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Asymmetric Synthesis of Amines Using Modular Heterocyclic Catalysts

A Dissertation Submitted for the Degree of Doctor of Philosophy

By Xianfu Li

Department of Chemistry

University of Sheffield

November 2011

In memory of my father

Imagination is more important than knowledge. For knowledge is limited to all we now know and understand, while imagination embraces the entire world, and all there ever will be to know and understand.

Albert Einstein

Declaration

This dissertation records the work carried out in the Department of Chemistry, University of Sheffield, between October 2008 and November 2011 and is original except where acknowledged by reference.

No part of this work is being, nor has been, submitted for a degree, diploma or any other qualification at any other university.

Publications

1. “Scope of the organocatalyzed asymmetric reductive amination of ketones with trichlorosilane” François-Moana Gautier, Simon Jones*, Xianfu Li, Stephen J Martin, *Org. Biomol. Chem*. **2011**, 9, 7860-7868.

Acknowledgements

First of all, I would like to express my gratitude to my supervisor Dr Simon Jones for offering me an opportunity to do a PhD in his research group, for teaching me a lot (not only chemistry) and for his instructive advice through my PhD research. I am greatly indebted to him for his consistent helps and careful proof reading through all the stages of my writing of this thesis.

Secondly, I would like to express my gratitude to current and previous members in Jones group for their helps. Thank them for making the stay here such enjoyable. Next, thanks would go to all the colleagues in E26. Of course, many thanks also belong to my colleagues in E74 and E75 for their helps over my first half of PhD study.

Furthermore, I would like to thank all the departmental staff members. Without their helps, the scientific work in this thesis could not have reached its present form.

I am greatly indebted to my family for their supporting over my PhD study. I would like to express the biggest "thank you" to my wife and two lovely daughters. Thank you for your love.

Abbreviations

Ac	Acetyl
BINAP	2-2'-Bis(diphenylphosphino)-1-1'-binaphtalene
BINOL	1-1'-Bi(2-naphthol)
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
BOX	Bis-oxazoline
t-Bu	*tert*-Butyl
CAN	Cerium ammonium nitrate
CBS	Corey-Bakshi-Shibata
COD	Cyclooctadiene
DCE	1,2-Dichloroethane
DIAD	Diisopropyl azodicarboxylate
DMF	Dimethylformamide
ee.	Enantiomeric excess
eq.	Equivalent
Et	Ethyl
FT-IR	Fourier Transform – Infrared
GC	Gas chromatography
HEH	1,4-dihydropyridine
HPLC	High performance liquid chromatography
h	Hour(s)
Me	Methyl
Ms	Mesyl
MS	Molecular Sieves
Min	Minute(s)
m.p.	Melting point
NMR	Nuclear Magnetic Resonance
c-Pent	Cyclopentyl
Ph	Phenyl
PMP	*Para*-Methoxyphenyl
nOe	Nuclear Overhauser effect
i-Pr	Isopropyl
Py	Pyridine
r.t.	Room temperature
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
t_R	Retention time
Ts	Tosyl (*p*-methylphenylsulfonyl)

Abstract

Catalyst **117** was previously reported in the Jones group and demonstrated to a very good catalyst at 1 mol% catalyst load. With the optimized conditions, a wide range of N-arylimines can be reduced in good yield and enantioselectivity by trichlorosilane. Followed this previous discovery, the project now is extending the application this methodology, investigating the mechanism and designing more efficient catalysts.

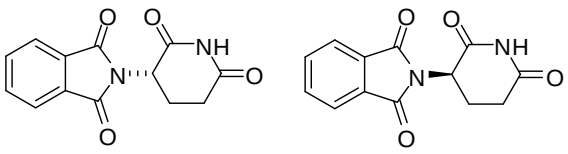
A chromatography process for the synthesis of catalyst **117** was developed. Asymmetric reduction of both *N*-aryl and *N*-alkyl ketimines can be performed using trichlorosilane catalyzed by **117** at 1 mol% catalyst loading. The scalability of this process was demonstrated. This catalyst can also facilitate the reduction of β-enamino esters by trichlorosilane with good yield and high enantioselectivity albeit with the necessity of a high catalyst loading and benzoic acid as an additive.

An asymmetric reductive amination of ketones with both aromatic and aliphatic amines was achieved in good yield and high enantioselectivity at 1 mol% catalyst loading. Sterically hindered ketones also undergo reductive amination in good yield and enantioselectivity by a two-step one-pot procedure. The asymmetric synthesis of (+)-NPS R-568 in good yield and high enantioselectivity using the two-step one-pot procedure demonstrated the potential utility of this catalyst to the pharmaceutical industry. Lewis acidic TMSOTf can improve the yield in direct reductive amination, but showed a negative effect on the enantioselectivity.

Initial investigations into the mechanism have resulted in unprecedented discoveries. Both the NMR study of catalyst **117** and the discovery of a new highly active catalyst **263** place the Matsumura transition state model into doubt. Although no signals were detectable to support the hypercoordinate silane species by NMR experiments, *in-situ* ReactIR data showed that there might be some interactions between trichlorosilane and catalysts. A new tentative transition state model was proposed according to the study of structure/activity of catalysts and the preliminary *in-situ* IR data.

1. Introduction

Enantiomers of a chiral molecule may display different biological activities, since interactions at a molecular level with intrinsically chiral receptors and related binding sites can lead to diastereomeric intermediates. In extreme cases, one enantiomer may be an effective therapeutic drug whereas the other exhibits toxicity. The catastrophic example of thalidomide is well-known (Figure 1). Thalidomide was chiefly sold and prescribed in the racemic form as an antiemetic medicine to combat morning sickness in pregnant women. Unfortunately, it had a tendency to induce birth defects, and from 1956 to 1962, approximately 10,000 children in Africa and Europe were born with severe malformations because their mothers had taken thalidomide during pregnancy. Further studies showed that the (*R*) enantiomer is effective against morning sickness while the (*S*) had devastating effects on the development of an unborn foetus.[1] More recently research disclosed that the (*R*) and (*S*) enantiomers of thalidomide can interconvert in blood plasma,[2] meaning that both isomers will be biologically available even if pure (*R*)-thalidomide or (*S*)-thalidomide is given to patients. Though administering only one enantiomer will not prevent the teratogenic effect, the case indicates how important it is to independently study biological and chemical behaviours of both enantiomers *in vivo* for the development of new medicines.



(*S*)-thalidomide **(*R*)-thalidomide**

Figure 1

The increased interest in asymmetric synthesis from both pharmaceutical industry and academia has enhanced the need for developing effective methods for the preparation of enantiopure chemicals. Among the various methods used to obtain enantiomerically pure chemicals, catalytic asymmetric synthesis is one of the most desirable yet the most challenging of methodologies, since use of a small amount of chiral catalyst can afford large

amounts of chiral product, just as enzymes do in biological systems.[3]

Chiral amines are widely distributed in Nature and medicine (Figure 2), with the amino group playing a significant role in their bioactivities.

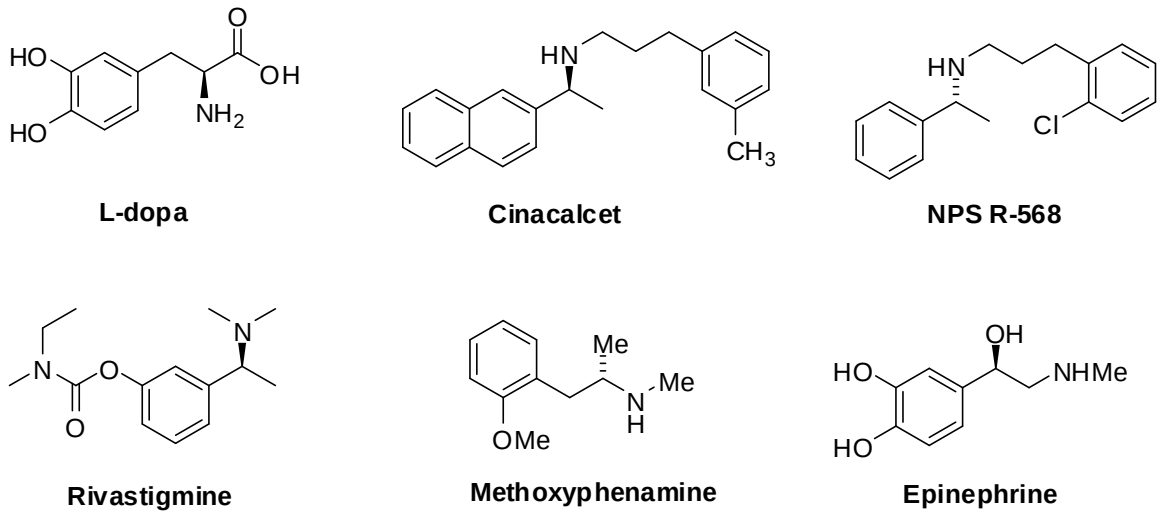


Figure 2

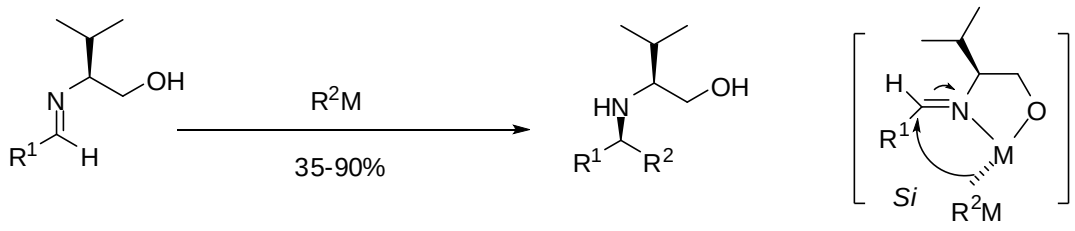
For the preparation of chiral amines, the use of starting materials containing a carbon-nitrogen double bond, including tautomeric β-enamino esters, has been widely explored. The desired products have been produced by asymmetric addition of nucleophiles including carbon based reagents (leading to chiral secondary or tertiary amines) or a reducing agent (leading to chiral secondary amines).

1.1 Nucleophilic addition to nitrogen-containing double bonds

The asymmetric addition of nucleophiles to the carbon-nitrogen double bond of an imine provides a convenient and efficient route to optically active amines bearing a stereogenic centre at the nitrogen α-position. Methodologies for asymmetric C-C bond formation by nucleophilic addition to a carbon-nitrogen double bond based on both chiral substituent induction and chiral ligand asymmetric induction have been developed.

Readily available enantiopure amines have been widely employed to prepare chiral imines,[4] usually by condensation with the corresponding carbonyl compounds. In 1982, Takahashi and co-workers reported the first example of a chiral substituent-controlled asymmetric

addition of organolithium or organomagnesium reagents to imines derived from aldehydes and (*S*)-valinol or phenylglycinol.[5] For example, benzylmagnesium chloride or aryllithium compounds can be added to imine **1** in moderate to high yields forming single diastereomeric adducts. The transition state was proposed to be a metallo-chelate **3**. Coordination of the alkoxy group and the lone electron pair on nitrogen of the imine was proposed to lead to a preferred *Si*-face addition of the organometallic reagent (Scheme 1).

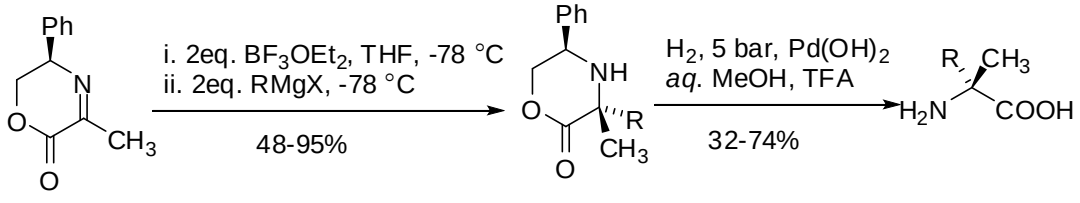


1 **2** **3**

R^1=Ph, 4-$MeOC_6H_4$, 2-and 3-thienyl, 2-furyl; de>98%
R^2=Bn, Ph, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-ClC_6H_4;
M=Mg, Li

Scheme 1

Asymmetric synthesis of enantiopure α-substituted alanine derivatives by addition of Grignard reagents to the cyclic imine **4** has been described by Harwood *et al.* Single diastereoisomers **5** were obtained in all cases with moderate to high yield.[6] Cleavage of the morpholinone was performed by hydrogenolysis to afford the α-substituted alanine derivatives **6** (Scheme 2).



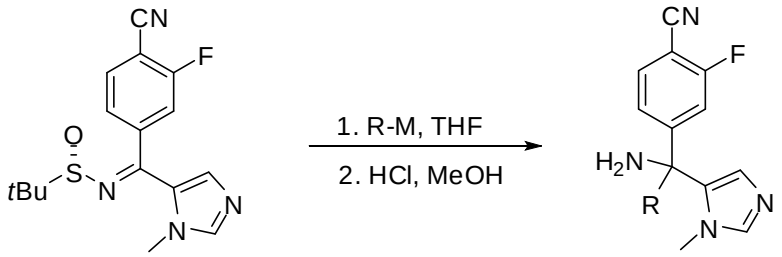
4 **5** **6**

R=Et, n-Hex, i-Pr, i-Bu, Bn single diastereomer

Scheme 2

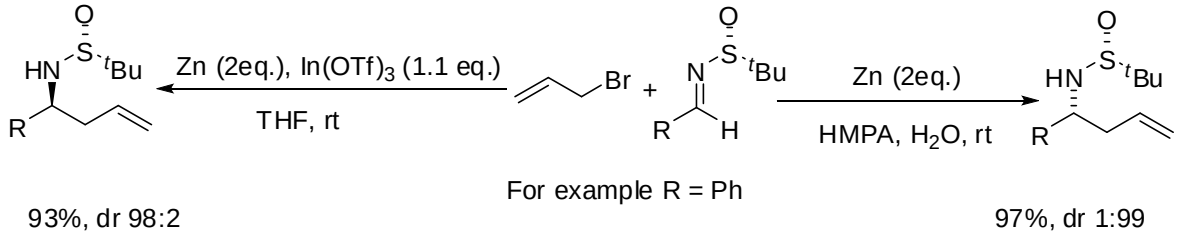
N-Chiral sulfinimines are versatile intermediates for the preparation of chiral amines.[7] Several strategically different methods have been developed for the synthesis of enantiomerically pure sulfinimines, such as the asymmetric oxidation of sulfenimines and

the condensation of enantiopure primary sulfinamides with aldehydes and ketones.[8] Organometallic reagents, such as organolithiums and Grignard reagents, add to sulfinimines to give sulfinamides in high diastereoselectivities and yields.[9] For example, Shaw and DeSolms at Merck applied this method to the synthesis of farnesyl protein transferase inhibitors **8** and it is quite interesting that reversals in diastereoselectivity are obtained in the Grignard versus alkyllithium addition to ketimine **7** (Scheme 3).[10]



Scheme 3

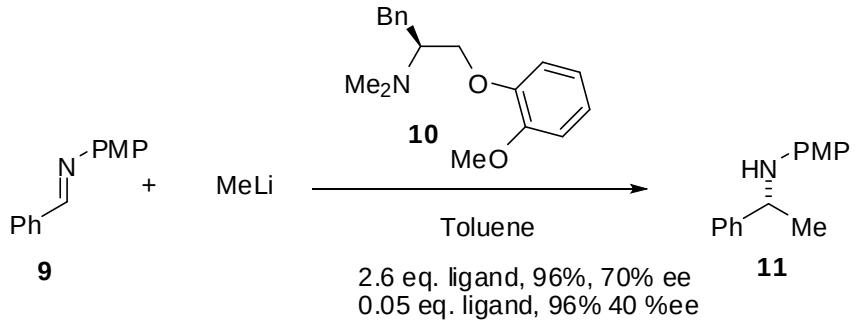
Lin and co-workers reported that the zinc-mediated allylation to chiral (*R*)-*N*-tert-butanesulfinyl imines derived from both aromatic and aliphatic aldehydes can be stereo-controlled by simply varying the reaction conditions (Scheme 4).[11] Two acyclic transition state models were proposed to explain the opposite diastereoselectivity rather than the six-membered ring transition state claimed by Ellman and Foubelo.[12]



Scheme 4

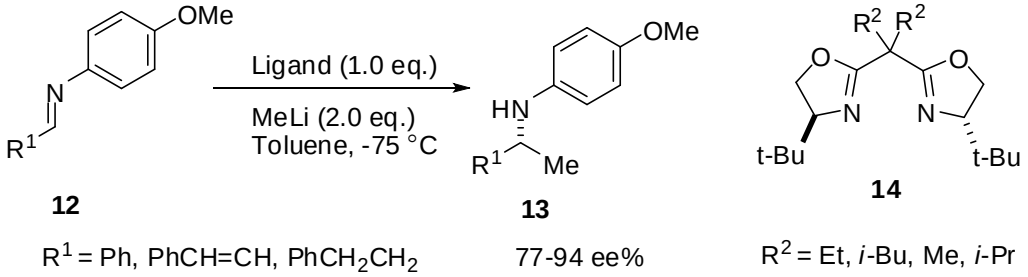
In 1990, Tomioka and co-workers reported the first catalytic asymmetric addition of organolithium reagents to carbon-nitrogen double bonds of imines, the stereochemistry of which was controlled by a chiral amino-ether ligand **10** (Scheme 5).[13] With 5 mol% of ligand **10**, enantiomerically enriched amine **11** was produced in moderate ee, but signified

the beginning of catalytic methods of asymmetric addition of organometallic reagents to carbon-nitrogen double bonds.



Scheme 5

Denmark and co-workers showed that bisoxazolines **14** can induce the asymmetric addition of lithium reagents to aromatic, olefinic and aliphatic aldimines (Scheme 6).[14] A systematic examination of the influence of the bridging group of the ligand was also carried out.[14c]

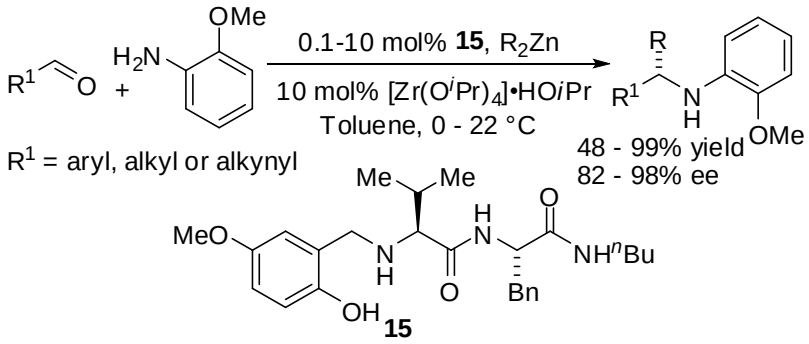


Scheme 6

Dialkylzinc reagents are less nucleophilic organometallic compounds and react slowly or not at all with imines due to the limited polarity of C-Zn bond. However, the mild reactivity means that dialkylzinc reagents have a high functional group tolerance compared to magnesium and lithium reagents. In the past few years, several chiral ligand-metal complexes such as copper,[15] zirconium or hafnium,[16] have been used to accelerate the addition of dialkylzinc reagents to the carbon-nitrogen double bonds of imines.

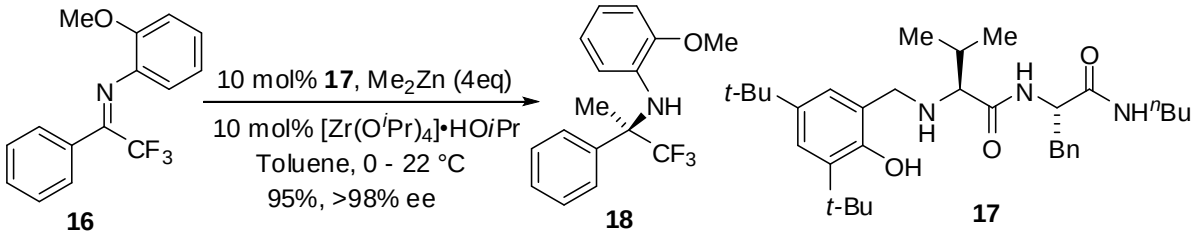
Hoveyda *et al*. reported catalytic asymmetric alkylation of aryl and alkylimines with alkyl zinc reagents activated by [Zr(O*i*Pr)$_4$]·HO*i*Pr and a small peptide ligand **15** derived from valine and phenylalanine (Scheme 7).[17] Thereafter, a three-component asymmetric alkylation

was also described by the same group, which involved imine formation from an aldehyde and *o*-anisidine, followed by enantioselective alkylation with the zinc reagent.[18]



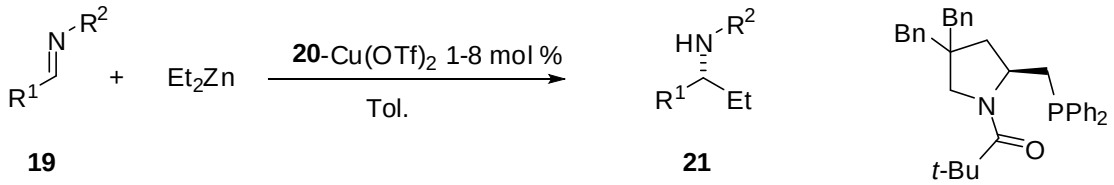
Scheme 7

Screening of a series of chiral peptide ligands derived from valine and phenylalanine allowed the alkylation of α-ketimine esters and trifluoromethylketimines to afford the amine products with quaternary carbon stereogenic centres in good yield and enantioselectivity.[19] For example, methylation of imine **16** employing the chiral ligand **17** gave the amine **18** in 95% yield with >98% ee (Scheme 8).



Scheme 8

Copper complexes have been widely used as catalysts in this area due to their ability to both activate a C=N double bond of an imine and facilitate alkyl group transfer.[20] Tomioka and co-workers reported the asymmetric addition of diethylzinc to imines using a copper complex with a chiral amidophosphine **20**.[21] Imines **19** bearing tosyl, mesyl, or 2-trimethylsilylethanesulfonyl groups on the nitrogen atom were used as substrates to afford the addition products **21** with high enantioselectivity and high chemical yield (Scheme 9).



