Non-Covalent Organocatalysis Utilizing Thiourea Derivatives: Understanding and Creating Organocatalyzed Reactions

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Für meine Familie

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Zusammenfassung

In der vorliegenden Arbeit werden neun Forschungsprojekte beschrieben. Beim ersten Projekt handelt es sich um eine kritische Übersicht über die zurzeit besten Methoden zur Durchführung verschiedener asymmetrischer Synthesen katalysiert durch Thioharnstoff-Derivate. Dieses Kapitel enthält Methoden für so wichtige Reaktionen wie Michael-Additionen, Desymmetrisierungen, Mannich-Reaktionen, Diels–Alder-Cycloadditionen und viele weitere. Somit zeigt dieses Kapitel, daß Thioharnstoff-Derivate wichtige und weithin nutzbare Katalysatoren für verschiedene Reaktionen sind.

Das zweite hier gezeigte Projekt handelt von der Wichtigkeit der Bis(trifluormethyl)-phenyl-Gruppe, die in vielen Thioharnstoff-Katalysatoren vorhanden ist. Durch extensive Untersuchungen mit Methoden wie (Tieftemperatur)-1D- und 2D-NMR-Techniken sowie 1D- und 2D-IR-Experimente und DFT-Rechnungen konnten wir drei signifikante Wirkweisen dieser Gruppe zeigen: Zunächst sind die stark elektronenziehenden CF_3-Gruppen für die Acidifizierung der Wasserstoff-Atome des Amins wichtig. Dies führt zur Ausbildung stärkerer Wasserstoffbrückenbindungen. Die zweite und dritte Funktion haben denselben Ursprung: nicht nur die Wasserstoffe des Amins werden acider sondern auch die Protonen in der *ortho*-Position. In der Konsequenz bildet sich eine Wasserstoffbrückenbindung zwischen dem acidifizierten *ortho*-Proton neben dem Schwefel-Atom und diesem Schwefel-Atom aus. Dies erhöht die Rigidität des aromatischen Thioharnstoff-Derivats. Außerdem kann das zweite *ortho*-Proton in Wasserstoffbrückenbindungen zu Substraten vergleichbar zu den Wasserstoff-Atomen des Amins einbezogen werden.

Das dritte Projekt handelt von den bevorzugten Konformationen von Evans-Auxiliar/$SnCl_4$-Komplexen. Hier gelang es uns durch extensive 2D-NMR- und IR-Studien sowie DFT-Rechnungen zu zeigen, daß das Evans-Auxiliar *N*-Crotonyl-oxazolidinon in Lösung eine antiperiplanare, s-*cis*-konfigurierte Konformation einnimmt. Dies steht im Gegensatz zu früheren Diskussionen hierüber. Wenn das Evans-Auxiliar durch Zinn(IV)-chlorid komplexiert wird, so bleibt die s-*cis*-Konfiguration erhalten, während sich die Amid-Bindung um 180° dreht.

Projekt Nummer vier handelt von mechanistischen Untersuchungen zur Alkoholyse von Styroloxiden. In vorherigen Untersuchungen hatten wir herausgefunden, daß Styroloxid schneller von Ethanol geöffnet wird in Anwesenheit von 2-Methyl-2-phenyloxiran. Daher wollten wir autokatalytische Effekte durch Zugabe von substöchiometrischen Mengen von 2-Methyl-2-phenyloxiran oder dem entsprechenden Ethanolyse-Produkt 2-Ethoxy-2-

phenyl-1-propanol zum ursprünglichen Katalysator-System bestehend aus *N*,*N*'-Bis[3,5-bis(trifluormethyl)phenyl]thioharnstoff und Mandelsäure untersuchen. Unsere Experimente zeigen, daß 2-Ethoxy-2-phenyl-1-propanol ein zusätzlicher Katalysator für die Ethanolyse von Styroloxiden ist.

Desweiteren wurden Versuche zur Entwicklung einer organokatalytischen Variante der Passerini-Reaktion durchgeführt; die Ergebnisse werden in Kapitel 5 beschrieben. Überraschenderweise konnten wir sieben Passerini-Produkte verschiedener Benzaldehyd-Derivate ohne die Verwendung eines Katalysators sogar bei niedrigen Temperaturen synthetisieren.

In Kapitel 6 zeigen wir unsere Experimente zur organokatalytischen Synthese von 1,4-Dioxepinen. Wir konnten sechs 1,4-Dioxepine aus Epoxiden und *α*,*β*-ungesättigten Aldehyden mit aromatischen sowie aliphatischen Substituenten durch Katalyse mit 2 mol% eines Thioharnstoff-Derivats synthestisieren. Die Reaktion mit Methylvinylketon führte nicht zur Bildung der gewünschten 1,4-Dioxepine mit allen drei Epoxiden. Leider konnten wir aufgrund ihrer Instabilität keine zufriedenstellende Reinigung der Produkte durch verschiedene Methoden erreichen. Sogar die Derivatisierung durch eine Diels–Alder-Cycloaddition mit Cyclopentadien half nicht bei der Lösung dieses Problems.

Das siebte Kapitel beschreibt unsere Versuche eine Art „organokatalytische Sharpless-Dihydroxylierung“ zu entwickeln. Wir verwendeten verschiedene Oxidationsmittel und verschiedene Lösungsmittel oder Lösungsmittel-Mischungen sowie einige Katalysatoren und Katalysator-Systeme. Leider waren wir bei der Lösung dieser Aufgabe nicht erfolgreich.

Unsere Versuche zur organokatalytischen Synthese von Oxazolidinon-Derivaten werden in Kapitel 8 beschrieben. Nur durch Verwendung des sehr reaktiven Chlorsulfonylisocyanats konnten wir die Bildung von Oxazolidinon beobachten. Dies geschieht allerdings auch in Abwesenheit eines Katalysators.

Abschließend beschreibt Kapitel 9 unser Projekt zur Entwicklung einer organokatalytischen Prins-Reaktion. Wir führten einige Experimente mit verschiedenen Katalysatoren oder Katalysator-Systemen durch. Mit allen waren wir nicht in der Lage einen Umsatz zu den gewünschten Produkten zu beobachten.

Summary

The present thesis describes nine projects performed during doctoral research. The first project deals with the critical review of the best methods available at this time for various asymmetric syntheses utilizing thiourea-derived catalysts. This chapter contains methods for important reactions such as Michael additions, desymmetrizations, Mannich reactions, Diels–Alder cycloadditions, and many more. Thus, the chapter proofs thiourea derivatives to be important and widely utilizable catalysts in various reactions.

The second project described herein deals with the importance of the bis(trifluoromethyl)-phenyl groups in many thiourea-derived catalysts. With extensive studies utilizing methods such as (low-temperature) 1D- and 2D-NMR techniques as well as 1D- and 2D-IR experiments and DFT computations we found three significant modes of action of this moiety: At first, acidification of the amine's hydrogen atoms by the strong electron-withdrawing CF_3 groups is of importance. This leads to stronger hydrogen-bonding abilities. The second and the third function have the same source: not only the amine's hydrogens are acidified but also the protons in the *ortho*-position. Consequently, a hydrogen bond between the acidified *ortho*-proton next to the sulphur atom and the sulphur atom is formed, enhancing rigidity of the aromatic thiourea derivative. Second, the other *ortho*-proton can be involved in hydrogen bonds to substrates akin to the amine's hydrogen atoms.

The third project deals with the preferred conformations of Evans auxiliary/$SnCl_4$ complexes. Here we were able to show with extensive 2D-NMR and IR studies as well as DFT computations that the Evans auxiliary *N*-crotonyloxazolidinone adopts only an antiperiplanar, s-*cis* configured conformation in solution in contrast to former discussions. When complexed by tin(IV) chloride this s-*cis* configuration remains while the amide bond rotates by 180°.

Project number four is about mechanistic studies on the alcoholysis of styrene oxides. In preliminary studies we found that styrene oxide is opened faster by ethanol in the presence of 2-methyl-2-phenyloxirane. Thus, we wanted to examine autocatalytic effects by adding substiochiometric amounts of 2-methyl-2-phenyloxirane or its respective ethanolysis product 2-ethoxy-2-phenyl-1-propanol to the original catalyst system consisting of *N*,*N*'-bis[3,5-bis(trifluoromethyl)phenyl]thiourea and mandelic acid. Our experiments show that 2-ethoxy-2-phenyl-1-propanol is working as an additional catalyst in the ethanolysis of styrene oxide.

An organocatalytic variant of the Passerini reaction was also attempted; the results are described in Chapter 5. We were able to synthesize seven Passerini products of various benzaldehyde derivatives, surprisingly, without the utilization of any catalyst even at lowered temperatures.

In Chapter 6 we show our experiments on the organocatalytic synthesis of 1,4-dioxepines. We were able to synthesize six 1,4-dioxepines from epoxides and α,β-unsaturated aldehydes with aromatic as well as aliphatic substituents catalyzed by 2 mol% of a thiourea derivative. The reaction with methyl vinyl ketone did not lead to the formation of the desired 1,4-dioxepines with all three epoxides. Unfortunately, we could not achieve a satisfying purification of the products by several methods because of their instability. Even the derivatization by a Diels–Alder cycloaddition with cyclopentadiene did not help in solving this task.

The seventh chapter describes our attempts to create a kind of "organocatalytic Sharpless dihydroxylation". We tried several oxidizing agents and several solvents or solvent mixtures as well as some catalysts and catalyst systems. However, unfortunately, in this task we did not succeed.

Our attempts on the organocatalytic synthesis of oxazolidinone derivatives are described in Chapter 8. Only with the utilization of the very reactive chlorosulfonyl isocyanate we were able to observe the formation of oxazolidinone but this happens as well in the absence of any catalyst.

Finally Chapter 9 lines out our project on the development of an organocatalytic Prins reaction. Here, we performed several experiments with various catalysts or catalyst systems. With all of these we were not able to observe any conversion to the desired products.

Abbreviations and Acronyms

1D	one-dimensional
2D	two-dimensional
3D	three-dimensional
abs.	absolute
Ac	acyl
AD	asymmetric dihydroxylation
anhyd	anhydrous
All	allyl
atm.	atmosphere
BCP	bond critical points
BINAM	(*R*)-(+)-binaphthalenediamine
Bn	benzyl
br	broad
Bz	benzoyl
calcd	calculated
Cbz	benzyloxycarbonyl
Conv.	conversion
COSY	correlated spectroscopy
m-CPBA	*meta*-chloroperbenzoic acid
CSP	chiral stationary phase
Cy	cyclohexyl
d	doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
de	diastereomeric excess
DFT	density functional theory
DHPM	dihydropyrimidin-2(1*H*)-one
$(DHQ)_2PHAL$	dihydroquinine 1,4-phthalazinediyl diether
$(DHQD)_2PHAL$	dihydroquinidine 1,4-phthalazinediyl diether

DKR	dynamic kinetic resolution
DMAP	4-(dimethylamino)pyridine
dr	diastereomeric ratio
ee	enantiomeric excess
equiv.	equivalent(s)
er	enantiomeric ratio
ESI	electrospray ionization
Et	ethyl
et al.	et alii
F-SPE	fluorous solid-phase extraction
FTIR	Fourier transform infrared spectroscopy
FWHM	full width at half maximum
GC	gas chromatography
h	hour(s)
HF	Hartree-Fock
HMPA	hexamethylphosphoric acid triamide
HOESY	heteronuclear Overhauser effect spectroscopy
HOMO	highest occupied molecular orbital
HPLC	high-performance liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
iBu	isobutyl
iPr	isopropyl
IR	infrared
LUMO	lowest unoccupied molecular orbital
m	*meta*
m	multiplet
M	molar, mol/L
MBH	Morita–Baylis–Hillman
Me	methyl
mg	milligram(s)
min	minute(s)
MOP	2-methoxypropene
MS	molecular sieve or mass spectrometry

MVK	methyl vinyl ketone
NBO	natural bond order
NCS	*N*-chlorosuccinimide
nm	nanometer(s)
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
Ns	*p*-nitrobenzenesulfonyl (nosyl)
o	*ortho*
OPA	optical parametric amplifier
p	*para*
P2D-IR	polarization-dependent two-dimensional infrared
PCM	polarizable continuum model
PE	petroleum ether
Ph	phenyl
PMP	*N*-*p*-methoxyphenyl
Pr	propyl
QTAIM	quantum theory of atoms in molecules
Ref	reference
ROESY	rotating-frame nuclear Overhauser effect spectroscopy
rr	regioisomeric ratio
rt	room temperature
s	singlet
sat.	saturated
SCRF	self-consistent reaction field
SDD	Stuttgart/Dresden effective core potential
SFC	supercritical fluid chromatography
t	triplet
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TBME	*tert*-butyl methyl ether
t-Bu	*tert*-butyl
TCBA	2,4,6-trichlorobenzoic acid
TEA	triethylamine

Temp	temperature
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
THP	tetrahydropyran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
t_R	retention time
Troc	2,2,2-trichloroethoxycarbonyl
Ts	*p*-toluenesulfonyl (tosyl)
UAHF	united atom Hartree-Fock
UAKS	united atom Kohn-Sham
ZPVE	zero-point vibrational energy

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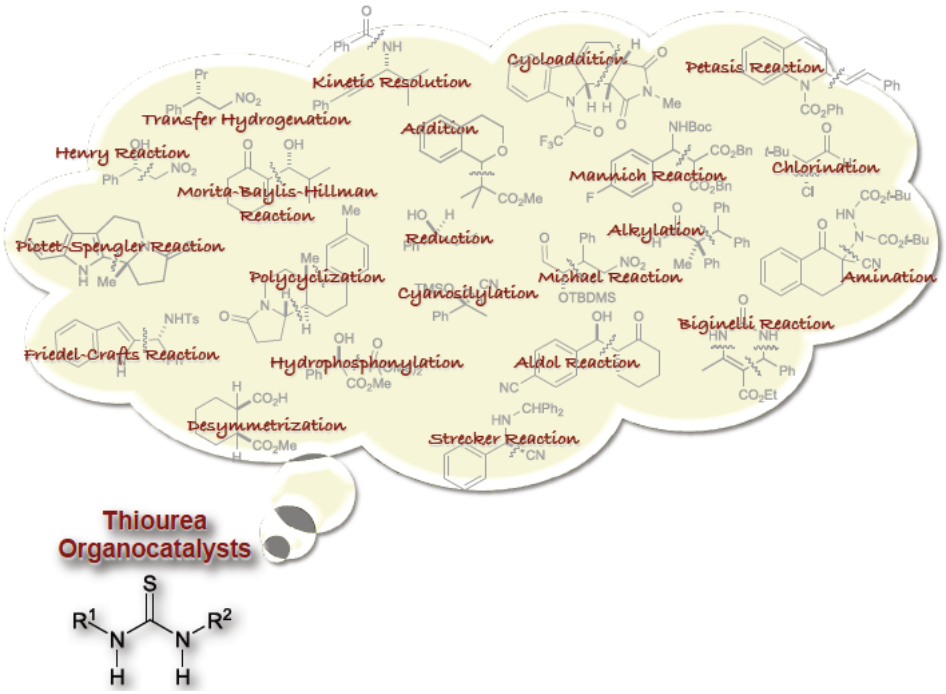
1 Hydrogen-Bonding Catalysts: Thiourea Catalysis



Chapter 1 presents the chapter **"Hydrogen-Bonding Catalysts: Thiourea Catalysis"** published in the book **"Asymmetric Organocatalysis Volume 2: Brønsted Base and Acid Catalysts, and Additional Topics"**. This book is part of a two-volume work for the Science of Synthesis Reference Library by the Georg Thieme Verlag KG, Stuttgart, and was edited by Keiji Maruoka (University of Kyoto). This book chapter will serve as an introduction to this thesis and is reprinted with the friendly permission of the **Georg Thieme Verlag KG, Stuttgart**, which is gratefully acknowledged.

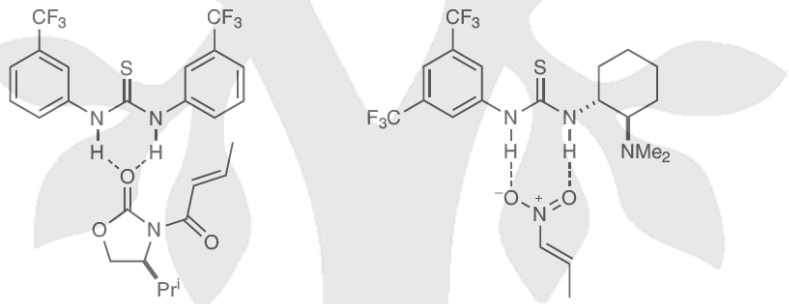
2.2.4 Hydrogen-Bonding Catalysts: (Thio)urea Catalysis

K. Hof, K. M. Lippert, and P. R. Schreiner

General Introduction

Over the last few years, thiourea derivatives have proven to be highly effective as organocatalysts in a wide variety of organic transformations.[1–6] The catalytic efficacy of such thiourea catalysts derives from them being weak Brønsted acids that allow the formation of tightly bound hydrogen-bonding complexes whose reactivity is chiefly determined by the nature of the catalyst.[7,8] In comparison with the corresponding urea derivatives, thiourea analogues are less prone to self-association because of the lower tendency of the thiocarbonyl group to accept hydrogen bonds.[1] Unsurprisingly, thiourea derivatives are excellent anion receptors,[5,9,10] and recognition motifs such as a double hydrogen-bonding interaction with neutral substrates (e.g., carbonyl or nitro compounds) have been proposed as the mode of action (Scheme 1).[1,7]

Scheme 1 Examples of Proposed Double Hydrogen-Bonding Interactions of Thiourea Derivatives with Carbonyl (Left)[7] or Nitro Compounds (Right)[11]

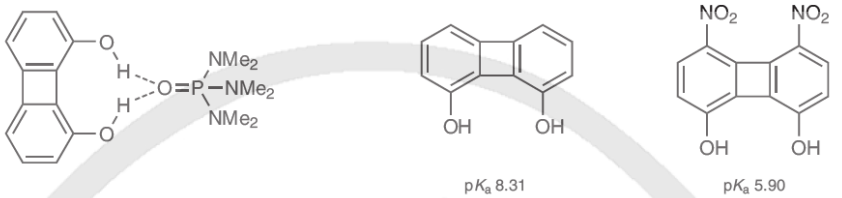


2.2.4.1 On the Way to Thiourea Organocatalysts

Several studies paved the way for the development of thiourea organocatalysts. Hine and co-workers showed in 1984 that the two hydroxy groups of biphenylene-1,8-diol bind to the same oxygen atom in hexamethylphosphoric triamide, 1,2,6-trimethylpyridin-4(1*H*)-one, or 2,6-dimethyl-4*H*-pyran-4-one (Scheme 2).[12] A year later, Hine and co-workers reported that biphenylene-1,8-diol catalyzes the reaction of an epoxide with a nucleophile via double hydrogen bonding.[13,14] In 1987, the same group reported that biphenylenediols with electron-withdrawing groups are better complexing agents than the unsubstituted diol due to more acidic hydroxy groups: biphenylene-1,8-diol has a pK_a value of 8.31, whereas the pK_a value of the 4,5-dinitro-substituted diol is 5.90 (in water per hydroxy group).[15]

for references see p 407

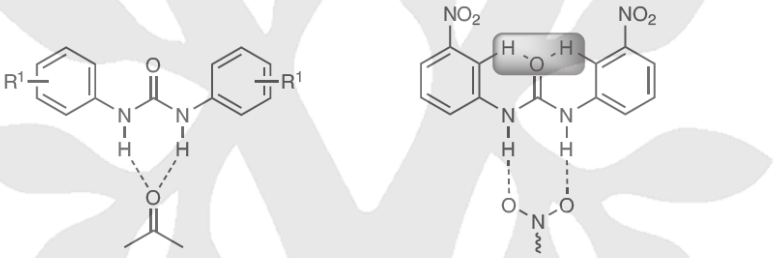
Scheme 2 Hine's Biphenylene-1,8-diol Binding to Hexamethylphosphoric Triamide (Left)[12] and pK_a Values of Biphenylene-1,8-diol and 4,5-Dinitrobiphenylene-1,8-diol (Right)[15]



pK_a 8.31 pK_a 5.90

In 1988, Etter and Panunto reported a urea derivative as a good proton donor.[16] In 1990, Etter and co-workers reported cocrystallization experiments with diarylurea derivatives[17] that showed double hydrogen bonding to the guest molecules (Scheme 3). They found that *meta*-substituted diarylureas have the ability to form cocrystals with hydrogen-bond acceptors. Etter and co-workers suggested that this effect is due to two very weak hydrogen bonds between the *ortho*-protons of the phenyl rings with the urea's carbonyl group.[17] This slight interaction lowers the affinity of self-association and opens the door for hydrogen-bond acceptors other than the urea itself.

Scheme 3 Etter's Cocrystal Consisting of a Urea Derivative and Acetone (Left) and Effect of the *meta*-Substitution Pattern (Right)[17]



In the same year, the Kelly group reported that biphenylenediols are catalysts for the Diels–Alder reaction of α,β-unsaturated aldehydes and ketones with dienes.[18] They suggested that the bidentate binding affords a more rigid geometry and thus minimizes conformational difficulties arising in the Diels–Alder reaction with monodentate catalysts.[18] Curran and Kuo published in 1995 a dipolar Claisen rearrangement catalyzed by a diarylurea.[19] In this article, thiourea derivatives were mentioned for the first time as catalysts. In the same year, Wilcox and co-workers reported their experiments on the association constants of aryl(thio)urea derivatives with 4-(tributylammonio)butane-1-sulfonate.[20] They found thiourea derivatives with electron-withdrawing substituents to be stronger binders than those without such groups, an effect that Hine and co-workers found 8 years previously for biphenylene-1,8-diols as well (see above). Another finding was that *para*-nitro substitution leads to stronger 1:1 complexation than having nitro groups in the *meta*-position. This finding was in contrast to that of Etter and co-workers in their cocrystallization studies of 1990.[17]

2.2.4.2 Thiourea Derivatives as Organocatalysts in Organic Synthesis

2.2.4.2.1 Nonstereoselective Transformations with Achiral Thiourea Derivatives

Achiral thiourea derivatives catalyze a variety of organic transformations. The most widespread catalyst is *N*,*N*′-bis[3,5-bis(trifluoromethyl)phenyl]thiourea (**1**), introduced as an organocatalyst by Wittkopp and Schreiner.[7,8] In proof-of-principle studies in 2002/2003, thiourea **1** was first utilized in Diels–Alder reactions; these studies laid the groundwork for the now ubiquitous (thio)urea double hydrogen-bonding motif.[7,8] The 3,5-bis(trifluoromethyl)phenyl group has proven essential in many catalytically active thiourea derivatives,[21] most likely due to its electron-withdrawing ability, required for substrate binding. Mesoporous silica nanoparticles functionalized with (thio)urea moieties were also applied in Diels–Alder reactions by the Lin group.[22] In 2003, Takemoto and co-workers developed a nonstereoselective nucleophilic addition of trimethylsilyl cyanide and ketene silyl acetals to nitrones and aldehydes also catalyzed by **1**.[23]

In 2004, Herrera, Ricci, and co-workers published a method for the Friedel–Crafts alkylation of indoles catalyzed by **1** or its urea analogue.[24] Connon and Maher first demonstrated in 2004 a (thio)urea-catalyzed and 1,4-diazabicyclo[2.2.2]octane-promoted Morita–Baylis–Hillman reaction.[25]

In 2006, Kotke and Schreiner reported a method for the acetalization of aldehydes utilizing **1** as catalyst; this was also the first report on a thiourea-assisted heterolysis (through binding of the counterion), in this case that of an ortho ester required for the acetalization.[26] This contribution also marks the departure from carbonyl group activation. Pettersen and Herrera published in 2006 a method for the conjugate addition of hydrazones and nitroalkenes utilizing **1** as organocatalyst.[27] In the same year, Kleiner and Schreiner published a method for the aminolysis of epoxides catalyzed by **1** in aqueous solution; contrary to expectation, water and hydrogen-bonding activation are not mutually exclusive but actually can enhance each other (through "hydrophobic amplification").[28] In 2006/2007, the List group reported methods for the acylcyanation of imines[29,30] as well as aldehydes and amines utilizing catalyst **1**.[31] The group of Hedrick and Waymouth developed methods for ring-opening polymerizations utilizing thiourea organocatalysts in 2005–2007.[32–35]

Hiersemann, Strassner, and co-workers published a diaryl(thio)urea-catalyzed Claisen rearrangement in 2007.[36] Thiourea **1** was shown to have only a very weak catalytic effect in various solvents, and the conversions of the ether in chloroform at 45 °C are in the same range as those of the reference experiments without catalyst **1**. DFT computations led to the conclusion that the energy gained through stabilization of the transition state is not sufficient to compensate for the additional energy needed for conformational changes and the formation of the reactive complex.[36] In 2007, Kotke and Schreiner reported the tetrahydropyranyl (THP) and 2-methoxypropan-2-yl (MOP) protection reactions of alcohols utilizing **1** with catalyst loadings down to 0.001 mol%.[37] Again, in this reaction the catalyst stabilizes the developing oxyanion hole in the transition structure for the addition of alcohols to 3,4-dihydro-2*H*-pyran or 2-methoxypropene. Procuranti and Connon published a method for the chemoselective reduction of 1,2-diketones catalyzed by a bifunctional thiourea derivative bearing an organic hydride donor.[38] Later in 2007, Costero and co-workers showed biphenylylthioureas to be good organocatalysts for electrochemical reductions of aromatic carboxylates.[39] Also in 2007, Zhang and Schreiner developed methods for the transfer hydrogenation of aldimines[40] and the reduction of conjugated nitroalkenes utilizing **1**,[41] thereby making a connection to biomimetic reductions (as, for example, with old yellow enzyme).

In 2008, the Khaksar group published the *tert*-butoxycarbonylation of amines catalyzed by thiourea.[42] The resulting *N*-*tert*-butoxycarbonyl-protected amines are obtained in excellent yields of 90–99%. Mechanistically, it was proposed that thiourea activates

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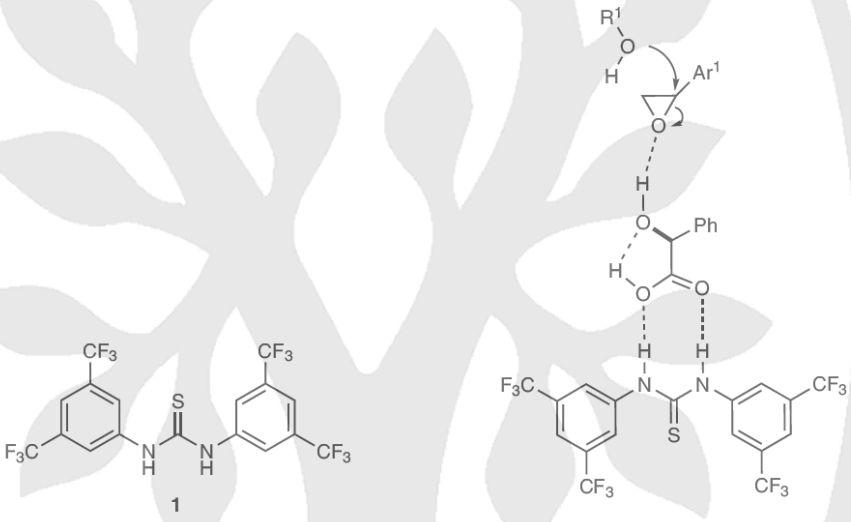
the di-*tert*-butyl dicarbonate via hydrogen-bonding interactions.[42] Also in 2008, Connon and co-workers reported a Corey–Chaykovsky reaction catalyzed by the urea analogue of thiourea derivative **1**.[43] The resulting epoxides are generally obtained in 90–96% yield, although in one case no epoxide could be obtained, and in two other cases the epoxides decompose during purification resulting in isolated yields of 57 and 75%. Schreiner and co-workers developed a completely regioselective alcoholysis of epoxides cooperatively catalyzed by thiourea derivative **1** and mandelic acid[44] (highlighted in *Synfacts*[45]). This was the first work employing two organocatalysts in a cooperative manner. Schreiner and co-workers proposed a ternary complex consisting of the thiourea derivative, mandelic acid, and the epoxide; an intramolecular hydrogen bond in mandelic acid acidifies the α-hydroxy proton (Scheme 4).[44] Russo and Lattanzi reported in 2009 a method for the oxidation of sulfides catalyzed by thiourea **1**.[46] The resulting sulfoxides are obtained in moderate to excellent yields of 69–99%. A mechanism was proposed in which the *tert*-butyl hydroperoxide is activated by a double hydrogen-bonding interaction with **1**.[46]

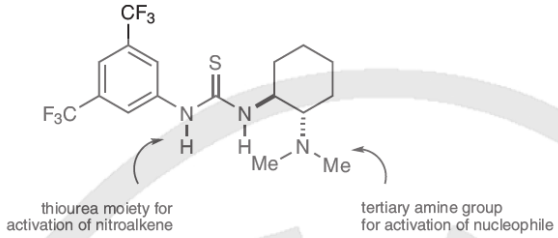
Scheme 4 Structure of *N,N′*-Bis[3,5-bis(trifluoromethyl)phenyl]thiourea and Its Proposed Ternary Complex in the Regioselective Alcoholysis of Styrene Oxides[44]



2.2.4.2.2 Stereoselective Transformations with Chiral Thiourea Derivatives

A rapidly growing field is the application of chiral and bifunctional thiourea organocatalysts in the asymmetric synthesis of organic compounds. These reactions are the subject of this chapter. In 2003, the first bifunctional thiourea organocatalyst was introduced by the Takemoto group for the enantioselective Michael reaction of malonates with nitroalkenes.[21] This organocatalyst **2** was conveniently derived from cyclohexane-1,2-diamine [Scheme 1 (right) and Scheme 5]. Takemoto and co-workers reasoned that a basic moiety in the thiourea catalyst would activate the nucleophile while the thiourea group activates the nitroalkene. A simultaneous activation could thus take place. The linking of these two different functionalities with a chiral spacer was supposed to introduce enantioselectivity. In their work they showed that the basic moiety has to be within the thiourea derivative; the addition of an external base leads to poor selectivities and reaction rates.[21]

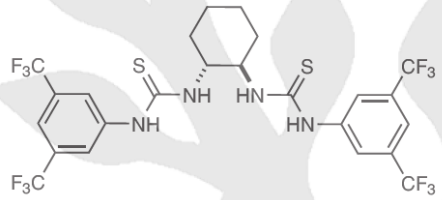
Scheme 5 The First Bifunctional Thiourea Derivative, Designed by the Takemoto Group[21]



2

The Nagasawa group introduced the first bisthiourea organocatalyst in 2004.[47] This organocatalyst **3** (Scheme 6) was designed for the enantioselective Morita–Baylis–Hillman reaction. It was reasoned that two thiourea moieties in one molecule would activate both reactants and would hold them together.[47]

Scheme 6 The First Bisthiourea, Developed by Nagasawa and Co-workers[47]



3

In 2005, the first thiourea derivative bearing a cinchona alkaloid moiety was implemented by Chen and co-workers,[48] followed by similar derivatives developed independently by the Connon group[49] as well as Soós and co-workers[50] in 2005. In the same year, the first 2,2′-diamino-1,1′-binaphthyl (BINAM) derived thiourea organocatalyst was presented by the Wang group.[51] A wide range of asymmetric reactions can be catalyzed by the aforementioned and other chiral and bifunctional thiourea derivatives. Among these are Michael reactions (Section 2.2.4.3), Mannich reactions (Section 2.2.4.4), desymmetrizations (Section 2.2.4.12), Diels–Alder cycloadditions (Section 2.2.4.14.1), Morita–Baylis–Hillman reactions (Section 2.2.4.7), and Strecker reactions (Section 2.2.4.8), to mention just a few examples covered in this chapter. Not covered are the methods for the thiourea-catalyzed Nazarov cyclization reported by Tius and co-workers in 2010,[52] and the "interrupted" Feist–Bénary reaction published by the Zhang group in the same year.[53]

2.2.4.3 Michael Addition

2.2.4.3.1 Michael Addition of 1,3-Dioxolan-4-ones to 1-Nitro-2-phenylethenes

In 2007, Dixon and co-workers published an organocatalytic diastereoselective and enantioselective Michael addition of 5-aryl-1,3-dioxolan-4-ones to 1-nitro-2-phenylethenes (β-nitrostyrenes) (Scheme 7).[54] An *epi*-9-amino-deoxy cinchona alkaloid derivative catalyzes the addition of a 1,3-dioxolan-4-one derived from mandelic acid to nitrostyrenes with diastereoselectivities of up to 98% and enantioselectivities of up to 89%. Substituents in the *ortho*-position increase reaction times (>250 h), although high enantioselectivities are observed. The best results for relatively short reaction times are shown in Scheme 7.

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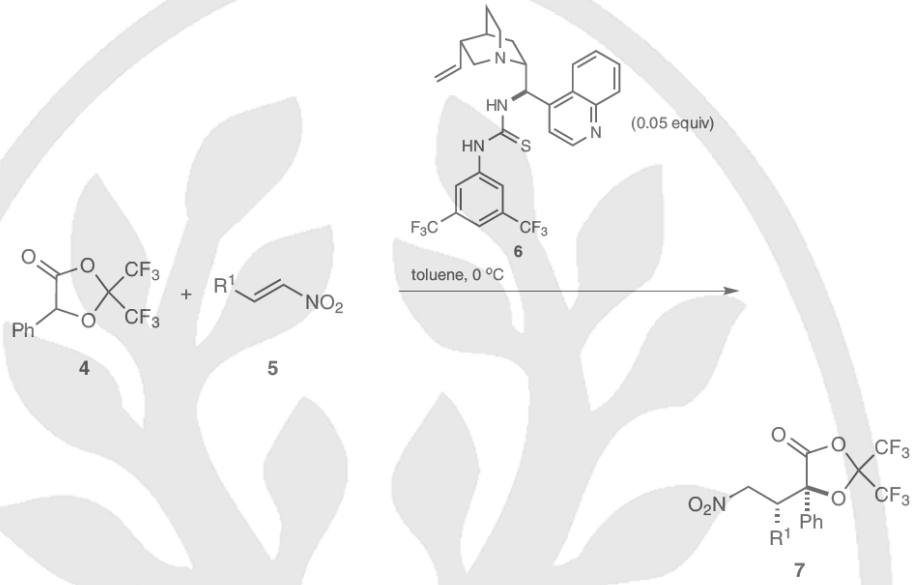
Subsequent aminolysis, alcoholysis, or hydrolysis of the ester moiety provides new chiral building blocks. In dichloromethane the reaction time decreases, but the enantioselectivities are not improved.

Scheme 7 Michael Addition of a Mandelic Acid Derived Dioxolanone to 1-Nitro-2-phenylethenes Using a Thiourea Catalyst at 0 °C[54]



R^1	Time (h)	Yield (%)	de (%)	ee (%)	Ref
Ph	–[a]	75	98	76	[54]
2-naphthyl	72	62	>97	75	[54]
2-$MeOC_6H_4$	72	65	>97	74	[54]
4-BrC_6H_4	72	59	>98	73	[54]
4-$MeOC_6H_4$	72	81	>97	73	[54]
4-Tol	40	67	>97	70	[54]
3-Tol	40	70	>98	69	[54]

[a] Conversion after 48 h was >98%.

(*R*)-5-(2-Nitroethyl)-5-phenyl-2,2-bis(trifluoromethyl)-1,3-dioxolan-4-ones 7; General Procedure:[54]

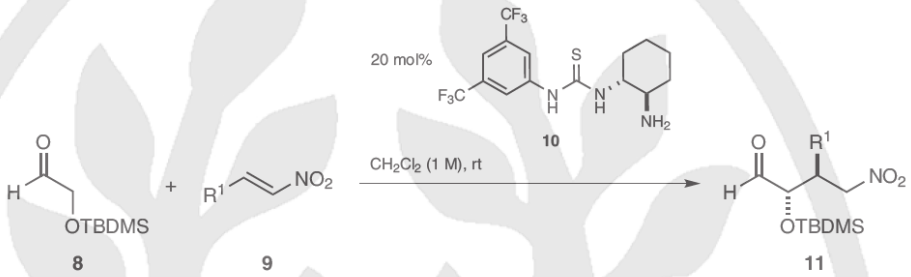
A reaction vessel was charged with the nitroalkene **5** (0.2 mmol), 5-phenyl-2,2-bis(trifluoromethyl)-1,3-dioxolan-4-one (**4**; 0.4 mmol), and toluene (0.2 mL). Catalyst **6** (11.2 mg, 0.02 mmol) was added and the mixture was stirred at 0 °C until full conversion was observed by TLC. Then, the solvent was removed under reduced pressure and the crude residue was purified by flash chromatography (silica gel, EtOAc/petroleum ether 1:20 to 1:16). The enantiomeric excess was determined by chiral HPLC (Chiralpak AD, OD, or IB; hexanes/iPrOH). The diastereomeric ratio was determined by ^1H NMR analysis.

2.2.4.3.2 Michael Addition of Aldehydes to Nitroalkenes

In 2009, Barbas and Uehara presented an *anti*-selective conjugate addition of aldehydes assisted by a bifunctional thiourea catalyst **10** (Scheme 8).[55] (*tert*-Butyldimethylsiloxy)-acetaldehyde (**8**) and the catalyst's secondary amine function form a *Z*-enamine that is stabilized through hydrogen bonding of the enamine hydrogen to the alkoxy group. The

thiourea moiety is proposed to activate the nitroalkene **9** through hydrogen bonding and approaches the *Z*-enamine in a synclinal fashion. The yield of isolated product **11** varies from 57 to 83%, with diastereomeric ratios (*syn*/*anti*) from 92:8 to 98:2 and excellent enantioselectivities of >97% (Scheme 8). The reaction works well for electron-deficient, electron-rich, and sterically hindered nitroalkenes. In 2010, Barbas and co-workers published a one-pot synthesis of carbohydrates and iminosugars with the Michael products as intermediates.[56,57]

Scheme 8 Michael Addition of (*tert*-Butyldimethylsiloxy)acetaldehyde to Nitroalkenes Using an Amino Thiourea Derived Catalyst[55]



R^1	Time (h)	Yield (%)	dr (*anti*/*syn*)	ee (%)	Ref
2-$F_3CC_6H_4$	24	74	98:2	99	[55]
Ph	4	83	98:2	98	[55]
4-BrC_6H_4	6	70	97:3	98	[55]
4-$MeOC_6H_4$	24	67	97:3	98	[55]
3,4-$Cl_2C_6H_3$	2	72	96:4	98	[55]
2,6-$Cl_2C_6H_3$	24[a]	68	98:2	98	[55]
4-Tol	6	81	97:3	97	[55]
3-BrC_6H_4	6	66	96:4	97	[55]
2-thienyl	6	75	97:3	97	[55]
$(CH_2)_6Me$	6[a]	57	92:8	97	[55]

[a] Using 50 mol% of catalyst **10**.

2-(*tert*-Butyldimethylsiloxy)-4-nitrobutanals 11; General Procedure:[55]
A 2-mL reaction vial was charged with catalyst **10** (15.4 mg, 40 μmol), the nitroalkene **9** (0.2 mmol), (*tert*-butyldimethylsiloxy)acetaldehyde (**8**; 114 μL, 0.6 mmol), and CH_2Cl_2 (0.2 mL) under a N_2 atmosphere. The soln was stirred at rt for the above-mentioned time (Scheme 8). Then, Et_2O and sat. aq NH_4Cl were added. After separation of the phases, the aqueous phase was extracted several times with Et_2O. The solvent of the organic phase was removed under reduced pressure. The diastereoselectivity was determined via ^1H NMR of the crude residue. The residue was then purified by flash chromatography [silica gel (ZEOprep 60 ECO, 40–63 Micron); hexanes/EtOAc or hexanes/toluene]. The enantiomeric excess was determined by chiral HPLC (Daicel Chiralpak IC, hexane/iPrOH 98:2).

2.2.4.3.3 Michael Addition of α-Cyano Ketones to α,β-Unsaturated Trifluoromethyl Ketones

In 2009, Zhu and co-workers utilized a tertiary amine derived thiourea catalyst **14** to synthesize α-(trifluoromethyl)dihydropyrans **15** via conjugate addition of α-cyano ketones **13** to α,β-unsaturated trifluoromethyl ketones **12** (Scheme 9).[58] Enantioselectivities of

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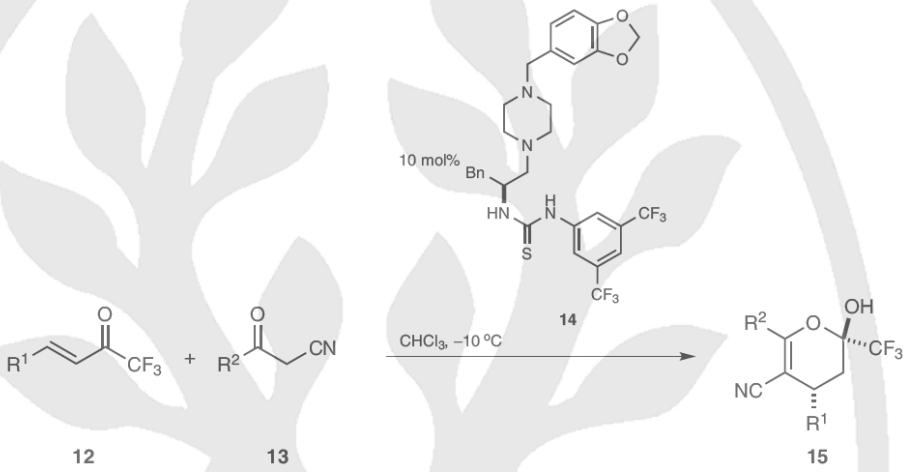
87–95% and diastereomeric ratios of up to >19:1 are observed. Various substituted benzene substituents with electron-donating groups for the α,β-unsaturated trifluoromethyl ketones as well as a range of cyano ketones with electron-withdrawing and electron-donating groups can be employed.

Zhao and co-workers also catalyzed an enantioselective Michael addition of α-substituted cyano ketones to β,γ-unsaturated α-keto esters using a tertiary amine thiourea catalyst to afford dihydropyran derivatives with good yields (91–95%, 70% in one case) and enantioselectivities of 87–96%.[59]

Scheme 9 Michael Addition of α,β-Unsaturated Trifluoromethyl Ketones to α-Cyano Ketones Using a Tertiary Amine Thiourea Derived Catalyst at −10 °C[58]



R^1	R^2	Yield (%)	dr	ee (%)	Ref
4-BrC_6H_4	4-BrC_6H_4	97	>19:1	94	[58]
Ph	Ph	99	>19:1	93	[58]
3-$MeOC_6H_4$	Ph	99	>19:1	93	[58]
4-Tol	Ph	99	>19:1	92	[58]
3-$MeOC_6H_4$	4-$MeOC_6H_4$	99	>19:1	92	[58]
4-Tol	4-$MeOC_6H_4$	99	>19:1	92	[58]
Ph	4-BrC_6H_4	99	>19:1	92	[58]
Ph	4-FC_6H_4	98	>19:1	92	[58]
4-$MeOC_6H_4$	Ph	99	>19:1	91	[58]
4-Tol	4-BrC_6H_4	99	>19:1	91	[58]

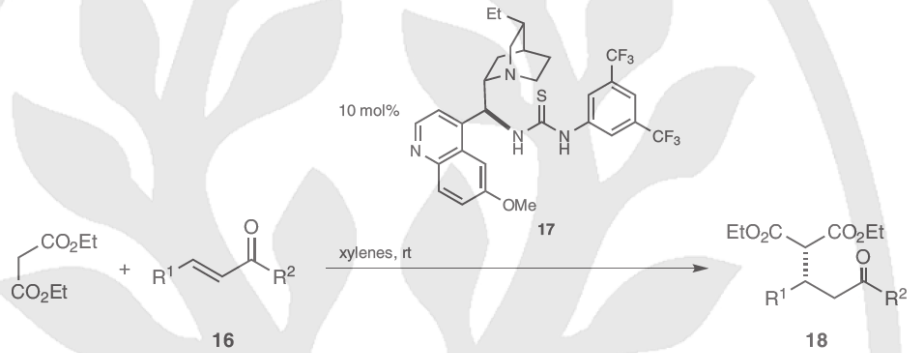
2-Hydroxy-2-(trifluoromethyl)-3,4-dihydro-2*H*-pyran-5-carbonitriles 15; **General Procedure:**[58]

A reaction vessel was charged with the α-cyano ketone **13** (0.2 mmol) and the catalyst **14** (6.2 mg, 0.01 mmol). $CHCl_3$ (2.0 mL) was added and the soln was cooled to −10 °C and stirred for 10 min. The α,β-unsaturated trifluoromethyl ketone **12** (0.01 mmol) was added and the mixture was stirred at rt for 5 h. Then, the mixture was purified by column chromatography (silica gel). The enantiomeric excess was determined by chiral HPLC analysis (hexane/iPrOH). The diastereomeric ratio was determined by ^{19}F NMR analysis of the crude product.

2.2.4.3.4 Michael Addition of Diethyl Malonate to (*E*)-Chalcones

In 2006, Wang and co-workers published a protocol for the Michael addition of various nucleophilic enol intermediates to chalcones **16** catalyzed by a cinchona alkaloid thiourea catalyst **17**. The reaction times are up to 144 hours, but the reaction provides good to excellent enantioselectivities (85–98%) and yields (61–99%).[60] Electron-withdrawing and electron-donating or heteroaromatic groups for R^1 of the chalcone are employed in the Michael reaction with diethyl malonate and give good enantioselectivities (Scheme 10). When a methyl group as R^2 is introduced, the reaction times are very long and the catalyst loading has to be increased to 30 mol%.

Scheme 10 Michael Addition of Diethyl Malonate to Chalcones Using a Cinchona Alkaloid Thiourea Derived Catalyst[60]



R^1	R^2	Time (h)	Yield (%)	ee (%)	Ref
4-FC_6H_4	4-Tol	120	90	98	[60]
2-thienyl	2-thienyl	144	85	96	[60]
Ph	4-ClC_6H_4	120	93	95	[60]
Ph	4-$MeOC_6H_4$	144	85	95	[60]
4-FC_6H_4	4-FC_6H_4	72	97	94	[60]
Ph	Me	96[a]	62	94	[60]
4-ClC_6H_4	Ph	108	95	93	[60]
2-ClC_6H_4	Ph	96	94	93	[60]
4-$MeOC_6H_4$	Ph	144	89	92	[60]
3-$O_2NC_6H_4$	Ph	120	92	90	[60]

[a] Reaction was performed with 30 mol% of catalyst **17**.

Wang and co-workers also performed a 1,4-conjugate addition of 1*H*-benzotriazoles to α,β-unsaturated ketones catalyzed by a bifunctional thiourea catalyst, but with enantioselectivities of only up to 64%.[61] Soós and co-workers utilized a cinchona alkaloid derived thiourea catalyst for the 1,4-addition of nitromethane to chalcone derivatives.[50] Enantioselectivities are up to 98% with 80–94% yield, but the reaction times are long (122 h). In 2007, Chen and co-workers reported a Michael reaction with chalcones and α-cyanoacetate catalyzed by bifunctional cinchona thiourea catalyst **17**.[62] The enantioselectivities are good (83–95%) and the obtained yields are 80–95%, but low diastereoselectivities are observed (dr 59:41 to 67:33). In 2009, Wang and Duan showed that an amino thiourea catalyst efficiently catalyzes the Michael addition of nitroalkanes to enones. The substrate scope is broad and the reaction gives high enantioselectivities of 92–99%, but low to moderate yields of 38–89%; a long reaction time of 5 days is necessary.[63] In 2010, Ye and co-workers

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showed that a cinchona alkaloid derived thiourea catalyst catalyzes the 1,4-addition of anthracen-9-one derivatives to chalcone derivatives with enantiomeric excess values of up to 93% and yields of 74–98%.[64]

In 2007, an aza-Michael reaction of *O*-benzylhydroxylamine with substituted (*E*)-chalcones, in the presence of a cinchona alkaloid based thiourea organocatalyst, was developed by Ricci and co-workers.[65] β-Keto hydroxylamines are obtained with moderate to good yields (35–94%) and low enantioselectivities (27–60%).

An enantioselective Michael addition of diethyl cyanomethylphosphonates to chalcones to form precursors of α-substituted β-aminophosphonates was reported in 2010.[66] The yields are variable (25–90%), with low diastereoselectivities (dr 52:48 to 56:44), and enantioselectivities in the range of 66–80%.

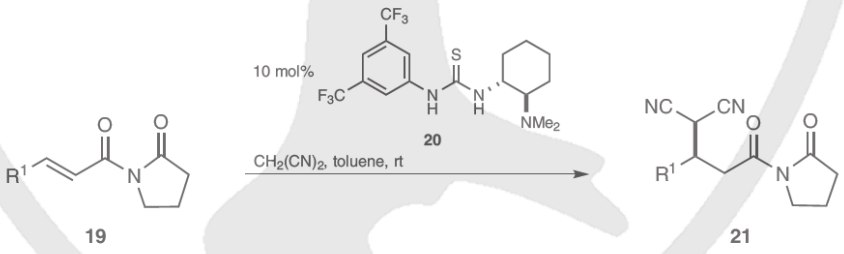
An enantioselective 1,4-addition of nitromethane to 1,5-diarylpenta-2,4-dien-1-ones catalyzed by bifunctional cinchona thiourea **17** provides high enantioselectivities of 87–99% and yields of 19–92%.[67] The reaction times are up to 7 days.

Diethyl 2-(3-Oxoalkyl)malonates 18; General Procedure:[60]
A reaction vessel was charged with diethyl malonate (1.4 mmol), the (*E*)-chalcone derivative **16** (0.25 mmol), and xylenes (0.1 mL). Catalyst **17** (15 mg, 0.025 mmol) was added at rt. The conversion was monitored via TLC. The mixture was stirred until completion of the reaction. The solvent was removed under reduced pressure and the crude residue was purified by flash column chromatography [silica gel (Merck 60), hexane/EtOAc]. The enantiomeric excess was determined by chiral HPLC analysis (Chiralcel OJ-H or Chiralpak AS-H, hexane/EtOH 70:30 or hexane/iPrOH 70:30).

2.2.4.3.5 Michael Addition of Malononitriles to α,β-Unsaturated 1-Acylpyrrolidinones

In 2005, Takemoto and co-workers developed an enantioselective Michael addition of malononitrile to α,β-unsaturated 1-acylpyrrolidinones **19** in the presence of a bifunctional tertiary amine thiourea catalyst **20** (Scheme 11).[68] The enantioselectivities (84–94%) and yields (77–99%) are good to excellent but the reaction times are long (up to 216 h). When the reactions are carried out at 0.1 M concentration instead of 0.5 M, with longer reaction times, the enantioselectivities increase.

Scheme 11 Michael Addition of Malononitrile to α,β-Unsaturated 1-Acylpyrrolidinones Catalyzed by a Bifunctional Tertiary Amine Thiourea Catalyst at Room Temperature[68]



R^1	Concentration (M) of **19**	Time (h)	Yield (%)	ee (%)	Ref
$(CH_2)_2Ph$	0.1	144	98	94	[68]
4-ClC_6H_4	0.1	192	88	93	[68]
1-naphthyl	0.1	168	87	93	[68]
Me	0.1	120	86	93	[68]
4-FC_6H_4	0.1	168	84	93	[68]
t-Bu	0.5	168	78	92	[68]

R^1	Concentration (M) of **19**	Time (h)	Yield (%)	ee (%)	Ref
Ph	0.5	60	93	87	[68]
2-furyl	0.5	192	79	85	[68]
4-$MeOC_6H_4$	0.5	216	77	85	[68]

(*R*)-2-[3-Oxo-3-(2-oxopyrrolidin-1-yl)-1-phenylpropyl]malononitrile (21, R^1 = Ph); **Typical Procedure:**[68]

CAUTION: *Malononitrile is classified as toxic by inhalation, in contact with skin, and if swallowed. It is very toxic to aquatic organisms and may cause long-term adverse effects in the aquatic environment.*

A reaction vessel was charged with α,β-unsaturated 1-acylpyrrolidinone **19** (R^1 = Ph; 43.1 mg, 0.2 mmol), malononitrile (26.4 mg, 2.0 equiv), and catalyst **20** (8.2 mg, 0.1 equiv). The substances were dissolved in anhyd toluene (0.4 mL) and stirred for 60 h at rt. Preparative TLC [silica gel (Merck 60), Et_2O] was used to isolate the product **21** as a colorless solid; yield: 52.3 mg (93%); 87% ee by chiral HPLC (Chiralcel AS-H, hexane/EtOH 80:20).

2.2.4.3.6 Michael Addition of Nitroalkanes to Nitroalkenes

Wulff and Rabalakos presented a Michael addition to form 1,3-diamino precursors by utilizing a 2,2′-diamino-1,1′-binaphthyl (BINAM) thiourea/4-(dimethylamino)pyridine derived catalyst.[69,70] Various nitroalkenes with electron-rich and electron-poor phenyl groups in combination with nitroalkanes can be transformed into the corresponding Michael adducts. The yields vary from 55 to 94% with very good enantioselectivities of 91–95%, but moderate diastereoselectivities (dr 74:26 to 90:10).[70] The successful addition of nitroalkanes **23** to nitroalkenes **22** was published by the group of Wang in 2009.[71] The resulting 1,3-dinitro compounds **25** are obtained with diastereomeric ratios of 55:45 of 98:2 and enantioselectivities generally in the range 80–99% (64% ee in one case). Yields vary from 60 to 92% (Scheme 12).

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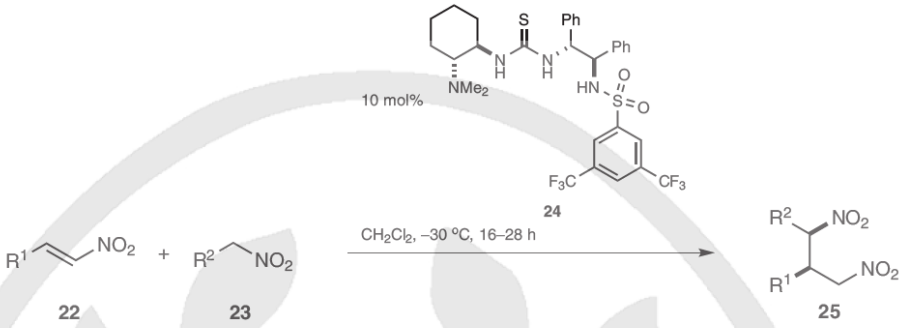
Scheme 12 Michael Addition of Nitroalkanes to Nitroalkenes Catalyzed by a Bifunctional Thiourea/Sulfonamide Catalyst at −30 °C[71]



R^1	R^2	Yield (%)	dr (*syn*/*anti*)	ee (%)	Ref
4-Tol	Et	89	97:3	99	[71]
2,4-$Cl_2C_6H_3$	Me	92	84:16	99	[71]
2-Tol	Me	92	91:9	98	[71]
Ph	Me	87	98:2	97	[71]
4-Tol	Me	89	92:8	97	[71]
1-naphthyl	Me	91	91:9	97	[71]
Ph	Et	92	95:5	96	[71]
Ph	Bn	89	96:4	95	[71]
2-ClC_6H_4	Me	87	93:7	95	[71]
2-furyl	Me	85	80:20	92	[71]

Ye and co-workers reported the Michael addition of nitroalkanes to α,β-unsaturated ketones with high enantioselectivities of up to 98% with yields of up to 98%.[72] In 2009, it was shown that 4-oxoalkenoates undergo a Michael addition with nitroalkanes catalyzed by a cinchona alkaloid thiourea derived catalyst in good yields (47–99%) and with good enantioselectivities (up to 98%).[73]

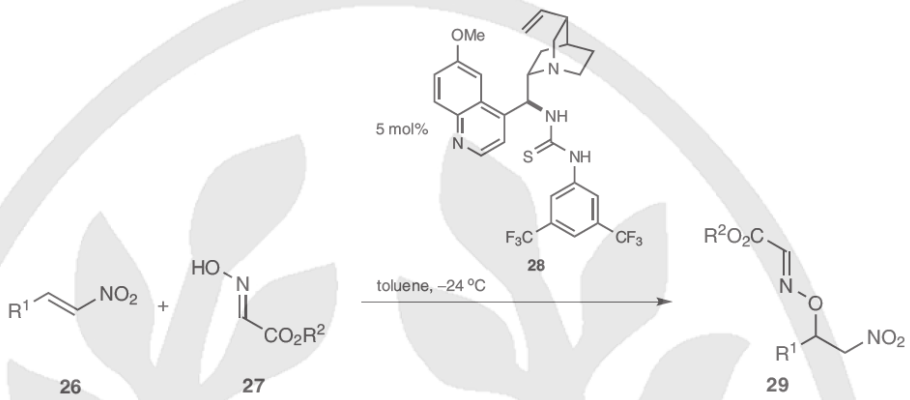
1,3-Dinitroalkanes 25; **General Procedure:**[71]
A reaction vial was charged with catalyst **24** (10 mg, 0.015 mmol) and the nitroalkene **22** (0.15 mmol). CH_2Cl_2 (0.6 mL) and the nitroalkane **23** (0.6 mmol) were added and the mixture was cooled to −30 °C. The conversion was monitored with TLC. After 16–28 h, the solvent was removed under reduced pressure and the crude residue was purified by flash chromatography. The enantiomeric excess was determined by chiral HPLC (Chiralcel OD-H or AS-H, or Chiralpak AD-H; hexane/iPrOH). The diastereomeric ratio was also determined by chiral HPLC or ^{1}H NMR analysis.

2.2.4.3.7 Michael Addition of Oximes to Aliphatic Nitroalkenes

In 2007, Pettersen and Herrera published the addition of hydrazones to nitroalkenes with an achiral thiourea-derived catalyst.[27] A Michael addition of formaldehyde *N*,*N*-dialkylhydrazones to β,γ-unsaturated α-keto esters was developed by Lassaletta, Fernández, and coworkers.[74] The enantioselectivities range from 58 to 80%. Jørgensen and co-workers presented a protocol for β-hydroxylation of nitroalkenes **26** with O-nucleophiles to afford precursors for nitro or amino alcohols (Scheme 13).[75] The reaction is catalyzed by a bifunctional cinchona alkaloid catalyst **28** bearing a thiourea moiety. The enantiopurities of the obtained products **29** are fairly good (48–93% ee), as are the yields (63–83%). The ab-

solute stereochemical configuration of the products was not determined. The product has to be purified on neutral Iatrobeads to diminish possible retro-Michael reactions.

Scheme 13 Michael Addition of Oximes to Nitroalkenes Catalyzed by a Thiourea Cinchona Alkaloid Derived Catalyst at −24 °C[75]



R^1	R^2	Yield[a] (%)	ee (%)	Ref
$(CH_2)_2CH{=}CHEt$	Et	79	93	[75]
$(CH_2)_4Me$	Et	79	91	[75]
$(CH_2)_4Me$	*t*-Bu	83	90	[75]
Cy	Et	82	90	[75]
t-Bu	Et	69[b]	90	[75]
Me	Et	63	90	[75]
$(CH_2)_2SMe$	Et	82	89	[75]
$(CH_2)_2Ph$	Et	68	89	[75]
$(CH_2)_4CO_2Me$	Et	68	89	[75]

[a] Unless otherwise stated, the reaction was performed with 5 mol% catalyst **28** (0.0125 mmol) in toluene (1 mL).
[b] Reaction was performed with catalyst **28** (0.025 mmol) in toluene (0.125 mL).

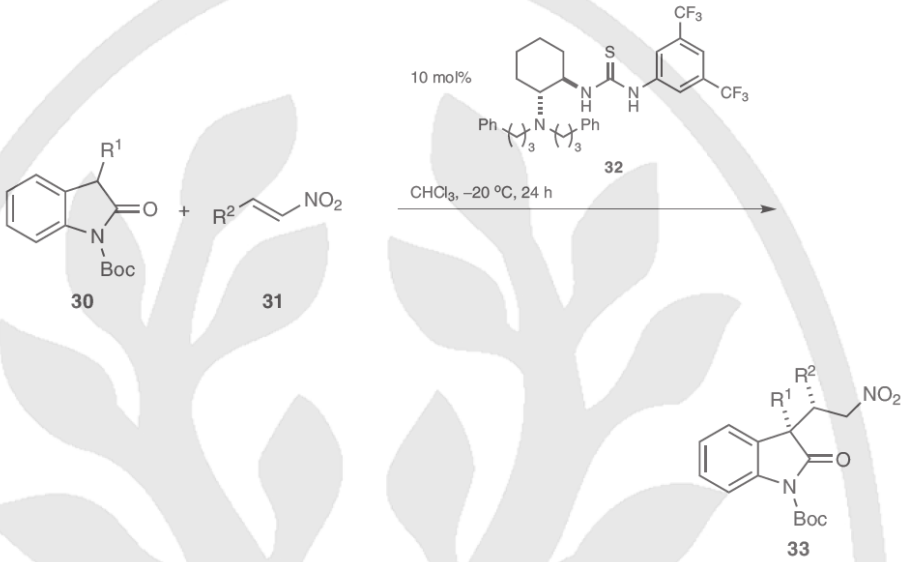
2-[*N*-(2-Nitroalkoxy)imino]acetates 29; General Procedure:[75]
A sample vial containing a magnetic stirrer bar was charged with catalyst **28** (0.0125 mmol, 5 mol%) and the nitroalkene **26** (0.25 mmol). After addition of toluene (1.0 mL), the mixture was stirred at −24 °C for 15 min. Then, the oxime **27** (0.5 mmol) was added and the conversion was monitored by TLC. After 16 h, when the reaction was complete, the mixture was directly purified by flash chromatography [Iatrobeads (6RS-8060)]. The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chiralpak AD, or Chiralcel OD or OJ).

2.2.4.3.8 Michael Addition of 3-Substituted Oxindoles to Nitroalkenes

In 2009, Barbas and co-workers developed an enantioselective addition reaction of 3-substituted oxindoles **30** to nitroalkenes **31** catalyzed by a thiourea derivative **32** (Scheme 14).[76] The developed methodology was utilized in the synthesis of (+)-physostigmine.[76] Various electron-rich and electron-deficient nitrostyrenes and heteroaromatic nitroal-

kenes combined with oxindoles bearing substituents at the C3-position can be utilized. The enantioselectivity is high (88–99% ee) and yields are in the range 68–97%. The diastereomeric ratios range from 3:1 to >20:1.

Scheme 14 Michael Addition of Oxindoles to Nitroalkenes Catalyzed by a Thiourea Derived Catalyst at −20 °C[76]



R^1	R^2	Yield (%)	dr	ee (%)	Ref
Me	Ph	96	10:1	99	[76]
$CH_2CH{=}CH_2$	2-furyl	97	6:1	99	[76]
Et	Ph	95	5:1	96	[76]
$CH_2CH{=}CH_2$	3-BrC_6H_4	91	9:1	95	[76]
$CH_2CH{=}CH_2$	$(CH_2)_6Me$	95	>20:1	94	[76]
$CH_2CH{=}CH_2$	Ph	89	6:1	94	[76]
$CH_2CH{=}CH_2$	$CH(OMe)_2$	68	>20:1	93	[76]
$CH_2CH{=}CHPh$	Ph	90	11:1	92	[76]
$CH_2CH{=}CH_2$	4-HOC_6H_4	92	7:1	92	[76]
$CH_2CH{=}CH_2$	4-BrC_6H_4	92	6:1	91	[76]

In 2010, Zhou and co-workers published a Michael addition of 3-substituted oxindoles to nitroalkenes with lower diastereomeric ratios (<5:1), but with good yields of 61–96%.[77] Melchiorre and co-workers obtained for the 1,4-addition of oxindoles to α,β-unsaturated compounds enantioselectivities of up to 99%. The reaction requires long reaction times of up to 5 days.[78] An asymmetric Michael addition of 3-substituted oxindoles to nitroalkenes was also investigated by Cheng and Luo.[79] In this case, the diastereoselectivities are lower (dr 1:1 to 19:1) but the enantioselectivities are high (53–98% ee and a racemic mixture in one case). Cheng and co-workers published a Michael addition of various vinyl ketones and vinyl sulfones to 3-aryloxindoles with yields of 48–99% and enantiomeric excesses of 17–91%.[80]

1-(*tert*-Butoxycarbonyl)-3-(2-nitroalkyl)-1,3-dihydro-2*H*-indol-2-ones 33; **General Procedure:**[76]

In a reaction vessel, the oxindole **30** (0.2 mmol, 1 equiv) and catalyst **32** (12.4 mg, 0.02 mmol, 0.1 equiv) were dissolved in anhyd $CHCl_3$ (0.3 mL). The soln was cooled to −20 °C, the nitroalkene **31** (0.22 mmol, 1.1 equiv) was added, and the soln was stirred at −20 °C for 24 h. Then, the mixture was first diluted with EtOAc and afterwards quenched with sat. aq NH_4Cl. After separation of the phases, the aqueous phase was extracted with EtOAc (4 ×). After drying of the combined organic phases ($MgSO_4$) and subsequent filtration, the solvent was removed under reduced pressure. The diastereomeric ratio was determined by ^1H NMR of the crude residue. The crude residue was purified by flash column chromatography [silica gel (EM Science, 230–400 mesh)]. The enantiomeric excess was determined by chiral HPLC (Daicel Chiralpak OD-H, AD, or OJ-H; hexane/iPrOH).

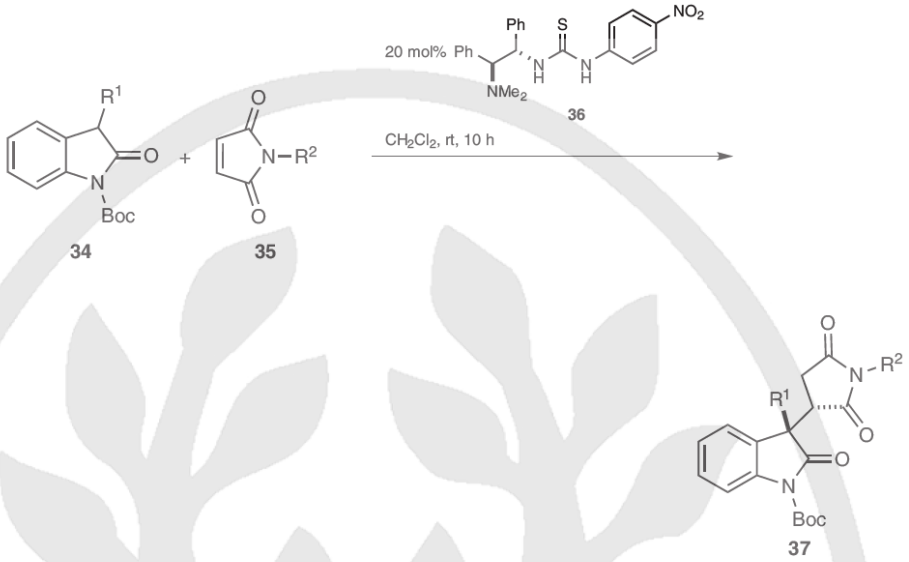
2.2.4.3.9 Michael Addition of Oxindoles to Maleimides

New quaternary centers in the C3-position of oxindoles are obtained through a Michael addition of oxindoles **34** to maleimides **35** catalyzed by a bifunctional tertiary amine thiourea derivative **36** (Scheme 15).[81] Moderate to high yields (45–92%), high diastereoselectivities (dr 63:37 to 99:1), and high enantioselectivities of 85–99% are obtained. Various *N*-(*tert*-butoxycarbonyl)-3-phenyloxindoles with various aliphatic and aromatic substituents can be utilized. The yields are lower with N-aliphatic maleimides than with N-aromatic maleimides. The *tert*-butoxycarbonyl group is crucial for the reactivity and stereocontrol.

In 2010, Yuan and co-workers presented an enantioselective protocol for the hydroxymethylation of oxindoles.[82] The products are obtained in up to 91% ee with yields of up to 99%.

for references see p 407

Scheme 15 Michael Addition of Oxindoles to Maleimides Catalyzed by a Bifunctional Tertiary Amine Thiourea Catalyst at Room Temperature[81]



R^1	R^2	Time (h)	Yield (%)	dr	ee (%)	Ref
3,5-$Me_2C_6H_3$	Ph	10	81	92:8	99	[81]
Ph	4-BrC_6H_4	10	89	91:9	98	[81]
Ph	4-Tol	10	92	96:4	97	[81]
4-PhC_6H_4	Ph	10	87	94:6	97	[81]
Bu	4-ClC_6H_4	24	65	95:5	97	[81]
Ph	3-$MeOC_6H_4$	10	92	95:5	96	[81]
4-FC_6H_4	Ph	10	80	94:6	95	[81]
iPr	Ph	36	67	99:1	94	[81]
Ph	$CH_2CH{=}CH_2$	10	64	89:11	91	[81]
Ph	iPr	10	45	94:6	85	[81]

3-[1-(*tert*-Butoxycarbonyl)-2-oxo-1,3-dihydro-2*H*-indol-3-yl]pyrrolidine-2,5-diones 37; General Procedure:[81]

CAUTION: *N-Phenylmaleimide is toxic if swallowed.*

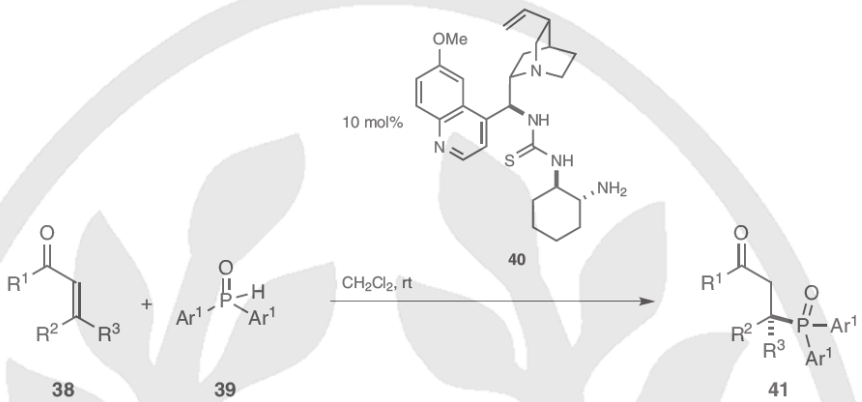
A reaction vessel was charged with the 3-substituted *N*-(*tert*-butoxycarbonyl)oxindole **34** (0.2 mmol), the N-substituted maleimide **35** (0.3 mmol), catalyst **36** (0.04 mmol), and anhyd CH_2Cl_2 (1 mL). The mixture was stirred at rt for 10 h (or longer if necessary), and subsequently purified by flash column chromatography (silica gel, petroleum ether/EtOAc). The enantiomeric excess was determined by HPLC analysis (Chiralcel OD-H, hexane/iPrOH 70:30; or Chiralcel AD-H, hexane/iPrOH 70:30 or hexane/iPrOH gradient).

2.2.4.3.10 Phospha-Michael Addition of Diarylphosphine Oxides to α,β-Unsaturated Ketones

In 2010, Ye and co-workers demonstrated functionalization of β,β-disubstituted α,β-unsaturated ketones **38** with pentavalent diarylphosphine oxides **39** through a phospha-Michael addition (Scheme 16).[83] Under optimized conditions, high yields (82–97%) and high enantioselectivities (84–98%) are achieved utilizing a primary amine/cinchona thiourea

catalyst **40**. Sterically hindered cyclohex-2-enone derivatives as well as various substituted aromatic enones can be used for the 1,4-addition reaction.

Scheme 16 Phospha-Michael Addition of Diarylphosphine Oxides to β,β-Disubstituted α,β-Unsaturated Ketones through a Bifunctional Thiourea Catalyst[83]



R^1	R^2	R^3	Ar^1	Time (d)	Yield (%)	ee (%)	Ref
$(CH_2)_3$		Me	Ph	6	96	98	[83]
$(CH_2)_2CMe_2$		H	Ph	2.5	95	98	[83]
$(CH_2)_2CMe_2$		H	2,4-$(MeO)_2C_6H_3$	2.5	90	98	[83]
$(CH_2)_3$		Bu	Ph	7[a]	85	97	[83]
$CH_2CMe_2CH_2$		Me	Ph	8	90	96	[83]
Me	H	4-BrC_6H_4	Ph	2	94	94	[83]
$(CH_2)_3$		Cy	2,4-$(MeO)_2C_6H_3$	4[a]	92	94	[83]
$(CH_2)_3$		Pr	Ph	6[a]	87	94	[83]
Me	H	4-$O_2NC_6H_4$	Ph	2	90	92	[83]
$(CH_2)_4$		H	Ph	6	87	90	[83]

[a] Reaction was performed with 20 mol% of catalyst **40** at 30 °C.

β-Phosphoryl Ketones 41; General Procedure:[83]
A soln of α,β-unsaturated ketone **38** (3.0 mmol) in anhyd CH_2Cl_2 (2 mL) was prepared in a reaction vessel. Then, the phosphine oxide **39** (1.0 mmol) and catalyst **40** (0.10 mmol) were added and the mixture was stirred at rt for the above-mentioned time (Scheme 16). The conversion was monitored by TLC. The product was purified by chromatography (silica gel). The enantiomeric excess was determined by chiral HPLC analysis (Chiralcel AS-H, or Chiralpak OD-H, AD-H, IA, or IC; hexane/EtOH or hexane/iPrOH).

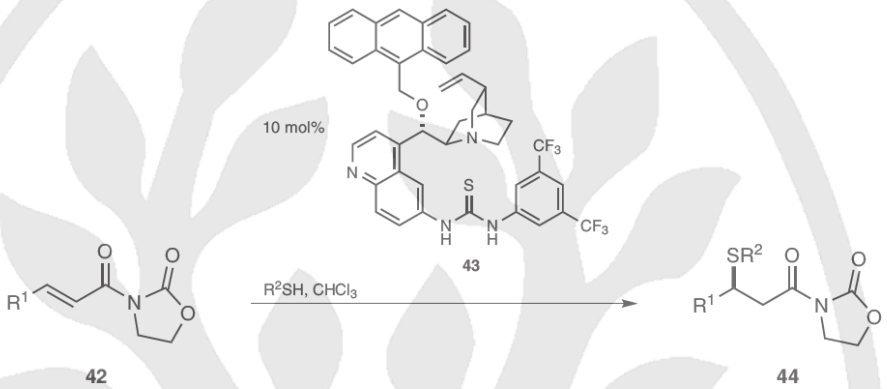
2.2.4.3.11 Sulfa-Michael Addition of Alkanethiols to α,β-Unsaturated N-Acylated Oxazolidin-2-ones

An addition reaction of arenethiols to α,β-unsaturated imides was developed by Chen and co-workers; poor to good enantioselectivities (55–77%) are observed.[48] The addition of arenethiols to α,β-unsaturated ketones gives enantioselectivities of up to 85%.[48] Wang and co-workers published, in 2006, an asymmetric 1,4-addition of thioacetic acid to enones, but with low enantioselectivities (up to 65%).[84] Thioacetic acid can also be used as nucleophile for the addition reaction to nitrostyrenes, with moderate enantioselectivities (up to 70%).[85] An enantioselective protocol for the 1,4-addition of various thiols to β-nitroacrylate derivatives was developed by Xiao and co-workers.[86] A bifunctional cinchona

for references see p 407

thiourea derivative is utilized to afford β[2,2]-amino acid precursors with yields of 89–100% and enantioselectivities of 87–98%. Deng and co-workers developed a synthesis of chiral sulfur compounds through a sulfa-Michael addition of alkanethiols to α,β-unsaturated N-acylated oxazolidin-2-ones **42** catalyzed by a bifunctional cinchona thiourea derived catalyst **43** (Scheme 17).[87] The conjugate addition protocol is efficient for several alkanethiols and variously substituted Michael acceptors; enantioselectivities span the range 87–96% and yields are 84–99%.

Scheme 17 Sulfa-Michael Addition of Alkanethiols to α,β-Unsaturated N-Acylated Oxazolidin-2-ones Catalyzed by a Bifunctional Cinchona Thiourea Derived Catalyst[87]



R	R^2	Temp[a] (°C)	Yield (%)	ee (%)	Ref
Me	PMB	−20	99	96	[87]
2-BrC_6H_4	$CH_2CH{=}CH_2$	−50[b]	91	96	[87]
$(CH_2)_4Me$	PMB	−20	96	95	[87]
Me	Bn	−20	98	94	[87]
Me	$CH_2CH{=}CH_2$	−20	97	94	[87]
$(CH_2)_5Me$	PMB	−20	97	94	[87]
Me	cyclopentyl	−20	96	94	[87]
Ph	$CH_2CH{=}CH_2$	−50[b]	93	94	[87]
Me	4-$ClC_6H_4CH_2$	−20	99	93	[87]
Me	$(CH_2)_2$OTBDMS	−20	97	93	[87]

[a] Unless otherwise stated, the reaction was conducted with 10 mol% (0.02 mmol) catalyst **43**.
[b] Reaction was performed with 20 mol% (0.04 mmol) of catalyst **43**.

3-[3-(Alkylsulfanyl)acyl]oxazolidinones 44; General Procedure:[87]

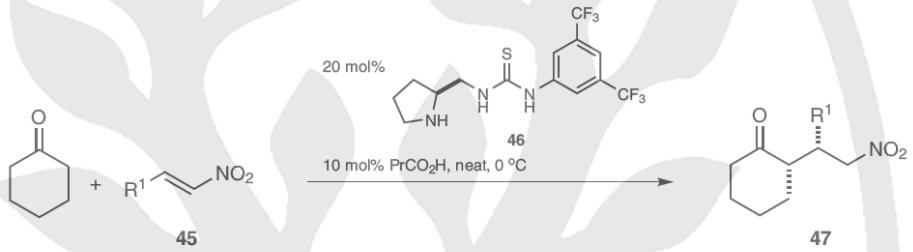
CAUTION: *Phenylmethanethiol is harmful if swallowed, toxic by inhalation, and very toxic to aquatic organisms with possible long-term adverse effects in the aquatic environment.*

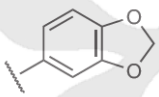
In a reaction vessel, a soln of catalyst **43** (15 mg, 0.02 mmol) and the α,β-unsaturated N-acylated oxazolidin-2-one **42** (0.2 mmol) in $CHCl_3$ (0.4 mL) was prepared. Then, the thiol (0.6 mmol, 3 equiv) was added and the soln was cooled to −20 or −50 °C for 72 h. The mixture was filtered through a short plug of silica gel, the plug was washed with Et_2O (5 mL), and the solvent was removed under reduced pressure; the crude residue was purified by flash chromatography (silica gel, hexanes/EtOAc). The enantiomeric excess was determined by chiral HPLC (Daicel Chiralcel OD or AD, hexanes/iPrOH).

2.2.4.3.12 Michael Addition of Cyclohexanone to Nitroalkenes

In 2006, Tang and co-workers utilized a secondary amine/pyrrolidine thiourea derivative **46** to catalyze the Michael addition of cyclohexanone to various (*E*)-1-aryl-2-nitroethenes **45** (Scheme 18).[88] The catalyst's efficiency is borne out by high enantioselectivities (88–98%) and diastereoselectivities (up to >99:1) with good to excellent yields (63–99%). A proposed mechanism assumes that the enone is first transformed into an enamine through the secondary amine function of the catalyst. The thiourea NH protons activate the nitroalkene through hydrogen bonding and the enamine double bond attacks the *Re*-face of the activated nitroalkene. The organic acid increases the reaction rate without lost of stereoinduction. Many groups have also provided efficient protocols for the enantioselective addition of cyclohexanone to nitroalkenes with excellent enantioselectivities, good diastereoselectivities, and high yields.[89–92]

Scheme 18 Michael Addition of Cyclohexanone to (*E*)-1-Aryl-2-nitroethenes Catalyzed by a Secondary Amine/Pyrrolidine Thiourea Derivative at 0 °C[88]



R^1	Time (h)	Yield (%)	dr (*syn*/*anti*)	ee (%)	Ref
	38	87	94:6	98	[88]
2,4-$Cl_2C_6H_3$	49	89	97:3	97	[88]
2-$O_2NC_6H_4$	38	95	96:4	97	[88]
2-BrC_6H_4	29	88	99:1	96	[88]
1-naphthyl	60	93	99:1	95	[88]
4-BrC_6H_4	38	90	95:5	95	[88]
iPr	144	63	>99:1	94	[88]
Ph	38	93	96:4	90	[88]
2-furyl	36	99	91:9	90	[88]
4-$MeOC_6H_4$	44	95	97:3	88	[88]

2-(2-Nitroalkyl)cyclohexanones 47; General Procedure:[88]
A reaction vial was charged with catalyst **46** (0.05 mmol), $PrCO_2H$ (0.0025 mmol), and predistilled cyclohexanone (0.5 mL, 20 equiv). The mixture was stirred for 15 min at 0 °C. Then, the nitroalkene **45** (0.25 mmol, 1 equiv) was added and the mixture was stirred for the above-mentioned time (Scheme 18); the conversion was monitored by TLC. After completion of the reaction, the mixture was concentrated under reduced pressure. The crude residue was purified by flash chromatography. The enantiomeric excess was determined by chiral HPLC (Chiralcel AS-H, AS, AD, or AD-H; hexane/iPrOH). The diastereomeric excess was determined by ^1H NMR analysis of the crude product.

