2 H), 7.27 (t, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.1, 49.2, 103.5, 115.3, 120.81, 129.1, 155.2.

HRMS: *m/z* calcd for $C_{10}H_{14}O_2$: 166.0993; found: 166.0979.

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.49; H, 8.73.

2-(1-Methoxy-1-methylethoxy)-2-methylpropane (13g)
Yellowish crude product, purification: basic alumina column (2.5 × 3 cm, *n*-pentane, ~8 mL, Et_2O, ~10 mL); the solvent was evaporated in vacuo (~200 mbar) and without warming.

Colorless oil, aromatic smell; yield: 94%.

IR (film): 2974, 1712, 1653, 1472, 1365, 1282, 1260, 1209, 1180, 1080, 1056, 994, 914, 827, 749 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.26 (s, 9 H), 1.38 (s, 6 H), 3.19 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.7, 30.6, 44.9, 54.6, 89.4.

HRMS: *m/z* calcd for $C_8H_{18}O_2$: 146.1306; found: 146.1328.

Anal. Calcd for $C_8H_{18}O_2$: C, 65.71; H, 12.41. Found: C, 65.82; H, 12.19.

Computations. Becke's gradient-corrected exchange functional[28] in conjunction with the Lee-Yang-Parr non-local correlation functional (B3LYP)[29] and a 6-31G(d,p) basis set as implemented in Gaussian03 were utilized for all optimizations.[30] The energies of the optimized structures were further refined at the coupled cluster level of theory including single, double, and perturbatively determined triple excitations [CCSD(T)][31] utilizing a cc-pVDZ basis set,[32] utilizing the frozen core (no deleted virtuals) approach. All optimized structures were characterized as stationary points by means of determining harmonic vibrational frequencies (with zero imaginary frequencies for minima and one imaginary frequency for transition structures). The xyz coordinates, structural drawings, and absolute energies as well as ZPVEs are available upon request from the authors.

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References

(1) (a) Baumeyer, G.; Dittus, G.; Muller, E. In *Houben-Weyl*, 4th ed., Vol. VI/4; Muller, G., Ed.; Georg Thieme Verlag: Stuttgart, **1963**, 368–374. (b) Miyashita, M.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772. (c) van Boom, J. H.; Herscheid, J. D. M.; Reese, C. B. *Synthesis* **1973**, 169.
(2) Branco, L. C.; Afonso, C. A. M. *Tetrahedron* **2001**, *57*, 4405.
(3) Kumar, P.; Dinesh, C. U.; Reddy, R. S.; Pandey, B. *Synthesis* **1993**, 1069.
(4) Campelo, J. M.; Garcia, A.; Lafont, F.; Luna, D.; Marinas, J. M. *Synth. Commun.* **1992**, *22*, 2335.
(5) Hoyer, S.; Laszlo, P.; Orlovic, M.; Polla, E. *Synthesis* **1986**, 655.
(6) Hajipour, A. R.; Pourmousavi, S. A.; Ruoho, A. E. *Synth. Commun.* **2005**, *35*, 2889.
(7) Shirini, F.; Zolfigolb, M. A.; Paktinat, M. *Synthesis* **2006**, 4252.
(8) Bartoli, G.; Giovannini, R.; Giuliani, A.; Marcantoni, E.; Massaccesi, M.; Merchiorre, P.; Paoletti, M.; Sambri, L. *Eur. J. Org. Chem.* **2006**, 1476.
(9) Kotke, M.; Schreiner, P. R. *Tetrahedron* **2006**, *62*, 434.
(10) (a) Magnusson, A.; Hult, K.; Holmquist, M. *J. Am. Chem. Soc.* **2001**, *123*, 4354. (b) Tantillo, D. J.; Houk, K. N. *J. Comput. Chem.* **2002**, *23*, 84.
(11) (a) Schreiner, P. R.; Wittkopp, A. *Org. Lett.* **2002**, *4*, 217. (b) Wittkopp, A.; Schreiner, P. R. *Chem. Eur. J.* **2003**, *9*, 407.
(12) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289.
(13) (a) Wenzel, A. G.; Lalonde, M. P.; Jacobsen, E. N. *Synlett* **2003**, 1919. (b) Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964.
(14) Fuerst, D. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 8964.
(15) Wittkopp, A.; Schreiner, P. R. In *The Chemistry of Dienes and Polyenes*, Vol. 2; Rappoport, Z., Ed.; John Wiley & Sons: Chichester, **2000**, 1029–1088.
(16) Yoon, T. P.; Jacobsen, E. N. *Science* **2003**, *299*, 1691.
(17) (a) Okino, T.; Hoashi, Y.; Takemoto, Y. *Tetrahedron Lett.* **2003**, *44*, 2817. (b) Gabriella, D.; Herrera, R. P.; Riccia, A. *Synlett* **2004**, 2374. (c) Hoashi, Y.; Yabuta, T.; Takemoto, Y. *Tetrahedron Lett.* **2004**, *45*, 9185. (d) Okino, T.; Nakamura, S.; Furukawa, T.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 625. (e) Berkessel, A.; Mukherjee, S.; Cleemann, F.; Muller, T. N.; Lex, J. *Chem. Commun.* **2005**, 1898. (f) Berkessel, A.; Cleemann, F.; Mukherjee, S. *Angew. Chem. Int. Ed.* **2005**, *44*, 7466. (g) Dove, A. P.; Pratt, R. C.; Lohmeijer, B. G. G.; Waymouth, R. M.; Hedrick, J. L. *J. Am. Chem. Soc.* **2005**, *127*, 13798. (h) Herrera, R. P.; Sgarzani, V.; Bernardi, L.; Ricci, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 6576. (i) Hoashi, Y.; Okino, T.; Takemoto, Y. *Angew. Chem. Int. Ed.* **2005**, *44*, 4032. (j) McCooey, S. H.; Connon, S. J. *Angew. Chem. Int. Ed.* **2005**, *44*, 6367. (k) Mosse, S.; Alexakis, A. *Org. Lett.* **2005**, *7*, 4361. (l) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X. N.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119. (m) Sohtome, Y.; Hashimoto, Y.; Nagasawa, K. *Adv. Synth. Catal.* **2005**, *347*, 1643. (n) Taylor, M. S.; Tokunaga, N.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2005**, *44*, 6700. (o) Wang, J.; Li, H.; Duan, W. H.; Zu, L. S.; Wang, W. *Org. Lett.* **2005**, *7*, 4713. (p) Wang, J.; Li, H.; Yu, X. H.; Zu, L. S.; Wang, W. *Org. Lett.* **2005**, *7*, 4293. (q) Xu, X. N.; Furukawa, T.; Okino, T.; Miyabe, H.; Takemoto, Y. *Chem. Eur. J.* **2005**, *12*, 466. (r) Ye, J. X.; Dixon, D. J.; Hynes, P. S. *Chem. Commun.* **2005**, 4481. (s) Yoon, T. P.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2005**, *44*, 466. (t) Connon, S. J. *Chem. Eur. J.* **2006**, *12*, 5418. (u) Bernardi, L.; Fini, F.; Herrera, R. P.; Ricci, A.; Sgarzani, V. *Tetrahedron* **2006**, *62*, 375. (v) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999. (w) Dixon, D. J.; Richardson, R. D. *Synlett* **2006**, 81. (x) Hao, L.; Zu, L. S.; Wang, J.; Wang, W. *Tetrahedron Lett.* **2006**, *47*, 3145. (y) Hoashi, Y.; Yabuta, T.; Yuan, P.; Miyabe, H.; Takemoto, Y. *Tetrahedron* **2006**, *62*, 365. (z) Sohtome, Y.; Takemura, N.; Iguchi, T.; Hashimoto, Y.; Nagasawa, K. *Synlett* **2006**, 144. (aa) Sohtome, Y.; Hashimoto, Y.; Nagasawa, K. *Eur. J. Org. Chem.* **2006**, 2894. (ab) Xu, X. N.; Yabuta, T.; Yuan, P.; Takemoto, Y. *Synlett* **2006**, 137. (ac) Yalalov, D. A.; Tsogoeva, S. B.; Schmatz, S. *Adv. Synth. Catal.* **2006**, *348*, 826.

(18) Tsogoeva, S. B.; Yalalov, D. A.; Hateley, M. J.; Weckbecker, C.; Huthmacher, K. *Eur. J. Org. Chem.* **2005**, 4995.
(19) Rueping, M.; Antonchick, A. P.; Theissmann, T. *Angew. Chem. Int. Ed.* **2006**, *45*, 6751.
(20) (a) Hoffman, C. H.; Wagner, A. F.; Wilson, A. N.; Walton, E.; Shunk, C. H.; Wolf, D. E.; Holly, F. W.; Folkers, K. *J. Am. Chem. Soc.* **1957**, *79*, 2316. (b) Pflieger, D.; Muckensturm, B. *Tetrahedron* **1989**, *45*, 2031. (c) Hassner, A.; Näumann, F. *Chem. Ber.* **1988**, *121*, 1823. (d) Hon, Y. S.; Lee, C. F.; Chen, R. J.; Szu, P. H. *Tetrahedron* **2001**, *57*, 5991. (e) Hamada, N.; Sato, T. *Synlett* **2004**, 1802.
(21) Sigman, M. S.; Vachal, P.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2000**, *39*, 1279.
(22) Vachal, P.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 867.
(23) (a) Williams, D. R.; Benbow, J. D. *Tetrahedron Lett.* **1990**, *31*, 5881. (b) Kliegel, W.; Nanninga, D. *Monatsh. Chem.* **1983**, *114*, 465. (c) Tosco, P.; Bertinaria, M.; Di Stilo, A.; Cena, C.; Sorba, G.; Frutteroa, R.; Gascoa, A. *Bioorg. Med. Chem.* **2005**, *13*, 4750.
(24) Miyabe, H.; Tuchida, S.; Yamauchi, M.; Takemoto, Y. *Synthesis* **2006**, 3295.
(25) Kjolberg, O.; Neumann, K. *Acta Chem. Scand.* **1994**, *48*, 80.
(26) (a) Pihko, P. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 2062. (b) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2006**, *45*, 1520.
(27) Weiss, K. L.; Alshafie, G.; Chapman, J. S.; Mershon, S. M.; Abou-Issa, H.; Clagett-Dame, M.; Robert, W.; Curley, J. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1583.
(28) Becke, A. D. *Phys. Rev. A: At., Mol., Opt. Phys.* **1988**, *38*, 3098.
(29) Lee, C. T.; Yang, W. T.; Parr, R. G. *Phys. Rev. B: Condens. Matter* **1988**, *37*, 785.
(30) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian version B.03*; Gaussian Inc.: Pittsburgh, **2003**.
(31) (a) Purvis, G. D.; Bartlett, R. J. *J. Chem. Phys.* **1981**, *75*, 1284. (b) Urban, M.; Noga, J.; Cole, S. J.; Bartlett, R. J. *J. Chem. Phys.* **1985**, *83*, 4041. (c) Bartlett, R. J.; Watts, J. D.; Kucharski, S. A.; Noga, J. *Chem. Phys. Lett.* **1990**, *165*, 513. (d) Raghavachari, K.; Trucks, G. W.; Pople, J. A.; Head-Gordon, M. *Chem. Phys. Lett.* **1989**, *157*, 479.
(32) (a) Dunning, T. H. Jr.; Peterson, K. A.; Woon, D. E. In *The Encyclopedia of Computational Chemistry*, Vol. 1; Schleyer, P. v. R.; Allinger, N. L.; Clark, T.; Gasteiger, J.; Kollman, P. A.; Schaefer, H. F.; Schreiner, P. R., Eds.; John Wiley & Sons: Chichester, **1998**, 88–115. (b) Dunning, T. H. Jr. *J. Chem. Phys.* **1971**, *55*, 716. (c) Dunning, T. H. Jr. *J. Chem. Phys.* **1989**, *90*, 1007.

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Cooperative Brønsted Acid-Type Organocatalysis: Alcoholysis of Styrene Oxides

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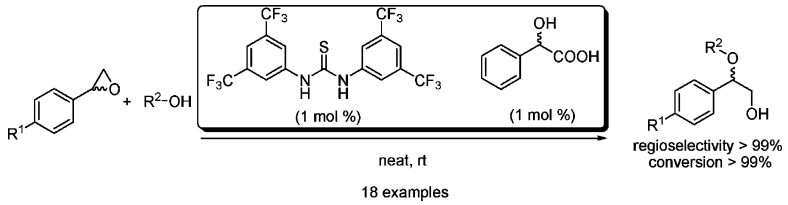
ABSTRACT



We present a mild and efficient method for the completely regioselective alcoholysis of styrene oxides utilizing a cooperative Brønsted acid-type organocatalytic system comprised of mandelic acid (1 mol %) and *N,N′*-bis-[3,5-bis-(trifluoromethyl)phenyl]-thiourea (1 mol %). Various styrene oxides are readily transformed into their corresponding *β*-alkoxy alcohols in good to excellent yields at full conversion. Simple aliphatic and sterically demanding, as well as unsaturated and acid-sensitive alcohols can be employed.

Catalytic epoxide ring opening reactions with neutral[1−3] and charged nucleophiles[1,2,4,5] provide access to a broad spectrum of valuable intermediates; the addition of alcohols leads to the synthetically important class of *β*-alkoxy alcohols.[2,4,6,7] Classical Brønsted acid catalysis is the most widely used method for epoxide openings through protonation of the basic epoxide oxygen that facilitates the ring opening with the nucleophile.[8] The use of strong mineral acids is naturally limited to acid-stable compounds; Lewis acids have also been widely used as catalysts for epoxide ring openings.[2,6] Nature, however, uses an entirely different path for epoxide hydrolysis, which is key for removing unsaturated toxic organic compounds (through epoxidation and subsequent hydrolysis).[9] There are numerous enzymes that catalyze this reaction, and a common motif is the activation of the epoxide through (double) hydrogen bonding to, e.g., tyrosine residues.[10] Such enzymatic ring opening reactions are mild but also often sensitive toward p*H* and solvent.[11,12] Recently, we have successfully utilized this motif, inter alia,[13] for epoxide

(1) Schneider, C. *Synthesis* **2006**, 3919−3944.

(2) Moghadam, M.; Tangestaninejad, S.; Mirkhani, V.; Shaibani, R. *Tetrahedron* **2004**, *60*, 6105−6111. Firouzabadi, H.; Iranpoor, N.; Jafari, A. A.; Makarem, S. *J. Mol. Catal. A-Chem.* **2006**, *250*, 237−242.

(3) Reetz, M. T.; Torre, C.; Eipper, A.; Lohmer, R.; Hermes, M.; Brunner, B.; Maichele, A.; Bocola, M.; Arand, M.; Cronin, A.; Genzel, Y.; Archelas, A.; Furstoss, R. *Org. Lett.* **2004**, *6*, 177−180. Yang, M. H.; Zhu, C. J.; Yuan, F.; Huang, Y. J.; Pan, Y. *Org. Lett.* **2005**, *7*, 1927−1930. Desai, H.; D'Souza, B. R.; Foether, D.; Johnson, B. F.; Lindsay, H. A. *Synthesis* **2007**, 902−910. Arai, K.; Salter, M. M.; Yamashita, Y.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 955−957. Yadav, J. S.; Reddy, A. R.; Narsaiah, A. V.; Reddy, B. V. S. *J. Mol. Catal. A: Chem.* **2007**, *261*, 207−212.

(4) Yarapathi, R. V.; Reddy, S. M.; Tammishetti, S. *React. Funct. Polym.* **2005**, *64*, 157−161.

(5) Vandeweghe, P.; Collin, J. *Tetrahedron Lett.* **1995**, *36*, 1649−1652. Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **1996**, *35*, 1995−1995. Albanese, D.; Landini, D.; Penso, M. *Tetrahedron* **1997**, *53*, 4787−4790. Schaus, S. E.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 1001−1004. Lau, E. Y.; Newby, Z. E.; Bruice, T. C. *J. Am. Chem. Soc.* **2001**, *123*, 3350−3357. Sabitha, G.; Babu, R. S.; Rajkumar, M.; Reddy, C. S.; Yadav, J. S. *Tetrahedron Lett.* **2001**, *42*, 3955−3958. Reddy, M. A.; Surendra, K.; Bhanumathi, N.; Rao, K. R. *Tetrahedron* **2003**, *59*, 2363−2363. Smitha, G.; Reddy, C. S. *J. Chem. Res., Synop.* **2004**, 300−301. Belokon, Y. N.; Chusov, D.; Borkin, D. A.; Yashkina, L. V.; Dmitriev, A. V.; Katayev, D.; North, M. *Tetrahedron: Asymmetry* **2006**, *17*, 2328−2333. Das, B.; Reddy, V. S.; Tehseen, F.; Krishnaiah, M. *Synthesis* **2007**, 666−668.

(6) Prestat, G.; Baylon, C.; Heck, M. P.; Mioskowski, C., *Tetrahedron Lett.* **2000**, *41*, 3829−3831. Chandrasekhar, S.; Reddy, C. R.; Babu, B. N.; Chandrashekar, G. *Tetrahedron Lett.* **2002**, *43*, 3801−3803. Kantam, M. L.; Jeyalakshmi, K. A. K.; Likhar, P. R. *Catal. Lett.* **2003**, *89*, 95−97. Bradley, D.; Williams, G.; Lawton, M. *Org. Biomol. Chem.* **2005**, *3*, 3269−3272. Gallo, J. M. R.; Teixeira, S.; Schuchardt, U. *Appl. Catal. A* **2006**, *311*, 199−203. Solodenko, W.; Jas, G.; Kunz, U.; Kirschning, A. *Synthesis* **2007**, 583−589.

(7) Iranpoor, N.; Mohammadpour Baltork, I. *Tetrahedron Lett.* **1990**, *31*, 735−738. Garcia, R.; Martinez, M.; Aracil, J. *Chem. Eng. Technol.* **1999**, *22*, 987−990. Matsunaga, S.; Ohshima, T.; Shibasaki, M. *Adv. Synth. Catal.* **2002**, *344*, 3−15. Robinson, M. W. C.; Buckle, R.; Mabbett, I.; Grant, G. M.; Graham, A. E. *Tetrahedron Lett.* **2007**, *48*, 4723−4725.

(8) Chapman, N. B.; Biggs, J.; Finch, A.; Wray, V. *J. Chem. Soc. B* **1971**, 55−63. Coxon, J. M.; Townsend, M. A. E. *Tetrahedron* **2007**, *63*, 5665−5668.

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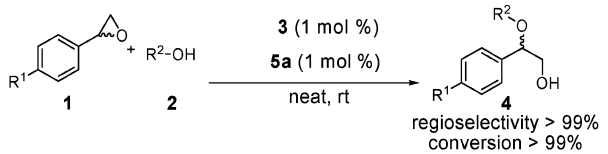
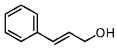
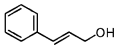
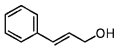
Table 1. Alcoholysis of Styrene Oxides with Mandelic Acid (**5a**)



1 2 4

no.[a]	R^1	1	alcohol (R^2-OH)	2	prod.	t [h]	%[d]
1	H	**1a**		**2a**	**4a**	18	85
2	H	**1a**		**2b**	**4b**	22	86
3	F	**1b**		**2b**	**4c**	24	57
4	*t*Bu	**1c**		**2b**	**4d**	15	65
5	H	**1a**		**2c**	**4e**	21	73
6[b]	H	**1a**		**2d**	**4f**	15	74
7[b]	F	**1b**		**2d**	**4g**	18	57
8[b]	*t*Bu	**1c**		**2d**	**4h**	16	65
9	H	**1a**		**2e**	**4i**	21	94
10	H	**1a**		**2f**	**4j**	20	73
11	H	**1a**		**2g**	**4k**	23	89
12	H	**1a**		**2h**	**4l**	18	80
13	H	**1a**		**2i**	**4m**	23	78
14[c]	H	**1a**		**2j**	**4n**	32	41
15	H	**1a**		**2k**	**4o**	16	65
16	F	**1b**		**2k**	**4p**	17	63
17	*t*Bu	**1c**		**2k**	**4q**	39	70
18[b]	H	**1a**		**2l**	**4r**	18	58

[a] Reaction conditions: 1 equiv of **1**, 12 equiv of alcohol, and 1 mol % of **3** and **5a** respectively; rt. All catalyzed reactions were accompanied by parallel reference experiments without **3**, as well as experiments with **3** and without acid co-catalyst under identical reaction conditions. No polymers of styrene oxide were detected. All reference experiments showed no conversion at the presented reaction time if not otherwise noted. Reactions were monitored by GC/MS. Regiochemistry was determined by NMR experiments (^3J CH-coupling) and fragmentation in MS. [b] At 50 °C. [c] 3 mol % of **5a**; 2 equiv of alcohol; at 50 °C. [d] Yield of isolated product.

openings with strong nucleophiles. We demonstrated that the effects of hydrogen-bonding organocatalysis and water as the solvent are *cooperative* and termed this "hydrophobic amplification".[14] Apparently, the approximately neutral p*H* and the presence of water also are key factors in THP-templated epoxide openings in cascade reactions leading to structures akin to Brevetoxin A.[12] As water can effectively compete with weaker nucleophiles, we set out to develop an alternative approach that relies on using *two* cooperative hydrogen-bonding catalysts. With regards to the choice of mild acid (**5**) to be used with *N*,*N*′-bis-[3,5-bis-(trifluoromethyl)phenyl]-thiourea (**3**),[15] we were helped by the fact that we observed that undistilled styrene oxide (**1a**) readily reacted with various alcohols while freshly distilled **1a** did not. As the oxidation product of **1a** is mandelic acid (**5a**),[9,16] this acid was our first choice. The initial results were very promising and encouraged us to examine this remarkable reaction further.

While carboxylic acids are known to increase the reaction rates of some nucleophilic organocatalytic reactions[17] this is a rare example of a cooperative Brønsted acid-type organocatalytic system.[18] Optimization of the reaction conditions led to a protocol that utilizes 12 equiv of the alcohol as nucleophile and solvent; this effectively suppresses the formation of byproducts resulting from attack of the product on **1** (see Supporting Information for details).

Styrene oxides can readily be transformed into β-alkoxy alcohols in good to excellent yields; all catalyzed reactions are completely regioselective and show full conversion. Both simple aliphatic and sterically demanding (Table 1, entries 1−10), as well as unsaturated (entries 12, 13) and especially acid-labile alcohols (entries 14−18) can be utilized. In general, the reaction times depend more on the nature of the epoxide substrate (**1**) than on the alcohol (**2**). The more reactive **1c** leads nearly in all cases to faster conversions (Table 1, entries 4 and 8); the sole exception is the reaction of cinnamyl alcohol (**2k**) with **1c**. An electron-deficient styrene oxide (**1b**) leads to longer reaction times and lower yields. The reactions of styrene oxides with *tert*-butanol (**2d**, entries 6−8) were all carried out at 50 °C and afforded yields from 57% to 74% without byproduct formation. All reference experiments for these reactions (entries 6−8) showed no conversion; even after 17 days the reference experiment of entry 8 without **3** showed less than 5% conversion. No decomposition or polymerization reactions could be detected for the acid-labile substrates **2j**, **2k**, and **2l**.

Table 2. Solvent Effect on the Alcoholysis of Styrene Oxide with Ethanol[a]

solvent	time [h]	temp. [°C]	conv. of **1** [%]
ethanol	22	rt	>99
acetonitrile	48	rt	–
acetonitrile	20	50	~9
THF	48	rt	>99
toluene	20	rt	–
toluene	16	50	>99
n-hexane	48	rt	>99

[a] Reaction conditions: 1 equiv of **1**, 2 equiv of **2b**, 2 vol equiv of solvent, and 1 mol % of **3** and **5a**, respectively, rt.

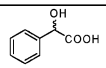
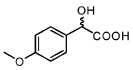
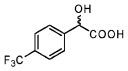
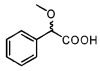
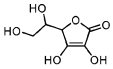
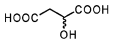
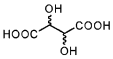
We examined various solvents for the conversion of solid alcohols or epoxides (Table 2) with our test reaction and

(9) Korn, M.; Wodarz, R.; Schoknecht, W.; Weichardt, H.; Bayer, E. *Arch. Toxicol.* **1984**, *55*, 59−63.
(10) Gallimore, A. R.; Stark, C. B. W.; Bhatt, A.; Harvey, B. M.; Demydchuk, Y.; Bolanos-Garcia, V.; Fowler, D. J.; Staunton, J.; Leadlay, P. F.; Spencer, J. B. *Chem. Biol.* **2006**, *13*, 453−460.
(11) Schreiner, P. R.; Wittkopp, A. *Org. Lett.* **2002**, *4*, 217−220. Schreiner, P. R., *Chem. Soc. Rev.* **2003**, *32*, 289−296. Wittkopp, A.; Schreiner, P. R., *Chem. Eur. J.* **2003**, *9*, 407−414.
(12) Vilotijevic, I.; Jamison, T. F. *Science* **2007**, *317*, 1189−1192.
(13) Kotke, M.; Schreiner, P. R. *Tetrahedron* **2006**, *62*, 434−439. Kotke, M.; Schreiner, P. R. *Synthesis* **2007**, 779−790. Zhang, Z.; Schreiner, P. R., *Synlett* **2007**, 1455−1457.
(14) Kleiner, C. M.; Schreiner, P. R. *Chem. Commun.* **2006**, 4315−4317.
(15) Pihko, P. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2062−2064. Takemoto, Y. *Org. Biomol. Chem.* **2005**, *3*, 4299−4306. Doyle, A. G.; Jacobsen, E. N., *Chem. Rev.* **2007**, *107*, 5713−5743.
(16) Ensign, S. A.; Allen, J. R. *Annu. Rev. Biochem.* **2003**, *72*, 55−76.
(17) Cao, C. L.; Ye, M. C.; Sun, X. L.; Tang, Y. *Org. Lett.* **2006**, *8*, 2901−2904.
(18) Yong-Ling Shi, M. S. *Adv. Synth. Catal.* **2007**, *349*, 2129−2135. Zuend, S. J.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129*, 15872−15883.

found a remarkable solvent effect. Reactions in ethanol were more than two times faster than reactions in nonpolar or aprotic solvents.[19] To optimize our cooperative catalyst system, we also varied the ratio between **3** and **5a**[20] and utilized various mandelic acid derivatives.[21]

Further Brønsted acid screening (Table 3) revealed that

Table 3. Brønsted Acid Screening

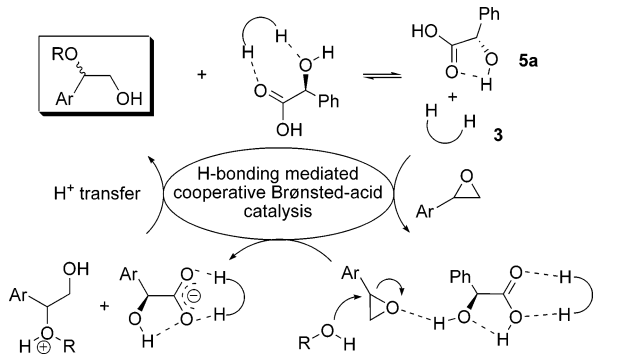
no.[a]	acid additive		pK_a	t [h]	conv. [%][b]
1		**5a**	3.37	22	> 99
2		**5b**	3.43[e]	19	> 99
3[c]		**5c**	3.01[e]	16	> 99
4		**5d**	4.05[e]	24	~5
5		**5e**	3.10[e]	26	--
6		**5f**	--[f]	26	--
7		**5g**	3.00	26	~12
8		**5h**	4.10	26	--
9[d]		**5i**	2.10[e]	12	> 99
10		**5j**	4.28	26	--
11		**5k**	3.41	26	--
12		**5l**	2.93	26	--

[a] Reaction conditions: 1 equiv of **1**, 12 equiv of ethanol, and 1 mol % of **3** and **5a**−**l**, respectively, rt. All catalyzed reactions were accompanied by parallel reference experiments without **3**, as well as experiments with **3** and without acid co-catalyst under identical reaction conditions. Reference experiments showed no conversion. [b] Reactions were monitored by GC/MS. [c] Reference without **3** showed 12% conversion after 18 h. [d] Reference without **3** showed 80% conversion after 15 h; remarkably, the reaction does not run to completion even after 3 days. [e] Calculated data. [f] No experimental or calculated data available.

only aromatic acids bearing a second coordination center in the α-position (hydroxy or carbonyl) led to appreciable conversions (entries 1−3, 9). The removal or blocking of the α-coordination center (**5j** and **5e**) or removal of the aromatic system dramatically reduces the conversion rates. Aqueous acidity (pK_a) appears not to be a good predictor for catalyst activity (entry 12).

Our experimental findings suggest an H-bonding-mediated cooperative Brønsted-acid catalysis mechanism (Scheme 1).

Scheme 1. Proposed Catalytic Cycle for Epoxide Alcoholysis through H-Bonding-Mediated Cooperative Catalysis



It is likely that co-catalyst **3** coordinates to the acid **5a** through double H-bonding, stabilizes **5a** in the chelate-like

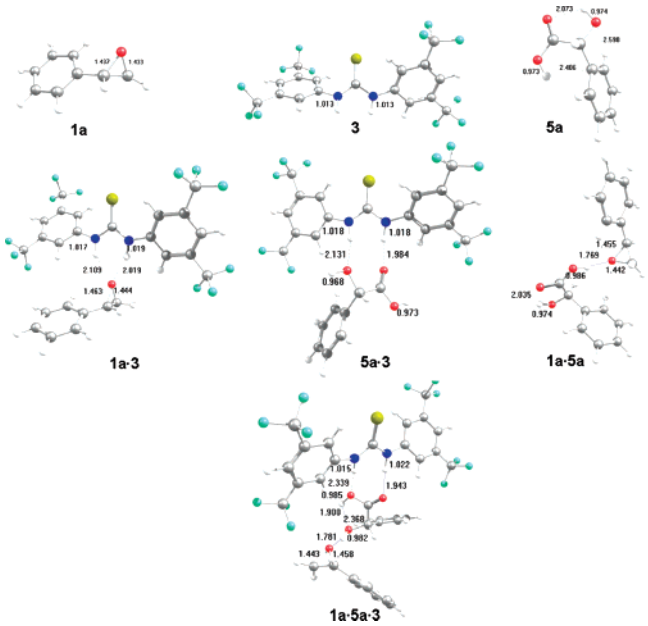


Figure 1. Minimum-energy structures of monomers **1a**, **3**, and **5a**, binary (**1a·3**, **5a·3**, and **1a·5a**) and ternary complexes (**1a·5a·3**) optimized at B3LYP/6-31+G(d,p).

cis-hydroxy conformation, and acidifies the α-OH proton via an additional intramolecular H-bond. The epoxide then is activated by a single-point hydrogen bond that facilitates regioselective nucleophilic attack of the alcohol at the benzylic position. Such monodentate binding was recently suggested for diol catalysts.[22] The incipient oxonium ion reprotonates the mandelate and affords the β-alkoxy alcohol product.

(19) Park, K. S.; Kim, J.; Choo, H.; Chong, Y. *Synlett* **2007**, 395−398. Shirakawa, S.; Shimizu, S. *Synlett* **2007**, 3160−3164.

(20) Suprisingly, reaction times in all cases are nearly equal, although GC/MS analysis after 15 h showed more than two times faster conversion in case of 7 mol % of **3** than in case of our standard protocol (1 mol % of **3**). The results are available in the Supporting Information.

(21) We observed a nonlinear catalytic effect for the ethanolysis of **1** with a notable rate enhancement in the second half of the reaction period. This is apparently not a case of autocatalysis through product **4b** because addition of 20 mol% of **4b** to our standard test reaction showed no variation relative to our standard protocol. Further mechanistic investigations are currently underway.

(22) McGilvra, J. D.; Unni, A. K.; Modi, K.; Rawal, V. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 6130−6133.

(23) Frisch; et al. *Gaussian 03* (for full reference see Supporting Information).

(24) Becke, A. D. *Phys. Rev. A* **1988**, *38*, 3098−3100. Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785−789.

Table 4. Stabilization Energies, H-Bond Distances and Bond Lengths at B3LYP/6-31+G(d,p)

complex	ΔH_0 [kcal/mol]	HB distance [Å]	bond length [Å]
1a·3	−9.2	NH···O 2.109	N−H 1.017
		NH···O 2.019	N−H 1.019
			C^1-O 1.463
			C^2-O 1.444
5a·3	−11.9	$NH^1\cdots O^1$ 2.131	$N-H^1$ 1.018
		$NH^2\cdots O^2$ 1.984	$N-H^2$ 1.018
			O−H 0.973
			O−H (α) 0.968
1a·5a	−5.7	OH···O 1.769	O−H 0.986
			O−H (α) 0.974
			C^1−O 1.455
			C^2−O 1.442
		$NH^2\cdots O^2$ 1.943	$N-H^2$ 1.022
		OH (α)···O 1.781	O−H 0.985
			O−H (α) 0.982
			C^1−O 1.458
			C^2−O 1.443
1a·5a·3	−20.0	$NH^1\cdots O^1$ 2.339	$N-H^1$ 1.015

DFT computations lend credibility to the suggested mechanism. At the B3LYP/6-31+G(d,p) level[23,24] a binary complex between **3** and **5a** is thermochemically favored by 2.7 and 6.2 kcal/mol as compared to complexes **1a·3** and **1a·5a** (Figure 1, Table 4). The rather strong complexation of epoxides with thiourea derivatives was recently found by us[14] and Connon et al.[25] The ternary complex has an overall binding energy relative to its components of remarkable 20.0 kcal/mol, and this explains the concept of cooperativity of the two catalysts. This prompted us to use an NMR titration to determine the **5a·3** complexation energy but found, even upon inclusion of elaborate DOSY experiments, that the binding is too strong to be measured with conventional means. Further experimental and computational studies are underway.

Acknowledgment. This work was supported by the Deutsche Forschungsgemeinschaft (SPP 1179) and the Fonds der Chemischen Industrie. We thank Dr. Heike Hausmann (JLU) for carrying out extensive NMR experiments and Volker Lutz (JLU) for helpful discussions and support in computational questions.

Supporting Information Available: Experimental and computational details as well as characterization of all new compounds. This material is free of charge via the Internet at http://pubs.acs.org.

OL800149Y

(25) Fleming, E. M.; Quigley, C.; Rozas, I.; Connon, S. J. *J. Org. Chem.* **2008**, *73*, 948−956.

Category

Organo- and Biocatalysis

Key words

styrene oxide

thioureas

cooperative catalysis

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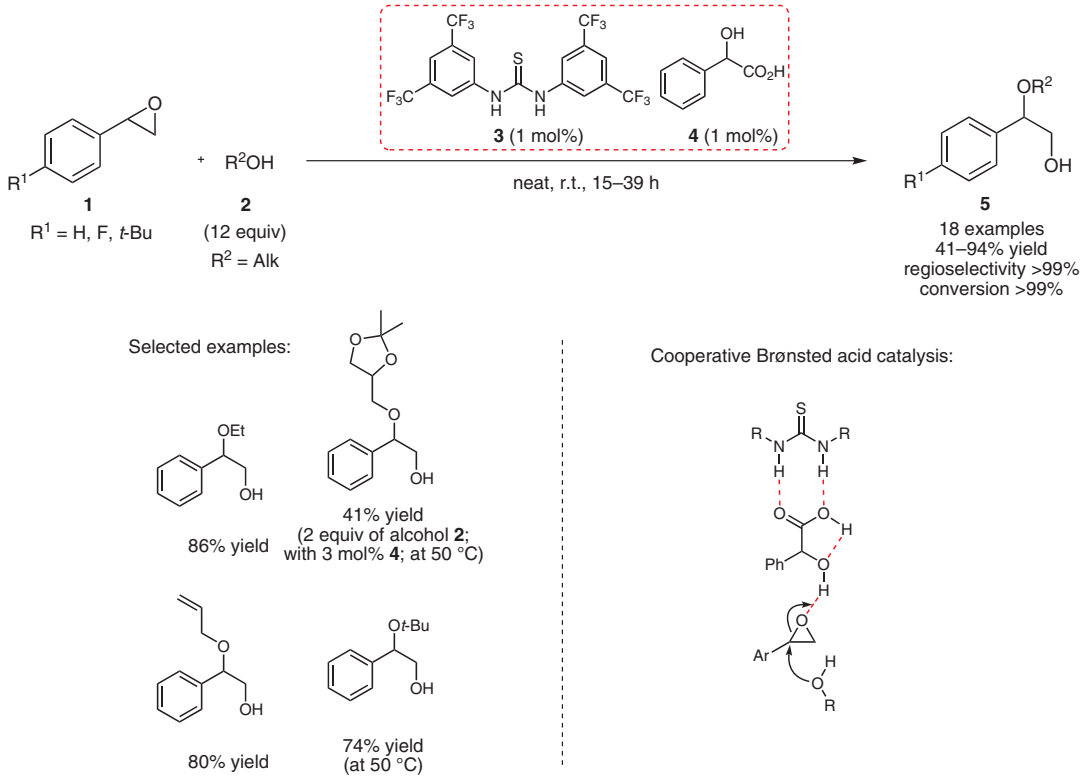
Cooperative Brønsted Acid-Type Organocatalysis: Alcoholysis of Styrene Oxides

Org. Lett. **2008**, *10*, 1513-1516.

Cooperative Brønsted Acid Catalysis



Significance: A completely regioselective alcoholysis of styrene oxides **1** has been accomplished utilizing a catalyst system comprised of *N*,*N*′-bis[3,5-bis(trifluoromethyl)phenyl]-thiourea (**3**, 1 mol%) and mandelic acid (**4**, 1 mol%). Both simple aliphatic and sterically demanding as well as unsaturated or acid-labile alcohols **2** can be used furnishing the corresponding β-alkoxy alcohols **5** in moderate to high yields. Thiourea **3** or mandelic acid (**4**) alone were both uneffective. The authors invoke an H-bonding-mediated cooperative Brønsted acid catalysis mechanism to rationalize their experimental findings (see scheme). Support is also provided by DFT computations.

