Organocatalytic Additions to C=X Bonds (X=O, C, and NR)

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An dieser Stelle möchte ich Herrn Prof. Dr. P. R. Schreiner für die Anregungen zu diesem Thema, sein stetes Interesse am Fortgang dieser Arbeit, die ausgezeichneten Arbeitsbedingungen und zahlreichen fördernden Diskussionen danken.

Für meine Frau Dan Li

This thesis is based on the following publications and manuscripts:

I. **Organocatalytic Reactions Mediated through Thiourea Derivatives**

Zhiguo Zhang, Peter R. Schreiner*

The introduction of this thesis is written as part of a review for *Chem. Soc. Rev.* and will be submitted soon.

II. **Thiourea-Catalyzed Transfer Hydrogenation of Aldimines**

Zhiguo Zhang, Peter R. Schreiner*

Synlett **2007**, 1455–1457.

III. **Organocatalytic Biomimetic Reduction of Conjugated Nitroalkenes**

Zhiguo Zhang, Peter R. Schreiner*

Synthesis **2007**, 2559–2564.

IV. **Trichlorosilane ($HSiCl_3$) – A Cheap and Convenient Reducing Agent**

Zhiguo Zhang

Submitted to *Synlett Spotlight* on Jan. 9, 2008.

V. **Organocatalytic Reduction of Imine Using Trichlorosilane as the Hydrogen Donor** (Manuscript in preparation)

VI. **Development of Thiourea-Catalyzed Cyanosilylation** (Manuscript in preparation)

VII. **Development of Organocatalytic Hydrophosphonylations** (Manuscript in preparation)

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Summary

In the present doctoral thesis, a series of novel chiral thiourea derivatives was firstly designed and synthesized, and their potential applications as organocatalysts were widely investigated in several important synthetic transformations, such as transfer hydrogenation of aldimines, biomimetic reduction of nitroolefins, cyanosilylation of ketones, and hydrophosphonylation of imines. Since the newly designed thiourea-based catalysts were generally inefficient for the promotion of reduction with trichlorosilane, various amino acids derived *N*-formamides were developed for the asymmetric reductions of ketimines using trichlorosilane as the hydrogen donor. The main results of this dissertation can be summarized as follows:

- Chapter 3 describes our efforts in organocatalytic reductions:

  3.1 challenging reported results from another group, we first reported that thiourea derivatives can catalyze transfer hydrogenation of aldimines through hydrogen bonding activation with Hantzsch ester as the hydrogen source.

  3.2 describes a thiourea-catalyzed biomimetic reduction of nitroolefins with Hantzsch ester as the hydrogen donor, which may provide insights into the mechanism of redox reactions in biological systems.

  3.5 a series of novel proline based *N*-formamides was firstly synthesized and characterized. Their catalytic efficiencies were investigated in asymmetric reductions of ketimines with trichlorosilane as the hydrogen source.

- In chapter 4, we firstly demonstrated that the asymmetric addition of TMSCN to ketones can be promoted by one chiral module involving thiourea and anion moieties. In addition, *n*-BuLi was found to be an efficient agent for initiating this transformation.

- In chapter 5, a one-pot three component addition of carbonyls, amines, and diethyl phosphite was found to proceed smoothly under neat conditions without catalysts and solvents. Moreover, the possibility of autocatalysis for the asymmetric addition of diethyl phosphite to imine was also investigated with kinetic and preparative methods.

Zusammenfassung

Im Rahmen dieser Dissertation wurden zahlreiche neue chirale Thioharnstoffderivate dargestellt und deren mögliche Anwendung als Organokatalysatoren für verschiedenste Reaktionen, wie zum Beispiel in der Transferhydrierung von Aldiminen, der biomimetischen Reduktion von Nitroolefinen, der Cyanosilylierung von Ketonen und Hydrophosphonylierung von Iminen untersucht. Da sich die dargestellten Thioharnstoff-basierten Katalysatoren als generell inaktiv für die Reduktion mit Trichlorsilan zeigten, wurden verschiedene von Aminosäuren abgeleitete *N*-Formamide synthetisiert und diese in der asymmetrischen Reduktion von Ketiminen, mit Trichlorsilan als Wasserstoffquelle, eingesetzt. Die wichtigsten Ergebnisse dieser Dissertation können wie folgt zusammengefasst werden:

- In Kapitel 2 wird organokatalytische Reduktion dargestellt:

  3.1 auf der Grundlage von bereits veröffentlichten Ergebnissen anderer Arbeitsgruppen wird beschrieben, wie ein zweifach substituierter Thioharnstoff die Transferhydrierung von Aldiminen über H-Brücken Katalyse beschleunigt. Hierbei dient der Hantzsch-Ester als Wasserstoffquelle.

  3.2 beschreibt die Thioharnstoff-katalysierte, biomimetische Reduktion von Nitroolefinen mit Hantzsch-Ester als Wasserstoffquelle. Diese Reaktion kann das Verständnis von Redoxmechanismen in biologischen Systemen verbessern.

  3.3 stellt die Darstellung von einer Bibliothek von neuen *N*-Formamiden vor. Deren katalytische Effizienz wurde für die asymmetrische Reduktion von Ketiminen mit Trichlorsilan als Wasserstoffquelle untersucht.

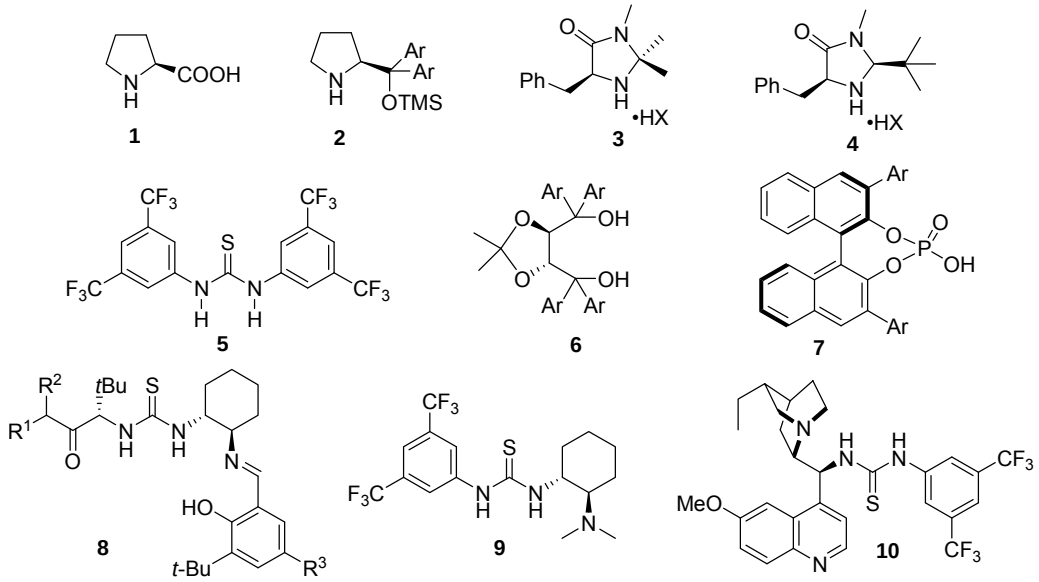
- In Kapitel 4 konnten wir erstmals zeigen, dass die asymmetrische Addition von TMSCN an Ketone durch ein chirales Katalysatorsystem, welches das Thioharnstoffmotiv und einen anionischen Rest enthält, beschleunigt werden kann. Zusätzlich zeigte sich *n*-BuLi als effizienter Initiator dieser Umsetzung.

- In Kapitel 5 wird die Ein-Topf-Drei-Komponenten-Synthese von Carbonylverbindungen, Aminen und Diethylphosphit unter lösungsmittel- und katalysatorfreien Bedingungen beschrieben. Weiterhin wurde die Möglichkeit der Autokatalyse für die asymmetrische Addition von Diethylphosphit an Imine mit experimentellen Methoden untersucht.

Chapter 1 Introduction and State-of-the-Art

1.1 Organocatalysis

Organocatalysis is defined as the acceleration of chemical reactions with a substoichiometric amount of organic molecules, which do not contain an active metal reaction center.[1] Although the roots of organocatalysis have run as deep as organic chemistry itself, asymmetric organocatalysis has just received much attention in the past few years as a result of organocatalysis has developed into a practical synthetic paradigm and started to serve as an important segment in common with biocatalysis and metal catalysis.[2] The operational simplicity, ready availability of these mostly inexpensive bench-stable catalysts, which are incomparably more robust than enzymes or other bioorganic catalysts makes organocatalysis an attractive method for the synthesis of complex structures. In contrast to any other system developed earlier, organocatalytic reactions provide a rich platform for multicomponent, tandem, or domino-type multistep reactions,[3-5] allowing the increase of the structural complexity of the product in a highly stereocontrolled manner. There are usually fewer toxicity issues associated with organocatalysis although this only applies when dealing with the more notorious metals and it should be pointed out that little is known about the toxicity of many of the organic catalysts. Moreover, there is no risk of metal leakage and also no expensive recovery process is required in the waste treatment. Such protocols are increasingly finding application in the synthesis of both biologically active natural products and therapeutically important synthetic compounds. Nowadays, the environmentally friendly "green" aspect of this chemistry coupled with the sustainability of the catalysts is considered widely for replacing standard, metal-based reactions.[6-11] Some representative organocatalysts are shown in Scheme 1.



Scheme 1. Some representative organocatalysts.

Our understanding of the mechanistic details of individual reaction pathway is improving. Organocatalytic reactions proceed usually either by a much "tighter" or a much "looser" transition structure than chiral metal complex mediated ones. The former class involves compounds which are acting as covalently (truly) bonded reagents such as enamine and iminium activation. The latter class includes reactions via noncovalent complexes such as ion pairing and hydrogen bonding. It should be noted that these two types of activation are often complementary and can therefore sometimes be used as alternatives in the same transformations.[12]

1.2 Organocatalysis mediated through hydrogen bonding

Hydrogen bonding acts as an ubiquitous glue to sustain the intricate architecture and functionality of proteins, nucleic acids and many supramolecular assemblies, and thus is responsible for the structure of much of the world around us.[13] In addition to its primacy as a structural determinant, hydrogen bonding also plays a crucial role in catalysis. Hydrogen bonding to an electrophile serves to decrease the electron density of this species, activating it toward nucleophilic attack. This principle is employed frequently by Nature's catalysts, enzymes, for the acceleration of a wide range of chemical processes. Recently, organic chemists have begun to appreciate the tremendous potential offered by hydrogen bonding as a mechanism for electrophile activation in small-molecule, synthetic catalyst systems. In particular, chiral hydrogen-bond donors have emerged as a broadly applicable class of catalysts for enantioselective synthesis.

Years of study have provided chemists with a relatively detailed understanding of catalysis by proton donors.[14-17] Brønsted acids can accelerate organic reactions by either of two fundamental mechanisms: reversible protonation of the electrophile in a pre-equilibrium step prior to nucleophilic attack (specific acid catalysis); or proton transfer to the transition state in the rate-determining step (general acid catalysis).

An increased appreciation of the scope of enzyme-catalyzed processes involving general acid catalysis likely contributed to the research efforts into synthetic H-bonding catalysts that began in the late 1990s. Organic chemists at this time also benefited from a relatively sophisticated understanding of the opportunities offered by H-bonding as a structural and functional element, due to research in several subdisciplines. Advances in supramolecular chemistry demonstrated that multiple, appropriately oriented H-bonds are sufficiently strong and directional to program the assembly of complex noncovalent structures, both in the solid state[18, 19] and in solution.[20] The ability of well-defined achiral hydrogen bond donors to catalyzed useful organic transformations was discovered in pioneering studies beginning in the mid 1980s. Rapid progress in other areas of organocatalysis, which occurred contemporaneously with early developments in chiral hydrogen-bond-donor catalysis,

rendered chemists keenly aware of the potential of simple organic molecules in asymmetric catalysis.[12, 21-25]

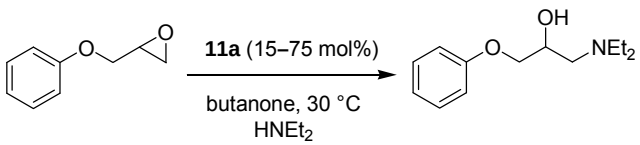
Although the concept of hydrogen donor catalysts has been widely accepted, information about the mechanism is quite limited. Jacobsen et al. classified this type of catalysts into three categories according to their features.[26]

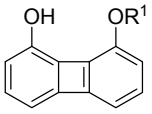
- Double hydrogen-bond-donor catalysts, such as ureas, thioureas, as well as guanidinium and amidinium ions.
- Bifunctional hydrogen-bond-donor catalysts, such as proline and amino thioureas.
- Single hydrogen-bond-donor catalysts, such as BINOL derived phosphoric acids.

1.3 Organocatalysts based on ureas and thioureas

1.3.1 General evolutions from biphenylenediols to efficient *N,N'*-diarylthio(urea) catalysts

The enormous potential of hydrogen bonding as an activating intermediate has been recognized only recently, but the notion that ureas and thioureas could act as catalysts by activating electrophiles through hydrogen bonding finds solid precedent in the work of a number of research groups. Detailed investigations into the mechanism of action of various enzymes identified a key role for hydrogen bonding (abbreviated H-bond) in electrophile activation.[13, 27, 28] Independently, and more of less simultaneously, well-defined achiral H-bond donors were discovered to catalyzed organic transformations. In pioneering studies, Hine and co-workers identified meta- and para-substituted phenols and biphenylenediols as catalysts for addition of diethylamine to phenyl glycidyl ether (Scheme 2).[29-32] Hine and co-workers proposed that the enhanced activity of the biphenylenediol (**11a**) in solution relative to phenol resulted from simultaneous donation of two H-bonds to the electrophile, a model that was given strong support from a solid-state 1:1 structure of the catalyst and substrate.[33-35]





11a R^1 = H
11b R^1 = Me

catalyst	p*K*a	*K*rel
phenol	9.98	1.0
m-nitrophenol	8.40	2.4
p-nitrophenol	7.15	2.8
catechol	9.49	2.0
11b	9.15	1.2
11a	8.00	12.5

Scheme 2. Biphenylenediol-Promoted Epoxide-Opening Reactions.

Later Kelly and co-workers reported the promotion of the Diels-Alder reaction between cyclopentadiene and α,β-unsaturated aldehydes and ketones by biphenylenediol derivatives, and proposed double hydrogen-bond donation to the dienophile (**12**; Figure 1) as an explanation for the catalysis observed.[36] This was consistent with a theory proposed by Jorgensen based on computational studies to rationalize the observed acceleration of Diels-Alder reactions and Claisen rearrangements in H_2O relative to nonprotic solvents (**13**; Figure 1).[37, 38]

Although the biphenylenediol catalysts possessed only moderate reactivity and solubility profiles, the pioneering work of Hine and Kelly established that general acid catalysis by conformationally restricted metal-free diprotic acids is a valid strategy upon which to base organocatalyst design. At around this time, Etter et al.[39, 40] observed hydrogen bond-directed co-crystallisation of *N,N'*-diaryureas (in particular 3,3'-dinitrocarbanilide (**14**) with compounds incorporating a wide variety of Lewis basic functional groups, such as nitroaromatics, ethers, ketones, and sulfoxides. In each case the bidentate nature of the binding interaction is particularly attractive because it removes some conformational degrees of freedom. To avoid entropic loss upon coordination, this also means that the hydrogen-bond donor must be relatively rigid.[41] The precedents set by the aforementioned studies for efficient catalysis by rigid bidentate hydrogen-bond donors and the demonstration of binding between (thio)ureas and Lewis bases provided the basis for the development of (thio)urea-based organocatalysts.

The first such example came from Curran et al. who found that substoichiometic amounts of diarylurea **15** enhanced both the yield and diastereoselectivity of the allylation of cyclic α-sulfinyl radicals with allyltributylstannane.[42] Later the same group reported the promotion of the Claisen rearrangement by using catalytic quantities of **15a** (Scheme 3).[43] For the first time thiourea derivatives (e.g., **15b**) were also shown to hold promise as hydrogen-bonding catalysts.

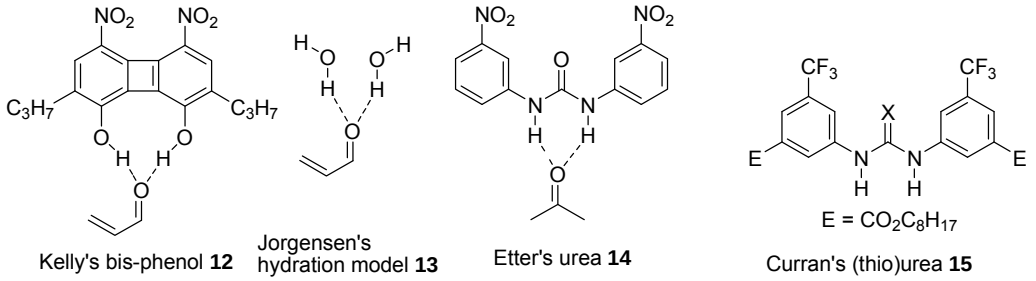
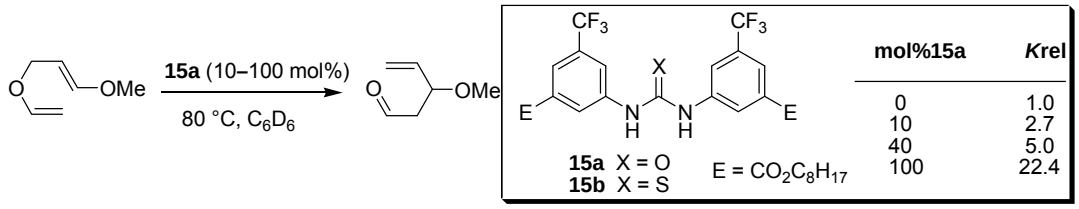
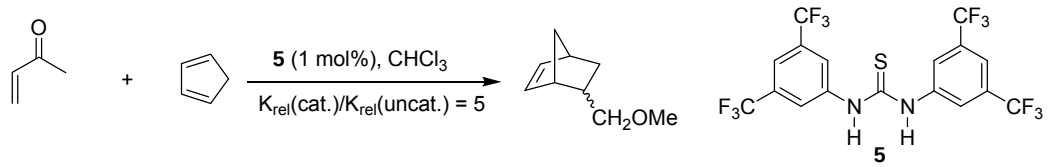


Figure 1. Bis-H-bond interaction.



Scheme 3. Diaryl(thio)urea catalysis of the Claisen rearrangement.

Schreiner's group took these ideas together and settled for using thioureas because they are a) more soluble in a variety of solvents, b) easier to prepare (thiophosgene is much easier to handle than phosgene) c) the thiocarbonyl group is a much weaker hydrogen-bond acceptor.[44, 45] As expected, the introduction of electron-withdrawing groups in the meta-position that not capable of much hydrogen bonding themselves, increases the catalytic efficiency; this observation is also in line with the fact that co-crystals are of higher quality when trifluoromethyl groups are present in the thiourea derivatives.[39] In a systematic study, *N,N'*-bis[3,5-bis(trifluoromethyl)phenyl]thiourea (**5**) was identified as the most active for the promotion of Diels-Alder and dipolar cycloaddition reactions, even with water as the reaction solvent (Scheme 4).



Scheme 4. Thiourea-catalyzed Diels-Alder reaction.

In view of the generally weak enthalpic binding between thioureas and carbonyl compounds,[46] the results were rationalised in terms of the importance of entropic effects; specially, it was proposed that the (computationally determined)[41] rotational barrier of catalyst **5** is relatively high due to an attractive interaction between the ortho-hydrogen atoms, which are polarised by the adjacent electron-withdrawing substituent, and the Lewis basic sulphur heteroatom (Scheme 4). This rigidifying interaction would minimise entropy loss upon binding of the substrate and thus facilitate catalysis. It is also likely, however, that enthalpic factors also contribute to the high activity of **5**; that is, the *m*-CF_3 substituents (σ_m = 0.46)[47] would significantly augment the acidity of the N–H protons.

To date, the applications of thiourea **5** have been extended for a wide range of useful organic transformations by our group as well as by other groups, such as nucleophilic addition,[48] Baylis-Hillman reactions,[49] Friedel-Crafts alkylation,[50] acetalization,[51] epoxide opening,[52] acyl-Strecker reaction,[53] as well as transfer hydrogenations[54, 55] Moreover, by incorporation of the electron-poor 3,5-bis(trifluorophenyl) thiourea moiety, various achiral/chiral mono-, bifunctional organocatalysts have been developed for a broad spectrum of reactions through H-bond activation.

1.3.2 Chiral (thio)ureas for asymmetric organocatalysis

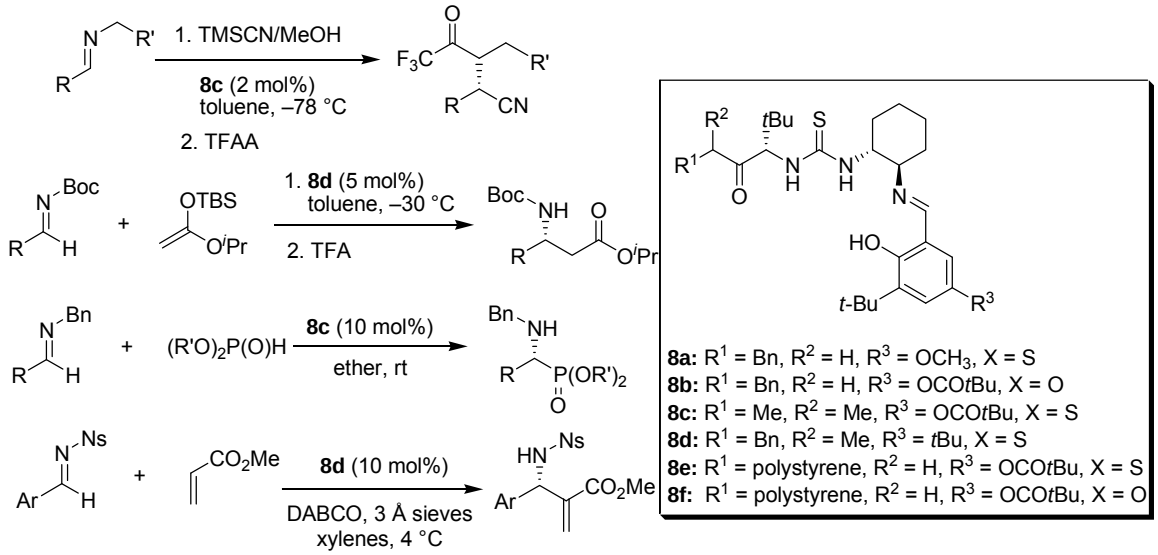
The ready availability of enantiopure chiral building blocks bearing primary amino functionalities from the chiral pool and other sources greatly facilitates the synthesis of asymmetric (thio)ureas. It is perhaps unsurprising that chiral analogues are rapidly emerging

as versatile, functional group tolerant and easily prepared/modified catalyst templates for the promotion of wide range of synthetically useful asymmetric carbon-carbon bond forming processes.

1.3.2.1 Double hydrogen-bond-donor (thio)ureas

The most remarkable advances in this field were achieved by Jacobsen's group.[56-61] Focusing on the activation of alkyl- or acyl-substituted imines, they identified and optimized a series of urea- and thiourea-containing Schiff-base catalysts for various types of asymmetric reactions such as Strecker, Mannich, hydrophosphonylation, nitro-Mannich, and acyl Pictet-Spengler reactions.

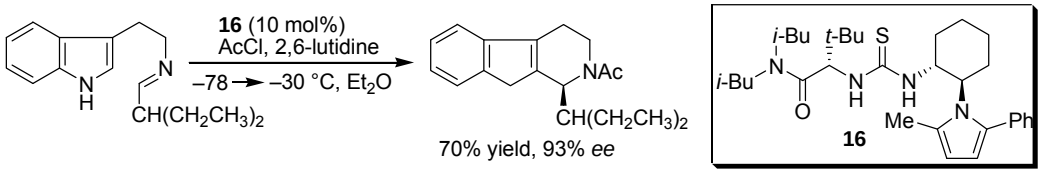
The discovery that Schiff bases **8a-c** catalyze asymmetric hydrocyanation reactions of a wide variety of imine substrates revealed for the first time that chiral urea and thiourea derivatives are capable of mediating highly enantioselective transformations (Scheme 5, eq. 1).[60-62] These compounds had been designed originally as potential ligands for Lewis acidic metals, and the observation that highest enantioselectivity was observed in the absence of metal additives was unanticipated. Systematic optimization led to identification of **8c** as remarkably general catalyst for the Strecker reaction. Furthermore, the catalyst can be reused without loss of either activity or enantioselectivity, and the immobilized catalysts **8e** and **8f** on a polystyrene bead facilitate Strecker product purification by simple filtration and solvent removal without impacting the enantioselectivity of the reaction. The mechanism by which these catalysts activate imines was subsequently investigated by using a number of approaches, such as structural modification, NMR, kinetic, and computational studies.[59] The data thus obtained were all consistent with a double H-bond between the acidic NH protons and the imine lone pair serving to activate the electrophile towards attack by cyanide. A very recent investigation by List and co-workers identified acetyl cyanide as the cyanation reagent for thiourea **8c**-catalyzed enantioselective acyl-Strecker reaction.[63, 64]



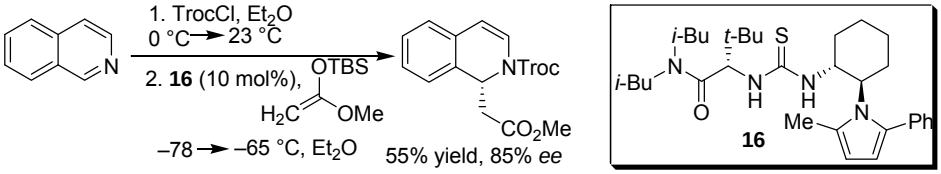
Scheme 5. (Thio)urea-catalyzed asymmetric reactions.

In addition to hydrogen cyanide, a number of nucleophiles undergo enantioselective addition to *N*-benzyl imines in the presence of thiourea catalysts **8**. Addition of di-(2-nitro-benzyl) phosphite to imines derived from aliphatic and aromatic aldehydes, followed by hydrogenolysis of the *N*- and *O*-benzyl groups, constitutes an efficient asymmetric synthesis of aminophosphoric acids (Scheme 4).[57] It is remarkable, however, that highly enantioselective additions to a range of functionally diverse electrophiles are promoted by thiourea catalysts. The first indications of this generality arose from studies of Mannich reactions of *N*-*tert*-butoxycarbonyl (Boc) imines, a reaction of interest for the preparation of enantioenriched β-amino acid derivatives. Thiourea **8d** catalyzes this reaction with high enantiomeric excess, despite the significant steric and electronic differences between *N*-Boc imines and the *N*-benzyl and *N*-allyl imines employed in the Strecker reaction (Scheme 4).[58] The scope of thiourea catalysis was extended to include *N*-(2-nitrobenzene)sulfonyl (nosyl, Ns) imines, useful substrates by virtue of their high electrophilicity and the ease of removal of the nosyl group (Scheme 4).[65] In the presence of **8d** and stoichiomeric quantities of diazabicyclo[2.2.2]octane (DABCO) as nucleophilic activator, *N*-nosyl imines undergo enantioselective aza-Baylis-Hillman reactions with methyl acrylate.

N-Acyliminium ions are among the most reactive imine derivatives, and methodology based upon these intermediates has been applied extensively to the synthesis of nitrogen-containing compounds.[66] The Jacobsen group discovered that pyrrole-containing thiourea **16** promotes the intramolecular addition of indoles to *N*-acyliminium ions generated *in situ* from imines and acetyl chloride (Scheme 6).[56] Subsequently, the same group found that catalyst **16** is also effective for Mannich-type additions of silyl ketene acetals to isoquinolines in the presence of 2,2,2-trichloroethyl chloroformate, providing access to enantioenriched dihydroisoquinoline products (Scheme 7).[67]



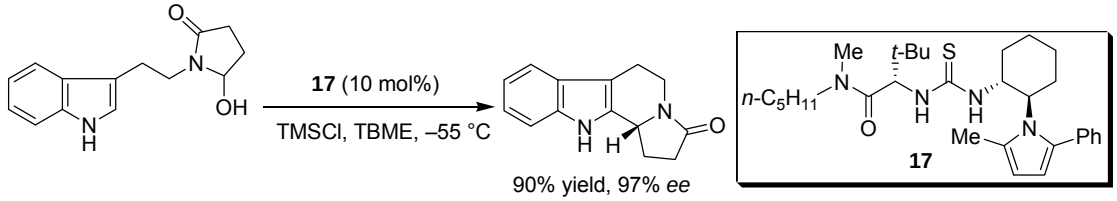
Scheme 6. Thiourea-catalyzed asymmetric acyl-Pictet-Spengler reaction.



Scheme 7. Thiourea-catalyzed addition to *N*-acyliminium ions.

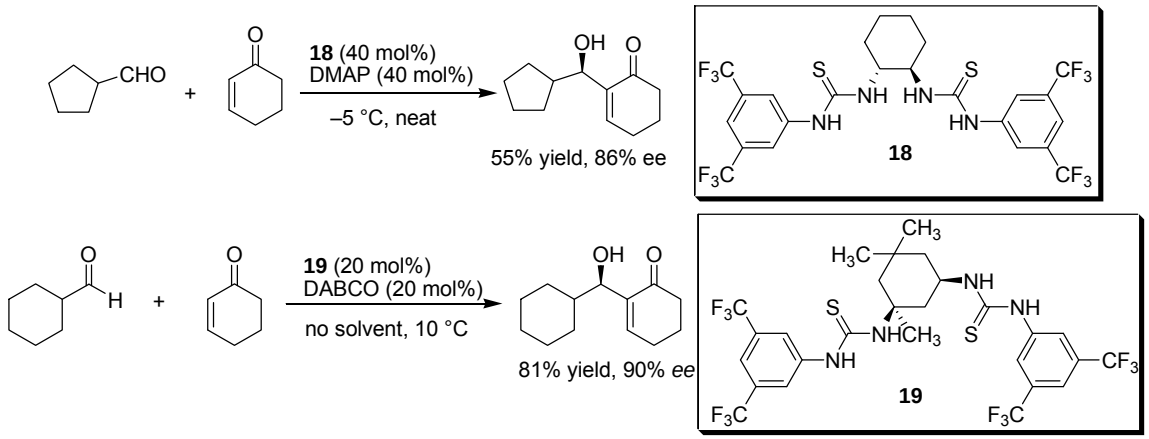
Formal dehydration of hydroxylactams provides an alternative synthetic route to *N*-acyliminium ions. Jacobsen and co-workers have shown that hydroxylactams, in the presence of TMSCl as a dehydrating agent, are substrates for thiourea **17**-catalyzed enantioselective Pictet-Spengler cyclizations (Scheme 8).[68] The observation of enhanced reactivity of

alkylated versus reduced derivatives suggests that an S_N2-type mechanism displacement of chloride is not operative in the cyclization reaction. In order to explain the reactivity and enantioselectivity with thiourea **17**-catylzed addition to *N*-acyliminium ions, the Jacobsen group proposed that the thiourea catalyst binds to the chloride counteranion of the charged electrophile. This proposal is consistent with the substitution and pronounced halide counteranion effects observed in the acyl-Pictet-Spengler and acyl-Mannich reactions (vide supra) and asymmetric catalysis via anion-transformations mechanism might be applicable to a wide variety of valuable transformations involving highly reactive cationic intermediates.



Scheme 8. Thiourea-catalyzed cyclization of hydroxylactams.

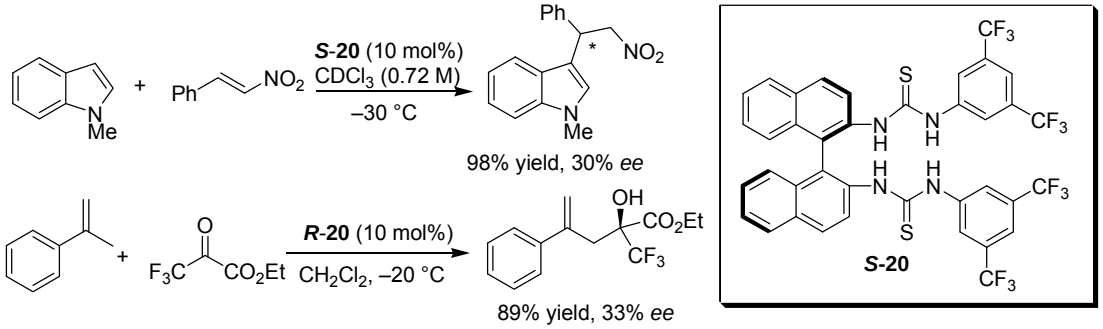
Nagasawa and co-workers found that *trans*-1,2-Diaminocyclohexane-derived bis-thiourea **18** promoted the *N*,*N*-4-dimethylaminopyridine (DMAP)-mediated addition of cyclohexenone to a range of activated aldehydes (Scheme 9, top).[69] Although detailed mechanistic studies were not reported, a proposal involving H-bonding to both the aldehyde electrophile and the enone (or enolate) was advanced. More recently, Berkessel and co-workers reported an improved bis-thiourea catalyst **19**, derived from the 1,4-diamine IPDA (3-(aminomethyl)-3,5,5-trimethyl-cyclohexyl-amine), for Baylis-Hillman reactions of aromatic and aliphatic aldehydes (Scheme 9, bottom).[70] Cyclohexenone and cyclopentenone were shown to be capable Michael acceptors for the enantioselective Baylis-Hillman reactions in the presence of **19** and DABCO as the nucleophilic promoter.



Scheme 9. Bis-thiourea-catalyzed Baylis-Hillman reaction.

Connon and co-workers developed an axially (*S*)-(+)-1,1'-Bi(2-naphthylamine) derived bis-thiourea catalyst **20** for asymmetric Friedel-Crafts type addition of *N*-methylindole to nitroolefins, affording the corresponding product in good yield and with comparable (albeit

lower) levels of enantioselectivity (Scheme 10, top).[71] It is noteworthy that the challenging nitroolefin substrates such as β-aliphatic substituents undergo FC addition with considerably higher enantioselectivity than the literature reported before. Recently, the enantiomer of **(*S*)-20** has also been used for catalytic asymmetric carbonyl-ene reaction (Scheme 10, bottom).[72]



Scheme 10. Axially bis-thiourea catalyzed FC addition and carbonyl-ene reactions.

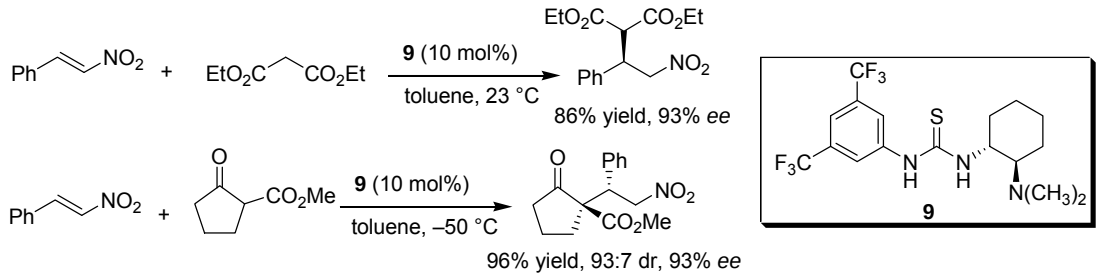
1.3.2.2 Chiral bifunctional (thio)ureas for asymmetric organocatalysis

The excellent functional group tolerance of the thio(urea) catalysts stem from their relatively weak enthalpic binding with organic Lewis basic nucleophiles, such as alcohols and amines. As is often the case, the penalty for high (chemo)selectivity can be a general lack of activity relative to benchmark metal(-ion)-based catalyst systems, often leading to restriction in reaction scopes. Recently the concept of exploiting the high functional group tolerance of these materials by incorporating a Lewis basic nucleophile-activating functionality into the catalyst structure has begun to be explored. Such bifunctional catalysts mimic natural enzymatic systems by activating both electrophile and nucleophile simultaneously,[73, 74] allowing scope for significantly improved catalytic activity, and perhaps, more importantly, allowing a greater degree of stereocontrol over the addition event. The majority of these prototype systems represent a hybrid strategy that borrows heavily from the design principles set down in the seminal work of Curran, Jacobsen, and Schreiner group outlined above involving the installation of readily tunable aromatic functionality (to maximize the catalyst's rigidity and hydrogen-bond-donating ability) at one (thio)urea nitrogen atom, and chiral (in this case Lewis basic) functionality at the other.

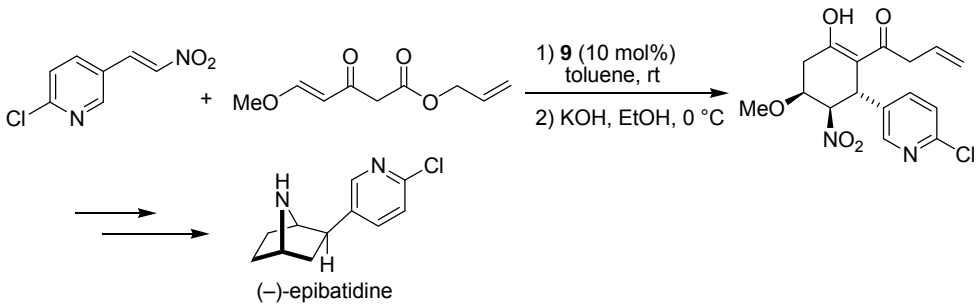
1.3.2.2.1 Tertiary amine-thiourea

In 2003, Takemoto and co-workers reported the first (thio)urea-based bifunctional catalyst **9** bearing a dimethyl amino group, which was capable of the efficient promotion of the addition of malonate esters to β-nitrostyrenes with excellent enantioselectivity (Scheme 11, eq. 1).[75] The authors found that both the tertiary amine and the thiourea moieties were requisite for efficient and selective catalysis. Reaction kinetic and catalyst modification studies are consistent with the mechanistic proposal that the catalyst serves to activate both nucleophile, by general base catalysis, and electrophile, by H-bonding to the nitro group. In subsequent

studies, a range of 1,3-dicarbonyl nucleophiles were shown to be compatible with the reaction conditions. Prochiral 1,3-dicarbonyl nucleophiles undergo C–C bond formation with the generation of adjacent tertiary and quaternary stereocenters in high enantio- and diastereoselectivity.[76] Additionally, γ,δ-unsaturated β-ketoesters undergo double Michael addition reactions, a transformation that was applied to the enantioselective synthesis of the medicinally relevant alkaloid (–)-epibatidine (Scheme 12).[77, 78] This reactivity has been extended to include diastereo- and enantioselective additions of substituted ketoesters, and double Michael additions of γ,δ-unsaturated β-ketoesters.[76, 77]



Scheme 11. Enantioselective conjugate addition reactions.

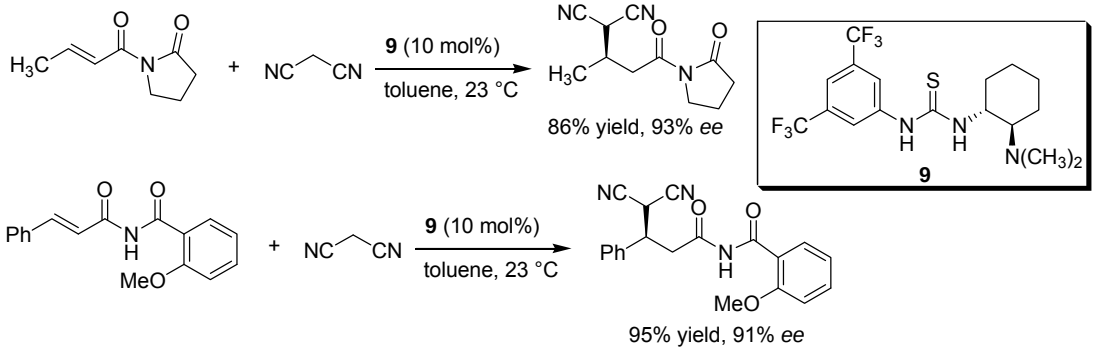


Scheme 12. Enantioselective synthesis of (–)-epibatidine.

Theoretical investigations conducted by Soós, Pápai, and co-workers support a dual activation mechanism of catalysis.[79] However, in contrast to qualitative models proposed by Takemoto and co-workers that involve electrophile activation through substrate binding of the thiourea,[75, 76] the authors proposed a reaction mechanism wherein the thiourea activates the deprotonated β-ketoesters nucleophile and the protonated amino group of the catalyst activates the nitroalkene electrophile.

Takemoto and co-workers have also reported the enantioselective addition of malononitrile to α,β-unsaturated imides in the presence of bifunctional catalyst **9**, furnishing the products with high enantioselectivity (Scheme 13).[80] It is of interest that while malononitrile is an excellent pronucleophilic substrate in the addition to α,β-unsaturated imides, it gave poor selectivtity in the addition to nitroolefins, while the best 1,3-dicarbonyl substrates for the nitroolefin addition reaction (vide supra) gave no reaction with α,β-unsaturated imides. Further studies demonstrated that the *N*-acylbenzamide derivatives are the best Michael acceptors, to which the addition of other carbonnucleophiles such as methyl

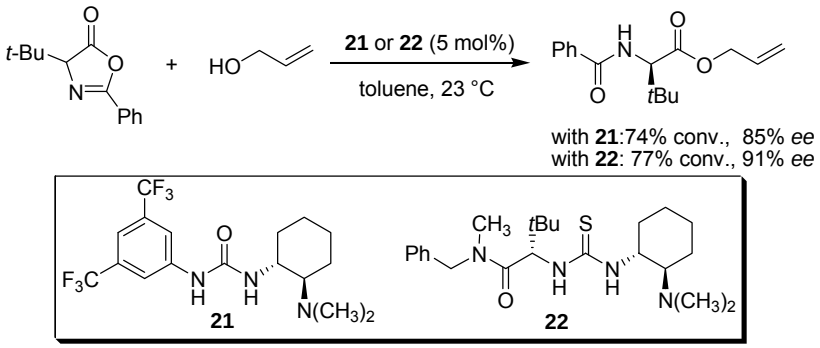
α-cyanoacetate and nitromethane proceeds at elevated temperature, giving the corresponding Michael adducts with good enantioselectivity (Scheme 13).[81]



Scheme 13. Enantioselecive Michael addition to α,β-unsaturated imides.

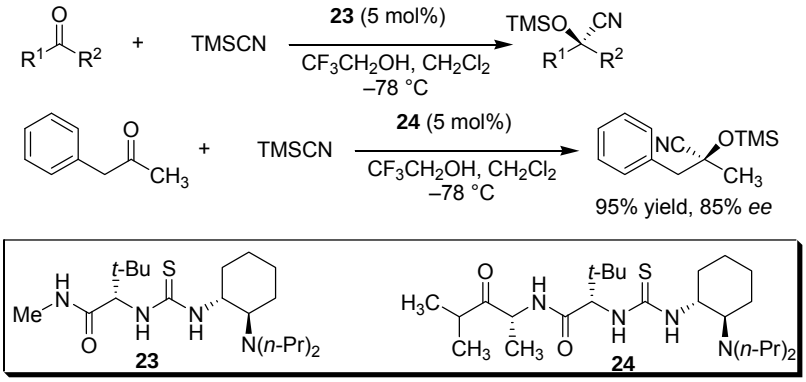
Recently, the scope of the Takemoto catalyst **9** has been expanded to encompass reactions in which both the nucleophile and electrophile differ substantially from those for which it was initially developed. Takemoto and co-workers applied catalyst **9** to promote nitro Mannich (aza Henry) reactions of *N*-phosphinoyl and *N*-Boc imines with nitroalkanes,[82, 83] as well as direct Mannich reaction.[84] Chen and co-workers reported that **9** catalyzes enantioselective conjugate additions of arenethiols to 2-cycloalkenones and α,β-unsaturated *N*-benzoyl imides.[85] Other recent results include asymmetric conjugate addition of thioacetic acid to β-nitrostyrenes[86] and enones[87], enantioselective domino Michael-aldol reactions between 2-mercaptobenzaldehydes and maleimides,[88] as well as Michael addition of α-substituted cyanoacetates to vinyl keotnes.[89] Remarkably, the catalyst **9** has also exhibited exceptional selectivity in the ring-opening polymerization of lactide for the synthesis of well-defined poly(lactide)s of narrow polydispersity, offering exciting opportunities for supramolecular recognition and the synthesis of well-defined polylactide architectures with end-group fidelity.[90]

Berkessel and co-workers have also employed bifunctional ureas for activation of carbonyl compounds, but in quite a different context: in the presence of urea **21** and allyl alcohol, chiral racemic azlactones undergo dynamic kinetic resolution, giving rise to protected, enantioenriched α-amino acid derivatives (Scheme 14).[91, 92] In the proposed mechanism for this transformation, the catalyst performs the general functions of a serine protease: the carbonyl group is activated by a double H-bond, while allyl alcohol is activated by general base catalysis. An improvement in selectivity was achieved with thiourea **22** incorporating the *tert*-leucine amide structural motif used frequently by Jacobsen group.



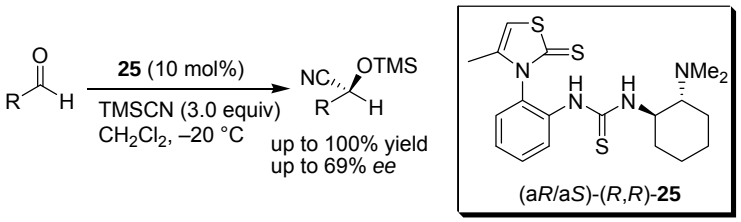
Scheme 14. Dynamic kinetic resolution of alzactones.

More recently, a thiourea-tertiary amine catalyst **23** was discovered by Fuerst and Jacobsen for the asymmetric cyanosilylation of carbonyl compounds (Scheme 15).[93] This represents one of the most effective and selective general cyanation catalysts for aromatic aldehydes and ketones. At this stage, this system is one of only a few examples of enantioselective thiourea catalysis in 1,2-carbonyl addition chemistry. DFT calculations of the catalytic system support a mechanism wherein the tertiary amino group of **23** activates HNC, the active nucleophile generated upon tautomerizaiton of HCN, toward 1,2-addition to a thiourea-bond ketone or aldehyde.[94] Calculated transition-state energies correlate well with the experimentally observed sense and degree of enantioinduction for a variety of ketone electrophiles. Insights from these studies have led to the design and evaluation of improved dipeptide catalyst **24** for substrates such as dialkyl ketones that underwent trimethylsilylcyanation with low ee's with **23**.



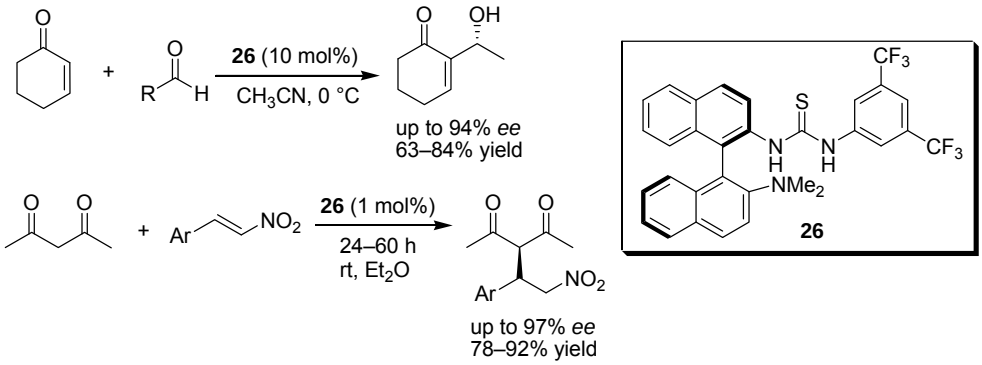
Scheme 15. Enantioselective, thiourea-catalyzed cyanosilylation of ketones.

Gennari and co-workers reported the use of a diastereomeric mixture of atropisomeric thioureas **25** as a bifunctional orgnocatalytic system for enantioselective cyanosilylation of aldehydes (Scheme 16).[95] It is noteworthy that the diastereomeric mixture performs better, in terms of enantioselectivity, than either of the single diastereomer alone. The authors suggested that this surprising effect may arise from a co-operation of the two diastereomeric thioureas in the transition state. In the presence of 10 mol% **25**, a variety of aldehydes were converted to the corresponding products in good to excellent yields with moderate enantioselectivities.



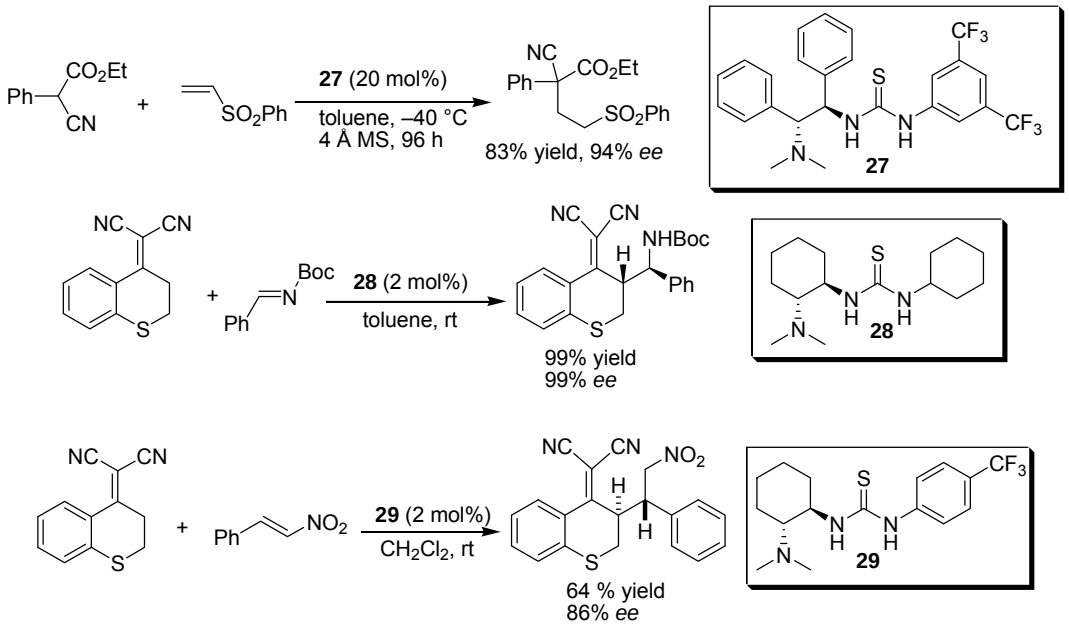
Scheme 16. Asymmetric cyanosilylation of aldehydes catalyzed by diastereomer **25**.

An axially binaphthyl-derived amine thiourea catalyst **26** has been recently developed by Wang et al. for the promotion of challenging enantioselective Morita-Baylis-Hillmann reactions. The addition of cyclohexenone to a wide range of aromatic and aliphatic aldehydes gave the corresponding products with good to excellent yields and selectivities (Scheme 17).[96] Compound **26** serves also as an efficient organocatalyst for asymmetric Michael addition of 2,4-pentadione to (*E*)-β-nitrostyrenes (Scheme 17).[97] Utilization of the catalyst in amounts as low as 1 mol% is sufficient for this transformation with comparable yields and enantioselectivities. Moreover, the Michael addition products can be readily converted into the valuable α-substituted-β-amino acids building blocks.



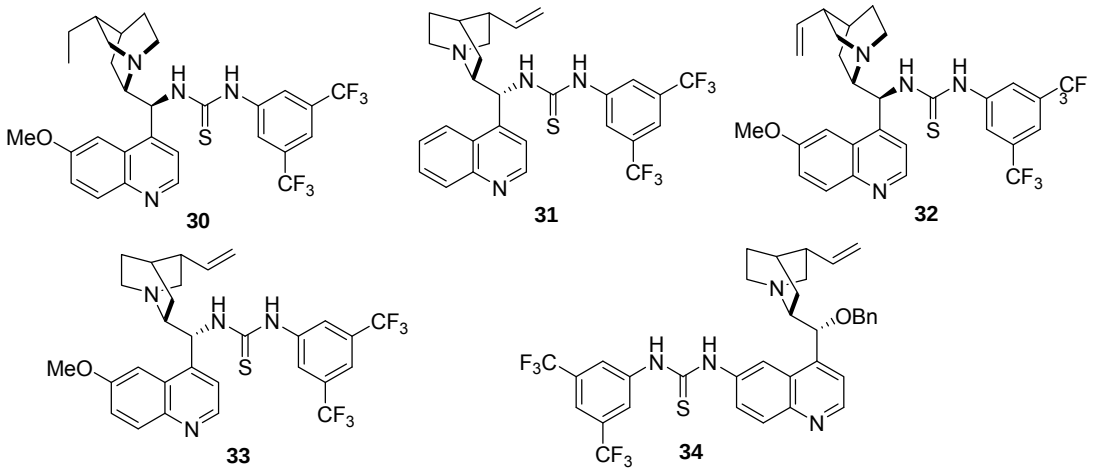
Scheme 17. Asymmetric Morita-Baylis-Hillman reaction and Michael addition.

Chen and co-workers discovered that the bifunctional thiourea-tertiary amine derivative **27** as highly enantioselective catalyst for the Michael addition of α-substituted cyanoacetates to vinyl sulfones, giving an efficient protocol for the construction of an all-carbon substituted quaternary stereocenter (Scheme 18).[98] Excellent enantioselectivities were achieved for both α-aryl and alkyl cyanoacetates in the presence of 20 mol% catalyst **27**. The authors proposed that a double-hydrogen bonding interaction between the NH of thiourea and a sulfone and tertiary amine functionalities might be indispensable for the activation of this reaction. Recently, Chen and co-workers reported that analogues of Takemoto's catalyst **28** and **29** are efficient for asymmetric direct vinylogous carbon-carbon bond formation, namely vinylogous Mannich and vinylogous Michael reactions respectively (Scheme 18).[99, 100]



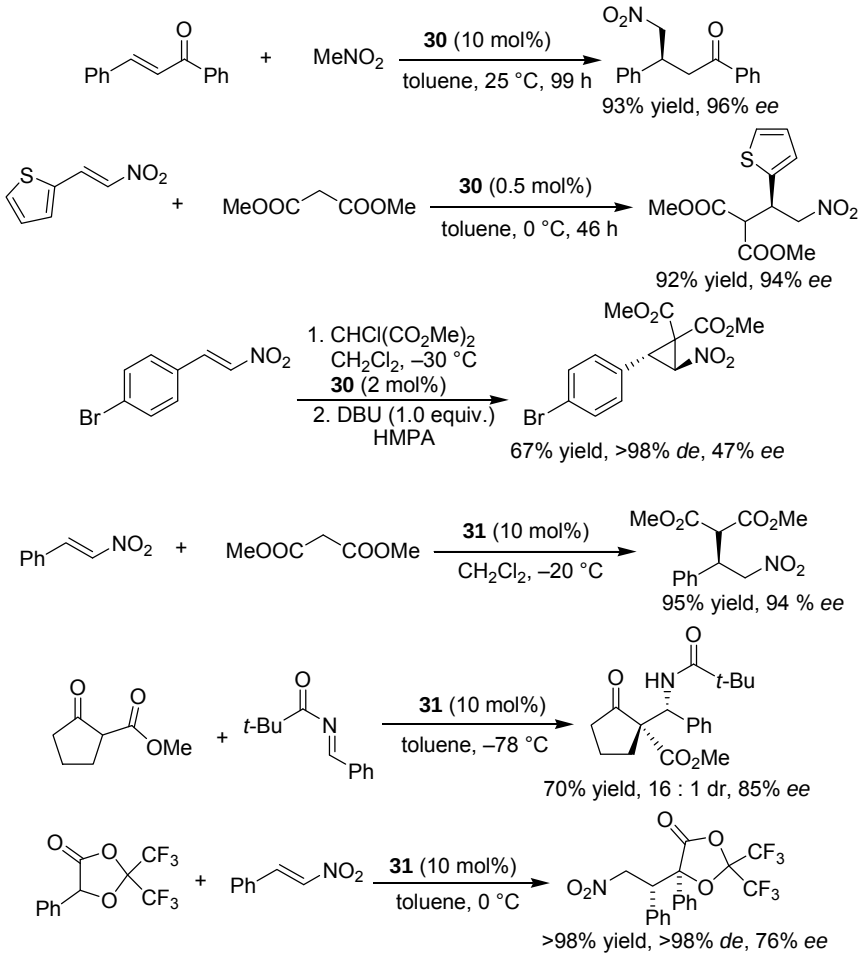
Scheme 18. Tertiary amine-thiourea catalyzed asymmetric reactions.

1.3.2.2.2 Cinchona alkaloids-thioureas



The groups of Soós, Connon, and Dixon independently developed H-bond donor catalysts by derivatizing C-9 hydroxy group of cinchona alkaloids with thiourea moiety. Soós and co-workers found that catalyst **30** promotes highly enantioselective Michael additions of nitroalkanes to chalcones, a reaction for which quinine itself is poorly reactive and only moderately enantioselective (Scheme 19).[101] This method offers a new alternative for highly enantioselective synthesis of pharmaceutically important γ-amino acids. It is noteworthy that the analogous quinine-derived catalyst was inactive, highlighting the importance of correct relative orientation of acidic and basic functional groups. Connon and McCooey prepared a range of (thio)urea-substituted derivatives of cinchona alkaloids for the asymmetric catalysis of the addition of dimethylmalonate to nitroolefins. They found that the thiourea moiety and its relative stereochemistry at C-8/C-9 were shown to be essential for the **30**-catalyzed enantioselective conjugate addition of dimethyl and diethylmalonate to aryl, heteroaryl, and alkyl β-substituted nitroalkenes (Scheme 19).[102] Interestingly, the analogous C-9 quinine-

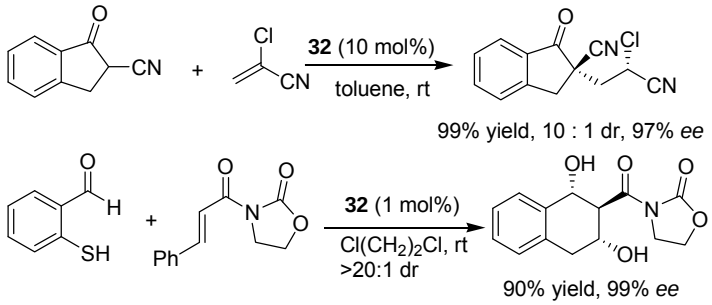
derived catalyst proved to be substantially less enantioselective and reactive than **30**. The catalyst is remarkably active and can be used in loading as low as 0.5 mol% without compromising the efficiency or selectivity of the transformations. Connon and co-workers extended the methodology to a one-pot conjugate addition-cyclization reaction with dimethyl chloromalonate to generate enantioenriched nitrocyclopropanes as single diasteromers.[103] Dixon et al. disclosed a similar results using cinchonine-derived catalyst **31** for addition of malonate esters to nitro olefins and further expanded the application to promote the addition of malonate and β-keto esters to *N*-Boc and *N*-Cbz aldimines (Scheme 14).[104, 105] Recently, they developed an efficient diastereo- and enantioselective Michael addition of 5-aryl-1,3-dioxane-4-ones to nitro olefins (Scheme 19).[106] Chen and co-workers recently reported cinchonine-derived catalyst **31** promoted effieciently asymmetric Michael-type Friedel-Crafts reaction of naphthols with nitroolefins and highly stereoselective direct vinylogous Mannich reactions.[99, 107]



Scheme 19. Cinchona alkaloid-thioureas catalyzed asymmetrc reactions.

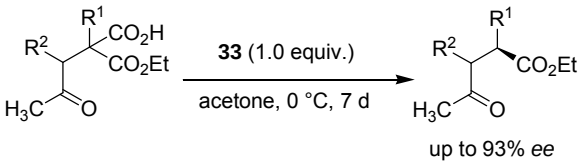
Recently, the cinchona-derived thioureas have represented an important and broadly applicable class of catalysts for enantioselective synthesis. Wang and co-workers reported the application of catalyst **30** in enantioselective 1,4-addition to enones. A variety of 1,3-dicarbonyl compounds are competent nucleophiles for **30**-catalyzed enantioselective additions

to chalchones.[108] Jørgensen and co-workers demonstrated the first catalytic highly stereoselective conjugate hydroxylation of nitroalkenes using oximes as easily accessible oxygen sources and **32** as catalyst.[109] This methodology gives access to both optically active nitro- and aminoalcohols. Deng and co-workers expanded applications of cinchona-thioureas in several reactions, such as asymmetric Mannich reaction,[110, 111] addition of *N*-Heterocycles to enones,[112] Friedel-Crafts reaction,[113] asymmetric Diels-Alder reaction.[114] The cinchona alkaloids C9-derived thioureas also demonstrated the efficacy in control of diastereoselectivity in asymmetric tandem reactions. Deng and co-workers developed an highly enantioselective catalytic conjugate addition with arylonitrile and an asymmetric tandem conjugate addition (Scheme 20).[115] It revealed that hydrogen-bonding-based cooperative catalysis not only is applicable to the development of highly enantioselective and diastereoselective tandem reactions but also could be manipulated to achieve diastereoselective control, thus allowing direct and stereoselective construction of two nonadjacent stereocenters. Wang and co-workers described an efficient, highly enantioselective and diastereoselective organocatalytic tandem Michael-aldol process for the preparation of synthetically useful and medicinally important chiral thiochromanes (Scheme 20).[116] The new one-pot process is promoted by using as low as 1 mol% of the cinchona alkaloid-derived thiourea **32** and closely mimicked the action mode of enzyme catalysis.



Scheme 20. Asymmetric tandem reaction catalyzed by cinchona-thiourea.

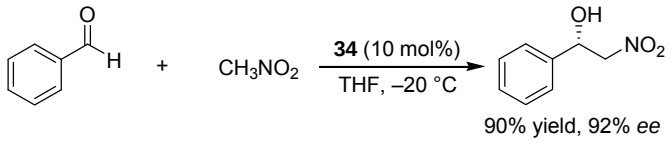
Rouden and co-workers found that thiourea derived cinchona alkaloid **33** promotes the asymmetric decarboxylative protonation of cyclic, acyclic, or bicyclic α-aminomalonate hemiesters in high yields and enantioselectivities up to 93% (Scheme 21).[117] This methodology offers a general applicability for the synthesis of α-amino acids, but requiring stoichiometric base (1 equiv.) and long reaction time (7 d).



Scheme 21. Enantioselective decarboxylation catalyzed by cinchona-thiourea.

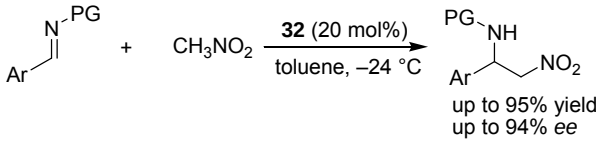
Hiemstra and co-workers reported that 6'-thiourea-substituted cinchona alkaloid derivative **34** serves as an effective enantioselective catalyst for addition of nitromethane to carbonyl

compounds (the Henry or nitroaldol reaction, Scheme 22).[118] Replacing the phenolic functional group with a thiourea led to an efficient catalyst for the Henry reaction. High asymmetric induction was observed for benzaldehyde and heteroaromatic aldehyde derivatives with 10 mol% of **34**. The highly enantioenriched products from the Henry reaction can be elaborated to aziridines, β-lactams, and α-alkylcysteines.



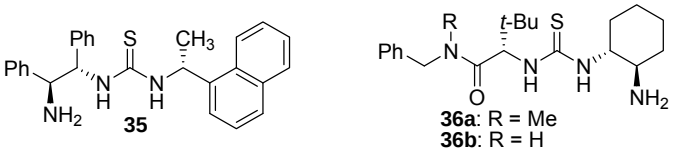
Scheme 22. Cinchona-thiourea for enantioselective Henry reaction.

Ricci and co-workers demonstrated that cinchona-based thiourea **32** catalyzes efficiently aza-Henry reaction using nitromethane and a range of aromatic and heteroaromatic differently protected imines, giving β-nitroamines in good to excellent yields with up to 94% *ee* (Scheme 23).[119]

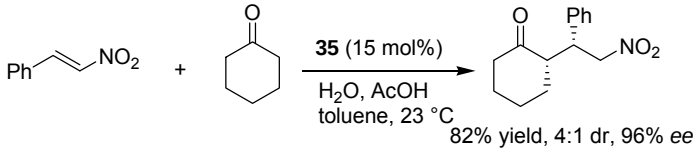


Scheme 23. Enantioselective aza-Henry reaction.

1.3.2.2.3 Primary amine-thiourea

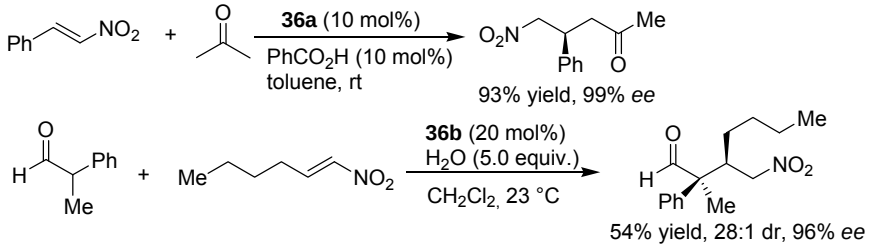


Primary amine-containing bifunctional thiourea catalysts have been identified recently for the direct addition of carbonyl nucleophiles to nitroalkenes. Primary amine catalysis is exploited in nature by enzymes such as type I aldolases that contain and active-site lysine residue.[120] Tsogeoeva and Wei reported the primary amine-thiourea catalyst **35** for the addition of ketones to aromatic nitroalkenes (Scheme 24).[121] In the presence of **35**, addition of cycloalkanones to β-nitrostyrene generates *syn* adducts whereas addition of unasymmetric acyclic dialkylketone such as methyl ethyl ketone generates *anti* adducts, both in moderate diastereoselectivity and very high enantioselectivity. Computational studies support a mechanism involving nitroalkene activation by dual H-bond donation to a single oxygen atom of the nitro group in the transition state.[122]



Scheme 24. Tsogoeva's primary amine thiourea catalyst.

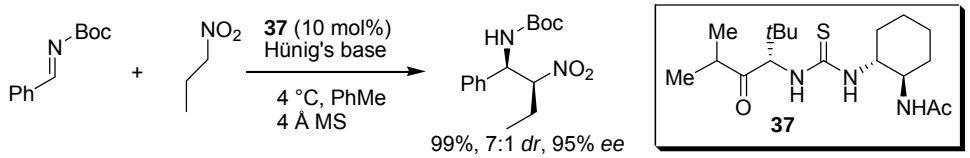
In independent studies, Huang and Jacobsen discovered that primary amine **36a** catalyzes the addition of ketones to nitroalkenes. The catalyst displays a strong bias for activation of ethyl ketones, allowing highly region- and anti-diastereoselective addition reactions of dialkyl ketones to β-alkyl and β-aryl nitroalkenes (Scheme 25).[123] Racemic α,α-disubstituted aldehydes also undergo conjugate addition to nitroalkenes in the presence of the closely related primary amine catalyst **36b** (Scheme 25).[124] Nitroalkenes bearing adjacent quaternary and tertiary stereocenters can be prepared by this method in high enantioselectivity with excellent scope for both the nitroalkene and aldehyde partner. In all examples of primary amine-catalyzed conjugate addition reactions reported, added water and acid was observed to increase the rate of catalysis, likely serving to facilitate catalyst turnover by imine and enamine hydrolysis.



Scheme 25. Jacobsen's thiouea primary amine catalysts.

1.3.2.2.4 Secondary amino-thioureas

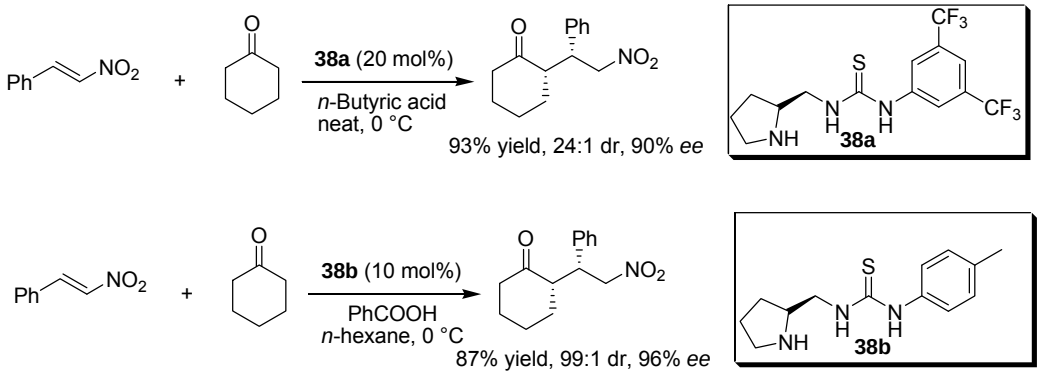
Yoon and Jacobsen found that the acetamide thiourea **37** is an excellent catalyst in the Henry (nitro-Mannich) reaction of *N*-Boc imines with nitroalkanes, offering the syn adducts with high enantio- and diastereoselectivity (up to 97% *ee* and 16/1 dr) in the presence of Hünig's base (Scheme 26).[125] In this study, they found that the addition of 4 Å molecular sieves improved the reproducibility of the process and provided higher diastereoselectivity in the products. Although the mechanism was not investigated in detail, dual activation of both reaction partners can not be excluded.



Scheme 26. Enantioselective nitro-Mannich reaction.

Recently, Tang and co-workers reported that the combination of thiouea and pyrrolidine in a chiral scaffold could result in an efficient bifunctional catalyst **38a** for asymmetric Michael additions of cyclohexanone to both aryl and alkyl nitroolefins (Scheme 27).[126] The high yield, high diastereoselectivity, and high enantioselectivity were observed in the presence of catalyst **38a** (20 mol%) under mild reaction conditions. Simultaneously, Xiao and co-workers reported a similar bifunctional pyrrolidine-thiourea catalyst **38b** for the direct Michael

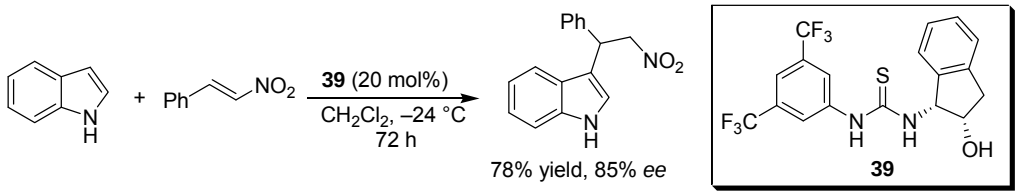
additions of cyclohexanone to various aromatic nitroolefins, giving the product with excellent enantio- and diastereoselectivities (Scheme 27).[127]



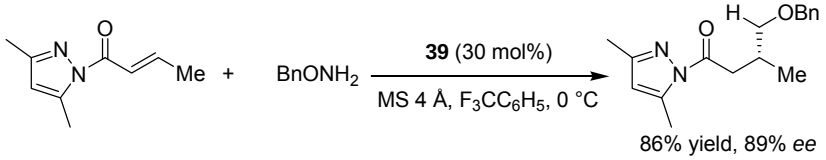
Scheme 27. Tang's secondary amino-thiourea for Michael addition.

1.3.2.2.5 Hydroxyl thioureas

Thiourea incorporating additional hydroxyl group also show promise as bifunctional catalysts. Ricci and co-workers demonstrated that catalyst **39** bearing both a thiourea and an adjacent hydroxyl group promotes asymmetric Friedel-Crafts addition of indoles to nitroalkenes (Scheme 28).[128] The optically active nitroalkane products were converted in a high-yielding reaction sequence to tryptamines and tetrahydro-β-carbolines without erosion in *ee*. Since only unprotected indoles underwent reaction in good enantioselectivity, the authors proposed that the role of hydroxyl group may be to activate the nucleophile by accepting a H-bond from the indole N-H. Recently, Sibi and Itoh extended the application of catalyst **39** in asymmetric conjugate amine additions (Scheme 29).[129] Amine addition to crotonate using 30 mol% of catalyst **39** is efficient yielding the product in high ee, which provides access to a variety of β-amino acid derivatives in high selectivity.

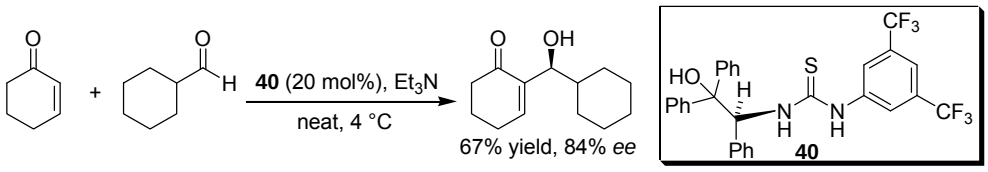


Scheme 28. Enantioselective Friedel-Crafts addition of indoles.



Scheme 29. Enantioselective conjugate amine additions.

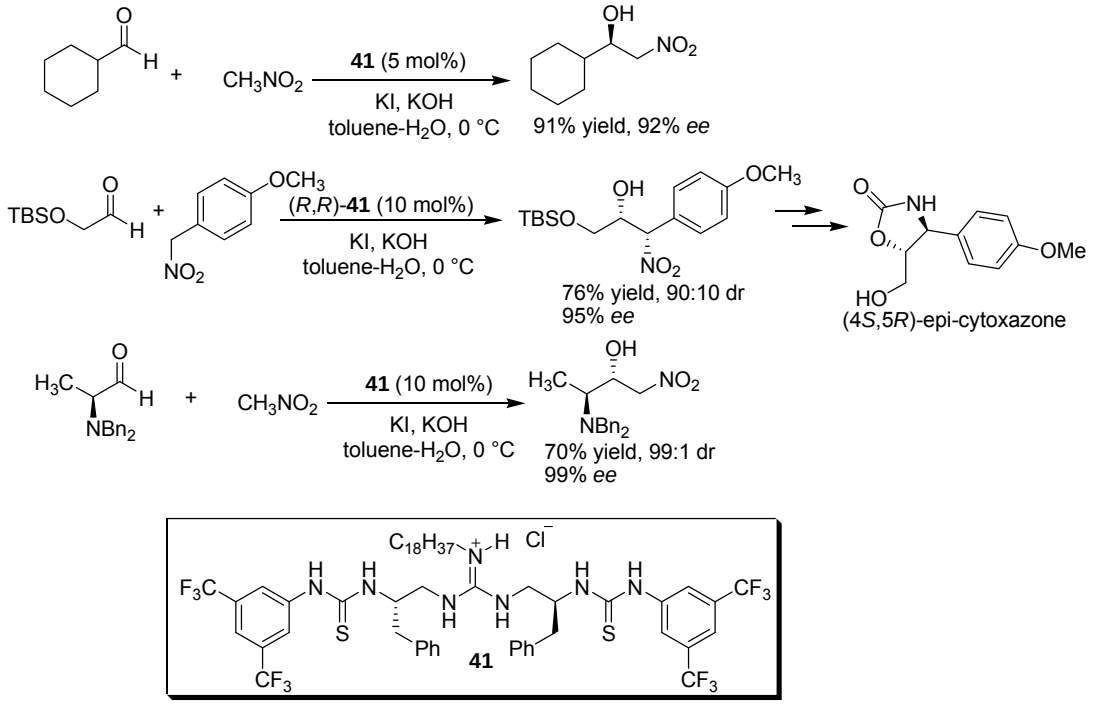
Lattanzi demonstrated that enantiopure amino alcohols derived thiourea **40** promotes the asymmetric Morita-Baylis-Hillman reaction of 2-cyclohexen-1-one and different aldehydes in the presence of triehtylamine under solvent-free conditions, affording the products in good to high yields and moderate to high enantioselecivity (Scheme 30).[130]



Scheme 30. Asymmetric Morita-Baylis-Hillman reaction.

1.3.2.2.6 Guanidino thiourea

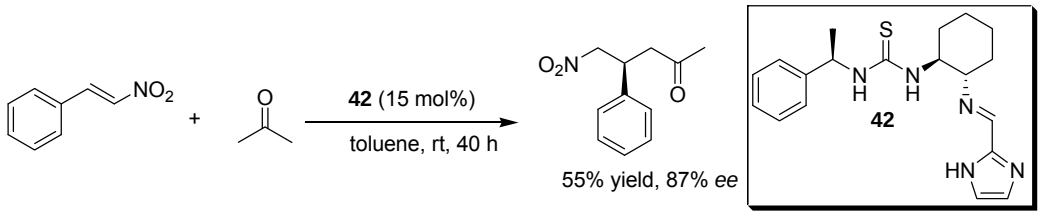
The bisthiourea-guanidinium ion **41** has been identified by Nagasawa and co-workers as an enantio- and diastereoselective catalyst for Henry reactions of achiral or chiral α-branched aliphatic aldehydes (Scheme 31).[131, 132] In addition to enantioselective nitromethane additions, catalyst **41** promotes highly *syn*-selective additions of nitroalkanes to functionalized aliphatic aldehydes.[133] Nagasawa and co-workers successfully utilized this reaction in an enantioselective synthesis of (4*S*,5*R*)-*epi*-cytoxazone, a type-2 cytokine selective inhibitor. A likely role of the thiourea is as activator of the aldehyde by dual H-bond donation while the guanidinium ion pairs with the nitronate nucleophile. In the presence of 10 mol% (*R,R*)-guanidinium thiourea **41**, optically active (*S*)-α-amino and α-alkoxy aldehydes react with nitromethane in high anti-diastereoselectivity, enhancing the otherwise moderate facial selectivity of the substrates. Further evidence for the hypothetical guanidine-thiourea cooperative reaction mode was obtained by using structural variants of **41**.[134] Drastic substituent effects on the guanidinium and chiral spacer moiety suggest a role of **41** as a chiral surfactant.