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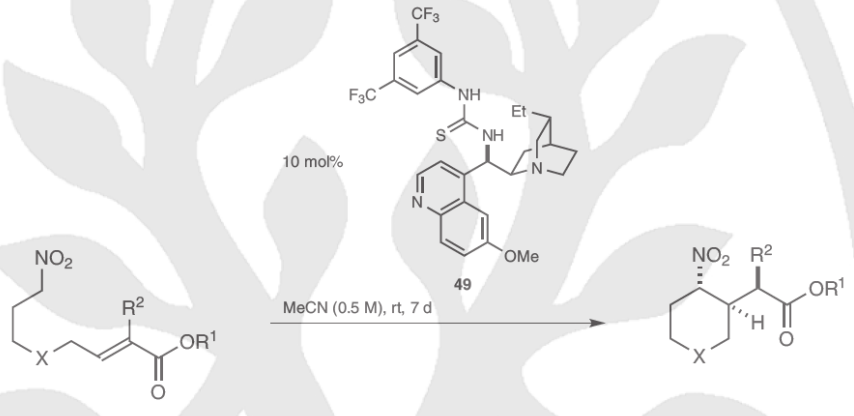
2.2.4.3.13 Intramolecular Michael Addition of Nitronates to Conjugated Esters

In 2009, Cobb and co-workers developed an intramolecular Michael addition reaction of nitronates to conjugated esters, precursors for cyclically constrained γ-amino acids (Scheme 19).[93] Up to three new stereogenic centers are introduced in the course of the reaction under catalysis by thiourea derivative **49**. The enantioselectivities are high (92–99%) and the yields are moderate to good (11–87%). Long reaction times of up to of 7 days derogate the efficiency of the reaction. Only reaction of the *E*-ester proceeds with good enantioselectivity. The *Z*-ester of **48** (e.g., R^1 = Et; R^2 = H; X = CH_2) produces the oppositely configured Michael adduct with lower enantioselectivity and diastereoselectivity (20% yield; 38% ee; dr 7:3).

Scheme 19 Intramolecular Michael Addition of Nitronates to α,β-Unsaturated Esters Using a Cinchona/Thiourea Derived Catalyst at Room Temperature[93]



R^1	R^2	X	Time (d)	Yield (%)	dr (*syn*/*anti*)	ee (%)	Ref
Et	Bn	CH_2	7	52	>19:4:1[a]	99	[93]
Bn	H	CH_2	7	66	4:1	98	[93]
Et	H	CH_2	7	87	>19:1	96	[93]
Et	H	CMe_2	2	76	>19:1	96	[93]
Me	H	CH_2	7	57	4:1	96	[93]
Et	NHCbz	CH_2	7[b]	65	2:1:<1[a]	95	[93]
Et	Me	CH_2	7	50	>19:6:1[a]	94	[93]
Et	H	O	7	69	>19:1	92	[93]

[a] Although four diastereomers are possible, a ratio of three diastereomers was given in ref [93] without explanation.
[b] Solvent not reported.

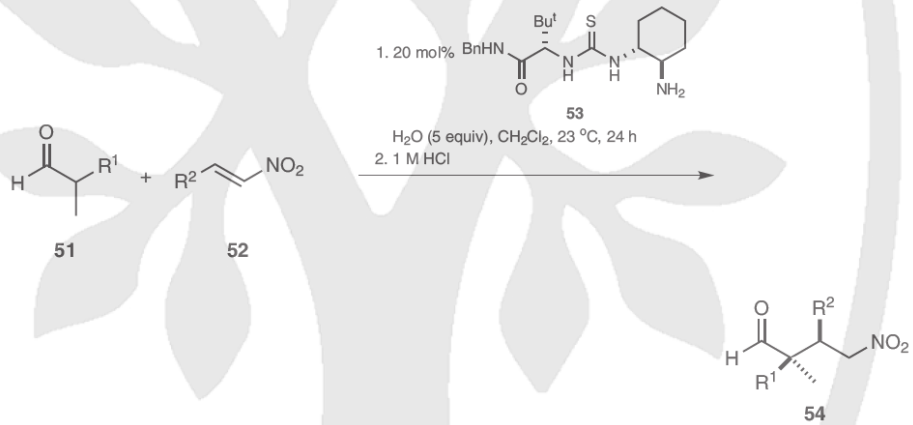
Nitrocarboxylic Acid Esters 50; General Procedure:[93]
A 0.5 M soln of nitronate **48** (1 equiv) in anhyd MeCN was prepared. The catalyst **49** (0.1 equiv) was added and the mixture was stirred for 7 d. Then, the solvent was removed under reduced pressure and the crude residue was purified by column chromatography [silica gel (type 60, 40–63 μm), hexane/Et_2O or hexane/EtOAc]. The enantiomeric excess was determined by chiral HPLC analysis (Chiralpak AD-H or Chiralcel OD, hexanes/iPrOH). Some of the products had to be reduced to the alcohol and protected with a benzyl group to determine the enantiomeric excess. The diastereomeric ratio was determined by ^{1}H NMR analysis of the crude product.

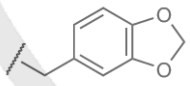
2.2.4.3.14 Michael Addition of α,α-Disubstituted Aldehydes to Nitroalkenes

In 2006, Jacobsen and Huang developed a Michael addition of ketones catalyzed through a thiourea derived primary amine catalyst **53** with yields of up to 94% and enantioselectivities of up to 99%.[94] The same primary amine thiourea derived catalyst **53** was utilized by Jacobsen and co-workers for the enantioselective and diastereoselective 1,4-addition of α,α-disubstituted aldehydes **51** to nitroalkenes **52** (Scheme 20).[95] The enantioselectivities are excellent (92–99% ee) for the *syn*- as well for the *anti*-product **54**; the best values are obtained with aldehydes bearing phenyl or ethereal α-substituents. The diastereoselectivities are moderate to good (dr 2.1:1 to >50:1) when the steric differentiation between α-substituents of the aldehyde and nitroalkene is high. A proposed mechanism describes enamine formation from the aldehyde and the primary amine function of the catalyst. The nitroalkene is activated by hydrogen bonding of the catalyst; subsequent nucleophilic attack of the enamine on the alkene with formation of a zwitterionic intermediate is proposed as the next step. The corresponding intermediate is hydrolyzed to form the Michael adduct.

The scope of this type of Michael reaction is very broad: various nitroalkenes, ketones, and aldehydes can be utilized. Many protocols afford excellent enantioselectivities and high diastereoselectivities.[94,96–111]

Scheme 20 Michael Addition of α,α-Disubstituted Aldehydes to Nitroalkenes Catalyzed by a Primary Amine Thiourea Derived Catalyst at 23 °C[95]



R^1	R^2	Yield (%)	dr (*syn*/*anti*)	ee (%) *syn*	ee (%) *anti*	Ref
	4-BrC_6H_4	81	3.8:1	99	99	[95]
Ph	CH_2OBn	87	>50:1	99	–	[95]
Ph	Me	91	23:1	99	–	[95]
Pr	Ph	98	2.1:1	99	97	[95]
$CH_2OTBDMS$	Ph	87	6.3:1	99	98	[95]
$CH_2OTBDMS$	2-thienyl	85	6.6:1	99	97	[95]
$CH_2OTBDMS$	3-pyridyl	94	5.6:1	99	96	[95]
Ph	CF_3	34	>50:1	97	–	[95]
Ph	Bu	54	28:1	96	–	[95]
OPMB	Ph	78	13:1	96	–	[95]

for references see p 407

4-Nitroalkanals 54**; General Procedure:**[95]
An oven-dried 25-mL flask fitted with a rubber septum, a gas inlet, and a magnetic stirrer bar was charged with catalyst **53** (75.3 mg, 0.2 mmol, 20 mol%) at rt under a slight pressure of N_2. The catalyst was dissolved in anhyd CH_2Cl_2 (6.7 mL), and then H_2O (90.1 μL, 5.0 mmol, 5.0 equiv) and the aldehyde **51** (2.0 mmol, 2 equiv; freshly distilled from $CaSO_4$/and or purified by column chromatography) were added. The clear soln was stirred for 2 min, then the nitroalkene **52** (1.0 mmol, 1.0 equiv) was added, and the rubber septum was exchanged for a polyethylene stopper. The resulting mixture was stirred at rt for 24 h. Then, 1 M aq HCl (7 mL) was added and the biphasic mixture was stirred at rt for 5 min and then transferred into a separatory funnel. Additional CH_2Cl_2 (30 mL) and 1 M aq HCl (30 mL) were then added. The phases were separated, the aqueous phase was extracted with CH_2Cl_2 (30 mL), and the combined organic phases were washed with aq $NaHCO_3$ (30 mL) and brine (30 mL), and dried (Na_2SO_4). After filtration, the solvent was evaporated under reduced pressure. The crude residue was purified by column chromatography [silica gel (EM Science 60, 230–400 mesh), hexanes/Et_2O]. The enantiomeric excess was determined by HPLC analysis (Chiralcel OD-H or Chiralpak AD-H, hexanes/iPrOH or hexanes/EtOH). The diastereomeric ratio was determined by ^1H NMR, SFC, or HPLC analysis.

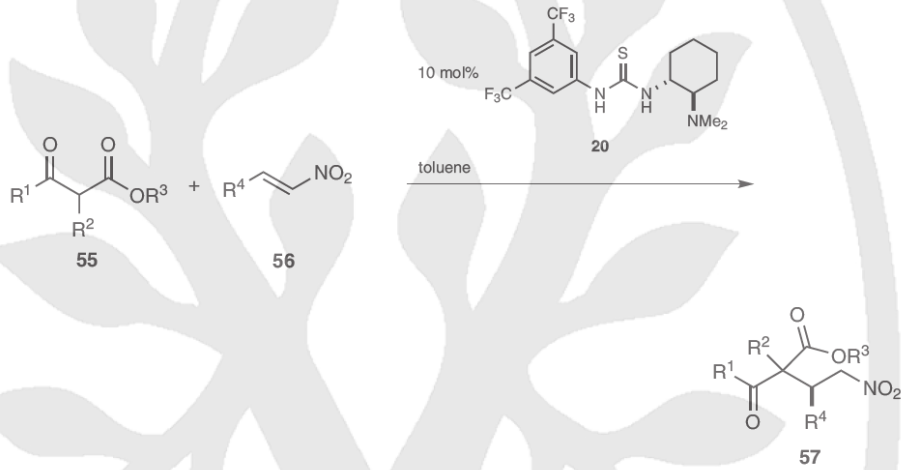
(2*S*,3*R*)-2-[(*tert*-Butyldimethylsiloxy)methyl]-2-methyl-4-nitro-3-(3-pyridyl)butanal (54, $R^1 = CH_2OTBDMS$; R^2 = 3-Pyridyl):[95]
An oven-dried 25-mL flask fitted with a rubber septum, a gas inlet, and a magnetic stirrer bar was charged with catalyst **53** (75.3 mg, 0.2 mmol, 20 mol%) at rt under a slight pressure of N_2. The catalyst was dissolved in anhyd CH_2Cl_2 (6.7 mL), and then H_2O (90.1 μL, 5.0 mmol, 5.0 equiv) and 3-(*tert*-butyldimethylsiloxy)-2-methylpropanal (**51**, R^1 = $CH_2OTBDMS$; 404.8 μg, 2.0 mmol, 2 equiv) were added by syringe. The clear soln was stirred for 2 min, then solid 3-(2-nitrovinyl)pyridine (**52**, R^2 = 3-pyridyl; 150.1 mg, 1.0 mmol, 1.0 equiv) was added, and the rubber septum was exchanged for a polyethylene stopper. The resulting yellow mixture was stirred at rt for 24 h. Then, 1 M aq HCl (7 mL) was added and the biphasic mixture was stirred at rt for 5 min. The soln was neutralized by adding solid $NaHCO_3$ portionwise. The mixture was transferred to a separatory funnel and then additional CH_2Cl_2 (30 mL) and sat. aq $NaHCO_3$ (30 mL) were added. The phases were separated, the aqueous phase was extracted with CH_2Cl_2 (30 mL), and the combined organic phases were washed with brine (30 mL), and then dried (Na_2SO_4). After filtration, the solvent was evaporated under reduced pressure. The crude residue was purified by column chromatography [silica gel (EM Science 60, 230–400 mesh), MeOH/$CHCl_3$ 1:99] to obtain a colorless to light yellow oil; yield: 332.3 mg (94%); dr 5.6:1; major diastereomer: 99% ee by HPLC (Chiralcel OD-H, EtOH/hexanes 2.5:97.5); minor diastereomer: 96% ee by SFC (Chiralcel OD-H, 2.0% MeOH/CO_2).

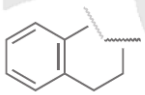
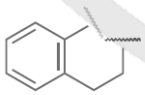
2.2.4.3.15 Michael Addition of 1,3-Dicarbonyl Compounds to Nitroalkenes

In reporting the addition reaction of 1,3-dicarbonyl compounds with nitroalkenes, Takemoto and co-workers opened a broad application field for tertiary amine thiourea catalyst **20**.[112] Various α-substituted keto esters undergo addition to (*E*)-1-nitro-2-phenylethene as Michael acceptor and furnish products with yields of 76–99% and good enantioselectivities (81–95% ee).[11] High enantioselectivities and yields are maintained even on variation of the substituents on the Michael acceptor, the nitroalkene, in combination with diethyl malonate.[11,21] The substrate scope and applicability of the Takemoto catalyst **20** is summarized in Scheme 21. Catalyst **20** is also very active in the Michael addition of malonic acid derivatives to various α,β-unsaturated imides; products are obtained in yields of 56–99% (and 28% in one case) with 62–93% ee.[113] The catalyst was also employed in a key step in a total synthesis of (*R*)-(−)-baclofen, affording the product with high enantioselectivi-

ty.[11] The total synthesis of (−)-epibatidine was additionally examined by Takemoto's group,[114,115] and they investigated the reaction of a polymer-bound variant of catalyst **20**.[116] Dixon and co-workers utilized a cinchona alkaloid thiourea derived catalyst for the Michael addition of dimethyl malonate to nitroalkenes, providing high enantioselectivities of up to 97%, and applicable in the total synthesis of (*R*)-rolipram (63% yield and >99% ee).[117,118] Connon and co-workers also utilized cinchona alkaloid thiourea derived catalysts and reached enantioselectivities of up to 99%.[49] Pedrosa and co-workers reported the addition of malonates to nitroalkenes using an amino acid derived thiourea catalyst, providing products of 79–99% ee.[119] Wang and co-workers also demonstrated the asymmetric addition of 1,3-dicarbonyl compounds to nitroalkenes, using a bifunctional rosin-derived amine thiourea catalyst.[105]

Scheme 21 Michael Addition of 1,3-Dicarbonyl Compounds to Nitroalkenes Using the Takemoto Thiourea Catalyst[11]



R^1	R^2	R^3	R^4	Temp (°C)	Time (h)	Yield (%)	dr (*syn*/*anti*)	ee (%)	Ref
		Me	2-BrC_6H_4	−40	0.5	94	92:8	95	[11]
OMe	OMe	Me	Ph	rt	28	89	–	94	[11]
OEt	H	Et	2-BrC_6H_4	rt	0.5	96	–	94[a]	[11]
OMe	Me	Me	Ph	rt	36	82	–	93[a]	[11]
$(CH_2)_3$		Me	Ph	−50	24	96	93:7	93	[11]
OEt	H	Et	2,6-$(MeO)_2C_6H_3$	rt	0.5	87	–	93	[11]
OEt	H	Et	1-naphthyl	rt	0.5	95	–	92[a]	[11]
OEt	H	Et	2-thienyl	rt	0.5	74	–	90[a]	[11]
		Me	2-thienyl	−20	0.5	98	99:1	90[a]	[11]
$(CH_2)_4$		Me	Ph	−20	36	93	96:4	85	[11]

[a] Absolute configuration was not determined.

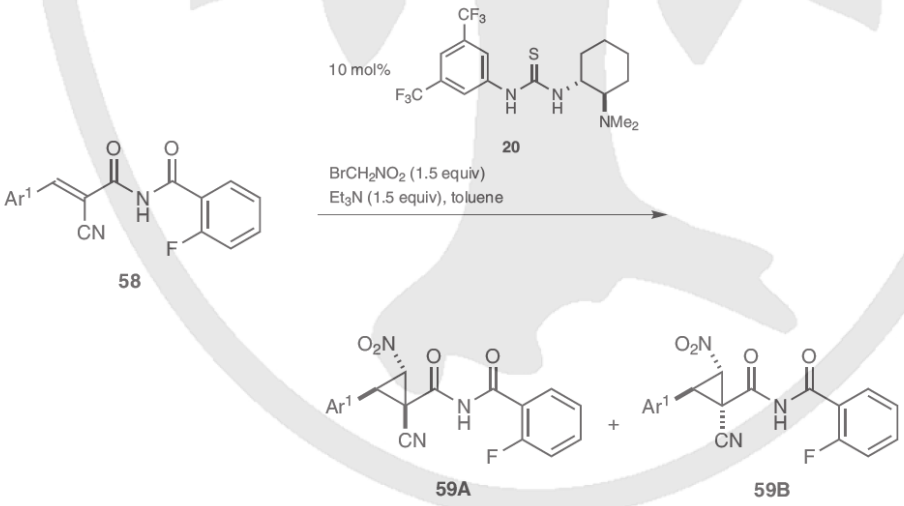
for references see p 407

2-Acyl-4-nitrocarboxylic Acid Esters 57**; General Procedure:**[11]
A reaction vessel was charged with the 1,3-dicarbonyl compound **55** (2 equiv), thiourea catalyst **20** (8.2 mg, 0.1 equiv), and anhyd toluene (0.4 mL). Then, the nitroalkene **56** (0.2 mmol) was added. After stirring at rt for 0.5 h (or the temperature/time noted in Scheme 21), the solvent was removed under reduced pressure. The crude residue was purified by column chromatography [silica gel (Kanto 60, spherical, 63–210 μm)]. The enantiomeric excess was determined by chiral HPLC analysis [Chiralpak AD-H, OJ-H, or OD-H (each 0.46 cm × 25 cm); hexane/EtOH or hexane/iPrOH]. The diastereomeric ratio was determined by ^{1}H NMR analysis.

2.2.4.3.16 Nitrocyclopropanation of α,β-Unsaturated α-Cyanoimides with Bromonitromethane

In 2006, the Connon group published a protocol for a thiourea-organocatalyzed conjugate addition of dimethyl chloromalonates to nitroalkenes to generate chiral functionalized nitrocyclopropanes.[120] The diastereoselectivities are high (de >98%) with good yields (64–73%), but only low enantioselectivities are attained. Highly toxic hexamethylphosphoric triamide is used in this synthesis, which limits general application. Takemoto and co-workers developed an enantioselective nitrocyclopropanation reaction with α,β-unsaturated α-cyanoimides **58** and bromonitromethane catalyzed by a bifunctional thiourea derivative.[112,121] The α,β-unsaturated α-cyanoimides are synthesized by Knoevenagel condensation of benzaldehydes and the appropriate α-cyanoimide. Two diastereomers **59A** and **59B** are afforded with various aryl groups (Ar^1), regardless of the electron-withdrawing or electron-donating nature of the substituents, with good total yields (>75%) and good enantioselectivities for the major diastereomer **59A** (98–99%) (Scheme 22). In 2010, Yan and co-workers published a nitrocyclopropanation of α,β-unsaturated ketones and bromonitromethane catalyzed by a thiourea derivative resulting in good enantioselectivities (88–99%) and moderate yields (31–98%). This procedure has only been applied to four substrates.[122]

Scheme 22 Enantioselective Thiourea-Catalyzed Nitrocyclopropanation of α,β-Unsaturated α-Cyanoimides[121]



Ar^1	Temp (°C)	Time (h)	Yield (%) of **59A** + **59B**	Ratio (**59A**/**59B**)	ee (%) of **59A**	Ref
4-Tol	−60	24	81	62:38	99	[121]
1-naphthyl	−20	1	81	73:27	98	[121]
3-ClC_6H_4	−20	2	80	50:50	98	[121]
2-ClC_6H_4	−20	1	79	63:37	98	[121]
4-BrC_6H_4	−20	5	76	58:42	98	[121]
4-ClC_6H_4	−20	4	75	60:40	98	[121]
Ph	−60	24	84	63:37	97	[121]

***N*-(1-Cyano-2-nitro-3-phenylcyclopropanecarbonyl)-2-fluorobenzamide (59, Ar^1 = Ph); Typical Procedure:**[121]

A reaction vessel was charged with α,β-unsaturated α-cyanoimide **58** (Ar^1 = Ph; 29.7 mg, 0.1 mmol) and thiourea **20** (4.7 mg, 10 mol%) in toluene (0.1 M). To this mixture, bromonitromethane (10 μL, 0.15 mmol, 1.5 equiv) and Et_3N (20 μL, 0.15 mmol) were added at −60 °C during a 24-h period (see Scheme 22 for temperatures and times for other substrates). The mixture was purified by column chromatography (silica gel, hexane/EtOAc 3:1) to afford the major product diastereomer **59A** (Ar^1 = Ph) as a white amorphous solid; yield: 19 mg (53%); 97% ee; and the minor product diastereomer **59B** (Ar^1 = Ph) as a brown oil; yield: 11 mg (31%); 90% ee. The enantioselectivity was determined by HPLC analysis (Daicel Chiralcel AS-H, hexane/iPrOH 90:10).

2.2.4.3.17 Michael Addition: Substrate Scope

Michael-type addition reactions provide a broad spectrum of possible reaction products. Various electrophiles and nucleophiles (e.g., nitroalkanes, malonate esters, 1,3-diketones, nitro esters, keto esters, 1,3-dinitriles, etc.) can be utilized to synthesize desirable molecules or important precursors.

In 2008, Falck and co-workers developed a protocol for the oxy-Michael addition of boronic acids to γ/δ-hydroxy α,β-enones utilizing a bifunctional catalyst.[123] In 2009, Takemoto and co-workers published a Michael addition of organoboronic acids to γ-hydroxy enones catalyzed by an iminophenol-type thiourea.[124] Vinyl adducts are obtained with high enantioselectivity (91–98% ee) and in yields of 64–99%.

Itoh and Sibi reported a synthesis of β-amino acid derivatives via a Michael addition of *O*-benzylhydroxylamines to pyrazole crotonates.[125] Yuan and co-workers demonstrated the addition of 1*H*-pyrazol-5(4*H*)-one derivatives to nitroalkenes,[126] and Goodman and Simón computationally investigated the reaction mechanism of the addition of hydroxylamines to 1-(but-2-enoyl)pyrazoles.[127]

In 2007, Scheidt and co-workers published an enantioselective protocol for the synthesis of flavones and other 2,3-dihydro-4*H*-1-benzopyran-4-ones, providing enantiomeric excesses of 65–97% and high yields of 80–94%.[128]

Wu and co-workers developed a very interesting Michael reaction of nitrodienes with methyl ketone derivatives catalyzed by a primary amino thiourea derived catalyst.[129] The products are obtained with high enantioselectivities (94–98% ee) and yields of 55–83% after a 4-day reaction time. Ma and co-workers reported a 1,4-addition of various ketones to nitrodienes or nitroenynes catalyzed by a primary amine/sugar thiourea derived catalyst.[130] The enantioselectivities range from 84 to 99% with moderate to high yields (15–98%).

In 2010, Bonne, Constantieux, and Rodriguez reported the functionalization of nitroalkenes with α-ketoamides using a bifunctional tertiary amine thiourea catalyst with very high enantioselectivities (85–99% ee), high diastereoselectivities (dr up to >20:1), and yields of 67–94%.[131]

for references see p 407

Yuan and co-workers developed a Michael addition of anthrones to nitroalkenes with enantioselectivities of 80–94% and in yields of 49–97%.[132] Du and co-workers observed high enantioselectivities (89–99% ee) for the addition of 2-hydroxy-1,4-naphthoquinones to nitroalkenes, with yields of 61–85%.[100]

2.2.4.4 Mannich Reaction

The Mannich reaction is named after C. Mannich, who transformed antipyrine, formaldehyde, and ammonium chloride into a tertiary amine in 1917.[133] This provided the basis for a generalized synthesis of β-amino ketones from CH-acidic compounds, carbonyl compounds, and primary or secondary amines.

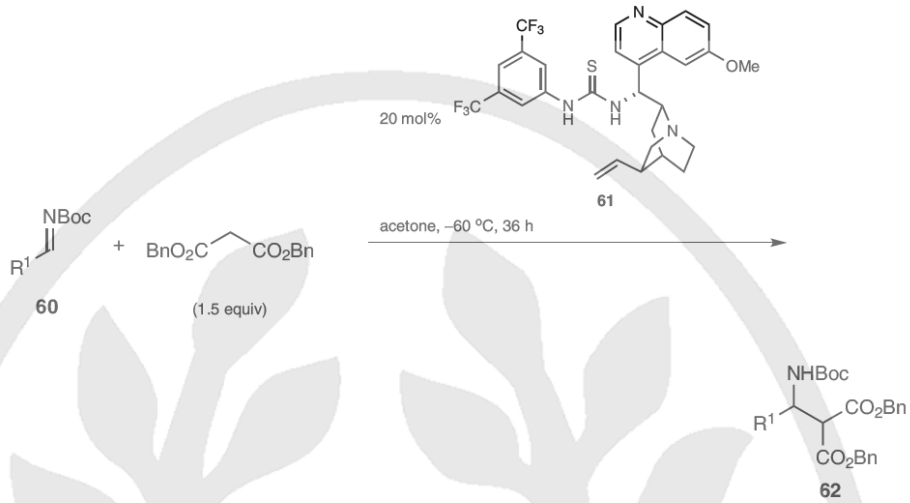
2.2.4.4.1 Mannich Reaction of Phosphorus Ylides with Imines

In 2008, the Chen group reported a sequential synthesis of β-(*tert*-butoxycarbonylamino)-α-methylene carboxylic acid esters consisting of a Mannich-type reaction catalyzed by a chiral bisthiourea and a subsequent Wittig reaction.[134] The esters are obtained in 35–87% yield with high enantiomeric excesses generally ranging from 83 to 96%. Only two examples were obtained with moderate enantiomeric excesses of 57 and 68%.

2.2.4.4.2 Mannich Reaction of Malonates with Imines

In 2006, the Dixon group reported a method for the addition of malonates to *tert*-butoxycarbonyl- and benzyloxycarbonyl-protected imines, utilizing a cinchona alkaloid derived thiourea as organocatalyst.[135] The products are obtained in yields of 81 to >99%, with 83–97% ee. Later in the same year, Deng and co-workers published a method for the enantioselective Mannich reaction of malonates to *tert*-butoxycarbonyl-protected imines **60** catalyzed by a similar thiourea derivative **61** with a cinchona alkaloid moiety.[136] For aromatic imines, enantiomeric excesses in the range 96–99%, and yields from 90 to 99% (in one case 81% yield) are obtained. The best results are presented in Scheme 23. The products of the reaction with alkyl imines are obtained with 88–92% ee and in moderate yields ranging from 55 to 64%. In 2007, Takemoto and co-workers presented their studies of Mannich reactions of *tert*-butoxycarbonyl-substituted imines with 1,3-dicarbonyl compounds.[137] In the six reported transformations, enantiomeric excesses generally span the range 83–96%, with 56% ee obtained in only one case.

Scheme 23 Enantioselective Mannich Reaction of Dibenzyl Malonate with *tert*-Butoxycarbonyl-Protected Imines Catalyzed by a Cinchona Thiourea Derivative[136]



R^1	Yield (%)	ee[a] (%)	Ref
4-FC_6H_4	99	99	[136]
4-ClC_6H_4	98	99	[136]
2-Tol	98	99	[136]
3-Tol	99	98	[136]
3,4-$(OCH_2O)C_6H_3$	99	98	[136]
2-furyl	99	97	[136]

[a] Absolute configuration of product with R^1 = Ph was determined to be *S*.

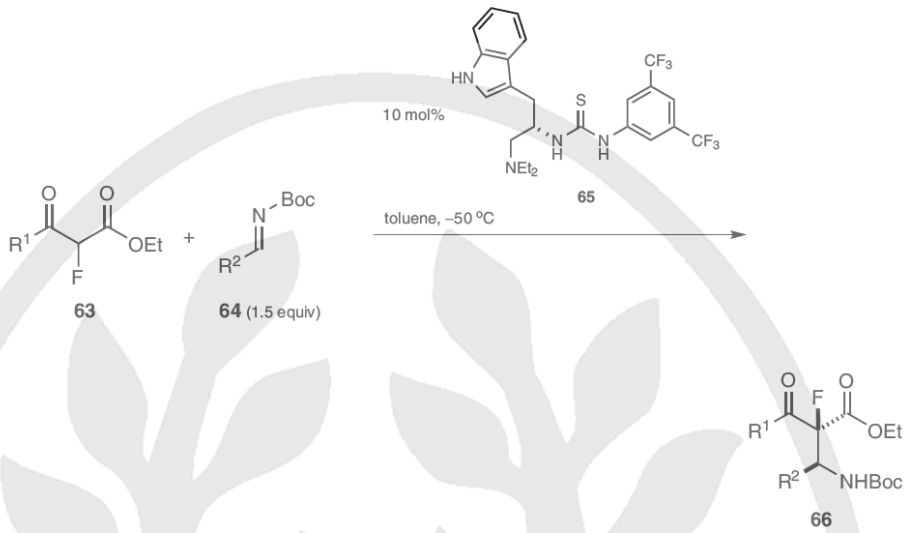
Dibenzyl 2-[2-(*tert*-Butoxycarbonylamino)alkyl]malonates 62; General Procedure:[136]
A soln of the imine **60** (0.20 mmol) and catalyst **61** (0.04 mmol, 20 mol%) in acetone (0.40 mL) was prepared. At –60 °C, dibenzyl malonate (0.30 mmol, 1.5 equiv) was added at once. After the mixture had been kept at this temperature for 36 h, it was diluted with Et_2O (5 mL), followed by filtration through a short column of silica gel. After concentration of the filtrate, the residue was purified by flash chromatography (silica gel) to afford the product **62**. The enantiomeric excess was determined by chiral HPLC analysis [Daicel Chiralpak AD or AS, Daicel Chiralcel OD, or (*R*,*R*)-Whelk-O 1; hexane/iPrOH, 1.0 or 0.5 mL·min^{-1}, λ = 220 nm].

2.2.4.4.3 Mannich Reaction of Fluorinated β-Keto Esters with Imines

In 2009, Huang, Lu, and co-workers reported a method for the addition of fluorinated β-keto esters **63** to *tert*-butoxycarbonyl-protected aldimines **64**.[138] This reaction is catalyzed by a tryptophan-derived thiourea **65**. Excellent enantiomeric excess values of 90–99% are mostly obtained, with 81–85% ee for only three of the reported cases. The diastereomeric ratios range from 1:1 to >19:1. The products **66** are afforded in generally excellent yields of 90–96% (in one case 70% yield). Scheme 24 shows 11 of the best results. In 2010, Kim and Lee reported a similar reaction of fluoromalonates with imines catalyzed by a cyclohexane-1,2-diamine-derived thiourea.[139] The obtained enantiomeric excesses (93–97%) are in a similar range to those previously reported by Huang, Lu, and co-workers,[138] but the reaction times are longer at 4–8 days.

for references see p 407

Scheme 24 Enantioselective Mannich Reaction of Fluorinated β-Keto Esters with Aldimines Catalyzed by a Thiourea Derivative[138]



R^1	R^2	Time (h)	Yield (%)	dr	ee[a] (%)	Ref
Ph	4-Tol	48	95	9:1	97	[138]
Ph	3-$O_2NC_6H_4$	20	92	8:1	99	[138]
4-Tol	4-Tol	72	92	12:1	97	[138]
Ph	4-FC_6H_4	20	95	10:1	97	[138]
Ph	4-$F_3CC_6H_4$	20	92	6:1	97	[138]
4-FC_6H_4	4-Tol	48	96	9:1	96	[138]
Ph	4-BrC_6H_4	20	92	8:1	96	[138]
2-naphthyl	4-Tol	24	93	5:1	96	[138]
Ph	Cy	20	92[b]	3:1	96	[138]
4-ClC_6H_4	4-Tol	24	95	8:1	95	[138]
4-BrC_6H_4	4-FC_6H_4	20	92	8:1	95	[138]

[a] Of the major diastereomer.
[b] The *N*-tosylimine was used.

Ethyl (2*S*,3*S*)-2-Benzoyl-3-(*tert*-butoxycarbonylamino)-2-fluoro-3-(4-tolyl)propanoate (66, R^1 = Ph; R^2 = 4-Tol); Typical Procedure:[138]

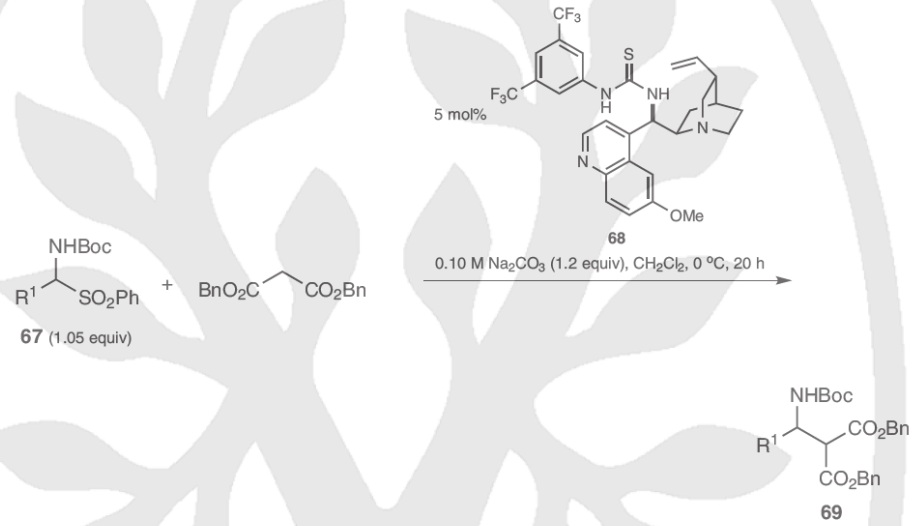
In a sample vial, fluorinated β-keto ester **63** (R^1 = Ph; 10.5 mg, 0.05 mmol) was added to a mixture of imine **64** (R^2 = 4-Tol; 16.43 mg, 0.075 mmol, 1.5 equiv) and catalyst **65** (2.5 mg, 0.005 mmol, 10 mol%) in toluene (1.0 mL). After capping of the vial, the mixture was stirred at −50 °C over a period of 48 h followed by removal of the solvent. The crude product was purified by column chromatography (silica gel, hexane/EtOAc 30:1 to 10:1) to yield the white, solid product; yield: 20.4 mg (95%); 97% ee by chiral HPLC [Chiralcel AD-H, iPrOH/hexane 15:85, 0.5 mL·min^{-1}, λ = 254 nm, t_R(major) = 23.4 min, 35.7 min].

2.2.4.4.4 Mannich Reactions of α-Amido Sulfones or Sulfonylimines

In 2009, Nagasawa and co-workers developed a method for the Mannich reaction of aromatic α-amido sulfones with malonates.[140] The synthesis of the utilized guanidine thiourea derivative requires the use of mercury(II) chloride. In 2010, Ayaz and Westermann published a Mannich reaction of naphthoquinone with α-amido sulfones.[141] Moderate

enantiomeric excesses of 31–66% are attained with a cyclohexane-1,2-diamine-derived thiourea bearing an adamantyl moiety, with yields that range from 56% to quantitative. Also in 2010, Coltart and co-workers developed a method for the enantioselective Mannich reaction of thioesters with sulfonylimines.[142] The utilized organocatalyst is a cinchona alkaloid derived thiourea, providing the products in moderate enantiomeric excesses (32–76% ee) with yields ranging from 41 to 95%. The diastereoselectivities are moderate to high, with diastereomeric ratios in the range from 83:17 to 98:2. In 2007, Deng and coworkers reported the Mannich reaction of aromatic α-amido sulfones **67** with malonates catalyzed by a cinchona alkaloid derived thiourea **68**.[143] Products **69** are obtained in 88–99% yield with 94–96% ee. The results are shown in Scheme 25.

Scheme 25 Mannich Reaction of Dibenzyl Malonate with α-Amido Sulfones Catalyzed by a Cinchona Alkaloid Thiourea Derivative[143]

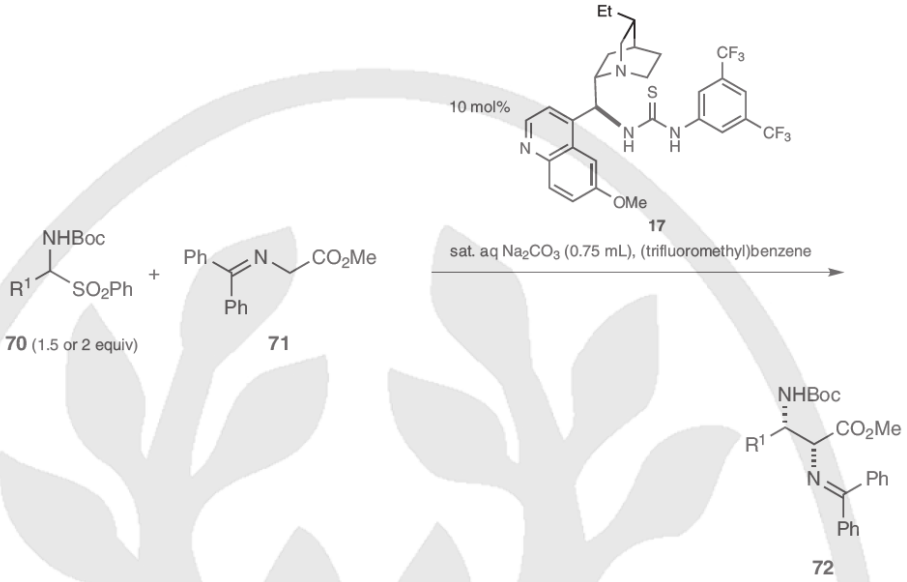


R^1	Yield (%)	ee (%)	Ref
2-furyl	90	96	[143]
Ph	89	96	[143]
4-Tol	97	95	[143]
2-Tol	96	95	[143]
3-Tol	88	95	[143]
4-$MeOC_6H_4$	90	95	[143]
4-FC_6H_4	99	94	[143]
2-thienyl	91	94	[143]

The Barbas group published the enantio- and diastereoselective Mannich reaction of α-amido sulfones **70** with imines (e.g., **71**) in 2010, using as organocatalyst a cinchona alkaloid thiourea derivative **17**.[144] The products **72** are obtained with excellent enantioselectivity (94 to >99% ee) and diastereoselectivity (dr >99:1), and in moderate to high yields (62–98%) (Scheme 26).

for references see p 407

Scheme 26 Enantio- and Diastereoselective Reaction of an Imine with α-Amido Sulfones Catalyzed by a Cinchona Alkaloid Thiourea Derivative[144]



R^1	Yield (%)	ee (%)	Ref
4-BrC_6H_4	90	>99	[144]
4-ClC_6H_4	87	>99	[144]
2-furyl	74	>99	[144]
Ph	73	99	[144]
1-naphthyl	80	98	[144]
4-$MeOC_6H_4$	62	98	[144]
4-$F_3CC_6H_4$	98	>97	[144]
4-Tol	89	>95	[144]
4-$O_2NC_6H_4$	86	94	[144]

Dibenzyl 2-[2-(*tert*-Butoxycarbonylamino)alkyl]malonates 69**; General Procedure:**[143]
A soln of catalyst **68** (0.025 mmol, 5 mol%), the amido sulfone **67** (0.525 mmol, 1.05 equiv), and dibenzyl malonate (0.50 mmol) in CH_2Cl_2 (1.0 mL) was prepared. After cooling to 0 °C, precooled 0.10 M aq Na_2CO_3 (6.0 mL, 1.2 equiv) was added at once followed by stirring for 20 h at this temperature. Then, the mixture was diluted with H_2O (10 mL). After extraction with Et_2O (3 × 25 mL), the combined organic phases were washed with brine (30 mL) and dried (Na_2SO_4). The soln was concentrated under reduced pressure, and the residue was purified by flash chromatography (silica gel, EtOAc/hexanes or hexanes/CH_2Cl_2). The enantiomeric excess was determined by chiral HPLC analysis [Daicel Chiralpak AD or AS, Daicel Chiralcel OD, or (*R*,*R*)-Whelk-O 1; hexanes/iPrOH, 1.0 mL·min^{-1}, 20 °C, λ = 220 nm].

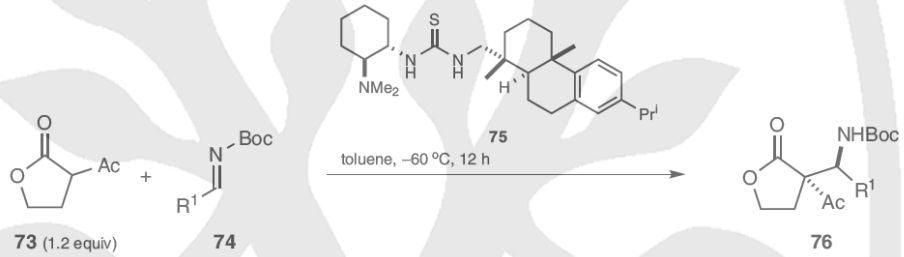
α-Aminated Imines 72**; General Procedure:**[144]
A soln of catalyst **17** (17.9 mg, 0.03 mmol, 10 mol%), the α-amido sulfone **70** (0.45 mmol, 1.5 equiv), and the imine **71** (75 mg, 0.3 mmol) in (trifluoromethyl)benzene (1.5 mL) was prepared. After addition of sat. aq Na_2CO_3 (0.75 mL) at 4 °C, the mixture was stirred over a period of 14 h at this temperature followed by stirring at rt for 28–48 h, and then quenching with H_2O. The aqueous phase was extracted with EtOAc (3 ×), and the organic phases

were combined. After drying ($MgSO_4$), the soln was concentrated, and the residue purified by flash chromatography (silica gel) to afford the *anti*-product (dr was determined by HPLC or ^1H NMR spectroscopy analysis after isolation and purification). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chiralpak AD-H, OD-H, or AD; hexane/iPrOH, 1.0 or 0.75 mL·min^{-1}, λ = 254 nm).

2.2.4.4.5 Mannich Reaction of Lactones with Imines

In 2010, Wang and co-workers reported the enantioselective addition of a lactone **73** to imines **74**.[145] The reaction is catalyzed by a cyclohexane-1,2-diamine-derived thiourea **75**. The mechanistic proposal consists of hydrogen-bonding activation of the aldimine by the thiourea moiety, while the acylated lactone in its enol form is activated by binding to the cinchona alkaloid's nitrogen.[145] The products **76** are generally obtained with high to excellent enantiomeric excesses of 81–99% (in one case 75% ee) and in 80–92% yield. The diastereomeric ratios are in all cases reported >20:1. The best results obtained are given in Scheme 27.

Scheme 27 Enantioselective Mannich Reaction of a Lactone with Imines Catalyzed by a Cyclohexane-1,2-diamine-Derived Thiourea[145]



73 (1.2 equiv) **74** **76**

R^1	Yield (%)	dr[a]	ee (%)	Ref
3-$MeOC_6H_4$	83	>20:1	99	[145]
4-Tol	82	>20:1	99	[145]
2-BrC_6H_4	85	>20:1	98	[145]
2-Tol	83	>20:1	93	[145]
2-thienyl	80	>20:1	93	[145]
Ph	86	>20:1	91	[145]

[a] The other diastereomer could not be detected by the analytical methods used (^1H NMR spectroscopy and HPLC analysis).

3-Acetyl-3-[(*tert*-butoxycarbonylamino)methyl]dihydrofuran-2(3*H*)-ones 76; General Procedure:[145]

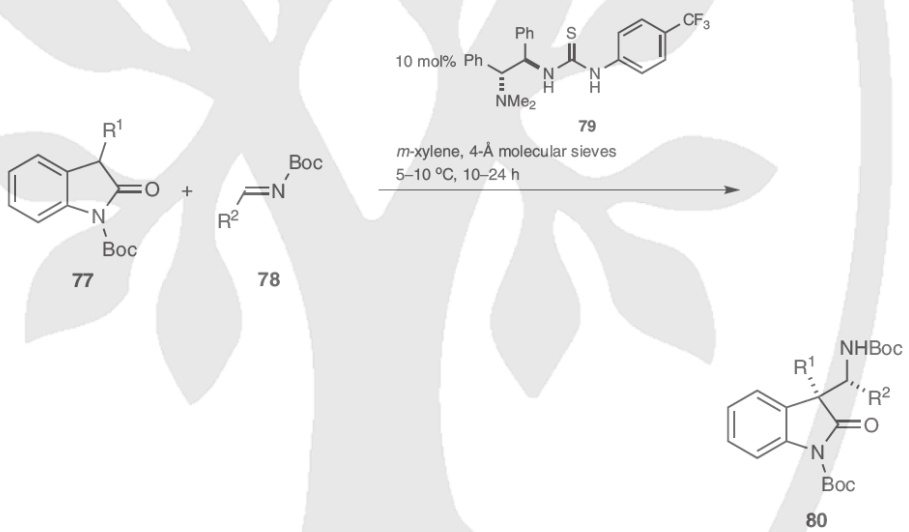
Method A: Under an atmosphere of argon, a stirred soln of catalyst **75** (0.015 mmol, 15 mol%), and the *N*-(*tert*-butoxycarbonyl)imine **74** (0.1 mmol) in anhyd toluene (1.0 mL) was prepared, followed by addition of lactone **73** (0.12 mmol, 1.2 equiv) to this soln over a period of 15 min at −60 °C. Then, the soln was stirred at this temperature over a period of 12 h. After completion of the reaction (TLC monitoring) and concentration under reduced pressure, the product was isolated by column chromatography (silica gel, EtOAc/hexane 1:8). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chiralcel AD-H or OJ-H, iPrOH/hexane, 0.8 or 1.0 mL·min^{-1}); the diastereomeric ratio was determined by ^1H NMR spectroscopy and HPLC analysis.

Method B: Under an atmosphere of argon, a stirred soln of catalyst **75** (0.015 mmol, 15 mol%), and the *N*-(*tert*-butoxycarbonyl)imine **74** (0.1 mmol) in anhyd toluene (1.0 mL) was prepared, followed by addition of lactone **73** (0.12 mmol, 1.2 equiv) to this soln over a period of 15 min at −60 °C. Then, the soln was stirred at this temperature over a period of 12 h resulting in a mixture. After completion of the reaction (TLC monitoring) and concentration under reduced pressure, the product was isolated by column chromatography (silica gel, EtOAc/hexane 1:10). After dissolution of the product in Et_2O, the soln was filtered. Removing the solvent under reduced pressure yielded the pure product. The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chiralcel AD-H or OJ-H, iPrOH/hexane, 0.8 or 1.0 mL·min^{-1}); the diastereomeric ratio was determined by ^{1}H NMR spectroscopy and HPLC analysis.

2.2.4.4.6 Mannich Reaction of Oxindoles with Imines

In 2008, the Chen group published the enantioselective addition of oxindoles **77** to imines **78** catalyzed by a 1,2-diamine-derived thiourea **79**.[146] The enantiomeric excesses are generally in the range of 82–95%, although in two reported cases less than 5% ee is obtained. The products **80** are afforded in 75–95% yield in most cases (40 and 60% for two examples), with diastereomeric ratios from >8.0:1 to >19.0:1 (Scheme 28).

Scheme 28 Enantioselective Mannich Reaction of Oxindoles with Imines Catalyzed by a 1,2-Diamine-Derived Thiourea[146]



R^1	R^2	Yield (%)	dr[a]	ee (%)	Ref
4-$FC_6H_4CH_2$	Ph	95	>19.0:1	95	[146]
Bn	Ph	94	>18.8:1	95	[146]
Bn	2-thienyl	90	12.8:1	94	[146]
Bn	3-ClC_6H_4	90	11.3:1	93	[146]
Pr	Ph	76	>15.0:1	92	[146]
Bn	4-FC_6H_4	95	>19.0:1	91	[146]
2-thienylmethyl	Ph	83	17.0:1	91	[146]
2-$ClC_6H_4CH_2$	Ph	85	>17.0:1	90	[146]

[a] Calculated from isolated yields of both diastereomers.

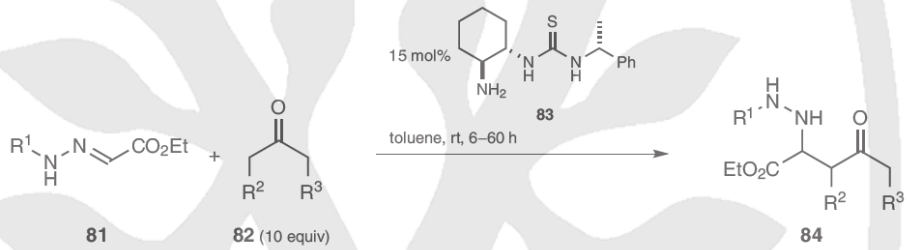
3-[(*tert*-Butoxycarbonylamino)methyl]-1,3-dihydro-2*H*-indol-2-ones 80; **General Procedure:**[146]

A mixture of catalyst **79** (4.5 mg, 0.01 mmol, 10 mol%), the oxindole **77** (0.1 mmol), and 4-Å molecular sieves (15 mg) in anhyd *m*-xylene (0.4 mL) was prepared, and then stirred at 5–10 °C. The *tert*-butoxycarbonyl-protected imine **78** (0.15 mmol, 1.5 equiv) in anhyd *m*-xylene (0.1 mL) was then added. After the reaction was complete (TLC monitoring), the product was isolated by flash chromatography (silica gel, EtOAc/petroleum ether). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chiralpak IC, AS, or AD, or Daicel Chiralcel OD; iPrOH/hexane, 1.0 mL·min^{-1}, $\lambda = 254$ nm).

2.2.4.7 Mannich Reaction of Ketones with Hydrazones

In 2008, the Tsogoeva group published a method for the enantioselective addition of ketones **82** to hydrazones **81** (Scheme 29).[147] A primary amine thiourea **83** derived from cyclohexane-1,2-diamine functions as organocatalyst. The products **84** are obtained in mostly excellent enantiomeric excesses of 90 to >99% (one product was obtained in 82% ee) with yields in the range of 45–89%.

Scheme 29 Enantioselective Addition of Ketones to Hydrazones in the Presence of a Thiourea Organocatalyst[147]



R^1	R^2	R^3	Yield (%)	de[a] (%)	ee (%)		Ref
					syn	*anti*	
Bz	H	Me	86[b]	–	>99		[147]
Bz	Me	H	–	40 (*anti*)	>99	>99	[147]
Bz	H	Et	80[c]	–	>99		[147]
Bz	Et	H	–	29 (*anti*)	>99	>99	[147]
Bz	Me	Me	82	72 (*anti*)	90	99	[147]
Bz	$(CH_2)_3$		87	8 (*syn*)	>96	>94	[147]
4-$O_2NC_6H_4CO$	$(CH_2)_3$		85	8 (*syn*)	>95	>90	[147]
4-BrC_6H_4CO	$(CH_2)_3$		89	8 (*syn*)	>94	>92	[147]
4-$MeOC_6H_4CO$	$(CH_2)_3$		83	9 (*syn*)	>93	>92	[147]
Bz	CH_2SCH_2		88	19 (*syn*)	>92	>82	[147]

[a] Configuration of major diastereomer shown in parentheses.
[b] Mixture of regioisomeric products **84** (R^2 = H; R^3 = Me) and **84** (R^2 = Me; R^3 = H) in 1.4:1 ratio.
[c] Mixture of regioisomeric products **84** (R^2 = H; R^3 = Et) and **84** (R^2 = Et; R^3 = H) in 13:1 ratio.

Ethyl 2-Hydrazino-4-oxoalkanoates 84; **General Procedure:**[147]

A stirred soln of catalyst **83** (0.15 equiv, 15 mol%) and hydrazone **81** (1 equiv) in anhyd toluene (4 mL/mmol hydrazone) was prepared, followed by addition of the ketone **82** (10 equiv) at rt. After stirring the mixture for 6–60 h under an argon atmosphere at rt,

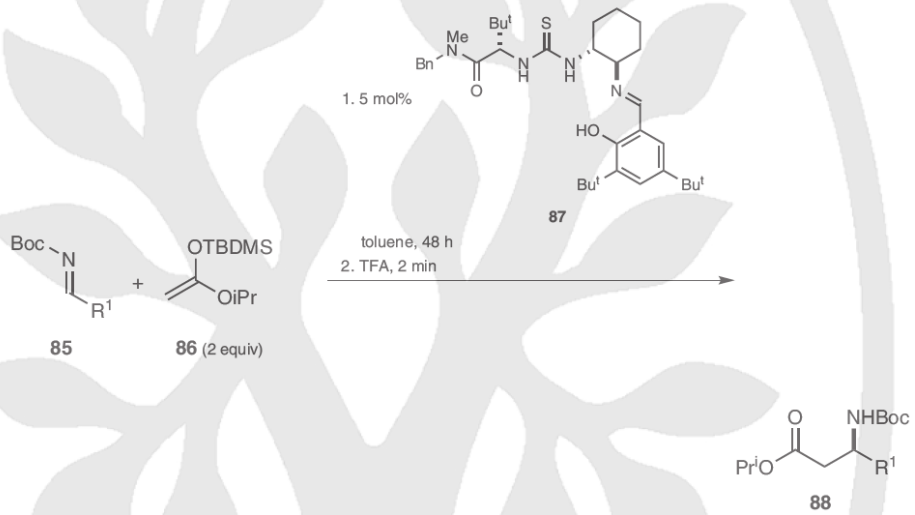
for references see p 407

the solvent was removed, followed by purification of the residue by flash chromatography (silica gel) to yield the product **84**. The enantiomeric excess and diastereomeric ratio were determined by chiral HPLC analysis (AD, OD, or IA column).

2.2.4.4.8 Mannich Reaction of Ketene Silyl Acetals with Imines

In 2002, Wenzel and Jacobsen reported a method for the enantioselective addition of a ketene silyl acetal **86** to imines **85** catalyzed by a thiourea **87** derived from cyclohexane-1,2-diamine.[148] High to excellent enantiomeric excesses in the range of 86–98% and excellent yields of 84–99% are obtained; Scheme 30 shows the best results. In 2003, the same group presented further studies on the structural dependence of the catalyst and the enantioselectivity obtained in the Mannich as well as Strecker reactions.[149]

Scheme 30 Enantioselective Mannich Reaction of a Ketene Silyl Acetal with Imines Catalyzed by a Cyclohexane-1,2-diamine-Derived Thiourea[148]



R^1	Temp (°C)	Yield (%)	ee (%)	Ref
3-pyridyl	−30	99	98	[148]
Ph	−40	95	97	[148]
3-quinolyl	−30	99	96	[148]
2-naphthyl	−30	88	96	[148]
4-Tol	−30	87	96	[148]
3-Tol	−30	98	94	[148]
4-BrC_6H_4	−30	93	94	[148]

Isopropyl 3-(*tert*-Butoxycarbonylamino)-3-phenylpropanoate (88, R^1 = Ph); Typical Procedure:[148]

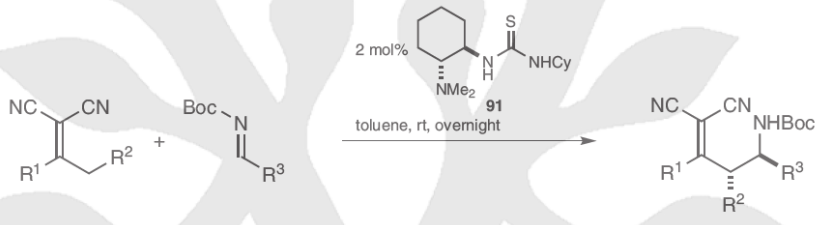
In a 5-mL round-bottomed flask, a mixture of catalyst **87** (15 mg, 0.025 mmol, 5 mol%) and anhyd toluene (250 μL) was prepared. To this mixture was added *tert*-butoxycarbonyl-protected imine **85** (R^1 = Ph; 100 mg, 0.50 mmol) at once under stirring. After homogeneity was reached, the soln was cooled to −40 °C (dry ice/acetone bath) followed by slow addition of ketene silyl acetal **86** (216 mg, 1.00 mmol, 2.0 equiv) along the flask wall over a period of 10 min. After the flask had been sealed under an atmosphere of N_2, the mixture was stirred for 48 h at −40 °C. For removal of excess **86**, the reaction was quenched at this temperature by the fast addition of a precooled (−20 °C) 3 M soln of TFA in toluene (500 μL).

The mixture was allowed to warm to ca. 5 °C followed by partition between sat. aq Na_2CO_3 and CH_2Cl_2 (1:1; 2 mL). After extraction of the aqueous phase with CH_2Cl_2 (3 × 2 mL), the combined organic phases were dried (Na_2SO_4) followed by filtration and concentration under vacuum. Then, purification of the residue by flash chromatography (silica gel, EtOAc/hexanes 2.5:97.5 to 10:90) afforded the pure product **88** (R^1 = Ph) as a white, crystalline solid; yield: 146 mg (95%); 97% ee by chiral HPLC analysis [(*R*,*R*)-Whelk-O 1, iPrOH/hexanes 5:95, 1.5 mL·min^{-1}, λ = 206 nm, t_R(minor) = 6.8 min, t_R(major) = 12.5 min].

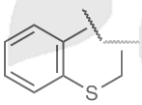
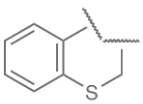
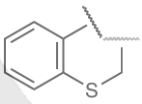
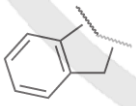
2.2.4.4.9 Vinylogous Mannich Reaction

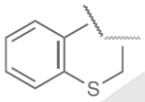
In 2007, Chen and co-workers published a method for the stereoselective vinylogous Mannich reaction catalyzed by a cyclohexane-1,2-diamine-derived thiourea **91**.[150] This bifunctional catalyst has the potential to activate both reaction components, i.e. the aldimine **90** and the dicyanoalkene **89**.[150] Excellent enantiomeric excesses of 96 to >99.5% and very good yields in the range 94–99% are obtained in most cases (Scheme 31). Lower yields of 67 and 74% are obtained for only two of the reported examples (not shown); the corresponding other diastereomers are obtained in 32 and 17% yield, respectively, with 78% ee.

Scheme 31 Stereoselective Vinylogous Mannich Reaction Catalyzed by a Cyclohexane-1,2-diamine-Derived Thiourea[150]



89 **90** (1.2 equiv) **92**

R^1	R^2	R^3	Yield (%)	ee (%)	Ref
		2-ClC_6H_4	99	>99.5	[150]
		4-FC_6H_4	94	>99	[150]
		Ph	99	99	[150]
		Ph	99	99	[150]
Ph	Me	Ph	99	99	[150]
4-FC_6H_4	H	Ph	99	99	[150]

R^1		R^2	R^3	Yield (%)	ee (%)	Ref
	$(CH_2)_4$		Ph	99	99	[150]
H		Et	Ph	99	99	[150]
			4-$MeOC_6H_4$	99	99	[150]

2-[3-(*tert*-Butoxycarbonylamino)propylidene]malononitriles 92**; General Procedure:**[150]
A mixture of catalyst **91** (0.002 mmol, 2 mol%), 1,1-dicyanoalkene **89** (0.1 mmol), and 4-Å molecular sieves (50 mg) in anhyd toluene (0.8 mL) was prepared and stirred at rt, followed by addition of the *N*-*tert*-butoxycarbonyl aldimine **90** (0.12 mmol, 1.2 equiv) in anhyd toluene (0.2 mL). After stirring overnight at rt, the product **92** was isolated by flash chromatography (silica gel, petroleum ether/EtOAc). The enantiomeric excess was determined by chiral HPLC analysis (Chiralcel AS, AD, or OD; hexane/iPrOH, 1.0 or 2.0 mL·min^{-1}, $\lambda = 254$ nm).

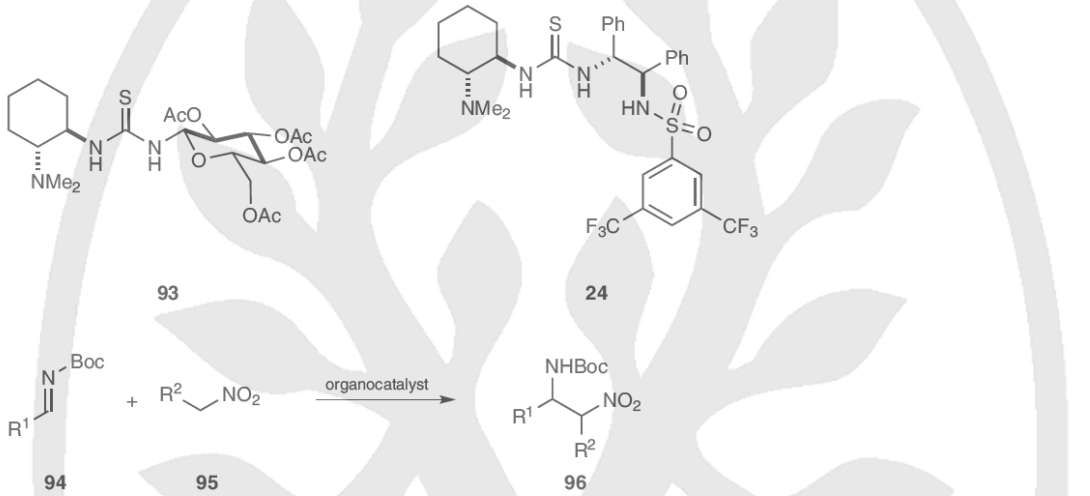
2.2.4.4.10 Nitro-Mannich Reaction/Aza-Henry Reaction

2.2.4.4.10.1 Nitro-Mannich/Aza-Henry Reaction of Nitroalkanes with Imines

Several groups have developed methods for the enantioselective addition of nitroalkanes to *tert*-butoxycarbonyl-protected imines. In 2004, the Takemoto group presented a nitro-Mannich/aza-Henry reaction of phosphinoyl-protected imines with nitromethane and nitroethane catalyzed by a cyclohexane-1,2-diamine-derived thiourea.[151] The products of the reaction with nitromethane are obtained with 63–76% ee in yields in the range 57–91%. In the case of nitroethane, the product is obtained in 83% yield with a diastereomeric ratio of 73:27; the major diastereomer is obtained with 67% ee. In 2005, Jacobsen and Yoon reported a nitro-Mannich/aza-Henry reaction of various aromatic imines with nitroethane utilizing a cyclohexane-1,2-diamine-derived thiourea.[152] The *syn*-products are obtained with 92–97% ee and in 79–99% yield, and the diastereomeric ratios range from 2:1 to 16:1. In 2006, Ricci and co-workers reported a method for the addition of nitromethane to aromatic *tert*-butoxycarbonyl- or (in one case) benzyloxycarbonyl-protected imines.[153] The products are obtained in 50–95% yield with enantiomeric excesses mostly between 80 and 94% (in two cases 44 and 63% ee were obtained). The Takemoto group reported an enantioselective addition of various nitroalkanes to aromatic *tert*-butoxycarbonyl-substituted imines also utilizing such a type of catalyst in 2006.[154] The enantiomeric excesses of the *syn*-products are in the range 89–99%; the products are obtained in 75–94% yield, and with diastereomeric ratios from 75:25 to 97:3. The same group reported an aza-Henry reaction catalyzed by polymer-supported thiourea catalysts in 2006.[116] In the same year, the Schaus group reported an enantioselective addition of nitromethane and nitroethane to aromatic acylimines with a cinchona alkaloid thiourea derivative.[155] The addition of nitromethane to acylimines furnishes the products in 60–98% yield, with the enantiomeric excesses ranging from 90 to 98%. The addition of nitroethane affords the *syn*-products with 90–97% ee in yields of 73–98%. The diastereomeric excesses are in the range 82–97%. In 2007, the Chang group published enantioselective aza-Henry reactions catalyzed by a dihydrooxazole (oxazoline) thiourea derivative.[156] The products were obtained in 68–97% yield and with 73–92% ee. In 2008, Rampalakos and Wulff reported an aza-Henry reaction catalyzed by a bisthiourea.[157] The reaction furnished the products with 65–91% ee and with yields in the range of 40 to 65%. Also in 2008, Zhou and co-workers developed an addition of nitromethane **95** ($R^2 = H$) to aromatic *N*-(*tert*-butoxycarbonyl)imines **94** catalyzed by a sugar-derived thiourea **93**.[158] The products are generally obtained in 84–95%

yield (in two cases yields of 69%, and 70% after recrystallization). The enantiomeric excesses range from 83 to >99%. Also in that year, Wang and co-workers reported an asymmetric, *anti*-selective addition of several nitroalkanes **95** to *N*-(*tert*-butoxycarbonyl)imines **94** utilizing a thiourea **24** derived from cyclohexane-1,2-diamine as organocatalyst.[159] The products **96** (R^2 = H) of the addition of nitromethane are afforded with 96–99% ee and in yields ranging from 85 to 99%. The products **96** (R^2 = Me, Et, Bn) for the addition of nitroethane, nitropropane, or 1-nitro-2-phenylethane are obtained with 96–99% ee, and in 88–99% yield. The diastereomeric ratios range from 93:7 to 99:1. The best results for nitro-Mannich/aza-Henry reactions are shown in Scheme 32.

Scheme 32 Enantioselective Nitro-Mannich/Aza-Henry Reaction of Nitroalkanes with Imines Catalyzed by Thiourea Derivatives[158,159]



R^1	R^2	Conditions	Yield (%)	dr[a]	ee (%)	Ref
1-naphthyl	H	**93** (15 mol%), CH_2Cl_2, −78 °C, 65 h	95	–	>99	[158]
4-ClC_6H_4	H	**93** (15 mol%), CH_2Cl_2, −78 °C, 60 h	93	–	>99	[158]
4-FC_6H_4	H	**93** (15 mol%), CH_2Cl_2, −78 °C, 65 h	91	–	>99	[158]
3-FC_6H_4	H	**93** (15 mol%), CH_2Cl_2, −78 °C, 39 h	87	–	>99	[158]
Ph	H	**93** (15 mol%), CH_2Cl_2, −78 °C, 60 h	86	–	>99	[158]
Ph	Bn	**24** (10 mol%), 4-Å molecular sieves, MeCN, −20 °C, 10–15 h	95	99:1	99	[159]
Ph	Et	**24** (10 mol%), 4-Å molecular sieves, MeCN, −20 °C, 10–15 h	94	99:1	99	[159]
4-Tol	Et	**24** (10 mol%), 4-Å molecular sieves, MeCN, −20 °C, 10–15 h	99	97:3	99	[159]
4-$F_3CC_6H_4$	Me	**24** (10 mol%), 4-Å molecular sieves, MeCN, −20 °C, 10–15 h	97	97:3	99	[159]
Ph	Me	**24** (10 mol%), 4-Å molecular sieves, MeCN, −20 °C, 10–15 h	92	97:3	99	[159]

[a] Determined by HPLC analysis. Minor *syn*-isomer was not detected by ^{1}H NMR analysis of crude product.

Takeda and Nagasawa reported an aza-Henry reaction utilizing a guanidine thiourea catalyst in 2009.[160] The products were obtained with excellent enantiomeric excesses of 90–99%, diastereomeric ratios in the range of 90:10 to 99:1, and with yields ranging from 81 to 96%, but the synthesis of the catalyst requires the use of highly toxic mercury(II) chloride. Also in that year, Wang, Zhou, and co-workers published the aza-Henry reaction of *N*-thiophosphorylimines with nitromethane furnishing the products with yields in the range of 78 to 94% and with 77–87% ee.[161]

for references see p 407

***N*-(*tert*-Butoxycarbonyl)-β-nitroamines 96 (R^1 = H); General Procedure Using Catalyst 93:**[158]

CAUTION: *Nitromethane is flammable, a shock- and heat-sensitive explosive, and an eye, skin, and respiratory tract irritant.*

In a flame-dried (under vacuum) vessel, nitromethane (**95**, R^2 = H; 270 μL, 5 mmol, 10 equiv) was added in one portion to a soln of the imine **94** (0.5 mmol) and catalyst **93** (40 mg, 0.075 mmol, 15 mol%) in CH_2Cl_2 at −78 °C. The mixture was stirred at that temperature and the course of the reaction was monitored by TLC. Then, the soln was concentrated followed by purification by column chromatography (silica gel, EtOAc/petroleum ether 1:12) to afford product **96** as a white solid. The enantiomeric excess was determined by chiral HPLC analysis (Chiralpak AD-H, hexane/iPrOH, 1.0 or 0.8 mL·min^{-1}, λ = 254 nm).

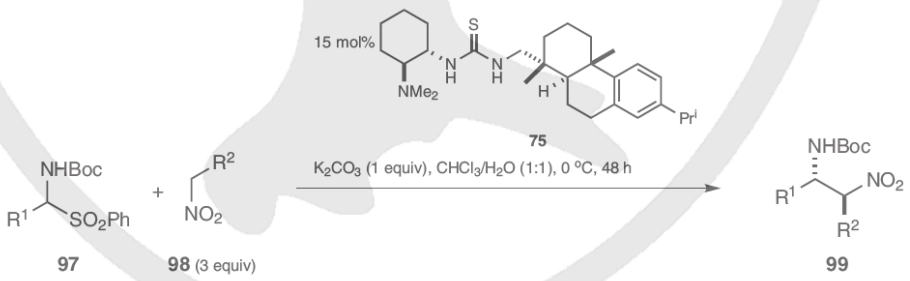
***N*-(*tert*-Butoxycarbonyl)-β-nitroamines 96 (R^2 = Me, Et, Bn); General Procedure Using Catalyst 24:**[159]

A mixture of the *N*-(*tert*-butoxycarbonyl)imine **94** (0.2 mmol) and the nitroalkane **95** (1.0 mmol, 5 equiv) in MeCN (0.5 mL) was prepared, followed by addition of catalyst **24** (13.5 mg, 0.02 mmol, 10 mol%) at −20 °C (note: the addition of 4-Å molecular sieves was not mentioned in the procedure). After the reaction was complete (TLC monitoring, 10–15 h), the mixture was concentrated under vacuum followed by purification by flash chromatography (silica gel) to yield the product **96**. The enantiomeric excess was determined by chiral HPLC analysis (Chiralcel AD-H or AS-H, iPrOH/hexane or EtOH/hexane, 1.0 or 0.5 mL·min^{-1}, λ = 210 or 220 nm).

2.2.4.4.10.2 Nitro-Mannich/Aza-Henry Reaction of Nitroalkanes with α-Amido Sulfones

In 2009, Wang and co-workers reported a method for the enantioselective nitro-Mannich/aza-Henry reaction of nitroalkanes **98** with α-amido sulfones **97** (Scheme 33).[162] As catalyst, a rosin-derived thiourea **75** is utilized. The (1*S*)-products **99** are obtained with 81–98% ee and in yields of 80–93%, with the exception of a nonaromatic amido sulfone example (R^1 = Cy), which gives only 15% of the (1*S*)- and 10% of the (1*R*)-product. The diastereomeric ratios of the products obtained via transformation with nitroethane range from 78:22 to 98:2. The (1*R*)-products are obtained by utilizing the opposite enantiomer of the catalyst, although the reported enantiomeric excesses and yields are on average not as high for these products as for the (1*S*)-analogues (78–97% ee, 80–90% yield).

Scheme 33 Enantioselective Nitro-Mannich/Aza-Henry Reaction of Nitroalkanes with α-Amido Sulfones Catalyzed by a Rosin-Derived Thiourea[162]



R^1	R^2	Yield (%)	dr (*anti*/*syn*)	ee (%)	Ref
4-FC_6H_4	H	83	–	98	[162]
4-ClC_6H_4	Me	93	78:22	95	[162]
4-ClC_6H_4	H	89	–	95	[162]
2-$MeOC_6H_4$	H	81	–	95	[162]

R^1	R^2	Yield (%)	dr (*anti*/*syn*)	ee (%)	Ref
Ph	H	86	–	93	[162]
1-naphthyl	H	82	–	93	[162]
3-$MeOC_6H_4$	H	80	–	93	[162]
2-FC_6H_4	H	92	–	92	[162]
2-FC_6H_4	Me	90	86:14	92	[162]

***tert*-Butyl 2-Nitro-1-phenylethylcarbamate (99, R^1 = Ph; R^2 = H); Typical Procedure:**[162]

CAUTION: *Nitromethane is flammable, a shock- and heat-sensitive explosive, and an eye, skin, and respiratory tract irritant.*

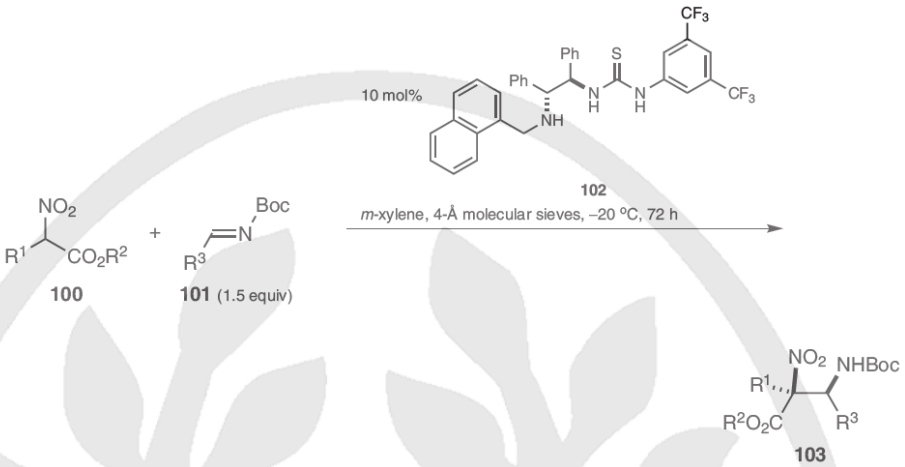
A mixture of catalyst **75** (7 mg, 0.015 mmol, 15 mol%) and α-amido sulfone **97** (R^1 = Ph; 34.7 mg, 0.1 mmol) was prepared in a mixture of $CHCl_3$ (1.0 mL) and H_2O (1.0 mL), followed by addition of K_2CO_3 (13.8 mg, 0.1 mmol, 1.0 equiv) under stirring. After addition of nitromethane (**98**, R^2 = H; 16.1 μL, 0.3 mmol, 3.0 equiv) under an argon atmosphere, the mixture was stirred at 0 °C. After completion of the reaction (TLC monitoring), the mixture was extracted with $CHCl_3$ (4 × 10 mL) followed by drying (Na_2SO_4). The soln was concentrated, and the residue was purified by flash chromatography (silica gel, EtOAc/hexane 1:8) to give product **99** (R^1 = Ph; R^2 = H); yield: 22.8 mg (86%); 93% ee by chiral HPLC analysis [Chiralpak AD, iPrOH/hexane 1:9, 0.6 mL·min^{-1}, λ = 210 nm, t_R(major) = 16.88 min, t_R(minor) = 17.91 min].

2.2.4.4.10.3 Nitro-Mannich/Aza-Henry Reaction of Nitroacetates with Imines

In 2008, Li, Chen, and co-workers reported a method for the enantioselective addition of nitroacetates **100** to *N*-*tert*-butoxycarbonyl-protected imines **101** utilizing a 1,2-diphenylethane-1,2-diamine-derived thiourea **102**.[163] High to excellent enantiomeric excesses of 91–96% and yields of 68–86% (38% in one reported case) are attained (Scheme 34). The diastereomeric ratios range from 3.8:1 to 17.2:1. In the case of R^1 = R^2 = Ph, the product **103** is labile.

for references see p 407

Scheme 34 Nitro-Mannich/Aza-Henry Reaction of Nitroacetates with Imines Catalyzed by a 1,2-Diphenylethane-1,2-diamine-Derived Thiourea[163]



R^1	R^2	R^3	Yield[a] (%)	dr[b]	ee (%)	Ref
Me	Me	Ph	86	17.2:1	96	[163]
Me	Me	4-Tol	86	14.3:1	96	[163]
Me	Me	4-FC_6H_4	78	9.8:1	96	[163]
iPr	Et	Ph	38	5.4:1	96	[163]
Me	Me	2-furyl	85	8.5:1	95	[163]
Me	Me	3-ClC_6H_4	83	10.4:1	95	[163]
Me	Me	3-Tol	85	17.0:1	94	[163]
Bn	Me	Ph	68	7.6:1	93	[163]
Me	Me	2-ClC_6H_4	79	7.9:1	91	[163]
Me	Me	2-thienyl	75	3.8:1	91	[163]

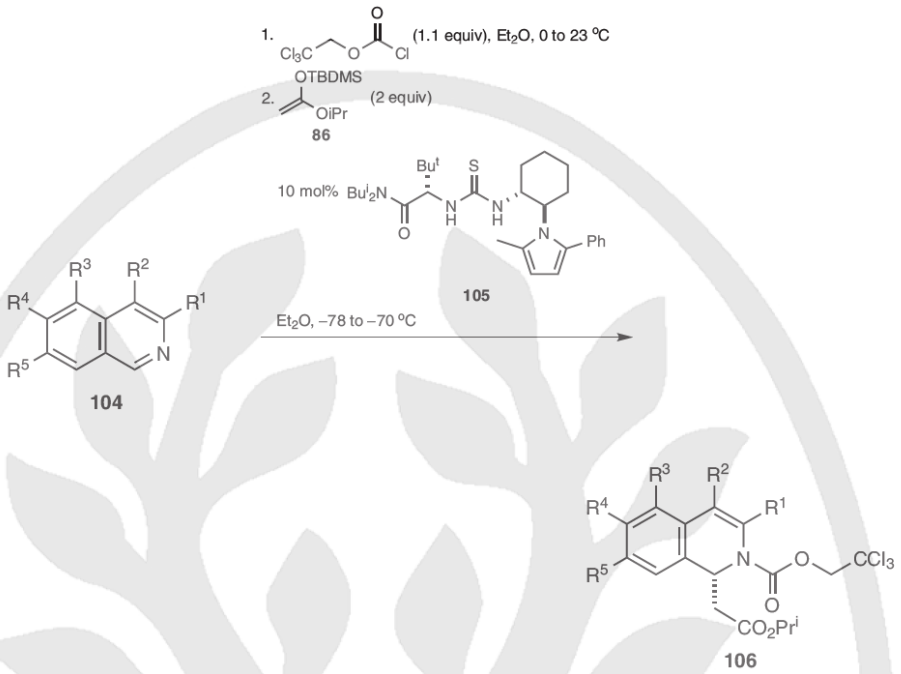
[a] Yield of isolated major product.
[b] Calculated from the yields of both isolated diastereomers.

3-(*tert*-Butoxycarbonylamino)-2-nitropropanoates 103**; General Procedure:**[163]
A mixture of catalyst **102** (9.3 mg, 0.015 mmol, 10 mol%), the imine **101** (0.23 mmol, 1.5 equiv), and 4-Å molecular sieves (40 mg) in freshly distilled *m*-xylene (0.50 mL) was prepared. After addition of the nitroacetate **100** (0.15 mmol) in one portion at −20 °C, the mixture was stirred at this temperature over a period of 72 h. The mixture was then filtered by passing through silica gel followed by concentration and purification via flash chromatography (silica gel, petroleum ether/EtOAc). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chiralpak AD, iPrOH/hexane, 1 mL · min^{-1}, λ = 220 nm).

2.2.4.4.11 Acyl-Mannich Reaction

In 2005, Jacobsen and co-workers developed a method for the enantioselective acyl-Mannich reaction of isoquinolines **104** catalyzed by a thiourea tertiary amine organocatalyst **105**.[164] This catalyst has the potential to activate a putative acyliminium ion via hydrogen-bonding interactions.[164] The resulting esters **106** are obtained in 67–86% yield with 60–92% ee. The six examples with the best enantiomeric excesses are shown in Scheme 35.