Comment: Epoxide hydrolysis in nature is commonly facilitated by the activation of the epoxide through (double) hydrogen bonding involving the phenolic protons of two tyrosine residues of epoxide hydrolases. By means of this motif, the Schreiner group has earlier developed epoxide openings with strong nucleophiles catalyzed by the Schreiner thiourea **3** (*Chem. Commun.* **2006**, 4315). Herein, they present an alternative approach which allows for the use of weaker nucleophiles. Further applications of the intriguing concept of cooperative Brønsted acid catalysis are highly desirable, especially in asymmetric catalysis.

SYNFACTS Contributors: Benjamin List, Corinna Reisinger
Synfacts 2008, 6, 0644-0644 Published online: 21.05.2008
DOI: 10.1055/s-2008-1072763; **Reg-No.:** B04108SF

– CHAPTER 3 –

Additional Research Projects on Organocatalysis

Preface

In course of the research efforts towards the design, the synthesis, and the identification of potential synthetic applications of explicit hydrogen-bonding (thio)urea organocatalysts numerous research projects have been evaluated on the level of proof-of-principle studies and were intensified to a different theoretical and experimental extend. Initial experiments including, e.g., Diels-Alder reactions of simple α,β-unsaturated carbonyl compounds with cyclopentadiene, diacetylations of carbonyl compounds, the syntheses of complexes between (a)chiral thiourea derivatives and hydrogen peroxide for potential asymmetric epoxidations, Claisen rearrangements, and Boc protections of primary amines turned out to be not feasible under the applied reaction conditions in the presence of preferably privileged organocatalyst *N,N′*-bis[3,5-(trifluoromethyl)phenyl]thiourea.
These studies are not reported in this PhD thesis.

In contrast, the strategic introduction of oxazoline-thioureas as potential hydrogen-bonding organocatalysts (3.1) as well as the development of an organocatalyzed formation of 1,3-dioxolanes from epoxides and carbonyl compounds (3.2) have provided promising results and deserve special attention. The current results pave the avenue for further investigations and applications that may lead to subsequent scientific publications and novel research projects (see also Chapter 5; “Outlook – Research Perspectives”).

Both these research projects are closely described in the following chapter.

3.1 Design and Synthesis of Novel Oxazoline-Thiourea Derivatives: Potential Organocatalysts

Various highly enantioselective bifunctional hydrogen-bonding (thio)urea organocatalysts derived from primary amine functionalized chiral scaffolds, which are incorporated as key moieties in enantiocontrolling ligands of organometallic catalytic systems (see Chapter 1; Section 1.1). These chiral scaffolds and building-blocks, respectively, such as *trans*-1,2-diaminocyclohexane, amino alcohols, 2,2′-binaphthol derivatives, and alkaloids have turned out to have both a strong impact on the bifunctional mode of action and the chirality transfer (enantiodifferentiation) of the respective (thio)urea organocatalysts. Chiral oxazolines and oxazoline-containing compounds have also received an extensive amount of attention as ligands in efficient asymmetric organometallic catalysis and are readily accessible from chiral 1,2-amino alcohols preferentially obtained by reduction of carboxylic acids and their suitable derivatives.[1, 2]

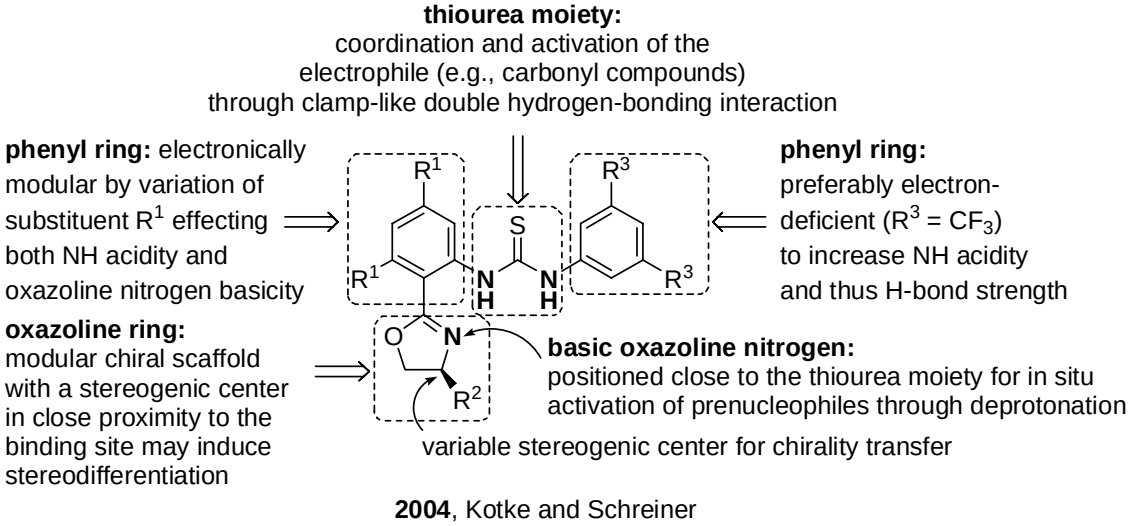
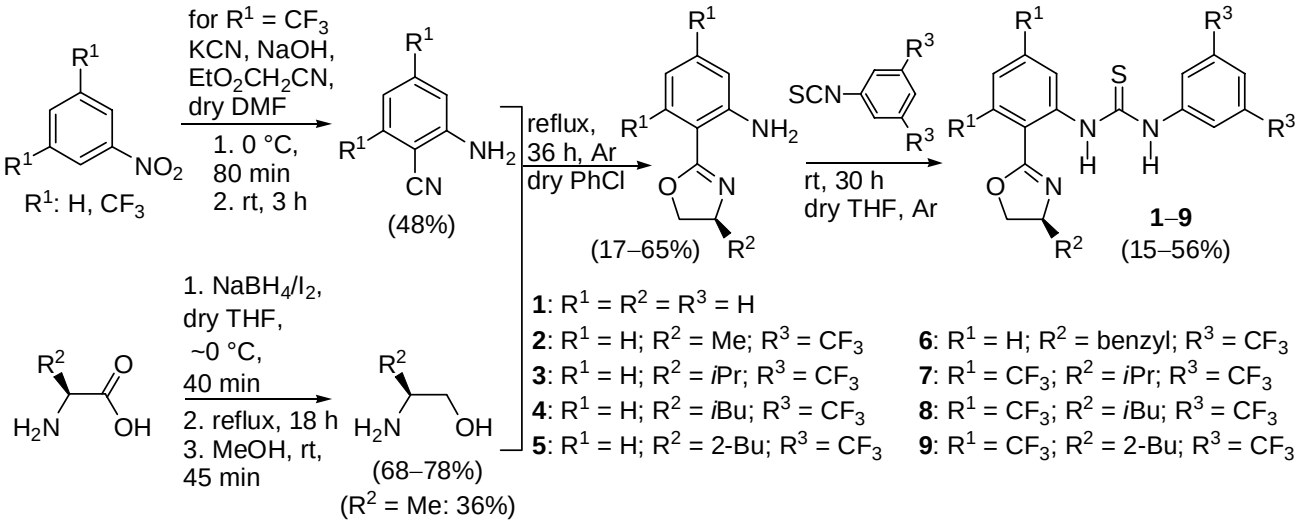


Figure 1. Design rationale and key moieties of chiral oxazoline-thioureas expected to operate as bifunctional double hydrogen-bonding thiourea organocatalysts. R^1, R^2, R^3: see Scheme 1.

Considering these aspects Schreiner and Kotke, in 2004, suggested the oxazoline-heterocyclus to be an attractive chiral scaffold for the design of a novel class of modular (thio)urea derivatives operating as bifunctional hydrogen-bonding organocatalysts such that the thiourea moiety could activate the electrophile, while the basic oxazoline nitrogen simultaneously activates the nucleophile (Figure 1). The synthetic strategy towards oxazoline-thioureas bases on the simple coupling reaction between the corresponding primary amine functionalized chiral phenyl-oxazoline component and predominantly 3,5-bis(trifluoromethyl)phenyl isothiocyanate.[3] For this reaction the respective 2-(aminophenyl)-2-oxazoline was obtained from a $ZnCl_2$-catalyzed condensation[4] of the precursors 2-aminobenzonitrile or 2-amino-4,6-bis(trifluoromethyl) benzonitrile[5] and an

enantiopure amino alcohol[6] readily accessible from 1-nitro-3,5-bis(trifluoromethyl)benzene and the corresponding enantiopure amino acid, respectively. This approach employs modified literature procedures.[4-6] Utilizing the straightforward four-step protocol shown in Scheme 1 developed and optimized by Kotke, in 2005, the desired oxazoline-thioureas **1**–**9** were isolated in analytical grade and in yields ranging from 15–56%; experimental details and the analytical data of both the novel thiourea derivatives and their precursors are reported elsewhere.[7]



Scheme 1. Straightforward synthetic route and reaction conditions for the synthesis of novel oxazoline-thioureas **1**–**9** utilizing inexpensive and commercially available chemicals. The yield of the respective product is given in parentheses.

The oxazoline-thioureas **1**–**9** were screened for catalytic efficiency in various organic transformations, e.g., Claisen rearrangements,[8] the aminolysis of terminal epoxides, the addition of TMSCN to benzaldehyde, and the addition of alcohols to ketenes.[9] Although the screening reactions were performed at variable conditions (loading, temperature, solvent, and stoichiometry) **1**–**9** turned out to be catalytically ineffective. This unexpected experimental finding is explained with a strong intramolecular hydrogen-bonding interaction between the basic oxazoline nitrogen and the contiguous amide proton, which displays a downfield-shifted ^{1}H-NMR signal in the region of 13.30–10.10 ppm ($CDCl_3$); in contrast, the signal of the second amide proton of the thiourea moiety is located in the region of 10.05–8.69 ppm ($CDCl_3$) (Figure 2). Computations[10] on the conformation of **1**–**9** support this interpretation and indicate that the intramolecular hydrogen bonding on the one hand stabilizes the *syn* orientation of the amide protons (*trans*/*trans* rotamer) required for double hydrogen-bonding interaction with the substrate; on the other hand, this *intra*molecular hydrogen-bonding remains even stable in the presence of an external hydrogen-bond acceptor (substrate) and inhibits the formation of the catalytically efficient *inter*molecular double

hydrogen-bonding interaction. This competition between intra- and intermolecular hydrogen bonding effects the catalytic inefficiency of the oxazoline-thioureas **1**–**9** and emphasizes the importance of double hydrogen-bonding interactions for (thio)urea organocatalysis. Consequently, the design rationale for (thio)urea organocatalysts should focus on both intra- and intermolecular interactions that could have an impact on catalytic activity. To verify this result and interpretation, respectively, **1**–**9** could be modified by incorporation of a methylene group destabilizing the intramolecular hydrogen bond owing to a seven- instead of a thermodynamically favored six-membered ring. Thus, intermolecular double hydrogen-bonding should be provided, when an adequate substrate approaches to the catalyst candidate. On the basis of this model oxazoline-thioureas derived from 2-aminomethyl-benzonitriles or (2-amino-phenyl)-acetonitriles and the resulting primary amine functionalized oxazolines, respectively, could exhibit catalytic efficiency in suitable model reactions (Figure 2).

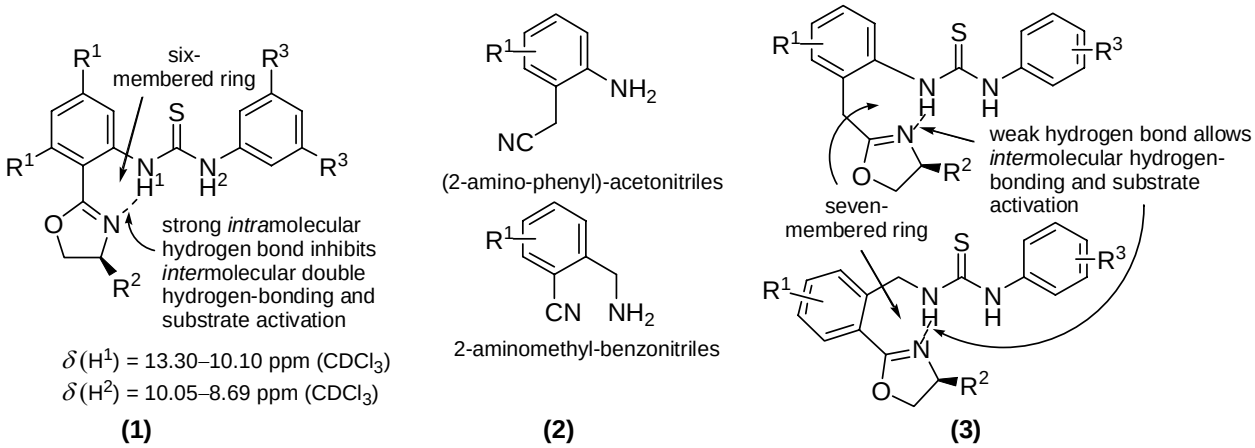
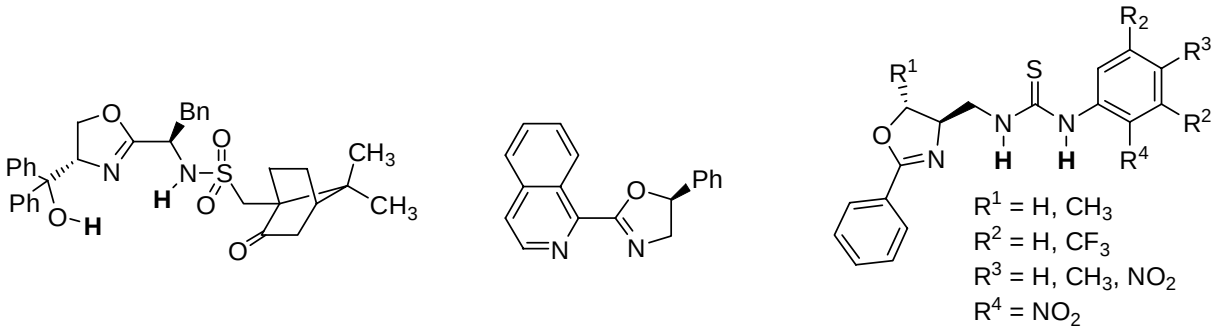


Figure 2. **(1)** A strong *intra*molecular hydrogen bond indicated by ^{1}H-NMR analysis and computations presumably inhibits double hydrogen-bonding of oxazoline-thioureas crucial for catalytic activity; **(2)** suitable starting materials for synthesis of modified oxazoline-thioureas; **(3)** modified oxazoline-thioureas, potential organocatalysts capable of providing an activating double hydrogen-bonding interaction with the substrate (see also Chapter 1; section 1.2.2.7).

While the spectrum and variety of organocatalysts derived from ligand scaffolds continuously increase (Chapter 1; Section 1.2.2) the readily accessible and modular oxazoline heterocyclus have not been established in organocatalysis to date. Only a few examples of oxazoline-organocatalysts have been reported. (Figure 3). In 2005, Sigman and Rajarman introduced a sulfonylamide-containing catalyst incorporating two hydrogen bond donating groups, a sulfonamide and a tertiary alcohol, across a rigid oxazoline scaffold.[11] This dual hydrogen bond donor representing the first oxazoline-organocatalyst was reported to activate aryl aldehydes for hetero-Diels-Alder reactions yielding dihydropyrones (42–80% yield; 71–92% *ee*; 20 mol% catalyst loading). Malkov and

Kočovský, in 2006, utilized isoquinoline-1-carboxylic acid and enantiopure (*S*)-configured mandelic acid to construct a (pyridyl)oxazoline-containing covalent organocatalyst applicable for hydrosilylations of aromatic ketones and ketimines giving secondary alcohols and amines (35–100% yield; 66–92% *ee*; 20 mol% catalyst loading), respectively.[12] The first catalytically efficient bifunctional hydrogen-bonding oxazoline-thiourea, however, was described by Chang et al., in 2007. This catalyst confirms the utility of the oxazoline scaffold for thiourea catalyst design realized by Schreiner and Kotke earlier (Figure 1 and 3) and was reported to promote asymmetric aza-Henry reactions between *N*-Boc-protected aryl imines and nitromethane affording the adducts in 68–97% yield (80–92% *ee*) (Chapter 1; Section 1.2.2.7).[13] Further research efforts on the development of hydrogen-bonding (thio)urea organocatalysts are desirable and should include systematic structure-efficiency studies employing both experimental and computational methodologies.



2005, Sigman, Rajaram
hetero-DA reactions

2006, Malkov, Kocovský
hydrosilylations

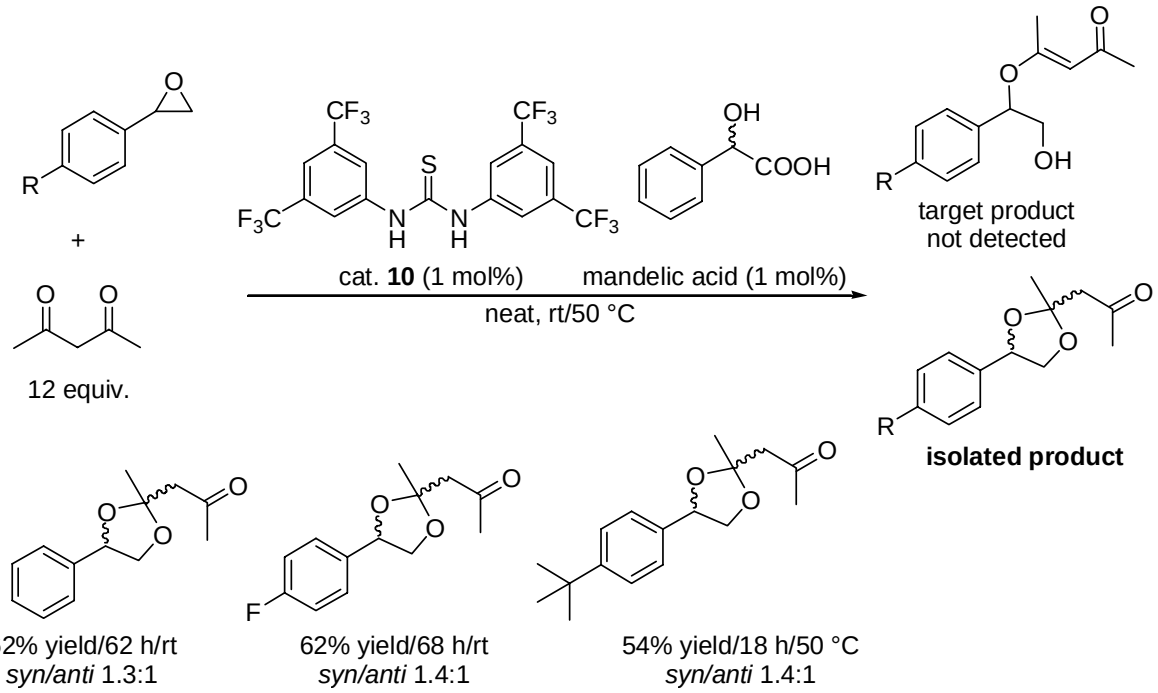
2007, Chang
aza-Henry reactions

Figure 3. Covalent and non-covalent organocatalysts incorporating the oxazoline moiety.

3.2 Organocatalytic 1,3-Dioxolane Formation from Styrene Oxides (Manuscript in preparation)

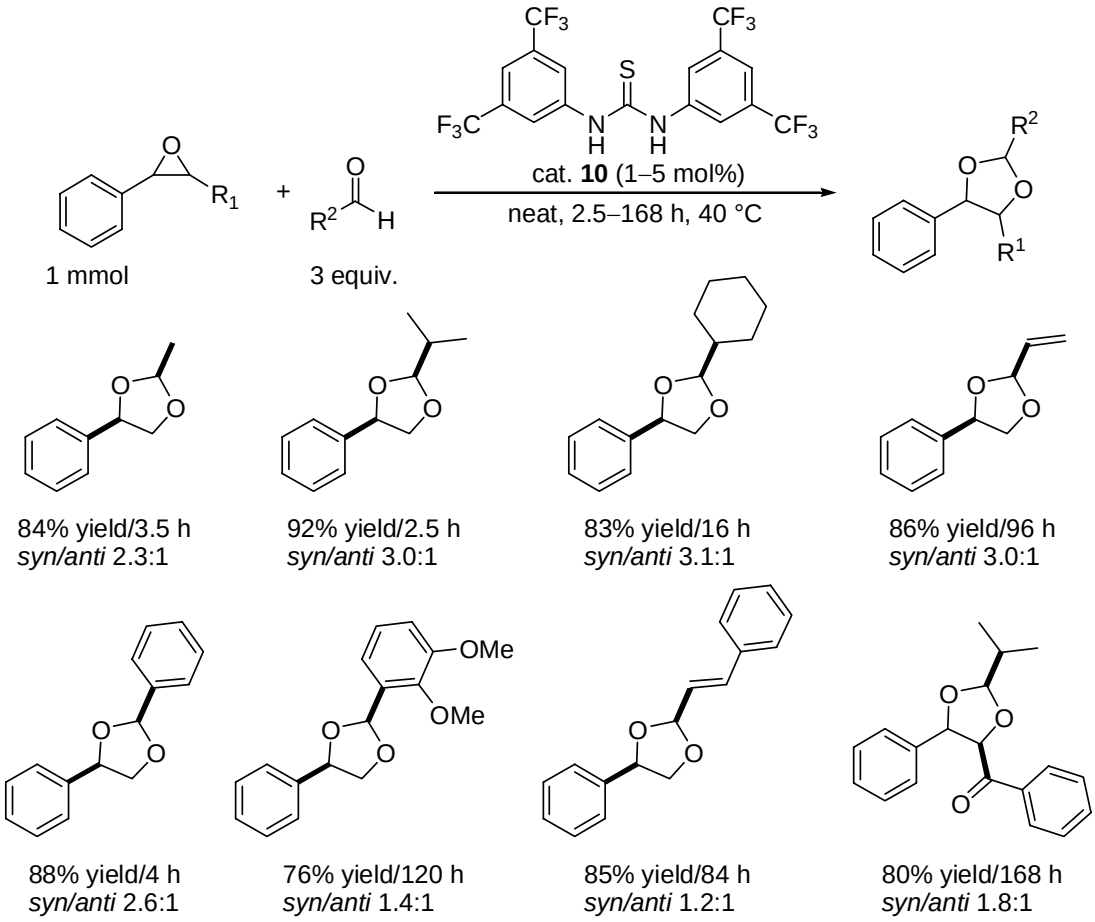
1,3-Dioxolanes (1,3-dioxiranes) are typically synthesized from carbonyl compounds and 1,2-ethanediol in the presence of an often stoichiometric amount of a Brønsted- or Lewis-acid catalyst under water-scavenging reaction conditions (e.g., orthoester, Na_2SO_4, molecular sieve, or water separator). These cyclic acetals are widely utilized protective groups for carbonyl functionalities in multistep syntheses,[14, 15] show antimuscarinic activity[16] and represent key building blocks and intermediates in the fragrance industry.[17] In 2006, Kotke and Schreiner introduced the first organocatalytic acetalization. This acid-free, practical method utilizes privileged hydrogen-bonding organocatalyst *N,N′*-bis[3,5-(trifluoromethyl)phenyl]thiourea **10** (0.01–1 mol% loading) to provide both acyclic and cyclic acetals in good to excellent yields (see Chapter 1,

Section 1.2.1.1 and Chapter 2.1).[18] Subsequent research efforts by Kotke and Schreiner led to the development of a generally applicable method for the organocatalytic tetrahydropyranylation of various hydroxy functionalities (Chapter 1, Section 1.2.1.1 and Chapter 2.2).[3] The resulting THP ethers are mixed acetals and expand the spectrum of acetals accessible in the presence of a substoichiometric amount of catalyst *N*,*N*′-bis[3,5-(trifluoromethyl)phenyl]thiourea. Both methodologies were optimized to provide the respective acetals predominantly at room temperature and at reasonable reaction times. Owing to the mild, acid-free reaction conditions both protocols tolerate substrates bearing acid-labile groups and give high product yields even for preparative acetalizations (up to 100 mmol scale). In course of the studies towards the substrate scope of the cooperative Brønsted acid-type organocatalytic styrene oxide alcoholysis[19] (Chapter 1, Section 1.2.1.1 and Chapter 2.3) Kotke and Weil, in 2007, suggested enolizable 1,3-diketones to react with styrene oxide via the hydroxy group of the enolate akin to secondary alcohols giving the respective β-alkoxy alcohol adducts.[19] To probe this hypothesis the model reaction between acetylacetone (12 equiv.) and styrene oxide was performed under the standard conditions of the epoxide alcoholysis protocol (1 mol% catalysts **10**, 1 mol% mandelic acid, rt, GC-MS analysis). Surprisingly, this experiment turned out to provide the corresponding 1,3-dioxolane (62% yield/62 h) instead of the target β-alkoxy alcohol (Scheme 2), which obviously underwent an intramolecular *oxy*-Michael cyclization. One electron-deficient and one electron-rich (at 50 °C) styrene oxide could be converted to 1,3-dioxolanes given in Scheme 2.[20]



Scheme 2. 1,3-Dioxolanes obtained from the reaction between acetylacetone and various styrene oxides. β-alkoxy alcohol formation could not be detected and uncatalyzed reference experiments showed no conversion under identical reaction conditions.

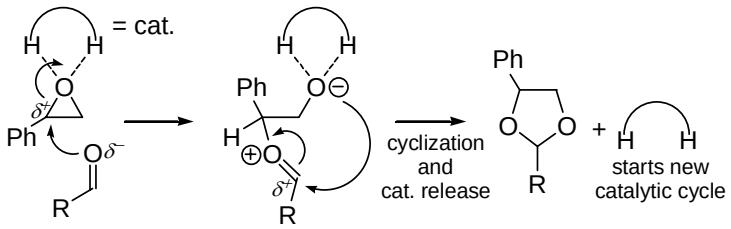
Various aldeyhdes (3 equiv.) including acid-labile acrolein and cinnamaldehyde could be converted with styrene oxide to the desired 1,3-dioxolanes (76%–92% yield) in the absence of mandelic acid, when *N*,*N*′-bis[3,5-(trifluoromethyl)phenyl]thiourea **10** (1–5 mol%) was employed as the catalyst (Scheme 3).[20] The transformations (1 mmol scale) proceeded smoothly under mild conditions (rt or 40 °C) without detectable (GC-MS analysis) side-products owing to, e.g., polymerizations and appeared superior to Brønsted- and Lewis-acid catalyzed procedures suffering from low yields and the intolerance towards acid-labile substrates.[21-26] The current protocol slightly favors the formation of the *syn*-diastereomers instead of the *anti*-products typically formed in the presence of Lewis-acid catalysts.



Scheme 3. Isolated 1,3-dioxolanes prepared from the acid-free, organocatalytic reaction between terminal epoxides and various aldehydes. Uncatalyzed reference experiments showed no conversion under identical reaction conditions.

Further investigations on this useful acid-free 1,3-dioxolane formation focus on the expansion of the substrate scope to ketones and internal epoxides, the optimization of the reaction conditions considering also a cooperative Brønsted acid-type organocatalytic approach (variation of both the thiourea catalyst and the Brønsted-acid component), and the elucidation of the mechanistic scenario

utilizing both experimental and computational methodologies. A preliminary mechanistic picture of this reaction, however, may originate from experimental studies by Wright et al. on the Lewis-acid (BF_3) catalyzed reaction of *cis*-but-2-ene-oxide and *trans*-but-2-ene-oxide, respectively, with O^{18}-labelled acetone.[27] Both the ketone and the epoxide are formally electrophilic and compete with the coordination and activation by the Lewis acid BF_3 (counterintuitive mechanism). The stereochemical outcome of this model reaction is reported to indicate a BF_3-epoxide complex, while the ketone acts as the nucleophile by attacking the epoxide with its carbonyl oxygen.[27] Since organocatalysts such as hydrogen-bonding *N,N'*-bis[3,5-(trifluoromethyl)phenyl]thiourea **10** were identified to operate as weak Lewis-acids[28] (Chapter 1; Section 1.2.1.1) the mechanism of the organocatalytic 1,3-dioxolane formation from aldehydes is proposed to occur comparably. Thiourea catalyst **10** activates styrene oxide (electrophile) through a clamp-like double hydrogen-bonding interaction and accordingly the more nucleophilic (less electrophilic) aldehyde attacks the more electrophilic (less nucleophilic) epoxide (Scheme 4). Subsequently, the hydrogen-bonded zwitterionic intermediate may undergo the product-forming cyclization in a fashion akin the nucleophilic alkoxide attack described for the orthoester assisted acetalization (Chapter 2.1).[18] This determination of the respective roles of the reaction components is ascribed to different complex stabilities and is consistent with the research result independently found by both the Schreiner group[29] and the Connon group[30] that hydrogen-bonding thiourea derivatives actually form more stable complexes with epoxides than with aldehydes or ketones.



Scheme 4. Preliminary mechanistic proposal for the **10**-catalyzed 1,3-dioxolane formation from aliphatic aldehydes and styrene oxide; zwitterionic intermediate undergoes cyclization.

3.3 References and Notes

[1] H. A. McManus, P. J. Guiry, *Chem. Rev.* **2004**, *104*, 4151–4202.
[2] G. Desimoni, G. Faita, K. A. Jørgensen, *Chem. Rev.* **2006**, *106*, 3561–3651.
[3] M. Kotke, P. R. Schreiner, *Synthesis* **2007**, *5*, 779–790.
[4] S. Cabaleiro, P. Pérez-Lourido, J. Castro, *Transition Met. Chem.* **2001**, *26*, 709–716.
[5] Y. Tomioka, K. Ohkubo, M. Yamazaki, *Chem. Pharm. Bull.* **1998**, *33*, 1360–1366.
[6] M. J. McKennon, A. I. Meyers, *J. Org. Chem.* **1998**, *58*, 3568–3571.
[7] Z. Zhang, PhD Thesis, Schreiner group, University Giessen, published online, **2008**.
[8] Claisen rearrangements in collaboration with the Hiersemann group, University Dormund, Germany, unpublished results, **2006**.
[9] Schreiner group, University Giessen, Germany, unpublished results, **2005**–**2008**.
[10] Computations performed by V. Lutz, Schreiner group, University Giessen, Germany, unpublished results, **2006**.
[11] S. Rajaram, M. S. Sigman, *Org. Lett.* **2005**, *7*, 5473–5475.
[12] A. V. Malkov, A. J. P. S. Liddon, P. Ramírez-López, L. Bendová, D. Haigh, P. Kocovský, *Angew. Chem. Int. Ed.* **2006**, *45*, 1432–1435.
[13] Y.-W. Chang, J.-J. Yang, J.-N. Dang, Y.-X. Xue, *Synlett* **2007**, *14*, 2283–2285.
[14] T. W. Greene, P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 3rd ed., Thieme, New York, **1999**.
[15] P. J. Kocienski, *Protecting Groups*, 3rd ed., Thieme, New York, **2005**.
[16] G. Marucci, P. Angeli, L. Brasili, M. Buccioni, D. Giardina, U. Gulini, A. Piergentili, G. Sagratini, *Med. Chem. Res.* **2005**, *14*, 274–296.
[17] C. Sell, *Understanding Fragrance Chemistry*, 1st ed., Allured Pub Corp, Carol Stream, Illinois, USA, **2008**.
[18] M. Kotke, P. R. Schreiner, *Tetrahedron* **2006**, *62*, 434–439.
[19] T. Weil, M. Kotke, C. M. Kleiner, P. R. Schreiner, *Org. Lett.* **2008**, *10*, 1513–1516.
[20] T. Weil, PhD Thesis, Schreiner group, University Giessen, Germany, published online, **2008**: Analytical data of the products obtained from the addition of acetylacetone to styrene oxides; the manuscript on the "Organocatalytic Formation of 1,3-Dioxolanes" is under preparation: C. M. Kleiner, M. Kotke, T. Weil, P. R. Schreiner, **2009**.
[21] D. S. Torok, J. J. Figueroa, W. J. Scott, *J. Org. Chem.* **1993**, *58*, 7274–7276.
[22] I. Bucsi, A. Meleg, A. Molnár, M. Bartók, *J. Mol. Catal. A: Chem.* **2001**, *168*, 47–52.
[23] M. H. Habibi, S. Tangestaninejad, V. Mirkhani, B. Yadollahi, *Catal. Lett.* **2001**, *75*, 205–207.
[24] J. R. Vyvyan, J. A. Meyer, K. D. Meyer, *J. Org. Chem.* **2003**, *68*, 9144–9147.
[25] A. Procopio, R. Dalpozzo, A. De Nino, L. Maiuolo, M. Nardi, B. Russoa, *Adv. Synth. Catal.* **2005**, *347*, 1447–1450.
[26] F. Benfatti, G. Cardillo, L. Gentilucci, A. Tolomelli, M. Monari, P. F., *Adv. Synth. Catal.* **2007**, *349*, 1256–1264.
[27] B. N. Blackett, J. M. Coxon, M. P. Hartshorn, A. J. Lewis, G. R. Little, G. J. Wright, *Tetrahedron* **1970**, *26*, 1311–1313.
[28] P. R. Schreiner, A. Wittkopp, *Org. Lett.* **2002**, *4*, 217–220.
[29] C. M. Kleiner, P. R. Schreiner, *Chem. Commun.* **2006**, 4315–4317.
[30] E. M. Fleming, C. Quigley, I. Rozas, S. J. Connon, *J. Org. Chem.* **2008**, *73*, 948–956.

– CHAPTER 4 –

Three Structurally Homologous Isothiocyanates Exert ‘‘Janus’’ Characteristics in Human HepG2 Cells

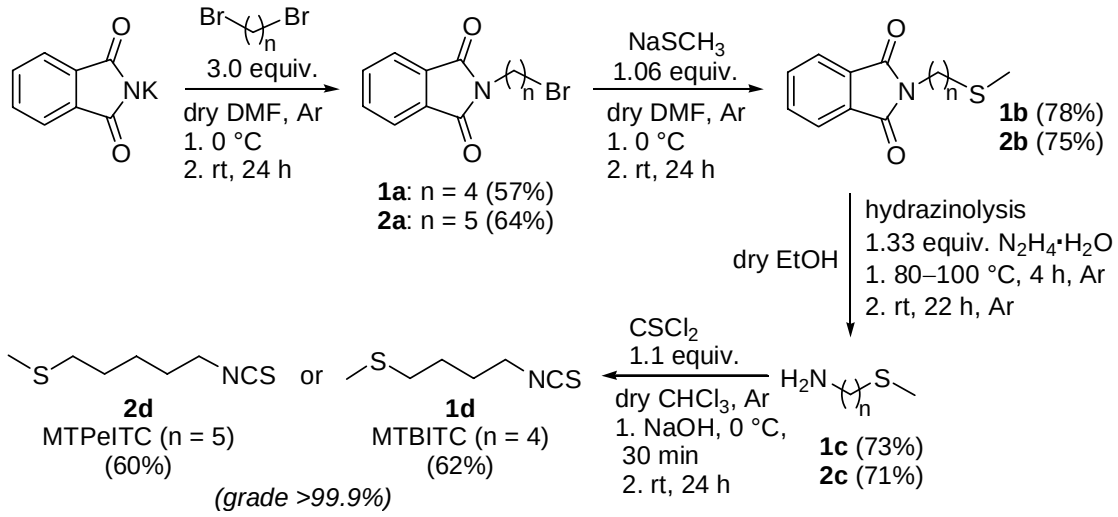
Interdisciplinary Research Project

Preface

In recent years, isothiocyanates (ITCs) including terminal methylthioalkyl isothiocyanates such as the homologous 4-(methylthio)butyl isothiocyanate (MTBITC) and 5-(methylthio)pentyl isothiocyanate (MTPeITC) have gained considerable attention for their role as potent chemopreventive agents.[1, 2] These ITCs can be isolated through extraction methods from, e.g., rocket plant (*Eruca sativa*), which is a member of the chemopreventive plant family Brassicaceae. However, a straightforward synthetic protocol have been desirable to provide these naturally occurring compounds in reproducible and high grade suitable for reliable human cell (e.g., HepG2) culture experiments and studies towards the origin of the chemopreventive potency. Kotke and Schreiner took various literature protocols[3-6] for methylthioalkyl ITCs together and developed an optimized four-step protocol affording MTBITC and MTPeITC, respectively, in high grade (>99.9%) (Scheme 1). Various successful cell culture studies, performed by Lamy, Mersch-Sundermann et al. rely on the quality of both MTBITC and MTPeITC prepared by Kotke utilizing this protocol.[1, 2]

This chapter reports the detailed protocol for the syntheses of the homologous terminal methylthioalkyl isothiocyanates MTBITC and MTPeITC; reaction parameters, observations, work-up, and also the full analytical data of the target ITCs are given to allow ready synthetic accessibility and reproducibility. The interdisciplinary research collaboration with the Lamy group (University Medical Center Freiburg/Germany) revealed ‘‘Janus’’ Characteristics of MTBITC and MTPeITC in human HepG2 cells. The results of these studies performed by Lamy et al. are published in the journal “Environmental and Molecular Mutagenesis” (available from Wiley InterScience). The abstract and introduction of this interdisciplinary research publication are mentioned below.

4.1 Synthesis of Homologous Terminal Methylthioalkyl Isothiocyanates (MTBITC; MTPeITC)



Scheme 1. Synthesis of the homologous aliphatic isothiocyanates 4-(methylthio)butyl isothiocyanate (MTBITC, Erucin) and 5-(methylthio)pentyl isothiocyanate (MTPeITC, Berteroin), respectively, employing inexpensive chemicals. The yields of the single steps are given in parentheses.