19 **21** **20**

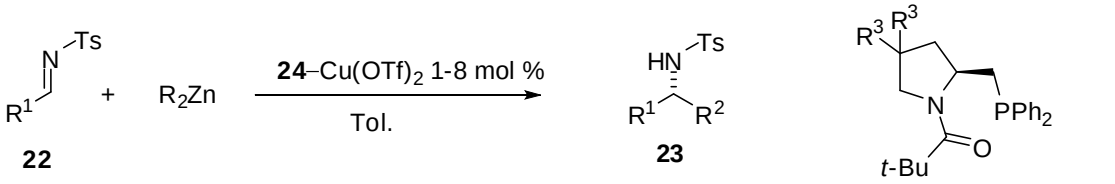
83-98%, 90-94% ee

R^1 = Ph, 4-ClC_6H_4, 3-ClC_6H_4, 2-ClC_6H_4, 4-$MeOC_6H_4$, 1-naphthyl, 2-naphthyl, 2-furyl

R^2=Ts, Ms, $TMS(CH_2)_2SO_2$

Scheme 9

The same group also reported the asymmetric addition of dimethylzinc and diisopropylzinc to *N*-tosyl imines **22** to give amines **23** with good enantioselectivity and high yield when the more bulky amidophosphane ligand **24** was employed (Scheme 10).[22]



22 **23**

R^1 = Ph, 4-$MeOC_6H_4$, 2-furyl, *o*-C_6H_{11}

R^2 = Me, *i*-Pr, Et

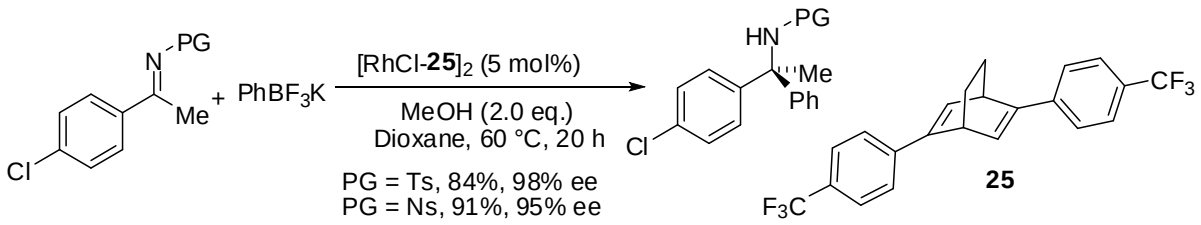
78-97%, 86-96% ee

R^3 = 2,4,6-*i*-$Pr_3C_6H_2CH_2$

24

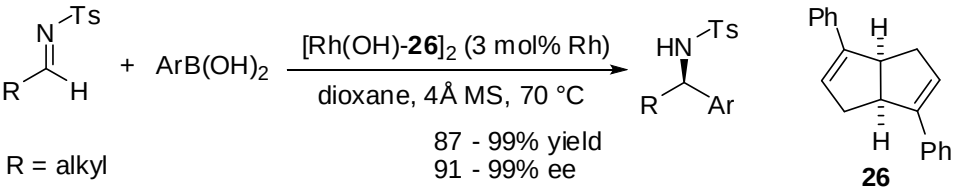
Scheme 10

The asymmetric synthesis of diarylmethylamines by arylation of *N*-tosyl and *N*-nosyl arylimines with arylboroxines, aryboronic acids and potassium organotrifluoroborates have recently been developed using rhodium-based catalysts.[23] Chiral dienes were reported to be highly effective ligands for this process. For example, Hayashi recently reported the highly enantioselective addition of potassium organotrifluoroborates to both *N*-tosyl and *N*-nosyl arylketimines with the chiral diene ligand **25** (Scheme 11).[24]



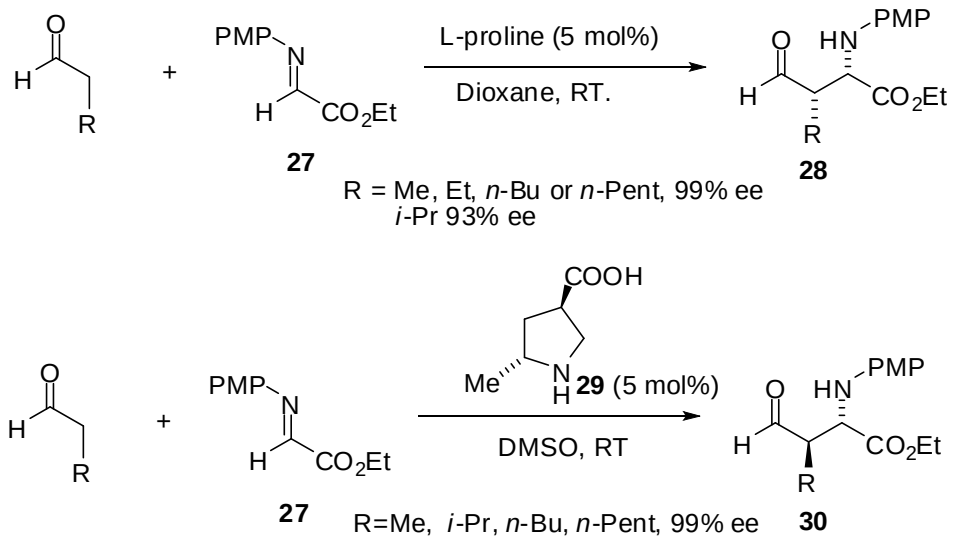
Scheme 11

Lin and co-workers recently reported that *N*-tosylalkylaldimines can be arylated with arylboronic acids in high yield and excellent enantioselectivity when chiral diene **26** was used as a ligand (Scheme 12).[25]



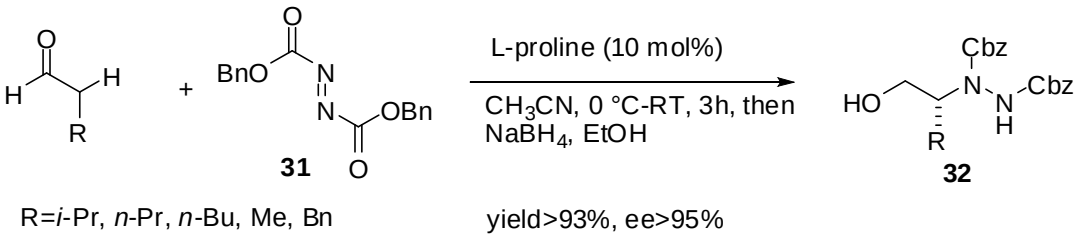
Scheme 12

An asymmetric Mannich reaction catalyzed by small organic molecules provides a facile route to optically active α- or β-amino acid derivatives and 1,3-amino alcohols.[26] Both *syn*- and *anti*-selective Mannich reactions have been developed. For example, Barbas *et al.* reported that reactions of aldehydes with *N*-*p*-methoxyphenyl (PMP)-protected glyoxylate imine **27** can afford enantiomerically enriched β-aminoaldehydes in the presence of proline-type catalysts at room temperature (Scheme 13).[27] The L-proline-catalyzed Mannich reactions afforded (2*S*, 3*S*)-*syn*-isomers **28** as the major products, while the (3*R*, 5*R*)-5-methyl-3-pyrrolidinecarboxylic acid **29** catalyzed the reactions to yield the (2*S*, 3*R*)-*anti*-products **30** in good yield with high enantioselectivities.



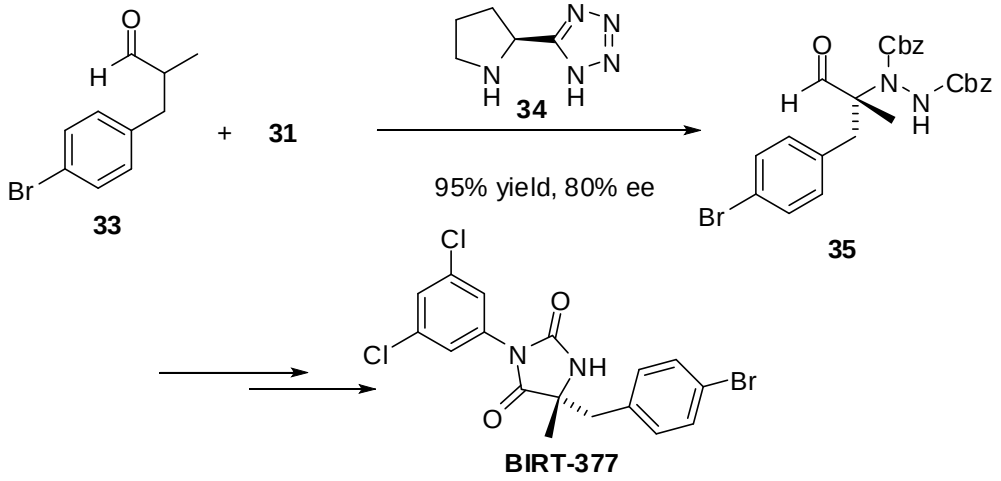
Scheme 13

Organocatalytic α-amination of aldehydes and ketones by addition to the electrophilic azodicarboxylates has also been developed. List reported that L-proline-catalyzed reactions of aldehydes with dibenzyl azodicarboxylate **31**, followed by $NaBH_4$ reduction, can afford β-amino-alcohols **32** in excellent yields and enantioselectivities (Scheme 14).[28]



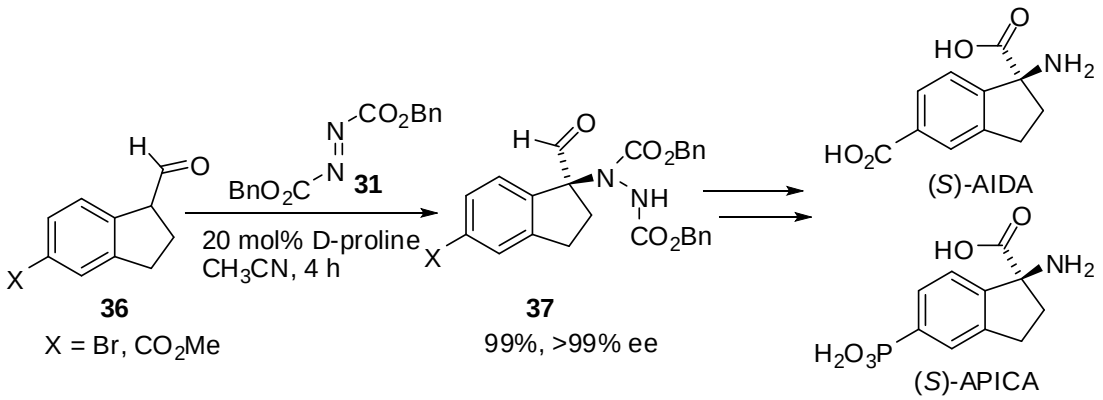
Scheme 14

Barbas and co-workers have applied the organocatalytic direct amination of aldehydes in a series of reports. For example, this methodology was used to construct the quaternary stereocentre in the enantioselective total synthesis of the cell adhesion inhibitor BIRT-377 (Scheme 15).[29] The L-proline-derived tetrazole **34** catalyzed the direct α-amination of 3-(4-bromophenyl)-2-methylpropanal **33** with dibenzyl azodicarboxylate **31** to give the amino aldehyde **35** in 95% yield and with 80% ee, from which BIRT-377 was prepared.



Scheme 15

Similarly, D-proline catalyzed amination of functionalized indane carboxaldehydes **36** was employed for the enantioselective synthesis of the metabotropic glutamate receptor ligands (*S*)-AIDA and (*S*)-APICA (Scheme 16).[30]



Scheme 16

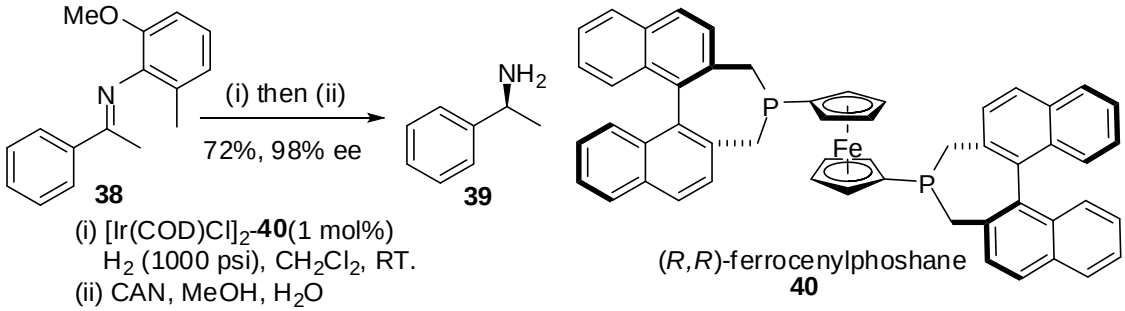
1.2 Asymmetric reduction of prochiral carbon-nitrogen double bonds

The reduction of a carbon-nitrogen double bond provides one of the most convenient methods for the synthesis of amines. When carbon-nitrogen double bond-containing compounds (generally imines) derived from unsymmetrical ketones are employed in this reaction, a new stereogenic centre is formed at the carbon connected to the nitrogen atom. A number of hydrogen sources have been used to perform this operation, including hydrogen gas, transfer hydrogenation agents, and hydride transfer agents. When a suitable chiral

catalyst or ligand is used, the reaction can be enantioselective.

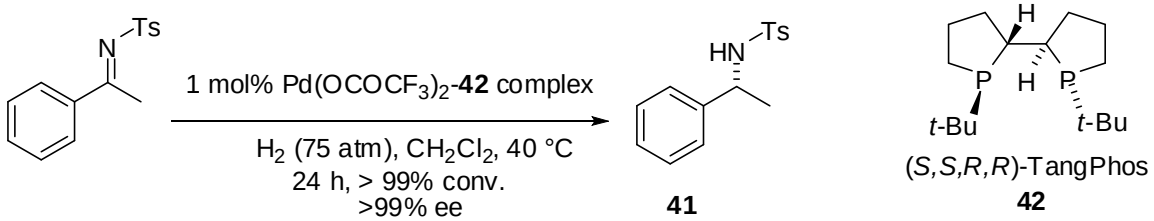
1.2.1 Asymmetric hydrogenation

Catalytic asymmetric hydrogenation, using chiral ligand-metal complexes as catalysts is a prime example of atom economy since both atoms of the hydrogen gas molecule are transferred to the product.[31] In the asymmetric hydrogenation of imines, chiral phosphine complexes of rhodium or iridium have frequently been used as catalysts. Zhang *et al.*[32] reported the hydrogenation of imine **38** using iridium-ferrocenylphosphane complex **40** as a catalyst delivering (*S*)-1-phenylethanamine **39** in high ee and good yield after deprotection with CAN (Scheme 17).



Scheme 17

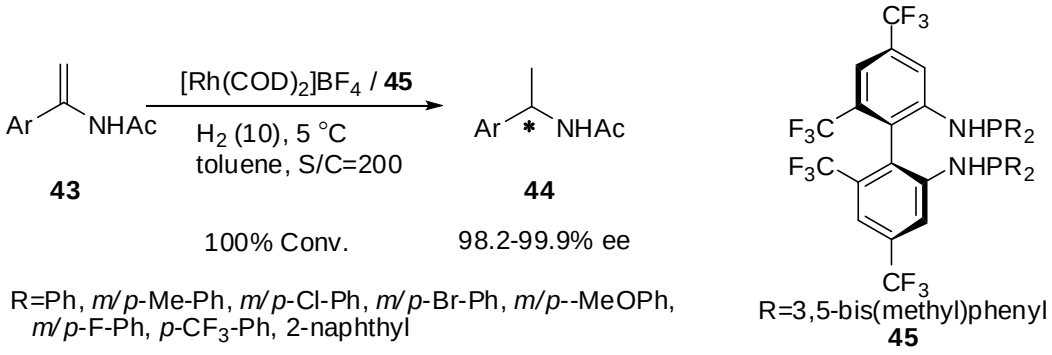
This same group has explored the asymmetric hydrogenation of *N*-tosylimines with many transition-metal-containing catalysts, in particular Rh, Ru, Ir, and Pd complexes.[33] A Pd-complex of ligand **42** was the best catalyst tested and for example at 1 mol % catalyst loading, the *N*-tosylamine **41** was obtained in high yield and excellent enantioselectivity (Scheme 18).



Scheme 18

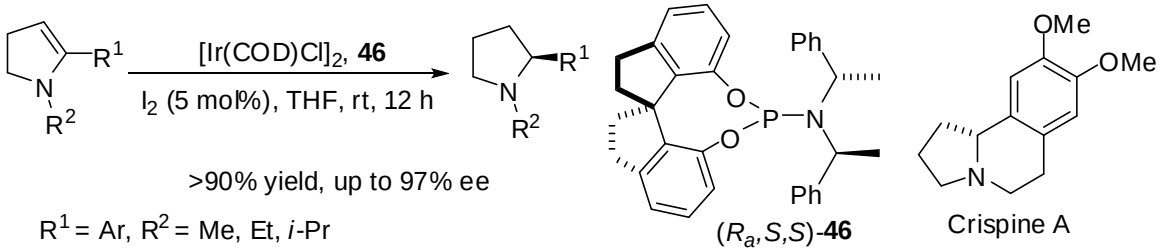
Wang and co-workers recently developed a C_2-symmetric bis(aminophosphine) ligand **45**.[34]

Aryl enamides **43** can be hydrogenated in high enantioselectivity to afford amines **44** by Rh(I)-catalyzed hydrogenation with ligand **45**. Remarkable enantioselectivity and catalytic activity were obtained with 0.5 mol % catalyst loading (Scheme 19).



Scheme 19

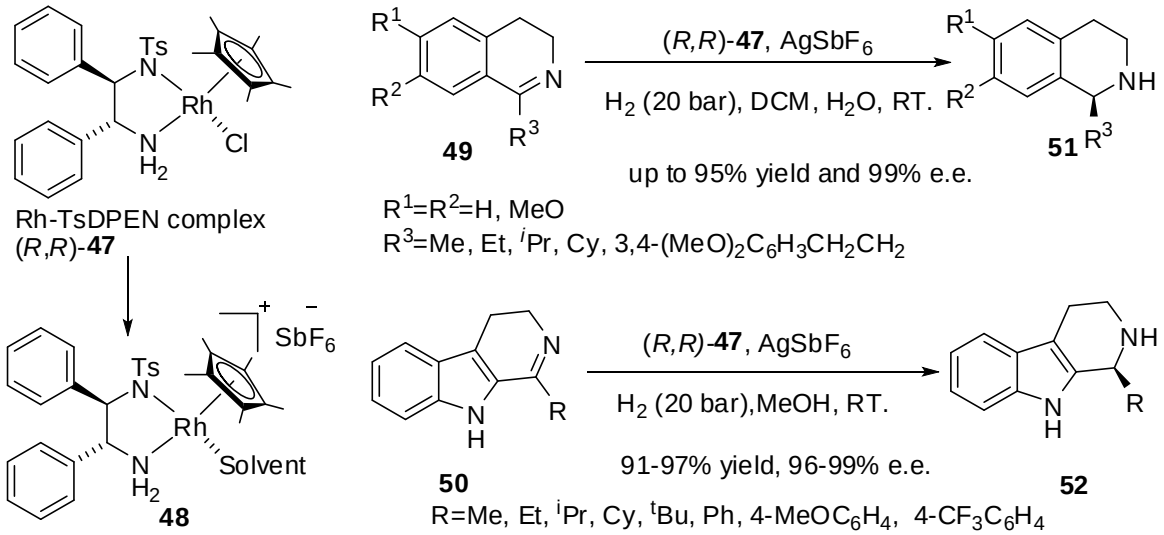
Recently, Zhou and co-workers reported the direct preparation of chiral tertiary amines in high yield and ee by catalytic asymmetric hydrogenation of the *N*, *N*-dialkyl enamines using an Ir(I) complex with ligand-**46**.[35] The natural product crispine A was synthesized in a 97% yield and 90% ee exploiting this method (Scheme 20).



Scheme 20

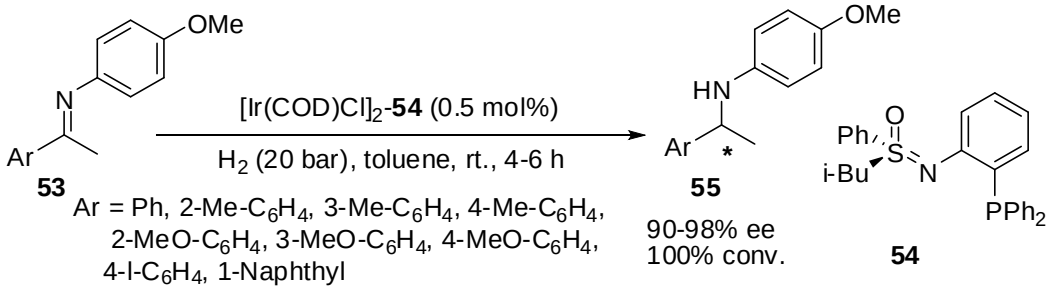
The Rh-TsDPEN complex (*R*,*R*)-**47** is a well-known catalyst for the asymmetric transfer hydrogenation of ketones and imines.[36] It was presumed that the corresponding cationic Rh (III) species might be more reactive towards hydrogen to form the necessary Rh-H hydride. Xiao *et al.* tested the effect of a range of silver salts on the hydrogenation, aiming to remove the chloride from coordination sphere to form the cationic Rh(III) species (Scheme 21).[37] In the presence of $AgSbF_6$, complex **47** was converted *in-situ* into catalyst **48**, the key species for hydrogen activation. Using this methodology, a range of isoquinoline-type imines **49** and **50** can be hydrogenated to afford the tetrahydroisoquinolines **51** and tetrahydro-*β*-carbolines

52 with excellent ee.