Scheme 35 Enantioselective Acyl-Mannich Reaction of Isoquinolines Catalyzed by a Thiourea Tertiary Amine Organocatalyst[164]



R^1	R^2	R^3	R^4	R^5	Yield (%)	ee (%)	Ref
Me	H	H	H	H	75	92	[164]
H	Br	H	H	H	78	91	[164]
H	H	Br	H	H	77	87	[164]
H	H	H	H	H	80	86	[164]
H	H	OTBDMS	H	H	77	83	[164]
H	H	H	OTf	H	67	83	[164]

2,2,2-Trichloroethyl 1-[(Isopropoxycarbonyl)methyl]-1*H*-isoquinoline-2-carboxylate (106, $R^1 = R^2 = R^3 = R^4 = R^5 = H$); Typical Procedure:[164]

CAUTION: *2,2,2-Trichloroethyl chloroformate is toxic by inhalation and causes burns.*

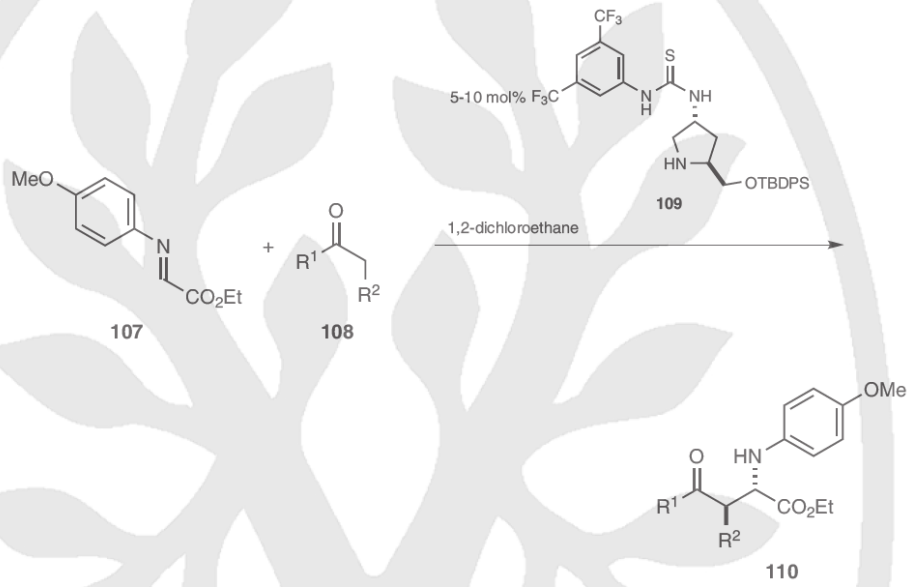
Under a N_2 atmosphere, a soln of isoquinoline **104** ($R^1 = R^2 = R^3 = R^4 = R^5 = H$; 97% pure; 61 μL, 0.50 mmol) in anhyd Et_2O (5.0 mL) was cooled to 0 °C in a flame-dried round-bottomed flask followed by the dropwise addition of 2,2,2-trichloroethyl chloroformate (TrocCl; 98% pure; 76 μL, 0.55 mmol, 1.1 equiv) via syringe resulting in a white suspension. The mixture was then warmed to 23 °C and stirred for 30 min. After cooling to −78 °C (dry ice/iPrOH bath), catalyst **105** (26.9 mg, 0.050 mmol, 10 mol%) in anhyd Et_2O (4.0 mL + 1.0 mL for rinsing) was added followed by addition of 1-(*tert*-butyldimethylsiloxy)-1-isopropoxyethene (**86**; 216 mg, 1.0 mmol, 2.0 equiv). The mixture was warmed to −70 °C (iPrOH bath equipped with immersion cooler) and stirred for 14 h. Then, the cooling bath was allowed to warm to 23 °C over a period of 3 h. The solvent was removed under vacuum, and the residue was purified by chromatography (silica gel, EtOAc/hexanes 0:100 to 5:95) affording **106** ($R^1 = R^2 = R^3 = R^4 = R^5 = H$) as a colorless oil; yield: 161 mg (80%); 86% ee by chiral SFC analysis [Chiralpak OD-H, 5% MeOH/CO_2, 5 mL·min^{-1}, 50 °C, λ = 285 nm, t_R(minor) = 2.23 min, t_R(major) = 2.66 min].

for references see p 407

2.2.4.4.12 *anti*-Mannich Reaction

In 2009, Peng and co-workers developed a method for the enantio- and diastereoselective *anti*-Mannich reaction of protected α-iminoacetate **107** with aldehydes or ketones **108** catalyzed by thiourea derivative **109**.[165] The resulting β-amino carbonyl compounds **110** are obtained in 63–94% yield and with enantiomeric excesses for the *anti*-products mostly ranging from 94 to >99% (in one case 81.5% ee). Diastereomeric ratios (*anti*/*syn*) vary from 55:45 to >99:1. Some of the best results are given in Scheme 36.

Scheme 36 Enantio- and Diastereoselective *anti*-Mannich Reaction Catalyzed by a Thiourea Derivative[165]



R^1	R^2	Temp (°C)	Time (min)	Yield (%)	dr (*anti*/*syn*)	ee (%)	Ref
H	iPr	−20	30	94	93:7	>99	[165]
H	$(CH_2)_5Me$	−20	20	93	>99:1	>99	[165]
H	Et	−20	120	93	96:4	>99	[165]
H	$(CH_2)_6Me$	−20	8	93	95:5	>99	[165]
H	$(CH_2)_4Me$	−20	20	87	97:3	>99	[165]
H	Pr	−20	20	84	93:7	>99	[165]

Ethyl 2-[(4-Methoxyphenyl)amino]-4-oxoalkanoates 110**; General Procedure:**[165]
The aldehyde **108** (R^1 = H; 1.0 mmol, 5 equiv) or ketone **108** (R^1 = organo; 2.0 mmol, 10 equiv) was added to a soln of ethyl 2-[(4-methoxyphenyl)imino]acetate (**107**; 0.2 mmol) in anhyd 1,2-dichloroethane (1.5 mL), and then catalyst **109** (0.01 mmol, 5 mol%; or 0.02 mmol, 10 mol%) was added. The mixture was stirred at the above-mentioned temperature for the indicated time (Scheme 36). After consumption of the imine (TLC monitoring), sat. aq NH_4Cl was added, and the mixture was extracted with EtOAc (3–4 ×). The combined organic layers were washed with brine and dried (Na_2SO_4). The filtrate was concentrated under vacuum, and purified by flash column chromatography (silica gel, EtOAc/petroleum ether 5:95 to 10:90) to afford the product **110**. The enantiomeric excess and diastereomeric ratio were determined by chiral-phase HPLC analysis (Chiralpak AS-H, hexane/iPrOH 90:10 or 98:2, 0.5 mL·min^{-1}, λ = 254 nm).

2.2.4.5 Henry Reaction/Nitroaldol Reaction

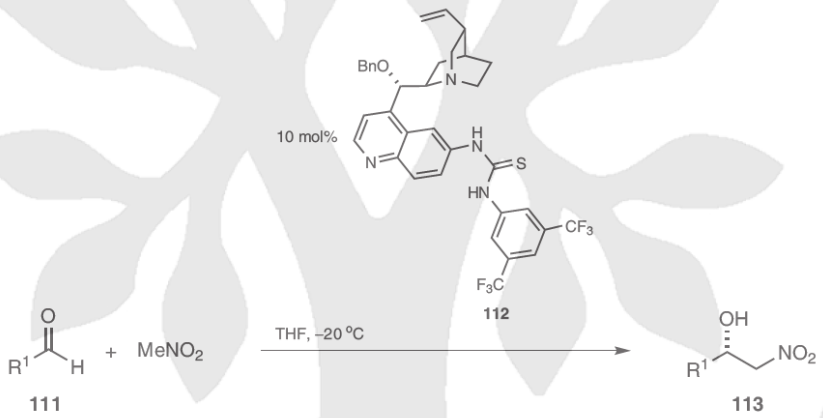
The reaction of aldehydes or ketones with nitroalkenes is known as the Henry or nitroaldol reaction. It is named after L. Henry, who reported this type of reaction in 1895.[133]

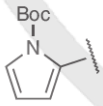
The Nagasawa group reported methods for the enantioselective Henry reaction catalyzed by a guanidine-derived thiourea.[166–170] However, the synthesis of this organocatalyst requires the use of highly toxic mercury(II) chloride.

In 2007, Shi and co-workers published an enantioselective Henry reaction of aromatic aldehydes with nitromethane,[171] utilizing a 2,2′-diamino-1,1′-binaphthyl (BINAM) derived bisthiourea as catalyst. The products are obtained with 22–75% ee in 65–99% yield.

Hiemstra and co-workers reported in 2006 an enantioselective organocatalytic Henry reaction of various aromatic aldehydes **111** with nitromethane catalyzed by a cinchona alkaloid thiourea derivative **112**.[172] In their mechanistic proposal, the thiourea group binds via double hydrogen bonding to the aldehyde, and thus activates the carbonyl compound by stabilizing the oxygen atom's partial negative charge. The nitrogen of the cinchona alkaloid activates the nitroalkane.[172] The resulting nitro alcohols **113** are obtained with high enantiomeric excesses of 85–92% in excellent yields ranging from 90 to 99% (Scheme 37). In 2007, Himo and co-workers published a computational study regarding the mechanism of this reaction.[173]

Scheme 37 Enantioselective Henry Reaction of Aromatic Aldehydes with Nitromethane Catalyzed by a Cinchona Alkaloid Thiourea Derivative[172]



R^1	Time (h)	Yield (%)	ee (%)	Ref
1-naphthyl	48	99	92	[172]
Ph	48	90	92	[172]
2-Tol	96	97	91	[172]
	24	95	91	[172]
4-$MeOC_6H_4$	168	94	89	[172]
4-$O_2NC_6H_4$	4	91	86	[172]
3-pyridyl	24	91	86	[172]
4-FC_6H_4	24	99	85	[172]

for references see p 407

Nitro Alcohols 113**; General Procedure:**[172]

CAUTION: *Nitromethane is flammable, a shock- and heat-sensitive explosive, and an eye, skin, and respiratory tract irritant.*

In a screw-capped vial, a mixture of the aldehyde **111** (1.0 mmol) and catalyst **112** (67 mg, 0.1 mmol, 10 mol%) in anhyd THF (1 mL) was prepared. After cooling of the soln to −20 °C in a freezer, nitromethane (536 μL, 10.0 mmol, 10 equiv) was added, and the soln was kept at this temperature for the time stated in Scheme 37. Then, the mixture was purified by column chromatography (silica gel, petroleum ether/EtOAc) to yield the product **113**. The enantiomeric excess was determined by chiral HPLC analysis (Chiralcel OD-H, iPrOH/heptane, 0.7 or 0.8 mL·min^{-1}, λ = 215 or 254 nm).

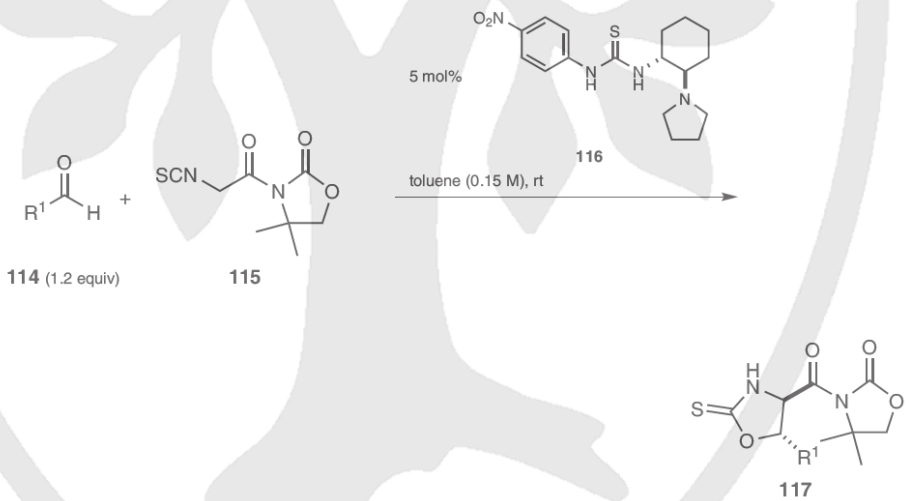
2.2.4.6 Aldol Reaction

An aldol reaction catalyzed by a thiourea derivative was applied in the synthesis of (+)-trachyspic acid by Hatakeyama and co-workers.[174]

2.2.4.6.1 Aldol Reaction of α-Isothiocyanato Imides with Aldehydes

In 2008, Seidel and co-workers disclosed the aldol reaction of α-isothiocyanato imide **115** with aldehydes **114**.[175] This aldol-type addition is catalyzed by a cyclohexane-1,2-diamine-derived thiourea **116**. The resulting thiocarbamate derivatives **117** are obtained with high enantiomeric excesses of 81–96% and in yields of 55–99%. The diastereomeric ratios are in the range 82:18 to 98:2. The eight best results are shown in Scheme 38.

Scheme 38 Enantioselective Aldol Reaction of an α-Isothiocyanato Imide with Aldehydes Catalyzed by a Cyclohexane-1,2-diamine-Derived Thiourea Derivative[175]



R^1	Time (h)	Yield[a] (%)	dr (*trans*/*cis*)	ee[b] (%)	Ref
4-$MeOC_6H_4$	3	76	97:3	96	[175]
4-FC_6H_4	8	97	95:5	94	[175]
4-BrC_6H_4	2	91	95:5	94	[175]
4-Tol	16	94	94:6	94	[175]
Ph	4	99	93:7	94	[175]

R^1	Time (h)	Yield[a] (%)	dr (*trans*/*cis*)	ee[b] (%)	Ref
1-naphthyl	72	60	93:7	94	[175]
4-$O_2NC_6H_4$	2	97	95:5	93	[175]
3-Tol	12	90	94:6	93	[175]

[a] Combined yield of both diastereomers.
[b] Determined by chiral HPLC analysis after transformation to the corresponding ethyl esters.

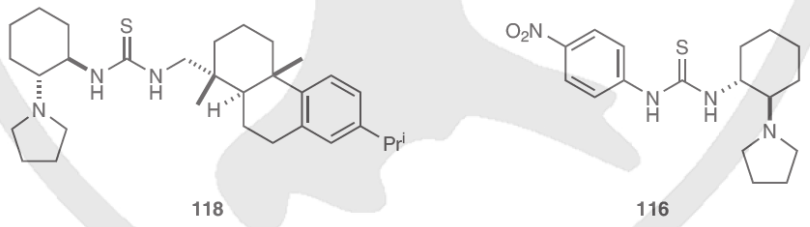
Thiocarbamate Derivatives 117**; General Procedure:**[175]
A soln of the aldehyde **114** (freshly distilled; 1.20 mmol, 1.2 equiv), catalyst **116** (17.5 mg, 0.05 mmol, 5 mol%), and α-isothiocyanato imide **115** (214 mg, 1.00 mmol) was prepared in toluene (6.67 mL) at rt. After imide **115** was consumed (TLC monitoring), the mixture was purified by flash chromatography (silica gel, CH_2Cl_2/EtOAc 50:1) to afford the product **117** as a mixture of diastereomers.

For transformation to the corresponding ethyl esters, a soln of the diastereomer mixture in anhyd THF (20 mL) was prepared. After cooling to 0 °C, a soln of MeMgCl (3 M in THF; 1.2 equiv) in EtOH (8 mL) was added with a syringe. To quench the reaction, aq phosphate buffer (pH 7; 8 mL) was added after 3 min. After concentration under vacuum, the residue was mixed with 1 M aq HCl (16 mL) and CH_2Cl_2 (20 mL). After separation, the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The extracts were combined and dried (Na_2SO_4). After concentration under reduced pressure, the crude product was purified by flash chromatography (silica gel, CH_2Cl_2/EtOAc 50:1). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chiralpak AS-H or AD-H, hexane/iPrOH, 1 mL·min^{-1}, λ = 254 nm).

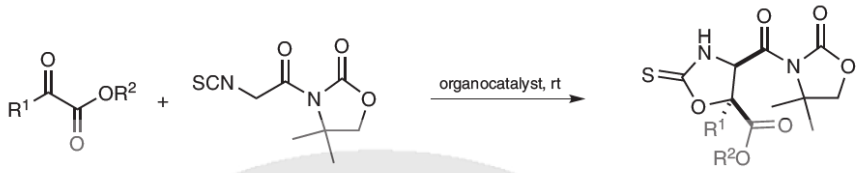
2.2.4.6.2 Aldol Reaction of α-Isothiocyanato Imides with α-Keto Esters

In 2010, the Wang group[176] as well as Seidel and co-workers[177] reported enantioselective aldol reactions of α-isothiocyanato imide **115** with α-keto esters **119**. They utilized cyclohexane-1,2-diamine-derived thioureas **118** and **116**, respectively, as organocatalysts for this addition. The resulting thiocarbamates **120** are obtained in 70–99% yield with 79–99% ee. The diastereomeric ratios range from 70:30 to 90:10. Ten of the best results are shown in Scheme 39.

Scheme 39 Enantioselective Aldol Reaction of an α-Isothiocyanato Imide with α-Keto Esters Catalyzed by Cyclohexane-1,2-diamine-Derived Thiourea Derivatives[176,177]



118 116



119 115 120

R^1	R^2	Conditions	Yield[a] (%)	dr	ee (%)	Ref
3-$MeOC_6H_4$	Me	**118** (1 mol%), toluene, 2.5 h	86	83:17	99	[176]
4-BrC_6H_4	Me	**118** (1 mol%), toluene, 2.5 h	84	85:15	98	[176]
3,4-$Cl_2C_6H_3$	Et	**116** (5 mol%), *t*-BuOMe (0.15 M), 1.5 h	99	83:17	98	[177]
4-ClC_6H_4	Et	**116** (5 mol%), *t*-BuOMe (0.15 M), 2.5 h	99	83:17	98	[177]
4-Tol	Me	**118** (1 mol%), toluene, 2.5 h	85	88:12	97	[176]
4-$F_3CC_6H_4$	Et	**116** (5 mol%), *t*-BuOMe (0.15 M), 12 h	95	85:15	97	[177]
3,5-$F_2C_6H_3$	Et	**116** (5 mol%), *t*-BuOMe (0.15 M), 2 h	96	80:20	97	[177]
2-naphthyl	Me	**118** (1 mol%), toluene, 5 h	78	90:10	96	[176]
4-*t*-BuC_6H_4	Et	**116** (5 mol%), *t*-BuOMe (0.15 M), 7 h	90	80:20	96	[177]
Ph	Et	**116** (5 mol%), *t*-BuOMe (0.15 M), 3 h	93	80:20	95	[177]

[a] Yield of isolated product (reactions using catalyst **118**), or yield of both isolated diastereomers combined (reactions using catalyst **116**).

Alkyl 4-(4,4-Dimethyl-2-oxooxazolidine-3-carbonyl)-2-thioxooxazolidine-5-carboxylates 120; General Procedure Using Catalyst 118:[176]

A soln of the α-keto ester **119** (0.24 mmol, 1.2 equiv) and catalyst **118** (0.002 mmol, 1.0 mol%) in anhyd toluene (1.0 mL) was prepared, followed by addition of a soln of α-isothiocyanato imide **115** (0.2 mmol) in anhyd toluene (0.1 mL) over a period of 10 min under an atmosphere of argon and with stirring. The soln was stirred for 2.5 h at rt (unless otherwise noted). After completion of the reaction (TLC monitoring), the mixture was concentrated under reduced pressure followed by purification by column chromatography (silica gel, EtOAc/hexane 1:2). The product was dissolved in Et_2O, and the soln was filtered. The product **120** was obtained after concentration under reduced pressure. The enantiomeric excess of the major diastereomer was determined by HPLC analysis (Chiralcel AD-H, iPrOH/hexane 1:4 or 1:9, 1.0 mL·min^{-1}).

Alkyl 4-(4,4-Dimethyl-2-oxooxazolidine-3-carbonyl)-2-thioxooxazolidine-5-carboxylates 120; General Procedure Using Catalyst 116:[177]

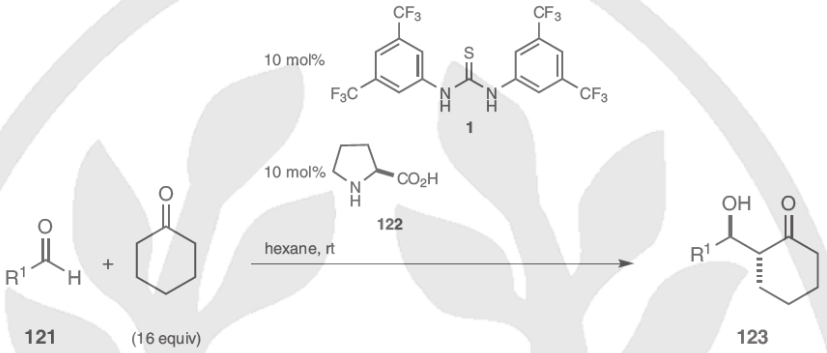
In a screw-capped vial, a soln of the α-keto ester **119** (0.55 mmol, 1.1 equiv) and catalyst **116** (0.025 mmol, 5 mol%) was prepared in anhyd *t*-BuOMe. Then, α-isothiocyanato imide **115** (0.50 mmol) was added. After imide **115** had been consumed (TLC monitoring), the solvent was removed under vacuum, followed by purification of the residue by flash chromatography (silica gel, EtOAc/CH_2Cl_2) to afford the product **120**. The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chiralpak AD-H, hexanes/iPrOH 9:1, 1 mL·min^{-1}, λ = 254 nm).

2.2.4.6.3 Aldol Reaction of Aromatic Aldehydes with Cyclohexanone

In 2009, Demir and co-workers reported the aldol reaction between aromatic aldehydes **121** and cyclohexanone.[178] The reaction is catalyzed by a complex between *N*,*N*′-bis[3,5-bis(trifluoromethyl)phenyl]thiourea (**1**) and proline (**122**). The desymmetrization of prochiral cyclohexanones with, and mechanistic studies on such a catalyst complex were un-

dertaken by Rios, Moyano, and co-workers in 2009/2010.[179,180] The resulting aldol adducts **123** are obtained in 75–98% yield with 97 to >99% ee.[178] The diastereomeric ratios are in the range from 60:40 to 94:6. Seven of the best results are shown in Scheme 40. In 2010, the same group reported further studies regarding this reaction.[181]

Scheme 40 Enantioselective Aldol Reaction of Aromatic Aldehydes with Cyclohexanone Catalyzed by *N*,*N*′-Bis[3,5-bis(trifluoromethyl)phenyl]thiourea and Proline[178]



R^1	Time (h)	Yield (%)	dr (*anti*/*syn*)	ee (%)	Ref
3-$O_2NC_6H_4$	16	94	92:8	>99	[178]
4-NCC_6H_4	16	98	93:7	99	[178]
4-$O_2NC_6H_4$	16	96	90:10	99	[178]
4-$F_3CC_6H_4$	24	93	94:6	99	[178]
4-ClC_6H_4	36	91	88:12	99	[178]
4-BrC_6H_4	36	87	90:10	99	[178]
2-ClC_6H_4	36	83	94:6	99	[178]

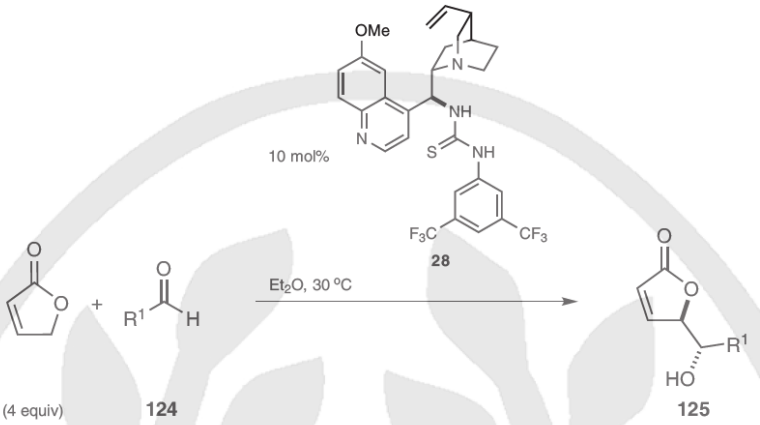
2-[Aryl(hydroxy)methyl]cyclohexanones 123**; General Procedure:**[178]
In a screw-capped vial, a mixture of proline (**122**; 2.9 mg, 0.025 mmol, 10 mol%) and thiourea derivative **1** (12.5 mg, 0.025 mmol, 10 mol%) in hexane (1.8 mL) was prepared, followed by the addition of cyclohexanone (0.4 mL, 4 mmol, 16 equiv). The mixture was stirred over a period of 15 min at rt, and then the aldehyde **121** (0.25 mmol) was added. After the reaction was complete (TLC monitoring), sat. aq NH_4Cl was added. Then, extraction of the whole mixture with EtOAc was accomplished. After washing with brine, the organic phase was dried and the solvent was removed. The crude product was purified by column chromatography (silica gel, hexane/EtOAc) to give the product **123**. The diastereomeric ratio was determined by ^1H NMR spectroscopic analysis of the crude product; the enantiomeric excess was determined by chiral HPLC analysis (Chiralpak AD-H or OD-H, hexane/iPrOH 90:10 or 95:5, 0.5 or 1.0 mL·min^{-1}).

2.2.4.6.4 Vinylogous Aldol Reaction

In 2010, the Feng group reported a method for the organocatalytic, enantioselective vinylogous aldol reaction.[182] As organocatalyst a cinchona alkaloid derived thiourea **28** is utilized. High yields of 73–93% are obtained in general (40% in only one case), and fairly good enantiomeric excesses ranging from 78 to 83% are attained. The best results can be found in Scheme 41.

for references see p 407

Scheme 41 Enantioselective Vinylogous Aldol Reaction Catalyzed by a Cinchona Alkaloid Derived Thiourea[182]



R^1	Time (h)	Yield (%)	dr (*anti*/*syn*)	ee[a] (%)	Ref
3-Tol	48	91	81:19	83	[182]
4-FC_6H_4	48	90	84:16	82	[182]
Ph	50	87	85:15	82	[182]
2-FC_6H_4	40	80	85:15	82	[182]
2-Tol	52	76	81:19	82	[182]
2-$MeOC_6H_4$	52	93	82:18	81	[182]
2-thienyl	48	91	85:15	81	[182]
4-ClC_6H_4	40	83	81:19	81	[182]
4-Tol	52	75	82:18	81	[182]

[a] Of *anti*-product.

5-[(4-Fluorophenyl)(hydroxy)methyl]furan-2(5*H*)-one (125, R^1 = 4-FC_6H_4); Typical Procedure:[182]

CAUTION: *Furan-2(5*H*)-one is irritating to the eyes, skin, and respiratory system.*

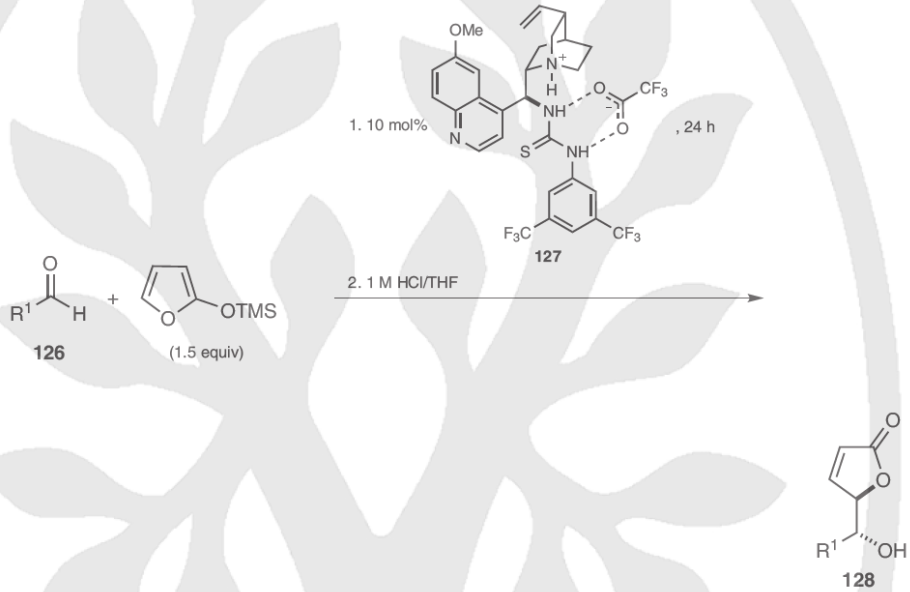
A mixture of 4-fluorobenzaldehyde (**124**, R^1 = 4-FC_6H_4; 11 μL, 0.1 mmol) and catalyst **28** (5.9 mg, 0.01 mmol, 10 mol%) in anhyd Et_2O (0.5 mL) was stirred over a period of 20 min at rt followed by addition of furan-2(5*H*)-one (28 μL, 0.4 mmol, 4 equiv). After stirring of the mixture for 48 h at 30 °C, the product **125** (R^1 = 4-FC_6H_4) was directly isolated by chromatography (silica gel, CH_2Cl_2/EtOAc 10:1); yield: 90%; dr (*anti*/*syn*) 84:16; 82% ee (*anti*) by chiral HPLC analysis (hexane/iPrOH 95:5, 1.0 mL·min^{-1}, λ = 210 nm; t_{R1} = 24.2 min, t_{R2} = 27.4 min, t_{R3} = 31.6 min, t_{R4} = 33.0 min).

2.2.4.6.5 Vinylogous Mukaiyama Aldol Reaction

In 2003, Takemoto and co-workers investigated a Mukaiyama aldol reaction of two aldehydes with a ketene silyl acetal catalyzed by *N*,*N*′-bis[3,5-bis(trifluoromethyl)phenyl]thiourea (**1**).[23] The aldol product of benzaldehyde is obtained in 36% yield, whereas the product of the reaction with 2,6-dimethoxybenzaldehyde is obtained in 65% yield. Ma, Wang, and co-workers reported an enantioselective Mukaiyama aldol reaction in 2010.[183] A cinchona alkaloid derived thiourea is utilized as organocatalyst and high enantiomeric excesses of 82–91% are achieved. Diastereomeric ratios range from 60:40 to 90:10 with yields of 72–90%. Later in 2010, Deng and co-workers also published the vinylogous Mukaiyama

aldol reaction catalyzed by a cinchona alkaloid thiourea derivative **127** (Scheme 42).[184] The presence of a carboxylic acid is necessary for the reaction. In the mechanistic proposal, the thiourea moiety builds in the first step a double-hydrogen-bonding complex with the carboxylate of the respective carboxylic acid. This carboxylate desilylates in the second step the dihydrofuran, which is bound by the cinchona alkaloid's NH.[184] For aromatic aldehydes **126** (R^1 = aryl), enantiomeric excesses are 90–95%, yields are in the range of 71–98%, and diastereomeric ratios vary from 84:16 to 96:4. The results for cinnamaldehyde and alkyl aldehydes are not as good as those for aromatic aldehydes. In these cases, 47–76% yield and 80–93% ee are attained, with diastereomeric ratios from 72:28 to 82:18. Seven of the best results are given in Scheme 42.

Scheme 42 Enantioselective Vinylogous Mukaiyama Aldol Reaction[184]



R^1	Temp (°C)	Time (h)	Yield (%)	dr (*anti*/*syn*)	ee[a] (%)	Ref
4-FC_6H_4	−20	96	95	96:4	95	[184]
2-naphthyl	−20	96	98	95:5	95	[184]
3-$MeOC_6H_4$	−50	36	96	95:5	95	[184]
Ph	−20	96	94	95:5	95	[184]
4-BrC_6H_4	−20	96	97	96:4	94	[184]
4-$F_3CC_6H_4$	−20	96	96	96:4	93	[184]
4-ClC_6H_4	−20	96	93	94:6	93	[184]

[a] Of *anti*-product.

5-(1-Hydroxyalkyl)furan-2(5*H*)-ones 128**; General Procedure:**[184]

CAUTION: *2-(Trimethylsiloxy)furan is highly flammable, and irritating to the eyes, skin, and respiratory system.*

The aldehyde **126** (0.25 mmol) was added to a soln of catalyst **127** (0.025 mmol, 10 mol%) in the appropriate solvent [Et_2O, 1,2-dichloroethane, or Et_2O/CH_2Cl_2 (1:1)]. After cooling to the temperature stated in Scheme 42, the mixture was stirred over a period of 15 min followed by addition of 2-(trimethylsiloxy)furan (0.37 mmol, 1.5 equiv). The mixture was stirred for the time mentioned in Scheme 42 at this temperature, and after dilution with

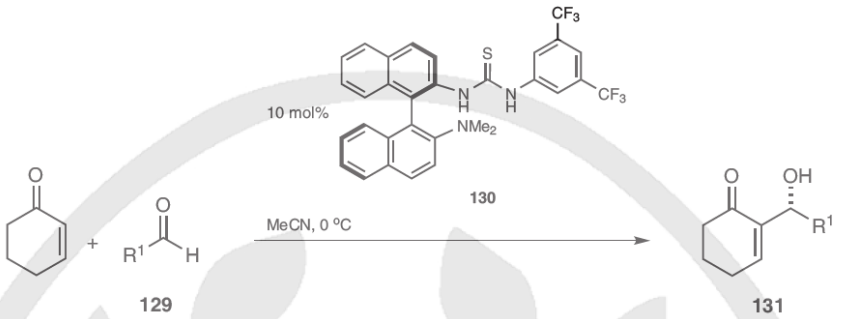
THF (1 mL) resulting in a soln, 1 M HCl (1 mL) was added. The soln was allowed to warm to rt. After stirring over a period of 15 min at rt, the mixture was neutralized by adding sat. aq $NaHCO_3$. The mixture was extracted with EtOAc (3 × 5 mL), and the organic layers were combined and washed with H_2O. After drying (Na_2SO_4), the soln was concentrated followed by filtration of the mixture through silica gel to remove the catalyst. The silica gel was rinsed with EtOAc (3–4 mL). The solvent was removed under vacuum and the crude product was purified by flash chromatography (silica gel, EtOAc/hexane) to afford the product **128**. The enantiomeric excess was determined by chiral HPLC analysis (Chiralpak AD-H or AS-H, hexanes/iPrOH, 1.0 mL·min^{-1}).

2.2.4.7 Morita–Baylis–Hillman Reaction

2.2.4.7.1 Morita–Baylis–Hillman Reaction of Cyclohex-2-enone with Aldehydes

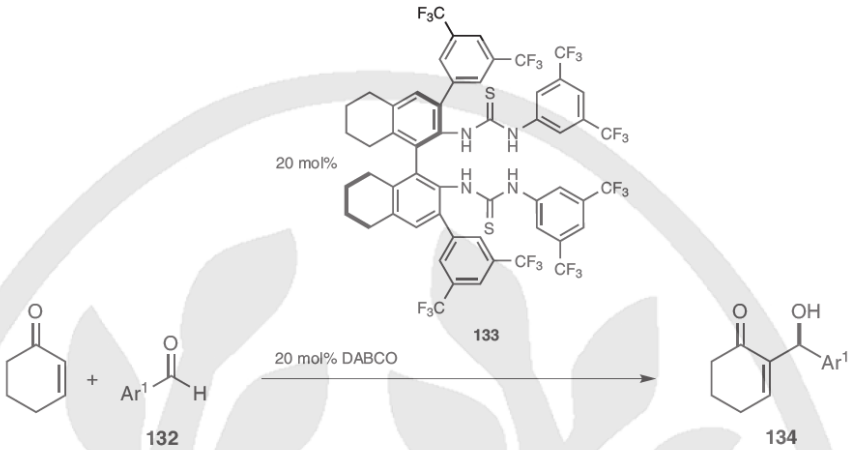
The Morita–Baylis–Hillman (MBH) reaction has been utilized by many groups to synthesize allylic alcohols from aldehydes and α,β-unsaturated systems.[185–189] The standard reaction requires a bulky, conformationally rigid, and basic tertiary amine, which acts as a Lewis base.[133] The Lewis base attacks in a nucleophilic Michael addition the α,β-unsaturated compound. This intermediate zwitterion attacks nucleophilically the aldehyde and after hydrogen transfer and elimination of the base an allylic alcohol forms. Brønsted additives such as (thio)urea derivatives can stabilize the intermediates and transition states that arise. Many groups have utilized tertiary amines and (thio)urea moieties combined in a single bifunctional catalyst, or added a chiral (thio)urea derivative to a tertiary amine. Connon and Maher first demonstrated, in 2004, a (thio)urea-catalyzed and 1,4-diazabicyclo[2.2.2]octane-promoted Morita–Baylis–Hillman reaction.[25] Philp and Clarke presented, in 2008, an achiral bis(thio)urea cocatalyst.[190] In 2009, Maseras, Eberlin, and Coelho investigated a thiourea-catalyzed Morita–Baylis–Hillman reaction by ESI-MS and DFT computations.[191,192] The groups of Berkessel,[193] Lattanzi,[194] and Nagasawa,[47,195] developed protocols for enantioselective thiourea-derivative catalyzed reactions, but good enantioselectivities were afforded only for some substrates. Wu and co-workers presented, in 2010, an enantioselective intramolecular Morita–Baylis–Hillman reaction with an amino acid derived phosphino thiourea derivative with good yields (63–100%) and enantioselectivities (45–84% ee and 5% ee in one case).[196] In 2005, Wang and co-workers used aliphatic aldehydes and a bifunctional thiourea catalyst **130** and obtained good yields (55–84%) and enantioselectivities of 60–94% (Scheme 43).[51] The best results are shown in Scheme 43 for simple aliphatic (linear) aldehydes **129** [R^1 = Bu, $(CH_2)_4Me$, $(CH_2)_5Me$, $(CH_2)_6Me$, $(CH_2)_2Ph$, (Z)-$(CH_2)_2CH{=}CHEt$] and for sterically demanding aldehydes **129** (R^1 = iPr, cyclopentyl, Cy). In 2008, Shi and Liu used cyclohex-2-enone and aromatic aldehydes **132** to afford the Morita–Baylis–Hillman adducts in good to excellent yields (50–99%) and with good enantioselectivities of 62–88% (Scheme 44).[197] They utilized a bis(thiourea) derivative **133** in combination with 1,4-diazabicyclo[2.2.2]octane; the best results are presented in Scheme 44.

Scheme 43 Enantioselective Morita–Baylis–Hillman Reaction of Cyclohex-2-enone and Aliphatic Aldehydes Catalyzed by a Bifunctional Thiourea Catalyst[51]



R^1	Temp (°C)	Time (h)	Yield (%)	ee (%)	Ref
Bu	0	48	84	81	[51]
$(CH_2)_4Me$	0	60	75	81	[51]
$(CH_2)_5Me$	0	72	71	80	[51]
$(CH_2)_6Me$	0	72	74	82	[51]
$(CH_2)_2Ph$	0	48	80	83	[51]
(*Z*)-$(CH_2)_2CH{=}CHEt$	0	72	82	81	[51]
iPr	0	72	63	94	[51]
cyclopentyl	0	96	71	90	[51]
Cy	0	120	67	92	[51]
iBu	0	72	72	80	[51]

Scheme 44 Morita–Baylis–Hillman Reaction of Cyclohex-2-enone and Aromatic Aldehydes Catalyzed by a Bis(thiourea) Derivative and 1,4-Diazabicyclo[2.2.2]octane[197]



Ar^1	Temp (°C)	Time (h)	Yield (%)	ee (%)	Ref
3-FC_6H_4	rt	72	79	88	[197]
3-ClC_6H_4	rt	72	67	86	[197]
4-ClC_6H_4	rt	72	90	85	[197]
4-FC_6H_4	rt	72	88	84	[197]
3-pyridyl	rt	72	99	83	[197]
4-BrC_6H_4	rt	72	95	83	[197]
3-BrC_6H_4	rt	72	71	83	[197]
Ph	rt	72	99	81	[197]
4-EtC_6H_4	rt	96	67	80	[197]

2-(1-Hydroxyalkyl)cyclohex-2-enones 131**; General Procedure Using Catalyst** 130:[51]

CAUTION: *2-Cyclohexen-1-one is toxic by inhalation and in contact with skin and harmful if swallowed.*

A reaction vial was charged with cyclohex-2-enone (36 μL, 0.374 mmol) in MeCN (1 mL) and the bifunctional catalyst **130** (10 mg, 0.019 mmol) was added at 0 °C. After stirring of the mixture for 10 min, the aldehyde **129** (0.187 mmol) was added and the mixture was stirred for the above-mentioned time (Scheme 43) at 0 °C. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography [silica gel (Merck 60), EtOAc/hexane 1:10 to 1:2 gradient]. The enantiomeric excess was determined by HPLC analysis (Chiralpak AS-H or Chiralcel OD-H, hexane/iPrOH 90:10).

2-[Aryl(hydroxy)methyl]cyclohex-2-enones 134**; General Procedure Using Catalyst** 133**/DABCO:**[197]

CAUTION: *1,4-Diazabicyclo[2.2.2]octane (DABCO) is highly flammable and is irritating to the eyes, respiratory system and skin. DABCO is harmful to aquatic organisms and may cause long-term adverse effects in the aquatic environment.*

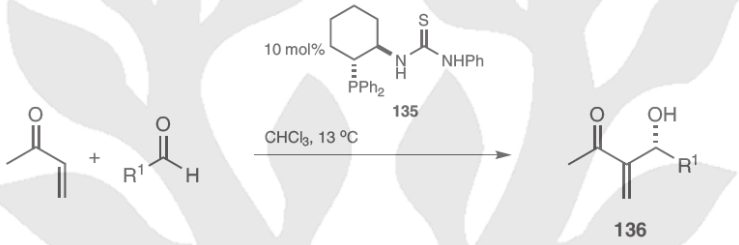
A reaction vessel was charged with the aromatic aldehyde **132** (0.15 mmol), DABCO (0.03 mmol), and catalyst **133** (0.03 mmol) in anhyd toluene under an argon atmosphere. Cyclohex-2-enone (0.45 mmol) was added and the mixture was stirred at rt for the above-mentioned time (Scheme 44). The solvent was evaporated under reduced pressure and the

crude product was purified by flash chromatography (silica gel, EtOAc/petroleum ether 1:4). The enantiomeric excess was determined by HPLC analysis (Daicel Chiralcel OJ-H or OD-H, hexane/iPrOH).

2.2.4.7.2 Morita–Baylis–Hillman Reaction of Methyl Vinyl Ketone with Aldehydes

In 2008, Wu and co-workers developed a protocol to transform methyl vinyl ketone and various aromatic aldehydes into allylic alcohols with a phosphino thiourea derivative, catalyst **135**. The yields vary from 15 to 91% but the enantioselectivities are good (87–94% ee) (Scheme 45).[198,199] In 2009, Wu and co-workers utilized a phosphino thiourea derivative with a range of acrylates and aromatic aldehydes to afford products in yields of up to 96% and with up to 83% ee.[200]

Scheme 45 Enantioselective Morita–Baylis–Hillman Reaction of Methyl Vinyl Ketone and Aromatic Aldehydes Catalyzed by a Phosphino Thiourea Derivative[198]



R^1	Time (h)	Yield (%)	ee (%)	Ref
4-$O_2NC_6H_4$	15	75	94	[198]
3-$O_2NC_6H_4$	20	71	94	[198]
2-$O_2NC_6H_4$	45	91	92	[198]
4-$F_3CC_6H_4$	60	65	92	[198]
4-BrC_6H_4	90	43	92	[198]
4-NCC_6H_4	30	63	90	[198]
Ph	180	48	90	[198]
4-ClC_6H_4	120	40	90	[198]
2-naphthyl	120	15	90	[198]
2,4-$Cl_2C_6H_3$	60	61	89	[198]

Methyl α-Methylene-β-hydroxy Ketones 136; General Procedure:[198]

CAUTION: *Methyl vinyl ketone is highly flammable, causes burns, is very toxic by inhalation, in contact with skin, and if swallowed, and may cause sensitization by skin contact. It is very toxic to aquatic organisms and may cause long-term adverse effects in the aquatic environment.*

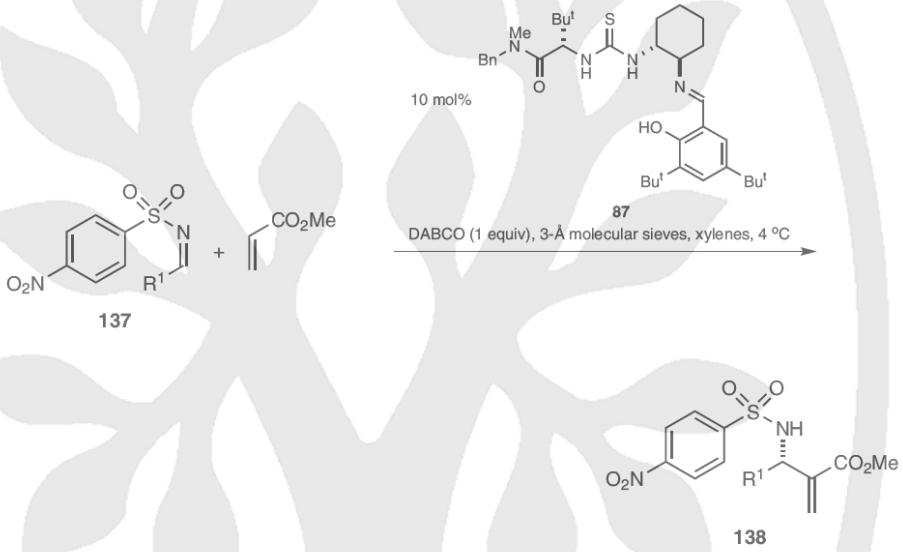
A reaction vessel was charged with catalyst **135** (12.6 mg, 0.03 mmol), anhyd $CHCl_3$ (1.0 mL), and methyl vinyl ketone (105 mg, 1.5 mmol). The mixture was stirred for 10 min at 13 °C. Then, the aldehyde [R^1CHO; 0.3 mmol; liquid aldehydes were freshly distilled; solid aldehydes were recrystallized (EtOH)] was added and the mixture was stirred for the above-mentioned time (Scheme 45) at 13 °C. After full completion, the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography [silica gel (300–400 mesh), EtOAc/petroleum ether]. The enantiomeric excess was determined by HPLC analysis (Chiralpak AS-H or AD-H, or Chiralcel OD-H; hexane/iPrOH).

for references see p 407

2.2.4.7.3 Aza-Morita–Baylis–Hillman Reaction of Imines with Acrylates or Methyl Vinyl Ketone

The groups of Jacobsen[201] and Shi[199,202] synthesized efficient catalysts for the aza-Morita–Baylis–Hillman (aza-MBH) reaction.[203] Jacobsen and Raheem used thiourea catalyst **87** in combination with 1,4-diazabicyclo[2.2.2]octane to produce products **138** from *N*-(4-nitrophenylsulfonyl)imines (*N*-nosylimines) **137** and methyl acrylate with good enantioselectivities (87–99%) and in marginal yields (25–49%) (Scheme 46).[201] Jacobsen and Raheem generated aza-Morita–Baylis–Hillman adducts from electron-donating, electron-withdrawing, and heteroaromatic substrates. The Supporting Information to ref[201] also provides a list of the benzenesulfonamides and transformation products of the aza-Morita–Baylis–Hillman imines. Furthermore a mechanistic proposal was formulated.

Scheme 46 Enantioselective Aza-Morita–Baylis–Hillman Reaction of Methyl Acrylate and *N*-(4-Nitrophenylsulfonyl)imines Catalyzed by a Chiral Thiourea at 4 °C[201]



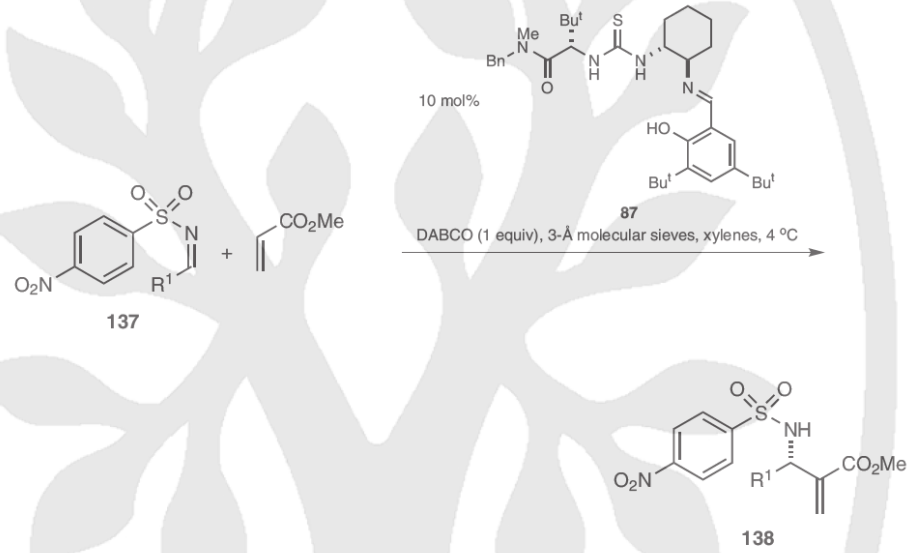
R^1	Time (h)	Yield (%)	ee (%)	Ref
2-thienyl	36	30	99	[201]
3-furyl	36	25	98	[201]
3-$MeOC_6H_4$	24	42	96	[201]
Ph	36	49	95	[201]
3-ClC_6H_4	16	33	94	[201]
3-Tol	24	40	93	[201]
3-BrC_6H_4	16	39	92	[201]
1-naphthyl	24	27	91	[201]
4-ClC_6H_4	24	36	87	[201]

The protocol of Shi and Shi requires the addition of benzoic acid to the bifunctional thiourea phosphine catalyst **140** to perform the aza-Morita–Baylis–Hillman reaction of a range of *N*-alkylidenebenzenesulfonamide derivatives **139** and methyl vinyl ketone (Scheme 47). Various aromatic imines and cinnamoyl imine give moderate to excellent results (67–97% ee, 61–98% yield). The enantiopurity of the products **141** is independent of the reaction time; no racemization of the product or autocatalysis is observed. The use

2.2.4.7.3 Aza-Morita–Baylis–Hillman Reaction of Imines with Acrylates or Methyl Vinyl Ketone

The groups of Jacobsen[201] and Shi[199,202] synthesized efficient catalysts for the aza-Morita–Baylis–Hillman (aza-MBH) reaction.[203] Jacobsen and Raheem used thiourea catalyst **87** in combination with 1,4-diazabicyclo[2.2.2]octane to produce products **138** from *N*-(4-nitrophenylsulfonyl)imines (*N*-nosylimines) **137** and methyl acrylate with good enantioselectivities (87–99%) and in marginal yields (25–49%) (Scheme 46).[201] Jacobsen and Raheem generated aza-Morita–Baylis–Hillman adducts from electron-donating, electron-withdrawing, and heteroaromatic substrates. The Supporting Information to ref[201] also provides a list of the benzenesulfonamides and transformation products of the aza-Morita–Baylis–Hillman imines. Furthermore a mechanistic proposal was formulated.

Scheme 46 Enantioselective Aza-Morita–Baylis–Hillman Reaction of Methyl Acrylate and *N*-(4-Nitrophenylsulfonyl)imines Catalyzed by a Chiral Thiourea at 4 °C[201]

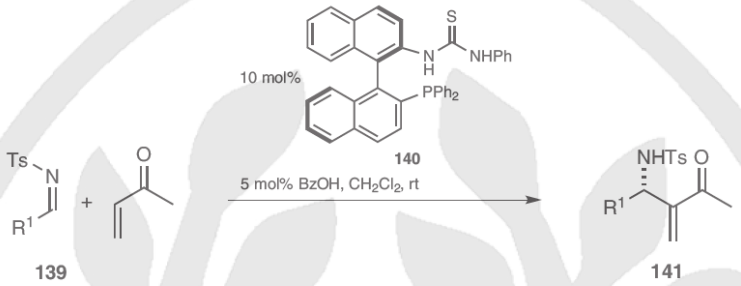


R^1	Time (h)	Yield (%)	ee (%)	Ref
2-thienyl	36	30	99	[201]
3-furyl	36	25	98	[201]
3-$MeOC_6H_4$	24	42	96	[201]
Ph	36	49	95	[201]
3-ClC_6H_4	16	33	94	[201]
3-Tol	24	40	93	[201]
3-BrC_6H_4	16	39	92	[201]
1-naphthyl	24	27	91	[201]
4-ClC_6H_4	24	36	87	[201]

The protocol of Shi and Shi requires the addition of benzoic acid to the bifunctional thiourea phosphine catalyst **140** to perform the aza-Morita–Baylis–Hillman reaction of a range of *N*-alkylidenebenzenesulfonamide derivatives **139** and methyl vinyl ketone (Scheme 47). Various aromatic imines and cinnamoyl imine give moderate to excellent results (67–97% ee, 61–98% yield). The enantiopurity of the products **141** is independent of the reaction time; no racemization of the product or autocatalysis is observed. The use

of propenal, ethyl vinyl ketone, and phenyl vinyl ketone results in lower enantioselectivities in comparison with the methyl vinyl ketone reactions (67–77% ee, 69–81% yield). A mechanism was proposed based on ^{31}P NMR spectroscopic investigations.

Scheme 47 Enantioselective Aza-Morita–Baylis–Hillman Reaction of Methyl Vinyl Ketone and *N*-Tosyl Aldimines Catalyzed by a Chiral Thiourea Phosphine at Room Temperature[202]



139 141

R^1	Time (h)	Yield (%)	ee (%)	Ref
3-ClC_6H_4	10	98	97	[202]
Ph	10	97	91	[202]
3-FC_6H_4	10	96	91	[202]
4-Tol	10	98	90	[202]
4-ClC_6H_4	10	98	90	[202]
4-FC_6H_4	10	94	90	[202]
4-BrC_6H_4	10	97	88	[202]
3-$O_2NC_6H_4$	5	95	88	[202]

Methyl 2-Methylene-3-(4-nitrophenylsulfonamido)alkanoates 138; General Procedure:[201]

CAUTION: *1,4-Diazabicyclo[2.2.2]octane (DABCO) is highly flammable and is irritating to the eyes, respiratory system and skin. DABCO is harmful to aquatic organisms and may cause long-term adverse effects in the aquatic environment.*

CAUTION: *Hydrogen chloride in dioxane is extremely flammable, causes severe burns, and may build explosive peroxides.*

An oven-dried 1.75-mL vial was charged with the *N*-(4-nitrophenylsulfonyl)-protected imine **137** (0.1 mmol, 1 equiv), catalyst **87** (6 mg, 0.01 mmol), DABCO (11.2 mg, 0.1 mmol, 1 equiv), and activated 3-Å molecular sieves (40 mg). The flask was evacuated and purged with N_2 gas. Precooled anhyd xylenes (700 μL) and methyl acrylate (75 μL, 0.8 mmol, 8 equiv) were added at 4 °C via syringe and the mixture was stirred for the above-mentioned time (Scheme 46). The mixture was diluted with anhyd MeOH (150 μL) and immediately afterwards with 4 M HCl in dioxane (60 μL). The crude adduct was purified by flash column chromatography [silica gel (EM Science 60, 230–400 mesh)] to afford solid product **138**. The enantiomeric excess was determined by HPLC [Chiralpak AS, iPrOH/hexanes 2:3 or EtOH/hexanes 1:9 (only for R^1 = 2-thienyl)].

for references see p 407

4-Methyl-*N*-(2-methylene-3-oxo-1-phenylbutyl)benzenesulfonamide (141, R^1 = Ph); Typical Procedure:[202]

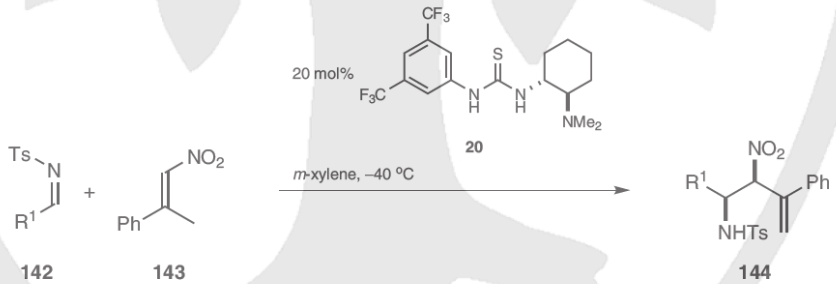
CAUTION: *Methyl vinyl ketone is highly flammable, causes burns, is very toxic by inhalation, in contact with skin, and if swallowed, and may cause sensitization by skin contact. It is very toxic to aquatic organisms and may cause long-term adverse effects in the aquatic environment.*

Under an argon atmosphere, a reaction vessel was charged with imine **139** (R^1 = Ph; 0.65 mg, 0.25 mmol), catalyst **140** (15 mg, 0.025 mmol), benzoic acid (0.15 mg, 0.0125 mmol), and predistilled CH_2Cl_2 (1.0 mL). To this soln, methyl vinyl ketone (42 μL, 0.5 mmol, 2 equiv) was added and the mixture was stirred at rt for 10 h. After completion of the reaction, the solvent was evaporated under reduced pressure. The crude residue was purified by column chromatography (silica gel, EtOAc/petroleum ether 1:5) to afford the colorless solid product **141** (R^1 = Ph); yield: 80 mg (97%); 91% ee by chiral HPLC (AD column, hexane/iPrOH 80:20).

2.2.4.7.4 Aza-Morita–Baylis–Hillman-Type Reactions of *N*-Tosylimines with Nitroalkenes

In 2009, Xu and co-workers published an aza-Morita–Baylis–Hillman-type reaction to produce β-nitro-γ-enamines **144** from *N*-tosyl-protected aryl imines **142** and nitroalkene **143** through activation by a bifunctional amino thiourea catalyst **20**.[204] The suggested reaction mechanism involves a Michael addition, aza-Henry addition, proton transfer, and β-elimination. Good yields (80–95%), and high enantioselectivities (72–91% ee) and diastereoselectivities (dr 35:65 to 1:99) are achieved; the best results are shown in Scheme 48. Protic solvents lower the yields and enantioselectivities. Aryl imines with electron-rich groups lead to higher enantioselectivities, as illustrated by the results for **144** (R^1 = 2-Tol, 3-Tol, 4-Tol, 4-$MeOC_6H_4$, 2-furyl) in Scheme 48, whereas electron deficiency decreases the enantiopurity of the obtained products. Only one aliphatic imine was used with good enantioselectivity and yield (84% ee and 87% yield).

Scheme 48 Diastereo- and Enantioselective Aza-Morita–Baylis–Hillman-Type Reaction of *N*-Tosylimines and a Nitroalkene under Thiourea Organocatalysis at −40 °C[204]



R^1	Time (h)	Yield (%)	dr (*anti*/*syn*)	ee (%)	Ref
Ph	45	91	3:97	91	[204]
3-Tol	90	95	9:91	91	[204]
2-furyl	72	92	<1:99	90	[204]
2-Tol	65	90	7:93	89	[204]
4-$MeOC_6H_4$	90	91	5:95	88	[204]
4-Tol	50	84	13:87	85	[204]
Pr	24	87	19:81	84	[204]

4-Methyl-*N*-(2-nitro-3-phenylbut-3-enyl)benzenesulfonamides 144**; General Procedure:**[204] An oven-dried reaction vial was charged with the *N*-tosylimine **142** (0.1 mmol), nitroalkene **143** (1 mmol, 10 equiv), and catalyst **20** (8.3 mg, 0.02 mmol); anhyd *m*-xylene (1.0 mL) was added under an argon atmosphere at −40 °C and the resulting mixture was stirred at −40 °C. The reaction times for the different substrates (based on TLC monitoring) are given in Scheme 48. The mixture was purified by flash gel column chromatography [silica gel (200–300 mesh), $CHCl_3$/petroleum ether/EtOAc 150:100:10 to 150:100:30] to afford a white solid. The enantiomeric excess was determined by chiral HPLC analysis (Chiralcel OD-H or AD-H, iPrOH/hexane). The diastereomeric ratio was determined by ^1H NMR analysis.

2.2.4.8 Strecker Reaction

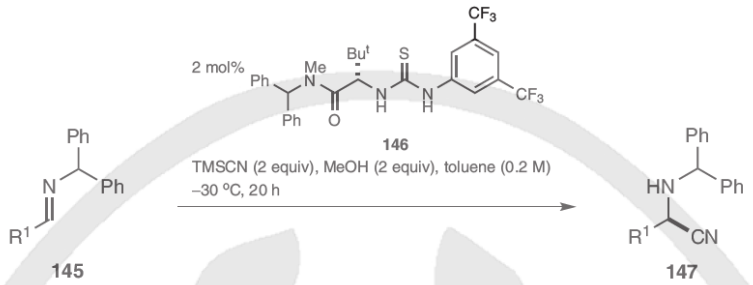
2.2.4.8.1 Strecker Reaction: Catalytic Addition of Hydrogen Cyanide or Trimethylsilyl Cyanide to Aldimines

The Strecker reaction, first reported in 1850, describes the synthesis of α-amino acids through the reaction of an imine with hydrogen cyanide in a C—C bond-forming process.[205–207] The first catalysts of the Jacobsen group featured thiourea and urea functions and a chiral cyclohexane-1,2-diamine moiety.[208] Enantiomeric excesses of >70% and yields of 65–92% are attained using a resin-bound catalyst.[208] A soluble thiourea catalyst gives higher enantioselectivities (77–97% ee) and yields of 65–99%.[209,210] Both aldimines[210] and ketimines[211] give rise to excellent enantioselectivities. Various allylic and benzylic aldimines can also be transformed into α-aminonitriles with 77–97% ee and in 65–99% yield and various ketimines can be transformed into α-aminonitrile precursors with up to 99.9% ee after recrystallization and in 45% to quantitative yield using the urea-derived catalyst.[210,211]

The effect of the catalyst structure was also investigated by Jacobsen and co-workers for the Strecker and Mannich reactions,[149,212] using as cyanide sources either hydrogen cyanide or trimethylsilyl cyanide/methanol.[213] Carboxamide thiourea organocatalyst **146** proved to be robust, compatible with aqueous cyanide salts, and amenable to scale-up.[212] Amide thiourea derived catalyst **146** provides in the enantioselective hydrocyanation at 1-mmol scale high enantioselectivities for alkyl and alkenyl imines (73–96% ee) and very good yields of >97% (Scheme 49). At 25–100-mmol scale, enantioselectivities of 87–90% are achieved. Using aryl and hetaryl imines **148**, similarly high enantioselectivities of 88–99% and yields of 96–99% are achieved (Scheme 50).

for references see p 407

Scheme 49 Enantioselective Hydrocyanation of Aliphatic Imines at −30 °C Using a Hydrogen-Bond Catalyst[212]

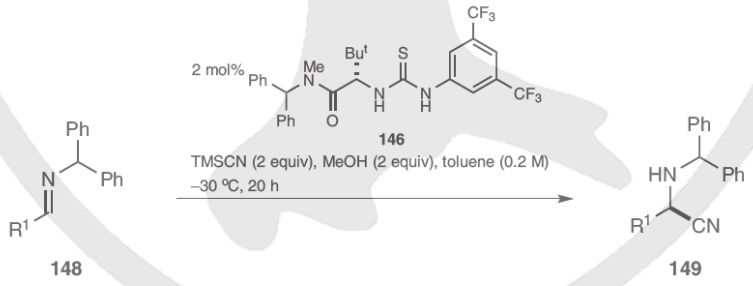


R^1	Yield[a] (%)	ee[b] (%)	Ref
$CMeEt_2$	99	96	[212]
1-methylcyclohexyl	99	95	[212]
cyclohex-1-enyl	99	95	[212]
(*E*)-CH=CHPh	99	95	[212]
t-Bu	99	93	[212]
1-adamantyl	99	93	[212]
(*E*)-CMe=CHEt	98	91	[212]
CMe_2Ph	97	85	[212]
Cy	99	74	[212]
(*E*)-CH=CHPr	97	73	[212]

[a] Yield of isolated product of 1-mmol scale reaction. Scale-up reaction (25–100-mmol scale, 87–90% ee) was also performed for R^1 = $CMeEt_2$, CHMeCy, and *t*-Bu under the following conditions: **146** (5 mol%), KCN, AcOH, H_2O, toluene, 0 °C, 4–8 h.

[b] Determined by chiral HPLC for product of 1-mmol scale reaction.

Scheme 50 Enantioselective Hydrocyanation of Aromatic and Heteroaromatic Imines at −30 °C Using a Hydrogen-Bond Catalyst[212]



Ar^1	Yield (%)	ee (%)	Ref
$4\text{-}MeOC_6H_4$	99	99	[212]
Ph	98	98	[212]
4-Tol	98	98	[212]
$4\text{-}ClC_6H_4$	97	98	[212]

Ar[1]	Yield (%)	ee (%)	Ref
3-furyl	98	97	[212]
2-BrC_6H_4	96[a]	97	[212]
4-$F_3CC_6H_4$	98[a]	96	[212]
2-thienyl	97[a]	95	[212]
2-furyl	99	93	[212]
4-NCC_6H_4	96[a,b]	93	[212]

[a] Reaction run at 0 °C.
[b] Reaction run with 10 mol% catalyst **146**.

In the same year (2009), mechanistic insights through DFT computations and experiments showed that the (thio)urea-derived catalyst promotes imine protonation by hydrogen cyanide and the formation of a catalyst-bound iminium/cyanide ion pair. The subsequent collapse of the ion pair and C—C bond formation furnishes the α-aminonitrile.[214,215] In 2007, Deslongchamps and co-workers also computationally investigated this process.[216]

Itoh and co-workers presented a synthesis of (*R*)-(+)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile, using a Jacobsen catalyst[217] for cyanation of a dihydroisoquinoline derivative with trimethylsilyl cyanide with 95% ee and in 86% yield.[218] In 2007, Kunz and co-workers reported the hydrocyanation of various aldimines with a glucosamine urea derived catalyst with 47–86% ee (0% ee for one example) and in 60–98% yield.[219] A pyridyl thiourea derivative[220] and an imidazole-based thiourea catalyst[221] can also be utilized in the Strecker reaction, but with low enantioselectivities.

α-[(Diphenylmethyl)amino]nitriles 147 **and** 149**; General Procedure at 1-mmol Scale:**[212]

CAUTION: *Trimethylsilyl cyanide is highly flammable, can liberate with water toxic HCN, and is very toxic by inhalation, in contact with skin, and if swallowed. During the reaction, protic methanol liberates HCN; working in a well-ventilated fume hood is mandatory. Waste aqueous solution should be kept at alkaline pH and stored in the fume hood.*

CAUTION: *Hydrogen cyanide can be absorbed through the skin and is extremely toxic.*

In a flame-dried 25-mL round-bottomed flask equipped with a stirrer bar, imine **145** or **148** (1.0 mmol, 1.0 equiv) and catalyst **146** (11.6 mg, 0.02 mmol, 0.02 equiv) were added, and the flask was flushed with N_2 and capped with a rubber septum. Via syringe under positive N_2 pressure, anhyd toluene (3.75 mL) was added. The mixture was stirred at rt until a homogeneous soln was formed. The flask was cooled in a dry ice/acetone bath (−78 °C) for 10 min. In an additional flame-dried 10-mL round-bottomed flask equipped with a stirrer bar, a HCN stock soln was prepared. The flask was capped with a rubber septum. Via syringe, anhyd toluene (1.25 mL) was added under a positive N_2 pressure. The soln was cooled with an ice–water bath for 10 min and predistilled TMSCN (0.27 mL, 2.0 mmol, 2 equiv) was added via syringe under positive N_2 pressure. MeOH (0.075 mL, 1.9 mmol, 1.9 equiv) was then added over 90 s. After stirring of the stock soln for 30 min at 0 °C, it was added via syringe to the stirred mixture within 2 min. The flask was sealed with Parafilm, placed in either a freezer (−30 °C) or a refrigerator (0 °C) (see Schemes 49 and 50), and left there for 20 h. The mixture was then transferred into a well-ventilated fume hood and the solvent was removed under reduced pressure (1 Torr). The crude residue was purified by flash column chromatography [silica gel (EM Science 60, 230–400 mesh), Et_2O/hexanes]. The enantiomeric excess of the α-aminonitrile was determined by chiral HPLC [AS-H, OD-H, (*S*,*S*)-Whelk, or AD-H; iPrOH/hexanes]. Before determination of

for references see p 407

the enantiomeric excess, the solid α-aminonitriles had to be carefully homogenized to avoid inaccurate enantiomeric excess determinations due to crystallization of the product.

(*R*)-2-[(Diphenylmethyl)amino]-3,3-dimethylbutanenitrile (147, R^1 = *t*-Bu); Scale-Up Procedure:[212]

CAUTION: *Cyanide salts can be absorbed through the skin and are extremely toxic.*

The reaction was performed in a well-ventilated fume hood. In a 250-mL round-bottomed flask equipped with a stirrer bar (length 4 cm), KCN (5.21 g, 80 mmol, 2.0 equiv) and anhyd toluene (76 mL) were added. The flask was capped with a rubber septum under a positive N_2 pressure. The mixture was cooled to 0 °C for 10 min. Sequentially, AcOH (2.75 mL, 48 mmol, 1.2 equiv) and H_2O (2.88 mL, 160 mmol, 4.0 equiv) were added via syringe. The N_2 inlet was removed and the resulting white heterogeneous mixture was stirred at 0 °C. After the cyanide-containing soln had been stirred for 5 min, the upper layer became clear; the lower aqueous soln contained a white precipitate. The mixture was stirred for an additional 20 min and the flask was connected again to the N_2 gas inlet. A stock soln of *N*-(2,2-dimethylpropylidene)-1,1-diphenylmethanamine (**145**, R^1 = *t*-Bu; 9.79–9.93 g, 40 mmol) and catalyst **146** (116 mg, 0.20 mmol, 0.0050 equiv) in anhyd toluene (24 mL) was prepared. The stock soln was added via syringe within 1 min to the mixture in portions (10 mL). The stock-soln flask was rinsed with anhyd toluene (2 × 3 mL) and the washings were added to the mixture. After removal of the N_2, the mixture was stirred for 4 h at 0 °C. The reaction could be monitored by ^{1}H NMR (method shown in Supplementary Information of the publication). The mixture was allowed to warm to rt and stirred for 5 min. The septum was removed and 0.2 g·mL^{-1} aq K_2CO_3 (50 mL) was added. The mixture was transferred to a 250-mL separatory funnel, the flask was rinsed with Et_2O (3 × 5 mL), and the rinsings were added to the separatory funnel. The phases were mixed and then separated. The organic layer was treated with further K_2CO_3 soln (50 mL) and brine (50 mL). The colorless and clear organic phase was dried (Na_2SO_4) and then decanted into a 500-mL round-bottomed flask. The drying salt was rinsed with Et_2O (3 × 5 mL) and the soln was concentrated to 100 mL using a rotary evaporator. Then, a stirrer bar (length 2 cm) was added and the flask was placed in a water bath at 25 °C. Most of the solvent was removed under reduced pressure in a cooled bath (dry ice/acetone, −78 °C) until a volume of 15 mL remained. A sample was taken for HPLC analysis (Chiralpak AS-H, iPrOH/hexanes 5:95); 87–88% ee. The soln was transferred into a 100-mL round-bottomed flask, the other flask was rinsed with CH_2Cl_2 (3 × 4 mL), and the solvent was removed under reduced pressure (ca. 30 to 1 Torr) to give a viscous oil (12 g) containing the product and toluene residue, which was used in the next step without purification.

(*R*)-2-[(Diphenylmethyl)amino]-2-(1-methylcyclohexyl)acetonitrile (147, R^1 = 1-Methylcyclohexyl); Scale-Up Procedure:[212]

CAUTION: *Cyanide salts can be absorbed through the skin and are extremely toxic.*

The reaction was performed in a well-ventilated fume hood. In a 250-mL round-bottomed flask equipped with a stirrer bar (length 4 cm), KCN (3.26 g, 50 mmol, 2.0 equiv) and anhyd toluene (48 mL) were added. The flask was capped with a rubber septum under a positive N_2 pressure. The mixture was cooled to 0 °C for 10 min. Sequentially, AcOH (1.72 mL, 30 mmol, 1.2 equiv) and H_2O (1.80 mL, 100 mmol, 4.0 equiv) were added via syringe. The N_2 inlet was removed and the resulting heterogeneous mixture was stirred at 0 °C. After the cyanide-containing soln had been stirred for 5 min, the upper layer became clear; the lower aqueous soln contained a white precipitate. The mixture was stirred for an additional 20 min and the flask was connected again to the N_2 gas inlet. A stock soln of (*E*)-*N*-[(1-methylcyclohexyl)methylene]-1,1-diphenylmethanamine (**145**, R^1 = 1-methylcy-

clohexyl; 7.29 g, 25 mmol, 1.0 equiv) and catalyst **146** (73 mg, 0.125 mmol, 0.0050 equiv) in anhyd toluene (15 mL) was prepared. The stock soln was added via syringe within 1 min to the mixture. The stock-soln flask was rinsed with anhyd toluene (2 × 2 mL) and the washings were added to the mixture. After removal of the N_2 inlet, the mixture was stirred for 4.5 h at 0 °C. The mixture was allowed to warm to rt and stirred for 5 min. The septum was removed and 0.2 g • mL^{-1} aq K_2CO_3 (50 mL) was added. The mixture was transferred to a 250-mL separatory funnel, the flask was rinsed with Et_2O (3 × 5 mL), and the rinsings were added to the separatory funnel. The phases were mixed and then separated. The organic layer was treated with further K_2CO_3 soln (50 mL) and brine (50 mL). The colorless and clear organic phase was dried (Na_2SO_4) and then decanted into a 500-mL round-bottomed flask. The drying salt was rinsed with Et_2O (3 × 5 mL) and the soln was concentrated to 70 mL using a rotary evaporator. Then, a stirrer bar (length 2 cm) was added and the flask was placed in a water bath at 25 °C. Most of the solvent was removed under reduced pressure in a cooled bath (−78 °C) until a volume of 10 mL remained. A sample was taken for HPLC analysis (AD-H column, iPrOH/hexanes 5:95); 89–90% ee. The soln was transferred into a 200-mL round-bottomed flask, the other flask was rinsed with CH_2Cl_2 (3 × 4 mL), and the solvent was removed under reduced pressure (ca. 30 to 1 Torr). The residue was additionally treated with CH_2Cl_2 (2 × 20 mL) and the solvent was again removed under reduced pressure (ca. 30 to 1 Torr) to give a viscous oil (8.6–8.7 g) containing the product, which was used in the next step without purification.

(*R*)-2-[(Diphenylmethyl)amino]-3-ethyl-3-methylpentanenitrile (147, **$R^1 = CMeEt_2$**); **Scale-Up Procedure:**[212]

CAUTION: *Cyanide salts can be absorbed through the skin and are extremely toxic.*

The reaction was performed in a well-ventilated fume hood. In a 250-mL round-bottomed flask equipped with a stirrer bar (length 4 cm), KCN (3.26 g, 50 mmol, 2.0 equiv) and anhyd toluene (48 mL) were added. The flask was capped with a rubber septum under a positive N_2 pressure. The mixture was cooled to 0 °C for 10 min. Sequentially, AcOH (1.72 mL, 30 mmol, 1.2 equiv) and H_2O (1.80 mL, 160 mmol, 4.0 equiv) were added via syringe. The N_2 inlet was removed and the resulting heterogeneous white mixture was stirred at 0 °C. After the cyanide-containing soln had been stirred for 5 min, the upper layer became clear; the lower aqueous soln contained a white precipitate. The mixture was stirred for an additional 20 min and the flask was connected again to the N_2 gas inlet. A stock soln of (*E*)-*N*-(2-ethyl-2-methylbutylidene)-1,1-diphenylmethanamine (**145**, $R^1 = CMeEt_2$; 6.90 g, 25 mmol, 1.0 equiv) and catalyst **146** (73 mg, 0.125 mmol, 0.0050 equiv) in anhyd toluene (15 mL) was prepared. The stock soln was added via syringe within 1 min. The stock-soln flask was rinsed with anhyd toluene (2 × 2 mL) and the washings were added to the mixture. After removal of the N_2, the mixture was stirred for 6 h at 0 °C. The mixture was allowed to warm to rt and stirred for 5 min. The septum was removed and 0.2 g • mL^{-1} aq K_2CO_3 (50 mL) was added. The mixture was transferred to a 250-mL separatory funnel, the flask was rinsed with Et_2O (3 × 5 mL), and the rinsings were added to the separatory funnel. The phases were mixed and then separated. The organic layer was treated with further K_2CO_3 soln (50 mL) and brine (50 mL). The colorless and clear organic phase was dried (Na_2SO_4) and then decanted into a 500-mL round-bottomed flask. The drying salt was rinsed with Et_2O (3 × 5 mL) and the soln was concentrated to 70 mL under reduced pressure (ca. 30 Torr). Then, a stirrer bar (length 2 cm) was added and the flask was placed in a water bath at 25 °C. Most of the solvent was removed under reduced pressure in a cooled bath (−78 °C) until a volume of 10 mL remained. A sample was taken for HPLC analysis (AS-H column, iPrOH/hexanes 1:99); 88% ee. The soln was transferred into a 200-mL round-bottomed flask, the other flask was rinsed with CH_2Cl_2 (3 × 4 mL), and the solvent was removed under reduced pressure (ca. 30 to 1 Torr). The residue was additionally treat-

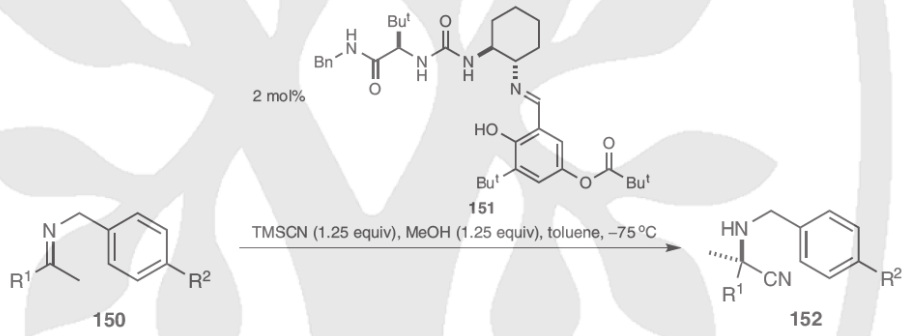
for references see p 407

ed with CH_2Cl_2 (2 × 20 mL) and the solvent was again removed under reduced pressure (ca. 30 to 1 Torr). A colorless oil [8.5 g, ca 90% (^{1}H NMR purity)] containing the product was obtained, which was used in the next step without purification.

2.2.4.8.2 Strecker Reaction: Catalytic Addition of Hydrogen Cyanide or Trimethylsilyl Cyanide to Ketimines

Various functionalized ketimines can be transformed into α-aminonitriles catalyzed by a Schiff base urea derivative **151** and give after formylation, hydrolysis, and debenzylation α-quaternary α-amino acids.[209,211] The enantioselectivities increase when *N*-benzyl-protected imines **150** are used; *N*-allyl-protected imines are unstable. The α-aminonitriles **152** obtained after recrystallization from hexanes typically are of >99% ee with yields of >75%. The influence of additional substituents at the *N*-benzyl-derived protecting group on enantioselectivities is small, as apparent from the reactions of **150** (R^1 = Ph; R^2 = Br, OMe, CF_3, *t*-Bu), which give products **152** of 89–99.9% ee (Scheme 51). Electron-withdrawing and electron-donating groups in the *para*-position of the ketimine result in products of 88–99.9% ee in yields of 75–98%. A 3-bromophenyl-substituted *N*-benzyl ketimine gives 91% ee after hydrocyanation. The corresponding 2-bromophenyl and aliphatic ketimines give lower enantioselectivity in the hydrocyanation (not shown).

Scheme 51 Addition of Hydrogen Cyanide to Ketimines Catalyzed by a Schiff Base Urea Derivative at −75 °C[211]



R^1	R^2	Time (h)	Yield (%)	ee (%)	Ref
4-$O_2NC_6H_4$	H	80	79[a]	99.9[a]	[211]
4-BrC_6H_4	H	80	76[a]	99.9[a]	[211]
4-$F_3CC_6H_4$	H	65	75[a]	99.9[a]	[211]
Ph	Br	40	75[a]	99.9[a]	[211]
Ph	OMe	36	97	93	[211]
Ph	CF_3	50	95	92	[211]
4-Tol	H	80	98	91	[211]
Ph	H	24	97	90	[211]
Ph	*t*-Bu	30	95	89	[211]
4-$MeOC_6H_4$	H	60	98	88	[211]

[a] After recrystallization from hexanes.