All chemicals were purchased from Aldrich, Acros Organics, Alfa Aesar, Merck, and Lancaster in the highest purity available and were used without further purification unless otherwise noted. All solvents used for extractions or filtrations were distilled once with a rotary evaporator. Drying followed established literature procedures. All dry liquid chemicals were stored under argon atmosphere and over activated molecular sieve (MS) in a brown bottle: Dichloromethane (drying agent P_2O_5, 3 h reflux, then distilled once, storage over MS 4 Å), chloroform (CaH_2, 6 h reflux, distilled once, MS 4 Å), ethanol (Na/diethyl phthalate, 3 h reflux, distilled once, MS 3 Å), *N*,*N*-dimethylformamide (CaH_2, 8 h reflux, distilled once at 80 mbar over 20 mm Vigreux column, storage over MS 4 Å); $CDCl_3$ and d_6-DMSO (99.8%, purchased from Deutero GmbH) were stored over MS 4 Å. TLC to monitor reaction progress was carried out on pre-coated Macherey-Nagel plastic sheets Polygram ALOX N/UV_{254} (40–80 mm) using UV light. GC/MS analyses were performed with a Quadrupol-MS HP MSD 5971(EI) and HP 5890A GC equipped with a J & W Scientific fused silica GC column (30 m × 0.250 mm, 0.25 micron DB–5MS stationary phase: 5% phenyl and 95% methyl silicone) using He (4.6 grade) as carrier gas; T-program standard 60–250 °C (15 °C/min heating rate), injector and transfer line 250 °C; ^{1}H and ^{13}C NMR spectra were recorded with Bruker spectrometer Avance II 200 MHz (AV 200) and Avance II 400 MHz WB (AV 400) using as the internal standard (chemical shift δ is given in ppm): TMS d(^{1}H) = 0.00, d(^{13}C) = 0.0; $CHCl_3$ [d(^{1}H) = 7.26], $CHCl_3$ [d(^{13}C) = 77.0]; ^{13}C signals were assigned with DEPT or APT (attached proton test) experiments. IR spectra were measured with Bruker IFS25 and IFS48 spectrophotometers. HRMS were recorded with a Sectorfield-MS: Finnigan MAT 95, CHN

analyses were obtained with a Carlo Erba 1106 (balance: Mettler Toledo UMX-2) analyzer. To keep reaction temperatures constant a standard mercury contact thermometer controlled by an IKAMAG RET-GS hot plate-stirrer was used.

N-(4-bromobutyl)-phthalimide **1a** and *N*-(5-bromopentyl)-phthalimide **2a**: In an oven-dried 250 mL three-necked flask equipped with thermometer, gas inlet, and magnetic stirring bar a homogeneous solution of 540 mmol (116.60 g, 63.7 mL) 1,4-dibromobutane or 540 mmol (124.18 g, 73.6 mL) 1,5-dibromobutane respectively, in dry DMF (60 mL) was prepared. Under argon atmosphere 178 mmol (32.98 g) phthalimide potassium salt was added in small portions to the well-stirred solution cooled at 0 °C to 2 °C (ice-bath). After addition, the resulting white suspension was allowed to stir 24 h at room temperature before the excess of the respective dibromoalkane and DMF was removed using vacuum distillation (~30 mbar, ~50 °C, oil bath) over a Liebig condenser giving a yellowish semi-solid residue. The Liebig condenser was replaced with a reflux condenser and the residue was dissolved under intensive stirring in a minimal volume (~450 mL) of a boiling EtAc/H_2O-mixture (1:1 ratio). After cooling of this mixture to room temperature the layers were separated, the aqueous layer was extracted with EtAc (2 × ~50 mL), and the combined organic layers were dried over anhydrous Na_2SO_4. After filtration and evaporation of the solvent with a rotary evaporator at reduced pressure (~30 mbar) the colorless solid crude product was purified once by recrystallization from diisopropyl ether (note: a white insoluble side-product was separated from the hot ether solution through filtration) affording colorless, needle-shaped crystals that were dried over P_2O_5 in a desiccator. Concentrating the mother liquor to a minimum volume and cooling in an ice box afforded an additional amount of the corresponding *N*-(bromoalkyl)-phthalimide. This procedure provided 28.40 g (101 mmol, 57% yield) *N*-(4-bromobutyl)-phthalimide **1a** or 33.62 g (114 mmol, 64% yield) *N*-(5-bromopentyl)-phthalimide **2a**, respectively, spectroscopically consistent with literature data.[4, 5]

N-[(4-methylthio)butyl]-phthalimide **1b** and *N*-[(5-methylthio)pentyl]-phthalimide **2b**: In an oven-dried 250 mL three-necked flask equipped with thermometer, gas inlet, and magnetic stirring bar a homogeneous solution of 73.9 mmol (5.17 g) sodium methylmercaptide (sodium thiomethoxide) in ice-cooled, dry DMF (160 mL) was prepared. At –4 °C to 2 °C (ice-bath) 70 mmol (19.68 g) *N*-(4-bromobutyl)-phthalimide **1a** or 70 mmol (20.66 g) *N*-(5-bromopentyl)-phthalimide **2a**, respectively, was slowly added to the well-stirred mixture giving an orange reaction solution. After vigorous stirring for 24 h at room temperature under argon atmosphere this solution was poured into 500 mL demineralized water (0 °C) leading to the precipitation of a white solid that was separated

with suction filtration. Washing with cold water (~ 80 mL) in small portions and drying over P_2O_5 in a desiccator provided 13.61 g (55 mmol, 78% yield) *N*-[(4-methylthio)butyl]-phthalimide **1b** or 13.83 g (53 mmol, 75% yield) *N*-[(5-methylthio)pentyl]-phthalimide **2b**, respectively, with NMR data identical to those reported in literature.[4, 5] The quality of the isolated crude product turned out to be suitable for subsequent hydrazinolysis; a higher product grade, however, could be obtained with recrystallization once from diisopropyl ether yielding colorless, needle-shaped crystals **1b** and **2b**, respectively.

4-(Methylthio)butylamine **1c** and 5-(methylthio)pentylamine **2c**: In an oven-dried 100 mL two-necked flask equipped with reflux condenser, gas inlet, and magnetic stirring bar a suspension of 21.7 mmol (5.42 g) *N*-[(4-methylthio)butyl]-phthalimide **1b** or 21.7 mmol (5.71 g) *N*-[(5-thiomethyl)pentyl]-phthalimide **2b**, respectively, in dry ethanol (30 mL) was prepared. At room temperature under argon atmosphere hydrazinolysis was initiated by slow addition of 28.9 mmol (1.45 g, 1.40 mL) hydrazine monohydrate via a plastic syringe. Warming the well-stirred reaction mixture approx. 15 min with an oil bath (~80 °C) led to the formation of a yellowish precipitation making further magnetic stirring impossible; after addition of 25 mL dry ethanol and controlled crushing of the solid with a spatula the suspension was stirred for 2.5 h at the same bath temperature. Acidification with 20 mL diluted (2 M) hydrochloric acid (pH value changed from 8 to ~4.5) gave a white suspension that could be readily stirred for further 1.5 h at 100 °C until heating was stopped and the reaction mixture was allowed to slowly (~2 h) cool to room temperature. After stirring at room temperature for 22 h the white solid was separated with suction filtration and was thoroughly washed with cold demineralized water (~60 mL). The remaining white water-insoluble phthalhydrazide side-product was poured into 80 mL demineralized water, the suspension was stirred for 15 min at room temperature to dissolve adhesive ammonium salt of product **1c** or **2c**, respectively, and phthalhydrazide was finally separated with filtration. The combined aqueous filtrates were neutralized with solid Na_2CO_3 and extracted with diethyl ether (4 × 80 mL), the addition of solid NaCl facilitated layer separation. The resulting organic layers were collected and dried over anhydrous Na_2SO_4/Na_2CO_3, the drying agent was separated by filtration and was washed intensively with diethyl ether (~100 mL) to reduce loss of product. Evaporation of the solvent (at ~40 °C and ~30 mbar) from the combined organic layers furnished a yellowish liquid with NMR data corresponding to the structure of 4-(methylthio)butylamine **1c** (1.89 g, 16 mmol, 73% yield) or 5-(methylthio)pentylamine **2c** (2.05 g, 15 mmol, 71% yield), respectively.[4, 5] The crude products showed only traces of solvent (EtOH and Et_2O) and could be utilized without further purification

for the synthesis of the target products 4-(methylthio)butyl isothiocyanate (MTBITC) **1d** and 5-(methylthio)pentyl isothiocyanate (MTPeITC) **2d**, respectively.

4-(Methylthio)butyl isothiocyanate (MTBITC) **1d** and 5-(methylthio)pentyl isothiocyanate (MTPeITC) **2d**: The formation of the respective isothiocyanate proceeded in an oven-dried 50 mL three-necked flask equipped with argon inlet, septum, thermometer, and magnetic stirring bar. 18.5 mmol (2.2 g) 4-(methylthio)butylamine **1c** or 18.5 mmol (2.46 g) 5-(methylthio)pentylamine **2c**, respectively, were dissolved in dry chloroform (18 mL) under argon atmosphere. This vigorously stirred solution was cooled (–2 °C to 0 °C) with an efficient ice/salt bath while a homogeneous solution of 20.3 mmol (2.33 g) thiophosgene in 5 mL dry chloroform was added dropwise within approx. 15 min via a plastic syringe. The mixture was stirred for 30 min at the same temperature before powdered 55 mmol (2.21 g) sodium hydroxide was slowly added at –2 °C to 5 °C resulting in an orange suspension that was allowed to warm to room temperature (within ~2 h); final stirring for 24 h at room temperature led to completion of the transformation (TLC control; eluent: *n*-hexane/EtAc). Evaporation of the solvent and subsequent fractionated distillation (10 cm Vigreux column) in vacuo (20 mbar) gave analytically pure (>99.9%; GC/MS analysis) yellowish transparent MTBITC **1d** (1.85 g, 11.5 mmol, 62% yield) or MTPeITC **2d** (1.95 g, 11.1 mmol, 60% yield), respectively. The observed spectroscopic data proved to be in line with literature values and supported the structure of **1d** and **2d**, respectively.[4, 5]

4-(Methylthio)butyl isothiocyanate (MTBITC, Erucin) **1d**:[4, 5] Yellowish transparent liquid, b.p. 135–136 °C/~20 mbar; IR (film): 2947, 2917, 2184, 2104 (NCS), 1451, 1371, 1348, 1273, 1030, 758 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, δ in ppm): 1.68–1.90 (m, 4H), 2.11 (s, 3H), 2.54 (t, 2H), 3.56 (t, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ in ppm): 15.4, 25.9, 28.8, 33.3, 44.7, 132.1 (C_q, NCS). HRMS: *m/z* calcd. for $C_6H_{11}NS_2$: 161.0333; found: 161.0339. CHN-analysis: calcd. C 44.68, H 6.87, N 8.68; found C 44.51, H 6.71, N 8.59.

5-(Methylthio)pentyl isothiocyanate (MTPeITC, Berteroin) **2d**:[4, 5] Yellowish transparent liquid, b.p. 151–152 °C/~20 mbar; IR (film): 2941, 2916, 2857, 2183, 2114 (NCS), 1451, 1437, 1346, 957 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, δ in ppm): 1.51–1.82 (m, 6H), 2.11 (s, 3H), 2.50 (t, 2H), 3.60 (t, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ in ppm): 15.5, 25.7, 28.3, 29.8, 33.9, 44.7, 131.7 (C_q, NCS). HRMS: *m/z* calcd. for $C_7H_{13}NS_2$: 175,0489; found: 175.0481. CHN-analysis: calcd. C 47.96, H 7.47, N 7.99; found C 47.73, H 7.31, N 7.65.

4.2 References and Notes

[1] E. Lamy, J. Schröder, S. Paulus, P. Brenk, T. Stahl, V. Mersch-Sundermann, *Food Chem. Toxicol.* **2008**, *46*, 2415–2421.
[2] E. Lamy, *PhD Thesis, "MTBITC-induced apoptosis and cell cycle arrest of human hepatoma (HepG2) cells: A link between p53 and human telomerase?"*, University Giessen, **2007**, available online from the electronic library. See also references cited therein.
[3] C. A. D'Souza, S. Amin, D. Dhimant, *J. Label. Compd. Radiopharm.* **2003**, *46*, 851–859.
[4] H. L. Holland, F. M. Brown, B. G. Larsen, M. Zabic, *Tetrahedron: Asymmetry* **1995**, *6*, 1569–1574.
[5] M. Vermeulen, B. Zwanenburg, G. J. F. Chittenden, H. Verhagen, *Eur. J. Med. Chem.* **2003**, *38*, 729–737.
[6] H. Schmid, P. Karrer, *Helv. Chim. Acta* **1948**, *31*, 1497–1505.

4.3 Abstract and Introduction of the Interdisciplinary Research Publication

Environ. Mol. Mutagen. **2009**, *50*, 164–170

Three Structurally Homologous Isothiocyanates Exert ''Janus'' Characteristics in Human HepG2 Cells

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Abstract

In this study, we used the single cell gel electrophoresis (SCGE) assay and the micronucleus (MN) test to investigate the DNA damaging effects and the antigenotoxic potencies of three structurally related ITCs in human HepG2 cells. The results show that all three ITCs possess the characteristic of a ''Janus'' compound, i.e., they exert both significant genotoxicity and antigenotoxicity, depending on the concentrations used in the test systems applied. Regression line analysis of the results derived by SCGE analysis showed genotoxic potency of the ITCs in the following order: 3-methylthiopropyl ITC (MTPITC) > 4-methylthiobutyl ITC (MTBITC) > 5-methylthiopentyl ITC (MTPeITC); however, this order in genotoxic potency was not confirmed by MN analysis. Additionally, the MN test showed significant mutagenicity of the test substances at higher concentrations when compared with the SCGE assay. Twenty-four hour-treatment of the cells with the ITCs, followed by a 1-hr recovery period, showed significant DNA repair in the SCGE assay at a concentration ≤10 μM MTPITC, ≤3 μM MTBITC, and ≤0.1 μM MTPeITC, respectively. In antigenotoxicity studies, the most effective concentration of MTPITC and MTPeITC toward

B(a)P-induced DNA damage was 0.1 μM in both test systems. MTBITC suppressed MN formation in B(a)P-treated cells to the background level at a concentration of 1 μM. The ambivalent character of the ITCs under study must be further clarified, especially in the possible context of high dose therapeutic applications.

Introduction

Methylthiopropyl isothiocyanate (MTPITC), Methylthiobutyl isothiocyanate (MTBITC), and Methylthiopentyl isothiocyanate (MTPeITC) belong to the isothiocyanate (ITC) class of chemopreventive compounds, which is a group of small molecules derived from vegetables of the Brassicaceae plant family. The three ITCs are for instance found in cabbage turnip or rocket plants [Fischer, 1992; Jirovetz et al., 2002; Lamy et al., 2008]. In numerous epidemiological and experimental data, ITCs have been shown to possess a potent inhibitory effect on cancer development and are effective protectors toward dietary carcinogens such as polycyclic aromatics hydrocarbons (PAHs) [Wattenberg, 1977; Hecht, 2000; Hecht et al., 2002]. It has been well-established that ITCs mediate their chemopreventive activities through multiple mechanisms depending on the concentrations applied. For some ITCs, it has been shown that at lower concentrations, i.e., <5 μM, inhibition of Phase I biotransformation enzymes and the upregulation of Phase II enzymes play a key role in their antigenotoxic action against procarcinogens such as benzo(a)pyrene (B(a)P) [Lamy et al., 2008] or aflatoxins [Manson et al., 1997]. Also, besides enzyme regulation, it has been proposed that cell survival could be enhanced through the Nrf2 signaling pathway by ITC-mediated expression of genes involved in the recognition and repair of damaged proteins, which, in turn, could provide secondary protection against DNA damage [Hu et al., 2006]. In contrast, ITC concentrations above 5–10 μM have been shown to initiate apoptotic response in various cancer cell lines through a multitude of signaling pathways, depending on the cell type, ITC, and experimental condition [Wu et al., 2006]. The other side of the coin is existing evidence that ITCs can exert genotoxic [Kassie and Knasmuller, 2000], cocarinogenic [Okazaki et al., 2003], and even carcinogenic [Dunnick et al., 1982; National Toxicology Program, 1982] effects. In this study, we investigated the genotoxicity and antigenotoxicity of MTPITC, MTBITC, and MTPeITC, three structurally homologous ITCs that differ only in the length of carbon chain. The precursor glucosinolates of these ITCs have been detected in the human diet, but, so far, no or only few data are available on the bioactivity of MTPITC and MTPeITC. MTBITC was recently shown by our group to possess strong antigenotoxic activity in a short term assay [Lamy et al., 2008]. In this study, the bioactivity of the

ITCs was investigated using the comet assay. This assay is a valuable tool for the detection of genotoxic damage, but it also has some disadvantages, i.e., the DNA damage detected does not necessarily correspond to fixed mutations. Therefore, to verify the comet assay results, we additionally used the micronucleus (MN) test, which detects clastogenic or aneugenic events. Because there was indeed a difference between the two short term genotoxicity assays, we additionally carried out a modified version of the comet assay to determine whether DNA repair could help explain this difference.

The entire research article including all references and notes not given above can be retrieved from the publisher Wiley InterScience.

– CHAPTER 5 –

Outlook – Research Perspectives

Preface

The outlook of this PhD thesis may provide aspects, inspirations, ideas, and practicable perspectives that could be impulses for innovative and challenging research projects on explicit hydrogen-bonding (thio)urea organocatalysts both in non-stereoselective and stereoselective organic transformations, applications, and methodologies. Chapter 1 “Hydrogen Bonding in Organic Synthesis”, the organocatalytic acetalization (Chapter 2.1), the organocatalytic tetrahyhydropyranylation (Chapter 2.2), the cooperatively organocatalyzed epoxide alcoholysis (Chapter 2.3), and also the organocatalyzed 1,3-dioxolane formation (Chapter 3.2) offer various seminal research results, reliable analytical strategies, optimized experimental procedures, reasonable mechanistic pictures, concepts, principles and guidelines. This well-founded “toolbox” help to visualize an optimistic picture of research objectives towards (thio)urea organocatalysis.

The “Summary and Outlook” section of chapter 1 (section 1.3) contributes a further critical and constructive look on the achievements of this research field including some important conceptual and practical points to be considered for successful and high-quality future research activities.

In the following novel potential hydrogen-bonding (thio)urea organocatalysts and their applications in organic synthesis are suggested and discussed such that the realization of these perspectives and research objectives, respectively, should appear desirable, encouraging, and mainly feasible.

5.1 Novel Potential Hydrogen-bonding (Thio)urea Organocatalysts

The rationale design, development, and identification of catalytically efficient (thio)urea derivatives for practical and useful applications remain timely and central research challenges in the field of non-covalent organocatalysis.[1, 2] Applying the structure principles and guidelines discussed in chapter 1 potential explicit hydrogen-bonding (thio)urea organocatalysts both non-stereoselective and stereoselective can be developed and readily synthesized from inexpensive commercially available and synthetically accessible building blocks. Since the most efficient catalyst architectures derive from privileged catalyst *N*,*N*′-bis[3,5-(trifluoromethyl)phenyl]thiourea **1** incorporating the 3,5-bis(trifluoromethyl)phenyl thiourea moiety novel catalyst candidates should preferably designed analogously. Catalytic efficiency regarding both significant rate enhancement and enantioinduction should be evaluated in suitable model reactions characterized by simple starting materials, stable, readily observable products, and reliable reaction monitoring and analysis (e.g., THP protection; Chapter 2.2). Figure 1 illustrates chiral mono- and bifunctional (thio)urea organocatalyst candidates predominantly derived from (*R*,*R*)-1,2-diaminocyclohexane, the isothiocyanates **2** and **3**, and primary amine functionalized thiourea **4** as the key building blocks.[3] The respective amine components such as enantiopure amino alcohols, protected amino acids, anthranilic acids, and amine-oxazolines (see Chapter 3; Section 3.1) are readily available. The preparations of **5**–**16** are feasible in a few synthetic steps and the modular structures allow access to small libraries of representative derivatives of these catalyst candidates. Systematic structure optimizations studies both experimentally (e.g., employing high-throughput screening approaches) and computationally should be utilized to indentify catalytically relevant structure features, to elucidate the catalyst's mode of action, the mechanistic picture, and may point the way for further optimizations, e.g., regarding reaction parameters (e.g., substrate choice, solvent, temperature, loading, stirring rate, scale). In analogy to the structures depicted in Figure 1 various (chiral) (vicinal) primary (di)amine and (chiral) isothiocyanate building blocks can be synthetically combined to obtain further potential hydrogen-bonding (thio)urea organocatalysts applicable for a broad spectrum of enantioselective organic reactions; limitations to only very special substrates and to rather similar transformation, respectively, may be acceptable for academic proof-of-principle studies, but will not lead to the broad establishment and maturity of (thio)urea organocatalysis. In conclusion, future research efforts should be driven by the ambitious research goal to develop privileged[4] and innovative (thio)urea organocatalysts, which can actually serve as attractive and powerful alternatives to metal-containing catalysts deserving popularity also in large-scale synthetic organic chemistry.

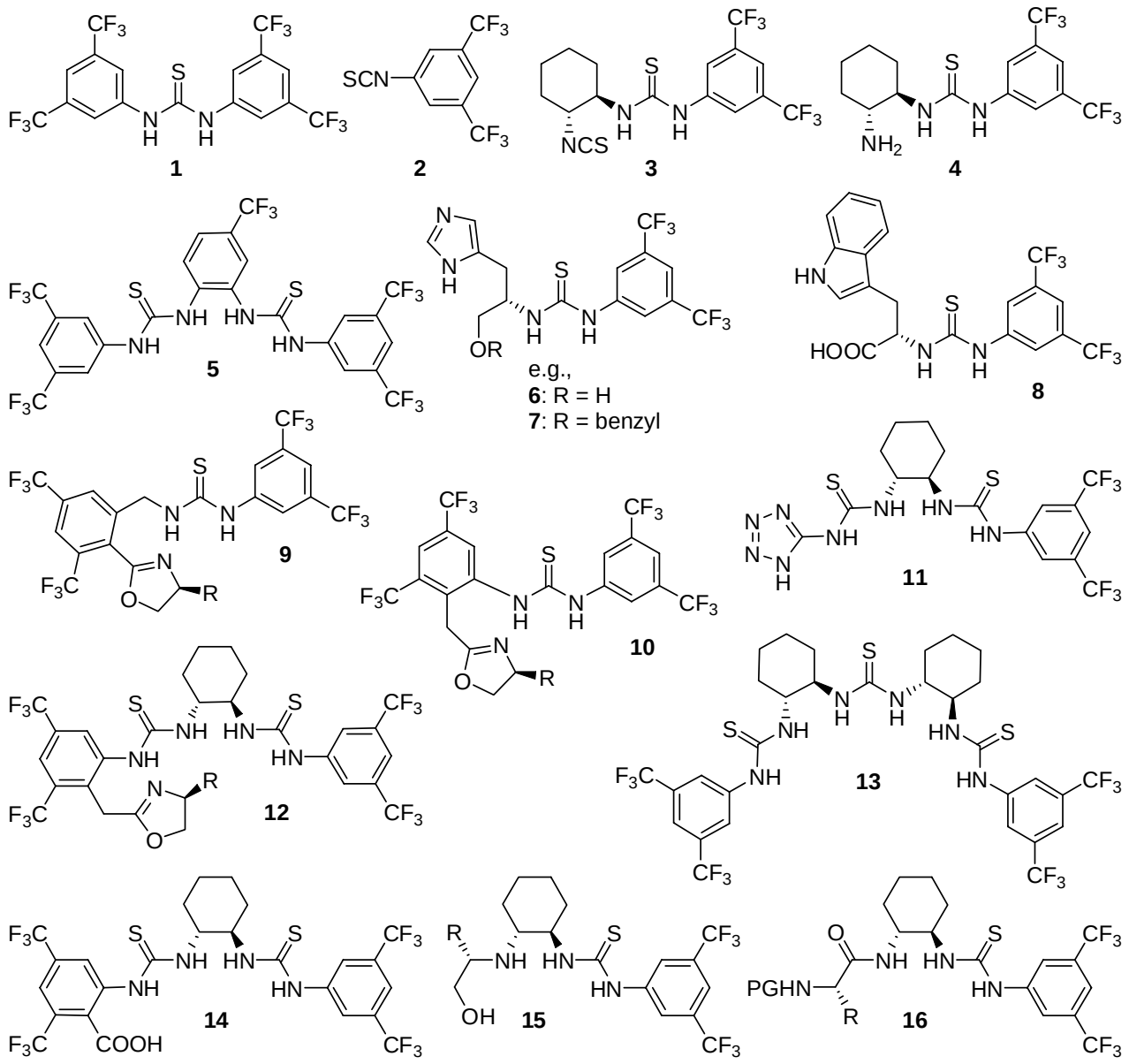
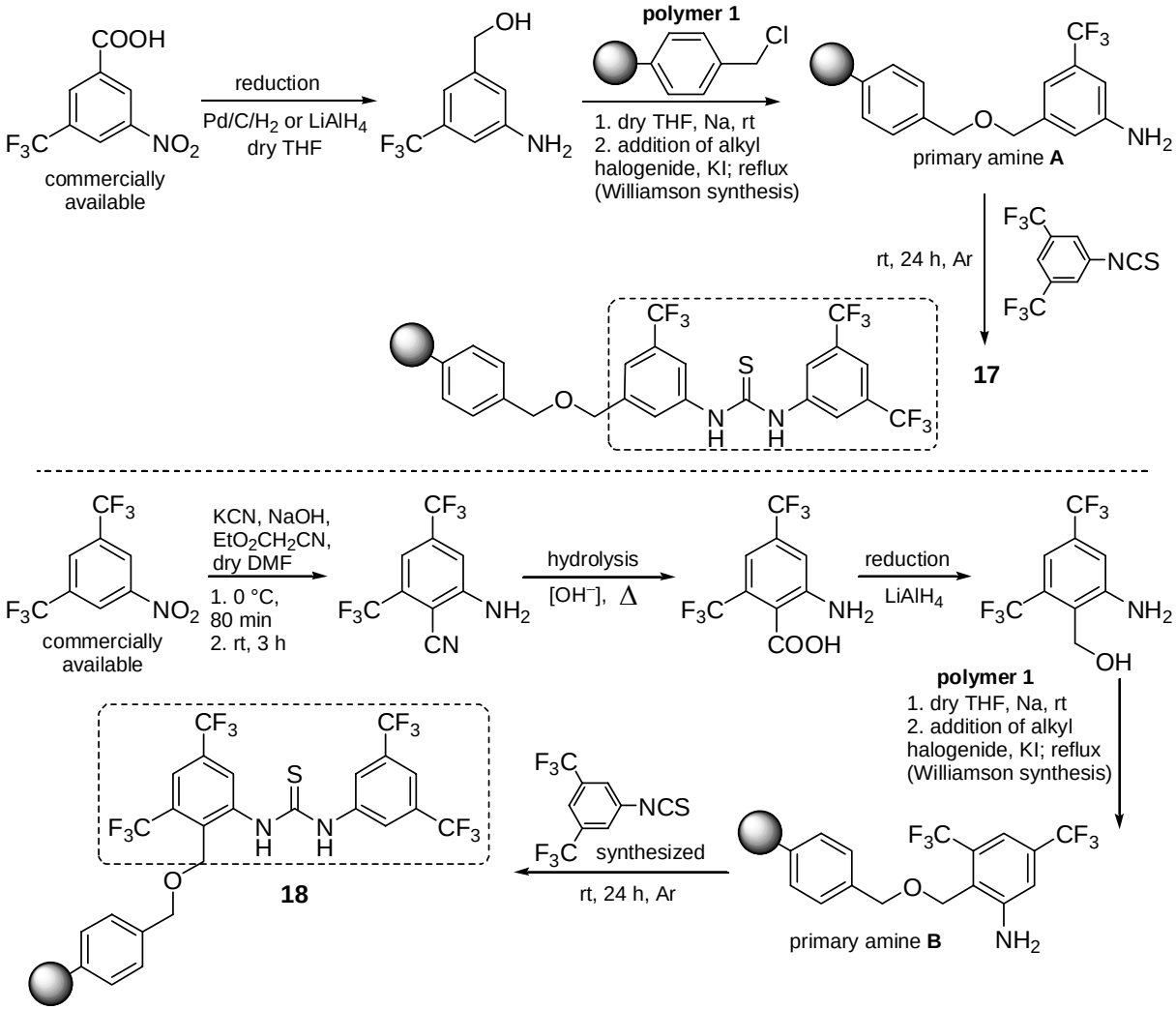


Figure 1. *N*,*N'*-bis[3,5-(trifluoromethyl)phenyl]thiourea catalyst **1**, key building blocks **2**–**4**, and structures of potential hydrogen-bonding thiourea organocatalysts **5**–**16**. An attractive catalyst is characterized by a reasonable compromise between its synthesis and efficiency.

Furthermore, this strategic catalyst design, tailoring, and utilization should be embedded in the discovery of new reaction principles and concepts such as the cooperative organocatalysis.[5] This conceptual approach should be intensified and mark the departure from the early "gold rush days" providing the tool kit for the realization of more sophisticated exploitations and developments leading to innovative and useful catalytic systems. The cooperative Brønsted acid-type organocatalysis introduced for the completely regioselective alcoholysis of styrene oxides (Chapter 2), e.g., utilizes the combination of thiourea derivative **1** and mandelic acid to accelerate the epoxide openings. The individual components, however, proved catalytically inactive

(in contrast to dual catalysis), while the cooperation leads to full conversion at low loadings of only 1 mol% each. This mode of action was rationalized through the formation of an active hydrogen-bonding complex with increased acidity and polarizability capable of catalysis. This novel catalysis concept paves the avenue for employing chiral natural compounds, e.g., amino acids, (carboxylic) acids, or alcohols that can be turned into catalysts by the addition of a simple achiral (thio)urea derivative being individually inactive in the respective reaction. In the other way round, (thio)urea derivatives displaying no or low catalytic efficiency in a reaction can be activated through addition of an adequate cooperating component extending the scope of the individual (thio)urea derivative for catalysis. This strategy of variable individual components that cooperatively match to each other may be utilized for reaction- and/or substrate-specific tuning or modulation (*activity tailoring*), respectively, of the catalytic effect of (thio)urea derivatives such that optimized accelerating effects and enantioinductions are achievable without time-consuming synthetic tailoring of the individual (thio)urea species.



Scheme 1. Polymer functionalization (e.g., SynPhase Lanterns®): Two synthetic pathways affording polymer-bound thiourea derivatives **17** and **18**, which are potentially applicable as heterogeneous hydrogen-bonding organocatalysts. The primary amines **A** and **B** can also be employed for coupling with various isothiocyanates to obtain further catalyst candidates.

Another practical improvement of (thio)urea organocatalysts is realized through catalyst immobilization on a solid support such as polystyrene beads or SynPhase Lanterns®.[6][7] The resulting insoluble polymer-bound organocatalysts (heterogeneous catalysts) offer an increased practicability owing to easy recovery and recycling (e.g., filtration- or centrifugation-washing sequence), facile product isolation, and reusability.[8] Despite these obvious advantages there have been reported only a few synthetically useful polymer-bound (thio)urea organocatalysts, e.g., the polystyrene-bound recyclable thiourea catalyst, which was introduced by Kotke and Schreiner to accelerate the THP protection of hydroxy functionalities (Chapter 2).[9] Chloromethyl (polymer 1) and aminomethyl (polymer 2) functionalized polystyrene beads are inexpensive, commercially available platforms for the attachment of the respective (thio)urea organocatalyst moiety using straightforward addition (coupling) or substitution reactions, respectively. Scheme 1 exemplarily visualizes two synthetic pathways towards the polystyrene-bound achiral thiourea derivatives **17** and **18** incorporating the efficient structure motif of homogeneous organocatalyst **1**. Employing achiral or chiral isothiocyanates such as **2** or **3** the primary amine functionalized intermediates **A** and **B** depicted in Scheme 1 can also be converted to corresponding polymer-bound thiourea derivatives, e. g., **20**, which are potentially applicable for organocatalysis (Figure 2). Additionally, primary amine-terminated polymers (e.g., PIB or P*t*BS) with an inverse temperature-dependent solubility appear to be useful for the synthesis of soluble polymer-bound hydrogen-bonding thiourea catalysts.[10, 11] The thermally reversible solubility of the polymer support should allow homogeneous catalysis at low reaction temperatures suitable for asymmetric catalysis, while heating leads to insolubility of the polymer and the attached catalyst unit, respectively, facilitating recovery and work-up. Under these aspects of synthetic accessibility, variability, and practicability polymer-supported thiourea organocatalysts represent refined catalysts with an increasing importance for

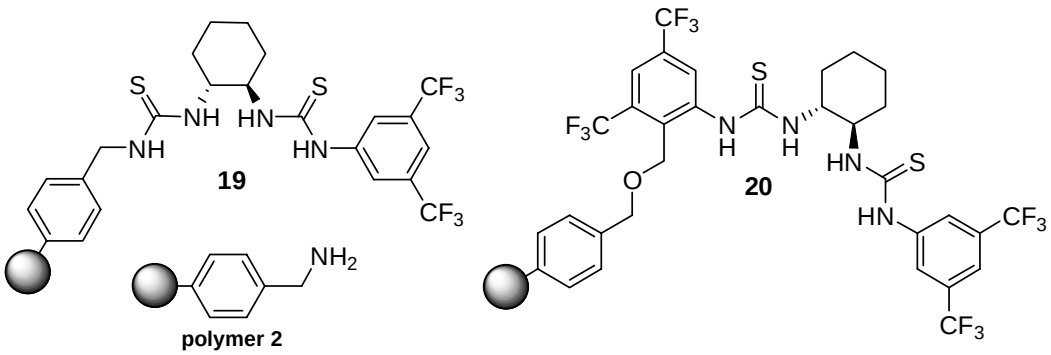


Figure 2. Representative chiral polystyrene-bound thiourea derivatives **19** (from aminomethyl functionalized polystyrene) and **20** (from primary amine **B**; Scheme 1) potentially applicable as enantioselective organocatalysts, e.g., in THP-protection and MBH reactions.

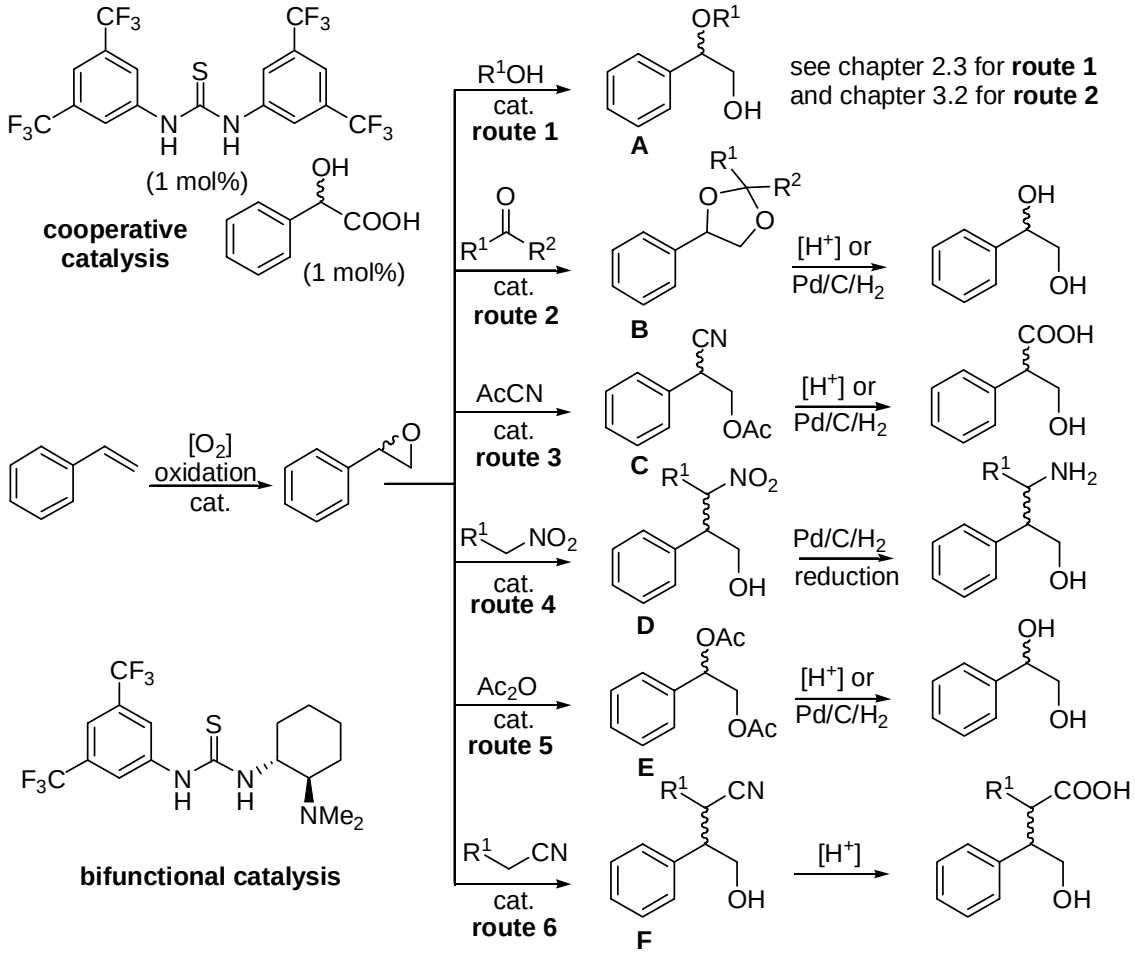
routine implementation. Therefore catalyst immobilization techniques and the development of such catalysts should remain in the focus of future research efforts, e.g., regarding the feasibility of cooperative catalysis with polymer-bound species (e.g., cooperation of polymer-bound derivatives of mandelic acid and thiourea **1**)

5.2 Applications of Hydrogen-bonding (Thio)urea Organocatalysts in Organic Synthesis

As long as a (thio)urea derivative has not been identified to significantly accelerate (referring to the uncatalyzed reference reaction and the TOF) an organic reaction the respective (thio)urea derivative remains in the status "potential catalyst" and is preliminarily useless for catalysis. That means, the synthetic value of a (thio)urea derivative strongly depends on the observed catalytic efficiency and also on both the substrate and the reaction type being activated and catalyzed, respectively. In the face of the self-conception of this PhD thesis really pioneering, innovative, and valuable research results on hydrogen-bonding (thio)urea organocatalysis therefore are not reached with standard reactions (e.g., simple Mannich, Michael and Henry additions), with standard substrates, and findings exclusively aiming at the introduction of only slightly modified catalysts; to actually increase the importance and utility of (thio)urea organocatalysts in organic synthesis in fact *novel* organic reactions should be investigated in systematic proof-of-principle studies revealing the feasibility of an organocatalytic approach. Subsequent optimizations of reaction parameters (reaction apparatus, catalyst, catalyst loading, solvent, temperature, reaction scale, stirring mode, stoichiometry) substrate screening, and reliability studies are essential and have to be performed towards routine laboratory applicability. In these efforts novel (thio)urea derivatives are not always obligatory to disclose novel routes and illuminate attractive perspectives. Depending on the conditions previous "potential catalysts" or even well-known catalysts such as privileged *N*,*N*′-bis[3,5-(trifluoromethyl)phenyl]thiourea (Chapter 1; Section 1.2.1.1) can display an unknown potential and activity providing very encouraging and promising impulses for ambitious and useful research objectives; this strategy is demonstrated, e.g., in the development of the cooperative catalysis concept (Chapter 2.3). This section of the outlook considers both novel substrates and reactions worth to be closely examined for (thio)urea organocatalysis.