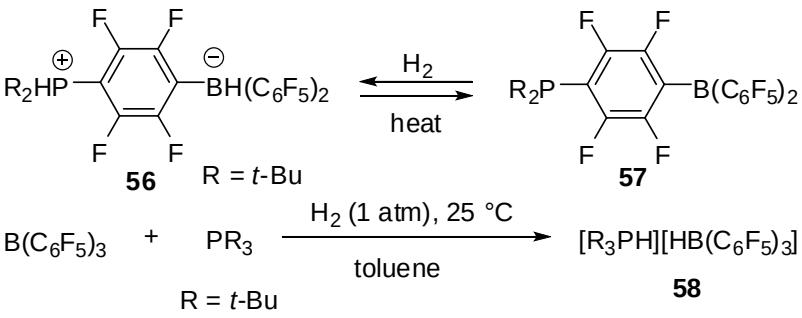
Scheme 21

Bolm *et al*. developed a chiral sulfoximine-phosphine complex **54** catalyst which facilitated the hydrogenation of a variety of *N*-(4-methoxyaryl) imines **53** to give amines **55** with high enantioselectivity and quantitative yield (Scheme 22).[38]



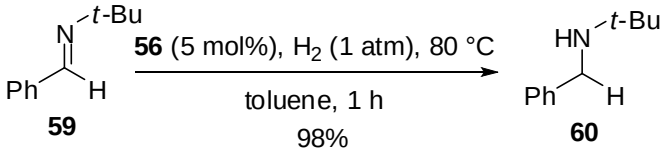
Scheme 22

In 2006, Stephan *et al*. first demonstrated that hydrogen can be activated via heterolytic cleavage by frustrated Lewis pairs (bulky Lewis acids and bases), in an intermolecular or intramolecular fashion (Scheme 23).[39]



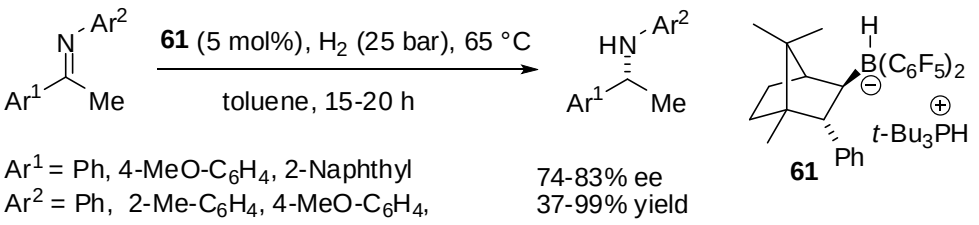
Scheme 23

Following this discovery of the metal-free hydrogen activation by frustrated Lewis pairs, Stephan and coworkers reported the catalytic hydrogenation of imines using 5 mol% Lewis pair **56** as a catalyst.[40] For example, imine **59** was reduced within 1 hour in 98% yield to afford amine **60** (Scheme 24).



Scheme 24

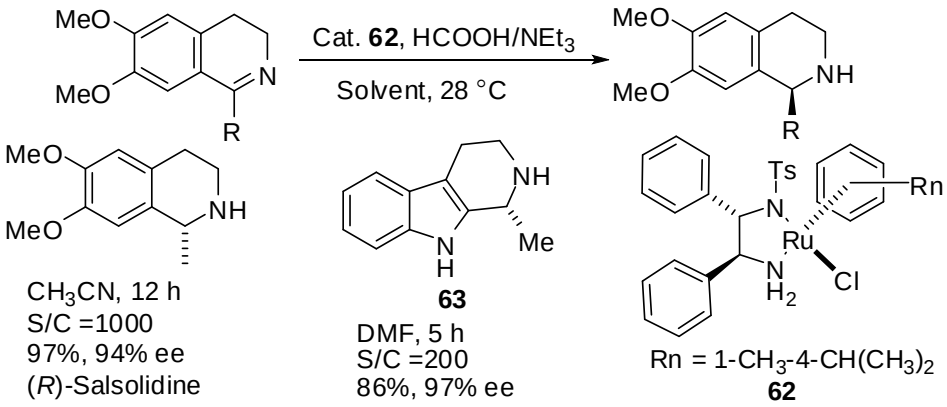
Later, the same group disclosed that electron rich imines can be hydrogenated with a Lewis acid $B(C_6F_5)_3$ without additional Lewis bases. In this case, the imine substrate acted as Lewis base to form a frustrated Lewis pair with $B(C_6F_5)_3$ to activate hydrogen. However, additional base was required for the reduction of electron poor imines.[41] Recently, Klankermayer extended these systems for asymmetric hydrogenation of ketimines.[42] A series of amines were obtained in good yield and enantioselectivity by hydrogenation of the corresponding imines at 5 mol% catalyst loading using chiral frustrated Lewis pair **61** (Scheme 25).



Scheme 25

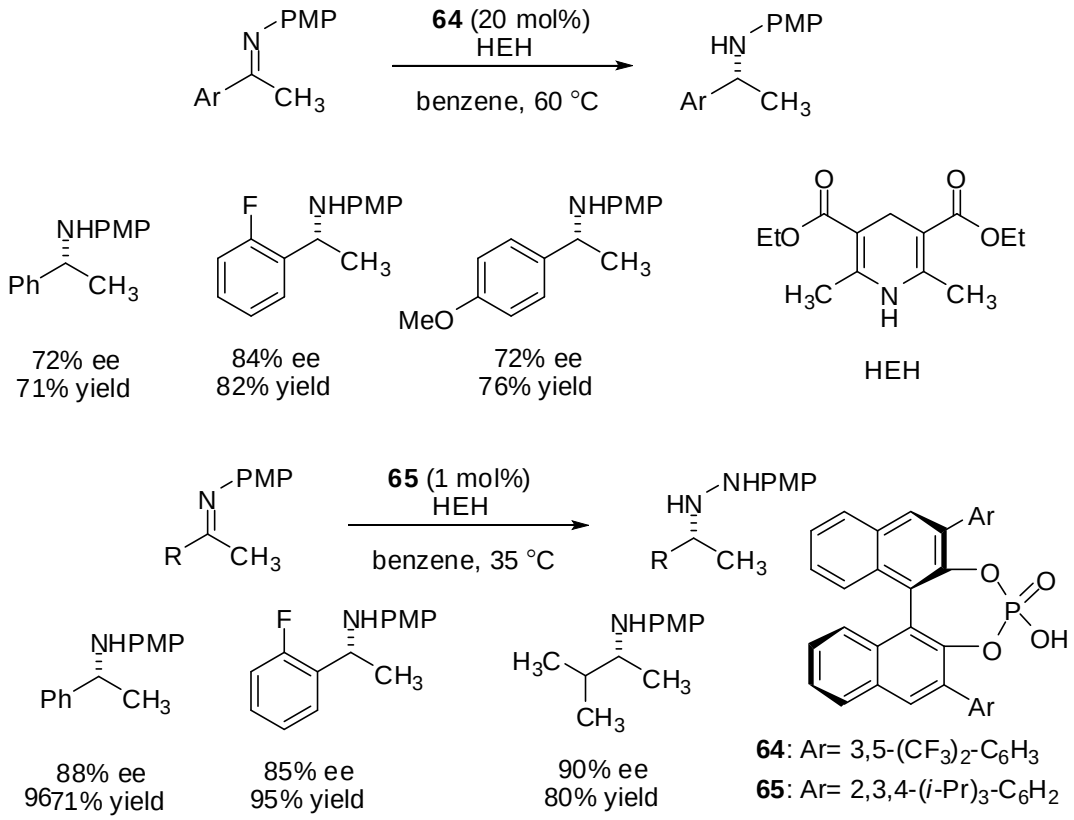
1.2.2 Asymmetric transfer hydrogenation

Asymmetric transfer hydrogenation using a stable organic hydrogen donor is a useful synthetic method. Although originally focused on ketone substrates, asymmetric transfer hydrogenation of imines has also been investigated. Noyori *et al.* reported that ketimines can be reduced with a 5:2 formic acid-triethylamine mixture in the presence of catalyst RuCl[(*S*,*S*)-Tsdpen](η^6-arene) **62**.[43] For example, (*R*)-salsolidine and indole derivative **63** were obtained in 95% ee and 97% ee respectively by reduction of the corresponding imines (Scheme 26).



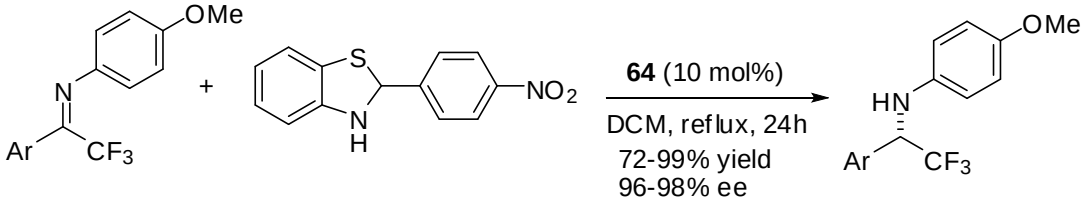
Scheme 26

Asymmetric organocatalytic transfer hydrogenation has also been developed employing a Hantzsch ester as the hydride source. Rueping and co-workers investigated the use of chiral binaphthyl-derived phosphoric acids for the enantioselective organocatalytic reduction of imines.[44] Chiral phosphoric acid **64** proved to be most enantioselective, allowing the reduction of a range of aromatic methyl ketimine substrates in 70-84% ee (Scheme 27).[44b] List and co-workers subsequently reported the efficiency and enantioselectivity can be improved using phosphoric acid **65** at 1 mol % catalyst loading.[45] Macmillan and co-workers later developed a reductive amination strategy with analogous chiral binaphthyl-derived phosphoric acids.[46]



Scheme 27

Akiyama *et al.* reported that benzothiazolines were also suitable hydride sources for the asymmetric transfer hydrogenation of ketimines and α-imino esters using chiral phosphoric acids as catalysts,[47] and more recently reported that trifluoromethylated imines can also be reduced in high enantioselectivity using chiral phosphoric acid **64** (Scheme 28).[48]

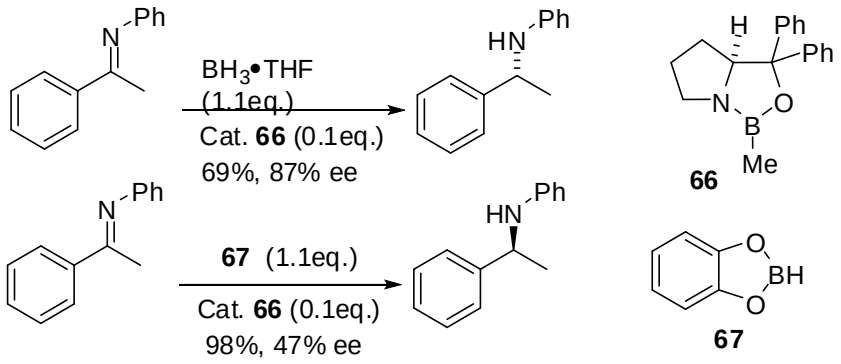


Scheme 28

1.2.3 Reduction of carbon-nitrogen double bonds with boranes

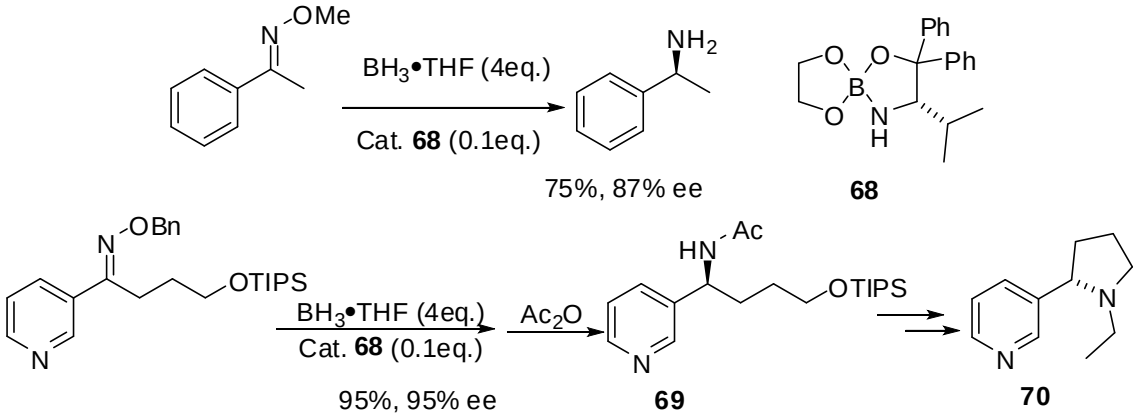
Asymmetric hydrometallation of ketimines and ketoxime ethers catalyzed by chiral transition-metal complexes or metal-free chiral ligands provides an effective route to optically active amines. Organoborane reagents, especially oxazaborolidine borane complexes, have been widely used for the asymmetric reduction of ketones due to their outstanding enantioselectivity and predictable stereochemical control,[49] and may also be

used for the reduction of ketoxime ethers.[50] In 2004, Field and co-workers reported the reduction of imines using a CBS catalyst **66** and a less reactive reducing agent catecholborane **67** (Scheme 29).[51] Their studies showed that the choice of reducing agent can affect the sense of asymmetric reduction, which was attributed to steric factors.



Scheme 29

Ortoz-Marciales and co-workers prepared a spiroborate ester **68** derived from diphenylvalinol, which has been successfully used for the asymmetric reduction of ketoxime ethers.[52] The same group found that the (*S*)-nicotine analogue **70** could be prepared in 97% ee from enantiopure **69** with 64% overall yield using the same strategy (Scheme 30).[53]

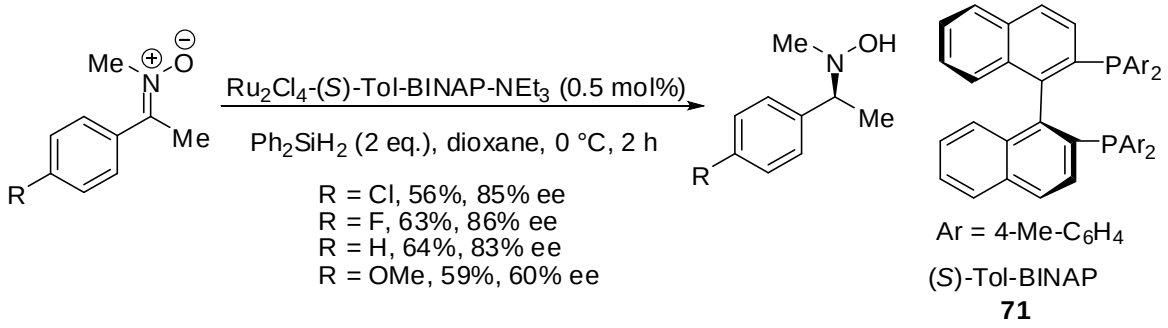


Scheme 30

1.2.4 Reduction of carbon-nitrogen double bonds with silanes

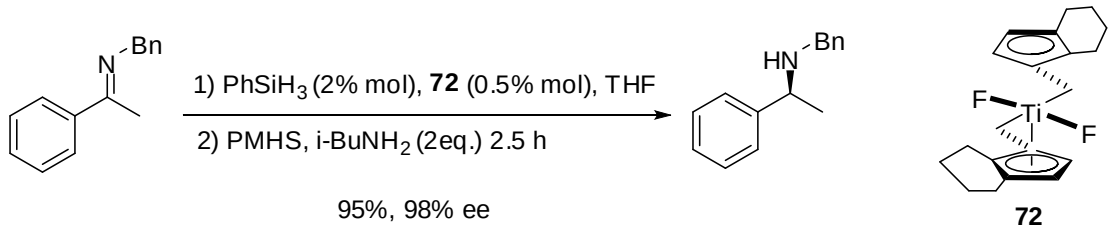
Several silanes have been used in the enantioselective reduction of nitrones, imines and enamines to afford chiral amines. Murahashi *et al.* reported that the enantioselective

hydrosilylation of carbon-nitrogen double bonds of nitrones with diphenylsilane (Ph_2SiH_2) using Ru_2Cl_4-(*S*)-Tol-BINAP-NEt_3 as catalyst at 0 °C afforded the corresponding optically active *N*,*N*-disubstituted hydroxylamines (Scheme 31).[54]



Scheme 31

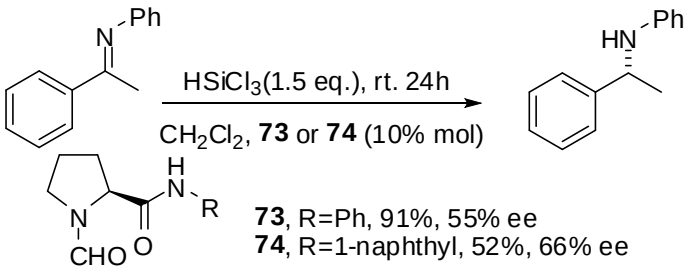
Polymethylhydrosiloxane (PMHS) is an attractive reducing agent because it is inexpensive, non-toxic and insensitive to air and moisture, leading to many applications in organic synthesis.[55] Buchwald *et al.* reported that a combination of titanocene **72** and PMHS can reduce imines to amines with excellent ee and high yields (Scheme 32).[56]



Scheme 32

Trichlorosilane ($HSiCl_3$, an inexpensive and relatively easy-to-handle reducing reagent) is more Lewis acidic than alkyl- and arylsilanes and can be activated by metal-free organic molecules, such as DMF, a discovery which made the organocatalytic asymmetric reduction of imines possible.[57] A series of chiral formamides based on amino acids have been developed as the activator by several groups. In 1999, Matsumura reported the first enantioselective reduction of ketones using trichlorosilane with proline-derived amides **73**, **74**.[58] In 2001, the same group expanded the scope of their catalysts to reduce ketimines in an asymmetric fashion (Scheme 33).[59] The *N*-formyl group proved to be crucial for the

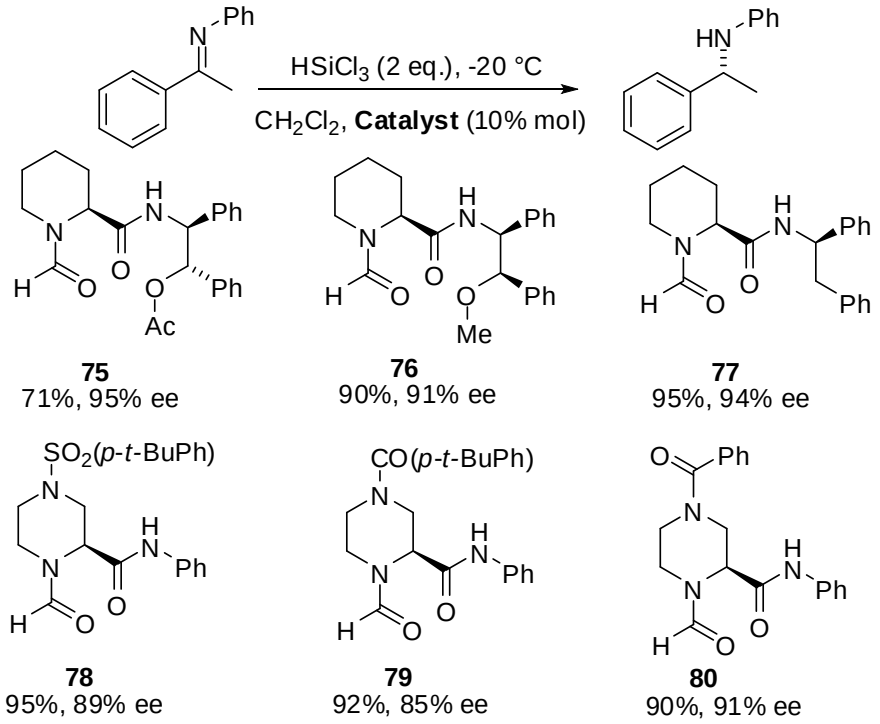
activation of $HSiCl_3$, as the corresponding *N*-methoxycarbonyl and acetyl group failed to initiate the reaction.



Scheme 33

Although moderate enantioselectivity was obtained, these studies gave impetus to the development of chiral activators for asymmetric reduction of imines with trichlorosilane. Several groups have been involved with the development of new chiral formamide catalysts.