2-(Benzylamino)propanenitriles 152**; General Procedure:**[211]

CAUTION: *Trimethylsilyl cyanide is highly flammable, can liberate with water toxic HCN, and is very toxic by inhalation, in contact with skin, and if swallowed. During the reaction, protic methanol liberates HCN; working in a well ventilated fume hood is mandatory. Waste aqueous solution should be kept at alkaline pH and stored in the fume hood.*

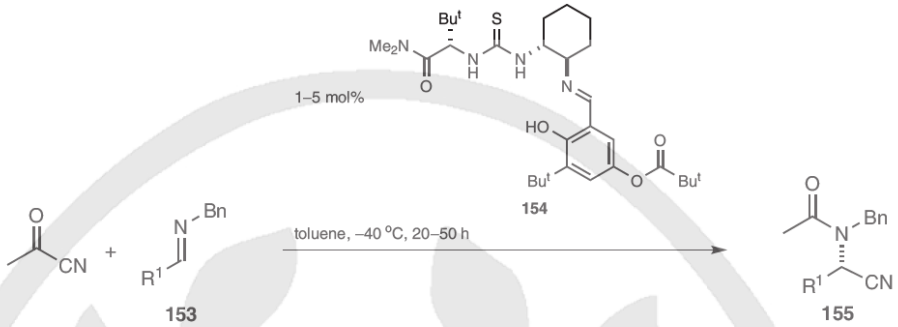
In a 10-mL round-bottomed flask equipped with a stirrer bar, catalyst **151** (3.7 mg, 0.006 mmol, 0.02 equiv), anhyd toluene (2 mL), and the imine **150** (0.03 mmol) were added. The mixture was cooled to −75 °C. In a 2-mL flask equipped with a stirrer bar were mixed anhyd toluene (1 mL) and distilled TMSCN (50 μL, 1.25 equiv). After cooling of this stock soln to 5 °C, anhyd MeOH (15 μL, 1.25 equiv) was added, and the resulting mixture was stirred at 5 °C for 2 h and then cooled to −78 °C. The stock soln was added via syringe to the mixture with the imine. ^{1}H NMR or HPLC analysis was used to monitor the conversion; reaction times are given in Scheme 51. At >99% conversion, the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography (silica gel or neutral alumina, EtOAc/hexanes 1:4) or by recrystallization (Scheme 51). The enantiomeric excess was determined by chiral HPLC analysis (Chiralcel OD, iPrOH/hexanes or EtOH/hexanes).

2.2.4.8.3 Strecker Reaction: Acylcyanation of Imines

In 1956, the first reaction of acyl cyanides with imines was reported by Dornow and coworkers.[222,223] In order to avoid highly volatile and highly toxic hydrogen cyanide, List and co-workers developed an achiral thiourea organocatalyzed reaction for the acylcyanation of imines with acyl cyanide in 2006.[29,224] In an asymmetric version, α-aminonitriles **155** are obtained in good yields and with good to excellent enantioselectivities (62–95% yield; 89–98% ee).[30] Scheme 52 shows results for aromatic, aliphatic, and alkenic imines **153**. Some substrates show a dependence on catalyst loading, as demonstrated by the observation that increasing the amount of catalyst from 1 to 5 mol% increases the enantioselectivity. An asymmetric version of the addition reaction of hydrogen cyanide to imines through a chiral Brønsted acid catalyst was developed by the Jacobsen group.[208,210–212,217]

for references see p 407

Scheme 52 Acylcyanation of Imines Catalyzed by a Schiff Base Thiourea Catalyst at −40 °C[30]



R^1	**154** (mol%)	Yield (%)	ee (%)	Ref
4-ClC$_6$H$_4$	1	87	98	[30]
cyclohex-1-enyl	5	82	98	[30]
4-MeOC$_6$H$_4$	1	95	96	[30]
Ph	1	94	96	[30]
2-naphthyl	1	92	96	[30]
t-Bu	5	62	96	[30]
iPr	5	87	95	[30]
(*E*)-CH=CHPh	1	83	94	[30]
Bu	5	76	94	[30]
Cy	1	88	92	[30]

2-[Acetyl(benzyl)amino]alkanenitriles 155; General Procedure:[30]

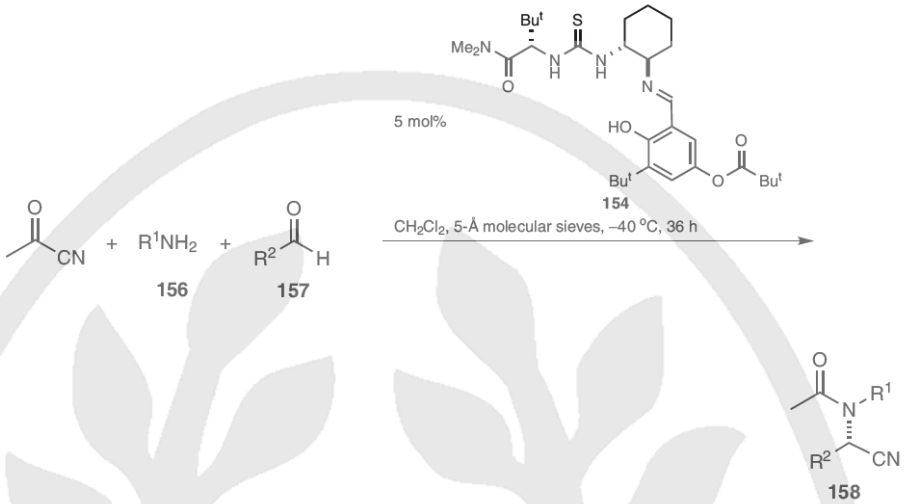
CAUTION: *Acetyl cyanide is highly flammable, toxic by inhalation or if swallowed, and irritating to respiratory system and skin. It is toxic to aquatic organisms and may cause long-term adverse effects in the aquatic environment.*

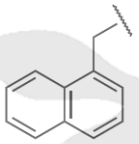
A dried Schlenk tube was charged with the imine **153** (0.5 mmol), catalyst **154** (1–5 mol%; see Scheme 52), and anhyd toluene (1 mL). Then, the mixture was cooled to −40 °C under a positive argon stream and stirred for 10 min. Acetyl cyanide (50 μL, 1.5 equiv) was added to the mixture, which was then stirred for an additional 20–50 h at −40 °C. The mixture was purified directly by flash chromatography [silica gel (Merck 60, 0.040–0.063 mm), EtOAc/hexanes]. The enantiomeric excess was determined by chiral HPLC analysis (ChiralPak AS-H or OJ-H, iPrOH/heptane).

2.2.4.8.4 Acyl-Strecker Reaction in One Pot

In 2007, List and co-workers reported an achiral three-component acyl-Strecker reaction in one pot using acyl cyanides as cyanide source.[31] An asymmetric one-pot α-aminonitrile synthesis is catalyzed by a thiourea catalyst **154** (Scheme 53).[225] Using the more manageable acyl cyanide avoids the use of highly toxic and volatile hydrogen cyanide. Good enantioselectivities (88–94% ee) and yields of 46–97% are afforded for aromatic and aliphatic aldehydes **157** with benzylamine. Various benzylamine derivatives **156** (R^2 = aryl) react with benzaldehyde in high yields of 92–95% and with good enantioselectivity (up to 94% ee). Allylic, aliphatic, and 2-furfuryl amines give enantioselectivities of <88%. To afford the α-amino acids, the nitriles **158** have to be hydrolyzed.

Scheme 53 Asymmetric Three-Component Acyl-Strecker Reaction Catalyzed by Jacobsen's Schiff Base Thiourea Catalyst at −40 °C[225]



R^1	R^2	Yield (%)	ee (%)	Ref
Bn	Ph	94	94	[225]
4-$MeOC_6H_4CH_2$	Ph	95	94	[225]
4-$ClC_6H_4CH_2$	Ph	93	94	[225]
Bn	2-naphthyl	92	94	[225]
	Ph	92	94	[225]
Bn	CH_2t-Bu	97[a]	92	[225]
Bn	iPr	92	92	[225]
Bn	4-$MeOC_6H_4$	88	92	[225]
Bn	(*E*)-CH=CHPh	82	92	[225]
Bn	4-ClC_6H_4	78	92	[225]

[a] With 10 mol% of catalyst **154**.

2-(Acetylamino)alkanenitriles 158**; General Procedure:**[225]

CAUTION: *Acetyl cyanide is highly flammable, toxic by inhalation or if swallowed, and irritating to respiratory system and skin. It is toxic to aquatic organisms and may cause long-term adverse effects in the aquatic environment.*

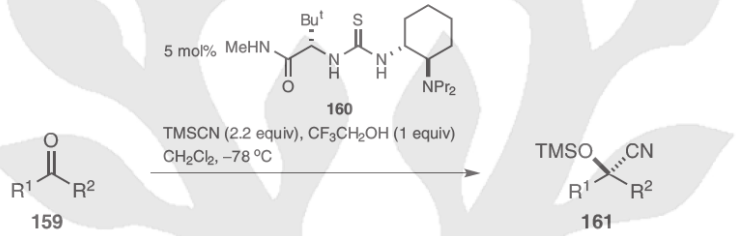
A dried Schlenk tube was charged with the aldehyde **157** (0.5 mmol), the amine **156** (0.5 mmol), and 5-Å molecular sieves (150 mg). Anhyd CH_2Cl_2 (2 mL) was added and the mixture was stirred at rt for 2 h. After addition of the catalyst **154** (5 mol%), the mixture was cooled the −40 °C and stirred for 10 min. Acetyl cyanide (0.75 mmol, 1.5 equiv) was added to the mixture, which was then stirred at −40 °C for a further 36–50 h. The mixture was purified directly by flash chromatography [silica gel (Merck 60, 0.040–0.063 mm), EtOAc/hexane]. The enantiomeric excess was determined by chiral HPLC analysis (Chiral-Pak AS-H or OJ-H, iPrOH/heptane).

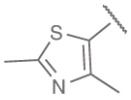
for references see p 407

2.2.4.9 Cyanosilylation

In 2003, Takemoto and co-workers developed a nonstereoselective nucleophilic addition reaction of trimethylsilyl cyanide and ketene silyl acetals to nitrones and aldehydes catalyzed by achiral *N*,*N*′-bis[3,5-bis(trifluoromethyl)phenyl]thiourea (**1**).[23] In 2005, Fuerst and Jacobsen developed a method for the asymmetric cyanosilylation of ketones.[226] Enantiomeric excesses in the range of 86–98% and yields of 81–98% are achieved. The 10 examples with the best enantiomeric excesses achieved are shown in Scheme 54. A mechanistic study regarding this reaction was published in 2007.[227] In 2006, Gennari, Piarulli, and co-workers developed a method for the cyanosilylation of aldehydes catalyzed by a mixture of atropisomeric thiourea derivatives.[228] Moderate enantiomeric excesses of 45–69% and yields from 30% to quantitative are obtained. Bernal, Fernández, and Lassaletta reported an asymmetric cyanosilylation of nitroalkenes in 2010, with enantiomeric excesses in the range 60–86% and yields from 19 to 98%.[229]

Scheme 54 Enantioselective Cyanosilylation of Ketones with Trimethylsilyl Cyanide Using a Chiral Thiourea Organocatalyst[226]



R^1	R^2	Time (h)	Yield (%)	ee (%)	Ref
2-Tol	Me	36[a]	96	98	[226]
2-thienyl	Me	48[b,c]	88	98	[226]
2-naphthyl	Me	12	98	97	[226]
3-$MeOC_6H_4$	Me	12[b]	97	97	[226]
Ph	Me	24	96	97	[226]
CBr=CH$(CH_2)_3$		12	95	97	[226]
	Me	48[b]	87	97	[226]
2-furyl	Me	48[b]	81	97	[226]
4-Tol	Me	36	97	96	[226]
(*E*)-CH=CHPh	Me	12	94	96	[226]

[a] Carried out on 10-mmol scale; other reactions were carried out on a 1-mmol scale.
[b] 10 mol% of catalyst was used.
[c] Carried out with 2.7 equiv of TMSCN and 1.5 equiv of 2,2,2-trifluoroethanol.

2-Phenyl-2-(trimethylsiloxy)propanenitrile (161**, R^1 = Ph; R^2 = Me); Typical Procedure:**[226]

CAUTION: *Trimethylsilyl cyanide is highly flammable, can liberate with water highly toxic HCN, and is very toxic by inhalation, in contact with skin, and if swallowed.*

In a flame-dried 5-mL round-bottomed flask sealed with a rubber septum and equipped with a magnetic stirrer bar, a soln of catalyst **160** (0.0192 g, 0.05 mmol, 5 mol%), acetophenone (**159**, R^1 = Ph; R^2 = Me; 0.117 mL, 1.00 mmol), and distilled TMSCN (0.294 mL, 2.20 mmol, 2.2 equiv) in anhyd CH_2Cl_2 (2.0 mL) was prepared. The septum was sealed with Parafilm M, and the soln was cooled to −78 °C in an immersion Cryocool. After stirring for 15 min, 2,2,2-trifluoroethanol (0.073 mL, 1.00 mmol) was added with a syringe to the mixture. After 24 h of stirring at −78 °C, the mixture was put under high vacuum for 5 min at this temperature for removal of excess HCN. The entire mixture was warmed to rt, and purified by column chromatography (silica gel, hexanes/EtOAc 20:1) to give the product as a clear, colorless oil; yield: 210 mg (96%); 97% ee by chiral GC [γ-TA, 100 °C isothermal, 48.3 kPa, t_R(minor) = 14.70 min, t_R(major) = 15.31 min].

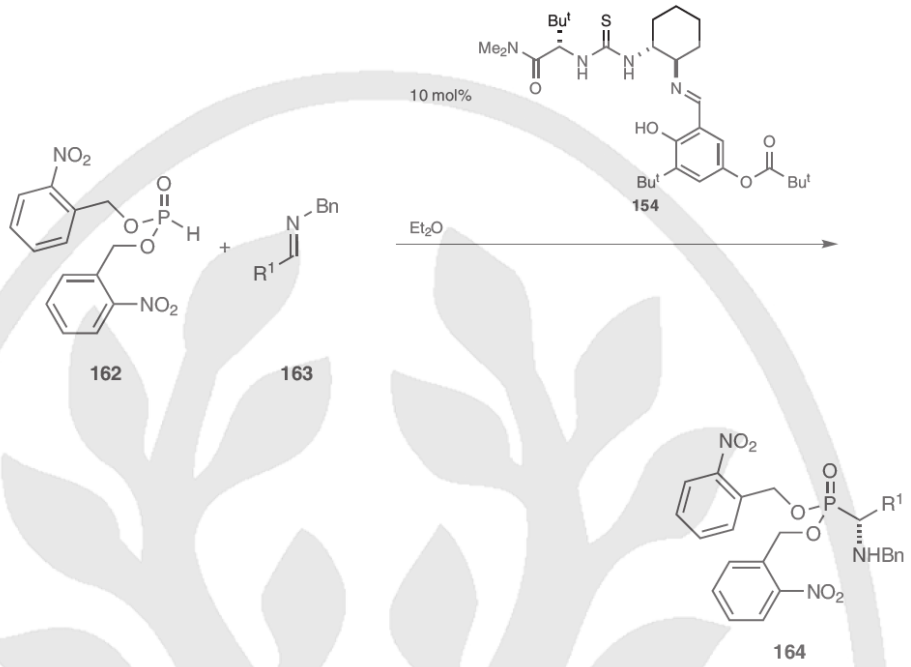
2.2.4.10 Hydrophosphonylation

2.2.4.10.1 Hydrophosphonylation of Imines

In 2004, Joly and Jacobsen developed an asymmetric method for the hydrophosphonylation of imines with bis(2-nitrobenzyl) phosphite (**162**) catalyzed by thiourea derivative **154**.[230] More-electron-deficient phosphites such as bis(2,2,2-trifluoroethyl) phosphite lead to configurationally unstable products.[230] The reaction affords the hydrophosphonylated products with 81–99% ee in yields of 52–93%. Aliphatic imines react faster with phosphite **162** than do aromatic ones; the temperature has to be increased to room temperature for reaction of aromatic imines in some cases. The best results are shown in Scheme 55.

for references see p 407

Scheme 55 Enantioselective Hydrophosphonylation of Imines with Bis(2-nitrobenzyl) Phosphite Catalyzed by a Schiff Base Thiourea Derivative[230]



R^1	Temp (°C)	Time (h)	Yield (%)	ee (%)	Ref
4-ClC_6H_4	4	72	87	99	[230]
4-FC_6H_4	4	72	89	98	[230]
Ph	4	72	87	98	[230]
2-naphthyl	4	72	86	98	[230]
3-ClC_6H_4	23	48	83	98	[230]
$CHEt_2$	4	24	90	96	[230]
4-MeOC_6H_4	4	48	90	96	[230]
4-Me$O_2CC_6H_4$	23	48	78	96	[230]
3-pyridyl	23	48	77	96	[230]

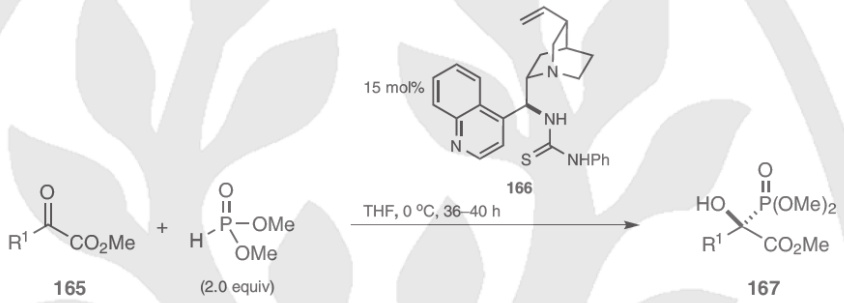
Bis(2-nitrobenzyl) (Benzylamino)(phenyl)methylphosphonate (164, R^1 = Ph); Typical Procedure:[230]

In an oven-dried 4-mL vial, phosphite **162** (0.177 g, 0.501 mmol, 1.0 equiv), catalyst **154** (0.0288 g, 0.0501 mmol, 10 mol%), and Et_2O (1.2 mL) were mixed. The vial was sealed with a plastic cap and cooled under stirring to 0 °C (ice–water bath). Imine **163** (R^1 = Ph; 0.0979 g, 0.501 mmol, 1.0 equiv) was added to this suspension (phosphite **162** is sparingly soluble). The mixture was warmed to 4 °C. After 72 h, a mixture of 1 M aq HCl (0.5 mL) and THF (0.5 mL) was added. This mixture was stirred at 4 °C for 1 h, and then partitioned between 1 M aq HCl and CH_2Cl_2 (1:1; 40 mL). The layers were mixed well and separated. The aqueous layer was extracted with CH_2Cl_2 (5 mL). The combined organic layers were washed with sat. aq Na_2CO_3 (20 mL). The Na_2CO_3 soln was extracted with CH_2Cl_2 (2 × 5 mL), and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (silica gel, hexanes/EtOAc 60:40) to provide the product **164** (R^1 = Ph) as a very pale yellow solid; yield: 0.239 g (87%); 98% ee by chiral HPLC analysis [Pirkle L-leucine, hexane/iPrOH 95:5, 1.0 mL·min^{-1}, λ = 208 nm, t_R(major) = 87.9 min, t_R(minor) = 100.1 min].

2.2.4.10.2 Hydrophosphonylation of α-Keto Esters

In 2009, Feng and co-workers developed a method for the hydrophosphonylation of α-keto esters **165** with dimethyl phosphite catalyzed by a thiourea derivative **166** bearing a cinchona alkaloid moiety.[231] It was proposed that the keto ester is activated by double hydrogen bonding through the thiourea group while the nitrogen atom of the cinchona alkaloid has the potential to shift the phosphite–phosphonate equilibrium to the phosphite via hydrogen-bonding interactions.[231] High yields of 85–94% and enantiomeric excesses in the range 88–91% are obtained (Scheme 56).

Scheme 56 Hydrophosphonylation of α-Keto Esters with Dimethyl Phosphite Catalyzed by a Cinchona Alkaloid Thiourea Derivative[231]



R^1	Yield (%)	ee (%)	Ref
2-thienyl	91	91	[231]
4-$MeOC_6H_4$	90	91	[231]
3-FC_6H_4	94	90	[231]
3-Tol	92	90	[231]
Ph	92	90	[231]
4-Tol	90	90	[231]
4-FC_6H_4	90	90	[231]
4-BrC_6H_4	87	90	[231]
4-ClC_6H_4	85	90	[231]
2-naphthyl	86	88	[231]

(+)-Methyl 2-(Dimethoxyphosphoryl)-2-hydroxy-2-phenylacetate (167, R^1 = Ph); **Typical Procedure:**[231]

CAUTION: *Dimethyl phosphite is a suspected carcinogen.*

Methyl 2-oxo-2-phenylacetate (**165**, R^1 = Ph; 15 μL, 0.1 mmol) was added to a soln of catalyst **166** (6.5 mg, 0.015 mmol, 15 mol%) in anhyd THF (0.4 mL) under stirring at 0 °C followed by addition of dimethyl phosphite (19 μL, 0.2 mmol, 2.0 equiv). The mixture was stirred for 36–40 h at 0 °C. Purification was accomplished by flash chromatography (EtOAc/petroleum ether 1:1) affording the product as a pale yellow liquid; yield: 25.2 mg (92%); 90% ee by chiral HPLC analysis [Chiralcel AD-H, hexane/iPrOH 95:5, 1.0 mL·min^{-1}, λ = 210 nm, 23 °C, t_R(major) = 18.08 min, t_R(minor) = 20.22 min].

for references see p 407

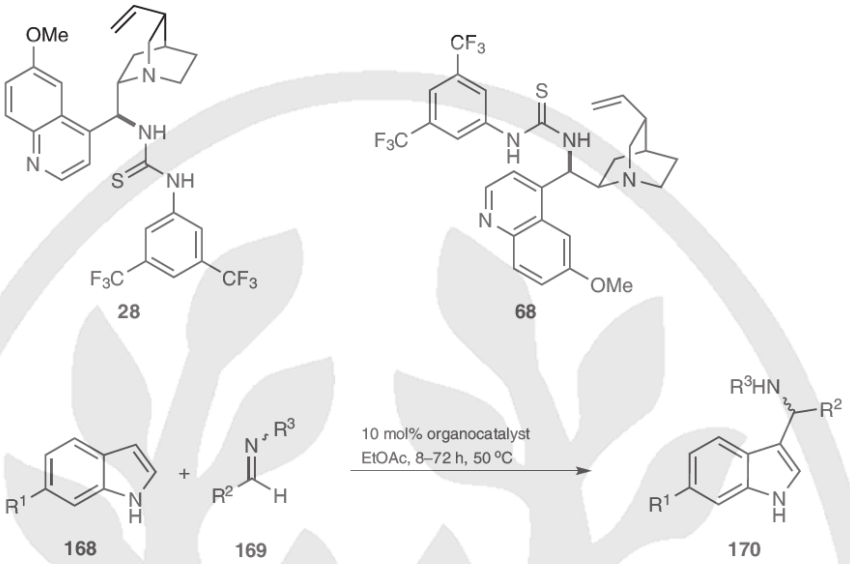
2.2.4.11 Friedel–Crafts Reaction

The Friedel–Crafts alkylation reaction of aromatic compounds with unsaturated compounds can be used as a method to synthesize enantioenriched aromatic compounds.[232,233] In 2008, Connon and his group utilized a thiourea-based organocatalyst for the addition 1,2-dimethylindoles to styrene oxide derivatives with very good yields of isolated products, but no enantioselectivity.[234,235] Additionally, they utilized a bis(thiourea) derivative catalyst in an addition reaction of nitroalkenes to 1-methylindoles with low enantioselectivities (12–50% ee) and moderate to high yields of 54–98%.[236] A planarchiral thiourea derivative employed by Paradies and co-workers also affords low enantioselectivities (<9% ee).[237] Nagasawa and Sohotome developed a protocol for a 1,4-type Friedel–Crafts reaction of nitroalkenes to phenols through a guanidine/bis(thiourea) organocatalyst.[238] The yields of isolated products are good to excellent (77–99%) and the enantioselectivities are also good (82–93% ee), but the synthesis of the catalysts requires the addition of very toxic mercury(II) chloride. In 2005, Ricci and co-workers first reported an asymmetric Friedel–Crafts reaction with nitroalkenes and indoles.[24,239] The yields of isolated products are marginal to good (37–88%), and the enantioselectivities are good (71–89%), but the substrate scope is narrow.[239]

2.2.4.11.1 Friedel–Crafts Reaction of Indoles with Imines

A bifunctional cinchona alkaloid derived thiourea organocatalyst **28** (and the opposite diastereomer **68**) was studied by the group of Deng in a Friedel–Crafts reaction of indoles **168** with imines **169** to synthesize indol-3-ylmethanamine derivatives **170** (Scheme 57).[240] Presumably, the bifunctional catalyst simultaneously activates the indole and imine through hydrogen bonding. Good enantioselectivities of 83–97% and yields of 53–99% are achieved. The applicability of the catalyst is broad, because it transforms aromatic as well as aliphatic imines with good enantioselectivities into indol-3-ylmethanamines. Electron-withdrawing and electron-donating groups on the indole have no influence on the enantioselectivity, as illustrated by the examples with R^1 = Br and OMe in Scheme 57. The enantioselectivity is likewise maintained when the protecting group of the imine changes from *N*-tosyl to *N*-phenylsulfonyl. *N*-*tert*-Butoxycarbonyl-protected imines, however, only give racemic products. Combining an electron-deficient indole with an electron-rich imine does not give as good results as do the other reactions. Aryl imines with various electron-withdrawing and electron-donating groups also show high enantioselectivities. A similarly good enantioselectivity is achieved with the diastereomeric catalyst **68**. 1-Methylindole shows no reactivity. A protocol for the deprotection of the products is also mentioned. In 2008, He and co-workers first reported a thiourea-derived cinchona catalyst on mesoporous silica as a recyclable heterogeneous catalyst for the Friedel–Crafts reaction.[241,242] This heterogeneous catalyst gives good enantioselectivities (90–99% ee), but lower yields of 30–80%.[243]

Scheme 57 Enantioselective Friedel–Crafts Reaction of Indoles with Protected Imines Using Bifunctional Thiourea Catalysts[240]



R^1	R^2	R^3	Organocatalyst	Time (h)	Yield (%)	ee (%)	Ref
H	2-furyl	Ts	**28**	12	88	96	[240]
Br	Ph	SO_2Ph	**28**	60	86	95	[240]
H	4-ClC_6H_4	Ts	**28**	28	98	94	[240]
H	Ph	Ts	**28**	60	96	94	[240]
H	Cy	Ts	**28**	48	86	94	[240]
H	Ph	SO_2Ph	**28**	36	87	94	[240]
OMe	Ph	SO_2Ph	**28**	36	89	92	[240]
H	4-Tol	SO_2Ph	**68**	46	96	94	[240]
H	4-$F_3CC_6H_4$	Ts	**68**	8	97	97	[240]
H	iBu	Ts	**68**	12	85	96	[240]

1-(1*H*-Indol-3-yl)methanamines 170**; General Procedure:**[240]

CAUTION: *1H-Indole is harmful in contact with skin and if swallowed, irritating to respiratory system and skin, and risk of serious damage to eyes. 1H-Indole is very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.*

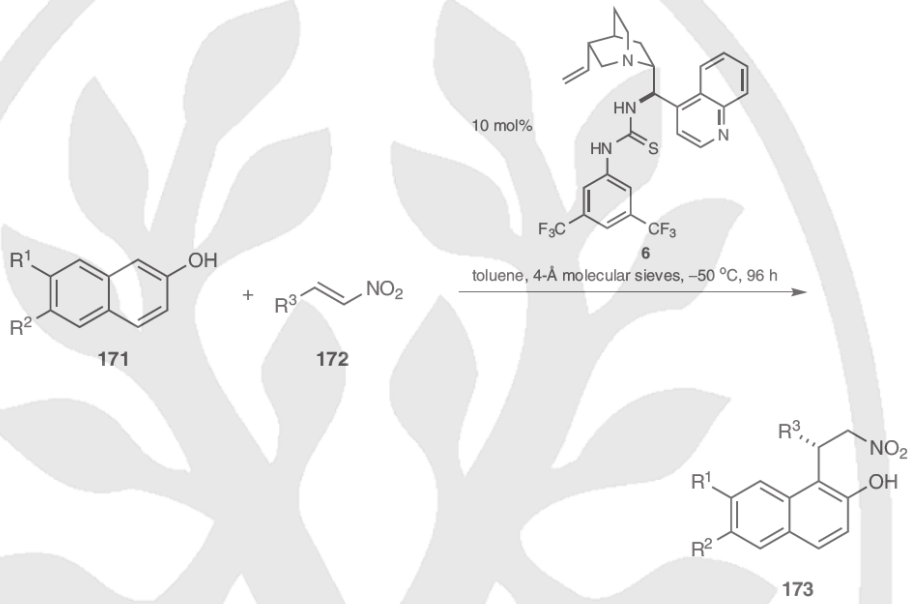
A reaction vessel was charged with the N-protected imine **169** (0.3 mmol), catalyst **28** or **68** (10 mol%), and EtOAc (0.15 mL). In one portion, the indole **168** (0.6 mmol) was added. The mixture was heated to 50 °C for 8–72 h (Scheme 57). Then, the mixture was directly purified by flash chromatography (silica gel, hexanes/EtOAc) to afford the product. The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chiralcel OD, hexanes/iPrOH 60:40).

2.2.4.11.2 Friedel–Crafts Reaction of Naphthols with Nitroalkenes

In 2007, Chen and co-workers developed a protocol for the Friedel–Crafts reaction of 1- and 2-naphthols with nitroalkenes utilizing a bifunctional thiourea amine derivative catalyst **6**.[244] The isolated yields range from 69 to 83% and the enantiomeric excess values from 85 to 95%. The enantioselectivities are excellent for nitroalkenes **172** with elec-

tron-withdrawing groups (Scheme 58), even in combination with electron-rich and electron-poor naphthols **171** (i.e., R^1 = OMe or R^2 = Br). Even hetaryl nitroalkenes **172** (R^3 = 2-thienyl, 2-furyl) provide good enantiomeric excess values. An interesting finding is the isolation of a byproduct through dimerization of product to *N*-(1,2-dihydronaphtho[2,1-*b*]furan-2-yl)hydroxylamine derivatives. Longer reaction times of 144 hours promote this reaction. The enantioselectivities are 99.5% and the yields 52–67%.

Scheme 58 Enantioselective Friedel–Crafts Reaction of Naphthol Derivatives with Nitroalkenes Using a Bifunctional Thiourea Tertiary Amine Catalyst[244]



R^1	R^2	R^3	Yield (%)	ee (%)	Ref
OMe	H	4-ClC_6H_4	83	95	[244]
H	H	4-ClC_6H_4	82	94	[244]
H	H	2-thienyl	79	94	[244]
H	H	Pr	69	94	[244]
H	H	Ph	80	93	[244]
OMe	H	Ph	81	91	[244]
H	H	3-Tol	72	91	[244]
H	H	2-furyl	77	90	[244]
H	Br	4-ClC_6H_4	77	90	[244]
H	Br	Ph	72	90	[244]

1-(2-Nitroethyl)-2-naphthols 173**; General Procedure:**[244]

CAUTION: *2-Naphthol is classified as harmful by inhalation and if swallowed and very toxic to aquatic organisms.*

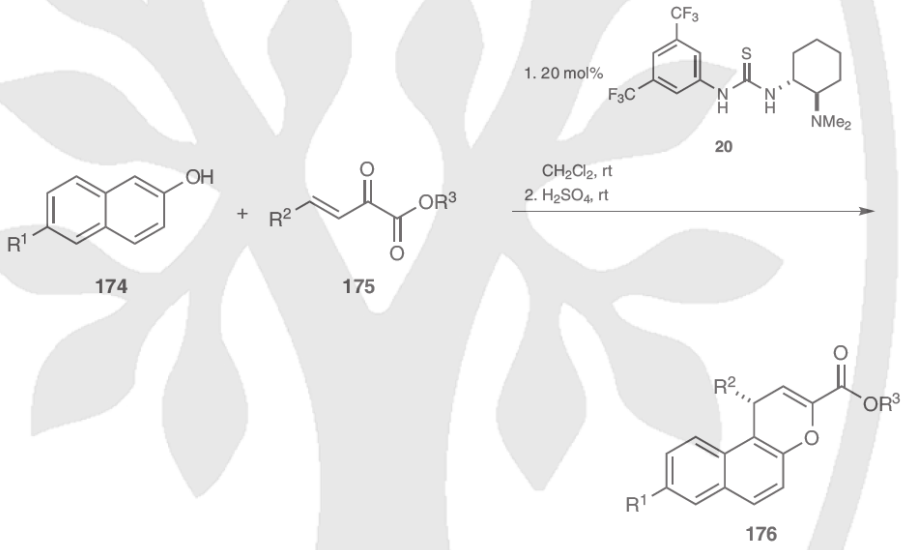
A reaction vessel was charged with catalyst **6** (5.6 mg, 0.01 mmol, 10 mol%), the naphthol derivative **171** (0.1 mmol), 4-Å molecular sieves (20 mg), and anhyd toluene (0.8 mL). The mixture was cooled to −50 °C under an argon atmosphere. The nitroalkene **172** (0.15 mmol) in anhyd toluene (0.8 mL) was added and the mixture was stirred for 96 h at −50 °C under an argon atmosphere. The mixture was saturated with cold petroleum ether to remove the starting material. The purification of product was performed by flash chro-

matography [silica gel (200–300 mesh), EtOAc/petroleum ether]. The enantiomeric excess was determined by chiral HPLC analysis (Chiralpak AS or OD, hexane/iPrOH 90:10 or 98:2).

2.2.4.11.3 Friedel–Crafts Reaction of Naphthols with β,γ-Unsaturated α-Keto Esters

Zhao, Yang, and co-workers developed a synthesis of naphthopyran derivatives **176** from 2-naphthol or its 6-bromo derivative **174** (R^1 = H, Br) and β,γ-unsaturated α-keto esters **175**[245] utilizing catalyst **20**.[246] In a one-pot reaction, the product naphthopyran is obtained in yields of 51–91% and with enantioselectivities of 57–90%. The ester alkyl group R^3 controls the reactivity, but has minor influence on enantioselectivity. The best results are obtained for substrates with electron-withdrawing groups in the 4- or 3-positions of the aryl group of the α-keto ester, i.e. for **175** (R^2 = 4-$O_2NC_6H_4$, 4-BrC_6H_4, 4-ClC_6H_4, 3-ClC_6H_4), as shown in Scheme 59. In 2008, Zhao and Yang published a Friedel–Crafts reaction of 2-naphthols and α,α-dicyanoalkenes with a bifunctional thiourea tertiary amine catalyst **20**, with enantiomeric excesses of the synthesized naphthopyrans in the range 56–99% and yields of 19–99%.[247]

Scheme 59 Asymmetric Friedel–Crafts Reaction of 2-Naphthols with β,γ-Unsaturated α-Keto Esters Using a Bifunctional Thiourea Tertiary Amine Catalyst at Room Temperature[246]



R^1	R^2	R^3	Yield (%)	ee (%)	Ref
H	4-$O_2NC_6H_4$	Me	78	90	[246]
H	4-BrC_6H_4	Me	91	87	[246]
H	4-ClC_6H_4	Me	89	87	[246]
H	Ph	Me	84	87	[246]
H	3-ClC_6H_4	Me	71	86	[246]
Br	Ph	Me	57	86	[246]

Alkyl 1*H*-Naphtho[2,1-*b*]pyran-3-carboxylates 176**; General Procedure:**[246]

CAUTION: *2-Naphthol is classified as harmful by inhalation and if swallowed and very toxic to aquatic organisms.*

A reaction vessel was charged with the naphthol derivative **174** (0.1 mmol), the β,γ-unsaturated α-keto ester **175** (0.1 mmol), thiourea organocatalyst **20** (0.02 mmol), and anhyd

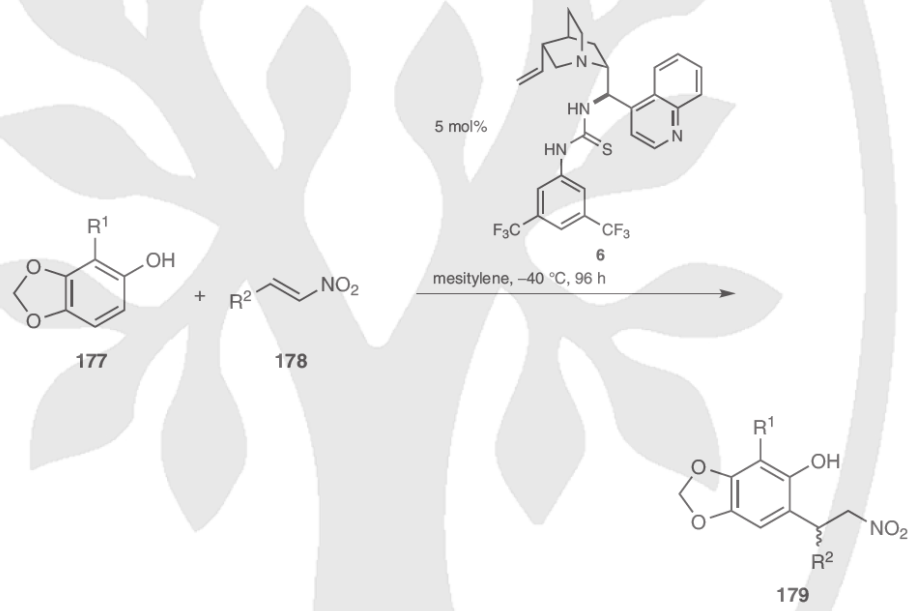
for references see p 407

CH_2Cl_2 (1.0 mL). The mixture was stirred at rt for 6–48 h (monitoring by TLC). A drop of concd (98%) H_2SO_4 was added and the mixture was stirred for an additional 30 min at rt. The mixture was purified by flash chromatography (silica gel) to obtain the product as a white solid. The enantiomeric excess was determined by chiral HPLC analysis (Chiralcel OD-H, hexane/iPrOH 9:1).

2.2.4.11.4 Friedel–Crafts Reactions of Sesamol with Nitrostyrenes

In 2010, Zhang and co-workers published a method for the enantioselective Friedel–Crafts reaction of electron-rich sesamol and 2-substituted sesamols (4-substituted 1,3-benzodioxol-5-ols) **177** with 1-aryl-2-nitroethenes using a thiourea tertiary amine catalyst **6**; good yields (75–97%) and enantioselectivities (59–90% ee) are attained.[248] The best results are obtained when the 1-aryl-2-nitroethenes bear substituents in the *meta*- or *para*-positions. Lower enantioselectivities result with substituents in the *ortho*-position (not shown). The best results are shown in Scheme 60.

Scheme 60 Friedel–Crafts Alkylation of Sesamol Derivatives with 1-Aryl-2-nitroethenes Using a Chiral Thiourea Catalyst[248]



R^1	R^2	Yield (%)	ee[a] (%)	Ref
I	Ph	88	90	[248]
H	4-ClC_6H_4	96	88	[248]
H	4-BrC_6H_4	96	86	[248]
H	3-BrC_6H_4	87	86	[248]
H	4-$MeOC_6H_4$	97	85	[248]
H	3-FC_6H_4	75	85	[248]

[a] The absolute configuration was not determined.

6-(2-Nitroethyl)-1,3-benzodioxol-5-ols 179**; General Procedure:**[248]
A 10-mL reaction tube was charged with catalyst **6** (5.6 mg, 0.01 mmol, 5 mol%), the 1,3-benzodioxol-5-ol **177** (0.2 mol), and the nitroalkene **178** (0.3 mmol). The mixture was

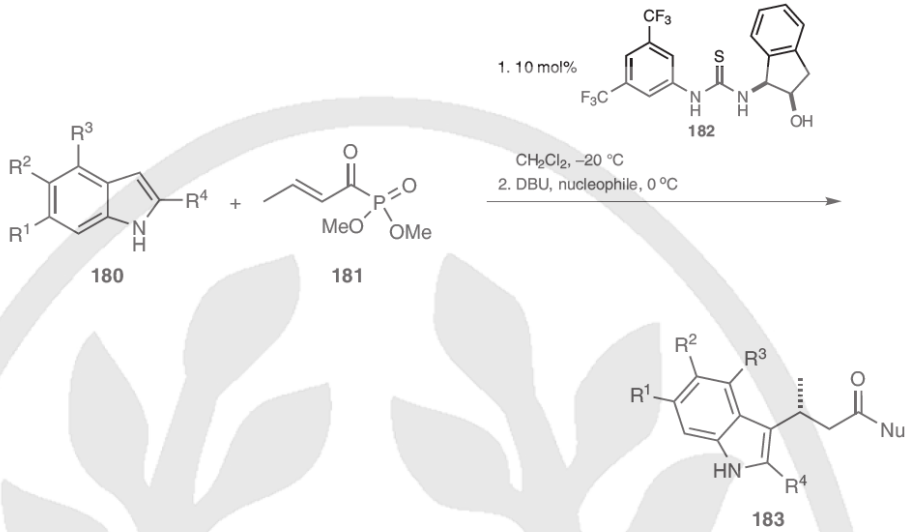
cooled to −40 °C under an argon atmosphere and anhyd mesitylene (4 mL) was added. After 96 h, the mixture was purified by flash chromatography [silica gel (type HG/T2345–92)] and a colorless oil was isolated. The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chiralpak AD-H, hexane/EtOH 70:30; or Daicel Chiralpak OD-H, hexane/iPrOH 80:20 or hexane/EtOH 70:30).

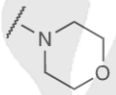
2.2.4.11.5 Friedel–Crafts Reaction of Indoles with Acylphosphonates

Jørgensen and co-workers published in 2010 the Friedel–Crafts alkylation of indoles with acylphosphonates as ester amide surrogates.[249] Thiourea organocatalyst **182**, containing a free hydroxy group, is suggested to activate dimethyl (*E*)-but-2-enoylphosphonate (**181**) through hydrogen bonding and the hydroxy group binds to the nitrogen atom of the indole **180** to synthesize β-indol-3-yl acylphosphonates. It is also suggested that in the transition state the thiourea catalyst arranges the nucleophilic indole next to the electrophilic acylphosphonate. After addition of the indole, the phosphonate is substituted by a nucleophile to afford β-hetarylated esters. Jørgensen and co-workers utilized thiourea **182** with broad substrate scope: Indoles with electron-donating substituents at various positions give good yields (ca. 90%) and enantioselectivities (82–90% ee). Indoles bearing electron-withdrawing groups lead to good enantioselectivities of 85–90% with yields of 72–86%. The best results are shown in Scheme 61. Due to the possibility of a second nucleophilic attack, the ester can racemize, but this strongly depends on the nucleophilicity and basicity of the nucleophile as well as reaction time.

for references see p 407

Scheme 61 Friedel–Crafts Alkylation of Indoles with an Alkenoylphosphonate[249]



R^1	R^2	R^3	R^4	Nucleophile	Nu	Yield (%)	ee (%)	Ref
H	H	H	H	morpholine		63	87	[249]
OMe	H	H	H	EtOH	OEt	93	90	[249]
H	Cl	H	H	EtOH	OEt	86	90	[249]
H	H	H	H	EtOH	OEt	68	90	[249]
H	H	H	H	MeOH	OMe	60	86	[249]
H	OMe	H	Me	EtOH	OEt	87	85	[249]
H	I	H	H	EtOH	OEt	70	85	[249]

3-(1*H*-Indol-3-yl)butanoates and -butanamides 183**; General Procedure:**[249]

CAUTION: *1H-Indole is harmful in contact with skin and if swallowed, irritating to respiratory system and skin, and risk of serious damage to eyes. 1H-Indole is very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.*

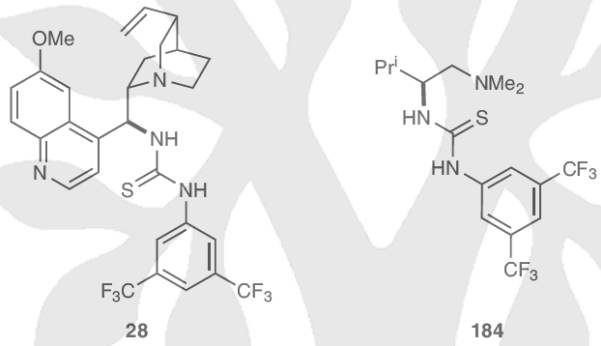
A reaction vial with a magnetic stirrer bar was charged with dimethyl (*E*)-but-2-enoylphosphonate (**181**; 0.2 mmol, 2 equiv), catalyst **182** (0.01 mmol, 0.1 equiv), and CH_2Cl_2 (2.0 mL). The mixture was stirred for 5 min, and then the indole **180** (0.1 mmol, 1 equiv) was added. The mixture was stirred at −20 C until full conversion was observed by TLC. The reaction times were usually 24–72 h. The nucleophile [alcohol (0.1 mL) or morpholine (0.2 mmol, 2 equiv)] and DBU (0.2 mmol, 2 equiv) were then added in sequence to the mixture at 0 °C. The mixture was stirred for additional 30 min, sat. aq NH_4Cl was added, and the resulting mixture was extracted with EtOAc (3 × 5 mL). The organic phase was dried ($MgSO_4$), the solvent was removed under reduced pressure, and the crude product was purified by flash chromatography [silica gel (Fluka 60, 230–400 mesh), pentane/EtOAc 4:1 to 2:1 gradient or pentane/EtOAc 4:1 to EtOAc gradient]. The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chiralpak OD, hexane/iPrOH).

2.2.4.12 Desymmetrizations

2.2.4.12.1 *meso*-Anhydride Desymmetrization

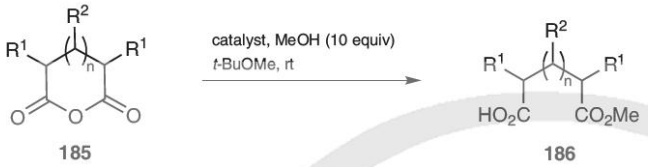
The groups of Chen,[250] Connon,[251] Pedrosa,[252] and Chin and Song[253,254] developed thiourea-catalyzed protocols for the desymmetrization of *meso*-anhydrides via alcoholysis to obtain enantioenriched hemiesters with high yields and good enantioselectivities; results from Connon[251] and Pedrosa[252] are shown in Scheme 62 and Table 1. Chen and Wang also reached enantioselectivities of 82–95% with good yields (88–97%), and utilized the developed protocol in a reaction step in the total synthesis of (+)-biotin.[250] Song and Chin also achieved high enantioselectivity of >91% with good yields of >88%, but the other groups demonstrated broader scope.[253] The desymmetrization of anhydrides requires simultaneous activation of the alcohol and the ester functions, and the bifunctional catalyst presumably assumes this role. The enantioselectivity is independent of the relative stereochemistry of the starting *meso*-anhydrides, because *endo*- as well as *exo*-tricyclic anhydrides react at the same carbonyl group (Table 1, entries 1, 2, 5, and 10). Huang and coworkers published a synthesis of an asymmetric dihydropyridin-2-one derivative utilizing an anhydride desymmetrization step.[255]

Scheme 62 Catalysts for Enantioselective Methanolysis of Anhydrides with Thiourea Catalysts[251,252]



for references see p 407

Table 1 Enantioselective Methanolysis of Anhydrides with Thiourea Catalysts[251,252]



185 186

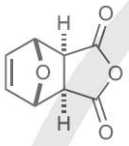
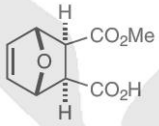
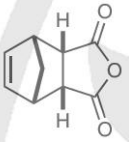
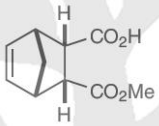
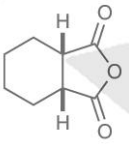
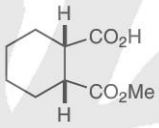
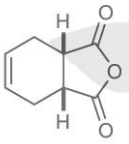
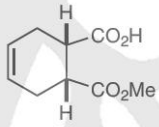
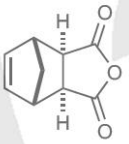
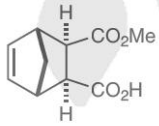
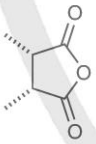
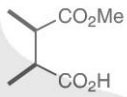
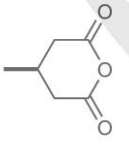
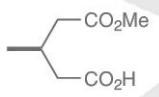
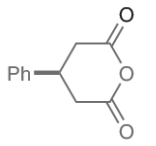
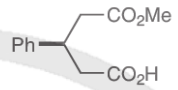
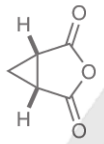
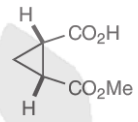
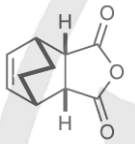
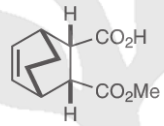
Entry	Starting Material	Catalyst	Temp (°C)	Time (h)	Product	Yield (%)	ee (%)	Ref
1		**184**	rt	32		95	>99[a]	[252]
2		**184**	rt	32		99	96[a]	[252]
3		**184**	rt	12		99	96[a]	[252]
4		**184**	rt	12		99	94[a]	[252]
5		**184**	rt	12		99	96[a]	[252]
6		**28**	rt	14		98	92[b]	[251]
7		**28**	0	50		94	90[b]	[251]

Table 1 (cont.)

Entry	Starting Material	Catalyst	Temp (°C)	Time (h)	Product	Yield (%)	ee (%)	Ref
8		**28**	0	26		95[c]	89[b]	[251]
9		**184**	4	60		94	86[a]	[252]
10		**184**	rt	120		55	50[a]	[252]

[a] Enantiomeric excess determined after derivatization to a 4-bromophenyl ester.
[b] Enantiomeric excess determined after derivatization with (*R*)-1-(1-naphthyl)ethylamine by ^{1}H-NMR analysis and/or confirmed by CSP-HPLC.
[c] The absolute configuration of the product was not determined.

Enantioenriched Hemiesters (Table 1, Entries 1–5, 9, and 10); General Procedure Using Catalyst 184:[252]

Under a N_2 atmosphere and at rt, anhyd MeOH (203 μL, 5.0 mmol) was added dropwise to a soln of the anhydride **185** (0.5 mmol) and catalyst **184** (10.0 mg, 0.025 mmol) in anhyd *t*-BuOMe (33 mL, 0.015 M). The mixture was stirred until complete conversion was observed. The solvent was evaporated, the residue was dissolved with CH_2Cl_2 (5 mL), and the soln was extracted with sat. aq Na_2CO_3 (2 × 5 mL). The combined aqueous phases were acidified with 2 M HCl and extracted with EtOAc (3 × 20 mL). The combined organic phases were dried ($MgSO_4$), and after removal of the drying agent by filtration, the solvent was evaporated under reduced pressure.

The enantiomeric excess was determined by optical rotation and/or HPLC analysis. After conversion of the hemiester **186** into the corresponding 4-bromophenyl esters, the enantiomeric excess was also determined by HPLC analysis [Daicel Chiralcel OD or Chiralpak AS-H or AD-H (each 250 × 4.6 mm); hexane/iPrOH].

Enantioenriched Hemiesters (e.g., Table 1, Entry 6); General Procedure Using Catalyst 28 **at Room Temperature:**[251]

The anhydride (0.3 mmol) was placed in a 40-mL vial equipped with a stirrer bar and catalyst **28** (1.8 mg, 0.003 mmol). A septum was fixed on the vial, which was flushed with argon and anhyd *t*-BuOMe (20 mL) was added. Anhyd MeOH (122 μL, 3.0 mmol) was added dropwise to the mixture through a syringe. The mixture was stirred at rt for the time given in Table 1. Full conversion was determined by TLC or ^{1}H NMR spectroscopy. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (particle size 0.04–0.063 mm). If full conversion was not observed, the mixture was quenched by adding 0.1 M HCl (10 mL). The aqueous phase was extracted with EtOAc (2 × 10 mL) and the combined organic phases were dried ($MgSO_4$). The solvent was removed under reduced pressure and the crude residue was purified by flash chromatography (particle size 0.04–0.063 mm).

for references see p 407

The enantiomeric excess was determined by ^{1}H NMR spectroscopy after derivatization with (*R*)-1-(1-naphthyl)ethylamine and/or by CSPC-HPLC analysis [OD-H column (4.6 mm × 25 cm), hexane/iPrOH 90:10] and by optical rotation.

Enantioenriched Hemiesters (Table 1, Entries 7 and 8); General Procedure Using Catalyst 28 at Low Temperature:[251]

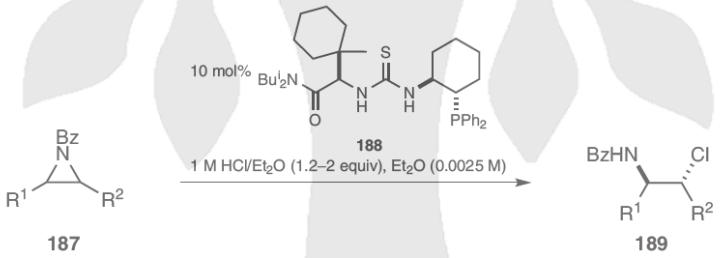
The anhydride (0.3 mmol) was placed in a 60-mL vial equipped with a stirrer bar and catalyst **28** (1.8 mg, 0.003 mmol). A septum was fixed on the vial, which was then flushed with argon. Anhyd *t*-BuOMe (40 mL) was added and the mixture was cooled to 0 °C. Anhyd MeOH (122 μL, 3.0 mmol) was added dropwise to the mixture through a syringe. The mixture was stirred at 0 °C for the time given in Table 1. Full conversion was detected by TLC or ^{1}H NMR spectroscopy. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography.

For determination of enantiomeric excess see room-temperature procedure above.

2.2.4.12.2 Ring Opening of Aziridines

In 2009, Mita and Jacobsen developed an asymmetric method for the desymmetrization of *meso*-aziridines **187** with hydrogen chloride.[256] In the mechanistic proposal, the phosphine moiety of the catalyst **188** is protonated by hydrogen chloride while the chloride anion is bound by the thiourea group. This leads to activation toward electrophilic addition. The oxygen of the aziridine's benzoyl group undergoes hydrogen-bonding interactions with the protonated phosphine moiety, thus bringing the aziridine and the chloride anion into proximity. This paves the way for an S_N2 reaction.[256] The resulting 2-chlorobenzamide derivatives **189** are obtained in excellent yields of 91–99% with moderate to high enantiomeric excesses of 70–92% (Scheme 63).

Scheme 63 Enantioselective Ring Opening of *meso*-Aziridines with Hydrogen Chloride Catalyzed by a Phosphino Thiourea Derivative[256]



R^1	R^2	Temp (°C)	Time (h)	Yield (%)	ee (%)	Ref
(CH$_2$)$_2$CH=CH(CH$_2$)$_2$		−78 to −50	13[a]	94	92	[256]
(CH$_2$)$_5$		−78 to −50	19[a]	96	90	[256]
(CH$_2$)$_6$		−78 to −50	84[a,b]	91	84	[256]
(CH$_2$)$_4$		−78	4	97	83	[256]
(CH$_2$)$_3$		−78	6	99	78	[256]
Me	Me	−78	1	96	70	[256]

[a] 20 mol% of catalyst was used.
[b] The reaction was conducted at 0.025 M concentration.

(1*R*,2*R*)-*N*-(2-Chlorocyclohexyl)benzamide [189, R^1,R^2 = $(CH_2)_4$]; Typical Procedure:[256]

CAUTION: *Hydrogen chloride in diethyl ether is extremely flammable, causes severe burns, and may build explosive peroxides.*

A 1 M soln of HCl in Et_2O (60 μL, 0.06 mmol, 1.2 equiv) was added to a soln of 7-azabicyclo-[4.1.0]heptane [**187**, R^1,R^2 = $(CH_2)_4$; 10.1 mg, 0.050 mmol] and catalyst **188** (3.0 mg, 0.005 mmol, 10 mol%) in Et_2O (20 mL, 0.0025 M) at −78 °C. After 4 h, the solvent was removed under reduced pressure. The residue was purified via automated column chromatography (silica gel, hexane/EtOAc 19:1 to 3:2) to afford the product as a colorless solid; yield: 11.6 mg (98%); 83% ee by chiral HPLC analysis [Daicel Chiralpak AD-H, iPrOH/hexane 1:10, 1.0 mL·min^{-1}, λ = 210 nm, and 254 nm, t_R(major) = 13.8 min, t_R(minor) = 23.4 min].

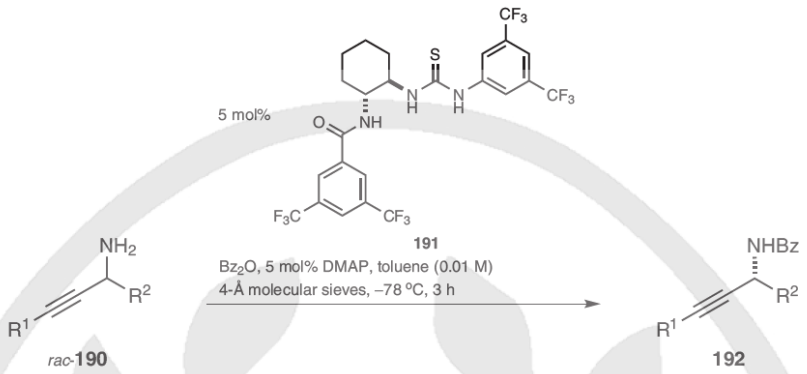
2.2.4.13 Kinetic Resolutions

2.2.4.13.1 Kinetic Resolution of Propargylic Amines

In 2009, the Seidel group published a protocol for the kinetic resolution of amines through benzoylation with good enantioselectivities (62–83%), and yields higher than 35% (*S*-factors between 7 and 24).[257] In 2010, they introduced a new thiourea amide catalyst **191**, a chiral anion acceptor for the achiral acyl pyridinium salt, which can benzoylate a broader spectrum of racemic propargylic amines **190** with good enantioselectivities (up to 91.8% ee and *S*-factors of 12–56).[258] The highest *S*-factors are obtained for propargylic amines **190** (R^1 = 3-ClC_6H_4, 3-Tol) with substituents in the *meta*-position of the aromatic ring (Scheme 64). Benzoylation of aliphatic propargylic amines, e.g. **190** (R^1 = Bu), gives lower enantioselectivities. Utilization of the new thiourea catalyst **191** on benzylamine derivatives results in higher *S*-factors (13–38) compared with those observed in the publication of 2009.

for references see p 407

Scheme 64 Dynamic Kinetic Resolution of Propargylic Amines[258]



R^1	R^2	Yield[a] (%)	ee[a] (%)	Ref
3-ClC_6H_4	Me	40	91.8	[258]
Ph	iPr	40	90.8	[258]
Ph	Et	45	89.5	[258]
4-Tol	Me	42	89.3	[258]
3-Tol	Me	42	89	[258]
4-ClC_6H_4	Me	36	88[b]	[258]
Ph	Me	43	87.8	[258]
4-$F_3CC_6H_4$	Me	41	86.8	[258]
Ph	Ph	29	78.6	[258]
Bu	$(CH_2)_2Ph$	41	76.2	[258]

[a] All reactions were run twice; the results of only the first run are presented here with no average of yields and enantiomeric excess.
[b] Absolute stereochemistry determined after recrystallization and crystal structure analysis.

Enantioenriched Propargylic Amides 192 **(R^1 = Aryl; R^2 = Me, Et, iPr); General Procedure:**[258]

Benzoic anhydride (34.0 mg, 0.150 mmol, 0.6 equiv) and 4-Å molecular sieves (100 mg) were placed in a flame-dried round-bottomed flask under a N_2 atmosphere. DMAP (1.52 mg, 0.0125 mmol, 0.05 equiv) dissolved in anhyd toluene (1 mL) and freshly distilled anhyd toluene (21.0 mL, 0.01 M) were added. The mixture was cooled to −78 °C and, after 15 min, a soln of catalyst **191** (7.82 mg, 0.0125 mmol, 0.05 equiv) in anhyd toluene (2 mL) was added. A soln of amine **190** (0.25 mmol) in anhyd toluene (1 mL) was added and the mixture was stirred at −78 °C for 3 h. The reaction was quenched with 3.0 M MeMgCl in THF (0.167 mL, 0.5 mmol) at −78 °C and the mixture was stirred for additional 10 min at this temperature. The excess of Grignard reagent was quenched with 1 M aq HCl (5 mL). After the mixture had warmed to rt, it was extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with 1 M HCl (5 mL) and brine and dried (Na_2SO_4). The solvent was evaporated under reduced pressure and the residue was flash chromatographed [silica gel (EM Reagent 60, 230–400 mesh)]. The enantiomeric excess was determined by optical rotation and by chiral HPLC analysis (Daicel Chiralpak OD-H or AD-H, hexane/iPrOH).

(*R*)-*N*-(1,3-Diphenylprop-2-ynyl)benzamide (192, **R^1 = R^2 = Ph):**[258]

Benzoic anhydride (34.0 mg, 0.150 mmol, 0.6 equiv) and 4-Å molecular sieves (100 mg) were placed in a flame-dried round-bottomed flask under a N_2 atmosphere. DMAP

(1.52 mg, 0.0125 mmol, 0.05 equiv) dissolved in anhyd toluene (1 mL) and freshly distilled anhyd toluene (21.0 mL, 0.01 M) were added. The mixture was cooled to −78 °C and, after 15 min, a soln of catalyst **191** (7.82 mg, 0.0125 mmol, 0.05 equiv) in anhyd toluene (2 mL) was added. A soln of (*R*)-*N*-(1,3-diphenylprop-2-ynyl)amine (**190**, $R^1 = R^2 = Ph$; 0.25 mmol) in anhyd toluene (1 mL) was added and the mixture was stirred at −78 °C for 8 h. The reaction was quenched with 3.0 M MeMgCl in THF (0.167 mL, 0.5 mmol) at −78 °C and the mixture was stirred for additional 10 min at this temperature. The excess of Grignard reagent was quenched with 1 M aq HCl (5 mL). After the mixture had warmed to rt, it was extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with 1 M HCl (5 mL) and brine and dried (Na_2SO_4). The solvent was evaporated under reduced pressure and the residue was flash chromatographed [silica gel (EM Reagent 60, 230–400 mesh)]. The product was obtained as a white solid; yield: 23.1 mg (29%); $[\alpha]_D^{20}$ −5.0 (*c* 1.0, $CHCl_3$); 78.6% ee by chiral HPLC analysis (Daicel Chiralpak AD-H, hexane/iPrOH 90:10).

Aliphatic Propargylic Amines, e.g. 192 (R^1 = Bu); Typical Procedure:[258]
Benzoic anhydride (34.0 mg, 0.150 mmol, 0.6 equiv) and 4-Å molecular sieves (100 mg) were placed in a flame-dried round-bottomed flask under a N_2 atmosphere. DMAP (1.52 mg, 0.0125 mmol, 0.05 equiv) dissolved in anhyd toluene (1 mL) and freshly distilled anhyd toluene (21.0 mL, 0.01 M) were added. The mixture was cooled to −78 °C and, after 15 min, a soln of catalyst **191** (7.82 mg, 0.0125 mmol, 0.05 equiv) in anhyd toluene (2 mL) was added. A soln of the aliphatic amine **190** (0.25 mmol) in anhyd toluene (1 mL) was added and the mixture was stirred at −78 °C for 3 h. The reaction was quenched with 3.0 M MeMgCl in THF (0.167 mL, 0.5 mmol) at −78 °C and the mixture was stirred for additional 10 min at this temperature. The excess of Grignard reagent was quenched with sat. aq NH_4Cl (5 mL). After the mixture had warmed to rt, it was extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with brine and dried (Na_2SO_4). The solvent was evaporated under reduced pressure and the residue was flash chromatographed [silica gel (EM Reagent 60, 230–400 mesh), hexane/EtOAc gradient]. The enantiomeric excess was determined by optical rotation and by chiral HPLC analysis (Daicel Chiralpak OD-H, AD-H, or OJ-H; hexane/iPrOH).

2.2.4.14 Cycloadditions

2.2.4.14.1 Diels–Alder Reaction

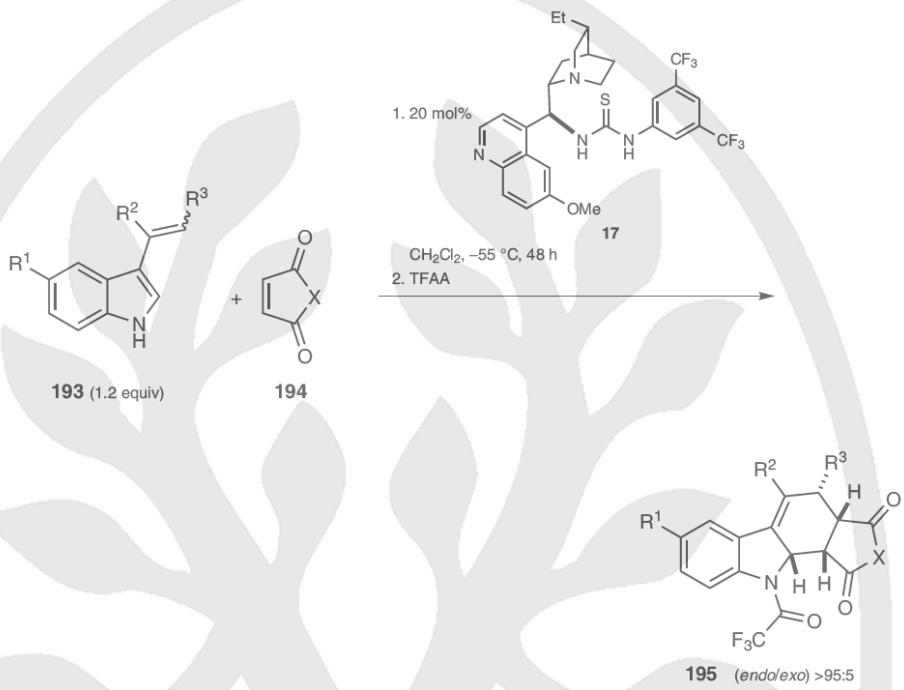
The Diels–Alder reaction is a [4+2] cycloaddition in which a diene and an alkene, the dienophile, react to give cyclohexene derivatives. It is named after O. Diels and K. Alder who reported for the first time the correct structure of the cycloadducts in the year 1928.[133] In 2002/2003, Wittkopp und Schreiner showed that thiourea derivatives such as *N*,*N*′-bis[3,5-bis(trifluoromethyl)phenyl]thiourea (**1**) act akin to Lewis acids by catalyzing Diels–Alder reactions.[7,8] Theoretical studies focusing on these types of Diels–Alder reactions catalyzed by thiourea derivatives were performed by Fu and Thiel in 2006,[259] as well as by Linder and Brinck in 2009.[260] In 2009, Kotsuki and co-workers published an organocatalytic hetero-Diels–Alder reaction.[261] Ketones bearing electron-withdrawing groups in the α-position are transformed into precursors of δ-lactones in the presence of catalyst **1** under high pressure (1.0 GPa). In 2010, Lin and co-workers reported Diels–Alder reactions catalyzed by mesoporous silica nanoparticles functionalized with urea or thiourea moieties.[22]

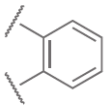
In 2008, Bernardi, Ricci, and co-workers developed an enantioselective method for the Diels–Alder reactions of 3-vinylindoles **193** catalyzed by a cinchona alkaloid derived thiourea **17** (Scheme 65).[262] It was proposed that the nitrogen of the cinchona alkaloid moiety binds to the indole's NH, thus raising the HOMO energy of the diene. The thiourea

for references see p 407

group interacts via double hydrogen bonding with the oxygen of the dienophile **194**, and lowers the LUMO energy.[262] In 2010, the scope of the reaction was extended to 2-vinylindoles.[263]

Scheme 65 Enantioselective Diels–Alder Reaction of 3-Vinylindoles Catalyzed by a Cinchona-Derived Thiourea[262,263]



R^1	R^2	R^3	X	Yield (%)	ee (%)	Ref
H	H	H	CH=CH	83	>99	[262,263]
H	H	H	NPh	91	98	[262,263]
H	H	H	NMe	89	98	[262,263]
H	H	H	NBn	89	96	[262,263]
H	Me	H	NPh	79	96	[262,263]
H	H	H		77	96	[262,263]
OMe	H	H	NPh	77[a]	96	[262,263]
H	H	Me	NPh	58[a,b]	92	[262,263]
Br	H	H	NPh	86[a]	90	[262,263]

[a] 2 equiv of diene was used.
[b] Ratio (*E*/*Z*) of diene: 50:50; the product was a single diastereomer (dr >95:5) from reaction of the *E*-isomer.

1,2-Fused 9-(2,2,2-Trifluoroacetyl)-2,3,9,9a-tetrahydro-1*H*-carbazolediones 195; **General Procedure:**[262]

The dienophile (0.15 mmol), CH_2Cl_2 (1.0 mL; previously passed through basic alumina), and then catalyst **17** (17.8 mg, 0.030 mmol, 20 mol%) were added to a test tube, and cooled to −55 °C. After addition of a precooled soln of the 3-vinylindole **193** (0.18 mmol, 1.2 equiv)

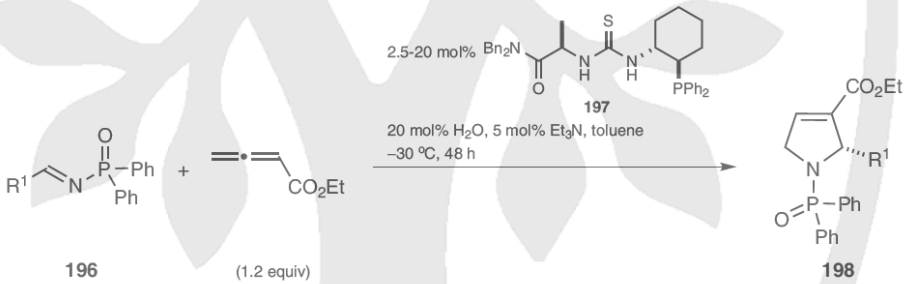
in CH_2Cl_2 (0.50 mL) with a syringe, the mixture was stirred at this temperature for 48 h without moisture or air exclusion, followed by the addition of a soln of TFAA (104 μL, 0.75 mmol, 5.0 equiv) in CH_2Cl_2 (1.5 mL). The mixture was allowed to warm to rt over a period of 1 h. Then, sat. $NaHCO_3$ soln was added slowly followed by extraction with CH_2Cl_2 (3 × 5 mL). After combining and drying of the organic layers (Na_2SO_4), the soln was filtered and concentrated (only the *endo*-cycloadduct was observed by ^1H NMR spectroscopy analysis). The residue was purified by chromatography (silica gel, CH_2Cl_2/Et_2O) to afford the product. The enantiomeric excess was determined by chiral stationary-phase HPLC analysis (Daicel Chiralpak AD-H or Chiralcel OJ-H, hexane/iPrOH 80:20 or 95:5, 0.75 mL • min^{-1}).

2.2.4.14.2 [3+2] Cycloaddition

In 2008, Takemoto and co-workers reported a formal [3+2] cycloaddition of azomethine ylides with nitroalkenes.[264] The reaction consists of two steps which are both catalyzed by the thiourea catalyst: a Michael addition and a subsequent aza-Henry reaction.

Fang and Jacobsen reported a method for the enantioselective [3+2] cycloaddition of imines with allenes in 2008.[265] The reaction is catalyzed by a phosphino thiourea derivative **197**. This bifunctional catalyst has the potential to activate the allene by binding to the phosphine moiety, and the phosphorylimine **196** by hydrogen bonding with the thiourea group.[265] Water and triethylamine as additives increase the reaction rates. The reaction proceeds in moderate to high yields of 68–90%, and with excellent enantiomeric excesses of 94–98%. The 10 best results are shown in Scheme 66.

Scheme 66 Enantioselective [3+2] Cyclization of *N*-Phosphorylimines with an Allene Catalyzed by a Phosphino Thiourea Derivative[265]



R^1	**197** (mol%)	Yield (%)	ee (%)	Ref
Ph	10	84	98	[265]
4-$MeOC_6H_4$	20	80	97	[265]
2-thienyl	20	77	97	[265]
4-PhC_6H_4	10	81	96	[265]
2-BrC_6H_4	10	90	95	[265]
3-pyridyl	10	85	95	[265]
2-BrC_6H_4	2.5	77	95	[265]
4-FC_6H_4	10	72	95	[265]
3-$O_2NC_6H_4$	10	70	95	[265]
3,4,5-$(MeO)_3C_6H_2$	20	70	95	[265]

for references see p 407

Ethyl (*S*)-1-(Diphenylphosphoryl)-2-phenyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate (198, R^1 = Ph); Typical Procedure:[265]

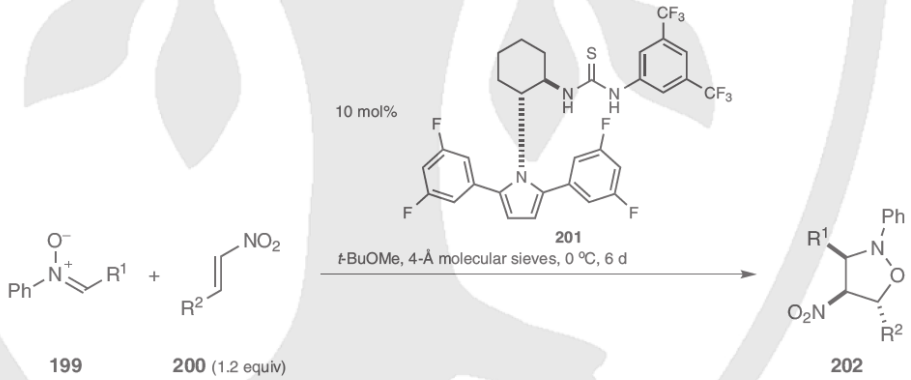
The imine **196** (R^1 = Ph; 0.0763 g, 0.25 mmol) and catalyst **197** (15 mg, 0.025 mmol, 10 mol%) were added to a 1-dram vial. After the vial had been sealed with a screw cap equipped with a Teflon septum, it was evacuated and flooded with N_2 (3 ×). Anhyd toluene (2.5 mL) and then H_2O (0.9 μL, 20 mol%) were added. After the mixture had been stirred vigorously at rt for 10 min, Et_3N (1.8 μL, 5 mol%) was added followed by immediate cooling to −30 °C (iPrOH bath). The mixture was stirred over a period of 15 min, and then ethyl buta-2,3-dienoate (35 μL, 0.3 mmol, 1.2 equiv) was added with a microsyringe. After stirring for 48 h at −30 °C, the resulting soln was rapidly purified by flash chromatography [silica gel (2.5 cm × 3 cm), EtOAc/hexanes 50:50 to 70:30 to 100:0]. The mixed fractions were further purified by preparative TLC (EtOAc/hexanes 75:25) to afford the product as a white foamy solid; yield: 0.0877 g (84%); 98% ee by chiral SFC analysis [Chiralpak AS-H, 5% MeOH/CO_2, 30 °C, 3 mL·min^{-1}, λ = 210 nm, t_R(minor) = 7.27 min, t_R(major) = 8.19 min)].

2.2.4.14.3 1,3-Dipolar Cycloaddition

In 2008, Zhang and co-workers reported the 1,3-dipolar cycloaddition of azomethine ylides with nitroalkenes catalyzed by a cinchona alkaloid thiourea derivative.[266] Moderate enantiomeric excesses of 46–65%, diastereomeric ratios from 85:15 to >99:1, and yields in the range 49–77% are obtained.

Later in 2008, the Chen group published a method for the enantioselective 1,3-dipolar cycloaddition of nitrones **199** to nitroalkenes **200**.[267] The reaction is catalyzed by a cyclohexane-1,2-diamine-derived thiourea **201**. High enantiomeric excesses of 80–88% are obtained, except for in a single reported case (40% ee). The yields are in the range 43–93%. Seven of the best results are shown in Scheme 67.

Scheme 67 Enantioselective 1,3-Dipolar Cycloaddition of Nitrones to Nitroalkenes Catalyzed by a Cyclohexane-1,2-diamine-Derived Thiourea[267]



R^1	R^2	Yield (%)	ee (%)	Ref
4-$MeOC_6H_4$	Et	78	88	[267]
Ph	Et	84	87	[267]
4-ClC_6H_4	Et	54	87	[267]
4-Tol	Et	71	86	[267]
Ph	Pr	93	84	[267]
2-ClC_6H_4	Et	78	84	[267]
Ph	$(CH_2)_5Me$	72	84	[267]

4-Nitro-2-phenylisoxazolidines 202**; General Procedure:**[267]
A mixture of the nitrone **199** (0.1 mmol), catalyst **201** (6.6 mg, 0.01 mmol, 10 mol%), and 4-Å molecular sieves (50 mg) was stirred in redistilled *t*-BuOMe (0.4 mL) at 0 °C. The nitroalkene **200** (0.12 mmol, 1.2 equiv) in *t*-BuOMe (0.1 mL) was added at the same temperature. After 6 d, the product was isolated by flash chromatography (silica gel, EtOAc/petroleum ether 1:15). The enantiomeric excess was determined by chiral HPLC analysis (Chiralpak AD or IC or Chiralcel OD or OJ, hexane/iPrOH, 1.0 mL·min^{-1}, $\lambda = 254$ nm).

2.2.4.15 Pictet–Spengler Reaction

In the presence of a protic or Lewis acid, the reaction of β-arylethylamines with carbonyl compounds leads to ring closure and thus to the formation of tetrahydroisoquinoline derivatives. This reaction was published by A. Pictet and T. Spengler in 1911 and is thus called the Pictet–Spengler reaction.[133]

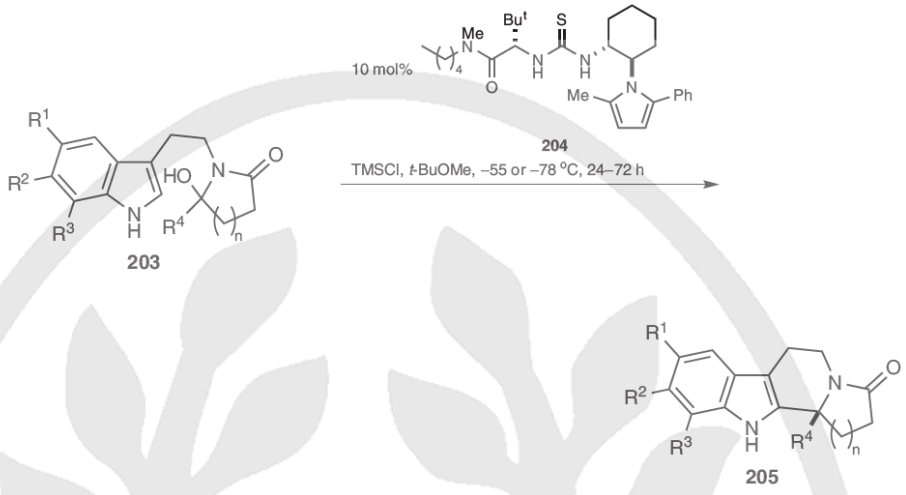
Pictet–Spengler reactions catalyzed by thiourea derivatives were successfully applied in the total syntheses of (+)-harmicine by cyclization of hydroxy lactams[268] (see below) and (+)-yohimbine, also developed by Jacobsen and co-workers.[269]

2.2.4.15.1 Cyclization of Hydroxy Lactams

In 2007, Jacobsen and co-workers reported the Pictet–Spengler-type cyclization of hydroxy lactams **203** catalyzed by a pyrrolyl thiourea derivative **204**.[268] An S_N1-type cyclization is proposed based on experiments and computational studies.[268] For n = 1, high to excellent enantiomeric excesses of 85–99% and yields of 51–94% are obtained (Scheme 68). For n = 2, products **205** are synthesized in 52–65% yield with 81–96% ee.

for references see p 407

Scheme 68 Enantioselective Pictet–Spengler-Type Cyclization of Hydroxy Lactams Catalyzed by a Pyrrolyl Thiourea Derivative[268]



R^1	R^2	R^3	R^4	n	Temp (°C)	Time (h)	Yield (%)	ee (%)	Ref
F	H	H	H	1	–55	48	89	99	[268]
H	H	H	Bu	1	–78	24	74	98	[268]
H	F	H	H	1	–55	48	94	97	[268]
H	H	H	H	1	–55	48	90	97	[268]
H	H	H	Me	1	–78	24	92	96	[268]
Br	H	H	H	1	–55	48	88	96	[268]
OMe	H	H	H	1	–55	48	86	95	[268]
H	H	Me	H	1	–55	48	91	93	[268]
OMe	H	H	Me	1	–78	24	84	91	[268]

1,2,5,6,11,11b-Hexahydroindolizino[8,7-*b*]indol-3-one (205, $R^1 = R^2 = R^3 = R^4 = H$); Typical Procedure for Cyclization of Hydroxy Lactams Prepared by Reduction of Imides:[268]
In an oven- or flame-dried 100-mL round-bottomed flask, a mixture of crude 5-hydroxy-1-[2-(1*H*-indol-3-yl)ethyl]pyrrolidin-2-one (**203**, $R^1 = R^2 = R^3 = R^4 = H$; 230 mg, 0.942 mmol), freshly distilled *t*-BuOMe (94.2 mL), and catalyst **204** (48 mg, 94.2 μmol, 10 mol%) was prepared. The flask was sealed with a rubber septum, and the mixture was stirred vigorously at rt for 1 min with a magnetic stirrer bar followed by cooling to −78 °C, whereupon the mixture was stirred vigorously for 3 min. Freshly distilled TMSCl (241 μL, 1.88 mmol, 2 equiv) was then added with a syringe, and the mixture was warmed to −55 °C. After rapid stirring at this temperature for 48 h, the reaction was quenched with precooled (−55 °C) Et_3N (650 μL, 4.71 mmol), and the mixture was poured quantitatively into sat. aq $NaHCO_3$ (100 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 75 mL), and the combined organic layers were dried (Na_2SO_4) and filtered. After concentration under reduced pressure, the crude product was purified by flash chromatography (silica gel, MeOH/CH_2Cl_2 2:98) to yield the product as an off-white solid; yield: 191 mg (90%); 97% ee by chiral SFC analysis [Chiralpak AS-H, 20% MeOH, 4.0 mL·min^{-1}, λ = 280 nm, t_R(minor) = 3.77 min, t_R(major) = 4.50 min].