Scheme 31. Guanidine thiourea catalyzed Henry reaction.

1.3.2.2.7 Imidazole thiourea

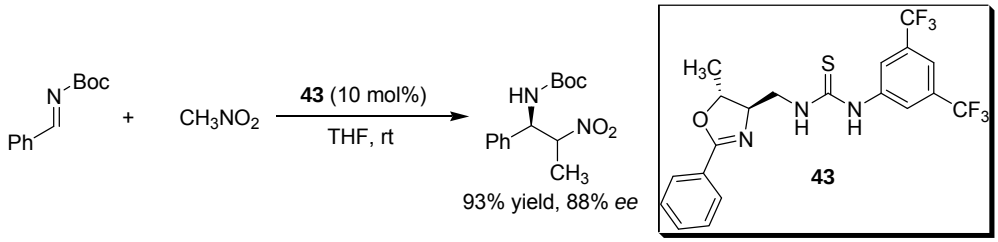
The bifunctional organocatalyst **42** bearing a thiourea moiety and an imidazole group on a chiral diaminocyclohexane scaffold was demonstrated by Tsogoeva and co-workers for asymmetric nitro-Michaeal reaction (Scheme 32).[135] Mechanism investigation by experiments showed that neither the imidazole ring nor the thiourea moiety is able to facilitate the Michael addition on their own. The authors proposed that the reactions are most likely promoted in a synergistic manner.



Scheme 32. Asymmetric Michael addition of acetone to nitrolefins.

1.3.2.2.8 Oxazoline thiourea

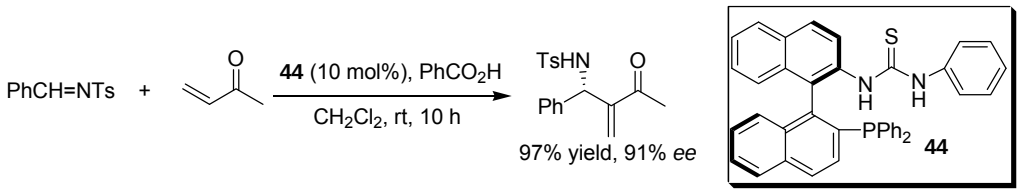
Chang and co-workers disclosed that oxazoline-thiourea catalyst **43** promotes aza-Henry reactions between *N*-Boc aryl imines and nitromethane (Scheme 33).[136] The reactions proceeded smoothly giving the products in moderate to high yields with high levels of enantioselectivity.



Scheme 33. Oxazoline-thiourea catalyzed aza-Henry reaction.

1.3.2.2.9 Phosphine thiourea

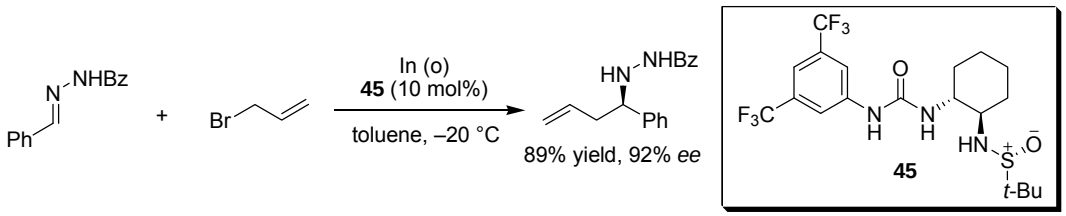
The phosphine-thiourea **44** was first reported by Shi group as a efficient catalyst for asymmetric aza-Morita-Baylis-Hillman reaction of *N*-sulfonated imines (Scheme 34).[137] Moderate to excellent *ee* and yields of the products were obtained in the presence of 10 mol% **44**. The authors proposed that **44** acts as a bifunctional organocatalyst in this reaction, in which the phosphine served as a nucleophile to initiate the reaction and the thiourea group served as a hydrogen-bonding donor to stabilize the *in situ* generated intermediate.



Scheme 34. Phosphine-thiourea catalyzed aza-Morita-Baylis-Hillman reaction.

1.3.2.2.10 Sulfinamido urea

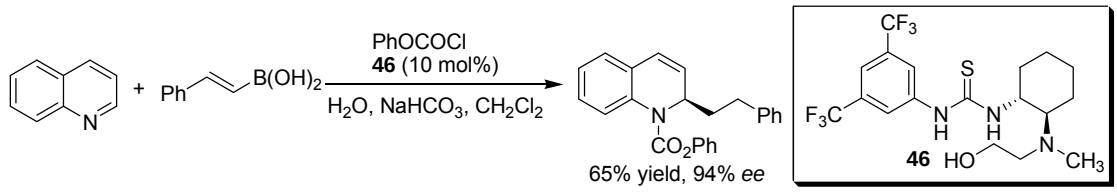
Addition of organometallic nucleophiles constitutes an important class of carbon-carbon bond-forming reactions, and substantial effort has been dedicated toward the discovery of enantioselective reactions of this type. The application of chiral H-bond donor catalysts to this problem is susceptible to several potential problems, including the possible incompatibility of organometallic agents with protic functional groups. Recent investigations by Jacobsen group of the addition of allylindium reagents to acylhydrazones demonstrate that despite these potential issues, bifunctional catalysis may be useful in this context (Scheme 35).[138] The optimal urea catalyst **45** bears a configurationally defined, Lewis basic sulfinamide group, which is postulated to activate the incoming allylindium nucleophile towards attack. An X-ray crystallographic analysis of **45** revealed that the sulfinamide N-H participates in an H-bond to the C=O of the urea in the solid-state structure. This interaction may serve to increase the Lewis acidity of the urea functionality and rigidify the catalyst structure. Given the well-studied ability of Lewis bases to activate organometallic and related reagents,[139] this general catalyst design may prove to have considerable utility for enantioselective methodology.



Scheme 35. Sulfinamido urea catalyzed allylation of hydrazones.

1.3.2.2.11 Amino-hydroxyl thiourea

Recently, Takemoto and co-workers developed a thiourea catalyst **46** bearing an amino-hydroxyl moiety for enantioselective Petasis reaction of quinolines by activation of nucleophilic organoboronic acids (Scheme 36).[140] In these reactions, catalyst modification studies have revealed that both the thiourea and the amino-hydroxyl moieties of the catalyst are necessary for reactivity and enantioselectivity. The authors proposed a dual activation mechanism of catalysis. The reactions with electron-rich boronic acids are more reactive and the reaction with electron-withdrawing boronic acid was remarkably ineffective, but high degrees of stereocontrol for both reactions were achieved.



Scheme 36. Asymmetric Petasis reaction of quinolines.

1.3.3 Conclusions and Outlook

Recent developments in the area of urea and thiourea-catalyzed reactions have been introduced. Due to their strong hydrogen-bonding properties, they can be used to recognize a series of Lewis base functionalities, such as carbonyls, imines, nitros, as well as other functionalities and activate them as a general acid catalyst. In addition, novel urea and thiourea derivatives have been demonstrated as an efficient catalyst for a variety of diastereo- and enantioselective reactions. However, the application of these catalysts to asymmetric reactions seems to be somewhat limited, owing to the weaker binding interaction. Dual activation strategies by incorporation of an additional functionality to known (thio)urea scaffold, not only greatly enhance the reaction rate via simultaneous activation of both the electrophile and nucleophile, but also allows greater steric control over the transition states and results in promising stereoselective outcome. However, rational design of multi-functional thiourea based H-bond donor catalyst is considerably difficult at this stage, since detailed mechanistic understanding of this chemistry is not available. Therefore, many techniques, such as kinetic, computation, state-of-the-art spectroscopic methods, crystallography, and reverse docking methods, have been brought to explain the action modes of thiourea catalysts. Moreover, mimicry of some enzyme systems involving H-bonding is also a powerful strategy in finding new catalysts and new transformations.

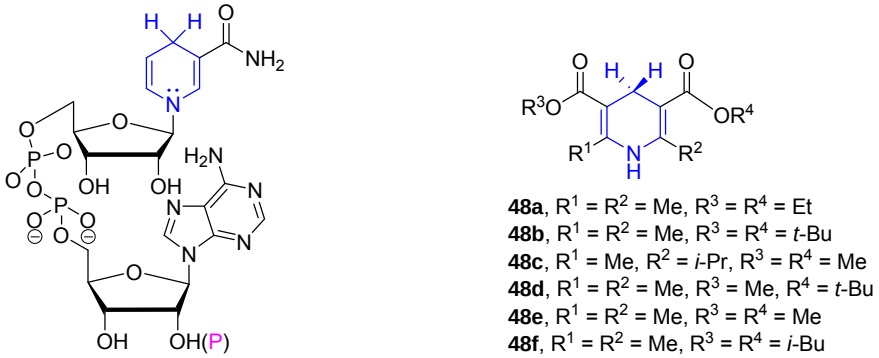
1.4 Organocatalyzed transfer hydrogenation with Hantzsch esters as the hydrogen source

1.4.1 Introduction

The synthesis of enantiopure products by asymmetric catalysis of organic reactions represents one of the most important areas in modern synthetic chemistry.[141] Among many successful asymmetric transformations, asymmetric hydrogenation of unsaturated organic compounds such as olefins, carbonyls, and imines, is currently becoming a standard procedure in both academia and industrial applications.[142-144] In the last few decades, all the methods developed for the reduction of organic compounds have been dominated by the use of metal catalysts surrounded by proper stereodiscriminating chiral ligands in conjunction with hydrogen gas,[145, 146] and in the case of transfer hydrogenation, isopropanol or formic acid.[147] Today, we are equipped with a plethora of different methods for the enantioselective reduction of unsaturated organic compounds, and thus the 2001 Nobel Prize in chemistry was

awarded to two prominent scientists in this field.[148, 149] However, science and industry are facing an unprecedented challenge today for achieving environmentally sustainable growth of economy. In the context of chemical synthesis, this challenge has posed stringent and compelling demands for green processes and for the developing of cost-effective and environmentally-benign solvents, catalysts and reagents.[150] Recently, a shift of this paradigm was made due to the discovery that small organic molecules such as ammonium salts and Brønsted acid could catalyze the chemo- and enantioselective reductions using Hantzsch dihydropyridine as the hydrogen source.[151-154]

Biological systems employ nicotinamide adenine dinucleotide (NADH, **47**) and flavin adenine dinucleotide ($FADH_2$) as cofactors in a diverse array of reduction reactions (Scheme 37).[155] A biomimetic approach that involves the utilization of Hantzsch esters **48** as NADH mimics and enzyme-like small organic molecules as catalysts was developed recently[151, 152, 156-166] to realize the highly enantioselective transfer hydrogenation of C=C, C=N, and C=O.

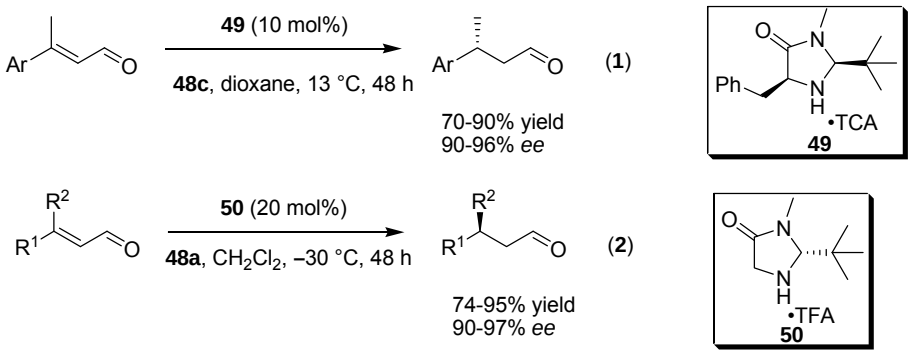


Scheme 37. Naturally occurring hydride-reduction cofactors and Hantzsch esters.

1.4.2 Developments and applications

1.4.2.1 Reductions of C=C bonds

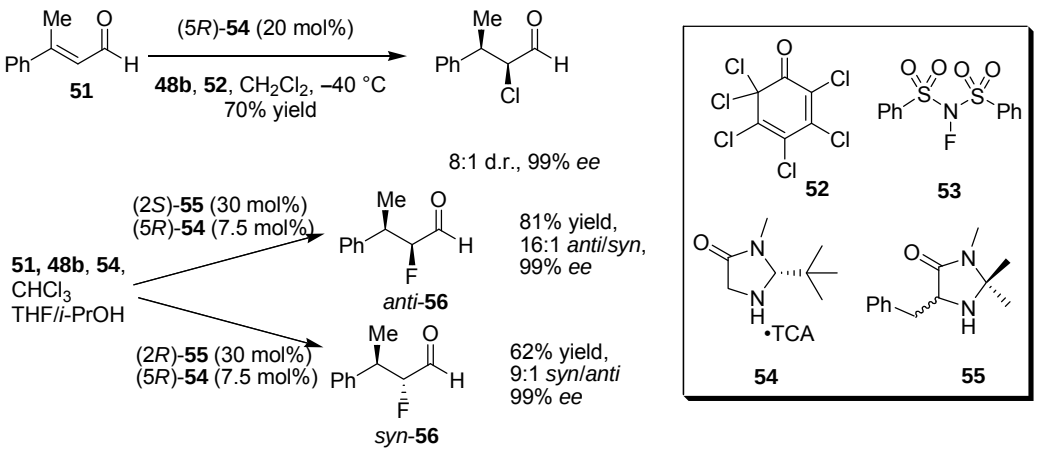
Reduction of the C=C bond of α,β-unsaturated aldehydes represents a formidable challenge in organic synthesis as reduction of the carbonyl group often occurs as the side reaction. By using the well-recognized iminium catalysts developed by MacMillan and co-workers together with Hantzsch esters, asymmetric transfer hydrogenation of α,β-unsaturated aldehydes was independently reported by List and MacMillan and their co-workers. List et al. found in the presence of 10 mol% of imidazolidinone salt **49**, treatment of α,β-unsaturated aldehydes with Hantzsch ester **48c** afforded aldehydes in 77–90% yield with 90–96% *ee* (Scheme 38, eq. 1). Almost simultaneously, MacMillan and co-workers reported the asymmetric reduction of various α,β-unsaturated aldehydes by using another imidazolidinone salt **50** as catalyst, developed in their own laboratory, to give the corresponding products in good yield and excellent *ee* (74–95% yield, 90–97% *ee* (Scheme 38, eq. 2).



Scheme 38. Asymmetric transfer hydrogenation of α,β-unsaturated aldehydes.

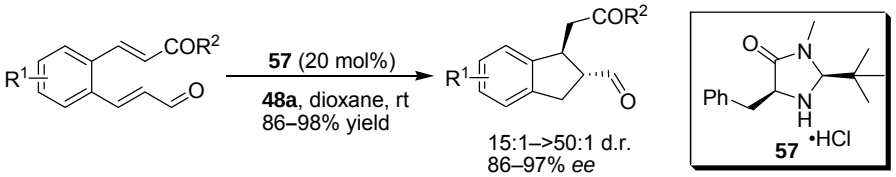
Interestingly, the geometry of the aldehyde olefin was found to have limited effect on the enantioselectivity; both conformations led to the same product enantiomer. The origin of stereoconvergence here is explained by the rapid *E*-*Z* isomerisation of the two iminium ions prior to the rate determining hydride attack from the dihydopyridine. Tolerance of the starting material with low geometric purity undoubtedly enhances the utility of this hydrogenation process.

A distinct difference between this Hantzsch ester hydrogenation process and that with hydrogen gas is the stepwise nucleophilic addition of hydride, which generates a new nucleophile and enables the "cascade catalysis" in the presence of an electrophile. Recently, this concept was realized independently by MacMillan[167] and List[158] and their co-workers. MacMillan and co-workers developed an enantioselective organo-cascade catalysis by combining transfer hydrogenation with Hantzsch esters and halogenation with electrophilic sources such as **52** and **53** (Scheme 39). Remarkably, the authors demonstrated rapid access to complex molecular architecture by using two different amine catalysts that can be easily modulated to produce the required diastereo- and enantioselective outcome. The mechanism pathway was proposed as a tandem process: the first cycle is a hydride transfer from the Hantzsch ester **48b** to the iminium intermediate, previously formed by the reaction of α,ß-unsaturated aldehyde **51** and chiral amine **54**, followed by hydrolysis to render an aliphatic aldehyde intermediate. The second one is the fluorination, which takes place by reaction of *N*-fluorobenzenesulfonimide **53** with the enamine formed by previous reaction of the aliphatic aldehyde intermediate and the chiral amine **55**. The final hydrolysis gave anti-**56** with a diastereomeric excess higher than 95% and enantiomeric excess more than 99%.



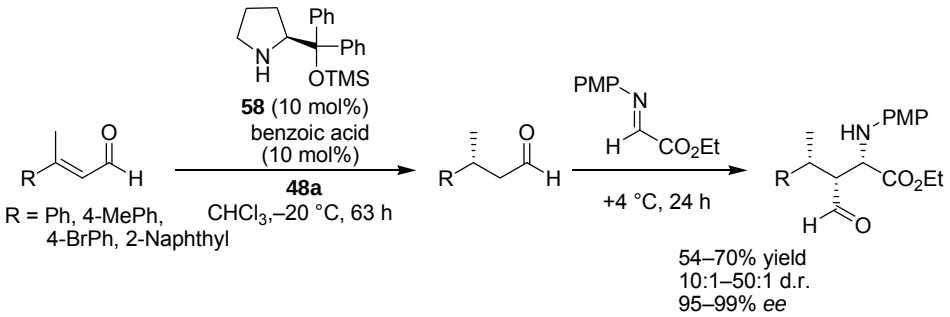
Scheme 39. Organo-cascade catalysis for asymmetric transfer hydrogenation and halogenation.

Instead of using electrophilic sources for halogenation, List and co-workers ulitized α,β-unsaturated ketones as the electrophilic acceptor to realize the asymmetric reductive Michael cyclization (Scheme 40).[158] In the presence of 20% mol of **57** and Hantzsch ester **48a**, a variety of enal enones underwent the reductive Michael cyclization to afford functionalized five- and six-membered rings with excellent diastereo- and enantioselectivities. The spacers used are not limited to substituted benzene rings; the cyclization of aliphatic enal in the presence of **57** provided the corresponding product with excellent diastereo- and enantioselectivities.



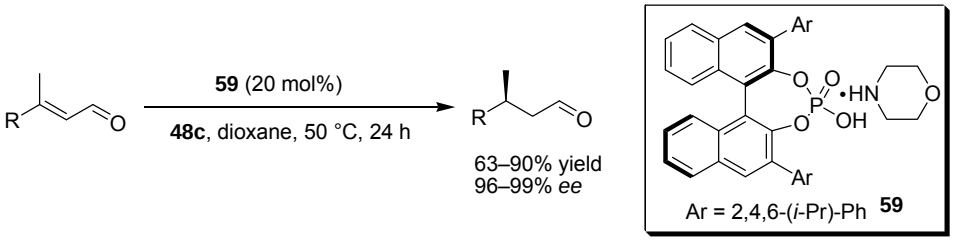
Scheme 40. Asymmetric reductive Michael cyclization.

Almost simultaneously, the asymmetric reductive Mannich-type reaction, another excellent example of cascade reactions, was introduced by Zhao and Cordova (Scheme 41).[168] Highly enantioselective direct organocatalytic asymmetric reductive Mannich-type reactions can be realized in the presence of 10 mol% **58** and 10 mol% benzoic acid as additive, furnishing three contiguous stereocenters in one step.



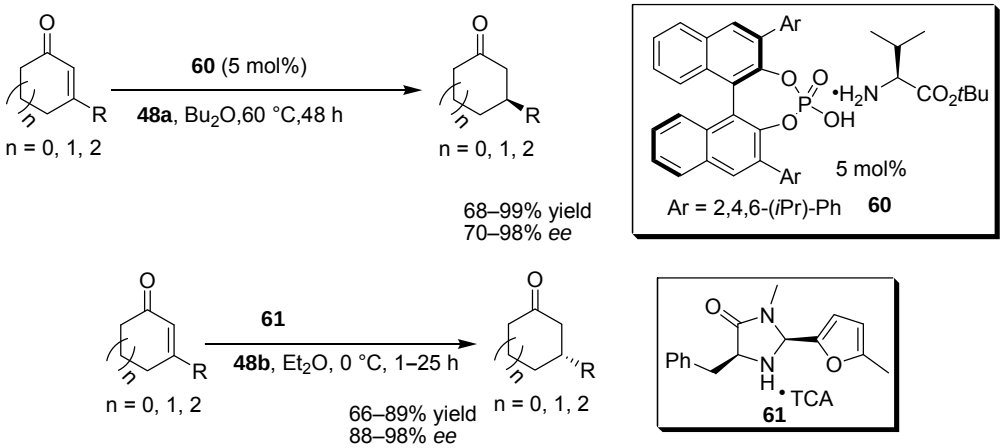
Scheme 41. Organocatalytic asymmetric reductive Mannich-type reactions.

In contrast to use a salt formed by a chiral amine and an achiral acid via iminium activation, List and co-workers elegantly developed a method that employs an achiral amine and a chiral Brønsted acid catalyst for transfer hydrogenation of α,β-unsaturated aldehydes, which was named by them as asymmetric counteranion-directed catalysis (ACDC) (Scheme 42). With 20 mol% of **59**, α,β-unsaturated aldehydes bearing substituents were reduced to their corresponding saturated aldehydes in moderate to good yields with excellent enantioselectivities (96–99% *ee*).



Scheme 42. Asymmetric transfer hydrogenation of α,β-unsaturated aldehydes by ACDC.

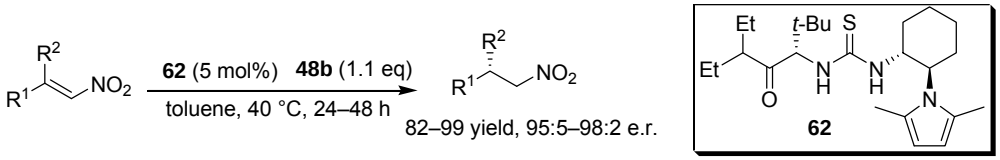
Transfer hydrogenation of α,β-unsaturated ketones were reported independently by List[159] and MacMillan[163] and their co-workers. During the search for an efficient catalyst, however, both aforementioned ACDC and chiral iminium catalysts failed to provide satisfying yields or enantioselectivities. Interestingly, ammonium phosphate **60**, derived from a chiral phosphoric acid and a valine *tert*-butyl ester, proved effective for this process (Scheme 43, top). Just before the aforementioned work was carried out, Macmillan and co-workers also found imindazolidinone salt **61** is an efficient catalyst for this transformation (Scheme 43, bottom).



Scheme 43. Asymmetric transfer hydrogenation of α,β-unsaturated ketones.

Over the past several years, the dominant strategy for enantioselective organocatalytic transfer reduction of C=C with Hantzsch esters as hydrogen source has involved activation by iminium catalysts, chiral Brønsted acids based on BINOL derived phosphoric acid, as well as ACDC discovered by List and co-workers. Thioureas have played an important role during the maturity of organocatalysis and have found a vast variety of applications in synthetic transformations, which can catalyzed the reactions through dative hydrogen bonding

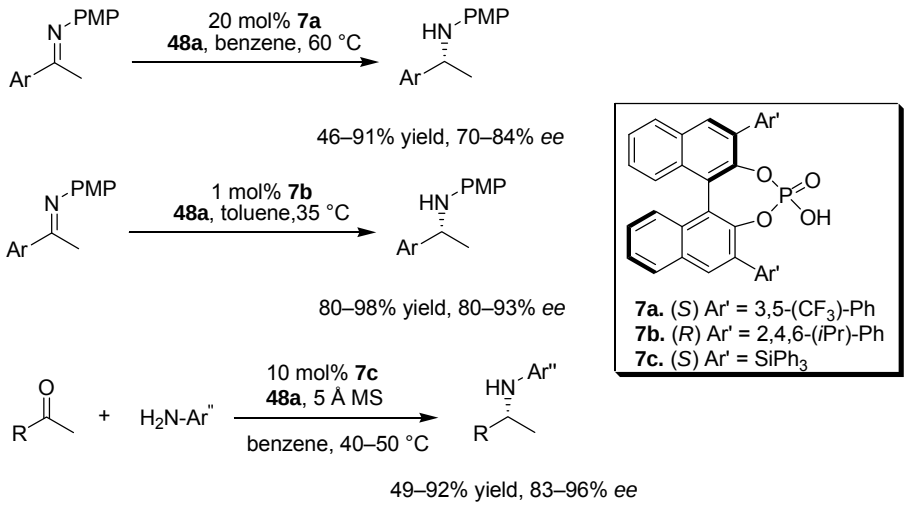
activation. However, less is known employing thioureas in transfer hydrogenation of C=C with Hantzsch esters as hydrogen source, due to the interaction through hydrogen bonding is too moderate to render the transformations occur. Very recently, during the course of our studies on non-conjugate catalysis based on thiourea derivatives mediated through hydrogen bonding activation, we demonstrated a biomimetic method in reducing a variety of conjugated nitroalkenes to their corresponding saturated nitroalkanes in moderate to good yields.[55] Independently, List and co-workers found that the enantioselective reduction of nitroolefins can be catalyzed by chiral thiourea derivative **62** designed by Jacobsen et al (Scheme 44).[169]



Scheme 44. Asymmetric transfer hydrogenation of nitroalkenes.

1.4.2.2 Reduction of C=N bonds (imines, quinolines, and pyridines)

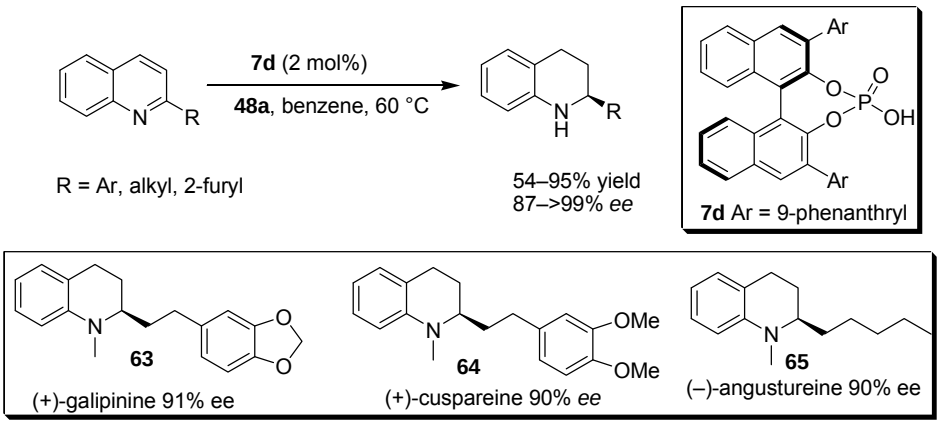
Besides the hydrogenation of C=C bonds, Hantzsch esters can also be applied in reduction of C=N bonds to their corresponding products. The first asymmetric example involving the use of an achiral Hantzsch ester was reported as early as 1989 by Singh et al.. Prochiral ketimines were reduced by Hantzsch ester **48a** in the presence of α-amino acid hydrochlorides or chiral acids to afford amines with moderate enantioselectivities (up to 63% *ee*).[170] Recently, Rueping et al. found that a chiral phosphoric acid is an effective catalyst for transfer hydrogenation of ketimines.[164] In the presence of **48a** and 20 mol% of **7a**, various aryl methyl ketimines were converted to the respective amines in 46–91% yield with 70–84% *ee* (Scheme 45, top). Subsequently, List and co-workers discovered another similar phosphoric acid for this transformation by changing the substituents at 3,3′-position to a more sterically hindered group. Good to excellent yields (80–98%) and enantioselectivities (80–93%) were attained for a variety of aryl methyl ketimines in the presence of **48a** and 1 mol% of **7b** (Scheme 45, middle).[156]



Scheme 45. Asymmetric transfer hydrogenation of imines and reductive aminations.

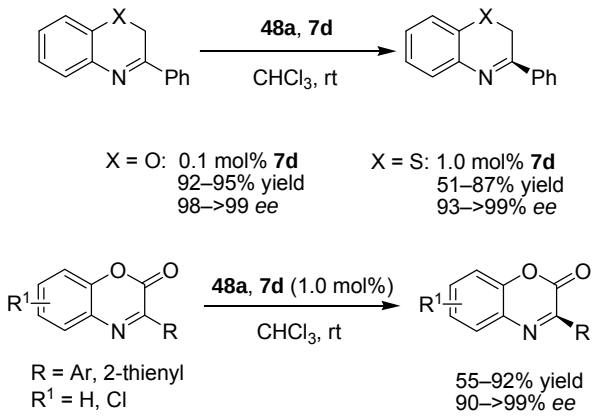
Soon after these results, a biomimetic reductive amination was successfully achieved and reported by MacMillan and co-workers (Scheme 45, bottom).[171] The newly designed phosphoric acid **7c**, which bears two triphenylsilyl groups on the 3- and 3′-positions of the binaphthyl scaffold, was found to be optimal for the reductive amination starting from ketone, amine and Hantzsch ester **48a**. In the presence of 10 mol% **7c** and MS 5 Å, a broad spectrum of structurally diverse amines was formed in moderate to excellent yields and enantioselectivities. It is noted that a single-crystal X-ray structure of **7c** bound with an imine substrate was also obtained, which provided direct insight into the origin of the enantiofacial discrimination.

Inspired by the Hantzsch ester mediated transfer hydrogenation of alkenes and imines, Rueping et al. demonstrated that phosphoric **7d** could catalyze transfer hydrogenation of quinolines, an important class of heteroaromatic compounds.[166] With Hantzsch ester **48a** as the hydrogen source, a proposed cascade-hydrogenation process afforded tetrahydroquinolines with excellent enantioselectivities of up to > 99% *ee* in the presence of 2 mol% of **7d**. This methodology has been applied to the synthesis of several biologically active tetrahydroquinoline alkaloids such as (+)-galipinine (**63**; 91% *ee*), (+)-cuspareine (**64**; 90% *ee*), and (–)-angustureine (**65**, 90% *ee*) (Scheme 46). This mild reaction conditions, operational simplicity, and relative low catalyst loading make this organocatalytic approach very attractive for the synthesis of enantio-enriched tetrahydroquinolines.



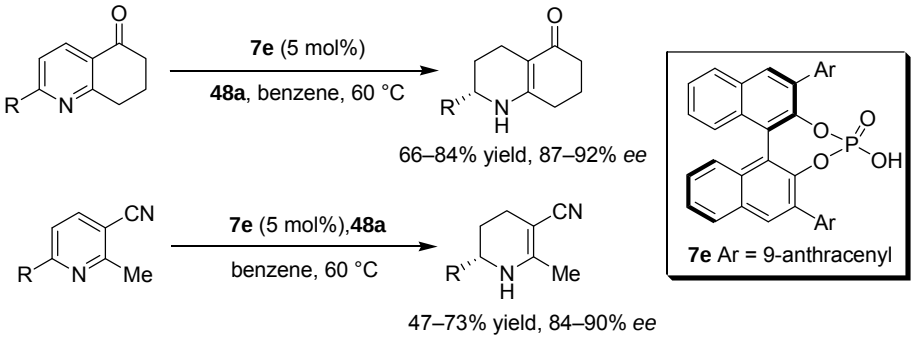
Scheme 46. Asymmetric transfer hydrogenation of quinolines.

The development of highly efficient organocatalyst for low catalyst loading still remains one of the biggest challenges in practical organocatalysis. Rueping and his group recently extended aforementioned approach to transfer hydrogenation of benzoxazines, benzothiazines, and benzoxazinones (Scheme 47).[165] Remarkably, the catalyst loading can be reduced to 0.1 mol% (or even 0.01 mol%) without a considerable loss in reactivity and selectivity. Highly enantioselectivities and low catalyst loading render this approach competitive with transition-metal-catalyzed hydrogenation, which are known to be poisonous by sulphur-containing substrates.



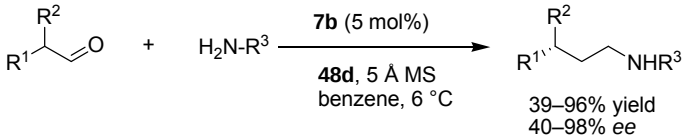
Scheme 47. Asymmetric transfer hydrogenation of benzoxazines, benzothiazines, and bezoxazinones.

With the success of highly enantioselective Brønsted acid catalyzed transfer hydrogenation of ketimines, quinolines, and so on, Rueping and co-workers recently explored this approach in reduction of pyridines, which today is still represents a great challenge. After evaluation of catalysts and optimization of reaction conditions, they indentified that in the presence of 5 mol% **7e** and Hantzsch ester **48a** as hydride source, the products, hexahydroquinolinones and tetrahydropyridines, are isolated in good yields and with excellent enantioselectivities (up to 92% *ee*) (Scheme 48).[172]



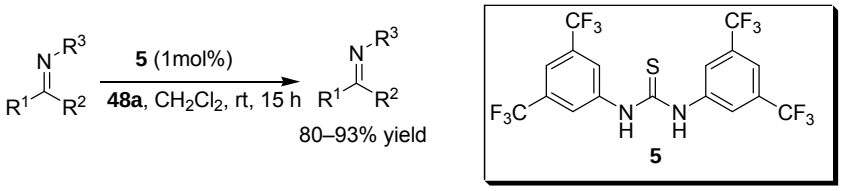
Scheme 48. Asymmetric transfer hydrogenation of pyridines.

Although organocatalytic selected asymmetric reductive amination of ketones to give α-branched amines has been reported, the reductive amination of α-branched aldehydes via dynamic kinetic resolution to give β-branched chiral amines is unexplored. Recently, List et al. successfully realized this concept (Scheme 49).[160] In the presence of 5 mol% of **7b**, a series of α-branched aldehydes with different anilines undertook reductive amination to afford β-branched chiral amines in 39–96% yield and with 40–98% *ee*.



Scheme 49. Asymmetric reductive amination of aldehydes.

The direct reductive amination of ketones and aldehydes were recently reported by Menche et al.[173-175] This approach requires catalytic amount of thiourea as hydrogen bond donor and **48a** as hydrogen source in the presence of 5 Å MS as dehydrating agent. After carefully investigation of their protocol and comparison with our catalyst, we found the catalytic effect arised from the unactivated MS instead of their claimed thiourea. Besides questioning their protocols, we presented a practical method for the thiourea-catalyzed transfer hydrogenation of aromatic as well as aliphatic aldimines with **48a** as hydrogen source (Scheme 50).[54]



Scheme 50. Thiourea-catalyzed transfer hydrogenation of aldimines.

1.4.3 Summary and outlook

Transfer hydrogenation of C=C and C=N functionalities can be realized in the presence of catalytic amount of organocatalysts such as imidazolidinones, phosphoric acid, ACDC, or thioureas and with Hantzsch esters as hydrogen sources. A variety of enantio-enriched organic compounds can be obtained under these protocols. Compared with the traditional reduction by transition metal combined with hydrogen gas or transfer hydrogenation by transition metal combined with isopropanol or formic acid, organocatalytic transfer hydrogenation mediated with Hantzsch esters as hydrogen sources showed quite superior such as mild reaction conditions, operational simplicity, and so on. All these make this biomimetic reductive process very attractive in synthetic chemistry. On the other hand, problems are still confronted with current approaches, such as problematic removal of the oxidized pyridine form of Hantzsch ester for industrial-scale and poor atom economy, as only two protons are used per molecule. Thus, efforts toward the easy separation and recycling of Hantzsch esters will be highly desirable. It is reasonable to believe that by overcoming the formidable drawbacks, the practical application of this biomimetic approach will be forthcoming.

1.5 Organocatalytic reduction with trichlorosilane

1.5.1 Introduction

Asymmetric hydrogenation, hydroboration, and hydrosilylation are the most frequently used catalytic methods for reduction of prochiral ketones and imines.[141] Although asymmetric hydrogenation remains favored by industry in general, it is not free of problems, namely, those associated with metal leaching, high pressure, and the cost of the catalyst and its regeneration. Stoichiometric borane reduction, catalyzed by chiral oxazoborolidine, avoids

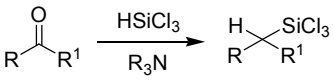
most of these problems and offers high levels of enantioselection,[141] but its cost is prohibitive for large-scale industrial application. The recently developed reduction of C=C and C=N, which uses the Hantzsch ester as a stoichiometric reducing agent and chiral imidazolidinone or chiral Brønsted acid as organocatalysts is also limited by removal of the pyridine form of Hantzsch ester and the cost implications.[151, 152, 156-167, 169, 171, 172] It is still worthwhile to exploit new methods, which can be carried out in industrial scale under mild conditions. One of such reagents may be trichlorosilane ($HSiCl_3$), a commercially available and abundant byproduct of the industrial Rochow process,[176] albeit some activators are necessary for $HSiCl_3$ to efficiently reduce ketones[177] and imines.[178, 179] In general, $HSiCl_3$ is an appealing alternative due to the environmentally and physiologically less toxic qualities. The reagent is volatile and can be pumped away under reduced pressure; alternatively, after workup with dilute aqueous saturated $NaHCO_3$, $HSiCl_3$ and its byproducts are converted to much less-harmful hydroxysilanes.

In view of its advantages, a variety methodologies have been developed for reduction of C=C, C=N and C=O. The currently most successful methods are based on use of transition metal-cetered hydrosilylation,[141] however, recent advance in organocatalytic alternative appeals to be very attractive and competitive with traditional methods. In this perspective, I attempt to offer a comprehensive overview of reduction with $HSiCl_3$ as reductant mediated by organocatalysts. Since for the most part it is still less known with precision about the catalytic mechanism, the advance in this field will be classified into different parts based on the organic molecules developed for the activation of $HSiCl_3$.

1.5.2 Developments and applications

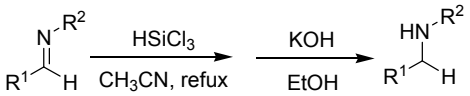
1.5.2.1 $HSiCl_3$-tertiary amine combinations

Prior to 1962, there were only three reports of $HSiCl_3$ additions to olefins catalyzed by tertiary amine.[180-182] Since then a vast majority of applications have been reported.[183] Organic halides, in the presence of $HSiCl_3$-tertiary amines, undergo a variety of transformations depending upon the reaction conditions. One of the most remarkable and useful transformations which the trichlorosilane-tertiary amine systems can effect is the removal of a carbonyl oxygen from a wide variety of compounds. Aromatic ketones, aldehydes, acid chlorides, acid amides, and aromatic acids all undergo such a reaction, which have termed, "reductive silylation". Pictorially, the reaction can be represented as the replacement of a carbonyl oxygen by the H and $SiCl_3$ moieties of trichlorosilane (Scheme 51).



Scheme 51. "Reductive Silylation" by the combination of $HSiCl_3$ with tertiary amine.

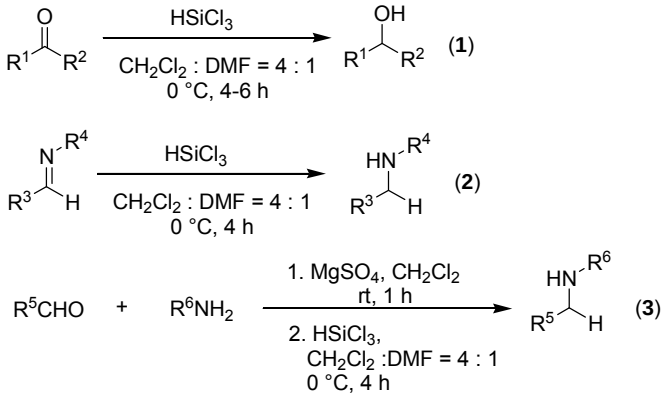
It has been amply demonstrated in previous work that the trichlorosilane and tertiary amine combination is a powerful reagent for a number of interesting and useful chemical transformations. In an effort to gain insight into this mechanism, Benkeser et al. found unexpected results when this approach was applied to carbon-nitrogen double bond. *N*-(benzylidene)aniline was treated with this system yielding the amine rather than cleavage product toluene after hydrolysis.[184] The reaction also proceeded well under reflux conditions in acetonitrile (Scheme 52).



Scheme 52. Reduction of aldimines under reflux conditions in acetonitrile.

1.5.2.2 Trichlorosilane-dimethylformamide ($HSiCl_3$-DMF) as an efficient reducing agent

In contrast to "reductive silylation" by the combination of trichlorosilane with tertiary amine, Kobayashi and co-workers developed another efficient reducing agent, triclorosilane-dimethylformamide ($HSiCl_3$-DMF), which is effective for reduction of aldehydes to alcohols, imines to amines, and also reductive amination of aldehydes under mild conditions (Scheme 53).[178] The reduction of aldehydes proceeded smoothly at 0 °C for 4–6 h with $HSiCl_3$ in DMF-dichloromethane to give the corresponding alcohols in high yields. As for the reduction of ketones, a longer reaction time was required, and the secondary alcohols were obtained in good to high yields (Scheme 53, eq. 1). Moreover, the reduction of imines (Scheme 53, eq. 2) and reductive amination (Scheme 53, eq. 3) of aldehydes were successfully carried out using $HSiCl_3$-DMF (Scheme 53, eq. 2 and 3).

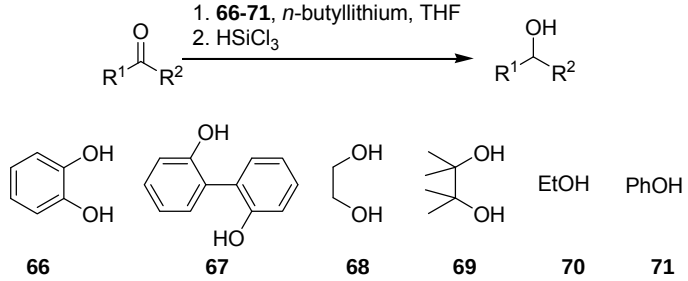


Scheme 53. Reductions with $HSiCl_3$-DMF.

1.5.2.3 Reduction of carbonyl compounds with pentacoordinate hydriodosilicates

Sakurai and Kira reported that bis(1,2-benzendiolato)hydridosilicate, prepared from trichlorosilane and dilithium catecholate, reduced aldehydes and ketones to afford the corresponding alcohols. Besides catechol (**66**), 2,2′-dihydroxybiphenyl (**67**) also provides a ligand which produces an effective reducing agent. However, aliphatic diols such as 1,2-

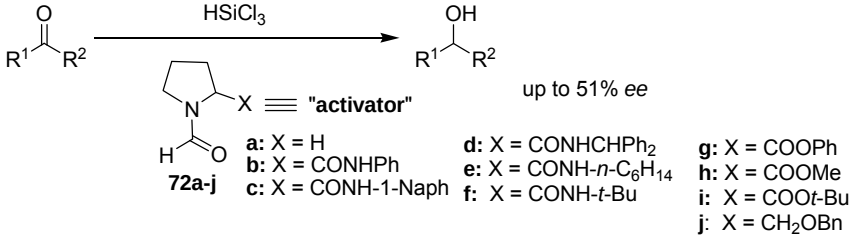
ethanediol (**68**) and pinacol (**69**) produce reducing agents which are less effective and monoalcohols (**70**, **71**) were totally ineffective to reduce ketones under the conditions (Scheme 54).



Scheme 54. Reduction of carbonyl compounds with pentacoordinate hydrodosilicates.

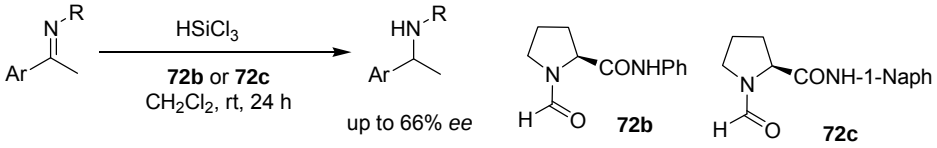
1.5.2.4 Asymmetric organocatalytic reduction with $HSiCl_3$

Based on the reduction with reducing agent $HSiCl_3$-DMF, Mstsumura and co-workers found some kinds of *N*-formyl cyclic amine derivatives to be effective activators for trichlorosilane to reduce ketones. Namely, a catalytic amount of these activators were sufficient to complete the reduction of ketones with trichlorosilane, and the reduction of ketones by trichlorosilane with optically active activators gave enantiomerically enriched *sec*-alcohols in some extent of optical yields (up to 51% *ee*) (Scheme 55).[177]



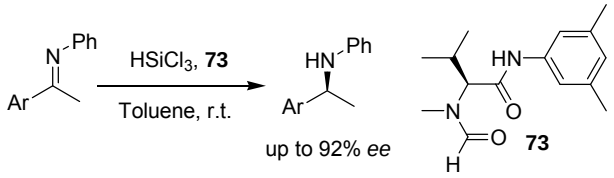
Scheme 55. Asymmetric reduction of ketones with $HSiCl_3$ catalyzed by *N*-formylated cyclic amine derivatives.

In the continuous exploration of the versatility of $HSiCl_3$ activated with *N*-formylpyrrolidine derivatives, the Matsumura group found trichlorosilane activated with *N*-formylpyrrolidine derivatives to be an effective reagent for chemo- and seteroselective reduction of imines (Scheme 56).[179] The reduction of imines using trichlorosilane activated with optically active *N*-formylproline derivatives gave enantiomerically enriched amines in moderate yields with up to 66% *ee*.



Scheme 56. Asymmetric reduction of imines with $HSiCl_3$ activated by *N*-formylpyrrolidine derivatives.

The work presented by Matsumura group in designing *N*-formyl pyrrolidine derivatives as $HSiCl_3$ activator can be considered as a milestone for the asymmetric reduction of ketones and imines using $HSiCl_3$ as reducing agent. Since then, considerable efforts have been devoted to the development of this transformation, and remarkable progress has been made. One important breakthrough was achieved by Malkov et al. They developed a new *N*-methyl-L-valine derived Lewis basic organocatalyst **73** for asymmetric reduction of ketimines with trichlorosilane to afford the corresponding products with high enantioselectivity (Scheme 57).[185] It is noteworthy that the rigid cyclic framework of proline may not always be an advantage. Among the methods designed to enhance enantioselectivity through structural variations, chiral relay represents an emerging new strategy where a conformationally flexible group, appropriated placed, effectively conveys the chiral information to the reaction center.[186, 187]



Scheme 57. Asymmetric reduction of ketimines with trichlorosilane catalyzed by **73**.

Generally, development of any new catalytic protocol include a delicate balancing of various factors, such as catalyst structure and loading, solvent, temperature, etc. Often, even minor changes in any of these characteristics can produce a dramatic effect on the stereochemical outcome of the reaction. Recently, Malkov et al. fully investigated the structure-reactivity of the reduction of imines with $HSiCl_3$ catalyzed by *N*-methyl-L-amino acid derivatives.[188] They designed a library of chiral DMF analogues based on the use of amino acids as the chiral scaffold, with the α-amino group converted into *N*-methyl formamide moiety and the amino acid carboxyl converted into another amide group, with either aromatic or aliphatic substituent adjacent to the nitrogen. After assessment of a variety of prepared *N*-methyl-L-amino acid in the reduction of ketimines, they draw some conclusions as follows: (1) The *N*-methyl formamide moiety of the catalyst is crucial for the enantioselectivity. (2) The anilide part of the catalyst and the *N*-aryl substituent of the substrate imine are crucial for the enantiodifferentiating process, suggesting arene-arene interaction. (3) The anilide moiety of the catalyst must constitute a secondary amide, with an NH group. (4) The reagent $HSiCl_3$ is apparently activated by the formamide moiety. (5) The nature of the amino acid side chain determines the configuration of the resulting product, apparently by controlling the conformation of the transition state. According the experiments, key features of the catalyst and the substrate was depicted (Figure 2).

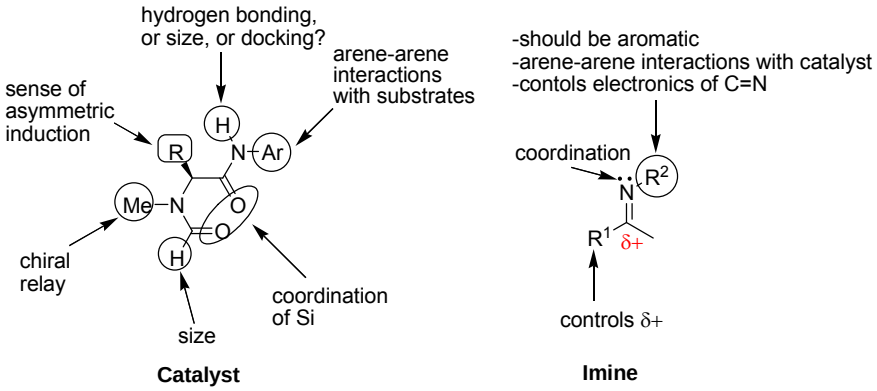
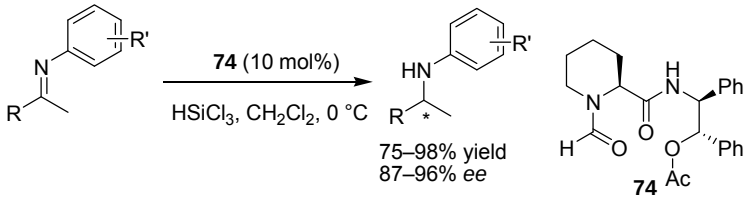


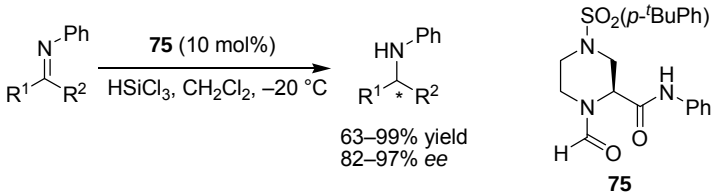
Figure 2. Key features of the catalyst and the substrate.

The search for efficient catalysts for highly enantioselective reductions of imines still remains a challenging task, due to the difference in reactivity among imines containing different nitrogen substituents, the existence of acyclic imines as inseparable mixtures of *E*/*Z* isomers, and the ease of interconversion between these two isomers in solution. Recently, Sun and co-workers developed the L-pipecolinic acid derived formamides as highly efficient and enantioselective Lewis basic organocatalysts for the reduction of *N*-aryl imines with trichlorosilane (Scheme 58).[189] A broad spectrum of *N*-aryl imines were reduced to their corresponding in high yields (up to 98%) and enantioselectivities (up to 96%).



Scheme 58. Asymmetric reduction of ketimines with trichlorosilane catalyzed by **74**.

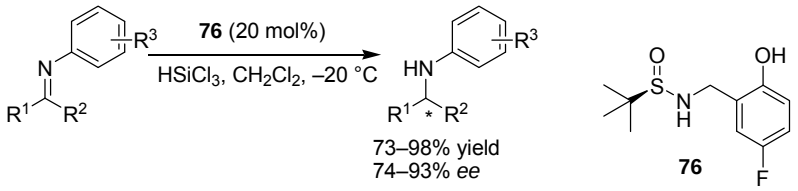
Soon after the aforementioned work, Sun and co-workers reported that L-piperazine-2-carboxylic derived *N*-formamide **75** is also highly enantioselective Lewis basic catalysts for the reduction of *N*-aryl imines with trichlorosilane (Scheme 59).[190] High isolated yields (up to 99%) and enantioselectivities (up to 97%) were obtained for a broad range of substrates, including aromatic and aliphatic ketimines, particularly those with R^2 as relatively bulky alkyl groups.



Scheme 59. Asymmetric reduction of ketimines with trichlorosilane catalyzed by **75**.

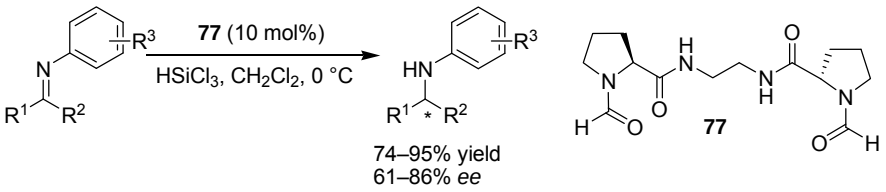
Several months later in the same year, the Sun group found that easily accessible chiral sulfinamide **76** was highly efficient and enantioselective organocatalyst for the reduction of

N-aryl ketimines with triclorosilane (Scheme 60).[191] In the presence of 20 mol% of **76**, a broad range of *N*-aryl ketimines were reduced by trichlorosilane to produce the corresponding amines in high yield (up to 98% yield) and enantioselectivity (up to 93% *ee*).



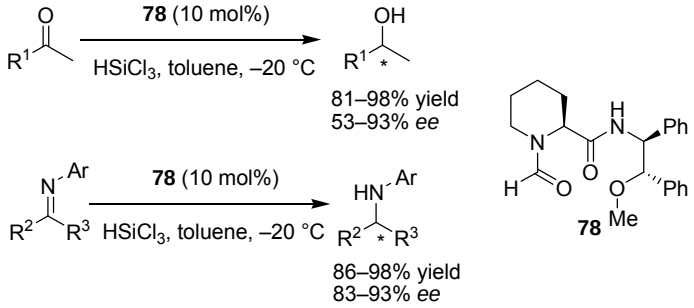
Scheme 60. Asymmetric reduction of ketimines with trichlorosilane catalyzed by **76**.

After successful development of **74**, **75**, and **76** as efficient catalyst for the reduction of ketimines with trichlorosilane, Sun and his group developed L-proline derived C_2-symmetric chiral tetraamide **77** as an effective Lewis basic catalyst in the enantioselective reduction of ketimines, affording high yields (up to 95%) and moderate to high enantioselectivities (up to 86% *ee*) (Scheme 61).[192]



Scheme 61. Asymmetric reduction of ketimines with trichlorosilane catalyzed by **77**.

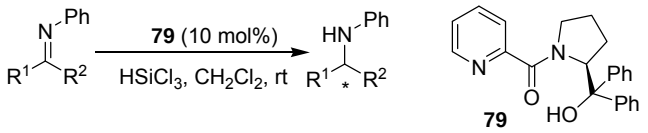
During the course of developing chiral Lewis basic *N*-formamide as highly effective organocatalyst for reductions with trichlorosilane, Sun et al. demonstrated that **78** arising from fine-tuning the structure of **74** was a first highly effective catalyst for the asymmetric reduction of aromatic and aliphatic ketones as well as aromatic and aliphatic ketimines in good to high enantioselectiviy (Scheme 62).[193]



Scheme 62. Asymmetric reduction of ketones and ketimines with trichlorosilane catalyzed by **78**.

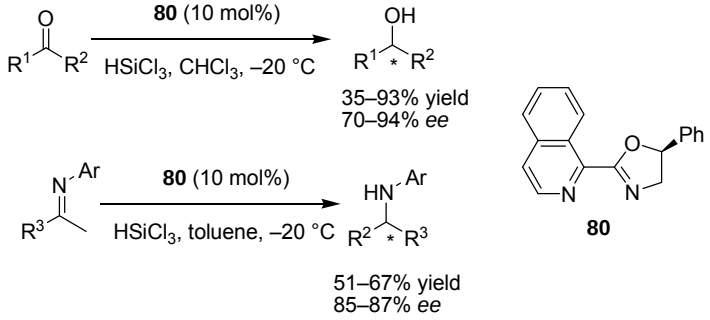
During the last several years, a variety of Lewis basic organic activators have been developed for asymmetric reductions with trichlorosilane. The noticeable feature in most of the activators was that *N*-formyl substituent was essential for those reductions. Recently, two other types of activators were independently disclosed by Matsumura and Malkov groups. Matsumura et al. developed **79** as organic activator in asymmetric reduction of imines to the

corresponding amines with trichlorosilane in moderate to good enantioselectivities (Scheme 63).[194]



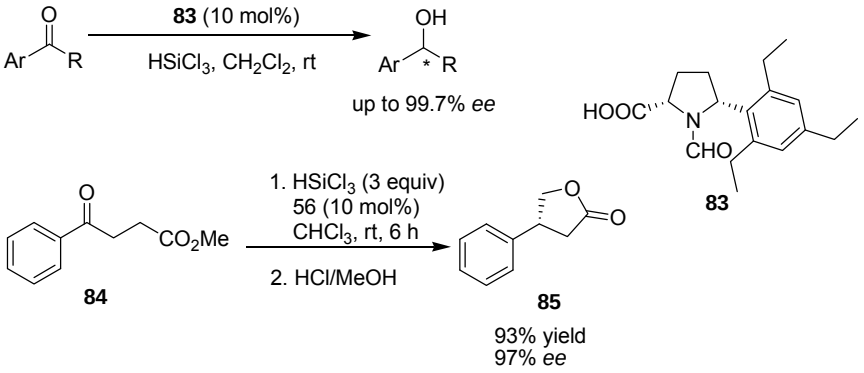
Scheme 63. Asymmetric reduction of ketimines with trichlorosilane catalyzed by **79**.

Simultaneously, Malkov and co-workers developed a new, practical, and efficient organocatalyst **80** for the enantioselective reduction of aromatic ketones (up to 94% *ee*) and ketimines (up to 87% *ee*) using trichlorosilane (Scheme 64).[195] It is noteworthy that the reaction is characterized by an unusual, long-ranging chiral induction.



Scheme 64. Asymmetric reduction of ketones and ketimines with trichlorosilane catalyzed by **80**.

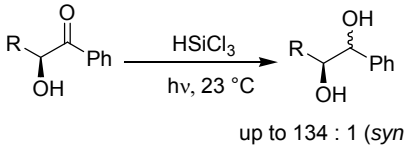
Recently, one remarkable progress in asymmetric reduction of aryl ketones using trichlorosilane was achieved by Matsumura and co-workers. In the presence of a catalytic amount of **83** aryl ketones were reduced to the corresponding alcohols with excellent enantioselectivity (up to 99.7% *ee*) (Scheme 65).[196] Also, by using this method, they succeeded in the preparation of an optically active lactone **84** from keto ester **85** in 93% yield with 97% *ee*. **85** is an important intermediate for a preparation of a wide variety of biologically active substance.



Scheme 65. Asymmetric reduction of aryl ketones with trichlorosilane catalyzed by **83**.

The aforementioned reductions using trichlorosilane activated by an organic activator is a well-established two-electron transformation, in which a hydride was transferred from

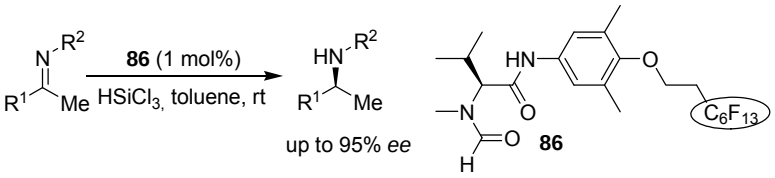
activated trichlorosilane to nucleophiles, such as imines or ketones. The related free-radical reduction remains a potentially valuable one-electron alternative to this reaction. Enholm et al. reported that the reduction of α-hydroxy ketones can be performed with trichlorosilane under neutral free radical conditions to anti-1,2-diols in high diastereoselectivities (Scheme 66).[197] This reduction provides a stereoselective, mild, one-electron alternative to the established two-electron methods that use hydride regents.



up to 134 : 1 (*syn* : *anti*)

Scheme 66. Trichlorosilane radical reduction of α-hydroxy ketones.

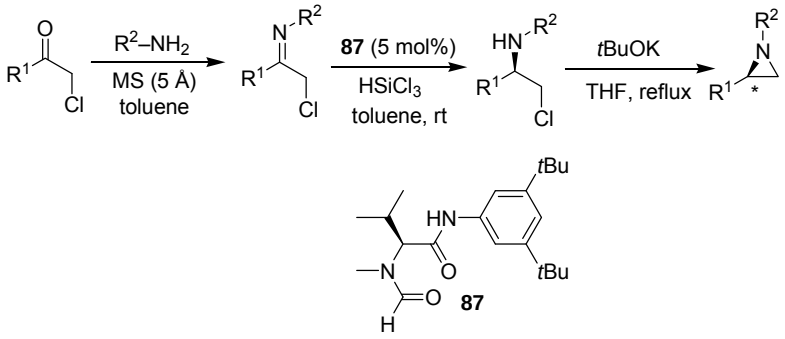
Recently, Malkov and co-workers continued to refine their valine-derived organocatalysts for the asymmetric reduction of *N*-aryl ketimines with trichlorosilane (Scheme 67).[198] The introduction of bulky groups into the anilide moiety of the catalysts resulted in an increase of enantioslectivity not only in the aromatic realm, but also for the nonaromatic imines. The catalyst loading can be reduced to 1 mol%, which is rather uncommon in general. In addition, they enhanced the practicality by fluorous tagging of the catalyst, which allows a very easy isolation of the product and an undemanding recovery of the catalyst that can be used in the next cycle.



up to 95% *ee*

Scheme 67. Asymmetric reduction of ketimines with trichlorosilane catalyzed by **86**.

Almost simultaneously, the same group of Malkov et al. developed a new, expedient protocol for the synthesis of 1,2-diaryl aziridines that have hot been prepared previously as pure enantiomers, in which the reductive amination of α-chloroacetophenone with trichlorosilane catalyzed by L-valine-derived formamide **87** is a crucial step (Scheme 68).[199]



Scheme 68. Enantioselective synthesis of 1,2-diarylaziridines.

1.5.3 Summary

In general, trichlorosilane, employed as the stoichiometric reducing agent for the reduction of ketones or imines, serves as a starting material in the silicon industry and is manufactured in bulk, so that its price is reduced almost to the level typical for common organic solvents. Although trichlorosilane is sensitive to water, the implications are rather modest and the reagent can be easily handled by using standard procedures for moisture-sensitive materials with minimum precautions (in principle, a $CaCl_2$ drying tube could be used instead of an inert atmosphere of nitrogen of argon). Since toluene was identified as an optimal solvent and the workup of the reaction with aqueous $NaHCO_3$ produces innocuous inorganic materials, namely NaCl and silica, this protocol represents a relatively low environment risk. In conjunction with the low catalyst loading, all these features suggest that the organocatalyzed reductions with $HSiCl_3$ may become an attractive alternative to the established industrial technologies for asymmetric reductions.

1.6 Organocatalyzed asymmetric cyanosilylation

1.6.1 Introduction

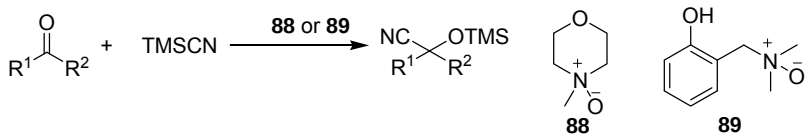
Cyanohydrins are of synthetic interest as they may be elaborated into a number of key functional groups, including α-hydroxyacids, β-hydroxyalcohol, and other valuable building blocks.[200, 201] Hydrogen cyanide (HCN) is the most commonly industrially used reagent for cyano transfer to carbonyl compounds.[202] However, due to its toxicity and difficulty in handling, new methods have been developed to substitute HCN with other potentially less harmful and yet easily manageable reagents. Trimethylsilyl cyanide (TMSCN) is widely used as a cyanide source with various catalysts. The use of TMSCN allows the desired cyanohydrin to be prepared directly as the corresponding trimethylsilyl ether. The stability of the TMS adduct, conferred by an energetically favourable Si-O bond, prevents the reverse cyanation reaction from occurring and hence removes a potential pathway for racemization. In 1973, Evans and Sundermeyer and their co-workers are among the first to report the addition of TMSCN to aldehydes, ketones, and acid chlorides catalyzed by thermal and Lewis acid respectively.[203, 204] Since then, a multitude of different catalysts has been reported in the literature for both the racemic and asymmetric addition of the cyanide to carbonyls.[200, 205, 206] Majority of these chiral catalysts are based on metallic Lewis acidic systems containing a variety of ligands that enable enantioselective transfer of CN^- to carbonyls. However, in view of environmental benign pressures, organocatalysts have received great attention in recent years.[12] This chapter describes the progress in organanocatalytic addition of TMSCN to carbonyls, mainly on the addition of aldehydes or ketones, which was ordered mainly in two parts: organocatalytic racemic addition of TMSCN to carbonyls and enantioselective addition of TMSCN to carbonyls.

1.6.2 Synthesis of racemic cyanohydrins with green approaches

1.6.2.1 Organocatalytic racemic addition of TMSCN to carbonyls

Before discussing enantiomerically enriched cyanohydrins, I would like to introduce the area by reviewing cyanohydrin synthesis in the absence of chiral control. This section therefore summarizes the preparation of racemic cyanohydrins.

Generally, in the absence of a catalyst, no reaction is observed between TMSCN and carbonyl compounds. Consequently, a variety of organic activators or promoters have been reported for the cyanation of carbonyl compounds with TMSCN. Element I_2, tertiary amines and quaternary ammonium salts have been used to catalyze the addition of TMSCN to aldehydes and ketones.[207-210] Interestingly, 1,2- or 1,4-adducts can be manipulated easily in the case of α,β-unsaturated ketones under specific conditions.[208, 209] Plumet et al. have reported racemic or diastereoselective cyanosilylation of carbonyl compounds with TMSCN using Tetrabutylammonium cyanide or methyltriphenylphosphonium iodide as catalysts.[210-212] A series of N-oxides including commercially available *N*-methylmorpholine *N*-oxide (NMO) and prepared tertiary amine and pyridine *N*-oxides are reported independently by Kim and Feng and their co-workers to be effective promoters for the addition of TMSCN to ketones (Scheme 69).[213, 214] The air-stable phenolic *N*-oxide **89** exhibited superior catalytic effect over **88**. In the presence of 5 mol% of **89**, ketones were quantitatively converted into corresponding cyanohydrin O-TMS ethers at mild temperature within short reaction time. Denmark and Chung conducted a brief survey of effective solvents, catalysts, and kinetics of Lewis base catalyzed addition of TMSCN to aldehydes.[215] Maruoka, Song, and Aoyama have reported the use of *N*-heterocarbenes (NHCs) as effective catalysts for the addition of TMSCN to carbonyl compounds.[216-218] Wilhelm and Blanrue have reported cyanosilylaiton of aldehydes with TMSCN using Imidazolium-carbodithionates as catalysts.[219] Verkade and Fetterly have reported the 1,2-addition of trialkylsilylcyanides to aldehydes and ketones in the presence of catalytic amounts of non-ionic strong base $P(RNCH_2CH_2)N$.[220] Feng et al. have reported catalytic cyanosilylation of ketones using 1,1,3,3-tetramethylguanidine as catalyst.[221] Takemoto et al. have reported thiourea-catalyzed addition of TMSCN and ketene silyl acetals to nitrones and aldehydes.[48] Recently, Olah and co-workers reported the cyanosilylaitons in demethylformamide (DMF) using nucleophilic catalysts such as carbonates and phosphates.[222] They found that the CN to carbonyl transfer in DMF can be carried out even in the absence of a catalyst. With the addition of K_2CO_3 or organic phosphate as catalyst, the rate of the reaction has been significantly enhanced.



Scheme 69. *N*-oxides catalyzed addition of TMSCN to ketones.

1.6.2.2 Cyanosilylation of carbonyl compounds through heterogeneous catalysis

The ever-increasing pressure of environmental pollutions has compelled chemists to research green chemistry and technology in order to replace currently existing pollution sources with clear manufacturing process. The rational way is to immobilize homogeneous catalysts with polymers or to pursue solid catalysts made from mineral materials affording heterogeneous catalysis, which is featured in recyclable use of the catalyst and simplified workup.

In the area of cyanosilylation synthesis, many efforts have been made to realize heterogeneous addition of TMSCN to ketones. Modified mineral materials were firstly utilized to catalyze cyanosilylation of ketones. Solid acidic cation-exchanged montmorillonites (M^{n+}-Mont, M^{n+} = Al^{3+}, Fe^{3+}, Sn^{4+}, Ca^{2+}, Ni^{2+}),[223-225] solid basic calcined hydrotalcite (HT, $Mg_6Al_2(OH)_{16}CO_3 \cdot 4H_2O$), $MgAlCO_3$-HT and hydroxyapatite ($Ca(PO_4)_6(OH)_2$), were employed as heterogeneous catalysts for the reaction in organic solvents.[223-226] Some inorganic metal oxides such as MgO and CaO were also used as heterogeneous promotors.[224, 225] CaF_2 can release cyanide from TMSCN as a result of the formation of Si-F bond, thus accelerate the addition of TMSCN to ketones.[223] In fact, all basic heterogeneous catalysts could promote this transformation due to the coordination between silicon atom of TMSCN and O^{2-} of those catalysts.[227]

Recently, diamine attached to commercially purchased mesoporous silica MCM-41 exhibited good catalytic capacity to cynosilylation of ketones as a green catalyst.[228]

Heterogeneous catalysis has received increasing interest in organic synthesis using inorganic salts as catalysts. Jenner has reported cyanosilylation of ketones with TMSCN using $LiClO_4$ or solution of $LiBF_4$ as catalysts.[229] Later, Saidi reported the use of $LiClO_4$ as catalyst for this reaction under solvent-free conditions, however, solvents was required for the workup stage.[230] Recently, Ohkuma et al. reported LiCl as a highly effective catalyst for cyanosilylation of aldehydes and ketones to the corresponding silylated cyanohydrins under solvent-free conditions.[231] The turnover frequency (TOF) can reach 28000 at a substrate/catalyst (S/C) 50000. K_2CO_3 was found as the efficient inorganic salt to catalyze the addition of TMSCN to ketones under solvent conditions.[232]

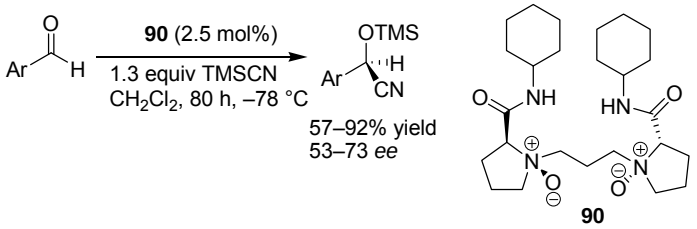
1.6.3 Asymmetric synthesis of cyanohydrins with TMSCN catalyzed by organocatalysts

Since cyanohydrins can serve as precursors to α-hydroxy acids, β-amino alcohols, and other valuable chiral building blocks, the catalytic asymmetric cyanation of carbonyl compounds ranks among the most important and well-studied reaction classes in asymmetric catalysis.[201] Whereas several outstanding catalyst systems have been identified for cyanation of aldehydes,[200] ketones present a greater challenge as a substrate class, and only recently have effective methods using chiral metal complexes,[200, 233-242] cinchona alkaloids,[243] chiral oxazaborolidinium ions,[244] amino acid salts,[245] mono- or bilithium salts of binols,[246-248]

and chiral thioureas[93] been devised. This part mainly covers the recent advancement in organocatalytic asymmetric addition of TMSCN to carbonyl compounds.

1.6.3.1 Organocatalytic asymmetric addition of TMSCN to aldehydes

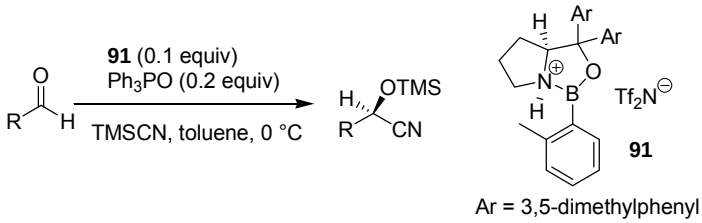
Feng and coworkers developed an asymmetric cyanosilylation of aldehydes catalyzed by proline-based chiral *N,N'*-dioxide (Scheme 70).[249] In the presence of 2.5 mol% **90**, a variety of aromatic aldehydes were converted to their corresponding products with good yields in up to 73% *ee*.



Scheme 70. Asymmetric cyanosilylation of aldehydes catalyzed by **90**.

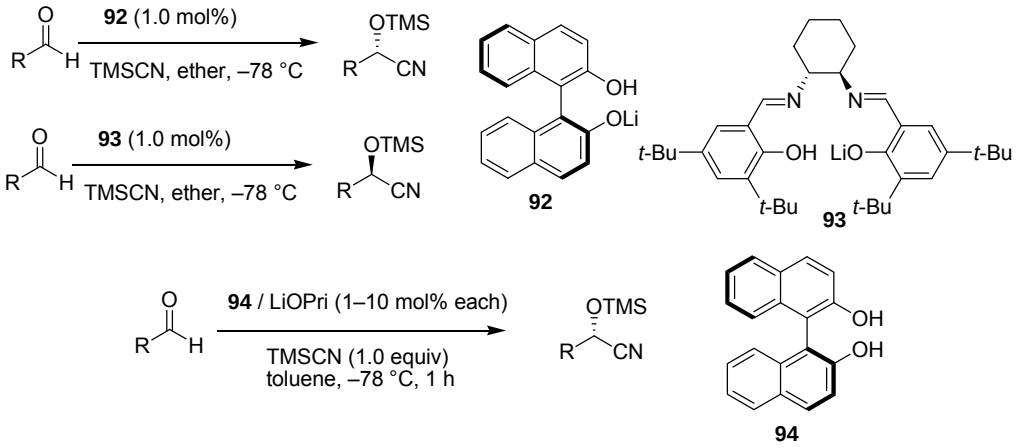
Gennari and co-workers reported the use of a diastereomeric mixture of atropisomeric thioureas **25** as a bifunctional orgnocatalytic system for enantioselective cyanosilylation of aldehydes (Section 1.3.2.2.1).[95]

Corey and Ryu described a new chiral system based on boron and Ph_3PO as a coreactant (Scheme 71).[250] A variety of aldehydes, aromatic and aliphatic, have been transformed into cyanohydrins with excellent yield in >90% *ee*. In addition, the chiral precursor of the catalyst is readily recoverable and the absolute stereochemical course of the reaction is predicted clearly by a well precedented mechanism.



Scheme 71. Asymmetric cyanosilylation of aldehydes catalyzed by **91**.

Kagan and coworkers have reported the use of mono- and dilithium salts binol for asymmetric addition of TMSCN to aldehydes (Scheme 72, top).[247, 248] It should be noted that the enantioselectivity and rate of reactions are very substrate specific. Recently, Ishiahara and coworkers have modified this system by introducing a water/alcohol mixture as a coactivator (Scheme 72 bottom).[246] A highly enantioselective cyanation of aromatic aldehydes can be obtained using a simple and inexpensive chiral lithium binaphtholate aqua or alcohols complexes. This system is suitable for process chemistry to ensure the practical gram-scale cyanohydrin synthesis in minimum solvent.

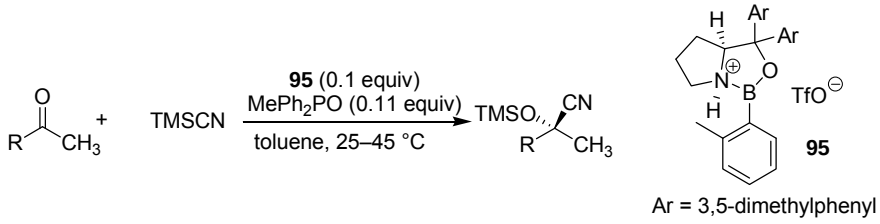


Scheme 72. Asymmetric cyanosilylation of aldehydes catalyzed monolithium salt **92**, **93**, or **94**.

1.6.3.2 Organocatalytic asymmetric cyanosilylation of ketones

The asymmetric cyanation of ketones has been historically considered as problematic. There is more steric hindrance around the carbonyl group of ketones than of aldehydes, significantly decreasing the propensity of the former to undergo cyanation. Despite this inherent problem, the area has received considerable attention as a consequence of the synthetic utility of homochiral cyanohydrins of ketones. This part mainly describes the recent progress in organocatalytic systems.

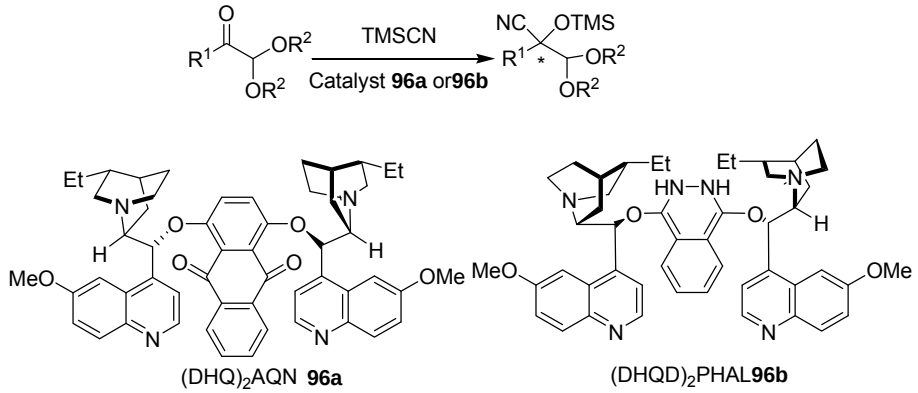
During the investigation of chiral oxazaborolidium ion as catalyst for asymmetric cyanosilylation of aldehydes, Corey and Ryu succeeded to extend this system to enantioselective cyanosilylation of methyl ketones (Scheme 73).[244] After optimizing the reaction parameters, in the presence of 10 mol% **95** and $MePh_2O$ as acoreactant, a range of methyl ketones can be converted to the corresponding cyanosilyl ether with good to high yield in high to excellent enantioselectivities. The absolute stereochemical course of these carbonyl addtions can be rationalized in a logical way. Interestingly, higher enantioselectivities result with the more electron-withdrawing groups, presumably considered that these favour early transition states and a stronger attractive interaction between the coordinated methyl ketone carbonyl and the neighboring π-electron-rich mexyl group of **95**. In contrast, electron-supplying groups have the opposite effect, leading to stereochemically variable pathways.