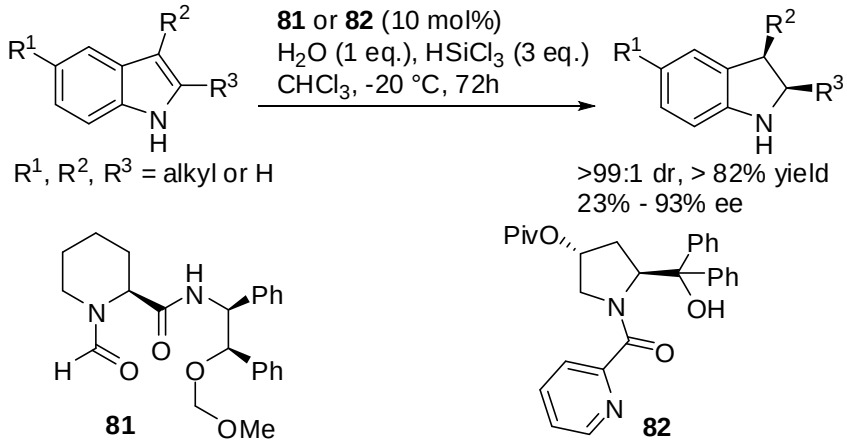
Sun and co-workers reported a series of catalysts by replacing the rigid proline core with pipecolinic acid and piperazine 2-carboxylic acid derivatives **75**-**80** (Scheme 34).[60]



Scheme 34

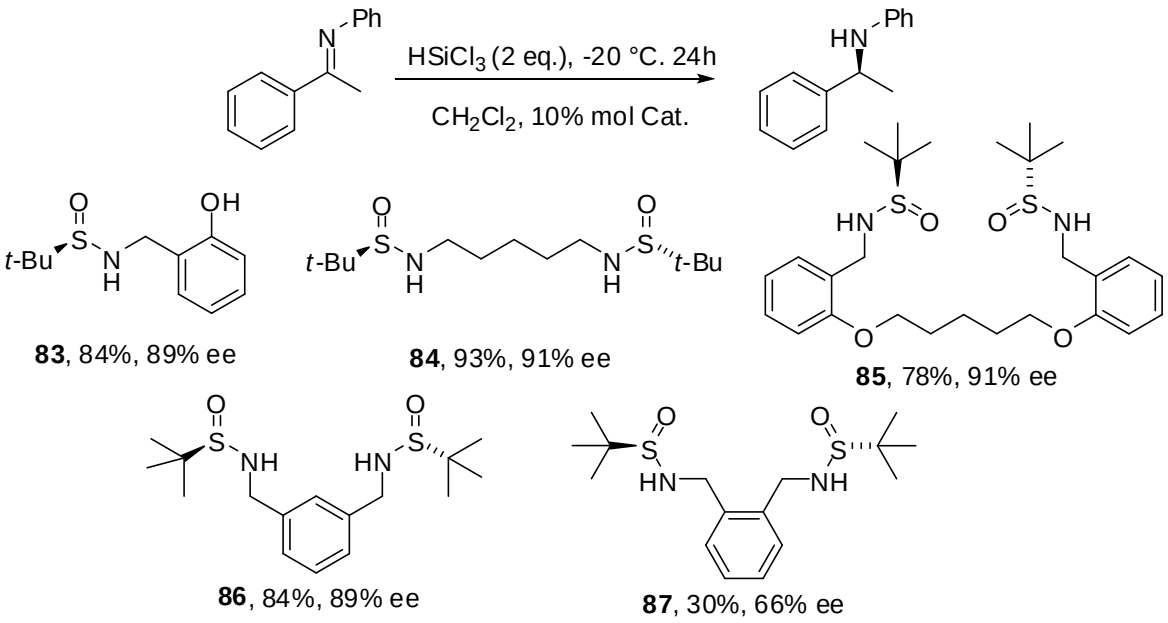
Most recently, the same group demonstrated that indoles can be reduced by trichlorosilane in

the presence of one equivalent of water and 10 mol% of the novel *N*-formyl L-pipecolinamide **81** or the *N*-formyl L-proline amide **82** (Scheme 35).[61]



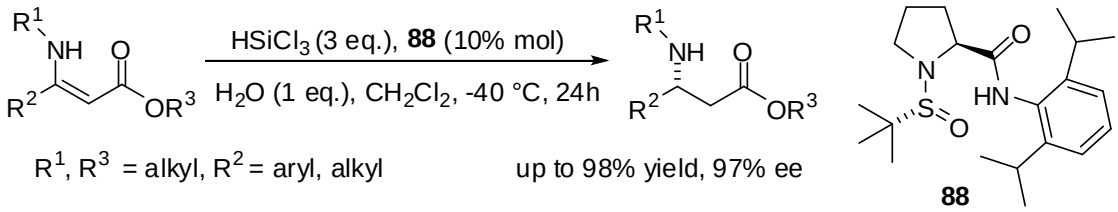
Scheme 35

Sun and co-workers also reported that catalysts **83-87** based on a chiral sulfinamide instead of chiral formamide worked efficiently for the asymmetric reduction of ketimines (Scheme 36).[62] A clear positive non-linear effect of the enantiomeric excess of catalyst **83** on the product enantioselectivity in the asymmetric reduction of ketimine was observed.[62a] This result suggested more than one molecule of monosulfinamide catalyst **83** was involved in the transition state. As expected for the bissulfinamide **84**, a linear correlation of catalyst ee on product ee was observed, which indicated in this case a single molecule participated in the transition state.[62b]



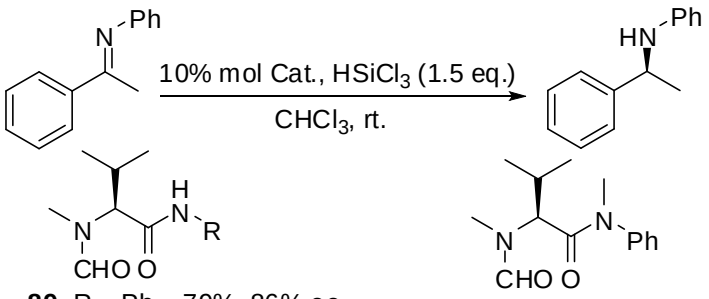
Scheme 36

The highly enantioselective reduction of *N*-alkyl β-enamino esters with trichlorosilane using a chiral sulfinamide derivative of L-proline **88** as catalyst was reported recently by the same group (Scheme 37).[63] The use of one equivalent of water as an additive proved to be crucial to achieve high reactivity and enantioselectivity; the HCl generated in situ was proposed to accelerate the enamine-imine tautomerization.



Scheme 37

Malkov *et al.* devised a range of chiral formamide catalysts **89**-**93**, employing acyclic *N*-methyl amino acids instead of cyclic amino acids as the core (Scheme 38).[64] Their studies showed that a conformationally restricted core, such as proline, was not necessary to achieve high enantioselectivity. Interestingly, despite the same configuration of the parent amino acids in catalysts **73**-**80** and **89**-**93**, the valine-based catalysts **89**-**93** induced the formation of the opposite enantiomer of product.

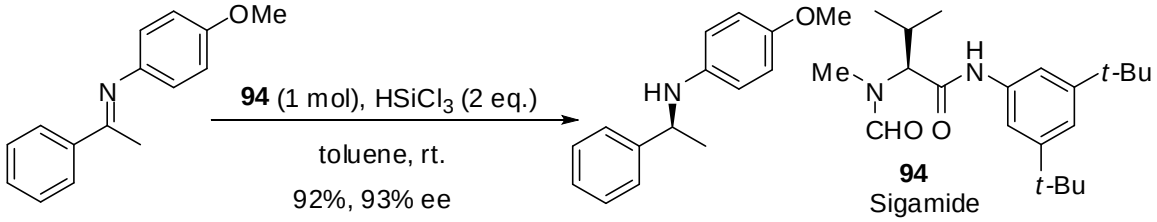


89, R = Ph, 79%, 86% ee
90, R = 4-MeOC$_6$H$_4$, 62%, 85% ee
91, R = 3,5-Me$_2$C$_6$H$_3$, 70%, 89% ee
92, R=^{n}Bu, 0%

93, 23%, 7% ee

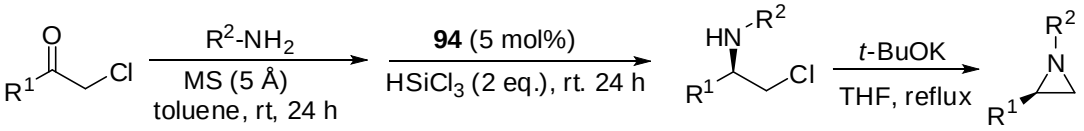
Scheme 38

A highly active *N*-formamide catalyst **94** (commercialized as Sigamide) based on (*S*)-valine was also reported by Malkov.[65] Benchmark imine substrates can be reduced in 92% yield and 93% ee by trichlorosilane in the presence of 1 mol% of catalyst **94** (Scheme 39).



Scheme 39

In 2007, Malkov *et al.* reported the reduction of α-chloro-imines using catalyst **94**.[66] Interestingly, α-chloro-imines generated *in-situ* from the corresponding α-chloro-ketones and aniline derivatives can be reduced directly in high yields and enantioselectivities following addition of trichlorosilane and catalyst. After further cyclization, the corresponding aziridines were obtained with high enantiopurities (Scheme 40).

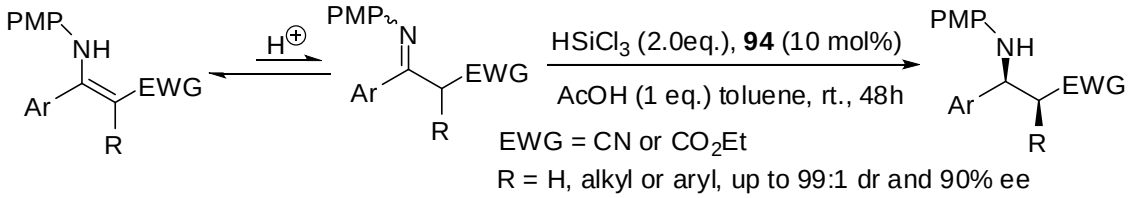


R$_1$ = Ph, 4-FC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$,4-CF$_3$C$_6$H$_4$,3-MeC$_6$H$_4$, 3-MeOC$_6$H$_4$,2-ClC$_6$H$_4$, 2-naphthyl
R$_2$ = Ph, 4-MeOC$_6$H$_4$, 4-FC$_6$H$_4$, 4-ClC$_6$H$_4$ 54-94% yield, 84-96% ee

Scheme 40

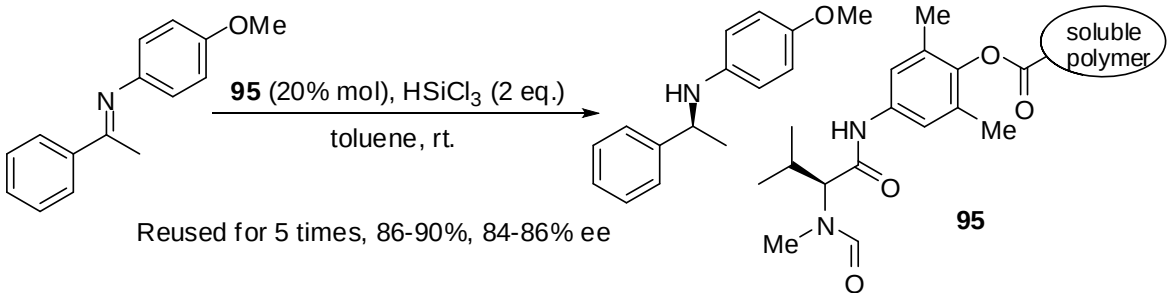
In 2008, catalyst **94** was extended to catalyze the asymmetric reduction of *β*-enamino esters with trichlorosilane.[67] α-Substituted *β*-enamino esters were also suitable substrates through a

dynamic kinetic resolution process. Since the reaction involved a crucial imine-enamine equilibrium, addition of 1 eq. of acetic acid to buffer the reaction medium was important to ensure good reproducibility (Scheme 41).



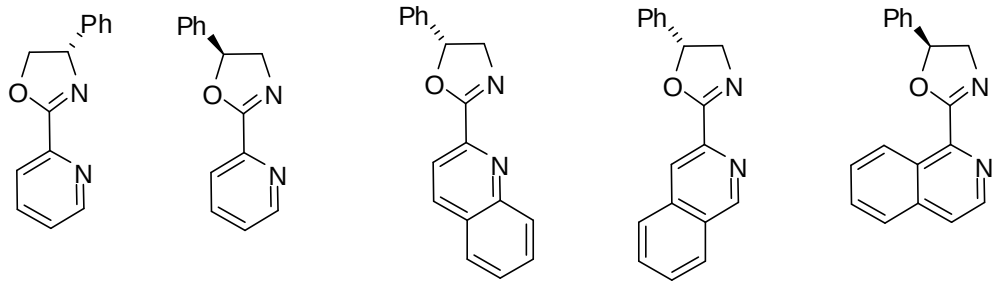
Scheme 41

Malkov and co-workers devised several recyclable catalytic systems of (*S*)-valine-derived organocatalysts by immobilising the catalytic species onto nanoparticles, resins, dendrons and fluorous tags.[65,68] For example, the soluble polymer-supported catalyst **95** exhibited high activity even after being reused 5 times (Scheme 42).[68a]



Scheme 42

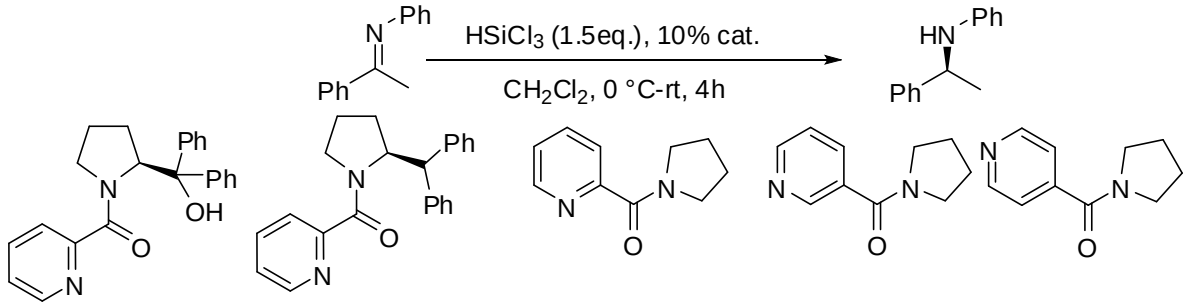
In 2006, the same group devised a series of mandelic acid derived oxazoline catalysts **96**-**100** (Figure 3).[69] Catalyst **100** provided the best enantioselectivities for the reduction of aryl ketones and was also found to exhibit high efficiency in the reduction of *N*-aryl imines with 20% catalyst loading (up to 67%, 87% ee).



96 **97** **98** **99** **100**

Figure 3

In 2006, Matsumura and co-workers developed a new non-formamide catalyst **101** based on (*S*)-α,α-diphenylprolinol and picolinoyl chloride (Scheme 43).[70] The relationship of the structure and activity of the catalysts was investigated using a series of structurally related catalysts **101-105**. Coordination of the silicon atom with both the nitrogen atom of picolinoyl group and the carbonyl oxygen was thought to play a significant role since the *N*-nicotinoylpyrrolidine **104** and *N*-(4-pyridylcarbonyl)-pyrrolidine **105** were less efficient activators than catalyst **101-103**. Furthermore, the fact that catalyst **101** afforded higher enantioselectivity than catalyst **102** suggests an important role of the hydroxyl group of catalyst **101**. According to these results, a transition state model was proposed (Figure 4). It is crucial that the formation of a hydrogen bond between the nitrogen of imine and the hydroxyl group in the catalyst **101** controls the stereochemistry.



101 **102** **103** **104** **105**

Scheme 43

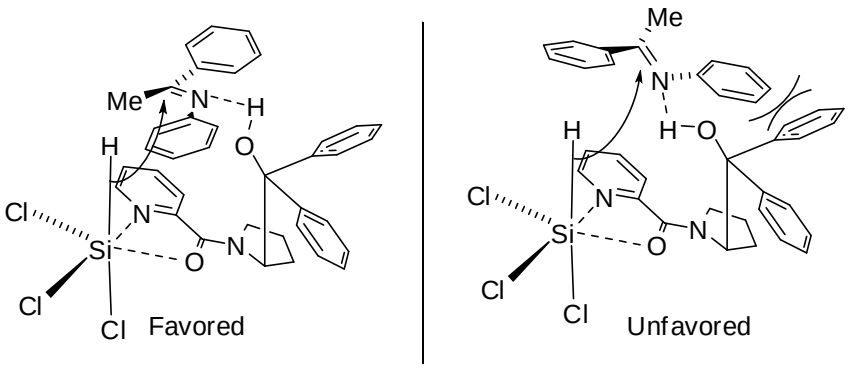
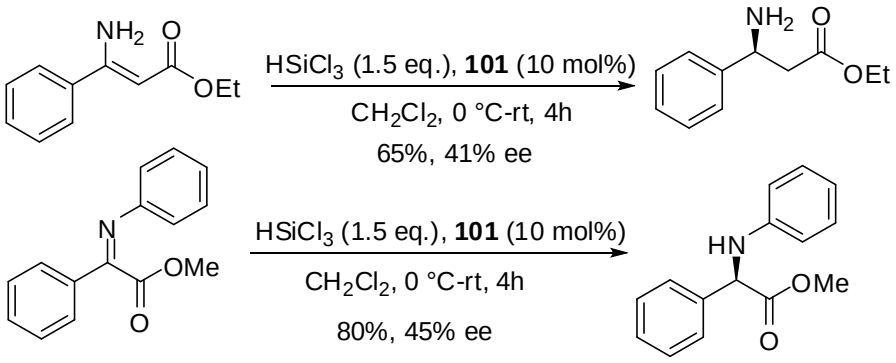


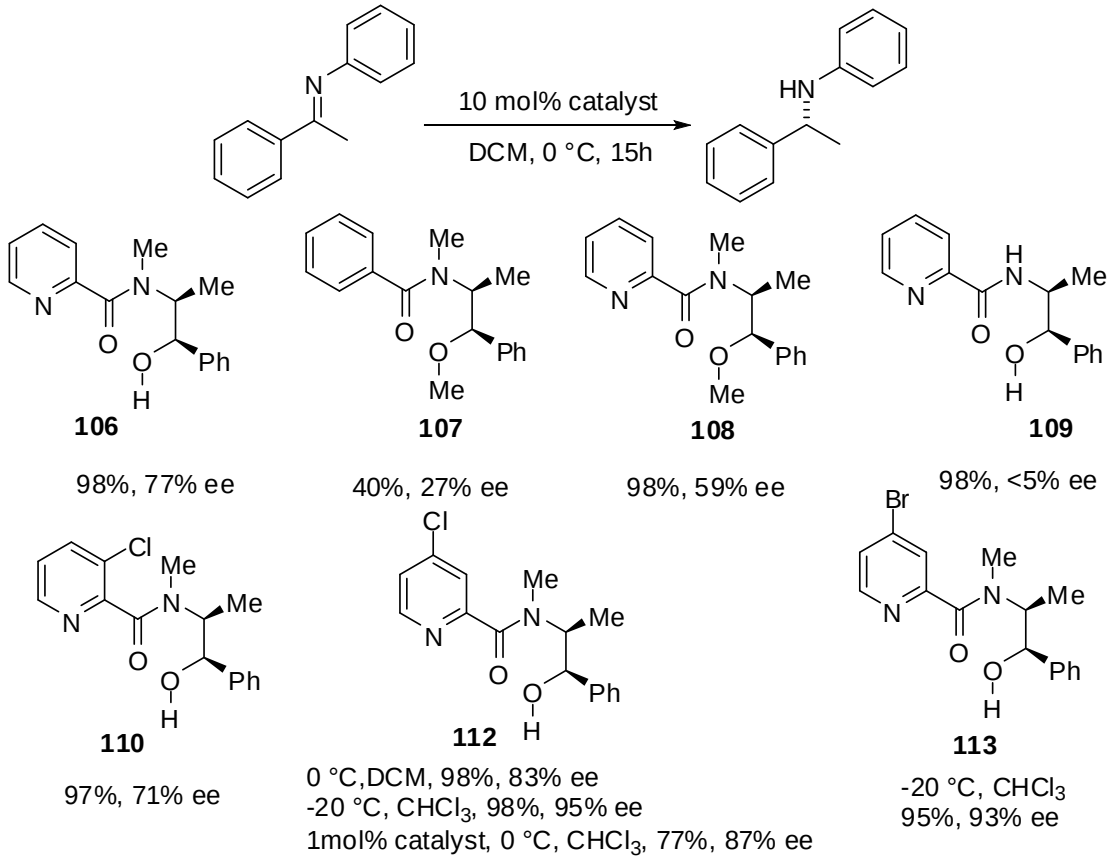
Figure 4

Matsumura demonstrated that both α-imino esters and β-enamino esters can be reduced with trichlorosilane using catalyst **101**, but only with moderate enantioselectivity (Scheme 44).



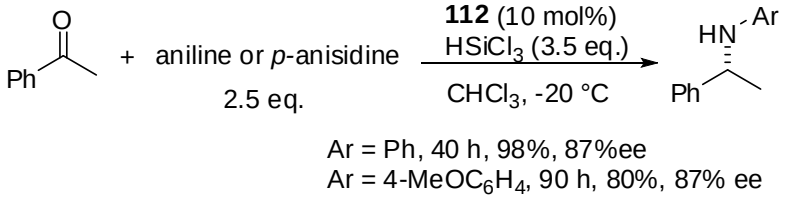
Scheme 44

A series of chiral *N*-picolinoyl aminoalcohol catalysts were prepared and screened for the asymmetric reduction of ketimines by both Benaglia's and Zhang's group.[71,72] Catalyst **106** proved to be one of the best catalysts tested by both groups. The structure/activity relationship studies carried out by Benaglia indicated that a pyridine ring, free hydroxyl group and *N*-alkyl substituent were necessary structural elements to obtain good stereoselectivity and high yield (Scheme 45). These results were similar to Matsumura's work (Scheme 43) and a transition state model proposed similar to this. The effect of introducing a substituent on the pyridine ring was also investigated; placement of a chlorine or bromine atom on the 4-position of the pyridine improved the catalyst efficiency. With a catalyst loading of 1 mol%, 4-chloropicolinic acid derivative **112** still maintained a high level of catalytic efficiency yielding the product in 77% yield and 87% ee.



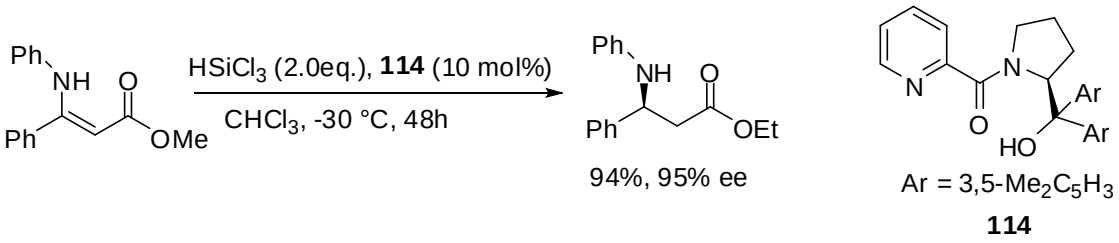
Scheme 45

The reductive amination of acetophenone with aniline and *p*-anisidine using 10 mol% of catalyst **112** was also reported although a long reaction time was necessary for achieving high yield by Benaglia *et al.* (Scheme 46).[72]



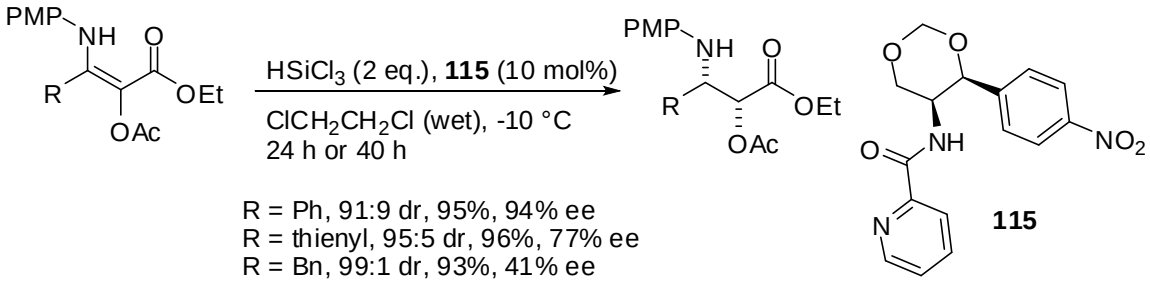
Scheme 46

Zhang *et al.* also reported the highly enantioselective reduction of *β*-enamino esters with trichlorosilane catalyzed by chiral *N*-picolinoyl aminoalcohol catalyst **114** as a chiral Lewis base activator (Scheme 47).[73]



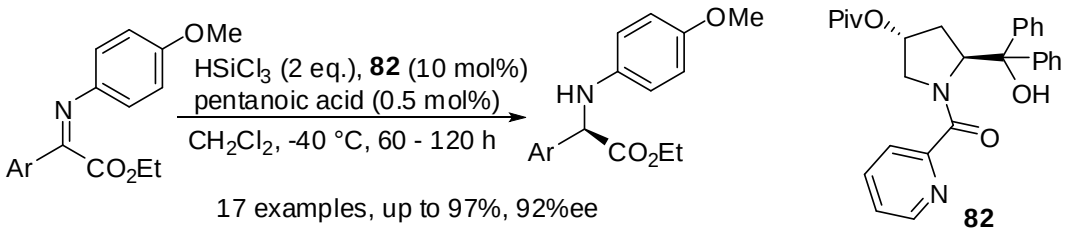
Scheme 47

Recently, the asymmetric reduction of α-acetoxy *β*-enamino esters with the picolinamide **115** as catalyst was reported by the same group (Scheme 48).[74] The use of unpurified solvent was necessary to generate HCl *in-situ* (from water and trichlorosilane) to promote the tautomerisation of enamine-imine.