5.2.1 Epoxidations and Epoxide Openings

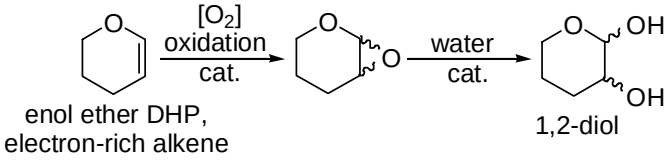
Epoxides have been found to be stronger hydrogen bond acceptors than carbonyl compounds[12, 13] (Chapter 2.3) and are important substrates and target compounds in organic synthesis. Surprisingly, epoxides are underrepresented substrates in (thio)urea organocatalysis, while carbonyl and carbonyl-analogue compounds dominate the typical substrate spectrum (Chapter 1.). The cooperative epoxide alcoholysis suggests that further epoxide openings could be catalyzed employing this novel concept. However, to realize and utilize the full potential of cooperative catalysis for the development of powerful protocols the mechanistic picture has to be elucidated further. An intensified combination of NMR experiments (e.g., titrations, temperature-dependent analyses), IR studies, and chemical computations may explain the interplay between thiourea component **1** and mandelic acid leading to the formation of the catalytically active (binary) complex and may identify the mechanistic origin of the observed high regioselectivity . At this stage preliminary experiments have provide no definite classification of the reaction type, as enantiopure styrene oxide and ethanol reacting under standard alcoholysis conditions give the respective 2-ethoxy-2-phenyl-ethanol in >95% *ee* and with inverted stereochemistry; this finding indicates no racemization expected for a S_N1-type mechanism. Racemic styrene oxide on the other hand does not afford stereochemically enriched products.[14] Scheme 2 depicts potential epoxide openings based on the protocol of the cooperative epoxide alkoholysis (route 1). The 1,3-dioxolane formation (route 2) have already found to be feasible (Chapter 3; Section 3.2) and should be extended to ketone nucleophiles. The proposed transformations employ acetyl cyanide (route 3), CH acidic nitroalkanes (route 4), acetanhydride or alternative less stable anhydrides (e.g., benzoic anhydride) (route 5), and nitriles (route 6) leading to the corresponding adducts **A**–**F**, which can be the target compounds themselves or precursors for further conversions. Applying mild conditions may yield synthetically important building blocks such as β-amino alcohols and β-hydroxy carboxylic acids. The formation of 1,2-diols resulting from route 2 and 6 represents an organocatalytic variant of the Sharpless' catalytic dihydroxylation.[15, 16] Initial proof-of-principle experiments should use styrene oxide as the model substrate and also the conditions developed for the alcoholysis protocol. Route 4, 5, and 6, however, may require the presence of a bifunctional thiourea catalyst for prenucleophile activation (e.g. Takemoto's tertiary amine functionalized thiourea **12**, Chapter 1) and an acylation catalyst (e.g., DMAP, pyridine) may be necessary for the activation of the anhydride in route 5; alternatively, the application of, e.g., catalyst candidate **7** could be successful (Figure 1) without any base additive. Each outlined regioselective epoxide opening may be coupled with an initial epoxidation of the respective alkene starting material such as styrene oxide (Scheme 2; Scheme 3 with DHP as model substrate[17]). The epoxidation step appears to be practicable in the presence of



Scheme 2. Proposals for epoxidation/epoxide opening sequences performed in the presence of (thio)urea organocatalysts; derivatizations of the adducts allow access to various synthetically useful product classes. Each hydroxy functionalized product (except for amino alcohols) can be MOP- or THP-protected. All reactions should be optimized for stereoinduction using conditions properly adjusted to retain induced product configurations (racemization-free conditions).

a single (thio)urea organocatalyst[13] along with an standard oxidizing reagent (DMDO,[17, 18] *t*BuOOH, aq. H_2O_2, *m*-CPBA) or in combination with permandelic acid (cooperative catalysis approach) potentially generated in situ from mandelic acid and H_2O_2.[19] Depending on the catalyst choice and the reaction conditions (catalyst stability, substrate and reagent tolerance) the resulting epoxidation/epoxide opening sequence (domino reaction; cascade reaction)[20] can be optimized for a practical one-pot procedure. Notably, all hydroxy functionalized compounds (expect for amino alcohols) given in Scheme 2 can be THP- or MOP-protected affording the respective THP- and MOP-ether, respectively (Chapter 2.2). In case of *meso*-1,2-diols obtained, e.g., from the opening of stilbene oxide or cyclohexene oxide (route 2 or 5) the organocatalytic THP protection could be applicable for desymmetrizations, when a chiral thiourea catalyst (e.g., catalyst **106** in chapter 1 or catalyst candidate **13**, Figure 1) is employed at reduced temperatures.[21, 22] This option may expand

the envisioned sequence further resulting in an epoxidation/epoxide opening/protection sequence. For example a variety of catalysts and catalyst combinations as well as reaction conditions can be utilized to initially realize non-stereoselective and then also stereoselective epoxide openings. The concept of cooperative catalysis allows combinations of achiral and chiral thiourea derivatives (e.g., **1**, **5**, **13**; Figure 1) with various chiral cooperating components. This may aid to identify the component, which is responsible for stereoinduction and the observed stereochemistry of the product, respectively. In addition to the development of enantioselective epoxidations (e.g., with enantiopure permandelic acid as the epoxidizing agent) and epoxide openings, respectively, the substrate scope should be expanded to aliphatic, internal, and sterically hindered epoxides. Furthermore, the opening of thiiranes and aziridines using adequate nucleophiles and subsequent manipulations of the respective adducts are imaginable as well. In conclusion, Scheme 2 and 3 provides various synthetic perspectives to offer both epoxides and epoxide conversions a more prominent role in the field of (thio)urea organocatalysis.

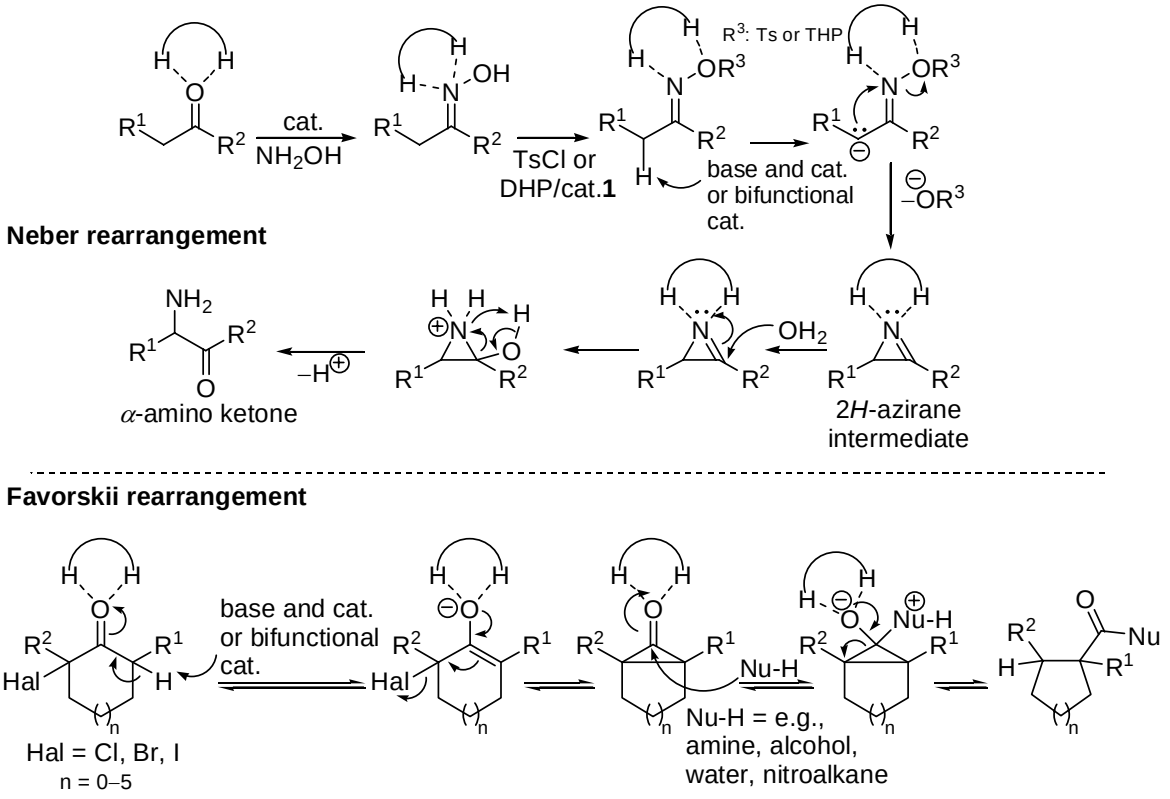


Scheme 3. Enol ether incorporate an electron-rich double bond that should be readily oxidizable with known epoxidizing reagents (see above) in the presence of catalysts suggested for the reactions in scheme 2. Subsequent hydrolysis may lead to the respective 1,2-diols. Alternative nucleophiles (e.g., alcohols, thiols, amines) are applicable. DHP appears to be a suitable model substrate to examine this reaction sequence regarding , e.g., stereochemistry.

5.2.2 Neber and Favorskii Rearrangements

While rearrangements represent elegant, atom-efficient, and widespread transformations in organic synthesis affording the respective target products in high yields and stereocontrol there are only a few examples catalyzed through hydrogen-bonding (thio)urea derivatives (see Chapter 1). Investigations on the Claisen rearrangement[23, 24] and modifications thereof such as the Johnson-Claisen orthoester rearrangement demonstrated that (thio)urea derivatives are inefficient for catalysis under the chosen reaction conditions. This research result may root in the increased reaction temperatures (often >100 °C) required for these rearrangements. Typical Brønsted- and Lewis-acid catalysts tolerate this temperature region and promote the transformations efficiently. Hydrogen-bonding (thio)urea organocatalysts, however, are proposed to behave catalytically inefficient owing to the missing formation of stable explicit hydrogen-bonding interactions with the respective substrate. In general, the successful application of these non-covalent organocatalysts is

predominantly limited to reaction temperatures below 60 °C as evidenced by numerous examples in chapter 1. The Neber[25] and the Favorskii[26] rearrangement are reported to proceed at room temperature and even at 0 °C depending on the substrate structure. Both these rearrangements are induced through protonation of the starting material (Neber: Tosylated ketoximes; Favorsikii: Acyclic or cyclic α-halo ketones) upon treatment with a base, preferably alkoxide or hydroxide, and were found to undergo mechanistically various potential hydrogen bond accepting intermediates, which could be activated or stabilized, respectively, through (bifunctional) hydrogen-bonding (thio)urea organocatalysts (e.g., Takemoto's tertiary amine thiourea; Chapter 1) (Scheme 4). This hypothesis appears to be promising since the Neber rearrangement have already been identified to occur in the presence of an alkaloid[27] or a phase-transfer catalyst;[28] both catalysts were suggested to operate through explicit hydrogen-bonding interactions. Initial experiments could employ catalysts **1** in combination with a base (e.g., DBU, DMAP, pyridine) to evaluate the accelerating effect. Subsequent studies should screen bifunctional (thio)urea derivatives both achiral and chiral under variable conditions to develop enantioselective versions. The tosylation of the Neber ketoxime (R^3 = Ts or THP) could be replaced with an organocatalytic THP-protection (Chapter 2.2) shown in Scheme 4 and even the oxime formation may be feasible organocatalytically, when an adequate water scavenger is applied.



Scheme 4. Mechanism of the Neber and Favorskii rearrangement, respectively, proposed to be catalyzed through double hydrogen-bonding (thio)urea organocatalysts. The clamp symbol stands for the respective catalyst and marks potential hydrogen-bonding interactions.

5.2.3 References and Notes

[1] S. J. Connon, *Synlett* **2009**, *3*, 354–376.
[2] Z. Zhang, P. R. Schreiner, *Chem. Soc. Rev.* **2009**, *38*, 1187–1198.
[3] Thiourea **4** is accessible without protective group chemistry. Notably, e.g., the mono-Boc protection of the diamine suffers from the instability of the thiourea moiety under the subsequent deprotection conditions. See: S. B. Tsogoeva et al., *Eur. J. Org. Chem.* **2005**, 4995–5000 and also B. Procuranti and S. J. Connon, *Chem. Commun.*, **2007**, 1421–1423.
[4] The term "privileged" was coined in analogy of pharmaceutical compound classes that are active against a number of different biological targets. See: T. P. Yoon, E. N. Jacobsen, *Science* **2003**, *299*, 1691–1693.
[5] T. Weil, M. Kotke, C. M. Kleiner, P. R. Schreiner, *Org. Lett.* **2008***, 10*, 1513–1516.
[6] SynPhase Lantern is a registered trademark of Perbio Science.
[7] S. W. Gerritz, M. H. Norman, L. A. Barger, J. Berman, E. C. Bigham, M. J. Bishop, D. H. Drewry, D. T. Garrison, D. Heyer, S. J. Hodson, J. A. Kakel, J. A. Linn, B. E. Marron, S. S. Nanthakumar, I. Navas, F. J., *J. Comb. Chem.* **2003**, *5*, 110–117.
[8] F. Cozzi, *Adv. Synth. Catal.* **2006**, *348*, 1367–1390.
[9] M. Kotke, P. R. Schreiner, Synth*esis* **2007**, *5*, 779–790.
[10] D. E. Bergbreiter, *Chem. Rev.* **2002**, *102*, 3345–3384.
[11] D. E. Bergbreiter, J. Tian, C. Hongfa, *Chem. Rev.* **2009**, *109*, 530–582.
[12] C. M. Kleiner, P. R. Schreiner, *Chem. Commun.* **2006**, 4315–4317.
[13] E. M. Fleming, C. Quigley, I. Rozas, S. J. Connon, *J. Org. Chem.* **2008***, 73*, 948–956.
[14] K. Hof, *Diploma Thesis,* unpublished results, Schreiner group, University Giessen, **2008**.
[15] T. Katsuki, K. B. Sharpless, *J. Am. Chem. Soc.* **1980***, 102*, 5974–5976.
[16] K. B. Sharpless, *Angew. Chem. Int. Ed.* **2002***, 41*, 2024–2032.
[17] S. D. Markad, S. Xia, N. L. Snyder, B. Surana, M. D. Morton, C. M. Hadad, M. W. Peczuh, *J. Org. Chem.* **2008***, 73*, 6341–6354.
[18] S. A. Grabovski, D. V. Kazakov, N. N. Kabalnova, S. L. Khursan, V. V. Shereshovets, *React. Kinet. Catal. Lett.* **1997***, 62, 179–183*.
[19] C. Bonini, G. A. Righi, *Tetrahedron* **2002**, *58*, 4981–5021.
[20] D. Enders, C. Grondal, M. R. M. Hüttl, *Angew. Chem. Int. Ed.* **2007***, 46*, 1570–1581.
[21] E. García-Urdiales, I. Alfonso, V. Gotor, *Chem. Rev.* **2005**, *105*, 313–354.
[22] C. E. Müller, L. Wanka, K. Jewell, P. R. Schreiner, *Angew. Chem. Int. Ed.* **2008***, 47*, 6180–6183.
[23] A. M. M. Castro, *Chem. Rev.* **2004***, 104*, 2939–3002.
[24] M. Kirsten, J. Rehbein, M. Hiersemann, T. Strassner, *J. Org. Chem.* **2007**, *72*, 4001–4011.
[25] F. Palacios, A. M. Ochoa de Retana, E. Martinez de Marigorta, M. de los Santos, *Eur. J. Org. Chem.* **2001**, 2401–2414.
[26] S. Moulay, *Chem. Ed.: Res. Pract. Eur.* **2002**, *3*, 33–64.
[27] M. M. H. Verstappen, G. J. A. Ariaans, B. Zwanenburg, *J. Am. Chem. Soc.* **1996***, 118,* 8491–8492.
[28] T. Ooi, K. Maruoka, *Angew. Chem. Int. Ed.* **2007**, *46*, 4222–4266.

– CHAPTER 6 –

Appendix

The appendix completes the chapters before and provides:

6.1 The **Crystal Structure** of the *N*,*N*′-bis[3,5-(trifluoromethyl)phenyl]thiourea Catalyst,

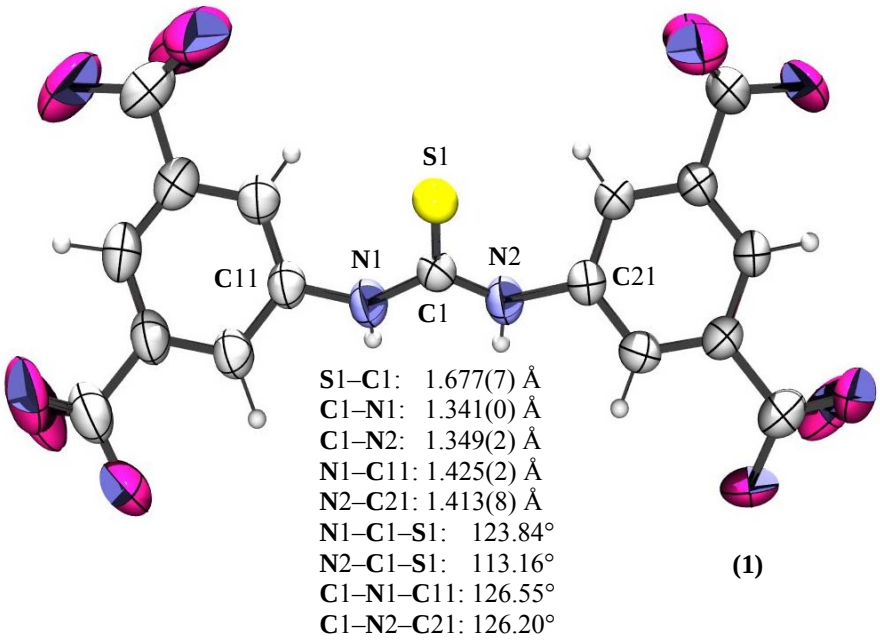
6.2 the **Supporting Information (SI)** of Chapter 2.3:
Cooperative Brønsted Acid-Type Organocatalysis: Alcoholysis of Styrene Oxides,

6.3 the **(Thio)urea Structure Index**,

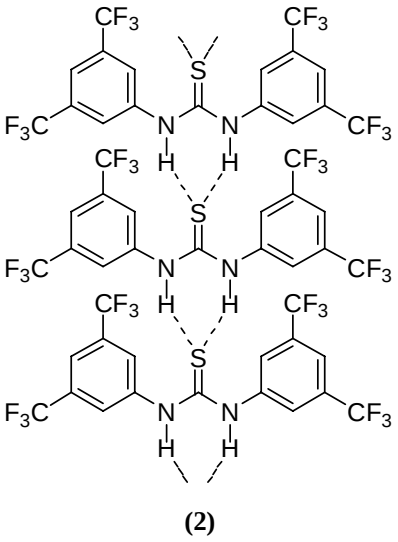
and

6.4 the list of **Abbreviations and Acronyms**

6.1 Crystal Structure of *N*,*N*′-bis[3,5-(trifluoromethyl)phenyl]thiourea Catalyst



(1)



(2)

Figure 1. **(1)** The crystal structure of *N*,*N*′-bis[3,5-(trifluoromethyl)phenyl]thiourea catalyst with selected bond lengths and angles; *syn* orientation of the NH protons (*trans*/*trans* rotamer). **(2)** Intermolecular double hydrogen-bonding interactions lead to the found layer crystal structure.

Table 1. Crystallographic key data of *N*,*N*′-bis[3,5-(trifluoromethyl)phenyl]thiourea. The structure was deposited as 1,3-bis(3,5-bis(trifluoromethyl)phenyl)thiourea (alternative IUPAC name) in the Cambridge Crystallographic Data Center (CCDC 206506) and can be retrieved from there.

Empirical formula	$C_{17}H_8F_{12}N_2S_1$
Formula weight; M [g mol^{-1}]	500.31
Habitus	needle crystal
Color	colorless
Melting point [K]	471–472
Crystal system	monoclinic
Space group	$P2_1/c$ (symmetry int. tables no.14)
Unit cell dimensions:	a = 15.178 Å α = 90°
	b = 8.2203 Å β =112.495°
	c = 17.399 Å γ = 90°
Volume; V [Å^3]	2005.66(1)
Formula units/cell; Z	4
F(000)	248
T [K]	298
ρ_{calcd} [g cm^{-3}]	1.657
$2\theta_{max}$ [°]	55.0
Reflections collected	17894
Unique reflections	4462
Number of parameters	430
R_1 [I>2σ(I)]	0.0981
wR_2 [I>2σ(I)]	0.1934
R-factor [%]	7.03
Goodness of fit on F^2	0.923
Residual electron density [e/Å^3]	0.06
Largest diff. peak and hole [e/Å^3]	1.54 and –0.28

6.1.1 Crystal Growth and X-ray Crystallography

N,*N*′-bis[3,5-(trifluoromethyl)phenyl]thiourea is highly soluble in ethers such as diethylether or tetrahydrofurane, but shows a low solubility in *n*-hexane. This fact was utilized to grow crystals of this thiourea derivative. In a standard test-tube a diluted solution of the analytically pure thiourea (~300 mg) in diethylether (~5 mL) was prepared and the same volume of *n*-hexane was slowly added via a syringe.[1] The resulting two-phase mixture was allowed to stay at ~25 °C in the test-tube sealed with Parafilm® until needle-shaped, colorless crystals were formed owing to the increasing evaporation of the ether (~4 days). A single crystal suitable for crystal X-ray diffraction was selectecd with a microscope and was positioned inside of a glass capillary. The X-ray crystallographic data were collected at room temperature on a STOE IPDS-diffractometer using Mo-K_α radiation (λ= 0.71069 Å) and the φ-oscillation mode. The structure solution employed Direct Methods in SHELXS-97;[2] structure refinement was achieved by full-matrix least squares using the program SHELXL-97.[2-4] The final crystal structure of this thiourea catalyst was visualized with the programs ORTEP-3 and POV-Ray.[5]

6.1.2 References and Notes

[1] Prior to use diethylether and *n*-hexane were dried according to established literature procedures.
[2] G. M. Sheldrick, *Acta Cryst.* **2008**, *A64*, 112–122.
[3] The SHELX-97 Homepage: http://shelx.uni-ac.gwdg.de/SHELX/
[4] The structure solution and refinement were performed by Ansgar Dülmer, formerly a member of the Institute of Inorganic Chemistry at the Justus-Liebig University, Giessen/Germany. His friendly support is highly acknowledged.
[5] The structure was deposited as 1,3-bis(3,5-bis(trifluoromethyl)phenyl)thiourea in the Cambridge Crystallographic Data Center (CCDC 206506) and can be retrieved from there. The structure have been published: a) Poster presentation at "Winter School on Organic Chemistry-WISOR", January **2003**, Bressanone/Italy; b) P. R. Schreiner, *Chem. Soc. Rev.*, **2003**, *32*, 289–296; c) P. R. Schreiner, A. A. Fokin, M. Kotke, T. Weil, *Ann. Polish Chem. Soc.* **2004**, *3*, 21–24.

6.2 Supporting Information of Chapter 2.3

Cooperative Brønsted Acid-Type Organocatalysis: Alcoholysis of Styrene Oxides

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1. General Experimental Details

All chemicals were purchased from Aldrich, Acros Organics, Alfa Aesar, Merck, and Lancaster in the highest purity available and were used without further purification unless otherwise noted. Liquid epoxides were distilled once over a 10 cm Vigreux column and stored until use in Schlenk tubes under an argon atmosphere at 8° C in a fridge. All carboxylic acids were used as purchased without further purification. All solvents used for extractions or filtrations were distilled once with a rotary evaporator. Drying followed established literature procedures: THF, *n*-hexane, and toluene were freshly distilled from Na/benzophenone ketyl; EtOH (Na/diethyl phthalate, reflux); PrOH, *i*-PrOH, BuOH (distilled once, 20 cm Vigreux column), and acetonitrile (5 h refluxed over P_2O_5 and distilled once over 30 cm column filled with Raschig rings). All dry chemicals were stored under an argon atmosphere and over activated 3 Å molecular sieve (MS) (alcohols and acetonitrile) and Na wire (THF, *n*-hexane, toluene), respectively: *t*-BuOH, allyl alcohol and BnOH were stored over MS 3 Å without prior distillation; $CDCl_3$ (99.8%, purchased from Deutero GmbH) was stored over MS 4 Å. TLC was carried out on pre-coated Macherey-Nagel plastic sheets Polygram SiO_2 N/UV254 (40–80 mm) using UV light for visualization. The progress of reactions was monitored by GC-MS analyses with a Quadrupol-MS HP MSD 5971(EI) and HP 5890A GC equipped with a J & W Scientific fused silica GC column (30 m × 0.250 mm, 0.25 micron DB–5MS stationary phase: 5% phenyl and 95% methyl silicone) using He (4.6 grade) as carrier gas; T-program standard 60–250 °C (15 °C/min heating rate), injector and transfer line 250 °C. ^{1}H and ^{13}C NMR spectra were recorded with Bruker spectrometer Avance II 200 Hz (AV 200) and Avance II 400 MHz (AV 400) using as the internal standard: TMS d(^{1}H) = 0.00, d(^{13}C) = 0.0; $CHCl_3$ [d(^{1}H) = 7.26], $CHCl_3$ [d(^{13}C) = 77.0]; ^{13}C-NMR signals were assigned with DEPT or APT (attached proton test) experiments. IR spectra were measured with Bruker IFS25 and IFS48 spectrophotometers. HRMS were recorded with a Sectorfield-MS: Finnigan MAT 95, CHN analyses were obtained with a Carlo Erba 1106 (balance: Mettler Toledo UMX-2) analyzer. To keep reaction temperature constant a standard mercury contact thermometer controlled by an IKAMAG RET-GS hot plate-stirrer was used. All analytical reaction mixtures were prepared in clean oven-dried one-necked 10 mL (5 mmol scale experiments) standard glass flasks (Schott DURAN) tightly sealed with a plastic plug. For experiments at 50 °C, reaction flasks were sealed with a clamped glass plug and were placed in a tempered oil bath (50 °C). For each test reaction thiourea derivative **3** and carboxylic acid **5a** or **5b-l**, respectively, were directly weighed out into the reaction flasks; liquid epoxides (5 mmol) were added via syringe (1 mL) and were dissolved in excess

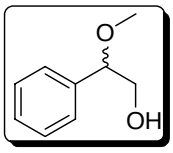
of alcohol (60 mmol). The quantity of additives (thiourea derivative **3** and carboxylic acid **5a-l**.) refers to the epoxide quantity that determines the scale of the experiment. If not otherwise noted all experiments were run in homogeneous solutions. For stirring, standard Teflon-coated magnetic stirring bars (1 to 1.5 cm) were used. Reaction temperature (25 or 50 °C) is given in Table 1. To determine the catalytic efficiency, all experiments were accompanied by parallel reference experiments under identical conditions, but without **3** or **5a-l** respectively. Sample volumes (~0.2 μL) were taken directly from the stirred reaction mixture via 10 μL Hamilton syringe and were injected immediately to record the GC-MS chromatogram. The course of each epoxide opening reaction was monitored by integrating the starting material and product signal; time-dependent conversion as a percentage was determined from the integral ratio of starting material and product signal. After completion of the reaction as confirmed by GC-MS, work-up followed according to the procedures described below.

All *ß*-alkoxy alcohols **4a-r** (see Table 1 in the article; Chapter 2) were isolated, purified, and characterized by ^{1}H and ^{13}C NMR, IR, and MS spectroscopy. New compounds are fully characterized and their data are listed below:

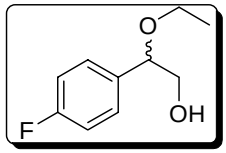
Representative protocol for alcoholysis of styrene oxides (1a-c):

Mandelic acid **5a** (7.6 mg, 0.05 mmol, 1 mol % loading) and thiourea derivative **3** (25 mg, 0.05 mmol, 1 mol % loading) were weighed out into an oven-dried, one-necked, 10 mL flask. After addition of styrene oxide **1a** (0.57 mL, 5 mmol) and dry ethanol (3.52 mL, 60 mmol) via a syringe the reaction flask was sealed with a plastic plug and the reaction solution was vigorously stirred with a magnetic stirring bar (1.5 cm) at room temperature. After full conversion (22 h, GC-MS analysis, see Table 1; Chapter 2) excess of ethanol was evaporated in vacuo and the crude product (yellow oil) was subjected to fractionated vacuum distillation over a 5 cm Vigreux column affording analytically pure *ß*-alkoxy alcohol (*ß*-ethoxy phenyl ethanol) **4b** (715 mg, 4.3 mmol, 86%, b.p. 52−54 °C/~0.1 torr); physical data were consistent with those reported in literature.

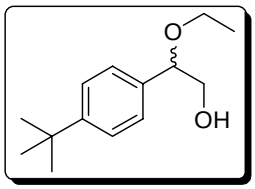
2. Representative and new compounds:



***rac*-2-Methoxy-2-phenyl-ethanol (4a)[1]:** High vacuum distillation of the crude residue afforded 646 mg of **4a** (4.25 mmol, 85 %) as colorless liquid, b.p.: 48−49 °C/~0.1 torr. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.41−7.30 (5H, m), 4.39−4.32 (1H, dd, *J* = 12.1, 8.0 Hz), 3.80−3.58 (2H, m), 3.34 (3H, s), 3.15−3.09 (1H, dd, *J* = 12.6 Hz, 8.3 Hz). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 138.4, 128.5, 128.1, 126.9, 84.9, 67.3, 56.9. **IR** (cm^{-1}): 3415 (br), 2930 (m), 2871 (m), 2824 (m), 1452 (m), 1109 (s), 1061 (s), 1025 (s), 756 (s), 700 (vs), 636 (m). **LRMS** {EI, 70 eV, m/z (%)}: 152 (1), 122 (15), 121 (100), 105 (9), 91 (29), 77 (34), 65 (3), 51 (5). **HRMS** (M^+, $C_9H_{12}O_2$): calcd.: 152.0837, found: 152.0834.

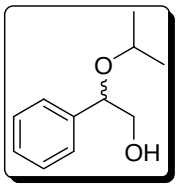


***rac*-2-Ethoxy-2-(4-fluorophenyl)-ethanol (4c, new compound):** High vacuum distillation of the crude residue furnished 526 mg of **4c** (2.85 mmol, 57 %) as slightly yellowish oil, b.p.: 53−57 °C/~0,1 torr. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.32−7.25 (2H, m), 7.08−7.00 (2H, m), 4.39 (1H, dd, *J* = 8.29 Hz, 3.99 Hz), 3.67−3.53 (2H, m), 3.52−3.35 (2H, m), 2.46 (1H, s, br, OH), 1.21 (3H, t, *J* = 14.07 Hz, 7.02 Hz). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 162.5 (d, *J* = –245.9 Hz), 134.8 (d, *J* = 3.0 Hz), 128.4 (d, *J* = 8.07 Hz), 115.4 (d, *J* = 21.8 Hz), 82.0, 67.3, 64.5, 15.3. **IR** (cm^{-1}): 3437.2 (br), 3070.5 (w), 2976.4 (s), 2930.3 (m), 2873.5 (s), 1896.1 (w), 1725.3 (w), 1685.0 (w), 1652.8 (w), 1604.7 (s), 1510.3 (vs), 1484.1 (m), 1445.3 (m), 1399.5 (s), 1370.5 (m), 1339.7 (m), 1296.2 (m), 1278.5 (m), 1225.3 (vs), 1190.3 (m), 1157.0 (s), 1106.3 (vs), 1071.1 (vs), 1047.7 (s), 1014.7 (m), 931.9 (m), 867.6 (s), 835.7 (vs). **HRMS:** calcd.: 184.0899, found: 184.0898.

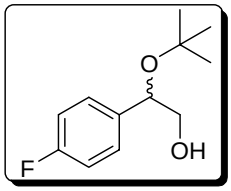


***rac*-2-Ethoxy-2-(4-*tert*-butylphenyl)-ethanol (4d, new compound):** High vacuum distillation of the crude residue afforded 722 mg of **4d** (3.25 mmol, 65 %) as colorless liquid, b.p.: 78−82 °C/~0.1 torr. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.29 (2H, d, *J* = 8.40 Hz), 7.16 (2H, d, *J* = 8.40 Hz), 4.32 (1H, dd, *J* = 8.45 Hz, 4.01 Hz), 3.63−3.48 (2H, m), 3.47−3.38 (1H, m), 3.36−3.26 (1H, m), 2.62 (1H, s, br, OH), 1.24 (9H, s), 1.14 (3H, t, *J* = 14.02 Hz, 7.02 Hz). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 150.9, 135.9, 126.5, 125.4, 82.5, 67.4, 64.4, 34.6, 31.4, 15.3. **IR** (cm^{-1}): 3441.1 (br), 3055.6 (w), 3027.2 (w), 2965.3 (vs), 2903.7 (s), 2869.3 (vs), 1910.1 (w), 1614.7 (w), 1509.9 (m), 1463.6 (m), 1397.2 (s), 1363.5 (m), 1340.8 (m), 1308.9

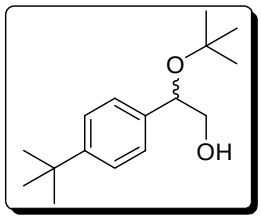
(m), 1270.0 (m), 1226.3 (m), 1202.9 (m), 1158.4 (m), 1119.7 (s), 1097.9 (vs), 1071.4 (s), 1047.8 (s), 933.1 (m), 867.3 (m), 831.2 (s). **HRMS:** calcd.: 222.1619, found: 222.1587.



***rac*-2-Isopropoxy-2-phenyl-ethanol (4e):**[2] High vacuum distillation of the crude residue yielded 658 mg of **4e** (3.65 mmol, 73 %) as colorless liquid, b.p.: 48 °C/~0.1 torr. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.25−7.14 (5H, m), 4.44−4.41 (1H, dd, *J* = 12.4 Hz, 8.4 Hz), 3.55−3.42 (3H, m), 2.76 (1H, s, br, OH), 1.10−1.08 (3H, d, *J* = 6 Hz), 1.03−1.01 (3H, d, *J* = 6.2 Hz). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 139.8, 128.4, 127.9, 126.9, 80.1, 69.5, 67.5, 23.5, 21.3. **IR** (cm^{-1}): 3426 (br), 2969 (m), 1452 (m), 1378 (m), 1123 (m), 1090 (s), 1055 (s), 969 (m), 756 (s), 700 (vs). **LRMS** {EI, 70 eV, m/z (%)}: 181 (1), 180 (5), 162 (4), 149 (49), 121 (8), 107 (100), 91 (12), 79 (49), 77 (17), 51 (5). **HRMS** (M-CH_2=OH^+, $C_{10}H_{13}O$): calcd.: 149.0961, found: 149.0970.

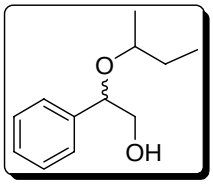


***rac*-2-*tert*-Butoxy-2-(4-fluorophenyl)-ethanol (4g, new compound):** High vacuum distillation of the crude residue afforded 610 mg of **4g** (2.85 mmol, 57 %) as colorless liquid, b.p.: 55 °C/~0.1 torr. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.34−7.28 (2H, m), 7.04–6.97 (2H, m), 4.59 (1H, dd, *J* = 8.45 Hz, 4.27 Hz), 3.54−3.40 (2H, m), 2.10 (1H, s, br, OH), 1.16 (9H, s). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 162.3 (d, *J* = –245.18 Hz), 138.0 (d, *J* = 2.95 Hz), 127.9, 127.8, 115.2, 115.0, 75.0, 74.5, 67.9 (diastereotopic), 67.8 (diastereotopic), 28.8. **IR** (cm^{-1}): 3439.5 (br), 3070.4 (w), 2975.8 (vs), 2903.7 (s), 2871.6 (m), 1892.7 (w), 1766.7 (w), 1726.8 (w), 1650.3 (w), 1605.7 (s), 1509.2 (vs), 1472.4 (m), 1462.4 (m), 1461.1 (m), 1391.6 (s), 1367.2 (s), 1295.8 (w), 1254.9 (m), 1223.0 (vs), 1192.8 (vs), 1155.3 (s), 1084.6 (vs), 1069.8 (vs), 953.9 (s), 864.1 (s), 834.3 (vs). **HRMS** ($C_{12}H_{17}FO_2$): calcd.: 212.1212, found: 212.1200.