Scheme 73. Asymmetric cyanosilylation of ketones catalyzed by **95**.

Deng et al. reported the first highly enantioselective cyanosilylation of ketones with modified cinchona alkaloids (Scheme 74).[243] Reasoning that acetal ketones serve not only as

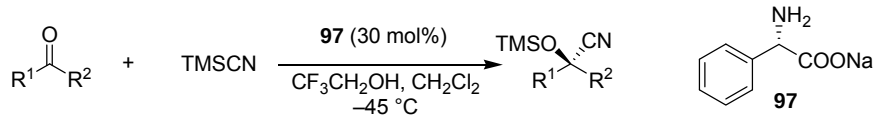
a versatile handle for synthetic elaboration of the product, but the acetal group also enhances the activity of the ketone toward the nucleophilic enantioselective cyanosilylation, cyanosilylation of a series of prepared acetal ketones was investigated with various cinchona alkaloid derivatives. In the presence of 2 mol% of $(DHQ)_2AQN$ (**96a**) in chloroform or 5–10 mol% of $(DHQ)_2PHAL$ (**96b**) in ethyl acetate, excellent enantioselectivity and yield is obtained with acetal ketones bearing a broad range of aryl, alkenyl, and alkyl substituents. In addition, both the isolation of product and the recovery of the **96a** were achieved in quantitative yield using a simple extractive procedure. These results were duplicated with the recovered **96a**. In general, this reaction provides a new, practical, and broadly applicable approach toward chiral building blocks bearing quaternary stereocenters. This is in marked contrast to the often highly exothermic, poorly selective reactions normally observed with the addition of TMSCN to unactivated ketones. Choi and coworkers investigated simple cinchona alkaloid systems as catalysts for the reaction of TMSCN with acetophenone. After the variation of a number of reaction parameters, including solvent and pressure, a maximum of 10% *ee* was obtained.[251]



Scheme 74. Asymmetric cyanosilylation of ketones catalyzed by **96a** or **96b**.

Jacobsen and Fuerst reported a significant new example of thiourea catalysis in the highly enantioselective cyanosilylation of ketones and aldehydes with a bifunctional thiourea-amine derivative (Section 1.3.2.2.1).[93]

Much differently from the known enzyme- and transition metal-based methods, Feng and coworkers developed a sodium salt of chiral amino acid **97** as catalyst for highly enantioselective cyanosilylation of ketones (Scheme 75).[245] In the presence of 30 mol% of **97** and add isopropanol, a variety of aromatic ketones were converted to their corresponding cyanosilyl ether in excellent yields and enantioselectivities, but only moderate *ee* values for aliphatic and α,β-unsaturated ketones. Notable features of the reaction are the utilization of commercially available and fully recyclable catalysts and employment of simple and convenient experiment procedures, which should render the reaction more attractive for industry application.



Scheme 75. Asymmetric cyanosilylation of ketones catalyzed by organic salt **97**.

1.6.4 Conclusions and outlook

Recent progress in organocatalytic addition of TMSCN to carbonyls was introduced. Generally, these organocatalysts include cinchona alkaloids, amino acid salts, mono- or bilithium salts of binols, *N*-oxides, as well as thiourea derivatives. However, operations of the present methods are considerably complicate and there are still less alternatives for efficient organocatalytic asymmetric cyanosilylation of ketones, due to steric hindrance around ketones. Since enantiomerically enriched cyanohydrins can be elaborated into a number of key functional groups, generally applicable and environmentally benign methodologies are still highly anticipated.

Chapter 2 Research Objectives

As outlined briefly above, thiourea-based catalysts have proven effective in promoting a variety of reactions. However, the development of "privileged" thiourea-based organocatalyst with general applications is still formidable.[252] One of the main targets of this present doctoral thesis is to develop novel thiourea-based chiral organocatalysts for several fundamentally important transformations, such as transfer hydrogenations, cyanosilylation, as well as hydrophosphonylation. First, we design and prepare a series of thiourea-based compounds with novel chiral modules via a short and straightforward synthetic route. General strategies are based on the following aspects: (1) incorporation of chiral oxazoline moieties into known achiral thiourea catalysts; (2) incorporation of additional Lewis base functionality; (3) preparation of analogues of reported catalysts; (4) exploration of new applications for reported catalysts. After the potential catalysts' library is set up, their catalytic efficacy will be investigated under optimized reaction conditions.

The applications of chiral *N*-formamides as metal-free catalysts have recently added to the advances in the field of organocatalysis. Another important goal of our study is to develop novel chiral *N*-formamide for asymmetric reduction of ketimines using trichlorosilane as the hydrogen donor. Since the detailed mechanisms of these reactions are not available, preliminary mechanistic studies will be considered, which involve the interception and characterization of reaction intermediates by means of experimental and computational methods. The implication of these mechanistic findings should provide information for rational design of novel chiral activators for trichlorosilane.

Chapter 3 Organocatalytic Reductions

General Remarks

The results achieved so far have been published in two papers, and the other unpublished attempts are introduced separately.

3.1 Thiourea-Catalyzed Transfer Hydrogenation of Aldimines

Zhiguo Zhang, Peter R. Schreiner*

Synlett **2007**, 1455–1457.

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On the question of some of the published literature protocols, we present a practical method for the thiourea-catalyzed reduction of aromatic as well as aliphatic aldimines with a Hantzsch ester as the hydrogen source.

3.2 Organocatalytic Biomimetic Reduction of Conjugated Nitroalkenes

Zhiguo Zhang, Peter R. Schreiner*

Synthesis **2007**, 2559–2564.

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A thiourea-catalyzed biomimetic metal- and acid-free reduction of conjugated nitroalkenes to the respective nitroalkanes utilizing a Hantzsch ester as the hydrogen source was developed.

3.3 Miscellaneous

The *in situ* regeneration of Hantzsch ester, development of chiral ammonium salts as potential catalysts, as well as search for other hydrogen sources were investigated.

3.4 Trichlorosilane ($HSiCl_3$) – A Cheap and Convenient Reducing Agent

Zhiguo Zhang

Submitted to *Synlett Spotlight* on Jan. 9, 2008.

An introduction to trichlorosilane was performed.

3.5 Asymmetric Organocatalyzed Reduction of Ketimines with $HSiCl_3$ (Manuscript in preparation)

Various novel chiral *N*-formamides derived from proline, valine, and pipecolinic acid were developed for the asymmetric reductions of ketimines using trichlorosilane as the hydrogen donor. The enantioselectivity up to 68% *ee* was so far obtained. The preliminary mechanism studies showed quite different features as described in the literature. Further work will be directed to elaborate the mechanism aspects by means of experimental and computational methods and develop more efficient catalysts.

LETTER 1455

Thiourea-Catalyzed Transfer Hydrogenation of Aldimines

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Abstract: The present letter reports on the thiourea-catalyzed transfer hydrogenation of imines through hydrogen-bonding activation with Hantzsch 1,4-dihydropyridine as the hydrogen source. A variety of aromatic as well as aliphatic aldimines can be reduced to give the respective amines under acid- and metal-free reaction conditions.

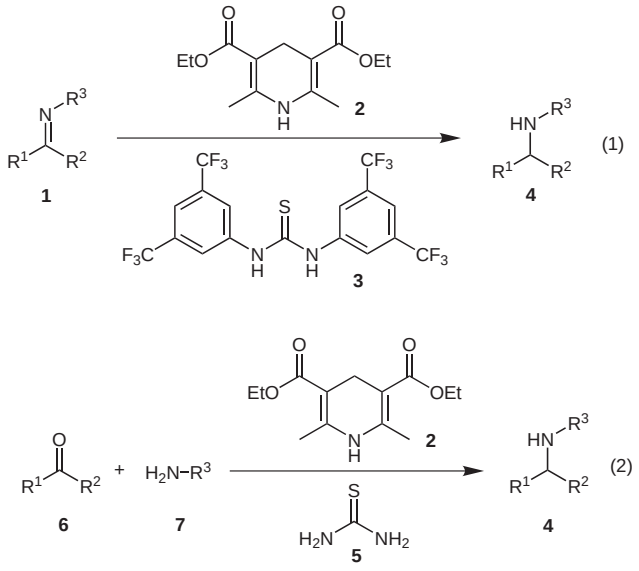
Key words: Hantzsch dihydropyridine, hydrogen bonds, organocatalysis, thiourea, transfer hydrogenation

The organocatalytic hydrogenation of imines and the reductive amination of carbonyl compounds represent a contemporary challenge.[1] There are many metal-based approaches to this transformation, and molecular hydrogen as the reductant activated by chiral metal complexes is a powerful method for the preparation of amines,[2] even on industrial scale.[3] Transfer hydrogenations using isopropyl alcohol or formic acid as sources of hydrogen also are effective.[4] However, expensive and toxic metal ions were used in most of these transformations, so that the organocatalytic hydrogenation of imines and reductive aminations were eagerly anticipated. These include hydrosilylations catalyzed by chiral Lewis bases[5] and hydrogen-transfer reactions catalyzed by chiral phosphoric acid derivatives in combination with the NADH analogous Hantzsch ester.[6]

In the course of our studies on noncovalent organocatalysis mediated through hydrogen bonding, we have demonstrated that thiourea derivatives catalyze Diels–Alder-reactions,[7] acetalizations,[8] epoxide openings[9] as well as several other reactions.[10] We envisioned that activation of imines **1** by hydrogen bonding with electron-poor biaryl thiourea **3** would promote hydrogen transfer from the Hantzsch ester **2** to generate amine **4** (Scheme 1, eq. 1).

Recent work by Menche et al. on the reductive amination of ketones[11] and aldehydes[12] with thiourea (**5**) itself (Scheme 1, eq. 2) encouraged us to utilize **3**, which has proven to be generally a more effective catalyst. First, we attempted to reproduce the findings by the Menche group and compared the catalytic activity of **3** and **5** (Table 1).

Much to our surprise, the reductive amination of acetophenone (**6a**) was ineffective (entries 6–8). When the reaction was carried out using *unactivated* 5 Å MS as dehydrating agent (entry 9), the conversion at 50 °C was



Scheme 1 Thiourea-catalyzed transfer hydrogenation

smooth (89%) even *without* a thiourea catalyst added. This is in stark contrast to the previous report by Menche et al. who reported a maximum yield of 5%;[11] the reasons for using unactivated MS is not clear to us but complies with the data given in the original publications.[11,12]

Conversely, activated MS gives the product in less than 5% yield in the presence of 10 mol% of **5**, while Menche et al. report 88% yield when using unactivated 5 Å MS. As a consequence, we conclude that commercially available 5 Å MS contains some water or other relatively volatile components that could catalyze the reaction as well.

Our attempts at reproducing the published protocol[12] for the reductive amination of aldehydes were equally puzzling at first (entries 1–5). We found that benzaldehyde (**6b**) could be condensed and reduced to the corresponding amine **4b** *without* catalyst with 78% yield in 24 hours! Naturally, we assumed that the auto-oxidation of **6b** had produced sufficient quantities of benzoic acid that could catalyze the reaction as well. Hence, upon addition of excess of base (10 mol% $NaHCO_3$), the reaction was completely suppressed (entry 1). The same reaction in the presence of **5** gave no product (entry 2). In contrast, over 80% yield of product can be realized within 24 hours with 5 mol% or 10 mol% of **3** (entries 3 and 4). Other substituted aryl aldehydes gave poor to moderate yields.

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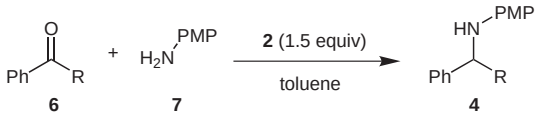
Table 1 Thiourea-Catalyzed Reductive Amination

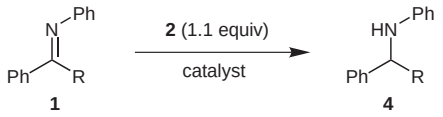


6 7 4

Entry	R	Catalyst (mol%)	Temp (°C)	Conditions	Yield (%)[a]
1	H	–	r.t.	base,[b] 24 h	trace
2	H	**5** (10)	r.t.	base,[b] 24 h	trace
3	H	**3** (10)	r.t.	base,[b] 24 h	86
4	H	**3** (5)	r.t.	base,[b] 24 h	84
5	H	–	70	5 Å MS,[c] 24 h	91 (93[12])
6	Me	–	50	5 Å MS,[d] 48 h	<5
7	Me	**5** (10)	50	5 Å MS,[d] 48 h	<5 (88[11])
8	Me	**3** (10)	50	5 Å MS,[d] 48 h	<5
9	Me	–	50	5 Å MS,[c] 48 h	89 (<5[11])

[a] Yield of **4** after column chromatography.
[b] 10 mol% of $NaHCO_3$ was added.[13]
[c] Unactivated (Acros organics, pellets, 4–8 mesh, product number: 197285000).
[d] Activated.

Table 2 Imine Reduction with Thioureas



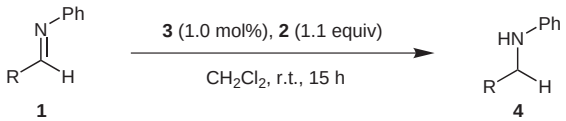
1 4

Entry	R	Catalyst (mol%)	Conditions	Yield (%)[a]
1	Me	–	toluene, 50 °C, 48 h	trace
2	Me	**5** (20)	toluene, 50 °C, 48 h	trace
3	Me	**3** (20)	toluene, 50 °C, 48 h	trace
4	H	–	CH_2Cl_2, r.t., 24 h	trace
5	H	**5** (10)	CH_2Cl_2, r.t., 24 h	trace
6	H	**3** (10)	CH_2Cl_2, r.t., 15 h	91
7	H	**3** (5)	CH_2Cl_2, r.t., 15 h	89
8	H	**3** (1)	CH_2Cl_2, r.t., 15 h	89
9	H	**3** (0.1)	CH_2Cl_2, r.t., 60 h	87

[a] Yield of **4** after column chromatography.

We therefore turned our attention to the reduction of isolated imines to further clarify the crucial step in the reported reductive amination. These were allowed to react with reductant **2** under thiourea catalysis (Table 2). While the ketimine derived from **6a** only gave traces of product, the aldimine **1b** produced the corresponding amine even at 1 mol% loading of **3** (entry 8), while **5** again had no catalytic effect (entries 2 and 5). Loadings as low as 0.1 mol% are also possible at the expense of longer reaction times (entry 9).

Table 3 Thiourea-Catalyzed Reduction of Aldimines



1 4

Entry	R	Yield (%)[a]
1	Ph	89
2	4-MeC_6H_4	92
3	4-$O_2NC_6H_4$	91
4	4-BrC_6H_4	93
5	3-HOC_6H_4	86
6	4-FC_6H_4	84
7	3-ClC_6H_4	90
8	2,6-$Cl_2C_6H_3$	86
9	3-$MeOC_6H_4$	84
10	*i*-Bu	80
11	*c*-Hex	87

[a] Yield of pure **4** after column chromatography.

Using dichloromethane as solvent and **3** (1 mol%) as catalyst we explored the scope of this acid- and metal-free transfer hydrogenation for the aldimines (Table 3).[14] In general, a variety of aromatic aldimines can be reduced, including electron-rich, electron-deficient, as well as *ortho*-, *meta*-, and *para*-substituted aryl aldehydes. In addition, aliphatic aldimines can also be reduced to give the respective amines with high yields (entries 10 and 11).

The present paper questions some of the published literature protocols[11,12] on the reductive amination of aldehydes and ketones. At the same time, we present a practical method for the thiourea-catalyzed reduction of aromatic as well as aliphatic aldimines with a Hantzsch ester as the hydrogen source.

Acknowledgment

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(13) Since it is difficult to avoid the formation of carboxylic acids generated from aldehydes during the reaction, 10 mol% of $NaHCO_3$ was added.

(14) **General Procedure for the Thiourea-Catalyzed Transfer Hydrogenation of Aldimines**
In a typical experiment the aldimine **1** (1.0 mmol), thiourea **3** (1 mol%) and Hantzsch dihydropyridine **2** (1.1 equiv) were suspended in anhyd CH_2Cl_2 (5 mL) in a flask. The resulting mixture was allowed to stir at r.t. for 15 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel using mixtures of PE and Et_2O to afford the pure corresponding amine **4**. All compounds were fully characterized on the basis of IR, ^1H NMR, ^{13}C NMR and HRMS.
Compound **4a**: light yellow oil. IR (film): 3418, 1699, 1602, 1505, 1179, 1064 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.20 (s, 2 H), 6.50–6.52 (d, 2 H, *J* = 8.71 Hz), 6.59–6.63 (t, 1 H, *J* = 7.41 Hz), 7.04–7.09 (t, 2 H, *J* = 7.40 Hz), 7.14–7.27 (m, 5 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 48.2, 112.8, 117.5, 127.1, 127.4, 128.5, 129.2, 139.4, 148.1. HRMS: *m/z* calcd for $C_{13}H_{13}N$: 183.10425; found: 183.10347.

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SPECIAL TOPIC 2559

Organocatalytic Biomimetic Reduction of Conjugated Nitroalkenes

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Abstract: A thiourea-catalyzed biomimetic reduction of conjugated nitroalkenes has been developed. Various aromatic and aliphatic conjugated nitroalkenes can be reduced to give the respective nitroalkanes with good yields under mild conditions. This protocol is not only practical, but may also provide insight into the mechanisms of redox transformations in biological systems.

Key words: biomimetic reduction, Hantzsch ester, hydrogen bonding, nitroalkenes, thiourea

Aliphatic nitroalkanes are valuable building blocks and intermediates in organic synthesis as well as in carbohydrate chemistry.[1] They are very useful tools for carbon–carbon bond formation or carbon skeleton elongation because the high electron-withdrawing power of the nitro group stabilizes α-carbanions and enables their reactions with electrophiles under mild conditions. Moreover, the nitro group itself can be transformed into other functionalities such as, amongst others, carbonyl, amino, oxime, and hydrogen moieties.[2] The preparation and subsequent reduction of conjugated nitroalkenes has been widely accepted as a straightforward route to nitroalkanes, thus, there are quite a number of reducing reagents and reduction methodologies employed in this transformation.[3] Commonly used reductants include borohydride derivatives, metal hydrides, and metal halides. However, the selective reduction of the conjugated double bond is rather difficult because nitro-group reduction often takes place simultaneously.[4] Though sodium borohydride primarily furnishes the corresponding nitroalkanes, these reactions are often accompanied by the formation of polymeric side products through Michael addition of the nitronate intermediate to the starting nitroalkene.[5] Zinc borohydride is reported to be an efficient reagent with which to convert nitroalkenes smoothly into the corresponding nitroalkanes.[6] Metal-catalyzed hydrogenations and transfer hydrogenation are also very effective, however, due to the difficulties in handling or the toxicity of metal ions, new efficient and environmentally friendly methods remain desirable.[7]

In contrast to the chemical conversions described above, biological redox transformations using reduced nicotinamide adenine dinucleotide (NADH) as a coenzyme to reduce unsaturated functionalities, proceeds smoothly under very mild conditions. The ease with which such reactions takes place has been a stimulus for the development of a wide range of NADH models for a variety of reductions.[8] Among these, Hantzsch esters are one of the most widely investigated biomimetic reductants because they are inexpensive, stable and readily available.[9] Recent advances in organocatalysis have shown considerable promise for employing Hantzsch esters as the hydrogen source in asymmetric reductions as well as reductive aminations;[10] however, there is no organocatalytic method for the reduction of conjugated nitroalkenes.[11]

Developments in biological and enzymatic catalysis have shown that isolated enzymes from baker's yeast or Old Yellow Enzyme (OYE), which was termed as nitroalkene reductase, can efficiently catalyze the NADPH-linked reduction of nitro-olefins. The crystal structure of OYE revealed that several amino acid residues around the active site of the enzyme affect catalysis and ligand binding. With a systematic study of the OYE-catalyzed reduction of nitrocyclohexene, a catalytic mechanism was proposed in which the nitrocyclohexene was activated by nitro-oxygen hydrogen bonds to His-191 and Asn-194 (Figure 1, A).[12] A hydride is then transferred to the β-position from the reduced flavin which, ultimately, originated from NADPH. The product is finally formed through proton transfer from the Tyr-196 hydroxyl to the α-position.[12]

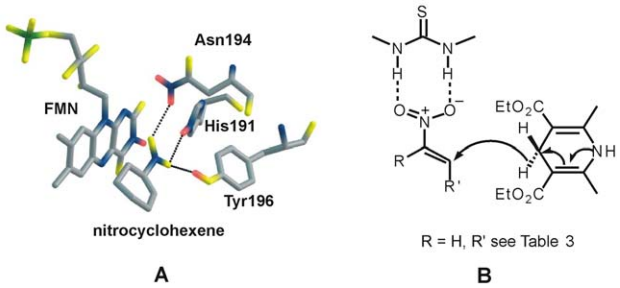

Figure 1 Thiourea-catalyzed biomimetic reduction of nitroalkenes. (A) Key interactions between the enzyme (OYE) and nitrocyclohexene (Protein Databank ID code 1OYB); (B) model of the thiourea-catalyzed biomimetic reduction of conjugated nitroalkenes.

This excellent study inspired us to mimic the procedure in preparative chemistry with an organocatalyst functioning as the 'reductase' and an NADPH analog such as a Hantzsch ester. During our efforts at developing noncovalent organocatalysis mediated through hydrogen bonding,[13] we recently found that thiourea **3** catalyzes the transfer hydrogenation of aldimines with Hantzsch ester **2** as the hydrogen source, at low catalyst loadings

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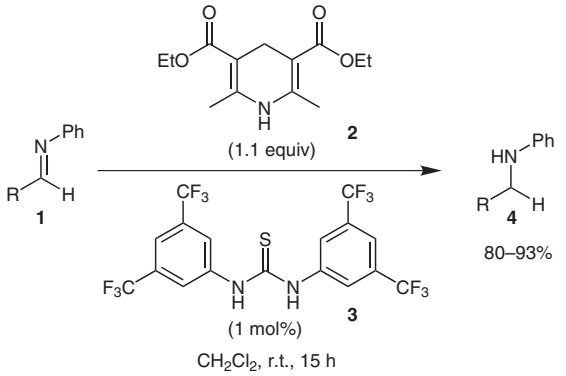
(Scheme 1).[14] We were hopeful that it would be possible to extend this procedure to other electron-deficient α,β-unsaturated conjugated olefins such as nitroalkenes (Figure 1, B). Here we report the first thiourea-catalyzed biomimetic reduction of conjugated nitroalkenes through hydrogen-bonding activation.



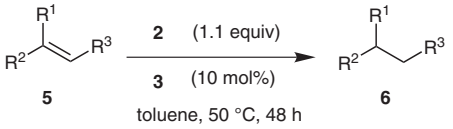
Scheme 1 Thiourea-catalyzed transfer hydrogenation of aldimines.[14]

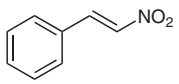
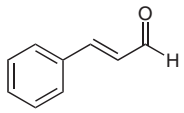
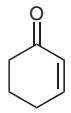
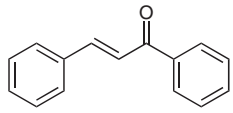
We first examined some representative electron-withdrawing, conjugated olefins such as nitrostyrene (**5a**), cinnamaldehyde (**5b**), 2-cyclohexenone (**5c**) and chalcone (**5d**) with the protocol described in Table 1. Only nitrostyrene could be reduced at 10 mol% loading of **3**; a decrease in the catalyst loading resulted in somewhat reduced yields (Table 1). The rationale behind this effective reduction may be that the nitro group, as the most electron-withdrawing substituent known,[15] forms strong hydrogen-bonding interactions between the nitro group and **3** and is thus very effective in lowering the LUMO energy of the olefin and thus accelerating the reaction.

We then evaluated solvent effects on the reduction of nitrostyrene (Table 2). Reductions in non-polar media such as benzene and toluene, as well as halogenated solvents, proceeded smoothly. Performing the reaction in more polar media led to sluggish reactions and considerably diminished yields. Surprisingly, a moderate yield was also obtained in the protic solvent methanol (entry 9). In order to further clarify this unusual phenomenon, the reaction was repeated in methanol without the addition of catalyst **3**; complete consumption of **5a** was observed and, in addition to the expected nitroalkane, the Michael addition product was also obtained (entry 10).

Using dichloromethane as solvent and **3** (10 mol%) as catalyst, we studied the general applicability of this procedure for reducing various nitroalkenes (Table 3). All aromatic nitroalkenes were smoothly reduced in good yields and varying the substituents had no marked effect on the outcome of this reaction. As expected, the reductions of electron-rich nitrostyrenes took longer and afforded the product in lower yield. Aliphatic nitroalkenes (**5q** and **5r**) were reduced to the corresponding nitroalkane in very good yield. Only the reduction of nitrocyclohexene gave the nitroalkane in poor yield even at 20 mol% load-

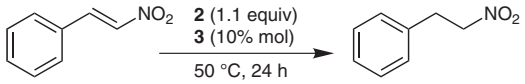
Table 1 Substrate Screening for Thiourea-Catalyzed Reductions



Substrate	Catalyst (mol%)	Product	Yield (%)[a]
 **5a**	–	**6a**	0
5a	**3** (10)	**6a**	87
5a	**3** (5)	**6a**	75
 **5b**	**3** (10)	**6b**	0
 **5c**	**3** (10)	**6c**	0
 **5d**	**3** (10)	**6d**	0

[a] Yield of product after column chromatography.

Table 2 Solvent Effects on the Reduction of Nitrostyrene

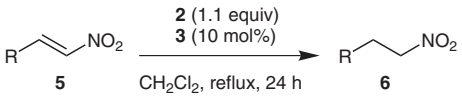


Entry	Solvent	Yield (%)[a]
1	toluene	78
2	benzene	84
3	CH_2Cl_2	88
4	$CHCl_3$	76
5	THF	39
6	1,4-dioxane	30
7	MeCN	39
8	DMF	31
9	MeOH	52
10	MeOH	45[b]

[a] Yield of product after column chromatography.
[b] The reaction was carried out in the absence of catalyst **3**.

ing. Reduction of the nitro group and polymerization of the olefins did not occur in any case.

Table 3 Biomimetic Reduction of Various Nitroalkenes



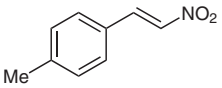
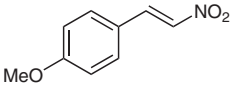
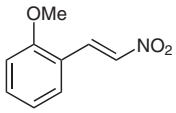
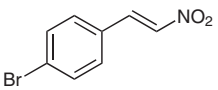
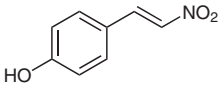
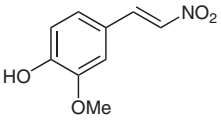
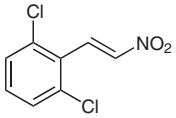
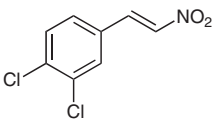
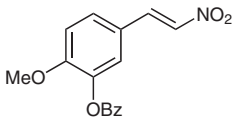
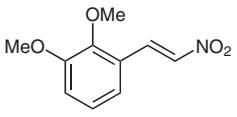
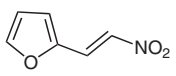
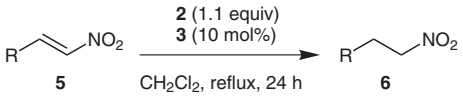
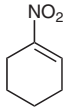
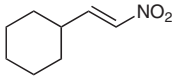
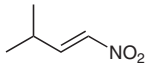
Nitroalkene	Product	Yield (%)[a]
 **5e**	**6e**	80
 **5f**	**6f**	72
 **5g**	**6g**	85
 **5h**	**6h**	79
 **5i**	**6i**	75
 **5j**	**6j**	71
 **5k**	**6k**	82
 **5l**	**6l**	89
 **5m**	**6m**	80
 **5n**	**6n**	71
 **5o**	**6o**	93

Table 3 Biomimetic Reduction of Various Nitroalkenes (continued)



Nitroalkene	Product	Yield (%)[a]
 **5p**	**6p**	37[b] 47[b,c]
 **5q**	**6q**	82
 **5r**	**6r**	87

[a] Yield of product after column chromatography.
[b] A mixture of **5p** and **6p** was isolated; yield was determined by ^{1}H NMR spectroscopy.
[c] 20 mol% of **3** was used.

In summary, we have developed a thiourea-catalyzed biomimetic metal- and acid-free reduction of conjugated nitroalkenes to the respective nitroalkanes utilizing a Hantzsch ester as the hydrogen source. A variety of aromatic and aliphatic conjugated nitroalkenes can be reduced to the respective nitroalkanes with good yields under mild conditions. This protocol is not only practical, but may also provide insights into transformations through hydrogen-bond activation in biological systems. The extension of this protocol to an asymmetric reduction of disubstituted or trisubstituted nitroalkenes, using chiral thiourea derivatives, is under investigation.

Unless otherwise noted, all materials were obtained from commercial suppliers and were used without further purification. Solvents for chromatography were of technical grade and were distilled prior to use. Solvents used in the reactions were reagent grade and were distilled from the indicated drying agents: toluene (P_2O_5), CH_2Cl_2 (P_2O_5), benzene (Na), Et_2O (Na), MeCN (P_2O_5), 1,4-dioxane (Na), DMF (CaH_2), $CHCl_3$ (P_2O_5), THF (Na). For TLC, silica gel coated aluminum plates (Merck, silica gel 60 F_{254}) were used and chromatograms were visualized by irradiation with UV light at 254 nm. Column chromatography was performed using J. T. Baker silica gel (particle size 0.063–0.200 mm). Solvent mixtures are understood as volume/volume. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AM 400 spectrometer at 298 K in 5 mm NMR tubes. The chemical shifts (δ values) were obtained in $CDCl_3$ solutions unless otherwise noted and referenced to residual $CHCl_3$ (^{1}H NMR: δ = 7.25 ppm, ^{13}C NMR: δ = 77.2 ppm). Data are presented as follows: chemical shift, multiplicity, coupling constant in Hertz (Hz), integration. IR spectra were reported in terms of frequency (cm^{-1}) and intensity of absorption (s = strong, m = medium, w = weak). HRMS were recorded on a Thermo Finnigan MAT 95. GC-MS analyses were carried out with a Quadrupole-MS HP MSD 5971 (EI) and HP 5890A gas chromatograph equipped with a J & W Scientific fused silica GC column (30 m × 0.250 mm, 0.25 micron DB-5MS stationary phase: 5% phenyl and 95% methyl silicone) using

He as carrier gas; T-program standard 60–250 °C (15 °C/min heating rate), injector and transfer line 250 °C.

Preparation of Nitro Alcohols; General Procedure

To a solution of the aldehyde (45.4 mmol) and nitromethane (2.5 mL, 46.2 mmol) in EtOH (10 mL) cooled to 0 °C, was added aq NaOH (10 M, 4.54 mL, 45.4 mmol) through a plastic syringe, dropwise, under vigorous stirring (necessary to prevent the formation of a solid mass). After 10 min, the reaction mixture became white and solidified. AcOH (2.6 mL, 45.4 mmol) and subsequently H_2O (20 mL) was added and the aqueous phase was extracted with Et_2O (2 × 500 mL). The combined organic phase was washed with H_2O (5 × 300 mL) until the pH of the washings was about 6. After drying over $MgSO_4$, filtration and concentration in vacuo, the nitro alcohol was obtained and used without further purification.

1-Nitro-2-cyclohexyl-2-ethanol

Colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88–1.18 (m, 5 H), 1.28–1.37 (m, 1 H), 1.50–1.56 (m, 2 H), 1.63–1.71 (m, 2 H), 2.65 (br, 1 H, OH), 3.92–3.98 (m, 1 H), 4.25–4.37 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.76, 25.88, 26.09, 27.97, 28.81, 41.45, 72.91, 79.38.

MS: *m*/*z* (%) = 112, 94, 83, 68, 55 (100).

1-Nitro-3-methyl-2-butanol

Yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91 (m, 6 H), 1.72 (m, 1 H), 3.16 (br, 1 H, OH), 4.04 (m, 1 H), 4.32–4.45 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.4, 18.3, 31.7, 73.5, 79.4.

MS: *m*/*z* (%) = 91, 90, 86, 73, 69 (100), 62, 55.

Preparation of Aliphatic Nitroalkenes (5q and 5r);[16] Typical Procedure

To a solution of 1-nitro-2-cyclohexyl-2-ethanol (5.06 g, 29.2 mmol) in CH_2Cl_2 (60 mL), cooled to 0 °C, were added successively TFAA (4.34 mL, 30.7 mmol) then, dropwise, Et_3N (8.56 mL, 61.4 mmol). The reaction mixture was allowed to warm to r.t. and stirred for 1 h. CH_2Cl_2 (40 mL) was added and the organic phase was washed successively with H_2O (20 mL), sat. aq NH_4Cl (20 mL) and brine (20 mL) then dried over $MgSO_4$. After filtration and concentration in vacuo, the product was distilled under reduced pressure.

5q

Yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.06–1.78 (m, 10 H), 2.19 (m, 1 H), 3.09 (m, 1 H), 6.86 (d, *J* = 13.6 Hz, 1 H), 7.15 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.4, 25.6, 31.4, 37.5, 138.3, 147.4.

MS: *m*/*z* (%) = 138, 97, 81, 79, 69, 57, 55 (100).

5r

Yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.14 (d, *J* = 6.79 Hz, 6 H), 2.58 (m, 1 H), 6.94 (m, 1 H), 7.22–7.28 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.0, 28.3, 138.1, 148.5.

MS: *m*/*z* (%) = 100, 67, 57 (100), 53, 51.

Biomimetic Reduction of Nitroalkenes; General Procedure

Nitroalkene (1.0 mmol), thiourea **3** (10 mol%) and Hantzsch ester (**2**; 1.1 equiv) were suspended in anhyd CH_2Cl_2 (5 mL) and the resulting mixture was allowed to reflux for 24 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel to afford the pure corresponding nitroalkanes. The yields are given in Table 3. ^{1}H NMR data for known compounds were identical to those in the literature: **6a**,[11e] **6f**,[11e] **6e**,[17] **6g**,[11e] **6i**,[18] **6l**,[19] **6m**,[5b] **6o**,[11e] **6p**,[20] and **6q**.[21] The ^{13}C NMR, IR, and MS data are given below. All new compounds or those that have not been well-described in the literature were fully characterized on the basis of IR, ^{1}H NMR, ^{13}C NMR, and HRMS.

6a

Colorless oil.

IR (film): 3031, 1551, 1455, 1379, 1083, 769, 752 cm^{-1}.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 33.4, 76.3, 127.4, 128.6, 129.2, 135.7.

HRMS: *m*/*z* calcd for $C_8H_9NO_2$: 151.06278; found: 151.06220.

6e

Colorless oil.

IR (film): 3025, 2923, 1905, 1551, 1517, 1433, 1379, 1181, 1115, 811 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.24 (s, 3 H), 3.19 (t, *J* = 7.39 Hz, 2 H), 4.49 (t, *J* = 7.39 Hz, 2 H), 7.03 (dd, J_1 = 8.17 Hz, J_2 = 10.31 Hz, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.1, 33.1, 76.5, 128.5, 129.6, 132.6, 137.1.

MS: *m*/*z* (%) = 165, 118 (100), 103, 91, 77, 65.

6f

Colorless oil.

IR (film): 3007, 2959, 2937, 2838, 1612, 1551, 1514, 1434, 1379, 1250, 1180, 866, 827 cm^{-1}.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 32.7, 55.3, 76.6, 114.4, 127.6, 129.6, 158.9.

HRMS: *m*/*z* calcd for $C_8H_{11}NO_3$: 181.07389; found: 181.07319.

6g

Colorless oil.

IR (film): 2941, 2839, 1603, 1589, 1551, 1465, 1380, 1120, 1031, 756 cm^{-1}.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.2, 55.3, 74.7, 110.4, 120.8, 123.9, 128.9, 130.7, 157.5.

HRMS: *m*/*z* calcd for $C_8H_{11}NO_3$: 181.07389; found: 181.07288.

6h

Colorless solid.

IR (KBr): 3029, 2974, 2957, 2911, 1719, 1565, 1488, 1425, 1336, 1295, 1009, 979, 803, 771 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.19 (t, *J* = 7.20 Hz, 2 H), 4.51 (t, *J* = 7.20 Hz, 2 H), 7.01 (d, *J* = 8.43 Hz, 2 H), 7.37 (d, *J* = 8.43 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 32.75, 75.90, 121.44, 130.31, 132.08, 134.66.

HRMS: *m*/*z* calcd for $C_8H_8BrNO_2$: 228.97384; found: 228.97034.

6i

Colorless oil.

IR (film): 3424, 2984, 1552, 1516, 1445, 1107, 772 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 3.13 (t, *J* = 7.41 Hz, 2 H), 4.47 (t, *J* = 7.41 Hz, 2 H), 6.70 (d, *J* = 8.42 Hz, 2 H), 6.94 (d, *J* = 8.42 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 32.7, 76.6, 116, 130, 155.6.

MS: *m*/*z* (%) = 167, 120 (100), 103, 91, 77, 65, 51.

6j
Colorless oil.

IR (film): 3505, 2941, 1613, 1551, 1517, 1453, 1433, 1033 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.17 (t, *J* = 7.31 Hz, 2 H), 3.80 (s, 3 H), 4.50 (t, *J* = 7.31 Hz, 2 H), 5.52 (br, 1 H, OH), 6.62 (m, 2 H), 6.78 (d, *J* = 7.96 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 33.3, 55.9, 76.7, 111.1, 114.8, 121.3, 127.4, 145.0, 146.7.

HRMS: *m*/*z* calcd for $C_9H_{11}NO_4$: 197.06826; found: 197.06995.

6k
Colorless oil.

IR (film): 3084, 2920, 1437, 1380, 1088, 1025, 779 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.59–3.63 (m, 2 H), 4.47–4.51 (m, 2 H), 7.08–7.13 (t, *J* = 8.04 Hz, 2 H), 7.25–7.27 (d, *J* = 8.04 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.0, 72.0, 128.6, 129.4, 131.4, 135.8.

HRMS: *m*/*z* calcd for $C_8H_7Cl_2NO_2$: 218.98483; found: 218.98395.

6l
Colorless oil.

IR (film): 2977, 2929, 1557, 1279, 865, 772, 566 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.17 (t, *J* = 7.19 Hz, 2 H), 4.52 (t, *J* = 7.19 Hz, 2 H), 6.96 (m, 1 H), 7.22 (m, 1 H), 7.28 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 32.2, 75.5, 123.0, 128.0, 130.5, 130.8, 135.9.

HRMS: *m*/*z* calcd for $C_8H_7Cl_2NO_2$: 218.98483; found: 218.98395.

6m
Yellow solid.

IR (KBr): 3345, 3038, 2936, 1664, 1590, 1516, 1380, 1349, 1010, 808 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.13 (t, *J* = 7.32 Hz, 2 H), 3.77 (s, 3 H), 4.43 (t, *J* = 7.32 Hz, 2 H), 5.04 (s, 2 H), 6.66 (m, 2 H), 6.75–6.77 (d, *J* = 8.00 Hz, 1 H), 7.17–7.35 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 32.9, 56.0, 71.2, 76.4, 112.1, 114.6, 121.4, 127.4, 127.9, 128.1, 128.5, 136.7, 148.2, 149.0.

HRMS: *m*/*z* calcd for $C_{16}H_{17}NO_4$: 287.11521; found: 287.11575.

6n
Colorless oil.

IR (film): 2941, 2838, 1588, 1551, 1484, 1278, 1083, 1007, 750 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.22 (t, *J* = 7.45 Hz, 2 H), 3.77 (s, 3 H), 3.79 (s, 3 H), 4.52 (t, *J* = 7.45 Hz, 2 H), 6.68 (m, 1 H), 6.78 (m, 1 H), 6.91 (t, *J* = 7.98 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.7, 55.7, 60.7, 75.2, 110.0, 119.3, 124.3, 129.2, 147.3, 152.7.

HRMS: *m*/*z* calcd for $C_{10}H_{13}NO_4$: 211.08391; found: 211.08459.

6o
Yellow oil.

IR (film): 2921, 1724, 1555, 1507, 1378, 1281, 1145, 741 cm^{-1}.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.0, 73.4, 107.4, 110.1, 143.8, 149.4.

MS: *m*/*z* (%) = 141, 94 (100), 83, 65, 55.

6p
Colorless oil; ratio **6p**/**5p** = 4:5.

IR (film): 2802, 2669, 1713, 1468, 1431, 1268, 1243, 1223, 1194, 1160 cm^{-1}.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.8, 24.6, 30.8, 84.6.

MS: *m*/*z* (%) = 84, 83, 81, 77, 67, 65, 55 (100).

6q
Colorless oil.

IR (film): 2926, 2854, 1554, 1449, 1385 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.84–0.93 (m, 2 H), 1.06–1.18 (m, 4 H), 1.57–1.66 (m, 5 H), 1.84 (q, *J* = 7.11 Hz, 2 H), 4.34 (t, *J* = 7.30 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.9, 26.2, 32.7, 34.6, 34.9, 73.8.

MS: *m*/*z* (%) = 138, 122, 111, 109, 99, 94, 81, 79, 67, 55 (100).

6r
Colorless oil.

IR (film): 2964, 2875, 1785, 1555, 1470, 1382, 1279, 1135 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.89 (d, *J* = 6.63 Hz, 6 H), 1.58–1.66 (m, 1 H), 1.85 (q, *J* = 7.27 Hz, 2 H), 4.34 (t, *J* = 7.39 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.0, 25.6, 36.0, 74.3.

MS: *m*/*z* (%) = 71, 69, 67, 62, 59, 55 (100).

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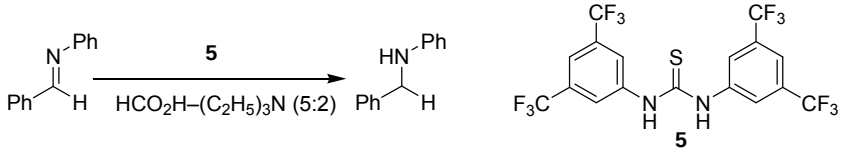
3.3 Miscellaneous

3.3.1 Hydrogen sources

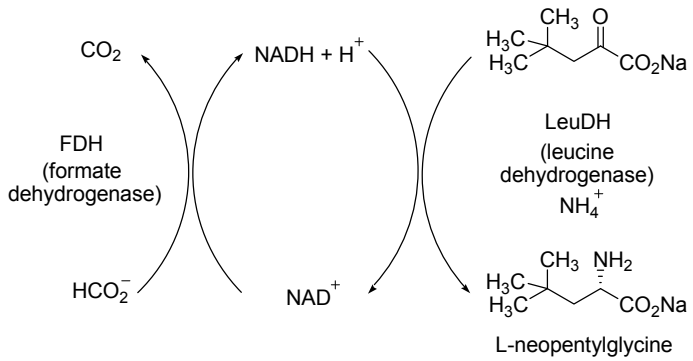
Transfer hydrogenation using stable organic hydrogen donors is an attractive alternative in view of operational simplicity, as well as possible high overall cost performance. Although such reductions has emerged as a convenient method for asymmetric transition metal-catalyzed saturation of C=C, C=O, as well as C=N linkages, the hydrogen sources for organocatalytic reduction are quite limited. The problematic removal of oxidized pyridine forms of Hantzsch esters prompt us to investigate other alternative hydrogen sources for thiourea catalyzed reduction. In this investigation, we selected as the model reaction the reduction of aldimine in the presence of thiourea catalyst **5**. First hydrogen donor was focused on a 5:2 formic acid-triethylamine azeotropic mixture (TEAF),[253] which has proven to be a useful source of hydrogen.[254-256] Owing to its solubility in organic solvent and decomposition to hydrogen and carbon dioxide during the reaction, TEAF, in contrast to other hydrogen donors, was applied to our test reaction (Scheme 1). Whatever we tried different reaction parameters such as solvents, temperatures, as well as catalyst loadings, unfortunately no transformation was observed.



Scheme 1. Investigation of TEAF as hydrogen donor for thiourea catalyzed reduction of imine.

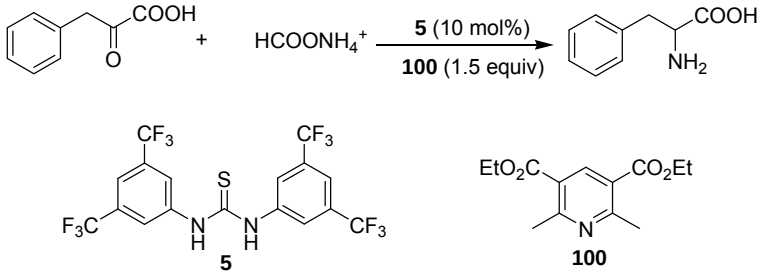
3.3.2 Biomimetic reductive amination

The reductive amination of α-keto acid or the sodium salt in the presence of two isolated enzymes, namely a leucine dehydrogenase and a formate dehydrogenase, is regarded to be one the most efficient routes for preparation of enantiomerically pure amino acid.[257, 258] The reaction concept is shown in Scheme 2.



Scheme 2. General reductive amination concept.

The reductive amination step under consumption of the cofactor NADH is catalyzed by a leucine dehydrogenase, forming the desired L-neopentylglycine as well as oxidized cofactor form, NAD^+. This oxidized cofactor form, NAD^+, is subsequently reduced under formation of NADH by means of a formate dehydrogenase-catalyzed oxidation of formate. This enzymatic reaction has already proven its technical feasibility on large scale. Since its operation is not familiar to most of synthetic chemists and the need for isolated, costly enzymes as well as the requirement for significant amounts of the expensive cofactor NAD^+, we wonder if it is possible to mimic this process in synthetic scale by using thiourea as functional enzymes and oxidized pyridine form of Hantzsch ester as NAD^+ (Scheme 3).



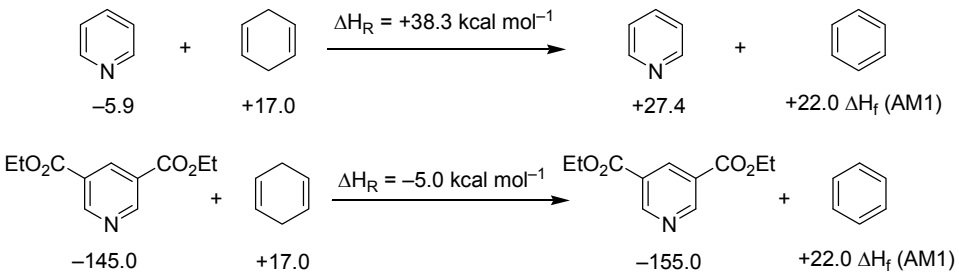
Scheme 3. Biomimetic reductive amination.

Experimental details:

To a mixture of phenylpyruvic acid (32.8 mg, 0.2 mmol), **100** (75.4 mg, 0.3 mmol), and **5** (10.0 mg, 10 mmol%) in 2 mL CH_2Cl_2 was added ammonium formate (37.8 mg, 0.6 mmol). The resulting mixture was stirred at room temperature and was monitored by TLC. No reaction was determined. Although we further investigated the reaction under different conditions such as temperature, solvents and catalyst loadings, no transformation was observed. The proposal was still under investigation.

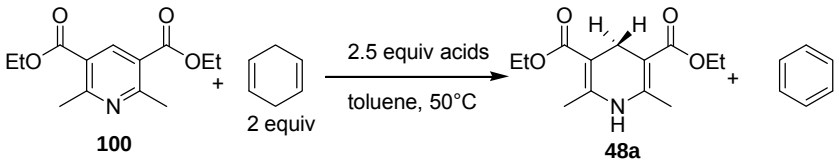
3.3.3 Regeneration of Hantzsch ester

The problematic removal of oxidized form of Hantzsch ester and poor atom economy prompt us to investigate the *in situ* regeneration of Hantzsch ester using an inexpensive and easily handling co-reductant. Theoretical calculation by Prof. Peter R. Schreiner has revealed that the oxidized form of Hantzsch ester can be potentially reduced with 1,4-cyclohexadiene (Scheme 4).



Scheme 4. Chemical calculation of the energy.

Experimental Section

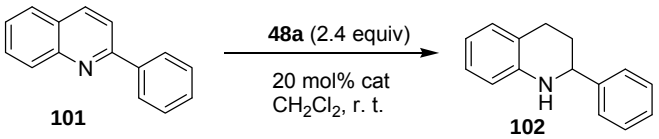


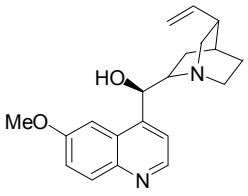
entry	acid	yield
1	CH_3COOH	-
2	HCl	-
3	CF_3COOH	-
4	H_3PO4	-
5	P-TSA	-
6	CSA	-
7	$HClO_4$	-
8	HBF_4	-

Under argon atmosphere, acid was added to a mixture of **100** (25.1 mg, 0.1 mmol) and 1,4-cyclohexadiene (16 mg, 0.2 mmol) in 0.5 mL toluene. The resulting mixture was stirred at 50 °C and monitored by TLC and GC-MS, no reaction was observed under activation of different acids.

3.3.4 Asymmetric ammonium salt catalyzed transfer hydrogenation of quinoline

Asymmetric counteranion-directed catalysis (ACDC), described by List and co-workers, has emerged as an effective strategy for asymmetric transfer hydrogenation of α,β-unsaturated aldehydes and ketones.[159, 259] Despite high conversion and enantioselectivity, however, the need for costly preparation of BINOL-derived phosphoric acid is a disadvantage. We turned our attention to prepare chiral ammonium salts, formed from commercially abundant quinine and acids, as catalysts for transfer hydrogenation of 2-phenylquinoline. Some of the formed ammonium salts do catalyze the transfer hydrogenation of 2-phenylquinoline, albeit no enantioselectivities (entries 2, 3, and 7).



Entry	Quinine	Acids	Ratio[a]	Yield (%)	*ee* (%)[b]
1		H_3PO4	1:1	0	-
2		*p*-toluenesulfonic acid	1:1	100	1.2
3		L-(+)-tartaric acid	1:1	80	0
4		L-(+)-tartaric acid	2:1	trace	-
5		L-(+)-lactic acid	1:1	trace	-
6		TFA	1:1	trace	-
7		(1*S*)-(+)-CSA	1:1	100	0

[a] The ratio represents quinine to the corresponding acids, general procedure for the preparation of organic salts is: acids was added to the solution of quinine in CH_2Cl_2, after stirring overnight, the solvent was evaporated under reduced pressure to provide the product, which was used as catalyst in the hydrogenation of quinoline. [b] Determined by chiral HPLC.

Experimental section

Reactions were performed with 2-phenylquinoline (20.5 mg, 0.1 mmol, 1.0 equiv.), Hantzsch ester (60.79 mg, 0.24 mmol) in CH_2Cl_2 (2 mL) using 20 mol% of formed organic salts (0.02 mmol, 0.2 equiv.) at room temperature. The reaction was monitored with GC-MS, GC and TLC.

Trichlorosilane ($HSiCl_3$) – A Cheap and Convenient Reducing Agent

Compiled by Zhiguo Zhang

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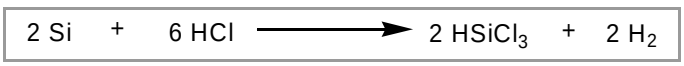
Dedicated to my research advisor Prof. Dr. Peter R. Schreiner

Introduction

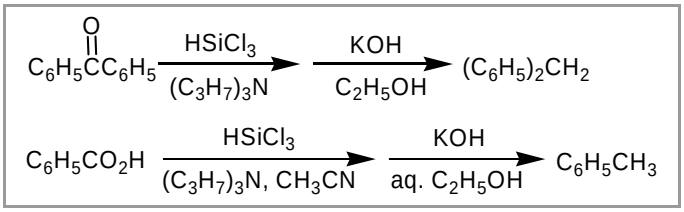
Trichlorosilane ($HSiCl_3$) is a cheap, stable, and commercially available reagent, which has been widely used as a stoichiometric reductant. In general, activators are necessary for $HSiCl_3$ to reduce efficiently C=C, C=O, C=N, and P=O functionalities. The currently most successful methodologies are based on transition metal-centered catalyzed hydrosilylation, however, recent advances in the field of organocatalysis have also provided a series of small organic molecules as efficient alternative catalysts for asymmetric reductions of ketones or imines with $HSiCl_3$. In this paper, reductions using $HSiCl_3$ are summarized.

A number of methods are available for the preparation of trichlorosilane in the laboratory, for example, by the reaction of dry HCl gas with silicon[1] or with metallic silicides.[2] The title compound is also an abundant by-product of the industrial Rochow process.[3]

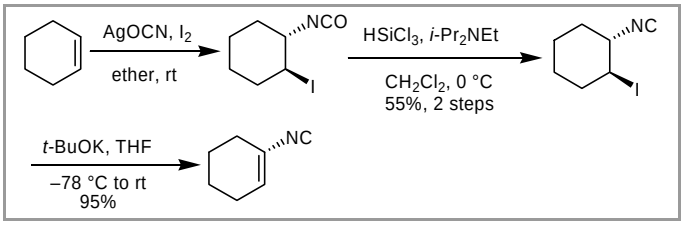


Abstracts

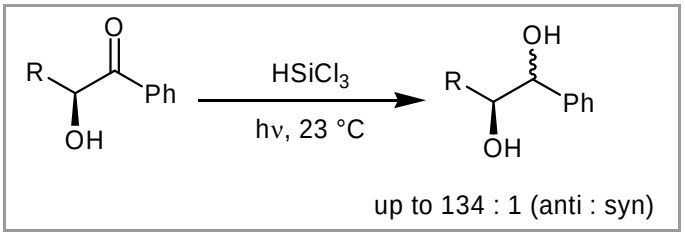
(A) Trichlorosilane has been often used together with tertiary amines to reduce carbonyl groups of aromatic aldehydes, ketones, acids, amides, acid chlorides, and anhydrides to give the corresponding benzylic trichlorosilane. This transformation was termed a "reductive silylation" through replacement of a carbonyl oxygen with H and $SiCl_3$.[4] This method provides a new way to form silicon-carbon bonds, and the benzylic trichlorosilane products can be can be further transformed to toluenes by base treatment.



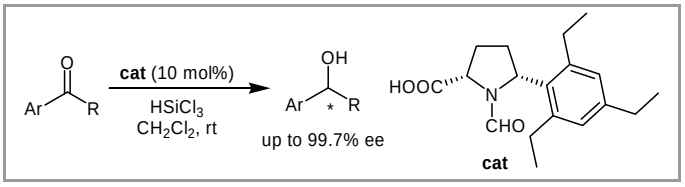
(B) Reduction of isocyanates with $HSiCl_3$ gives the corresponding isocyanides in high yield under mild conditions.[5] This provides a relatively simple method for the synthesis of vinyl isocyanides from alkenes.[6]



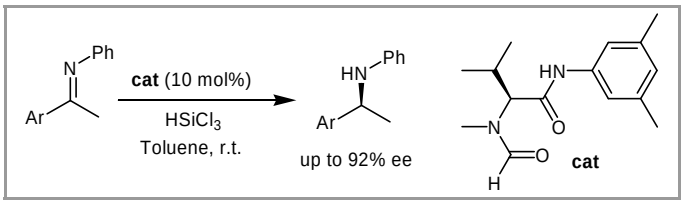
(C) Highly diastereoselective reduction of α-hydroxyl ketones can be achieved using $HSiCl_3$ as the reductant under neutral free-radical conditions.[7] This reduction provides a diastereoselective, mild, one-electron alternative to the established two-electron methods that employ hydride reagents.

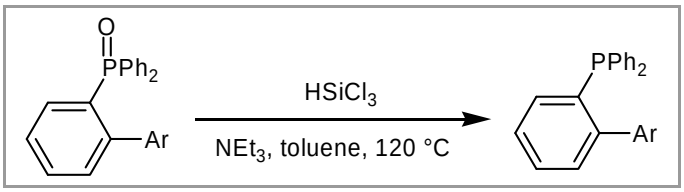


(D) The catalytic enantioselective reduction of aryl ketones by $HSiCl_3$ gives the corresponding alcohols with excellent enantioselectivity in the presence of catalytic amounts of *N*-formyl-α′-(2,4,6-triethylphenyl)-L-proline as the activator.[8]

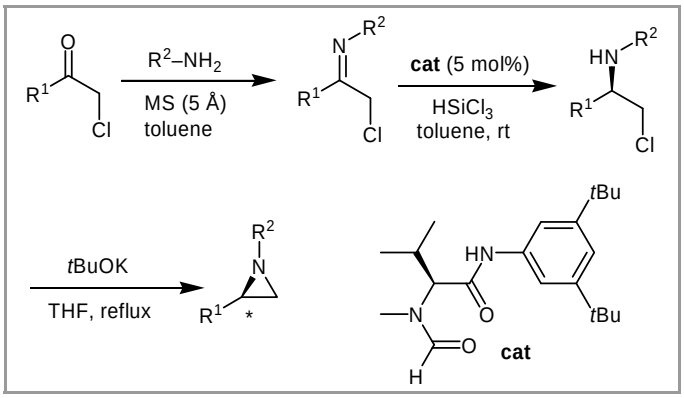


(E) Asymmetric reduction of ketimines with trichlorosilane can be catalyzed by a new *N*-methyl-L-valine derived Lewis basic organocatalyst, affording the respective secondary amines with high enantioselectivity.[9]

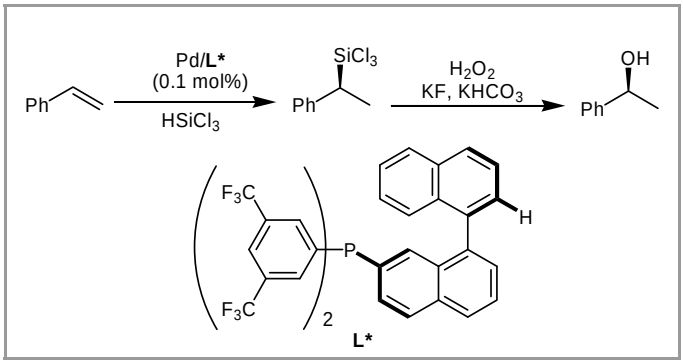




(F) The *N*-methylvaline derived Lewis basic formamide catalyzed reductive amination of α-chloroketones is a key step in the enantioslective synthesis of 1,2-diarylaziridines that had not been prepared previously as pure enantiomers.[10] This provides an efficient and environmentally friendly methodology for the preparation of enantiopure aziridines.



(G) The preparation of optically active alcohols from prochiral styrenes can be realized by the palladium-MOP complex catalyzed asymmetric hydrosilylation of styrenes with trichlorosilane.[11]



(H) Trichlorosilane is an often-used reducing agent for converting phosphine oxides to phosphines, which play an extremely important role as ligands in homogeneous catalysis.[10]

References

(1) (a) Friedel, C.; Ladenburg, A. *Ann. Chem.* **1867,** *143*, 118. (b) H., B.; Wöhler, F. *Ann. Chem.* **1857,** *104*, 94.

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(3) Rochow, E. G. *J. Am. Chem. Soc.* **1945,** *67*, 963.

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(10) Malkov, A. V.; Stoncius, S.; Kocovsky, P. *Angew. Chem. Int. Ed.* **2007,** *46*, 3722.

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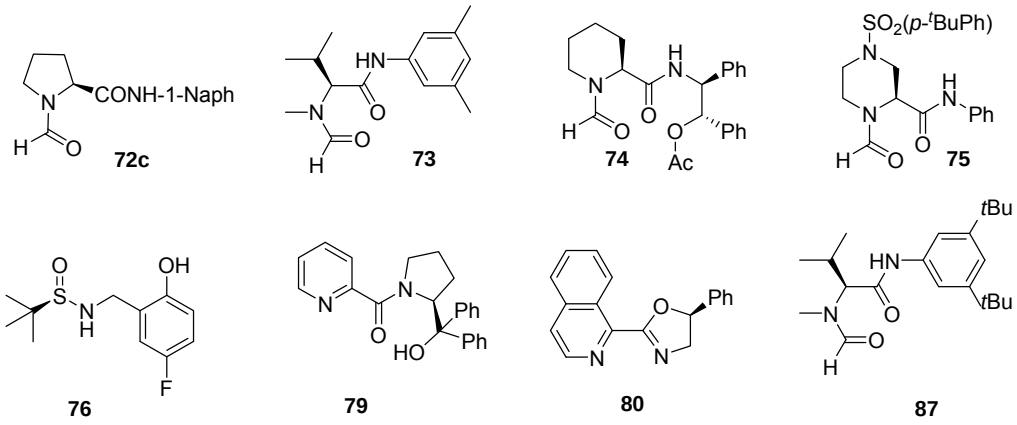
3.5 Asymmetric Organocatalyzed Reduction of Ketimines with $HSiCl_3$

Introduction

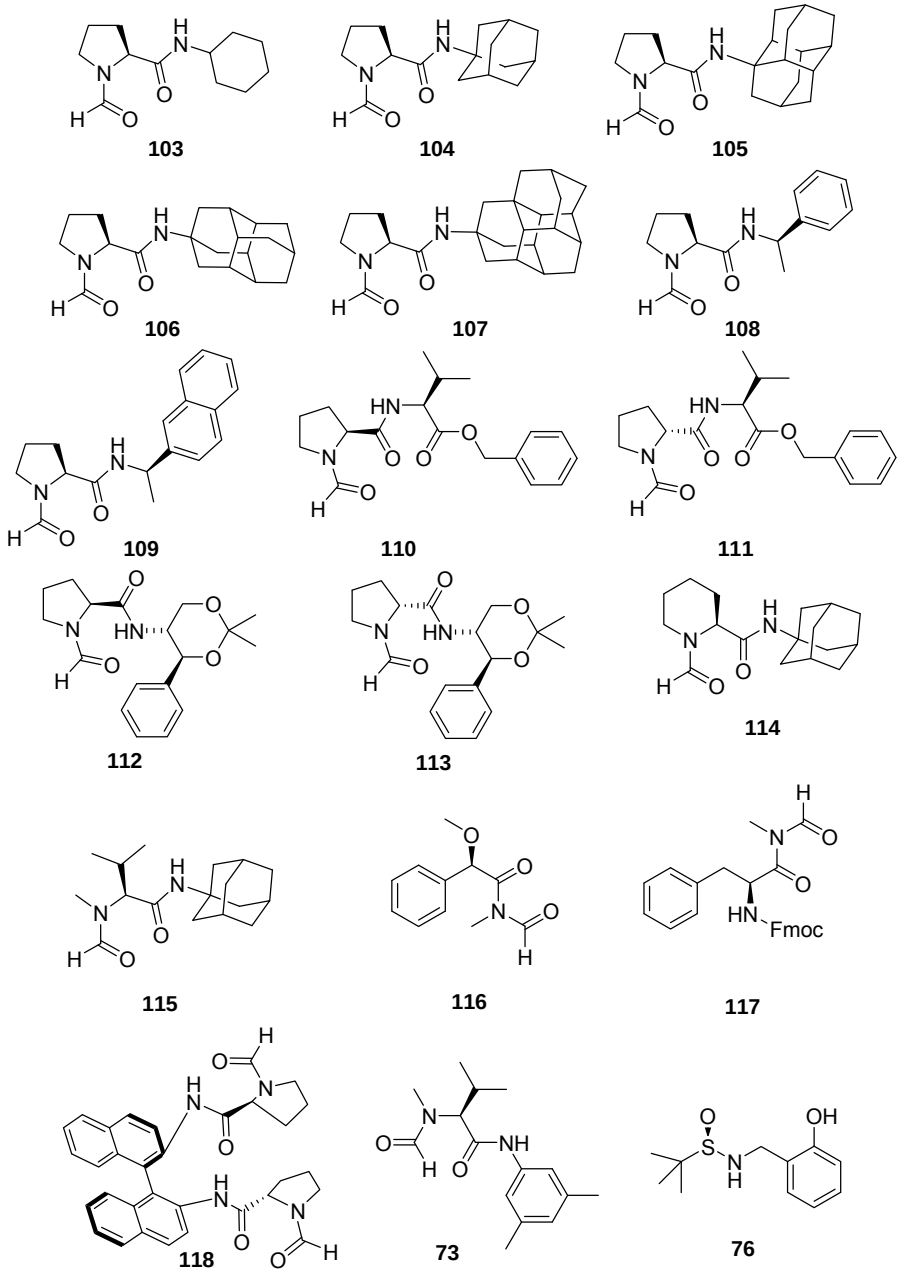
Asymmetric hydrogenation, hydroboration, and hydrosilylation are the most frequently used catalytic methods for reduction of prochiral ketones and imines.[141] Although asymmetric hydrogenation remains favored by industry in general, it is not free of problems, namely, those associated with metal leaching, high pressure, and the cost of the catalyst and its regeneration. Stoichiometric borane reduction, catalyzed by chiral oxazoborolidine, avoids most of these problems and offers high levels of enantioselection,[141] but its cost is prohibitive for large-scale industrial application. The recently developed reduction of C=C and C=N, which uses the Hantzsch ester as a stoichiometric reducing agent and chiral imidazolidinone or chiral Brønsted acid as organocatalysts is also limited by removal of the pyridine form of Hantzsch ester and the cost implications.[151, 152, 156-167, 169, 171, 172] It is still worthwhile to exploit new methods, which can be carried out in industrial scale under mild conditions. One of such alternative developments may be asymmetric reductions with trichlorosilane ($HSiCl_3$), a cheap and commercial available reagents, albeit some activators are necessary for promoting $HSiCl_3$ to efficiently reduce unsaturated functionalities. The currently most successful methods are based on the use of transition metal-centered hydrosilylation,[141] however, recent advances in organocatalysis appeal to be very attractive and competitive with traditional methods. The first asymmetric organocatalytic reduction of ketimines using trichlorosilane was reported by Matsumura and co-workers in 2001.[179] During the past few years, various chiral activators have been studied and reported by several laboratories (Scheme 1).[185, 188-191, 194, 195] Representative organocatalysts for this transformation are listed in Scheme 1. This part describes our studies on this subject.



Scheme 1. Some examples of chiral organic activators.

Initial design of catalysts

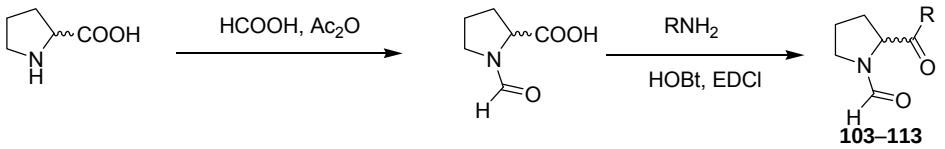
Our search for chiral organic activators for trichlorosilane was initially based on the following general strategies: (1) *N*-formyl proline is used as basic chiral modular, with the carboxyl converted into amide group by incorporation of aliphatic amino compounds in various molecular sizes; (2) *N*-formyl proline derived diastereomeric activators involving more than one chiral centers; (3) extension of amino acids from proline to valine or pipecolinic acid scaffold; (4) introduction of *N*-formyl proline to an axially C_1-symmetric scaffold; (5) it was also intended to prepare 1,3-dicarbonyl *N*-formamide as potentially "six ring" activators; (6) two reported catalysts were prepared for comparison. On the basis of these considerations, a series of compounds (**103–120**) were designed and prepared as reservoir for potential trichlorosilane activators (Scheme 2).



Scheme 2. Synthesized compounds.

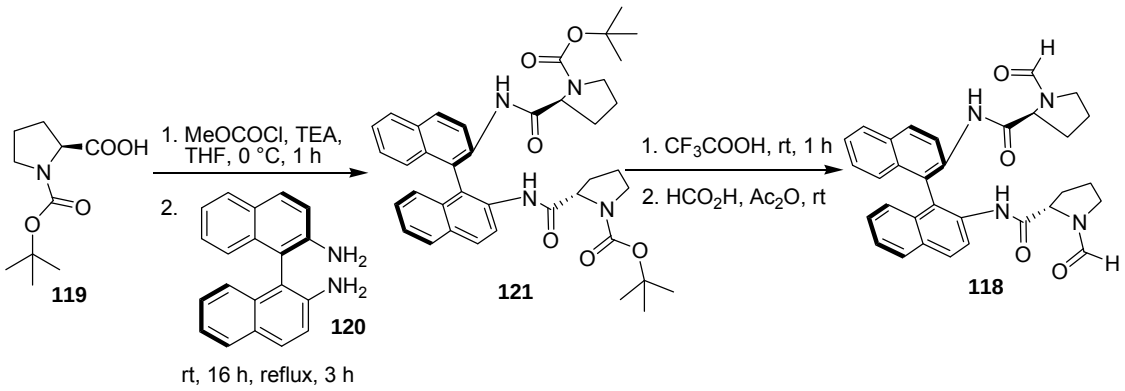
Synthesis

The synthesis of proline-derived formamides started with the formylation of proline in the presence of acetyl anhydride and formic acid, which afforded *N*-formyl proline in 90% yield. The carbonyl of the latter derivative was then converted into a series of secondary amides by reaction with respective primary amines, employing 1-hydoxy-benzhotriazole hydrate (HOBt) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) as coupling reagents (Scheme 3). This method is applicable to all primary aliphatic amines, namely compounds **103–113**. The same strategy was also employed for the synthesis of L-pipecolinic acid derived *N*-formamide **114** and proved to be equally efficient as for proline.



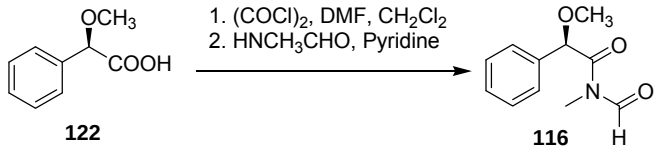
Scheme 3. Catalyst synthesis.

The synthesis of **118** commenced with conversion of Boc-protected L-proline **119** to active anhydride, which generated *in situ* from **119** and methyl chloroformate and then reacted with axially (*R*)-(+)-1,1′-Bi(2-naphthyl)amine (BINAM, **120**) to give product **121** (64%). Boc-deprotection with TFA followed by formylation with a mixed anhydride, generated *in situ* from formic acid and acetic anhydride, to produce the desired axially C_1-symmetric activator **118** (Scheme 4).

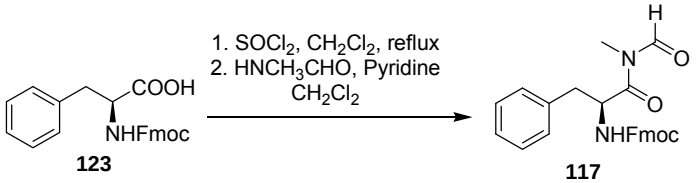


Scheme 4. Catalyst preparation.

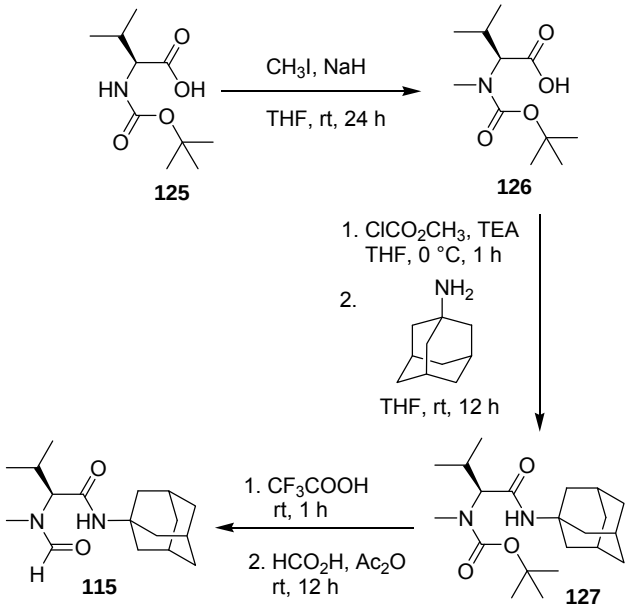
The synthesis of **116**, started with the conversion of (*R*)-2-methoxyphenyl acetic acid **122** to acid chloride with oxalyl chloride in the presence of catalytic amount DMF, followed by reaction with *N*-methylformamide (Scheme 5). The phenyl alanine derived formamide **117** prepared through the same manner failed to produce the corresponding product, due to serious side reactions. An alternative method for conversion of Fmoc-protective L-phenyl alanine **123** to acid chloride **124** was carried out with $SOCl_2$, followed by reaction with *N*-methylformamide, giving the desired product, albeit in low yield (Scheme 6).



Scheme 5. Catalyst synthesis.



Scheme 6. Catalyst synthesis.



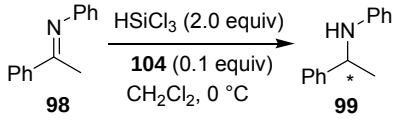
The synthesis of **115** commenced with *N*-methylation of the BOC-protected L-valine **125** with MeI in the presence of NaH, which afforded the BOC-protected *N*-methyl valine **126**. The latter was then converted to **127** through the reaction of 1-aminoadmantane with the mixed anhydride, generated in situ from **126** and methyl chloroformate. BOC-deprotection with TFA was followed by formylation with formic acid and acetic anhydride to produce **115** (Scheme 7). The known compounds **73** and **76** were prepared according to the literature reported.[185, 260]

Scheme 7. Catalyst synthesis.

Asymmetric reduction of ketimines with $HSiCl_3$

A typical reaction is performed firstly by the reduction of ketimine **98** (derived from acetophenone and aniline) with $HSiCl_3$ in CH_2Cl_2 at 0 °C in the presence of L-proline-derived catalyst **104** (10 mol%), affording the corresponding amine in high yield with 67% *ee* (Table 1, entry 1). We next examined the influence of other reaction parameters on the reaction outcome. Interestingly, when the reaction was run at –18 °C and room temperature, both the *ee* values of product **99** decreased to 45% *ee* and 58% respectively (entry 2 and 3), and the yields was almost unchanged. Toluene was found to afford the same level of enantioselectivity as dichloromethane at –18 °C (Table 1, entry 4). The lower enantioselectivities obtained in Et_2O and THF clearly indicate that the reaction requires nonpolar solvents (Table 2, entries 5 and 6). The reaction in $CHCl_3$ also shows inferiority (Table 3, entry 7). No enantioselectivity was observed when the reaction was run in DMF (Table 4, entry 8).

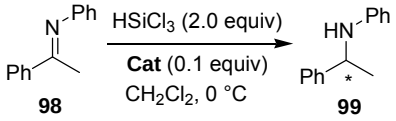
Table 1. Solvent and Temperature Survey in the Reduction of Imin-1 with Trichlorosilane in the presence of **104** (10 mol%).



entry	temperature	solvent	yield (%)	*ee* (%)
1	0 °C	CH_2Cl_2	82	67
2	-18 °C	CH_2Cl_2	80	45
3	rt	CH_2Cl_2	80	58
4	-18 °C	toluene	78	45
5	-18 °C	Et_2O	75	33
6	-18 °C	THF	79	31
7	0 °C	$CHCl_3$	81	60
8	0 °C	DMF	85	0

We then investigated the role of the amide functionality in the catalyst by running the reaction in CH_2Cl_2 at 0 °C, using the designed compounds as catalysts at 10 mol% loading (Table 2). In general, reduction of imin-1 with $HSiCl_3$ using different synthesized compounds as catalysts except **116** and **117**, gives the corresponding product in good to high yields. Variation of the molecular size of the amide functionality in catalysts had a dramatic effect on the stereochemical outcome. The enantioselectivites increased when the substituents changed from cyclohexane to diamantane (Table 2, entries 1–3), however, catalyst **107** with 1-amino triamantane was found to be slightly less efficient, affording the product in lower yield with 65% *ee* (Table 2, entry 5), indicating the importance of steric interaction between the amide functionality and substrate for the reaction outcome. Catalysts involving one more chiral centers proved to be generally inefficient in achieving higher enantioselectivities. The conformation of α-position in proline is crucial for the absolute configuration of the corresponding product (Table 2, entries 8 and 9, 10 and 11). "Six ring" activators 1,3-dicarbonyl formamides **116** and **117** proved to be sluggish catalysts, which suggest that the proposed simultaneous coordination of two carbonyls with one silyl group may be not correct (Table 2, entries 17 and 18). Interestingly, catalyst **114** derived from L-pipecolinic acid and 1-amino admantane gives the product in racemic form (Table 2, entry 12). According to the literature reported, *N*-formamide catalysts derived from L-pipecolinic acid exhibited significantly higher reactivity and selectivity than its congener derived from L-proline.[190] This unexpected phenomenon prompted me to investigate the optical purity of L-pipecolinic acid, which is exactly the same optical activity as reported. The search for more proofs is still in progress, which may help in gaining insight into the mechanism. In addition, the reaction for the reduction of imines using reported catalysts **73** and **76** can be repeated (Table 2, entries 14 and 15).