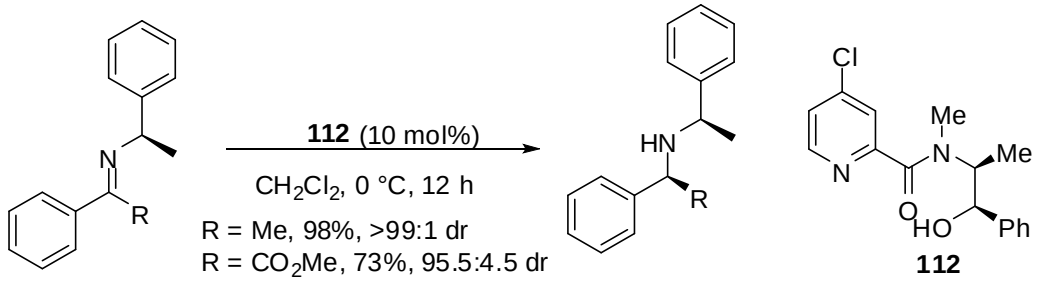
Scheme 48

The same group has reported that the asymmetric reduction of α-imino esters can be achieved with 10% mol of chiral *N*-picolinoyl aminoalcohol catalyst **82** (Scheme 49).[75] Pentanoic acid (0.5 mol%) was required as an additive to activate the substrates.



Scheme 49

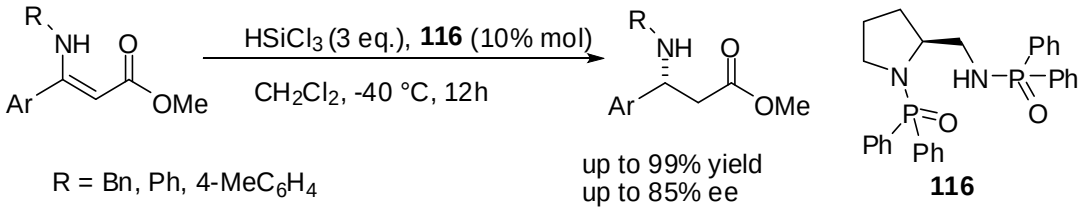
Benaglia *et al*. recently reported that the asymmetric reduction of imines and α-imino esters derived from enantiopure 1-phenylethylamine can be achieved in high diastereoisomeric excess with catalyst **112**.[76]



Scheme 50

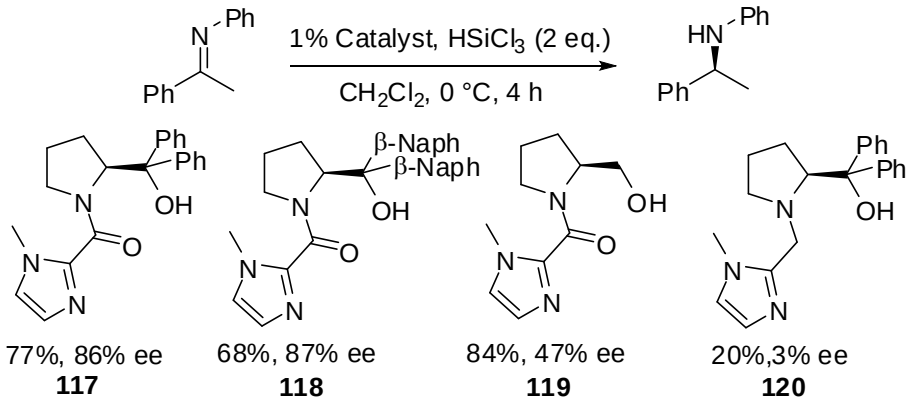
Subsequently, this methodology was extended to the reduction of β-enamino esters derived from enantiopure amines using the same catalyst **112**.[77] Further conversion of the product provided a route to β-lactams.

Most recently, the same group demonstrated that a range of chiral bis-phosphinamides derived from L-proline were active catalysts for the reduction of β-enamino esters.[78] The best catalyst **116** facilitated the reduction of β-enamino esters in up to 99% yield and 85% ee (Scheme 51).



Scheme 51

In Jones' group, a new bifunctional catalyst **117** was developed featuring an imidazole ring, which can facilitate the asymmetric reduction of a variety of ketimines within 4 hours at a low catalyst loading (1 mol%).[79] A structure-activity study was carried out by testing the activity of catalysts **117**-**120** (Scheme 52). Two coordination sites are necessary for highly catalytic activities, since catalyst **120** exhibited very low catalytic activity and no selectivity. This observation was similar to Matsumura's result (Scheme 43). Using the *gem*-diphenyl and *gem*-β-dinaphthyl prolinol derivatives **117** and **118** as catalysts, the product was obtained in good yield and ee, while prolinol derivative **119** showed low enantioselectivity but high yield. Apparently, the steric hindrance effect of the geminal groups played a key role in controlling the enantioselectivity.



Scheme 52

1.3 Project aims

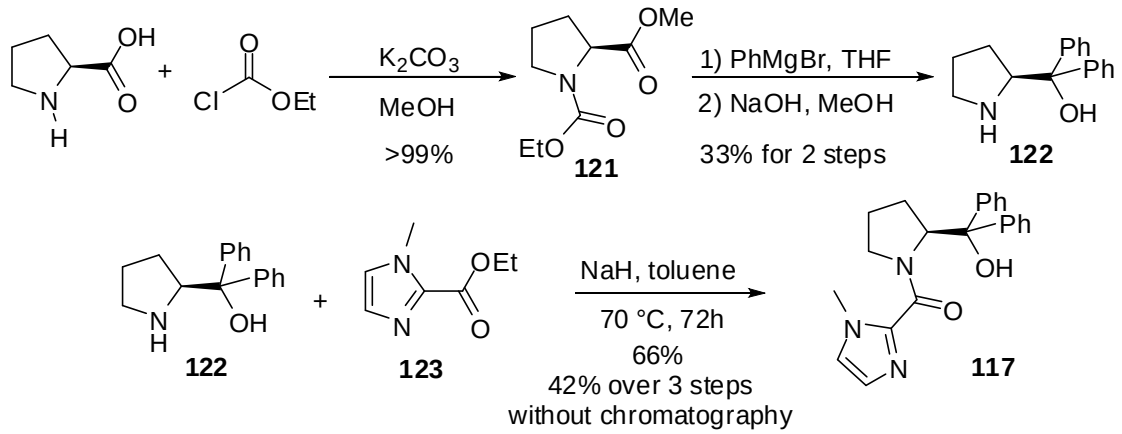
A number of synthetic strategies to prepare chiral amines have been developed. The processes catalysed by a biocatalyst are expensive, require aqueous reaction media, and the concentration of substrates is limited to a low level since most organic substrates are poorly soluble in the aqueous phase. The reduction of imines by transition metal catalytic hydrogenation or transfer hydrogenation has been extensively investigated. However, it can suffer from metal-leaching in the product which is a non-negligible issue in the pharmaceutical industry. Organic catalysts have emerged as a promising method. Phosphoric acid catalysed reduction of imines using Hantzsch esters as hydrogen source has been reported by several groups. Clearly, this method is less atom-economical due to the stoichiometric pyridine derivative produced as waste, removal of which is not trivial in some cases. Trichlorosilane is now well placed to take up the baton as an economic hydrogen source. A catalyst **117** developed in Jones' group proved to be efficient for asymmetric reduction of various *N*-phenyl and *N*-*p*-methoxyphenyl ketimines at a very low catalyst loading (1% mol). Continuing this research, the main aims of the project are therefore as follows:

- Expand the substrate scope of catalyst **117**
- Develop an asymmetric reductive amination protocol using catalyst **117**
- Investigate the mechanism and devise new catalysts

2. Investigation of the scope of asymmetric reduction of imines

2.1 Optimisation of synthesis of catalyst

Catalyst **117** was prepared by four steps starting from L-proline and ethyl chloroformate (Scheme 53). The key intermediate of α,α-diphenylprolinol **122** was synthesized in 33% yield by addition of four equivalents of phenylmagnesium bromide to proline methyl ester **121**, followed by hydrolysis of the carbonate according to a literature procedure. Pure α,α-diphenylprolinol **122** was obtained after purification by silica chromatography. The condensation of α,α-diphenylprolinol **122** with ethyl 1-methylimidazole-2-carboxylate **123** afforded catalyst **117** in 66% yield after purification by chromatography and recrystallization.



Scheme 53

During the preparation of catalyst **117**, the main by-product was found to be biphenyl from the preparation of α,α-diphenylprolinol **122**, formed by homo-coupling during the formation of phenylmagnesium bromide. Additionally, catalyst **117** was poorly soluble at room temperature in ethyl acetate whereas the impurities were soluble. Therefore, it was possible to conduct the final three steps without purification until the last step, followed by recrystallisation. In order to reduce the homo-coupling by-product, a solution of proline methyl ester in THF was added dropwise to a solution of freshly prepared phenylmagnesium bromide (3 eq. instead of 4 eq.) in THF. The following steps were then carried forward without purification of the intermediates. Gratifyingly, catalyst **117** was obtained after two

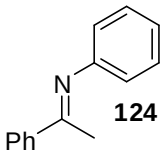
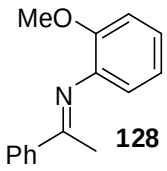
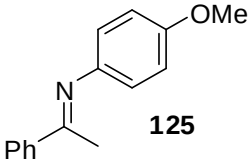
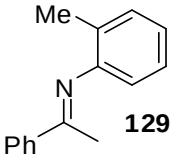
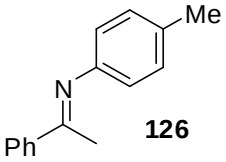
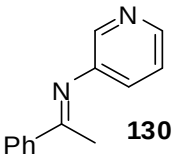
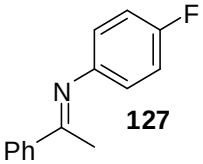
crystallizations from ethyl acetate in 42% yield over the final three steps (Scheme 53). This process for synthesis of catalyst **117** is scalable with good overall yield without purification by chromatography.

2.3 Evaluation of the influence of *N*-protecting group on the reduction of imines

The generality of catalyst **117** has been previously demonstrated by asymmetric reduction of an array of acyclic imines bearing a phenyl or *p*-MeO-phenyl ring on the nitrogen atom. Thus, in this project, the effect of varying the electronic and steric properties of imine protecting group would be explored in the first instance.

A series of *N*-arylimines were prepared as single isomers by the condensation of the corresponding ketone and aniline derivative in the presence of 4Å molecular sieves at room temperature in toluene, followed by purification by recrystallisation or vacuum distillation (Table 1). These imines were assumed to be the more stable *trans*[i] isomers.

Table 1: Preparation *N*-arylimines[a]

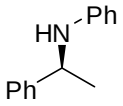
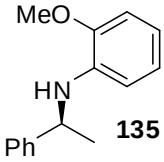
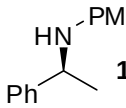
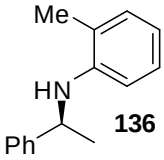
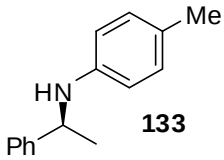
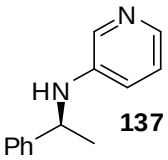
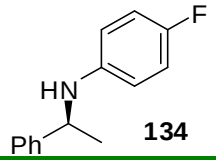
Imine	Yield (%)	Imine	Yield (%)
 **124**	51	 **128**	44
 **125**	52	 **129**	48
 **126**	72	 **130**	17
 **127**	46		

[a] The mixture of ketone (50 mmol), amine (60 mmol) and 4Å MS (20 g) in toluene (40 mL) stirred at room temperature for 24 hours.

[i] In this thesis, the *trans* isomer of an imine is defined as the isomer in which the bulky groups of imine lie on opposite side of the double bond of an imine. In contrast, the *cis* isomer of imine has the bulky groups on the same side of the double bond.

The reductions were performed under the optimized conditions developed in Jones' group, which were imine (1 mmol), trichlorosilane (2 eq.) and catalyst **117** (0.01 mmol) in dichloromethane (0.5 mL), stirring for 4 hours at 0 °C (Table 2).[79] Both electronic rich and poor imines were reduced in high yields and good enantioselectivies (amines **131-134**). In contrast, exceptionally high enantioselectivities were obtained with *ortho*-substituted *N*-aryl imines but with lower yields (amines **135-136**). These results indicated that electronic factors had little effect on the activity and enantioselectivity; however, steric interactions close to the nitrogen atom played an important role on the activity and enantioselectivity. The reduction of *N*-pyridinyl imine **130** can yield amine **137** in 40% yield and 47% ee; the enantioselectivity was slightly improved (60% ee) when increasing the catalyst loading to 10 mol%. It should be mentioned that a suspension formed upon the addition of trichlorosilane for the reduction of imine **130**.

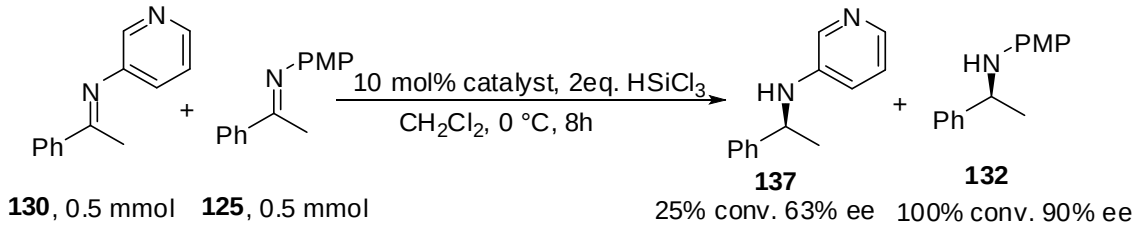
Table 2: The asymmetric reduction of *N*-arylimines[a]

Amine	Yield (%)	Ee (%)	Amine	Yield(%)	Ee(%)
 **131**	98	85	 **135**	35	96
 **132**	100	90	 **136**	64	97
 **133**	100	87	 **137**	40 (44)[b]	47 (60)[b]
 **134**	96	87			

[a] A solution of imine (1 mmol) and catalyst **117** (0.01 ~ 0.1 mmol) in CH_2Cl_2 (0.5 mL) was cooled to 0 ºC and $HSiCl_3$ (2 mmol) was added, and then the mixture was stirred for 4 h at 0 ºC; [b] Reduction was performed for 8 h at 10 mol % catalyst for data in parentheses.

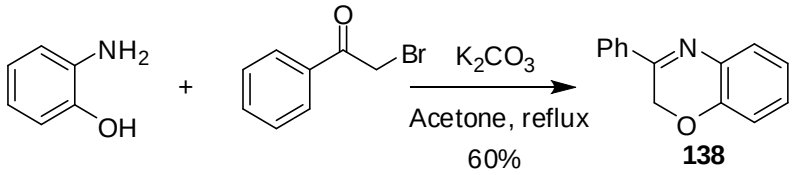
A control experiment was performed in order to rationalise why the *N*-3-pyridinylimine **130** was reduced with poor enantioselectivity and low yield (Scheme 54). A mixture of amine

130 and **125** was reduced with 10 mol% catalyst. Low conversion (25%) for reduction of *N*-3-pyridinylimine **130** was observed with 63% ee, while imine **125** was reduced completely in 90% ee. Therefore, the poor enantioselectivity obtained when using imine **130** as a substrate was not attributable to it acting as a competitive catalyst, although the possibility of it reacting in an intramolecular fashion cannot be ruled out. The low yield perhaps could be attributable to coordination with trichlorosilane removing it from reaction since it is known that pyridine derivatives with trichlorosilane can form low solubility complexes.[80]



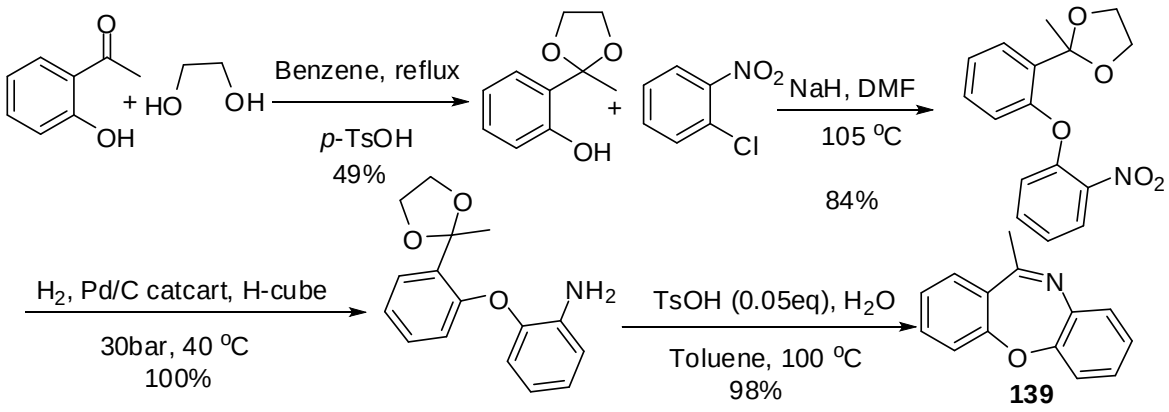
Scheme 54

To determine whether the imine geometry was important, a series of geometrically constrained substrates were prepared. Cyclic imine **138** was successfully prepared by condensation of 2-aminophenol and 2-bromoacetophenone in reflux acetone with potassium carbonate in 60% yield (Scheme 55).



Scheme 55

The seven-membered ring imine **139** was synthesized from *o*-hydroxy-acetophenone in 4 steps (Scheme 56). It should be mentioned that the protection of the carbonyl group of *o*-hydroxyacetophenone was necessary for the following S_NAr reaction with *o*-chloronitrobenzene, otherwise a C-arylation product **140** formed through a Smiles-type rearrangement (Figure 5).[81]



Scheme 56

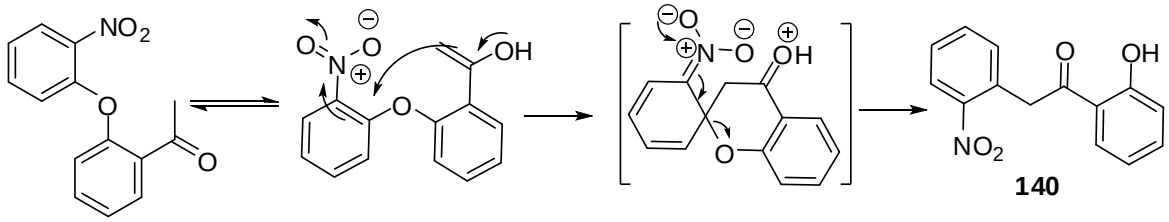
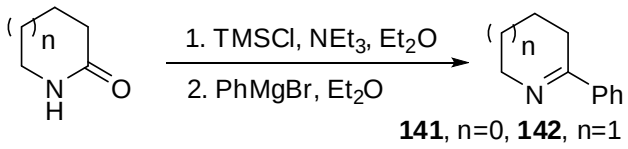


Figure 5

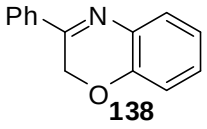
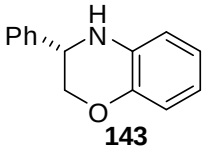
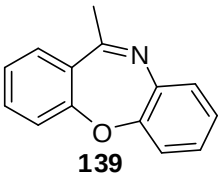
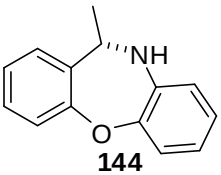
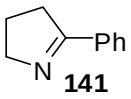
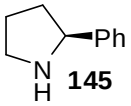
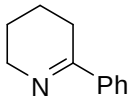
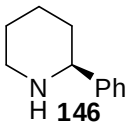
Cyclic imines **141** and **142** were prepared according to known procedures reported in the literature (Scheme 57**)**.[82]



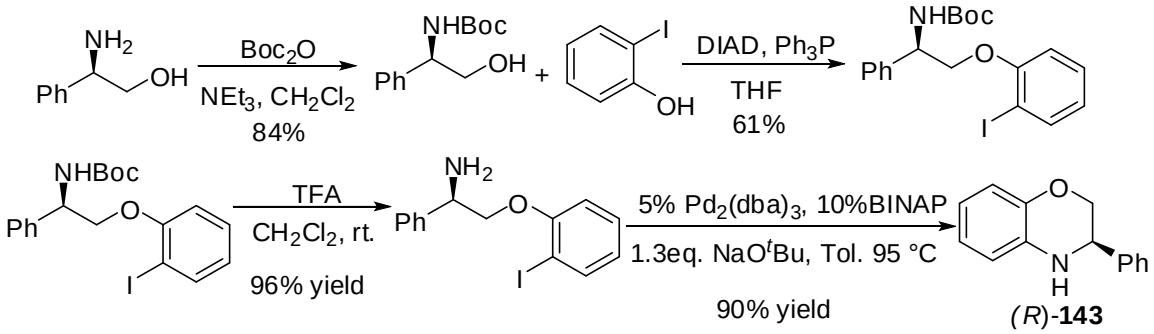
Scheme 57

The asymmetric reduction of these cyclic imines was then tested (Table 3). *cis*-Imine **139** was reduced in 86% conversion and 99% ee, however, under the same conditions only 26% of *trans*-imine **138** was reduced in 21% ee. Amines **145** and **146** were isolated in 81% yield, 82% ee and 53% yield, 73% ee, respectively, after reduction of *trans*-imines **141** and **142**. The absolute configuration of amine **144** was assigned to (*S*) by X-ray crystal analysis of the salt with (1*S*)-(+)-camphor-10-sulfonic acid (see Appendix 1). The configuration of amines **145** and **146** was confirmed to be (*S)* by comparison of the specific rotation with compounds of known configuration. Amine **143** was confirmed as (*S*) by comparing the retention time on HPLC with the optically pure amine (*R*)-**143** prepared from (*R*)-2-phenylglycinol (Scheme 58).