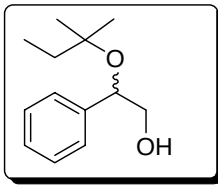


***rac*-2-*tert*-Butoxy-2-(4-*tert*-butylphenyl)-ethanol (4h, new compound):** High vacuum distillation of the crude residue afforded 810 mg of **4h** (3.25 mmol, 65 %) as colorless solid, b.p.: 62−67 °C/ ~0.1 torr. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.25 (2H, d, *J* = 8.33 Hz), 7.18 (2H, d, *J* = 8.33 Hz), 4.52 (1H, dd, *J* = 8.40 Hz, 4.52 Hz), 3.48−3.36 (2H, m), 2.18 (1H, s, br, OH), 1.24 (9H, s), 1.10 (9H, s). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 150.2, 139.0, 126.0, 125.1, 74.9, 74.8, 67.9, 34.5, 31.4, 28.8. **IR** (cm^{-1}): 3393.6 (br), 3087.5 (w), 3056.8 (w), 2966.0 (s), 2921.7 (s), 2869.0 (m), 2797.2 (w), 2740.7 (w), 1913.4 (w), 1726.7 (w), 1508.1 (m), 1470.3 (m), 1407.5 (m), 1389.7 (m), 1377.9 (m), 1365.9

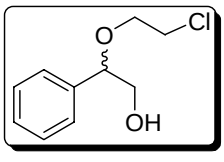
(s), 1342.2 (m), 1314.5 (w), 1259.9 (m), 1236.3 (m), 1192.9 (m), 1185.8 (m), 1106.6 (m), 1083.5 (vs), 1072.3 (vs), 1051.4 (s), 1016.6 (m), 957.4 (m), 862.6 (m), 828.1 (s). **HRMS** ($C_{16}H_{26}O_2$): calcd.: 250.1933, found: 250.1930.



***rac*-2-sec-Butoxy-2-phenyl-ethanol (4i, new compound):** High vacuum distillation of the crude residue gave 931 mg of **4i** (4.70 mmol, 94 %) as colorless liquid, b.p.: 64 °C/~0.1 torr. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.37−7.27 (5H, m), 4.57–4.51 (1H, m), 3.68−3.56 (2H, m), 3.46−3.41 (1H, m), 3.37−3.32 (1H, m), 2.66 (1H, s, br, OH), 1.70−1.38 (2H, m), 1.18−1.17 (1.5H, d, *J* =6 Hz), 1.07–1.05 (1.5H, d, *J* = 6 Hz), 0.95−0.90 (1.5H, t, *J* = 15 Hz, 7.5 Hz), 0.87–0.83 (1.5H, t, *J* = 15 Hz, 7.5 Hz). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 140.0, 128.4, 127.2, 126.9, 80.7, 79.6, 75.1, 73.9, 67.6, 67.4, 30.3, 28.3, 20.4, 18.7, 10.1, 9.4. **IR** (cm^{-1}): 3442 (br), 2967 (vs), 2931 (s), 2877 (s), 1492 (m), 1453 (s), 1379 (m), 1092 (vs), 1059 (vs), 757 (s), 701 (vs). **LRMS** {EI, 70 eV, m/z (%)}: 194 (0.04), 163 (30), 121 (17), 107 (100), 91 (9), 79 (24), 77 (10), 65 (2), 57 (5), 51 (3). **HRMS** (M-CH_2=OH^+, $C_{11}H_{15}O$): calcd.: 163.1127, found: 163.1128.

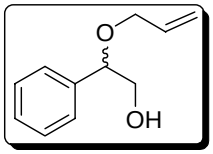


***rac*-2-(1,1-Dimethyl-propoxy)-2-phenyl-ethanol (4j, new compound):** High vacuum distillation of the reaction mixture furnished 760 mg of **4m** (3.65 mmol, 73 %) as colorless liquid, which became a white solid at ambient pressure; b.p.: 101 °C/~0.1 torr. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.27−7.13 (5H, m), 4.49 (1H, t, *J* = 12.54 Hz, 6.27 Hz), 3.39 (2H, d, *J* = 6.27 Hz), 2.89 (1H, br, s), 1.41 (2H, m), 1.02 (3H, s), 0.89 (3H, s), 0.77 (3H, t, *J* = 15.01 Hz, 7.51 Hz). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 142.6, 128.2, 127.4, 126.6, 77.2, 74.9, 67.9, 34.9, 29.3, 25.8, 8.7. **IR** (cm^{-1}): 3311.5 (br), 3061.6 (s), 3030.0 (s), 2965.6 (s), 2931.2 (s), 2879.3 (s), 2363.7 (w), 2337.7 (w), 1958.9 (w), 1895.1 (w), 1878.6 (w), 1808.8 (w), 1603.5 (m), 1504.4 (w), 1494.5 (s), 1451.1 (vs), 1386.6 (m), 1366.5 (m), 1350.5 (m), 1313.3 (m), 1228.2 (m), 1195.2 (m), 1177.1 (m), 1134.4 (m), 1088.4 (s), 1056.8 (s), 1026.7 (s), 1000.7 /m), 914.0 (m), 896.5 (m), 833.5 (m), 758.8 (s), 700.4 (s). **HRMS:** calcd.: 208.1463, found 208.1465.

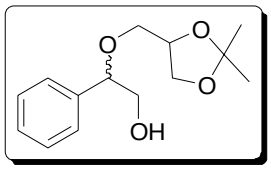


***rac*-2-(2-Chloro-ethoxy)-2-phenyl-ethanol (4k, new compound):** High vacuum distillation of the crude residue afforded 892 mg of **4j** (4.45 mmol, 89 %) as colorless liquid, b.p.: 82 °C/~0.1 torr. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.39−7.29 (5H, m), 4.49−4.46 (1H, dd, *J* = 12.3 Hz, 8.7 Hz), 3.75−3.59 (6H, m), 2.59 (1H, s, br, OH). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 138.0, 128.7, 128.4, 126.8,

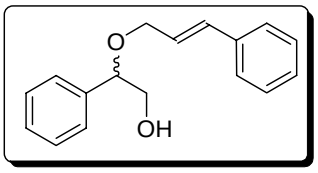
83.6, 69.1, 67.4, 43.2. **IR** (cm^{-1}): 3439 (br), 2872 (m), 1493 (m), 1453 (m), 1116 (vs), 1046 (s), 759 (s), 702 (vs). **LRMS** {EI, 70 eV, m/z (%)}: 200 (0.2), 171 (35), 169 (100), 121 (6), 107 (29), 105 (18), 91 (8), 84 (16), 79 (21), 77 (14), 65 (9), 63 (29), 51 (4). **HRMS** (M-CH_2=OH^+, $C_9H_{10}ClO$): calcd.: 169.0424, found: 169.0434



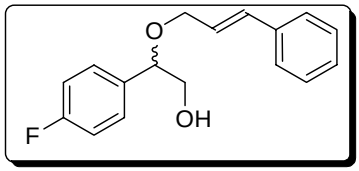
***rac*-2-Allyloxy-2-phenyl-ethanol (4l)[2]:** High vacuum distillation of the crude residue afforded 712 mg of **4k** (4.0 mmol, 80 %) as colorless liquid, b.p.: 56−57 °C/~0.1 torr. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.44−7.29 (5H, m), 6.01−5.91 (1H, m), 5.32−5.31 (0.5H, q, *J* = 4.9 Hz, 3.3 Hz), 5.28−5.27 (0.5H, q, *J* = 4.9 Hz, 3.3 Hz), 5.22−5.21 (0.5H, q, *J* = 4.2 Hz, 2.9 Hz), 5.18−5.17 (0.5H, q, *J* = 4.2 Hz, 2.8 Hz), 4.54−4.51 (1H, dd, *J* = 8.4 Hz, 3.8 Hz), 4.07−4.06 (0.25H, t, *J* =12.8 Hz, 6.2 Hz, 5.2 Hz, 1.5 Hz), 4.06−4.05 (0.25H, t, *J* = 12.8 Hz, 6.2 Hz, 5.2 Hz, 1.5 Hz), 4.04−4.03 (0.25H, t, *J* = 12.8 Hz, 6.2 Hz, 5.2 Hz, 1.5 Hz), 4.03−4.02 (0.25H, t, *J* = 12.8 Hz, 6.2 Hz, 5.2 Hz, 1.5 Hz), 3.92−3.91 (0.25H, t, *J* = 12.8 Hz, 6.2 Hz, 5.2 Hz, 1.3 Hz), 3.90−3.89 (0.25H, t, *J* = 12.8 Hz, 6.2 Hz, 5.2 Hz, 1.3 Hz), 3.89−3.88 (0.25H, t, *J* = 12.8 Hz, 6.2 Hz, 5.2 Hz, 1.3 Hz), 3.87−3.86 (0.25H, t, *J* = 12.8 Hz, 6.2 Hz, 5.2 Hz, 1.3 Hz), 3.78−3.73 (1H, dd, *J* = 11.8 Hz, 8.4 Hz), 3.67−3.62 (1H, dd, *J* = 11.8 Hz, 3.8 Hz), 3.02 (1H, s, br, OH). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 138.7, 134.6, 128.5, 128.1, 126.9, 117.2, 82.3, 69.8, 67.3. **IR** (cm^{-1}): 3405 (br), 2863 (m), 1492 (m), 1451 (m), 1343 (m), 1097 (s), 1040 (vs), 1027 (vs), 922 (s), 756 (s), 699 (vs). **LRMS** {EI, 70 eV, m/z (%)}: 178 (0.4), 148 (9), 147 (100), 121 (8), 105 (72), 91 (55), 79 (10), 77 (27), 65 (5), 51 (8), 41 (80). **HRMS:** (M-CH_2=OH^+, $C_{10}H_{11}O$): calcd.: 147.0810, found: 147.0803.



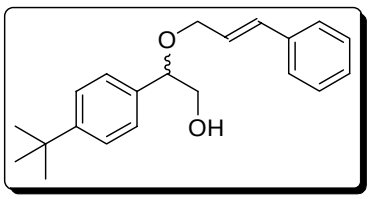
***rac*-2-(2,2-Dimethyl-[1,3]dioxolan-4-ylmethoxy)-2-phenyl-ethanol (4n [1:1 mixture of diastereomers], new compound)**: High vacuum distillation of the crude residue afforded 521 mg of **4n** (2.05 mmol, 41 %) as colorless oil, b.p.: 115−118 °C/~0.5 torr. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.41−7.27 (5H, m), 4.47 (1H, m), 4.37−4.26 (1H, m), 4.08−4.01 (1H, m), 3.83−3.39 (5H, m), 2.42 (1H, s, br, OH), 1.41 (3H, s), 1.36 (3H, s). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 138.3, 138.2, 128.6, 128.5, 128.3, 128.2, 126.8, 109.6, 109.5, 84.1, 83.8, 74.9, 74.7, 70.9, 69.9, 67.4, 66.7, 66.4, 26.7, 26.6, 25.3, 25.2. **IR** (cm^{-1}): 3454.3 (br), 3029.5 (w), 2985.7 (s), 2933.3 (s), 2872.6 (m), 1493.1 (m), 1453.1 (m), 1380.8 (s), 1371.0 (s), 1277.7 (m), 1256.0 (m), 1214.2 (s), 1157.1 (m), 1112.5 (s), 1053.6 (vs), 843.3, (m), 758.5 (m), 702.0 (m). **HRMS** (M-CH_2=OH^+, $C_{13}H_{17}O_3$): calcd.: 221.1172, found: 221.1176.



***rac*-2-Phenyl-2-(3-phenyl-allyloxy)-ethanol (4o, new compound):** High vacuum distillation of the crude residue yielded 833 mg of **4o** (3.27 mmol, 65 %) as colorless oil, b.p.: 155 °C/ ~0.3 torr. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.36−7.15 (10H, m), 6.50 (1H, d, *J* = 15.67 Hz), 6.21 (1H, m), 4.48 (1H, dd, *J* = 8.64 Hz, 3.79 Hz), 4.11 (1H, dd, *J* = 12.55 Hz, 5.59 Hz), 3.96 (1H, dd, *J* = 12.61 Hz, 6.67 Hz), 3.67 (1H, dd, *J* = 11.85 Hz, 8.54 Hz), 3.58 (1H, dd, *J* = 11.85 Hz, 3.77 Hz), 2.24 (1H, br, s, OH). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 138.5, 136.6, 132.7, 131.2, 128.6, 128.2, 127.7, 126.9, 126.5, 125.7, 82.2, 69.5, 63.8. **IR** (cm^{-1}): 3385.4 (br), 3083.6 (m), 3061.8 (m), 3029.0 (m), 2924.9 (m), 2872.3 (m), 1953.7 (w), 1883.6, (w), 1811.3 (w), 1719.0 (m), 1675.8 (m), 1625.3 (w), 1601.8 (w), 1577.3 (w), 1559.5 (w), 1540.5 (w), 1494.7 (s), 1452.2 (s), 1395.7 (m), 1347.0 (m), 1308.6 (m), 1278.2 (m), 1197.7 (m), 1132.5 (m), 1093.3 (s), 1069.3 (s), 1027.3 (s), 968.5 (m), 914.8 (w), 889.5 (w), 835.1 (w), 751.2 (s), 700.4 (vs). **HRMS:** calcd.: 254.1307, found: 254.1317.

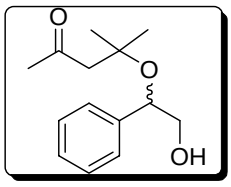


***rac*-2-(4-Fluor-phenyl)-2-(3-phenyl-allyloxy)-ethanol (4p, new compound).** High vacuum distillation of the crude residue yielded 858 mg of **4p** (3.15 mmol, 63 %) as colorless oil, b.p.: ~152 °C/~0.3torr. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.32−7.14 (7H, m), 6.92−7.02 (2H, m), 6.47 1H, d, *J* = 15.81 Hz), 6.19 (1H, m), 4.44 (1H, dd, *J* = 8.34 Hz, 3.73 Hz), 4.07 (1H, dd, *J* = 12.55, 5.69 Hz), 3.93 (1H, dd, *J* = 12.55 Hz, 6.62 Hz), 3.63 (1H, dd, *J* = 11.84 Hz, 8.39 Hz), 3.54 (1H, dd, *J* = 12.02 Hz, 3.46 Hz), 2.35 (1H, s, br, OH). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 162.6 (d, *J* = –246.3 Hz), 136.5, 134.3 (d, *J* = 2.97 Hz), 132.8, 128.6, 127.9, 126.5, 125.6, 115.7, 115.5, 81.5, 69.5, 67.3. **IR** (cm^{-1}): 3431.9 (br), 3060.9 (m), 3028.3 (m), 2920.7 (m), 2867.6 (m), 1895.4 (w), 1703.2 (w), 1657.1 (w), 1604.9 (s), 1577.9 (w), 1508.7 (vs), 1449.7 (m), 1393.5 (m), 1343.0 (m), 1296.6 (m), 1224.0 (vs), 1156.9 (m), 1101.5 (s), 1049.1 (s), 968.3 (m), 835.4 (s), 736.0 (s), 693.2 (s). **HRMS:** calcd.: 272.1220, found: 272.1222

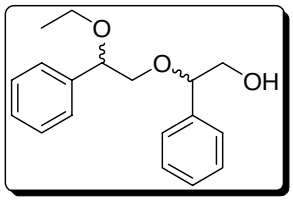


***rac*-2-(4-*tert*-Butyl-phenyl)-2-(3-phenyl-allyloxy)-ethanol (4q, new compound).** High vacuum distillation of the crude residue yielded 1080 mg of **4q** (3.47 mmol, 70 %) as colorless oil, b.p.: 168−173 °C/~0.3 torr. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.37−7.13 (9H, m), 6.51 (1H, d, *J* = 15.72 Hz), 6.21 (1H, m), 4.44 (1H, dd, *J* = 8.44 Hz, 3.39 Hz), 4.11 (1H, dd, *J* = 12.63 Hz, 6.39 Hz), 3.95 (1H, dd, *J* = 12.63 Hz, 6.39 Hz), 3.66

(1H, m), 3.55 (1H, m), 2.25 (1H, br, s, OH), 1.25 (9H, s). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 151.2, 136.6, 135.4, 132.5, 128.6, 127.7, 126.7, 126.5, 125.9, 125.5, 82.0, 69.5, 67.4, 34.6, 31.4. **IR** (cm^{-1}): 3422.5, (br), 3082.6 (m), 3058.7 (m), 3027.0 (m), 2962.3 (vs), 2904.7 (m), 2867,7 (m), 1910.3 (w), 1717.9 (w), 1653.7 (w), 1612.5 (w), 1599.3 (w), 1577.0 (w), 1508.7 (m), 1495.9 (m), 1462.2 (m), 1449.5 (m), 1393.4 (m), 1363.2 (m), 1343.2 (m), 1309.1 (m), 1269.7 (m), 1203.4 (m), 1185.5 (m), 1101.6 (s), 1043.7 (s), 967.1 (m), 875.8 (w), 831.8 (m), 744.8 (m), 693.2 (m). **HRMS:** calcd.: 310.1933, found: 310.1973.

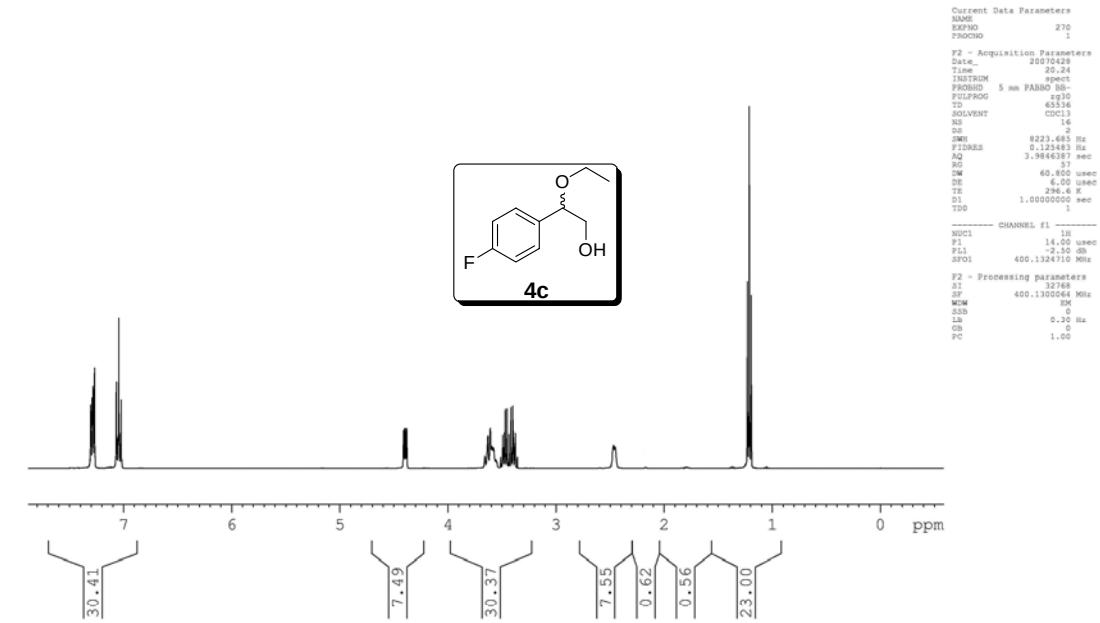


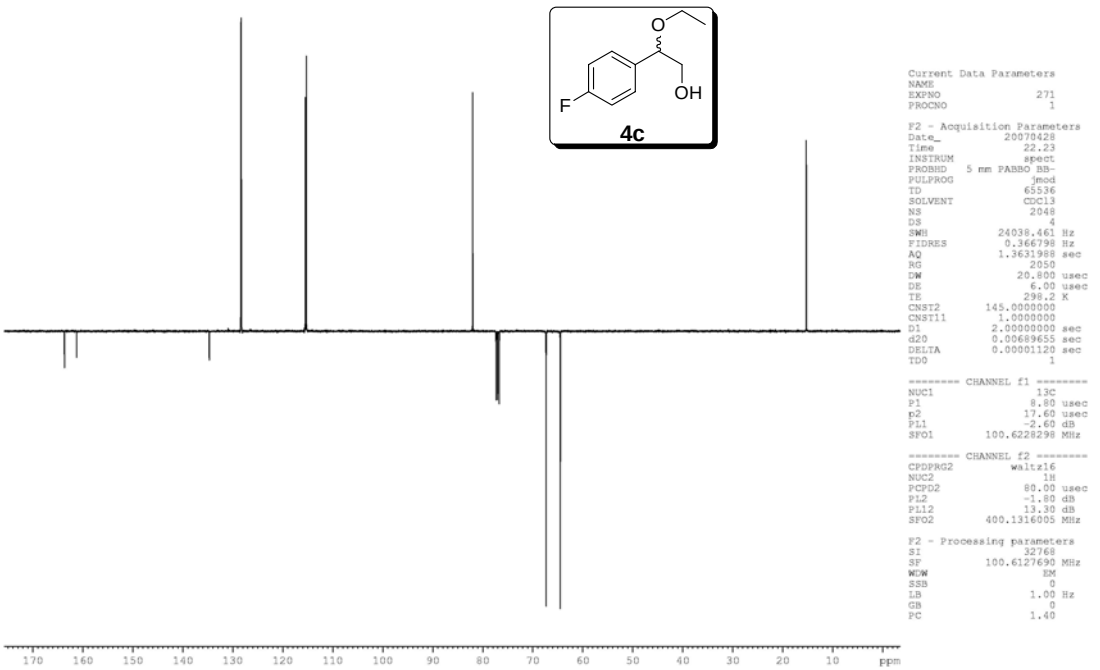
***rac*-4-(2-Hydroxy-1-phenyl-ethoxy)-4-methyl-pentan-2-one (4r, new compound)**: Separation of the crude residue by HPLC (diol phase, 20% TBME/ 80% *n*-Hexane) afforded 685 mg of **4r** (2.90 mmol, 58 %) as colorless oil, b.p.: 91−96 °C/~0.1 torr. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.34−7.22 (5H, m), 4.65 (1H, t, *J* = 10.62 Hz, 3.50 Hz), 3.53 (1H, s, br, OH,), 3.52 (2H, d, *J* = 3.50 Hz), 2.67 (2H, d, *J* = 2.06 Hz), 2.21 (3H, s),1.24 (3H, s), 1.16 (3H, s). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 208.4, 141.7, 128.3, 127.5, 126.3, 75.9, 75.8, 68.2, 53.4, 32.8, 27.9, 26.0. **IR** (cm^{-1}): 3429.5 (br), 2974.1 (s), 2933.7 (s), 2868.4 (m), 1704.4 (vs), 1492.9 (m), 1452.6 (s), 1386.1 (s), 1367.3 (s), 1312.5 (m), 1218.4 (m), 1146.5 (m), 1085.4 (vs), 1060.5 (vs), 963.3 (m), 758.0 (m), 702.6 (vs). **LRMS** {EI, 70 eV, m/z (%)}: 221 (8), 205 (5), 163 (58), 121 (15), 107 (40), 91 (17), 77 (14), 65 (4), 51 (6), 43 (100). **HRMS:** ($M\text{-}CH_2{=}OH^+$, $C_{13}H_{17}O_2$): calcd.: 205.1232, found: 205.1213.

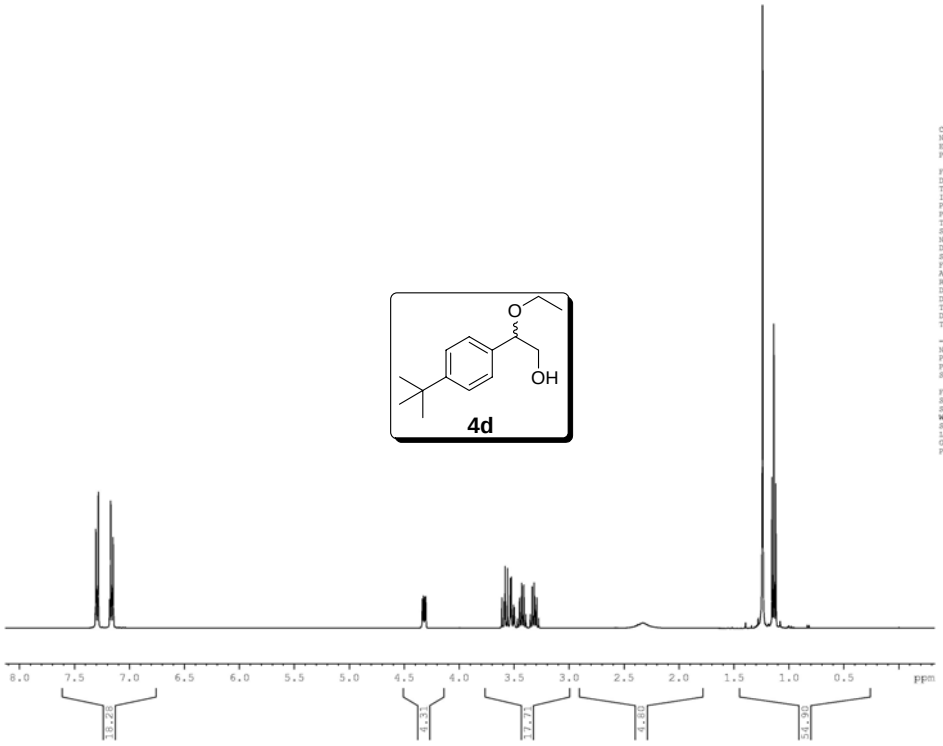


***rac*-2-(2-Ethoxy-2-phenyl-ethoxy)-2-phenyl-ethanol (4s, by-product formed at non-optimized reaction conditions [1:1 mixture of diastereomers], new compound)**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.29 (10H, m), 4.53 (1H, m), 4.46 (1H, dd, *J* = 8.79, 3.75 Hz), 3.80–3.35 (6H, m), 2.89 (1H, br, s, OH), 1.23 (1.5H, t, *J* = 14.03 Hz, 7.01 Hz), 1.20 (1.5H, t, *J* = 14.03 Hz, 7.01 Hz). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 139.6, 139.1, 138.9, 138.4, 128.4, 128.0, 126.9, 126.8, 126.7, 126.6, 84.7, 83.1, 81.9, 80.4, 74.9, 73.2, 67.7, 67.3, 64.6, 64.5, 15.3, 15.2. **IR** (cm^{-1}): 3441.3 (br), 3085.2 (m), 3062.2 (m), 3029.8 (m), 2973.7 (m), 2869.3 (s), 1954.1 (w), 1883.3 (w), 1810.7 (w), 1722.7 (m), 1652.5 (w), 1603.1 (w), 1585.5 (w), 1558.2 (w), 1493.0 (m), 1452.8 (s), 1398.0 (m), 1369.9 (m), 1346.1 (m), 1311.6 (m), 1278.5 (m), 1223.4 (m), 1197.5 (m), 1176.7 (m), 1156.8 (m), 1107.9 (vs), 1071.1 (vs), 1027.9 (s), 1001.9 (w), 943.2 (w), 915.1 (w), 892.9 (w), 861.2 (w), 758.5 (s), 701.0 (vs). **HRMS:** ($M\text{-}CH_2{=}OH^+$, $C_{17}H_{19}O_2$): calcd.: 255.1379, found: 255.1381.

4. ^{1}H- and ^{13}C-NMR spectra





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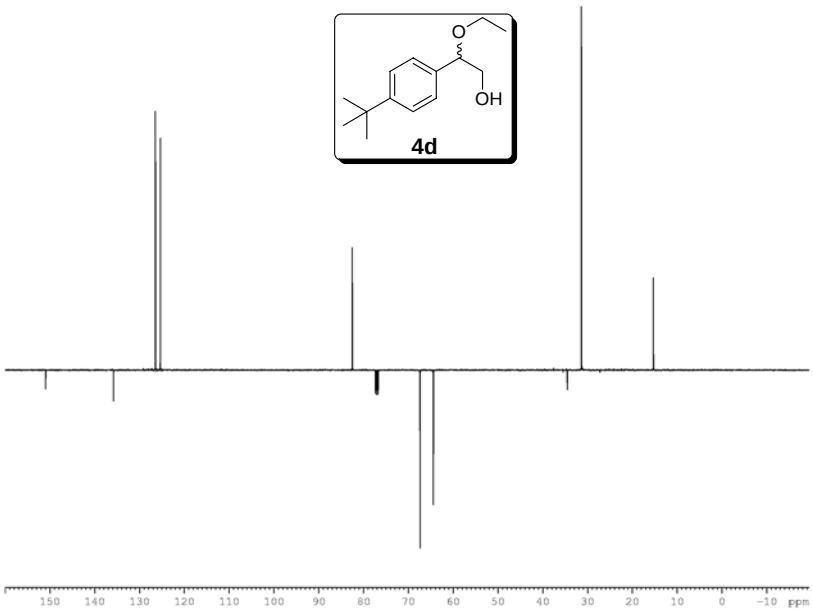


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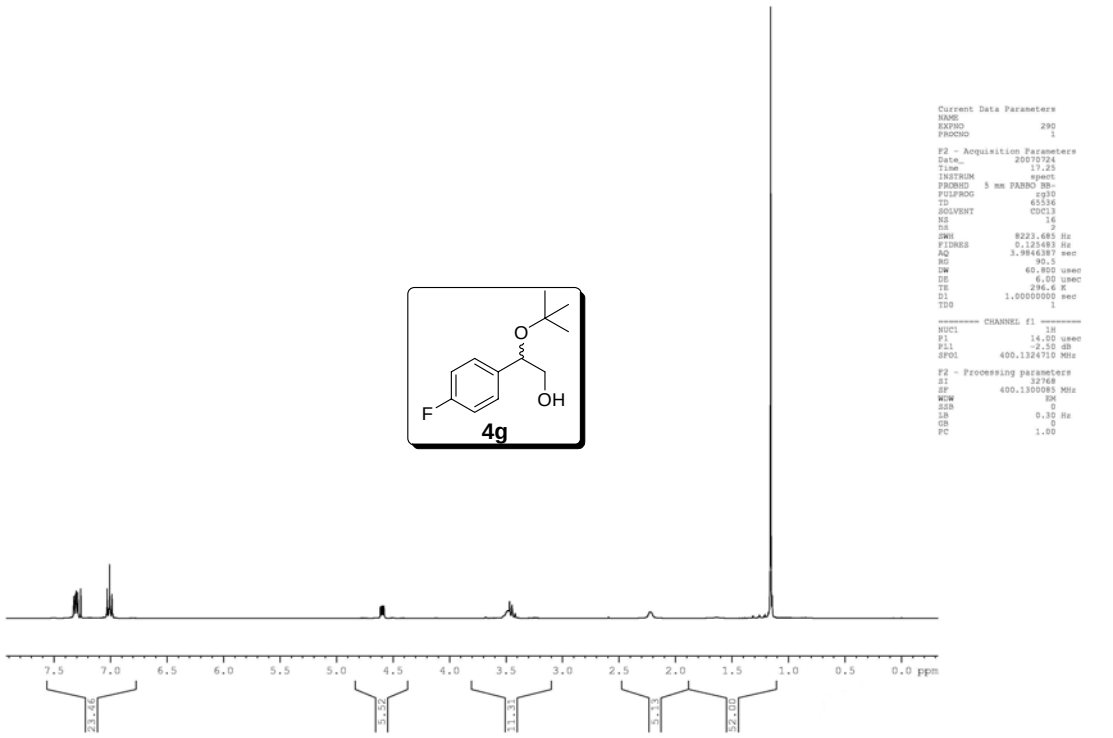
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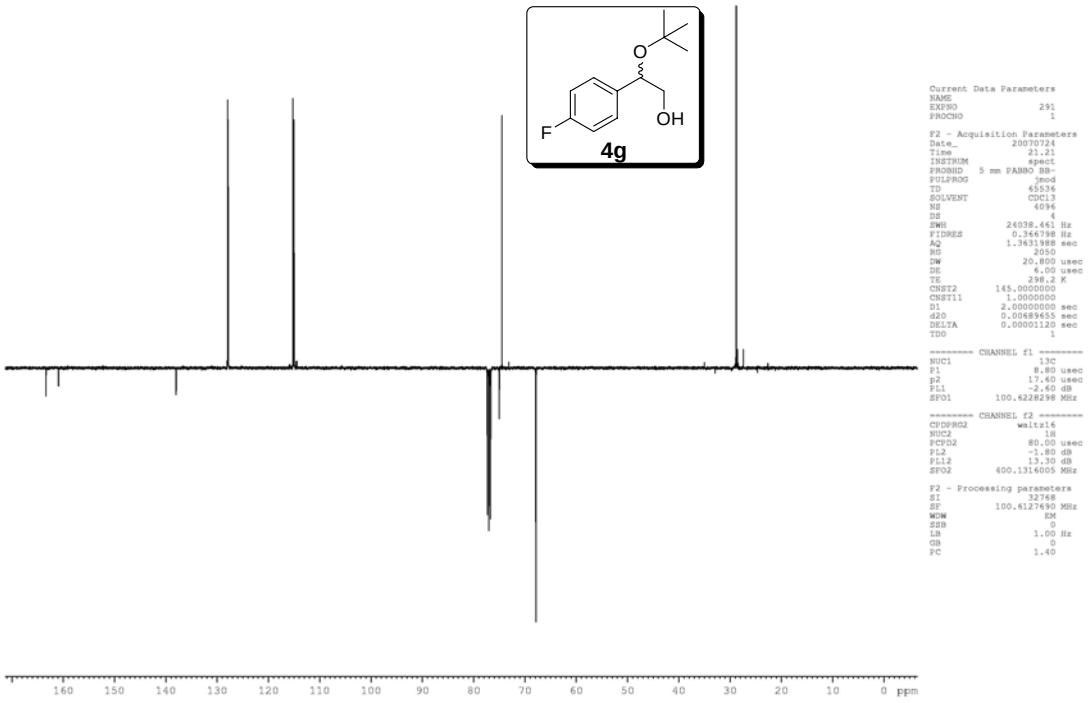
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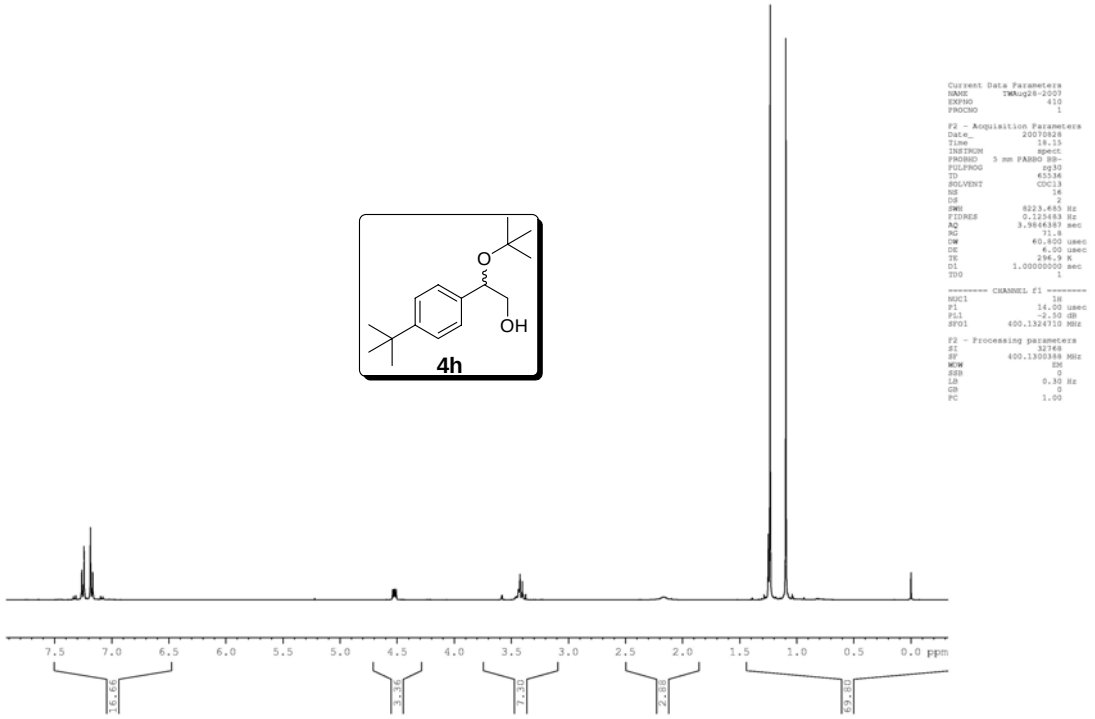
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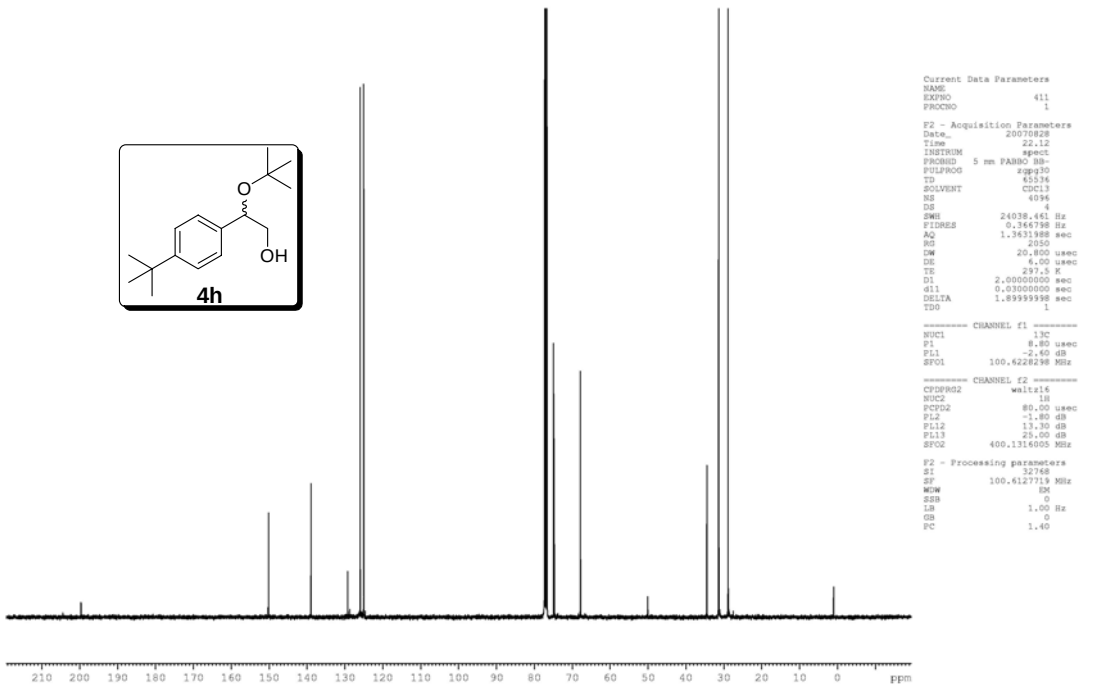
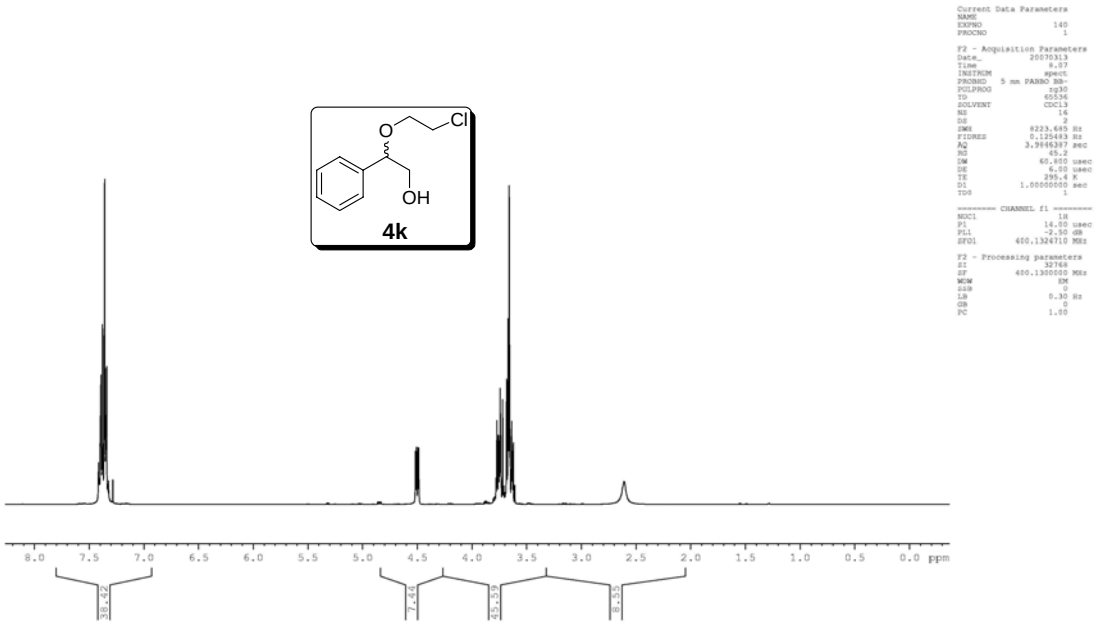
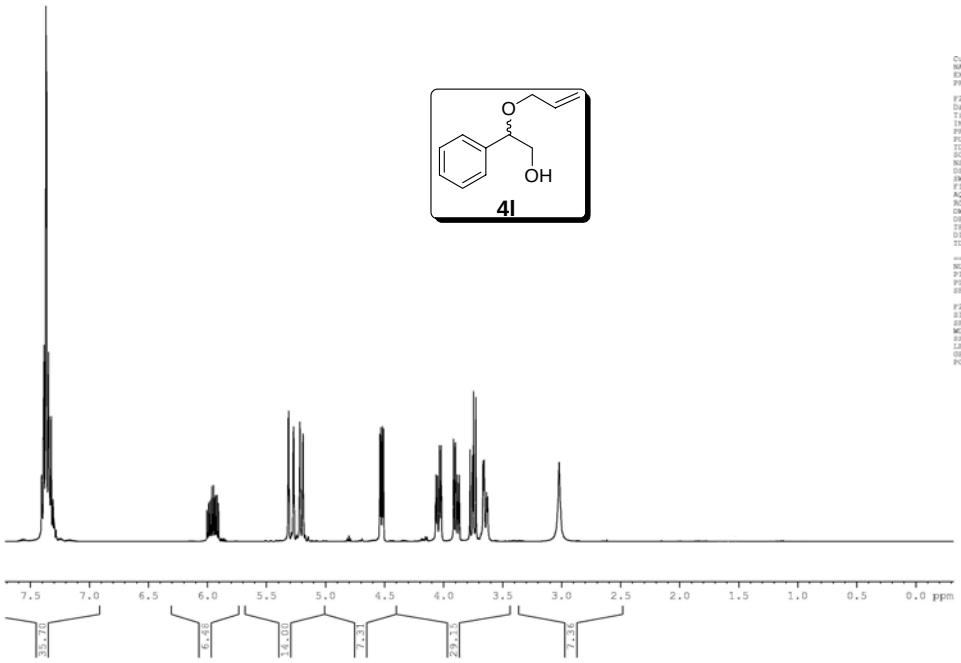
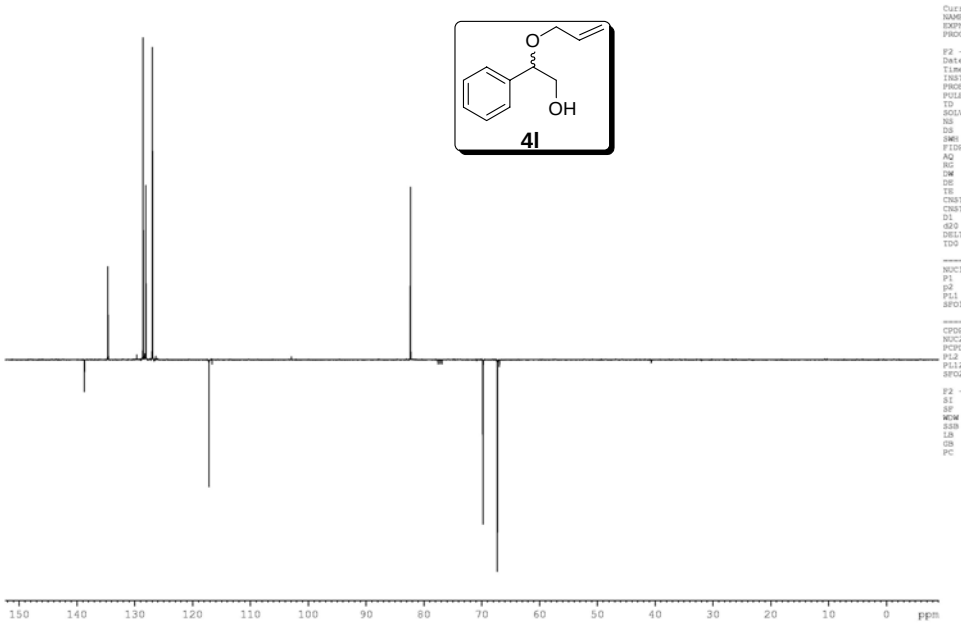
2.08
59.80