Table 2. Catalyst Screening of Reduction of **98** with Trichlorosilane.[a]

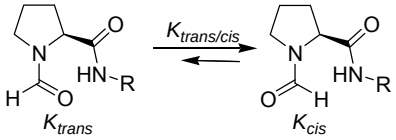


entry	catalysts	solvent	yield (%)[b]	*ee* (%)[c]	config[d]
1	**103**	CH_2Cl_2	79	42	R
2	**104**	CH_2Cl_2	85	67	R
3	**105**	CH_2Cl_2	81	68	R
4	**106**	CH_2Cl_2	78	60	R
5	**107**	CH_2Cl_2	52	65	R
6	**108**	CH_2Cl_2	87	65	R
7	**109**	CH_2Cl_2	83	61	R
8	**110**	CH_2Cl_2	78	28	R
9	**111**	CH_2Cl_2	78	45	S
10	**112**	CH_2Cl_2	70	30	R
11	**113**	CH_2Cl_2	76	15	S
12	**114**	CH_2Cl_2	80	0	-
13	**115**	CH_2Cl_2	89	54	R
14	**76**	CH_2Cl_2	82	86	S
15	**73**	CH_2Cl_2	91	95	S
16	**118**	CH_2Cl_2	82	30	S
17	**116**	CH_2Cl_2	43	0	-
18	**117**	CH_2Cl_2	39	0	-

[a] The reaction was carried out on a 0.2 mmol scale with 10 mol% loading of catalysts and 2 equivalent of $HSiCl_3$ in CH_2Cl_2 at 0 °C. [b] Yield of isolated product. [c] Determined by chiral GC analysis and HPLC. [d] Absolute configuration was referred to literature.[185] reported.

Structure features

^{1}H-NMR spectroscopy shows that all the *N*-formamide catalysts are mixtures of *trans*- and *cis*-isomers (Scheme 8). We found that the value of $K_{trans/cis}$, as determined by ^{1}H-NMR spectroscopy, is actually >1 in $CDCl_3$. Two main factors may be considered to be determinant of the preference of the *N*-formyl group in *trans*-conformation.[261] Hyperconjugative delocalization of a nonbonding pair of electrons (*n*) from the formyl oxygen to the C–O bond is the most well-known factor in stabilizing molecular conformation. The intramolecular hydrogen bonding between amide and *N*-formyl oxygen can not be ruled out. Analysis of the ROESY NMR gives further information about the conformations (Fig. 1). Correlation between formyl-**H** and C5-C**H$_2$** represents the existence of *trans* isomer, while the correlation between formyl-**H** and C2-C**H** means the *cis* isomer.



Scheme 8. Catalyst conformations.

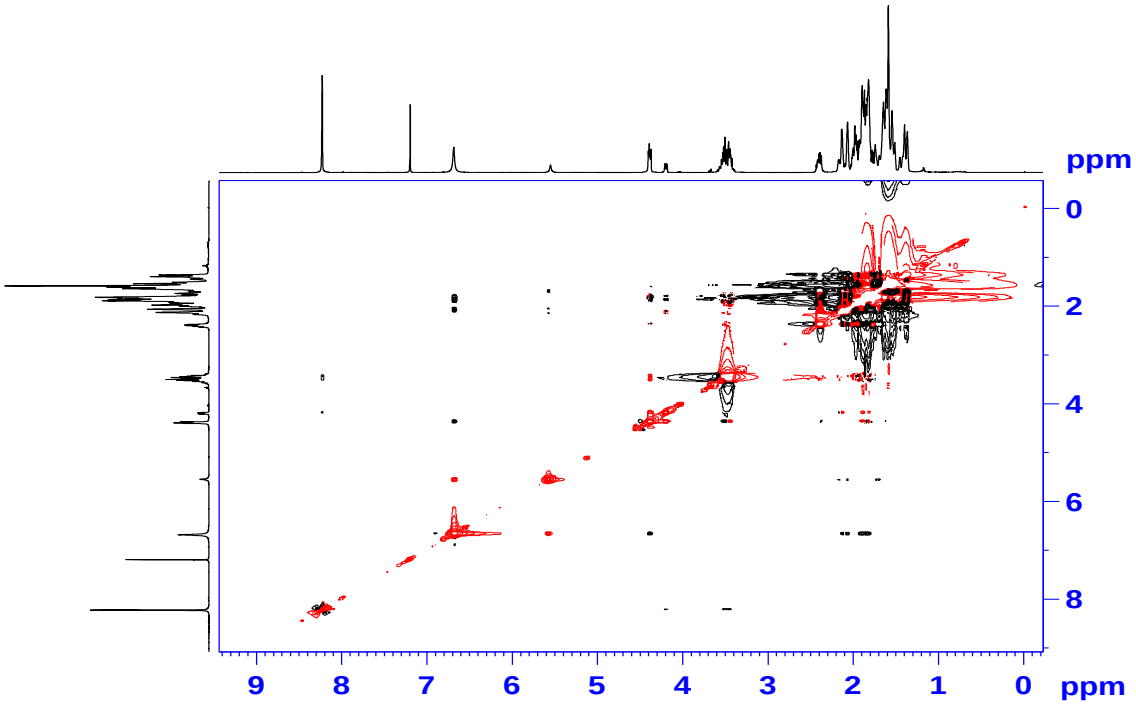


Fig. 1. ROESY spectrum of compound **105**.

Mechanistic consideration

The reduction of imin-1 with $HSiCl_3$ in the presence of catalysts **104**, **114**, and **115** afforded **99** in high yield with 67% *ee*, 0, and 53% *ee* respectively, and the product catalyzed by **104** had opposite configuration to that catalyzed by **115**, even the configuration of the catalyst was identical. Interestingly, no *ee* was observed with catalyst **116**. These results suggest that the enantiodifferentiation steps for proline-, pipecolinic acid-, and valine-derived catalyst are different.

Since no mechanism details on this reaction were known at this stage, which provides difficulties in rational design and development of efficient catalysts. Malkov and co-workers proposed a possible mechanism based on their empirical experience.[188] However, the inferiorities of catalysts **116** and **117** revealed for the first time that the assumption of coordination of two amide groups with $HSiCl_3$ as donors may not be correct. An intensive study on the mechanism was performed by means of experimental and computer methods (note: the part of chemical calculation was being performed by Dr. Parham Rooshenas). To probe the mechanism for this reaction, a "six ring" transition state was firstly proposed, in which DMF was regarded as proton transporter and $HSiCl_3$ as proton donor (Figure 1). The reduction of **98** was performed as before in the presence d_1-DMF as catalyst. No deuterated product **99** was determined either in ^{1}H-NMR or GC-MS. It indicates that this type of "six ring" transition state may be ruled out.

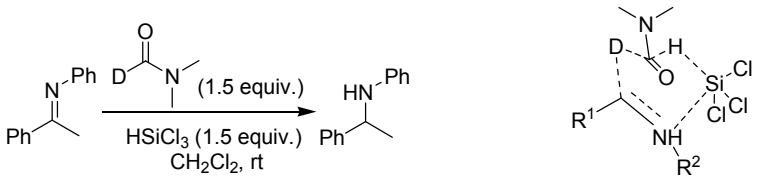


Figure 2. Proposed "six ring" proton transporter.

The chemical calculation by Dr. Parham Rooshenas so far proposed a "seven ring" transition state using *N*-methyl formamide as stoichiometric catalyst (Figure 3). The imine was stabilized and reduced by a hypercovalent silicate formed between catalyst and $HSiCl_3$. More proofs are still needed to confirm this hypothesis, such as kinetic and NMR studies.

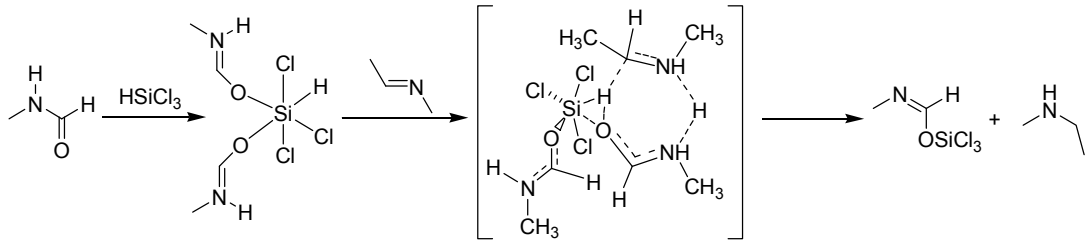


Figure 3. Proposed transition state by chemical computation.

In addition, in the ^{1}H-NMR spectrum of a 1:2 mixture of catalyst **104** and $HSiCl_3$, shift of ~0.1 ppm to downfield was only observed for the corresponding signal of the formamide proton in *cis* conformation, no formamide proton shift was found for *trans* conformation, suggesting that *cis* conformation of proline-derived catalysts may play a crucial role in promoting the reduction with $HSiCl_3$ (Fig. 4). All these features observed do show that the proposed transition state in literature should be improved. Further efforts will focus on elaboration of the mechanism and development of more efficient catalysts.

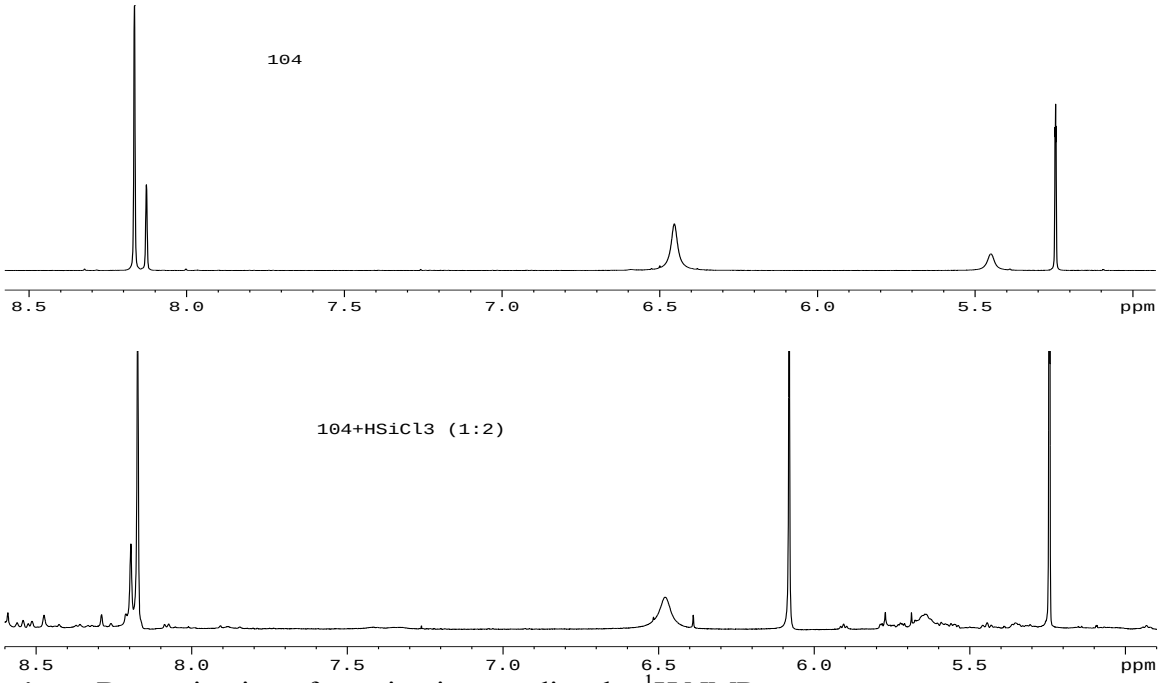


Fig. 4. Determination of reaction intermediate by ^{1}H NMR.

Summary and outlook

We have designed a series of novel chiral organocatalysts derived from proline, valine, and pipecolinic acid for asymmetric reduction of ketimine with $HSiCl_3$ to afford the corresponding secondary amine. The enantioselectivity up to 68% *ee* was observed in the presence of catalyst **105** formed by *N*-formyl-L-proline and 1-aminodiamantane. Variety in catalyst structures clearly demonstrated determinant role of amino acids scaffold for the action mode in enantiodifferentional step. The preliminary mechanism studies showed quite different feature as in the literature. Further work will be directed to elaborate the mechanism aspects and develop more efficient catalysts.

Chapter 4 Development of Thiourea-Catalyzed Cyanosilylation

Introduction

Cyanohydrins are of synthetic interest as they may be elaborated into a number of key functional groups, including α-hydroxyacids, β-hydroxyalcohol, and other valuable building blocks.[200, 201] Hydrogen cyanide (HCN) is the most commonly industrially used reagent for cyano transfer to carbonyl compounds.[202] However, due to its toxicity and difficulty in handling, new methods have been developed to substitute HCN with other potentially less harmful and yet easily manageable reagents.

Trimethylsilyl cyanide (TMSCN) is widely used as a cyanide source with various catalysts. The use of TMSCN allows the desired cyanohydrin to be prepared directly as the corresponding trimethylsilyl ether. The stability of the TMS adduct, conferred by an energetically favourable Si-O bond, prevents the reverse cyanation reaction from occurring and hence removes a potential pathway for racemization. In 1973, Evans and Sundermeyer and their co-workers are among the first to report the addition of TMSCN to aldehydes, ketones, and acid chlorides catalyzed by thermal and Lewis acid respectively.[203, 204] Since then, a multitude of different catalysts has been reported in the literature for both the racemic and asymmetric addition of the cyanide to carbonyls.[200, 205, 206]

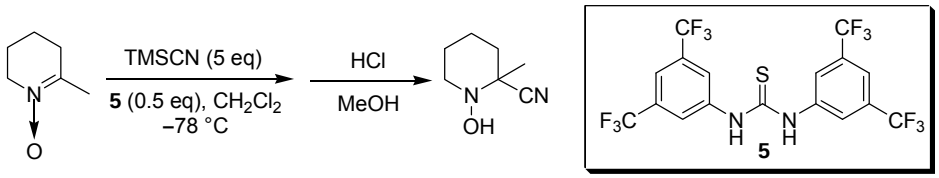
Generally, in the absence of a catalyst, no reaction is observed between TMSCN and carbonyl compounds. Consequently, a variety of activators or promoters have been reported for the cyanation of carbonyl compounds with TMSCN including Lewis acids, Lewis bases, peptides and enzymes. In recent years, Shibasaki and co-workers developed Lewis acid-Lewis base bifunctional catalysts for the enantioselective addition of TMSCN to aldehydes.[262] However, in view of environmental benign pressures, organocatalysts and heterogeneous catalysts have received great attention in recent years.[12] Among of them, Jacobsen and Fuerst reported a significant new example of thiourea catalysis in the highly enantioselective cyanosilylation of ketones and aldehydes with a bifunctional thiourea-amine derivative.[93] Ishihara and co-workers reported chiral lithium binaphtholate was efficient catalyst for the asymmetric addition of TMSCN to aldehydes.[246] All of these developments have significantly advanced the frontier of enantioselective cyanohydrin synthesis.

In view of our continuing interest in the use of thiourea derivatives for asymmetric transformations, we undertook the development of bifunctional catalysts bearing thiourea moieties and lithium phenolate in one chiral modular molecule. Herein, we described the first example of chiral thiourea bearing oxygen anion as bifunctional catalyst for asymmetric cyanosilylation of ketones.

Results and discussion

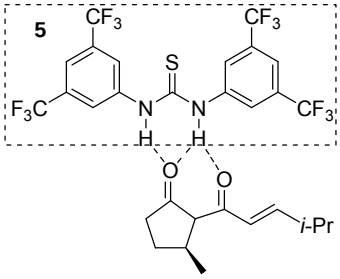
Catalyst design and synthesis

As we started the program on thiourea catalyzed asymmetric cyanosilylation in 2004, there was only one report on nucleophilic addition of TMSCN to nitrones catalyzed by thiourea **5** in Takemoto group (Scheme 1).[48]

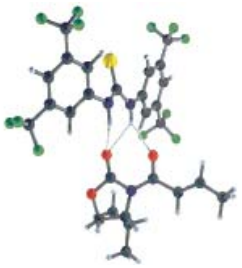


Scheme 1. Thiourea-catalyzed nucleophilic addition of TMSCN to nitrone.

Besides this application, thiourea **5** has also proven to be an active Lewis acid-like catalyst in promoting Diels-Alder reaction through cooperative hydrogen bonding interaction with unsaturated 1,3-diketones (Scheme 2).[41, 45, 263]

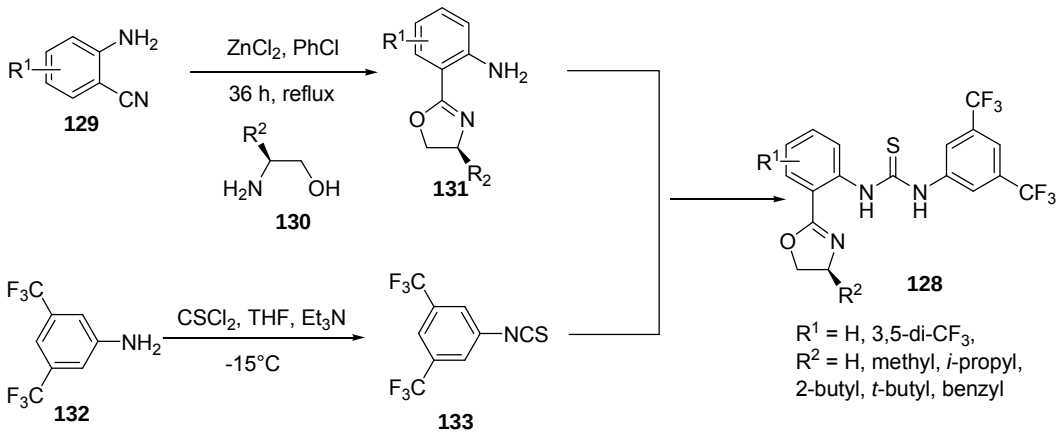


Scheme 2a. Proposed system



Scheme 2b. Computed system

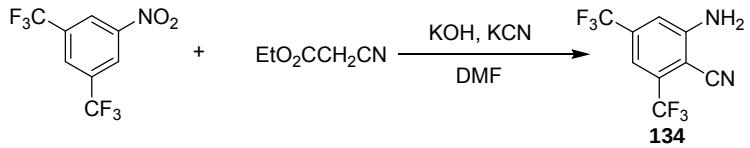
Inspired by the general ability for activation of a series of functionalities by thiourea derivatives via a double hydrogen bonding "clamp", we set out to design second-generation chiral thiourea derivatives for asymmetric cyanosilylations, in which chiral oxazoline moieties are used as stereogenic center and placed much close to the binding site. On the basis of this strategy, various oxazoline based thiourea derivatives **128** were prepared in a straightforward route (Scheme 3).



Scheme 3. Synthetic routes to oxazoline thiourea organocatalysts.

The oxazoline derivatives **131** can conveniently be synthesized through zinc-catalyzed condensation of 2-aminobenzonitrile or 4,6-ditriflurometh yl-2-aminobenzonitrile **129** with chiral amino alcohols **130** that are readily accessible form the respective (natural) amino acid.[264] Coupling compounds **131** with isothiocyanato-3,5-ditrifluoromethylbenzene gives the desired products **128** in considerably yields. For purification of the intermediates and final products please refer to the experimental section. As we had proposed, one of the thiourea N–H hydrogens resonates at much lower field in the NMR spectrum (>12.5 ppm), indicating the desired hydrogen-bond interaction between N–H hydrogen and lone pair electron of nitrogen in oxazoline ring.

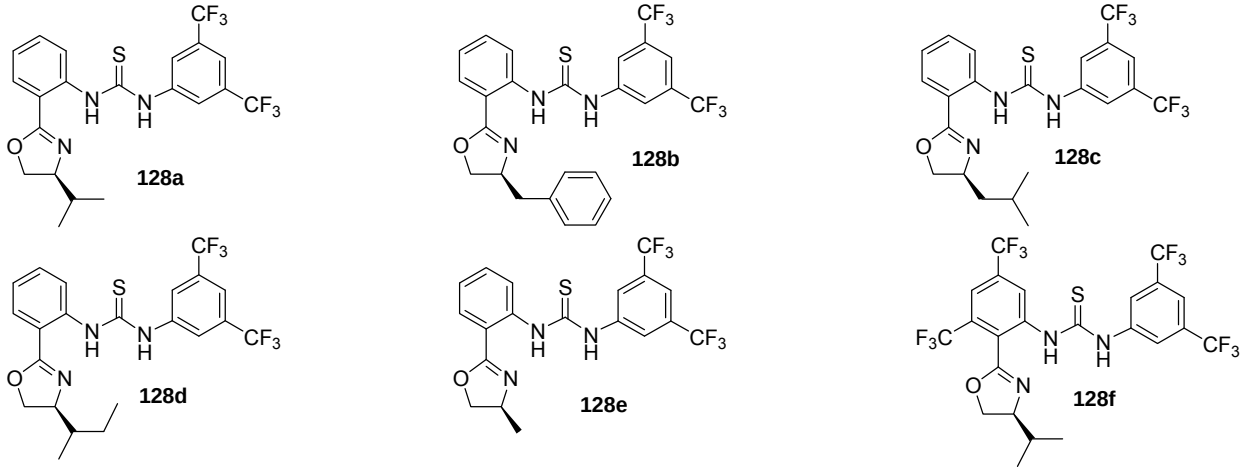
In order to increase the N–H hydrogen donor properties, electron deficient 4,6-ditrifluoromethyl-2-aminobenzonitrile **134** was prepared by a known method (Scheme 4). Treating 1-nitro-3,5-ditrifluoromethylbenzene with EtO_2CCH_2CN, KOH, as well as KCN in DMF followed by aqueous workup affords the crude product, which was further purified by column chromatography with chloroform as eluent.[265] For details refer to experimental section.

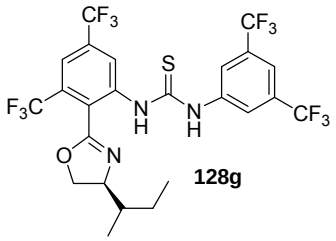


Scheme 4. Synthesis of 4,6-ditrifluoromethyl-2-aminobenzenonitrile.

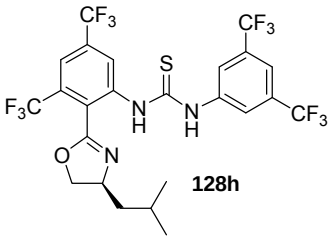
Chiral amino alcohols were obtained through reduction of natural amino acid with $NaBH_4$-I_2 mixture in THF as reported in literature,[266] in the exception of (*S*)-2-amino-propanol using $LiAlH_4$ as reductant.[267] Although 3,5-ditrifluoromethylbenzylisothiocyanate is commercially available, a modified method was carried out in our group by dropwise addition of the cold and diluted solution of 3,5-bifluoromethylaniline $CSCl_2$ at about –15 °C. All newly oxazoline-based thiourea derivatives are listed in Table 1.

Table 1. List of oxazoline-based thiourea derivatives 128.[a]





128g



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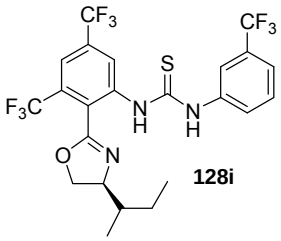
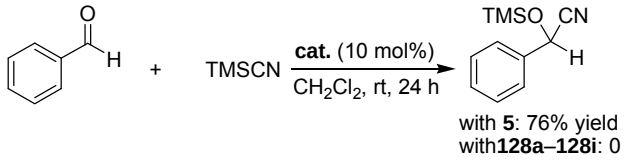


128i

[a] For experimental details, please refer to the experimental section.

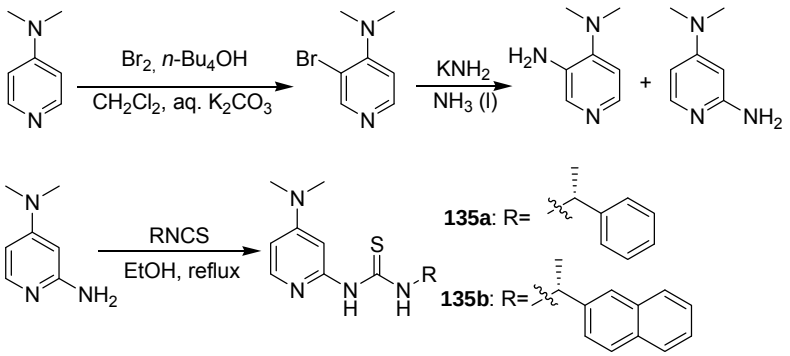
In a first set of experiments, catalytic efficiency of these novel thiourea derivatives was tested in the addition of TMSCN to benzaldehyde, the results are depicted in Scheme 5.



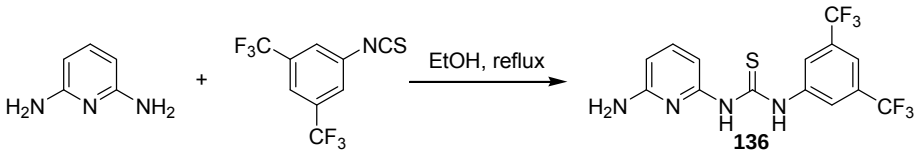
Scheme 5: Cyanosilylation of benzaldehyde.

These results showed that the designed novel thiourea derivatives displayed no catalytic activity in promotion of the addition of TMSCN to benzaldehyde. In comparison, good yield can be obtained with thiourea **5** as catalyst. Presumably the hydrogen-bond interaction between thiourea N–H hydrogen and lone pair electron of nitrogen in oxazoline ring dramatically decrease the binding ability of thiourea derivatives. In addition, it was also revealed that the bidentate hydrogen bond binding is requisite for thiourea's catalytic effect.

The presence of basic functionalities for thourea-based catalysts is desirable for many reactions because they may synergistically activate both nucleophile and electrophile at an appropriate arrangement of transition state, giving rise to enantioselective outcome. It should be noted that these basic sites should be placed in a way so that they can not effectively compete with the electrophile for binding to the thiourea clamp. Our strategy involves the preparation of 4-*N*,*N*-dimehylaminopyridine (DMAP) based thiourea **135a**, **135b**, and 2,6-diaminopyridine based thiourea **136**. The synthesis of these thiourea derivatives is shown in Scheme 6.

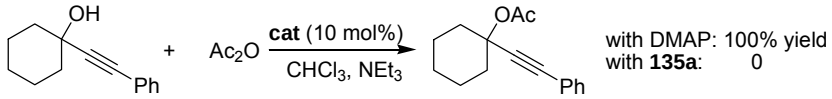


Scheme 6. Synthesis of **135a**, **135b**, and **136**.

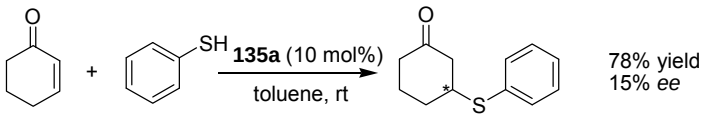


Scheme 6. Synthesis of **135a**, **135b**, and **136**.

The synthesis of **135** started with bromination of DMAP, followed by amination under the homogeneous aminating conditions of KNH_2 in NH_3 (l), affording a mixture of 2-amino-4-dimethylaminopyridine and 3-amino-4-dimethylaminopyridine. The major product 2-amino-4-dimethylaminopyridine was refluxed with isothiocyanate in ethanol to give the desired product **135a** and **135b** respectively. The preparation of **136** was achieved by refluxing 2,6-diaminopyridine with equimolar isothiocyanate **133**. **135a**, **135b**, and **136** were tested as catalyst for the cyanosilylation of benzaldehyde with TMSCN in CH_2Cl_2 at room temperature. With a catalyst loading of 10 mol%, no conversion was observed within 24 h. After we optimized other reaction parameters such as catalyst loading, temperature, and solvents, no conversion was detected, either. A possible reason for this unexpected result may be the low nucleophilicity of aromatic amine functionalities or less of synergetic effect due to steric arrangement of amino- and thiourea-functionalities. Both **135a** and **135b** were also tested in acylation of alcohol as acyl-transfer catalysts, but no conversion was determined (Scheme 7). The only catalytic effect of **135a** was found in Michael addition of thiophenol to 2-cyclohexenone (Scheme 8). With a catalyst loading of 10 mol% of **135a**, the product was obtained in 78% yield and 15% *ee* at room temperature. After lowering the reaction temperature to –40 °C, no increase in enantiomeric excess was obtained.



Scheme 7. Acylation of alcohol.

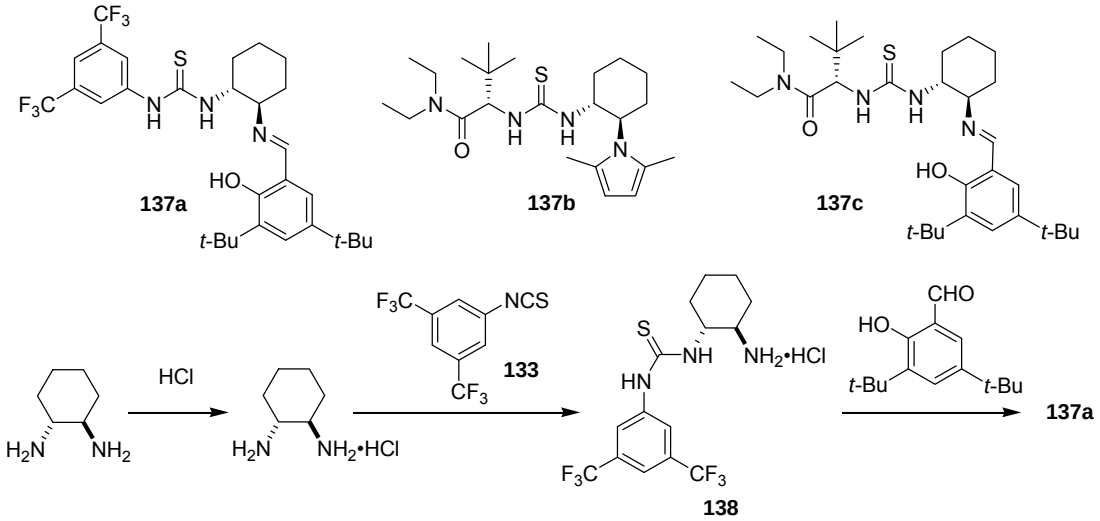


Scheme 8. Michael addition.

Preparation of Jacobsen's catalyst analogue.

Jacobsen and co-workers have developed a series of urea- and thiourea-containing Schiff-base catalysts for various types of asymmetric reactions such as Strecker, Mannich, hydrophosphonylation, nitro-Mannich, and acyl-Pictet-Spengler reactions.[26] Ishihara and co-workers reported chiral lithium binaphtholate was efficient catalyst for the asymmetric addition of TMSCN to aldehydes.[246] In accordance with these previous reports, we envisioned that catalyst **137b** and **137c** developed by Jacobsen group may serve as a bifunctional catalysts for cyanosilylation, when it was used in combination with a base

cocatalyst. In addition, we also prepared a Jacobsen's catalyst analogue **137a** by exchanging the tertiary amide with more electron deficient thioureas (Scheme 9). First we tried to prepare **137a** by reacting (*R*,*R*)-1,2-diaminocyclohexane with equimolar of isothiocyanate **133** followed by addition of equimolar of 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde or in contrary sequence, but both methods afforded only symmetric products such as bis-thiourea or bis-Schiff base instead of the desired product. We then protected one amino group with hydrochloride and then coupled with isothiocyanate **133**, affording the crude intermediate **138**, which can be further purified by column chromatography. Treating **138** with K_2CO_3 solution, followed by refluxing with 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde give product **137a** in excellent yield. For experimental details, please refer to experimental section.



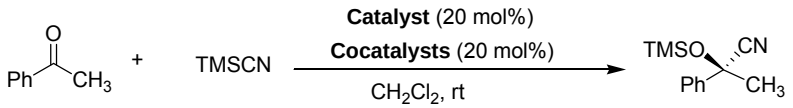
Scheme 9. Synthesis of Jacobsen's catalysts and analogue.

Survey of efficient catalyst systems

The asymmetric cyanation of ketones has been historically considered as problematic. Initial catalyst screening revealed that none of these chiral thiourea derivatives tested alone can catalyze the addition of TMSCN to acetophenone. In light of these molecular scaffolds bearing phenol moiety, we envisioned that metal phenolate complex may promote the cyanation of ketone through Si-O bonding activation. Therefore, systematic study was performed using **137a**, **137b**, and **137c** as chiral scaffold and variable metalli bases as additives. These results were shown in Table 2. Interestingly, using Jacobsen's catalysts **137b** and **137c** in combination with various metalli bases, the product can be obtained in excellent yield with no enantioselectivity (Table 2, entries 2, 3, 5, 6, 8, 9). Amongst others, with **137a** and LiOH as catalytic system, product with *ee* up to 36% was obtained in high yield (Table 2, entry 4). Ph_3PO has been used by Ryu and Corey to convert TMSCN to a more reactive reactive cyanide donor, $Ph_3P(OTMS)(N{=}C{:})$, in chiral oxazaborolidinium catalyzed cyanosilylation of adehydes and ketones.[244, 250] Inspired by the previous reports, we applied Ph_3PO as co-catalysts along with chiral thiourea derivatives for the cyanosilylaiton

of ketones. After the reaction was run at room temperature for 60 h, no conversion was observed (Table 2, entries 15–17).

Table 2. Survey of catalytic systems on the asymmetric addition of TMSCN to acetophenone.[a]



Entry	Catalyst	Cocatalyst	T (℃)	Time (h)	Conversion[b] (%)	ee(%)[c]
1	**137q**	n-BuLi	r.t	15	100	0
2[d]	**137b**	n-BuLi	r.t	15	100	0
3[d]	**137c**	n-BuLi	r.t	15	100	0
4	**137a**	LiOH	r.t	15	80	36
5[d]	**137b**	LiOH	r.t	15	100	0
6[d]	**137c**	LiOH	r.t	15	100	0
7	**137a**	$LiOPr^i$	–20 °C	15	97	11
8[d]	**137c**	$LiOPr^i$	–20 °C	15	94	0
8	**137a**	$LiOH·H_2O$	–20 °C	15	21	0
9[d]	**137c**	$LiOH·H_2O$	–20 °C	15	79	4
10	**137a**	KOH	r.t	60	trace	-
11	**137a**	NaOH	r.t	60	9	0
12	**137a**	CaH	r.t	60	63	6
13	**137a**	NaH	r.t	60	32	7
14	**137a**	NaOMe	r.t	60	35	7
15[d]	**137a**	Ph_3PO	r.t	60	0	-
16[d]	**137b**	Ph_3PO	r.t	60	0	-
17[d]	**137c**	Ph_3PO	r.t	60	0	-

[a] The reaction was carried out on a 0.1 mmol scale with 20 mol% catalyst **4.11**, 20 mol % cocatalyst and 1.2 eq TMSCN at room temperature. [b] Yield of isolated product. [c] Determined by chiral GC analysis. [d] 10 mol% of catalysts and cocatalysts were used.

Survey of n-BuLi as catalyst

Although the combination of n-BuLi and thiourea derivatives showed appreciable catalytic activity, there was no asymmetric induction, presumably the catalytic effect is ascribed from the metal specie. n-BuLi alone was then assessed as catalyst at 10 mol% loading and it is interesting of note that the quantitative conversion of acetophenone was observed with TLC and GC-MS. To our knowledge, there is so far no report on n-BuLi catalyzed cyanosilylation. Two possible catalytic cycles were proposed, one mechanism cycle is that n-BuLi itself acts as nucleophilic catalyst, that is, the formed TMSCN and n-BuLi complex serves as active

species and cyano transfer to acetophenone led to the lithium salt, which then reacted with trimethyl-n-butylsilane affording the corresponding product (Figure 1). However, the regeneration of n-BuLi through the reaction of lithium salt with silane under common conditions is forbidden due to the high energy consumption. Thus, another catalytic cycle was proposed as Figure 2, the lithium enolate salt arising from the reaction of acetophenone with n-BuLi works as the active catalyst, which activates TMSCN and thus promote cyano transfer to acetophenone giving the corresponding product and regenerating the active catalytic specie. The latter appears more plausible but needs to be verified by further investigation.

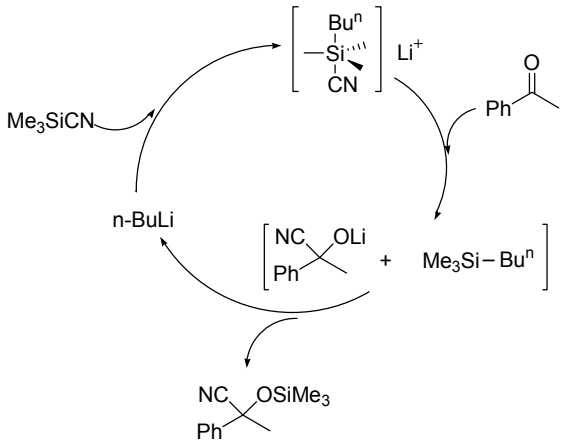


Figure 1. Proposed catalytic cycle 1.

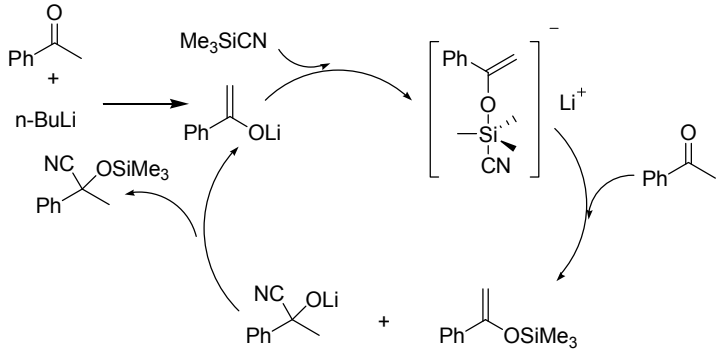


Figure 2. Proposed catalytic cycle 2.

Summary

Despite the low reactivity of chiral thiourea derivatives alone for cyanosilylation of ketones, it was revealed for the first time that one molecular bearing a thiourea functionality and phenolate in a chiral scaffold can act as a bifunctional organocatalyst for cyanosilylation of ketones, yielding the product with up to 36% *ee*. In addition, n-BuLi was found to be an effective catalyst for the cyanosilylation of ketones. Moreover, plausible mechanism is also proposed for cyanosilylation of ketone catalyzed by n-BuLi based on empirical experiment.

Chapter 5 Development of Organocatalytic Hydrophosphonylations

Introduction

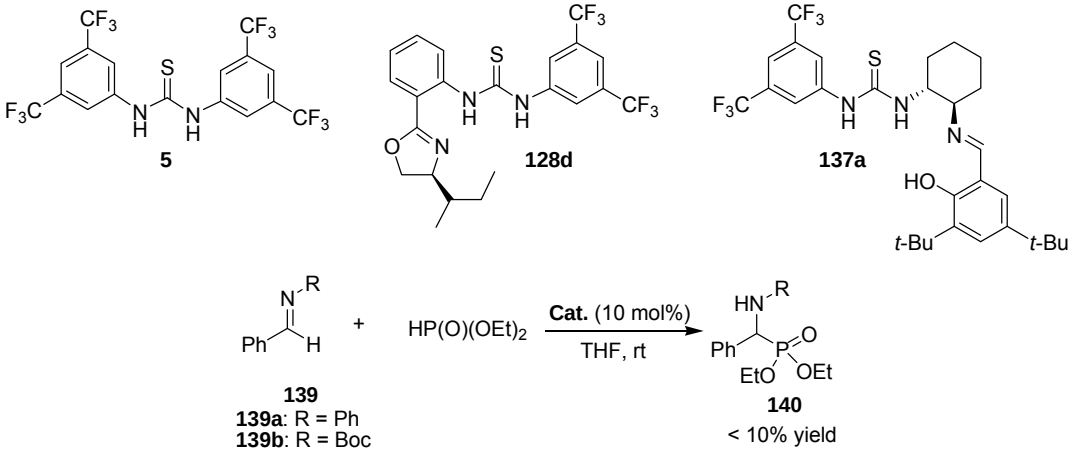
Optically active α-amino phosphonic acids serve as isosteric or bio-isosteric analogues of the corresponding amino acids, in which the planar and less bulky carboxylic acid group is replaced by a tetrahedral phosphoric acid functionality. α-Amino phosphonic acids and short peptides bearing the functionalities display interesting biological and biochemical properties giving rise to antibacterial and antifungal agents, a wide range of proteolytic enzyme inhibitors, and haptens for catalytic antibodies.[268-271] Therefore, this class of compounds has received considerable attention and resulted in intense efforts directed towards the development of suitable synthetic methodologies for their preparation. The addition of phosphites to imines (hydrophosphonylation) is probably the most general and direct approach to α-amino phosphonates. Generally, these transformation can be promoted by an alkali metal alkoxide or acids.[272, 273] NaOEt has been mainly used for this purpose since the pioneering work of Pudovik[274] and Lewis acids such as $SnCl_2$, $SnCl_4$, and BF_3•Et_2O have also found to be effective.[275] However, satisfactory yields can not be achieved using these reagents or catalysts. Although the yields can be strongly improved in the catalysis of $ZnCl_2$ or $MgBr_2$, one-pot operation with a carbonyl compound, amine, and dialkyl phosphite can not be carried out because the presence of amines and water can decompose or deactivate these Lewis acids.[276] After the first one-pot synthesis of α-amino phosphonates in the presence of lanthanide triflates/$MgSO_4$,[277] a variety of reagents or catalysts involving $InCl_3$[278], $In(OTf)_3$[279], $TaCl_5/SiO_2$[280], $ZrCl_4$[281], GaI_3[282], $BiCl_3$[283], $LiClO_4$[284], SmI_2[285], $Na_2CaP_2O_7$[286], $YbCl_3$[287], $Mg(ClO_4)_2$[288, 289]and surface mediated reactions on Al_2O_3[290, 291] have been developed for this transformation. In view of today's environmental consciousness, there is still a need to develop efficient, practically potential and environmentally benign methodologies. Ionic liquid turned to be promising medium for such three-component couplings.[292, 293] Recent advances in organocatalysis have so far provided alternatives for enantioselective preparation of α-amino phosphonates.[57, 294, 295] Ranu and co-workers reported a simple one-pot three-component synthesis of α-aminophosphonates through condensation of carbonyl compound, amine, and diethylphosphite at 75–80 °C under neat conditions without any solvent and catalyst.[296]

We took these ideas together and set out to investigate this one-pot transformation focusing mainly on two aspects: 1) could this transformation be catalyzed by some other novel thiourea derivatives? 2) is this type of transformation autocatalytic reaction? Herein, we disclose that the reaction of aldehydes, amines, and diethyl phosphate proceeds smoothly under solvent- and catalyst-free conditions *without* heating affording the corresponding α-aminophosphonates at high yields. In addition, some key elements for rate acceleration were

also demonstrated through dynamic study on reaction procedure, which may provide insights into the reaction mechanism. In most cases, phosphonates have been used as P-nucleophiles.

Results and Discussions

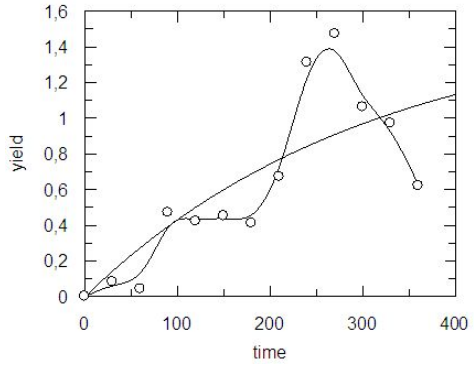
Inspired by the successful application of thiourea Schiff-base derivatives as organocatalysts for hydrophosphonylation of imines, we envisioned that electron-poor thiourea derivatives developed in our group may promote the nucleophilic addition of phosphites to imines mediated through hydrogen bonding activation. To test our proposal, representative reaction was performed between imines (**139a** or **139b**) and diethyl phosphite in the presence of thiourea derivatives **5**, **128d**, or **137a** (10 mol%) in THF at room temperature (Scheme 1). Surprisingly, the control reaction proceeded even faster than the one in the presence of thiourea derivatives, though poor conversions were observed in all reactions (<10%). After optimization of reaction conditions, it was found that the reaction proceeds smoothly to afford the corresponding α-amino phosphate **140a** in high yield (89%) under neat conditions without solvent and catalysts. The completion of this reaction can be easily determined by visualization as the reaction mixture is solidified. The product can be purified through recrystallization from mixture of ethyl acetate and hexane according to the procedure reported.[296] This avoids use of large quantities of volatile solvents usually required for work-up and purification in many existing procedures. On the other hand, no catalyst used in this process make easier waste disposal.



Scheme 1. Thiourea-catalyzed hydrophosphonylation.

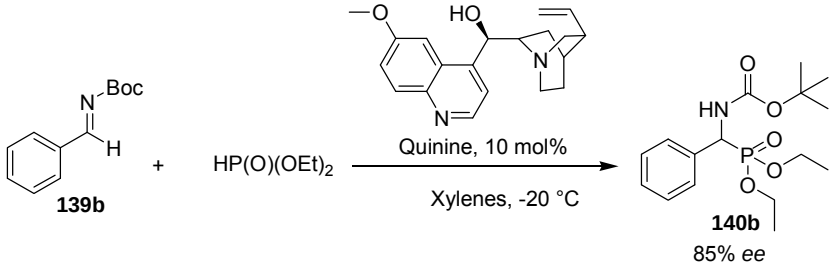
These results led us to pose the question of whether the product itself is the catalyst for this reaction, namely autocatalysis. If the autocatalysis is true, the graph for these reactions should be a sigmoid curve, that is, the rate of reaction increases progressively as the amount of catalysts increases and it again slows down as the reactant concentrations decreases. We first initiate a dynamic study monitored by GC using *n*-dodecane as internal standard. Unfortunately, it is difficult to measure the ratio between reactants and *n*-dodecane, since *n*-dodecane is insoluble in the reaction mixture. As we know, the reaction sparingly proceeds in

the solvents without the addition of catalysts. We then run this reaction parallel using the solution of *n*-dodecane in EtOAc as external standard to quench the reaction at specific time and monitored by GC. These results are depicted as graph **1**. The reaction procedure has mainly two stages. The reaction rates increased dramatically from 30 min to 60 min and from 180 min to 250 min respectively. The reaction was reversible as the product will decompose to reactants at extending the reaction time after 5 h. In addition, it was also found that the amount of diethyl phosphite influences the reaction rate since the reaction proceeded dramatically faster with a small excess of diethylphosphite (6 h) than substoichiometric diethyl phosphite (15 h).



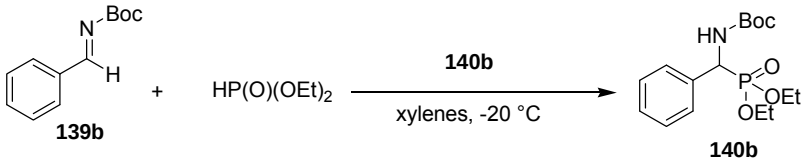
Graph 1. Dynamic study on the reaction procedure between benzylideneaniline **139a** and diethyl phosphite.

Although the reaction between benzylideneaniline and diethyl phosphate did not show automatic effect, we turned our attention to another reactant *N*-Boc-imine (**139b**). The origin of the homochirality of biomolecules (e.g., amino acids and carbohydrates) is still puzzling. It is still not clear how these generally small enantiomeric excesses could have been amplified under prebiotic conditions. As an analogue to amino acids, α-phosphoric acids cause our attention to be investigated for help to explain this interesting phenomenon. An initial experiment was carried out to prepare **140b** at different enantiomeric excesses by known method (Scheme 2) and then employ **140b** as catalyst for the addition of diethylphosphite to *N*-Boc-Imine **139b**. Independent of the addition amount of product **140b**, the isolated products were almost the same amount and the *ee* were varied with the addition amount of enantiomeric enriched product. It was demonstrated that the product **140b** has probably no influence on the outcome of this reaction. These results were recorded in Table 1.



Scheme 1. Preparation of enantiomeric enriched **140b**.

Table 1. Investigation of autocatalysis.

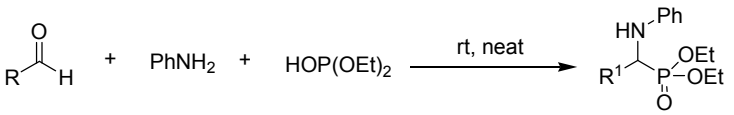


entry	Catalyst loading (mol%)	Conversion[a]* (%)		yield (%)[b]	*ee* (%)[c]
		18 h	40 h		
1	30	35	64	3	60
2	20	52	93	6	56
3	10	45	63	21	28
4	1	62	72	27	11

[a] Conversion was determined by GC (*n*-dodecane as internal standard). [b] Yield after subtraction of the initially added product catalyst. [c] Enantioselectivities was determined by chiral HPLC (Chiralpak AD-H). * Only rough value because of the instability of the educt.

From a synthetic point of view, we wonder that imines, generated *in situ* from aldehydes and amines, may immediately react with phosphites to afford α-amino phosphonates in one-pot way under neat conditions without solvent and catalysis. The reaction of benzaldehyde, aniline, and diethyl phosphite took place smoothly affording the desired α-amino phosphonates in 83% yield after 6 h at room temperature under neat conditions. A wide variety of structurally diverse aldehydes and amines were subjected to this procedure and converted into the corresponding α-amino phosphonates in high to excellent yields. The results are summarized in Table 2. This procedure is equally effective for conversion of open-chain, heterocyclic, cyclic and aromatic aldehydes. The presence of electron-withdrawing or electron-donating substituents on the aromatic ring did not show obvious influence on the course of the reaction.

Table 2. One-pot synthesis of α-amino phosphonates under neat conditions.



entry	R	time (h)	yield (%)[a]
1	Ph	6	89
2	4-NO_2Ph	4	86
3	4-BrPh	6	82
4	4-OHPh	6	78

[a] yield of isolated product.

In general, three-component reaction of aldehydes, amines, and diethylphosphite proceeded smoothly to afford the corresponding α-amino phosphonates under neat conditions without the involvement of any catalyst and solvent. The present procedure provides a very simple, efficient, and cost-effective methodology. Systematic dynamic study and

enantioselective reaction using product itself as additive have clearly excluded the possible autocatalysis. In addition, diethylphosphite was found to play important role in the acceleration of reaction rate, though the real features of diethylphosphite are still needed to be investigated.

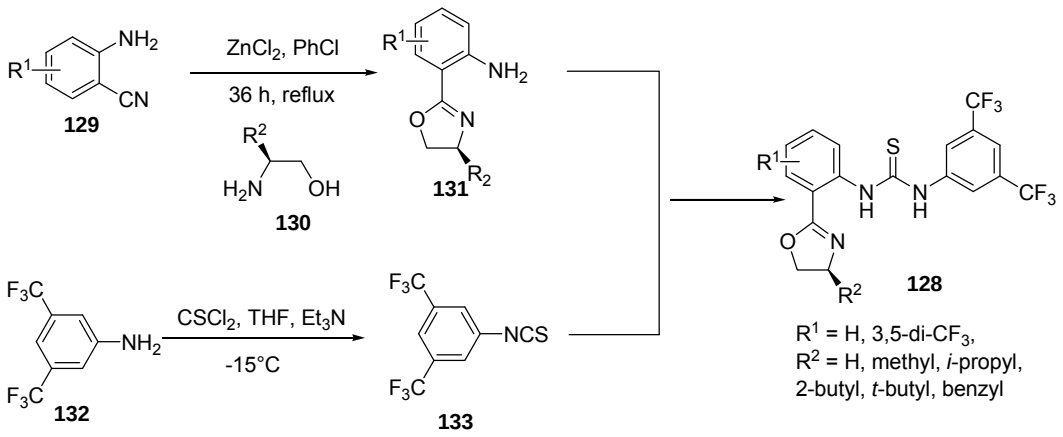
General experimental procedure

A mixture of aldehyde, amine, and diethyl phosphite was stirred at room temperature under neat conditions. After completion of the reaction as indicated by TLC and GC-MS, the solid ones were recrystallized from mixture of ethyl acetate and hexane (4:1) and the liquid products were isolated by direct distillation under reduced pressure. All the products are known compounds and the characterizations of these compounds are identical with the literature reports.

Chapter 6 Summary and Outlook

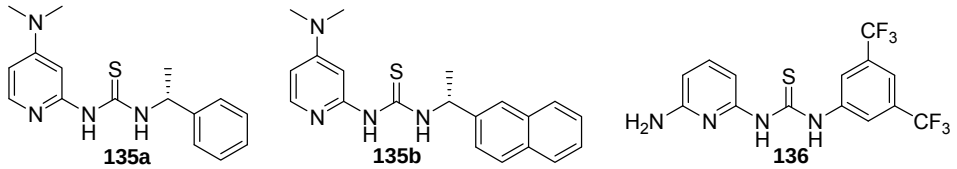
As introduced in this thesis, a series of novel chiral thiourea derivatives were firstly designed and synthesized, and their potential applications as organocatalysts were investigated in several fundamentally important transformations, such as transfer hydrogenation of imines, biomimetic reduction of nitroolefins, cyanosilylation of ketones, as well as hydrophosphonylation of imines.

Inspired by the general activation ability of thiourea derivatives via a double hydrogen bonding "clamp", one class of chiral thiourea derivatives were designed by incorporation of chiral oxazoline moieties closely into the binding site. On the basis of this strategy, various oxazoline based thiourea derivatives were prepared in a short and straightforward route (Scheme 1). Unfortunately, no catalytic effects were observed in all test reactions, presumably due to the competitive intramolecular hydrogen-bond interaction.



Scheme 1. Synthesis of oxazoline-based thiourea derivatives.

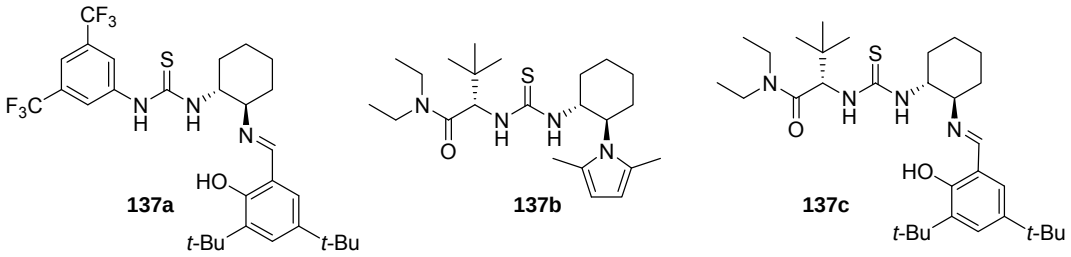
The presence of basic functionalities for thiourea-based catalysts is desirable for many reactions because they may synergistically activate both nucleophile and electrophile at an appropriate arrangement of transition state, giving rise to enantioselective outcome. Our strategy involves the preparation of DMAP based thiourea **135a**, **135b**, and 2,6-diaminopyridine based thiourea **136**. The catalytic effect was only found in Michael addition of thiophenol to 2-cyclohexenone. With a catalyst loading of 10 mol% of **135a**, the product was obtained with 15% *ee*.



Scheme 2. Bifunctional thiourea derivatives.

Besides the preparation of Jacobsen's catalysts **137b** and **137c**, we also prepared a Jacobsen's catalyst analogue **137a** by exchanging the tertiary amide with more electron

deficient thioureas (Scheme 3). It was revealed for the first time that one molecular bearing a thiourea functionality and phenolate in one chiral scaffold can act as a bifunctional organocatalyst for cyanosilylation of ketones, yielding the product with up to 36% *ee*. In addition, n-BuLi was found to be an efficient substoichiometric initiator for the cyanosilylation of ketones.



137a **137b** **137c**

Scheme 3.

Thiourea-catalyzed transfer hydrogenations with Hantzsch ester as the hydrogen source were reported. On the question of some of the published literature protocols, we present a practical method for the thiourea-catalyzed reduction of aromatic as well as aliphatic aldimines with a Hantzsch ester as the hydrogen source. The loadings of catalyst **5** as low as 0.1 mol% is sufficient for this transformation.

A thiourea-catalyzed biomimetic reduction of conjugated nitroalkenes has been developed. Various aromatic and aliphatic conjugated nitroalkenes can be reduced to give the respective nitroalkanes with good yields under mild conditions. This protocol is not only practical, but may also provide insight into the mechanisms of redox transformations in biological systems.

In addition, some other efforts concerned with the *in situ* regeneration of Hantzsch ester, development of chiral ammonium salts as potential catalysts, as well as search for other hydrogen sources were also investigated.

Since the newly designed thiourea-based catalysts were generally inefficient for the promotion of reduction with trichlorosilane, various novel chiral *N*-formamides derived from proline, valine, and pipecolinic acid were developed for the asymmetric reductions of ketimines using trichlorosilane as the hydrogen donor. The enantioselectivity up to 68% *ee* was so far obtained. The preliminary mechanism studies showed quite different feature as described in the literature. Further work will be directed to elaborate the mechanism aspects by means of experimental and computational methods and develop more efficient catalysts.

Thiourea-catalyzed addition of diethyl phosphite to imines was also investigated. Generally, no catalytic effects were observed for our designed thiourea derivatives. In contrast, three-component reaction of aldehydes, amines, and diethylphosphite proceeded smoothly to afford the corresponding α-amino phosphonates under neat conditions without the involvement of any catalyst and solvent. Dynamic study and enantioselective evaluation with product itself as additive have clearly excluded the possibility of autocatalysis. In

addition, diethylphosphite was found to play an important role in the reaction rate, though the real features of diethylphosphite are still needed to be investigated.

Chapter 7 Experimental Section

7.1 Chemicals and solvents

Chemicals

Unless otherwise noted, chemicals were purchased from commercial suppliers (Acros, Aldrich, Fluka, Lancaster, or Merck) and were used without further purification.

2,6-diaminopyridine and p-anisidine were purified by sublimation. 1-aminodiamantane and 4-aminodiamantane were prepared by Dipl.-Chem. Hartmut Schwertfeger. 1-Aminotriadmantane was prepared by Anika Merz.

Solvents

Solvents for chromatography, recrystallization, and reaction workup were of technical grade and were distilled prior to use. Dry Solvents were prepared in the following manner:

Table I. Preparation of dry solvents

entry	solvent	dry conditions
1	THF	predried with KOH and then distilled over sodium/benzophenone suspension under argon
2	CH_2Cl_2	predried with $CaCl_2$ and then distilled over phosphorous pentoxide under argon
3	toluene	predried with $CaCl_2$ and then distilled over phosphorous pentoxide under argon
4	benzene	distilled over sodium/benzophenone suspension under argon
5	diethyl ether	predried with $CaCl_2$ and distilled over sodium/benzophenone suspension under argon
6	$CHCl_3$	distilled over phosphorus pentoxide under argon
7	DMF	distilled from calcium hydride under argon and stored over 4 Å MS
8	1,4-dioxane	predried with KOH and then distilled from sodium/benzophenone suspension under argon
9	CH_3OH	predried with sodium and distilled over magnesium under argon and stored over 4 Å MS
10	xylenes	predried with $CaCl_2$ and then distilled over phosphorus pentoxide

General procedures

All reactions involving air sensitive chemical were performed under an argon atmosphere. Glassware was heated *in vacuo* with heating gun or in oven and subsequently purged with argon. Plastic syringes with steel cannulae were used to transfer air and moisture sensitive liquids. Column chromatography was conducted using J. T. Baker silica gel (particle size 0.063–0.200 mm), or for flash chromatography, Merck silica gel 60 (particle size 0.040–0.063 mm). Solvent mixtures are understood as volume/volume. For thin-layer chromatography (TLC), silica gel plates coated aluminium plates (Merck, silica gel 60 F_{254}) were used and chromatograms were visualized by iodine or irradiation with UV light at 254 nm.

7.2 Instrumentation and methods

NMR spectroscopy

Proton nuclear magnetic resonance (^{1}H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) were recorded on a Bruker AM 400, 200, or 600 spectrometer at 298 K in 5 mm NMR tubes. The chemical shifts (δ values) were obtained in deuterated solutions unless otherwise noted and referenced to respective solvent or TMS residual signals. Data are presented as follows: chemical shift, integration, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, cm = complex multiplet) and coupling constant in Hertz (Hz).

IR spectroscopy

Infrared (IR) spectra were obtained using a Bruker IFS25 or IFS48 spectrometer. The measurements were carried out on a film between two plates of KBr for liquids and KBr pressing for solids. Data are represented in terms of frequency of absorption (cm^{-1}) and intensity of absorption (s = strong, m = medium, w = weak).

GC-MS

GC-MS analyses were carried out with a Quadrupol-MS HP MSD 5971 (EI) detector and HP 5890A gas chromatograph equipped with a J & W scientific fused silica GC column (30 m × 0.250 mm, 0.25 micron DB-5MS stationary phase: 5% phenyl and 95% methyl silicone) using He as carrier gas; T-program standard 60–250 °C (15 °C/min heating rate), injector and transfer line 250 °C.

HRMS

High resolution mass spectroscopy (HRMS) was recorded on a Thermo Finnigan MAT 95 sectorfield spectrometer.

Elemental analysis

Elemental analyses were performed on a Carlo Erba 1106 CHN analyzer.

Optical rotations

Optical rotations were measured using a 5 mL cell with a 1 dm path length on a Jasco P-2000 digital polarimeter.

Melting points

Melting points were measured on a Bunsen burner melting point apparatus and were not corrected.

Chiral HPLC

Chiral high performance liquid chromatography (HPLC) analyses were performed on a Dionex machine using Diacel Chiralcel OD-H, Chirapak IA, IB, or Nucleocell Delta column.
2-phenyl-1,2,3,4-tetrahydroquinoline (102): Nucleocell Delta, 254 nm, hexane/isopropanol 60:40, flow rate 1.0 mL/min, t_{R1} = 6.64 min, t_{R2} = 8.38 min.
***N*1-(1-phenylethyl)aniline (99)**: Chiracel OD-H, 254 nm, hexane/isopropanol 99:1, flow rate 1 mL/min, t_{R1} = 11.7 min, t_{R2} = 14.5 min; Chirapak IB, 254 nm, hexane/isopropanol 98:2, flow rate 0.7 mL/min, t_{R1} = 9.7 min, t_{R2} = 10.9 min
***N*1-(1-phenylethyl)-4-methoxyaniline**: Chirapak IB, 254 nm, hexane/isopropanol 98:2, flow rate 0.6 mL/min, t_{R1} = 14.9 min, t_{R2} = 16.2 min
***tert*-butyl(diethoxyphosphoryl)(phenyl)methylcarbamate (140b)**: Chirapak IA, 254 nm, hexane/isopropanol 98:5, flow rate 1.0 mL/min, t_{R1} = 14.4 min, t_{R2} = 17.0 min
***N*1-benzyl-*N*1-cyano(phenyl)methylacetamide**: Chiralpak IA, 254 nm, hexane/isopropanol 80:20, flow rate 0.7 mL/min, t_{R1} = 10.05 min, t_{R2} = 12.62 min

Chiral GC

Chiral gas chromatography (GC) analyses were performed on a Hewlett-Packard 5890 gas chromatography using a Hydrodex-β-6-TBDM, Chiraldex G-TA column, or Lipodex E.
***N*1-(1-phenylethyl)aniline (99)**: Hydrodex-β-6-TBDM, 130–175 °C, 1 °C/min, t_{R1} = 38.13 min, t_{R2} = 38.46 min
2-phenyl-2-(trimethylsilyloxy)acetonitrile: Hydrodex-β-6-TBDM, 100–150 °C, 2 °C/min, t_{R1} = 19.78 min, t_{R2} = 20.07 min

2-phenyl-2-(trimethylsilyloxy)acetonitrile: Hydrodex-β-6-TBDM, 100–170 °C, 2 °C/min, t_{R1} = 14.34 min, t_{R2} = 14.63 min

3-phenylsulfanyl-1-cyclohexanone: Hydrodex-β-6-TBDM, 180 °C, isothermal 30 min, t_{R1} = 25.54 min, t_{R2} = 25.15 min

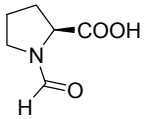
2-nitropropyl)benzene: Chiraldex G-TA, 100–180 °C, 5 °C/min, t_{R1} = 12.77 min, t_{R2} = 13.12 min

(1-nitropropane-2-yl)benzene: Chiraldex G-TA, 100–180 °C, 5 °C/min, t_{R1} = 13.62 min, t_{R2} = 13.96 min

7.3 Synthesis of *N*-formamides

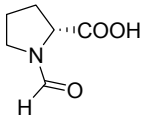
7.3.1 General Procedure for the preparation of *N*-formyl amino acids.

_N_-formyl-L-proline[261]



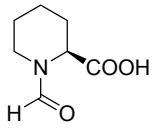
L-proline (4.0 g, 34.8 mmol) was dissolved in 98% formic acid (50 mL) and the resulting solution was cooled to 0 °C. The cooled solution was added to a mixture of acetic anhydride (40 mL, 436 mmol) in 98% formic acid (50 mL) at 0 °C. The resulting solution was allowed to warm to room temperature overnight. The solvent was then removed under reduced pressure. The residue was purified by flash column chromatography (30 g silica gel, 10% v/v methanol in chloroform). Fractions containing *N*-formyl-L-proline were pooled, and the solvent was removed under reduced pressure to yield compound **1** (4.5 g, 90%) as a clear oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.26 (s, 1 H, COOH), 8.22 (s, 0.6 H, CHO), 8.18 (s, 0.4 H, CHO), 4.45–4.42 (m, 1 H), 3.63–3.77 (m, 1 H), 3.45 (t, *J* = 7.22 Hz, 1 H), 2.29–2.20 (m, 2 H), 1.87–2.08 (m, 2 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 173.7, 173.6, 163.2, 162.2, 58.9, 56.6, 46.8, 44.1, 29.4, 29.0, 23.6, 22.5.

_N_-formyl-D-proline[297]



D-proline (600 mg, 5.21 mmol) was dissolved in 85% formic acid (11 mL) and cooled to 0°C. Acetic anhydride (3.6 mL) was added and the resulting mixture was stirred at room temperature for 2 h. Ice cold water (4.2 mL) was then added and the solvent was removed under reduced pressure. The residue pale yellow oil was purified by flash column chromatography (10% v/v methanol in chloroform) to give compound **2** (663.9 mg, 89%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.54 (s, 1 H), 8.21 (s, 0.6 H), 8.18 (s, 0.4 H), 4.35–4.40 (m, 1 H), 3.56–3.64 (m, 1 H), 3.46 (apparent triplet, *J* = 7.22 Hz, 1 H), 2.14–2.25 (m, 1 H), 1.83–2.06 (m, 3 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 174.2, 173.8, 163.2, 167.2, 59.2, 57.0, 47.0, 44.3, 29.3, 23.9, 22.8.

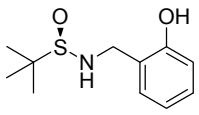
_N_-formyl-L-pipecolinic acid[298]



Acetic anhydride (0.662 mL, 7.0 mmol) was added dropwise to a stirred and cooled (0~5 °C) solution of L-pipecolinic acid (129.2 mg, 1.0 mmol) in 1.0 mL of 98% formic acid. Stirring was continued for 1 h at room temperature. Water (0.8 mL) was added and the solution was evaporated to dryness to give 125 mg of crude product as yellow oil, which was purified by flash column chromatography (10% v/v methanol in chloroform) to yield the product **3** (97 mg, 62%) as a colorless oil.

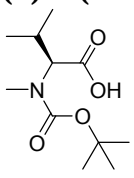
7.3.2 Synthesis of known catalysts 73 and 76

(*R*)-*N*-(2-hydroxybenzyl)-*tert*-butanesulfinamide (76)[260]



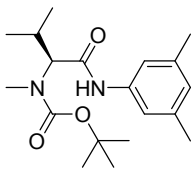
To a stirred solution of (*R*)-(+)-2-methyl-2-propanesulfinamide (121.2 mg, 1.0 mmol) in dry toluene (5 mL) at 45 °C was added anhydrous $KHSO_4$ (272 mg, 2.0 mmol) and salicylaldehyde (213 µl, 2.0 mmol). After 24 h, the reaction mixture was filtered and concentrated in high vacuum to afford sulfimine as white yellow solid 224 mg. The solid was dissolved in THF (10 mL), and $NaBH_4$ (57 mg, 1.5 mmol) was added. Once the addition was completed, the mixture became yellow and was stirred for additional 2 h at 0 °C. The solution turned colorless before saturated aqueous NH_4Cl, was added to quench the reaction. The resulting mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to give crude product as a colorless oil (260 mg), which was purified by flash column chromatography on silica gel (2 : 1 (v/v) hexane/ ethyl acetate) to yield **76** (156 mg, 69%) as a white solid. The resulting solid was recrystallized with ethyl acetate/hexanes to afford highly pure **76** as a needle crystal. $[\alpha]^{20}_D$ = -86.8 (c = 0.45, EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.64 (s, 1 H), 7.03–7.06 (m, 2 H), 6.70–6.80 (m, 2 H), 4.25–4.30 (m, 2 H), 4.08–4.14 (m, 1 H), 1.17 (s, 9 H) . **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 155.7, 129.6, 129.5, 124.0, 119.6, 116.4, 56.2, 46.9, 22.6.

(*S*)-2-(*tert*-Butoxycarbonyl-methyl-amino)-3-methyl-butyric Acid (126)



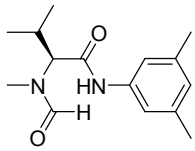
Sodium hydride (60% dispersion in mineral oil; 3.0 g, 138 mmol) was added in small portions to a stirred solution of (*S*)-2-tert-butoxycarbonylamino-3-methyl-butyric acid (**125**) (3.0 g, 13.8 mmol) and iodomethane (19.6 g, 138 mmol) in anhydrous THF (60 mL) at 0 °C. The mixture was allowed to stir at room temperature for 24 h under an argon atmosphere. The reaction was then quenched with water (15 mL), ethyl acetate (10 mL) and evaporated *in vacuo*. The residue was diluted in water (300 mL) and washed with ethyl acetate (150 mL). The aqueous solution was acidified to pH 3.5 with a solution of 5% citric acid and extracted with ethyl acetate (200 mL). The extract was washed with brine (100 mL), dried over anhydrous $MgSO_4$, and evaporated *in vacuo* to give the compound **126** as a yellow oil, which was used in the following step without further purification.

(*S*)-*N*-(3,5-Dimethylphenyl)-2-(*tert*-butoxycarbonyl-methyl-amino)-3-methyl-butyric Amide.



Methylchloroformate (0.55 mL, 7.15 mL) was added dropwise to a stirred solution of **125** (1.40 g, 6.05 mmol) and triethylamine (1.0 mL, 7.15 mmol) in anhydrous THF (30 mL) at 0 °C under an argon atmosphere and the mixture was stirred at that temperature for 2 h. The precipitation was removed by filtration *in vacuo* and the filtrate was added dropwise to a solution of 3,5-dimethylaniline (1.06 mL, 8.5 mmol) and triethylamine (1.0 mL, 7.15 mmol) in anhydrous THF (30 mL) at 0 °C. The mixture was allowed to stir at room temperature overnight under an argon atmosphere and the solvent was then removed under reduced pressure. The residue was purified using flash column chromatography on silica gel with a hexane-ethyl acetate (4 : 1) to afford the compound (958 mg) as a yellow oil.

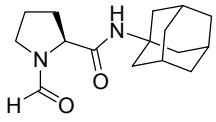
(*S*)-*N*-(3,5-Dimethylphenyl)-2-(formyl-methyl-amino)-3-methyl-butyric Amide (**73**).



The BOC derivative (344 mg, 1.03 mmol) was dissolved in trifluoroacetic acid (2.0 mL) at room temperature. After 1 h, the reaction mixture was evaporated *in vacuo*, the residue was dissolved in 98% formic acid (1.5 mL) and the resulting solution was cooled to 0 °C. Acetic anhydride (0.68 mL, 7.21 mmol) was added dropwise and the mixture was allowed to stir at room temperature overnight. The solvent was then removed by reduced pressure. Purification using column chromatography on silica gel with a hexanes-ethyl acetate mixture (1 : 1) afforded the compound **73** (175 mg) as a colorless oil.

7.3.3 General precedure for the formation of *N*-formamides

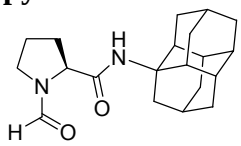
***N*2-(1-adamantyl)-(2*S*)-1-formyltetrahydro-1*H*-2-pyrrolecarboxamide (104)**



Triethylamine (1.12 mL, 8.02 mmol) was added dropwise to a cooled (0 °C) solution of *N*-formyl-L-proline (760 mg, 5.35 mmol) in dry dichloromethane (50 mL). 1-Aminoadmantane (970.4 mg, 6.4 mmol) was added, followed by 1-hydoxy-benzhotriazole hydrate (HOBt; 1.07 g, 6.96 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI; 1.33 g, 6.96 mmol). The mixture was stirred at 0 °C for 1 h, and then at room temperature for 20 h. The mixture was diluted with ethyl acetate (250 mL) and washed successively with water (100 mL), cold 0.5 M HCl (2 × 100 mL), saturated $NaHCO_3$ (2 × 100 mL), and brine (100 mL) and dried over $MgSO_4$, filtered and evaporated to afford crude product 884 mg as a yellow oil, which was purified by column chromatography on silica gel with a chloroform-methanol mixture (20 : 1) to give **104** (585 mg, 39.7%) as a white solid. **IR** (KBr): 3306, 2906, 2849, 1684, 1639, 1539, 1384, 612 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$, *cis* and *trans* forms): δ 8.24 (s, 1 H, CHO), 6.68 and 5.53 (2 × s, br, 1 H, NH), 4.34–4.37 and 4.17–4.20 (2 × q, J = 3.75, 1 H), 3.40–3.61 (m, 2 H), 2.36–2.43 (m, 0.7 H), 1.77–2.16 (m, 13.3 H), 1.62 (m, 6 H). **^{13}C NMR** (100 MHz,

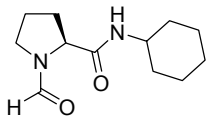
$CDCl_3$): δ = 170.3, 169.1, 162.3, 162.1, 61.6, 58.5, 56.4, 56.2, 46.9, 44.4, 41.5, 41.3, 39.3, 39.1, 38.9, 38.85, 38.8, 38.7, 38.6, 38.1, 37.8, 37.4, 37.3, 37.2, 37.0, 36.8. **HRMS**: *m/z* calcd for $C_{16}H_{24}N_2O_2$: 276.18323; found: 276.18317. **Elemental anal.:** calcd (%) for $C_{16}H_{24}N_2O_2$ (276.38): C 69.53, H 8.75, N 10.13; found: C 69.50, H 8.74, N 10.24.

_N_2-pentacyclo[7.3.1.1^{4,12}.0^{2,7}.0^{6,11}]tetradec-1-yl-1-formyltetrahydro-1_H_-2-pyrrolecarboxamide (105)



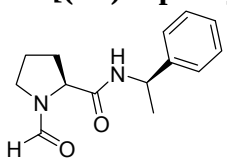
The general procedure described above was performed on 0.50 mmol scale, using 1.0 equivalent of 1-aminodiadmantane. After workup, the crude product was purified by column chromatography on silica gel with a chloroform-methanol mixture (15 : 1) to give **105** (116 mg, 71%) as a white solid, mp = 191 °C. **IR** (KBr): 3311, 2899, 2852, 1676, 1640, 1534, 1395, 629 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$, *cis* and *trans* forms): δ 8.24 (s, 1 H, CHO), 6.70 and 5.56 (2 × s, br, 1 H, NH), 4.38–4.41 and 4.20–4.22 (2 × m, 1 H), 3.43–3.58 (m, 2 H), 2.39–2.43 (m, 0.8 H), 1.38–2.18 (m, 22 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 170.0, 168.9, 162.2, 162.1, 61.4, 58.5, 52.3, 51.9, 46.9, 44.3, 44.3, 41.5, 41.4, 30.5, 29.4, 29.36, 26.9, 24.2, 22.9. **HRMS**: *m/z* calcd for $C_{20}H_{28}N_2O_2$: 328.21453; found: 328.21329. **Elemental anal.:** calcd (%) for $C_{20}H_{28}N_2O_2$ (328.46): C 73.14, H 8.59, N 8.53; found: C 72.03, H 8.42, N 8.36.

_N_2-cyclohexyl-(2_S_)-1-formyltetrahydro-1_H_-2-pyrrolecarboxamide (103)



The general procedure described above was performed on 0.50 mmol scale, using 1.2 equivalents of cyclohexylamine. After workup, the crude product was purified by column chromatography on silica gel with a chloroform-methanol mixture (15 : 1) to give **103** (75 mg, 7%) as a white solid. **IR** (KBr): 3288, 2985, 2933, 2852, 1668, 1646, 1554, 1373, 691 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$, *cis* and *trans* forms): δ 8.27 (s, 1 H, CHO), 6.89 and 5.84 (2 × s, br, 1 H, NH), 4.41–4.44 and 4.29–4.32 (2 × quinlets, *J* = 3.83, 1 H), 3.63–3.79 (m, 1 H), 3.43–3.61 (m, 2 H) 2.43–2.50 (m, 0.8 H), 1.05–2.24 (m, 15 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 170.2, 169.2, 162.3, 162.2, 61.0, 58.0, 48.5, 48.3, 46.9, 44.4, 33.1, 33.0, 32.8, 32.7, 30.4, 26.9, 25.5, 25.4, 24.8, 24.6, 24.2, 22.8. **HRMS**: *m/z* calcd for $C_{12}H_{20}N_2O_2$: 224.15193; found: 224.15179. **Elemental anal.:** calcd (%) for $C_{12}H_{20}N_2O_2$ (224.30): C 64.26, H 8.99, N 12.49; found: C 64.21, H 8.93, N 12.52.