Table 3: Asymmetric reduction of cyclic imines

Entry	Imine	Amine	Conv. (%)	Ee (%)
1[a]	 **138**	 **143**	26	21
2[a]	 **139**	 **144**	86	99
3[b]	 **141**	 **145**	81[c]	82
4[b]	 **142**	 **146**	53[c]	73

[a] 1.2 mL of CH_2Cl_2, 1 mol% **117**, 2 eq. $HSiCl_3$, 4 h 0 °C; [b] 1 mL of CH_2Cl_2, 1 mol% **117**, 2 eq. $HSiCl_3$, 12 h 0 °C; [c] Isolated yield.

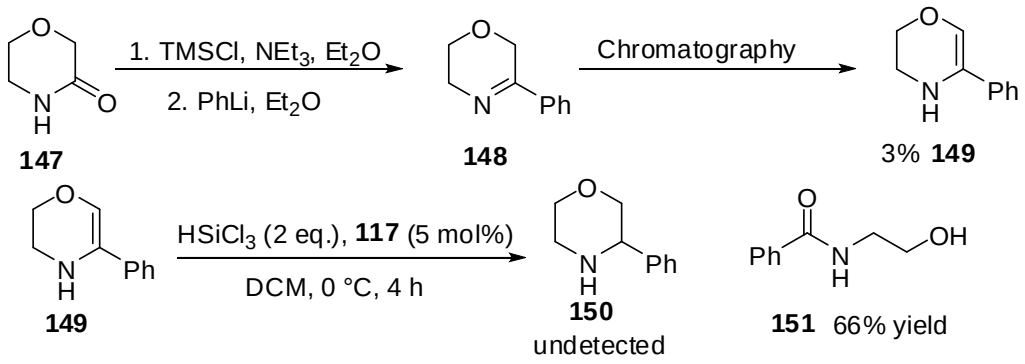


Scheme 58

It was quite interesting that *trans* cyclic imine **138** resulted in the opposite stereoselectivity compared to the *trans* cyclic imines **141**, **142** and acyclic imines **124-130** (attention: Cahn-Ingold-Prelog priority changes). The opposite selectivity of an analogue of imine **148** compared to acyclic imines was also observed using catalyst **117** for this process reported by Malkov and co-workers, although a wrong configuration was assigned in their paper.[83] It is notable that the reduction of *cis* cyclic imine **139** also shows the same stereoselectivity as the *trans* cyclic imines **141**, **142** and *trans* acyclic imines **124-130**, which could be a result of locked conformation of the fused rings. It is therefore likely that the stereoselectivity is related to the reactive conformation of the imine.

The opposite selectivity of *trans*-imine **148** may have been as a consequence of the fused

benzene ring since both *trans*-imine **141** and **142** have the same selectivity with acyclic imines **124**-**130**. Therefore, preparation of imine **148** was attempted by the procedure for imines **141** and **142** (Scheme 59). Imine **148** did form according to the ^{1}H NMR spectrum of the crude product. However, after purification by chromatography, only enamine **149** was isolated in 3% yield. This was then used for the reduction and unexpected amide **151** was isolated in 66% yield instead of amine **150**, with no trace amount of expected product **150** detected. But it is not clear how amide **151** was formed.



Scheme 59

Similar to the reduction of *N*-3-pyridinylimine **130**, a suspension was also observed after addition of trichlorosilane in the reduction of imine **141** and this suspension disappeared after stirring for 9 h at 0 °C. The solid was proposed to be an imine-trichlorosilane pentacoordinate or hexacoordinate complex (Figure 6).[80] Sun also explored the reduction of imine **141** with trichlorosilane using chiral sulfonamide catalysts, however, imine **141** was totally inactive and no explanation was disclosed.[62b]

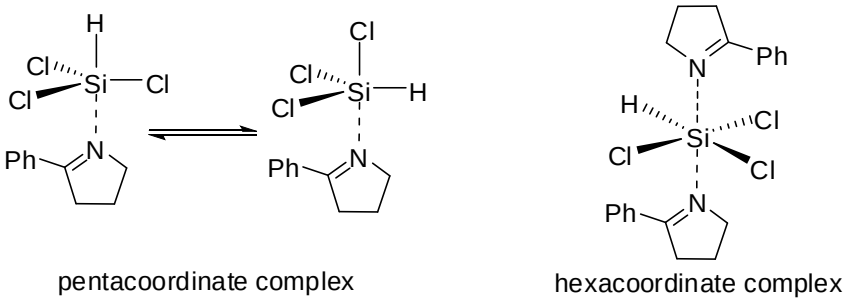
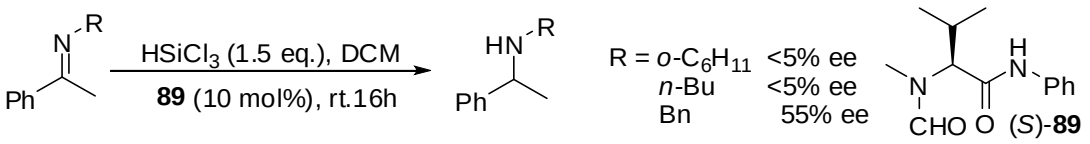


Figure 6: Proposed complexes formed from trichlorosilane and imine **151**

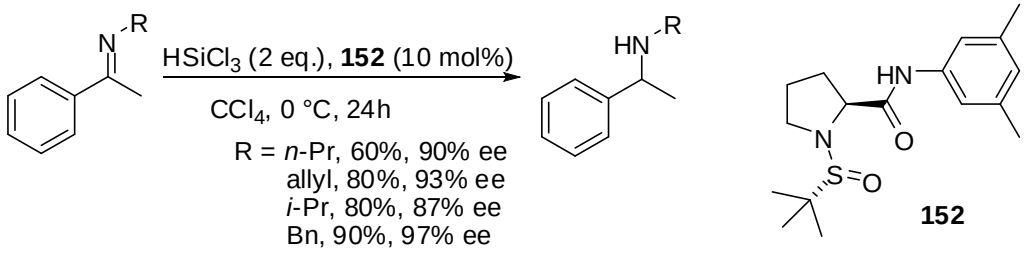
2.4 Asymmetric reduction of *N*-alkyl ketimines with trichlorosilane

There are many chiral amines used as therapeutic drugs possessing one or two alkyl groups on the nitrogen atom and thus highly enantioselective reduction of *N*-alkyl ketimines could provide a straight-forward pathway to this type of chiral amine, circumventing *N*-deprotection and *N*-alkylation steps. Although reduction of imines with trichlorosilane catalysed by an organic Lewis base has been achieved with good to excellent enantioselectivities and yields, there are only a few reports exploiting *N*-alkyl ketimine substrates.[64,72] The first reported example of reduction of *N*-alkyl ketimines with trichlorosilane used formamide (*S*)-**89** as a catalyst by Malkov and coworkers, however, the products were obtained with low enantioselectivity (Scheme 60).[64]



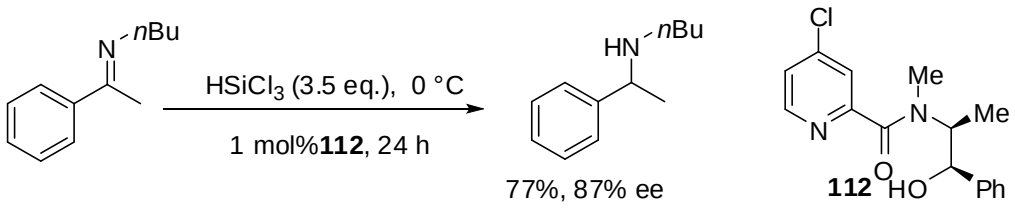
Scheme 60

In 2008, Sun made a breakthrough with a catalyst **152** that reduced a number of *N*-benzyl, allyl and alkyl imines with high enantioselectivities and yields (Scheme 61). [84]



Scheme 61

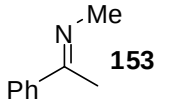
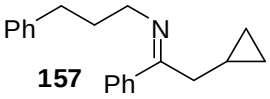
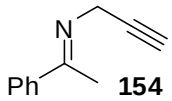
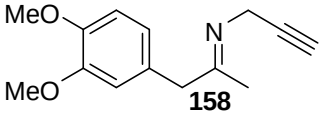
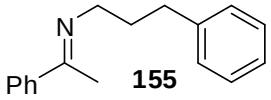
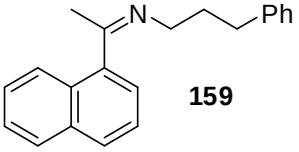
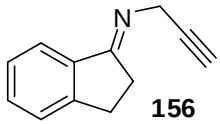
Benaglia recently disclosed that 4-chloropicolinic acid derivative **112** can also catalyse the reduction of the *N*-butyl ketimine of acetophenone in good yield and enantioselectivity at low catalyst loading but only this one substrate was tested (Scheme 62).[72]



Scheme 62

Catalyst **117** has already shown high catalytic efficiency in the reduction of *N*-aryl ketimines. The potential utility of catalyst **117** for the asymmetric reduction of *N*-alkyl ketimines with trichlorosilane was examined. The *N*-alkyl ketimines were prepared from the corresponding ketones and amines using molecular sieves to trap the water (method A) or under Dean-Stark conditions with a catalytic amount of *p*-TsOH (method B) and were isolated as isomeric mixtures of *trans* and *cis* imines by distillation or crystallization (Table 4).

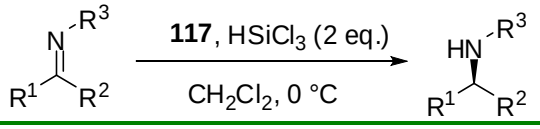
Table 4: Preparation of *N*-alkyl ketimines[a]

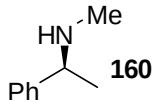
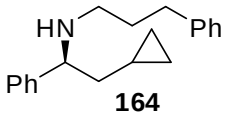
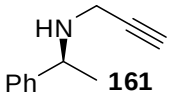
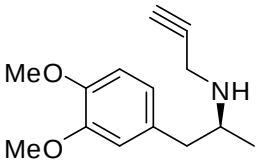
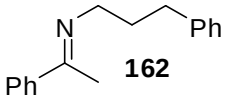
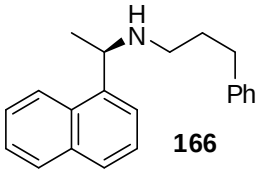
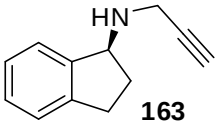
Imine	Isomer ratio	Yield % (method)	Imine	Isomer ratio	Yield % (method)
 **153**	16:1	77(A)	 **157**	3:2	61(B)
 **154**	10:1	45(A)	 **158**	5:1	100(A)
 **155**	2:1	17(A)	 **159**	3:1	47(B)
 **156**	1:0	47(A)			

[a] Method A: A mixture of ketone (50 mmol), amine (60 mmol) and 4Å MS (20 g) in toluene (40 mL) stirred at room temperature for 24 hours. [b] Method B: A mixture of ketone (10 mmol), amine (1.1 ~ 1.3 eq.) and *p*-toluene sulfonic acid (0.05 eq.) in toluene (50 mL) was heated at reflux under Dean-Stark condition for 24 hours.

Most of *N*-alkyl ketimines were reduced smoothly under the standard conditions (Table 5). The *N*-alkyl ketimines derived from acetophenone were reduced in high yield and reasonable enantioselectivity and the ee was slightly improved when increasing catalyst loading from 1 to 10 mol% (amines **160**-**162**). The amine **163** was isolated in high enantioselectivity (88% ee) but only moderate yield, even if the reaction time was prolonged to 24 h at a 10 mol% catalyst loading (Table 5).

Table 5 : Asymmetric reduction of *N*-alkyl ketimines[a]



Amine	Cat. loading	Time	Yield (ee)%	Amine	Cat. loading	Time	Yield (ee)%
 **160**	1%	4 h	93 (67)	 **164**	1%	8 h	67 (56)
	10%	4 h	89 (77)				
 **161**	1%	4 h	60 (90)	 **165**	1%	8 h	77 (53)
	1%	8 h	87 (91)		10%	8 h	73 (49)
 **162**	1%	8 h	89 (79)	 **166**	1%	8 h	8[b] (23)
	10%	8 h	94 (85)		10%	24 h	40 (50)
 **163**	1%	4 h	9 (69)				
	10%	24 h	44 (88)				

[a] A solution of imine (1 mmol) and catalyst **117** (0.01 ~ 0.1 mmol) in CH_2Cl_2 (0.5 mL) was cooled to 0 ºC and $HSiCl_3$ (2 mmol) was added, and then the mixture was stirred at 0 ºC; [b] Conversion based on integration of appropriate signals in the ^{1}H NMR spectrum.

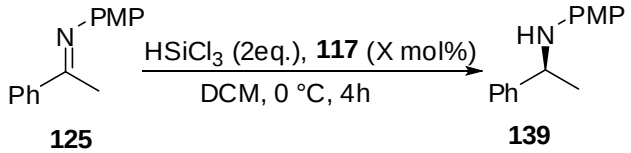
Amines **164-165** were obtained in moderate enantioselectivity, which could be attributable to less steric differences of ketimines **157-158**. Imine **159** derived from 1-acetonaphthalene was reduced to give amine **166** in both low yield and poor enantioselectivity, which could be a result of *peri*-interaction in naphthalene derivatives.

2.5 Investigations of the scalability and solvent influence

After demonstrating catalyst **117** to be an excellent catalyst for the reduction of certain types of both *N*-aryl and *N*-alkyl imines, attention was then turn to the scalability of the process. The reduction of imine **125** can be performed at a 0.02 mol scale in dichloromethane with a complete conversion after 10 hours at 1 mol% catalyst loading, which yielded the amine **139** without any decrease in term of enantioselectivity compared to a 1 mmol scale (Table 6, entry 1-2). Toluene was proven to be a suitable solvent, albeit with slightly lower

enantioselectivity (entry 3). Finally, it was found that the catalyst loading can be decreased to 0.1 mol% with no obvious decrease in term of enantioselectivity (entry 4). Acetonitrile was also a suitable solvent although a slightly lower enantioselectivity was observed (entry 5-7).

Table 6: Scale-up investigation of the reduction of imine **125**

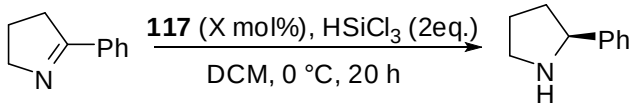


125 **139**

Entry	Solvent (mL)	Cat. loading	Scale	Time	Yield (%)	Ee (%)
1	DCM (0.5)	1 %	1 mmol	4 h	100	90
2	DCM (10)	1 %	20 mmol	10 h	95	91
3	Toluene (20)	1 %	20 mmol	8 h	98	85
4	DCM (5)	0.1 %	10 mmol	4 h	74	86
5	CH_3CN (1)	1 %	1 mmol	4 h	99	84
6	CH_3CN (0.5)/DCM (0.5)	1 %	1 mmol	4 h	96	88
7	CH_3CN (0.5)/toluene (0.5)	1 %	1 mmol	4 h	95	88

The scalability of reduction of cyclic imine **141** was then explored at a 10 mmol scale (Table 7). The concentration of substrate had a significant effect on the enantioselectivity. As mentioned earlier, a suspension was formed upon addition of trichlorosilane when smaller amounts of dichloromethane (<10 mL) were used, but the suspension disappeared after stirring for 2-4 hours. When the amount of dichloromethane was increased to 20 mL, no suspension was observed. With a more diluted substrate, a higher enantioselectivity was also observed (entry 1-3). Improved enantioselectivity was observed when increasing the catalyst loading (entry 2 vs 4). Gratifying, the higher enantioselectivity can be also achieved by slow addition of a solution of imine **141** (10 mmol in 10 mL dichloromethane) at a rate of 2 mL/h using a syringe pump at a 1 mol% catalyst loading.

Table 7: Scale-up investigation of the reduction of imine **151**

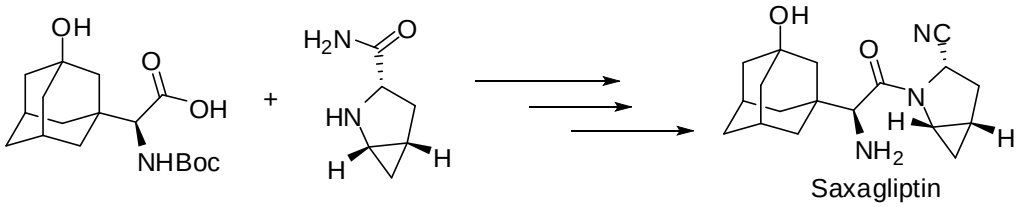


141 **145**

Entry	DCM (mL)	Cat. Loading (%)	Conversion (%)	Ee %
1	5	1	>95	65
2	10	1	>95	72
3	20	1	>95	80
4	10	10	>95	86
5	10+10	1	>95	85

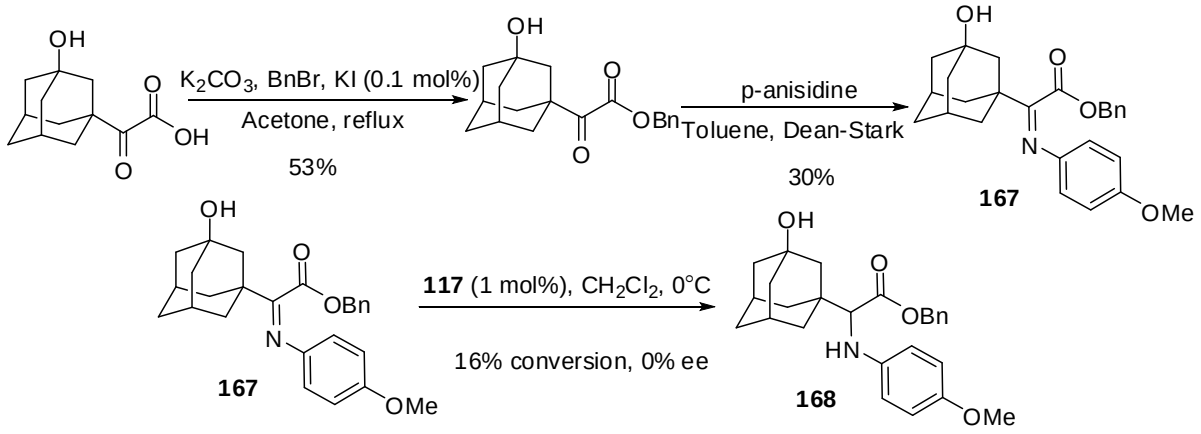
2.6 Applications toward the synthesis of precursor of Saxagliptin

Saxagliptin, a new anti-diabetic drug approved as the trade name Onglyza by FDA for treatment of type II diabetes mellitus, is produced industrially from *N*-Boc-3-hydroxyadamantylglycine and methanoprolineamide, both of these being optically pure amino acid derivatives (Scheme 63).[85] The possibility of preparing the adamantyl α-amino acid by asymmetric reduction of the corresponding α-imino ester with trichlorosilane using catalyst **117** was explored.



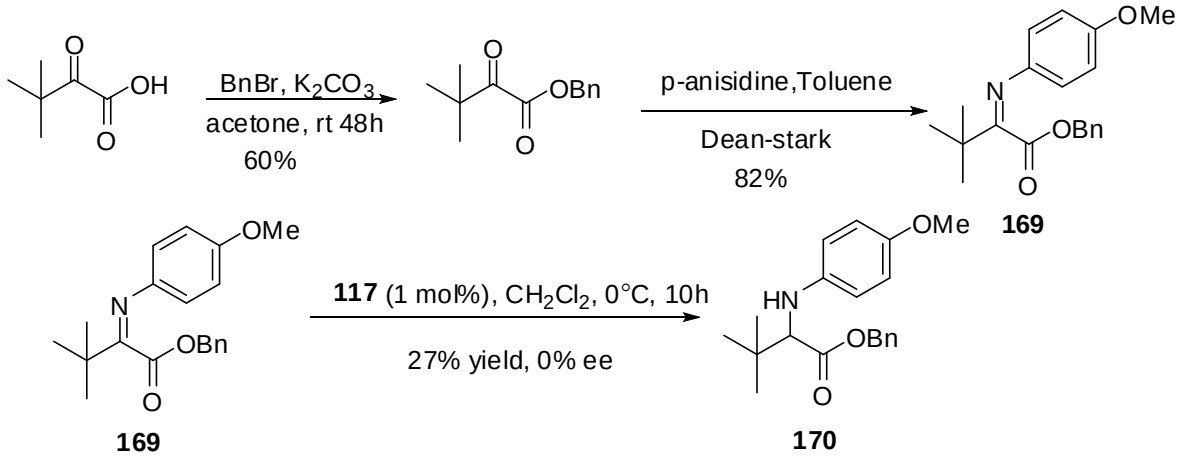
Scheme 63

α-Imino ester **177** was prepared from the corresponding keto acid in two steps in acceptable yield (Scheme 64). Unfortunately the reduction of α-imino ester **167** offered the α-amino ester **168** in a 16% conversion and without any optical activity.



Scheme 64

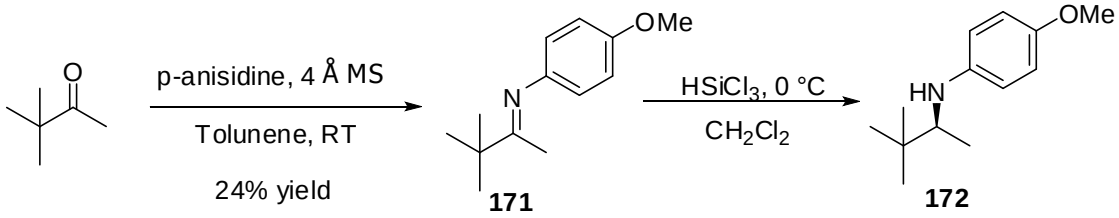
α-Imino ester **169** was also prepared using a similar general procedure as for the preparation of α-imino ester **167** in good yield (Scheme 65). As in the case of the reduction of α-imino ester **167**, low conversion and no asymmetric induction were observed in the reduction of α-imino ester **169**.