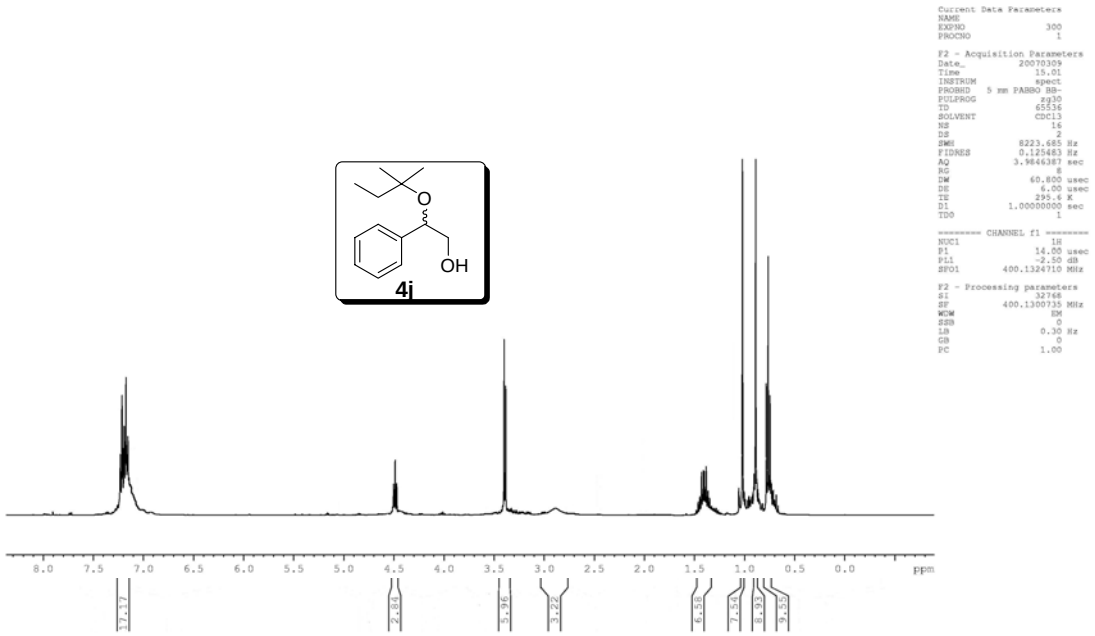

4h
Current Data Parameters
NAME
EXPNO 411
PROCNO 1
F2 - Acquisition Parameters
Date_ 20070828
Time 22.12
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 4096
DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631988 sec
RG 2050
DW 20.800 usec
DE 6.00 usec
TE 297.5 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 8.80 usec
PL1 -2.60 dB
SFO1 100.6228298 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 -1.80 dB
PL12 13.30 dB
PL13 25.00 dB
SFO2 400.1316005 MHz
F2 - Processing parameters
SI 32768
SF 100.6127719 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

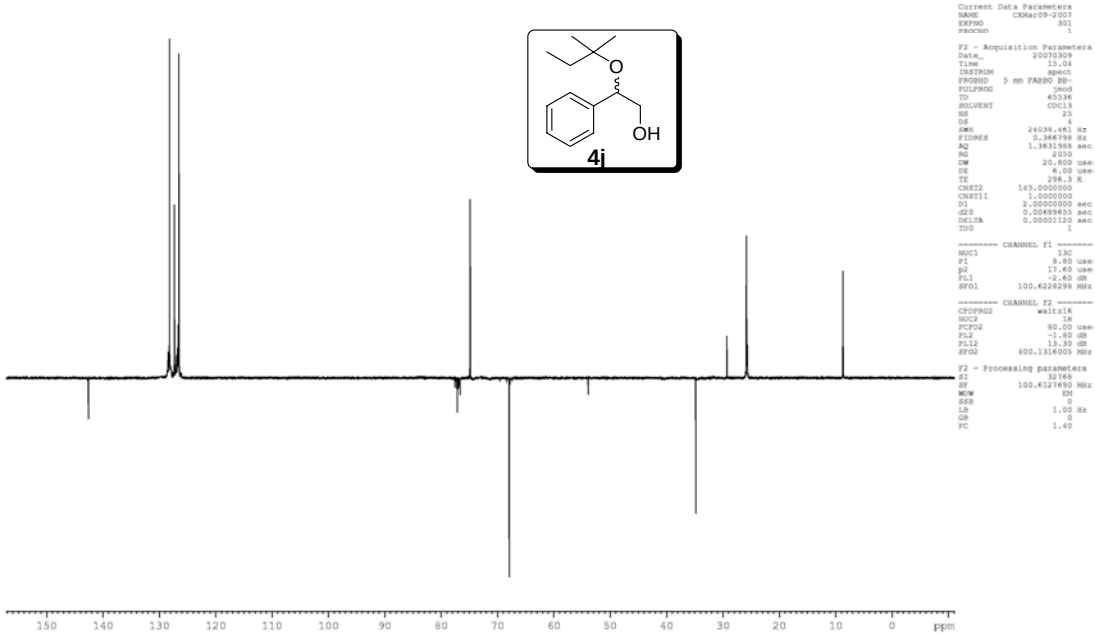

Cl
O
OH
4k
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm

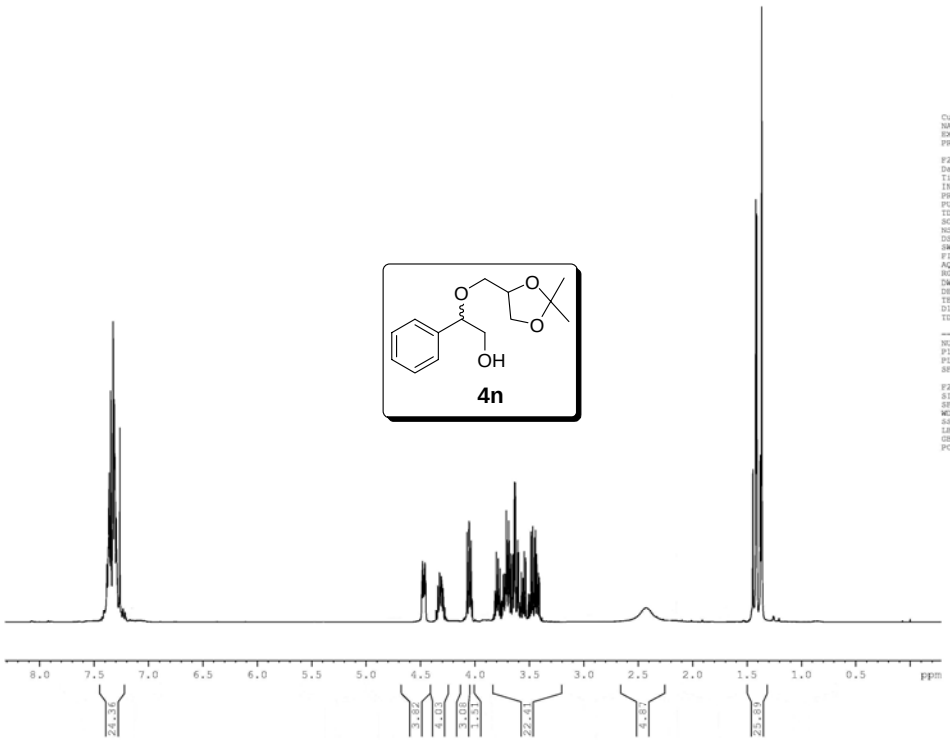

Cl
O
OH
4k
140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 ppm


O
OH
4l
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
35.70
6.48
14.00
7.31
29.17
7.36

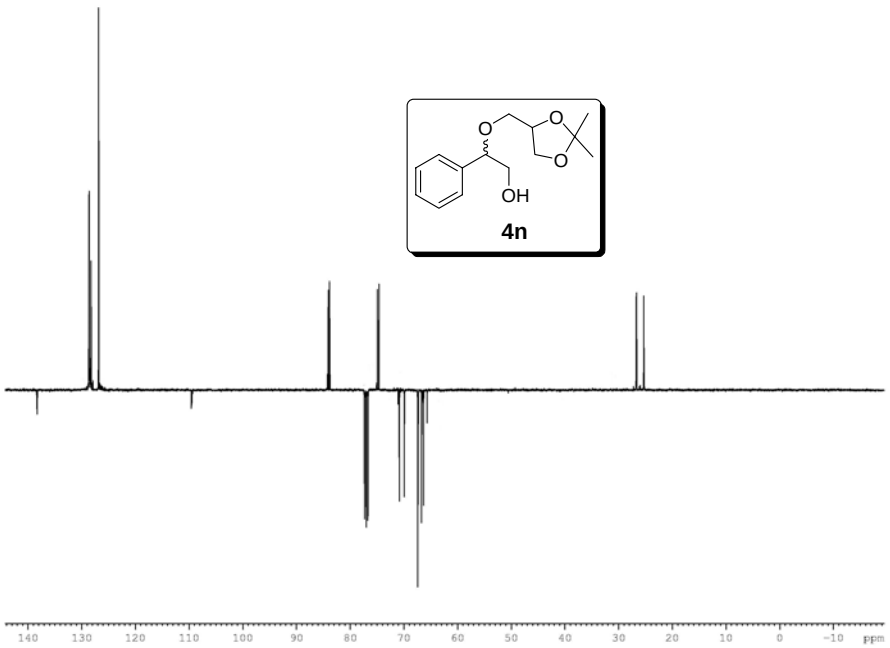

O
OH
4l
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


O
OH
4j
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
7.17
2.84
3.96
3.22
6.58
7.54
8.93
9.55

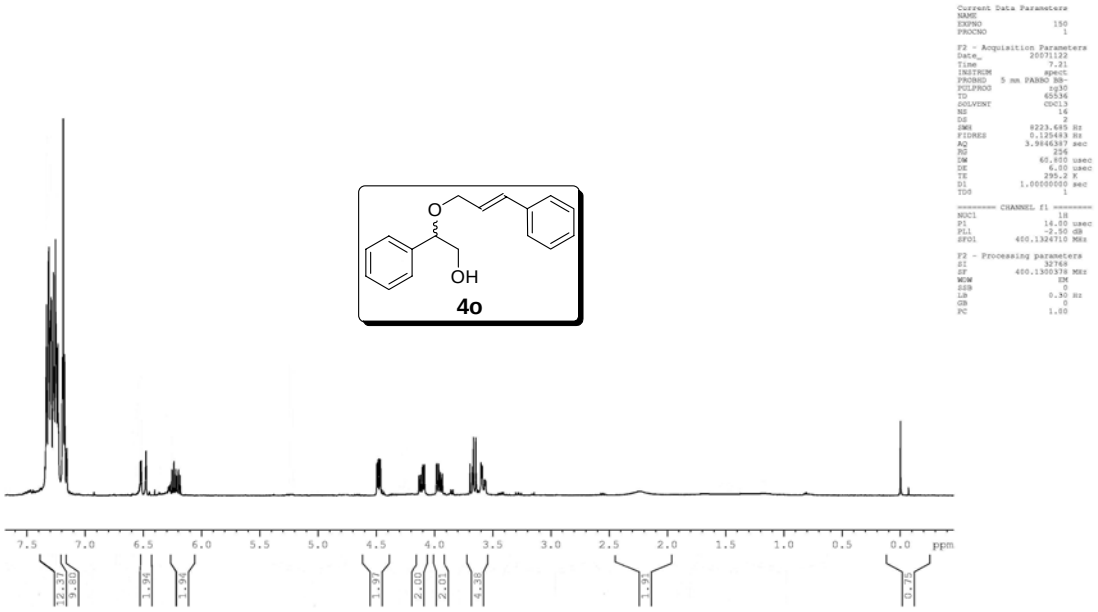

O
OH
4j
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

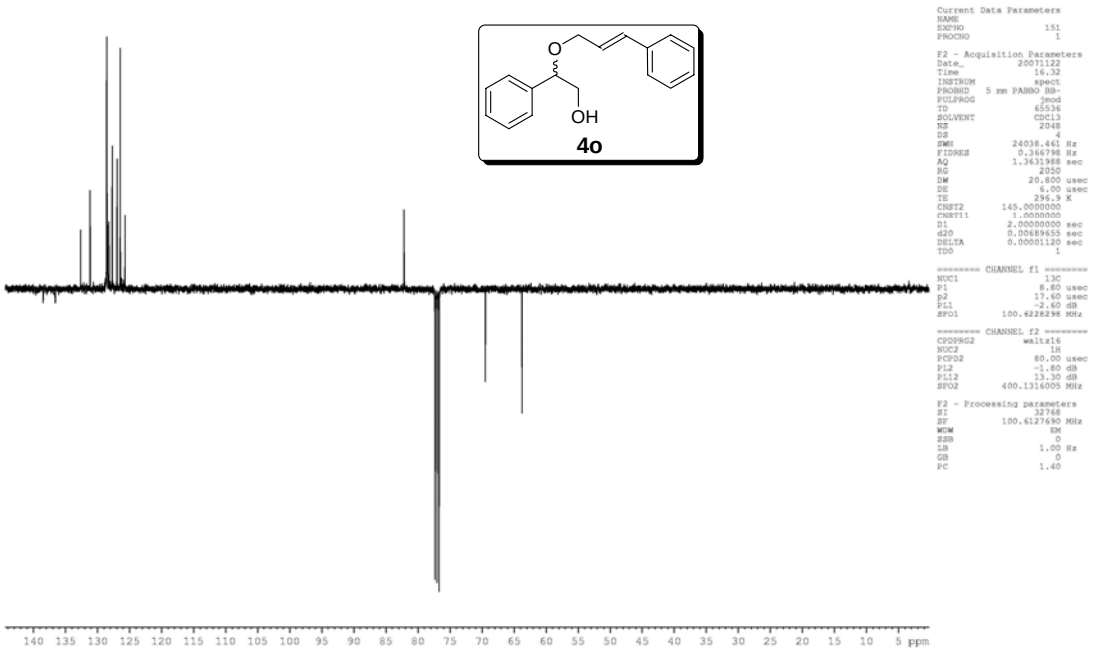


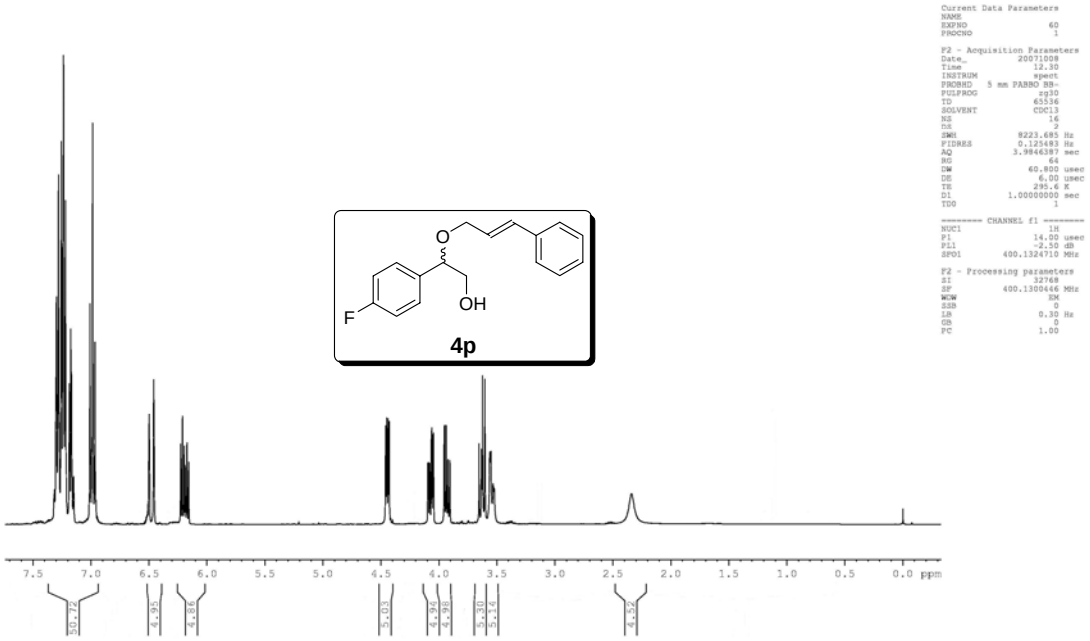

```
Current Data Parameters
NAME
EXPNO                  210
PROCNO                   1

F2 - Acquisition Parameters
Date_               20071002
Time                   10.40
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                       16
DS                        2
SWH                8223.685 Hz
FIDRES             0.125483 Hz
AQ                 3.9846387 sec
RG                      90.5
DW                    60.800 usec
DE                     6.00 usec
TE                    296.1 K
D1                 1.00000000 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                    1H
P1                    14.00 usec
PL1                   -2.50 dB
SFO1          400.1324710 MHz

F2 - Processing parameters
SI                     32768
SF                400.1300085 MHz
WDW                       EM
SSB                        0
LB                      0.30 Hz
GB                         0
PC                      1.00
```

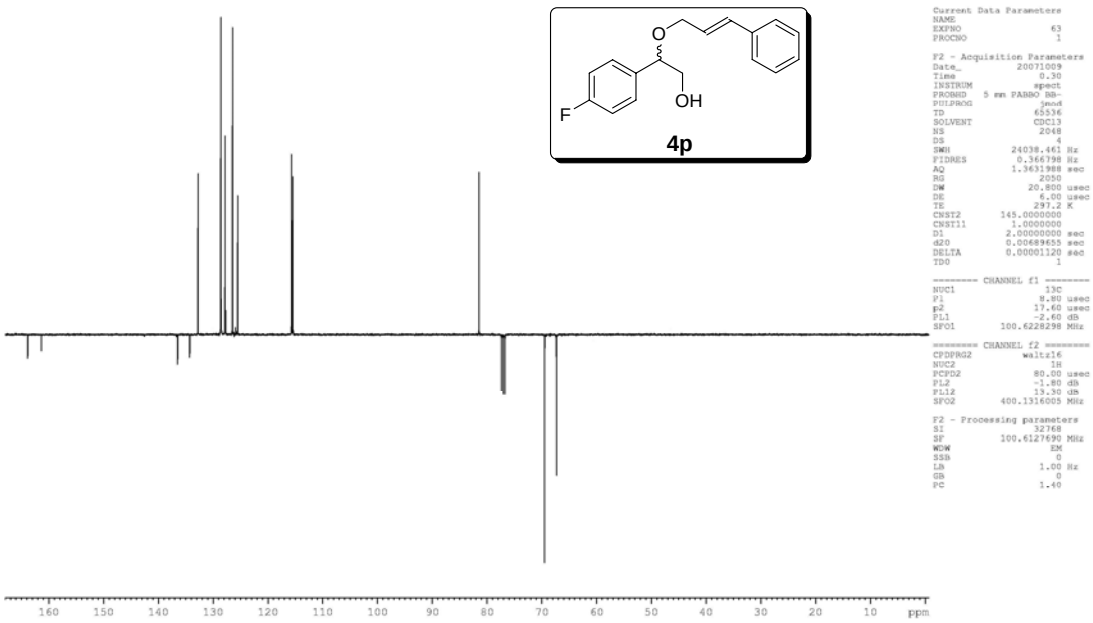


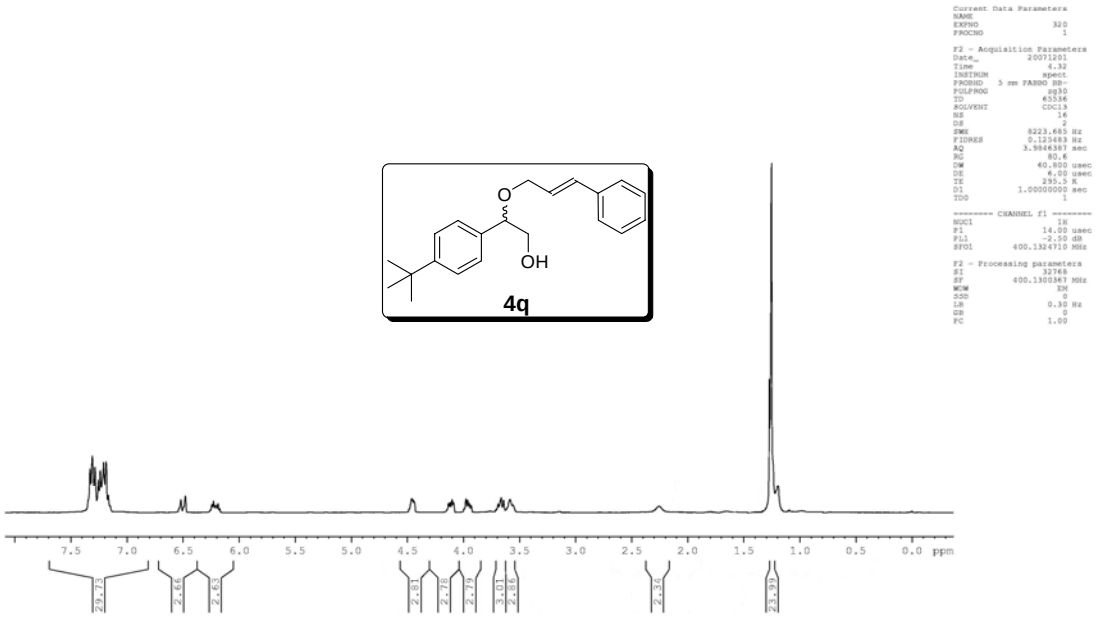

```
Current Data Parameters
NAME
EXPNO                  213
PROCNO                   1

F2 - Acquisition Parameters
Date_               20071003
Time                   13.23
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG                zgpg30
TD                    65536
SOLVENT               CDCl3
NS                     8000
DS                        4
SWH               24038.461 Hz
FIDRES             0.366798 Hz
AQ                 1.3631988 sec
RG                      2050
DW                    20.800 usec
DE                     6.00 usec
TE                    298.1 K
CNST2             145.0000000
CNST11              1.0000000
D1                  2.00000000 sec
d20                 0.00689655 sec
DELTA               0.00001120 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                   13C
P1                     8.80 usec
p2                    17.60 usec
PL1                   -2.60 dB
SFO1          100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2             waltz16
NUC2                    1H
PCPD2                 80.00 usec
PL2                   -1.80 dB
PL12                  13.30 dB
SFO2          400.1316005 MHz

F2 - Processing parameters
SI                     32768
SF                100.6127690 MHz
WDW                       EM
SSB                        0
LB                     1.00 Hz
GB                         0
PC                      1.40
```

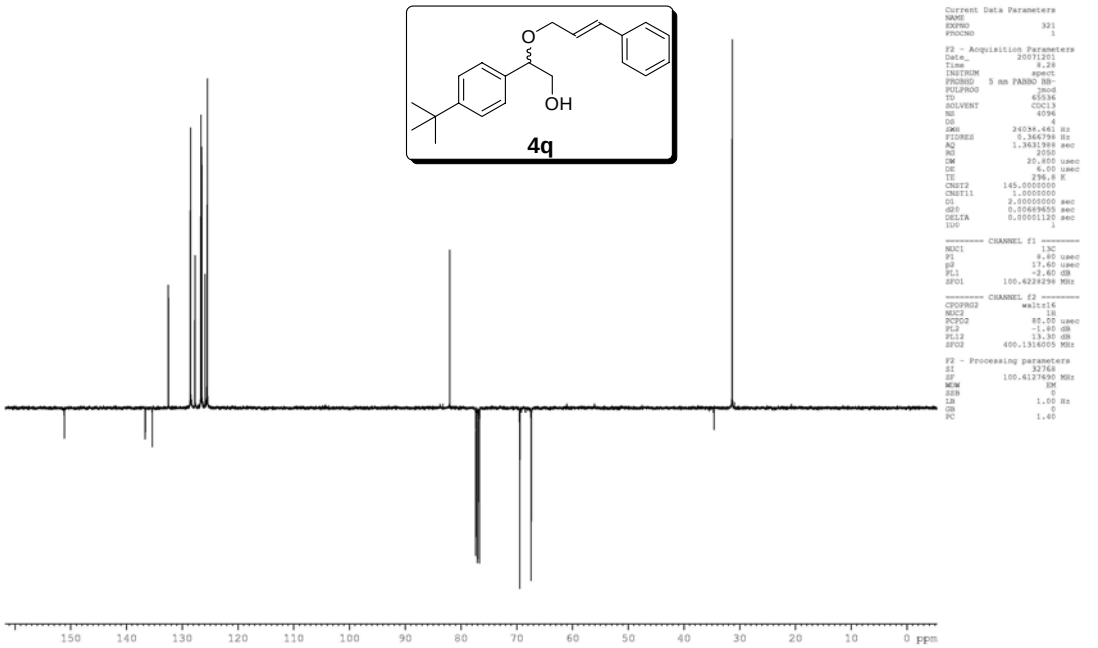

O
OH
4o
ppm

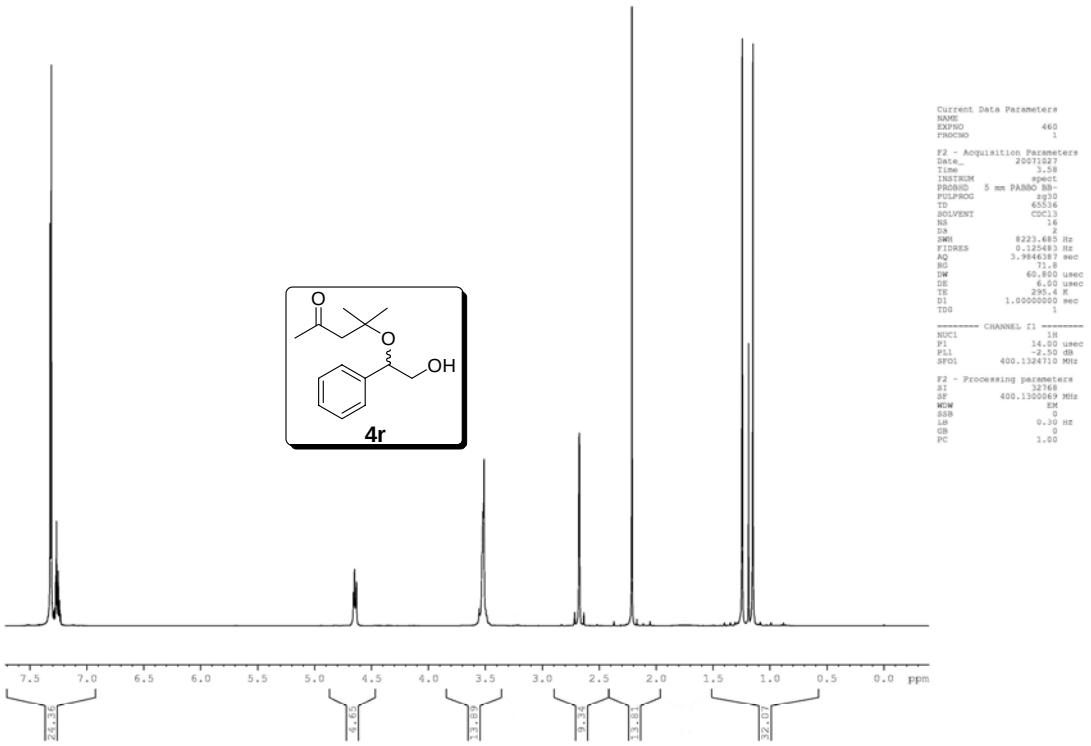

O
OH
4o
ppm

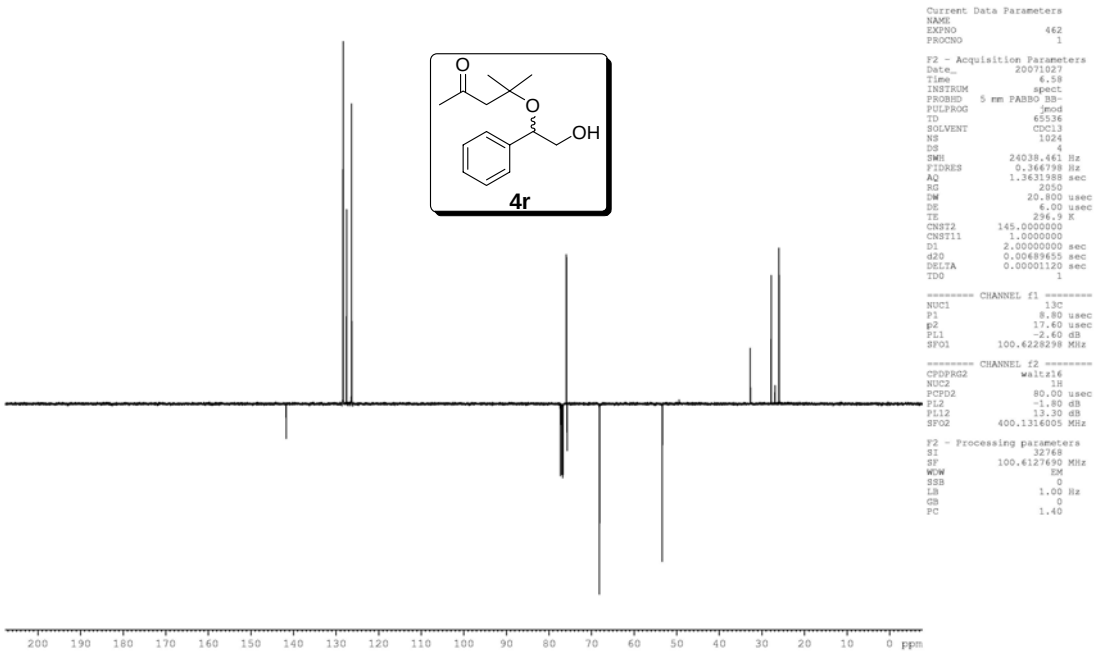

O
F
OH
4p
Current Data Parameters
NAME
EXPNO 60
PROCNO 1
F2 - Acquisition Parameters
Date_ 20071008
Time 12.30
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8223.685 Hz
FIDRES 0.125483 Hz
AQ 3.9846387 sec
RG 64
DW 60.800 usec
DE 6.00 usec
TE 295.6 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 14.00 usec
PL1 -2.50 dB
SFO1 400.1324710 MHz
F2 - Processing parameters
SI 32768
SF 400.1300446 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
50.72
4.95
4.68
5.03
4.98
4.98
5.30
5.14
4.52

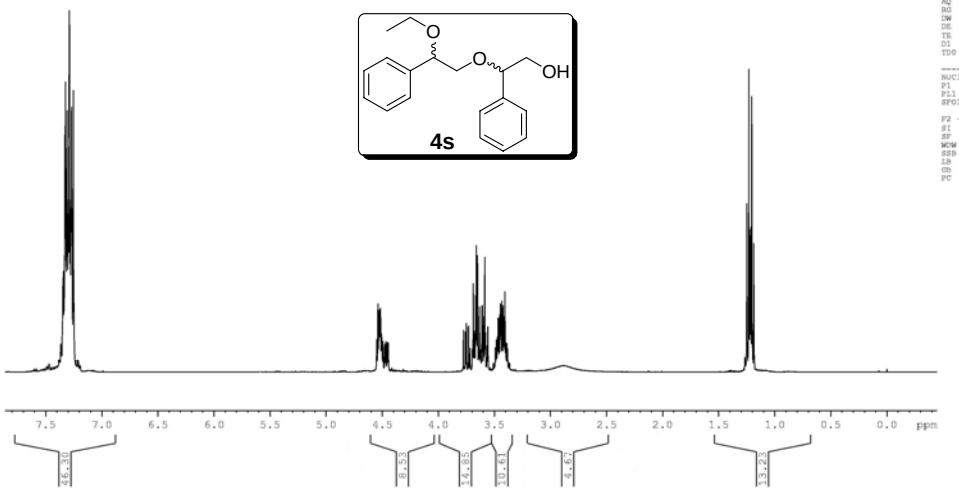

O
F
OH
4p
Current Data Parameters
NAME
EXPNO 63
PROCNO 1
F2 - Acquisition Parameters
Date_ 20071009
Time 0.30
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg6
TD 65536
SOLVENT CDCl3
NS 2048
DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631988 sec
RG 2050
DW 20.800 usec
DE 6.00 usec
TE 297.2 K
CNST2 145.0000000
CNST11 1.0000000
D1 2.00000000 sec
d20 0.00689655 sec
DELTA 0.00001120 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 8.80 usec
p2 17.60 usec
PL1 -2.60 dB
SFO1 100.6228298 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 -1.80 dB
PL12 13.30 dB
SFO2 400.1316005 MHz
F2 - Processing parameters
SI 32768
SF 100.6127690 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