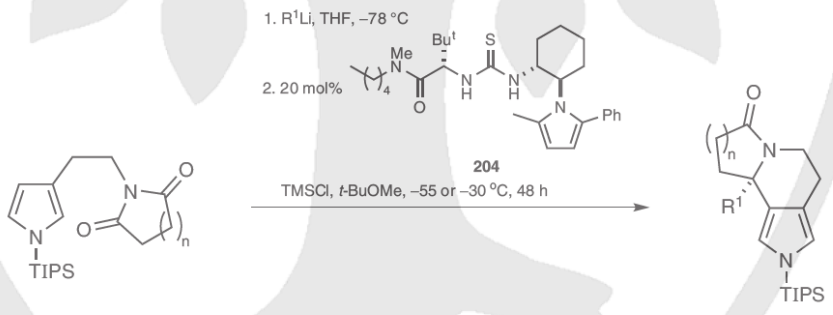
11b-Methyl-1,2,5,6,11,11b-hexahydroindolizino[8,7-*b*]indol-3-one (205, $R^1 = R^2 = R^3 = H$; $R^4 = Me$); Typical Procedure for Cyclization of Hydroxy Lactams Prepared by Alkylation of Imides:[268]

In an oven- or flame-dried 50-mL round-bottomed flask, a mixture of crude 5-hydroxy-1-[2-(1*H*-indol-3-yl)ethyl]-5-methylpyrrolidin-2-one (**203**, $R^1 = R^2 = R^3 = H$; $R^4 = Me$; 330 mg, 1.28 mmol), freshly distilled *t*-BuOMe (32 mL), and catalyst **204** (65 mg, 128 μmol, 10 mol%) was prepared. The flask was sealed with a rubber septum, and the mixture was stirred vigorously at rt for 1 min with a magnetic stirrer bar followed by cooling to −78 °C, whereupon the mixture was stirred vigorously for 3 min. Freshly distilled TMSCl (330 μL, 2.56 mmol, 2 equiv) was then added with a syringe. After rapid stirring at this temperature for 24 h (unless otherwise noted), the reaction was quenched with precooled (−78 °C) Et_3N (890 μL, 6.4 mmol), and the mixture was poured quantitatively into sat. aq $NaHCO_3$ (100 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 75 mL), and the combined organic layers were dried (Na_2SO_4) and filtered. After concentration under reduced pressure, the crude product was purified by flash chromatography (silica gel, MeOH/CH_2Cl_2 2:98) to yield the product as an off-white solid; yield: 283 mg (92%); 96% ee by chiral SFC analysis [Chiralpak AD-H, 20% MeOH, 4.0 mL·min^{-1}, λ = 230 nm, t_R(major) = 2.02 min, t_R(minor) = 3.30 min].

2.2.4.15.2 Cyclization of Pyrroles onto *N*-Acyliminium Ions

In 2008, the Jacobsen group developed a method for the Pictet–Spengler type cyclization of pyrroles **206** catalyzed by a chiral pyrrolyl thiourea derivative **204**.[270] C2- as well as C4-cyclizations can be accomplished. The C4-cyclizations generally proceed in 49–77% yield and with enantiomeric excesses of 92–97% (Scheme 69), although in one case the enantiomeric excess was 70% and a mixture of two regioisomers is formed in a ratio of 1.7:1 favoring the C4-product. The results for the C2 cyclization are not as good as for the C4 case: yields in the range 51–86% and enantiomeric excesses of 52–93% are obtained.

Scheme 69 Enantioselective C4 Cyclization of Pyrroles Catalyzed by a Chiral Pyrrolyl Thiourea Derivative[270]



n	R^1	Yield (%)	ee (%)	Ref
2	Bu	70	97	[270]
1	Bu	69	96	[270]
1	iBu	68	96	[270]
1	iPr	49	93	[270]
1	Me	77	92	[270]
1	Ph	63	92	[270]

for references see p 407

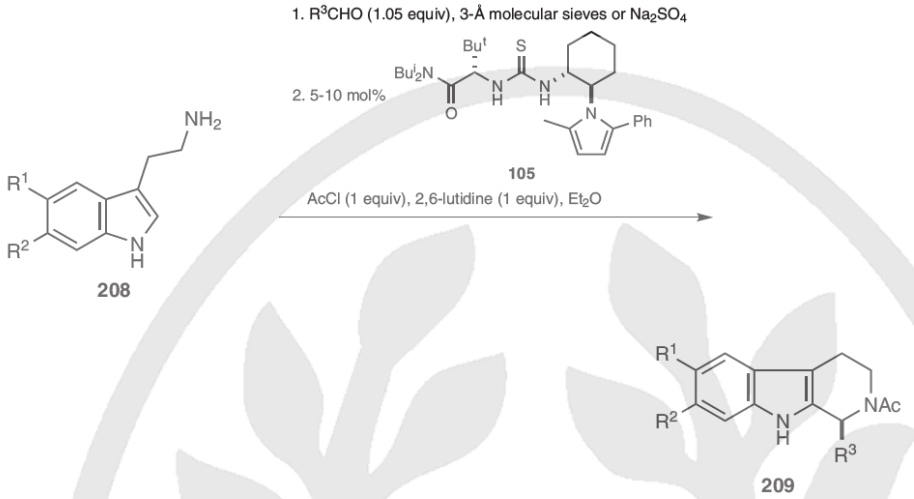
9a-Methyl-2-(triisopropylsilyl)-4,5,9,9a-tetrahydro-2*H*-pyrrolo[3,4-*g*]indolizin-7(8*H*)-one (207, n = 1); Typical Procedure:[270]

In a flame-dried 100-mL round-bottomed flask equipped with a magnetic stirrer bar, a mixture of 1-{2-[1-(triisopropylsilyl)-1*H*-pyrrol-3-yl]ethyl}pyrrolidine-2,5-dione (**206**, n = 1; 90.5 mg, 0.26 mmol) and anhyd THF (26 mL) was prepared. After the flask had been sealed with a rubber septum, the mixture was cooled to −78 °C (dry ice/acetone bath), and 1.6 M MeLi in THF (0.244 mL, 0.39 mmol, 1.5 equiv) was added in one portion with a syringe. After vigorous stirring for 2 h at −78 °C, the flask was removed from the cooling bath, and sat. aq $NaHCO_3$ (2.0 mL) was added dropwise under vigorous stirring for quenching. CH_2Cl_2 (30 mL) was added to this mixture, and after vigorous stirring at rt for 3 min, the mixture was poured into sat. aq $NaHCO_3$ (50 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (20 mL). The organic layers were combined, dried (Na_2SO_4), and filtered (a small amount of the organic phase was taken for ^1H NMR analysis; see below). Concentration of the organic layer under reduced pressure, and then under high vacuum for 5 min, yielded the crude hydroxy lactam (>95% pure; 95 mg, 0.26 mmol). This was immediately suspended in anhyd *t*-BuOMe (26 mL) in a 50-mL round-bottomed flask. Under stirring, catalyst **204** (26.6 mg, 0.052 mmol, 20 mol%) was added, and the mixture was cooled to −78 °C (dry ice/acetone bath). After the addition of anhyd TMSCl (0.166 mL, 1.3 mmol) with a syringe in one portion, the mixture was warmed to −55 °C, and stirred for 48 h at this temperature [^1H NMR analysis of a small amount of the hydroxy lactam was performed to guarantee that no racemic cyclization occurred; basified $CDCl_3$ (>2 weeks), DMSO-d_6, or acetone-d_6 was used to prevent acid-catalyzed cyclization]. The reaction was quenched with precooled (−55 °C) Et_3N (10 equiv), and the mixture was poured quantitatively into sat. aq $NaHCO_3$ (50 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic layers were dried (Na_2SO_4) and filtered. After concentration under reduced pressure, the crude product was purified by flash chromatography (silica gel, MeOH/CH_2Cl_2 1:99) to yield the product as a light yellow oil; yield: 69 mg (77%); 92% ee by chiral SFC analysis [Chiralcel OD-H, 5% MeOH/CO_2, 4.0 mL·min^{-1}, λ = 230 nm, t_R(major) = 3.88 min, t_R(minor) = 5.58 min].

2.2.4.15.3 Acyl-Pictet–Spengler Reaction

In 2004, Taylor and Jacobsen developed a method for the enantioselective acyl-Pictet–Spengler reaction catalyzed by tertiary amine-thiourea derivative **105**.[271] High enantiomeric excesses of 85–95% and yields in the range 65–81% are obtained (Scheme 70).

Scheme 70 Enantioselective Acyl-Pictet–Spengler Reaction Catalyzed by a Chiral Pyrrolyl Thiourea Derivative[271]



R^1	R^2	R^3	Conditions (Step 1)	**105** (mol%)	Temp (Step 2) (°C)	Yield[a] (%)	ee (%)	Ref
H	H	$(CH_2)_4Me$	Na_2SO_4, CH_2Cl_2/Et_2O	10	−78 to −60	65	95	[271]
OMe	H	$CHEt_2$	3-Å molecular sieves, CH_2Cl_2	5	−78 to −40	81	93	[271]
H	H	iBu	Na_2SO_4, CH_2Cl_2/Et_2O	10	−78 to −60	75	93	[271]
H	H	$CHEt_2$	3-Å molecular sieves, CH_2Cl_2	5	−78 to −30	65	93	[271]
H	H	$(CH_2)_2OTBDPS$	Na_2SO_4, CH_2Cl_2/Et_2O[b]	10	−78 to −60	77	90	[271]

[a] Yield of isolated products over two steps after chromatography (0.25-mmol scale).
[b] With slight modification.

(*S*)-2-Acetyl-1-(pentan-3-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (209, $R^1 = R^2 = H$; $R^3 = CHEt_2$); Typical Procedure Using Molecular Sieves and 5 mol% Catalyst:[271]

Spherical 3-Å molecular sieves (250 mg) were flame-dried under vacuum and cooled to 23 °C under N_2. Anhyd CH_2Cl_2 (1.25 mL) was added to the molecular sieves followed by tryptamine (**208**, $R^1 = R^2 = H$; 40 mg, 0.25 mmol). After the dropwise addition of 2-ethylbutanal (32 μL, 0.275 mmol, 1.05 equiv) with a syringe to this suspension, the mixture was allowed to stand for 7 h at 23 °C. Occasional swirling guaranteed mixing of the contents. A round-bottomed flask plugged by a rubber septum was flame-dried under an atmosphere of N_2, and the prepared soln mentioned above was transferred into this with a cannula, and thus filtered. The remaining desiccant was washed with anhyd CH_2Cl_2 (2 × 5 mL). The rinses were transferred into the flask with a cannula as well, and combined with the filtrate. After concentration under vacuum, the afforded imine, a pale brown oil, was dissolved in anhyd Et_2O (5.0 mL), and catalyst **105** (6.7 mg, 0.013 mmol, 5 mol%) was added. The soln was cooled to −78 °C (dry ice/acetone bath), and 2,6-lut (29 μL, 0.25 mmol, 1.0 equiv) followed by AcCl (18 μL, 0.25 mmol, 1.0 equiv) were added dropwise with a syringe. The mixture was stirred at −78 °C for 5 min, and after warming to −30 °C stirred for an additional 22 h, after which the resulting heterogeneous mixture was allowed to warm to 23 °C. After concentration under vacuum, the residue was purified by column chromatography (silica gel, EtOAc/CH_2Cl_2 20:80) to afford the white, solid product; yield: 46 mg (65%); 93% ee by chiral HPLC analysis [(*S*,*S*)-Whelk-O 1 (Pirkle), EtOH/hexanes 10:90, 1.2 mL·min^{-1}, λ = 220 nm, t_R(minor) = 9.9 min, t_R(major) = 12.1 min].

for references see p 407

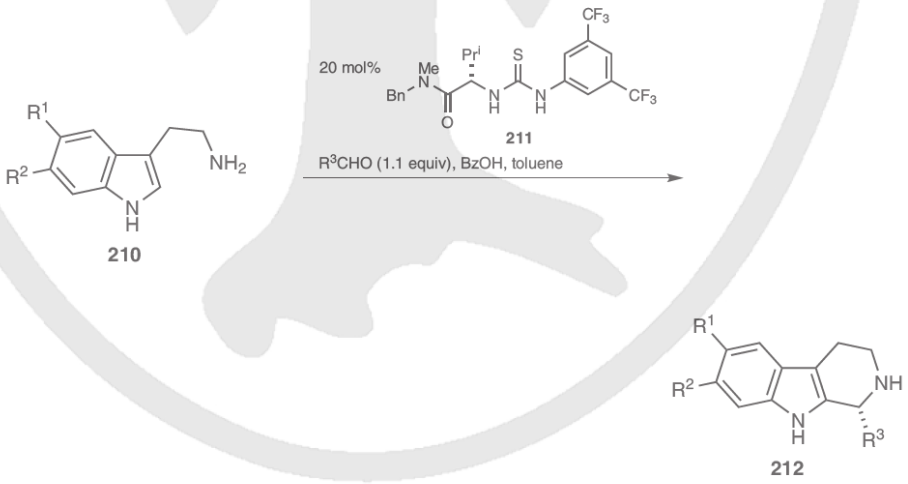
(*S*)-2-Acetyl-1-pentyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole [209, $R^1 = R^2 = H$; $R^3 = (CH_2)_4Me$]; Typical Procedure Using Sodium Sulfate and 10 mol% Catalyst:[271]

In a flame-dried round-bottomed flask plugged with a rubber septum, a soln of tryptamine (**208**, $R^1 = R^2 = H$; 40 mg, 0.25 mmol) in anhyd CH_2Cl_2/anhyd Et_2O (3:1 v/v; 12.5 mL) was prepared under a N_2 atmosphere. After the dropwise addition of hexanal (32 μL, 0.275 mmol, 1.05 equiv) with a syringe at 23 °C, the mixture was stirred at this temperature for 90 min. Na_2SO_4 (500 mg) was added and the mixture was stirred for additional 30 min. A round-bottomed flask plugged by a rubber septum was flame-dried under a N_2 atmosphere, and the prepared soln mentioned above was transferred into this with a cannula and thus filtered. The remaining desiccant was washed with anhyd CH_2Cl_2 (2 × 5 mL). The rinses were transferred into the flask with a cannula as well, and combined with the filtrate. After concentration under vacuum, the afforded imine, a pale brown oil, was immediately dissolved in anhyd Et_2O (5.0 mL), and catalyst **105** (13.5 mg, 0.025 mmol, 10 mol%) was added. The soln was cooled to −78 °C (dry ice/acetone bath), and 2,6-lut (29 μL, 0.25 mmol, 1.0 equiv) followed by AcCl (18 μL, 0.25 mmol, 1.0 equiv) were added dropwise with a syringe. The mixture was stirred at −78 °C for 5 min, and after warming to −60 °C stirred for an additional 23 h, after which the resulting heterogeneous mixture was allowed to warm to 23 °C. After concentration under vacuum, the residue was purified by chromatography (silica gel, EtOAc/hexanes 1:2) affording the product as a white solid contaminated with 2% enamide byproduct; yield: 47 mg (65%); 95% ee by chiral HPLC analysis [Pirkle L-leucine, EtOAc/hexanes 10:90, 1.2 mL·min^{-1}, t_R(minor) = 10.4 min, t_R(major) = 12.3 min].

2.2.4.15.4 Protio-Pictet–Spengler Reaction

In 2009, the Jacobsen group developed an enantioselective protio-Pictet–Spengler reaction catalyzed in a cooperative manner by thiourea derivative **211** and benzoic acid.[272] It was proposed that thiourea derivative **211** coordinates the carboxylic acid. Its proton is transferred to the tryptamine and is thus activating this toward cyclization, while the thiourea stabilizes the counterion by anion binding.[272] High to excellent enantiomeric excesses of 85–99%, and yields from a modest 39 to a very good 94%, are obtained (Scheme 71).

Scheme 71 Enantioselective Protio-Pictet–Spengler Reaction[272]



R^1	R^2	R^3	BzOH (mol%)	Time (h)	Yield (%)	ee[a] (%)	Ref
OMe	H	2-BrC_6H_4	40	87	82[b]	99	[272]
H	OMe	2-BrC_6H_4	20	11	74	95	[272]
H	OMe	iPr	0	88	90[c]	94	[272]
H	OMe	3-BrC_6H_4	20	19	87	94	[272]
H	OMe	4-BrC_6H_4	20	74	79	94	[272]
H	OMe	4-ClC_6H_4	20	66	78	94	[272]
H	OMe	4-FC_6H_4	20	78	81	92	[272]

[a] Determined by chiral SFC analysis of the *N*-*tert*-butoxycarbonyl derivative.
[b] Reaction performed at 35 °C.
[c] Modified procedure.

(*R*)-1-(4-Chlorophenyl)-7-methoxy-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (212, R^1 = H; R^2 = OMe; R^3 = 4-ClC_6H_4); Typical Procedure:[272]

A homogeneous soln of 4-chlorobenzaldehyde (1.00 g, 7.14 mmol) in CH_2Cl_2 (10 mL; dried by passing through activated alumina) was prepared in a separatory funnel and washed with 4 M aq NaOH (3 × 10 mL). The organic layer was dried (Na_2SO_4), filtered, concentrated, and put under high vacuum (<133 Pa) for 10 min to afford a white, semicrystalline solid. The so-prepared 4-chlorobenzaldehyde (77 mg, 0.55 mmol, 1.1 equiv) was placed immediately in a flame-dried 50-mL round-bottomed flask equipped with a magnetic stirrer bar together with 6-methoxytryptamine (**210**, R^1 = H; R^2 = OMe; 95 mg, 0.50 mmol) and catalyst **211** (49 mg, 0.1 mmol, 20 mol%). The mixture was put under high vacuum (<133 Pa) for 5 min; the flask was purged with N_2 and capped with a rubber septum. Toluene (10 mL; dried by passing through activated alumina) and benzoic acid (12 mg, 0.1 mmol, 20 mol%) were added and the cloudy white suspension was stirred for 66 h at rt. The heterogeneous mixture was quenched by addition of sat. aq $NaHCO_3$ (10 mL) followed by extraction with EtOAc (4 × 5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The crude product was purified by chromatography [silica gel (short, wide column: 30 cm × 20 cm), MeOH/CH_2Cl_2 0:100 to 5:95] to afford the product as a pale yellow solid; yield: 120 mg (78%).

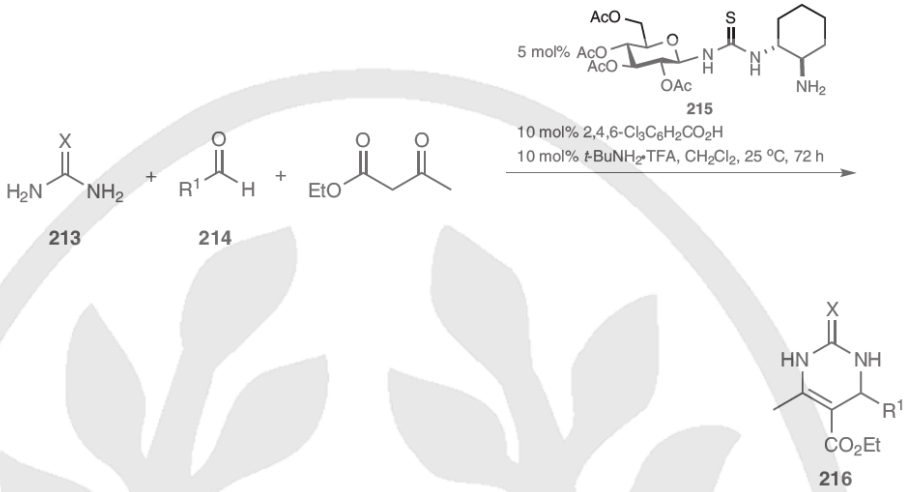
2.2.4.16 Biginelli Reaction

2.2.4.16.1 Biginelli Reaction of (Thio)ureas with Benzaldehydes and Ethyl Acetoacetate

3,4-Dihydropyrimidin-2(1*H*)-ones (DHPMs) are important targets because of their broad applicability in medicinal compounds.[273] In 2009, Chen, Miao and co-workers developed a protocol for a highly enantioselective synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones with urea (**213**, R^1 = O) or thiourea (**213**, R^1 = S), a benzaldehyde derivative **214**, and ethyl acetoacetate utilizing a bifunctional primary amine thiourea derivative catalyst **215**.[273] The products are obtained in good yields and with moderate to good enantioselectivities; the best results are depicted in Scheme 72. Butanal shows low enantioselectivity (ca. 15% ee).

for references see p 407

Scheme 72 Synthesis of Dihydropyrimidines through Enantioselective Biginelli Reaction Utilizing a Primary Amine Thiourea Derivative Catalyst[273]



R^1	X	Yield (%)	ee[a] (%)	Ref
4-ClC_6H_4	O	72	>99	[273]
3-Tol	O	78	>99	[273]
2-furyl	O	89	95[b]	[273]
Ph	O	93	94	[273]
4-FC_6H_4	O	85	93	[273]
Ph	S	91	93	[273]
4-Tol	O	83	89	[273]
3-FC_6H_4	S	86	87	[273]
3-FC_6H_4	O	88	80	[273]
4-BrC_6H_4	O	77	74	[273]

[a] Absolute configuration was *S* unless otherwise stated.
[b] Absolute configuration was *R*.

Ethyl 6-Methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates 216; **General Procedure:**[273]

CAUTION: *2-Furaldehyde is classified as toxic by inhalation and if swallowed, harmful in contact with skin and irritating to eyes, respiratory system and skin. 2-Furaldehyde shows limited evidence of a carcinogenic effect.*

CAUTION: *Thiourea is harmful if swallowed and shows limited evidence of a carcinogenic effect and possible risk of harm to the unborn child. Thiourea is toxic to aquatic organisms and may cause long-term adverse effects in the aquatic environment.*

A reaction vessel was charged with the aldehyde **214** (0.75 mmol), urea/thiourea **213** (0.05 mmol), 2,4,6-trichlorobenzoic acid (0.0112 g, 0.05 mmol), and *t*-$BuNH_2$•TFA (0.009 g, 0.05 mmol) in anhyd CH_2Cl_2 (1 mL), and the mixture was stirred at 25 °C for 1 h. Sequentially, catalyst **215** (0.013 g, 0.025 mmol) and ethyl acetoacetate (0.195 g, 1.5 mmol) were added. After the mixture had been stirred at rt for 3 d, the crude product precipitated. The product was collected by filtration under suction and washed with precooled EtOAc (2 ×). This isolated product was a white solid. The enantiomeric excess was determined by HPLC

analysis (Daicel Chiralcel OD-H or Chiralpak AS-H or AD-H, hexane/iPrOH) and by optical rotation.

2.2.4.17 Petasis Reaction

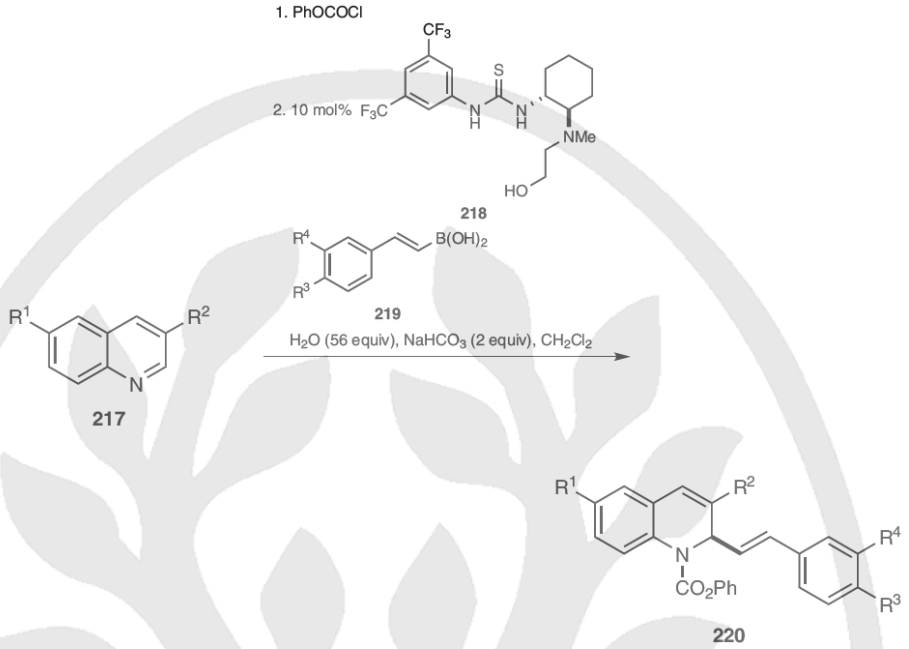
2.2.4.17.1 Petasis-Type 2-Vinylation of Quinolines

In 2007, Takemoto and co-workers developed a Petasis-type reaction protocol to synthesize dihydroquinolines **220** from quinolines **217** and vinylboronic acids **219** through thiourea catalysis (Scheme 73).[274] The asymmetric synthesis of quinolines is a contemporary challenge, because the resonance stability of heteroaromatic compounds complicates the asymmetric addition. Shibasaki developed the first enantioselective additions to quinolines using Lewis acid and Lewis base catalysis.[275,276] Alexakis and co-workers engineered an organolithium addition to quinolines as well as to isoquinolines,[277–279] while Jacobsen and co-workers succeeded in the addition of ketene silyl acetals to isoquinolines.[164]

In the reaction illustrated in Scheme 73, nucleophilic attack of the quinoline on phenyl chloroformate presumably activates the substrate for nucleophilic attack of the thiourea-activated boronic acid **219**; the activation of the latter occurs through the attack of the terminal hydroxy function in catalyst **218** onto the boronic acid moiety.[274] The addition of aqueous sodium hydrogen carbonate regenerates the catalyst and removes the boronic acid. The reaction proceeds smoothly when the quinoline bears a methyl group in the 3-position. More-electron-rich boronic acids are more reactive, whereas with a trifluoromethyl group the reaction is sluggish, but gives high stereoinduction.

for references see p 407

Scheme 73 Petasis-Type Reaction of Quinolines with Vinylboronic Acids in the Presence of a Hydroxy Thiourea Catalyst[274]



R^1	R^2	R^3	R^4	Temp (°C)	Yield (%)	ee (%)	Ref
H	H	OMe	H	−78	70	97	[274]
H	Me	H	H	−78	70	96	[274]
CO_2t-Bu	H	H	H	−65	61	96	[274]
Br	H	H	H	−65	78	95	[274]
Me	H	H	H	−65	75	95	[274]
H	H	CF_3	H	−40	28	95	[274]
H	H	H	H	−65	65	94	[274]
Cl	H	H	H	−65	63	94	[274]
H	H	Me	H	−65	60	91	[274]
H	H	OMe	OMe	−78	60	89	[274]
H	H	OCH_2O		−78	59	82	[274]

2-(2-Arylvinyl)-1,2-dihydroquinolines 220; General Procedure:[274]

CAUTION: *Phenyl chloroformate is very toxic. It causes burns, is very toxic by inhalation, and is harmful if swallowed.*

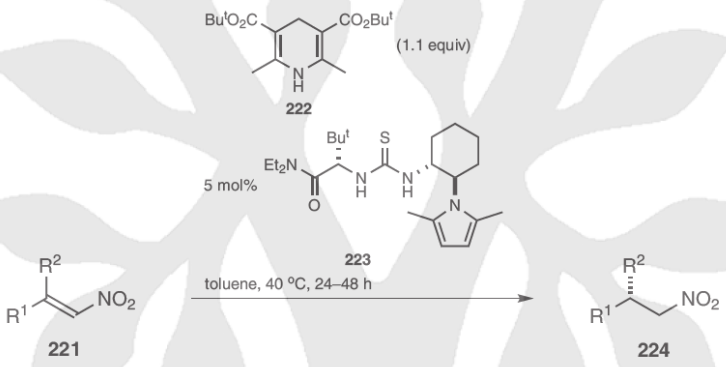
Phenyl chloroformate (0.051 mL, 0.4 mmol) and H_2O (0.2 mL) were added to a cooled soln of the quinoline derivative **217** (0.2 mmol), the vinylboronic acid **219** (0.4 mmol), thiourea derivative **218** (0.02 mmol), and $NaHCO_3$ (34 mg, 0.4 mmol) in CH_2Cl_2 (2 mL) under an argon atmosphere, and the mixture was stirred for 24 h at the appropriate temperature (Scheme 73). Then, the mixture was diluted with $CHCl_3$ and washed with 1 M NaOH, 1 M HCl, and H_2O. The organic phase was dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc 10:1). The enantiomeric excess was determined by HPLC analysis (Chiralcel OD-H or AD-H, hexane/iPrOH).

2.2.4.18 Transfer Hydrogenation

2.2.4.18.1 Transfer Hydrogenation of Nitroalkenes

In 2007, Schreiner and Zhang developed a protocol for the synthesis of nitroalkenes using an achiral thiourea catalyst.[41] In the same year, List and co-workers presented their results on a highly enantioselective organocatalytic transfer hydrogenation of β,β-disubstituted nitroalkenes **221** through a thiourea-derived catalyst.[280] They applied a Jacobsen-type catalyst **223**[271] and the Hantzsch ester **222** as reagent (Scheme 74). The reaction is performed at 40 °C for better solubility of the Hantzsch ester. Aliphatic, heteroaromatic, and various aromatic alkenes are tolerated and give good yields as well as enantioselectivities (>82% yield and >90% ee). The results for **221** (R^1 = Et; R^2 = Me) and **221** (R^1 = Me; R^2 = Et) (Scheme 74) show that the enantioselectivity depends on the geometry of the alkene: the *E*-enriched isomer **221** (R^1 = Et; R^2 = Me) gives more *S*-enantiomer, whereas the *Z*-enriched isomer **221** (R^1 = Me; R^2 = Et) gives more *R*-enantiomer. In 2010, Paradies and co-workers also demonstrated transfer hydrogenation of nitroalkenes, using a planar chiral thiourea derivative, but with low yields and enantioselectivities.[237]

Scheme 74 Transfer Hydrogenation of Nitroalkenes with a Thiourea-Derived Organocatalyst and a Hantzsch Ester[280]



R^1	R^2	Yield[a] (%)	ee (%)	Ref
Ph	Pr	>99	96	[280]
4-Tol	Me	99	94	[280]
4-ClC_6H_4	Me	99	94	[280]
Ph	Me	97	94	[280]
Ph	Et	94	94	[280]
2-naphthyl	Me	>99[b]	92	[280]
2-furyl	Me	84[b]	92	[280]
t-Bu	Me	82[b]	92	[280]
4-NC_6H_4	Me	99[b]	90	[280]

for references see p 407

R^1	R^2	Yield[a] (%)	ee (%)	Ref
3-ClC_6H_4	Me	97	90	[280]
Et	Me	97[b,c,d]	64	[280]
Me	Et	95[b,c,e]	12	[280]

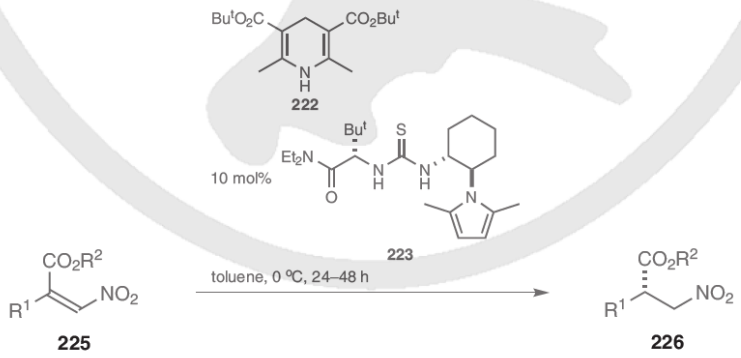
[a] Isomeric purity of nitroalkene was >98:2 unless stated otherwise.
[b] With 10 mol% of catalyst **223**.
[c] Yield and enantiopurity of product determined by GC (volatile products).
[d] Ratio (*E*/*Z*) in starting material 93:7.
[e] Ratio (*E*/*Z*) in starting material 14:86.

Nitroalkanes 224**; General Procedure:**[280]
In an oven-dried flask, the catalyst **223** (8.2 mg, 0.020 mmol, 0.05 equiv) and Hantzsch ester **222** (132.6 mg, 0.429 mmol, 1.1 equiv) were added to a soln of β,β-disubstituted nitroalkene **221** (0.390 mmol) in anhyd toluene (0.3 mL, 1.3 M). After stirring of the mixture under an argon atmosphere at 40 °C for 48 h, the solvent was removed under reduced pressure. The residue was purified by flash column chromatography [silica gel (Merck 60, 0.040–0.063 mm), pentane/Et_2O]. The enantiomeric excess was determined by chiral GC [Ivadex 1/PS086 or G-TA or BGB 176/SE], polarimetry, or chiral HPLC (Chiralcel AS-H, heptane/iPrOH 90:10).

2.2.4.18.2 Transfer Hydrogenation of β-Nitroacrylates

List and co-workers developed, in 2008, an alternative protocol to synthesize β-nitro esters **226** as precursors for β^2-amino acids through hydrogenation of β-nitroacrylates **225** with Hantzsch esters (e.g., **222**) and a chiral thiourea catalyst **223** (Scheme 75).[280,281] Gellman and co-workers obtained β-amino aldehydes via Mannich aldehydes, which also can be converted into β^2-amino acids.[282,283] Direct palladium/carbon-catalyzed hydrogenation of the β-nitro esters gives the free β^2-amino acids.[281] The yield is high in all cases, but the enantioselectivity increases slightly with size and bulkiness of the ester moiety.[281] Other aryl and hetaryl groups can also be utilized and give good enantioselectivity (>89% ee). List and co-workers also tested the influence of *E*- and *Z*-nitroalkenes, and observed that the *E*-isomer of **225** (R^1 = Me; R^2 = Et) gives the opposite enantiomer as product. Mixtures of *E*- and *Z*-isomers of nitroalkenes **225** give racemic β-nitro esters.

Scheme 75 Transfer Hydrogenation of β-Nitroacrylates Using a Chiral Thiourea Catalyst[281]



R^1	R^2	Yield[a] (%)	ee (%)	Ref
$(CH_2)_4Me$	Et	91[b]	95	[281]
Ph	iPr	91	95	[281]
Ph	*t*-Bu	92	94	[281]
Me	Et	97[b]	94	[281]
Ph	Bn	91	94	[281]
4-Tol	Et	92	93	[281]
2-thienyl	Et	81	93	[281]
iPr	Et	92	93	[281]
Ph	Et	95	92	[281]
$4\text{-}FC_6H_4$	*t*-Bu	85	92	[281]

[a] Isomeric purity >98:2 in the starting nitroacrylate; the *Z*-alkene was used unless otherwise stated.
[b] *E*-Alkene was used.

β-Nitro Esters 226; General Procedure:[281]

CAUTION: *Di-tert-butyl azodicarboxylate has specific target organ toxicity properties for single exposure. It is irritating to the eyes, respiratory system, and skin.*

Hantzsch ester **222** (92.8 mg, 0.3 mmol, 1.0 equiv) and the catalyst **223** (12.6 mg, 0.03 mmol, 0.1 equiv) were added to a soln of the β-nitroacrylic ester **225** (0.3 mmol) in toluene (0.3 mL, 1.0 M) in oven-dried glassware under an argon atmosphere. The mixture was stirred for 24–48 h at 0 °C. After removal of the solvent under reduced pressure, the residue was purified by flash column chromatography [silica gel (Merck 60, 0.040–0.063 mm), pentane/Et_2O].

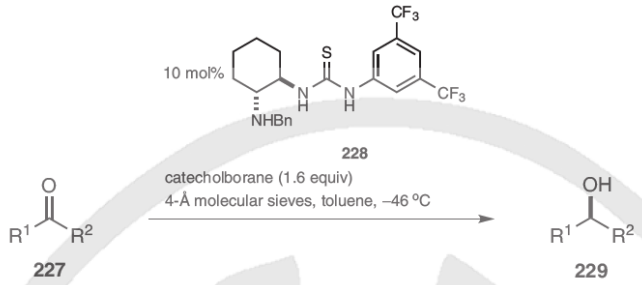
If the reaction was not complete, the Hantzsch ester was destroyed at 0 °C with di-*tert*-butyl azodicarboxylate (DBAD). In this way the non-enantioselective background reactions during solvent evaporation were avoided. The enantiomeric excess was determined by chiral HPLC analysis (Chiralcel AS-H, heptane/iPrOH 80:20) or chiral GC (G-TA, BGB-176/BGB-15, IVADEX 1/PS086, or LIPODEX G) and polarimetry.

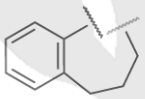
2.2.4.19 Reduction of Ketones

Procuranti and Connon published a method for the chemoselective reduction of 1,2-diketones catalyzed by a bifunctional thiourea derivative bearing an organic hydride donor in 2007.[38] Later in the same year, Costero and co-workers showed biphenylylthioureas to be good organocatalysts for electrochemical reductions of aromatic carboxylates.[39] In 2010, the Falck group developed a method for the enantioselective reduction of various ketones **227** catalyzed by cyclohexane-1,2-diamine-derived thiourea **228**.[284] It was proposed that the thiourea moiety activates the carbonyl group by double hydrogen bonding while the secondary amine functionality activates the borane by forming a boronate–amine complex.[284] For aryl ketones, moderate to high yields (66–95%) and excellent enantiomeric excesses (95–99%) are achieved (Scheme 76). The results for alkenyl and alkyl ketones are not as good: reduction affords the corresponding alcohols in 60–92% yield with 47–97% ee.

for references see p 407

Scheme 76 Enantioselective Reduction of Ketones[284]



R^1	R^2	Time (h)	Yield (%)	ee (%)	Ref
4-BrC_6H_4	Me	22	95	99	[284]
4-ClC_6H_4	Me	22	94	99	[284]
Ph	Et	24	86	99	[284]
Ph	Pr	24	86	99	[284]
		24	86	99	[284]
4-FC_6H_4	Me	20	84	99	[284]
Ph	Me	24	88	98	[284]

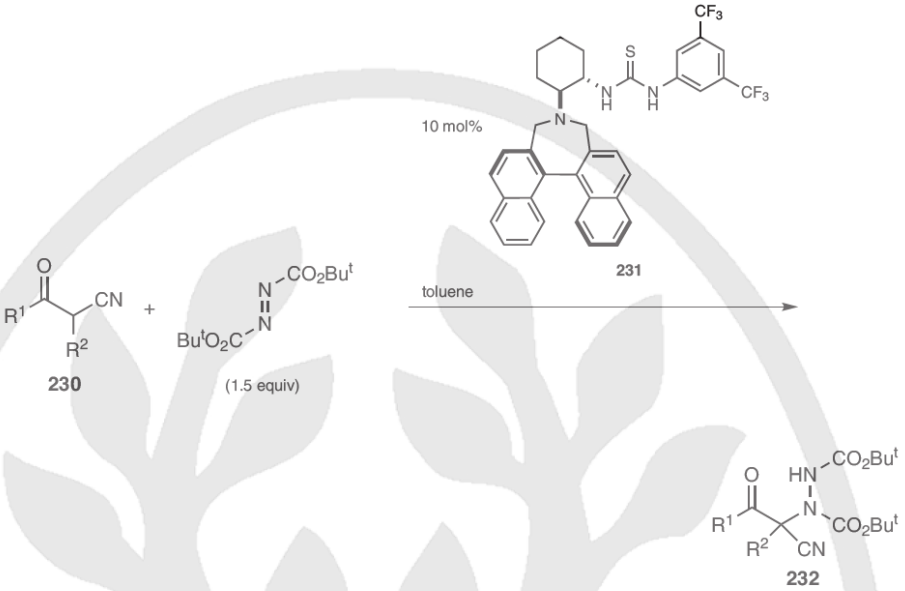
(*S*)-1-Phenylethanol (229, R^1 = Ph; R^2 = Me); Typical Procedure:[284]
Under an argon atmosphere, a mixture of acetophenone (**227**, R^1 = Ph; R^2 = Me; 30 mg, 0.25 mmol), catalyst **228** (12 mg, 0.025 mmol, 10 mol%), and freshly activated 4-Å molecular sieves (250 mg) in anhyd toluene (0.7 mL) was cooled to −78 °C. A 1.0 M soln of catecholborane in toluene (0.4 mL, 0.4 mmol, 1.6 equiv) was added slowly and the mixture was placed in a bath at a temperature of −46 °C. The soln was stirred for 24 h at this temperature followed by addition of first MeOH (1 mL) and then 3 M NaOH soln (1 mL). The mixture was warmed to rt gradually, stirred for 1 h, and extracted with Et_2O (3 × 20 mL). The extracts were combined, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexanes/EtOAc 6:1) to yield (*S*)-1-phenylethanol as a colorless oil; yield: 27 mg (88%); 98% ee by chiral HPLC [Chiralcel OD, iPrOH/hexane 2:98, 1 mL·min^{-1}, λ = 254 nm, t_R(minor) = 15.0 min, t_R(major) = 19.2 min].

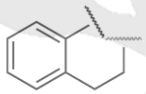
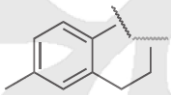
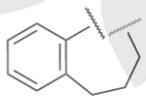
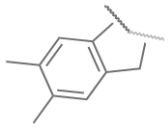
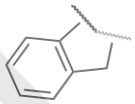
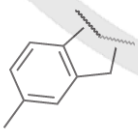
2.2.4.20 α-Amination

2.2.4.20.1 α-Amination of α-Cyano Ketones

Kim and co-workers published in 2008 a method for the enantioselective α-amination of α-cyano ketones **230** with azodicarboxylates catalyzed by a tertiary amine thiourea derivative **231**.[285] High to excellent enantiomeric excesses of 87–99% and mostly high yields of 77–95% (45% in one case) are obtained. The seven best results can be found in Scheme 77.

Scheme 77 Enantioselective α-Amination of α-Cyano Ketones with Di-*tert*-butyl Azodicarboxylate Catalyzed by a Tertiary Amine Thiourea Derivative[285]



R^1	R^2	Temp (°C)	Time	Yield (%)	ee (%)	Ref
		−35[a]	21 h	94	99	[285]
		−78	48 h	94	99	[285]
Ph	4-$MeOC_6H_4$	−30	36 h	93	99	[285]
		−30	8 d	77	99	[285]
		−78	24 h	85	98	[285]
		−20[a]	0.5 h	95	97	[285]
		−78	20 h	92	97	[285]

[a] 1 mol% catalyst.

for references see p 407

Di-*tert*-butyl 1-(2-Cyano-1-oxo-2,3-dihydro-1*H*-inden-2-yl)hydrazine-1,2-dicarboxylate (232, R^2,R^1 = 2-$CH_2C_6H_4$); Typical Procedure:[285]

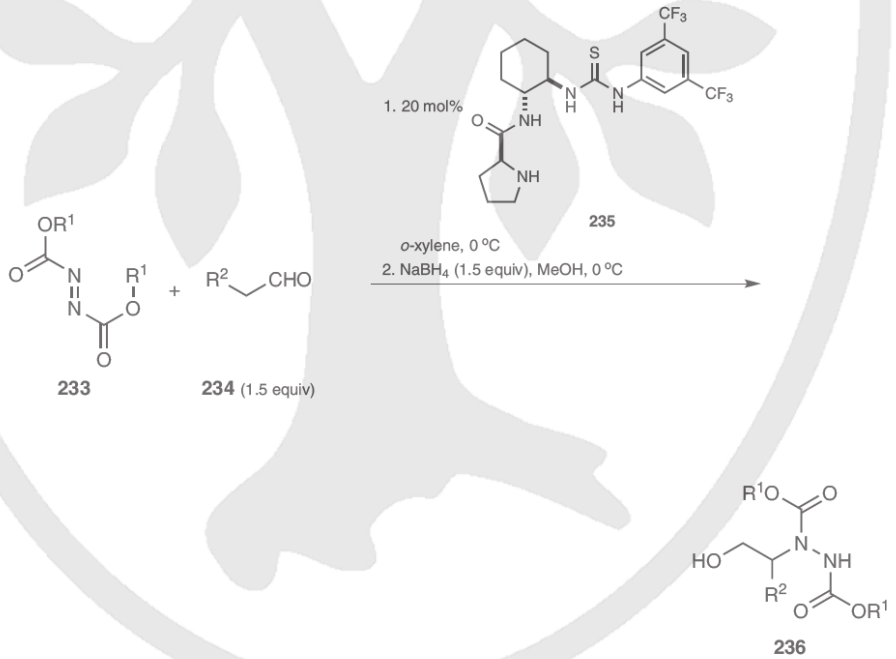
CAUTION: *Di-*tert*-butyl azodicarboxylate has specific target organ toxicity properties for single exposure. It is irritating to the eyes, respiratory system, and skin.*

A soln of 1-oxo-2,3-dihydro-1*H*-indene-2-carbonitrile (**230**, R^2,R^1 = 2-$CH_2C_6H_4$; 47.15 mg, 0.3 mmol) and catalyst **231** (1.99 mg, 0.003 mmol, 1 mol%) in toluene (0.3 mL) was prepared followed by the dropwise addition of a soln of di-*tert*-butyl azodicarboxylate (103.6 mg, 0.45 mmol, 1.5 equiv) in toluene (0.3 mL) under stirring at −20 °C. After stirring over a period of 30 min at this temperature, the mixture was concentrated, and then purified by flash chromatography (EtOAc/hexane 1:4) to yield the product; yield: 110.4 mg (95%); 97% ee by HPLC analysis [Chiralpak AD, hexane/iPrOH 4:1, λ = 254 nm, 1.0 mL·min^{-1}, t_R(minor) = 5.8 min, t_R(major) = 7.7 min].

2.2.4.20.2 α-Amination of Aldehydes

In 2010, Wang, Xu, and co-workers reported the enantioselective α-amination of aldehydes.[286] The amination reaction is catalyzed by a bifunctional catalyst **235** bearing both a proline amide and a thiourea moiety. It was proposed that this kind of catalyst activates the azodicarboxylate **233** by double hydrogen bonding to the thiourea moiety and the aldehyde **234** by enamine formation through the pyrrolidine group.[286] Yields in the range 65–97% and enantiomeric excesses of 77–99% are obtained. Some results are given in Scheme 78.

Scheme 78 Enantioselective α-Amination of Aldehydes with Azodicarboxylates Catalyzed by a Proline Amide Thiourea[286]



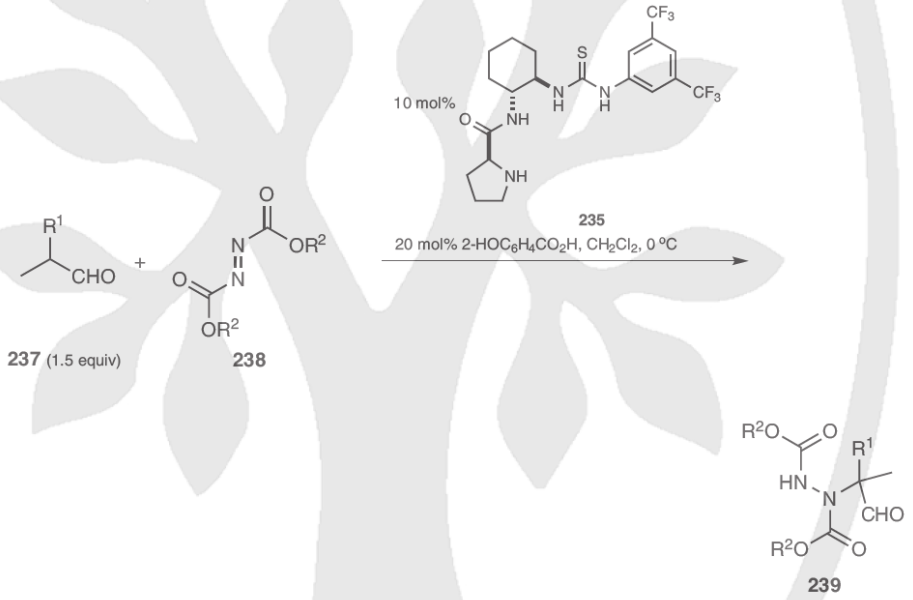
R^1	R^2	Time[a]	Yield (%)	ee (%)	Ref
Et	iPr	1 min	97	99	[286]
Et	iPr	9.5 h[b]	96	99	[286]
iPr	iPr	40 min	89	99	[286]

R^1	R^2	Time[a]	Yield (%)	ee (%)	Ref
Bn	iPr	10 min	70	98	[286]
Bn	Et	9 h	73	97	[286]
Et	Me	2 min	89	96	[286]
Bn	Me	9 h	82	91	[286]

[a] For the amination reaction.
[b] With 2.0 mL of *o*-xylene.

Later in 2010, the same group reported the enantioselective α-amination of branched aldehydes **237**.[287] As organocatalyst, the above-mentioned proline amide thiourea derivative **235** is also utilized. 2-Hydroxybenzoic acid (20 mol%) is employed as an additive to increase yields; under these conditions, yields of 30–99% and enantiomeric excesses of 80–97% are obtained (except for two cases, where no reaction was observed or the product was only obtained in traces). The seven results with the best enantiomeric excesses obtained are given in Scheme 79.

Scheme 79 Enantioselective α-Amination of Branched Aldehydes with Azodicarboxylates Catalyzed by a Proline Amide Thiourea[287]



R^1	R^2	Time (h)	Yield (%)	ee (%)	Ref
4-BrC_6H_4	iPr	32	92	97	[287]
Ph	iPr	32	87	97	[287]
2-ClC_6H_4	iPr	56	30	97	[287]
Ph	Et	23	96	96	[287]
4-FC_6H_4	iPr	32	94	96	[287]
4-Tol	iPr	20	85	96	[287]
2-naphthyl	iPr	15.5	90	95	[287]

for references see p 407

Dialkyl 1-(1-Alkyl-2-hydroxyethyl)hydrazine-1,2-dicarboxylates 236; **General Procedure:**[286]

CAUTION: *Diethyl azodicarboxylate is irritating to eyes, skin, and the respiratory system. It can explode when heated, and is harmful if inhaled.*

CAUTION: *Diisopropyl azodicarboxylate is irritating to eyes, skin, and the respiratory system. It is a suspected carcinogen. Health can be seriously damaged by prolonged exposure. It is harmful by swallowing and if inhaled.*

CAUTION: *Dibenzyl azodicarboxylate is irritating to eyes, skin, and the respiratory system.*

A stirred soln of catalyst **235** (0.04 mmol, 20 mol%) and the aldehyde **234** (0.3 mmol, 1.5 equiv) in anhyd *o*-xylene (0.8 mL) was prepared, and cooled to 0 °C followed by addition of the azodicarboxylate **233** (0.2 mmol) (dibenzyl azodicarboxylate synthesized from hydrazine had a purity of 90%). The mixture was stirred at this temperature for the time given in Scheme 78. After consumption of **233** (TLC monitoring; the color of **233** also vanishes), $NaBH_4$ (11 mg, 0.3 mmol) in anhyd MeOH (0.8 mL) was added. After 20 min, the reaction was quenched by addition of 2 M NH_4Cl soln (3 mL) followed by extraction with EtOAc (3 × 2.5 mL). The combined organic layers were dried ($MgSO_4$) and filtered. After concentration under vacuum, the residue was purified by column chromatography (silica gel, petroleum ether/EtOAc 10:1 to 4:1) to yield the product. The enantiomeric excess was determined by chiral HPLC (Chiralpak AD-H or AS-H, or Whelk-O 1; iPrOH/hexane 10:90 or 5:95) or GC analysis (CP-Chirasil Dex CB).

Dialkyl 1-(1-Alkyl-1-methyl-2-oxoethyl)hydrazine-1,2-dicarboxylates 239; **General Procedure:**[287]

CAUTION: *Diethyl azodicarboxylate is irritating to eyes, skin, and the respiratory system. It can explode when heated, and is harmful if inhaled.*

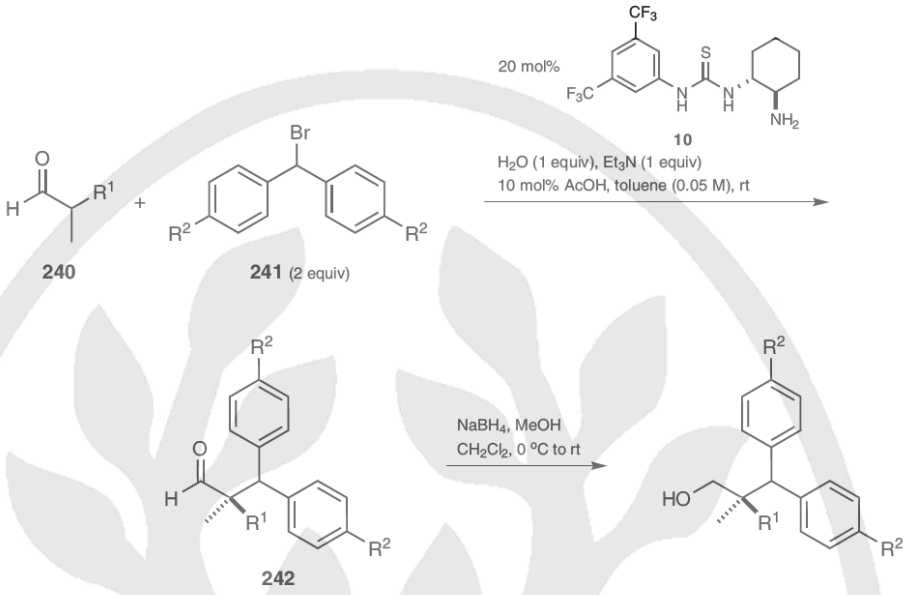
CAUTION: *Diisopropyl azodicarboxylate is irritating to eyes, skin, and the respiratory system. It is a suspected carcinogen. Health can be seriously damaged by prolonged exposure. It is harmful by swallowing and if inhaled.*

A soln of catalyst **235** (0.02 mmol, 10 mol%), 2-hydroxybenzoic acid (0.04 mmol, 20 mol%), and the aldehyde **237** (0.3 mmol, 1.5 equiv) in anhyd CH_2Cl_2 (1.0 mL) was prepared, and cooled to 0 °C followed by addition of the azodicarboxylate **238** (0.2 mmol) under stirring. The mixture was stirred at this temperature for the time given in Scheme 79. After consumption of **238** (TLC monitoring; the color of **238** also vanishes), the mixture was concentrated under reduced pressure, and the residue was purified by column chromatography (silica gel, petroleum ether/EtOAc 8:1) to yield the product. The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chiralpak AD-H, AS-H, AS, or OD-H, or Whelk-O 1; iPrOH/hexane).

2.2.4.21 α-Alkylation of Aldehydes

In 2010, the Jacobsen group developed an enantioselective α-alkylation of aldehydes **240** catalyzed by a bifunctional thiourea derivative **10**, bearing a cyclohexane-1,2-diamine moiety.[288] The electrophile could in principle be activated by halogen abstraction (S_N1-type) or coordination by the thiourea derivative (S_N2-type). Based on kinetic isotope effects, competition experiments, and catalyst structure–activity studies, an S_N1 mechanism was proposed based on anion binding to the catalyst.[288] High enantiomeric excesses (85–94%) as well as moderate yields in the range 52–70% are obtained (Scheme 80).

Scheme 80 Enantioselective α-Alkylation of Aldehydes Using a Cyclohexane-1,2-diamine Thiourea Derivative as Catalyst[288]



R^1	R^2	Time (d)	Yield[a] (%)	ee[b] (%)	Ref
4-BrC_6H_4	H	4	56	94	[288]
4-FC_6H_4	H	4	57	92	[288]
2-naphthyl	H	2	68	92	[288]
Ph	H	3	70	91	[288]
Ph	Cl	3	61	91	[288]
Ph	Br	3	61[c]	91	[288]
Ph	F	3	60[c]	90	[288]

[a] Yield of isolated alcohol after reduction with $NaBH_4$ unless otherwise indicated.
[b] Determined by HPLC analysis of alcohol following reduction with $NaBH_4$.
[c] Yield of isolated aldehyde **242**.

α-Alkylated Aldehydes 242**; General Procedure:**[288]

For preparation of the stock soln, the bromodiphenylmethane **241** (0.750 mmol, 2 equiv) was added to a flame-dried 10-mL Schlenk flask under a N_2 atmosphere. The flask was sealed with a rubber septum, and then evacuated and flooded with N_2 (4×). After addition of the aldehyde **240** (0.375 mmol), AcOH (2.1 μL, 0.0375 mmol, 10 mol%), anhyd Et_3N (52 μL, 0.375 mmol, 1 equiv), and anhyd toluene (7.5 mL), the septum was replaced by a glass plug under a positive N_2 pressure, and the mixture was degassed (three freeze–pump–thaw cycles). The glass plug was replaced by a rubber septum.

A flame-dried 10-mL Schlenk flask was charged with catalyst **10** (22.4 mg, 0.058 mmol, 20 mol%) under a N_2 atmosphere. The flask was sealed with a rubber septum, and then evacuated and flooded with N_2 (4×). N_2 was bubbled through deionized H_2O (ca. 1 mL) for 10 min in a GC vial; a portion of this H_2O (5.2 μL, 0.29 mmol, 1 equiv) was transferred to the Schlenk flask using a gastight microsyringe, followed by addition of the stock soln (6 mL, 0.29 mmol aldehyde, 0.58 mmol bromide). Care was taken on rinsing the H_2O from the flask wall. Under a positive N_2 flow, the rubber septum was replaced by a glass plug, the Schlenk flask was sealed, and the mixture was stirred at rt.

for references see p 407

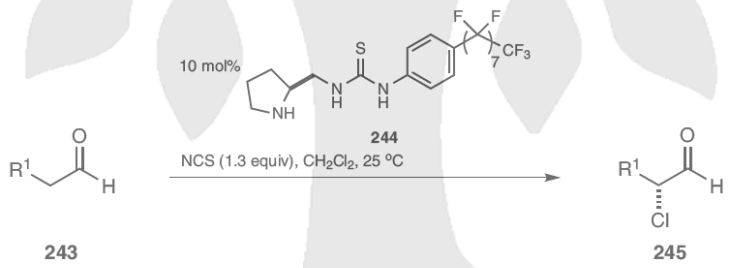
Workup procedure for isolation of the aldehyde product: After addition of 1 M aq HCl (3 mL) to the mixture, the resultant mixture was stirred for 15 min followed by extraction with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried (Na_2SO_4). After concentration under reduced pressure, the residue was purified by flash chromatography (silica gel) to yield the aldehyde product.

Workup procedure for isolation of the alcohol product: After addition of 1 M aq HCl (3 mL), the mixture was stirred for 15 min followed by extraction with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried (Na_2SO_4). After concentration under reduced pressure, MeOH (ca. 10 mL) and CH_2Cl_2 (ca. 5 mL) were added to the residue followed by cooling to 0 °C. After addition of $NaBH_4$ (113 mg, 3.0 mmol), the mixture was stirred for 15 min at 0 °C. Then, the mixture was allowed to warm to rt followed by stirring for an additional 30 min. After addition of H_2O (ca. 10 mL), the mixture was again stirred for 30 min followed by extraction with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried (Na_2SO_4). After concentration under reduced pressure, the residue was purified by flash chromatography (silica gel) to afford the alcohol product. The enantiomeric excess was determined by chiral HPLC analysis [OD-H or (*S*,*S*)-Whelk, iPrOH/hexanes 2:98, 1.0 mL·min^{-1}].

2.2.4.22 α-Chlorination of Aldehydes

In 2010, Cai and Zhang showed (*S*)-pyrrolidine thiourea **244** to be an efficient catalyst for the α-chlorination of aldehydes **243**.[289] It was proposed that an enamine is built from the aldehyde and the catalyst's pyrrolidine moiety while one carbonyl group of *N*-chlorosuccinimide is bound to the thiourea moiety.[289] The resulting 2-chloroaldehydes **245** are obtained in yields ranging from 91 to 99% with enantiomeric excesses from 85 to 95% (Scheme 81).

Scheme 81 Enantioselective α-Chlorination of Aldehydes with *N*-Chlorosuccinimide Catalyzed by a Chiral Pyrrolidine Thiourea Derivative at 25 °C[289]



243 245

R^1	Time (h)	Yield[a] (%)	ee[b] (%)	Ref
t-Bu	2	92	95	[289]
$(CH_2)_5Me$	3	96	92	[289]
$(CH_2)_8Me$	3	95	91	[289]
iPr	2	97	90	[289]
$CH_2CH{=}CH_2$	3	91	89	[289]

R^1	Time (h)	Yield[a] (%)	ee[b] (%)	Ref
Pr	2	95	87	[289]
Et	2	99	86	[289]
Bn	3	99	85[c]	[289]

[a] Measured by GC using benzyl methyl ether as internal standard.
[b] Determined by chiral GC unless otherwise stated.
[c] Determined by chiral HPLC after reduction to the corresponding alcohol.

2-Chloro-3-phenylpropanal (245, R^1 = Bn); Typical Procedure:[289]
Catalyst **244** (32.65 mg, 0.05 mmol, 10 mol%) and then NCS (87 mg, 0.65 mmol, 1.3 equiv) were added to a stirred and cooled (ice bath) soln of 3-phenylpropanal (**243**, R^1 = Bn; 65.8 μL, 0.5 mmol) in CH_2Cl_2 (1.0 mL) and the mixture was stirred for 1 h. Then, the mixture was allowed to warm to 25 °C. After the reaction was completed (ca. 2 h, GC analysis, internal standard: benzyl methyl ether), the mixture was concentrated and loaded onto a FluoroFlash silica gel cartridge (2 g) for F-SPE [eluents: THF/H_2O (80:20; 10 mL) for non-fluorous products, then THF (5 mL) for the fluorous catalyst]. The THF/H_2O fraction filtrates were combined and extracted with hexane, and the extracts were dried (Na_2SO_4) and concentrated to give the pure product; yield: 99%. The fluorous catalyst dissolved in the THF fraction could easily be recovered by evaporating the solvent.

The aldehyde was dissolved in MeOH (2 mL) and $NaBH_4$ (100 mg, 2.6 mmol) was added in several portions for reduction to the corresponding alcohol. After 10 min of stirring, the reaction was quenched by addition of H_2O and the mixture was extracted with EtOAc. The separated organic layer was dried (Na_2SO_4). The solvent was evaporated and the product was purified by flash chromatography (pentane/EtOAc 4:1); 85% ee by chiral HPLC analysis [Daicel Chiralpak OD-H, hexane/iPrOH 98:2, t_R(minor) = 11.38 min, t_R(major) = 12.18 min].

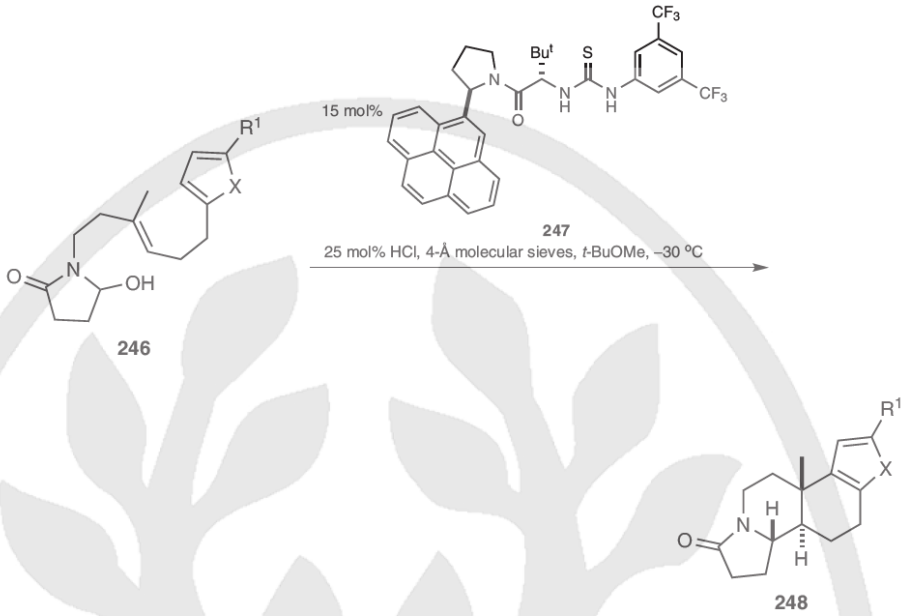
2.2.4.23 Cationic Polycyclization

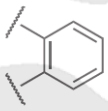
2.2.4.23.1 Cationic Polycyclizations of Lactam Derivatives

The Jacobsen group developed an efficient method for the asymmetric biscyclization of hydroxy lactams catalyzed by a thiourea organocatalyst **247**.[290] Presumably, in the conversion of the lactam into a chloro lactam with hydrogen chloride, the thiourea stabilizes the chloride through hydrogen bonding, while the cationic center is stabilized through cation–π interactions. 4-Substituted phenyl derivatives show high enantioselectivities and reactivities (Scheme 82). Substrates with more-electron-rich arenes or modifications of the nonaromatic portions of the molecule result in lower enantioselectivity and reactivity. More information and additional substrates are found in the Supporting Information to the relevant reference.[290]

for references see p 407

Scheme 82 Enantioselective Thiourea-Catalyzed Cationic Polycyclizations[290]



X	R^1	Time (h)	Yield (%)	ee (%)	Ref
CH=CH	OMe	72	72	94	[290]
	H	72[a]	75	92	[290]
CH=CH	Me	96	62	91	[290]
S	Cl	72[b]	77	91	[290]
CH=CH	*t*-Bu	96	71	91	[290]
CH=CH	Ph	117[c]	54	91	[290]
CH=CH	H	96	51	89	[290]

[a] Reaction run with 50 mol% HCl.
[b] Reaction run at −10 °C.
[c] Reaction run with addition of TMSCl (2 equiv); single procedure.

7,8-Fused 6a-Methyldecahydropyrrolo[2,1-*a*]isoquinolin-3(2*H*)-ones 248; **General Procedure:**[290]

CAUTION: *Hydrogen chloride in diethyl ether is extremely flammable, causes severe burns, and may build explosive peroxides.*

An oven-dried round-bottomed flask (25 mL) was filled with the hydroxy lactam **246** (0.25 mmol, 1.0 equiv), thiourea catalyst **247** (0.375 mmol, 0.15 equiv), 4-Å molecular sieves (160 mg), and anhyd *t*-BuOMe (10 mL). The mixture was cooled to −78 °C and a 2 M soln of HCl (0.0625 to 0.125 mmol, 0.25 to 0.50 equiv) in Et_2O was added dropwise. The mixture was then placed in a Cryocool at −30 °C and stirred for 72–96 h at this temperature. Then, the mixture was quenched with a precooled 20% v/v soln of Et_3N in EtOAc (ca. 1 mL). The mixture was filtered through a pipet containing silica gel, which was rinsed with acetone. The solvents were removed under reduced and the residue was purified

chromatographically [silica gel (EM Science 60, 230–400 mesh)]. The enantiomeric excess was determined by SFC analysis (Chiralpak AS, AD-H, or OD-H).

(4b*S*,10a*S*,10b*R*)-4b-Methyl-3-phenyl-5,6,9,10,10a,10b,11,12-octahydrobenzo[*f*]pyrrolo-[2,1-*a*]isoquinolin-8(4b*H*)-one (248, **X = CH=CH; R^1 = Ph**):[290]
An oven-dried round-bottomed flask (25 mL) was filled with the hydroxy lactam **246** (X = CH=CH; R^1 = Ph; 0.25 mmol, 1.0 equiv), anhyd CH_2Cl_2 (2.5 mL), and anhyd Et_3N (0.78 mmol, 3.1 equiv). Into the cooled (0 °C) mixture, AcCl (0.73 mmol, 2.9 equiv) was added dropwise under stirring. The mixture was stirred at rt for 1.5 h. The light yellow suspension was filtered through an alumina plug and rinsed with acetone. Then, the remaining solvent and reagents were evaporated under reduced pressure. An oily residue was afforded in the flask, which was charged with the thiourea catalyst **247** (0.375 mmol, 0.15 equiv), 4-Å molecular sieves (160 mg), and anhyd *t*-BuOMe (10 mL). The mixture was cooled to −78 °C and TMSCl (63.5 μL, 0.50 mmol, 2 equiv) was added dropwise. The flask was placed in a Cryocool at −30 °C and the mixture was stirred for 117 h. After quenching at −30 °C with a precooled 20% v/v soln of Et_3N in EtOAc (ca. 1 mL), the mixture was filtered through a pipet containing silica gel, which was rinsed with acetone. The solvents were evaporated under reduced pressure and the residue was purified chromatographically [silica gel (EM Science 60, 230–400 mesh)] to give the product as a white foam; yield: 44.9 mg (54%). The enantiomeric excess was determined by SFC analysis (Chiralpak AS-H, 20% MeOH).

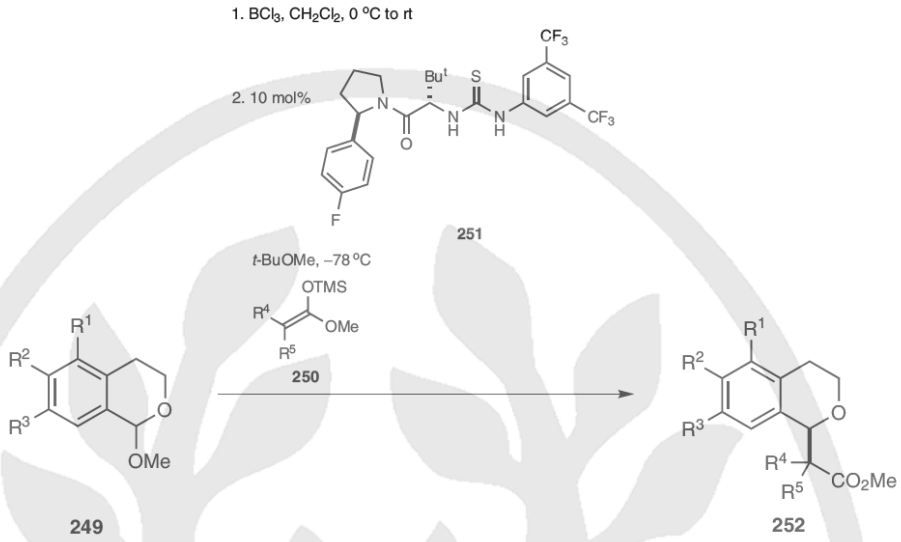
2.2.4.24 Addition to Oxocarbenium Ions

2.2.4.24.1 Addition to Oxocarbenium Ions: Synthesis of 3,4-Dihydro-1*H*-2-benzopyran Derivatives

Schreiner and co-workers reported the first use of a double hydrogen bonding thiourea organocatalyst in acetalization reactions.[5,26] The thiourea catalyst in this case assists the heterolysis of an ortho ester through stabilization of an oxyanion through hydrogen bonding. The stabilized oxyanion is then transferred to a carbonyl moiety to complete the acetalization. In 2008, Jacobsen reported a protocol for the use of asymmetric counterion catalysis in nucleophilic additions to oxocarbenium ions.[291] A thiourea catalyst **251**, a ketene silyl acetal **250**, and 1-chloro-3,4-dihydro-1*H*-2-benzopyrans (or 1-methoxy-3,4-dihydro-1*H*-2-benzopyrans **249** with boron trichloride) are used to synthesize several 3,4-dihydro-1*H*-2-benzopyran derivatives **252** with excellent enantioselectivity (Scheme 83).

for references see p 407

Scheme 83 Synthesis of 3,4-Dihydro-1*H*-2-benzopyran Derivatives under Thiourea Organocatalysis through Asymmetric Addition of Nucleophiles to Oxocarbenium Ions[291]



R^1	R^2	R^3	R^4	R^5	Time (h)	Yield (%)	ee (%)	Ref
Me	H	H	$(CH_2)_2O(CH_2)_2$		24	74	97	[291]
H	F	H	$(CH_2)_2O(CH_2)_2$		24	70	95	[291]
H	H	H	$(CH_2)_5$		24	84	94	[291]
H	Me	H	$(CH_2)_2O(CH_2)_2$		24	76	94	[291]
H	H	H	$(CH_2)_2O(CH_2)_2$		24	87	93	[291]
H	H	H	Me	Me	24	92	92	[291]
H	H	H	$(CH_2)_4$		24	85	92	[291]
H	H	Me	$(CH_2)_2O(CH_2)_2$		20	70	92	[291]
Me	H	H	H	H	7.5	71	90	[291]
H	F	H	H	H	21	70	90	[291]

Methyl 2-(3,4-Dihydro-1*H*-2-benzopyran-1-yl)alkanoates 252**; General Procedure:**[291]
An oven-dried flask flushed with N_2 was charged with the anhyd 1-methoxy-3,4-dihydro-1*H*-2-benzopyran **249** (0.30 mmol, 1.0 equiv) and anhyd CH_2Cl_2 (0.4 mL). After cooling of the mixture to 0 °C, a 1.0 M soln of BCl_3 in hexanes (0.10 mL, 0.35 equiv) was added dropwise. The mixture was warmed to rt and stirred for an additional 1.5 h. The solvent was removed under reduced pressure. The crude residue was kept under vacuum (1 Torr) for 30 min. Anhyd *t*-BuOMe (2.0 mL) was added under a N_2 atmosphere. After cooling of the flask to −78 °C, thiourea catalyst **251** (0.03 M stock soln in anhyd *t*-BuOMe; 1.0 mL, 0.03 mmol, 0.1 equiv) and the ketene silyl acetal **250** (0.45 mmol, 1.5 equiv) were added. After temporary stirring (see Scheme 83) at this temperature, the reaction was quenched by addition of 0.5 M NaOMe in MeOH (0.2 mL) at −78 °C. Then, the mixture was diluted with of Et_2O/hexanes (1:1; 2 mL). To hydrolyze the remaining ketene silyl acetal, the mixture was filtered through a 10-mL fritted funnel containing silica gel. The silica gel was rinsed with Et_2O/hexanes (1:1; 15 mL). The solvent was evaporated to afford the crude residue, which was purified by chromatography [silica gel (EM Science 60, 230–400 mesh), hexanes/EtOAc or hexanes/Et_2O]. The enantiomeric excess was determined by chiral HPLC analysis [(*S*,*S*)-Whelk-O 1, Chiralpak AS-H or AD-H, or Chiralcel OD-H; hexanes/iPrOH or hexanes/EtOH] or GC analysis (β-cyclodex, 20 m × 0.25 mm).

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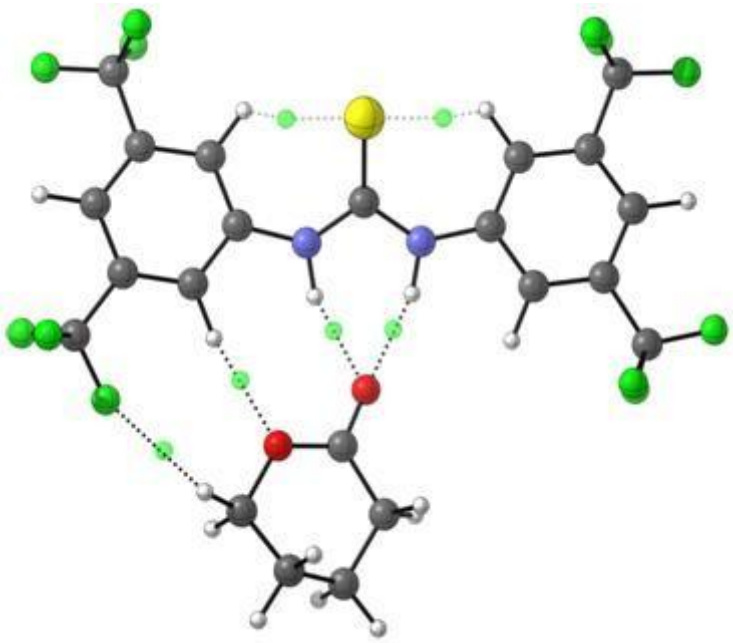
2 Hydrogen-Bonding Thiourea Organocatalysts: The Privileged 3,5-Bis(trifluoromethyl)phenyl Group



The second chapter presents the publication named **"Hydrogen-Bonding Thiourea Organocatalysts: The Privileged 3,5-Bis(trifluoromethyl)-phenyl Group"**. Herein, we examined complexes between thiourea derivatives and carbonyl compounds revealing the mode of action of thiourea organocatalysts bearing bis(triflouromethyl)phenyl groups. This study was published in the **European Journal of Organic Chemistry**. The Supporting Information accompanying this publication can be downloaded free of charge (see footnote on publication's first page). The permission to show this publication herein was friendly given by the **Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim**, which is gratefully acknowledged.

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FULL PAPER

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Hydrogen-Bonding Thiourea Organocatalysts: The Privileged 3,5-Bis(trifluoromethyl)phenyl Group

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Keywords: Density functional theory computations / IR spectroscopy / NMR spectroscopy / Organocatalysis / Thiourea derivatives

We present evidence that the privileged use of the 3,5-bis(trifluoromethyl)phenyl group in thiourea organocatalysis is due to the involvement of the *ortho*-CH bond in the binding event with Lewis-basic sites. We utilized a combination of low-temperature IR spectroscopy, 2D NMR spectroscopy, nano-MS (ESI) investigations, as well as density functional theory computations [M06/6-31+G(*d*,*p*), including solvent corrections as well as natural bond orbital and atoms-in-molecules analyses] to support our conclusions that bear implications for catalyst design.

Introduction

Urea and thiourea derivatives are popular hydrogen-bonding catalysts that have been utilized successfully in a large variety of organocatalytic transformations.[1] Many catalysts display the 3,5-bis(trifluoromethyl)phenyl group[2] that was first introduced as a key structural motif in thiourea catalysis in 2002.[3] Remarkably, this moiety is also present in some of the most active proline and phosphoric acid derived catalysts (Figure 1).[4] It appears that the 3,5-bis(trifluoromethyl)phenyl moiety generally has beneficial effects on organocatalysts. This may inter alia involve an increase in catalyst polarity, polarizability, acidity,[5] and π–π interactions[2k,6] through the highly polarized aryl groups. Here we describe that the involvement of the highly polar *ortho*-CH bond is also quite important for catalyst–substrate interactions in the case of thiourea catalysis.[2k,7] Evidence for

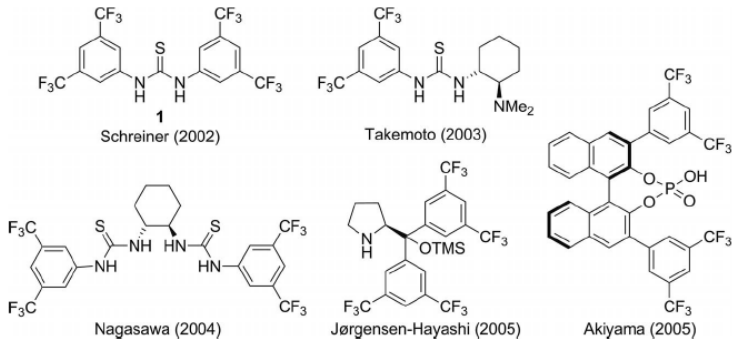

Figure 1. Selection of catalysts bearing a 3,5-bis(trifluoromethyl)phenyl group.

the non-negligible role of CH–heteroatom interactions comes from early IR and NMR spectroscopic studies.[8] Such interactions increase with increasing carbon *s*-content in the hybridization and in the presence of electron-withdrawing groups.[8,9] Hydrogen-bonding interactions of polar aromatic CH bonds with Lewis basic sites have been well studied but,[9,10] to the best of our knowledge, not in the context of hydrogen-bonding organocatalysis.