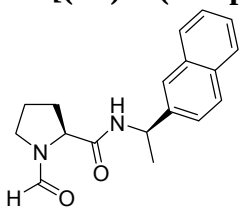
_N_2-[(1_R_)-1-phenylethyl]-(2_S_)-1-formyltetrahydro-1_H_-2-pyrrolecarboxamide (108)



The general procedure described above was performed on 0.50 mmol scale, using 1.2 equivalents of (*R*)-1-methyl-benzylamine. After evaporation of the solvent, the residue was directly purified by column chromatography on silica gel with a chloroform-methanol mixture (20 : 1) to give **108** (96 mg, 78%) as a white solid, mp = 103 °C. **IR** (KBr): 3284, 2982, 2966, 1649, 1528, 1376, 768, 706, 544 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$, *cis* and *trans* forms): δ 8.23 and 8.22 (2 ×s, 1 H,

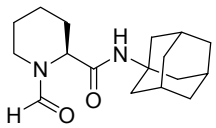
CHO), 7.40 and 6.21 (2 × d, J = 6.6, 1 H, NH), 7.14–7.29 (m, 5 H), 5.04–5.11 and 4.94–5.01 (2 × m, 1 H), 4.46–4.49 and 4.28–4.31 (2 × dd, *J* = 7.7 and 3.6, 1 H), 3.46–3.56 (m, 1 H), 3.34–3.42 (m, 1 H), 2.42–2.50 (m, 0.8 H), 1.70–2.12 (m, 3.5 H), 1.63 (s, 0.7 H), 1.43 and 1.40 (2 × d, *J* = 7.37, 3 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 170.3, 169.1, 162.4, 162.3, 143.5, 142.6, 128.8, 128.6, 127.6, 127.0, 125.9, 125.8, 61.0, 57.9, 49.2, 48.9, 46.9, 44.4, 30.4, 26.7, 24.1, 22.9, 22.7, 21.5. **HRMS**: *m/z* calcd for $C_{14}H_{18}N_2O_2$: 246.13628; found: 246.13662**.** **Elemental anal.:** calcd (%) for $C_{14}H_{18}N_2O_2$ (246.31): C 68.27, H 7.37, N 11.37; found: C 67.08, H 7.39, N 11.37.

***N*2-[(1*R*)-1-(2-naphthyl)ethyl]-(2*S*)-1-formyltetrahydro-1*H*-2-pyrrole-carboxamide (109)**



The general procedure described above was performed on 0.50 mmol scale, using 1.2 equivalents of (*R*)-1-methyl-2-naphthylethylamine. After evaporation of the solvent, the residue was directly purified by column chromatography on silica gel with a chloroform-methanol mixture (20 : 1) to give **109** (120 mg, 81%) as a white solid. **IR** (KBr): 3313, 2972, 1673, 1642, 1534, 1398, 752 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$, *cis* and *trans* forms): δ 8.24 and 8.21 (2 ×s, 1 H, CHO), 7.72–7.76 (m, 3 H), 7.64 (s, 1 H), 7.50 and 6.31 (2 × d, *J* = 8.0, 1 H, NH), 7.28–7.44 (m, 3 H), 5.24 and 5.13 (2 × m, 1 H), 4.50 and 4.30 (2 × dd, *J* = 7.7 and 3.6, *J* = 8.2 and 3.3, 1 H), 3.44–3.53 (m, 1 H), 3.33–3.40 (m, 1 H), 1.62–2.16 (m, 4 H), 1.51 and 1.48 (2 × d, J = 7.0, 3 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 170.4, 169.2, 162.4, 162.3, 140.9, 139.9, 133.4, 133.3, 132.8, 132.6, 128.8, 128.4, 128.0, 127.9, 127.7, 127.6, 126.4, 126.1, 126.08, 125.7, 124.6, 124.45, 124.43, 124.3, 61.0, 58.0, 49.4, 49.0, 46.9, 44.4, 30.4, 29.7, 26.7, 24.2, 22.9, 22.6, 21.4. **HRMS**: *m/z* calcd for $C_{18}H_{20}N_2O_2$: 296.15193; found: 296.15029. **Elemental anal.:** calcd (%) for $C_{18}H_{20}N_2O_2$ (296.37): C 72.95, H 6.80, N 9.45; found: C 72.68, H 6.77, N 9.45.

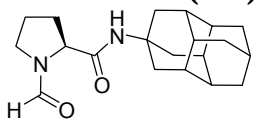
***N*2-(1-adamantyl)-(2*S*)-1-formylhexahydro-2-pyridinecarboxamide (114)**



The general procedure described above was performed with 0.62 mmol of *N*-formyl-L-pipecolinic acid and 1.2 equivalents of 1-aminoadmantane. After workup, the crude product was purified by column chromatography on silica gel with a chloroform-methanol mixture (15 : 1) to give **114** (145 mg, 81 %) as a white solid, mp = 123 °C. **IR** (KBr): 3418, 2911, 2850, 1690, 1667, 1653, 1503, 1410, 549 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$, *cis* and *trans* forms): δ 8.01 (s, 1 H, CHO), 5.61 and 5.52 (2 × s, br, 1 H, NH), 4.8 and 4.01 (2 × d, *J* = 5.6, 1 H), 4.31 and 3.46 (2 × dd, *J* = 13.3 and 3.0, 1 H), 3.16 and 2.63 (2 × td, *J* = 13.0 and 3.0, 1 H), 2.43 and 2.2 (2 × m, 1 H), 2.00 (s, 3 H), 1.60–1.92 (m, 16 H), 1.27–1.5 (m, 2 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 168.8, 168.0, 162.4, 162.3, 58.1, 53.4, 52.4, 51.9, 51.3, 44.3, 41.6, 41.5, 41.3, 38.6, 36.3, 36.2, 36.1, 29.6, 29.5, 29.3, 29.2, 26.8, 25.7, 25.1, 24.5, 21.2, 20.9. **HRMS**: *m/z* calcd for

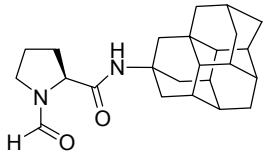
$C_{17}H_{26}N_2O_2$: 290.19888; found: 290.19754. **Elemental anal.:** calcd (%) for $C_{17}H_{26}N_2O_2$ (290.41): C 70.31, H 9.02, N 9.65; found: C 68.67, H 9.04, N 9.22.

*N*2-pentacyclo[7.3.1.1^{4,12}.0^{2,7}.0^{6,11}]tetradec-4-yl-1-formyltetrahydro-1*H*-2-pyrrole-carboxamide (106)



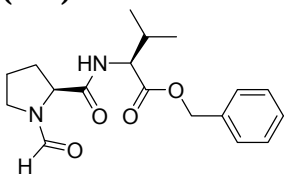
The general procedure described above was performed on 0.50 mmol scale, using 1.0 equivalent of 4-aminodiadmantane. After workup, the crude product was purified by column chromatography on silica gel with a chloroform-methanol mixture (20 : 1) to give **106** (108 mg, 66%) as a white solid. The resulting product was purified again with column chromatography on silica gel with hexane-ethyl acetate mixture (2 : 1) to obtain highly pure product (98 mg, 60%) as a white solid, mp = 214 °C. **IR** (KBr): 3439, 3303, 2884, 2849, 1682, 1638, 1536, 1461, 1348, 1232, 1051, 630 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$, *cis* and *trans* forms): δ 8.22 (s, 1 H, CHO), 6.65 and 5.49 (2 × s, br, 1 H, NH), 4.33 and 4.16 (2 × dd, *J* = 7.8 and 3.9, 1 H), 3.37–3.59 (m, 2 H), 2.34–2.41 (m, 0.8 H), 1.65–2.14 (m, 22 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 170.4, 169.2, 162.2, 162.1, 61.4, 58.5, 51.2, 50.7, 46.9, 44.3, 42.0, 41.9, 38.5, 38.4, 37.3, 37.2, 36.4, 36.3, 30.4, 26.8, 25.6, 25.4, 24.1, 22.8. **HRMS**: *m/z* calcd for $C_{20}H_{28}N_2O_2$: 328.21453; found: 328.21512. **Elemental anal.:** calcd (%) for $C_{20}H_{28}N_2O_2$ (328.46): C 73.14, H 8.59, N 8.53; found: C 72.79, H 8.64, N 8.26.

*N*2-heptacyclo[7.7.1.1^{3,15}.0^{1,12}.0^{2,7}.0^{4,13}.0^{6,11}]octadec-9-yl-1-formyltetrahydro-1*H*-2-pyrrolecarboxamide (107)



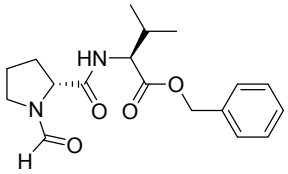
The general procedure described above was performed on 0.50 mmol scale, using 1.0 equivalent of 4-aminotiadmantane. After workup, the crude product was purified by column chromatography on silica gel with a chloroform-methanol mixture (20 : 1) to give **107** (164 mg) as a colorless oil. The resulting product was purified again with column chromatography on silica gel with hexane-ethyl acetate mixture (2 : 1) to obtain highly pure product (121 mg, 64%) as a white solid, mp = 191 °C. **IR** (KBr): 3453, 3290, 3051, 2968, 2873, 1679, 1643, 1540, 1425, 1387, 1333, 1264, 1232, 1221, 1196, 1083, 1058, 1025, 992, 782, 647, 509, 457 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$, *cis* and *trans* forms): δ 8.20 (s, 1 H, CHO), 6.67 and 5.50 (2 × s, br, 1 H, NH), 4.33 and 4.16 (2 × dd, *J* = 8.0 and 4.2, 1 H), 3.37–3.58 (m, 2 H), 2.35–2.42 (m, 0.8 H), 1.75–2.14 (m, 10 H) 1.56–1.63 (m, 10 H), 1.49 (s, 2 H), 1.37 (s, 2 H), 1.24 (s, 2 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 170.4, 169.2, 162.3, 162.1, 61.4, 58.5, 52.3, 51.9, 48.7, 48.6, 46.9, 45.75, 45.74, 45.64, 45.62, 44.8, 44.7, 44.3, 41.9, 41.8, 41.7, 39.1, 39.0, 38.0, 37.8, 37.7, 37.6, 37.4, 37.3, 34.9, 34.8, 34.7, 34.6, 34.1, 34.0, 30.5, 27.25, 27.18, 26.8, 24.2, 22.9. **HRMS**: *m/z* calcd for $C_{24}H_{32}N_2O_2$: 380.24638; found: 380.24370. **Elemental anal.:** calcd (%) for $C_{24}H_{32}N_2O_2$ (380.53): C 75.75, H 8.48, N 8.26; found: C 73.59, H 8.27, N 7.04.

Benzyl (2*S*)-2-[(2*S*)-1-formyltetrahydro-1*H*-2-pyrrolylcarboxamido]-3-methyl-butanoate (110)



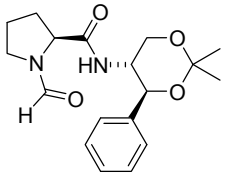
The general procedure described above was performed on 1.0 mmol scale, using 1.0 equivalent of L-valine benzyl ester hydrochloride and 4.3 equivalents of triethylamine. After workup, the crude product was purified by column chromatography on silica gel with a chloroform-methanol mixture (15 : 1) to give **110** (232 mg, 67%) as a colorless oil. **IR** (KBr): 3305, 3064, 2966, 2878, 1740, 1661, 1540, 1383, 1193, 751, 700 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$, *cis* and *trans* forms): δ 8.25 and 8.21 (2 × s, 1 H, CHO), 7.24–7.38 (m, 6 H), 5.03–5.15 (m, 2 H), 4.41–4.54 (m, 2 H), 3.42–3.60 (m, 2 H), 2.39 and 2.13 (2× m, 2 H), 1.78–2.04 (m, 3 H), 0.75–0.85 (m, 6 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 171.5, 171.4, 171.2, 170.3, 162.1, 162.0, 135.5, 135.1, 128.8, 128.7, 128.6, 128.57, 128.5, 128.4, 128.3, 127.0, 125.1, 120.2, 109.4, 85.1, 67.3, 66.9, 60.8, 57.8, 57.6, 57.1, 46.9, 44.3, 31.1, 31.0, 30.5, 27.0, 24.2, 22.9, 19.1, 19.08, 17.6, 17.5. **HRMS**: *m/z* calcd for $C_{18}H_{24}N_2O_4$: 332.17306; found: 332.17052. **Elemental anal.:** calcd (%) for $C_{18}H_{24}N_2O_4$ (332.40): C 65.05, H 7.28, N 8.43; found: C 62.92, H 7.09, N 9.02.

Benzyl (2*S*)-2-[(2*R*)-1-formyltetrahydro-1*H*-2-pyrrolylcarboxamido]-3-methyl-butanoate (111)



The general procedure described above was performed with 1.0 equivalent of *N*-formyl-D-Proline, 1.0 equivalent of L-valine benzyl ester hydrochloride and 4.3 equivalents of triethylamine. After workup, the crude product was purified by column chromatography on silica gel with a chloroform-methanol mixture (15 : 1) to give **111** (76 mg, 23%) as a colorless oil. **IR** (Film): 3294, 3034, 2965, 2877, 1740, 1661, 15391382, 670 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$, *cis* and *trans* forms): δ 8.21 and 8.13 (2 × s, 1 H, CHO), 7.45 and 6.38 (2× d, *J* = 9.2, 1 H, NH), 7.26 (m, 5 H), 4.97–5.15 (m, 2 H), 4.50 (m, 1 H), 4.34 and 4.43 (m, 1 H), 3.44 and 3.31 (2 × m, 2 H), 2.14 and 2.40 (2× m, 2.7 H), 1.72–1.94 (m, 3.3 H), 0.75–0.89 (m, 6 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 171.5, 171.4, 171.3, 171.2, 171.1, 170.3, 162.3, 162.0, 135.5, 135.4, 135.0, 128.6, 128.5, 128.4, 128.3, 128.27, 128.24, 128.19, 128.17, 124.9, 120.0, 109.3, 85.0, 67.1, 66.7, 66.6, 60.6, 59.2, 57.5, 57.4, 57.3,. 57.0, 48.0, 46.6, 44.2, 30.8, 30.6, 30.5, 26.8, 26.7, 24.8, 23.9, 22.7, 22.2, 19.0, 17.44, 17.39. **HRMS**: *m/z* calcd for $C_{18}H_{24}N_2O_4$: 332.17306; found: 332.17072. **Elemental anal.:** calcd (%) for $C_{18}H_{24}N_2O_4$ (332.40): C 65.05, H 7.28, N 8.43; found: C 64.89, H 7.28, N 8.71.

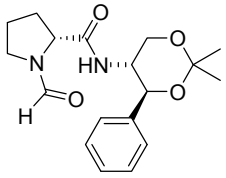
***N*2-[(4*R*,5*R*)-2,2-dimethyl-5-phenyl-1,3-dioxan-4-yl]-(2*S*)-1-formyltetrahydro-1*H*-2-pyrrolecarboxamide (112)**



The general procedure described above was performed on 0.5 mmol scale, using 1.0 equivalent of (4*S*,5*R*)-2,2-dimethyl-4-phenyl-1,3-dioxan-5-amine. After workup, the crude product was purified by column chromatography

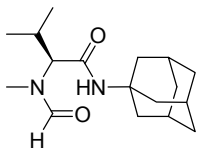
on silica gel with a chloroform-methanol mixture (20 : 1) to give **112** (78 mg, 47%) as a white solid. **IR** (KBr): 3253, 2984, 2873, 1676, 1651, 1552, 1378, 1204, 1076, 700 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$, *cis* and *trans* forms): δ 8.20 and 7.76 (2 × s, 1 H, CHO), 7.37 and 6.36 (2 × d, *J* = 8.8, 1 H, NH), 7.15–7.32 (m, 5 H), 5.17 and 5.10 (2× s, 1 H), 3.96–4.22 (m, 3 H), 3.78 and 3.75 (2 × s, 1 H), 3.37–3.49 (m, 2 H), 1.62–2.00 (m, 4 H), 1.46–1.51 (m, 6 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 170.8, 169.9, 162.0, 161.9, 138.6, 138.1, 128.4, 128.3, 128.1, 127.8, 127.5, 125.7, 125.2, 125.1, 99.6, 99.5, 77.4, 77.1, 76.7, 72.2, 71.6, 64.6, 64.4, 64.3, 60.4, 57.5, 47.4, 47.3, 46.7, 45.5, 44.2, 30.4, 29.8, 29.6, 23.9, 22.7, 18.6, 18.5. **HRMS**: *m/z* calcd for $C_{18}H_{24}N_2O_4$: 332.17306; found: 331.16577 (M^+–1). **Elemental anal.:** calcd (%) for $C_{18}H_{24}N_2O_4$ (332.40): C 65.05, H 7.28, N 8.43; found: C 64.51, H 7.07, N 8.13.

*N*2-[(4*R*,5*R*)-2,2-dimethyl-5-phenyl-1,3-dioxan-4-yl]-(2*R*)-1-formyltetrahydro-1*H*-2-pyrrolecarboxamide (113)



The general procedure described above was performed with 0.5 mmol of *N*-formyl-D-proline and 1.0 equivalent of (4*S*,5*R*)-2,2-dimethyl-4-phenyl-1,3-dioxan-5-amine. After workup, the crude product was purified by column chromatography on silica gel with a chloroform-methanol mixture (20 : 1) to give **113** (78 mg, 47%) as a white solid. **IR** (KBr): 3253, 2984, 2873, 1676, 1651, 1552, 1378, 1204, 1076, 700 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$, *cis* and *trans* forms): δ 8.04 and 8.02 (2 × s, 1 H, CHO), 7.70 and 6.38 (2 × d, J = 9.2, 1 H, NH), 7.14–7.29 (m, 5 H), 5.18 and 5.10 (2 × s, 1 H), 4.49 and 4.40 (2 × d, J = 7.7, 1 H), 4.04–4.22 (m, 2 H), 3.77–3.85 (m, 1 H), 3.35 and 3.25 (2 × m, 1 H), 3.06 and 2.87 (2 × m, 1 H), 2.21 (m, 0.7 H), 1.46–1.97 (m, 10 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 170.7, 170.4, 169.6, 162.1, 162.0, 139.1, 138.9, 138.3, 128.4, 128.3, 127.7, 127.1, 127.0, 125.5, 125.4, 125.2, 124.9, 124.8, 99.7, 99.5, 71.6, 71.3, 71.1, 64.6, 64.4, 64.1, 62.2, 60.7, 59.0, 57.2, 47.6, 47.4, 47.2, 47.0, 46.8, 46.5, 46.1, 45.5, 44.1, 31.6, 30.0, 29.7, 29.6, 26.2, 26.0, 24.5, 23.5, 22.3, 22.0, 18.6, 18.5. **HRMS**: *m/z* calcd for $C_{18}H_{24}N_2O_4$: 332.17306; found: 331.16303 (M^+–1). **Elemental anal.:** calcd (%) for $C_{18}H_{24}N_2O_4$ (332.40): C 65.05, H 7.28, N 8.43; found: C 64.76, H 7.29, N 8.28.

*N*1-(1-adamantyl)-(2*S*)-3-methyl-2-methylformamidobutanamide (115)

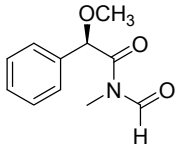


Triethylamine (0.4 mL, 3.0 mmol) was added dropwise to a cooled (0 °C) solution of **126** (462.6 mg, 2.0 mmol) in dry dichloromethane (20 mL). 1-aminoadmantane (302.4 mg, 2.0 mmol) was added, followed by 1-hydoxy-benzhotriazole hydrate (HOBt; 468 mg, ca. 2.6 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI; 500 mg, 2.6 mmol). The mixture was stirred at 0 °C for 1 h, and then at room temperature for 20 h. The mixture was diluted with ethyl acetate (100 mL) and washed successively with water (40 mL), cold 0.5 M HCl (2 × 40 mL), saturated $NaHCO_3$ (2 × 40 mL), and brine (40 mL) and dried over $MgSO_4$, filtered and evaporated to afford crude product (750 mg), which was purified by column

chromatography on silica gel with a hexane-ethyl acetate mixture (6 : 1) to give **127** (585 mg, 80 %) as a colorless oil.

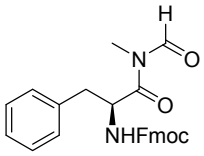
127 (364.5 mg, 1.0 mmol) was then treated with 20% (v/v) trifluoroacetic acid in CH_2Cl_2 (10 mL). After stirring for 1 h at room temperature, the solution was concentrated under reduced pressure to give a TFA salt as an oil, which was dissolved in 98% formic acid (1.5 mL). The solution was cooled down to 0 °C, acetic anhydride (0.68 mL, 7.21 mmol) was added dropwise at the same temperature. The resulting mixture was allowed to stir at room temperature overnight, and then evaporated to dryness. The residue was purified by column chromatography on silica gel with a hexane-ethyl acetate mixture (2 : 1) to give **115** (121 mg, 41%) as a colorless oil. **IR** (KBr): 3525, 3457, 3279, 2966, 2908, 2850, 1672, 1650, 1562, 1063 cm⁻11. **^{1}H NMR** (400 MHz, $CDCl_3$, *cis* and *trans* forms): δ 8.05 and 8.03 (2 × s, 1 H, CHO), 5.70 and 5.39 (2 × s, 1 H, NH), 4.08 and 3.13 (2 × d, *J* = 11.3, 1 H), 2.89 and 2.82 (2 × s, 3 H), 2.19–2.32 (m, 1 H), 1.98 (s, 3 H), 1.90 (s, 6 H), 1.59 (s, 6 H), 0.90 (d, J = 6.6, 3 H), 0.76 (d, *J* = 6.8, 3 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 168.1, 167.8, 163.6, 163.1, 69.2, 62.4, 53.4, 52.5, 52.1, 41.4, 41.38, 36.3, 36.2, 31.2, 29.5, 29.4, 29.2, 27.2, 26.7, 25.3, 19.7, 19.4, 18.9, 18.5. **HRMS**: *m/z* calcd for $C_{17}H_{28}N_2O_2$: 292.21453; found: 292.21292. **Elemental anal.:** calcd (%) for $C_{17}H_{28}N_2O_2$ (292.42): C 69.83, H 9.65, N 9.58; found: C 69.16, H 9.79, N 9.70.

(*R*)-*N*-formyl-*N*-methyl-2-phenylpropanamide (116)



To (*R*)-2-methoxyphenyl acetic acid (**122**) (166.2 mg, 1.0 mmol) and 1 drop DMF in anhydrous CH_2Cl_2 (3 mL) was added dropwise oxalyl chloride (186.1 µl, 2.2 mmol). The resulting solution was stirred for 2 h at room temperature. After removal of the solvent and excess oxalyl chloride under reduced pressure, the residue was dissolved in anhydrous CH_2Cl_2 (2 mL) and cooled to –5 °C under ice-salt bath. Anhydrous pyridine (97.7 µl, 1.2 mmol) was dropwise added, followed by dropwise addition of a solution of *N*-methylformamide (64.3 µl, 1.1 mmol) in anhydrous CH_2Cl_2 (2 mL). The reaction was allowed to stir at room temperature for 2 h. The solvent was then removed *in vacuo*, and the residue was purified by column chromatography on silica gel with hexane-ethyl acetate mixture (3 : 1) to afford the product **116** (115 mg, 56%) as a colorless oil. **IR** (Film): 3386, 2994, 2940, 2830, 1726, 1675, 1283, 1075, 700 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.27 (s, 1 H, CHO), 7.26–7.35 (m, 5 H) 5.17 (s, 1 H), 3.43 (s, 3 H), 3.03 (s, 3 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 172.7, 163.4, 134.7, 129.1, 129.0, 126.2, 85.0, 58.0, 26.6. **HRMS**: *m/z* calcd for $C_{11}H_{13}NO_3$: 207.08899; found: 207.08919. **Elemental anal.:** calcd (%) for $C_{11}H_{13}NO_3$ (207.22): C 63.76, H 6.32, N 6.76; found: C 63.34, H 6.33, N 6.58.

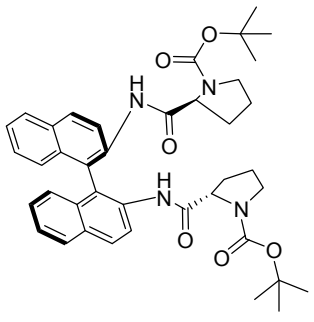
(*S*)-(9H-fluoren-9-yl)methyl 1-(*N*-methylformamido)-1-oxo-3-phenylpropane-2-ylcarbamate (117)



Under an argon atmosphere, $SOCl_2$ (0.729 mL, 10.0 mmol) was added to a suspension of Fmoc-Phe-OH (**123**) (387.4 mg, 1.0 mmol) in anhydrous CH_2Cl_2 (5 mL). The resulting mixture was refluxed for 2 h and the solvent was then removed under reduced pressure. The residue was reevaporated 3 times with addition of CH_2Cl_2 to give white solid. The white solid was dissolved in anhydrous CH_2Cl_2 (2 mL) and another hexane was added to cause precipitations, which was filtered and washed with hexane several times, dried in desiccator under *vacuo* to give the corresponding chloride as white solid.

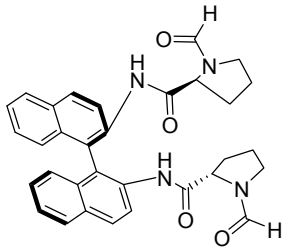
Fmoc-Phe-OH chloride (276 mg, 0.68 mmol) was dissolved in anhydrous CH_2Cl_2 (2 mL) and cooled to 0 °C, followed by the addition of pyridine (66 µl, 0.82 mmol). To the resulted solution was dropwise added a solution of *N*-methylformamide (43.7 µl, 0.75 mmol) in anhydrous CH_2Cl_2 (2 mL). The reaction was allowed to stir at room temperature overnight. The mixture was diluted with ethyl acetate (25 mL), washed with water (10 mL), cold 0.5 M HCl (2 × 10 mL), saturated aqueous $NaHCO_3$ (2 × 10 mL), brine (10 mL), dried over MgSO4, filtered and evaporated to give crude product as an oil, which was purified by column chromatography on silica gel with hexane-ethyl acetate mixture (3 : 1) to afford the product **117** (52 mg, 17.8%) as a white solid. **IR** (KBr): 3346, 1694, 1665, 1533, 760, 742, 701 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$, *cis* and *trans* forms): δ 9.00 and 8.55 (2 × s, 1 H, CHO), 7.04–7.71 (m, 16 H) 5.02 (m, 1 H), 4.29–4.39 (m, 2 H), 3.01 (d, J = 7.1, 2 H), 2.94 (s, 3 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 161.6, 155.6, 143.4, 143.3, 140.6, 136.3, 129.0, 127.9, 127.2, 126.6, 126.3, 124.8, 124.7, 119.4, 67.2, 54.1, 47.1, 39.7, 27.1. **HRMS**: *m/z* calcd for $C_{26}H_{24}N_2O_4$: 428.17306; found: 428.17208. **Elemental anal.:** calcd (%) for $C_{26}H_{24}N_2O_4$ (428.49): C 72.88, H 5.64, N 6.54; found: C 68.61, H 5.01, N 5.57.

Synthesis of *N*2-(*R*)-(1-2-[(2*S*)-1-formyltetrahydro-1*H*-2-pyrrolylcarboxamido]-1-naphthyl-2-naphthyl)-(2*S*)-1-formyltetrahydro-1*H*-2-pyrrolecarboxamide (118)



To a solution of Boc-L-proline (**119**) (344.4 mg, 1.6 mmol) and TEA (223.2, 1.6 mmol) in anhydrous THF (8.0 mL) was added dropwise methyl chloroformate (123.6 µl, 1.6 mmol) at 0 °C under an argon atmosphere. After stirring for 1 h, (*R*)-(+)-1,1′-Bi(2-naphthylamine) (**120**) (227.4 mg, 0.8 mmol) was introduced in small potions. The resulting solution was continued to stir at 0 °C for 1 h, at room temperature for 16 h, and then at reflux for 3 h. After filtration and removal of solvents under reduced pressure, the residue was dissolved in small amount of CH_2Cl_2 and purified by column chromatography on silica gel with hexane-ethyl acetate mixture (1 : 1) to afford **121** (347 mg, 64%) as white solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.00–8.54 (m, 14 H), 3.92–4.08 (m, 2 H), 2.92 (s, br, 2 H), 2.42 (s, br, 2 H), 1.77 (s, br, 4 H), 1.49 (s, br, 3 H), 1.09 (s, br, 20 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 171.4, 170.9,

154.8, 153.6, 134.4, 132.1, 131.2, 129.8, 128.4, 127.8, 125.8, 124.9, 124.4, 121.0, 120.3, 80.1, 61.8, 61.3, 60.4, 46.8, 46.3, 31.0, 29.6, 28.1, 24.0, 23.2, 21.1, 14.2.

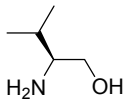


121 (243 mg, 0.36 mmol) was then treated with 20% (v/v) trifluoroacetic acid in CH_2Cl_2 (4 mL). After stirring for 1 h at room temperature, the solution was concentrated under reduced pressure to give a TFA salt as a white solid, which was dissolved in 98% formic acid (1.5 mL). The solution was cooled down to 0 °C, acetic anhydride (1 mL) was added dropwise at the same temperature. The resulting mixture was allowed to stir at room temperature overnight, and then evaporated to dryness. The yellow residue was purified by column chromatography on silica gel and eluted gradually with CH_2Cl_2-Methanol mixture (50 : 1 (100 mL); 40 : 1 (100 mL); 30 : 1 (100 mL); 20 : 1 (200 mL)) to afford **118** (146 mg, 76%). **IR** (KBr): 3380, 3250, 3055, 2974, 2878, 1657, 1502, 819 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.36 (s, 0.4 H, CHO), 7.80–8.15 (m, 7 H), 7.05–7.47 (m, 7 H), 3.95–4.22 (m, 2 H), 1.18–2.02 (m, 8 H), 2.54–3.18 (m, 4 H). **^{13}C NMR** (150 MHz, $CDCl_3$): δ = 170.8, 170.0, 169.4, 166.7, 164.0, 163.1, 161.4, 159.5, 158.6, 155.9, 134.6, 134.3, 134.0, 133.5, 132.5, 132.4, 132.2, 132.1, 132.0, 131.9, 131.6, 129.6, 129.5, 129.2, 128.3, 127.9, 127.6, 127.1, 127.0, 126.5, 125.8, 125.4, 125.0, 123.9, 123.4, 61.0, 58.4, 58.3, 58.0, 57.6, 46.0, 45.9, 45.7, 43.8, 43.4, 30.1, 29.9, 29.7, 28.3, 27.8, 27.6, 26.8, 26.7, 23.6, 23.5, 23.0, 22.4, 22.1, 21.7, 20.7. **HRMS**: *m/z* calcd for $C_{32}H_{30}N_4O_4$: 534.22616; found: 534.22622. **Elemental anal.:** calcd (%) for $C_{32}H_{30}N_4O_4$ (534.62): C 71.89, H 5.65, N 10.48; found: C 69.21, H 5.69, N 9.97.

7.4 Synthesis of oxazoline thioureas(In cooperation with Mike Kotke)

7.4.1 Synthesis of L-amino alcohols[266]

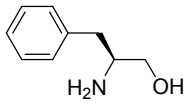
(2*S*)-2-amino-3-methylbutan-1-ol (130a)



A 1-L three-neck round-bottom flask was fitted with a magnetic stirbar, a reflux condenser, and an additional funnel. The flask was charged with sodium borohydride (9.11 g, 240.8 mmol) and 200 mL of anhydrous THF. L-valine (11.72 g, 100 mmol) was added in one portion. The remaining neck was sealed with a septum and an argon line attached, and the flask was cooled to 0 °C in an ice bath. A solution of iodine (25.38 g, 100 mmol) in THF (66 mL) was poured into the addition funnel and added slowly and dropwise over 30 min resulting in vigorous evolution of hydrogen. After addition of the iodine was complete and gas evolution had ceased, the flask was heated to reflux for 18 h and then cooled to room temperature, and methanol was added cautiously until the mixture became clear. After stirring 30 min, the solvent was removed by rotary evaporation leaving a white paste which was dissolved by addition of 200 mL of 20% aqueous KOH. The solution was stirred for 4 h and extracted with methylene chloride (3 × 200 mL). The organic extracts

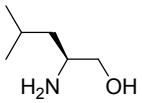
were dried over sodium sulfate and concentrated *in vacuo*, the residue was distilled under reduced pressure to yield **130a** (8.03 g, 78 %) as a colorless solid, mp 32 °C.

(2*S*)-2-amino-3-phenylpropan-1-ol (130b)



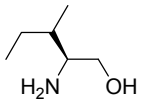
L-Phenylalaninol was prepared from L-phenylalanine by the general procedure described above. The crude material was recrystallized from toluene to yield 70% of **130b** as a colorless crystal: mp 90–92 °C, **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.15–7.30 (m, 5 H), 3.60 (dd, *J* = 10.8, 4.0, 1 H), 3.36 (dd, *J* = 10.4, 7.0, 1 H), 3.08 (m, 1 H), 2.76 (dd, *J* = 13.4, 5.1, 1 H), 2.49 (dd, *J* = 13.4, 8.6, 1 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 138.7, 129.2, 128.6, 126.4, 66.4, 54.1, 41.0.

(2*S*)-2-amino-4-methylpentan-1-ol (130c)



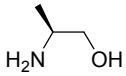
130c was prepared from L-isoleucine by the general procedure described above. The crude product was distilled under reduced pressure to yield 68% of **130c** as a colorless solid: mp 38–40 °C, **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.53–3.57 (dd, *J* = 10.6, 3.9, 1 H), 3.22–3.26 (dd, *J* = 10.6, 7.9, 1 H), 2.91 (m, 1 H), 2.63 (br, 3 H, NH and OH), 1.70 (m, 1 H), 1.19 (m, 2 H), 0.93 (d, *J* = 6.4, 3 H), 0.90 (d, *J* = 6.4, 3 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 66.6, 50.4, 43.2, 24.5, 23.2, 22.0.

(2*S*)-2-amino-3-methylpentan-1-ol (130d)



130d was prepared from L-isoleucine by the general procedure described above. The crude product was distilled under reduced pressure to yield 78% of **130d** as a colorless solid: mp 32 °C, **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.60–3.64 (dd, *J* = 10.7, 3.8, 1 H), 3.28–3.33 (dd, *J* = 10.7, 8.4, 1 H), 2.65 (m, 1 H), 1.45 (m, 1 H), 1.37 (m, 1 H), 1.16 (m, 1 H), 0.86–0.91 (m, 6 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 64.1, 56.9, 38.1, 25.2, 15.0, 11.2.

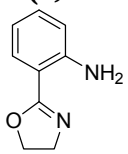
(2*S*)-2-aminopropan-1-ol (130e)[267]



Lithium aluminum hydride (17.0 g, 0.43 mmol) was suspended in 600 mL of anhydrous THF at 0 °C. L-Valine (20.0 g, 0.22 mmol) was added slowly in small portions. The reaction mixture was refluxed overnight and then cooled to room temperature. Saturated K_2CO_3 solution was added slowly. Filtration and evaporation of solvent gave a colorless oil. Distillation of the crude oil under reduced pressure yielded **130e** (6.0 g, 36%) as a light yellowish oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.50 (m, 1 H), 3.23 (m, 1 H), 2.99 (br, 4 H), 1.04 (m, 3 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 67.7, 48.1, 19.2.

7.4.2 General procedure for oxazoline formation.

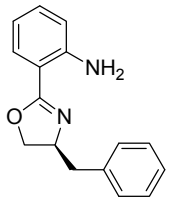
2-(4,5-Dihydro-1,3-oxazol-2-yl)aniline (131a)



An oven-dried 50 mL 2-neck round-bottom flask was fitted with a magnetic stirbar and a reflux condenser. Under argon atmosphere, the flask was charged

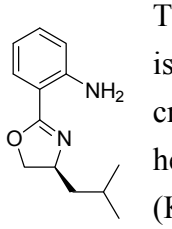
with anthranilonitrile (2.95 g, 25 mmol) and 2-aminoethanol (4.6 g, 75 mmol), in anhydrous PhCl (40 mL), using $ZnCl_2$ (0.51 g, 3.75 mmol) as a catalyst. The mixture was refluxed about 36 h to give a red solution. The solvent was removed and the crude product was dissolved in CH_2Cl_2. After washing with H_2O, the organic layer was dried over Na_2SO_4 and the solvent was removed *in vacuo*. The residue was purified by column chromatography on silica gel using hexane/EtOAc (19:1) as eluent to yield **131a** (1.46, 36%) as a yellow solid. IR (KBr): 3388, 3269, 2934, 2875, 1631, 750 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.70 (dd, *J* = 7.9, 1.6, 1 H), 7.20 (m, 1 H), 6.70 (dd, *J* = 8.3, 0.8, 1 H), 6.66 (m, 1 H), 6.06 (br, 2 H, NH), 4.31 (t, *J* = 9.4, 2 H), 4.10 (t, *J* = 9.4, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.9, 148.5, 132.0, 129.6, 115.8, 115.5, 109.2, 65.8, 55.0.

2-[(4*S*)-4-Benzyl-4,5-dihydro-1,3-oxazol-2-yl]aniline (131b)



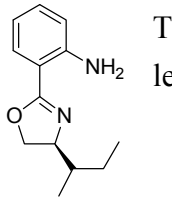
This compound was prepared from anthranilonitrile (3.0 g, 25.0 mmol) and L-phenylalanol (11.2 g, 74.1 mmol) by the general procedure described above. The crude product was purified by column chromatography on silica gel using hexane/EtOAc (10:1) as eluent to yield **131b** (1.5 g, 23.8%) as a white solid. **IR** (KBr): 3395, 3273, 2909, 1630, 751 cm^{-1}. **^1H NMR** (400 MHz, $CDCl_3$): δ 7.65 (dd, *J* = 7.9, 1.7, 1 H), 7.17–7.32 (m, 6 H), 6.61–6.69 (m, 2 H), 6.08 (br, 2 H, NH), 4.59 (m, 1 H), 4.26 (m, 1 H), 4.01 (m, 1 H), 3.12 (dd, *J* = 13.7, 6.2, 1 H), 2.75 (dd, *J* = 13.7, 7.9, 1 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 164.3, 148.9, 138.6, 132.3, 129.8, 129.4, 128.7, 126.6, 116.2, 115.9, 109.2, 70.4, 68.3, 42.4. **HRMS**: *m/z* calcd for $C_{16}H_{16}N_2O$: 252.12571; found: 252.12260. **Elemental anal.:** calcd (%) for $C_{16}H_{16}N_2O$ (252.32): C 76.16, H 6.39, N 11.10; found: C 76.16, H 6.32, N 11.07.

2-[(4*S*)-4-Isobutyl-4,5-dihydro-1,3-oxazol-2-yl]aniline (131c)



This compound was prepared from anthranilonitrile (2.95 g, 25.0 mmol) and L-isoleucinol (8.78 g, 75.0 mmol) by the general procedure described above. The crude product was purified by column chromatography on silica gel using hexane/EtOAc (9:1) as eluent to yield **131c** (0.9 g, 16.5%) as a white solid. **IR** (KBr): 3416, 3278, 2953, 1640, 746 cm^{-1}. **^1H NMR** (400 MHz, $CDCl_3$): δ 7.68 (dd, *J* = 7.9, 1.6, 1 H), 7.19 (m, 1 H), 6.63–6.70 (m, 2 H), 6.10 (br, 2 H, NH), 4.33–4.42 (m, 2 H), 3.86 (m, 1 H), 1.86 (m, 1 H), 1.65 (m, 1 H), 1.39 (m, 1 H), 0.98 (t. *J* = 6.4, 6 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 163.4, 148.5, 131.8, 129.5, 116.0, 115.6, 109.3, 71.4, 65.2, 45.8, 25.7, 22.9, 22.6. **HRMS**: *m/z* calcd for $C_{13}H_{18}N_2O$: 218.14136; found: 218.14213. **Elemental anal.:** calcd (%) for $C_{13}H_{18}N_2O$ (218.30): C 71.53, H 8.31, N 12.83; found: C 71.65, H 8.29, N 12.75.

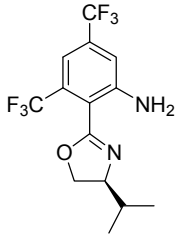
2-[(4*S*)-4-(*sec*-Butyl)-4,5-dihydro-1,3-oxazol-2-yl]aniline (131d)



This compound was prepared from anthranilonitrile (2.95 g, 25.0 mmol) and L-leucinol (8.78 g, 75.0 mmol) by the general procedure described above. The

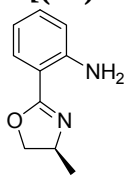
crude product was purified by column chromatography on silica gel using hexane/EtOAc (9:1) as eluent to yield **131d** (2.3 g, 42.1%) as a white solid. **IR** (KBr): 3464, 3287, 2962, 1638, 749 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.66 (dd, *J* = 7.8, 1.5, 1 H), 7.16 (m, 1 H), 6.61–6.67 (m, 2 H), 6.10 (br, 2 H, NH), 4.27 (m, 2 H), 4.19 (m, 1 H), 3.97 (m, 1 H), 1.62 (m, 2 H), 1.22 (m, 1 H), 0.93 (t. *J* = 7.4, 3 H), 0.86 (d, *J* = 6.7, 3 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 163.4, 148.5, 131.8, 129.5, 115.9, 115.5, 109.1, 71.5, 68.3, 39.5, 26.0, 14.7, 11.4. **HRMS**: *m/z* calcd for $C_{13}H_{18}N_2O$: 218.14136; found: 218.41210. **Elemental anal.:** calcd (%) for $C_{13}H_{18}N_2O$ (218.30): C 71.53, H 8.31, N 12.83; found: C 71.07, H 8.31, N 12.83.

2-[(4*S*)-4-Isopropyl-4,5-dihydro-1,3-oxazol-2-yl]-3,5-di(trifluoromethyl)aniline (131e)



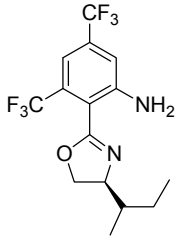
This compound was prepared from anthranilonitrile-2 (2.54 g, 10.0 mmol) and L-valinol (3.09 g, 30.0 mmol) by the general procedure described above. The crude product was purified by column chromatography on silica gel using hexane/EtOAc (9:1) as eluent to yield **131e** (1.5 g, 44.2%) as a white solid. **IR** (KBr): 3452, 3324, 3203, 2974, 1667, 698 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.24 (s, 1 H), 7.10 (s, 1 H), 5.57 (br, 2 H, NH), 4.41 (dd, *J* = 9.1, 7.6, 1 H), 4.10–4.21 (m, 2 H), 1.83–1.91 (m, 1 H), 1.04 (d, *J* = 6.7, 3 H), 0.97 (d, *J* = 6.9, 3 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 160.9, 148.3, 133.2, 132.9, 132.6, 132.3, 132.2, 131.9, 131.6, 131.2, 127.2, 124.5, 121.8, 115.7, 112.0, 72.8, 70.0, 32.7, 18.8, 18.4. **HRMS**: *m/z* calcd for $C_{14}H_{14}N_2OF_6$: 340.10103; found: 340.10040. **Elemental anal.:** calcd (%) for $C_{14}H_{14}F_6N_2O$ (340.26): C 49.42, H 4.15, N 8.23; found: C 49.38, H 4.03, N 8.56.

2-[(4*S*)-4-Methyl-4,5-dihydro-1,3-oxazol-2-yl]aniline (131f)



This compound was prepared from anthranilonitrile (2.96 g, 25.0 mmol) and L-alaninol (5.6 g, 74.5 mmol) by the general procedure described above. The crude product was purified by column chromatography on silica gel using hexane/EtOAc (9:1) as eluent to yield **131f** (2.4 g, 54.5%) as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.67 (dd, *J* = 7.9, 1.5, 1 H), 7.16 (m, 1 H), 6.61–6.66 (m, 2 H), 6.06 (br, 2 H, NH), 4.33–4.43 (m, 2 H), 3.80 (m. 1 H), 1.31 (d, *J* = 6.4, 3 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 163.4, 148.4, 131.8, 129.5, 115.9, 115.5, 109.0, 72.1, 62.0, 21.6.

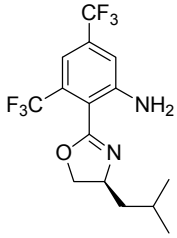
2-[(4*S*)-4-(*sec*-Butyl)-4,5-dihydro-1,3-oxazol-2-yl]-3,5-di(trifluoromethyl)aniline (131g)



This compound was prepared from anthranilonitrile-2 (2.0 g, 7.87 mmol) and L-leucinol (2.76 g, 23.61 mmol) by the general procedure described above. The crude product was purified by column chromatography on silica gel using hexane/EtOAc (9:1) as eluent to yield **131g** (1.34 g, 48.0%) as a white solid. **IR** (KBr): 3432, 3321, 3199, 2979, 1668, 874 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.21 (s, 1 H), 7.07 (s, 1 H), 5.54 (br, 2 H, NH), 4.36 (m, 1 H), 4.26 (m, 1 H), 4.09 (m, 1 H), 1.69 (m, 1 H), 1.58 (m, 1 H), 1.22 (m, 1 H), 0.94 (t, *J* = 7.5, 3 H),

0.88 (d, *J* = 6.8, 3 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 160.8, 148.3, 133.2, 132.9, 132.6, 132.23, 132.19, 131.9, 131.5, 131.2, 127.2, 127.1, 124.5, 124.4, 121.8, 121.7, 119.0, 115.7, 112.0, 111.7, 71.3, 69.5, 39.0, 26.1, 14.5, 11.4. **HRMS**: *m/z* calcd for $C_{15}H_{16}F_6N_2O$: 354.11613; found: 354.11649. **Elemental anal.:** calcd (%) for $C_{15}H_{16}F_6N_2O$ (354.30): C 50.85, H 4.55, N 7.91; found: C 50.90, H 4.44, N 7.62.

2-[(4*S*)-4-Isobutyl-4,5-dihydro-1,3-oxazol-2-yl]-3,5-di(trifluoromethyl)aniline (131h)

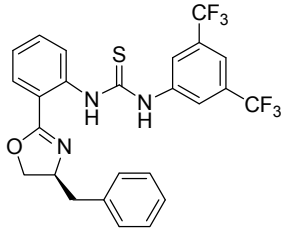


This compound was prepared from anthranilonitrile-2 (2.0 g, 7.87 mmol) and L-isoleucinol (2.76 g, 23.61 mmol) by the general procedure described above. The crude product was purified by column chromatography on silica gel using hexane/EtOAc (9:1) as eluent to yield **131h** (1.8 g, 64.5%) as a white solid. **IR** (KBr): 3440, 3325, 3201, 2967, 1668, 1642, 696 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.22 (s, 1 H), 7.08 (s, 1 H), 5.46 (br, 2 H, NH), 4.46 (dd, *J* = 9.4, 7.9, 1 H), 4.38 (m, 1 H), 3.96 (t. J = 7.9, 1 H), 1.81 (m, 1 H), 1.66 (m, 1 H), 1.40 (m, 1 H), 0.96 (t, *J* = 6.9, 6 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 160.7, 148.2, 132.9, 132.6, 131.9, 131.5, 124.5, 124.4, 121.8, 121.7, 115.74, 115.71, 112.1, 112.0, 111.9, 72.8, 65.1, 45.4, 25.6, 22.8, 22.6. **HRMS**: *m/z* calcd for $C_{15}H_{16}F_6N_2O$: 354.11613; found: 354.11653. **Elemental anal.:** calcd (%) for $C_{15}H_{16}F_6N_2O$ (354.30): C 50.85, H 4.55, N 7.91; found: C 51.03, H 4.48, N 7.65.

7.4.3 General procedure for thiourea formation

One oven-dried two-neck round-bottom flask was fitted with magnetic stirbar and an addition funnel. Under an argon atmosphere, the flask was charged with ISO-1 (1.08 g, 4.0 mmol) and anhydrous THF (5 mL), followed by dropwise addition of a solution of oxazoline (1.0 equiv.) in anhydrous THF (15 mL) under 0 °C. The resulting mixture was stirred overnight at room temperature. The solvent was removed by rotary evaporation and the residue was purified by column chromatography on silica gel using hexane/EtOAc (5:1) as eluent to yield the corresponding product.

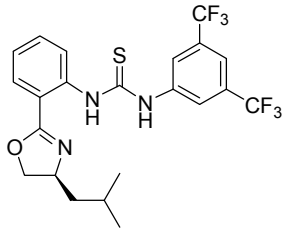
2-[(4*S*)-4-Benzyl-4,5-dihydro-1,3-oxazol-2-yl]anilino-3,5-di(trifluoromethyl)anilino methanethione (128b)



This compound was prepared from **131b** (1.16 g, 4.6 mmol) and **133** (1.0 equiv.) by the general procedure described above. The crude product was purified by column chromatography on silica gel using hexane/EtOAc (5:1) as eluent to yield **128b** (0.9 g, 43.0%) as a white solid. **IR** (KBr): 3345, 2909, 2791, 1634, 1276, 1120, 699 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 13.03 (s, 1 H, NH), 9.06 (d, *J* = 8.5, 1 H, NH), 7.83–7.87 (m, 2 H), 7.71 (s, 1 H), 7.52 (m, 1 H), 7.10–7.32 (m, 8 H), 4.49 (m, 1 H), 4.40 (m, 1 H), 4.09 (m, 1 H), 2.78 (m, 1 H), 2.66 (m, 1 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 178.9, 164.0, 140.1, 137.8, 132.0, 129.4, 129.0, 128.6, 126.8, 124.6, 123.4, 121.0, 114.5, 71.1, 67.4, 41.9. **HRMS**:

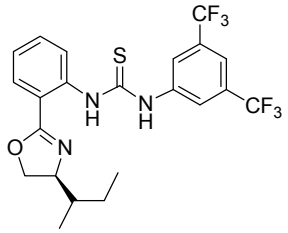
m/z calcd for $C_{25}H_{19}F_6N_3OS$: 523.11475; found: 523.11217. **Elemental anal.:** calcd (%) for $C_{25}H_{19}F_6N_3OS$ (523.49): C 57.36, H 3.66, N 8.03; found: C 57.47, H 3.53, N 7.98.

3,5-Di(trifluoromethyl)anilino-2-[(4*S*)-4-isobutyl-4,5-dihydro-1,3-oxazol-2-yl]aniline methanethione (128c)



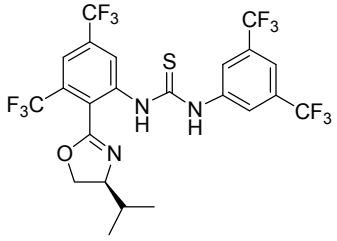
This compound was prepared from **131c** (0.87 g, 4.0mmol) and **133** (1.0 equiv.) by the general procedure described above. The crude product was purified by column chromatography on silica gel using hexane/EtOAc (5:1) as eluent to yield **128c** (0.6 g, 30.6%) as a white solid. **IR** (KBr): 3190, 2965, 2929, 1640, 1275, 682 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 13.16 (s, 1 H, NH), 8.94 (d, *J* = 8.4, 1 H, NH), 8.07 (s, 1 H), 7.84 (m, 3 H), 7.68 (m, 1 H), 7.52 (m, 1 H), 7.17 (m, 1 H), 4.34 (m, 1 H), 4.03 (m, 1 H), 3.85 (m, 1 H), 1.37 (m, 1 H), 1.11 (m, 2 H), 0.80 (m, 6 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 178.8, 163.0, 139.7, 139.3, 133.0, 131.7, 129.3, 123.7, 123.2, 121.4, 118.8, 118.76, 118.7, 115.2, 71.8, 64.6, 45.0, 25.3, 22.5, 22.3. **HRMS**: *m/z* calcd for $C_{22}H_{21}F_6N_3OS$: 489.13040; found: 489.13256. **Elemental anal.:** calcd (%) for $C_{22}H_{21}F_6N_3OS$ (489.48): C 53.98, H 4.32, N 8.58; found: C 53.43, H 4.28, N 8.59.

3,5-Di(trifluoromethyl)anilino-2-[(4*S*)-4-(*sec*-butyl)-4,5-dihydro-1,3-oxazol-2-yl]aniline methanethione (128d)



This compound was prepared from **131d** (0.87 g, 4.0mmol) and **133** (1.0 equiv.) by the general procedure described above. The crude product was purified by column chromatography on silica gel using hexane/EtOAc (5:1) as eluent to yield **128d**(1.08 g, 55.6%) as a white solid. **IR** (KBr): 3169, 2966, 1637, 1377, 1277, 682 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 13.10 (s, 1 H, NH), 8.89 (d, *J* = 8.3, 1 H, NH), 8.12 (s, 1 H), 7.80–7.82 (m, 3 H), 7.66 (s, 1 H), 7.50 (m, 1 H), 7.15 (m, 1 H), 4.24 (m, 1 H), 4.00 (t, *J* = 8.3, 1 H), 3.88 (m, 1 H), 1.19 (m, 2 H), 0.86 (m, 1 H), 0.78 (m, 3 H), 0.61 (m, 3 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 178.9, 163.1, 139.7, 139.4, 133.0, 132.7, 131.7, 129.3, 123.7, 123.4, 121.5, 118.8, 115.2, 70.8, 68.6, 38.8, 25.7, 14.0, 11.2. **Elemental anal.:** calcd (%) for $C_{22}H_{21}F_6N_3OS$ (489.48): C 53.98, H 4.32, N 8.58; found: C 54.00, H 4.25, N 8.59.

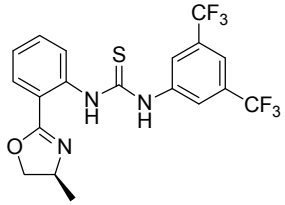
3,5-Di(trifluoromethyl)anilino-2-[(4*S*)-4-isopropyl-4,5-dihydro-1,3-oxazol-2-yl]-3,5-di(trifluoromethyl)anilinomethanethione (128f)



This compound was prepared from **131e** (1.02 g, 3.0mmol) and **133** (1.0 equiv.) by the general procedure described above. The crude product was purified by column chromatography on silica gel using hexane/EtOAc (5:1) as eluent to yield **128f** (0.22 g, 14.8%) as a white solid. **IR** (KBr): 3418, 2971, 1377, 1279, 1131, 683 cm^{-1}. **^{1}H NMR** (400 MHz, d_6-DMSO): δ 10.79 (s, 1 H, NH), 10.05 (s, 1 H, NH), 8.41 (s, 1 H), 8.26 (s, 2 H), 8.08 (s, 1 H), 7.89 (s, 1 H), 4.47 (m, 1 H), 4.16

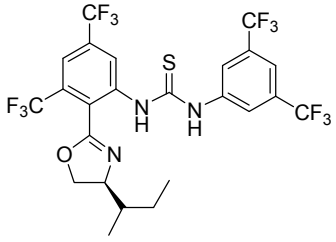
(m, 1 H), 4.08 (m, 1 H), 1.75 (m, 1 H), 0.90 (t, *J* = 6.6, 3 H), 0.86 (d, *J* = 6.8, 3 H). **^{13}C NMR** (100 MHz, d_6-DMSO): δ = 180.7, 157.3, 140.9, 140.1, 130.6, 130.5, 130.3, 130.2, 130.0, 129.8, 129.7, 127.3, 124.4, 123.7, 121.7, 120.8, 117.8, 72.7, 70.6, 31.8, 18.4, 18.1. **HRMS**: *m/z* calcd for $C_{23}H_{17}F_{12}N_3OS$: 611.08952; found: 611.09362. **Elemental anal.:** calcd (%) for $C_{23}H_{17}F_{12}N_3OS$ (611.45): C 45.18, H 2.80, N 7.07; found: C 45.33, H 2.67, N 6.75.

3,5-Di(trifluoromethyl)anilino-2-[(4*S*)-4-methyl-4,5-dihydro-1,3-oxazol-2-yl]aniline methanethione (128e)



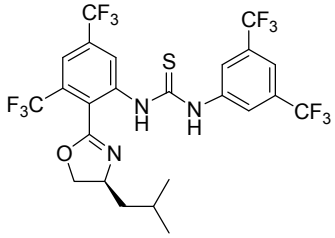
This compound was prepared from **131f** (1.76 g, 10.0 mmol) and **133** (1.0 equiv.) by the general procedure described above. The crude product was purified by column chromatography on silica gel using hexane/EtOAc (5:1) as eluent to yield **128e** (2.08 g, 46.5%) as a white solid. **IR** (KBr): 3198, 3042, 2976, 2898, 1639, 1618, 891, 683 cm^{-1}. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 12.96 (br, 1 H, NH), 8.94 (d, *J* = 8.3, 1 H), 8.69 (br, 1 H, NH), 7.86 (s, 2 H), 7.80 (dd, *J* = 7.9, 1.5, 1 H), 7.72 (s, 1 H), 7.51 (m, 1 H), 7.15 (m, 1 H), 4.36 (t, *J* = 8.8, 1 H), 3.99 (m, 1 H), 3.79 (t, *J* = 8.0, 1 H), 0.90 (d, *J* = 6.7, 3 H). **^{13}C NMR** (150 MHz, $CDCl_3$): δ = 179.0, 163.1, 139.6, 139.1, 133.1, 132.9, 132.7, 132.5, 131.7, 124.7, 123.8, 121.8, 119.4, 115.3, 72.9, 61.4, 20.9. **HRMS**: *m/z* calcd for $C_{19}H_{15}F_6N_3OS$: 447.08345; found: 447.08155. **Elemental anal.:** calcd (%) for $C_{19}H_{15}F_6N_3OS$ (447.40): C 51.01, H 3.38, N 9.39; found: C 50.80, H 3.23, N 9.62.

3,5-Di(trifluoromethyl)anilino-2-[(4*S*)-4-(*sec*-butyl)-4,5-dihydro-1,3-oxazol-2-yl]-3,5-di(trifluoromethyl)anilinomethanethione (128g)



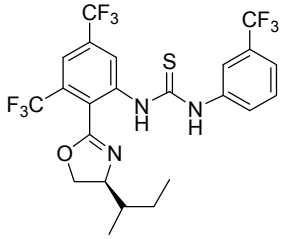
This compound was prepared from **131g** (0.77 g, 2.17 mmol) and **133** (1.1 equiv.) by the general procedure described above. The crude product was purified by column chromatography on silica gel using hexane/EtOAc (5:1) as eluent to yield **128g** (0.69 g, 51.0%) as a white solid. **IR** (KBr): 3427, 3179, 2972, 1375, 1279, 683 cm^{-1}. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 10.81 (br, 1 H, NH), 10.10 (br, 1 H, NH), 8.42 (s, 1 H), 8.26 (s, 2 H), 8.08 (s, 1 H), 7.89 (s, 1 H), 4.46 (m, 1 H), 4.16 (m, 1 H), 1.48–1.58 (m, 2 H), 1.06–1.13 (m, 1 H), 0.79–0.81 (m, 6 H). **^{13}C NMR** (150 MHz, $CDCl_3$): δ = 180.7, 157.3, 140.9, 140.1, 130.7, 130.6, 130.4, 130.2, 130.0, 129.9, 129.7, 127.1, 125.8, 124.0, 123.6, 123.4, 122.2, 121.8, 121.5, 120.9, 120.4, 117.8, 71.3, 70.2, 38.2, 25.2, 14.2, 11.1. **HRMS**: *m/z* calcd for $C_{24}H_{19}F_{12}N_3OS$: 625.10537; found: 625.10179. **Elemental anal.:** calcd (%) for $C_{24}H_{19}F_{12}N_3OS$ (625.47): C 46.09, H 3.06, N 6.72; found: C 46.08, H 2.82, N 6.70.

3,5-Di(trifluoromethyl)anilino-2-[(4*S*)-4-isobutyl-4,5-dihydro-1,3-oxazol-2-yl]-3,5-di(trifluoromethyl)anilinomethanethione (128h)



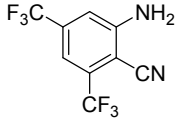
This compound was prepared from **131h** (1.06 g, 3.0 mmol) and **133** (1.1 equiv.) by the general procedure described above. The crude product was purified by column chromatography on silica gel using hexane/EtOAc (5:1) as eluent to yield **128h** (0.93 g, 42.1%) as a white solid. **IR** (KBr): 3428, 3177, 2972, 1375, 683 cm^{-1}. **^{1}H NMR** (400 MHz, d_6-DMSO): δ 10.71 (s, 1 H, NH), 10.03 (br, 1 H, NH), 8.35 (s, 1 H), 8.27 (s, 2 H), 8.03 (s, 1 H), 7.83 (s, 1 H), 4.50 (t, *J* = 8.8, 1 H), 4.28 (m, 1 H), 3.99 (t, *J* = 7.9, 1 H), 1.70 (m, 1 H), 1.48 (m, 1 H), 1.30 (m, 1 H), 0.83 (d, *J* = 6.5, 3 H), 0.86 (d, *J* = 6.6, 3 H). **^{13}C NMR** (100 MHz, d_6-DMSO): δ = 177.3, 159.1, 158.6, 156.2, 150.4, 150.2, 149.3, 141.5, 140.6, 131.3, 131.0, 130.6, 130.3, 124.9, 124.5, 124.0, 122.2, 121.8, 118.6, 118.0, 116.4, 115.2, 112.8, 107.0, 72.4, 64.8, 62.2, 60.9, 25.0, 22.7. **HRMS**: *m/z* calcd for $C_{24}H_{19}F_{12}N_3OS$: 625.10537; found: 625.10243. **Elemental anal.:** calcd (%) for $C_{24}H_{19}F_{12}N_3OS$ (625.47): C 46.09, H 3.06, N 6.72; found: C 46.16, H 2.86, N 6.78.

2-[(4*S*)-4-(*sec*-butyl)-4,5-dihydro-1,3-oxazol-2-yl]-3,5-di(trifluoromethyl)anilino-3-trifluoromethylanilinomethanethione (128i)



This compound was prepared from **131g** (1.06 g, 3.0mmol) by the general procedure described above. The crude product was purified by column chromatography on silica gel using hexane/EtOAc (5:1) as eluent to yield **128i** (0.86 g, 51.2%) as a white solid. **IR** (KBr): 3179, 2968, 1670, 1537, 1136, 699 cm^{-1}. **^{1}H NMR** (400 MHz, d_6-DMSO): δ 10.71 (s, 1 H, NH), 9.88 (s, 1 H, NH), 8.52 (s, 1 H), 7.99 (s, 2 H), 7.76 (d, *J* = 7.8, 1 H), 7.60 (dd, *J* = 9.1, 7.8, 1 H), 7.52 (d, J = 7.8, 1 H), 4.43 (m, 1 H), 4.15 (m, 1 H), 1.44–1.55 (m, 2 H), 1.03–1.13 (m, 1 H), 0.76–0.82 (m, 6 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 180.2, 157.4, 140.3, 139.4, 130.2, 129.8, 129.4, 129.2, 127.4, 125.8, 121.5, 121.1, 119.9, 71.1, 70.0, 25.2, 14.1, 11.2. **HRMS**: *m/z* calcd for $C_{23}H_{20}F_9N_3OS$: 557.11779; found: 557.11459. **Elemental anal.:** calcd (%) for $C_{23}H_{20}F_9N_3OS$ (557.48): C 49.55, H 3.62, N 7.54; found: C 49.09, H 3.45, N 7.41.

Synthesis of 2-amino-4,6-di(trifluoromethyl)benzonitrile (134)

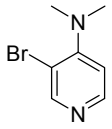


Under an argon atmosphere, to a 3-neck round-bottom flask equipped with magnetic stirbar and thermometer was added ethyl cyanoacetate (13.84 g, 0.12 mmol, 98%), anhydrous powder KOH (2.60 g, 0.04 mol), and dry DMF (120 mL). The resulting mixture was stirred vigorously at room temperature, and then was cooled down to 0 °C and stirred for 60 min. The solvent was removed *in vacuo*. The residue was mixed with 80 mL of 5% NaOH solution and refluxed for 60 min. The reaction was cooled down to room temperature and chloroform (180 mL) was added. After separation of the organic phase, the aqueous phase was extracted with chloroform (2 × 100 mL). The

combined organic phase was dried over Na_2SO_4, filtered, and evaporated to afford the crude product as a brown solid, which was purified by column chromatography on silica gel using chloroform as eluent, yielding the product (4.89 g, 48.1%) as a yellow solid. **IR** (KBr): 3509, 3359, 3247, 2234, 1647, 1584 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.26 (s, 1 H), 7.21 (s, 1 H), 5.02 (br, 2 H, NH). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 151.6, 136.0, 135.7, 135.4, 135.0, 134.8, 134.4, 134.1, 133.8, 126.5, 126.0, 115.3, 113.3, 111.6, 94.6.

7.5 Synthesis of bifunctional thioureas

3-Bromo-4-dimethylaminopyridine.



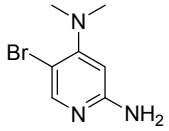
A 1000 mL-round-flask equipped with a magnetic stirbar and a dropping funnel was charged sequentially with 4-dimethylaminopyridine (DMAP, 20.0 g, 164.0 mmol), CH_2Cl_2 (400 mL), saturated aqueous K_2CO_3 (400 mL) and 1.3% (w/w) nBu_4OH (20 mL). The resulting mixture was stirred vigorously while a solution of Br_2 (20.8 mL, 328 mmol) in 100 mL of CH_2Cl_2 was added dropwise over 30 min. The reaction mixture was stirred at room temperature for 15 h, the layers were separated, and the organic phase was washed with H_2O (3 × 400 mL), dried over Na_2SO_4, filtered and rotary evaporated to give the crude product as a yellow oil, which was purified by column chromatography on silica gel (EtOAc as eluent) followed by distillation to yield 3-bromo-4-dimethylaminopyridine (9.2 g, 30%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.0 (s, 1 H, C**H**-2), 8.28 (d, J = 5.8 Hz, 1 H, C**H**-6), 6.78 (d, J = 5.8 Hz, 1 H, C**H**-5), 3.00 (s, 6 H, C**H**$_3$). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 156.9, 153.4, 148.7, 113.7, 112.4, 42.4. **MS** *m*/*z* (%): 202, 201 (100), 200, 199 (100), 119, 78. The physical data were in accordance with the literature reported.

General Amination Procedure.

Description to the reaction instruments. A 500 mL three necked round-bottom flask was equipped with mechanic stirring and cooling trap, dried three times and then flushed with argon. The flask was cooled to –78 °C by adding liquid nitrogen to acetone.

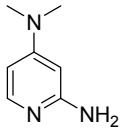
A 0.7 M solution of KNH_2 (3–5 equivalents) in NH_3 (l) was prepared by adding K (s) (4.86 g, 124.4 mmol) in small pieces to NH_3 (l) (178 mL) containing a catalytic amount of $Fe(NO_3)_3$•$9H_2O$ at –78 °C, after the K (s) disappeared, the solution was warmed to -33 °C until the blue colour was dissipated, then cooled down to -78 °C. The 3-bromo-4-dimethylaminopyridine (5.0 g, 24.9 mmol) was added dropwise as a 0.7 M solution in anhydrous Et_2O. After the reaction was complete, the reaction was quenched by the addition of NH_4Cl (excess) in small portion, the NH_3 allowed to evaporate at room temperature, and the residue dissolved in CH_3OH and filtered from insolubles. The product mixture was purified by column chromatography on silica gel ($CHCl_3$: CH_3OH: CH_3COOH = 40: 10 :1) to give 2-amino-5-bromo-4-dimethylaminopyridine, 2-amino-4-dimethylpyridine.

2-Amino-5-bromo-4-dimethylaminopyridine



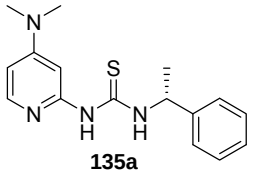
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (s, 1 H), 6.09 (s, 1 H), 3.02 (s, 6 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 159.5, 155.4, 141.7, 98.2, 96.1, 42.5.

2-Amino-4-dimethylaminopyridine



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (d, *J* = 7.4, 1 H), 6.58 (br, 2 H, NH), 6.14 (dd, *J* = 7.4, 2.5, 1 H), 5.94 (d, *J* = 2.5, 1 H), 3.10 (s, 6 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 157.2, 153.5, 134.1, 100.1, 88.4, 39.9.

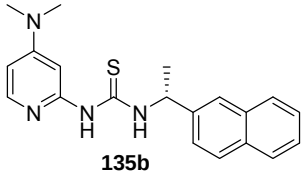
4-dimethylamino-2-pyridylamino-(1*R*)-1-phenylethylamino-methanethione (135a)



135a

To a stirred solution of 2-aminoDMAP (480 mg, 3.5 mmol) in ethanol (17.5 mL) was added $NaHCO_3$ (294 mg, 305 mmol). The mixture was suspended and vigorously stirred while (*R*)-1-phenylethylisothiocyanate (572 mg, 3.5 mmol) was added in one portion. The resulting mixture was heated to reflux overnight. After the reaction complete, the solvent was evaporated *in vacuo* and the residue was purified by column chromatography on silica gel (*n*-hexane : EtOAc = 4:1~2:1) to afford **135a** (300 mg, 30%) as a white solid, mp = 139 °C. **IR** (KBr): 3428, 3224, 2973, 1624, 1507, 695 cm^{-1}. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 12.56 (br, 1 H, NH), 8.36 (br, 1 H, NH), 7.80 (d, *J* = 6.0, 1 H), 7.40 (d, *J* = 7.3, 2 H), 7.33 (t, *J* = 7.4, 2 H), 7.24 (m, 1 H), 6.23 (dd, *J* = 6.0, 1.5, 1 H), 5.84 (s, 1 H), 5.68 (m, 1 H), 2.95 (s, 6 H), 1.64 (d, *J* = 6.9, 3 H). **^{13}C NMR** (150 MHz, $CDCl_3$): δ = 179.0, 155.8, 154.5, 145.8, 143.3, 128.6, 127.0, 126.2, 103.0, 92.2, 54.9, 39.2, 29.7, 22.5. **HRMS**: *m/z* calcd for $C_{16}H_{20}N_4S$: 300.14086; found: 300.13898. **Elemental anal.:** calcd (%) for $C_{16}H_{20}N_4S$ (300.42): C 63.97, H 6.71, N 18.65; found: C 63.57, H 6.74, N 19.06.

4-dimethylamino-2-pyridylamino-(1*R*)-1-(2-naphthyl)ethylamino-methanethione (135b)

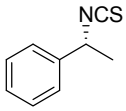


135b

This compound was prepared from 2-aminoDMAP (480 mg, 3.5 mmol) and (*R*)-2-naphthalen-2-yl-ethylisothiocyanate (740 mg, 3.5 mmol) according to the above procedure. The product was purified by column chromatography on silica gel (*n*-hexane : EtOAc = 4:1~1:1) to afford **135b** (150 mg, 12%) as a white solid, mp = 190 °C. **IR** (KBr): 3445, 3234, 2925, 1624, 1506, 811 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 12.70 (d, *J* = 8.0, 1 H, NH), 8.81 (s, 1 H, NH), 7.79 (m, 5 H), 7.53 (dd, *J* = 8.5, 1.8, 1 H), 7.41–7.45 (m, 2 H), 7.25 (s, 1 H), 6.18 (dd, *J* = 6.3, 2.4, 1 H), 5.93 (d, *J* = 2.3, 1 H), 5.86 (m, 1 H), 2.82 (s, 6 H), 1.72 (d, *J* = 6.9, 3 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 179.1, 155.8, 154.7, 145.6, 140.8, 133.4, 132.6, 128.3, 128.0, 127.6, 126.0, 125.6, 124.9, 124.6, 102.9, 92.6, 54.8, 39.1, 22.5. **HRMS**: *m/z* calcd for $C_{20}H_{24}N_4S$: 350.15597; found: 350.15598. **Elemental anal.:** calcd (%) for $C_{20}H_{22}N_4S$ (350.48): C 68.54, H 6.33, N 15.98; found: C 67.95, H 6.27, N 15.84.

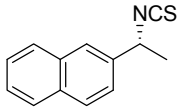
Synthesis of Isothiocyanate.[299]

(*R*)-1-Phenylethyl isothiocyanate



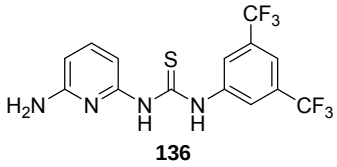
To a solution of *R*-(+)-1-phenylethylamine (5.0 mL, 39.3 mmol) in anhydrous ether (50 mL) at –10 °C were added CS_2 (15.0 mL, 249 mmol) and DCC (8.1 g, 39.3 mmol). The reaction mixture was allowed to warm slowly to room temperature during a period of 3 hrs and stirred for a further 12 hrs at room temperature. The thiourea which precipitated was removed by filtration and the solvent removed under vacuum. The residue was taken up in ether and more of thiourea was filtered. Evaporation of the solvent and rapid filtration on silica gel (eluent: *n*-hexane) gave product (3.2 g, 50%) as a yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30–7.43 (m, 5 H), 4.93 (q, 1 H), 1.69 (d, J = 6.6, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.0, 128.8, 128.1, 125.3, 56.9, 24.8.

(1*R*)-1-(2-naphthyl)ethyl isothiocyanate



This compound was prepared from *R*-(+)-1-naphthalen-2-yl-ethylamine (1.33 g, 7.75 mmol) according the above procedure. Evaporation of the solvent and rapid filtration on silica gel (eluent: *n*-hexane) gave product (1.25 g, 76%) as a white solid. **IR** (KBr): 2983, 2131, 1599, 1507, 1453, 1367, 1369 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.84–7.89 (m, 3 H), 7.77 (s, 1 H), 7.50–7.55 (m, 2 H), 7.43 (dd, J = 8.5, 2.0, 1H), 5.08 (q, J = 6.7, 1 H), 1.76 (d, J = 6.7, 3 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 137.5, 133.2, 133.0, 129.0, 128.0, 127.8, 126.7, 126.5, 124.4, 123.3, 57.2, 24.9. **HRMS**: *m/z* calcd for $C_{13}H_{11}NS$: 213.06067; found: 213.06138.

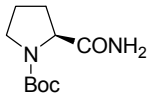
6-amino-2-pyridylamino-3,5-di(trifluoromethyl)anilinomethane-thione (136).



136

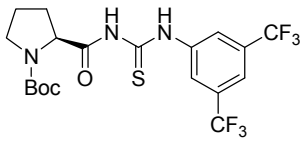
133 (1.16 g, 4.28 mmol) was added to a stirred solution of 2,6-diaminopyridine (0.467 g, 4.28 mmol) in ethanol (20 mL). The reaction mixture was heated to reflux for 8 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (*n*-hexane : ethyl acetate = 4 : 1) to give **136** (689 mg, 42%) as a yellow solid, mp = 181 °C. **IR** (KBr): 3428, 3335, 3220, 1610, 1125, 677 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$ + d_6-DMSO): δ 13.81 (s, 1 H, NH), 9.99 (s, 1 H, NH), 8.00 (s, 2 H), 7.30 (s, 1 H), 7.01 (t, J = 8.4, 7.9, 1 H), 6.04 (d, J = 7.9, 1 H), 5.85 (d, J = 8.4, 1 H), 5.27 (br, 2 H, NH). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 178.4, 155.9, 151.3, 140.2, 139.2, 130.4, 130.1, 124.2, 121.1, 117.3, 101.7, 99.7. **HRMS**: *m/z* calcd for $C_{14}H_{10}F_6N_4S$: 380.05249; found: 380.05249. **Elemental anal.:** calcd (%) for $C_{14}H_{10}F_6N_4S$ (380.31): C 44.21, H 2.65, N 14.73; found: C 43.91, H 2.59, N 14.56.

Miscellaneous: Synthesis of *tert*-butyl (2*S*)-2-carbamoyltetrahydro-1*H*-1-pyrrolecarboxylate (141)[300, 301]



To a stirred solution of L-Boc-proline (2.15 g, 10.0 mmol, 1.0 equiv.), pyridine (0.5 mL) and $(Boc)_2O$ (3.0 g, 13 mmol, 1.3 equiv.) in anhydrous 1,4-dioxane (50 mL) was added ammonium dicarbonate (1.0 g, 13.0 mmol, 1.3 equiv.). After stirring at room temperature for 18 h, the solvent was evaporated under reduced pressure and the residue was taken up in 50 mL of AcOEt, washed with 50 mL of an aqueous solution of citric acid (20% w/w) and 50 mL of brine. The aqueous layers were mixed and extracted with AcOEt (3 × 100 mL). The organic phases were pooled and dried over $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography on silica gel (CH_2Cl_2 : CH_3OH = 10 : 1) yielding the product **141** (1.85 g, 86%) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$, *cis* and *trans* forms): δ 6.80, 6.14, and 5.90 (3 × br, 2 H, CONH), 4.26 and 4.14 (2 × br, 1 H), 3.31–3.44 (br, 2 H), 1.82–2.26 (m × br, 4 H), 1.42 (br, 9 H). **^{13}C NMR** (100 MHz, $CDCl_3$, *cis* and *trans* forms): δ = 176.2, 175.2, 155.6, 154.6, 80.3, 61.0, 59.7, 47.1, 46.9, 31.1, 29.0, 28.6, 28.4, 27.8, 24.5, 23.7.