Scheme 65

The absence of asymmetric induction in these reductions could be attributable to racemisation during basic workup or from the steric hindrance which could impede the access to the catalyst-activated trichlorosilane. In order to examine this issue, the bulky imine **171** was prepared and used as a substrate (Scheme 66). As expected, the α-amino ester **172** was observed in low enantioselectivity (28% ee). The absolute configuration of **172** was presumed to *S* isomer by analog. Since this is unlikely to undergo racemisation during the

basic workup, steric hindrance is probably the main reason behind the low selectivity and yield observed.



1 mol% **117**, 4h, 22% yield and 28% ee
10 mol% **117**, 21h, 74% yield and 33% ee

Scheme 66

2.7 Conclusions and future work

A scalable process for the preparation of catalyst **117** was developed in four steps from commercially available L-proline without chromatography. Asymmetric reduction of both *N*-aryl and *N*-alkyl ketimines can be performed using trichlorosilane catalyzed by **117** at low catalyst loading. The scalability of this reducing system was demonstrated by the reduction of acyclic imine **125** and cyclic imine **141**, although the reduction of sterically bulky α-imino esters was inefficient. Future work will focus on employing this methodology to develop processes for the preparation of some pharmaceutically important chiral amine intermediates.

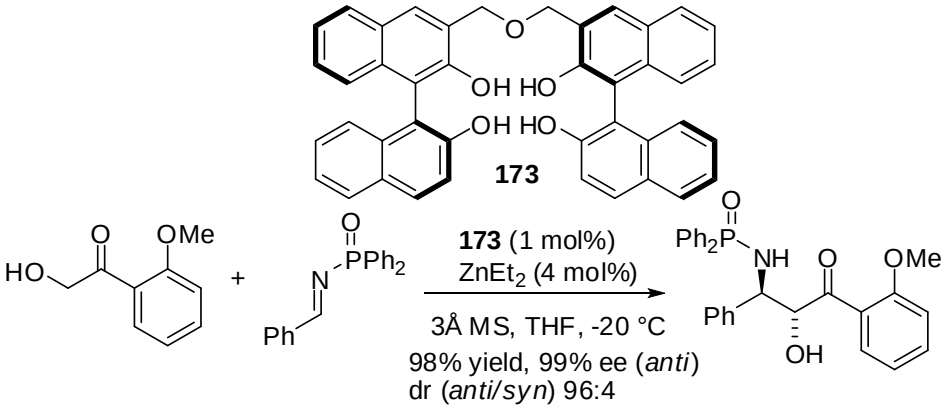
3 Asymmetric reductions of β-enamino esters

3.1 Background

Optically active β-amino acids and their derivatives are common structures in Nature and are also widely used as building blocks for the synthesis of β-lactams and other biologically active compounds.[86] It is not surprising then that much interest has focused on the development of methodologies for the preparation of enantioenriched β-amino acids and their derivatives.[87] The catalytic asymmetric synthesis of β-amino acids and their derivatives using both transition metal catalysts and organocatalysts have been developed in recent decades.

3.1.1 Asymmetric C-C bond-forming reactions

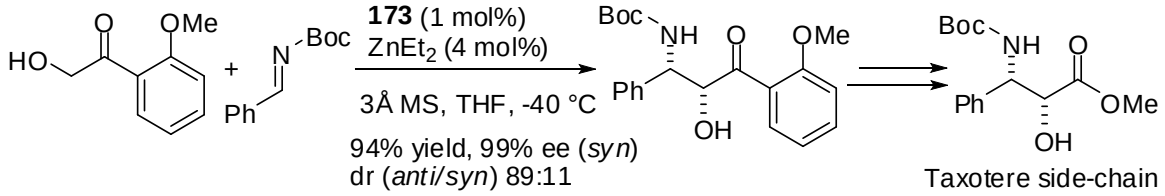
The asymmetric C-C bond-forming reaction to form the bond between α-carbon and β-carbon atoms are important methods to synthesize β-amino acids.[88] Asymmetric Mannich reactions have been widely investigated to prepare chiral β-amino carbonyl derivatives.[89] Shibasaki and co-workers reported a catalyst system formed *in situ* from diethylzinc and (*S*,*S*)-linked BINOL ligand **173** for the direct addition of α-hydroxyl aromatic ketones to *N*-diphenylphosphinoyl imines (Scheme 67).[90] In the presence of 1 mol% of the ligand, a range of *N*-protected α-hydroxyl-β-amino ketones were isolated in excellent yield and enantioselectivity with high *anti*-selectivity.



Scheme 67

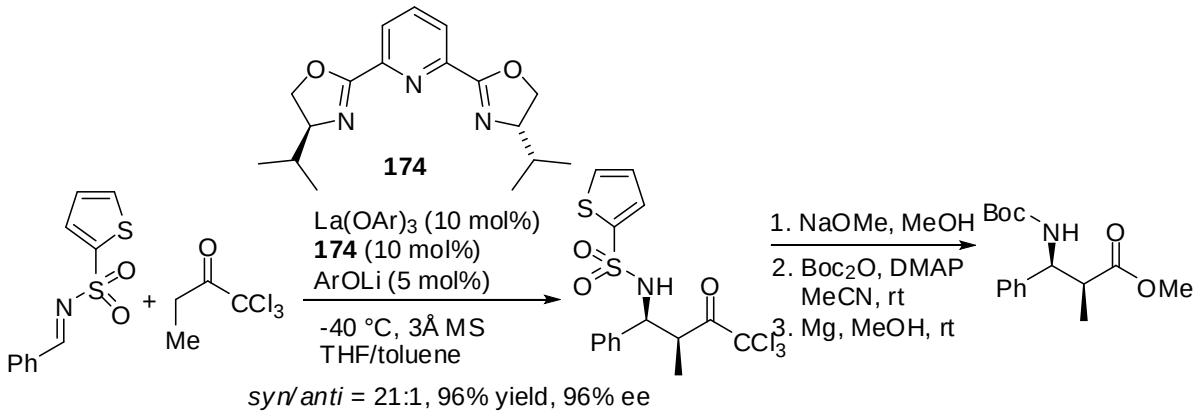
The same authors later demonstrated that catalyst **173** produced highly *syn*-selective

products when *N*-Boc-imines were used (Scheme 68).[91] Subsequently, Baeyer-Villiger oxidation of the products afforded the α-hydroxyl-β-amino esters, which form the basis of important targets, such as the Taxotere side-chain.



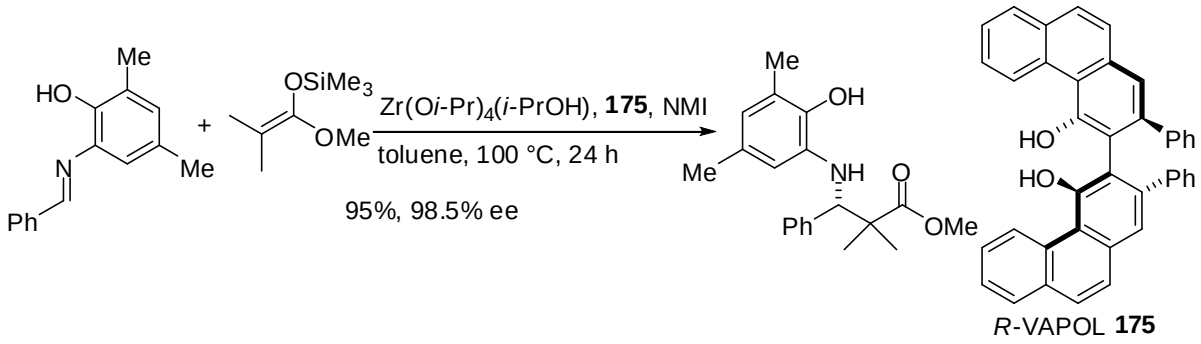
Scheme 68

Shibasaki and co-workers disclosed that the reaction of trichloromethyl alkyl ketones and *N*-thienylsulfonyl imines can be promoted by La(OAr)$_3$-pybox **174** complex to produce the corresponding β-amino trichloromethylketones in excellent yield and stereoselectivity with high *syn*-selectivity (Scheme 69).[92] The β-amino trichloromethylketones can be transformed into β-amino-α-substituted esters without epimerization by hydrolysis and subsequent protecting group interconversion.



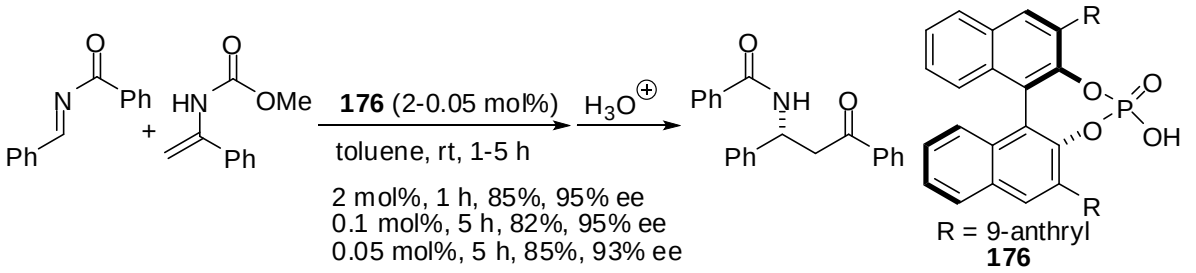
Scheme 69

The addition of silyl enol ethers to imines has also been studied.[93] For example, Wulff and co-workers reported the highly stereoselective addition of silyl ketene acetal **175** to a range of aromatic imines with 2 mol% catalyst which was pre-generated by the combination of Zr(*i*-PrO)$_4$·*i*-PrOH, *R*-VAPOL and *N*-methyl imidazole (Scheme 70).[94]



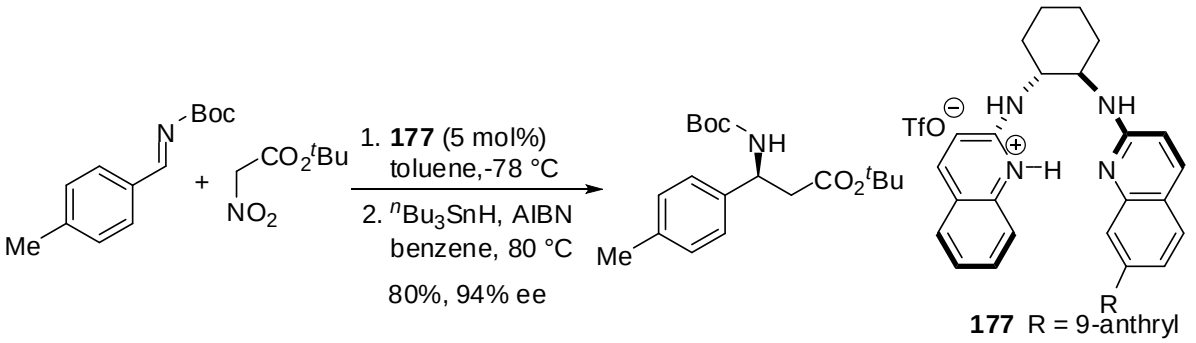
Scheme 70

Proline-type organocatalysts have also been shown to promote Mannich reaction of aldehydes and imines, the product of which are the precursors of β-amino acids (Scheme 13, page 9). Chiral Brønsted acids can be used as catalysts for highly asymmetric Mannich reactions. For example, Terada has used the highly steric-hindered phosphoric acid **176** to affect the addition of enecarbamates to imines at a very low catalyst loading (Scheme 71).[95]



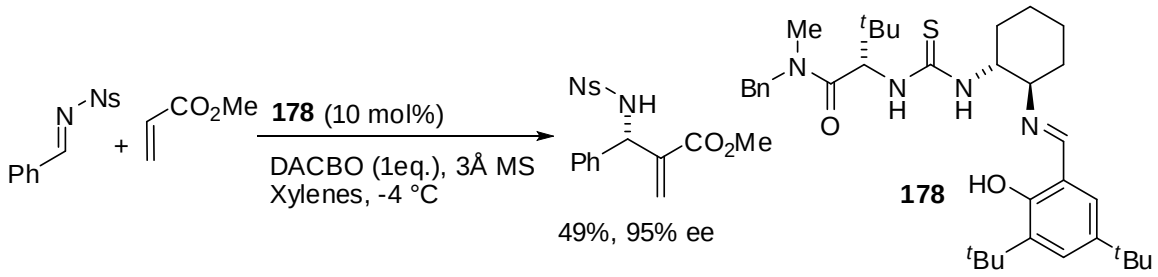
Scheme 71

Johnston *et al*. demonstrated that enantioselective synthesis of β-phenyl alanine derivatives can be achieved by addition of nitroacetic acid esters to *N*-Boc imines under the catalysis of 5 mol% catalyst **177**, followed by denitration (Scheme 72).[96]



Scheme 72

The dual activation system consisting of DABCO and thiourea **178** has been used for highly enantioselective asymmetric aza-Morita-Baylis-Hillman reaction between *N*-nosyl imines and methyl acrylate albeit in moderate yield by Jacobsen and co-workers (Scheme 73).[97]

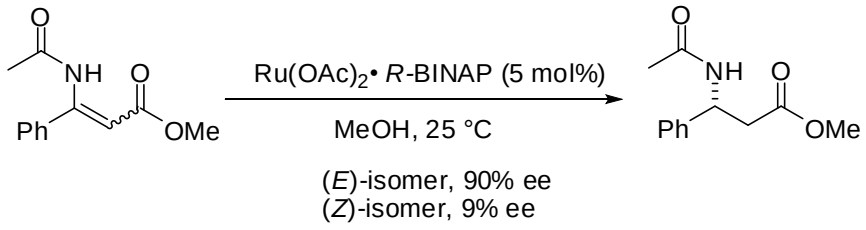


Scheme 73

3.1.2 Asymmetric reduction of β-enamino esters

Asymmetric catalytic reduction of β-enamino esters provides a direct route to access β-amino acid derivatives. Strategies employing transition metal-catalyzed asymmetric hydrogenation and organocatalytic hydride-transfer have been extensively investigated for the asymmetric catalytic reduction of β-enamino esters.[87]

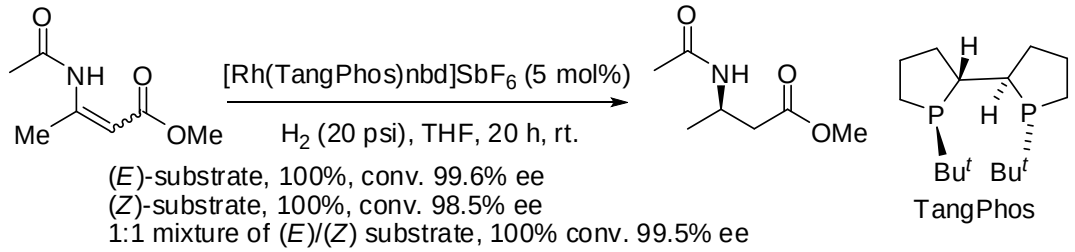
Noyori *et al*. reported the highly enantioselective hydrogenation of *N*-acyl-β-enamino esters using a catalyst system of $Ru(AcO)_2$ and *R*-BINAP.[98] Although high enantioselectivities can be achieved in the hydrogenation of (*E*)-*N*-acyl-β-enamino esters, unsatisfactory results were obtained in the hydrogenation of (*Z*)-*N*-acyl-β-enamino esters (Scheme 74). Similar results were produced using related catalyst systems.[99]



Scheme 74

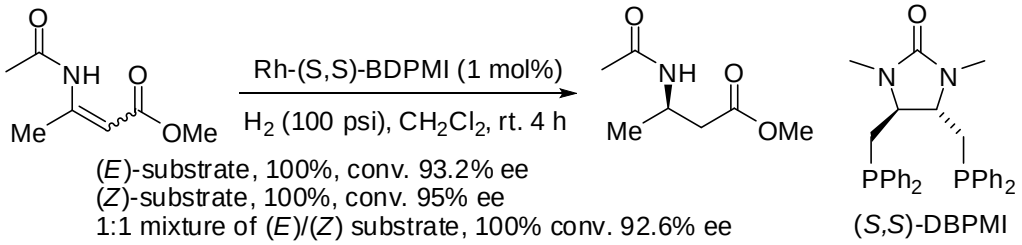
Zhang *et al*. reported that highly enantiopure β-amino esters can be obtained by asymmetric hydrogenation of both (*Z*)- and (*E*)-*N*-acyl-β-enamino esters or a mixture of these two isomers using a Rh-TangPhos catalyst system (Scheme 75).[100] The same group later

extended this catalyst system to the asymmetric hydrogenation of *N*-aryl β-enamino esters.[101]



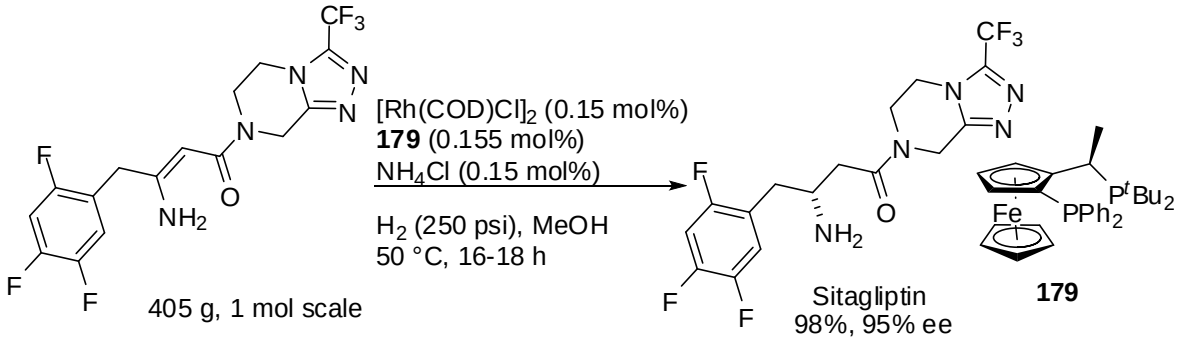
Scheme 75

The Rh-Me-BDPMI complex was also reported to be an effective catalyst for the hydrogenation of both (*Z*)- and (*E*)-*N*-acyl-β-enamino esters by Lee and co-workers (Scheme 76).[102]



Scheme 76

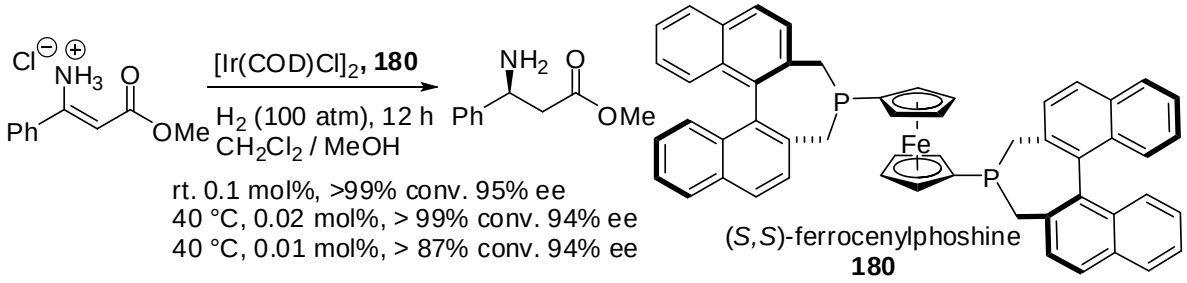
Hsiao *et al.* disclosed that unprotected β-enamino esters can also be hydrogenated in high yield and enantioselectivity using Josiphos (**179**)-Rh complex as catalyst.[103] Recently, this catalyst system has been successfully applied to the synthesis of Sitagliptin on a mole scale (Scheme 77).[104]



Scheme 77

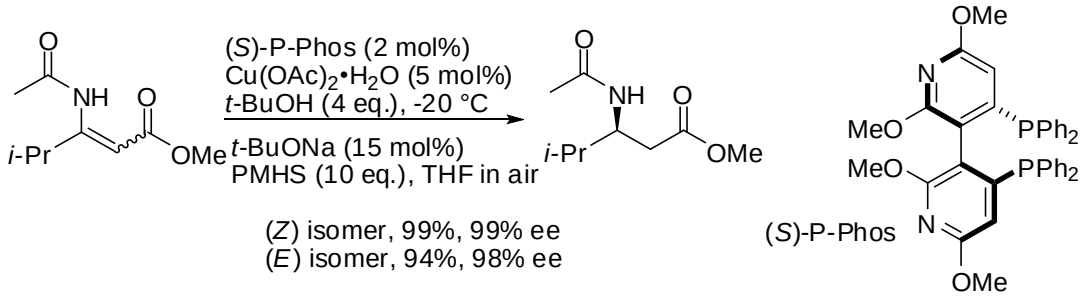
More recently, Zhang and co-workers reported the asymmetric hydrogenation of a variety of enamino hydrochloride esters can also be achieved in good to excellent enantioselectivity

using the iridium-ferrocenylphoshine **180** catalyst system.[105] High enantioselectivity still can be obtained at 0.01 mol% catalyst loading albeit with slightly lower conversion (Scheme 78).