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Results and Discussion

We utilized low-temperature NMR and IR techniques as well as modern density functional theory (DFT) computations[11] to corroborate our findings. While there are numerous complexes of anions and neutrals with (thio)urea derivatives, we are unaware of reports on the involvement of C–H bonding in the binding event.[1g,12] A pertinent example in the context of thiourea binding to neutrals comes from the work of Waymouth and Hedrick, who examined effects of supramolecular recognition for living polymerization of lactide by utilizing catalysts bearing the 3,5-bis(trifluoromethyl)phenyl motif.[7d,13] To elucidate the structural changes upon binding between catalyst and substrate, we examined the interactions of thiourea derivatives **1**–**4** with neutrals **5**–**9** (Figure 2).

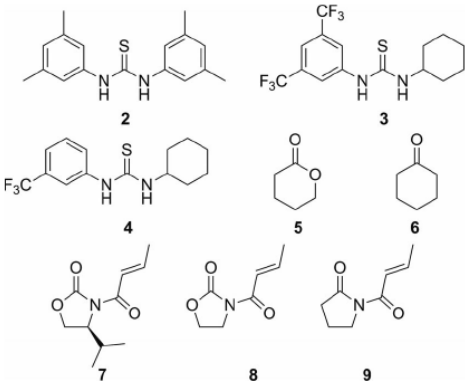

Figure 2. Investigated thiourea derivatives and substrates **5**–**9**.

Individual Components

In the absence of a Lewis basic donor, structure **2**, which has not been employed as a catalyst, displays two conformers with *E*,*Z*- (**2**_*E*,*Z*) and *Z*,*Z*-orientations (**2**_*Z*,*Z*) of the N–H bonds (Figure 3), with the **2**_*E*,*Z* form being slightly more stable as derived from computations and its crystal structure. However, our NMR spectroscopic studies imply that in [D$_8$]toluene at room temperature, conformer **2**_*Z*,*Z* is preferred, whereas **2**_*Z*,*E* predominates at temperatures below 200 K; that is, the rotation around the C–N bonds is facile (cf. Supporting Information, Figure S29).

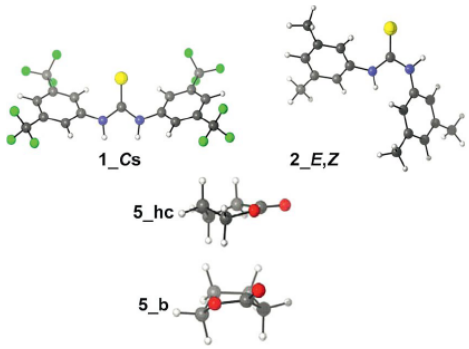

Figure 3. The lowest-lying conformers of **1**, **2**, and **5** computed at M06/6-31+G(*d*,*p*) at 0 K. Compounds **1**_Cs and **2**_*E*,*Z* are also present in the crystal structure.

Catalyst **1** prefers a *Z*,*Z*-orientation of the N–H protons (Figure 3) in solution, in the crystal, and computationally. At temperatures below 190 K in [D$_8$]THF, **1** transforms into the *Z*,*E*-conformation, as evident from the separated signals of the N–H protons (Figure 4). A ^{1}H–^{15}N HSQC spectrum

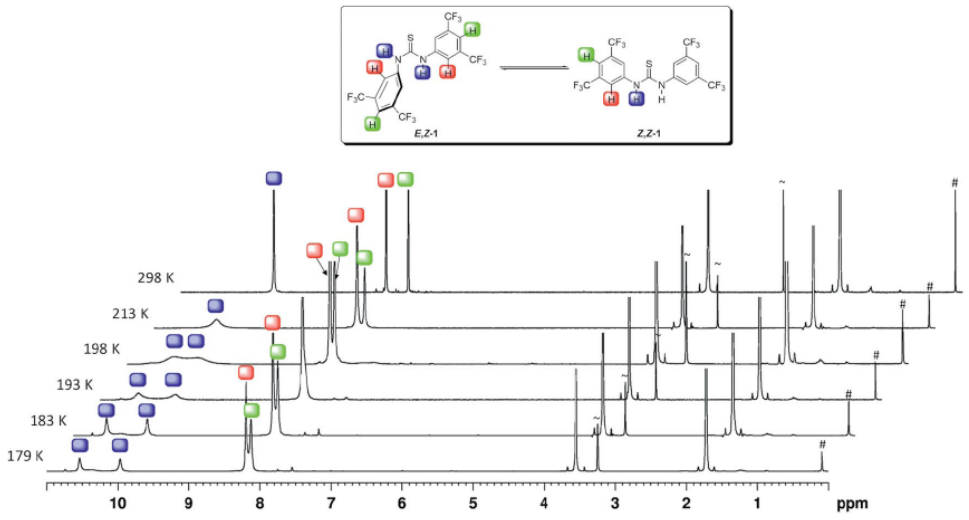

Figure 4. Stacked ^{1}H NMR (600 MHz) spectra of **1** (0.01 mmol, 13.3 mM) in [D$_8$]THF.

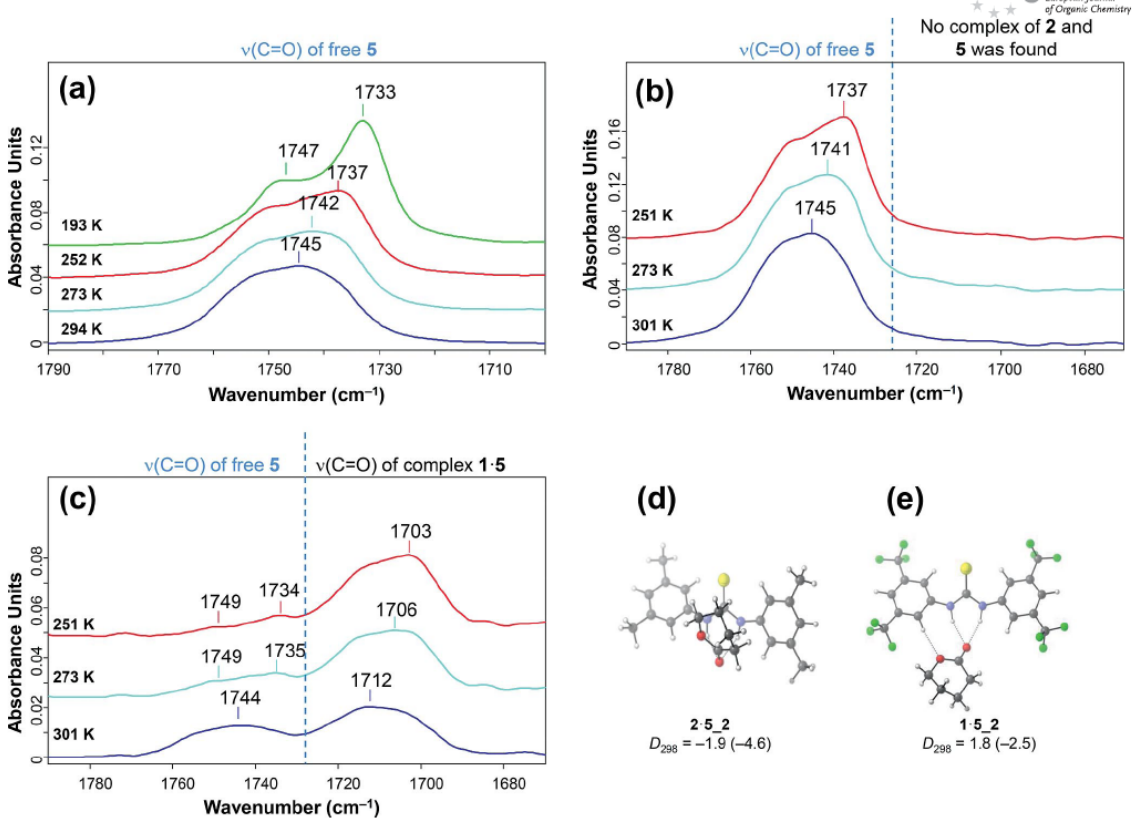

Figure 5. (a)–(c) Selected ranges of the IR spectra in [D_8]toluene; temperatures are given above each IR spectrum. (a) **5** (10 mM); (b) **2** (10 mM) and **5** (10 mM); (c) **1** (10 mM) and **5** (10 mM). (d) Lowest-lying complex of **2**·**5**. (e) Lowest-lying complex of **1**·**5**. Both complexes were computed at the M06/6-31+G(*d*,*p*) level of theory. Dissociation energies (D_{298}) given in kcal mol^{-1}. Values in parentheses were computed with the PCM model for toluene employing UAHF radii.

at 183 K clearly identifies two species with different N–H proton shifts (cf. Supporting Information, Figure S8). Again, C–N bond rotation is facile.

The half-chair (i.e., **5**_hc) conformer of uncomplexed lactone **5** is preferred computationally by 1.1 kcal mol^{-1} over the boat conformer (**5**_b, Figure 3). IR measurements in [D_8]toluene at room temperature show a broad C=O band wh a shoulder (Figure 5a, at 1745 cm^{-1}) implying a mixture of **5**_hc and **5**_b. At low temperatures, the concentration of **5**_hc increases, as evidenced from the growing band at 1733 cm^{-1}.

Complexation Studies

Turning to mixtures of the thiourea derivatives and the Lewis basic substrates we find that the ^{1}H NMR and ^{13}C NMR spectra of **2** in [D_8]toluene at room temperature in the absence and presence of **5** are rather similar (Figure 6a,b; ^{13}C NMR spectra are depicted in Figure 7) indicating that a complex does not form under these conditions. This is also supported by the absence of NOE cross peaks (Figure 8a) and the virtually unchanged (relative to free **5**) variable-temperature IR spectra (Figure 5b). M06/6-31+G(*d*,*p*) computations in the gas phase and in solution at room temperature give negative dissociation energies so that complex formation of **2**·**5** seems rather unlikely. On the contrary, the corresponding NMR spectra for **1** show large changes in the chemical shifts ($\Delta\delta \approx 1.8$ ppm) for the NH protons (Figure 6c,d) but also for the *ortho*-protons ($\Delta\delta \approx 0.7$ ppm). The same applies to the ^{13}C NMR absorptions (Figure 7) of the carbonyl ($\Delta\delta \approx 3.2$ ppm) and methylene carbon atoms next to the ring oxygen ($\Delta\delta \approx 1.4$ ppm).[7d] The NOESY (Figure 8b), ^{19}F–^{1}H HOESY (Figure 9), and IR spectra equally indicate **1**·**5** complex formation. The observed ^{19}F coupling with the hydrogen atoms of the methylene group next to the ring oxygen clearly indicate a very close spatial relationship between the *ortho*-C–H and the ring oxygen. The IR spectra of a 1:1 mixture of **1** and **5** in [D_8]toluene reveal a band at 1744 cm^{-1} originating from free **5** and a redshifted band at 1712 cm^{-1}, indicating a hydrogen-bonded complex of **1**·**5** (Figure 5c). These findings are also supported by MS (ESI) measurements (cf. Supporting Information) where the mass of [**1**·**5**+H]$^+$ = 601.08 was identified. M06/6-31G+(*d*,*p*) computations (Figure 5e) in

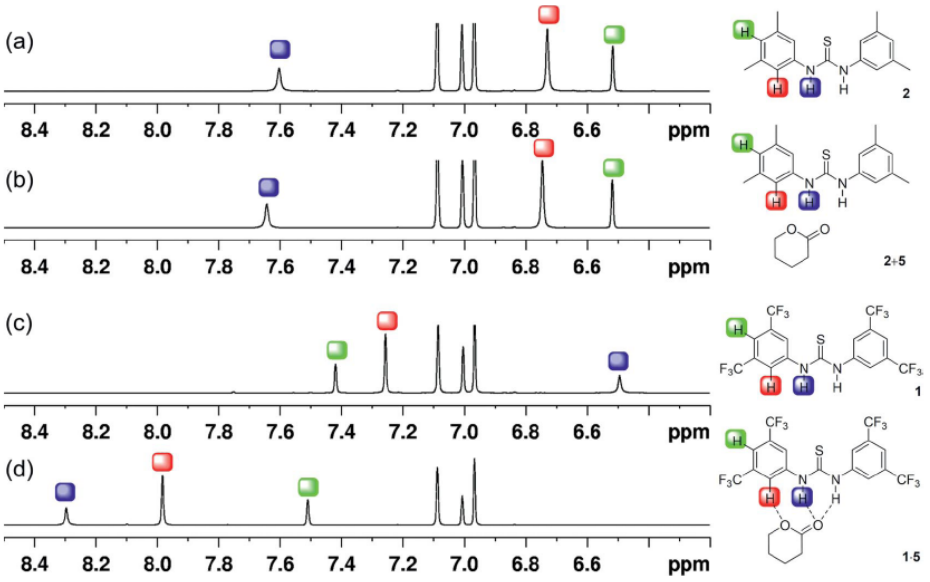

Figure 6. Sections of the ^{1}H NMR spectra in [D$_8$]toluene at 298 K. (a) Free **2** (13.3 mM); (b) complex **2**·**5** (**2**, 13.3 mM; **5**, 13.3 mM); (c) free **1** (13.3 mM); (d) complex **1**·**5** (**1**, 13.3 mM; **5**, 13.3 mM).

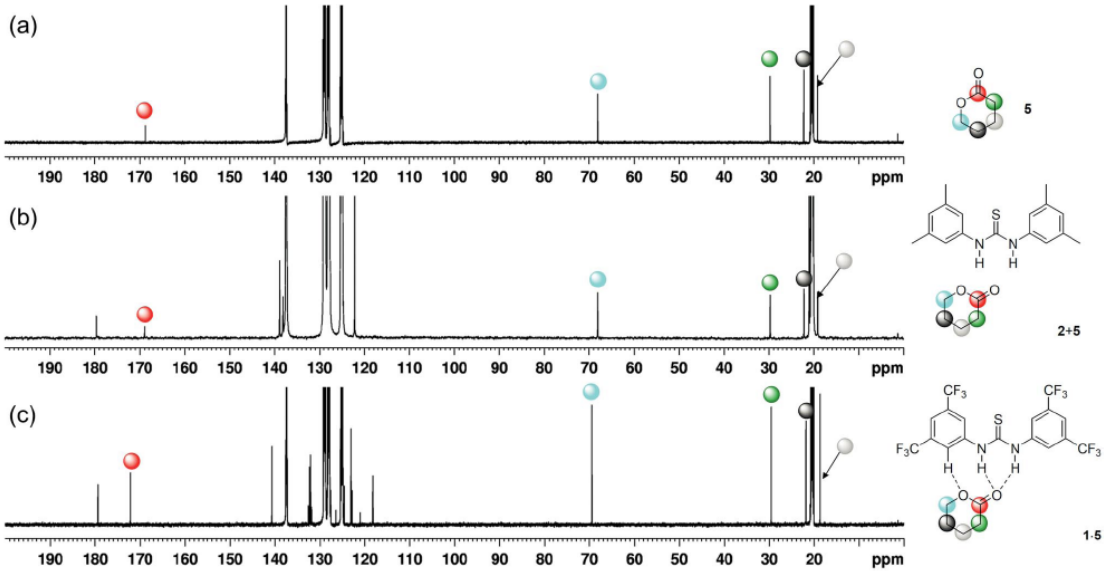

Figure 7. Sections of the ^{13}C NMR spectra in [D$_8$]toluene at 298 K. (a) Free **5** (13.3 mM); (b) complex **2**·**5** (**2**, 13.3 mM; **5**, 13.3 mM); (c) complex **1**·**5** (**1**, 13.3 mM; **5**, 13.3 mM).

the gas phase give D_{298} = 1.8 kcal mol^{-1} (in solution D_{298} = –2.5 kcal mol^{-1}) so that complex formation of **1**·**5** is preferred at room temperature, with **1** binding through double hydrogen bonding to the C=O group and the *ortho*-proton binding to the ring oxygen.

Natural bond order (NBO) analysis confirmed the N–H···O=C as well as the C–H···O$_{ring}$ interactions in **1**·**5**, with the C–H···O$_{ring}$ oxygen lone pair interaction with the C–H σ* orbital being energetically ≈2.5-fold weaker than the N–H···O=C interaction. This is confirmed through a quantum theory of atoms in molecules (QTAIM)[14] study by utilizing AIMAll:[15] an analysis of the electron density reveals bond critical points (BCPs) for the interactions noted above. In particular, we found a BCP for a hydrogen bond between the ring oxygen and the *ortho*-proton of $\rho \approx 1.20 \times 10^{-2}$ au, which is in the range of weak hydrogen bonds; there is also

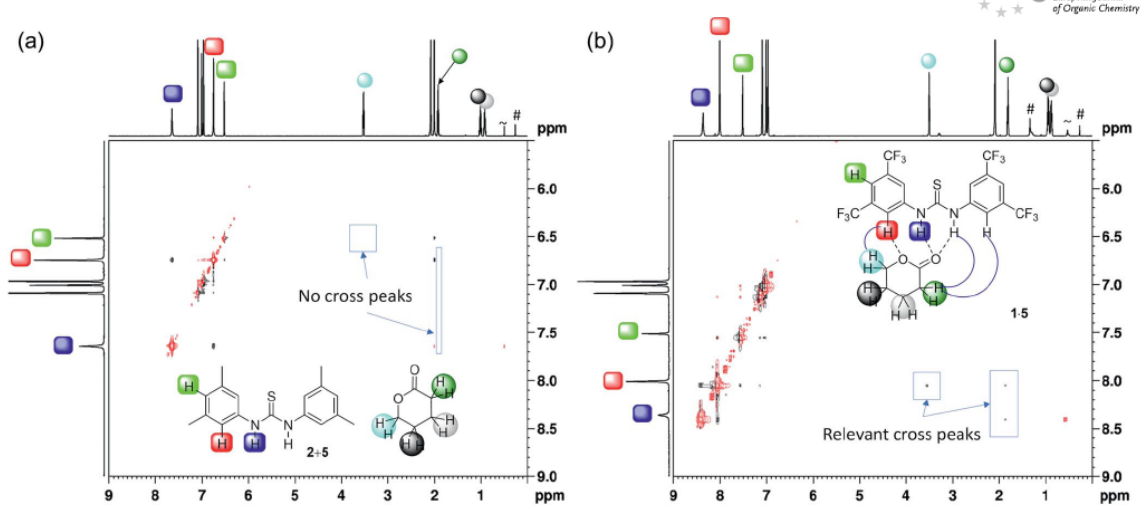

Figure 8. Sections of the NOESY spectra of 1:1 mixtures of thiourea derivatives and **5** in [D_8]toluene at 298 K. (a) **2** (13.3 mM) and **5** (13.3 mM); (b) **1** (13.3 mM) and **5** (13.3 mM). Expected and observed NOE signals are highlighted with a blue frame.

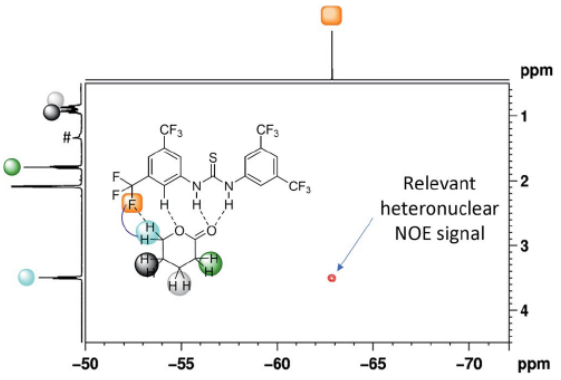

Figure 9. Section of the ^{19}F–^{1}H HOESY spectrum of a 1:1 mixture of **1** and **5** in [D_8]toluene at 298 K showing the cross peak between the fluorine of the CF_3 group and the methylene group protons adjacent to the ring oxygen; **1** (13.3 mM) and **5** (13.3 mM).

a BCP between the fluorine and the methylene proton adjacent to the ring oxygen.[14]

Thiourea derivatives **3** and **4** also bind to **5**, but the IR spectra (at the same concentrations, cf. Supporting Information) show that the amounts of complexes **3·5** and **4·5** are much lower than for **1·5**. NMR cross-peaks were only observed for **3·5**, and it can equilibrate between two low-energetically lying complexes (cf. Supporting Information). NBO analysis revealed both C–H···O_{ring} interactions through the *ortho*- or cyclohexyl methylene protons with the ring oxygen owing to an interaction of the ring oxygen's lone pair with the C–H σ* orbital (cf. Supporting Information, Figure S52 and Figure 10), similar to that found for **1·5** but weaker.[16] The hydrogen bonding in **3·5** is also evident from the downfield shifts of the NH- and *ortho*-protons. These downfield shifts correlate well with the thiourea NH acidities,[5b] and as catalytic acidity also qualitatively correlates with these pK_a values, the chemical shift differences (Δδ) may be suggestive of the potential activity of a particular catalyst. This correlation is evident from the presence of acidifying CF_3 groups, for which the pK_a values and Δδ differences follow the order **1** > **3** > **4** > **2**.[5b]

Next we investigated the complexation of **1** with **6**–**9**. Although **6** bears no ring oxygen as an additional hydrogen-bonding contact point, we identified an NH···O=C hydrogen-bonded complex through NOESY as well as IR measurements and DFT computations (Figure 10 and the Supporting Information). Both NH- and the *ortho*-protons of **1** bind to the carbonyl oxygen of **6**, because we find cross-peaks between the α-protons of **6** with the NH proton as well as with the *ortho*-proton. Computing the NBOs we found no C–H···O interaction, but this should be a consequence of long distance between the *ortho*-proton and the C=O group and according to that no correlation between the oxygen and C–H σ* orbital was visible; there is no C–H···O BCP.[17] Carbonyl derivatives bearing two C=O groups and a ring oxygen (i.e., **7** and **8**) lead to complexes as identified by IR and MS (ESI) techniques (Figure 10). The ring C=O IR redshift implies a hydrogen-bonded complex with the oxazolidinone ring. The NH and the *ortho*-protons of **1** bind to the ring C=O group of **7** and **8**, respectively. Computations reveal interactions of the *ortho*-protons with the ring oxygen for **1·7** and **1·8**. Without the ring oxygen structure **9** binds to **1** through the crotonyl C=O group (Figure 10). Complex **1·9** was found by NMR and IR spectroscopy and MS (ESI) measurements as well as DFT computations.

In the last years, many catalysts bearing the 3,5-bis(trifluoromethyl)phenyl moiety were reported and used in various hydrogen-bond-assisted organocatalytic reactions.[18] Many provide high enantioselectivities and high yields. Nevertheless, reactions for some systems fail due to a lack of substrate-specific interactions with the catalyst and show

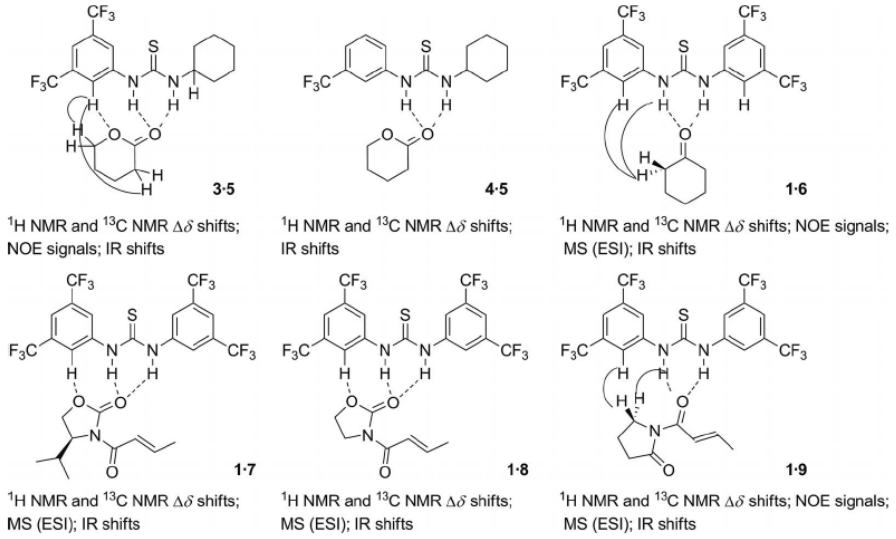

Figure 10. Complexes as identified by the indicated methods through NMR and IR spectroscopy and/or MS (ESI). Possible hydrogen bonds (dashed lines) where drawn for each complex demonstrated by relevant shortened distances between thiourea and carbonyl derivative by comparing NMR and computational results.

better results with alternatively functionalized catalysts.[5a,7b,19] For example, a phase-transfer catalyst bearing 3,4,5-trifluorophenyl substituents leads to higher enantioselectivities than a phase-transfer catalyst with pentafluorophenyl substituents[20] possibly due to the lack of polarized *ortho*-protons.[21]

Conclusions

As implied in many organocatalytic reactions utilizing **1** and its many derivatives, we find that it readily forms hydrogen-bonded complexes with Lewis basic substrates. The binding interactions do not only arise from interactions of the highly polar NH protons but also from the *ortho*-protons with Lewis bases. This is evident from NMR and IR spectroscopy, mass spectrometry (ESI), and DFT investigations and bears important implications for catalyst design.

Experimental Section

General Methods: 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 δ-valerolactone was freshly distilled and stored in a Schlenk tube under an argon atmosphere in the freezer. The thiourea and *N*-crotonyl derivatives were synthesized as noted below[22] or by literature-known procedures.[13c,23] Thiourea and solid *N*-crotonyloxazolidinone derivatives were stored under reduced pressure over P_2O_5. All solvents used for filtrations were distilled once. Drying was performed by following established literature procedures: THF and toluene were freshly distilled from Na/benzophenone ketyl; CH_2Cl_2 was distilled from CaH_2 and stored over (4 Å) molecular sieves (MS) and under an argon atmosphere. All deuterated chemicals {[D_8]THF, [D_8]toluene (99.8%, purchased from Deutero GmbH or euroisotop GmbH)} were stored over (4 Å) MS. TLC was carried out on precoated Macherey–Nagel plastic sheets Polygram SiO_2 N/UV254 (40–80 mm) by using UV light for visualization. ^{1}H NMR and ^{13}C NMR were recorded with Bruker spectrometer Avance II (AV 400) [D_6]DMSO [$\delta(^1H)$ = 2.50 ppm], [D_6]DMSO [$\delta(^{13}C)$ = 39.5 ppm]. 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.

***N*,*N*′-Bis[3,5-(trifluoromethyl)phenyl]thiourea (1):** To a mixture of 1,1′-thiocarbonyldiimidazole[24] (1.50 g, 8.43 mmol) in CH_2Cl_2 (dried, 8 mL) was added carefully 3,5-bistrifluoromethylaniline (2.74 mL, 17.70 mmol, 2.1 equiv.) under an argon atmosphere. The resulting solution was stirred for 24 h at room temperature. The solvent was evaporated and diethyl ether (70 mL) was added to the yellowish oil. The organic phase was extracted with HCl (1 M, 3 × 20 mL), aqueous $NaHCO_3$ (saturated, 3 × 20 mL), and brine (3 × 20 mL). The organic phase was dried with Na_2SO_4. After removing the drying agent and the solvent, the light yellow solid was recrystallized from $CHCl_3$. The filtrate was concentrated under reduced pressure, and the residue was recrystallized from $CHCl_3$ again. The white solid was dried under vacuum in a desiccator over P_2O_5. A white solid (2.29 g, 61.3%) was afforded. Physical data were consistent with those reported in the literature.[25]

***N*,*N*′-Bis(3,5-dimethylphenyl)thiourea (2):** To a mixture of 1,1′-thiocarbonyldiimidazol[24] (1.50 g, 8.43 mmol) in CH_2Cl_2 (dried, 8 mL) was added carefully 3,5-dimethylaniline (2.21 mL, 2.14 g, 17.7 mmol, 2.1 equiv.) under an argon atmosphere. The resulting solution was stirred for 24 h at room temperature. The solvent was evaporated and ethyl acetate (150 mL) was added to the brown oil; the solution was poured into a 250-mL separatory funnel. The organic phase was extracted with HCl (aqueous, 1 M, 3 × 40 mL), aqueous $NaHCO_3$ (saturated, 3 × 40 mL), and brine (3 × 40 mL). The organic phase was dried with Na_2SO_4. After removing the dry-

ing agent and the solvent, the light yellow solid was heated at reflux in diethyl ether (70 mL in a 250-mL flask) for 0.5 h. The solid was pumped off and washed with small portions of cooled diethyl ether to give a white solid (1.38 g, 57.6%). ^{1}H NMR (400 MHz, [D$_6$]-DMSO): δ = 9.56 (s, 2 H, N-*H*), 7.04 (s, 4 H, C-*H*$_{ortho}$), 6.76 (s, 2 H, C-*H*$_{para}$), 2.24 (s, 12 H, C*H*$_3$) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]-DMSO): δ = 179.35 (*C*q), 139.16 (*C*q), 137.39 (*C*q), 126.00 (*C*-H), 121.50 (*C*-H), 20.93 ppm. IR (KBr disc): $\tilde{\nu}$ = 3360.0, 3195.5, 3017.5, 2972.2, 2913.7, 1610.2, 1537.7, 1516.6, 1470.0, 1432.3, 1342.3, 1313.3, 1270.9, 1227.6, 1166.3, 1037.0, 862.2, 847.0, 715.3, 652.3, 482.7 cm^{-1}. HRMS: calcd. for $C_{14}H_{17}F_3N_2S_1$ [M]$^+$ 284.1347; found 284.1348.

***N*-Cyclohexyl-*N*′-[3-(trifluoromethyl)phenyl]thiourea (4):** To a 10-mL flask with a gas inlet charged with dried CH_2Cl_2 (5 mL) was added cyclohexylamine (0.3 mL, 0.27 mg, 2.7 mmol) and 3-(trifluoromethyl)phenylisothiocyanate (0.41 mL, 0.55 mg, 2.7 mmol), and the mixture was stirred at room temperature under an argon atmosphere for 12 h. Afterwards the solvent was evaporated and the precipitate was washed with hexane/CH_2Cl_2 (4:1). The solvent was then removed. The white solid of **4**[26] (0.5 g, 1.64 mmol, 60%) was dried under vacuum over P_2O_5. M.p. 140–141 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 9.59 (s, 1 H, N-*H*), 8.05 (s, 1 H, C-*H*$_{ortho}$), 7.91 (s, 1 H, N-*H*), 7.66 (d, *J* = 7.88 Hz, 1 H, C-*H*$_{para}$), 7.51 (t, *J* = 8.9, 8.9 Hz, 1 H, C-*H*$_{meta}$), 7.39 (d, *J* = 7.55 Hz, 1 H, C-*H*$_{ortho}$), 4.10 (s, 1 H, C-*H*), 1.91 (m, 2 H, C*H*$_2$), 1.69 (m, 2 H, C*H*$_2$), 1.51 (m, 1 H, C*H*$_2$), 1.28 (m, 1 H, C*H*$_2$) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 179.18 (*C*q), 140.64 (*C*q), 129.45 (*C*-H), 128.87 (q, *J* = 30.70 Hz), 125.78 (*C*-H), 124.01 (q, *J* = 271.19 Hz), 119.67 (*C*-H), 118.27 (*C*-H), 52.07 (*C*-H), 31.70 (*C*H$_2$), 25.09 (*C*H$_2$), 24.42 (*C*H$_2$) ppm. IR (KBr disc): $\tilde{\nu}$ = 3230.8, 3076.2, 2932.7, 2852.9, 1602.4, 1543.3, 1484.8, 1459.3, 1327.4, 1273.3, 1212.0, 1163.8, 1117.3, 1093.0, 1072.8, 984.4, 887.0, 795.5, 715.6, 700.0, 654.8, 588.3 cm^{-1}. HRMS: calcd. for $C_{14}H_{17}F_3N_2S_1$ [M]$^+$ 302.1065; found 302.1088. Elemental analysis: calcd. C 55.61, H 5.67, N 9.26; found C 55.36, H 5.65, N 9.29.

NMR Spectroscopic Data Collection and Processing: The NMR spectra (^{1}H, ^{13}C, ^{1}H–^{15}N HSQC, NOESY, and ROESY) were recorded with a 600 MHz spectrometer equipped with a 5-mm broadband z-gradient probe (maximum gradient strength 53.5 G cm^{-1}). The phase-sensitive ^{1}H NOESY spectra were recorded by using a mixing time of 1 s; the ROESY had a spin-lock pulse of 70 ms. The ^{1}H–^{15}N HSQC spectra were acquired with pulsed field gradients. The delay was adjusted to a coupling constant of $^1J(^1H,^{15}N)$ = 60.8 MHz. ^{1}H: 600.13 MHz. ^{13}C: 150.90 MHz; when necessary using as the internal standard: TMS $d(^1H)$ = 0, $d(^{13}C)$ = 0, [D$_8$]-toluene [$\delta(^1H)$ = 2.09, 6.98, 7.00, 7.09 ppm], [D$_8$]toluene [$\delta(^{13}C)$ = 18.3, 25.2, 78.7 ppm], [D$_8$]THF [$\delta(^1H)$ = 1.73, 3.58 ppm], [D$_8$]THF [$\delta(^{13}C)$ = 25.37, 67.57 ppm]. ^{19}F–^{1}H HOESY measurements were performed with a 400 MHz Bruker Avance II spectrometer equipped with a 5-mm BBFO probe with *z*-gradient. For the ^{19}F–^{1}H HOESY experiments the hoesyph pulse sequence was used and 1 K data points were acquired in the directly detected dimension. All experiments were run under fluorine detection. A mixing time of 800 ms was used for the non-degassed samples and 64 scans were taken for each of the 256 T_1 increments. The delay between increments was set to 3 s. The ^{19}F signals are recorded relative to the resonance of a sample of $CFCl_3$.

IR Spectroscopic Studies: We used a Bruker IFS 25 IR or a Bruker IFS 55 FTIR spectrometer and a low-temperature cell with CaF_2 windows. Solutions of the various pure compounds and compound mixtures in [D$_8$]toluene were loaded into a low-temperature CaF_2 cell (*d* = 0.1 mm). The cell was cooled from room temperature to –95 °C with liquid nitrogen because at this temperature the solvent ([D$_8$]toluene) froze. Absorbance spectra were recorded at 2 cm^{-1} resolution (40 scans) with pure solvent at the respective temperature as reference.

Computational Studies: All computations were performed with the Gaussian09 suite of programs.[27] Geometry optimizations and frequency computations were performed using the M06 density functional in conjunction with 6-31+G(*d*,*p*) basis set. The M06 functional is recommended for computations of organometallic species and for studies of noncovalent interactions, thermochemistry, and kinetics.[11] Additional geometry optimizations and frequency computations for the determination of solvent effects were also performed by using the M06/6-31+G(*d*,*p*) method with a self-consistent reaction-field (SCRF) model.[28] SCRF methods treat the solute at the quantum mechanical level, while the solvent is represented as a dielectric continuum. Specifically, we chose the polarizable continuum model (PCM) developed by Tomasi and co-workers to describe the bulk solvent.[28,29] PCM computations were modified by using the UAHF model, a United Atom Topological Model applied on radii optimized for the HF/6-31G(*d*) level of theory.[29,30] We found shifts of the stretching vibrations of the cyclohexyl methine CH bonds of about ≈100–400 cm^{-1}; at this time the reasons for these unphysical shifts are unclear, but we note that they only occur when using the UAHF model in solvent computations. ΔH_0 values are corrected for zero-point vibrational energies (ZPVEs). All computed minima displayed only real vibrational frequencies (no imaginary frequencies). The quantum theory of atoms in molecules (QTAIM)[14] analysis was performed using AIMAll.[15] Computational results were depicted with CYLview.[31]

MS (ESI) Studies: The formation of thiourea–guest complexes was also investigated by mass spectrometry using a linear ion trap/Fourier transform orbital trapping mass spectrometer (LTQ Orbitrap Discovery, Thermo Scientific GmbH, Bremen, Germany) equipped with a nanoelectrospray ion source (Nanospray Ion Source, Thermo Scientific GmbH, Bremen, Germany).[32] Sample solutions were prepared by dissolving the host (thiourea derivative *c* = 20 mM) and guest (carbonyl derivative *c* = 20 mM) in toluene (dried). Analysis was performed in positive ion mode. Complex formation was confirmed by determination of the accurate mass of the protonated complex and of its constituents (protonated) after intentional destruction of the complex via collision induced dissociation (CID).

X-ray Crystallographic Analysis: CCDC-868394 (for **2**), -868395 (for **4**), and -206506 (for **1**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. The crystal structure of **1** was previously published by Kotke and Schreiner.[25]

Supporting Information (see footnote on the first page of this article): Experimental details, remarks on NMR spectroscopic data collection and processing, matrix isolation studies, computational studies, as well as all NMR, IR, matrix-isolation IR, and mass spectra.

Acknowledgments

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[17] Computing complex **1·6_4** (cf. Supporting Information, Figures S76 and S77), which would be preferred at 0 K, we found a charge-transfer interaction from the oxygen's lone pair to the C–H σ* orbital. QTAIM computations also revealed a BCP ($\rho \approx 1.12 \times 10^{-2}$ au) in **1·6_4** through an interaction of the *ortho*-proton with the carbonyl oxygen, but this interaction is not visible in **1·6_2**.

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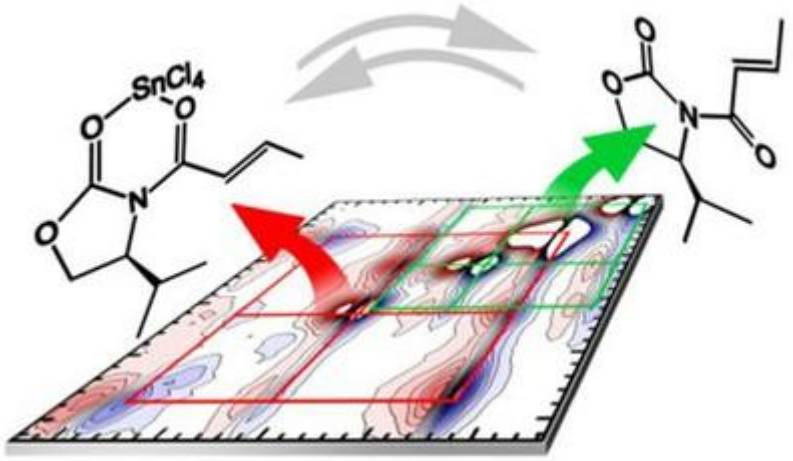
3 Two-Dimensional Infrared Spectroscopy Reveals the Structure of an Evans Auxiliary Derivative and Its $SnCl_4$ Lewis Acid Complex



In this third chapter the publication **"Two-Dimensional Infrared Spectroscopy Reveals the Structure of an Evans Auxiliary Derivative and its $SnCl_4$ Lewis Acid Complex"** is presented. This study was published in **Chemistry – A European Journal**. The Supporting Information accompanying this publication can be downloaded free of charge (see footnote on publication's first page). The permission to show this publication herein was friendly given by the **Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim**, which is gratefully acknowledged.

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Two-Dimensional Infrared Spectroscopy Reveals the Structure of an Evans Auxiliary Derivative and Its $SnCl_4$ Lewis Acid Complex

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Abstract: Determining the structure of reactive intermediates is the key to understanding reaction mechanisms. To access these structures, a method combining structural sensitivity and high time resolution is required. Here ultrafast polarization-dependent two-dimensional infrared (P2D-IR) spectroscopy is shown to be an excellent complement to commonly used methods such as one-dimensional IR and multidimensional NMR spectroscopy for investigating intermediates. P2D-IR spectroscopy allows structure determination by measuring the angles between vibrational transition dipole moments. The high time resolution makes P2D-IR spectroscopy an attractive method for structure determination in the presence of fast exchange and for short-lived intermediates. The ubiquity of vibrations in molecules ensures broad applicability of the method, particularly in cases in which NMR spectroscopy is challenging due to a low density of active nuclei. Here we illustrate the strengths of P2D-IR by determining the conformation of a Diels–Alder dienophile that carries the Evans auxiliary and its conformational change induced by the complexation with the Lewis acid $SnCl_4$, which is a catalyst for stereoselective Diels–Alder reactions. We show that P2D-IR in combination with DFT computations can discriminate between the various conformers of the free dienophile *N*-crotonyloxazolidinone that have been debated before, proving antiperiplanar orientation of the carbonyl groups and s-*cis* conformation of the crotonyl moiety. P2D-IR unequivocally identifies the coordination and conformation in the catalyst–substrate complex with $SnCl_4$, even in the presence of exchange that is fast on the NMR time scale. It resolves a chelate with the carbonyl orientation flipped to synperiplanar and s-*cis* crotonyl configuration as the main species. This work sets the stage for future studies of other catalyst–substrate complexes and intermediates using a combination of P2D-IR spectroscopy and DFT computations.

Keywords: chiral auxiliaries · density functional calculations · homogeneous catalysis · IR spectroscopy · structure elucidation

Introduction

Rational design and optimization of chemical reactions requires detailed knowledge about the structures that occur along the course of the reaction. To guide a reaction to the desired product, auxiliaries and catalysts are frequently used that control molecular conformation and accessibility of the reactive moiety. The combination of a Lewis acid catalyst and the chiral Evans auxiliary (a chiral oxazolidin-2-one derivative)[1,2] has frequently been used in asymmetric synthesis to induce predictable stereochemistry in reactions of prochiral moieties, such as *N*-acyloxazolidinones (Figure 1).[3] Early showcase examples are Lewis acid catalyzed enantioselective aldol additions[1,4] and Diels–Alder reactions of **1**.[5] The stereochemical outcome of these types of reactions is determined by a bulky group on the oxazolidinone auxiliary that shields one side of the molecule so that the reagent (e.g., cyclopentadiene in a Diels–Alder reaction) can only approach from the other side of the reactive moiety.[6] As illustrated in Figure 1, it is essential to control the rotational degrees of freedom of the connection between the chiral auxiliary and the reactive moiety to guide the reaction towards the desired product.[6] According to the mechanism proposed by Evans, the major Diels–Alder product originates from the conformer **1-spc**. Metal ion chelation, which locks the conformation of the *N*-acyl bond (transition state in Figure 1), is commonly used to rationalize the observed high diastereoselectivities of these and related reactions. An

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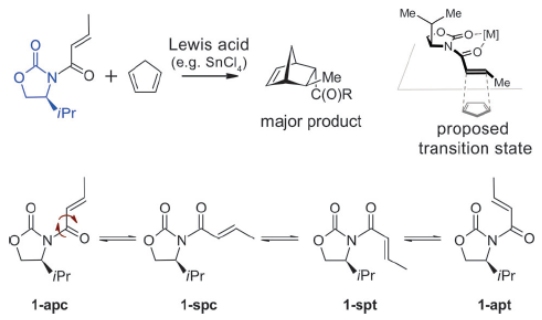

Figure 1. Top: The reaction of the *N*-crotonyloxazolidinone (4*S*)-3-[(*E*)-2-butenoyl]-4-(1-methylethyl)-2-oxazolidinone (**1**) with cyclopentadiene, an example for highly diastereoselective Diels–Alder reactions employing the Evans auxiliary (blue, abbreviated as R).[6] The transition structure commonly used to explain the observed stereoselectivity, a chelate of **1** with the Lewis acid, is shown on the right. Bottom: Conformers of **1** (including their shorthand notation: ap and sp denote the antiperiplanar and synperiplanar orientations of the two carbonyl groups relative to each other; c and t relate to the s-*cis* and s-*trans* configurations of the sp^2–sp^2 single bond of the crotonyl moiety).

alternative mechanism that questions the exclusive role of chelates has recently been proposed in a study using diethylaluminium chloride as a Lewis acid.[7]

There have been numerous attempts to determine the solution structures of these complexes and of the free *N*-crotonyloxazolidinones, for which the conformational equilibria in Figure 1 have been discussed in the literature.[7–11] Temperature and concentration-dependent one-dimensional nuclear magnetic resonance (1D-NMR) experiments on the complexes of **1** with $SnCl_4$ do not provide 3D structure information but agree with the proposed selectivity model,[8] although the selectivity is low with this particular Lewis acid.[6] Optimal selectivity was observed with >1.4 equivalents diethylaluminium chloride, for which Et_2Al^+ complexes with **1** were also studied using 1D-NMR.[9] Previous attempts to determine the structure of free **1** and its complexes with Lewis acids containing aluminium and magnesium in solution were done using two-dimensional (2D) NMR spectroscopy by through-space magnetization transfer (nuclear Overhauser effect spectroscopy, NOESY) and correlated spectroscopy (COSY).[7,10,11] NOE signals indicate the spatial proximity of nuclei,[12] whereas COSY determines vicinal couplings that can be used to deduce bond angles.[13,14] A source of difficulty that is frequently encountered in small- to medium-sized molecules is a low density of active nuclei, such that no suitable NOEs or through-bond couplings can be obtained. Accordingly, 2D-NMR experiments for **1** provide incomplete structural assignments because of the small number of useful cross peaks, which prevents the accurate determination of the conformational preferences. Furthermore, fast exchange processes occur under certain experimental conditions and preclude NMR structure determination (see the Supporting Information chapter 4.2).

Polarization-dependent 2D infrared (P2D-IR) spectroscopy offers a complementary approach to NMR spectroscopy, because it features sub-picosecond time resolution and allows the deduction of structural information from vibrations.[15–18] In a P2D-IR experiment, a vibration is selectively excited and the induced absorption change of this and other vibrations is probed. Similar to a 2D-NMR spectrum, the spectrum spans two frequency axes, one for the excitation frequency (*y* axis) and one for the probe frequency (*x* axis). Interactions between two vibrations, that is, couplings, lead to cross peaks between the vibrations that contain information about their proximity and relative orientations.[19,20] A very useful parameter for determining conformations is the angle between the transition dipole moments of two vibrations. This angle is accessible using P2D-IR spectroscopy.[17,21] Careful design of our experiment allows an accuracy for the angle as low as ±2°. Since vibrations are present in all molecules, structure determination using P2D-IR will be particularly helpful in systems with a sparse distribution of NMR-active nuclei, such as **1** and its $SnCl_4$ complexes.

Because of its sub-picosecond time resolution, P2D-IR spectroscopy is particularly well suited for structure determination in the presence of dynamic processes that occur on time scales faster than the intrinsic time resolution of an NMR experiment (typically milliseconds). Fast time scales are common for flexible molecules and conformational changes that occur upon complex formation, for example, substrate–catalyst association in the present case. NMR spectra of such fast processes are motionally averaged and the NMR parameters do not directly correspond to any of the involved species. In these situations, the P2D-IR spectra show the signals of the individual species, because the dynamics of these processes are essentially frozen.

In the following we show that P2D-IR spectroscopy in combination with computations using density functional theory (DFT) allows complete resolution of the conformational degrees of freedom of **1** that are important for controlling diastereoselectivity. The major conformer of **1** is determined and upper limits for the concentrations of the other conformers in Figure 1 are given. We unequivocally identify the coordination and conformation of **1** in the catalyst–substrate complex that forms upon addition of $SnCl_4$. In particular, the structural details of **1** and its complexes are resolved, even in the presence of dynamics that are fast on the NMR time scale. The structures identified for free and complexed **1** are in agreement with the relative free energies computed by DFT.

Results and Discussion

Solution structure of *N*-crotonyloxazolidinone: The conformers shown in Figure 1 have been previously discussed as potential solution structures of **1**.[7,10] They equilibrate through rotations around the σ bond of the crotonyl moiety and the amide bond and differ considerably in the relative orientation of the alkenyl and the two carbonyl groups. We show that P2D-IR spectroscopy in the spectral range of the vibrations involving these groups therefore allows the deter-

mination of the conformational preferences in solution; the corresponding bands are located at 1638 (ν_1), 1686 (ν_2), and 1776 cm^{-1} (ν_3). Figure 2a shows the P2D-IR spectra of **1** in CH_2Cl_2 for parallel (left) and perpendicular polarizations (right) of the pump and probe pulses; the IR absorption spectrum is shown on top for orientation.

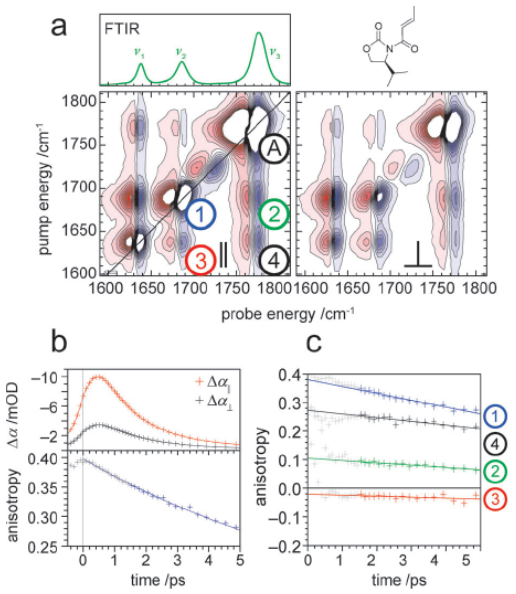

Figure 2. a) P2D-IR spectra of **1** in CH_2Cl_2 (1.5 ps). Left: parallel polarization and right: perpendicular polarization of the pump and probe pulses. The contour lines are spaced by 0.05 mOD. Signals larger than ±0.5 mOD are truncated. The FTIR spectrum is shown in the top panel for reference. b) Top: Time dependence of the diagonal peak intensity (negative signal) of ν_3 (see pos. A) for parallel (red) and perpendicular polarizations (black) in CH_2Cl_2; Bottom: Time dependence of the anisotropy calculated from the data points shown in the top panel (blue line: exponential fit to the data points with a time delay of more than 1.5 ps (blue), gray data points indicate the region when the pump and probe pulses overlap in time). c) Time dependence of the anisotropy for the signals labeled in Figure 2a. The straight lines show a linear fit to the data from 1.5 to 5 ps. For exponential fits of the data until 20 ps see the Supporting Information chapter 2.4.2. Diagonal peak ν_2: blue (see pos. 1); cross peak ν_2/ν_3: green (see pos. 2); cross peak ν_1/ν_2: red (see pos. 3); cross peak ν_1/ν_3: black (see pos. 4).

The P2D-IR spectra of **1** show three intense peaks along the diagonal, where the pump and probe pulses interact with the same vibration. The spectral positions of the diagonal peaks correspond to those in the absorption spectrum. Each peak consists of a positive (red) and negative (blue) contribution. The negative signal is caused by depopulation of the vibrational ground state after the vibration is excited to the first excited state. From there, stimulated emission occurs and also contributes to the negative signal. The positive signal is caused by absorption in the excited state. Positive and negative signals are separated by the vibrational anharmonicity.[15,22] A fourth, much weaker, diagonal peak is located at approximately 1725 cm^{-1}, which is redshifted by about 50 cm^{-1} from the diagonal peak at position A. This peak is assigned as a ^{13}C satellite of the peak at position A (see the Supporting Information chapter 2.4.3). In addition to the diagonal peaks, cross peaks between all three stretching vibrations occur, indicating that the vibrations are coupled to each other and are not localized on one individual bond.[15,23] By analyzing the polarization dependence of these cross peaks, the angles between the vibrational transition dipole moments are obtained from which the structure can be derived.

The size of the P2D-IR signal, $\Delta\alpha$, depends strongly on the relative polarization of pump and probe pulse. The difference can be quantified by the anisotropy $r(t)$ calculated as shown in Equation (1):

$$r(t) = \frac{\Delta\alpha_{||}(t) - \Delta\alpha_{\perp}(t)}{\Delta\alpha_{||}(t) + 2\Delta\alpha_{\perp}(t)} \quad (1)$$

in which $\Delta\alpha_{||}(t)$ and $\Delta\alpha_{\perp}(t)$ are the signal intensities for parallel and perpendicular polarization. For a fixed isotropic distribution of molecules in space, the anisotropy gives direct access to the angle θ between the transition dipole moments of the vibrations of the molecule through the relation given in Equation (2):[24]

$$\theta = \cos^{-1}\sqrt{\frac{5r+1}{3}} \quad (2)$$

Figure 2b shows the time-dependent signals $\Delta\alpha_{||}(t)$ and $\Delta\alpha_{\perp}(t)$ for the diagonal peak of ν_3 and the time-dependent anisotropy, $r(t)$, calculated from them. As the molecules rotate on the time scale of the time delay between the pump and probe pulses in a 2D-IR measurement, the anisotropy decays (Figure 2b, bottom) and it is essential to extrapolate the anisotropy to a delay time of $t=0$ to obtain exact values for θ.[25] Typical rotational correlation times for molecules of the size studied here are in the range from a few picoseconds to tens of picoseconds.[26,27]

The time dependence of the anisotropy of the diagonal and cross peaks labeled in Figure 2a (pos. 1 to 4, negative part of the signals) is shown in Figure 2c. The anisotropy of the diagonal peak of the vibration ν_2 (blue, see Figure 2a pos. 1) linearly extrapolates to 0.379(4), which is in good agreement with the exact value of 0.4 for a diagonal peak (angle 0°) and serves as an intrinsic validation of the experiment (see the Supporting Information chapter 2.4.1 for a detailed discussion). The anisotropy data points where the pump and probe pulses overlap (gray) were not used for the analysis. For the cross peak between ν_2 and ν_3 (see Figure 2a pos. 2), which is shown in green, we observed an anisotropy of 0.104(3) for zero delay time. Using Equation (2), this translates into an angle between the transition dipole moments of (44±3)°. Similar analysis of the cross peaks between the vibrations ν_1 and ν_2 (red, see Figure 2a pos. 3) and between ν_1 and ν_3 (black, see Figure 2a pos. 4) results in angles of (57±2)° and (28±3)°, respectively.

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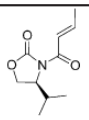
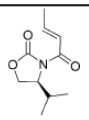
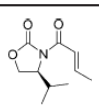
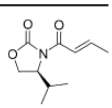
Table 1. Comparison between experimentally determined angles of **1** from P2D-IR in CH_2Cl_2 and the results of DFT computations (M06/6-31+G(d,p)/PCM/Bondi). The overall deviation of the three angles is expressed by the sum of the single deviations Δ_{total}.

					
	exptl	**1-apc**	**1-apt**	**1-spt**	**1-spc**
ν_1/ν_2 [°]	57±2	64 (Δ=7)	33 (Δ=24)	74 (Δ=17)	67 (Δ=10)
ν_1/ν_3 [°]	28±3	21 (Δ=7)	54 (Δ=26)	65 (Δ=37)	42 (Δ=14)
ν_2/ν_3 [°]	44±2	43 (Δ=1)	40 (Δ=4)	52 (Δ=8)	71 (Δ=27)
$\Delta_{total}=\Sigma\lvert\Delta_i\rvert$ [°]		15	54	62	51
ΔG_{298} [kcal mol^{-1}]		0	3.6	6.0	3.3

In the ideal case when the vibrations are localized on individual bonds, the angles between the transition dipole moments correspond directly to the bond angles of the molecule. However, in most cases the vibrations are delocalized over more than one bond[28] and the direction of the transition dipole moment with respect to the molecule is required to determine the structure. This can be accomplished using quantum chemical computations, for example, using DFT (see Computational Methods). The transition dipole moments were computed for the four conformers of **1** shown in Figure 1; Table 1 summarizes the DFT results and compares the computed angles with the measured angles.

The experimentally determined angles agree very well with the computations for the conformer **1-apc**. All other conformers show large differences compared with the measured values for at least one angle (up to 37° for the angle between ν_1/ν_3 in the case of **1-spt**). The measured IR frequencies also match best with those computed for **1-apc** (see the Supporting Information chapters 2.2 and 2.3). The small difference between the computed and experimental angles for **1-apc** may be due to the fact that although the computed structure is the energy minimum at 0 K, there is thermal motion at the finite temperatures of the experiment. Additionally, the DFT computations use the harmonic approximation, which may affect the transition dipole moment orientations.

The same measurements and analyses were performed for **1** in MeCN (see the Supporting Information chapter 2.4.2). Changing the solvent had little effect on the measured angles and the same conformer dominates in both solvents. This finding is in agreement with the similarity of the IR absorption spectra in the two solvents as well as with the relative free energies computed using DFT.

The P2D-IR measurements in combination with DFT computations clearly show that **1-apc** is the preferred conformer. By evaluating the P2D-IR signals at the frequencies determined from the computations for the other three conformers, we estimate the upper limit for the sum of their concentrations to be less than 5% (for a detailed analysis see the Supporting Information chapter 2.4.4). In particular, the population of **1-spc**, which is the precursor conformer used to rationalize the typically observed stereochemistry of the Diels–Alder reaction (Figure 1), is less than 0.2%. This is in agreement with a computed ΔG_{298} of 3.3 kcal mol^{-1} relative to **1-apc**. The conformational preference observed in solution was also seen in the crystal structure of **1** (see the Supporting Information chapter 2.6, CCDC-867200 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif). The DFT computations are in excellent agreement with the structural parameters obtained from crystallography. The results of NMR studies[7,10,11] (see the Supporting Information chapter 2.5) agree with the structure determined using P2D-IR. While NMR studies were inconclusive because they were based on the absence of cross peaks, the combination of P2D-IR spectroscopy and DFT computations allows for the distinction between all possible conformers and therefore the unambiguous determination of the structure of **1**.

Solution structure of the *N*-crotonyloxazolidinone tin(IV) chloride complex: Complexation of the dienophile **1** by the Lewis acid increases the reactivity and diastereoselectivity in Diels–Alder reactions.[6] There are two Lewis basic carbonyl groups in **1** and two important conformational degrees of freedom with a potential influence on diastereoselectivity. Accordingly, various 1:1 and 1:2 complexes have been discussed in the literature (Table 2).[6–8] As for free **1**, the complexes differ considerably in their transition dipole moment angles and we show that distinguishing between them using P2D-IR spectroscopy is therefore possible.

The carbonyl and alkenyl stretching vibrations of **1** shift to lower wavenumber upon complexation with $SnCl_4$ and are located at 1567 (ν'_1), 1633 (ν'_2), and 1726 cm^{-1} (ν'_3) (Figure 3a). The peaks in the P2D-IR spectrum shown in Figure 3a are altered compared with Figure 2a accordingly. The spectrum of the **1**·$SnCl_4$ complex is dominated by three intense diagonal peaks, as is the case for **1**. The cross peaks II and IV become more intense due to the increased extinction coefficient of the vibration ν'_3 and are as intense as the diagonal peaks. Minor signals on the diagonal originate from isotopologues and possibly from minor conformers (less than 15%); these are discussed in the Supporting Information (chapter 3.3). Here, we focus on the signals of the major conformer.

Figure 3b shows the time dependence of the anisotropy of the peaks labeled in Figure 3a (I: diagonal peak, II–IV: cross peaks). The changes compared with free **1** are apparent (see Figure 2c). First, the measured anisotropies are very different, reflecting a considerable change in the angles between the transition dipole moments. For instance, the ex-

Table 2. Comparison of the experimentally determined angles between the vibrations of **1**·$SnCl_4$ in CH_2Cl_2 and the results of DFT computations (M06/6-31+G(*d*,*p*)/SDD/PCM/Bondi).

	exptl	**1-spc**-κ²*O*,*O*′	**1-spt**-κ²*O*,*O*′	**1-apc**-κ*O*	**1-apc**-κ*O*′	**1-apt**-κ*O*′	**1-apc**-*1*κ*O*,*2*κ*O*′
ν'_1/ν'_2 [°]	11±6	16 (Δ=5)	24 (Δ=13)	56 (Δ=45)	81 (Δ=70)	38 (Δ=27)	84 (Δ=73)
ν'_1/ν'_3 [°]	45±2	46 (Δ=1)	20 (Δ=25)	80 (Δ=35)	20 (Δ=25)	44 (Δ=1)	5 (Δ=40)
ν'_2/ν'_3 [°]	49±2	61 (Δ=12)	42 (Δ=7)	44 (Δ=5)	61 (Δ=12)	38 (Δ=11)	89 (Δ=40)
$\Delta_{total}=\Sigma\lvert\Delta_i\rvert$ [°]		18	45	85	107	39	153
ΔG_{298} [kcal mol^{-1}]		0	6.5	8.4	6.7	10.2	–[a]

[a] The free energy of the di-tin-complex cannot be set into relation with the monocomplexes.

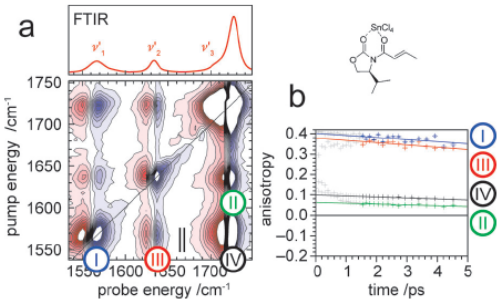


Figure 3. a) P2D-IR spectrum (parallel polarization, 1.5 ps) of the complex **1**·$SnCl_4$) in CH_2Cl_2 (c_1=6 mM; c_{SnCl4}=47 mM). The contour lines are spaced by 0.03 mOD; signals larger than ±0.3 mOD are truncated. The FTIR spectrum is shown in the top panel for reference. b) Anisotropy time dependence of the signals labeled in Figure 3a. Diagonal peak ν'_1: blue (see pos. I); cross peak ν'_2/ν'_3: green (see pos. II); cross peak ν'_1/ν'_2: red (see pos. III); cross peak ν'_1/ν'_3: black (see pos. IV).

trapolated anisotropy of the cross peak between the two low frequency modes (ν'_1/ν'_2) of **1**·$SnCl_4$ is 0.379(8) (see Figure 3b, red data points), whereas the corresponding cross peak for **1** (ν_1/ν_2) has an anisotropy of −0.021(5) (see Figure 2c, red data points). Second, the anisotropy of the diagonal peak (blue) decays approximately two times more slowly than that for **1** (see the Supporting Information chapter 3.3.3). This slowing of the rotational diffusion reflects the larger size of the complex.

As for free **1**, the anisotropy is obtained by linear extrapolation to zero time delay (straight lines) and provides the angles between the vibrational transition dipole moments, which are compared to DFT computations (Table 2).

The comparison shows that the chelate **1-spc**-κ²*O*,*O*′·$SnCl_4$ is the major complex. All other computed complexes show much larger deviations from the experimentally determined angles. The computed vibrational frequencies (see the Supporting Information chapter 3.2) support this conclusion. The computed free energies (Table 2) are consistent with **1-spc**-κ²*O*,*O*′·$SnCl_4$ being mainly populated. Previously published 1D-NMR studies of **1**·$SnCl_4$ concluded that a hexacoordinate Sn chelate with **1** formed.[8] This agrees with the structure determined using P2D-IR. As an important piece of additional information to define the diastereoselectivity of reactions with **1** as a substrate, P2D-IR spectroscopy revealed that the crotonyl conformation remains s-*cis* upon complex formation. Our 2D-NMR studies (see the Supporting Information chapter 3.4) support these conclusions and agree with studies of related systems that use Lewis acids other than $SnCl_4$.[7,10,11] Using diethylaluminium chloride as a Lewis acid, Santos and co-workers have identified a dimetal complex of **1** as the major species, leading to the proposal of an alternative selectivity model that is not based on chelation.[7] We rule out the presence of the corresponding Sn species, **1-apc**-*1*κ*O*,*2*κ*O*′·$SnCl_4$, based on the concentration dependence of our signals and the mismatch of the determined angles. Additional signals in the 2D-IR spectra (see the Supporting Information chapter 3.3.2) indicate a minor population (≤15%) of the s-*trans* conformer (**1-spt**-κ²*O*,*O*′·$SnCl_4$), which is not visible in the NMR spectra. The presence of this conformer may be the reason for a reduced diastereoselectivity of the reaction when using the Lewis acid $SnCl_4$.

Structure analysis in dynamic equilibrium: The P2D-IR data in Figure 3 used for structure determination were recorded with a large excess of $SnCl_4$ so that no uncomplexed **1** remained in solution. However, under the typical reaction conditions a mixture of rapidly interconverting species cannot be excluded. The ability to carry out structure analysis under such conditions is of particular interest and requires a method with faster time resolution than NMR spectroscopy. NMR data for an equimolar mixture of **1** and $SnCl_4$ recorded at room temperature show motional averaging and do not allow separate analysis of free **1** and the various **1**·$SnCl_4$ species that might coexist (see the Supporting Information chapter 4.2). P2D-IR spectroscopy on the other hand allows the distinction between interconverting species under these conditions (Figure 4). Compared with the ultrafast time resolution of the 2D-IR experiment, isomerization and complexation are slow and, therefore, motional averaging does not occur. Consequently, the spectrum can be thought of as the sum of the spectra of the different species present in the sample. Signals that belong to the same molecule are connected by a coupling pattern, as highlighted in Figure 4 by the colored grids. The 2D-IR signals of free **1**

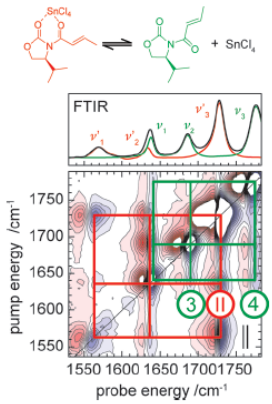


Figure 4. P2D-IR spectrum (parallel polarization) of an equimolar **1**:$SnCl_4$ mixture in CH_2Cl_2 (c_1 = 24 mM; c_{SnCl4} = 24 mM). The contour lines are spaced by 0.05 mOD. Signals larger than ±0.5 mOD are truncated. The signals that belong to the same molecule are connected by the grids. Green: free **1**; red: **1**·$SnCl_4$. The FTIR spectra of the mixture (black), **1** (green), and **1**·$SnCl_4$ (red) are shown in the top panel for orientation.

are connected with the green grid and are identical to the signals shown in Figure 2a. The signals of **1**·$SnCl_4$ are highlighted with the red grid and correspond to the signals shown in Figure 3a. Analyzing the cross peak anisotropies provides the same angles within the experimental error (see the Supporting Information chapter 4.1). The chelate **1**-spc-κ^2O,O'·$SnCl_4$, which is also found with an excess of $SnCl_4$, remains the dominant complex. This example demonstrates the possibility of analyzing the structures of several species interconnected by fast dynamic processes. Analysis is even possible when some of the absorption bands overlap completely, as is the case here for the bands ν'_2 (**1**-spc-κ^2O,O'·$SnCl_4$) and ν_1 (free **1**). Extracting the transition dipole moment angles is possible because the cross peaks are well separated for the different molecules (see Figure 4 pos. 3, 4, and II).

Conclusion

Using P2D-IR spectroscopy, *N*-crotonyloxazolidinone, which is a showcase example for the application of the Evans auxiliary in enantioselective Diels–Alder reactions, is determined to exist in the apc conformation in solution. Other conformations that have been previously discussed are not observed. Upon complexation with the Lewis acid $SnCl_4$, the amide bond rotates by 180°, as proposed by Evans. In the major complex structure identified using P2D-IR the sp^2–sp^2 single bond of the crotonyl moiety remains in the s-*cis* conformation, which supports the proposed selectivity model. Additional signals in the 2D-IR spectra indicate a minor population of the s-*trans* conformer (spt), potentially leading to the reduced diastereoselectivity using the Lewis acid $SnCl_4$. The structures formed in the presence of other common Lewis acid catalysts, such as Me_2AlCl, are under debate as well and will be investigated using a future P2D-IR setup capable of low temperature measurements.

The present study of the structures of the free *N*-crotonyloxazolidinone and its Lewis acid complex demonstrates that ultrafast P2D-IR spectroscopy provides detailed information about molecular structures, even when fast dynamic processes occur and when the molecules are highly functionalized, which can cause a low proton density for NMR structure determination. P2D-IR spectroscopy is therefore an excellent complement to NMR spectroscopy and particularly useful in cases where detailed structure information is highly desired, that is, in reactive, medium-sized molecules and short-lived intermediates, which often contain a number of heteroatoms and unsaturated moieties that lead to pronounced vibrational transitions. With the strengths demonstrated here, P2D-IR spectroscopy has the potential to become an integral part of organic chemists' toolboxes for structure determination and the elucidation of reaction mechanisms.

Experimental Section

Sample preparation: All materials were obtained from commercial suppliers and were used without further purification, unless otherwise noted. (*S*)-4-Isopropyl-oxazolidin-2-one was prepared as described by Benoit et al.[29] (4*S*)-3-[(*E*)-2-Butenoyl]-4-(1-methylethyl)-2-oxazolidinone (**1**) was synthesized following the protocol of Evans et al.[6] and stored under reduced pressure in a desiccator over P_2O_5. The enantiomeric purity was determined by polarimetry and was identical to that previously reported.[6] Tetrahydrofuran was dried over KOH, then distilled from sodium and stored under argon over sodium. Purification of **1** was achieved by flash chromatography (silica gel 60; particle size 230–400 mesh).

For the P2D-IR and FTIR measurements of **1** a 37 mM solution in the denoted solvent was used. The **1**·$SnCl_4$ complex was prepared by dissolving **1** (6.3 mM) and tin(IV) chloride (47 mM) in dichloromethane (CH_2Cl_2). Partial complexation was achieved in a 1:1 solution of **1** and $SnCl_4$ (24 mM) in CH_2Cl_2. The sample solutions were filled into a flow cell with CaF_2 windows and an optical path length of 100 μm (measurements of **1**) or 250 μm (tin complex measurements).[30]

P2D-IR spectroscopy: Mid-IR pulses (($\approx$2.4 μJ pulse^{-1}, center frequency $\approx$1660 cm^{-1}, bandwidth $\approx$200 cm^{-1} FWHM, pulse duration $\approx$150 fs) were generated in an optical parametric amplifier (OPA) with subsequent difference frequency generation.[31] The OPA was pumped by a Ti:sapphire-oscillator/amplifier system (Spectra Physics, Spitfire XP, 800 nm, 120 fs, 1 kHz; see the Supporting Information chapter 1.4 for the details of the mid-IR generation). In the pump-probe 2D-IR setup, which is based on the concept of Hamm et al.,[32] the probe and reference beams (both $\approx$50 nJ pulse^{-1}) were separated from the pump beam using a barium fluoride wedge and focused with an off-axis parabolic mirror into the sample (spot size $\approx$80 μm FWHM). The pump beam was spectrally narrowed by a computer controlled Fabry–Perot filter (6th order, $\approx$11 cm^{-1} FWHM, pulse length $\approx$1.2 ps), passed over a computer-controlled delay line and was mechanically chopped with 500 Hz. It was focused into the sample with a spot size of $\approx$130 μm (FWHM) in spatial overlap with the probe beam. Special care was taken to obtain proper polarization of the beams. The polarization of the pump beam was rotated by 45° relative to the probe and reference beam polarization.[25,33,34] The polarization contrast at the sample position was >1400:1 for the pump beam and >1200:1 for the probe and reference beam. Directly after the sample, the probe and reference beams passed through a motorized, computer-controlled polarizer and were then collimated. Since the motorized polarizer swapped its position every 300 laser shots between +45° and −45°, it was possible to quasi-simultaneously measure the spectra for parallel and perpendicular

polarization.[25,33,35] Both beams were then frequency dispersed in a spectrometer onto a 2×32 pixel mercury–cadmium–telluride detector array.

All spectra shown were measured in four blocks to span the whole spectral region of interest with sufficient resolution. All four blocks were measured directly after each other with minimal changes to the setup, that is, no changes of the mid-IR spectrum of the OPA. Subsequently the blocks were set together to the final spectrum without further treatment, that is, no scaling of the signal intensities.

Computational methods: All computations were performed using the Gaussian 09 suite of programs, using DFT with Truhlar's hybrid *meta*-exchange-correlation functional M06 in conjunction with the 6-31+G(d,p) basis set.[36,37] Computations on Sn containing species were performed using a 6-31+G(d,p) basis set with Stuttgart/Dresden effective core potentials (SDD) on the Sn atoms.[38] The M06 functional has been recommended for computations of organometallic species and for studies of non-covalent interactions, thermochemistry, and kinetics.[37] The 6-31+G(d,p) basis set has been chosen because a further increase of basis set size and thus computational cost led to only minor changes in the computed transition dipole moment angles (Figure S1 in the Supporting Information). The solvent was taken into account by the self-consistent reaction field (SCRF) method, using the polarizable continuum model (PCM) with van der Waals radii of Bondi with the Gaussian 09 default scaling of 1.1 and explicit hydrogen atoms.[39,40] The frequently used united atom topological models UAHF and UAKS do not take into account hydrogen atoms explicitly to create the solute cavity. Computations using these models in some cases resulted in unphysically long C–H bond lengths and low C–H stretching frequencies and were therefore not used.

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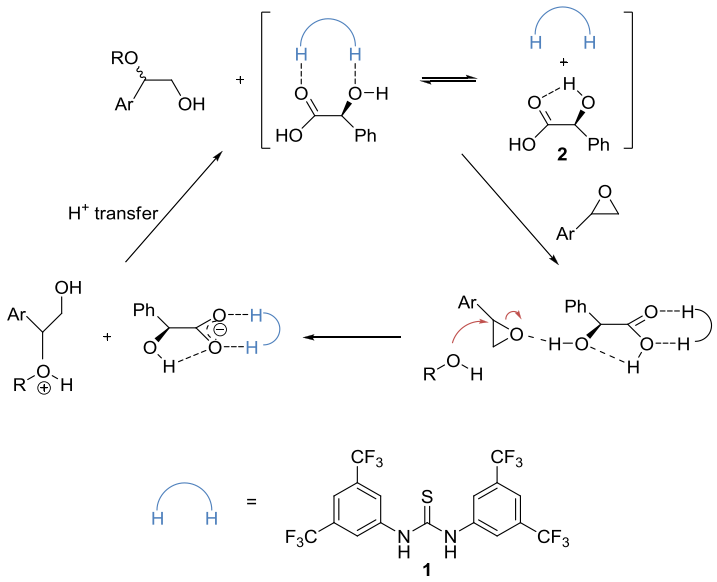
4 Mechanistic Studies on the Organocatalytic Alcoholysis of Styrene Oxides

Introduction

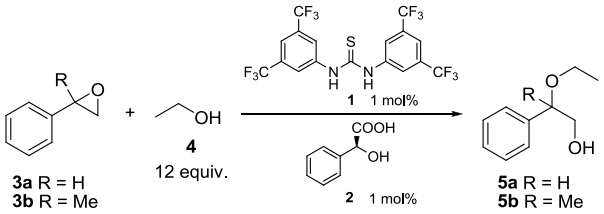
The versatility of epoxide openings has led to a widespread utilization of these reactions in organic syntheses.[1-3] Typically, the opening of epoxides by nucleophiles is catalyzed by Brønsted or Lewis acids. Some examples for this are the use of metal salts such as magnesium perchlorate or calcium chloride,[4] iron(III) montmorillonite,[5] a phosphaferrocene,[6] $BF_3{\cdot}Et_2O$,[7] or aluminum triflate,[8] and many more Lewis acids. Some very recent examples include titanoniobate nanosheets co-doped with sulfur or iron,[9] palladium nanoparticles,[10] or a mixture of gallium(III) chloride and polyvinylpyrrolidone.[11] The group around Iranpoor performed numerous studies on the alcoholysis of epoxides using, *e.g.*, ceric(IV) ammonium nitrate,[12] 2,3-dichloro-5,6-dicyano-*p*-benzoquinone,[13] iron(III) chloride,[14] tris[trinitratocerium(IV)]paraperiodate,[15] $TiCl_3(OTf)$ and $TiO(TFA)_2$,[16] or aluminumdodecatungstophosphate ($AlPW_{12}O_{40}$).[17]

The first organocatalytic conversion of epoxides was reported in 1985 when Hine *et al.* showed 1,8-biphenylenediol to be a catalyst for the opening of epoxides with nucleophiles.[18-19] In 2006, Kleiner and Schreiner were able to develop an organocatalyzed aminolysis of epoxides utilizing *N*,*N*'-bis[3,5-bis(trifluoromethyl)phenyl]thiourea (**1**).[20] Further studies focused on the alcoholysis of epoxides. In 2008, our group published a regioselective alcoholysis of styrene oxides.[21] This reaction was only feasible when catalyzed cooperatively by *N*,*N*'-bis[3,5-bis(trifluoromethyl)phenyl]thiourea (**1**) and mandelic acid (**2**, pK_a = 3.41[22]). The proposed mechanism involves a ternary complex between **1**, **2** and styrene oxide (Scheme 1).



Scheme 1 Proposed mechanism for the regioselective alcoholysis of styrene oxides cooperatively catalyzed by **1** and **2**

Interestingly, the course of the reaction is not a linear process. There is a moment in which the reaction is accelerated. Thus, we started the investigation of the reaction's mechanism utilizing styrene oxide (**3a**) and 2-methyl-2-phenyloxirane (**3b**) (Scheme 2).[23]



Scheme 2 Organocatalytic, regioselective ethanolysis of **3a** and **3b**

Based on these preliminary studies – including the surprising result that styrene oxide (**3a**) had been opened by ethanol within 3 h instead of 22 h in a competition experiment with **3b** – we extended our studies to the observation of autocatalytic effects. Such effects could not be observed by Weil *et al.* when they added the respective *β*-alkoxy alcohol to the reaction mixture.[21]

Results and Discussion

In course of the present thesis we repeated the competition experiment done in our preliminary studies on this reaction. This competition experiment was done to compare the reaction times of styrene oxide (**3a**) and 2-methyl-2-phenyloxirane (**3b**). Figure 1 shows the simulta-

neous ethanolysis of **3a** and **3b** catalyzed by 1 mol% **1** and 1 mol% **2**. The opening of styrene oxide takes place within 4 h consistent with our previous experiment. The ethanolysis of styrene oxide without **3b** needs 22 h until completion. Figure 2 shows a graphical comparison of these findings. Thus, the presence of **3b** or the corresponding alcohol 2-ethoxy-2-phenyl-1-propanol (**5b**) is shown to be promoting the ethanolysis of styrene oxide.

In the next step, we performed the reaction upon addition of 10 mol% of **3b**. Under these conditions, the ethanolysis of styrene oxide took place within 7 h. This confirms **3b** or the corresponding alcohol **5b** to be a catalyst for this reaction. A graph depicting the course of this reaction is shown in Figure 3.