Synthesis of *tert*-butyl (2*S*)-2-[3,5-di(trifluoromethyl)anilino(thioxo)methyl carbamoyl]tetrahydro-1*H*-1-pyrrolecarboxylate (142).



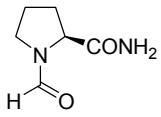
Under argon atmosphere, to a solution of **141** (857 mg, 4.0 mmol) in anhydrous THF (20 mL) was added NaH (480 mg, 20.0 mmol) in several portions. After stirring at room temperature for 10 min, 3,5-di(trifluoromethyl)phenyl isothiocyanate **133** (1.2 g, 4.4 mmol, 1.1 equiv.) was dropwise added to the solution. The reaction mixture was allowed to stir overnight and quenched by cautious addition of ethanol (10 mL). The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel (n-hexane : EtOAc = 4 : 1) to give **142** (1.05 g, 54 %) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$, *cis* and *trans* forms): δ 12.54, 10.64, 10.24, and 9.26 (4 × br, 2 H, NH), 8.21, 7.91, 7.68, and 7.34 (4 × br, 3 H, ArH), 4.53 (br, 1 H), 3.41–3.63 (m, 2 H), 1.92–2.29 (m, 4 H), 1.52 and 1.51 (2 × s, 9 H). **^{13}C NMR** (100 MHz, $CDCl_3$, *cis* and *trans* forms): δ = 178.7, 173.3, 171.2, 156.1, 140.0, 139.1, 132.3, 132.0, 131.6, 131.3, 127.1, 127.0, 124.4, 124.3, 123.5, 121.7, 121.6, 119.6, 118.9, 118.6, 116.5, 81.9, 81.2, 60.6, 47.4, 47.2, 29.0, 28.4, 28.3, 27.9, 24.5.

Boc deprotection (all the following methods failed).

1. 25% TFA (v/v) in DCM.
2. 98% H_2SO_4 in DCM.
3. 2 M HCl in AcOEt.
4. CAN in acetone at 0 °C.
5. $BiCl_3$ in CH_3CN/H_2O.
6. 25% TFA in DCM, Scavengers ($S(CH_3)_2$) was added.

Note added in proof: while proline-derived thioureas was in preparation, some analogues were reported by other groups.[121, 126]

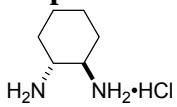
Synthesis of (2*S*)-1-formyltetrahydro-1*H*-2-pyrrolecarboxamide (143)



To a stirred solution of *N*-formyl-L-Proline (589 mg, 4.1 mmol), pyridine (0.21 mL), and $(Boc)_2O$ (1.42 g, 6.5 mmol) in anhydrous 1,4-dioxane (21 mL) was added ammonium dicarbonate (0.42 g, 5.35 mmol). After stirring at room temperature for 18 h, the precipitation was filtered and dried to yield the product (0.41 g, 70%) as a white solid. IR (KBr): 3331, 3166, 2978, 2879, 1653 cm^{-1}. **^{1}H NMR** (400 MHz, d_6-DMSO, *cis*/*trans* = 1:1): δ 8.18 and 8.06 (2 × s, 1 H, CHO), 7.54, 7.35, 7.17, and 6.96 (4 × br, 2 H, NH), 4.32 and 4.13 (2 × dd, *J* = 8.2 and 4.0, *J* = 8.4 and 4.0, 1 H), 3.55–3.61 and 3.47–3.53 (2 × m, 1 H), 3.22–3.39 (m, 1 H), 2.07–2.17 (m, 1 H), 1.67–1.99 (m, 3 H). **^{13}C NMR** (100 MHz, d_6-DMSO, *cis*/*trans* = 1:1): δ = 173.6, 173.2, 161.5, 161.0, 58.9, 57.1, 46.2, 43.6, 30.1, 29.6, 23.5, 22.5. **HRMS**: *m/z* calcd for $C_6H_{10}N_2O_2$: 142.07368; found: 142.07496.

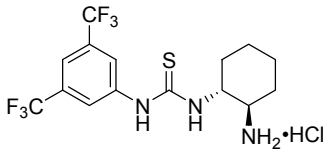
7.6 Synthesis of Schiff-base thioureas

Preparation of monoammonium salts of (*R*,*R*)-1,2-diaminocyclohexane. [302, 303]



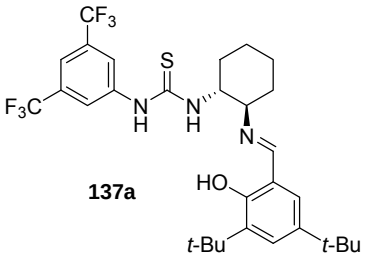
(*R*,*R*)-1,2-diaminocyclohexane (810 mg, 7.1 mmol) was dissolved in ether (25 mL). The solution was stirred vigorously while anhydrous HCl in ether (2.35 mL, 2.9 M, 7.1 mmol, 1.0 equiv.) was added dropwise over 15 min. An exothermic reaction was observed upon the addition of the acid, and a precipitate was formed. After complete addition of the acid, the mixture was allowed to stir at room temperature for 10 h. The precipitation was collected by vacuum filtration, washed with excess ether and dried *in vacuo* to give **1** (900 mg, 84%) as a white solid. **^{1}H NMR** (400 MHz, D_2O): δ 2.29 (br, 2 H), 1.67 (d, *J* = 10.4, 2 H), 1.40 (br, 2 H), 0.96 (m, 4 H). **^{13}C NMR** (100 MHz, D_2O): δ = 54.5, 32.2, 24.2.

Preparation of 138



(*R*,*R*)-1,2-diaminohexane mono (hydrogen chloride) (453 mg, 3.0 mmol) was dissolved in a mixture of methanol and ethanol (50/50, v/v, 25 mL). **133** (814 mg, 3.0 mmol, 1.0 equiv.) was added to the reaction, and the reaction mixture was stirred at room temperature for 40 h. The solvents were evaporated under reduced pressure and the residue was purified by column chromatography on silica gel (CH_2Cl_2 : CH_3OH = 10 : 1~4 : 1) to give **138** (739 mg, 71%) as a white solid. **IR** (KBr): 3247, 3051, 2948, 2869, 1553, 1277, 681. **^{1}H NMR** (200 MHz, d_6-DMSO): δ 8.93 (br, 1 H), 8.41 (s, 2 H), 7.78 (s, 1 H), 4.38 (br, 1 H), 3.12 (m, 1 H), 2.56 (m, 1 H), 1.96–2.15 (m, 2 H), 1.77 (m, 2 H), 1.15–1.59 (m, 4 H). **^{13}C NMR** (50 MHz, d_6-DMSO): δ = 180.8, 142.1, 131.0, 130.3, 130.0, 129.7, 129.0, 125.9, 121.7, 120.5, 115.9, 54.8, 53.0, 30.4, 29.3, 23.8, 23.1.

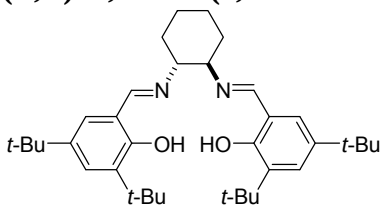
(1*R*,2*R*)-2-(*E*)-1-[3,5-di(*tert*-butyl)-2-hydroxyphenyl] methylidene aminocyclohexyl-amino-3,5-di(trifluoromethyl)anilinomethanethione (137a)



137a

A 50 mL two-necked flask equipped with a reflux condenser and an addition funnel was charge with **2** (168.7 mg, 0.4 mmol), K_2CO_3 (55.2 mg, 0.4 mmol) and distilled water (8.0 mL). The mixture was stirred until dissolution was achieved, then ethanol (8.0 mL) was added. The resulting colorless solution was heated to reflux (75~80 °C), and a solution of 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde in ethanol (4.0 mL) was added dropwise over 15 min. The yellow solution was stirred at reflux 2.5 h before heating was discontinued. Distilled water (8.0 mL) was added and the stirred mixture was cooled to less than 5 °C under ice bath and maintained at that temperature overnight. The product was collected by vacuum filtration and dried under vacuum to give **137a** (168 mg, 70%) as a yellow solid, mp = 153 °C. **IR** (KBr): 3274, 2968, 2865, 1628, 1539, 1279, 1138 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 13.04 (br, 1 H, OH), 8.45 (s, 1 H), 7.69 (s, 1 H), 7.61 (s, 1 H), 7.52 (s, 2 H), 7.39 (d, *J* = 2.4, 1 H), 7.13 (d, *J* = 2.4, 1 H), 6.23 (br, 1 H), 3.96 (br, 1 H), 3.11 (m, 1 H), 2.28 (m, 1 H), 1.73–1.95 (m, 4 H), 1.22–1.59 (m, 22 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 181.4, 167.2, 157.5, 141.0, 139.6, 136.7, 132.3, 128.2, 126.9, 126.4, 125.5, 124.1, 121.4, 119.7, 117.4, 59.1, 34.8, 34.2, 33.5, 31.7, 31.4, 29.4, 29.3, 29.1, 24.6, 23.8. **HRMS**: *m/z* calcd for $C_{30}H_{37}F_6N_3OS$: 601.25614; found: 601.25503. **Elemental anal.:** calcd (%) for $C_{30}H_{37}F_6N_3OS$ (601.69): C 59.88, H 6.20, N 6.98; found: C 59.87, H 6.18, N 7.18.

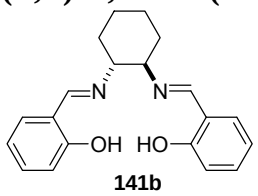
(*R*,*R*)-*N*, *N'*-Bis(3,5-di-*tert*-butyl-salicylidene)-1,2-cyclohexane- diamine (141a).[304]



141a

To a stirred solution of (*R*,*R*)-1,2-diaminohexane (228.4 mg, 2.0 mmol) in anhydrous methanol (8 mL) was added activated MS 5 Å (2.0 g) and 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde (0.94 g, 4.0 mmol) under an argon atmosphere. The reaction mixture was stirred at room temperature for 60 min, and then filtered through a pad of silica gel and rinsed with methanol several times. The yellow filter cake was then washed with CH_2Cl_2 (3 × 25 mL). The CH_2Cl_2 organic phase was collected together and washed with water (2 × 30 mL) and brine (30 mL). After dried over Na_2SO_4, the solvent was removed under vacuo, and the product **141a** was isolated as a yellow powder (1.01 g, 93%), mp = 209 °C. **IR** (KBr): 3439, 2962, 2871, 1630 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 13.73 (s, 2 H), 8.32 (s, 2 H), 7.32 (d, *J* = 2.4, 2 H), 7.00 (d, *J* = 2.4, 2 H), 3.33 (m, 2 H), 1.48–2.00 (m, 6 H), 1.43 (s, 20 H), 1.25 (s, 18 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 165.8, 158.0, 139.9, 136.4, 126.7, 126.0, 117.9, 72.4, 35.0, 34.1, 33.3, 29.5, 24.4. **HRMS**: *m/z* calcd for $C_{36}H_{54}F_6N_2O_2$: 546.41851; found: 546.42225. **Elemental anal.:** calcd (%) for $C_{36}H_{54}N_2O_2$ (546.83): C 79.07, H 9.95, N 5.12; found: C 78.87, H 10.00, N 4.91.

(*R*,*R*)-*N*, *N'*-Bis(salicylidene)-1,2-cyclohexanediamine (141b)

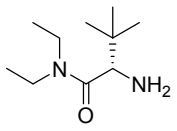


141b

This compound was prepared on a 2.0 mmol scale according to the above procedure. After work up, **141b** was obtained in 89.0% yield. **^{1}H NMR** (200 MHz, $CDCl_3$): δ 13.33 (br, 2 H), 8.25 (s, 2 H), 7.11–7.28 (m, 4 H), 6.74–6.90 (m, 4 H), 3.23–3.37 (m, 2 H), 1.21–1.96 (m, 8 H). **^{13}C NMR** (50 MHz, $CDCl_3$): δ = 164.7, 160.3, 132.1, 131.5, 118.6, 116.8, 72.6, 33.1, 24.2.

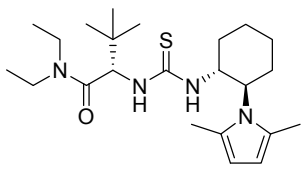
Synthesis of Jacobsen catalyst (137b and 137c)

Coupling of Boc-L-tert-leucine with diethylamine, followed by deprotection



N-Boc-L-*tert*-leucine (4.00 g, 17.29 mmol) in CH_2Cl_2 (159 mL) was added *O*-benztriazole-1-*N*,*N*,*N'*,*N'*-tetraethyluromium hexafluorophosphate (HBTU, 7.20 g, 19.03 mmol, 1.1 equiv). The white suspension was stirred for 5 minutes, followed by the addition of diisopropylethylamine (3.5 mL, 20.75 mmol, 1.2 equiv) and diethylamine (2.0 mL, 19.03 mmol). The reaction mixture was then stirred for 48 h at room temperature. The mixture was combined with CH_2Cl_2 and water and the organic layer was separated, washed with 1N hydrochloric acid (3 times), and dried over $MgSO_4$. The solvent was removed *in vacuo* to afford the crude Boc-protected amide as a colorless oil. The oil was dissolved in trifluoroacetic acid (TFA, 20 mL) at 0 °C. The reaction mixture was then stirred for 1 h at room temperature. All volatile compounds were removed *in vacuo* and the residue was dissolved in water and treated with KOH (10% aqueous solution) at 0 °C. The resulting mixture was extracted with CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$. After filtration and then evaporation of the solvent, the crude product was purified by flash chromatography (5-10% EtOAc in hexanes) yielding L-*tert*-leucine diethylamide as a colorless oil (2.90 g, 15.57 mmol, 90%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.72–3.63 (m, 1 H, C**H**$_2$CH$_3$), 3.60–3.52 (m, 1 H, C**H**$_2$CH$_3$), 3.37 (s, 1 H, C**H**NH$_2$), 3.22–3.12 (m, 1 H, C**H**$_2$CH$_3$), 3.10–2.99 (m, 1 H, C**H**$_2$CH$_3$), 1.74 (br s, 2 H, N**H**$_2$), 1.19–1.14 (m, 3 H, CH$_2$C**H**$_3$), 1.11–1.07 (m, 3 H, CH$_2$C**H**$_3$), 0.95 (s, 9 H, C(C**H**$_3$)$_3$). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 173.8, 57.7, 53.8, 42.8, 42.4, 40.3, 35.1, 26.4, 14.7, 13.0.

Preparation of 137b[169]

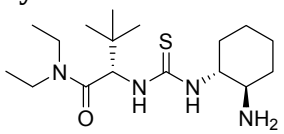


Saturated aqueous $NaHCO_3$ (5 mL) was added to a solution of L-*tert*-leucine diethylamide (300 mg, 1.61 mmol) in CH_2Cl_2 (9 mL) at 0 °C. The mixture was stirred for 30 minutes, then the stirring was stopped and thiophosgene (141 μL, 1.78 mmol, 1.1 equiv) was added to the organic phase by syringe. The resulting orange mixture was stirred at 0 °C for 1 h. CH_2Cl_2 (22.5 mL) was added, and the organic phase separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried over $MgSO_4$

and concentrated, yielding (*S*)-2-isothiocyanato-*N*,*N*-diethyl-3,3-dimethylbutanamide as a solid, which was used without further purification.

The crude product was dissolved in CH_2Cl_2 (15 mL) and (*1R*, *2R*)-2-(2,5-dimethyl-pyrol-1-yl)cyclohexylamine (369 mg,1.93 mmol,1.2 equiv) was added in different portions. The reaction mixture was allowed to stir for 14 h at room temperature. All volatile compounds were removed *in vacuo* and the residue was purified via flash chromatography (10-20% EtOAc in hexanes) yielding the compound **137b** as light salmon solid (600 mg, 1.43 mmol, 89%), mp = 128 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.32 (br d, J = 8.4 Hz, N**H**), 5.82 (br s, 1 H, N**H**), 5.70 (s, 2 H, Ar**H**), 5.44 (br s, 1 H, C**H**$(CH_3)_3$), 4.36 (m, 1 H, C**H** cycl.), 3.86–3.79 (m, 1 H, C**H** cycl.), 3.73–3.62 (m, 2 H, C**H**$_2$CH$_3$), 3.31 (m, 1 H, C**H**$_2$CH$_3$), 3.04 (m, 1 H, C**H**$_2$CH$_3$), 2.48–2.20 (m, 8 H, ArC**H**$_3$, C**H**$_2$ cycl), 2.02–1.79 (m, 4 H, C**H**$_2$ cycl.), 1.48–1.33 (m, 2 H, C**H**$_2$ cycl.), 1.24 (t, J = 7.1 Hz, 3 H, NCH$_2$C**H**$_3$), 1.10 (t, J = 7.1 Hz, 3 H, NCH$_2$C**H**$_3$), 0.95 (s, 9 H, C$(CH_3)_3$). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 181.9, 170.7, 128.7, 127.1, 108.5, 105.9, 60.0, 59.4, 55.8, 42.9, 40.1, 36.3, 33.9, 32.3, 26.8, 25.8, 24.7, 14.6, 12.9. **HRMS**: *m/z* calcd for $C_{23}H_{40}N_4OS$: 420.29173; found: 420.28980. **Elemental anal.:** calcd (%) for $C_{23}H_{40}N_4OS$ (420.66): C 65.67, H 9.58, N 13.32; found: C 65.14, H 9.54, N 13.68.

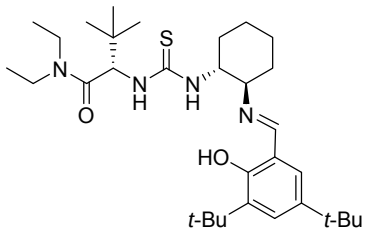
Synthesis of Jacobsen catalyst (137c).[59]



Saturated aqueous $NaHCO_3$ (10 mL) was added to a solution of L-*tert*-leucine diethylamide (600 mg, 3.22 mmol) in CH_2Cl_2 (18 mL) at 0 °C. The mixture was stirred for 30 minutes, then the stirring was stopped and thiophosgene (282 µL, 3.54 mmol, 1.1 equiv) was *added to the organic phase by syringe.* The resulting orange mixture was stirred at 0 °C for 1 h. CH_2Cl_2 (30 mL) was added, and the organic phase separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated, yielding (*S*)-2-isothiocyanato-*N*,*N*-diethyl-3,3-dimethylbutanamide as a solid, which was used without further purification.

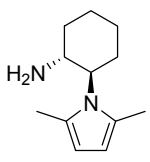
The crude isothiocyanate was dissolved in freshly distilled dichloromethane (30 mL) and (*R*,*R*)-1,2-diaminocyclohexane (404.5 mg, 3.54 mmol, 1.1 equiv) was added in one portion. The reaction mixture was allowed to stir at room temperature for 30 min and concentrated in vacuo. Crude product was purified by flash chromatography on silica gel (Eluent: 2 M solution of ammonia in methanol/dichloromethane = 1/9, stain with ninhydrine) to afford the corresponding amine (776 mg, 70%) as a straw yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.71 (br s, 1 H, N**H**), 6.50 (br s, 1 H, N**H**), 5.46 (d, J = 8.8 Hz, 1 H, C**H**$(CH_3)_3$), 3.74–3.63 (m, 2 H, C**H**$_2$CH$_3$), 3.38–3.29 (m, 1 H, C**H**$_2$CH$_3$), 3.00–2.91 (m, 1 H, C**H**$_2$CH$_3$), 2.47–2.42 (m, 1 H, C**H** cycl.), 2.18–1.96 (m, 6 H, C**H**$_2$ cycl. N**H**$_2$), 1.86–1.83 (m, 1 H, C**H** cycl.), 1.64 (m, 2 H, C**H**$_2$ cycl.), 1.24 (t, J = 7.1 Hz, 3 H, CH$_2$C**H**$_3$), 1.06 (t, J = 7.1 Hz, 3 H, CH$_2$C**H**$_3$), 0.98 (s, 9 H, C(C**H**$_3$)$_3$). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 182.7, 171.0, 55.8, 50.6, 43.0, 40.0, 36.2, 34.8, 32.3, 27.0, 24.8, 14.6, 12.8.

Schiff base formation (137c).



A 25 mL-round-bottom flask equipped with a stirbar was charged with amine **2** (300 mg, 0.876 mmol) prepared in the previous step and anhydrous methanol (4 mL) was added with stirring. Once the solution became homogeneous, oven dried sodium sulphate (1.0 g) was added. In a separate flask, 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde (205.2 mg, 0.876 mmol, 1.0 equiv) was dissolved in anhydrous methanol (4 mL), then transferred to the reaction mixture. An additional 3 mL of methanol was used to effect quantitative transfer of the aldehyde into the reaction mixture. The reaction mixture was stirred for 90 min, than concentrated under reduced pressure with the sodium sulphate still present. The resulting mixtures was combined with *n*-hexane (25 mL) and filtered through a fine, glass frit, and the solids were rinsed with n-hexane (25 mL). The filtrate was concentrated *in vacuo* to yield 476.6 mg of **JK-2** as a bright yellow solid (97% yield), mp = 131 °C. (Spectra data are referred to *JACS* **2002**, *124*, 12964. Compounds exists as a ~7 : 1 mixture of rotamers: the major rotamer is donated by *. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 13.38 (br s, 1 H, O**H***), 11.63 (br s, 1 H, O**H**), 9.86 (s, 1 H, C**H**=N), 8.37 (s, 1 H, C**H**=N*), 7.58 (d, J = 2.4 Hz, 1 H, Ar**H**), 7.33 (d, J = 2.3 Hz, 1 H, Ar**H***), 7.05 (d, J = 2.3 Hz, 1 H, Ar**H***), 6.56 (br s, 1 H, N**H***), 6.40 (br s, 1 H, N**H***), 5.51 (d, J = 9.35, 1 H, C**H**(CH_3)*), 3.87 (br s, 1 H, C**H** cycl.*), 3.74–3.60 (m, 2 H, C**H**$_2$CH$_3$*), 3.34–3.25 (m, 1 H, C**H**$_2$CH$_3$*), 3.16 (br s, 1 H, C**H** cycl.*), 3.00–2.92 (m, 1 H, C**H**$_2$CH3*), 2.12 (m, 1 H, C**H**$_2$ cycl.*), 1.88–1.62 (m, 4 H, C**H**$_2$ cycl.*), 1.47–1.35 (m, 3 H, C**H**$_2$ cycl.*), 1.42 (s, 9 H, C(C**H**$_3$)$_3$), 1.40 (s, 9 H, C(C**H**$_3$)$_3$*), 1.32 (s, 9 H, C(C**H**$_3$)$_3$), 1.26 (s, 9 H, C(C**H**$_3$)$_3$*), 1.22 (t, J = 7.1 Hz, 3 H, CH$_2$C**H**$_3$), 1.07 (t, J = 7.1 Hz, 3 H, CH$_2$C**H**$_3$), 0.90 (s, 9 H, C(C**H**$_3$)$_3$*), 0.87 (s, 9 H, C(C**H**$_3$)$_3$). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 197.4, 181.2, 170.8, 166.0, 159.1, 158.0, 141.6, 139.9, 137.6, 136.4, 131.9, 127.9, 127.0, 126.2, 120.0, 117.9, 71.1, 60.2, 56.7, 42.9, 40.1, 36.3, 35.02, 35.0, 34.2, 34.1, 33.1, 31.6, 31.5, 31.3, 31.1, 29.5, 29.3, 27.1, 26.8, 24.1, 23.5, 22.7, 14.6, 14.1, 12.9, 12.7. **Elemental anal.:** calcd (%) for $C_{32}H_{54}N_4O_2S$ (558.86): C 68.77, H 9.74, N 10.02; found: C 68.52, H 9.82, N 9.48.

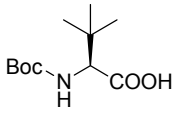
Preparation of 2-pyrrolylcyclohexylamines.[56]



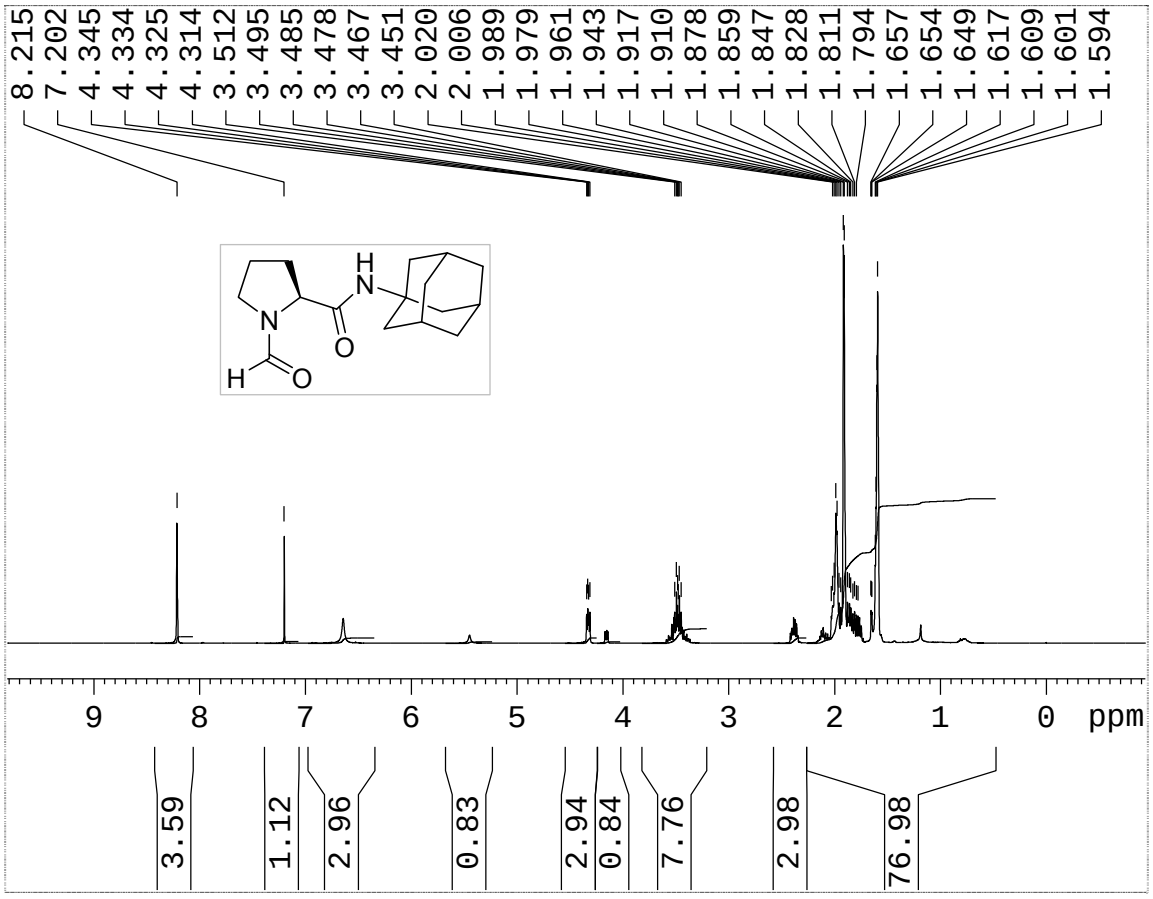
In a round-bottomed flask equipped with relux condenser, acetic acid (302 µL, 5.28 mmol, 1.0 equiv.) and 2,5-hexanedione (620 µL, 5.28 mmol, 1.0 equiv.) were added sequentially to a solution of (*R,R*)-diaminocyclohexane (604 mg, 5.28 mmol, 1.0 equiv.) in methanol (26 mL). The mixture was heated to 50 °C and stirred for 60 minutes, then cooled to 23 °C and concentrated *in vacuo*. The residue was partitioned between dichloromethane (100 mL) and 4 M aqueous sodium hydroxide (100 mL). The organic phase was separated, and the aqueous extracted twice with dichloromethane (100

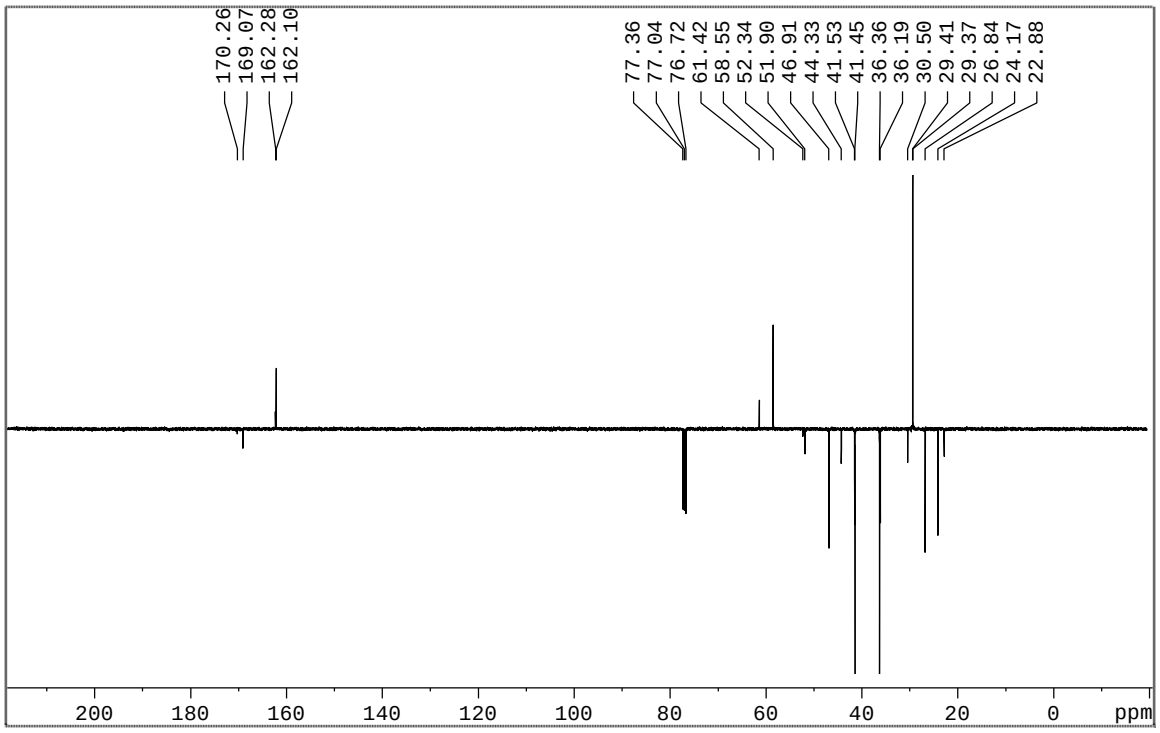
mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was purified by chromatography on silica (5% methanol in dichoromethane), yielding the product as a yellow oil (409 mg, 2.13 mmol, 81% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.76 (d, J = 11.5 Hz, 2 H, Ar**H**), 3.64–3.57 (m, 1 H, NH_2C**H**), 3.28–3.22 (m, 1 H, NC**H**), 2.36 (br s, 3H, C**H**$_3$), 2.23 (br s, 3 H, C**H**$_3$), 2.07–2.03 (m, 1 H, C**H** cycl.), 1.94–1.78 (m, 4 H, C**H**$_2$ cycl.), 1.46 (br s, 2 H, N**H**$_2$), 1.40–1.34 (m, 2 H, C**H** cycl.), 1.26–1.16 (m, 1 H, C**H** cycl.) . **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 129.8, 126.8, 107.9, 105.3, 63.6, 52.9, 35.4, 31.3, 26.2, 25.1, 15.3, 13.7.

Boc-L-*tert*-leucine.[305]

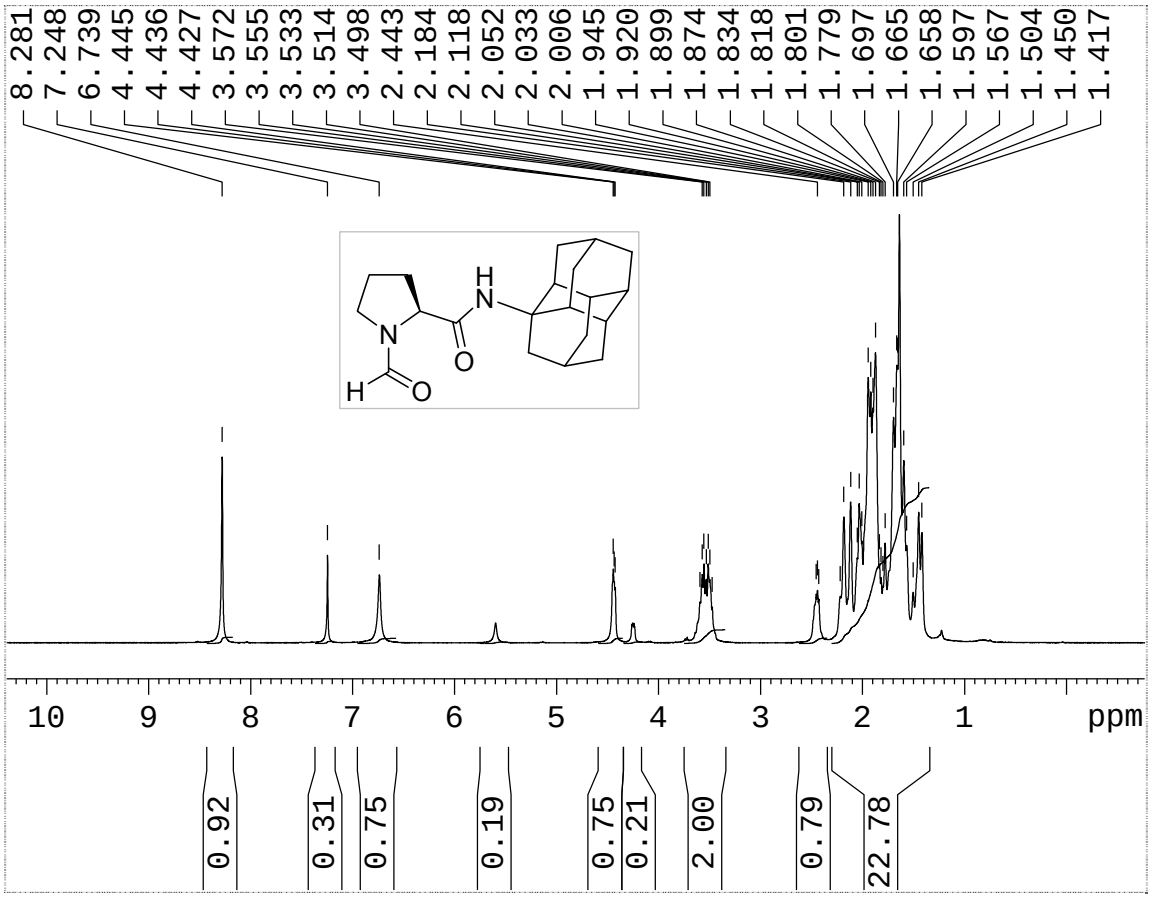


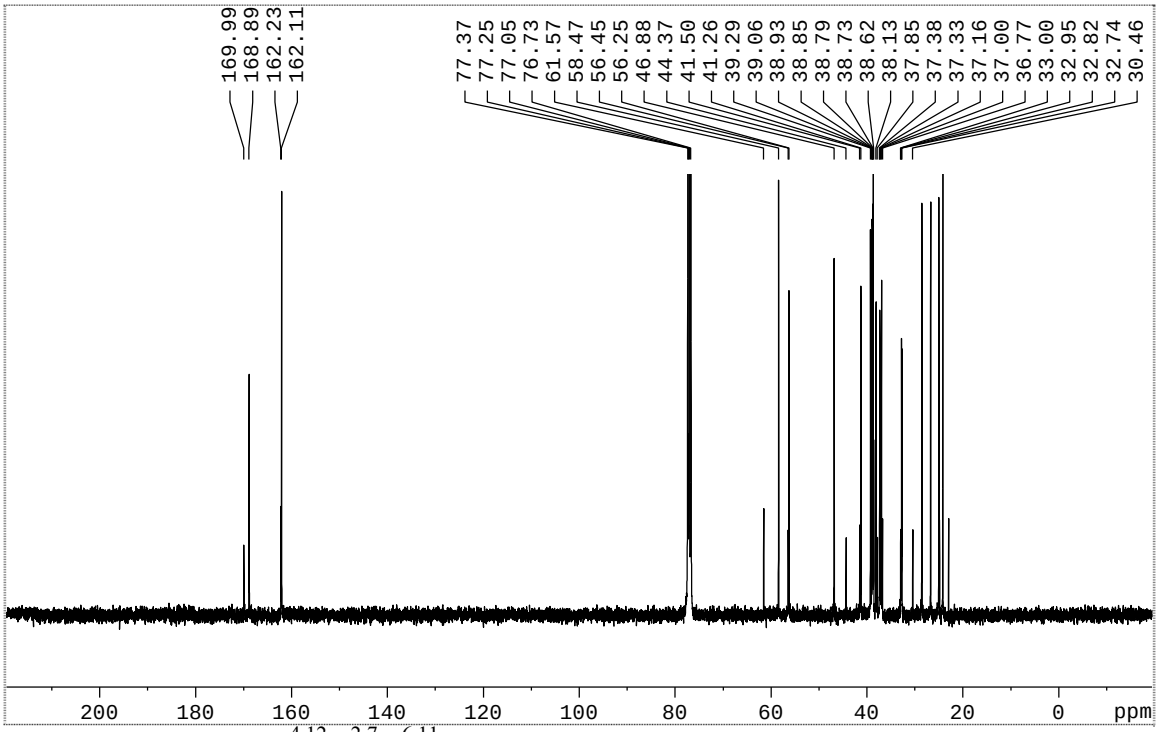
$(Boc)_2O$ (3.64 g, 16.68 mmol) was added to a solution of L-*tert*-leucine (2.00 g, 15.25 mmol) and NaOH (0.67, 16.80 mmol) in water/*tert*-butyl alcohol (20 mL/20 mL). The reaction mixture was stirred overnight at room temperature and was then extracted three times with 50 mL of ethyl acetate. The combined organic layers were washed with satd $NaHCO_3$ solution (50 mL), and the combined water phases were acidified to pH 1.5–2.0 with 6 M HCl. The water phase was extracted four times with 50 mL of ethyl acetate, and the combined organic layers were washed with brine (2 × 50 mL), dried over Na_2SO_4, and evaporated *in vacuo* to give Boc-L-tert-leucine (2.85 g, yield 81.0%) as a colorless solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 10.54 (br, 1 H), 5.14 (d, J = 9.5 Hz, 1 H), 4.14 (d, J = 9.5 Hz, 1 H), 1.46 (s, 9 H), 1.03 (s, 9 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 176.8, 155.6, 80.0, 61.6, 34.5, 28.3, 26.5.



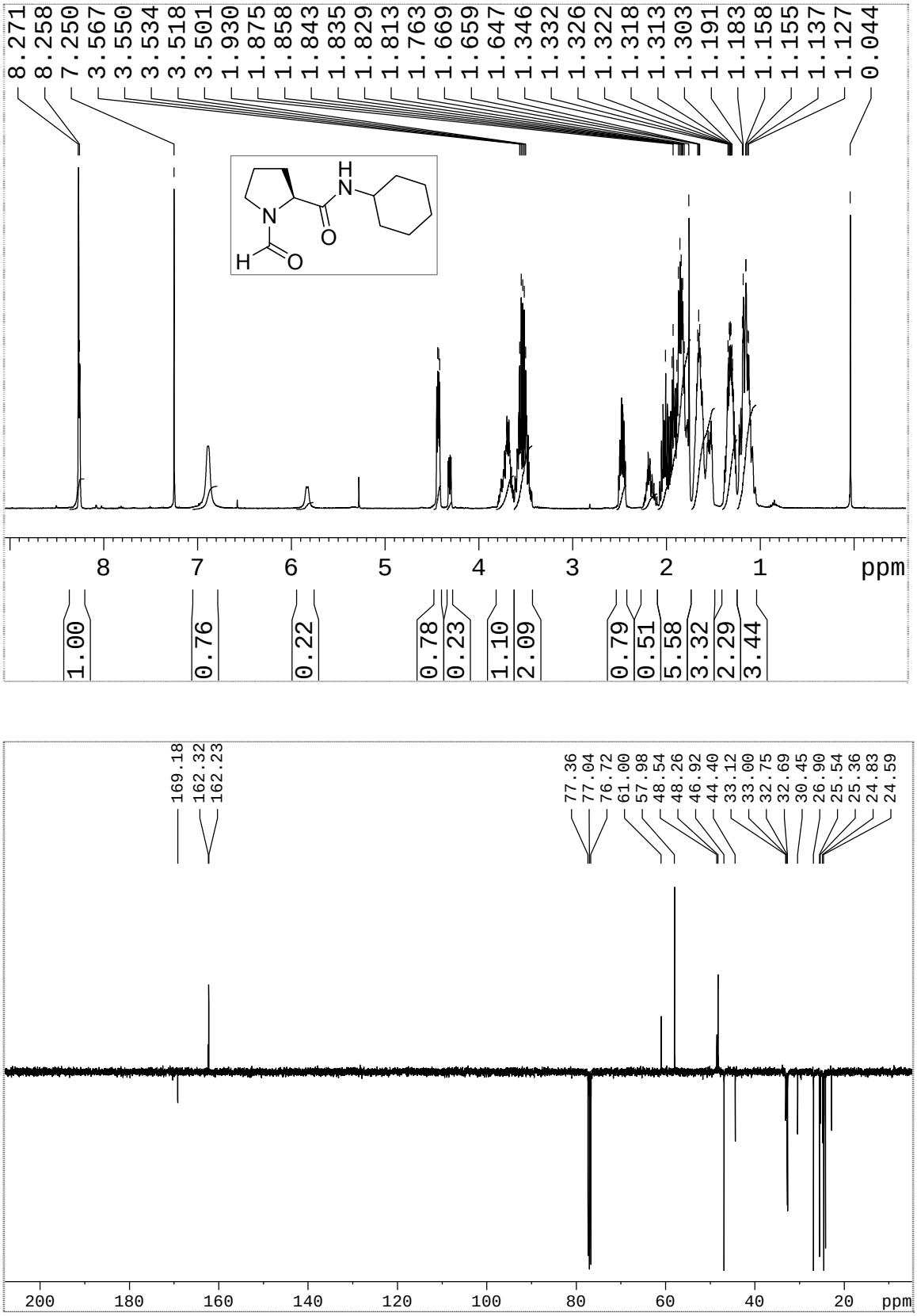


*N*2-(1-adamantyl)-(2*S*)-1-formyltetrahydro-1*H*-2-pyrrolecarboxamide (**104**)

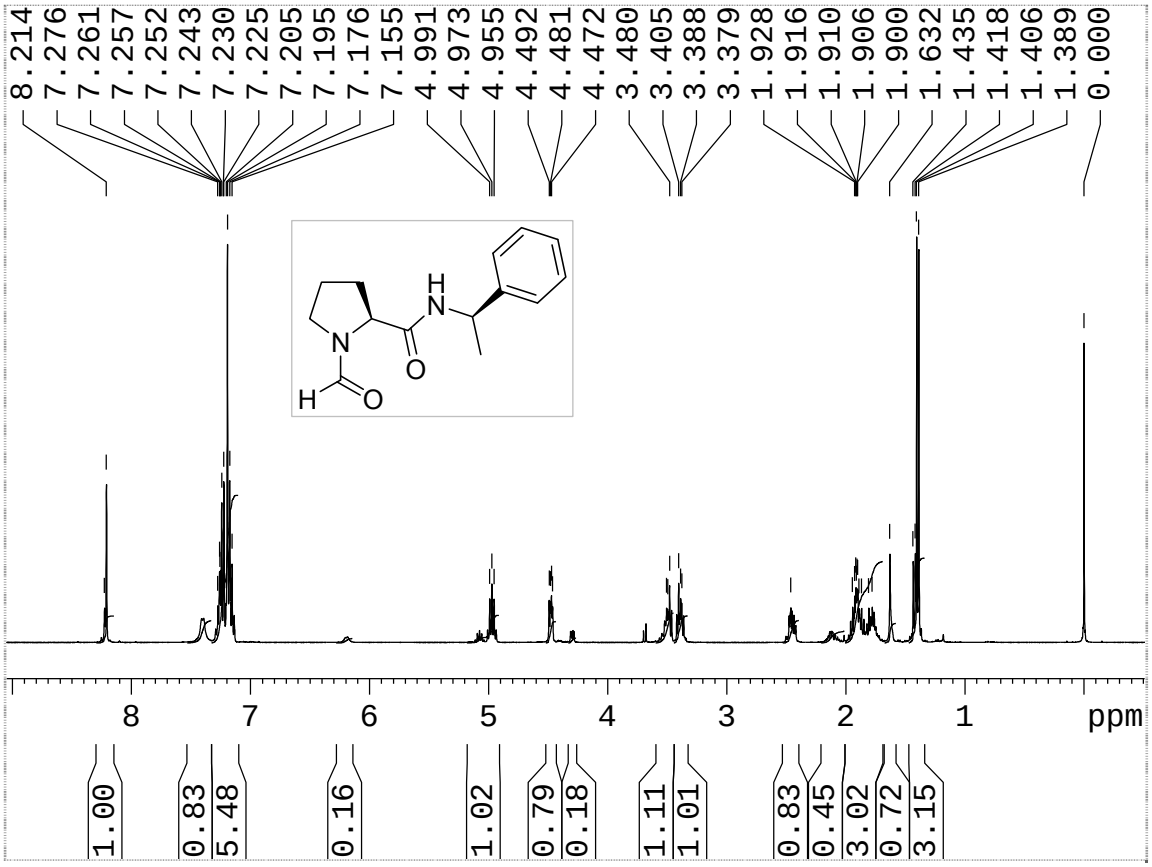


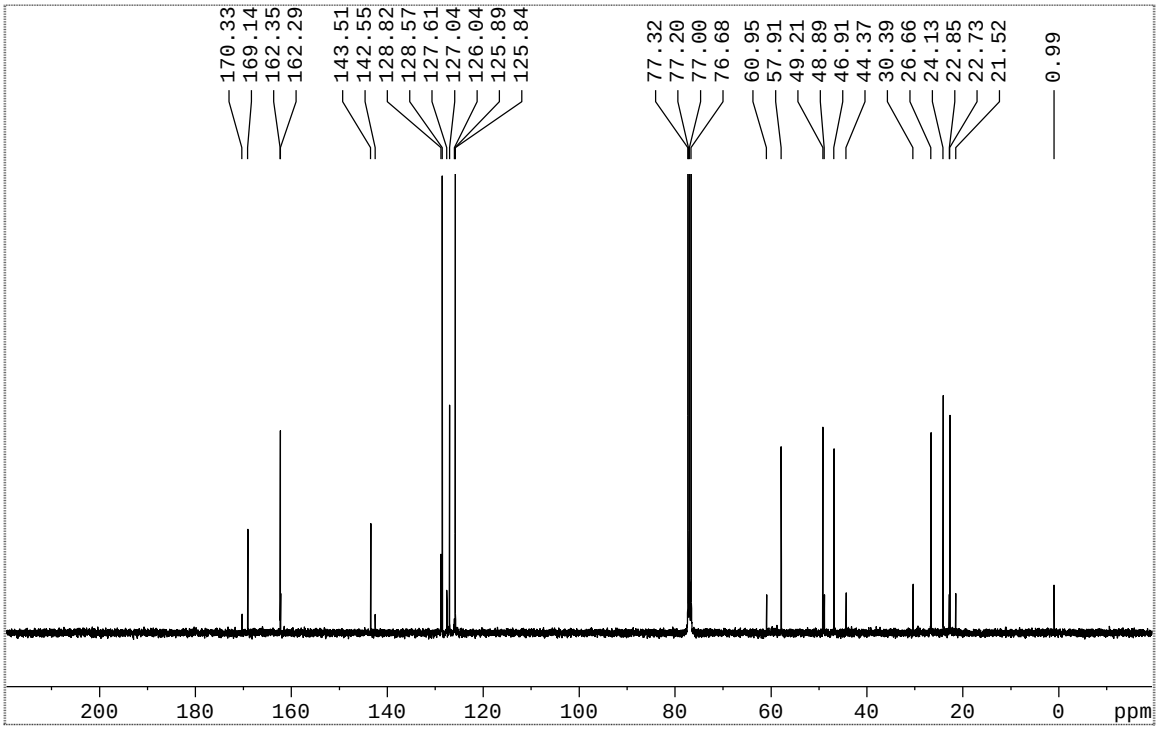


*N*2-pentacyclo[7.3.1.1^{4,12}.0^{2,7}.0^{6,11}]tetradec-1-yl-1-formyltetrahydro-1*H*-2-pyrrole-carboxamide (**105**)

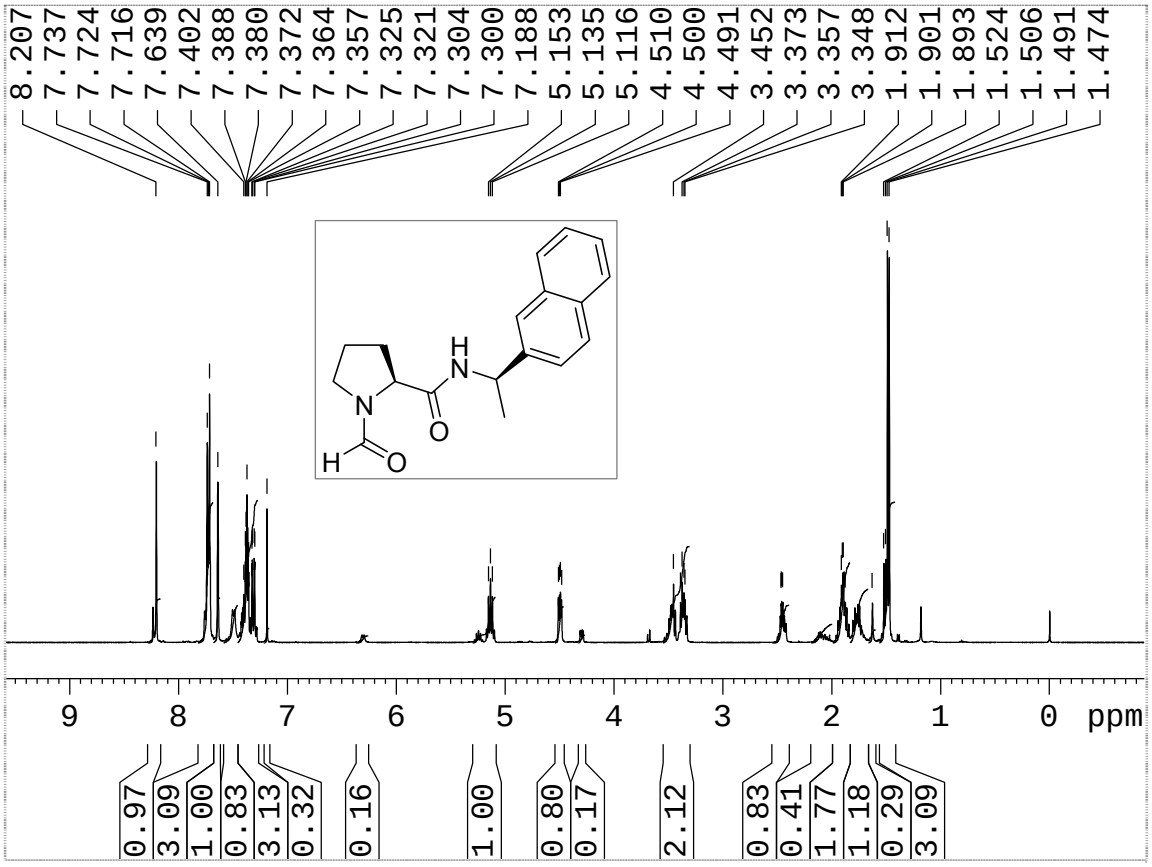


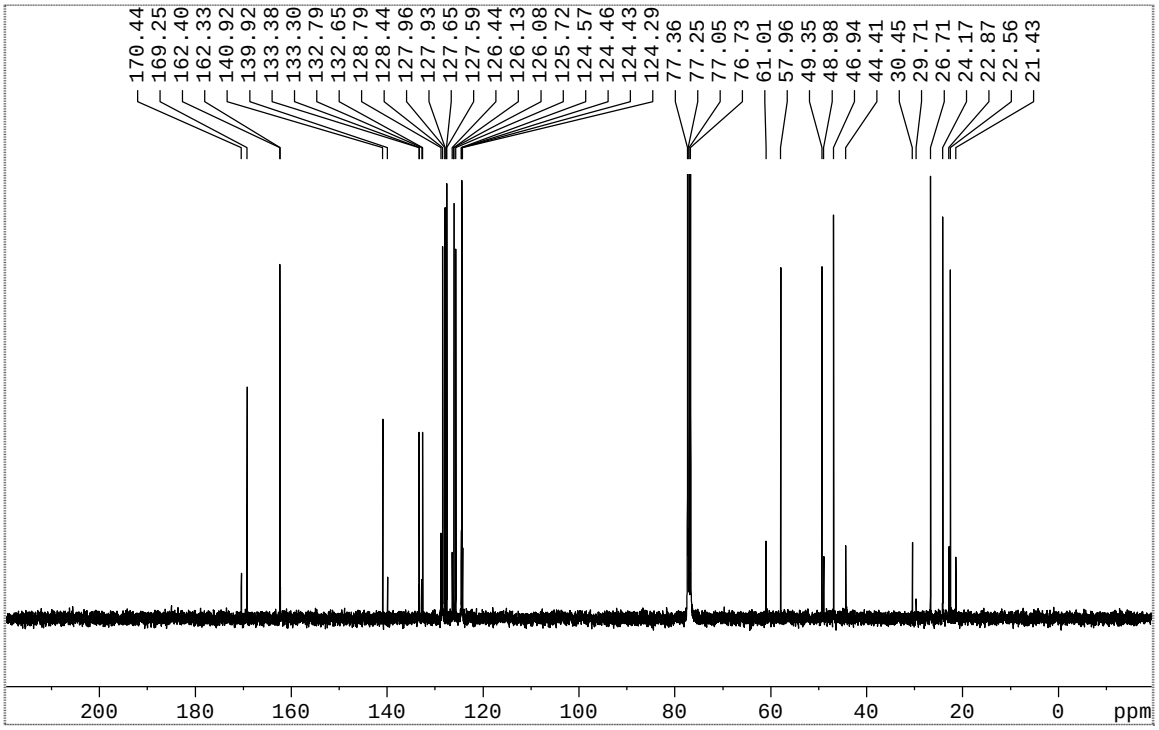
*N*2-cyclohexyl-(2*S*)-1-formyltetrahydro-1*H*-2-pyrrolecarboxamide (**103**)



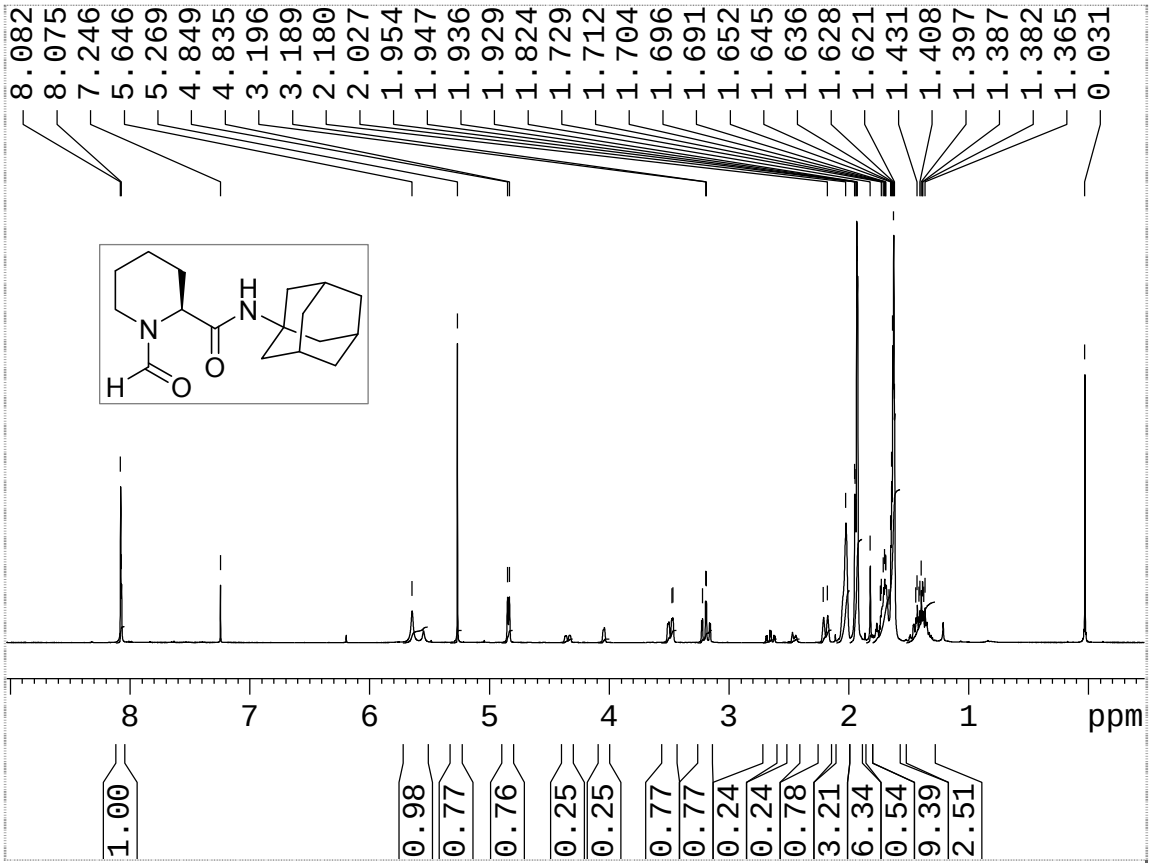


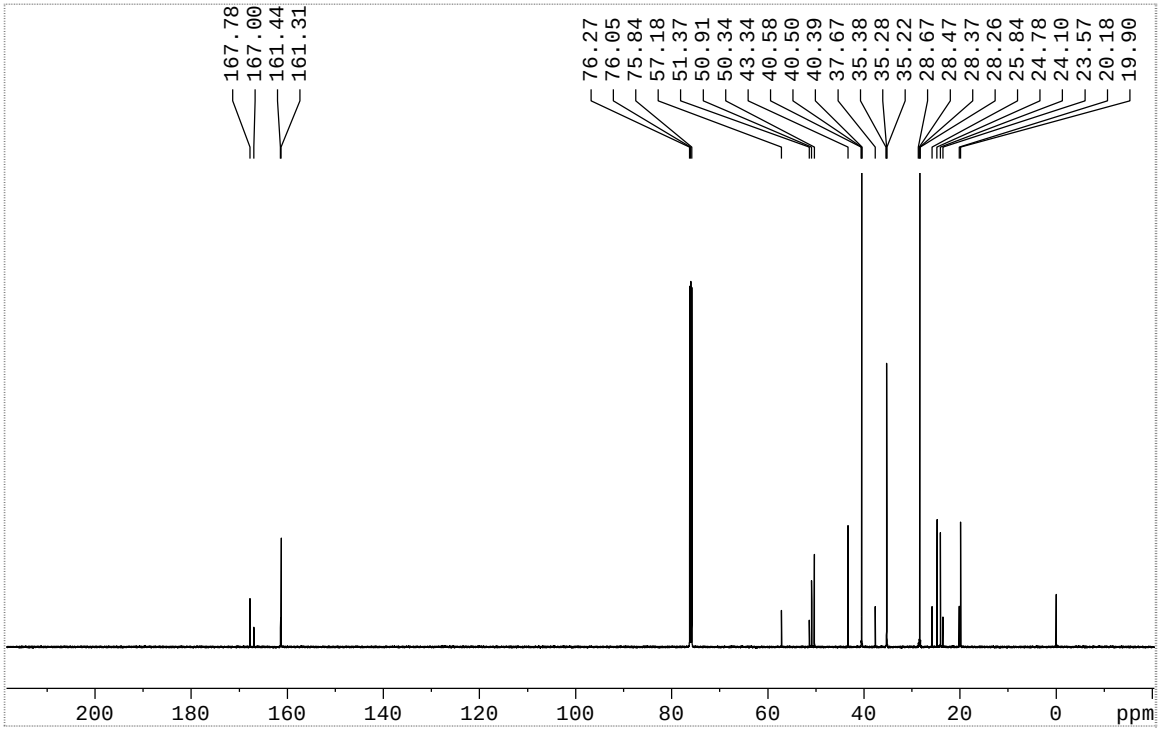
*N*2-[(1*R*)-1-phenylethyl]-(2*S*)-1-formyltetrahydro-1*H*-2-pyrrolecarboxamide (**108**)



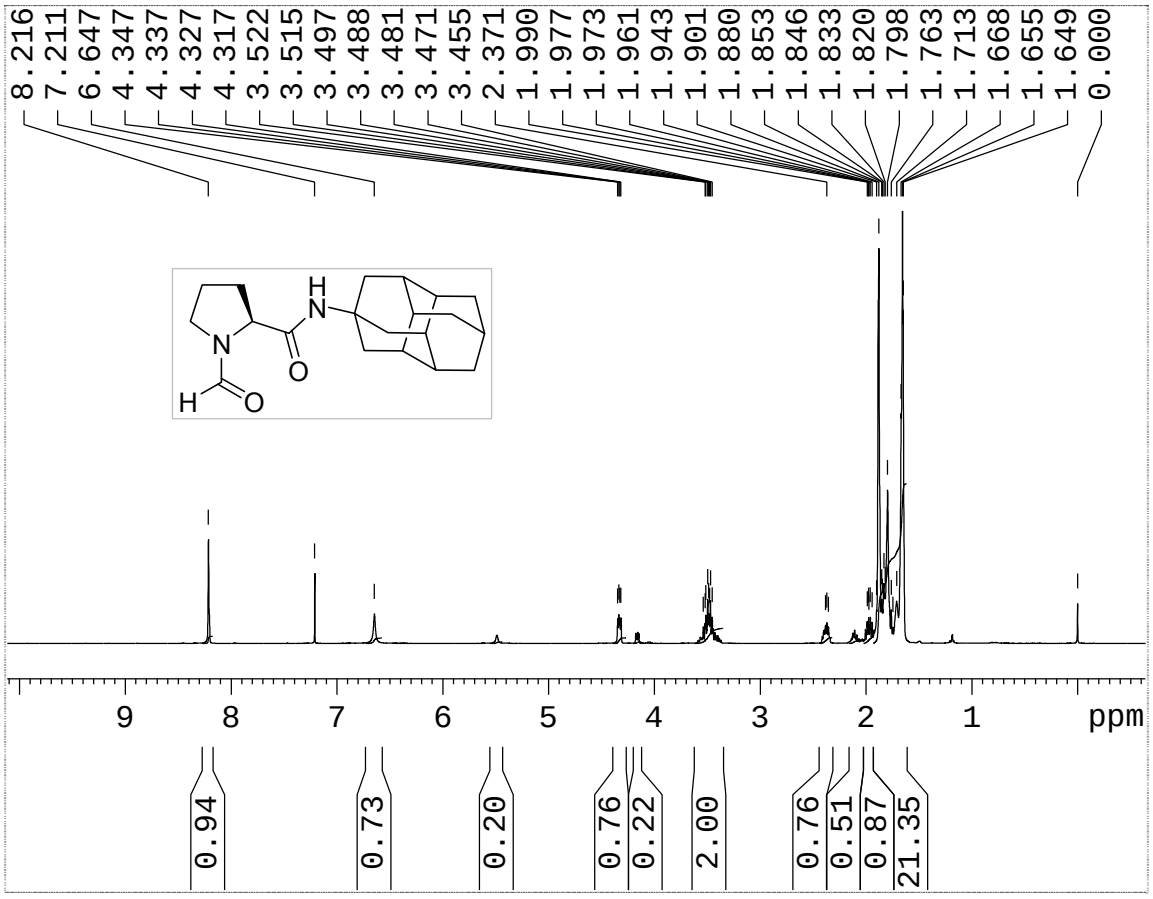


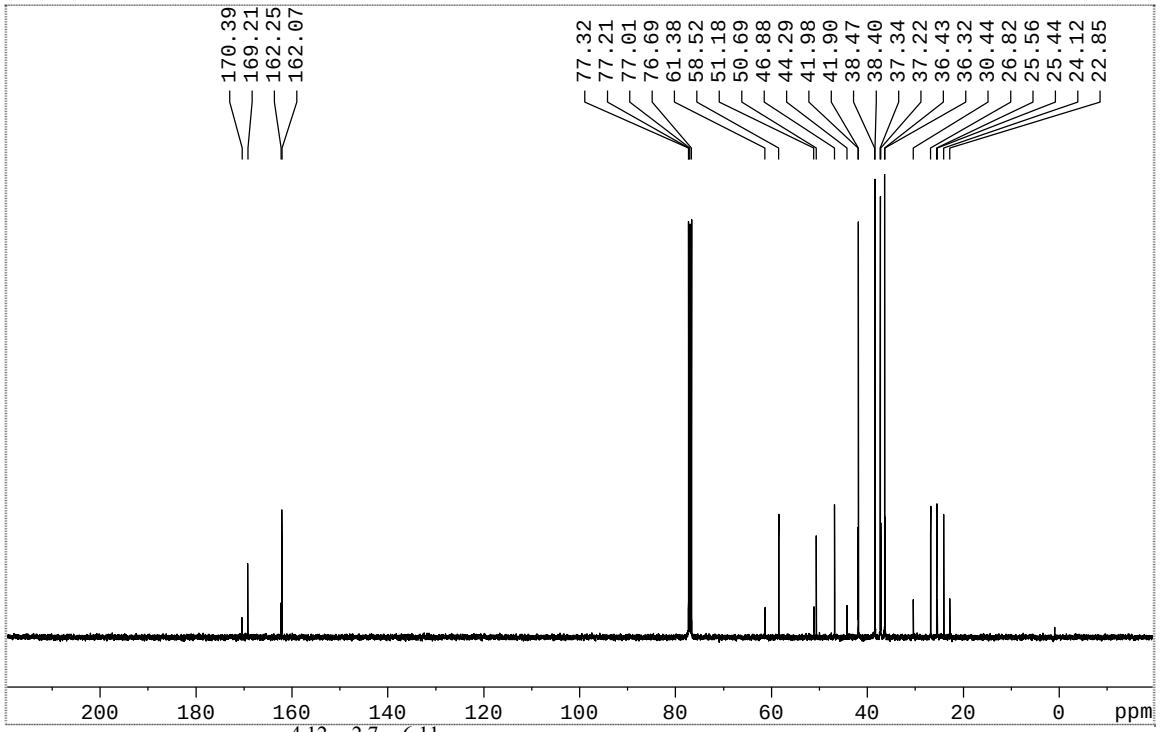
*N*2-[(1*R*)-1-(2-naphthyl)ethyl]-(2*S*)-1-formyltetrahydro-1*H*-2-pyrrolecarboxamide (**109**)



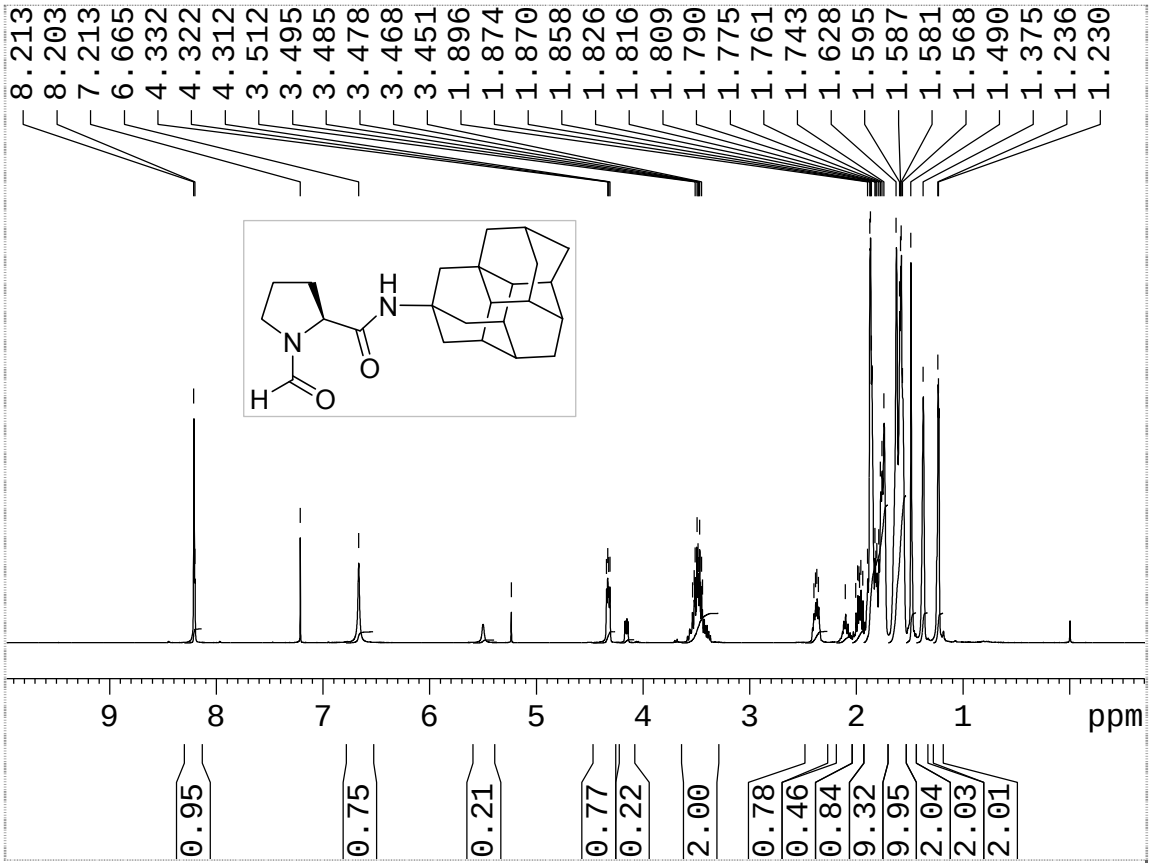


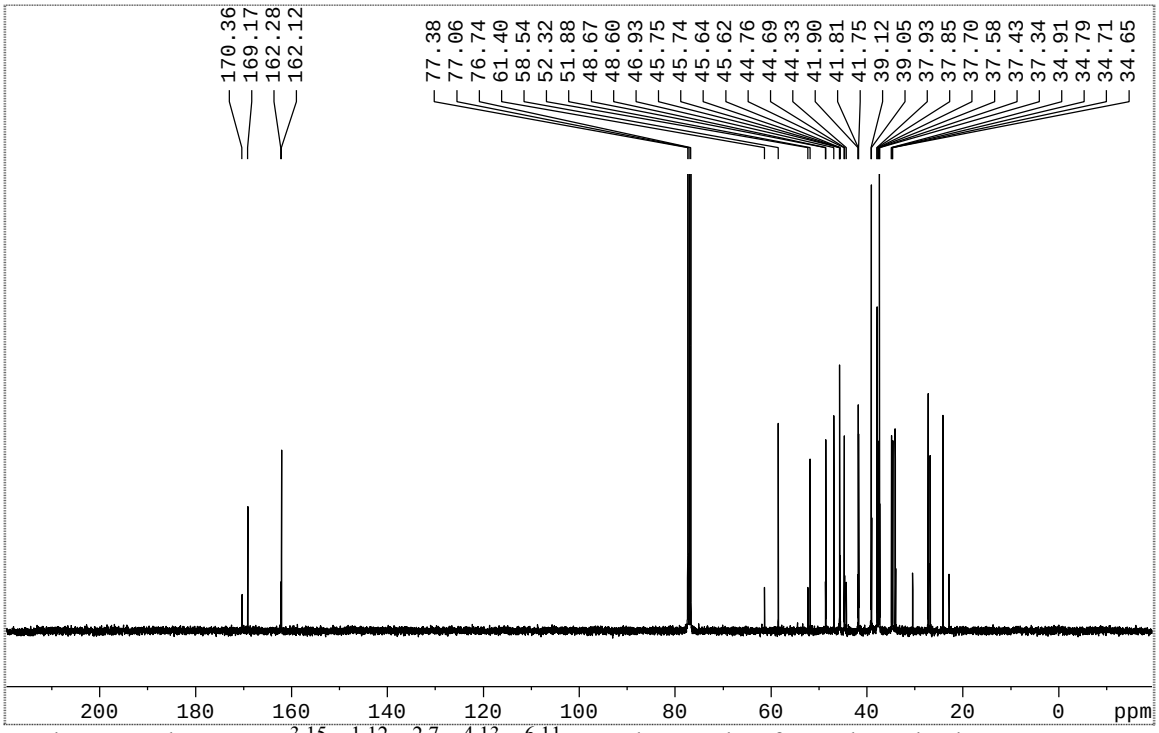
*N*2-(1-adamantyl)-(2*S*)-1-formylhexahydro-2-pyridinecarboxamide (**114**)



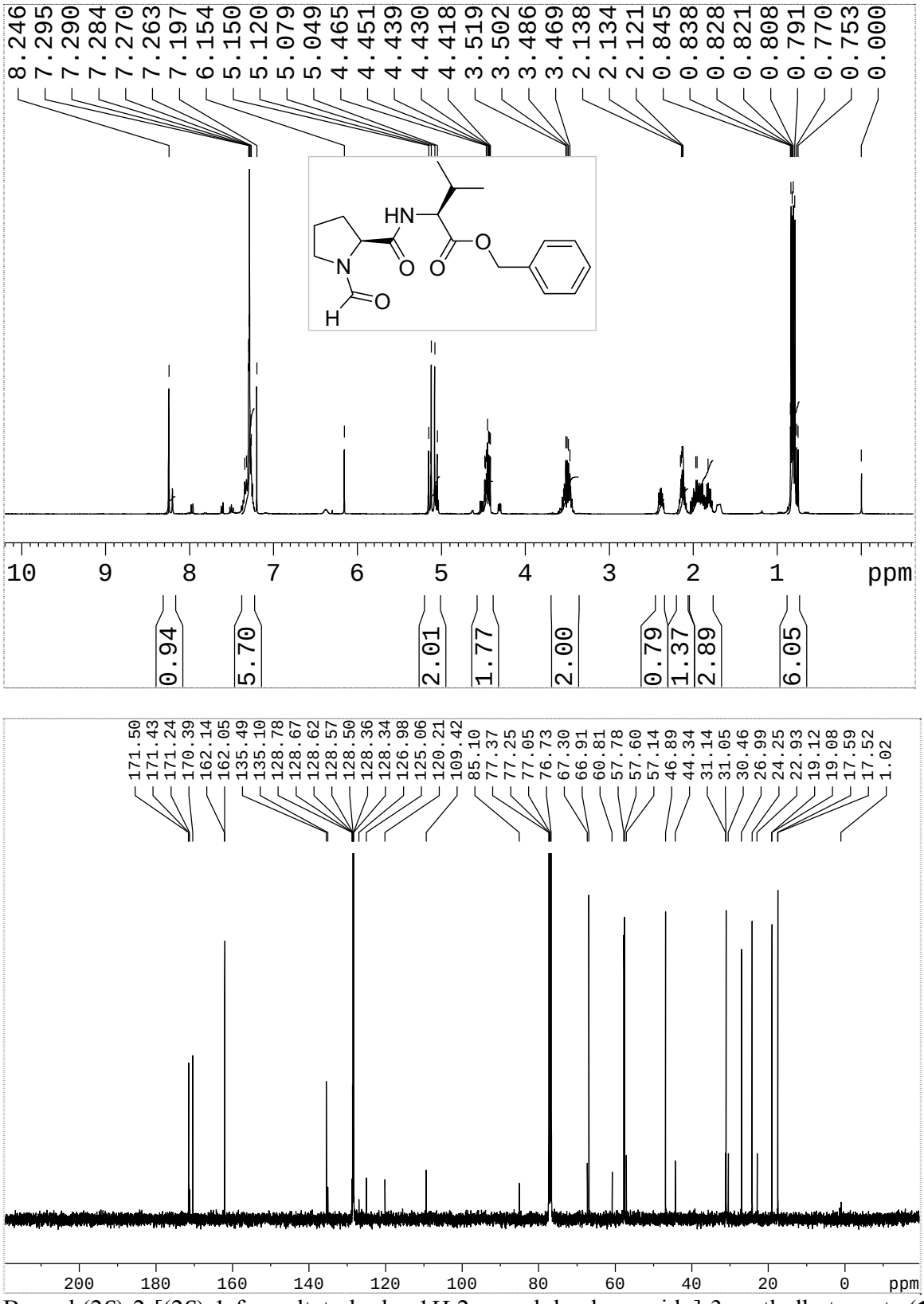


*N*2-pentacyclo[7.3.1.1^{4,12}.0^{2,7}.0^{6,11}]tetradec-4-yl-1-formyltetrahydro-1*H*-2-pyrrole-carboxamide (**106**)