O
OH
4q
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
29.75
2.66
2.60
2.61
2.78
2.71
3.01
2.68
2.36
23.99

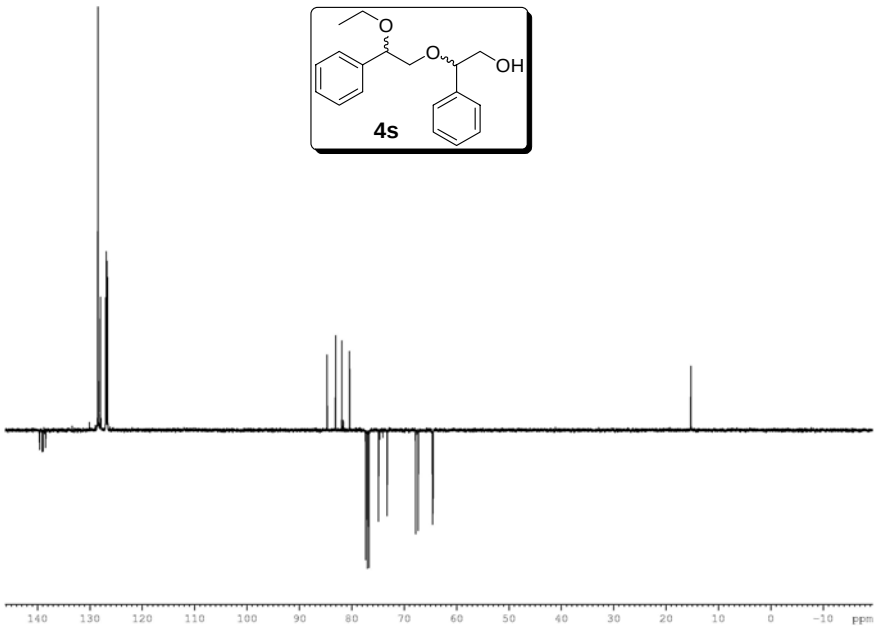

O
OH
4q
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


4r
Current Data Parameters
NAME
EXPNO 460
PROCNO 1
F2 - Acquisition Parameters
Date_ 20071027
Time 3.58
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8223.685 Hz
FIDRES 0.125483 Hz
AQ 3.9846387 sec
RG 71.8
DW 60.800 usec
DE 6.00 usec
TE 295.4 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 14.00 usec
PL1 -2.50 dB
SFO1 400.1324710 MHz
F2 - Processing parameters
SI 32768
SF 400.1300069 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
2.45
4.65
13.68
9.41
13.48
32.01


4r
Current Data Parameters
NAME
EXPNO 462
PROCNO 1
F2 - Acquisition Parameters
Date_ 20071027
Time 6.58
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG jmod
TD 65536
SOLVENT CDCl3
NS 1024
DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631988 sec
RG 2050
DW 20.800 usec
DE 6.00 usec
TE 296.9 K
CNST2 145.0000000
CNST11 1.0000000
D1 2.00000000 sec
d20 0.00689655 sec
DELTA 0.00001120 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 8.80 usec
p2 17.60 usec
PL1 -2.60 dB
SFO1 100.6228298 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 -1.80 dB
PL12 13.30 dB
SFO2 400.1316005 MHz
F2 - Processing parameters
SI 32768
SF 100.6127690 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm




```
Current Data Parameters
NAME
EXPNO                 190
PROCNO                  1

F2 - Acquisition Parameters
Date_              20071122
Time                  12.38
INSTRUM               spect
PROBHD   5 mm PABBO BB-
PULPROG               zg30
TD                   65536
SOLVENT              CDCl3
NS                      16
DS                       2
SWH               8223.685 Hz
FIDRES            0.125483 Hz
AQ                3.9846387 sec
RG                     90.5
DW                  60.800 usec
DE                   6.00 usec
TE                  295.2 K
D1                1.00000000 sec
TD0                     1

======== CHANNEL f1 ========
NUC1                   1H
P1                  14.00 usec
PL1                 -2.50 dB
SFO1          400.1324710 MHz

F2 - Processing parameters
SI                   32768
SF                400.1300103 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.00
```

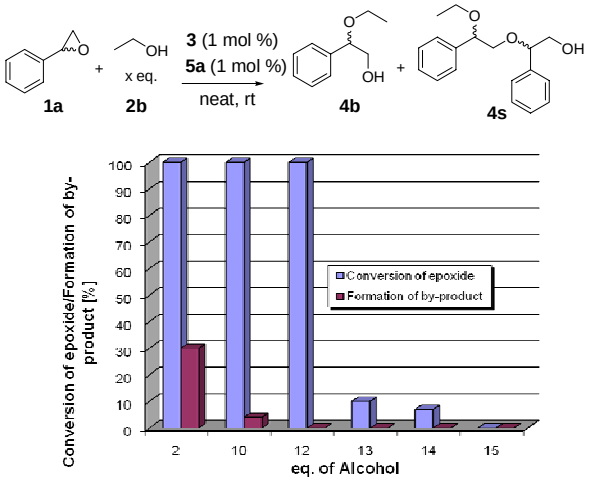



```
Current Data Parameters
NAME
EXPNO                 191
PROCNO                  1

F2 - Acquisition Parameters
Date_              20071122
Time                  20.40
INSTRUM               spect
PROBHD   5 mm PABBO BB-
PULPROG             jmod
TD                   65536
SOLVENT              CDCl3
NS                    2048
DS                       4
SWH              24038.461 Hz
FIDRES            0.366798 Hz
AQ                1.3631988 sec
RG                    2050
DW                  20.800 usec
DE                   6.00 usec
TE                  296.9 K
CNST2           145.0000000
CNST11            1.0000000
D1                2.00000000 sec
d20               0.00689655 sec
DELTA             0.00001120 sec
TD0                     1

======== CHANNEL f1 ========
NUC1                   13C
P1                   8.80 usec
p2                  17.60 usec
PL1                 -2.60 dB
SFO1          100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2             waltz16
NUC2                   1H
PCPD2               80.00 usec
PL2                 -1.80 dB
PL12                13.30 dB
SFO2          400.1316005 MHz

F2 - Processing parameters
SI                   32768
SF            100.6127690 MHz
WDW                     EM
SSB                      0
LB                    1.00 Hz
GB                       0
PC                    1.40
```

5. Optimization experiments

5.1 To minimize formation of by-product **4s**, we studied a dilution series and optimized the reaction conditions (Figure S1). It turned out that a ratio of 1 eq. of styrene oxide and 12 eq. of ethanol avoids formation of the side product completely. Further dilution led to reduced conversion.

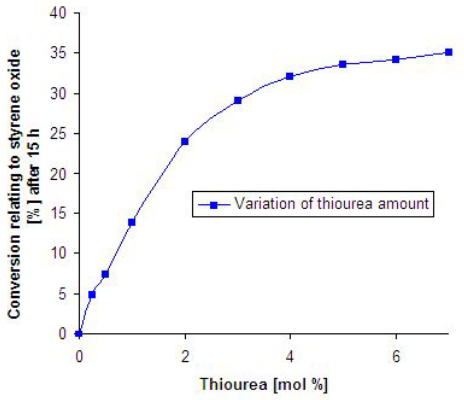
Figure S1. Optimization of the reaction conditions[a]



[a] Reaction time: 22 h

5.2 For further optimization of our cooperative catalyst system we also varied the ratio between **3** and **5a** (Figure S2). A loading of Brønsted acid **5a** in 1 mol % amount was kept constant in order to maintain mild reaction conditions. Surprisingly, reaction times in all cases are nearly equal, although GC-MS analysis after 15 h showed more than two times faster conversion in case of

Figure S2. Variation of **3**



7 mol % of **3** than in case of our standard protocol (1 mol % **3**). These results are consistent with the observation of a non-linear catalytic effect with a dramatic rate enhancement in the second half of the reaction period when a 1:1 mixture of **3** and **5a** was utilized.

6. Table S1. Absolute energies (Hartree) and zero point vibrational energies (ZPVE, kcal/mol) at the B3LYP/6-31+G(d,p) level of theory[3].

Structure	Absolute energy (Hartree)	ZPVE (kcal/mol)
1a	-384.87389	87.0
3	-2358.57744	150.3
5a	-535.38169	92.9
1a·3	-2743.46792	238.5
5a·3	-2893.97976	244.3
1a·5a	-920.26586	180.8
1a·5a·3	-3278.86852	332.5

Table S2. Cartesian coordinates (B3LYP/6-31+G(d,p))

Structure 1a

C	-2.153232000	1.027993000	0.051952000
C	-0.787739000	1.303556000	-0.051506000
C	0.147133000	0.260621000	-0.103952000
C	-0.306130000	-1.065560000	-0.070653000
C	-1.671351000	-1.340341000	0.028223000
C	-2.598933000	-0.295812000	0.093764000
H	-2.867158000	1.845677000	0.092731000
H	-0.446215000	2.335247000	-0.093203000
H	0.415167000	-1.873645000	-0.144132000
H	-2.012365000	-2.371618000	0.047182000
H	-3.660676000	-0.512018000	0.168508000
C	1.602837000	0.581398000	-0.187746000
C	2.601161000	0.004294000	0.737737000
O	2.494603000	-0.461948000	-0.613528000
H	1.833604000	1.557800000	-0.616556000
H	2.267172000	-0.700515000	1.498530000
H	3.511176000	0.557768000	0.968245000

Structure 3

C	2.941424000	0.248121000	0.975786000
C	4.304320000	0.536820000	1.076551000
C	5.224479000	0.020152000	0.164724000
C	4.760560000	-0.802624000	-0.864391000
C	3.402562000	-1.088248000	-0.990269000
C	2.486479000	-0.562281000	-0.069539000
H	2.245228000	0.644784000	1.701745000
H	6.279999000	0.246073000	0.258649000
H	3.056662000	-1.713063000	-1.806963000
C	5.758291000	-1.379655000	-1.837720000
C	4.773640000	1.450390000	2.183875000
F	6.644063000	-2.199932000	-1.216072000
F	6.487976000	-0.410333000	-2.442643000
F	5.165960000	-2.104843000	-2.816331000
F	6.091639000	1.293031000	2.449670000
F	4.100598000	1.229315000	3.339581000
F	4.587807000	2.756536000	1.866533000
N	1.130399000	-0.939124000	-0.197852000
H	0.987514000	-1.807062000	-0.700231000
C	0.000717000	-0.154565000	-0.027735000
S	0.006862000	1.490428000	0.201098000
N	-1.132979000	-0.948664000	-0.075973000
H	-0.991266000	-1.925057000	0.153506000
C	-2.488747000	-0.550044000	-0.090521000
C	-2.946629000	0.526132000	-0.857413000
C	-4.310403000	0.828765000	-0.869477000
C	-5.228657000	0.070471000	-0.144097000
C	-4.761535000	-1.011933000	0.605627000
C	-3.403114000	-1.319400000	0.641980000
H	-2.251853000	1.116646000	-1.438465000
H	-6.284211000	0.313371000	-0.166137000
H	-3.054575000	-2.150982000	1.245426000
C	-4.778063000	2.021628000	-1.669082000
C	-5.756070000	-1.856020000	1.363373000
F	-4.536738000	3.186062000	-1.015778000
F	-6.106815000	1.978199000	-1.922031000
F	-4.143122000	2.106082000	-2.864240000
F	-6.588625000	-1.097807000	2.116830000
F	-6.542508000	-2.575934000	0.521258000
F	-5.155208000	-2.740744000	2.194517000

Structure 5a

C	3.062821000	-0.045540000	-0.371008000

C	2.516287000	-0.953471000	0.537508000
C	1.173376000	-0.840391000	0.914621000
C	0.365698000	0.171598000	0.376816000
C	0.923316000	1.084784000	-0.528933000
C	2.264625000	0.976748000	-0.896982000
H	4.106450000	-0.125498000	-0.660253000
H	3.133245000	-1.737736000	0.966048000
H	0.762037000	-1.526670000	1.652558000
H	0.304544000	1.884325000	-0.922952000
H	2.689603000	1.691702000	-1.595429000
C	-1.107183000	0.243444000	0.739635000
H	-1.256581000	-0.308870000	1.684551000
C	-2.012780000	-0.471174000	-0.291448000
O	-3.084544000	-0.005823000	-0.608033000
O	-1.591323000	-1.653292000	-0.771816000
H	-0.666675000	-1.810548000	-0.513280000
O	-1.541846000	1.575017000	0.877916000
H	-2.447879000	1.610101000	0.522964000

Structure 1a·3

C	-3.364756000	-1.424607000	0.675913000
C	-4.759094000	-1.462096000	0.781553000
C	-5.572701000	-0.531968000	0.139373000
C	-4.959777000	0.463361000	-0.628258000
C	-3.576236000	0.516072000	-0.752485000
C	-2.759575000	-0.429595000	-0.103659000
H	-2.754820000	-2.157582000	1.183331000
H	-6.650508000	-0.578156000	0.231903000
H	-3.121766000	1.288215000	-1.364179000
C	-5.811808000	1.517098000	-1.287451000
C	-5.379297000	-2.573039000	1.595710000
F	-6.179598000	2.488392000	-0.407738000
F	-6.955373000	1.003823000	-1.797334000
F	-5.164366000	2.143487000	-2.303595000
F	-6.687174000	-2.344291000	1.864371000
F	-4.750083000	-2.740751000	2.784211000
F	-5.312405000	-3.764269000	0.947604000
N	-1.375848000	-0.254616000	-0.274517000
H	-1.142850000	0.644125000	-0.693279000
C	-0.299707000	-1.079421000	-0.028095000
S	-0.374329000	-2.647564000	0.542718000
N	0.879065000	-0.418149000	-0.319596000
H	0.806653000	0.579569000	-0.502826000
C	2.204145000	-0.895672000	-0.236271000
C	2.582446000	-2.174812000	-0.673038000
C	3.923203000	-2.550879000	-0.615388000
C	4.907907000	-1.675453000	-0.145743000
C	4.524156000	-0.402342000	0.268790000
C	3.182214000	-0.012795000	0.234258000
H	1.839208000	-2.858603000	-1.056749000
H	5.946937000	-1.978356000	-0.112564000
H	2.894808000	0.974427000	0.582619000
C	4.322672000	-3.943373000	-1.039379000
C	5.550074000	0.595493000	0.739061000
F	4.373242000	-4.793940000	0.018435000
F	5.553060000	-3.963011000	-1.611224000
F	3.457560000	-4.477012000	-1.932497000
F	6.764828000	0.040798000	0.939799000
F	5.720776000	1.601439000	-0.168193000
F	5.182469000	1.195158000	1.899810000
C	1.778123000	5.658911000	1.859761000
C	0.708809000	5.125808000	1.135363000
C	0.941116000	4.266201000	0.053671000
C	2.262694000	3.938655000	-0.287742000
C	3.329986000	4.463705000	0.440623000
C	3.089783000	5.327459000	1.514974000
H	1.584312000	6.323983000	2.695828000
H	-0.311373000	5.378152000	1.413528000
H	2.460803000	3.265099000	-1.116732000
H	4.347355000	4.194894000	0.173823000
H	3.922096000	5.733590000	2.081607000
C	-0.225222000	3.726969000	-0.700208000
C	-0.196996000	3.401706000	-2.137812000
O	-0.150845000	2.340155000	-1.159334000
H	-1.196888000	3.970959000	-0.272856000
H	0.725530000	3.541587000	-2.697078000
H	-1.115371000	3.446506000	-2.720369000

Structure 5a·3

C	2.345331000	-2.797030000	-0.137795000
C	3.676081000	-3.217886000	-0.242139000
C	4.731303000	-2.314108000	-0.319936000
C	4.432768000	-0.947040000	-0.296094000
C	3.119130000	-0.504806000	-0.202395000
C	2.055075000	-1.426151000	-0.120227000
H	1.541779000	-3.516661000	-0.073839000
H	5.755143000	-2.658811000	-0.397895000
H	2.907217000	0.558423000	-0.198035000
C	5.563766000	0.042829000	-0.403688000
C	3.952373000	-4.702595000	-0.217290000
F	6.167382000	-0.008012000	-1.619434000
F	6.532447000	-0.194749000	0.516313000
F	5.153217000	1.324217000	-0.223556000
F	5.221020000	-4.996328000	-0.590723000
F	3.123715000	-5.386886000	-1.040665000
F	3.779072000	-5.219494000	1.027959000
N	0.773194000	-0.861380000	-0.007857000
H	0.798574000	0.141616000	0.166908000
C	-0.492123000	-1.398038000	-0.117126000
S	-0.877123000	-3.021056000	-0.214305000
N	-1.424701000	-0.379612000	-0.158496000
H	-1.071714000	0.544501000	-0.400494000
C	-2.829534000	-0.462657000	-0.135083000
C	-3.533092000	-1.368879000	0.672421000
C	-4.927274000	-1.336398000	0.688638000
C	-5.646353000	-0.411380000	-0.073945000
C	-4.937059000	0.493960000	-0.861777000
C	-3.541837000	0.468185000	-0.902302000
H	-2.997489000	-2.082847000	1.281847000
H	-6.728455000	-0.394448000	-0.047789000
H	-3.001520000	1.166542000	-1.532867000
C	-5.671665000	-2.347101000	1.526644000
C	-5.661318000	1.552800000	-1.651113000
F	-5.857863000	-3.515276000	0.859665000
F	-6.901579000	-1.903079000	1.885665000
F	-5.007551000	-2.651245000	2.668313000
F	-6.973990000	1.277315000	-1.812932000
F	-5.587606000	2.770078000	-1.037779000
F	-5.127999000	1.722548000	-2.887812000
C	2.678805000	4.183678000	-0.106064000
C	3.735563000	5.085691000	-0.229499000
C	3.866924000	6.141638000	0.678684000
C	2.939979000	6.291155000	1.712289000
C	1.883523000	5.385195000	1.839383000
C	1.747034000	4.328263000	0.932545000
H	2.583861000	3.362605000	-0.811241000
H	4.455991000	4.963994000	-1.032469000
H	4.690847000	6.842072000	0.581260000
H	3.039030000	7.107406000	2.421362000
H	1.162367000	5.504365000	2.644000000

C	0.607344000	3.334423000	1.087973000
H	0.011585000	3.613563000	1.968747000
C	-0.357365000	3.362666000	-0.095865000
O	-0.602638000	2.424186000	-0.829342000
O	-0.932342000	4.565885000	-0.223022000
H	-1.546862000	4.535899000	-0.976999000
O	1.058097000	1.984666000	1.204059000
H	1.702586000	1.947469000	1.924747000

Structure 1a·5a

C	4.240734000	1.076692000	1.119024000
C	3.105159000	0.355481000	0.749188000
C	3.202868000	-0.680200000	-0.192279000
C	4.451140000	-0.972667000	-0.759039000
C	5.588893000	-0.255872000	-0.381151000
C	5.485648000	0.771195000	0.559507000
H	4.150692000	1.883070000	1.840624000
H	2.143871000	0.619369000	1.178324000
H	4.533628000	-1.764511000	-1.499599000
H	6.549818000	-0.494455000	-0.827295000
H	6.366779000	1.335733000	0.849706000
C	2.024951000	-1.495267000	-0.606238000
C	0.965251000	-1.940514000	0.320145000
O	0.708413000	-0.874794000	-0.617315000
H	2.189983000	-2.111680000	-1.489197000
H	1.011643000	-1.628484000	1.361847000
H	0.414778000	-2.857788000	0.121686000
C	-3.979993000	-2.233150000	0.902446000
C	-3.234835000	-2.374503000	-0.269970000
C	-2.652750000	-1.252401000	-0.868629000
C	-2.811089000	0.017766000	-0.304133000
C	-3.565137000	0.153054000	0.870781000
C	-4.143948000	-0.965126000	1.471309000
H	-4.436395000	-3.102201000	1.367649000
H	-3.114493000	-3.353745000	-0.725204000
H	-2.077571000	-1.363585000	-1.783890000
H	-3.705368000	1.136654000	1.310804000
H	-4.726035000	-0.848057000	2.380891000
C	-2.218328000	1.245646000	-0.990232000
H	-1.587398000	0.908352000	-1.823890000
C	-1.340619000	2.055111000	-0.016271000
O	-1.710943000	3.135832000	0.398569000
O	-0.177714000	1.524621000	0.367366000
H	0.040407000	0.670890000	-0.075712000
O	-3.226961000	2.093704000	-1.504795000
H	-3.204376000	2.904064000	-0.964076000

Structure 1a·5a·3

N	1.941342000	0.984338000	-0.056888000
C	1.259177000	2.181708000	-0.010396000
N	-0.047633000	1.987108000	-0.420820000
C	-1.202783000	2.780283000	-0.336208000
S	1.924625000	3.633365000	0.481147000
C	3.312936000	0.732168000	0.136395000
C	4.328044000	1.598679000	-0.290067000
C	5.664080000	1.232639000	-0.113915000
C	6.016421000	0.015679000	0.470858000
C	4.996931000	-0.848859000	0.875225000
C	3.657378000	-0.497818000	0.718403000
C	-2.390794000	2.178951000	-0.792665000
C	-3.598319000	2.870087000	-0.749003000
C	-3.663814000	4.173161000	-0.250732000
C	-2.482613000	4.763655000	0.197092000
C	-1.258269000	4.092182000	0.161614000
C	6.743788000	2.195894000	-0.542436000
F	6.985923000	3.136253000	0.407762000
F	6.411355000	2.864066000	-1.673949000
F	7.922603000	1.569516000	-0.779867000
C	5.355229000	-2.152018000	1.541886000
F	5.616272000	-1.987518000	2.866551000
F	6.462114000	-2.716115000	0.998824000
F	4.357444000	-3.067617000	1.455562000
C	-2.528566000	6.153083000	0.787535000
F	-1.401209000	6.855975000	0.539274000
F	-2.676748000	6.112485000	2.139569000
F	-3.569539000	6.876779000	0.305922000
C	-4.855037000	2.171374000	-1.194801000
F	-5.828603000	3.033669000	-1.561397000
F	-4.640104000	1.336793000	-2.242898000
F	-5.382630000	1.395985000	-0.197537000
H	1.368053000	0.137855000	-0.060411000
H	-0.228952000	1.079593000	-0.837708000
H	4.079174000	2.539937000	-0.758582000
H	7.057015000	-0.258686000	0.592416000
H	2.875451000	-1.178711000	1.036270000
H	-2.364202000	1.167669000	-1.184765000
H	-4.601645000	4.713283000	-0.225222000
H	-0.353188000	4.574946000	0.500195000
O	-2.226562000	-3.110096000	-1.929207000
C	-1.142748000	-3.197643000	-1.013945000
C	-0.485008000	-1.809122000	-0.899115000
O	0.313908000	-1.494086000	-0.037563000
O	-0.869805000	-0.934266000	-1.840525000
C	-0.118485000	-4.227469000	-1.481807000
C	0.921781000	-4.613127000	-0.624979000
C	1.871149000	-5.544031000	-1.048873000
C	1.787084000	-6.099666000	-2.329344000
C	0.747888000	-5.720387000	-3.181271000
C	-0.204206000	-4.786324000	-2.761534000
H	-3.039559000	-2.858740000	-1.440023000
H	-1.493545000	-3.459831000	-0.008352000
H	-1.541589000	-1.399499000	-2.390552000
H	0.994470000	-4.181958000	0.369017000
H	2.674157000	-5.834534000	-0.378209000
H	2.525944000	-6.824462000	-2.658111000
H	0.673580000	-6.150748000	-4.175729000
H	-1.018549000	-4.500258000	-3.417278000
O	-4.344496000	-2.000134000	-0.583738000
C	-4.959029000	-2.068965000	0.736418000
C	-5.777742000	-2.135537000	-0.488847000
C	-4.639179000	-3.250498000	1.587294000
C	-4.447596000	-4.529823000	1.041937000
C	-4.152917000	-5.612644000	1.870697000
C	-4.050509000	-5.432727000	3.254321000
C	-4.238615000	-4.162874000	3.803906000
C	-4.525343000	-3.076655000	2.973224000
H	-4.932510000	-1.109978000	1.251209000
H	-6.167765000	-3.098565000	-0.812605000
H	-6.331812000	-1.257516000	-0.812735000
H	-4.521181000	-4.681794000	-0.031321000
H	-4.003061000	-6.596937000	1.437115000
H	-3.821849000	-6.277068000	3.897572000
H	-4.155409000	-4.014037000	4.876240000
H	-4.661111000	-2.087843000	3.403881000

7. Full Reference Gaussian03

Gaussian 03, Revision C.02, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, Jr., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; and Pople, J. A.; Gaussian, Inc., Wallingford CT, 2004.

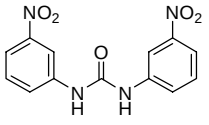
8. References

1. Robinson, M. W. C.; Buckle, R.; Mabbett, I.; Grant, G. M.; Graham, A. E., *Tetrahedron Lett.* **2007,** *48*, 4723–4725.
2. Kumar, G. D. K.; Baskaran, S., *J. Org. Chem.* **2005,** *70*, 4520–4523.

6.3 (Thio)urea Structure Index

Note: This index illustrates all (thio)urea derivatives discussed in chapter 1, 3, and 5; the numbering of each structure results from its order of appearance in the respective chapter of this PhD thesis.

(Thio)urea structures of chapter 1 "(Thio)urea Organocatalysts"



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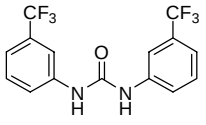

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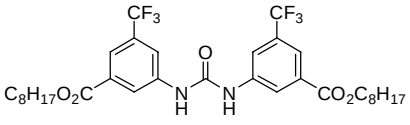

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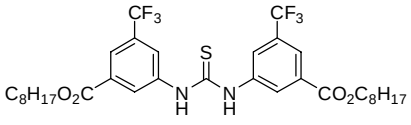

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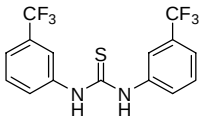

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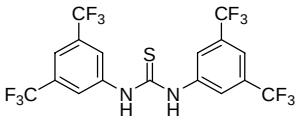

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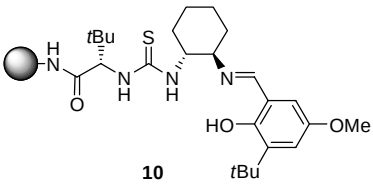

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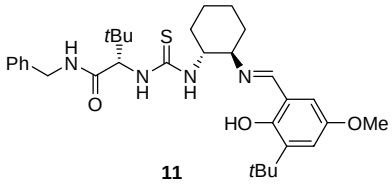

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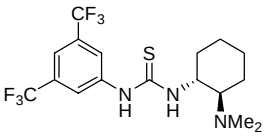

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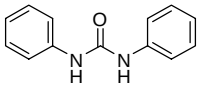

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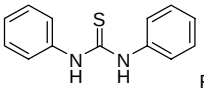

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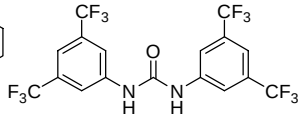

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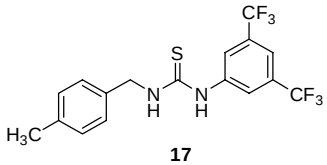

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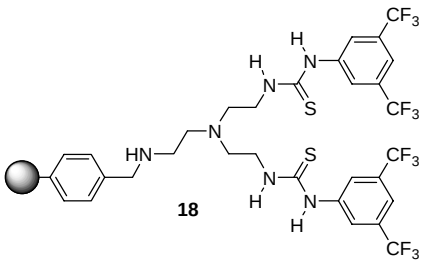

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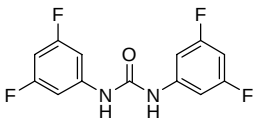

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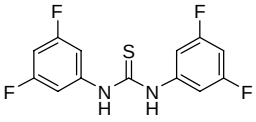

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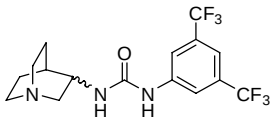

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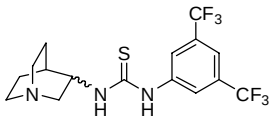

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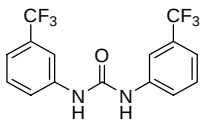

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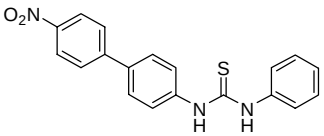

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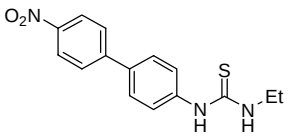

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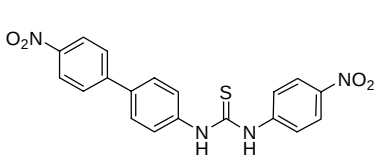

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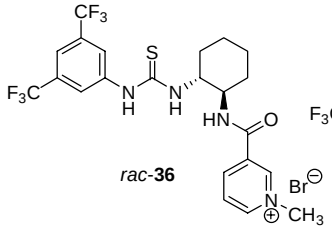

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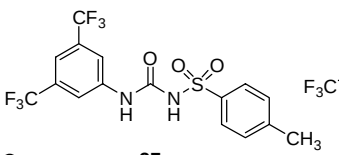

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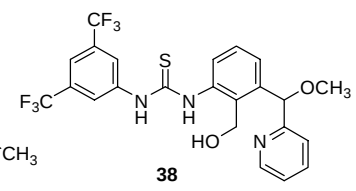

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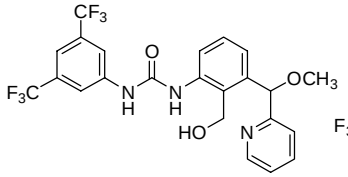

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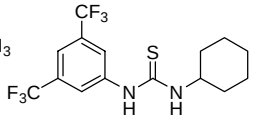

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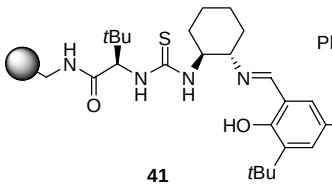

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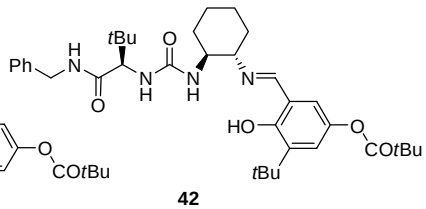

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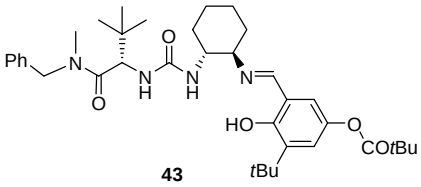
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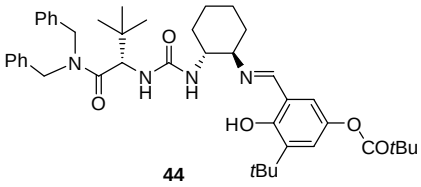
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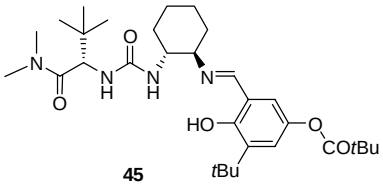
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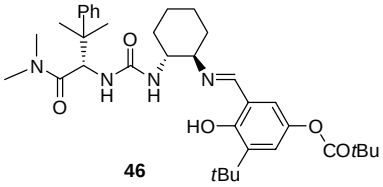
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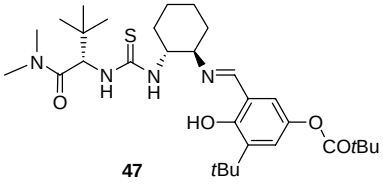
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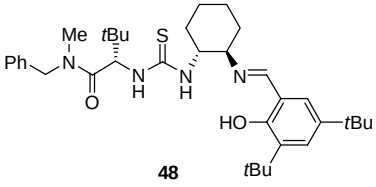
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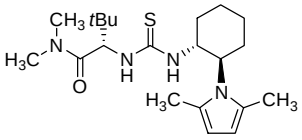
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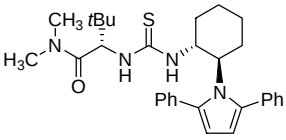
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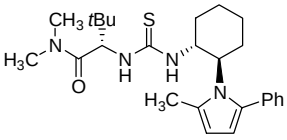
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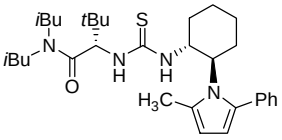
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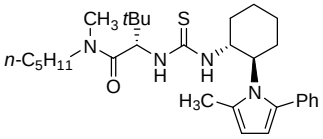
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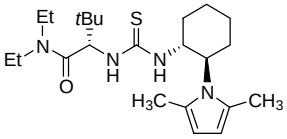
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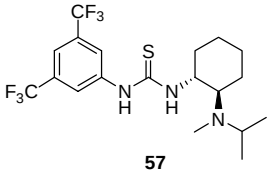
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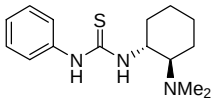
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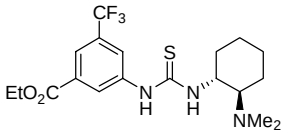
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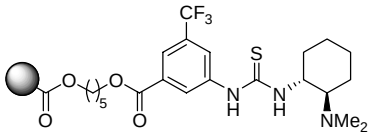
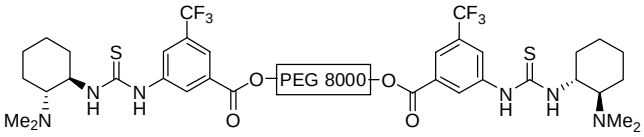

60 = carboxypolystyrene HL resin
61 = TentalGel carboxy resin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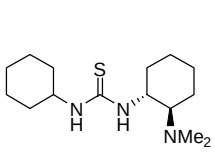
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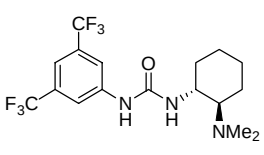
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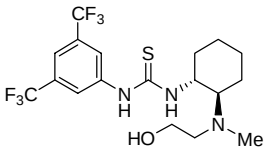
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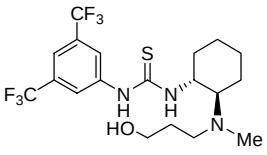
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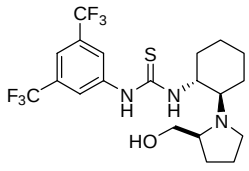
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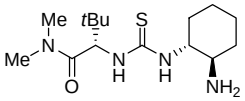
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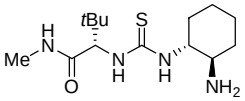
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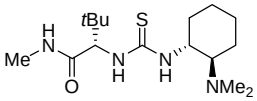
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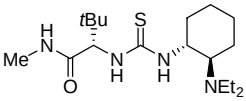
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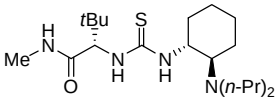
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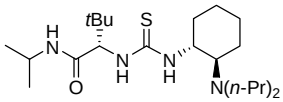
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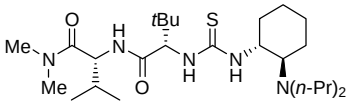
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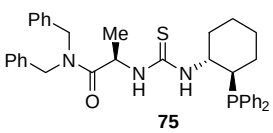
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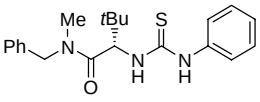
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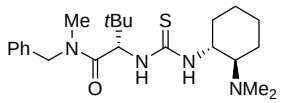
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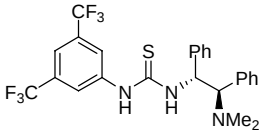
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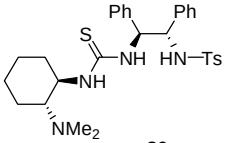
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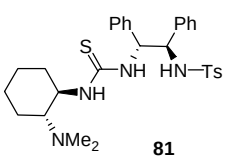
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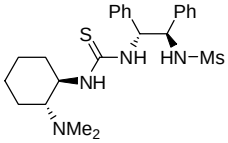
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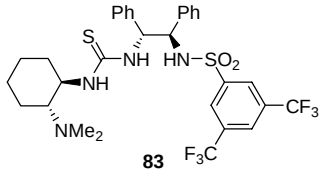

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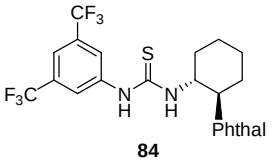

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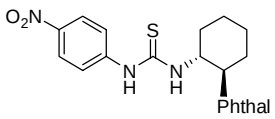

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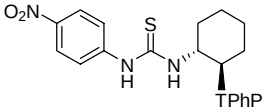

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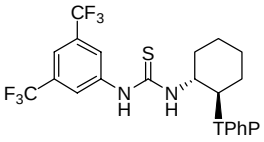

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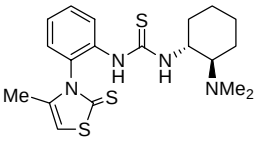
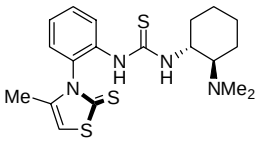


(*aR*/*aS*)-(*R*,*R*)-**88**



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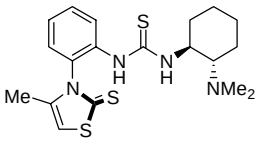

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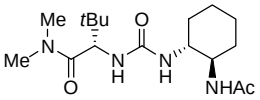

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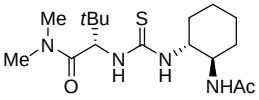

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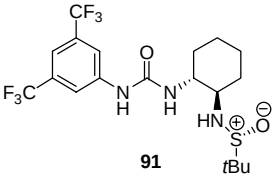

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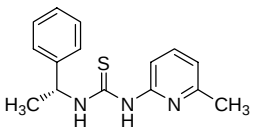