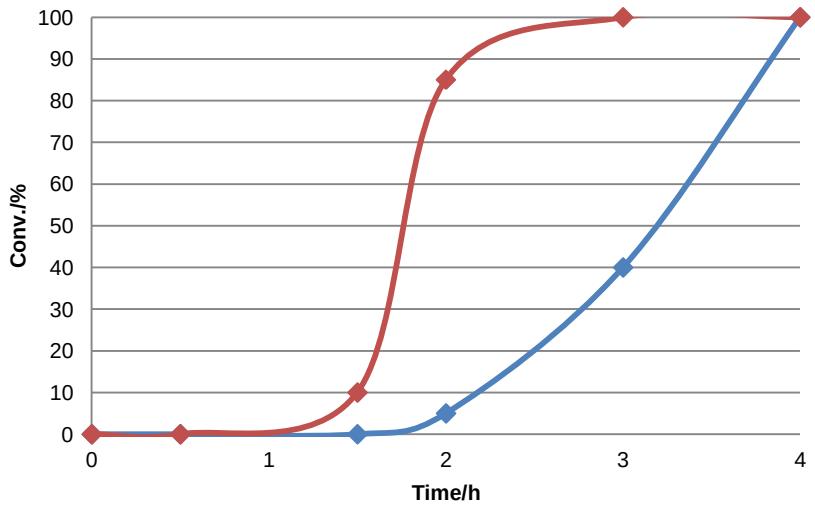


Figure 1 Temporary course of the simultaneous ethanolysis of equimolar amounts of styrene oxide (**3a**, blue) and 2-methyl-2-phenyloxirane (**3b**, red) catalyzed by 1 mol% **1** and 1 mol% **2** at rt under ambient atmosphere (determined by GC/MS analysis)

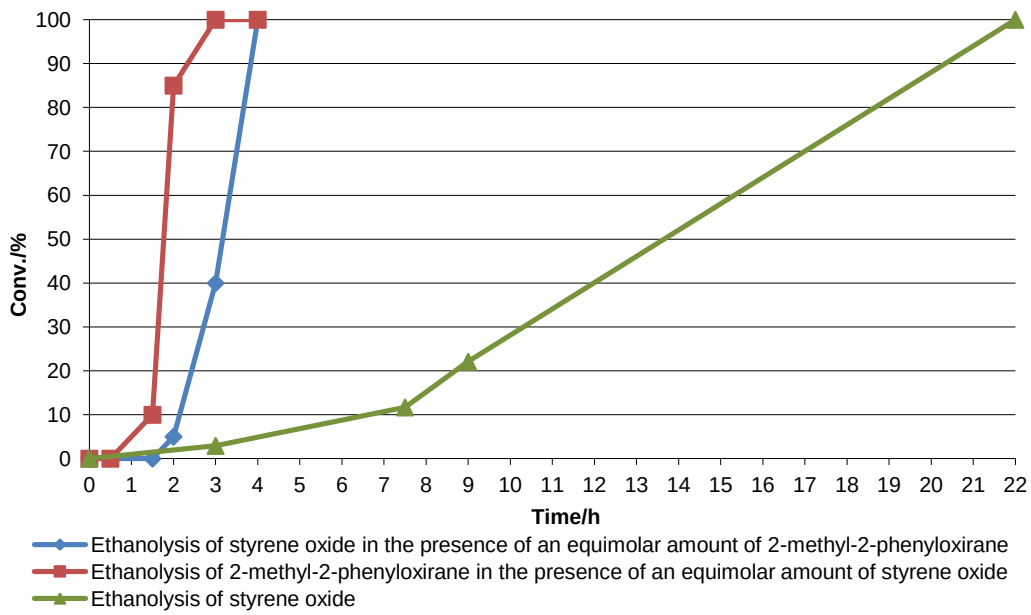


Figure 2 Comparison of the competition experiment (*cf.* Figure 1) and the ethanolysis of styrene oxide catalyzed by 1 mol% **1** and 1 mol% **2** at rt under ambient atmosphere (determined by GC/MS analysis)

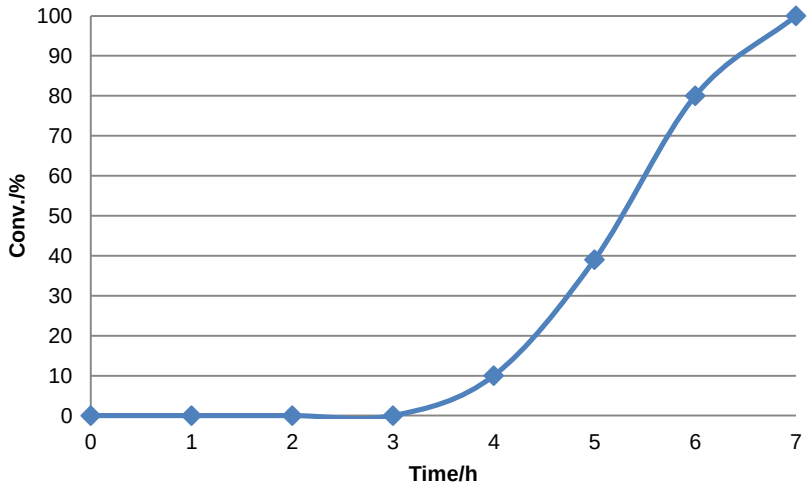


Figure 3 Temporary course of the ethanolysis of styrene oxide (**3a**) catalyzed by 1 mol% **1**, 1 mol% **2**, and 10 mol% of 2-methyl-2-phenyloxirane (**3b**) at rt under ambient atmosphere (determined by GC/MS analysis)

To complete these studies on autocatalysis we examined the opening of styrene oxide with ethanol under four different conditions (Figure 4). First of all, we reacted styrene oxide (**3a**) in the presence of 1 mol% **1** and 1 mol% **2** as well as 10 mol% of 2-ethoxy-2-phenyl-1-propanol (**5b**). The GC/MS analysis showed a full conversion of **3a** within 10 h. Our next test reaction was performed under the presence of 1 mol% **1** and 10 mol% **5b**. In this case, no conversion was observed within 13 h. In a third experiment we tried the addition of 1 mol% **2** and 10

mol% **5b**. Under these conditions, a conversion of less than 10% of the epoxide could be observed after 13 h. In the last case, only 10 mol% of **5b** were added. As in the second case, no conversion was observable within 13 h. Thus, 2-ethoxy-2-phenyl-1-propanol (**5b**) increases the reaction rate of the organocatalyzed ethanolysis of styrene oxide whereas **5a** was not capable to do this at all.[21]

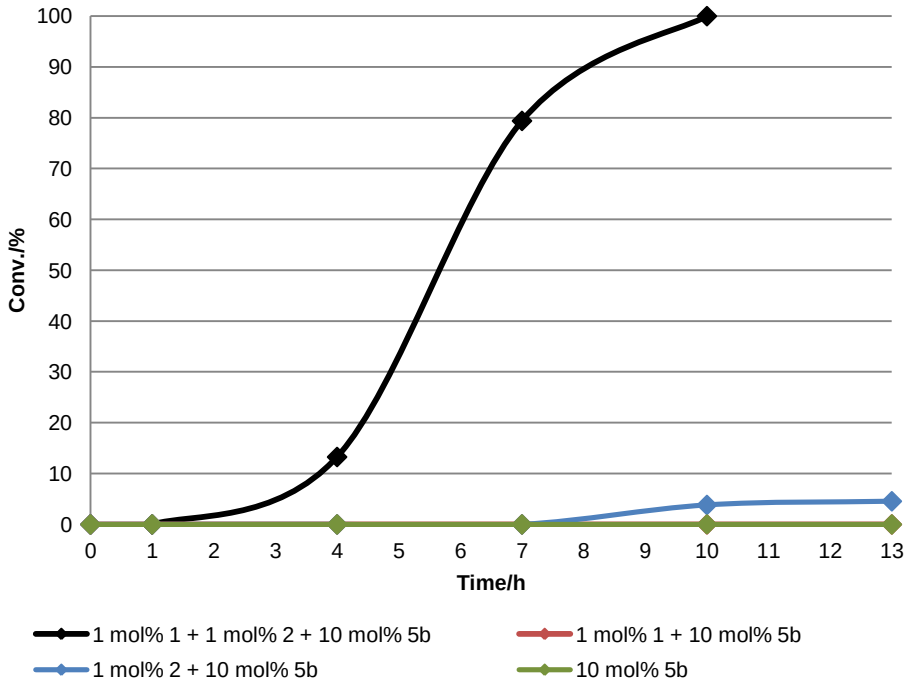
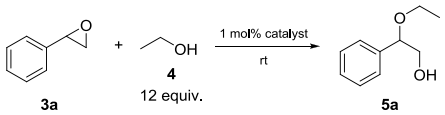
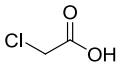
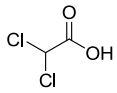
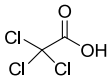


Figure 4 Temporary course of the ethanolysis of styrene oxide (**3a**) catalyzed by 1 mol% **1**, 1 mol% **2**, and/or 10 mol% **5b** at rt under ambient atmosphere (determined by GC/MS analysis) [The red line is hidden under the green one]

In a last panel of experiments, we screened three chloroacetic acids with decreasing pK_a values as sole catalysts in the ethanolysis of styrene oxide (Table 1). This was done to find out if the acid's pK_a value is an important fact for the epoxide opening. Using monochloroacetic (pK_a = 2.86)[24] the conversion of styrene oxide (**3a**) was only 13% after 22.5 h. When we utilized dichlororacetic acid (pK_a = 1.29)[24] full conversion of **3a** could be observed within 24 h. However, when we tried trichloroacetic acid (pK_a = 0.65)[24] a conversion of 80% after 28 h was found leading to the assumption that there is an optimal pK_a of the acid employed as a (co)catalyst in the ethanolysis of styrene oxides. Thus, we propose a mechanism where the complexation of mandelic acid (**2**) by thiourea derivative **1** lowers the acid's pK_a to the range where the alcoholysis of the epoxide is catalyzed smoothly.

Table 1 Ethanolysis of styrene oxide (**3a**) with 1 mol% of a chloroacetic acid



Catalyst	pK_a	Time/h	Conv./%[a]
	2.86	22.5	13
	1.29	24	100
	0.65	28	80

[a] GC/MS analysis

Conclusions

With a series of experiments we were able to show that the presence of 2-ethoxy-2-phenyl-1-propanol (**5b**) catalyzes the ethanolysis of styrene oxide (**3a**). Furthermore, we proposed based on our experiments with carboxylic acids that the pK_a value of the acid employed seems to be important for the reaction.

Experimental Section

General Remarks

All chemicals were purchased from Acros Organics, Alfa Aesar, Fluka, Merck, and Sigma Aldrich in the highest purity available. Argon (99.99%) was purchased from Messer-Griesheim. Styrene oxide was distilled *in vacuo* over a Vigreux column. 2-Methyl-2-phenyloxirane was synthesized according to the method of Wallace and Battle.[25] Ethanol was distilled from sodium/phthalic acid diethyl ester. Distilled chemicals were stored under an Argon atmosphere over molecular sieve 3 Å. All reactions were run in oven-dried, single-necked 10 mL flasks (Schott DURAN®) with PTFE-coated magnetic stirring bars. Mandelic acid was directly weighed into the reaction flasks; the thiourea derivative was weighed into an Eppendorf cup and added to the flask. Liquid chemicals were transferred with 1 mL syringes with thin cannulas. The reaction outcome was determined by GC/MS analyses with a Quadrupol-MS HP MSD 5971 and a HP 5890A GC equipped with a HP5 crosslinked silica GC column (25 m × 0.2 mm, 0.33 micron stationary phase: 5% phenyl and 95% methyl silicone) using helium as carrier gas; temperature program: 60–250 °C (heating rate: 15 °C/min),

injector and transfer line 250 °C. Samples were taken directly from the stirred reaction mixture with a 10 µL Hamilton syringe and were injected immediately.

Typical Procedure

Mandelic acid (**2**, 1.5 mg, 1 mol%) was weighed into an oven-dried, one-necked 10 mL flask followed by addition of **1** (5.2 mg, 1 mol%). Then, the mixture was dissolved in ethanol (**4**, 0.7 mL, 12 mmol, 12 equiv.) under stirring at rt. After this, styrene oxide (**3a** 0.11 mL, 1 mmol) and 2-methyl-2-phenyloxirane (**3b**, 13.16 µL, 10 mol%) were added simultaneously.

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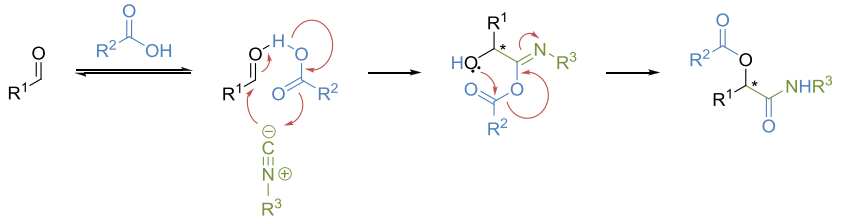
5 An Uncatalyzed Passerini Reaction

Introduction

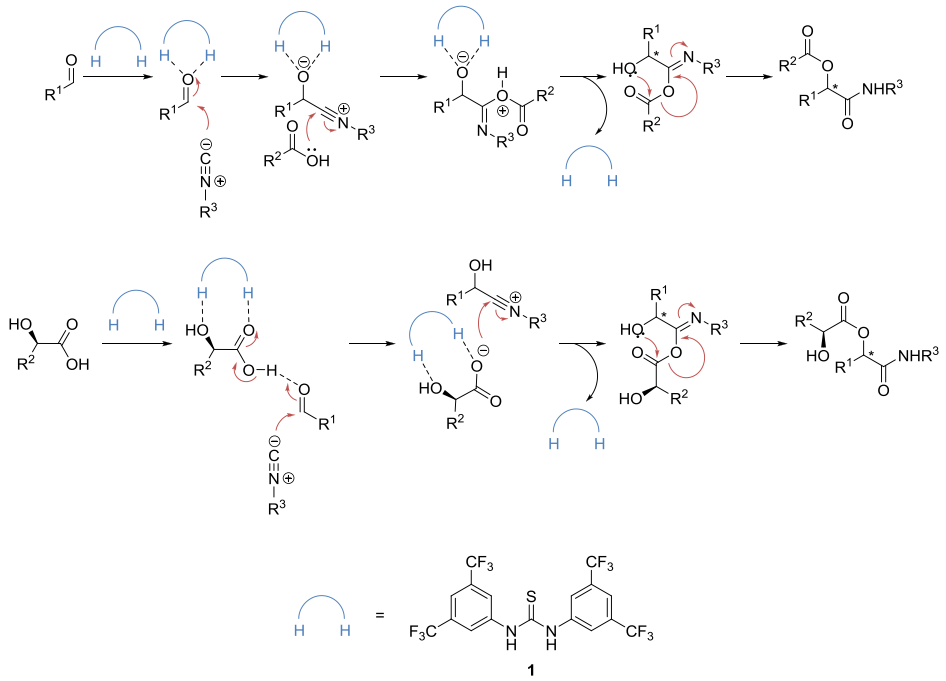
The three-component reaction between an aldehyde, a carboxylic acid and an isocyanide today is called the Passerini reaction.[1-3] The reaction is named after Passerini who published a reaction between *p*-isonitrilazobenzene with acetone, acetic acid and hydrogen peroxide in acetone in 1921.[4-5] The mechanism involves a hydrogen-bonding interaction between the carbonyl compound and the carboxylic acid (Scheme 1).[3]



Scheme 1 Mechanism of the Passerini reaction

In 2002, Xia and Ganem published a variant of the Passerini reaction where the carboxylic acid had been replaced by zinc(II) triflate; this reaction furnished new heterocycles.[6] Das Sarma and Pirrung were able to show that water accelerates Passerini and Ugi reactions.[7] In 2004, Schreiber and coworkers published a stereocontrolled Passerini reaction catalyzed by 20 mol% of a tridentate Cu(II) Lewis acid catalyst.[8] They achieved moderate to high ee's of 62–98%. Mironov *et al.* found *N*-hydroxy succinimide to be an accelerant for Passerini reactions.[9] Ngouansavanh and Zhu published a method for the utilization of alcohols instead of aldehydes in the Passerini reaction.[10] They were able to convert the alcohols in the presence of *o*-iodobenzoic acid to the Passerini products. Denmark and Fan found a system consisting of silicon tetrachloride and a chiral bisphosphoramide to be an efficient catalyst for enantioselective Passerini reactions.[11] Andrade *et al.* were able to conduct Passerini reactions in ionic liquids or polyethylene glycol.[12] In 2008, Wang, Zhu and coworkers identified an aluminum(III) salen complex as a catalyst for an enantioselective Passerini reaction.[13] This system was leading to ee's of 63 to >99%.

Thiourea derivatives are known for their analogy to Lewis acids and for coordinating aldehydes or carboxylic acids.[14-17] Hence we reasoned that an organocatalytic variant of the Passerini reaction involving hydrogen bonding mimicking Lewis acid catalysis could be feasible. Scheme 2 shows two possible mechanisms for a hypothetic organocatalytic variant of the Passerini reaction.

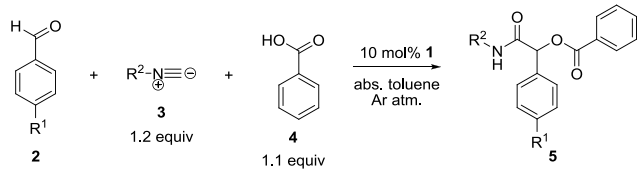


Scheme 2 Possible mechanisms for a hypothetic organocatalyzed Passerini reaction

Results and Discussion

At first, we screened various benzaldehyde derivatives and isocyanides in the Passerini reaction. The first reactions we performed at room temperature. In these cases, the reaction was furnishing the products even without any catalyst. Thus, we decided to lower the temperature to 0 °C. Even at this lower temperature the products formed without the addition of a catalyst. Therefore, we lowered the reaction temperature to –10 °C. Still, precipitation of substances without any catalyst could be observed; *via* NMR spectroscopy these substances could be identified – as in the former cases – as the desired products. Interestingly, the reaction of 4-hydroxybenzaldehyde with cyclohexylisocyanide at 0 °C did not furnish any product. Only the starting compounds could be found.

Table 1 Passerini reaction of various aldehydes with isocyanides and benzoic acid



R^1		R^2		Temperature	Product
Cl	**2a**	4-OMe-Ph	**3a**	rt	**5a**
Cl	**2a**	2-Naphthyl	**3b**	rt	**5b**
Cl	**2a**	*n*-Bu	**3c**	rt	**5c**
Cl	**2a**	Cy	**3d**	rt	**5d**
OH	**2b**	Cy	**3d**	rt	**5e**
Cl	**2a**	Cy	**3d**	0 °C	**5d**
Br	**2c**	Cy	**3d**	0 °C	**5f**
OH	**2b**	Cy	**3d**	0 °C	-[a]
Cl	**2a**	Cy	**3d**	–10 °C	**5d**
OH	**2b**	Cy	**3d**	–10 °C	**5e**
Br	**2c**	Cy	**3d**	–10 °C	**5f**
H	**2d**	Cy	**3d**	–10 °C	**5g**

[a] Only the substrate 4-hydroxybenzaldehyde (**2b**) could be observed in the NMR spectrum

Conclusions

Surprisingly, the Passerini reaction is feasible without any catalyst with most of the starting compounds we screened, even at relatively low temperatures. We were able to synthesize seven Passerini products, all of which were isolated and fully characterized *via* NMR and IR spectroscopy as well as HRMS and CHN analysis.

Experimental Section

General Remarks

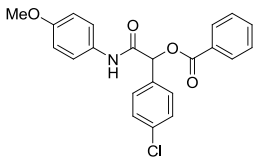
All chemicals were purchased from Acros Organics, Alfa Aesar, Fluka, Merck, and Sigma Aldrich in the highest purity available and were used – unless otherwise noted – without further purification. DMSO-d_6 was purchased from Deutero GmbH and stored over MS 3 Å. Argon (99.99%) was purchased from Messer-Griesheim. Benzaldehyde was used after distillation *in vacuo*. Toluene was distilled from sodium/benzophenone ketyl and stored under an Argon atmosphere over molecular sieve 3 Å. Cleaning of glassware and stirring bars was done in a laboratory washer with first Extran© (Merck), then phosphoric acid, and last fresh water. Drying was done in an oven. All reactions were run in oven-dried 10 mL Schlenk

flasks or reaction tubes (Schott DURAN®) with PTFE-coated magnetic stirring bars. The flasks and tubes – sealed with glass plugs equipped with PTFE thin wall sleeves – were heated with a heatgun *in vacuo*, and flushed with Argon (3×). The thiourea derivative, benzoic acid, solid isocyanides, and solid aldehydes were weighed into Eppendorf cups and then transferred into the reaction vessels. Benzaldehyde and liquid isocyanides were transferred with Eppendorf pipettes. The reaction outcome was determined by NMR analyses with a Bruker Avance II 400 MHz (AV 400) spectrometer using as standard the solvent residual peaks of DMSO-d_6 [$\delta(^1H)$ = 2.50 ppm; $\delta(^{13}C)$ = 39.5 ppm]. IR spectra were measured with Bruker IFS25 and IFS48 spectrophotometers. HRMS were recorded with a Sectorfield-MS: Finnigan MAT 95. ESI-MS was performed with a Bruker MicroTOF. CHN analyses were obtained with a Carlo Erba 1106 (balance: Mettler Toledo UMX-2) analyzer.

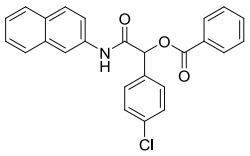
Typical Procedure

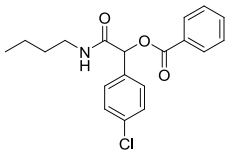
A reaction tube flushed with Argon and filled with toluene (5 mL) was cooled to 0 °C by a cryostat. 4-Bromobenzaldeyde (**2c**, 1 mmol, 184.9 mg), thiourea derivative **1** (49.7 mg, 0.1 mmol, 10 mol%), and benzoic acid (**4**, 134.6 mg, 1.1 mmol, 1.1 equiv.) were weighed into Eppendorf cups, and transferred into a reaction tube under positive Argon pressure. Then, cyclohexylisocyanide (98%, **3d**, 149.2 µL, 1.2 mmol, 1.2 equiv.) was added. The reaction mixture was stirred overnight at rt which was leading to precipitation of a colorless solid. The solid was filtered off, washed with toluene, and dried in an evacuated desiccator over Sicapent® and paraffin. The solid was identified as product **5f** by NMR analysis.

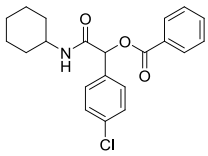
α-(Benzoyloxy)-4-chloro-*N*-(4-methoxyphenyl)benzeneacetamide (5a). New compound.



Brown solid. **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 8.06 (d, 2H, *J* = 7.2 Hz), 7.70 (d, 3H, *J* = 8.1 Hz), 7.59 (d, 2H, *J* = 7.8 Hz), 7.54 (d, 3H, *J* = 8.8 Hz), 7.47 (d, 2H, *J* = 9.1 Hz), 6.88 (d, 2H, *J* = 9.1 Hz), 6.22 (s, 1H), 3.71 (s, 3H) ppm. **^{13}C NMR** (100 MHz, DMSO-d_6): δ = 134.3 (C_q), 133.8 (C_q), 129.5 (CH), 129.2 (CH), 129.2 (CH), 128.9 (CH), 128.7 (CH), 128.5 (CH), 120.9 (CH), 113.9 (CH), 55.1 (C_q) ppm. **IR** (KBr disc): $\tilde{\nu}$ = 3443, 3292, 1732, 1666, 1542, 1514, 1249, 708 cm^{-1}. **HRMS**: calcd for $C_{22}H_{18}ClNO_4$ $[M]^+$ 395.0924, found 395.0917. **CHN analysis**: calcd C 66.75, H, 4.58, N 3.54; found C 65.72, H 4.65, N 3.88.

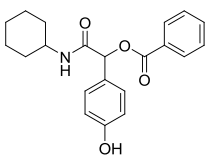
α-(Benzoyloxy)-4-chloro-*N*-(2-naphthyl)benzeneacetamide (5b). New compound. Brown solid.  **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 8.25 (s, 1H), 7.95 (d, 1H, *J* = 8.2 Hz), 7.90–7.78 (m, 4H), 7.71 (d, 1H, *J* = 7.5 Hz), 7.62–7.54 (m, 6H), 7.53–7.38 (m, 4H), 6.32 (s, 1H) ppm. **^{13}C NMR** (100 MHz, DMSO-d_6): δ = 166.5 (C_q), 135.8 (C_q), 130.0 (C_q), 129.5 (CH), 129.3 (CH), 128.9 (CH), 128.8 (CH), 128.5 (CH), 127.5 (CH), 127.3 (CH), 126.5 (CH), 124.9 (CH), 119.8 (CH), 115.8 (CH), 75.1 (CH) ppm. **IR** (KBr disc): $\tilde{\nu}$ = 3444, 1728, 1666, 1632, 1605, 1272, 1250, 710 cm^{-1}. **HRMS**: calcd for $C_{25}H_{18}ClNO_3$ $[M]^+$ 415.0975, found 415.0969. **CHN analysis**: calcd C 72.20, H, 4.36, N 3.37; found C 70.24, H 4.43, N 3.83.

α-(Benzoyloxy)-4-chloro-*N*-(*n*-butyl)benzeneacetamide (5c). New compound. Colorless solid.  **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 8.39 (t, 1H, *J* = 5.6 Hz), 8.05 (d, 2H, *J* = 7.7 Hz), 7.70 (t, 1H, *J* = 7.4 Hz), 7.61 (d, 2H, *J* = 8.3 Hz), 7.56 (t, 2H, *J* = 7.4 Hz), 7.50 (d, 1H, *J* = 8.8 Hz) ppm. **^{13}C NMR** (100 MHz, DMSO-d_6): δ = 167.5 (C_q), 165.0 (C_q), 135.2 (C_q), 133.9 (C_q), 133.5 (CH), 131.3 (CH), 129.7 (CH), 129.3 (C_q), 129.2 (CH), 129.0 (CH), 128.9 (CH), 128.7 (CH), 75.1 (CH), 38.4 (CH_2), 31.2 (CH_2), 19.5 (CH_2), 13.8 (CH_3) ppm. **IR** (KBr disc): $\tilde{\nu}$ = 3427, 3279, 1726, 1657, 1261 cm^{-1}. **HRMS**: calcd for $C_{19}H_{20}ClNO_3$ $[M]^+$ 345.1132, found 345.1119. **CHN analysis**: calcd C 65.99, H, 5.83, N 4.05; found C 64.22, H 5.53, N 3.53.

α-(Benzoyloxy)-4-chloro-*N*-cyclohexylbenzeneacetamide (5d). Colorless solid. **^{1}H NMR**  (400 MHz, DMSO-d_6): δ = 8.29 (d, 1H, *J* = 7.7 Hz), 8.04 (d, 2H, *J* = 7.7 Hz), 7.70 (t, 1H, *J* =7.5 Hz), 7.62 (d, 2H, *J* =8.6 Hz), 7.56 (t, 2H, *J* = 7.7 Hz), 7.50 (d, 2H, *J* = 8.5 Hz), 6.06 (s, 1H), 3.50 (m, 1H), 1.81–1.47 (m, 5H), 1.31–1.01 (m, 5H) ppm. **^{13}C NMR** (100 MHz, DMSO-d_6): δ = 166.7 (C_q), 165.0 (C_q), 135.2 (C_q), 133.9 (CH), 133.4 (C_q), 129.7 (CH), 129.3 (C_q), 129.2 (CH), 129.0 (CH), 128.7 (CH), 75.0 (CH), 47.9 (CH), 33.4 (CH_2), 32.2 (CH_2), 25.3 (CH_2), 24.6 (CH_2), 24.5 (CH_2) ppm. **IR** (KBr disc): $\tilde{\nu}$ = 3443, 3276, 1726, 1655, 1565, 1264, 1118 cm^{-1}. **HRMS**: calcd for $C_{21}H_{22}ClNO_3$ $[M]^+$ 371.1288, found 371.1256. **CHN analysis**: calcd C 67.83, H, 5.96, N 3.77; found C 67.06, H 5.84, N 3.64.

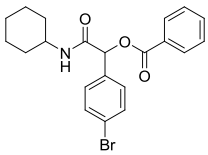
These values are comparable to the ones mentioned by Sotelo *et al*.[18]

α-(Benzoyloxy)-4-hydroxy-*N*-cyclohexylbenzeneacetamide (5e). New compound. Colorless



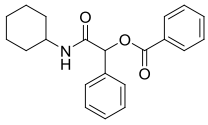
solid. **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 9.58 (s, 1H), 8.11 (d, 1H, *J* = 8.0 Hz), 8.01 (d, 2H, *J* = 8.0 Hz), 7.68 (t, 1H, *J* = 7.5 Hz), 7.54 (t, 2H, *J* = 7.7 Hz), 7.37 (d, 2H, *J* = 8.7 Hz), 6.78 (d, 2H, *J* = 8.8 Hz), 5.94 (s, 1H), 3.50 (br s, 1H), 1.81–1.45 (m, 5H), 1.33–0.99 (m, 5H) ppm. **^{13}C NMR** (100 MHz, DMSO-d_6): δ = 187.0 (C_q), 167.1 (C_q), 165.1 (C_q), 165.0 (C_q), 157.7 (C_q), 133.5 (CH), 129.4 (CH), 129.3 (CH), 128.8 (CH), 128.7 (CH), 126.3 (CH), 115.1 (CH), 75.4 (CH), 47.6 (CH), 32.2 (CH_2), 32.0 (CH_2), 25.1 (CH_2), 24.5 (CH_2), 24.4 (CH_2) ppm. **IR** (KBr disc): $\tilde{\nu}$ = 3373, 3312, 2933, 1723, 1662, 1615, 1599, 1548, 1517, 1451, 1260, 1174, 1109, 1095, 1070, 711 cm^{-1}. **HRMS** (ESI, positive mode): calcd for $C_{21}H_{23}NaNO_4$ $[M+Na]^+$ 376.1519, found 376.1525. **CHN analysis**: calcd C 71.37, H, 6.56, N 3.96; found C 67.89, H 6.92, N 3.88.

α-(Benzoyloxy)-4-bromo-*N*-cyclohexylbenzeneacetamide (5f). New compound. Colorless



solid. **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 8.27 (d, 1H, *J* = 7.9 Hz), 8.03 (d, 2H, *J* = 7.7 Hz), 7.69 (t, 1H, *J* = 7.4 Hz), 7.63 (d, 2H, *J* = 8.4 Hz), 7.58–7.50 (m, 4H), 6.04 (s, 1H), 3.53–3.44 (m, 1H), 1.80–1.46 (m, 5H), 1.29–1.02 (m, 5H) ppm. **^{13}C NMR** (100 MHz, DMSO-d_6): δ = 166.6 (C_q), 165.0 (C_q), 135.6 (C_q), 133.9 (CH), 131.6 (CH), 129.6 (CH), 129.5 (CH), 129.3 (C_q), 129.0 (CH), 122.0 (C_q), 75.0 (CH), 47.9 (CH), 32.4 (CH_2), 32.2 (CH_2), 25.3 (CH_2), 24.6 (CH_2), 24.5 (CH_2) ppm. **IR** (KBr disc): $\tilde{\nu}$ = 3443, 3287, 2934, 1726, 1657, 1561, 1265, 1119 cm^{-1}. **HRMS**: calcd for $C_{21}H_{22}BrNO_3$ $[M]^+$ 415.0783, found 415.0769. **CHN analysis**: calcd C 60.59, H, 5.33, N 3.36; found C 60.52, H 5.28, N 3.38.

α-(Benzoyloxy)-*N*-cyclohexylbenzeneacetamide (5g). New compound. Colorless solid. **^{1}H**



NMR (400 MHz, DMSO-d_6): δ = 8.37–8.21 (m, 1H), 8.16–8.00 (m, 2H), 7.78–7.53 (m, 5H), 7.52–7.4 (m, 3H), 6.05 (s, 1H), 3.51 (br s, 1H), 1.88–1.47 (m, 5H), 1.37–1.02 (m, 5H) ppm. **^{13}C NMR** (100 MHz, DMSO-d_6): δ = 166.8 (C_q), 164.9 (C_q), 136.0 (C_q), 133.6 (CH), 129.4 (CH), 129.2 (C_q), 128.8 (CH), 128.5 (CH), 128.4 (CH), 127.1 (CH), 75.5 (CH), 47.7 (CH), 32.2 (CH_2), 32.0 (CH_2), 25.1 (CH_2), 24.4 (CH_2), 24.3 (CH_2) ppm. **IR** (KBr disc): $\tilde{\nu}$ = 3423, 1657, 1026, 1000 cm^{-1}. **HRMS**: calcd for $C_{21}H_{23}NO_3$ $[M]^+$ 337.1678, found 337.1653. **CHN analysis**: calcd C 74.75, H, 6.87, N 4.15; found C 73.30, H 6.73, N 4.16.

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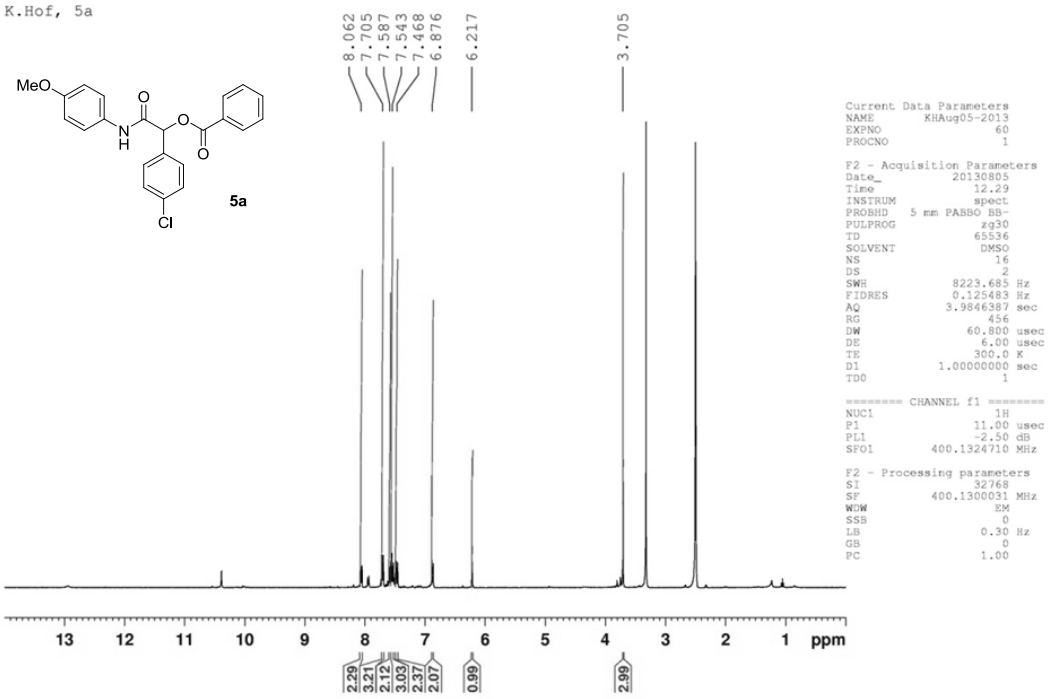
NMR Spectra


K.Hof, 5a
MeO
N
H
O
O
O
Cl
5a
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7.587
7.543
7.468
6.876
6.217
3.705
13 12 11 10 9 8 7 6 5 4 3 2 1 ppm
2.29
3.21
2.12
3.03
2.37
2.07
0.99
2.99
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PROCNO 1
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RG 456
DW 60.800 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
TD0 1
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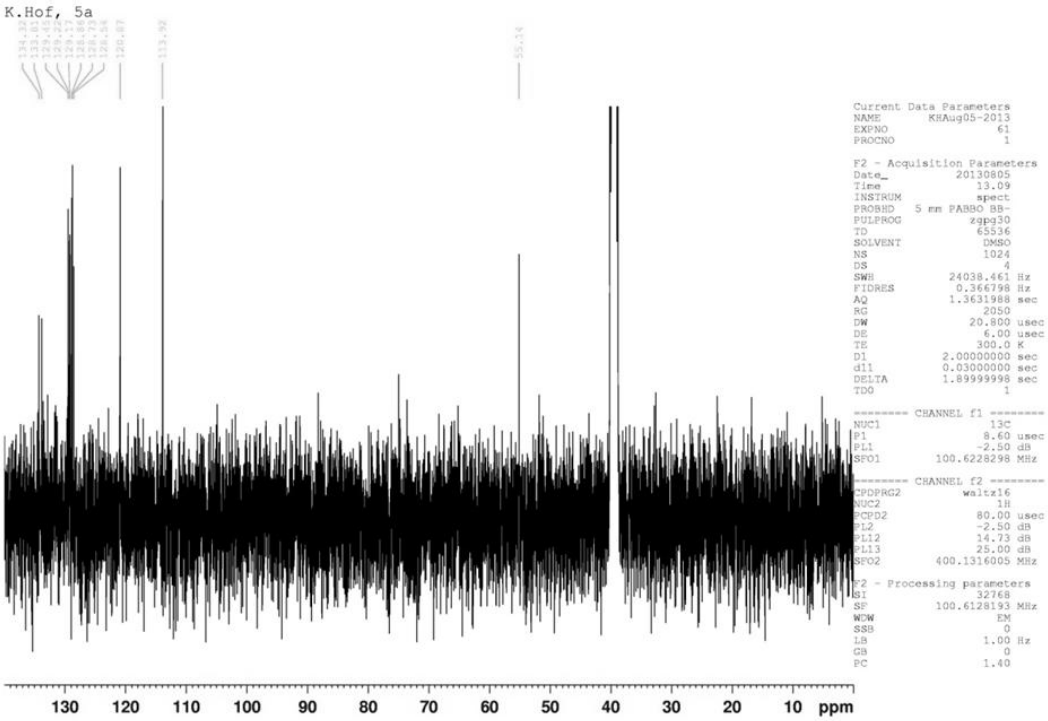
SF 400.1300031 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00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PROCNO 1
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RG 2050
DW 20.800 usec
DE 6.00 usec
TE 300.0 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1
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SFO1 100.6228298 MHz
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NUC2 1H
PCPD2 80.00 usec
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PL12 14.73 dB
PL13 25.00 dB
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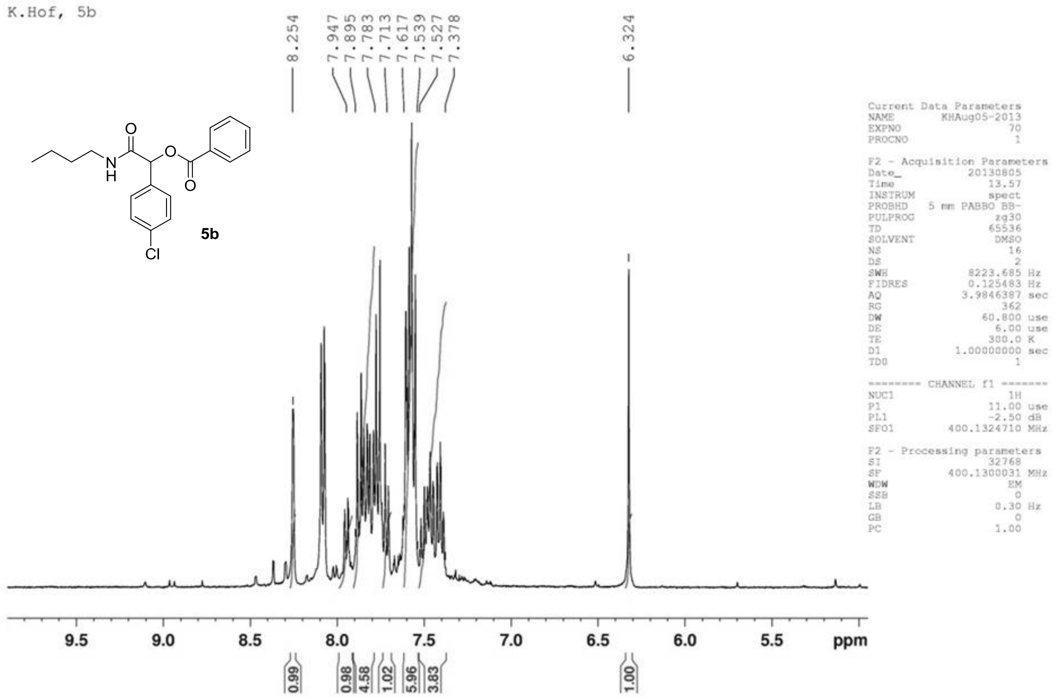
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7.617
7.539
7.527
7.378
6.324
5b
Cl
O
N
H
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PROCNO 1
F2 - Acquisition Parameters
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RG 362
DW 60.800 use
DE 6.00 use
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D1 1.00000000 sec
TD0 1
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F2 - Processing parameters
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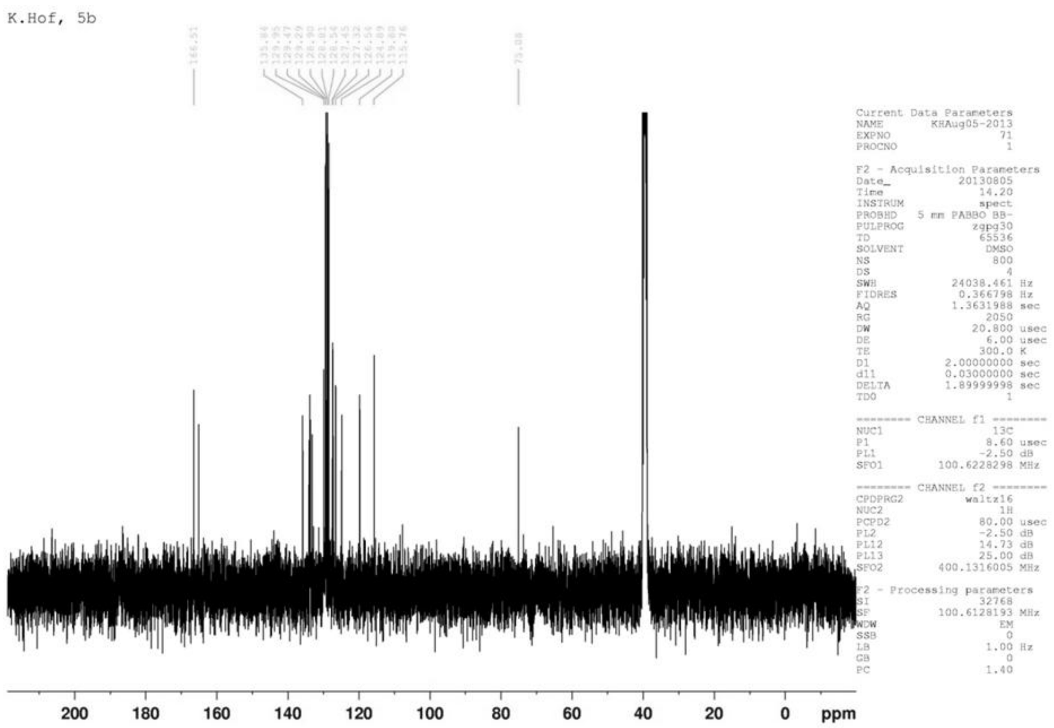
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FIDRES 0.366798 Hz
AQ 1.3631988 sec
RG 2050
DW 20.800 usec
DE 6.00 usec
TE 300.0 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1
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PL1 -2.50 dB
SFO1 100.6228298 MHz
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NUC2 1H
PCPD2 80.00 usec
PL2 -2.50 dB
PL12 14.73 dB
PL13 25.00 dB
SFO2 400.1316005 MHz
F2 - Processing parameters
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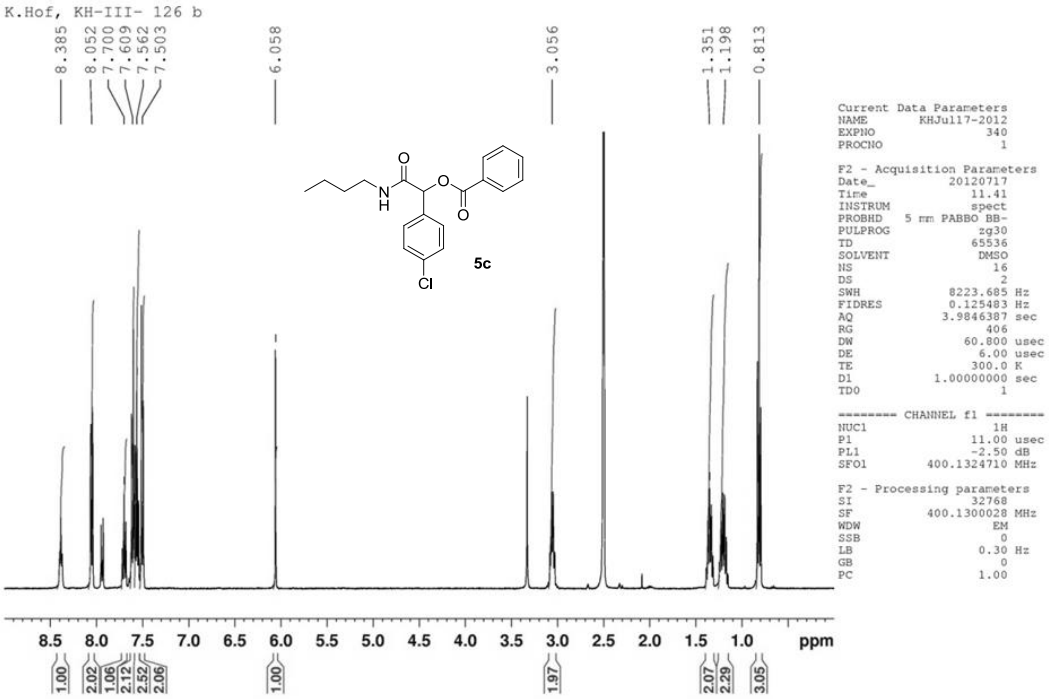
K.Hof, KH-III- 126 b
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5c
Cl
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FIDRES 0.125483 Hz
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RG 406
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DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
TD0 1
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P1 11.00 usec
PL1 -2.50 dB
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F2 - Processing parameters
SI 32768
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WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
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1.00
1.97
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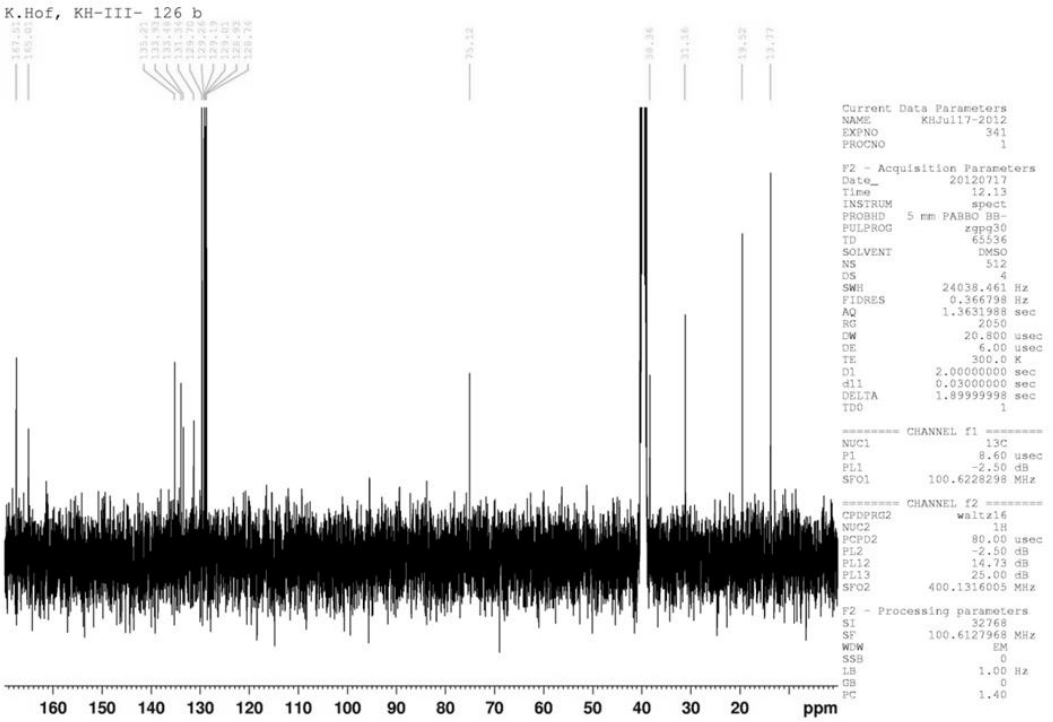
2.29
3.05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FIDRES 0.366798 Hz
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RG 2050
DW 20.800 usec
DE 6.00 usec
TE 300.0 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 8.60 usec
PL1 -2.50 dB
SFO1 100.6228298 MHz
======== CHANNEL f2 ========
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NUC2 1H
PCPD2 80.00 usec
PL2 -2.50 dB
PL12 14.73 dB
PL13 25.00 dB
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F2 - Processing parameters
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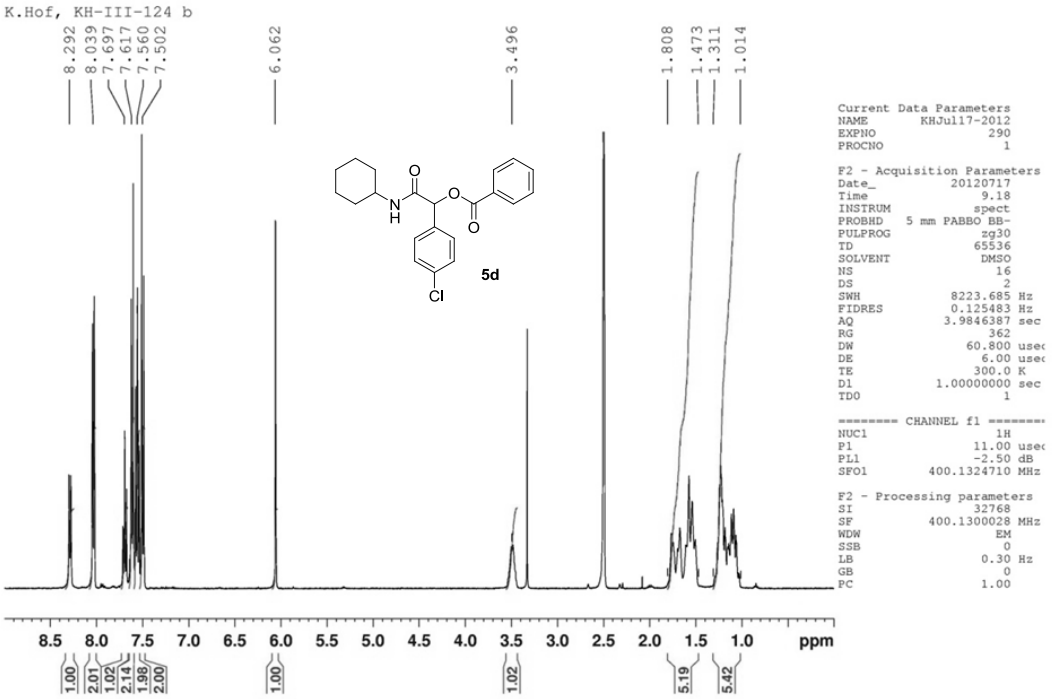
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5d
Cl
Current Data Parameters
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PULPROG zg30
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DS 2
SWH 8223.685 Hz
FIDRES 0.125483 Hz
AQ 3.9846387 sec
RG 362
DW 60.800 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
TD0 1
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NUC1 1H
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SFO1 400.1324710 MHz
F2 - Processing parameters
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1.98
2.00
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1.02
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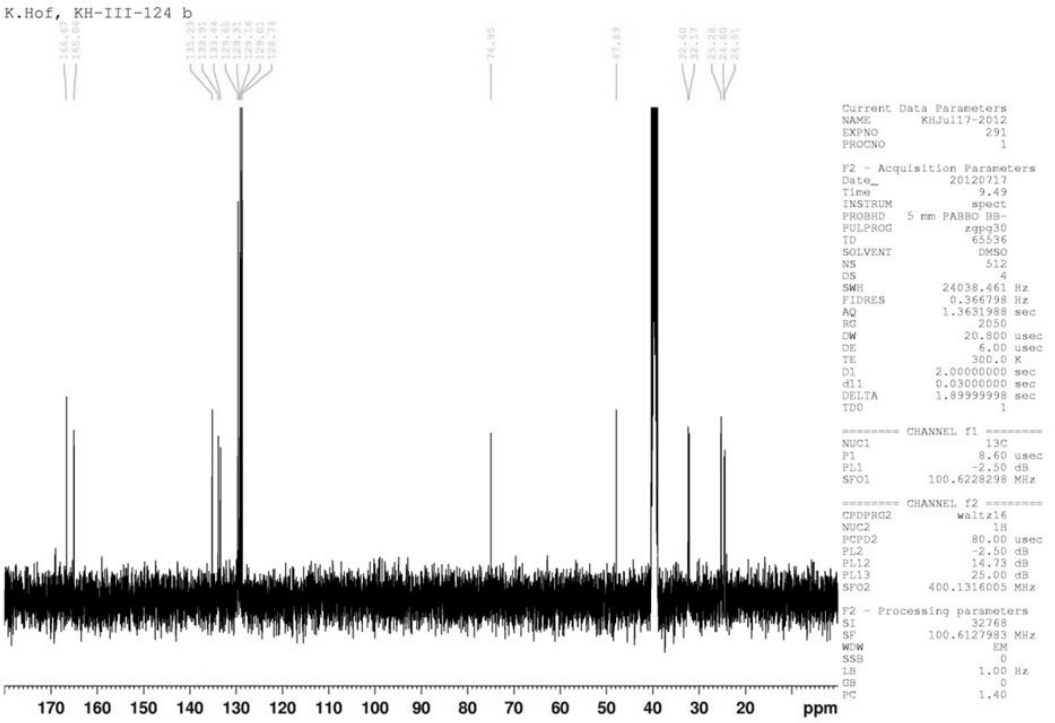
5.42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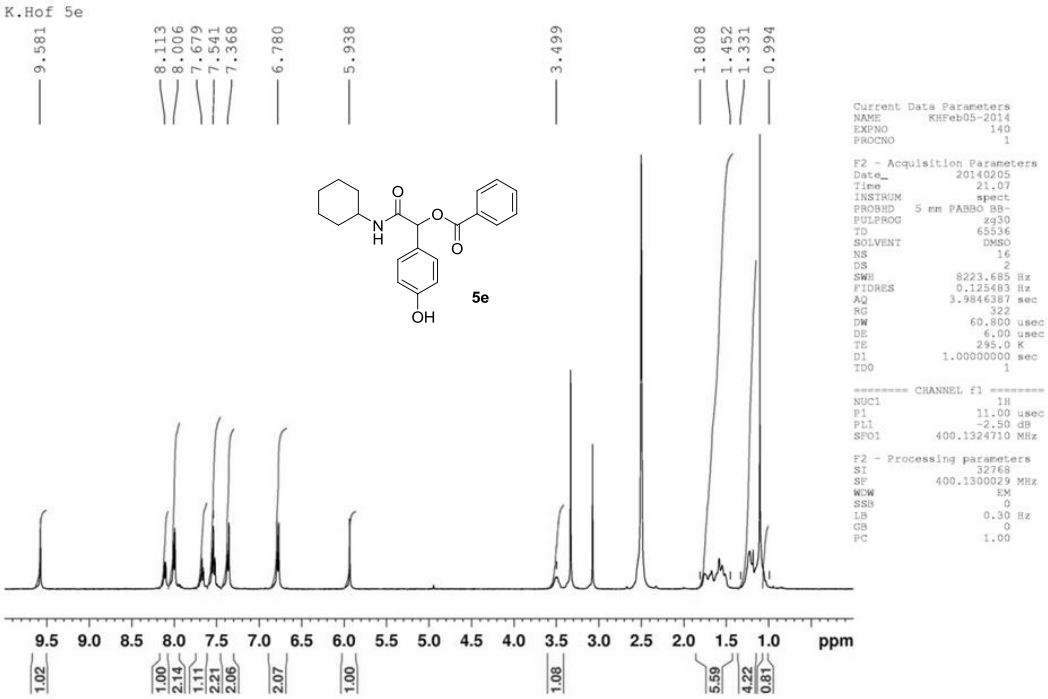
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0.994
5e
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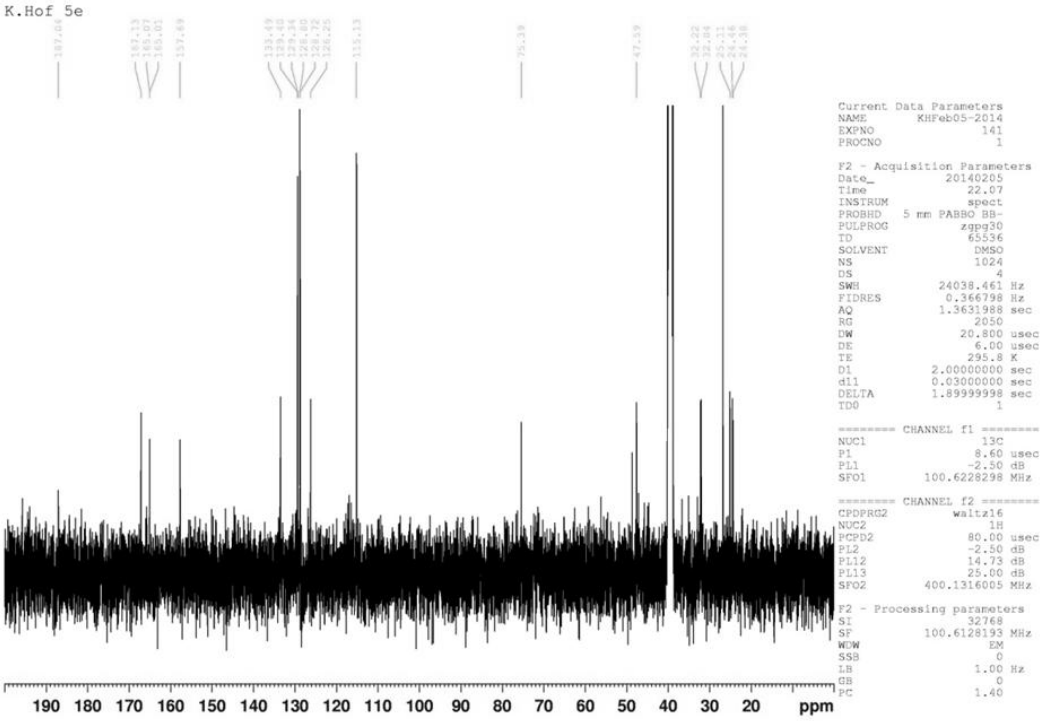
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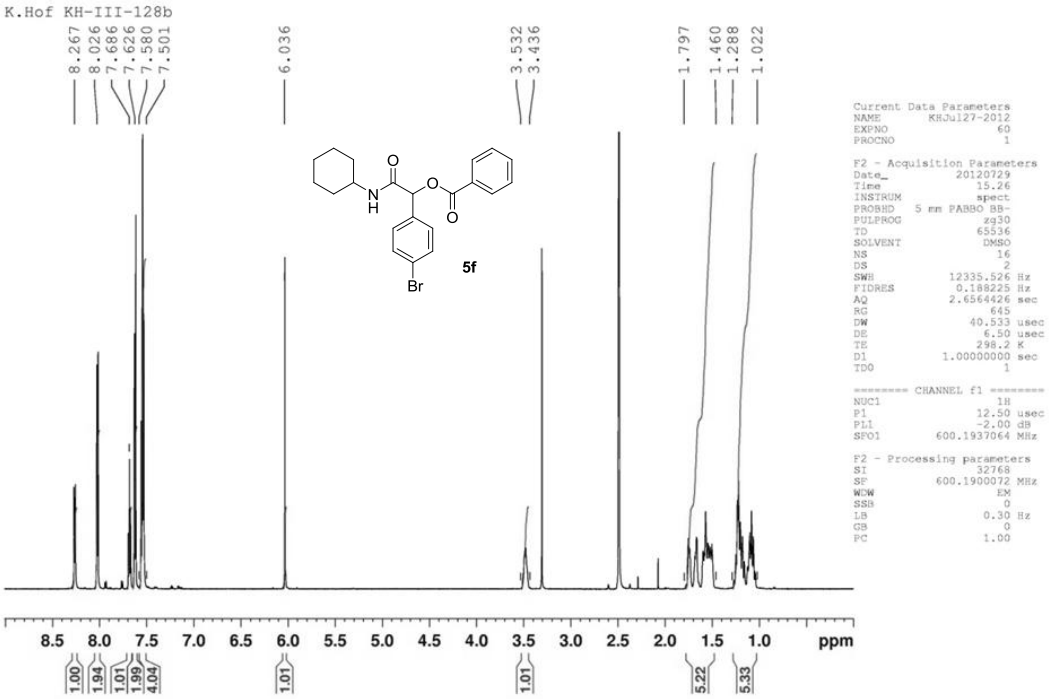
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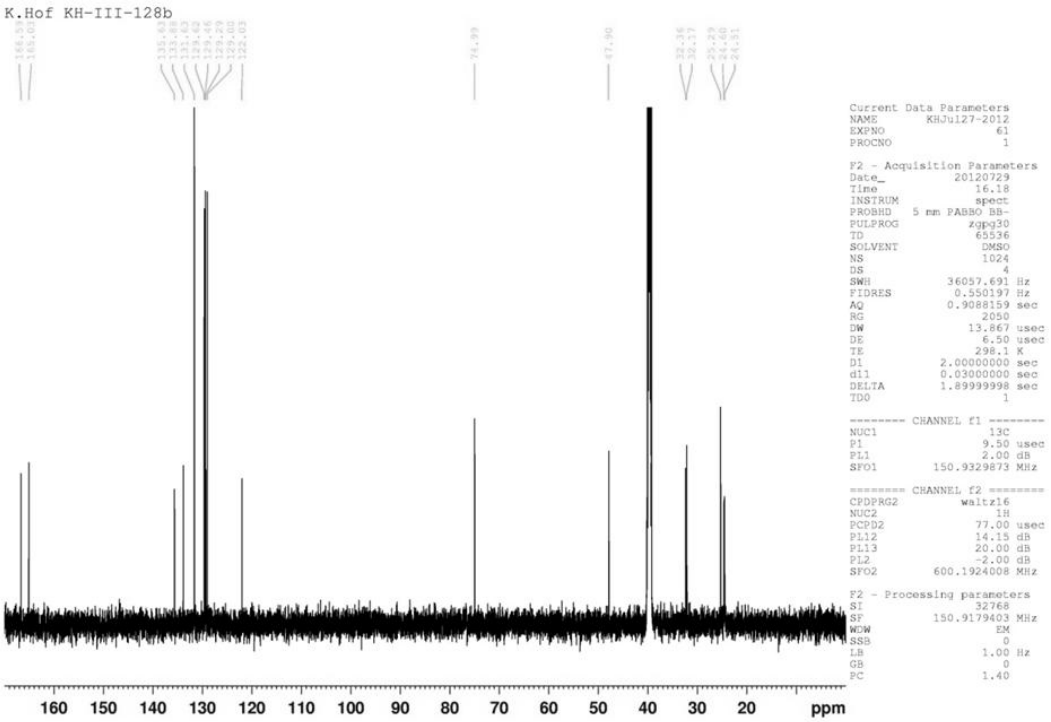
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D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
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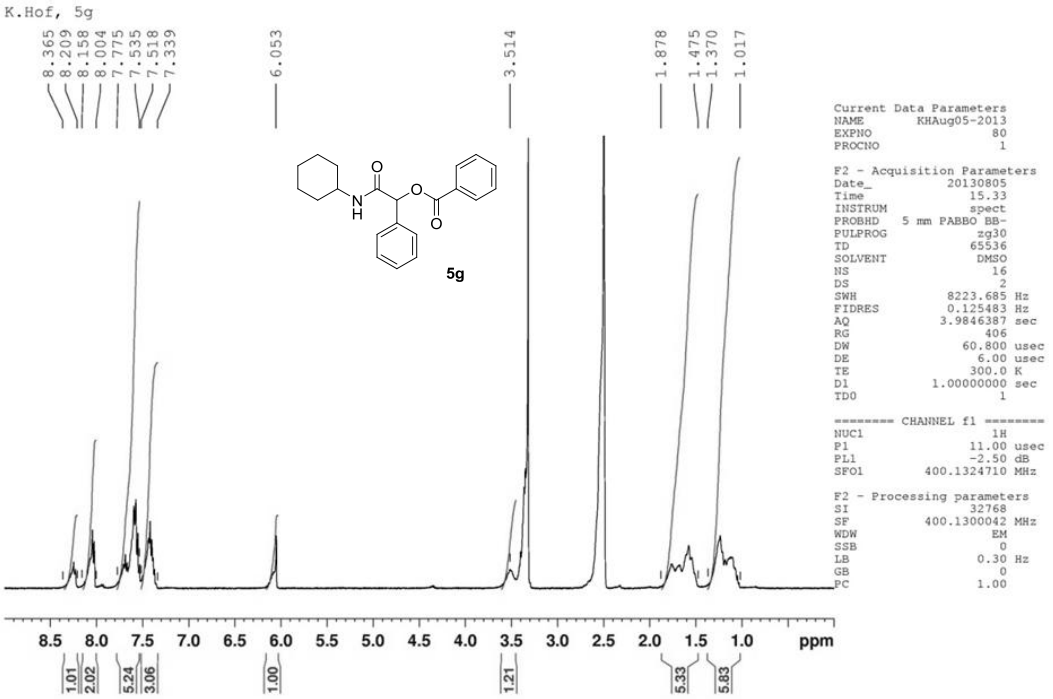
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DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
TD0 1
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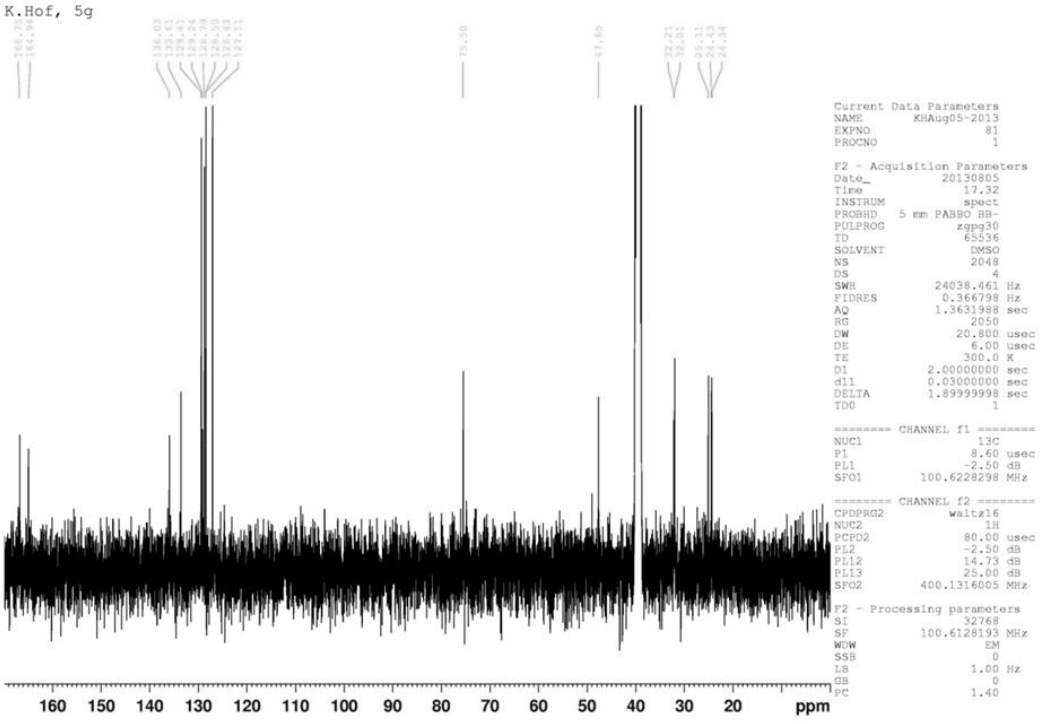
5.83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DE 6.00 usec
TE 300.0 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
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======== CHANNEL f1 ========
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P1 8.60 usec
PL1 -2.50 dB
SFO1 100.6228298 MHz
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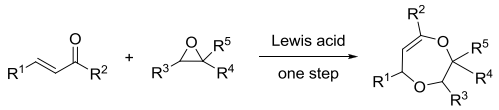
NUC2 1H
PCPD2 80.00 usec
PL2 -2.50 dB
PL12 14.73 dB
PL13 25.00 dB
SFO2 400.1316005 MHz
F2 - Processing parameters
SI 32768
SF 100.6128193 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

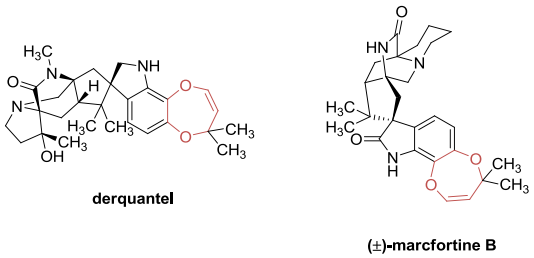
6 Organocatalytic Synthesis of 1,4-Dioxepines

Introduction

In our group efforts were made towards an organocatalytic method for the synthesis of 1,3-dioxolane derivatives from epoxides and aldehydes.[1-4] In 2012, the Wang group revealed that the Lewis acid-catalyzed version utilizing *α,β*-saturated aldehydes can furnish 1,4-dioxepine derivatives (Scheme 1).[5] The 1,4-dioxepine core is present in some substances like derquantel, used against parasites in animals,[6] and (±)-marcfortine B, used for the same purpose as anthelmintic substance[7] (Scheme 2).

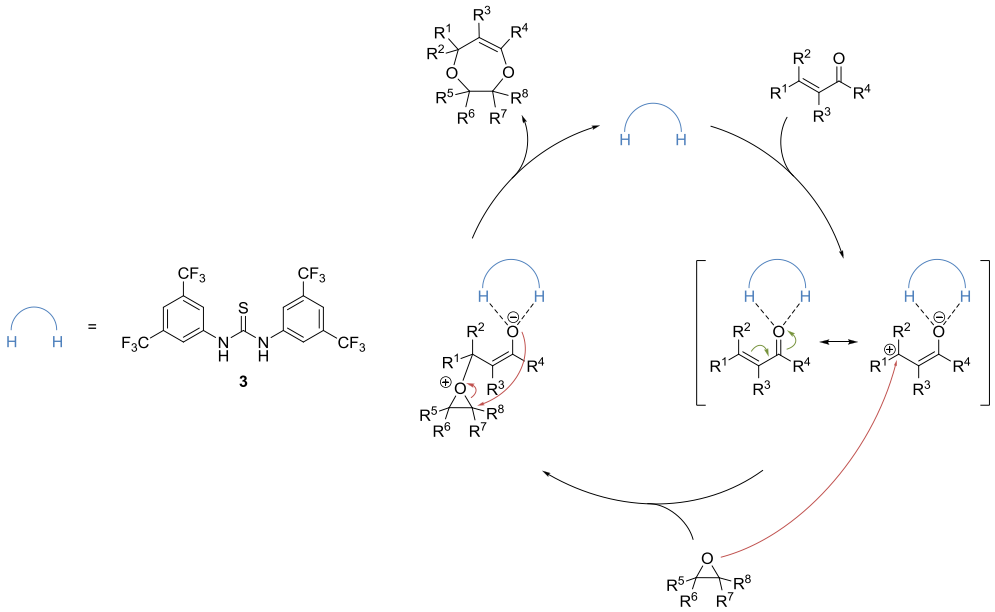


Scheme 1 Lewis acid-catalyzed synthesis of 1,4-dioxepines



Scheme 2 Structures of derquantel and (±)-marcfortine B

It was reasoned in our group that it could be possible to develop an organocatalyzed variant of this [4+3] cycloaddition, and the first examinations dealing with this reaction led to positive results utilizing 12 equivalents of cinnamaldehyde and 5 mol% of *N,N*'-bis[3,5-bis(trifluoromethyl)phenyl]thiourea (**3**).[8] Scheme 3 shows a mechanistic proposal for the organocatalytic variant according to the Lewis acid-catalyzed version.



Scheme 3 Mechanistic proposal for the organocatalytic synthesis of 1,4-dioxepines

Results and Discussion

We started with the optimization of the reaction conditions. For this purpose, we performed five experiments with amounts of thiourea **3** varying from 1 mol% to 5 mol%. These experiments showed 2 mol% to be sufficient for catalyzing the reaction within 24 h at room temperature (Figure 2).

In the next step, we performed six experiments varying the equivalents of aldehyde; we used 2, 4, 6, 8, 10, and 12 equivalents. With 2 mol% of **3** and 10 equivalents of aldehyde we achieved full conversion after 24 hours at room temperature (Figure 2).

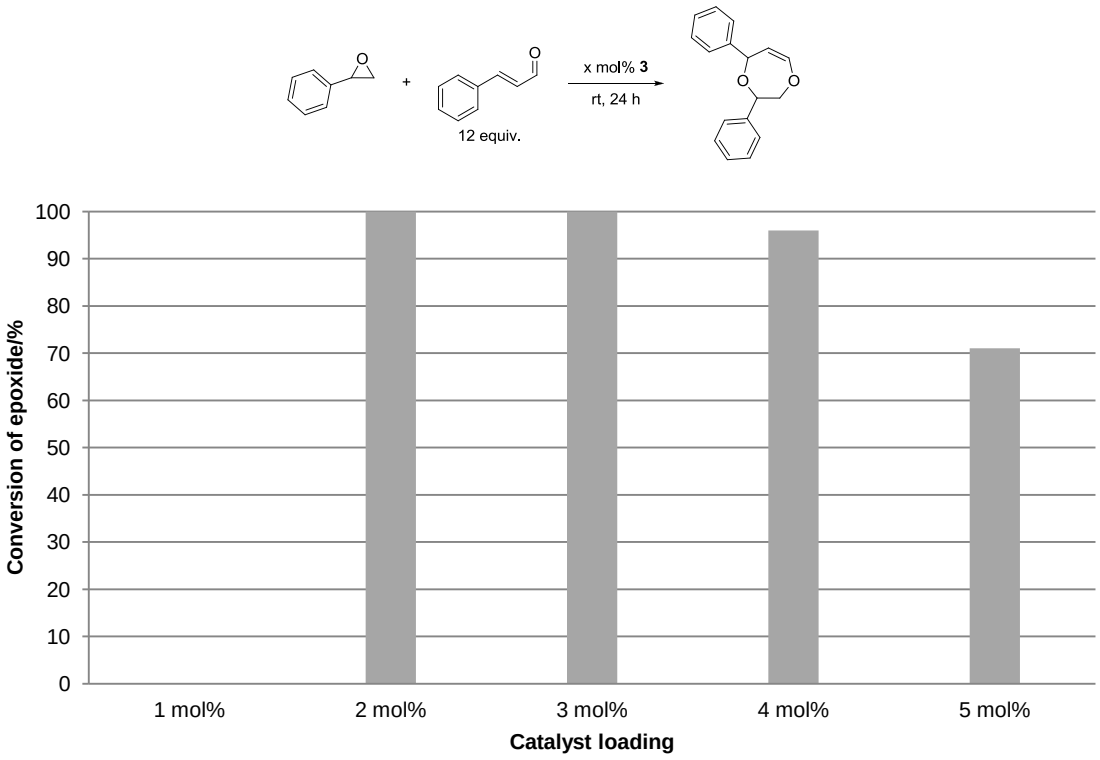


Figure 1 Results of the optimization of catalyst loading

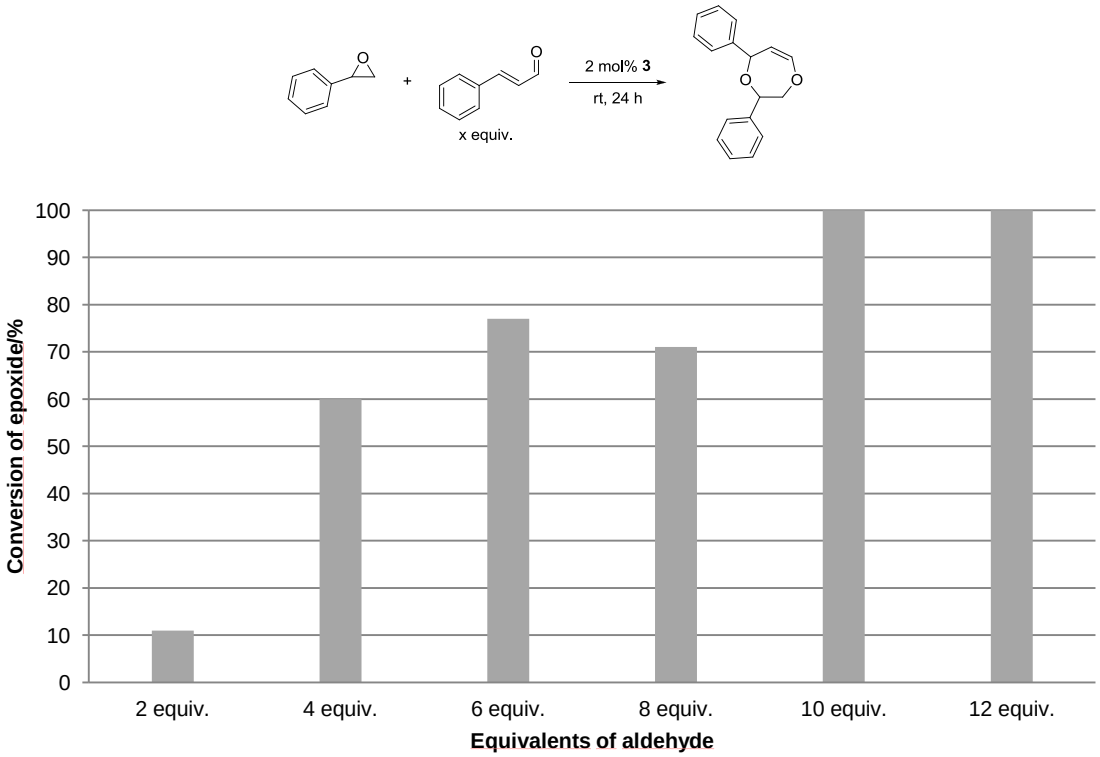


Figure 2 Results of the optimization of aldehyde equivalents

After having optimized the reaction conditions, we focused on the scope of the reaction. Here, we examined two *α,β*-unsaturated aldehydes and a ketone – crotonaldehyde (**1a**) as the aliphatic, cinnamaldehyde (**1b**) as the aromatic aldehyde variant, and methyl vinyl ketone (**1c**) – as well as three epoxides – the aromatic, monosubstituted styrene oxide (**2a**), the 1,1-disubstituted, aliphatic isobutylene oxide (**2b**), and the aliphatic, 1,2-disubstituted cyclohexene oxide (**2c**). With this selection of substrates we wanted to examine the influence of substitution pattern and the substituent's nature.

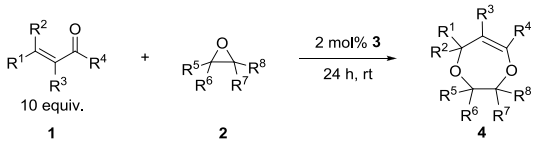
Table 1 summarizes our results. The reaction of styrene oxide (**2a**) with aldehyde **1a** led to full conversion within the given reaction time of 24 h. Almost the same result could be observed with aldehyde **1b**. Interestingly, this finding is in contrast to Wang *et al*. They reported that the utilization of aliphatic *α,β*-unsaturated aldehydes did not work with their variant maybe due to the "higher reactivity of these enolizable aldehydes".[5] In both cases, we could observe two diastereomers *via* GC/MS analysis with *cis*- and *anti*-standing methyl and phenyl group or two phenyl groups, respectively. The reaction with ketone **1c** did not lead to any conversion within 24 h.

In case of isobutylene oxide (**2b**) full conversion with aldehyde **1a** as well as with **1b** could be observed within 24 h *via* GC/MS analysis. According to our finding in the first experiments with epoxides **2a**, no conversion of **2b** could be observed in the reaction with methyl vinyl ketone (**1c**).

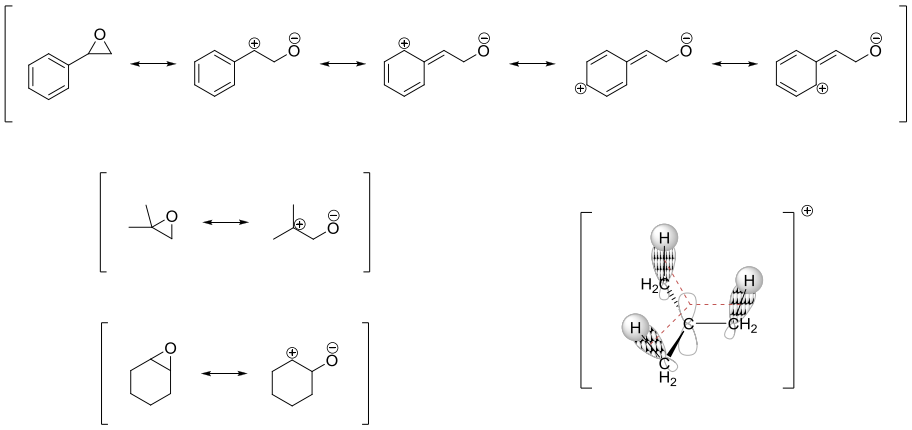
In a last series of experiments we observed the reaction between cyclohexene oxide (**2c**) with these two aldehydes and this ketone. The conversion of **2c** in the experiments with **1a** and **1b** were far lower than in the cases where epoxides **2a** and **2b** were used instead. The reaction of **2c** with **1c** showed – as in the reactions with this ketone before – no conversion at all.

We think these results are due to the epoxides' corresponding ionic structures (Scheme 1). The positive charge in styrene oxide is placed in a benzylic position. This leads to stabilization by mesomerization. The positive charges in the isobutylene and cyclohexene oxide mesomers are stabilized by C–H-hyperconjugation effects. The positive charge in isobutylene oxide is stabilized by three, the one in cyclohexene oxide by "only" two of these effects. Because of this the reaction of cyclohexene oxide with the utilized aldehydes is far slower than with styrene or isobutylene oxide.