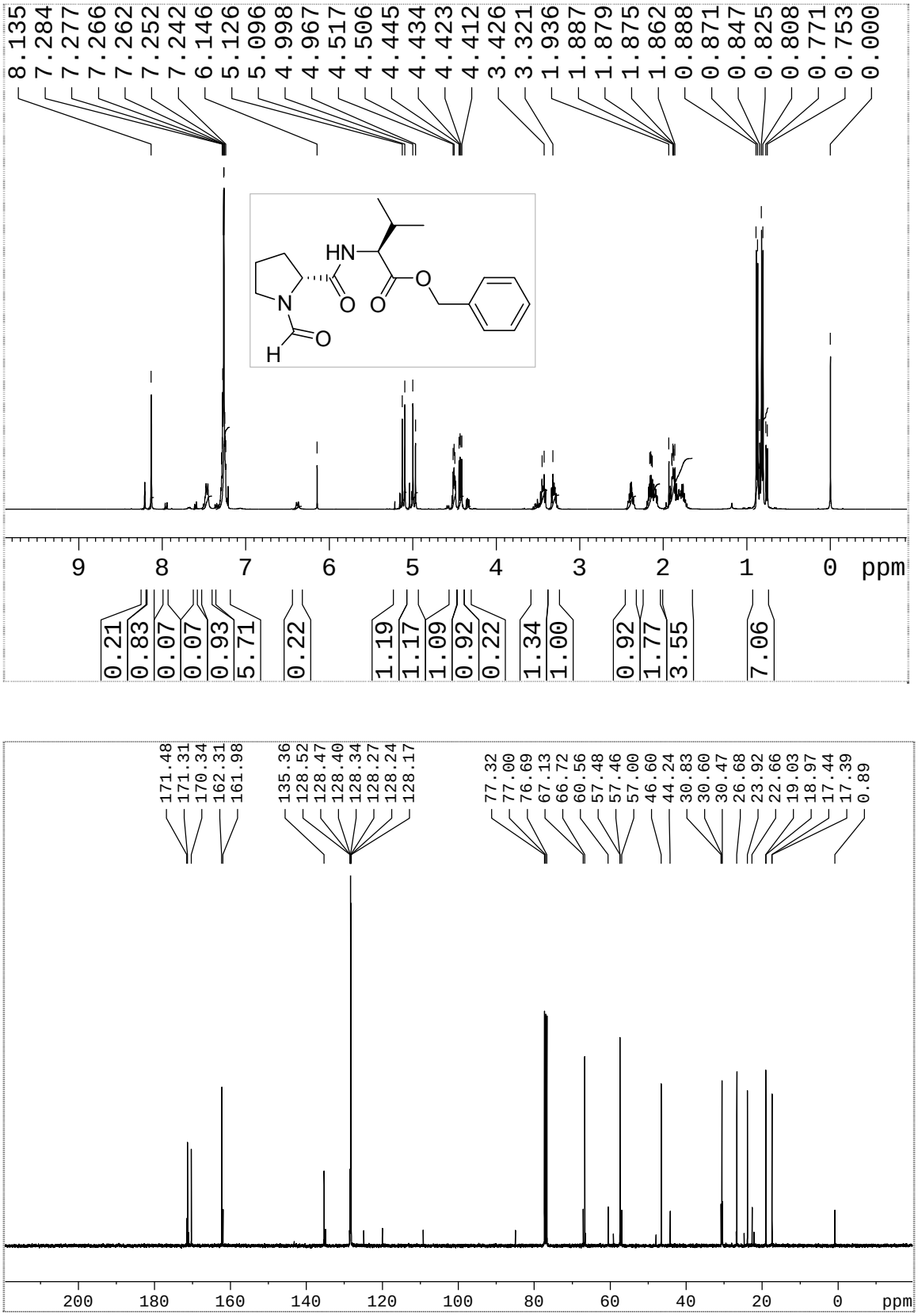




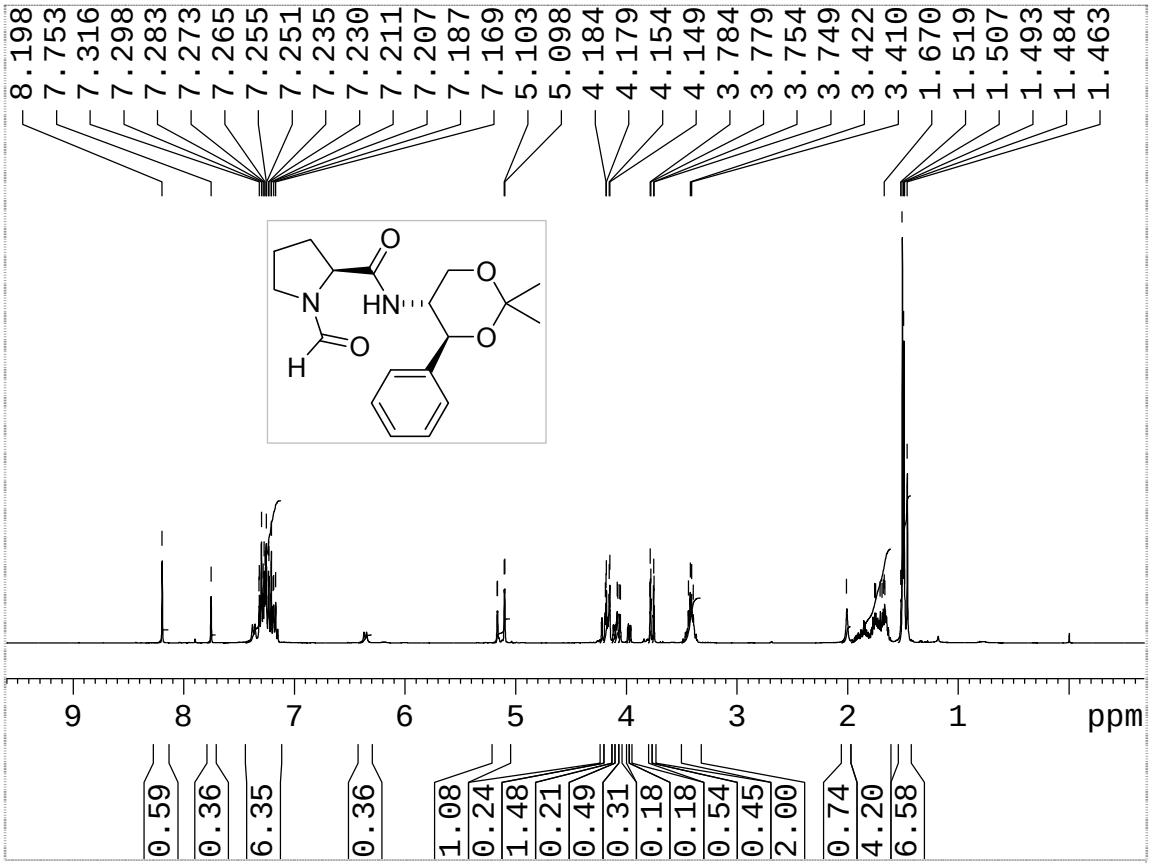
*N*2-heptacyclo[7.7.1.1^{3,15}.0^{1,12}.0^{2,7}.0^{4,13}.0^{6,11}]octadec-9-yl-1-formyltetrahydro-1*H*-2-pyrrolecarboxamide (**107**)

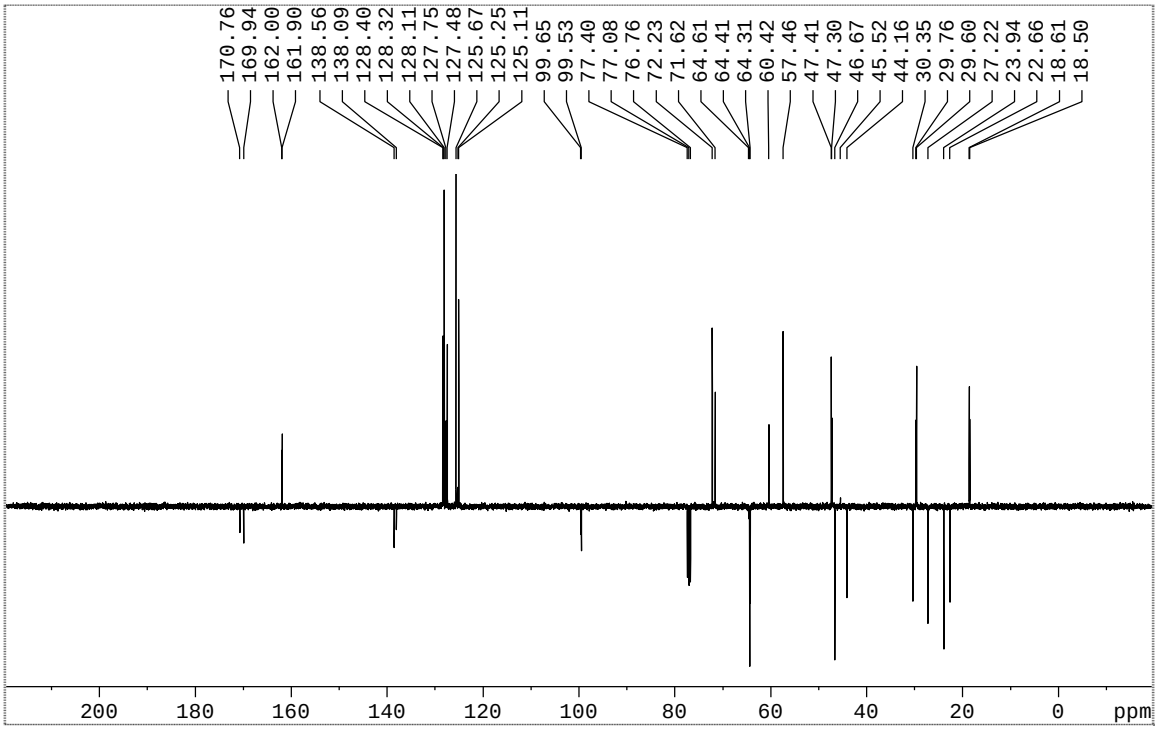


Benzyl (2*S*)-2-[(2*S*)-1-formyltetrahydro-1*H*-2-pyrrolylcarboxamido]-3-methylbutanoate (**110**)

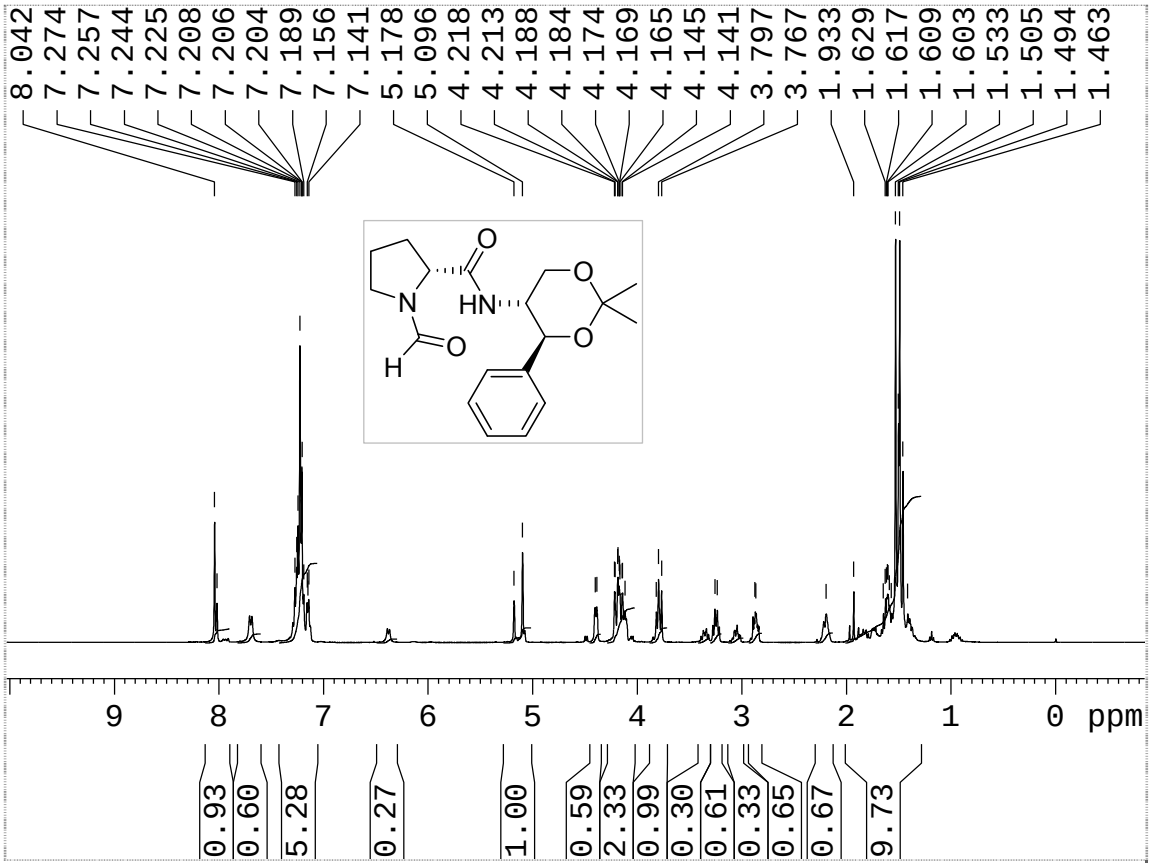


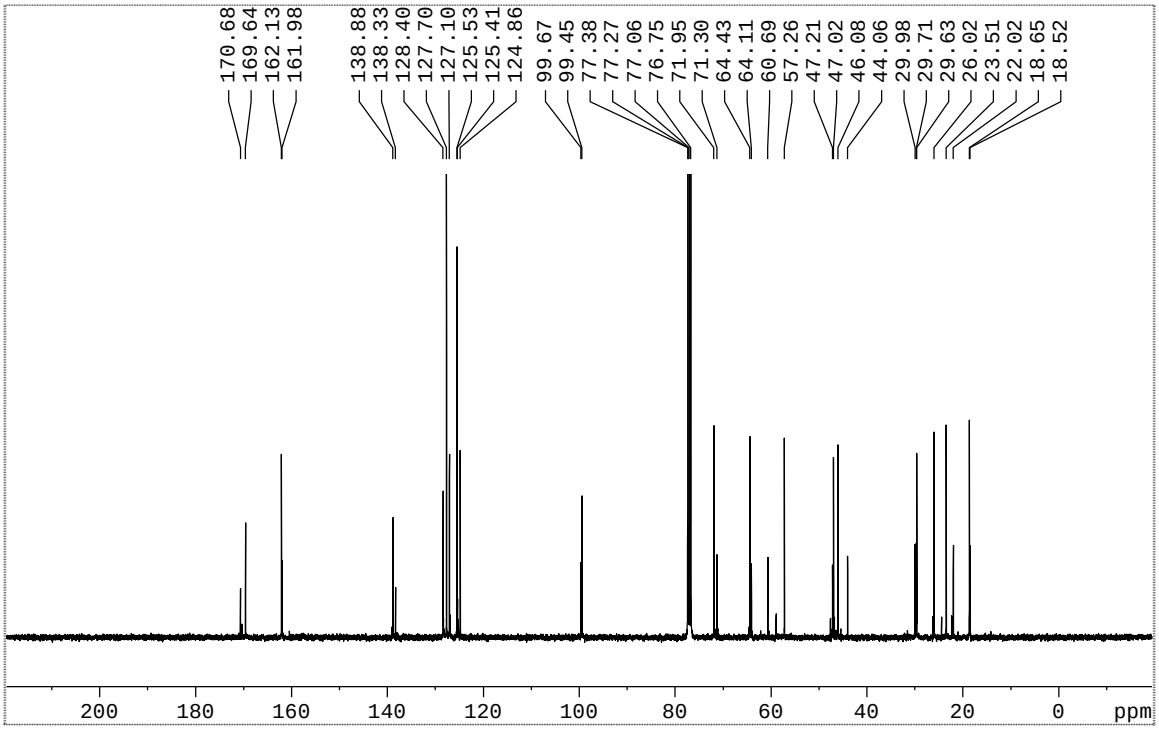
Benzyl (2*S*)-2-[(2*R*)-1-formyltetrahydro-1*H*-2-pyrrolylcarboxamido]-3-methylbutanoate (**111**)



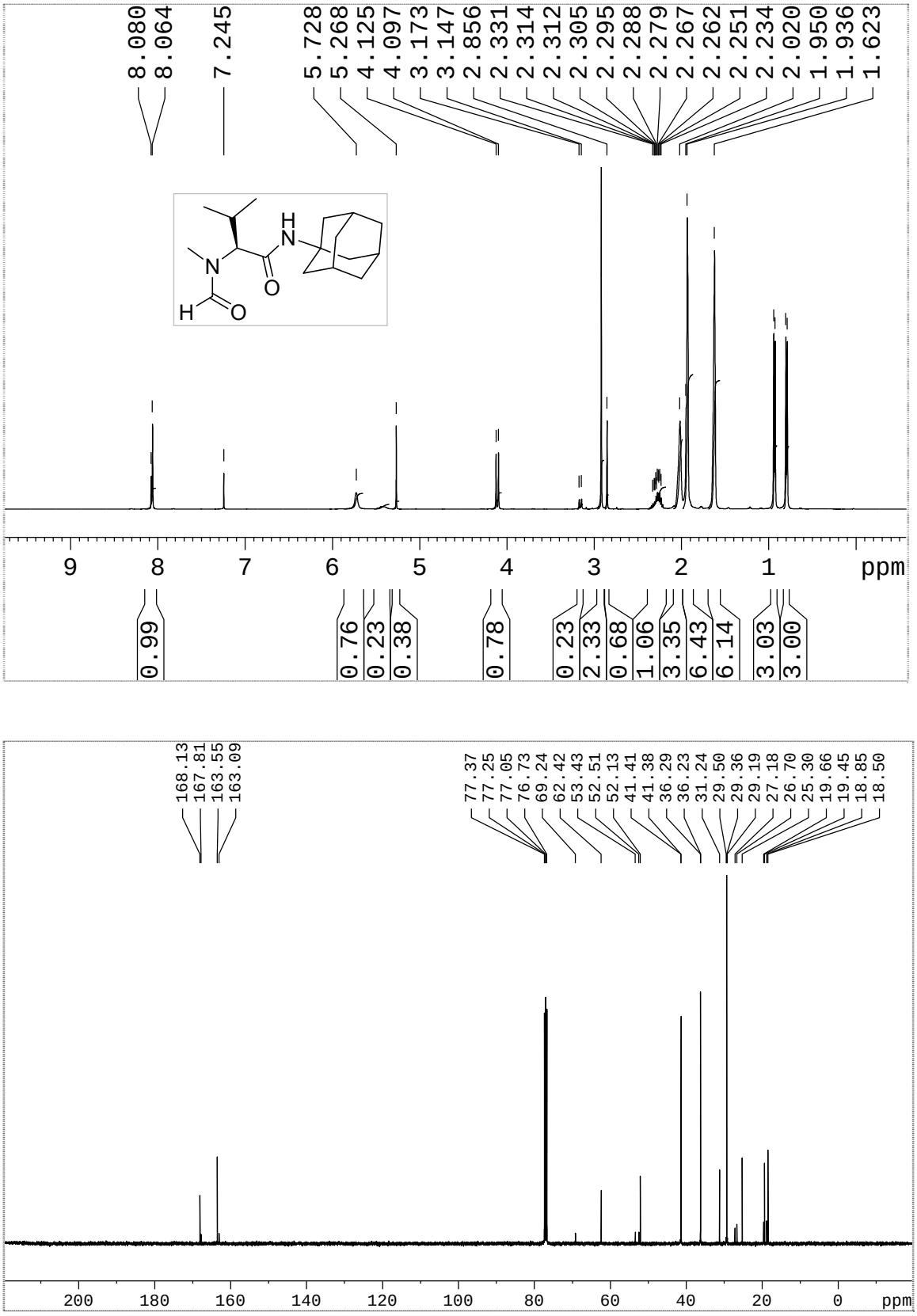


*N*2-[(4*R*,5*R*)-2,2-dimethyl-5-phenyl-1,3-dioxan-4-yl]-(2*S*)-1-formyltetrahydro-1*H*-2-pyrrolecarboxamide (**112**)

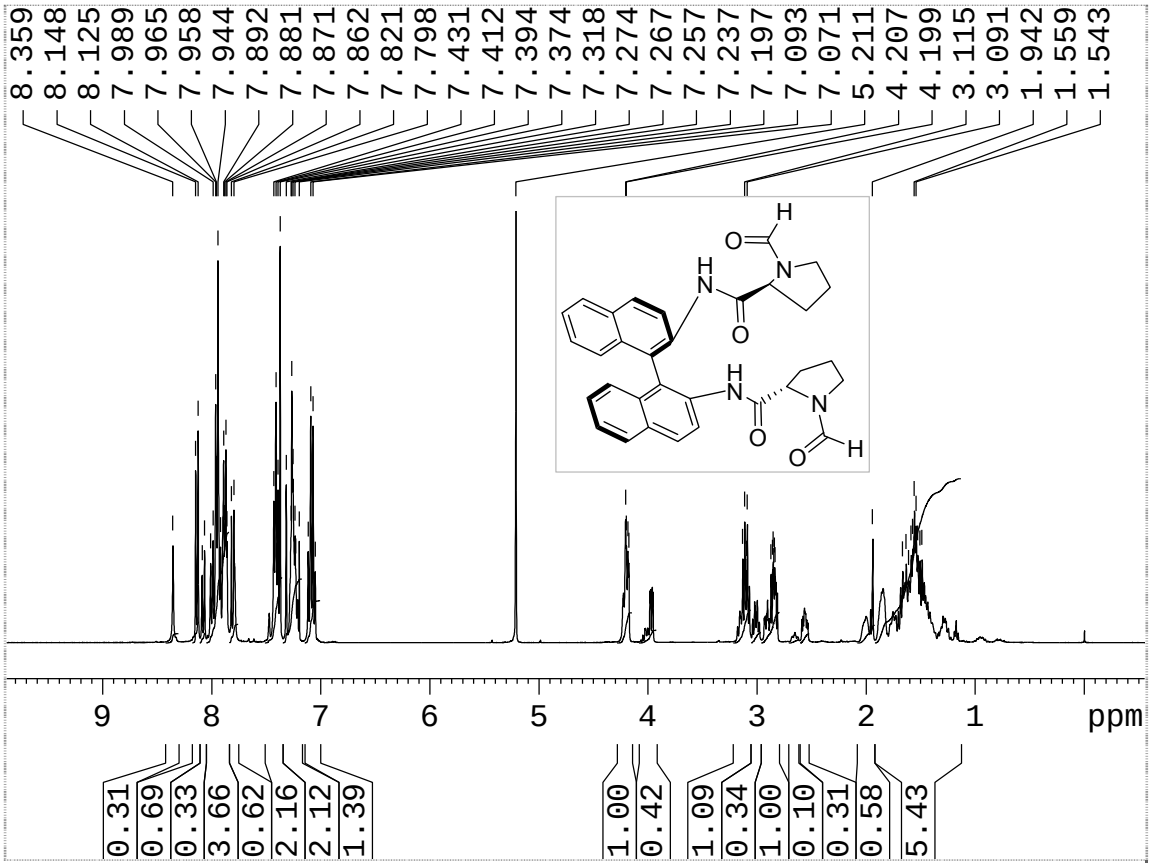


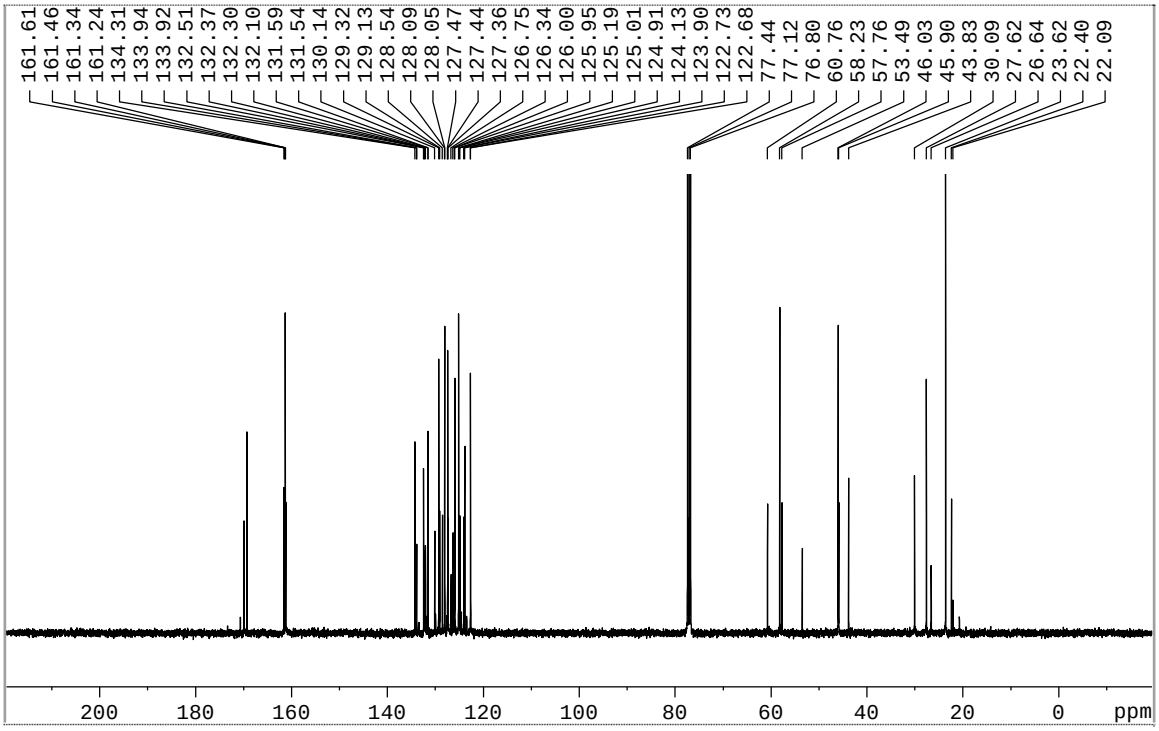


*N*2-[(4*R*,5*R*)-2,2-dimethyl-5-phenyl-1,3-dioxan-4-yl]-(2*R*)-1-formyltetrahydro-1*H*-2-pyrrolecarboxamide (**113**)

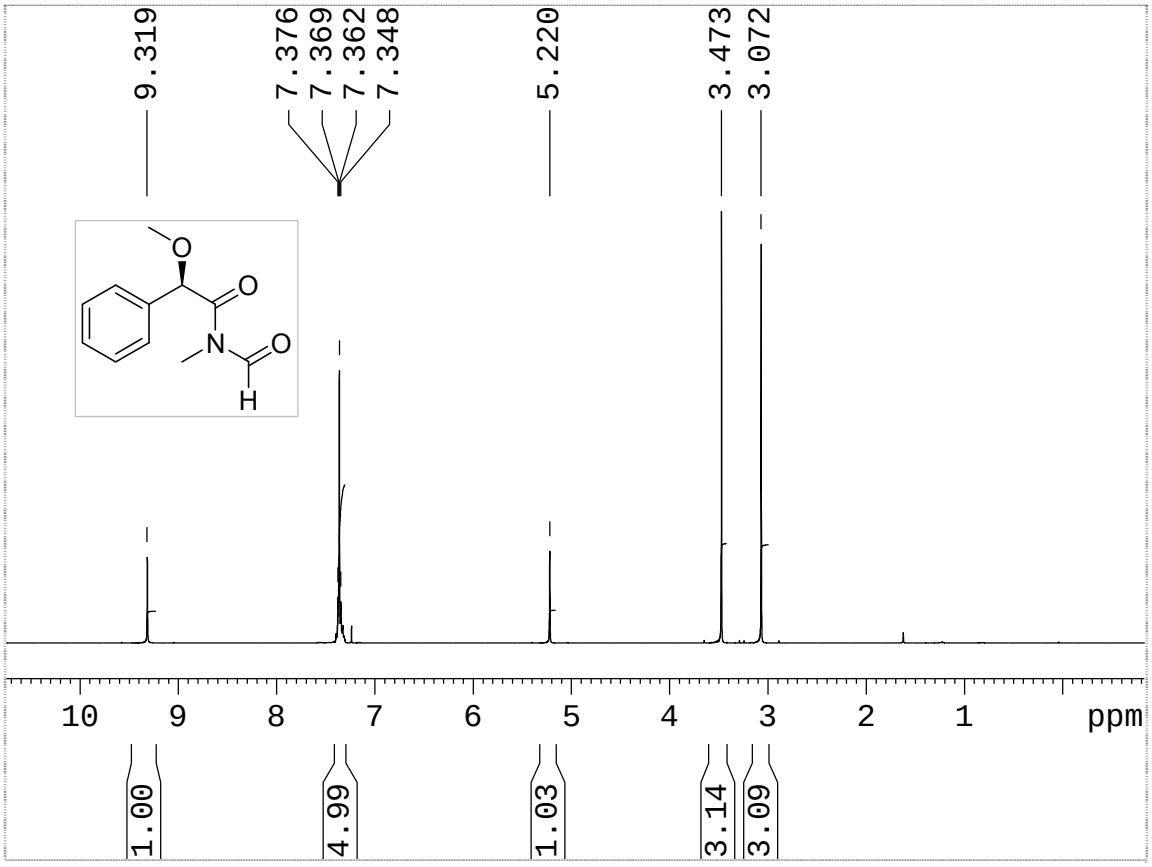


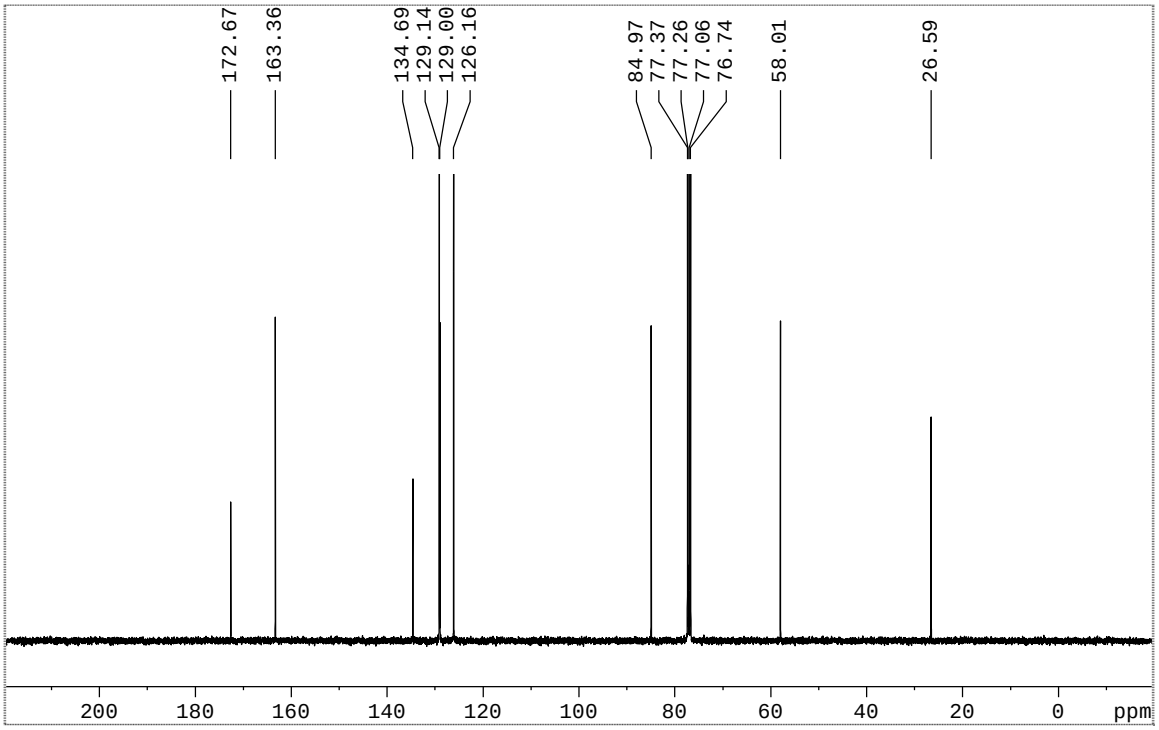
*N*1-(1-adamantyl)-(2*S*)-3-methyl-2-methylformamidobutanamide (**115**)



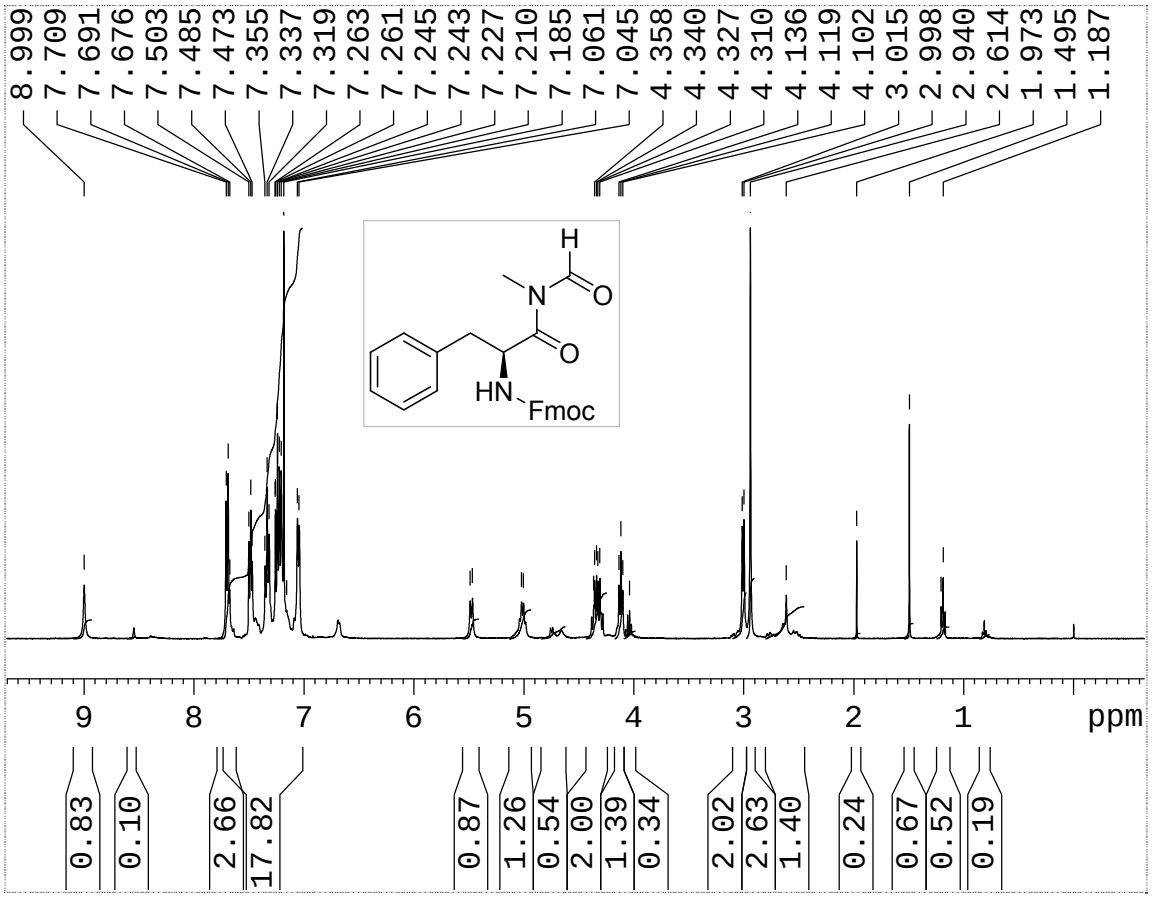


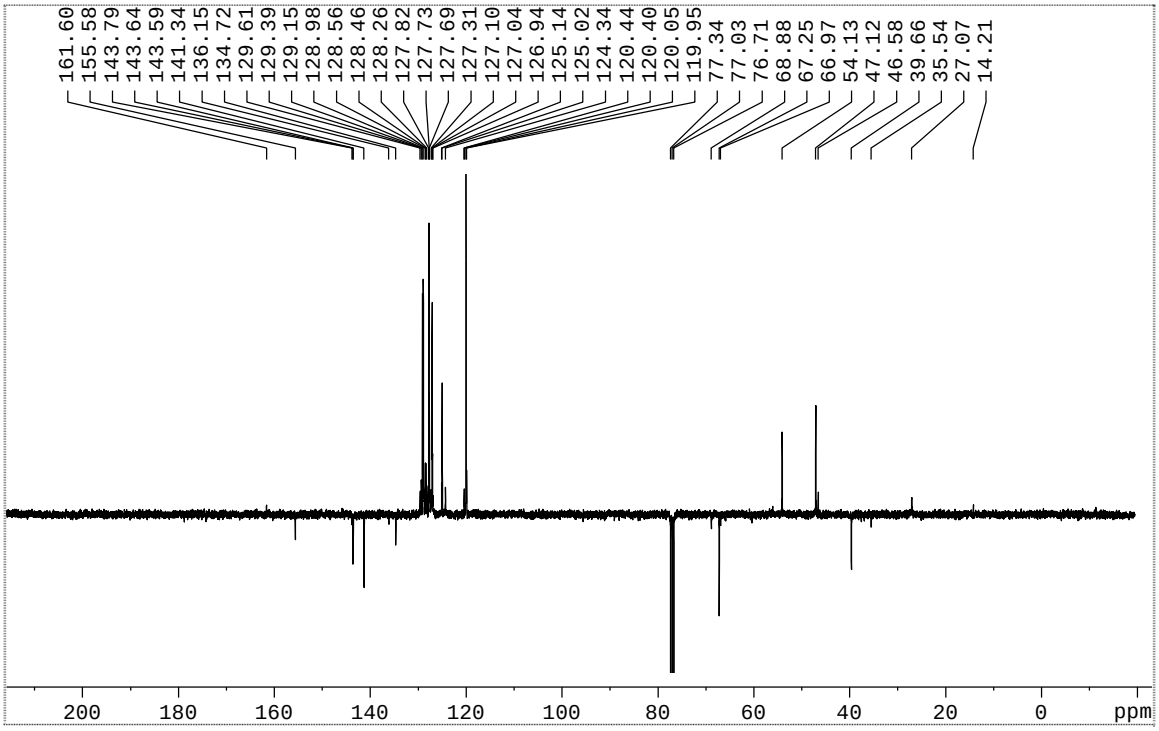
*N*2-(*R*)-(1-2-[(2*S*)-1-formyltetrahydro-1*H*-2-pyrrolylcarboxamido]-1-naphthyl-2-naphthyl)-(2*S*)-1-formyltetrahydro-1*H*-2-pyrrolecarboxamide (**118**)



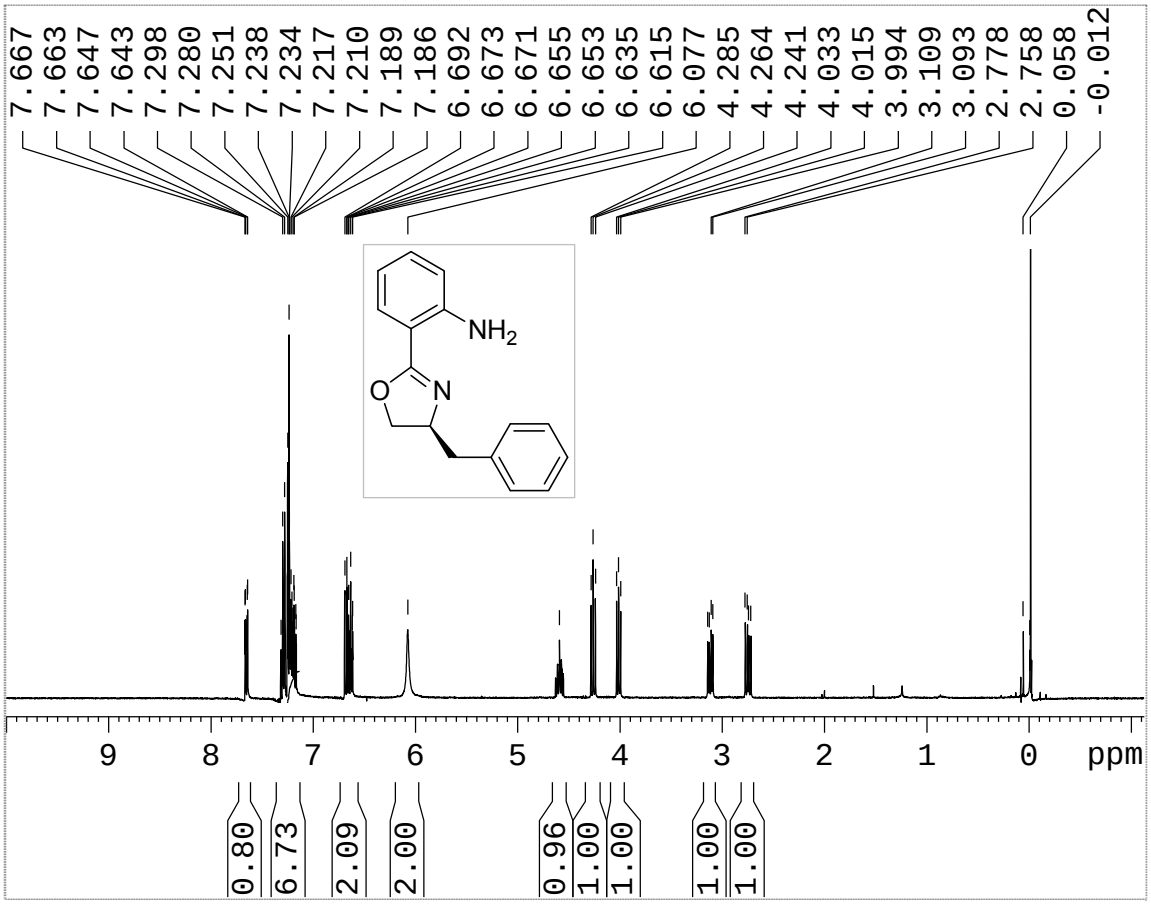


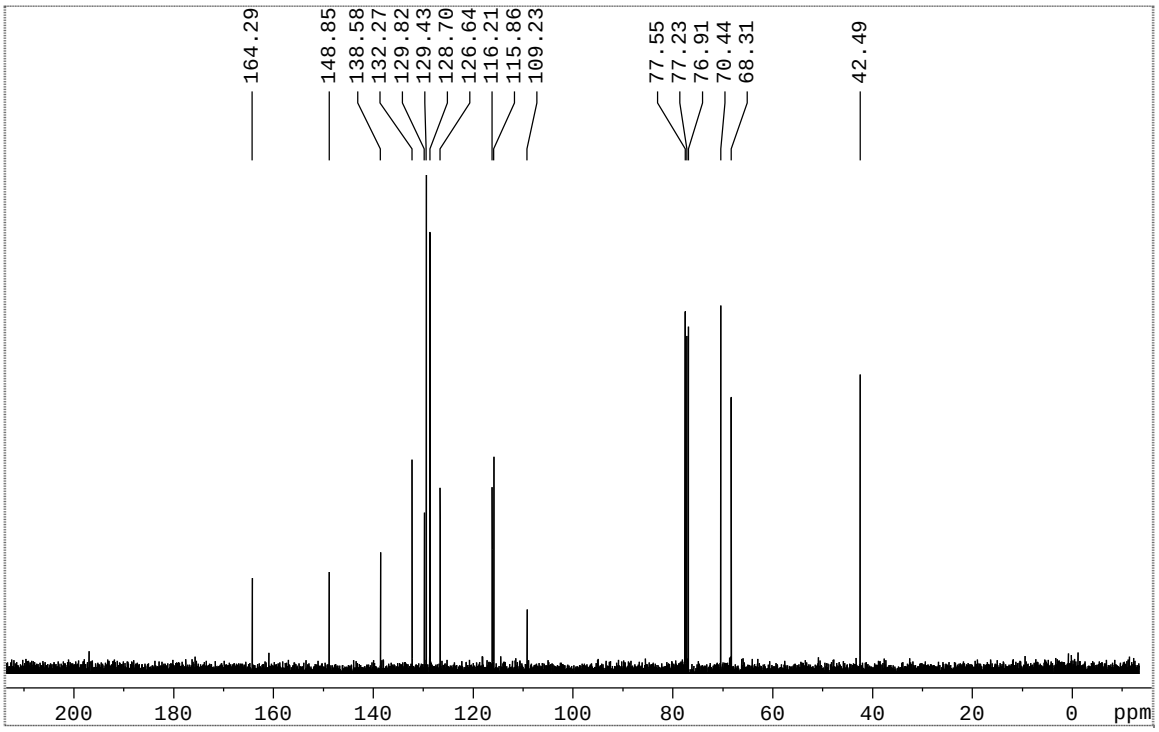
(*R*)-*N*-formyl-*N*-methyl-2-phenylpropanamide (**116**)



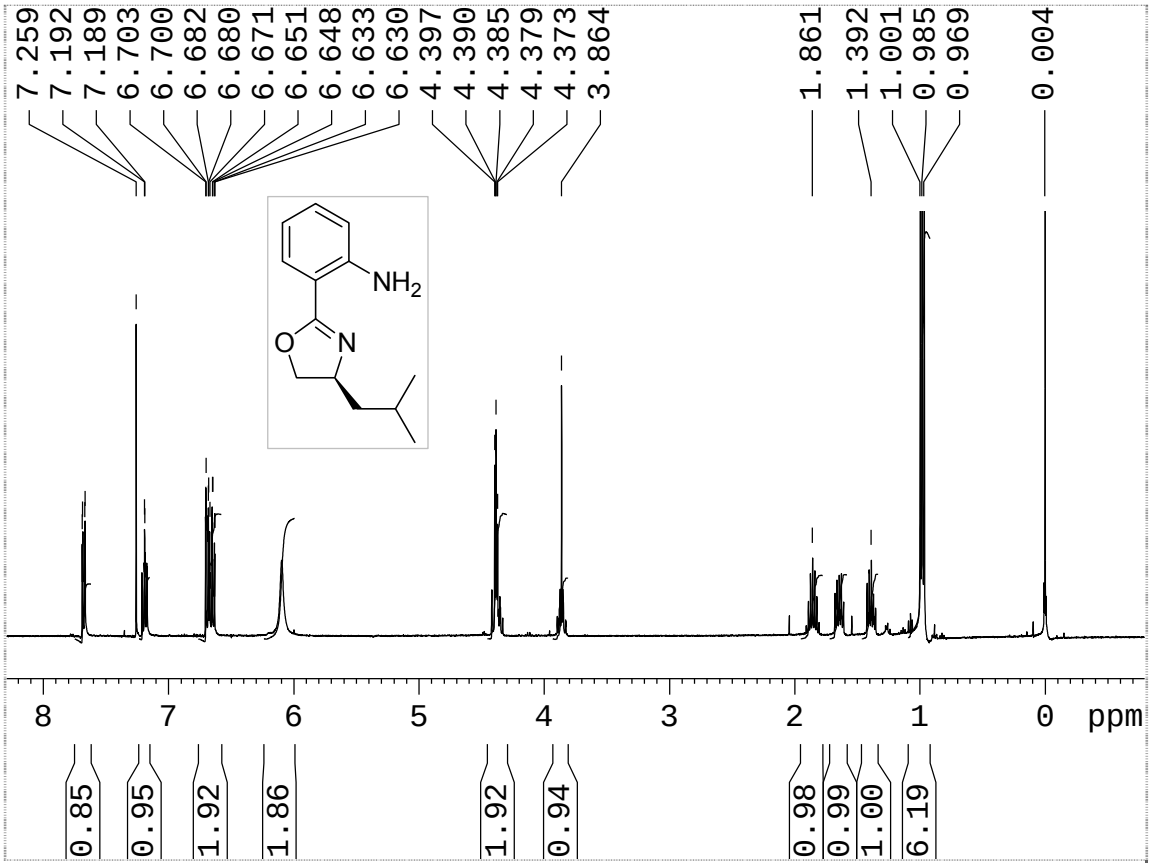


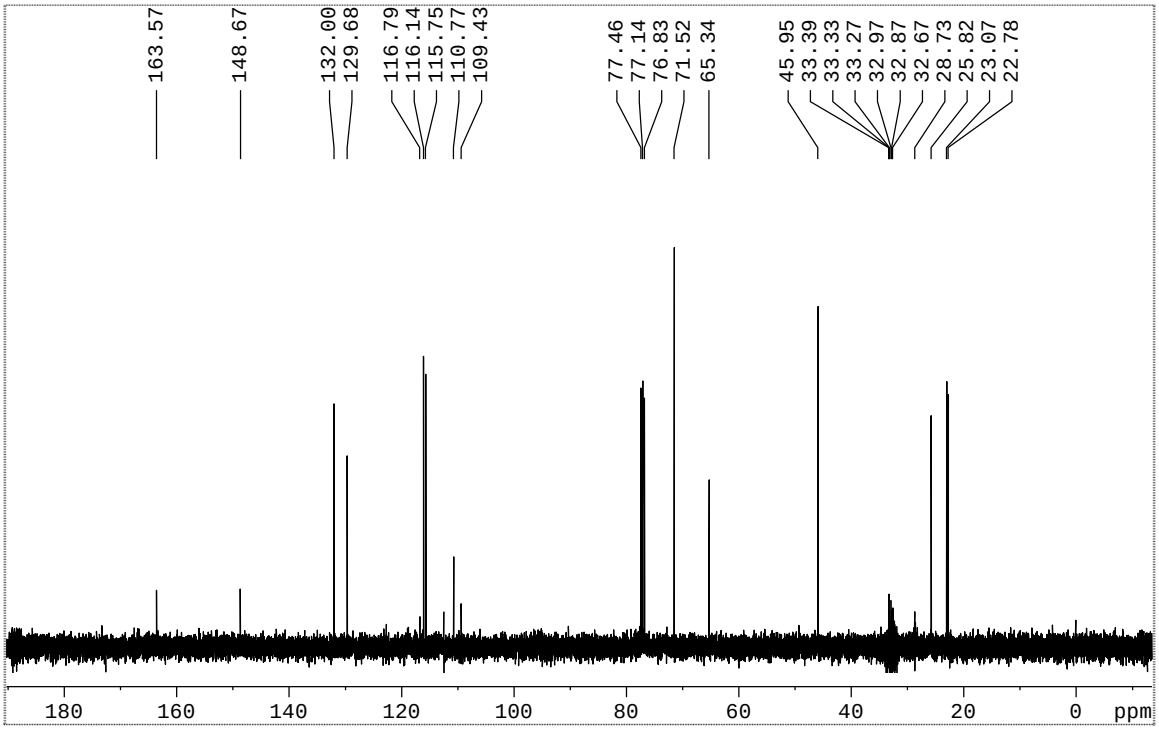
(*S*)-(9H-fluoren-9-yl)methyl 1-(*N*-methylformamido)-1-oxo-3-phenylpropane-2-yl-carbamate (**117**)



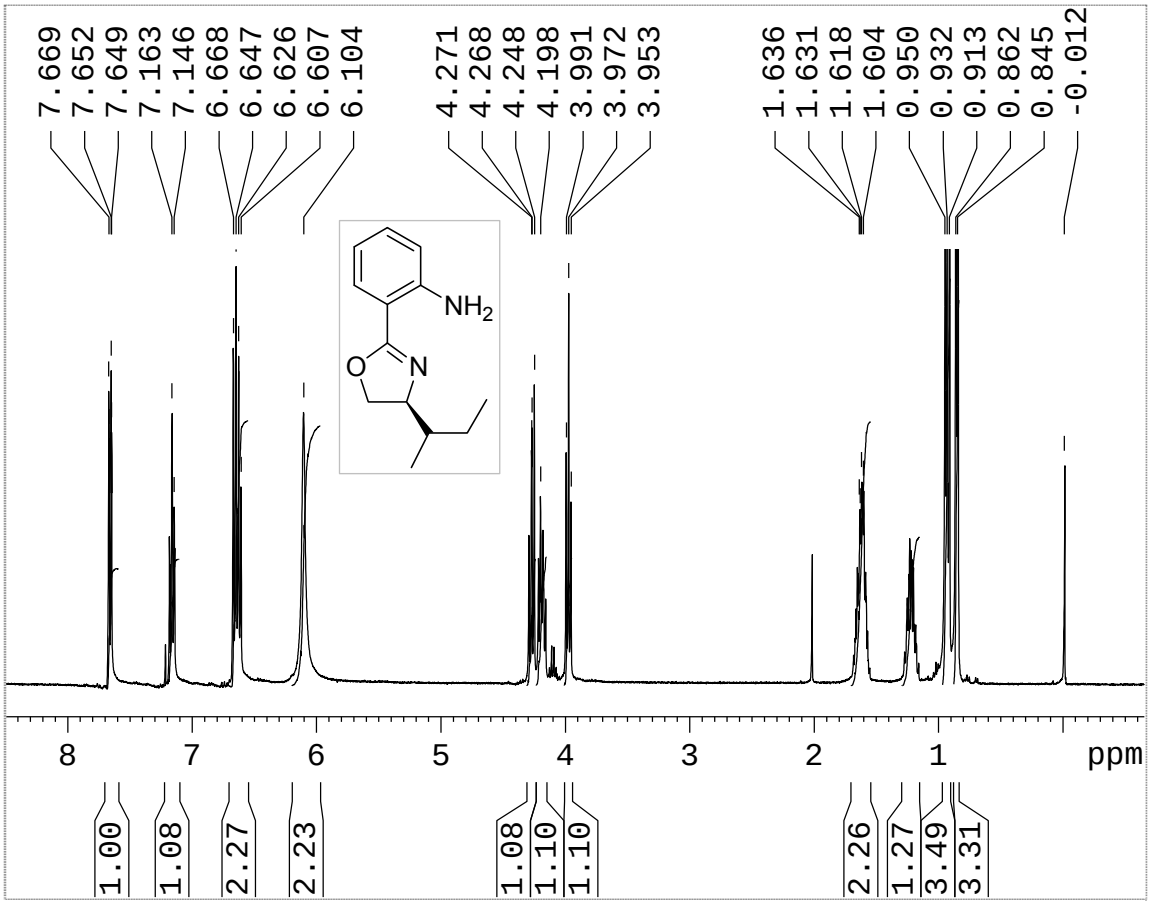


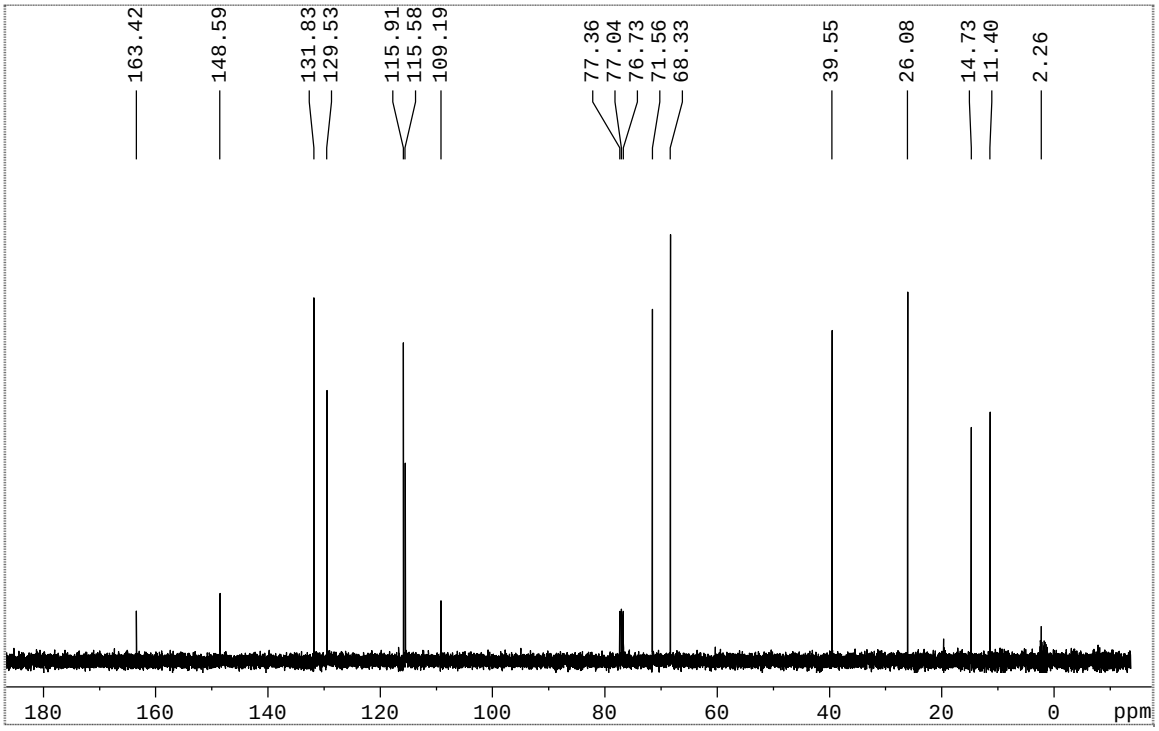
2-[(4*S*)-4-Benzyl-4,5-dihydro-1,3-oxazol-2-yl]aniline (**131b**)



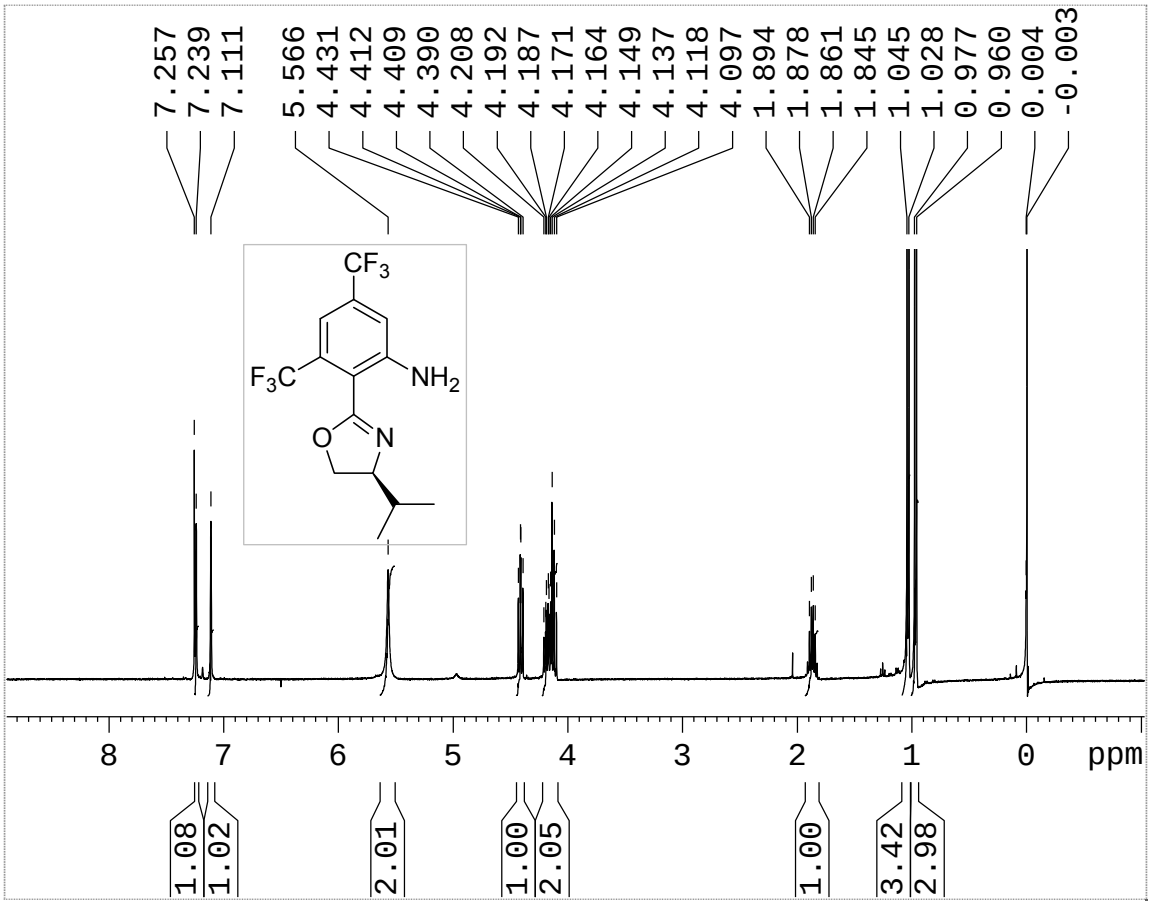


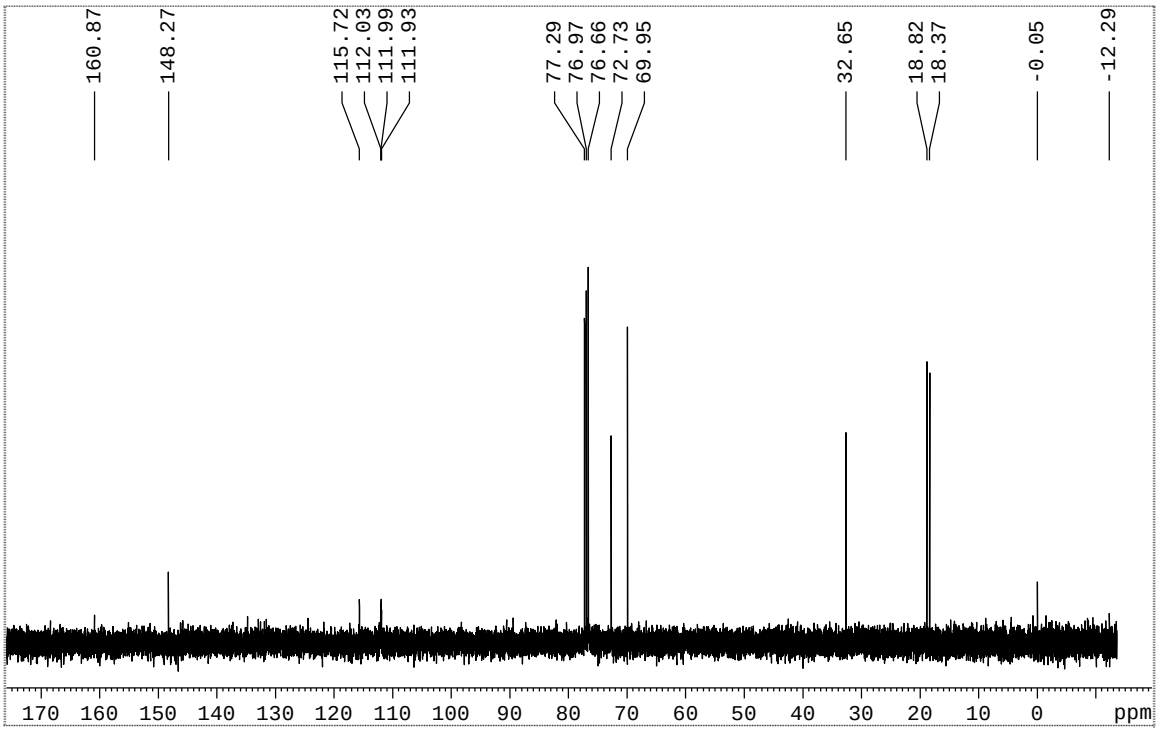
2-[(4*S*)-4-Isobutyl-4,5-dihydro-1,3-oxazol-2-yl]aniline (**131c**)



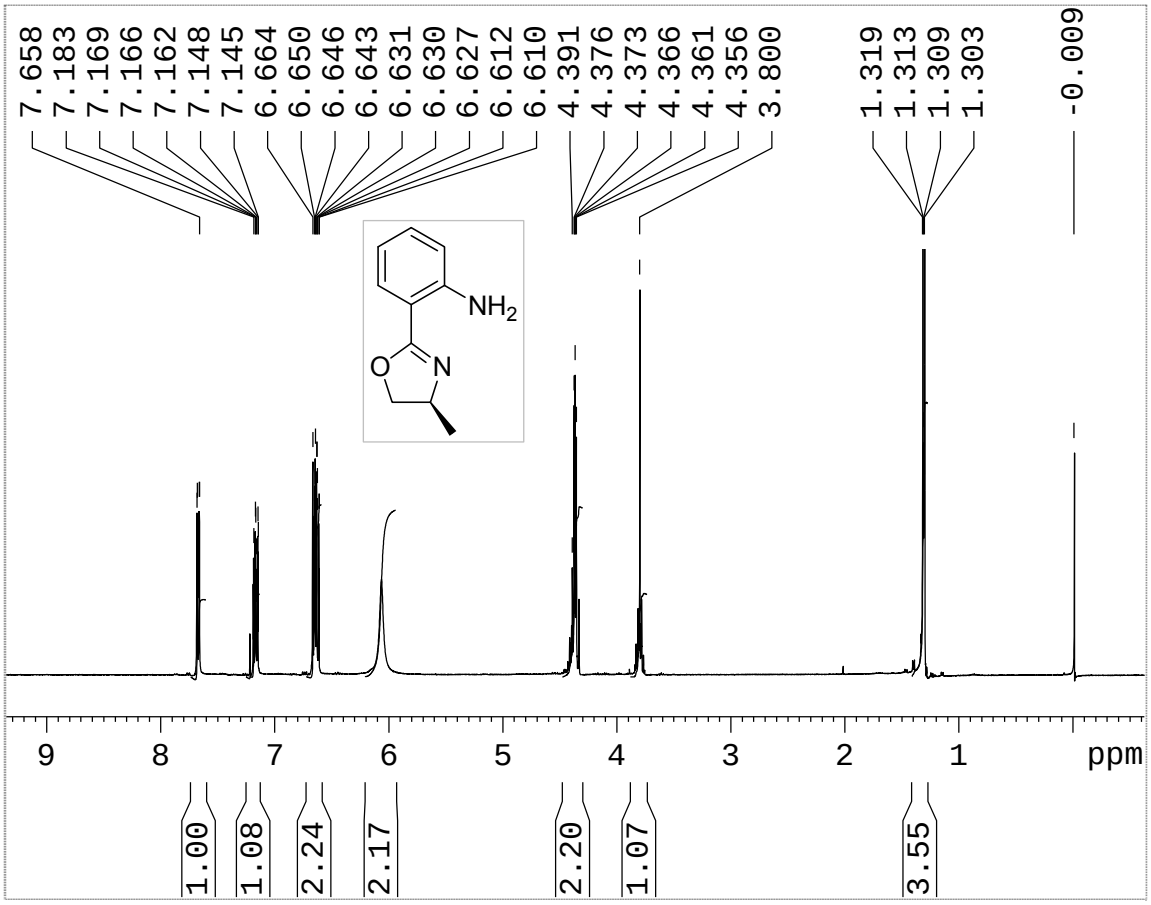


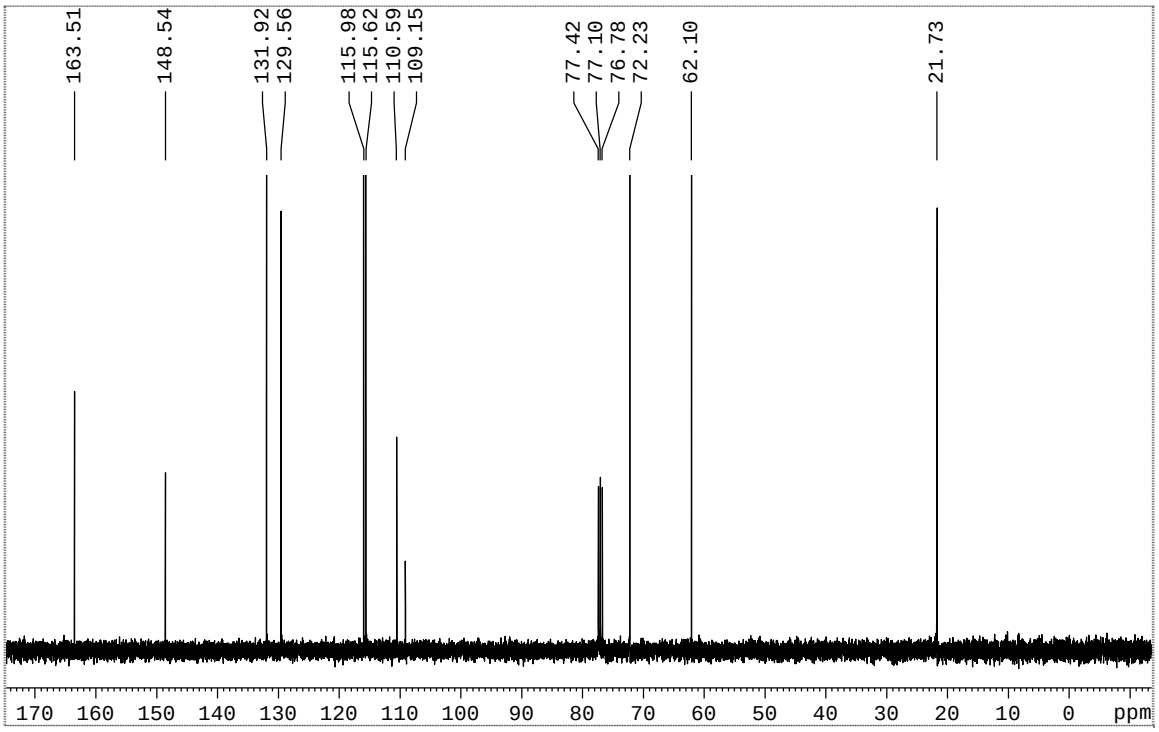
2-[(4*S*)-4-(*sec*-Butyl)-4,5-dihydro-1,3-oxazol-2-yl]aniline (**131d**)



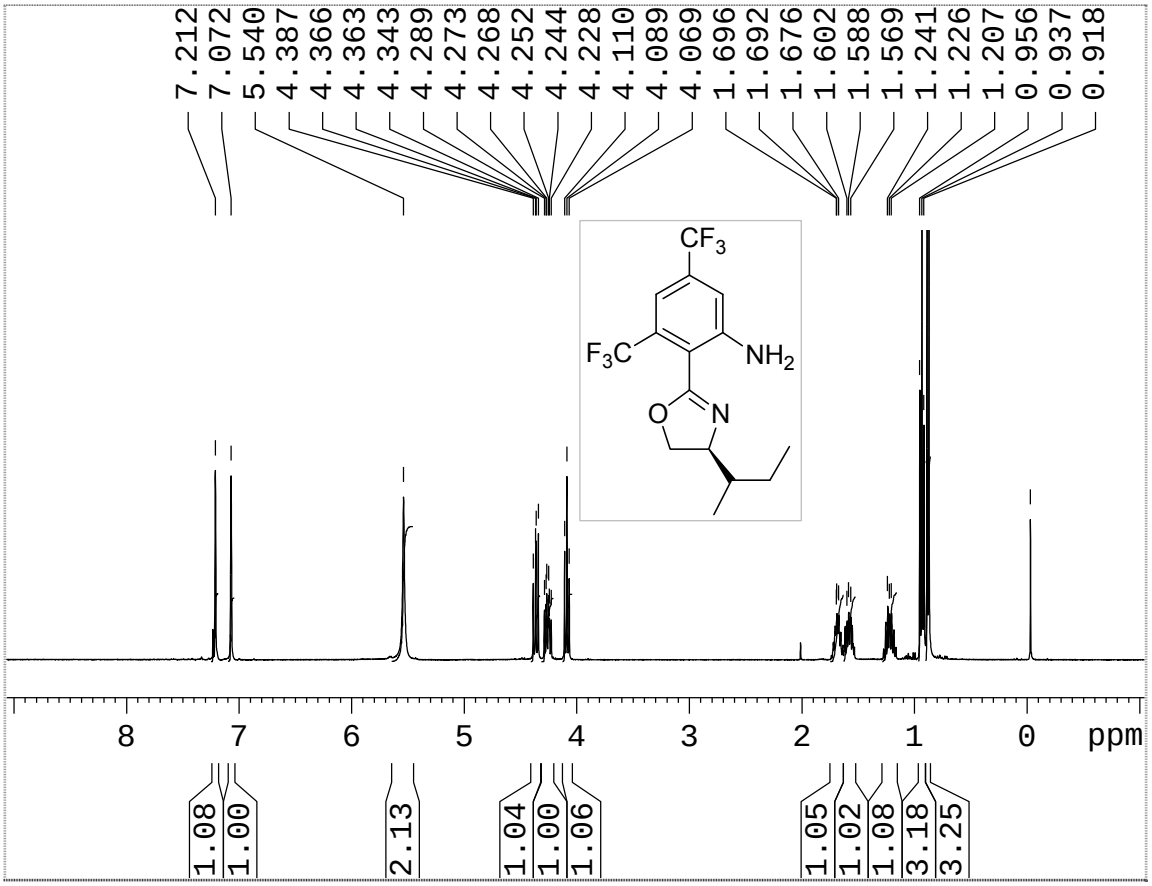


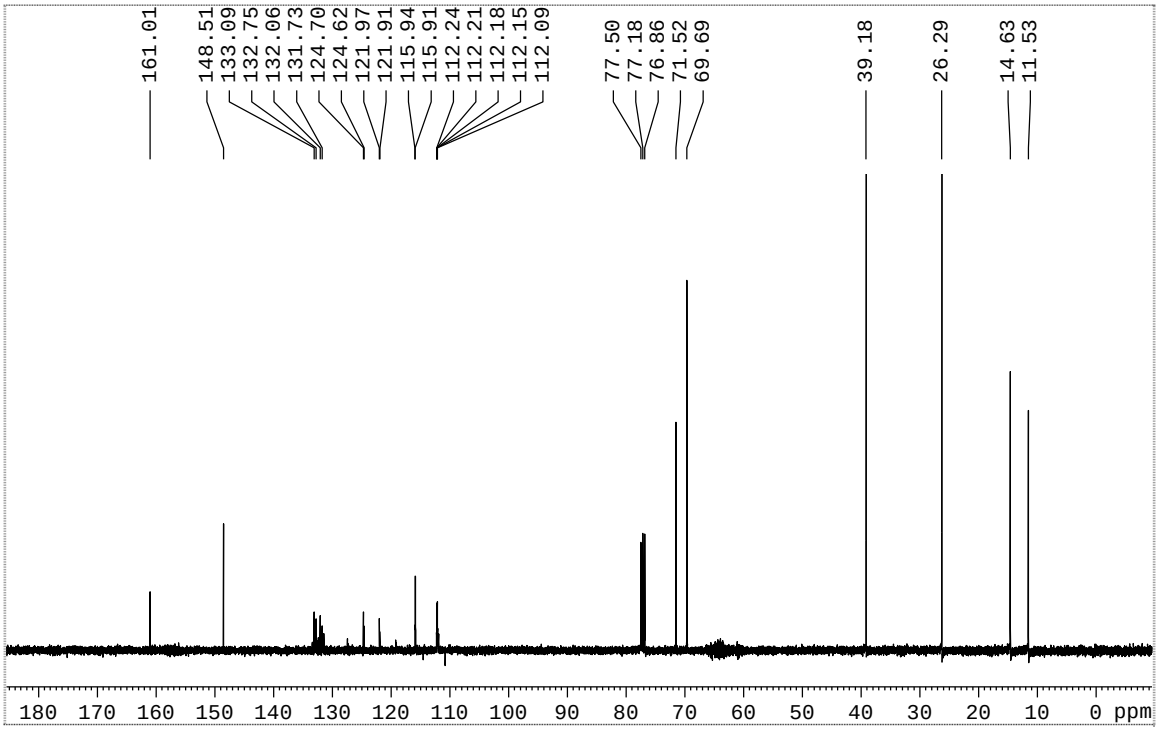
2-[(4*S*)-4-Isopropyl-4,5-dihydro-1,3-oxazol-2-yl]-3,5-di(trifluoromethyl)aniline (**131e**)