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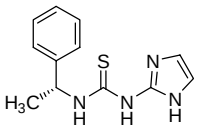

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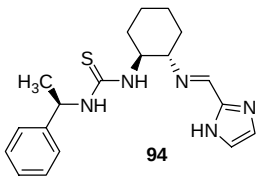

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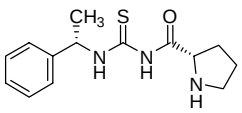

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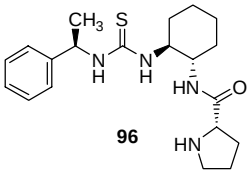

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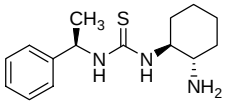

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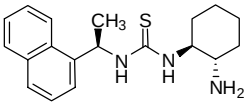

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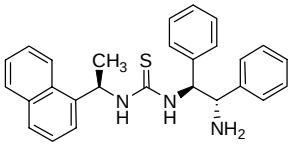

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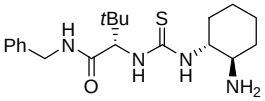

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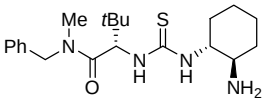

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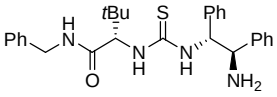

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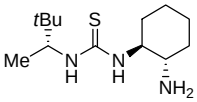

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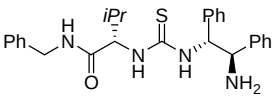

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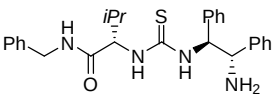

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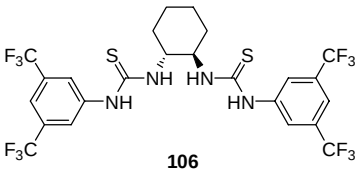

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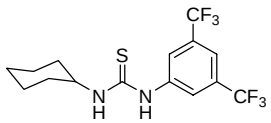

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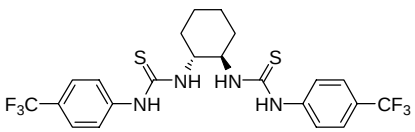

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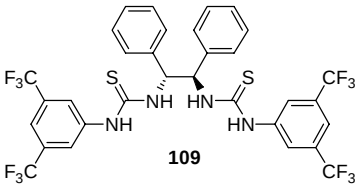

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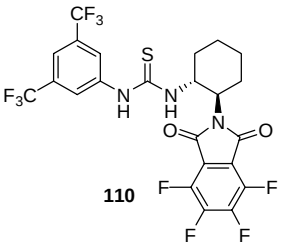

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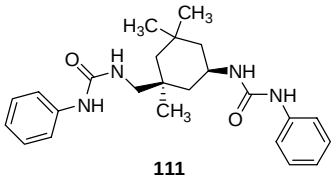

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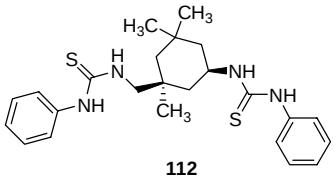

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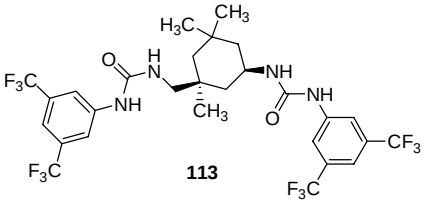

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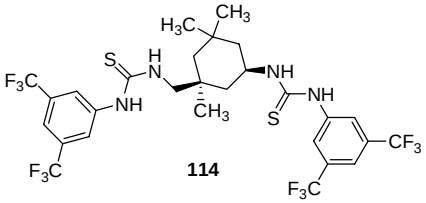

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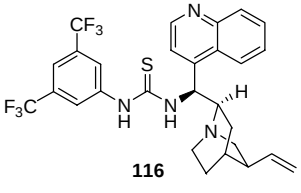

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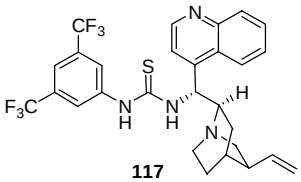
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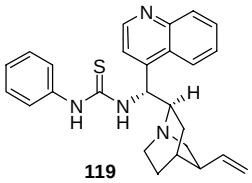
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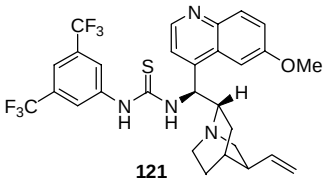
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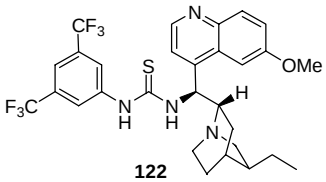
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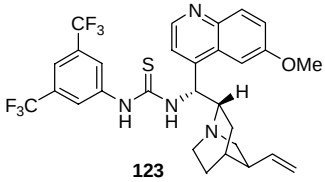
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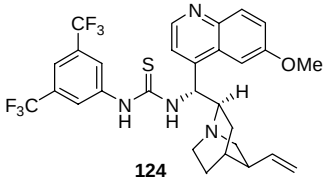
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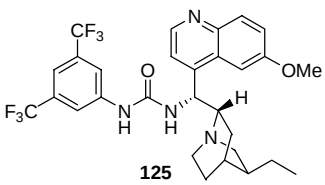
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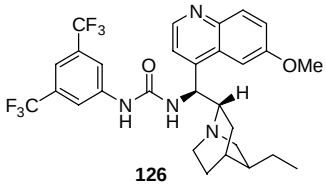
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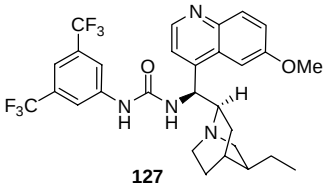
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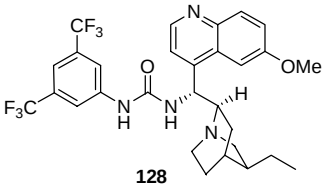
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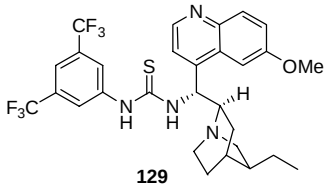
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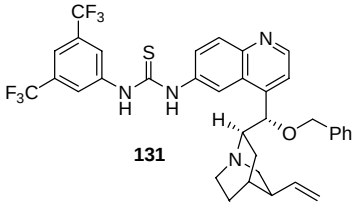
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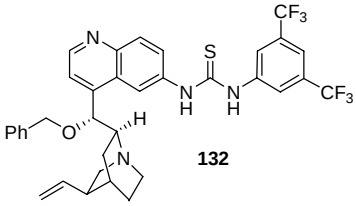
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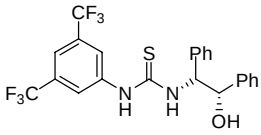
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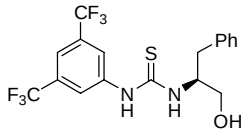
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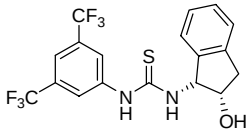
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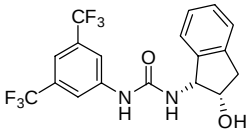
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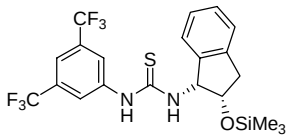
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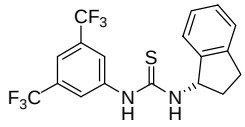
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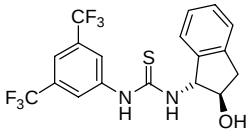
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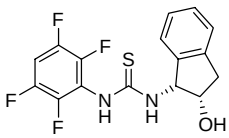
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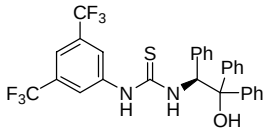
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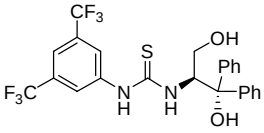
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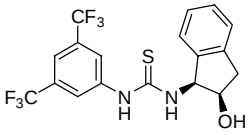
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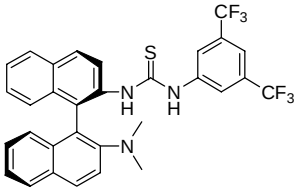
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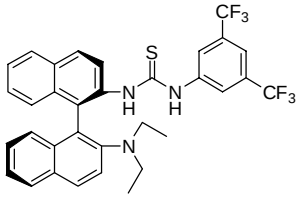
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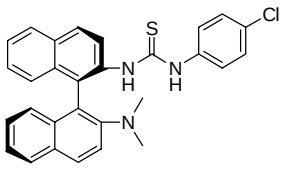
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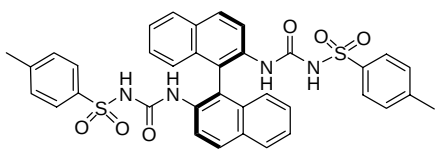
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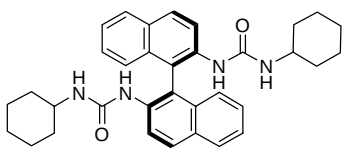
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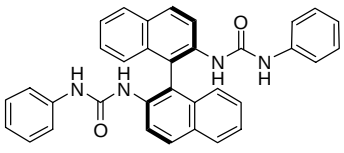
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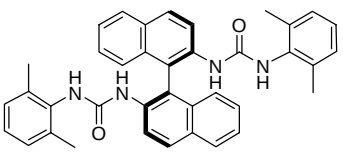

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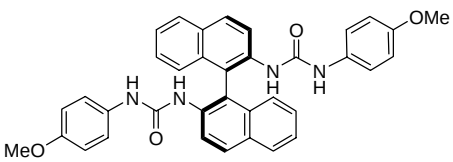

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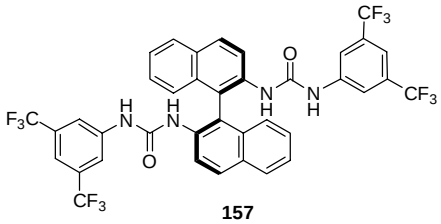

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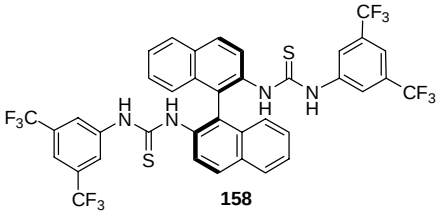

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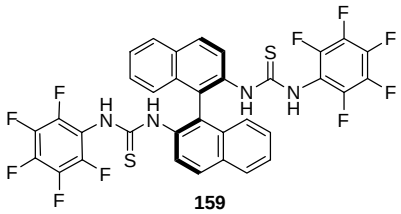

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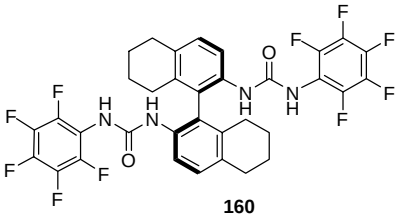

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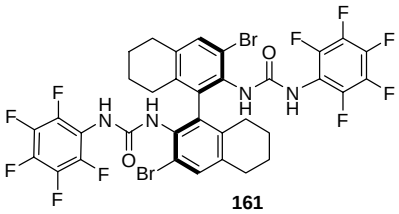

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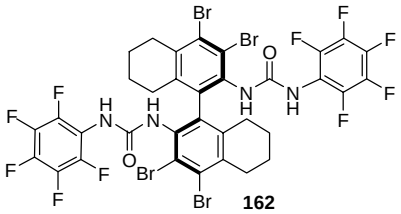

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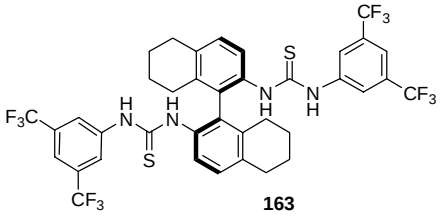

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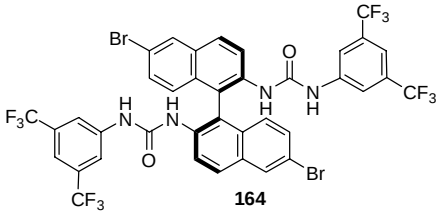

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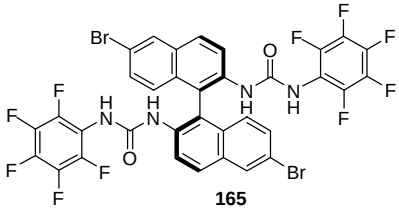

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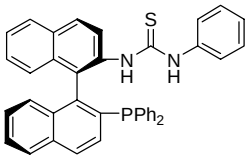

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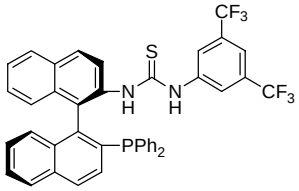

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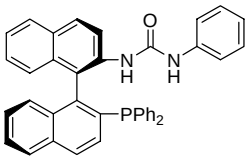

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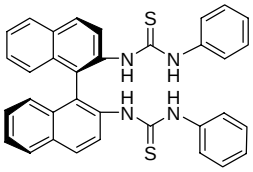

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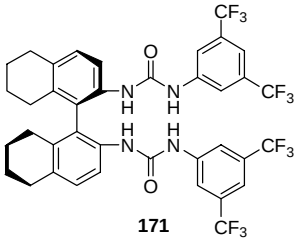

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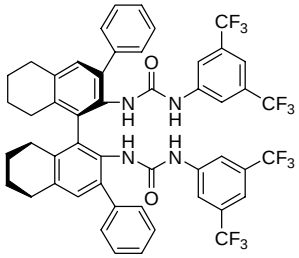

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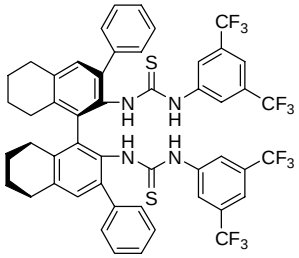

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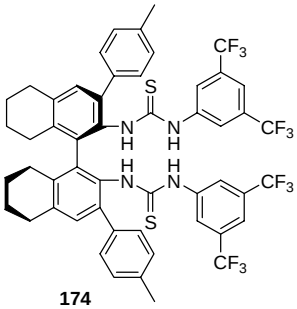

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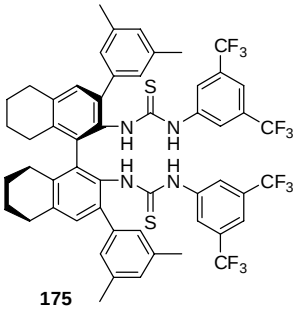

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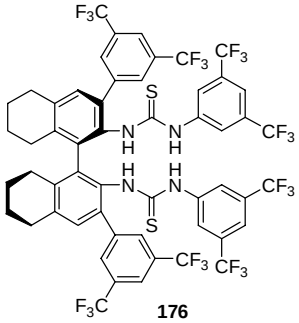

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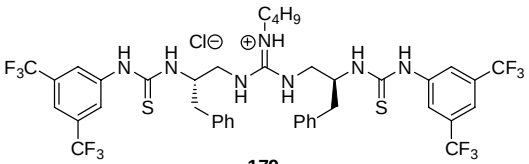

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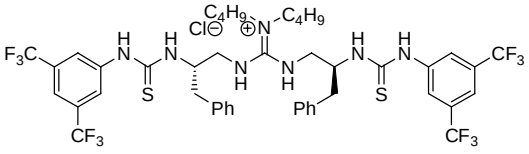

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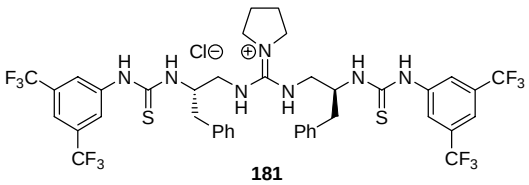

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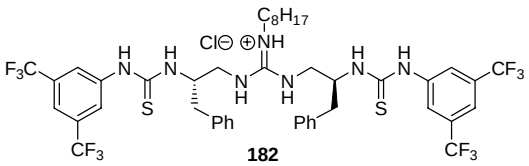

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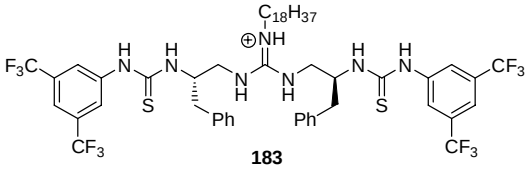

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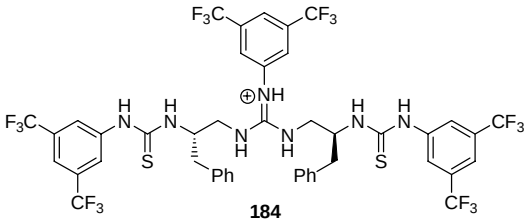

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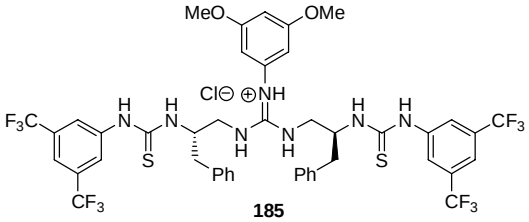

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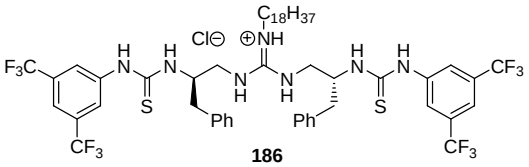

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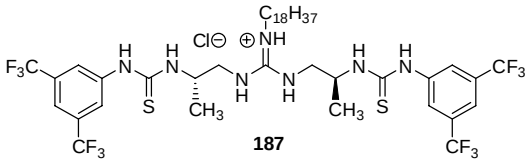

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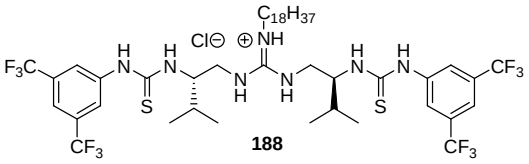

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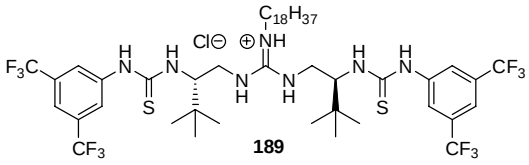

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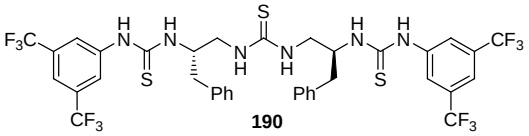

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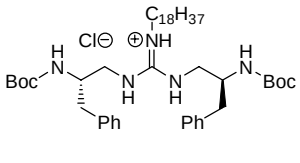

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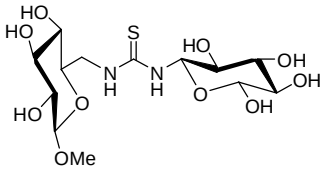

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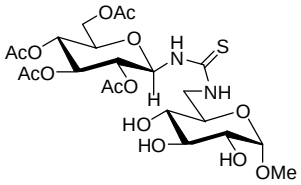

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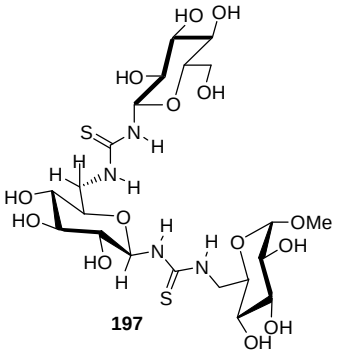

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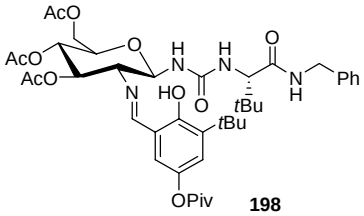

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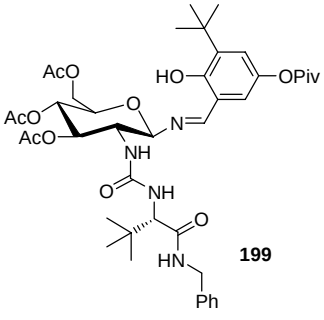

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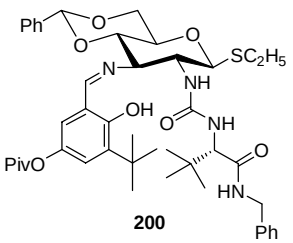

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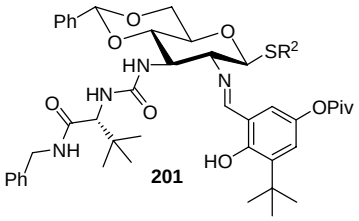

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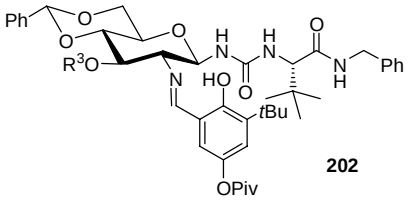

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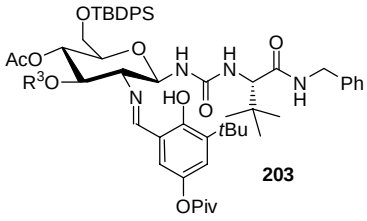

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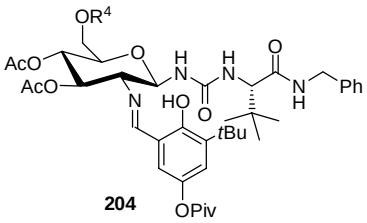
R^2 = -$(CH_2)_4$COOEt; R^3 = -(CO)$(CH_2)_2$(CO)O$(CH_2)_8$O(CO)Ps



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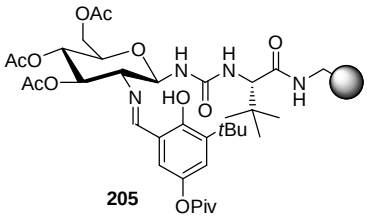

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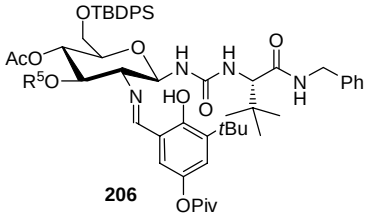

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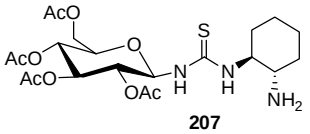
R^5 = -(CO)$(CH_2)_9$OTBDS



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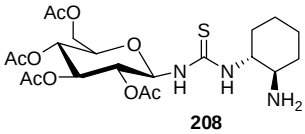

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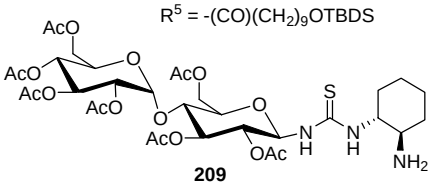

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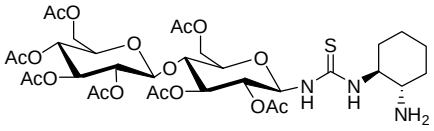

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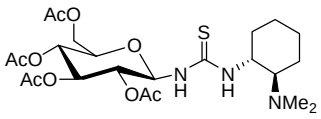

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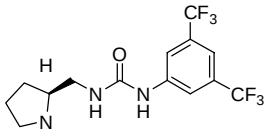

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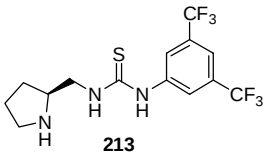

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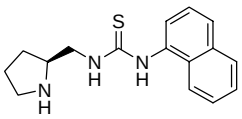

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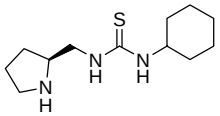

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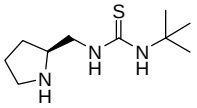

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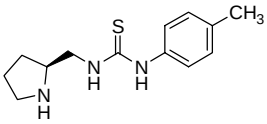

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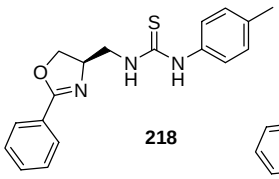

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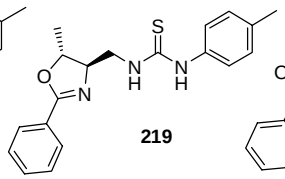

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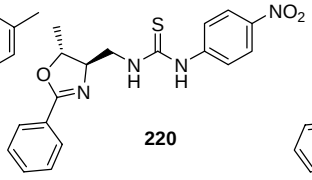

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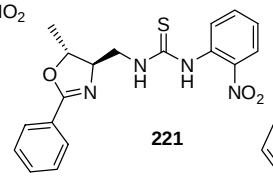

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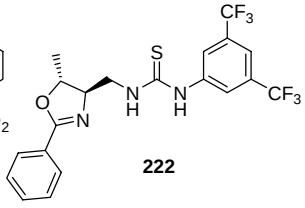

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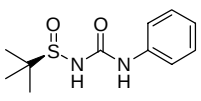

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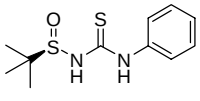

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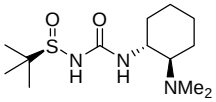

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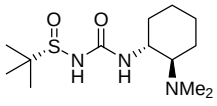

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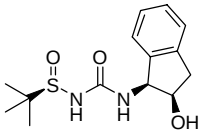

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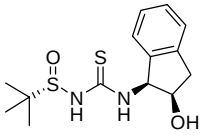

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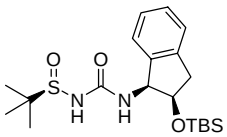

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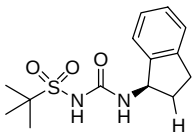

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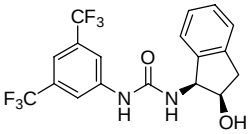

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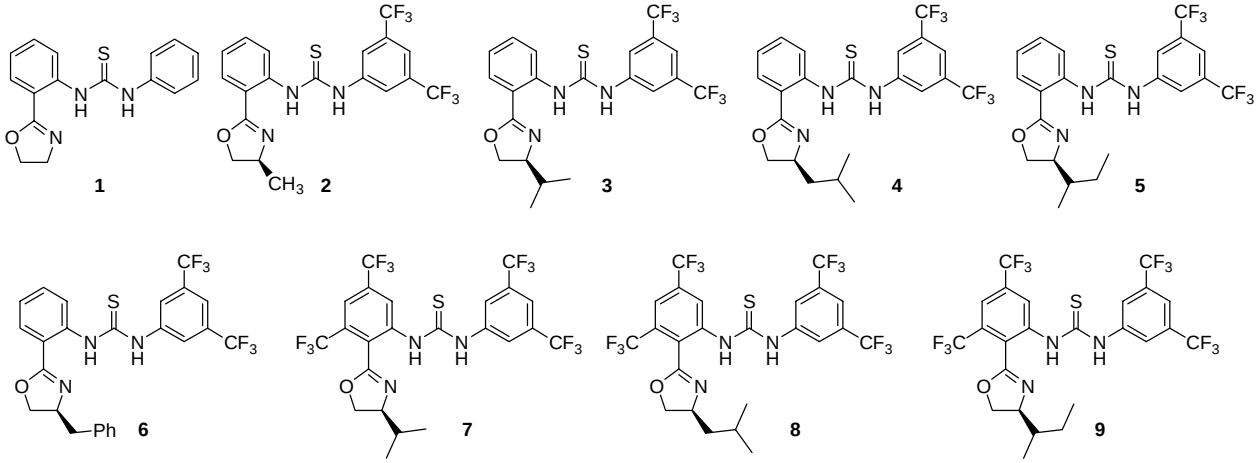
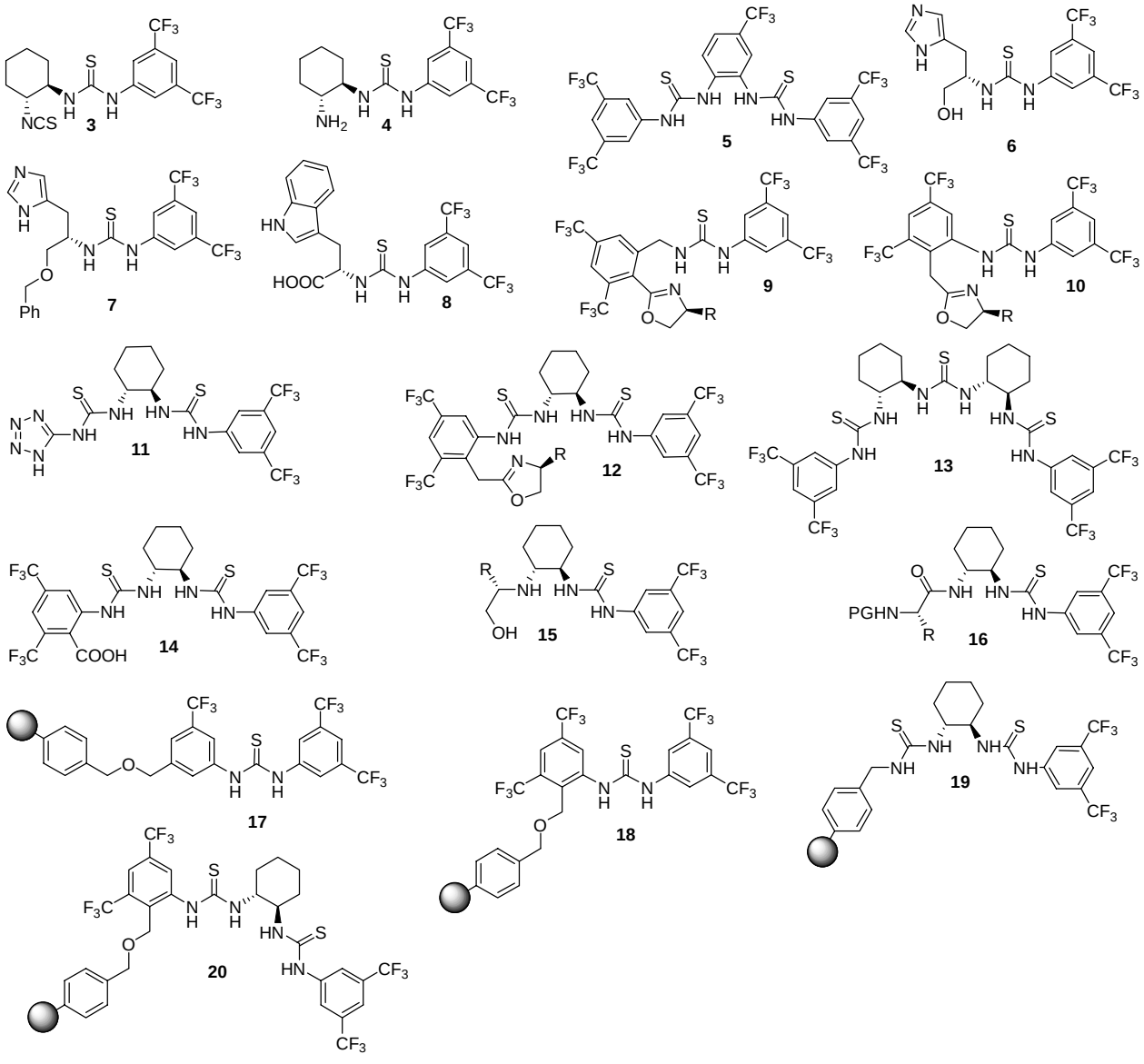
(Thio)urea structures of chapter 3 "Additional Research Projects on Organocatalysis"



(Thio)urea structures of chapter 5 "Outlook – Research Perspectives"



6.4 Abbreviations and Acronyms

Ac	acetyl
9-AECN	9-amino(9-deoxy) epicinchonine
AOT	sodium bis(2-ethylhexyl) sulphosuccinate
approx.	approximately
APT	attached proton test
aq.	aqueous
Ar	aromatic substituent
asym.	asymmetric
BINAM	(*R*)-(+)-binaphthalenediamine
BINOL	1,1′-bi-2,2′-naphthol
Bn	benzyl
Boc	*tert*-butoxycarbonyl
b.p./bp	boiling point
br	broad
Bs	brosyl (*p*-bromobenzenesulfonyl)
Bu	butyl
Bz	benzoyl
cat.	catalyst
calcd.	calculated
Cbz	benzyloxycarbonyl
CD	cinchonidine
CN	cinchonine
comp.	compound(s)
conc.	concentration
config. not det.	configuration not determined
conv.	conversion
COSY	correlation spectroscopy
Cp	cyclopentadiene
CPD	cupreidine
CPN	cupreine
CTAB	cetyltrimethylammonium bromide (cetyl: 1-hexadecanol)
d	doublet
dd	doublet of doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DCM	dichloromethane
de	diastereomeric excess

decomp.	decomposition
DEPT	distortionless enhancement by polarization transfer
DFT	density functional theory
DHP	3,4-dihydro-2*H*-pyran
DHQD	dihydroquinidine
DHQN	dihydroquinine
DIPEA	diisopropylethylamine (Hünig's base)
DKR	dynamic kinetic resolution
DMDO	dimethyl dioxirane
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
DOSY	diffusion ordered spectroscopy
DPP	diphenylphosphinoyl
dr	diastereomeric ratio
ee	enantiomeric excess
epi	epimeric
equiv./eq.	equivalent
er	enantiomeric ratio
FC	Friedel-Crafts
fw	formula weight [g mol^{-1}]
GC/MS	gas chromatography/mass spectrometry
ΔG_{rot}	Gibbs energy for rotation; rotational barrier [Kcal mol^{-1}]
HMPA	hexamethylphosphoramide
HOMO	highest unoccupied molecular orbital
HPG2	human hepatocellular liver carcinoma cell line
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
HTS	high-throughput screening
i	*iso*-
*i*Bu	*iso*-butyl
*i*Pr	isopropyl
IR	infrared
ITC	isothiocyanate
k_{obs}	observed rate constant
KR	kinetic resolution
k_{rel}	relative rate constant (relative to uncatalyzed rct.)
LRMS	low resolution mass spectroscopy
LUMO	lowest unoccupied molecular orbital
m	multiplet

M	molarity [mol L^{-1}]; molecular mass [g mol^{-1}]
MBH	Morita-Baylis-Hillman
m-CPBA	meta chloroperbenzoic acid
Me	methyl
MOP	2-methoxypropene; 2-methoxypropenyl
MS	molecular sieve; mass spectrometry
Ms	mesyl (methanesulfonyl)
MTBE	methyl *tert*-butyl ether
MVK	methyl vinyl ketone
MW	microwave
M_w	number-average molecular weight
NADH	dihydronicotinamide adenine dinucleotide
NADPH	nicotinamide adenine dinucleotide phosphate
*n*Bu	*n*-butyl
NCS	*N*-chlorosuccinimide
nd; not det.	not determined
NMR	nuclear magnetic resonance
NOE	nuclear overhauser effect
NOESY	nuclear overhauser enhancement spectroscopy
Nu	nucleophile
oxid.	oxidation
oxone®	potassium hydrogen peroxymonosulfate sulfate, triple salt $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$
PDI	polydispersity index = weight-average molecular weight (M_w)/number-average molecular weight (M_n) ≤ 1.07
PEG	poly(ethylene glycol)
PG	protective group
Ph	phenyl
Phthal	phthalimide
PIB	polyisobutylene
PMP	*p*-methoxyphenyl
ppm	parts per million
Pr	propyl
Ps	polystyrene
P*t*BS	poly(4-*tert*-butylstyrene)
PTMC	poly(trimethylene carbonate)
QD	quinidine
QN	quinine
quant.	quantitative
R*	chiral organic residue
rac	racemic

Ra-Ni	Raney nickel
rct.	reaction
recryst.	recrystallization
rel.	relative
ROESY	rotational frame nuclear overhauser effect spectroscopy
ROP	ring-opening polymerization
rr	regioisomer ratio
rt	room temperature
s	singlet
SDS	sodium dodecyl sulfate
t	triplet
t	*tert*-; tertiary
TBAA	tetrabutylammonium acetate
TBDMS (TBS)	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TBME	*tert*-butylmethyl ether
TBSCN	*tert*-butylsilyl cyanide
*t*Bu	*tert*-butyl
TEA	triethylamine
tert	tertiary
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFAA	trifluoroacetic acid
THF	tetrahydrofuran
THP	2-tetrahydropyranyl
TLC	thin layer chromatography
TMC	trimethylene carbonate
TMG	1,1,3,3-tetramethylguanidine
TMS	trimethylsilyl
TMSCN	trimethylsilyl cyanide
TMSOF	2-trimethylsilyloxyfuran
TOF	turnover frequency [h^{-1}]; TOF = n (product)/n (cat.)/ time
TON	turnover number
TPhP	tetraphenylphthalimide
Triton® X-100	octyl phenol ethoxylate
Troc	2,2,2-trichloroethoxycarbonyl
TrocCl	2,2,2-trichloroethyl chloroformate
Ts	tosyl (*p*-toluenesulfonyl)
UV/Vis	ultraviolet-visible
yl.	yield

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Eidesstattliche Erklärung
(Affirmation)

„Ich erkläre: Ich habe die vorgelegte Dissertation mit dem Titel

"Hydrogen-Bonding (Thio)urea Organocatalysts

in Organic Synthesis:

State of the Art and Practical Methods for Acetalization,

Tetrahydropyranylation, and Cooperative Epoxide Alcoholysis"

selbstständig und ohne unerlaubte fremde Hilfe und nur mit den Hilfen angefertigt, die ich in der Dissertation angegeben habe. Alle Textstellen, die wörtlich oder sinngemäß aus veröffentlichten Schriften entnommen sind, und alle Angaben, die auf mündlichen Auskünften beruhen, sind als solche kenntlich gemacht. Bei den von mir durchgeführten und in der Dissertation erwähnten Untersuchungen habe ich die Grundsätze guter wissenschaftlicher Praxis, wie sie in der „Satzung der Justus-Liebig-Universität Gießen zur Sicherung guter wissenschaftlicher Praxis" niedergelegt sind, eingehalten."

Ort, Datum	Mike Kotke