Table 1 Organocatalytic synthesis of 1,4-dioxepines



R^1	R^2	R^3	R^4		R^5	R^6	R^7	R^8		Product
Me	H	H	H	**1a**	H	H	H	Ph	**2a**	**4a**
Me	H	H	H	**1a**	H	H	Me	Me	**2b**	**4b**
Me	H	H	H	**1a**	H	-$(CH_2)_4$-		H	**2c**	**4c**
Ph	H	H	H	**1b**	H	H	H	Ph	**2a**	**4d**
Ph	H	H	H	**1b**	H	H	Me	Me	**2b**	**4e**
Ph	H	H	H	**1b**	H	-$(CH_2)_4$-		H	**2c**	**4f**
H	H	H	Me	**1c**	H	H	H	Ph	**2a**	-
H	H	H	Me	**1c**	H	H	Me	Me	**2b**	-
H	H	H	Me	**1c**	H	-$(CH_2)_4$-		H	**2c**	-



Scheme 1 Ionic structures of the epoxides
and visualization of the hyperconjugation effect

Conclusions

Out of nine desired products we were able to synthesize six 1,4-dioxepine derivatives. Unfortunately, we were not capable of satisfyingly purify these products.

Experimental Section

General Remarks

All chemicals were purchased from Acros Organics, Alfa Aesar, Fluka, Merck, and Sigma Aldrich in the highest purity available and were used – in case of liquids – after distillation over 5, 10, or 20 cm Vigreux columns (*in vacuo* if needed). Distilled chemicals were stored

under an argon atmosphere over MS 3 Å. $CDCl_3$ was purchased from Deutero GmbH and stored over MS 3 Å. Glassware and stirring bars were cleaned in a laboratory washer with first Extran© (Merck), then phosphoric acid, and last fresh water. Glassware was then dried in an oven at 120 °C. All reactions were run in 10 mL single-necked flasks (Schott DURAN®) with PTFE-coated magnetic stirring bars. The flasks were sealed with plastic plugs. Thiourea derivative **3** was directly weighed into the reaction flasks. Liquid chemicals were transferred with 1 mL or 5 mL syringes, respectively, with thin cannulas. The reaction outcome was determined by GC/MS analyses with a Quadrupol-MS HP MSD 5971 and a HP 5890A GC equipped with a HP5 crosslinked silica GC column (25 m × 0.2 mm, 0.33 micron stationary phase: 5% phenyl and 95% methyl silicone) using helium as carrier gas; temperature program: 60–250 °C (heating rate: 15 °C/min), injector and transfer line 250 °C. Samples were taken directly from the stirred reaction mixture with a 10 µL Hamilton syringe and were injected immediately. ^{1}H NMR and ^{13}C NMR spectra were recorded with Bruker Avance II (AV 400) or Bruker Avance III (600 MHz) spectrometers using $CDCl_3$ as a solvent and the solvent residual peaks [$\delta(^1H)$ = 7.26 ppm], $\delta(^{13}C)$ = 77.0 ppm] as well as TMS [$\delta(^1H)$ = 0.00 ppm], $\delta(^{13}C)$ = 77.0 ppm] as standard.

Typical Procedure

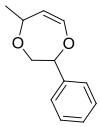
Thiourea derivative **3** (20.1 mg, 0.02 mmol, 2 mol%) was weighed directly into a 10 mL one-necked flask. Then crotonaldehyde (**1a**, 1.6 mL, 10 mmol, 10 equiv.) and styrene oxide (**2a**, 0.24 mL, 1 mmol) were added under stirring at rt. The resulting colorless solution was allowed to be stirred for 24 h. Then the solution was objected to GC/MS analysis.

Attempts towards Purification

First of all, we tried the purification via column chromatography on silica gel using ethyl acetate/*n*-pentane 1:5 as described by Wang *et al*. As this turned out not to be working, we tried column chromatography on neutral aluminum oxide. Again, we could not receive the desired product with a satisfying purity. We then focused on preparative TLC. Here, we were not able to separate the several fractions akin to the experiments with column chromatography. We tried to distill the reaction solutions to remove the excess component. This was leading to decomposition. In the next step, we objected the reaction solutions to HPLC. We were able to separate one product quite well. The four other products had been decomposed before the separation could be started. In the next step, we tried column chromatography again, but this time with longer and thinner columns. Also, this was not leading to properly purified prod-

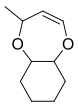
ucts. Then, we tried to use a gradient (ethyl acetate/*n*-pentane 1:30 → 1:25 → 1:20 → 1:15 → 1:10 → 1:5, each time ca. 100 mL) to elute the products. In these cases the yields were very low and sometimes the products had been decomposed before analytics could be run. The idea of performing preparative GC was rejected because of the products' instability. As *ultima ratio*, we tried the derivatization of these enol ether-like products *via* a Diels–Alder cycloaddition. This made the situation worse. We added 10.5 equivalents of freshly cracked cyclopentadiene, because not only the desired product but the remaining 9 equivalents of *α*,*β*-unsaturated aldehyde were supposed to react with the diene as well. *Via* GC/MS analysis we could observe the dimer of cyclopentadiene, two adducts of crotonaldehyde with cyclopentadiene and styrene oxide. The desired dioxepine–diene-adduct could not be observed. So we made TLC analysis of the reaction mixture in six different eluents. We were not able to find any spot clearly assigned to the desired adduct.

(***Z***)**-5-Methyl-2-phenyl-3,5-dihydro-2*H*-1,4-dioxepine (4a)**. New compound. R_f = 14.73 min and 14.86 min (two diastereomers). Molecular weight calcd for $C_{12}H_{14}O_2$ 190.24, found 190.

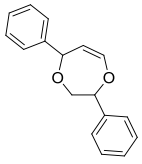


(*Z*)-2,2,5-Trimethyl-3,5-dihydro-2*H*-1,4-dioxepine (4b). New compound. R_f = 7.85 min. Molecular weight calcd for $C_8H_{14}O_2$ 142.20, found 142.

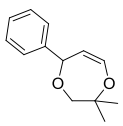
(*Z*)-2-Methyl-5a,6,7,8,9,9a-hexahydro-2*H*-benzo[*b*][1,4]dioxepine (4c). New compound. R_f = 12.67 min. Molecular weight calcd for $C_{10}H_{16}O_2$ 168.23, found 168.



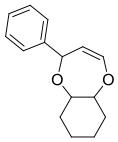
(*Z*)-2,5-Diphenyl-3,5-dihydro-2*H*-1,4-dioxepine (4d). New compound. R_f = 21.07 min and 21.58 min (two diastereomers). Molecular weight calcd for $C_{17}H_{16}O_2$ 252.31, found 193.



(*Z*)-2,2-Dimethyl-5-phenyl-3,5-dihydro-2*H*-1,4-dioxepine (4e). R_f = 15.56 min. Molecular weight calcd for $C_{13}H_{16}O_2$ 204.26, found 204.



(*Z*)-2-Phenyl-5a,6,7,8,9,9a-hexahydro-2*H*-benzo[*b*][1,4]dioxepine (4f). New compound. R_f = 18.89 min. Molecular weight calcd for $C_{15}H_{18}O_2$ 230.30, found 231.



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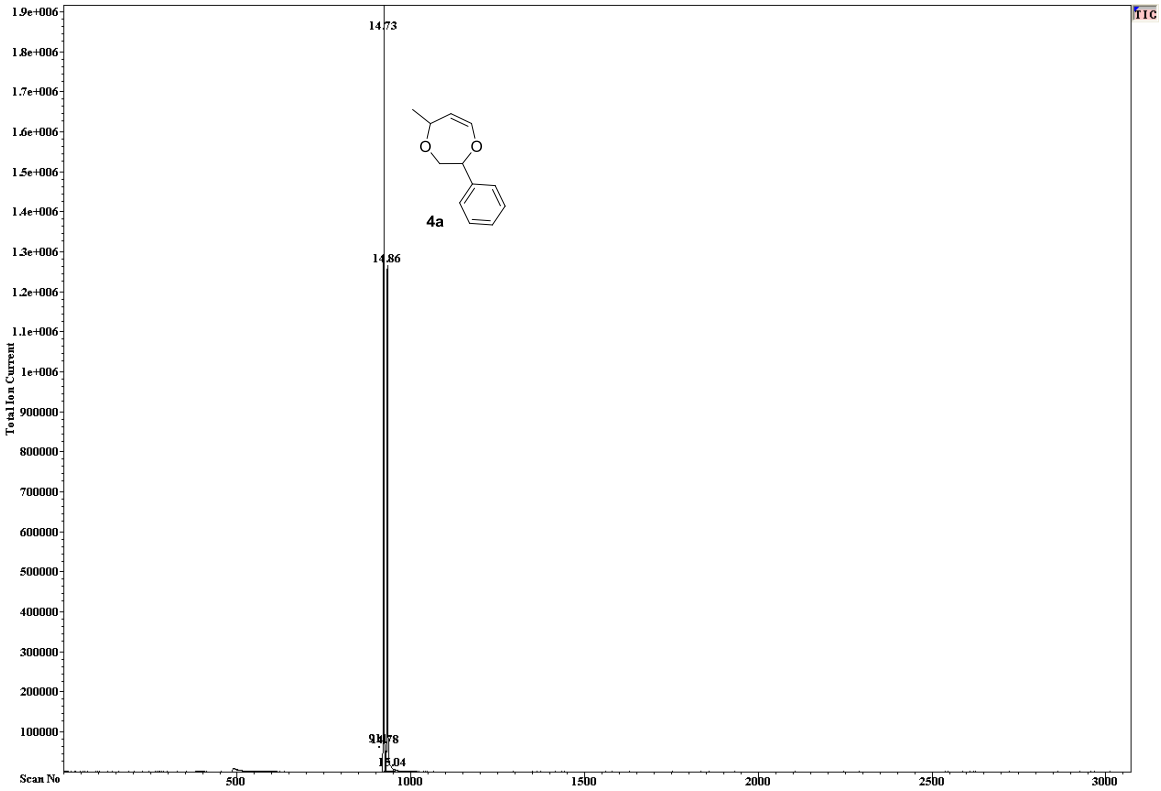
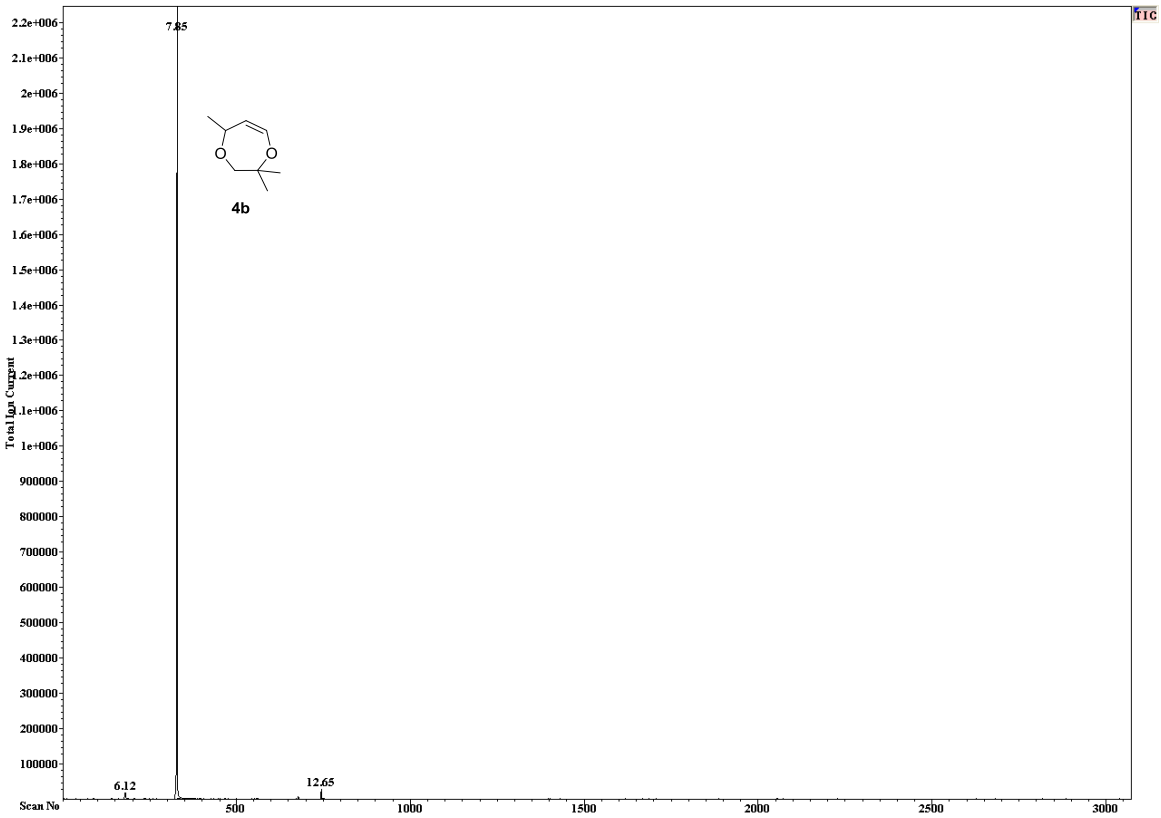
Chromatograms and Mass Spectra

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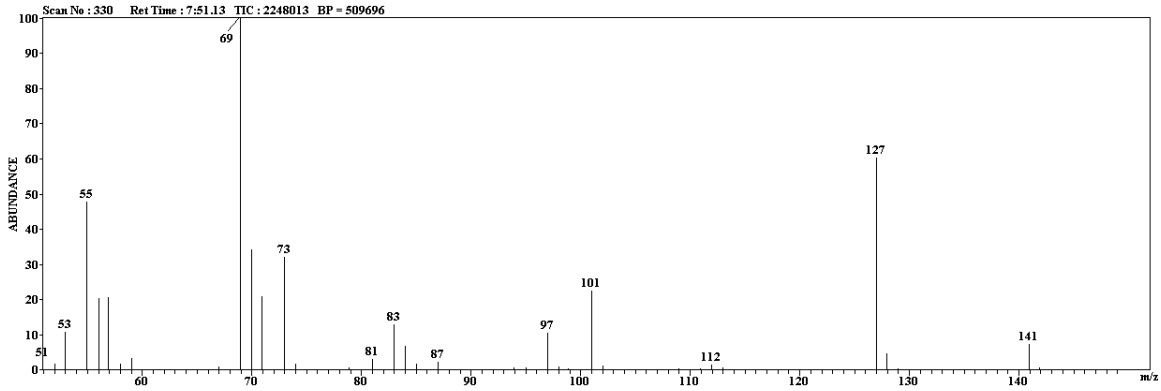
6.12
12.65
Total Ion Current
Scan No
4b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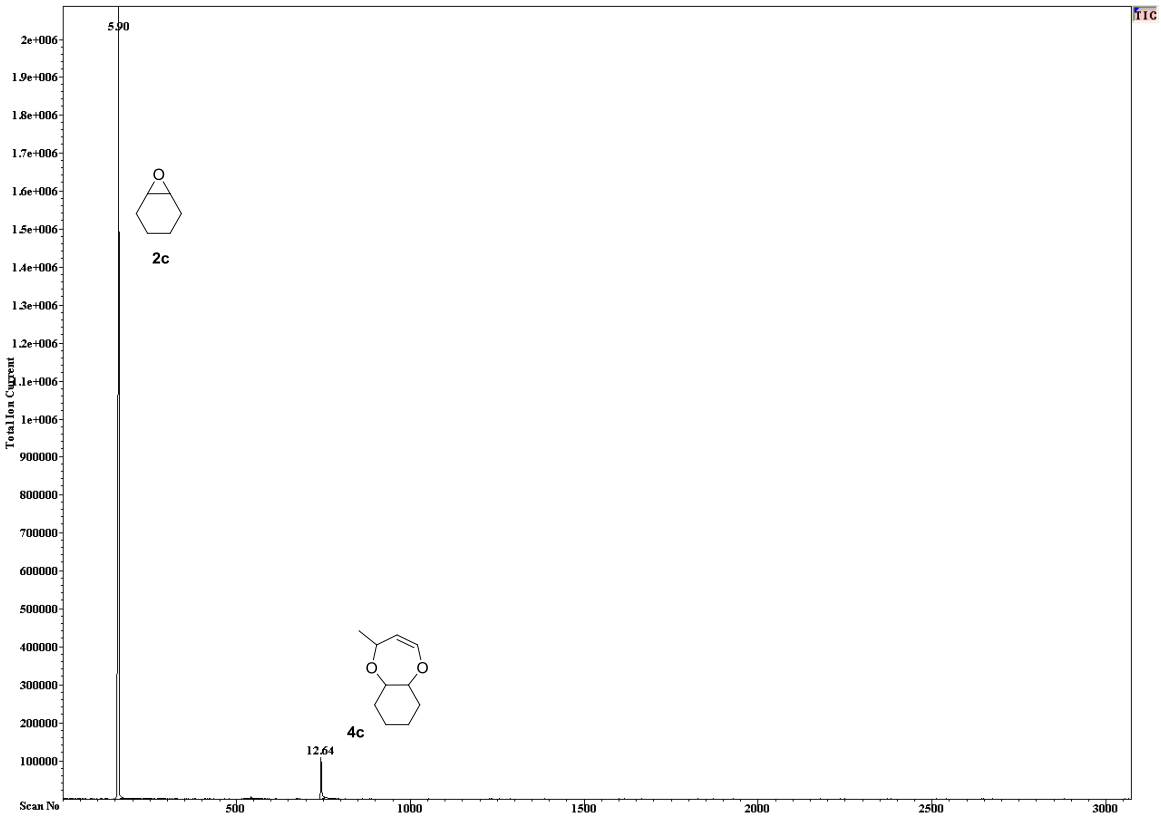
ABUNDANCE
m/z
69
55
73
53
83
81
87
97
101
112
127
141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2c
4c
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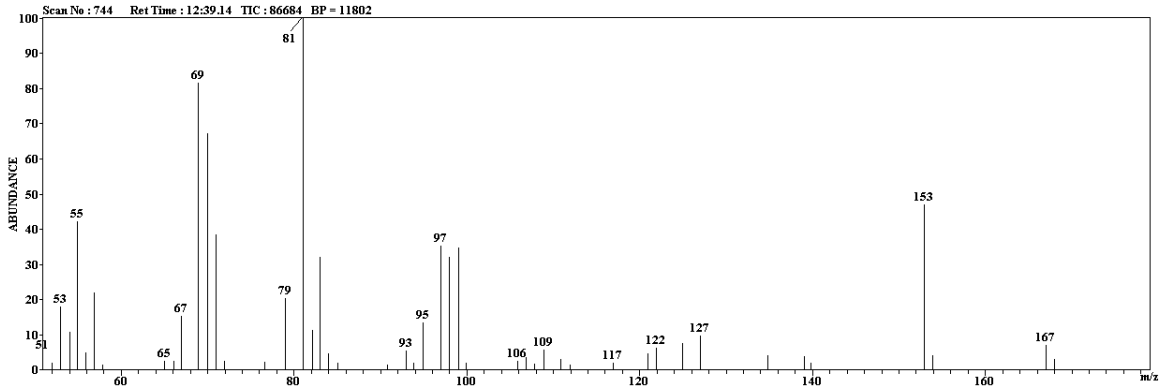
Scan No : 744 Ret Time : 12:39.14 TIC : 86684 BP = 11802
ABUNDANCE
m/z
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69
55
153
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122
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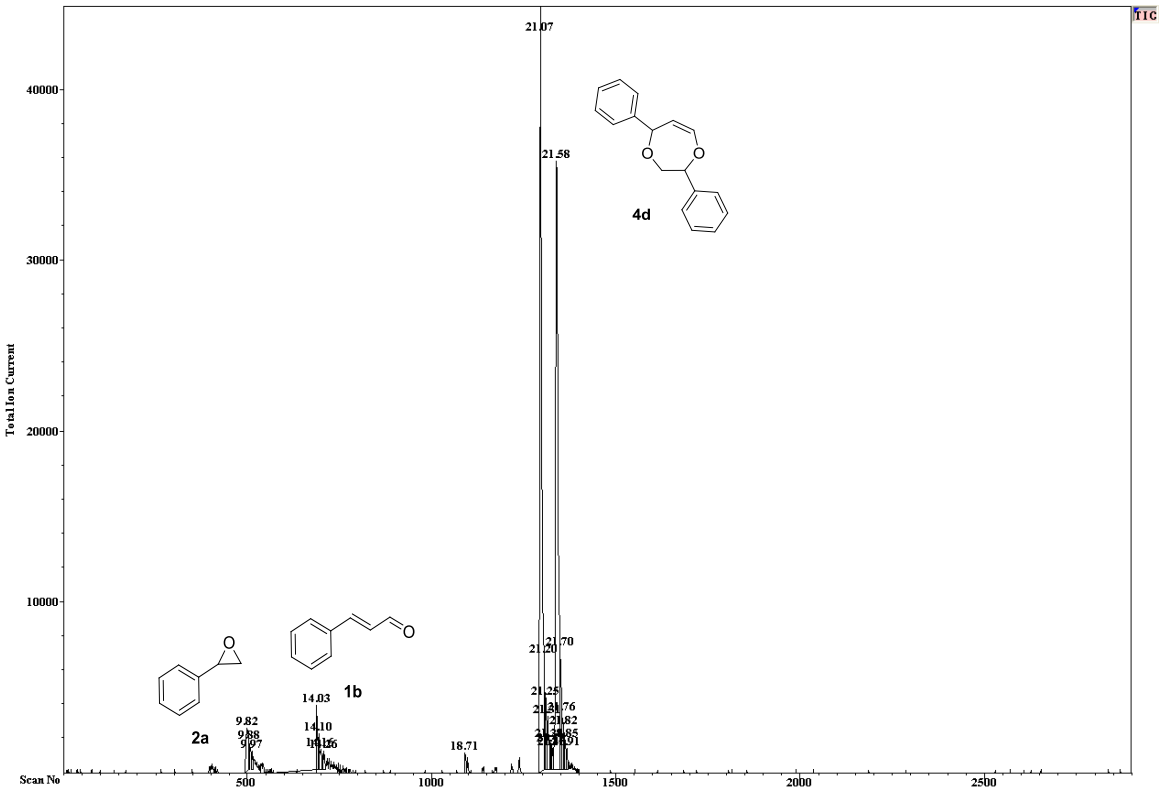
65
93
106
117
51


TIC
21.07
21.58
4d
1b
2a
14.03
14.10
9.82
9.88
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21.70
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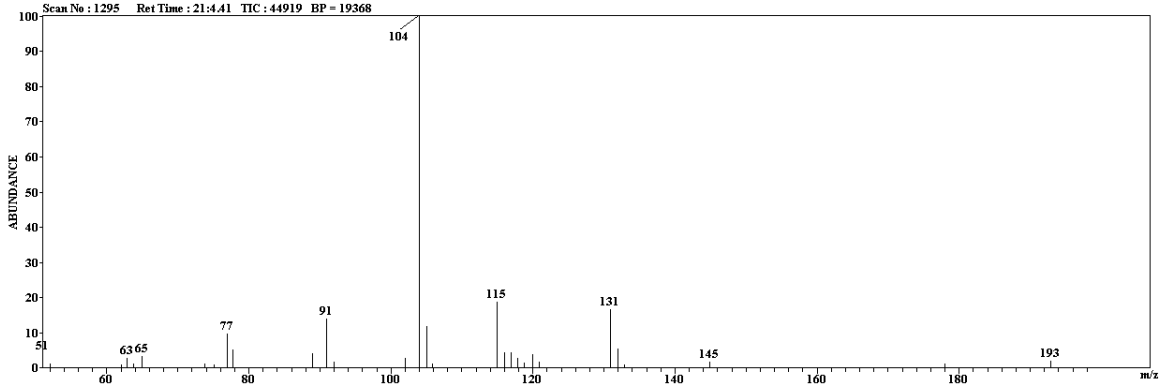
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131
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77
63
65
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145
193
ABUNDANCE
m/z
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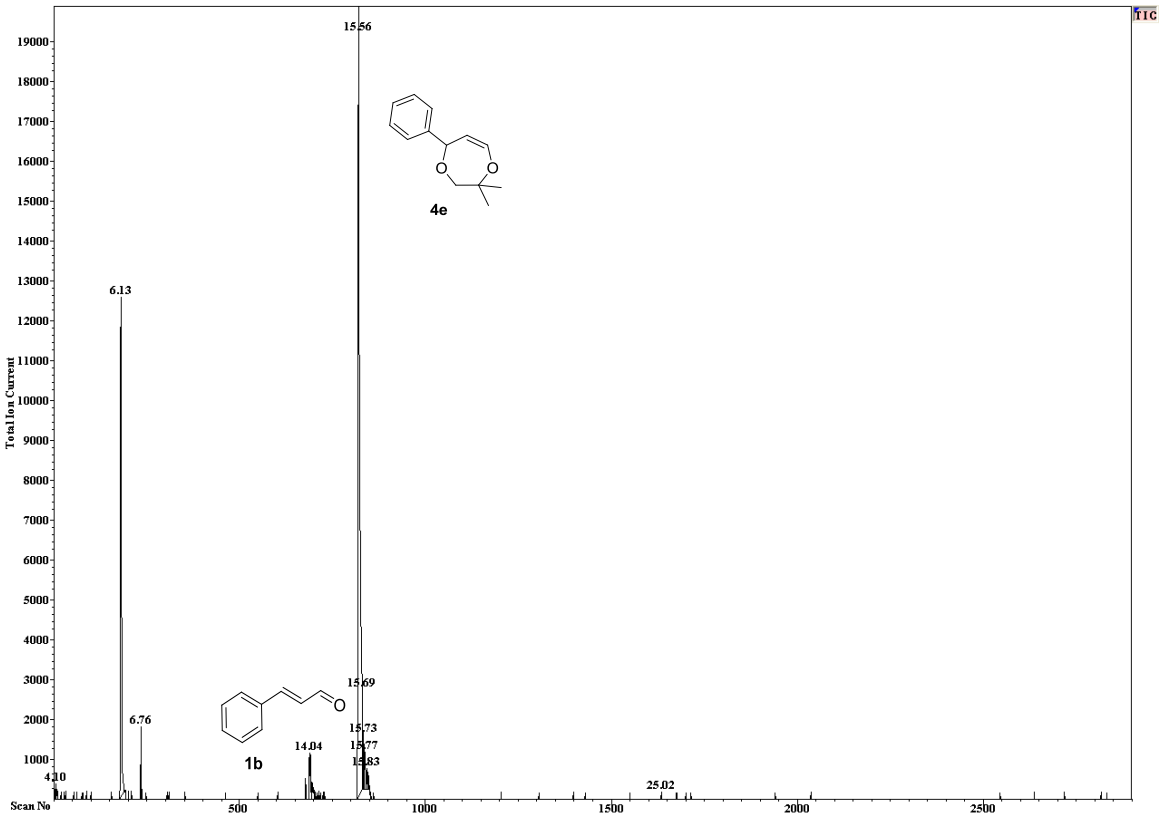
100
120
140
160
180


TIC
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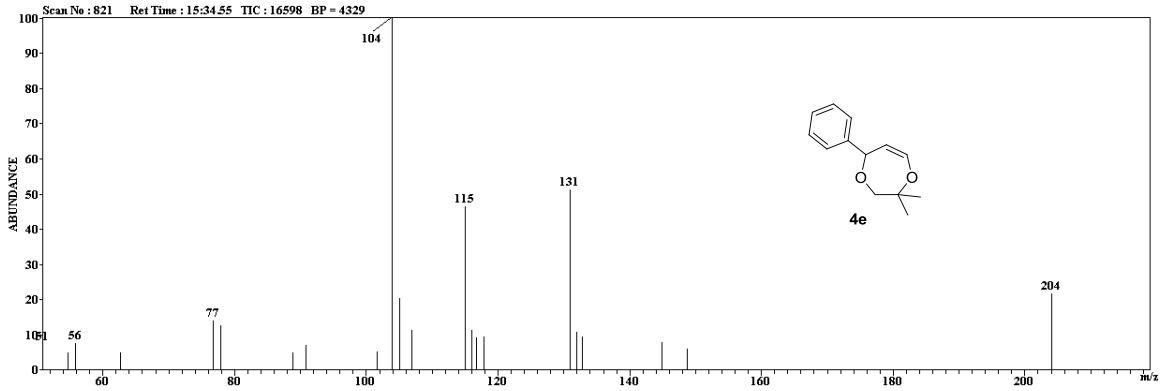
15.69
15.73
15.77
15.83
25.02
1b
4e
Total Ion Current
Scan No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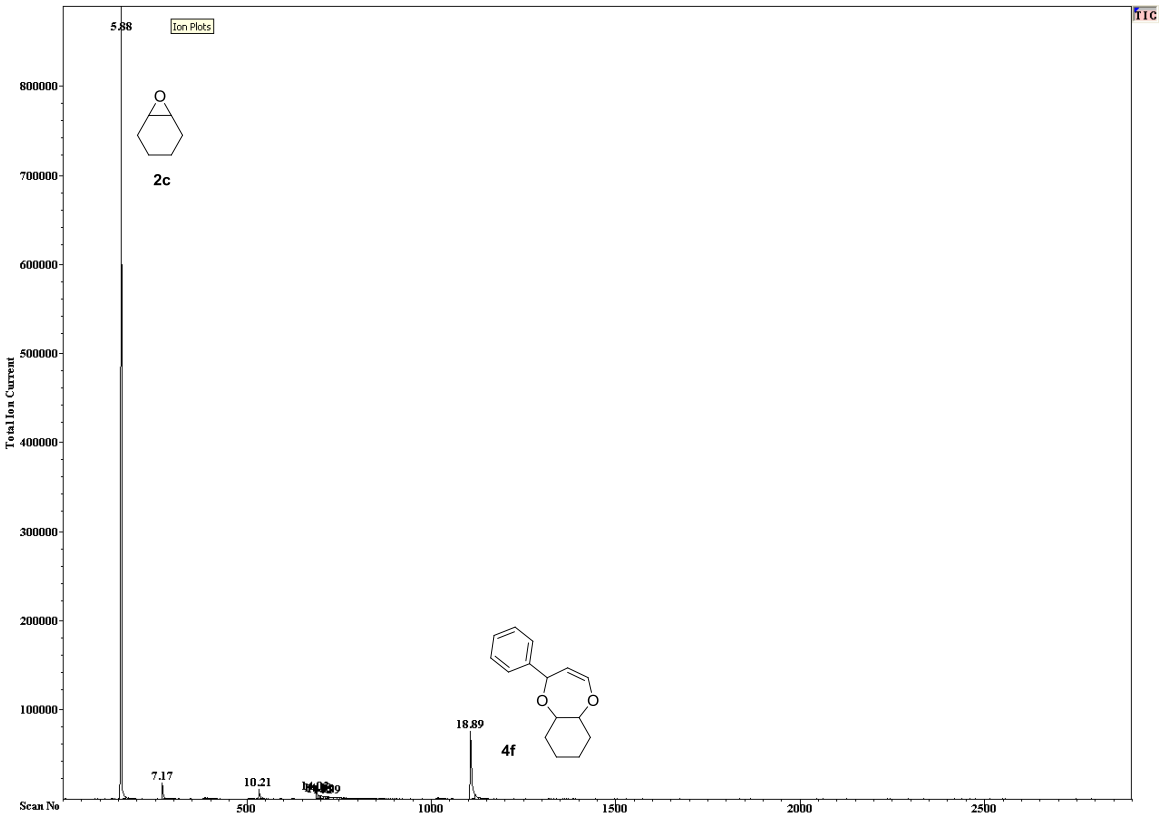
104
115
131
77
56
204
4e
ABUNDANCE
m/z


TIC
Ion Plots
5.88
2c
18.89
4f
7.17
10.21
Total Ion Current
Scan No
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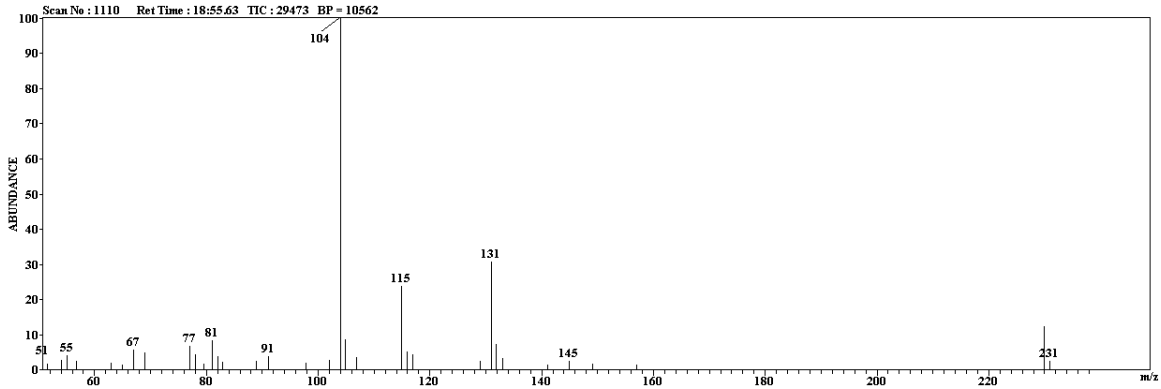
700000
600000
500000
400000
300000
200000
100000
500
1000
1500
2000
2500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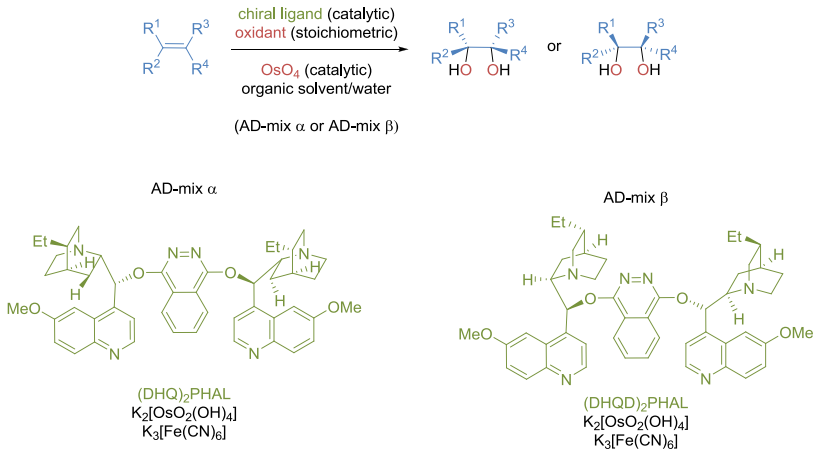
ABUNDANCE
m/z
104
131
115
67
77
81
91
55
51
145
231
100
90
80
70
60
50
40
30
20
10
0
60
80
100
120
140
160
180
200
220

7 Attempts towards the Bishydroxylation of Alkenes *via* Epoxide Intermediates

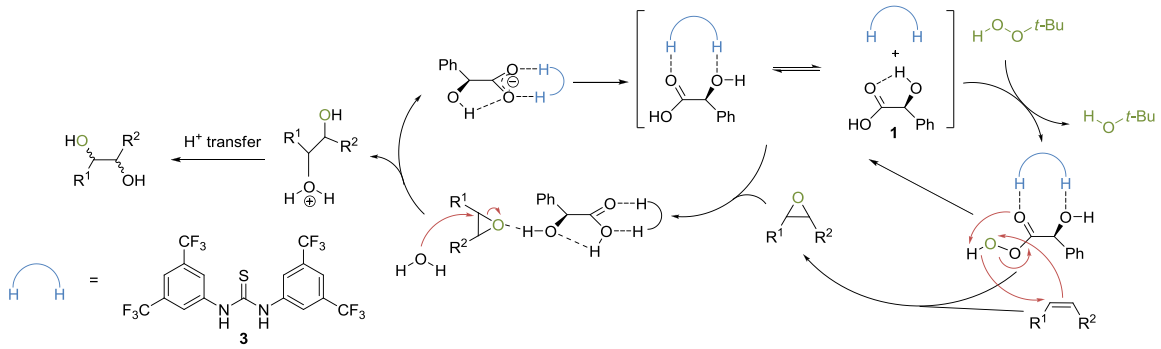
Introduction

Over a period of 20 years, the group around Sharpless developed an asymmetric dihydroxylation of alkenes (Scheme 1).[1] First, they utilized *tert*-butyl hydrogen peroxide as the oxidant in an alkaline solution instead of metal chlorates or hydrogen peroxide.[2] In the next step, they found out that diethylammonium acetate can be used in acetone for base-sensitive substrates.[3] The improvement of this reaction went on with the utilization of cinchona alkaloids as chiral ligands[4-5] and the slow addition of the olefin.[6-7] Their studies concluded with the development of new ligands.[8-10] In the year 2001, Sharpless was awarded the Nobel Prize in Chemistry – together with Knowles and Noyori – "for his work on chirally catalysed oxidation reactions".[11-12]



Scheme 1 The asymmetric dihydroxylation developed by Sharpless *et al.*[1]

The aim of the project described in this chapter was to develop a kind of "organocatalytic Sharpless dihydroxylation". With the concept of the cooperative alcoholysis of styrene oxides[13] (*vide supra*) in mind, we reasoned that to achieve this goal it should be possible to first oxidize an alkene to the respective epoxide. This epoxides could subsequently be opened by water under catalysis with a (chiral) thiourea derivative, and – if necessary – mandelic acid (Scheme 2).

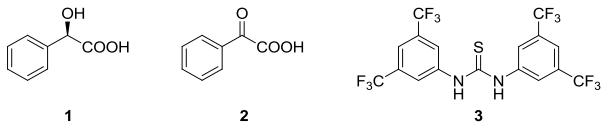


Scheme 2 Hypothesis for an "organocatalytic Sharpless dihydroxylation"

The opening of epoxides by water is a well-known reaction.[14-17] The miscibility of epoxides with water is very good.[18] Vilotijevic *et al.* as well as Wang *et al.* described water-promoted hydrolyses of epoxides.[17, 19]

Results and Discussion

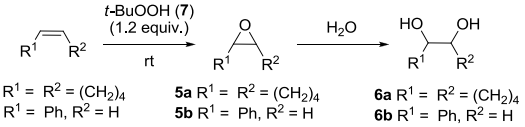
The catalysts or catalytic systems we utilized consisted of mandelic acid (**1**), phenylglyoxylic acid (**2**), and *N*,*N*'-bis[3,5-bis(trifluoromethyl)phenyl]thiourea (**3**) (Scheme 3).



Scheme 3 Catalysts utilized in the attempted conversions shown below

In the first experiments we tried *tert*-butyl hydroperoxide as the oxidant. As solvents we chose various substances or substance mixtures such as water or a water/THF mixture (Table 1). In all cases a conversion to the respective vicinal diol could not be observed; however, in some cases considerable amounts of cyclohexene oxide and traces of styrene oxide were detected *via* GC/MS analysis.

Table 1 Conditions for the attempted bishydroxylation utilizing *tert*-butylhydroperoxide as the oxidant



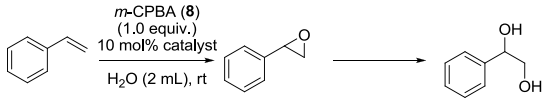
R^1	R^2	Catalyst(s)	Solvent	Time
-$(CH_2)_4$-		**1**[b]	H_2O[f]	6 d
-$(CH_2)_4$-		**1**[b]	H_2O/THF (1:1 Vol)[f]	5 d
-$(CH_2)_4$-		**1**[b]	H_2O/DCM (1:1 Vol)[g]	25 h
Ph	H	**1**[b]	H_2O[f]	6 d
Ph	H	**1**[b]	H_2O/THF (1:1 Vol)[f]	5 d
Ph	H	**1**[b]	H_2O/DCM (1:1 Vol)[g]	26 h
Ph	H	**1** + **3**[c]	H_2O[h]	7 d
Ph	H	**1**[a, d, e]	abs. DCM[g]	7 d
Ph	H	**2**[b, d]	abs. DCM[g]	19 h

[a] 1.0 equiv. [b] 10 mol% [c] 1 mol% [d] 1.0 equiv. *t*-BuOOH [e] 5 mol% [f] 2 mL [g] 1 mL [h] 12 equiv.

Thus, we tried in the next step to use *m*-CPBA as the oxidant; as solvent we chose water. In all five cases shown in Table 2 the respective diol **6b** could be observed *via* GC/MS analysis, even without any catalyst. We suggest these results are due to *m*-chlorobenzoic acid being present due to reduction of *m*-CPBA. This acid is strong enough (pK_a = 3.83)[20] to catalyze the conversion of the intermediate epoxides to the respective diol with water in contrast to *tert*-butanol (pK_a = 17.0)[20]. In 5 mL of water, the reaction shows a conversion of only 79% even after 65 h. We believe this is due to the 2.5-fold higher dilution decreasing the likeliness of reactive collisions between the reactants.

Thus, in a third series of experiments, we utilized hydrogen peroxide (**9**) as an oxidant in water. The results are summarized in Table 3. As in the experiments with *tert*-butyl hydrogen peroxide the desired product could not be observed *via* GC/MS analyses; however, in a few examples we detected benzaldehyde in our reaction mixtures.

Table 2 Results for the attempted dihydroxylation utilizing *m*-CPBA as the oxidant

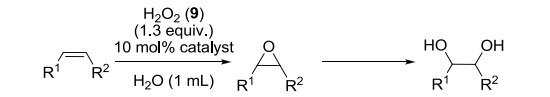


4b 5b 6b

Catalyst	Time/h	Conv./%[b]	Product
1	20	100	**6b**
2	21,5	100	**6b**
-	21	100	**6b**
-	22,5	100	**6b**
-[a]	65	79	**6b**

[a] 5 mL H_2O [b] GC/MS analysis

Table 3 Conditions and results of the attempted dihydroxylation of alkenes utilizing hydrogen peroxide as the oxidant



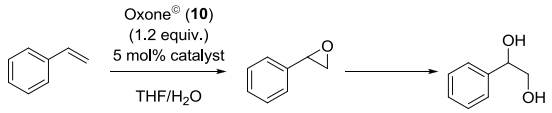
4a R^1 = R^2 = $(CH_2)_4$ **5a** R^1 = R^2 = $(CH_2)_4$ **6a** R^1 = R^2 = $(CH_2)_4$
4b R^1 = Ph, R^2 = H **5b** R^1 = Ph, R^2 = H **6b** R^1 = Ph, R^2 = H

R^1	R^2	Catalyst(s)	Temperature	Time
Ph	H	**2**	rt	22 h
-$(CH_2)_4$-		**2**	rt	7 d
Ph	H	**2**	50 °C	6 d
-$(CH_2)_4$-		**2**	50 °C	6 d
Ph	H	**2** + **3**[a]	rt	6 d
-$(CH_2)_4$-		**2** + **3**[a]	rt	6 d
Ph	H	**2** + **3**[a]	50 °C	7 d
-$(CH_2)_4$-		**2** + **3**[a]	50 °C	7 d

[a] 1.5 equiv. of H_2O_2

The forth oxidant we tried was oxone. Again, a conversion of styrene to the respective vicinal diol was not observable (Table 4).

Table 4 Conditions and results of the attempted dihydroxylation of alkenes utilizing oxone as the oxidant



4b 5b 6b

Catalyst(s)	Temperature	Time/d
1 + **3**	rt	6
1	rt	6
3	rt	6
1 + **3**	50 °C	5
1	50 °C	5
3	50 °C	5
2 + **3**	rt	8
2	rt	8
3	rt	8
2 + **3**	50 °C	5
2	50 °C	5
3	50 °C	5

[a] GC/MS analysis

Conclusions

An "organocatalytic Sharpless dihydroxylation" could not be developed. Four different oxidants were tried to make the reaction feasible in an "organocatalytic mode" without any success. Nevertheless, the reaction was feasible utilizing *m*-CPBA as the oxidant but without any catalyst differing from the respective *m*-chlorobenzoic acid built in the course of the reaction.

Experimental Section

General Remarks

All chemicals were purchased from Acros Organics, Alfa Aesar, Fluka, Merck, and Sigma Aldrich in the highest purity available and were used – in case of liquids – after distillation *in vacuo* over Vigreux columns, or without further purification in case of solid chemicals. Distilled chemicals were stored under an argon atmosphere. All reactions were run in 10 mL single-necked flasks (Schott DURAN®) with PTFE-coated magnetic stirring bars. The flasks were sealed with glass plugs equipped with PTFE thin wall sleeves. The thiourea derivative,

mandelic acid, phenylglyoxylic acid, and oxone were directly weighed into the reaction flasks. Liquid chemicals were transferred with 1 mL syringes with thin cannulas. The reaction outcome was determined by GC/MS analyses with a Quadrupol-MS HP MSD 5971 and a HP 5890A GC equipped with a HP5 crosslinked silica GC column (25 m × 0.2 mm, 0.33 micron stationary phase: 5% phenyl and 95% methyl silicone) using helium as carrier gas; temperature program: 60–250 °C (heating rate: 15 °C/min), injector and transfer line 250 °C. Samples were taken directly from the stirred reaction mixture with a 10 μL Hamilton syringe and were injected immediately.

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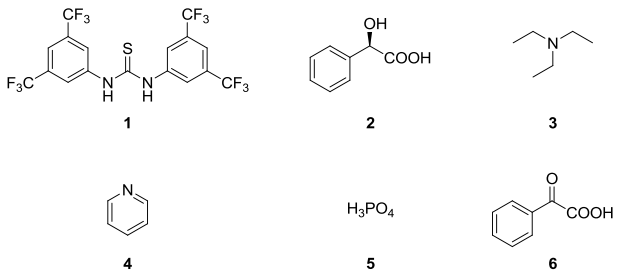
8 Attempts towards the Synthesis of Oxazolidinones *via* the Organocatalytic Opening of Epoxides with Isocyanates

Introduction

As already mentioned in Chapter 4, epoxides are very useful substrates in organic transformations.[1-3] The opening of epoxides with isocyanates is a long-known reaction; it leads to oxazolidinone derivatives.[4-9] Some oxazolidinone derivatives have antimicrobial properties.[10-12] Thus, synthesizing oxazolidinone derivatives is of some interest. Especially an asymmetric variant would be important for the synthesis of chiral oxazolidinone derivatives such as Evans auxiliaries. Unsurprisingly, this epoxide opening reaction is usually catalyzed by Lewis acids. Catalysts reported thus far include tetraphenylstibium iodide,[13] lanthanide salts,[14] or lithiumbromide/tributyl-phosphonium oxide[15] – to mention just a few examples. In 2008, Janssen and coworkers published a synthesis of enantiopure oxazolidinones through the opening of epoxides with isocyanates which was catalyzed by halohydrin dehalogenase.[16] Encouraged by this enzyme-catalyzed epoxide opening, we envisioned that an organocatalyzed oxazolidinone synthesis utilizing thiourea derivatives could be feasible.

Results and Discussion

Scheme 1 summarizes the catalysts we utilized in trying the oxazolidinone synthesis. Additionally to thiourea catalyst **1** and mandelic acid (**2**), we tried triethylamine (**3**), pyridine (**4**), phosphoric acid (**5**) and phenylglyoxylic acid (**6**).

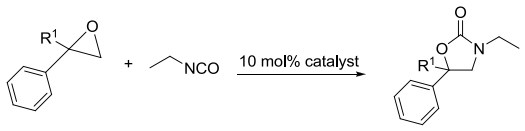


Scheme 1 Catalysts used in our attempts to synthesize oxazolidinones

We tried to run the reaction with thiourea catalyst **1**, catalysts **1** and mandelic acid (**2**), **1** in addition with triethylamine (**3**), **1** and pyridine (**4**), as well as with the catalysts **3**, **4**, and **5** alone. The reactions were done in DCM or in toluene. Furthermore, we tried four different temperatures between 0 and 50 °C; additionally, in two cases we worked under Argon atmos-

phere. In all these cases a conversion to the respective oxazolidinone derivative could not be observed *via* GC/MS analysis even after several days (Table 1).

Table 1 Attempted conversion of various epoxides with ethyl isocyanate and different catalysts/catalyst systems as well as various conditions



7a R^1 = H
7b R^1 = Me

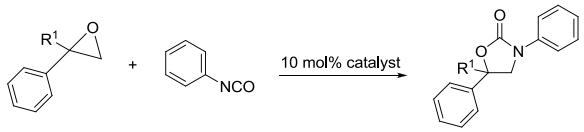
8

9a R^1 = H
9b R^1 = Me

R^1	Catalyst(s)	Conditions	Time/d
H	**1**	DCM, rt	12
H	**1**	DCM, 30 °C	9
H	**1**	DCM, Ar atm., rt	7
H	**1** + **2**	DCM, rt	5
H	**1** + **2**	DCM, Ar atm., 30 °C	4
H	**1** + **3**	DCM, rt	3
H	**3**	DCM, rt	3
H	**1** + **4**	DCM, rt	3
H	**4**	DCM, rt	3
H	**1** + **2**	toluene, 50 °C	2
H	**1** + **2**	DCM, 0 °C	3
H	**1** + **3**	toluene, Ar atm., 50 °C	2
H	**5**	DCM, rt	10
H	**5**	toluene, 50 °C	6
H	**1**	toluene, 50 °C	3
H	**1** + **4**	toluene, 50 °C	3
Me	**1**	DCM, rt	7

In the next step, we changed ethyl isocyanate to phenyl isocyanate. Again, we tried various catalysts under various conditions. We tried catalyst **1**, catalyst **1** in addition to mandelic acid (**2**), catalyst **1** in addition to phenylglyoxylic acid (**6**), only **2** or only **5**. The reaction was done at rt as well as 50 °C; as solvents we used DCM or toluene. In three cases, we worked under an Argon atmosphere. Even after several days, we were not able to detect any desired products by GC/MS analysis (Table 2).

Table 2 Attempted conversion of various epoxides with phenyl isocyanate and different catalysts/catalyst systems as well as various conditions



7a R^1 = H
7b R^1 = Me

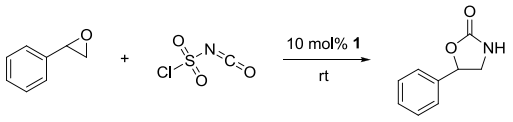
10

11a R^1 = H
11b R^1 = Me

R^1	Catalyst(s)	Conditions	Time/d
H	**1**	DCM, Ar atm., rt	4
H	**1** + **6**	DCM, Ar atm., rt	2
H	**1** + **6**	toluene, Ar atm., 50 °C	2
H	**5**	DCM, rt	5
H	**5**	toluene, 50 °C	6
H	**1**	toluene, 50 °C	3
Me	**1**	DCM, rt	14
Me	**1**	toluene, 50 °C	6
Me	**1** + **2**	DCM, rt	6
Me	**2**	DCM, rt	6

To finish this project, we made a last attempt using chlorosulfonyl isocyanate, a very reactive isocyanate, in addition to styrene oxide (Table 3). After three days in case of DCM or around 23 h in THF at rt, a conversion to the desired product could be seen; but this happens to be the case even without any catalyst.

Table 3 Attempted conversion of styrene oxide with chlorosulfonyl isocyanate



7a **12** **13**

Solvent	Time
DCM	3 d
THF	22 h 45 min

Conclusions

We did not succeed in synthesizing oxazolidinone derivatives in an organocatalyzed manner.

Experimental Section

General Remarks

All chemicals were purchased from Acros Organics, Alfa Aesar, Fluka, Merck, and Sigma Aldrich in the highest purity available and were used – in case of liquids – after distillation *in vacuo* over Vigreux columns, or without further purification in case of solid chemicals. DCM was distilled from CaH_2, toluene from sodium/benzophenone. Distilled chemicals were stored under an argon atmosphere. All reactions were run in 10 mL single-necked or two-necked flasks (Schott DURAN®) with PTFE-coated magnetic stirring bars. The flasks were sealed with glass plugs equipped with PTFE thin wall sleeves. Solid chemicals were directly weighed into the reaction flasks. Liquid chemicals were transferred with 1 mL syringes with thin cannulas or Eppendorf pipets. The reaction outcome was determined by GC/MS analyses with a Quadrupol-MS HP MSD 5971 and a HP 5890A GC equipped with a HP5 crosslinked silica GC column (25 m × 0.2 mm, 0.33 micron stationary phase: 5% phenyl and 95% methyl silicone) using helium as carrier gas; temperature program: 60–250 °C (heating rate: 15 °C/min), injector and transfer line 250 °C. Samples were taken directly from the stirred reaction mixture with a 10 µL Hamilton syringe and were injected immediately.

Typical Procedure

1 (49.8 mg, 0.1 mmol, 10 mol%) was weighed directly into a 10 mL one-necked flask followed by addition of 2 mL of DCM. Afterwards, styrene oxide (**7a**, 0.11 mL, 1 mmol) and ethyl isocyanate (**8**, 79.2 µL, 1 mmol, 1 equiv.) were added. The then clear and colorless solution was allowed to stir for the above mentioned time at rt.

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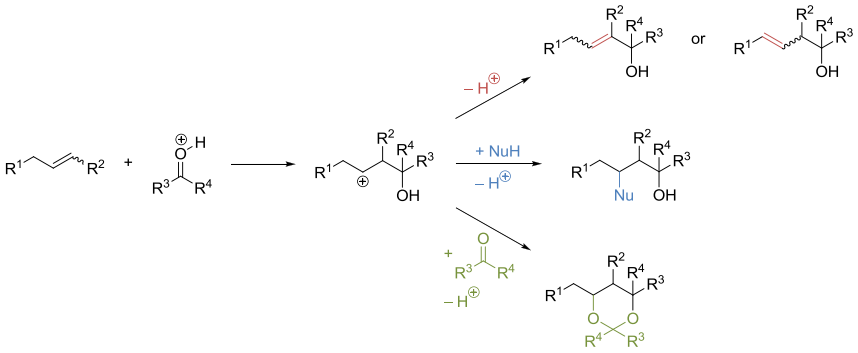
9 Attempts towards an Organocatalyzed Prins Reaction

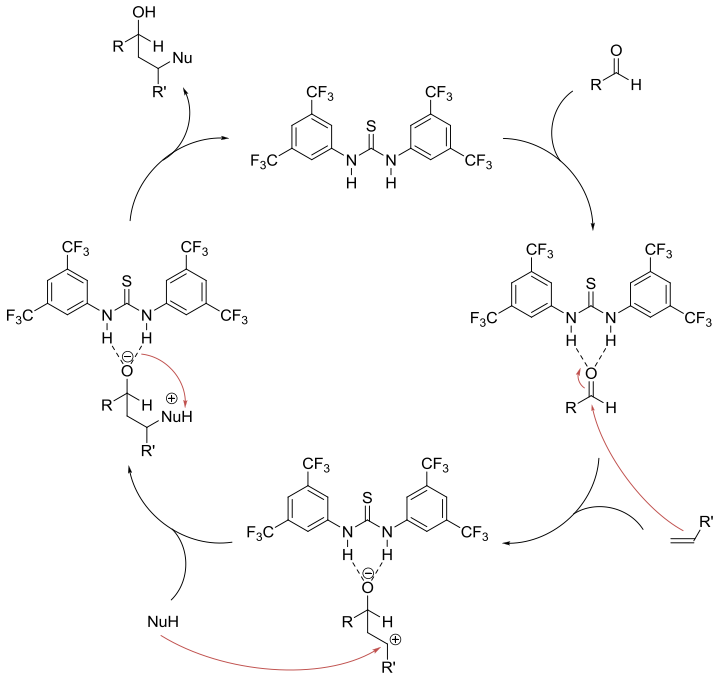
Introduction

In 1919, Prins published his findings “over de condensatie van formaldehyd met eenige onverzadigde verbindingen” (about the condensation of formaldehyde with some unsaturated compounds).[1-2] He reacted formaldehyde with styrene, anethol, isosafrol and some terpenes in the presence of acidic acid. Thus, the Prins reaction is a carbon–carbon bond forming reaction between an alkene and an aldehyde or ketone; it is typically catalyzed by Brønsted or Lewis acids.[3-4] Which product is formed is dependent on the reaction conditions. The formation of *α,β*-unsaturated alcohols, alcohols with nucleophilic substituents in the *γ*-position as well as the formation of acetals is possible (Scheme 1).[4] The Prins reaction can be catalyzed by Lewis acids[5]; Brønsted acidic ionic liquids have been applied as catalysts as well.[6] The Prins reaction and the Prins cyclization are important tools for the synthesis of natural products like Beraprost[4] (used against pulmonary arterial hypertension),[7] Leucascandrolide A (a substance with antifungal and cytotoxic properties)[8] core,[4] or Chatancin[4] (a platelet activating factor antagonist).[9] In 2012, Fache and coworkers published a solvent- and metal-free method for the Prins cyclization.[10]



Scheme 1 The possible products formed in a Prins reaction

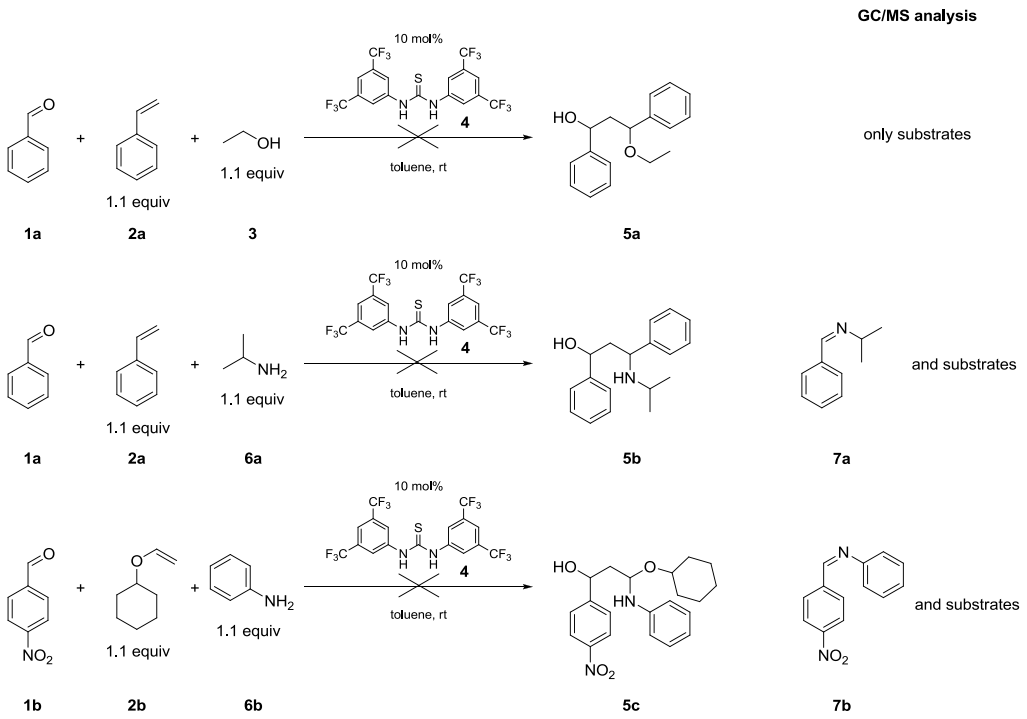
Because of thiourea derivatives being weak Brønsted acids and acting akin to Lewis acids,[11] we envisioned that an organocatalyzed method utilizing thiourea derivatives should be possible to build γ-substituted alcohols or acetals (Scheme 2).



Scheme 2 Hypothetic Mechanism for an Organocatalyzed Prins Reaction

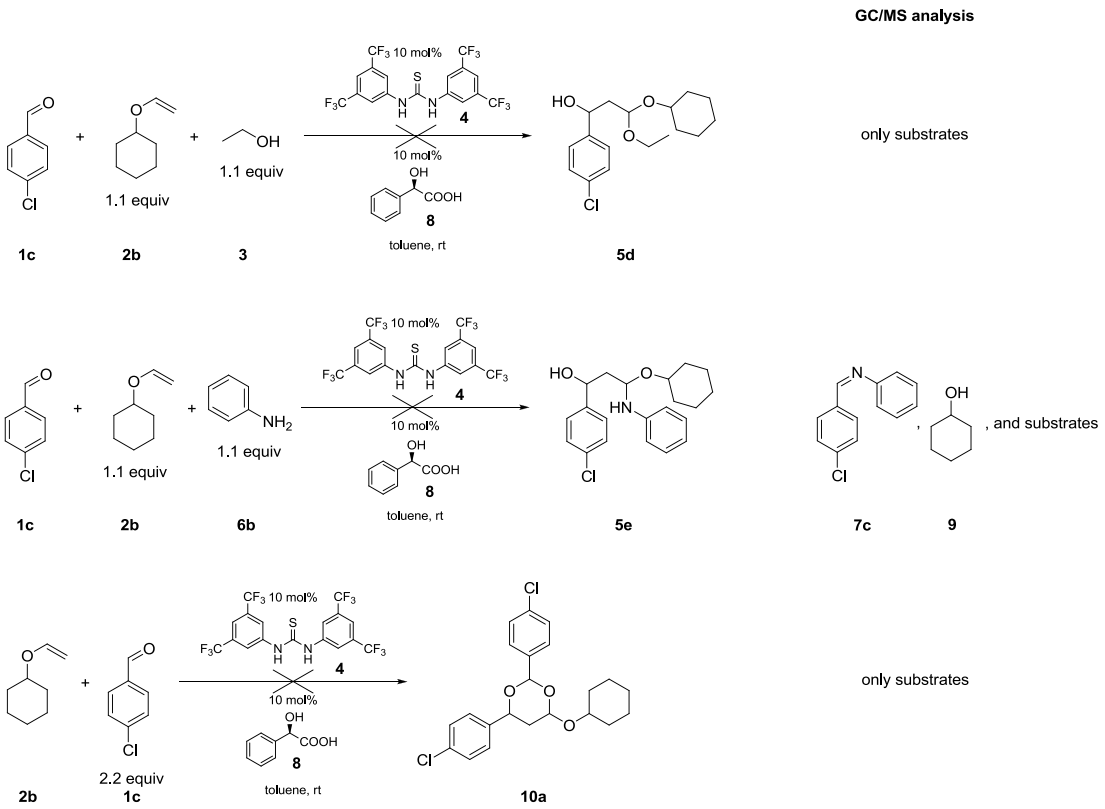
Results and Discussion

First, we tried to convert benzaldehyde (**1a**) with styrene (**2a**) and ethanol (**3**) to the respective product **5a** under catalysis with *N*,*N*'-bis-3,5[bis(trifluoromethyl)phenyl]thiourea (**4**). The GC/MS analysis showed only educts. Therefore, we chose to utilize better nucleophiles such as amines. We tried a reaction between **1a**, **2a**, and isopropylamine (**6a**). This was just leading to the formation of imine **7a**. In the next step, we envisioned that we had to make the reaction between aldehyde and alkene faster. Thus, we changed from styrene (**2a**) to cyclohexylvinylether (**2b**) – thinking the oxygen would make it a better nucleophile. But again, with vinylether **2b** and aniline (**6b**) in hand, we only saw the respective imine **7b** as a product *via* GC/MS analysis (Scheme 3).



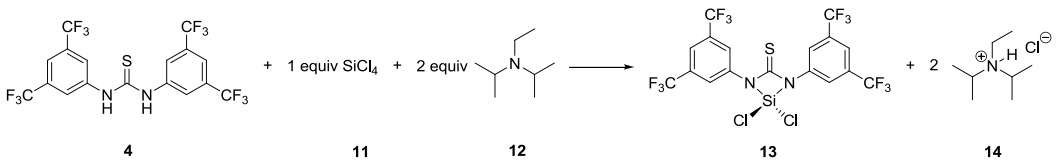
Scheme 3 Attempted Prins reactions catalyzed by thiourea derivative **4**

After we saw that thiourea derivative **4** alone would not be working as a catalyst we thought to use the cooperative catalysis system of **4** with mandelic acid (**8**) created in our group.[12] First, we tried a reaction between *p*-chlorobenzaldehyde (**1c**), vinyl ether **2b** and ethanol (**3**). The GC/MS analysis only showed the substrates. In the next step, we replaced the nucleophile ethanol by aniline (**6b**). In this case, the respective imine **7c**, cyclohexanol (**9**) and the substrates could be observed *via* GC/MS analysis. Finally, we thought to try the acetal formation of **2b** with **1c**. However, only the substrates could be detected with GC/MS analysis (Scheme 4).

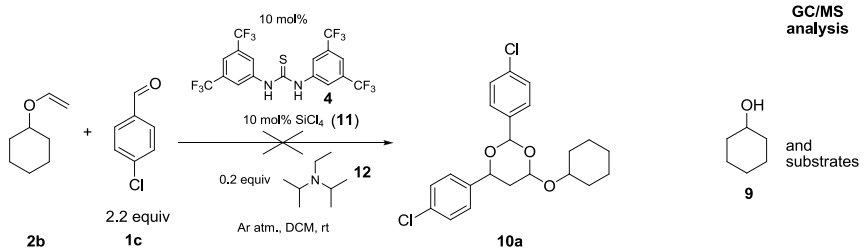


Scheme 4 Attempted Prins reactions catalyzed by thiourea derivative **4** and mandelic acid (**8**)

In 2011, a thiourea–silicon Lewis acid was developed in our group.[13] Scheme 5 shows the formation of this novel Lewis acid. We envisioned that the Prins reaction could be feasible with this Lewis acid. Thus, we tried to convert vinyl ether **2b** with aldehyde **1c** to the respective acetal. Again, only cyclohexanol (**9**) and the substrates were observable *via* GC/MS analysis (Scheme 6).



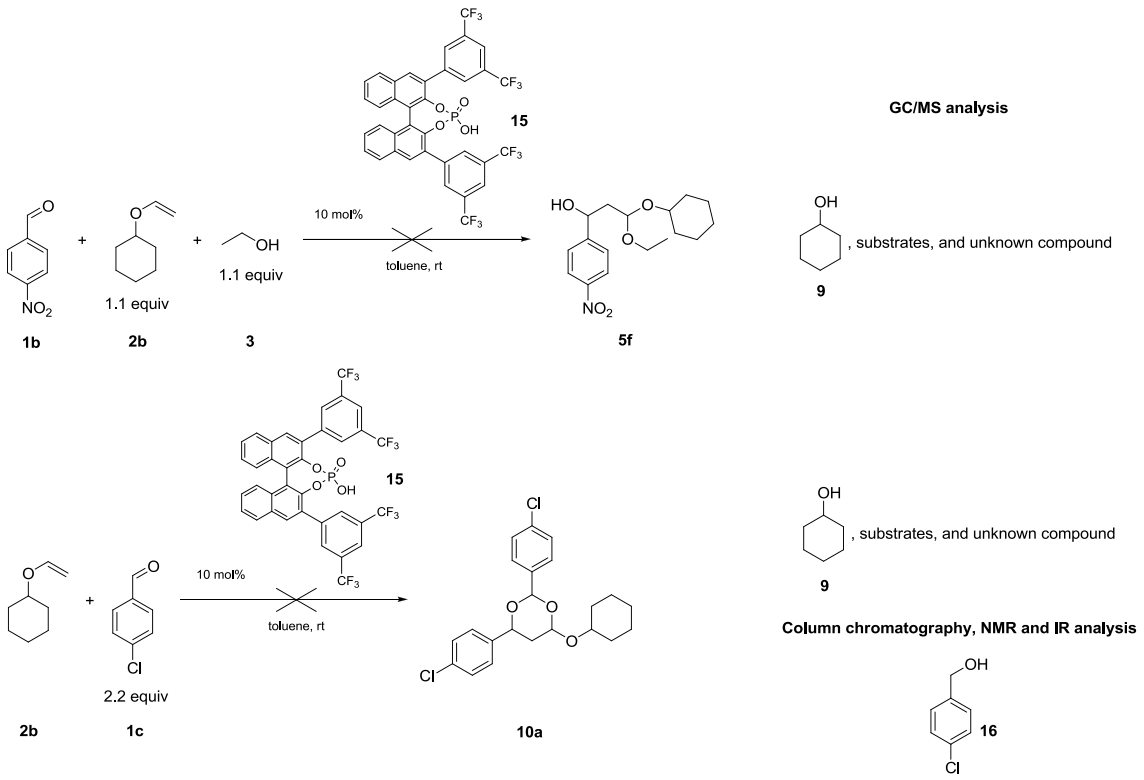
Scheme 5 Formation of thiourea–silicon Lewis acid **13**



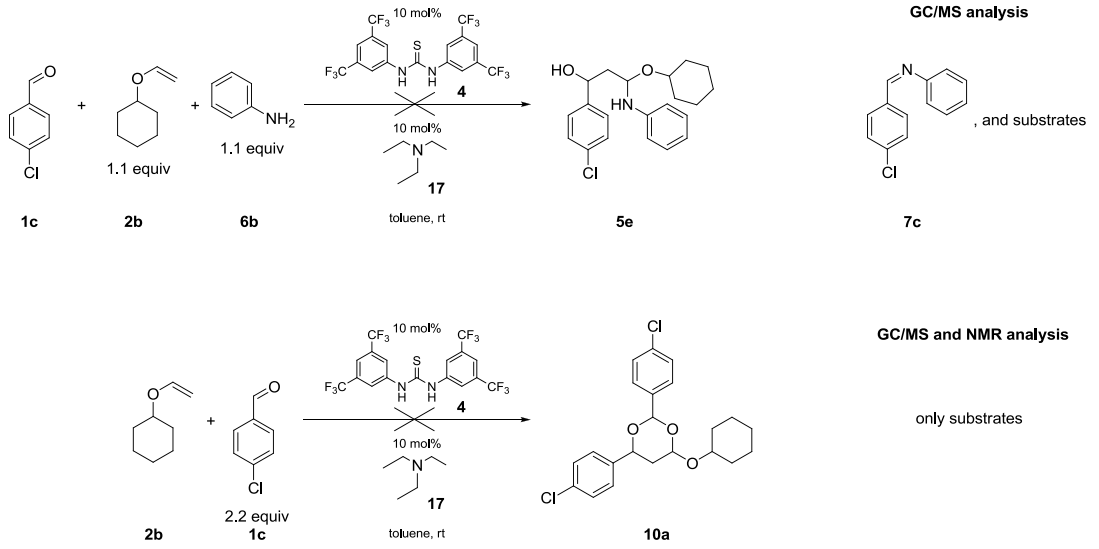
Scheme 6 Attempted Prins reactions catalyzed by thiourea derivative **4** and silicon tetrachloride (**11**)

Next, we thought to get away from thiourea derivatives and to come to a chiral phosphoric acid (CPA). We tried Akiyama's CPA, developed in 2005,[14] bearing bis(trifluoromethyl)phenyl groups like the thiourea derivative utilized in the first experiments. Again, we tried to convert aldehyde **1b** with vinyl ether **2b** and ethanol (**3**). GC/MS analysis identified cyclohexanol (**9**), the substrates, and an unknown compound. Next, we tried the acetal formation between **2b** and **1c**. Cyclohexanol (**9**), the substrates, and an unidentified compound could be observed *via* GC/MS analysis. Hence, the reaction mixture was purified by column chromatography, and the isolated compounds were analyzed by NMR and IR spectroscopy. We could identify *p*-chlorobenzyl alcohol as a product, however, it is not identical with the unknown compound seen by GC/MS analysis (Scheme 7).

Finally, we tried to utilize a catalyst system consisting of thiourea derivative **4** and trietylamine (**17**), and a bifunctional thiourea derivative – Takemoto's catalyst developed in 2003[15] – bearing both a bis(trifluoromethyl)phenyl as well as a chiral dimethylated cycloheyldiamine moiety. With both catalysts/catalyst systems we tried the identical reactions – the conversion of aldehydes **1c** with **2b** and aniline (**6b**) and the acetal formation of **2b** with **1c**. In case of catalyst system **4**/**17** we observed in the first reaction the respective imine **7c** and the substrates *via* GC/MS analysis. The GC/MS as well as the NMR analysis of the acetal formation's reaction mixture revealed only the starting compounds (Scheme 8).

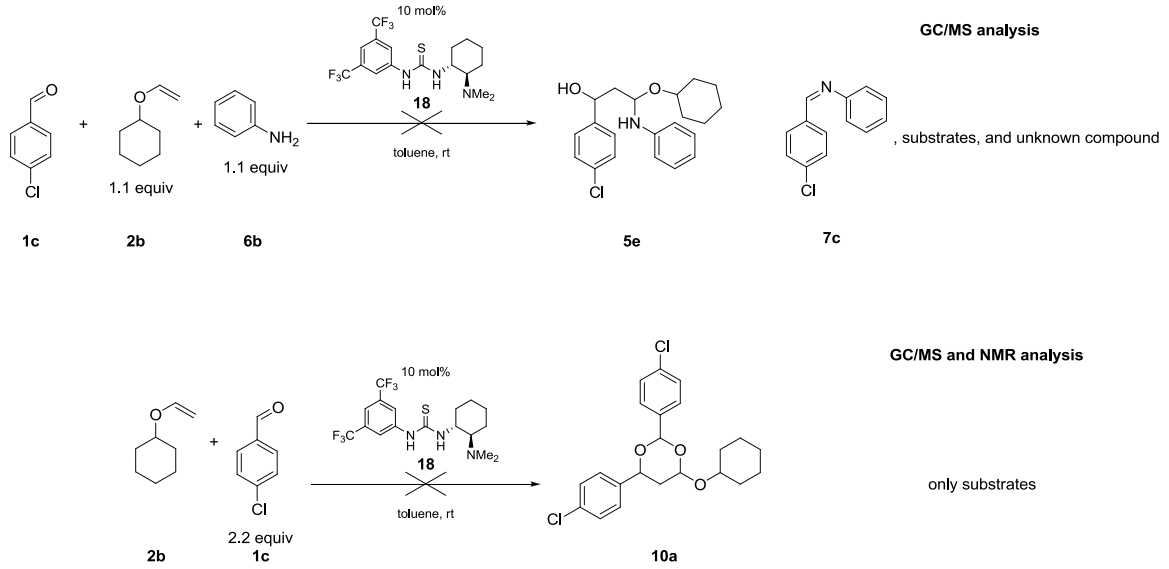


Scheme 7 Attempted Prins reactions catalyzed by chiral phosphoric acid **15**



Scheme 8 Attempted Prins reactions catalyzed by thiourea derivative **4** and triethylamine (**17**)

With Takemoto's thiourea derivative as a catalyst we could observe the imine **7c**, the substrates, and an unknown compound by GC/MS analysis in the first reaction. In case of the acetal formation only the substrates could be found by GC/MS as well as NMR analysis (Scheme 9).



Scheme 9 Attempted Prins reactions catalyzed by thiourea derivative **18**

Conclusions

An organocatalytic Prins reaction is not feasible with the catalysts and catalyst systems we tried.

Experimental Section

General Remarks

All chemicals were purchased from Acros Organics, Alfa Aesar, Fluka, Merck, and Sigma Aldrich in the highest purity available and were used – in case of liquids – after distillation *in vacuo* over Vigreux columns, or without further purification in case of solid chemicals. Distilled chemicals were stored under an argon atmosphere. Cleaning of glassware and stirring bars was done in a laboratory washer with first Extran© (Merck), then phosphoric acid, and last fresh water. Drying was done in an oven. All reactions were run in 10 mL single-necked flasks (Schott DURAN®) with PTFE-coated magnetic stirring bars. The flasks were sealed with glass plugs equipped with PTFE thin wall sleeves. The thiourea derivative, mandelic acid, the chiral phosphoric acid, and solid aldehydes were directly weighed into the reaction flasks. Liquid aldehydes, alkenes, and alcohols or amines, respectively, were transferred with 1 mL syringes with thin cannulas. The reaction outcome was determined by GC/MS analyses with a Quadrupol-MS HP MSD 5972 and a HP 5890 GC equipped with a HP5 crosslinked silica GC column (23 m × 0.2 mm, 0.5 micron stationary phase: 5% phenyl and 95% methyl silicone) using helium as carrier gas; temperature program: 60–250 °C (heating rate: 15 °C/min), injector and transfer line 250 °C. Samples were taken directly from the stirred reaction mixture with a 10 µL Hamilton syringe and were injected immediately.

Typical Procedure

4-Chlorobenzaldeyde (**1c**, 140.9 mg, 1 mmol), thiourea derivative **4** (50.3 mg, 0.1 mmol, 10 mol%), and (*R*)-(–)-mandelic acid (**8**, 15.2 mg, 0.1 mmol, 10 mol%) were weighed into a 10 mL one-necked flask at rt followed by addition of toluene (5 mL). Then, cyclohexylvinylether (**2b**, 0.16 mL, 1.1 mmol, 1.1 equiv.) and aniline (**6b**, 0.10 mL, 1.1 mmol, 1.1 equiv.) were added *via* syringe. The reaction mixture was stirred overnight at rt.

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10 Outlook

Building up a connection between the NMR titrations as well as the IR studies (Chapter 2) and the mechanistic studies on the alcoholysis of styrene oxides (Chapter 4) described in this thesis can be considered as the first step to advance further examinations. Observation of the complexation between thiourea derivative **1** and mandelic acid (**2**) as well as 2-methyl-2-phenyloxirane (**3**) or the respective *β*-alcoxy alcohols **4** (Figure 1) could enlighten the remarkable temporary progress of the epoxide ring-opening by alcohols. A ternary complex built of thiourea derivative **1**, madelic acid (**2**) and styrene oxide(s) was proposed as an important part in the reaction mechanism.[1]

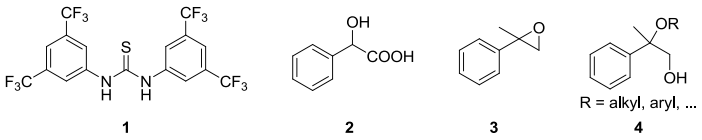


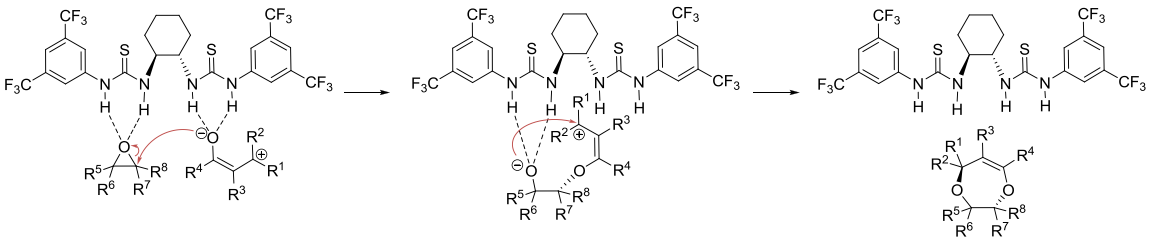
Figure 1 Substances for further NMR and IR complexation studies

We learned that with NMR titration experiments and IR studies it is possible to observe a complexation between thiourea derivatives and carbonyl compounds. If we transfer this finding to the alcoholysis of styrene oxides it could be possible to observe a complexation between these three substances and thus provide a proof for the existence of the proposed ternary complex. Furthermore the IR studies described in Chapter 2 could be developed further into a rapid method of screening for libraries of organocatalysts.[2] This method can deliver data on the activity of the possible catalyst very quickly just by the "degree of complexation", *i.e.*, the amount of complexed species, observed *via* IR spectroscopy. The more complexed species can be observed, the more likely is the catalyst to be a highly active organocatalyst.

In case of the Passerini reaction – which worked even at lowered temperatures of –10 °C – one could lower the temperature even further to, *e.g.*, –78 °C. If the reaction would not work without a catalyst but works with one at this temperature it would be possible to keep an eye on the creation of an asymmetric variant of this reaction. The utilization of a chiral or bifunctional thiourea derivative or a chiral phosphoric acid, for instance, could furnish enantiomerically enriched products then.

The next step in the synthesis of 1,4-dioxepines also is the development of a diastereo- and enantioselective version of this reaction. Possible catalysts for these conversions could be chiral and/or bifunctional thiourea derivatives. Because of the reaction's hypothetic mechanism the Nagasawa catalyst[3] appears as a promising choice for this system. The Nagasawa

catalyst incorporates two thiourea moieties thus giving the possibility of complexing two substances at once. This brings the two substances nearer together and provides the attack of the anion by one site (Scheme 1).



Scheme 1 The Nagasawa catalyst as a choice for the asymmetric synthesis of 1,4-dioxepines

However, the purification of these 1,4-dioxepine derivatives will remain a challenging task. To avoid decomposition of the substances it would be maybe helpful to silanize all glassware utilized in this reaction. This could prevent decomposition of the products by protons attached to the glassware walls.[4]

To follow these studies up will widen and deepen the understanding of thiourea organocatalysts' mode of action as well as pave the way for the creation of organocatalyzed reactions and novel organocatalysts.

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