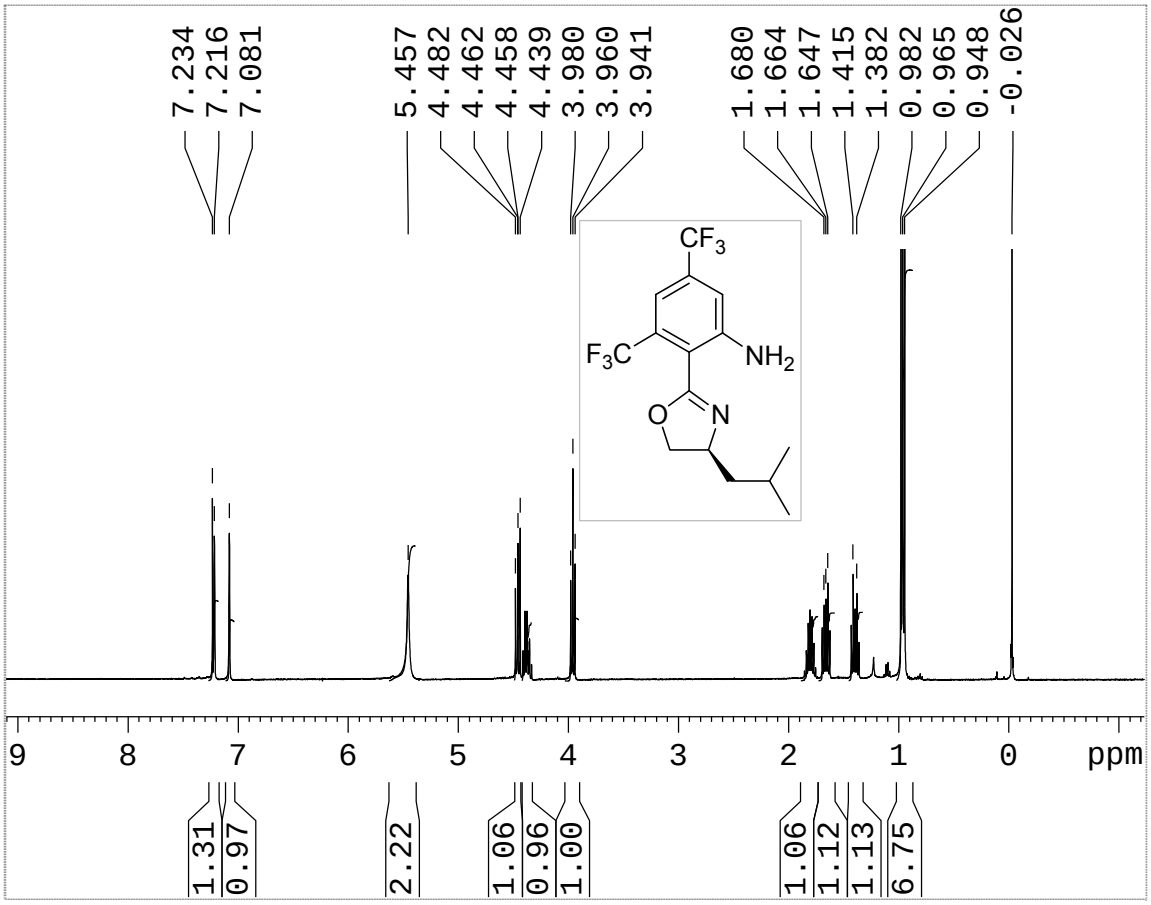


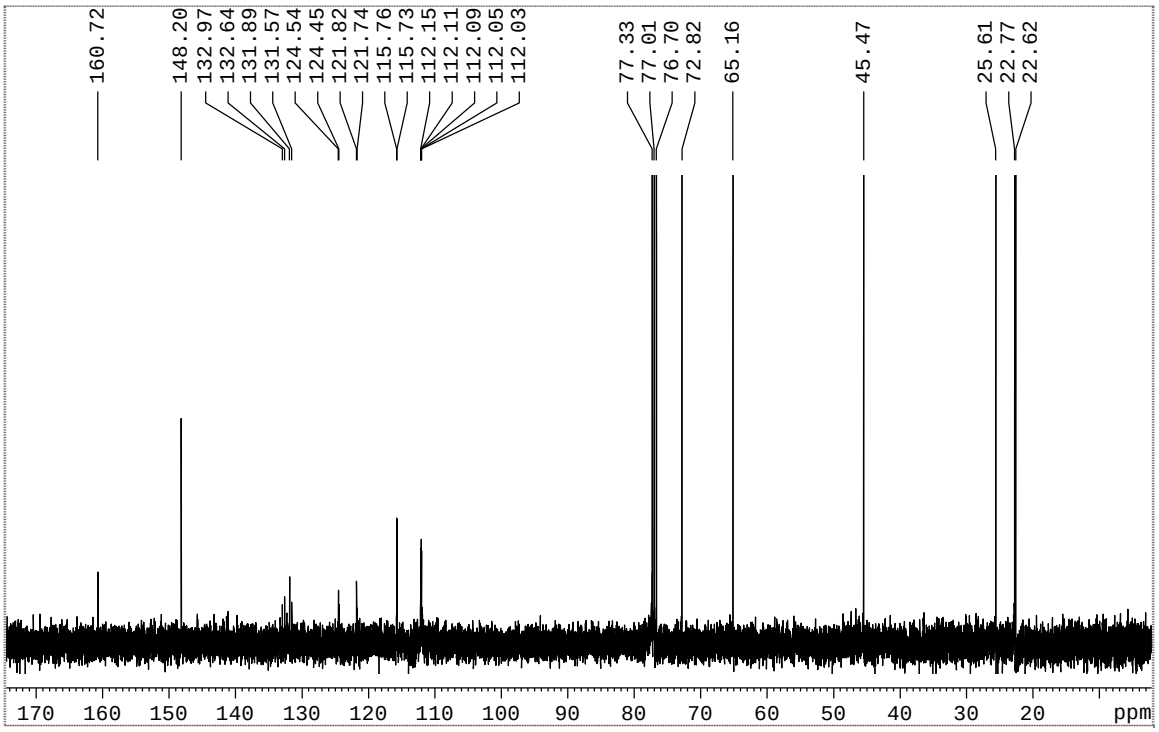
2-[(4*S*)-4-Methyl-4,5-dihydro-1,3-oxazol-2-yl]aniline (**131f**)



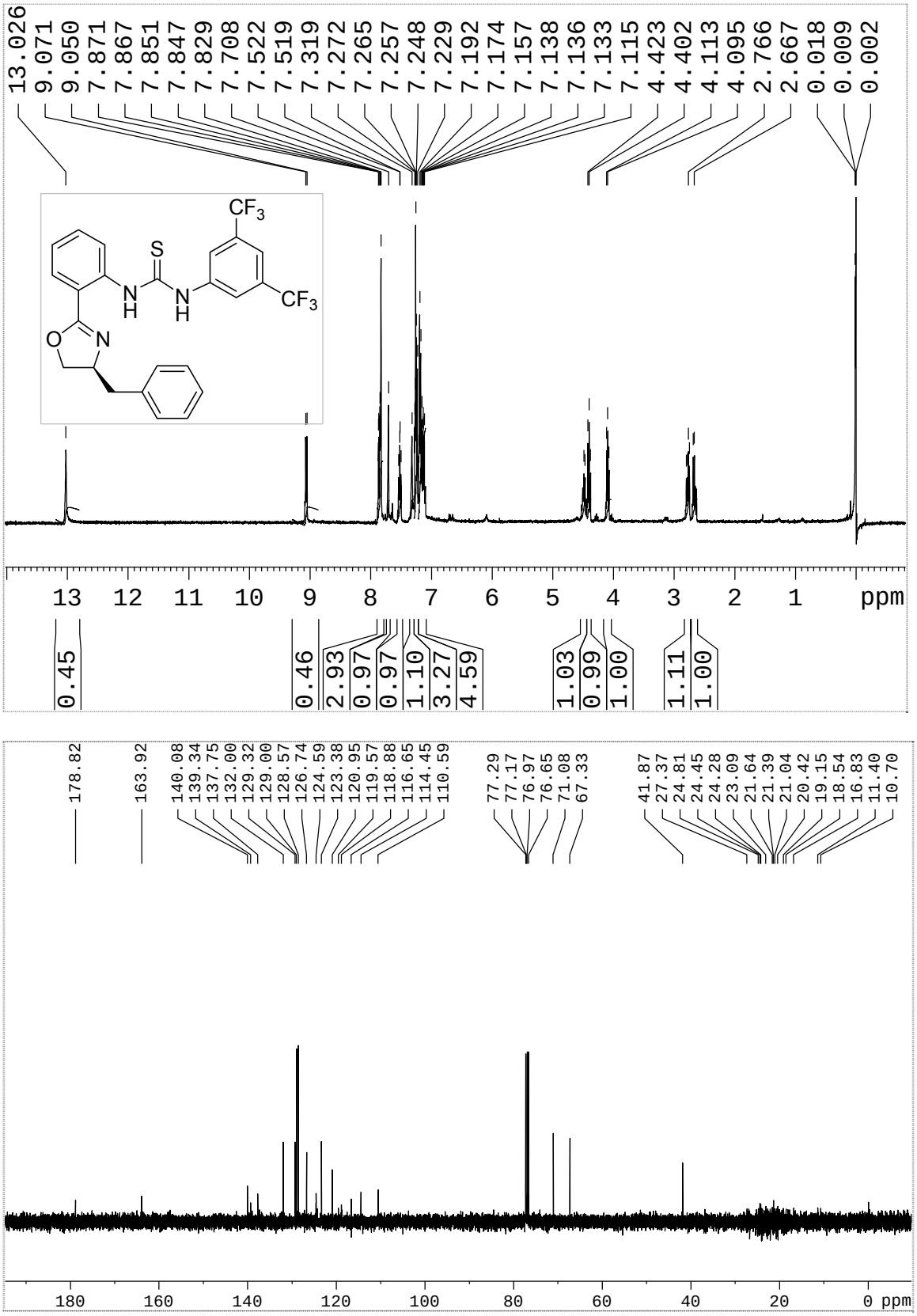


2-[(4*S*)-4-(*sec*-Butyl)-4,5-dihydro-1,3-oxazol-2-yl]-3,5-di(trifluoromethyl)aniline (**131g**)

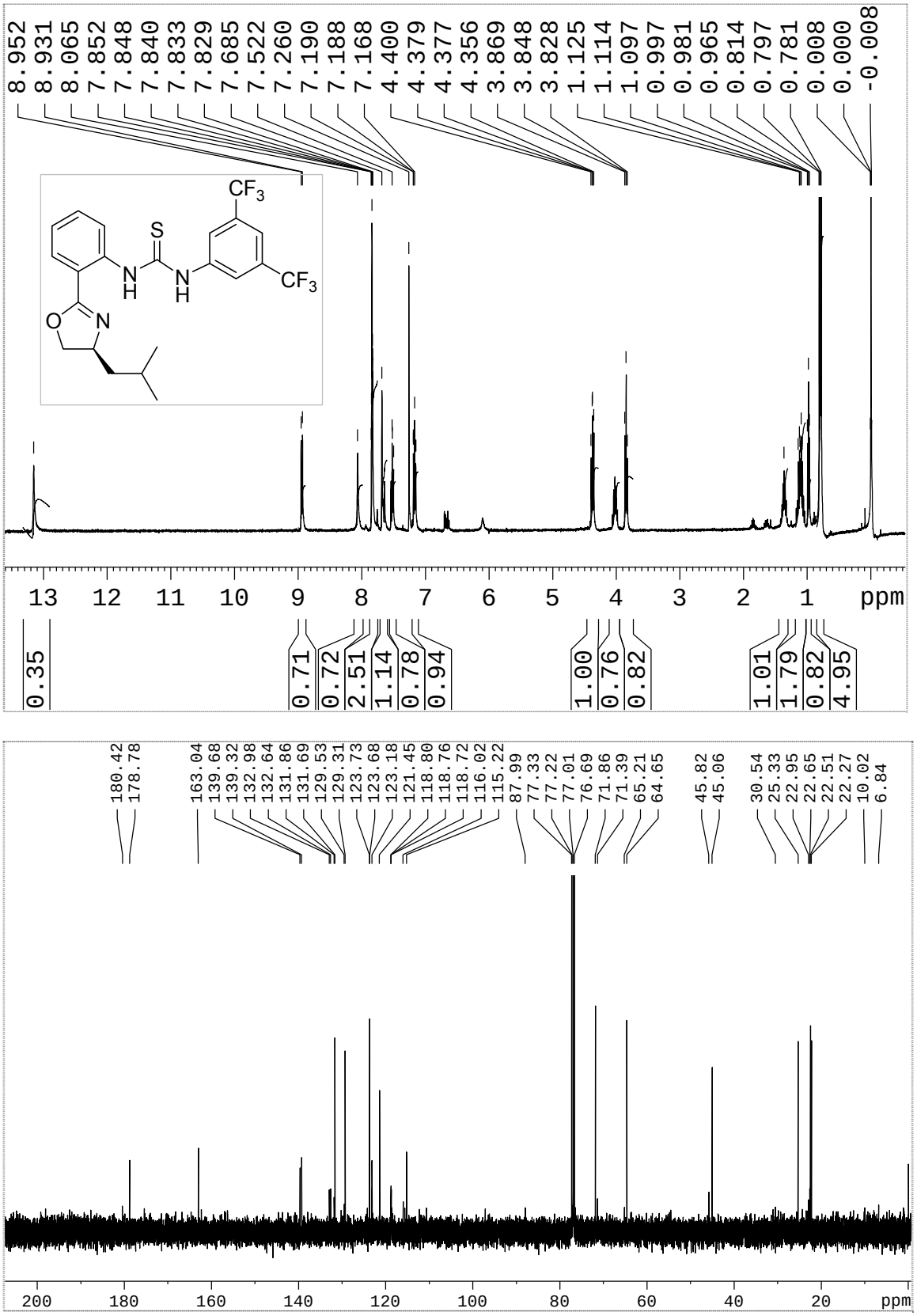




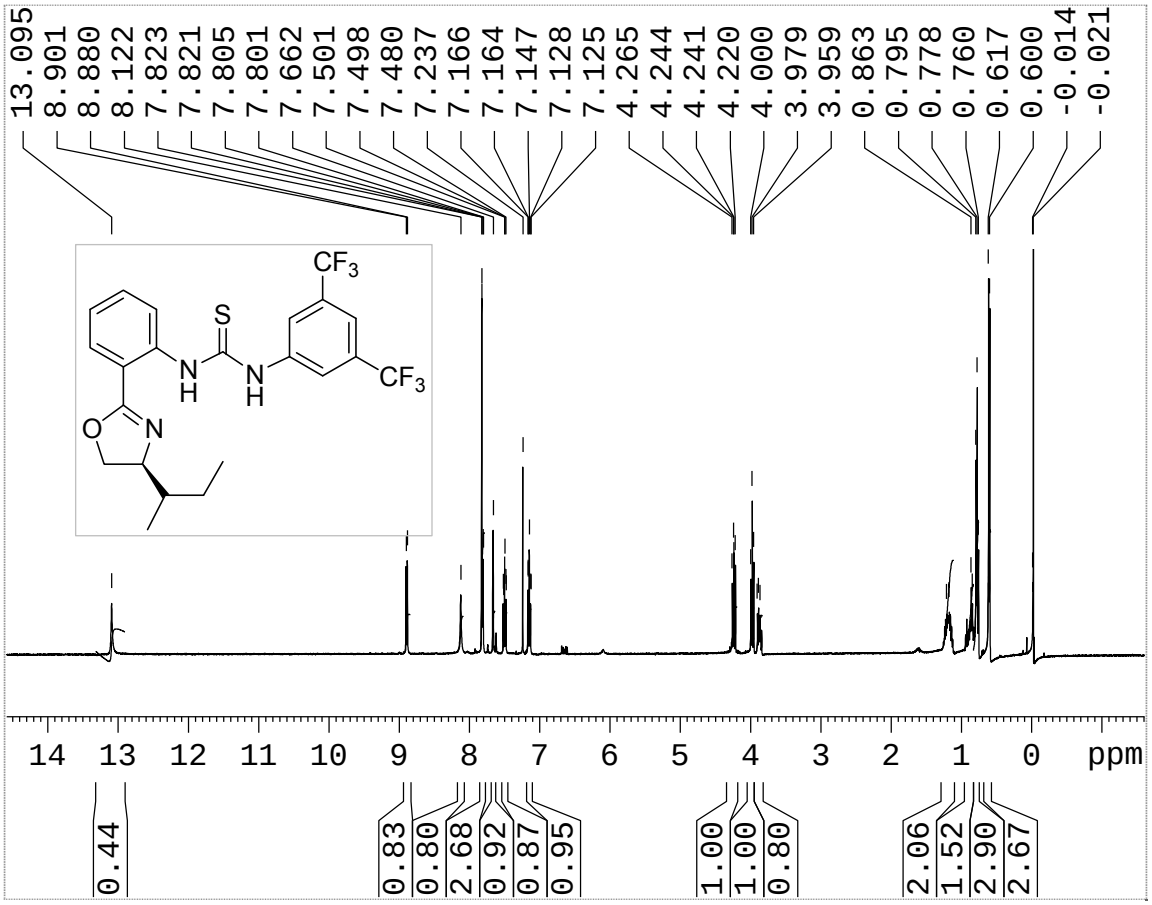
2-[(4*S*)-4-Isobutyl-4,5-dihydro-1,3-oxazol-2-yl]-3,5-di(trifluoromethyl)aniline (**131h**)

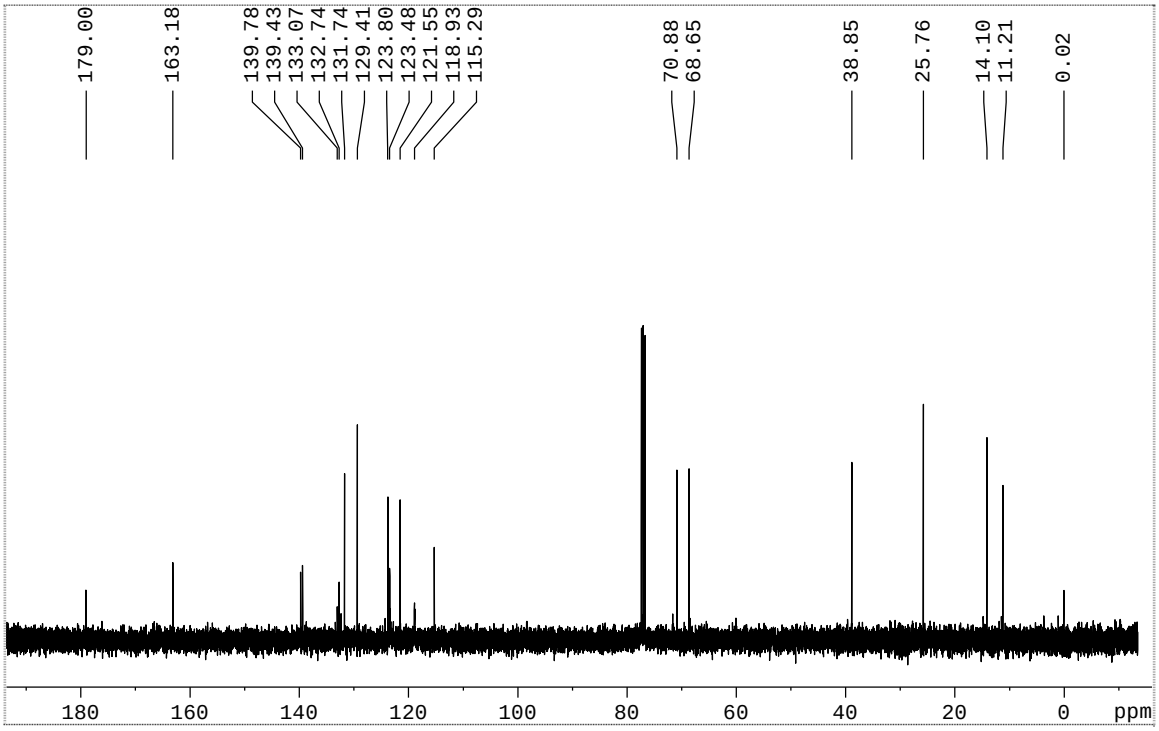


2-[(4*S*)-4-Benzyl-4,5-dihydro-1,3-oxazol-2-yl]anilino-3,5-di(trifluoromethyl)anilino-methanethione (**128b**)

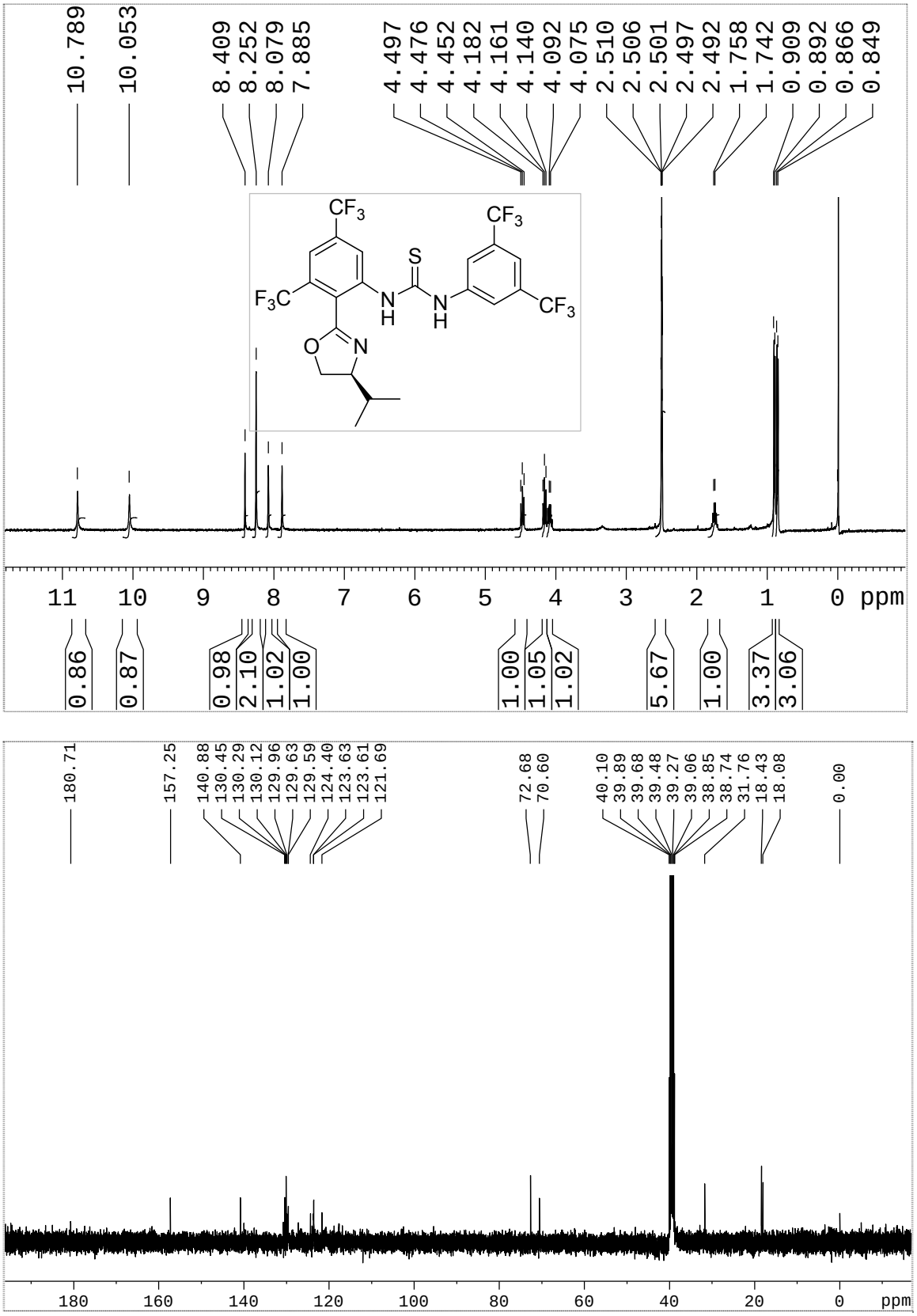


3,5-Di(trifluoromethyl)anilino-2-[(4*S*)-4-isobutyl-4,5-dihydro-1,3-oxazol-2-yl]aniline-methanethione (**128c**)

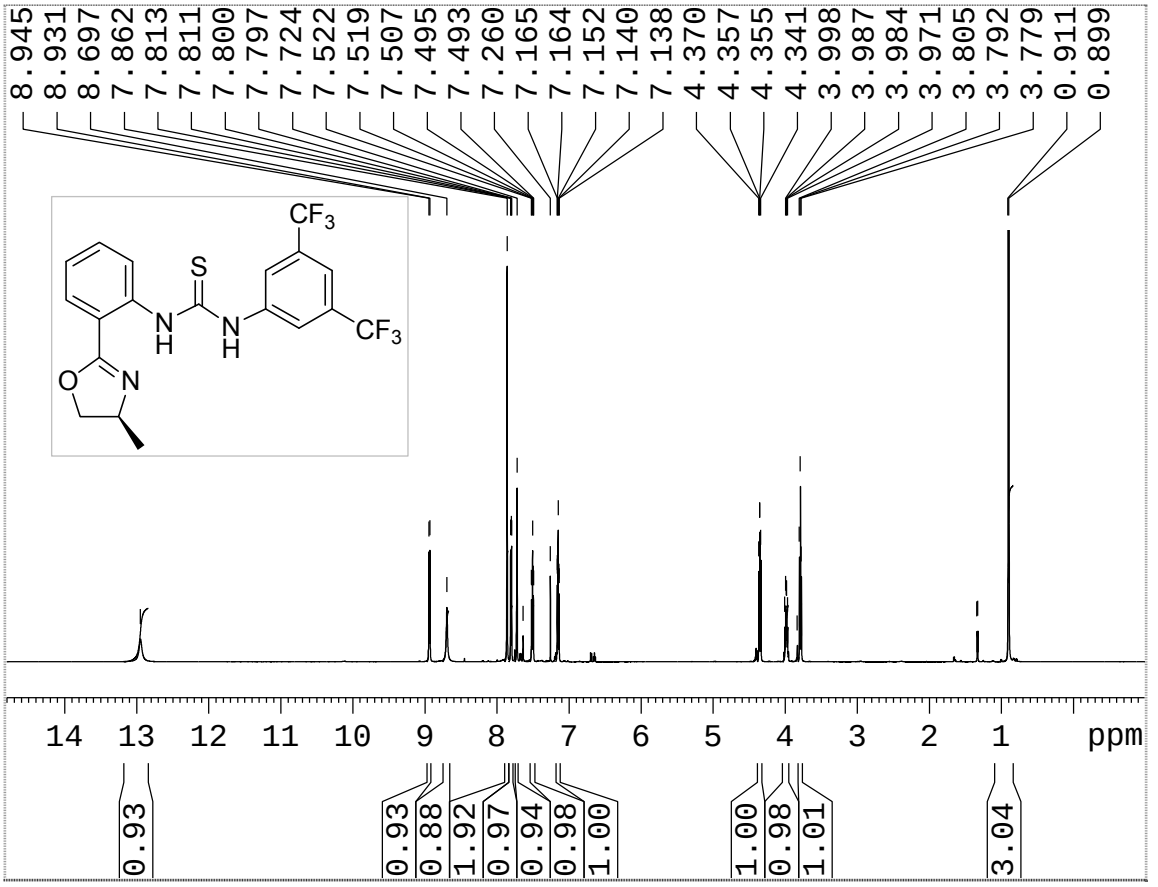


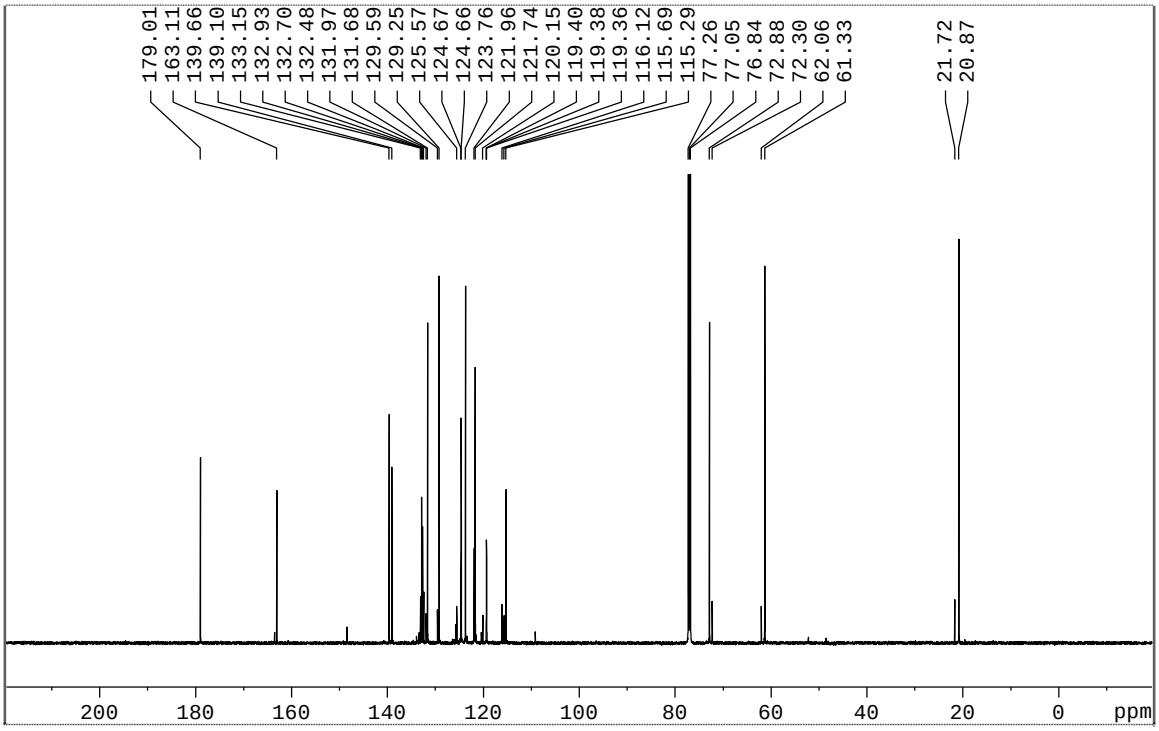


3,5-Di(trifluoromethyl)anilino-2-[(4*S*)-4-(*sec*-butyl)-4,5-dihydro-1,3-oxazol-2-yl]aniline methanethione (**128d**)

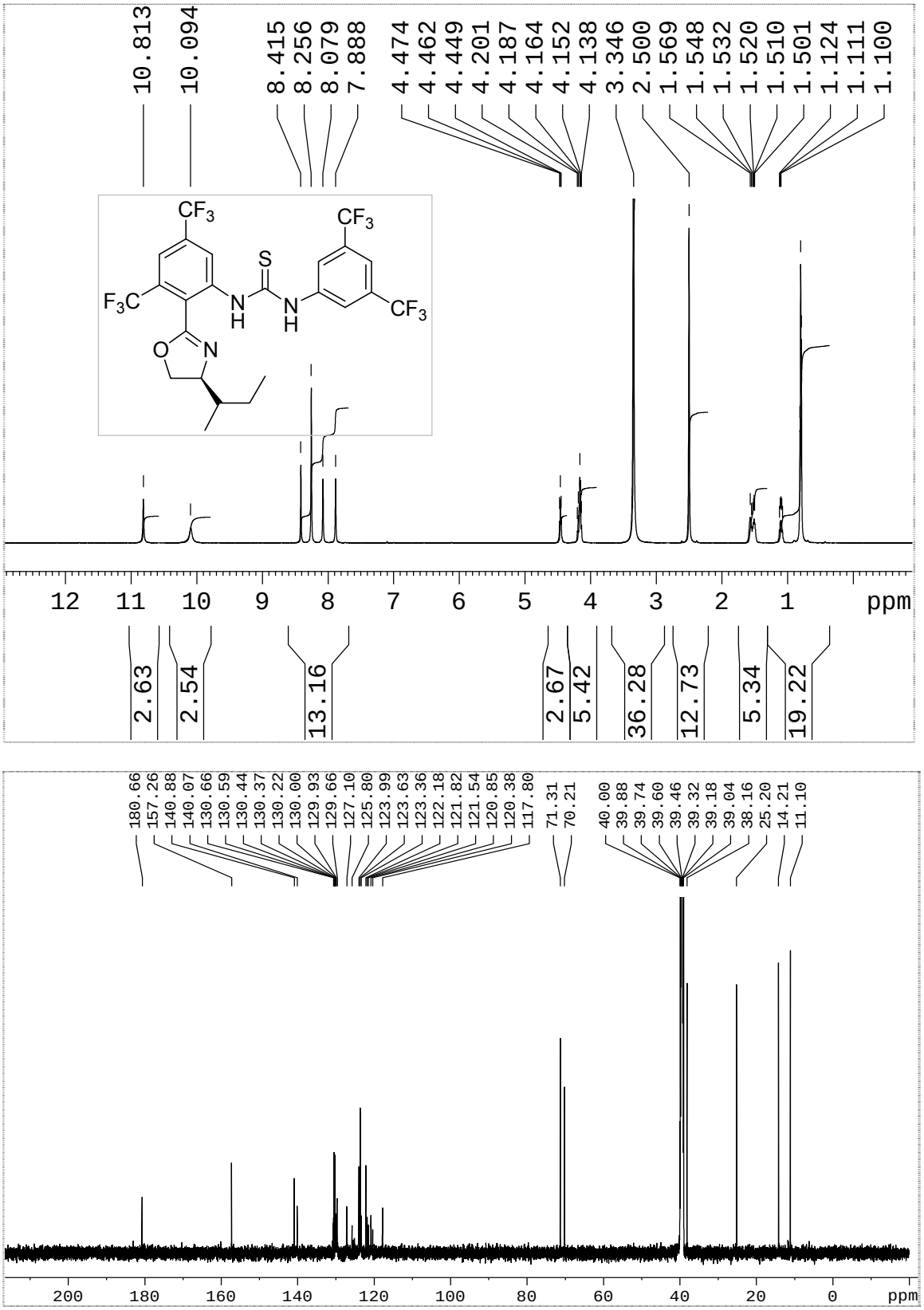


3,5-Di(trifluoromethyl)anilino-2-[(4*S*)-4-isopropyl-4,5-dihydro-1,3-oxazol-2-yl]-3,5-di(trifluoromethyl)anilinomethanethione (**128f**)

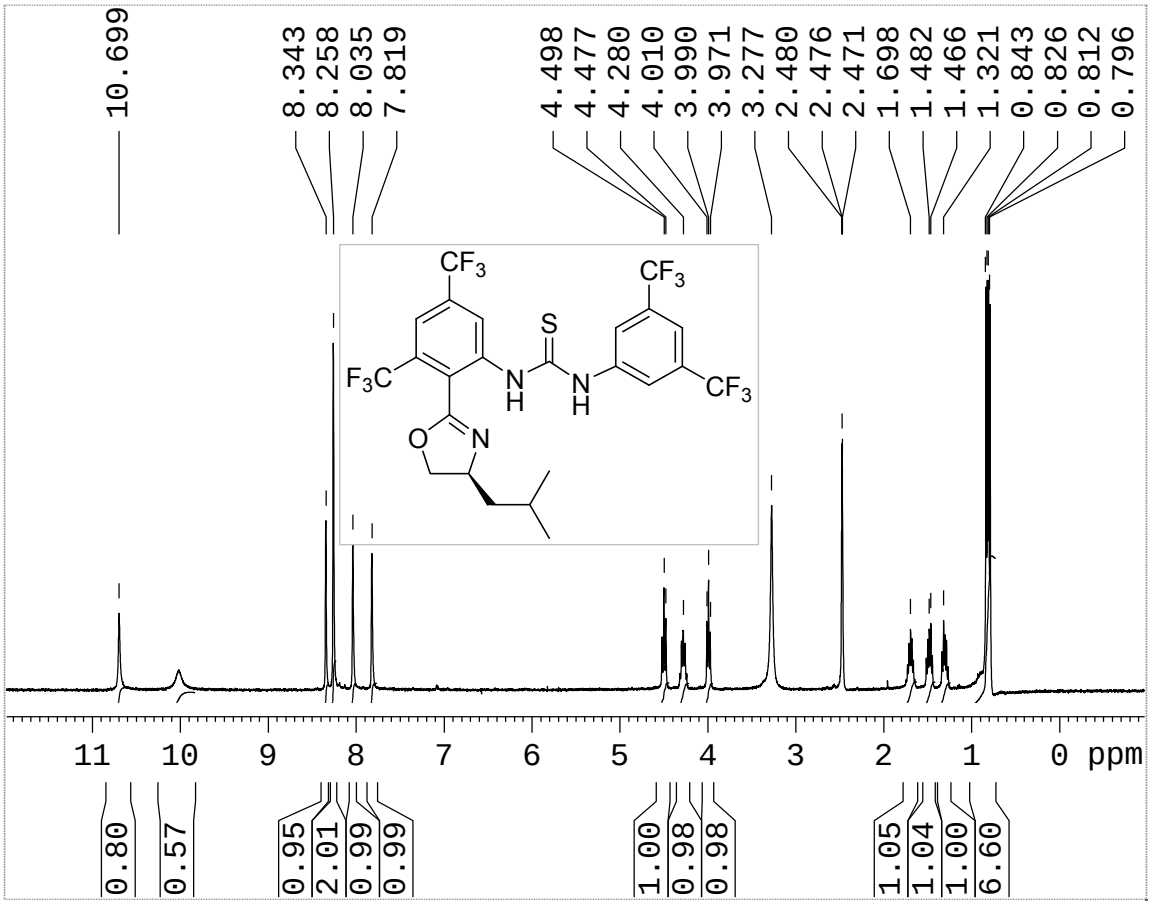


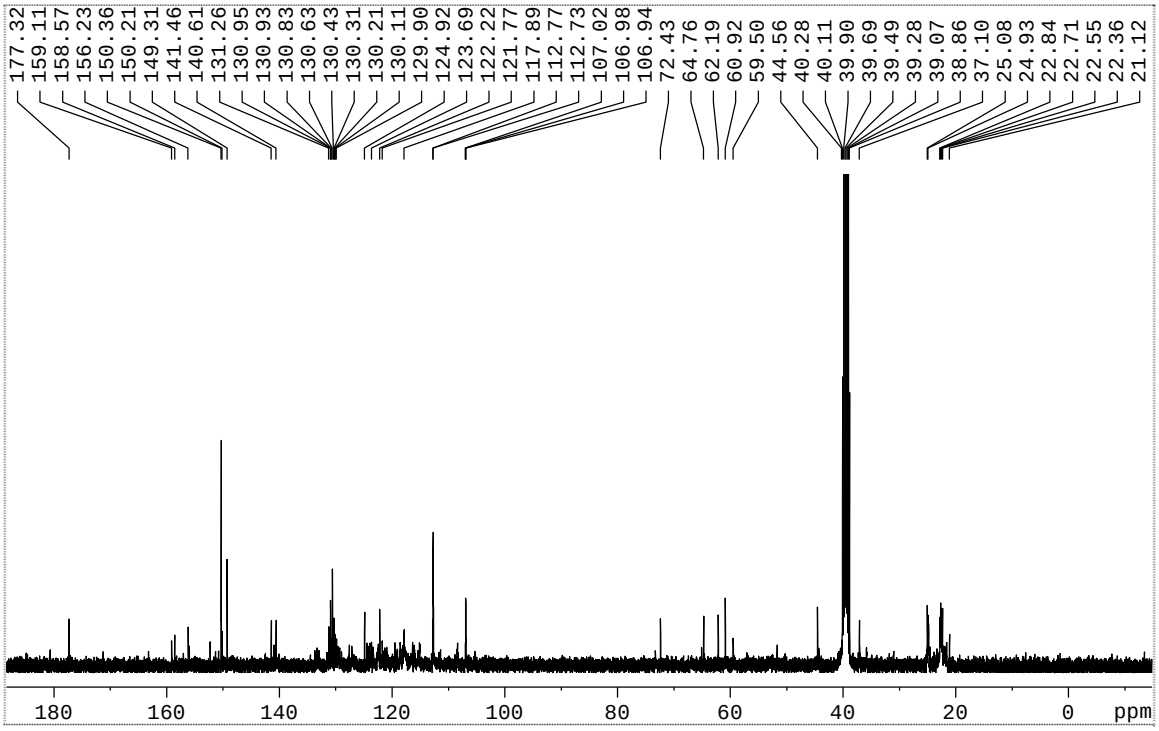


3,5-Di(trifluoromethyl)anilino-2-[(4*S*)-4-methyl-4,5-dihydro-1,3-oxazol-2-yl]aniline-methanethione (**128e**)

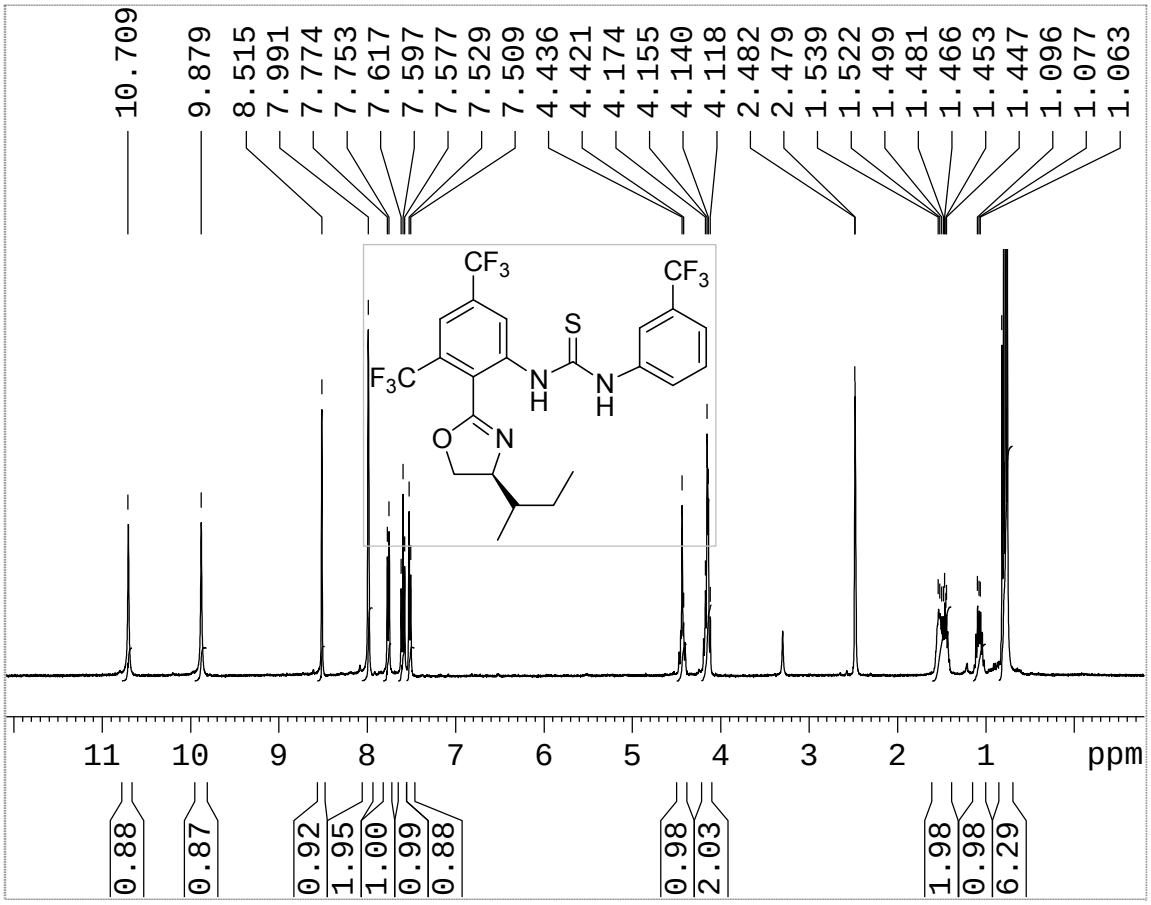


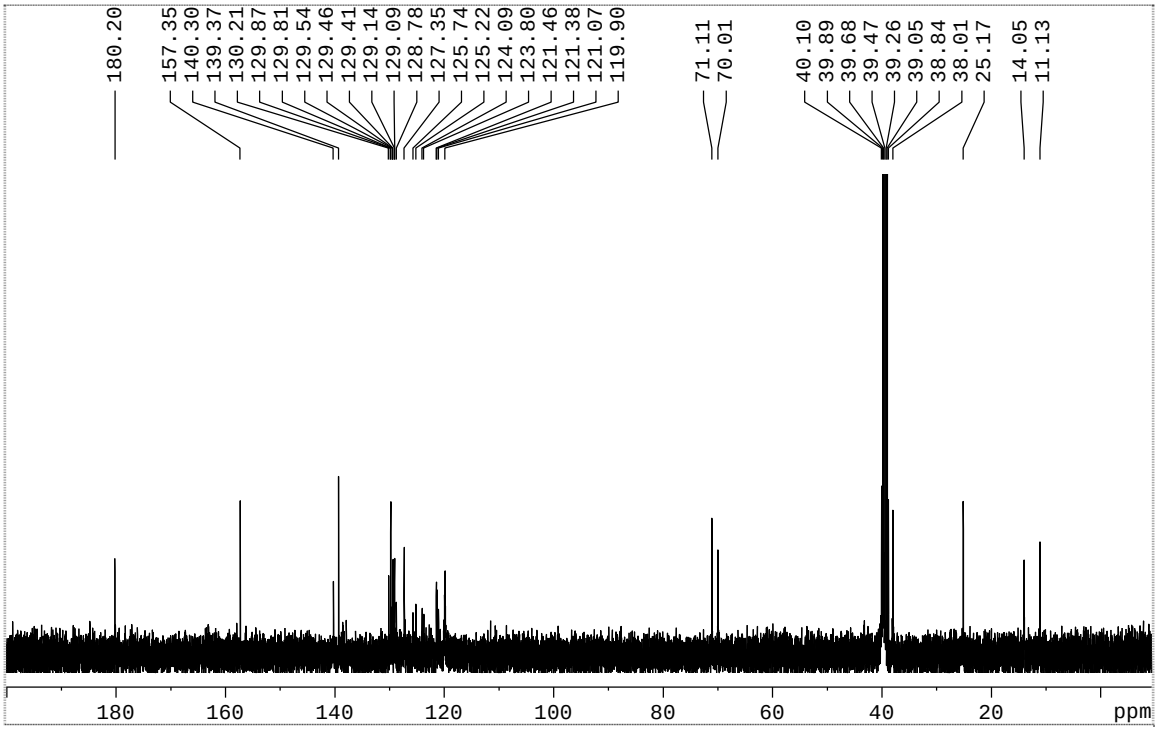
3,5-Di(trifluoromethyl)anilino-2-[(4*S*)-4-(*sec*-butyl)-4,5-dihydro-1,3-oxazol-2-yl]-3,5-di(trifluoromethyl)anilinomethanethione (**128**g)



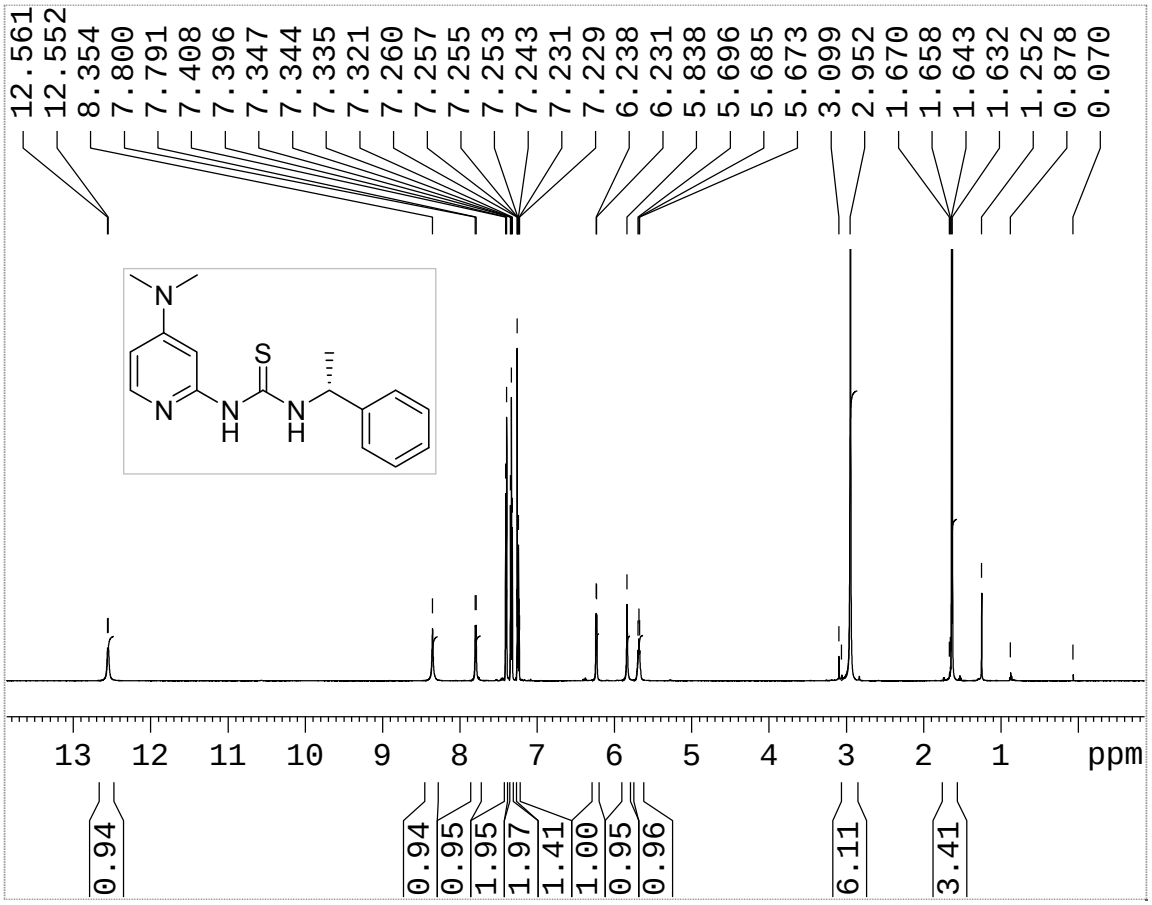


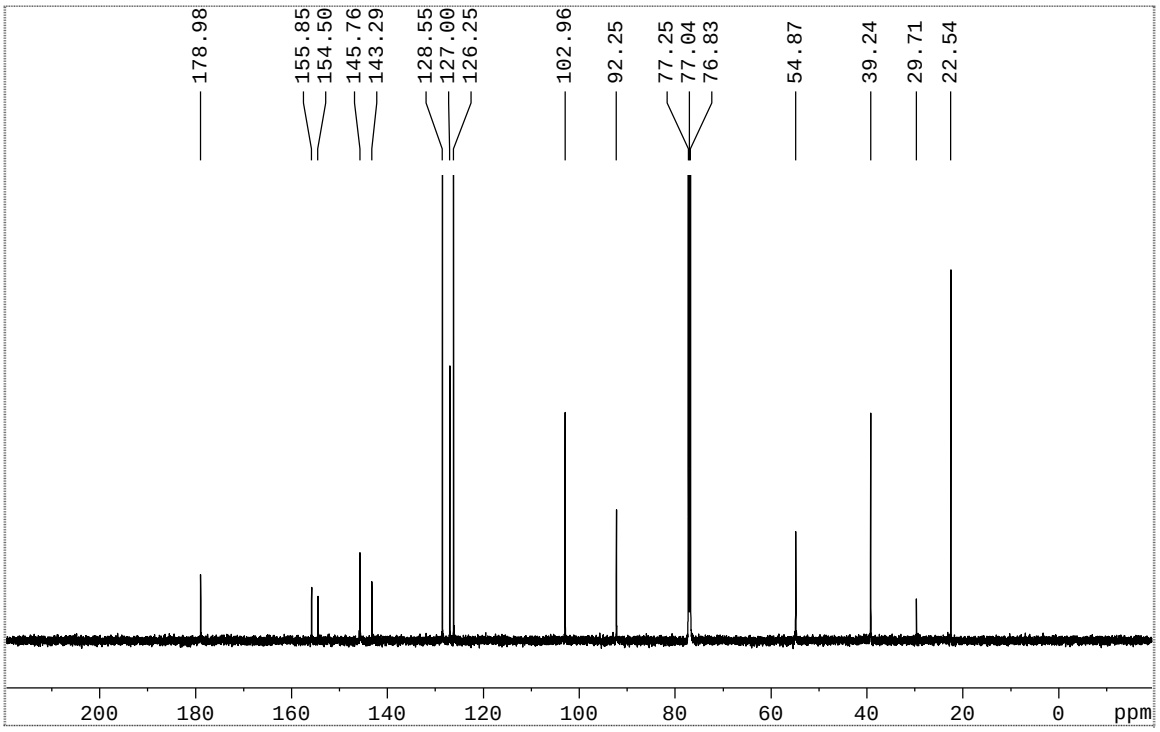
3,5-Di(trifluoromethyl)anilino-2-[(4*S*)-4-isobutyl-4,5-dihydro-1,3-oxazol-2-yl]-3,5-di(trifluoromethyl)anilinomethanethione (**128h**)



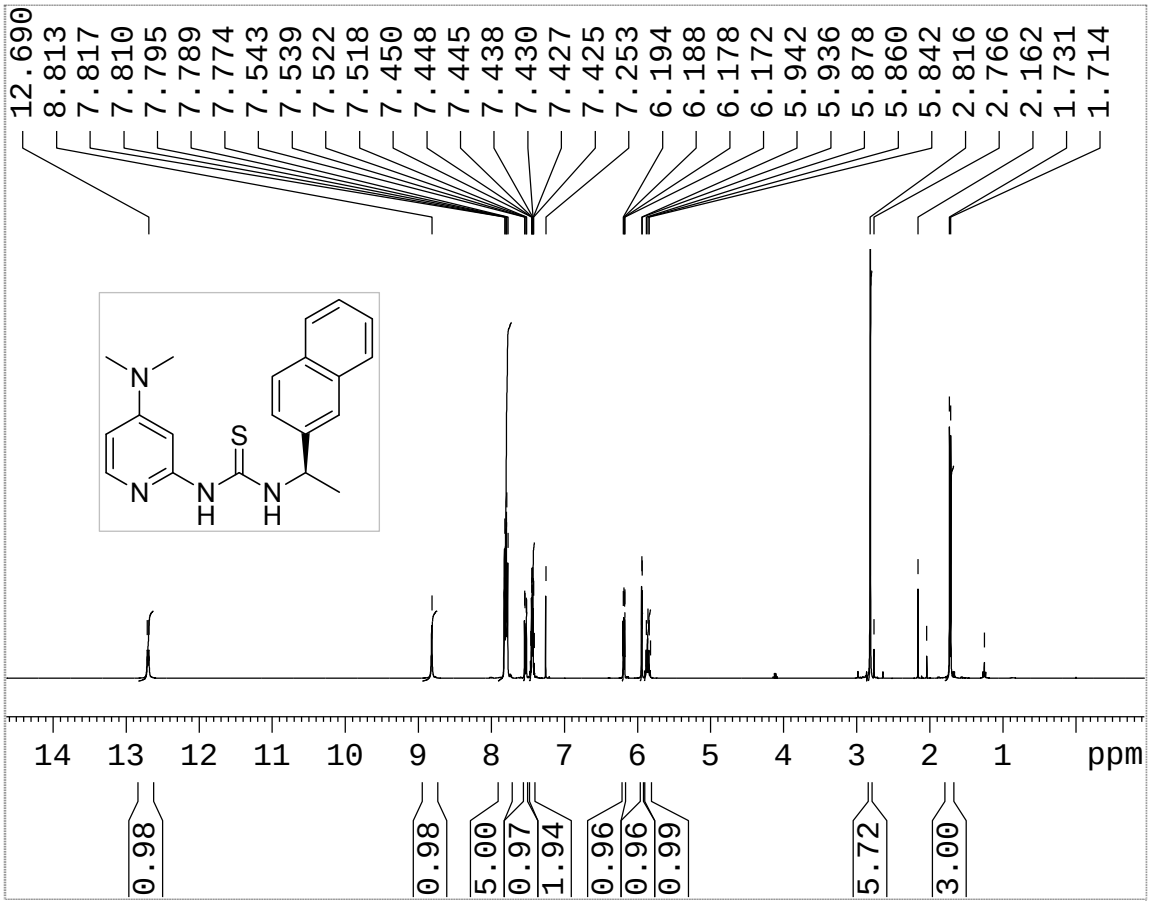


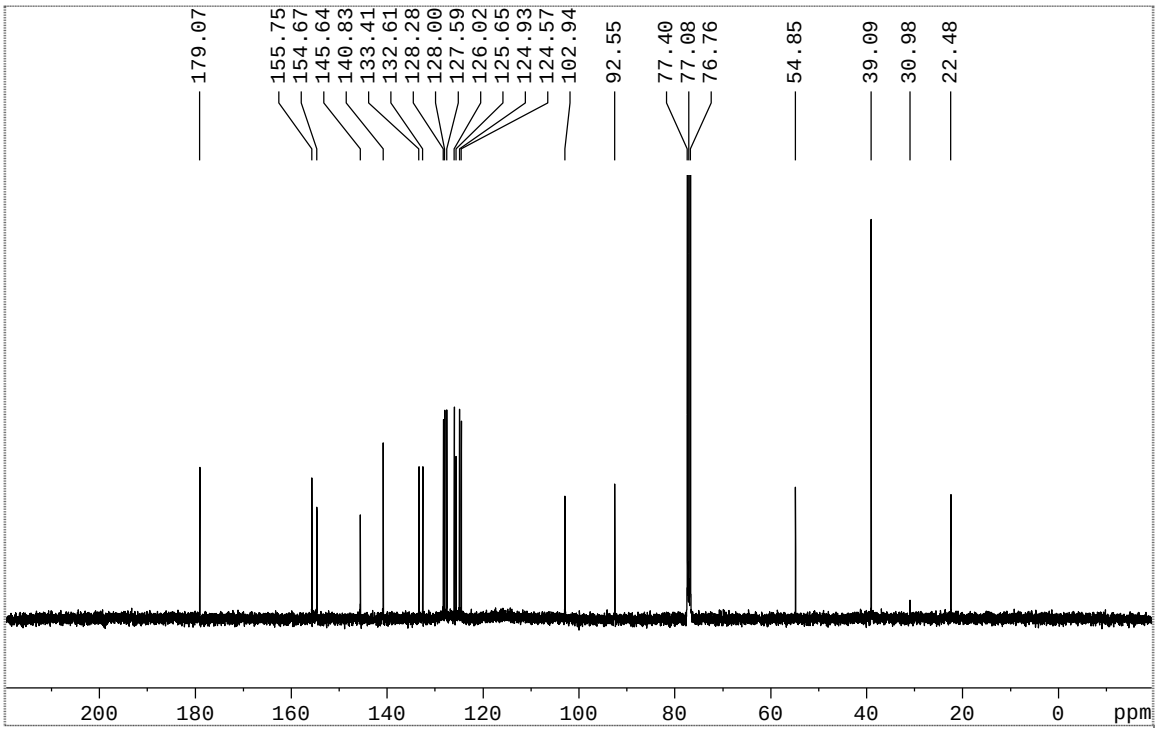
2-[(4*S*)-4-(*sec*-butyl)-4,5-dihydro-1,3-oxazol-2-yl]-3,5-di(trifluoromethyl)anilino-3-trifluoromethylanilinomethanethione (**128i**)



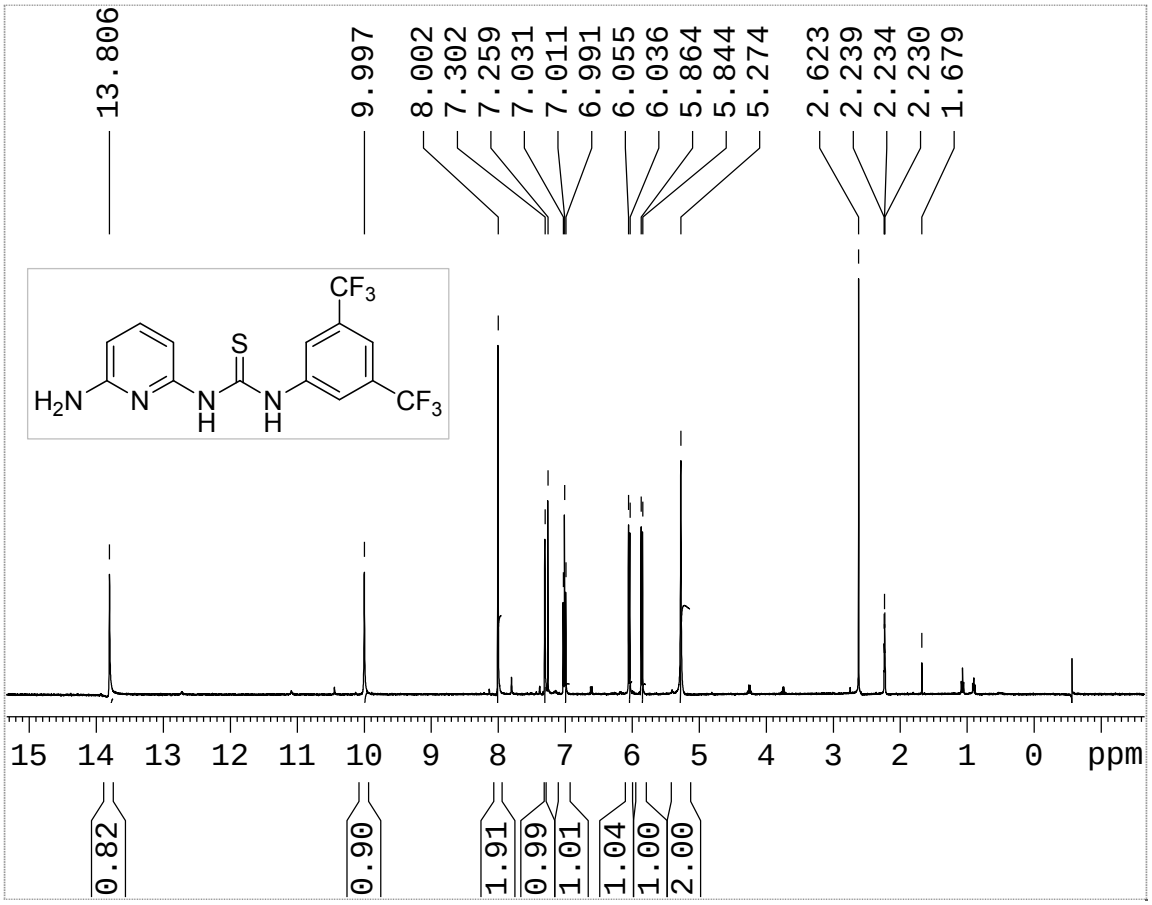


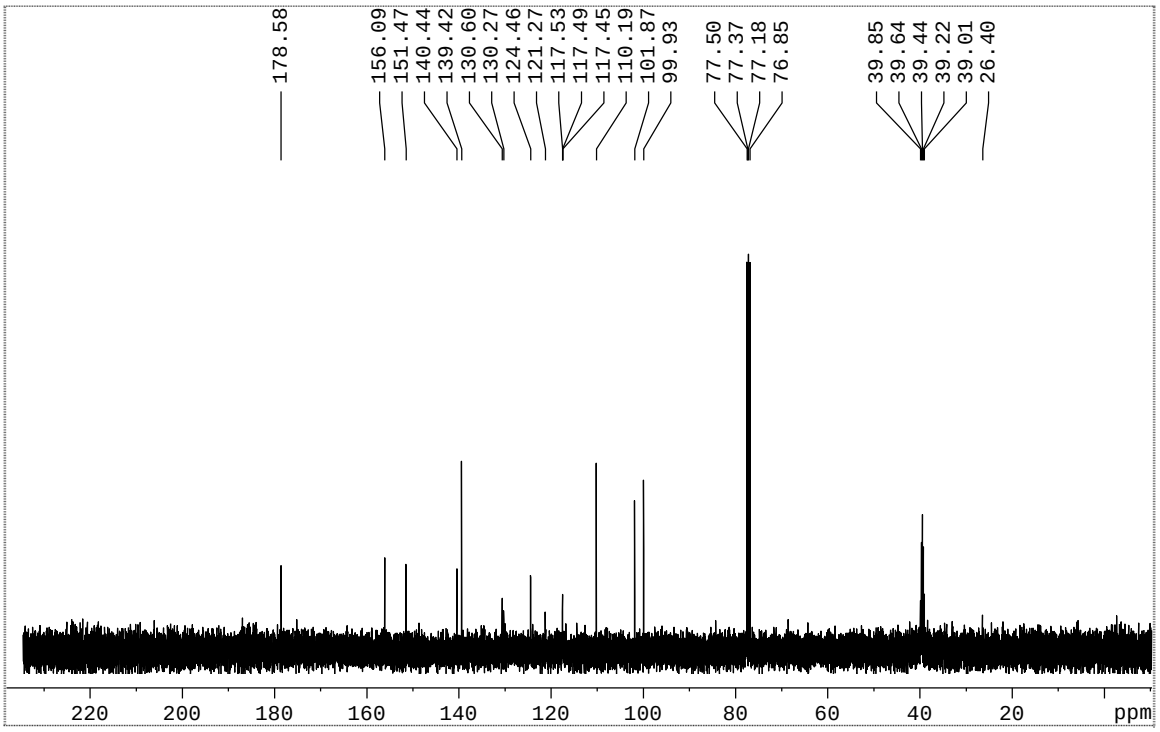
4-dimethylamino-2-pyridylamino-(1*R*)-1-phenylethylamino-methanethione (**135a**)



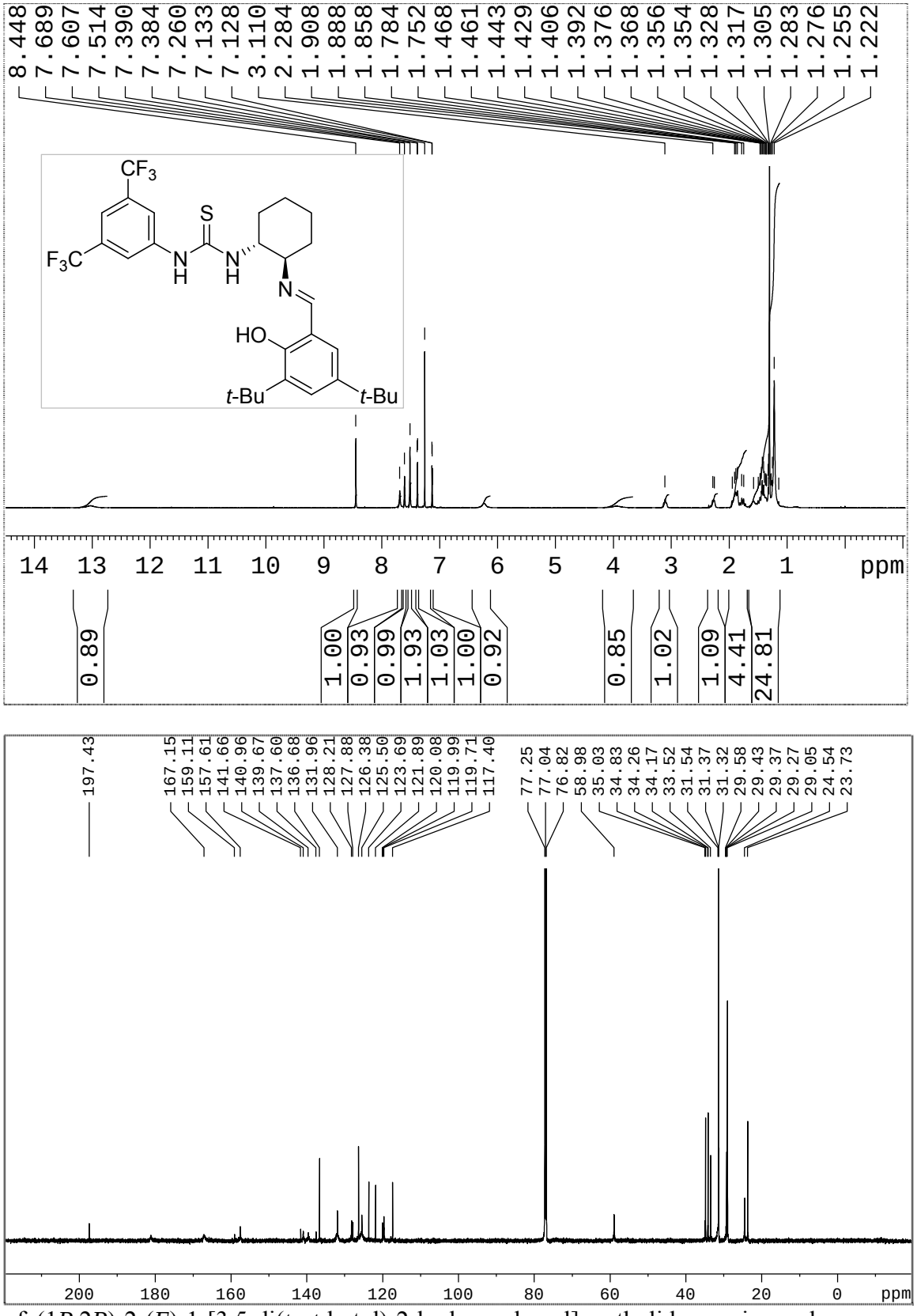


4-dimethylamino-2-pyridylamino-(1*R*)-1-(2-naphthyl)ethylamino-methanethione (**135b**)





6-amino-2-pyridylamino-3,5-di(trifluoromethyl)anilinomethane thione (**136**)



of (1*R*,2*R*)-2-(*E*)-1-[3,5-di(*tert*-butyl)-2-hydroxyphenyl] methylideneaminocyclohexylamino-3,5-di(trifluoromethyl)anilinomethanethione (**137a**)

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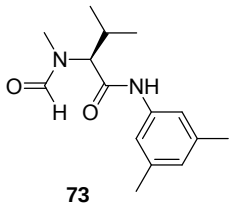
List of Symbols and Abbreviations

δ	NMR chemical shift/ppm
J	NMR coupling constant/Hz
λ	Wavelength/nm
Å	Angstrom
Ac	Acetyl
Ar	Arene
Bn	Benzyl
Boc	*t*-Butyloxycarbonyl
Bu	Butyl
Bz	Benzoyl
C	Celsius
c	Concentration
Cbz	Carbobenzyloxy
Cat.	Catalyst
CSA	Camphorsulfonic Acid
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexyl Carbodiimide
de	Diastereomeric excess
DFT	Density functional theory
DIPEA	*N*-Ethyl-*N*,*N*-Diisopropylamine
dist.	distilled
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
ee	Enantiomeric excess
eq	equivalent
er	Enantiomeric ratio
Fmoc	9-Fluorenylmethoxycarbonyl
GC	Gas chromatography
GC-MS	Gas chromatography coupled with a mass spectrometer
HBTU	Tetramethyluromiumhexafluorophophate
HOBt	Hydroxybenzotriazol
HOMO	The highest occupied molecular orbital
HPLC	High Performance Liquid Chromatography
IR	Infrared
Lit.	Literature
LUMO	The lowest unoccupied molecular orbital
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser Effect
NOESY	Nuclear Overhauser Effect Spectroscopy.
Ph	Phenyl
Phe	Phenylalanine
ppm	Parts per million
Pro	Proline
PTC	Phase Transfer Catalysis
ROESY	Rotational Frame Nuclear Overhauser Effect Spectroscopy

r.t.	Room temperature
SET	Single electron transfer
Tf	Triflate
TFA	2,2,2-Trifluoroacetic acid
TFAA	Trifluoroacetic acid anhydride
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
t_R	Retention time
Ts	Tosyl

Compound Index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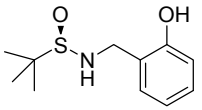
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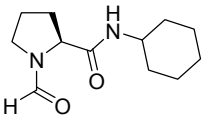
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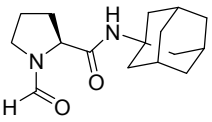
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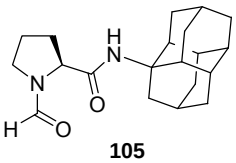
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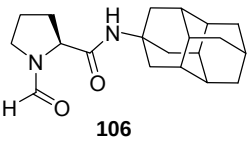
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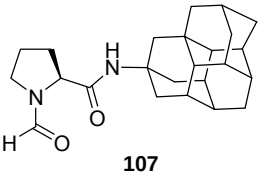
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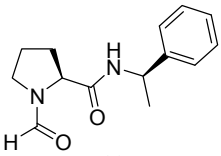
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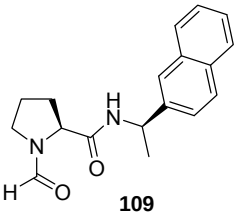
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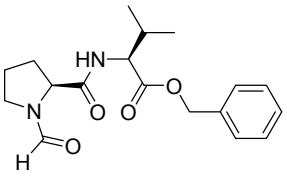
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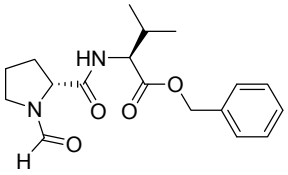
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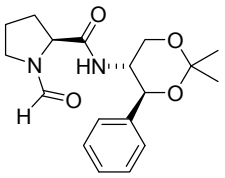
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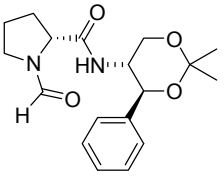
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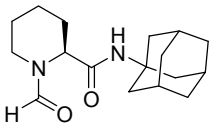
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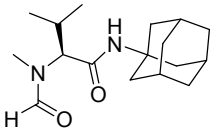
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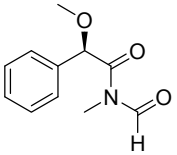
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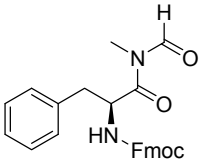

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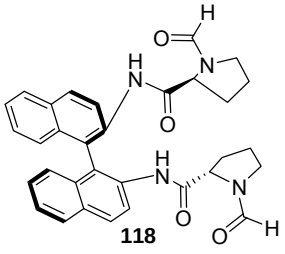
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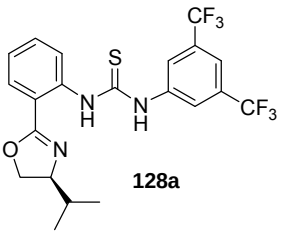
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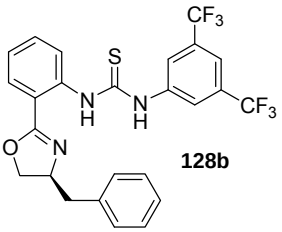
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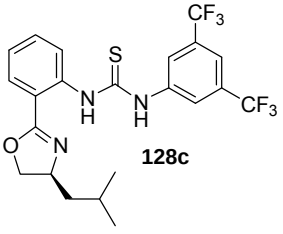
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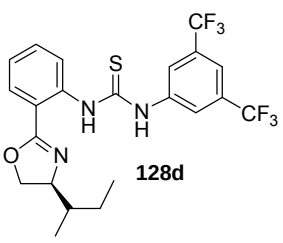
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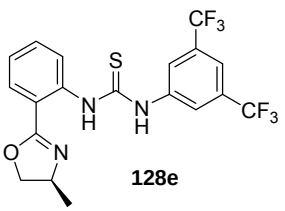
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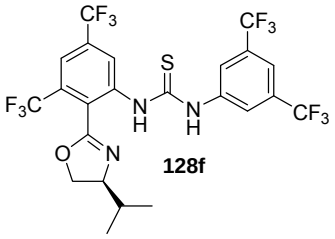

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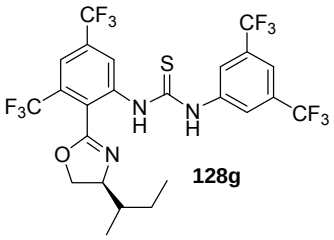

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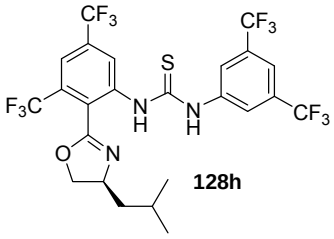

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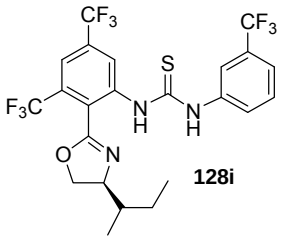

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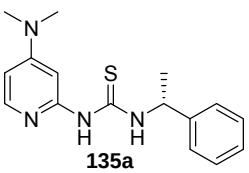

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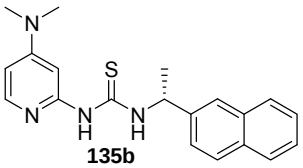

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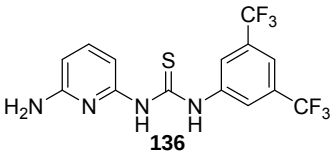

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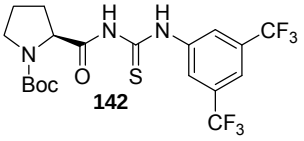

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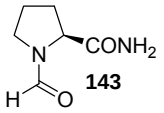
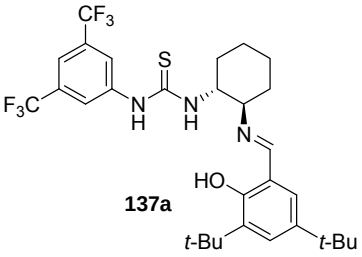


143



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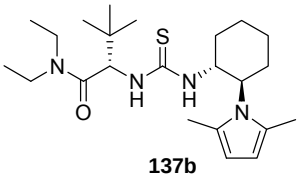
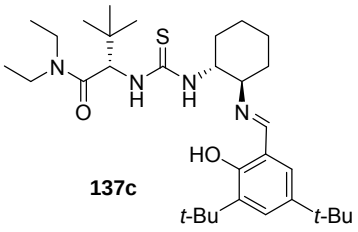


137b



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Publications

1. *"Thiourea-Catalyzed Transfer Hydrogenation of Aldimines"*
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3. *"Preparation and Antiasthmatic Activities of Seratrodast-coupling Derivatives"*
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3. *"Organocatalytic Reduction of Imine Using Trichlorosilane as the Hydrogen Donor"* (*in preparation*)

4. *"Thiourea-Catalyzed Cyanosilylation of Ketones"* (*in preparation*)

Posters Presented

1. *"Functional Thiourea Organocatalysts"*
   Zhiguo Zhang, Peter R. Schreiner
   The 1st Berichtskolloquim für das Schwerpunktprogramm Organokatalyse (SPP 1179) im Max-Planck-Institut für Kohlenforschung in Mühlheim/Ruhr, Feb. 9 – Feb. 10, 2006, Germany.

2. *"Novel Thiourea Catalyzed Reactions of Carbonyl Derivatives"*
   Zhiguo Zhang, Peter R. Schreiner
   GDCh Tagung, Orchem, Sep. 7 – Sep. 9, 2006, Bad Nauheim, Germany.