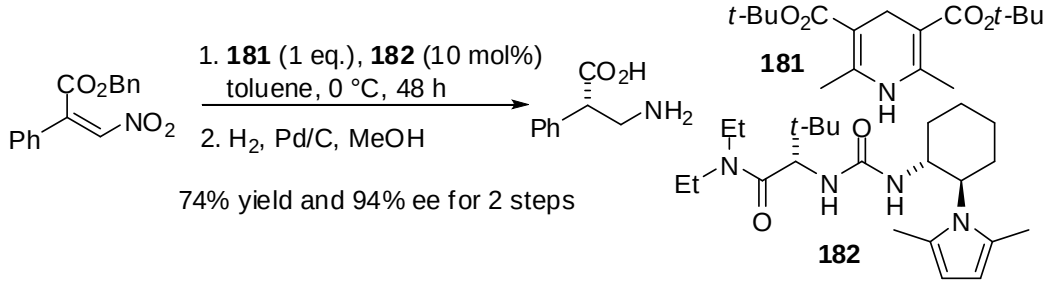
Scheme 78

A catalyst system of $Cu(OAc)_2$ and enantiopure (*S*)-P-phos was used in combination with PMHS (polymethylhydrosiloxane) as hydride source for the asymmetric reduction of *N*-acyl-β-enamino esters. Both (*Z*)- and (*E*)-isomers were reduced in good yield and enantioselectivity (Scheme 79).[106]



Scheme 79

List and co-workers reported that β-amino acid precursors can be synthesized by transfer hydrogenation of nitroalkenes with a Hantzsch ester catalyzed by thiourea **182.**[107] High enantioselectivities were obtained from both (*E*)-alkene and (*Z*)-alkene, but with opposite stereoselectivity. Hydrogenation of the β-nitro ester in the presence of Pd/C directly affords the free β-amino acid (Scheme 80).

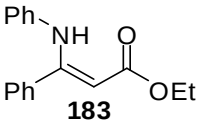
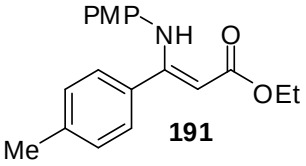
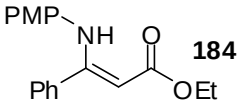
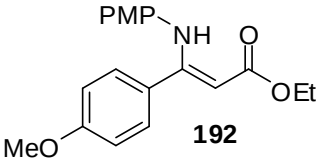
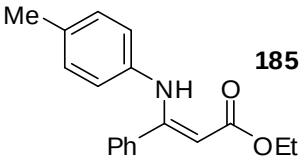
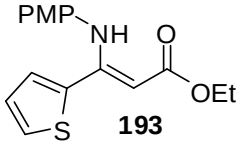
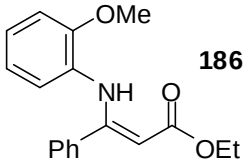
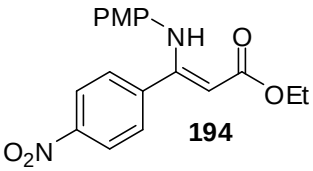
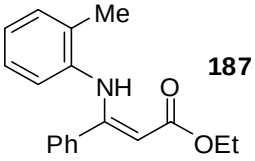
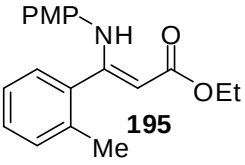
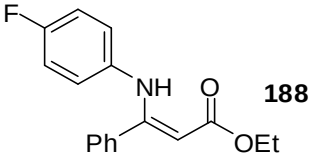
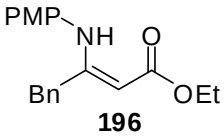
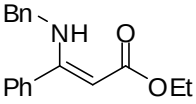
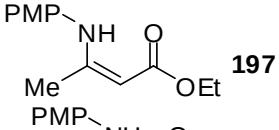
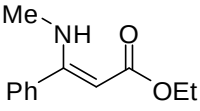
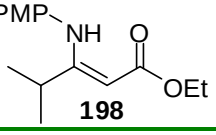


Scheme 80

3.2 Asymmetric reduction of β-enamino esters with trichlorosilane

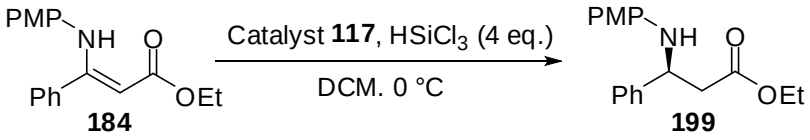
Asymmetric reduction of β-enamino esters with trichlorosilane catalysed by chiral Lewis bases has also been reported (see Chapter 1.24, page 17). In order to examine the activity of catalyst **117** in this respect, a range of *N*-aryl-β-enamino esters was prepared by condensation of the corresponding β-ketoester and amine or its acetate salt in the presence of a catalytic amount of *p*-TsOH at reflux in ethanol. Pure products were obtained by chromatography or recrystallisation (Table 8).

Table 8: Synthesis of β-enamino esters

β-Enamino esters	Yield %	β-Enamino esters	Yield %
 **183**	37	 **191**	41
 **184**	60	 **192**	50
 **185**	56	 **193**	26
 **186**	40	 **194**	82
 **187**	41	 **195**	11
 **188**	59	 **196**	56
 **189**	42	 **197**	66
 **190**	55	 **198**	42

The β-enamino ester **184** was used as a model substrate for the optimisation of reaction conditions (Table 9). The reaction was performed in dichloromethane at 0 °C at 10 mol% of **117**. With 1 eq. acetic acid or water as additives, the yields of product **199** were improved, but with serious erosion of enantioselectivity (entry 1-3). High yield is observed when 20% salicylic acid used as an additive but with low enantioselectivity (entry 4). Using 20% of benzoic acid and phenol as independent additives gave good enantioselectivity but unsatisfactory yield (entry 5-6). Further increasing the amount of benzoic acid additive to 30 mol% gave a drop in enantioselectivity (entry 7). Higher enantioselectivity was achieved when using 10 mol% of benzoic acid, however, the yield was not acceptable and could not be improved by prolonging the reaction time (entry 8-9). The highest enantioselectivity was achieved using 5 mol% of benzoic acid as an additive (half amount of catalyst loading), albeit in unsatisfactory yield (entry 10). The optimal conditions in term of both enantioselectivity and yield obtained were thus use of 20 mol% catalyst **117** and 10 mol% benzoic acid as additive. Using these conditions, product **199** was isolated in 76% yield and 91% ee after 10 h at 0 °C (entry 9). This represents the shortest reaction time in the literature for the reduction of β-enamino esters with trichlorosilane catalysed by Lewis bases.

Table 9: Optimisation for reduction of β-enamino ester **183**



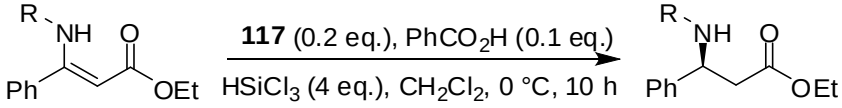
184 **199**

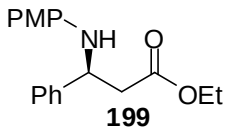
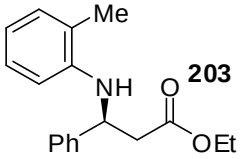
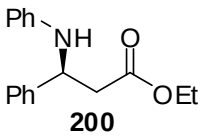
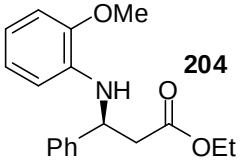
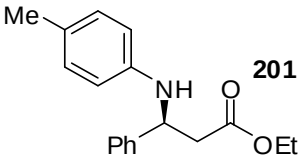
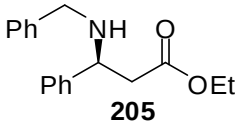
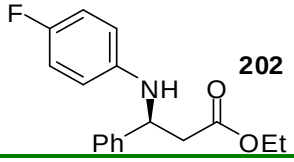
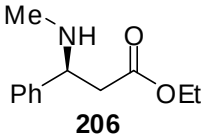
Entry	Additive	Reaction time	Yield %	Ee %
1	no	10h	55	84
2	AcOH, 100%	10h	93	42
3	H_2O, 100%	10h	74	51
4	Salicylic acid, 20%	10h	87	65
5	PhOH, 20%	10h	68	85
6	$PhCO_2H$, 20%	10h	70	83
7	$PhCO_2H$, 30%	10h	83	75
8	$PhCO_2H$, 10%	10h	60	88
9	$PhCO_2H$, 10%	24h	62	88
10	$PhCO_2H$, 5%	10h	58	91
11[a]	$PhCO_2H$, 10%	10h	76	91

[a] 20 mol% catalyst was used.

Under the optimised reaction conditions (Table 9, entry 11), a series of *N*-aryl phenyl enamino esters were used as substrates to evaluate the generality of this methodology (Table 10). Excellent enantioselectivity was obtained for most substrates, although slightly lower enantioselectivity was observed for the β-amino ester **202**, which has an electron-deficient aromatic ring attached to the nitrogen atom (71% ee). The catalyst system was found to be very sensitive to the steric properties of the substrates since reduction of *N*-2-methoxyphenyl enamino ester **186** exhibited a low reactivity and enantioselectivity compared to *N*-2-methylphenyl enamino **197** ester (β-amino ester **203** vs **204**). It was notable that *N*-alkyl β-enamino esters were suitable substrates, the reduction of which showed good reactivity and excellent enantioselectivity (β-amino esters **205** -**206**).

Table 10: Reduction of β-enamino esters

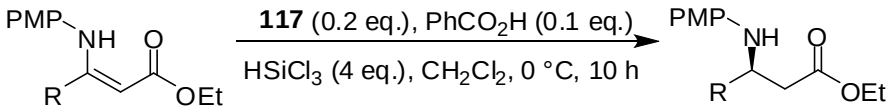


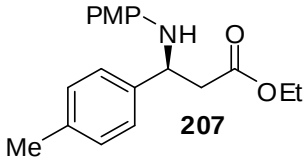
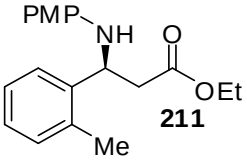
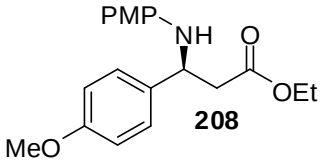
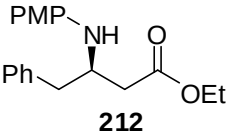
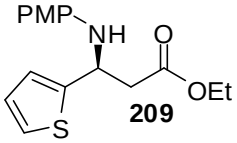
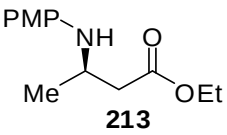
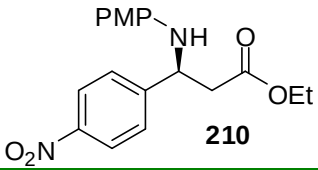
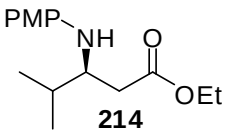
Product	Yield %	Ee %	Product	Yield %	Ee %
 **199**	76	91	 **203**	53	86
 **200**	64	85	 **204**	41	13
 **201**	69	87	 **205**	57	93
 **202**	59	71	 **206**	59	95

With the same reaction conditions (Table 9, entry 11), the reduction of a series of β-aryl/alkyl *N*-*p*-anisidine enamino esters was further explored (Table 11**)**. β-Aryl *N*-*p*-anisidine enamino esters bearing an electron-donating group were reduced with excellent enantioselectivity, although electron-deficient substrate **194** afforded the product in a slightly

lower yield and enantioselectivity (β-amino ester **210**). Reduction of the β-aryl enamino ester containing an *o*-methyl group gave a surprisingly low yield of product with poor enantioselectivity (β-amino ester **211**). Reduction of β-alkyl β-enamino esters afforded the products with low enantioselectivity (β-amino esters **212-214**).

Table 11: Reduction of *N*-*p*-anisolyl β-aryl or β-alkyl enamino esters



Product	Yield (%)	Ee (%)	Product	Yield (%)	Ee (%)
 **207**	75	92	 **211**	27	3
 **208**	70	91	 **212**	56	30
 **209**	66	90	 **213**	63	20
 **210**	50	82	 **214**	44	56

The mechanism of the process is not clear at present. It is likely that the enamino esters tautomerize to the corresponding imines in the acidic reaction environment and then reduced to the amino esters by trichlorosilane. The observation of low enantiopurity of β-amino ester **204** cannot be attributable to simple steric effects, since β-amino ester **203** was obtained in high ee (Table 10). It is perhaps more likely that intramolecular stabilization of the enamine occurs through interaction with the oxygen lone pair, limiting the imine/enamine equilibrium (Figure 7). In this enamine tautomeric form, unselective reduction then occurs. This proposal was in accordance with the observation that β-enamino ester **215** existing exclusively in enamine tautomeric form, was also reduced in good yield under the optimized conditions, but the reduction occurred in a racemic fashion (Scheme 81).

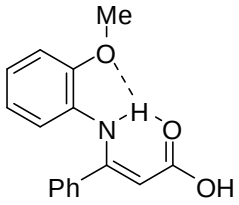
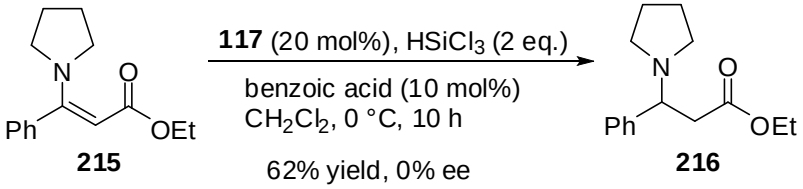


Figure 7: Stable tautomer of β-enamino ester **204**



Scheme 81

It seems that the conjugation of aromatic ring and double bond of enamine is required for the reduction since β-enamino ester **195** was only reduced to give β-amino ester **211** in fairly low yield and negligible enantioselectivity. In this case, β-enamino ester **195** could exist mainly in the frustrated conjugated conformation to reduce steric clashes between *o*-methyl group and the hydrogen or aromatic ring attached to the nitrogen atom (Figure 8).

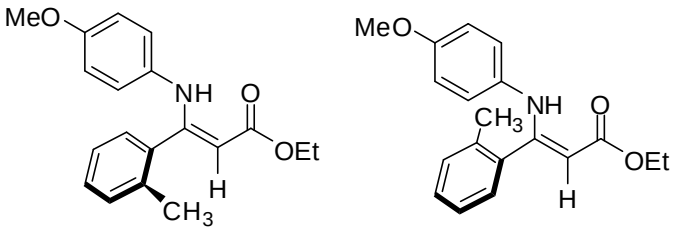


Figure 8: Frustrated conjugated confirmations of β-enamino ester **195**

β-Alkyl β-amino esters **212-214** obtained in low enantioselectivity could be a result of the smaller steric difference of the two alkyl groups compared to that of aryl and alkyl groups.

3.3 Conclusion and future work

In summary, the results obtained so far demonstrate that catalyst **117** can facilitate the reduction β-enamino esters with trichlorosilane with high enantioselectivity. It is notable that both *N*-aryl and *N*-alkyl substrates are suitable for the reduction with this catalytic system in high enantioselectivity although catalyst activity is not very efficient compared to the reduction of imines and high catalyst loading was necessary to achieve good results. Acidic

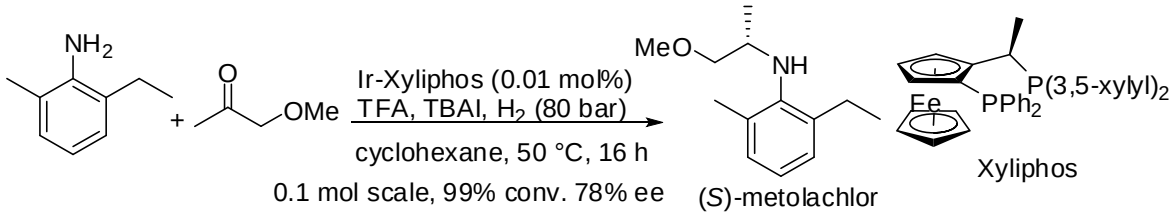
additives can accelerate the reduction, but a negative effect on enantioselectivity was observed when a large amount of additives was used. It is also important to note that the identification of the additives used depends greatly on the catalyst that is being used. Those additives that have been successful in the literature (one equivalent of H_2O or AcOH) were not very successful with catalyst **117**. Thus, although the methodology delivered the desired targets, better alternative strategies exist in the literature to access these compounds.

4. Asymmetric reductive amination of ketones

4.1 Background

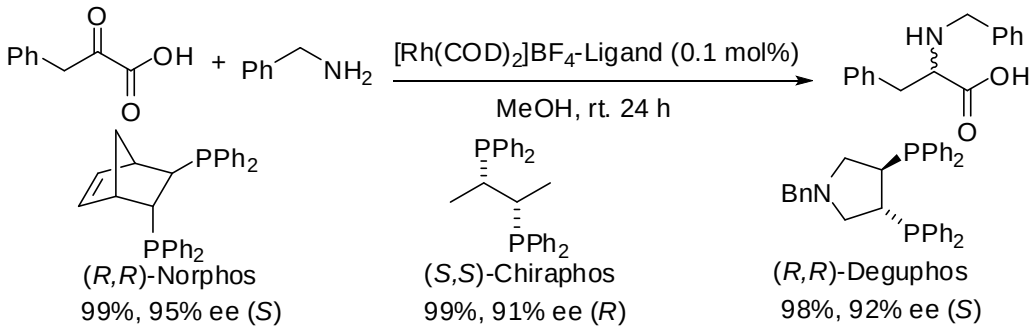
Asymmetric reduction of imines has proved to be an efficient route to access chiral amines, but can be hampered by the sometimes non-trivial preparation and stability of imine precursors, resulting in a low overall yield. Alternatively, asymmetric reductive amination of ketones provides a convenient, economical and time-efficient strategy by circumventing this problem. It is not surprising that direct asymmetric reductive amination of ketones has been investigated using both transition-metal catalytic hydrogenation and organocatalysed transfer hydrogenation with Hantzsch esters as hydride source.

Blaser *et al.* reported the first example of asymmetric reductive amination using Ir-Xyliphos complex as catalyst.[108] The synthesis of the herbicide (*S*)-metolachlor was achieved in good yield and ee by this process from methoxyacetone and 2-methyl-6-ethyl-aniline (Scheme 82).



Scheme 82

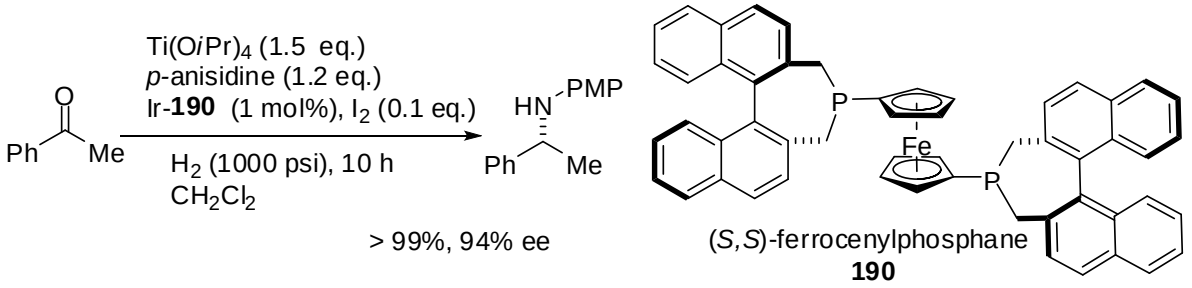
Börner reported the highly enantioselective reductive amination of keto-acids with benzylamine using Rh(I)-complexes as catalysts.[109] Three highly efficient P-ligands were obtained by high-throughput screening of 96 chiral ligands (Scheme 83).



Scheme 83

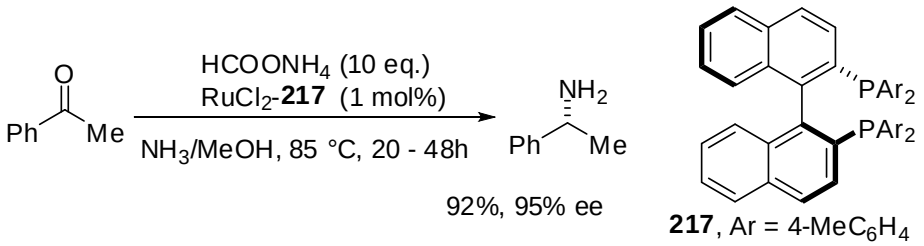
Zhang and co-workers reported the highly enantioselective reductive amination of aryl

ketones in the presence of Ti(O*i*Pr)$_4$ and iodine using a Ir-f-phosphane complex as catalyst (Scheme 84).[110]



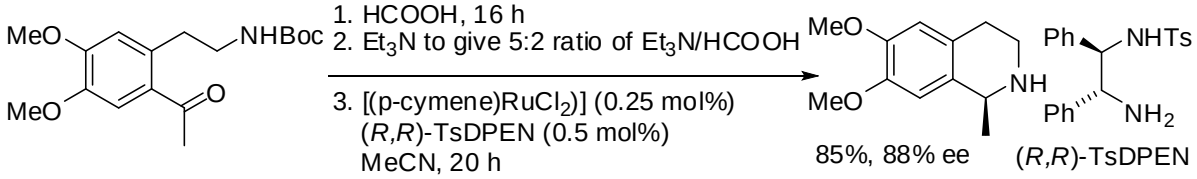
Scheme 84

Kadyrov reported the asymmetric hydrogen-transfer reductive amination of aryl ketones using ammonium formate as the hydrogen donor. Under optimal conditions, highly enantiopure primary amines were produced using 1 mol% of catalyst prepared *in situ* from $RuCl_2$ and tol-BINAP **217** (Scheme 85).[111]



Scheme 85

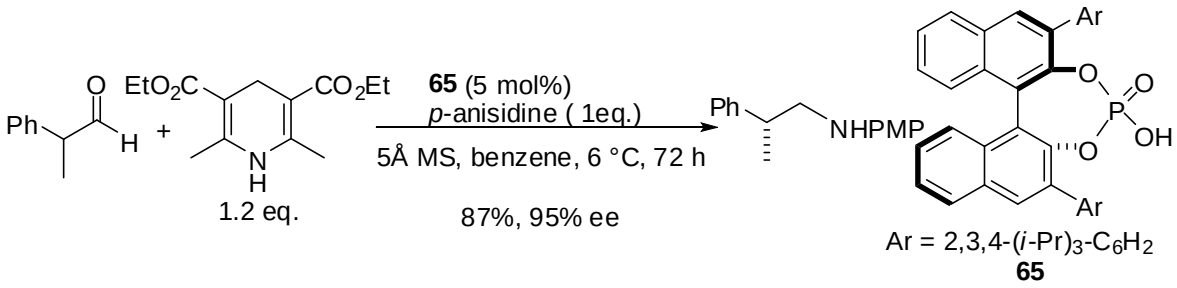
Wills and co-workers reported an intramolecular reductive amination to prepare cyclic amines under transfer hydrogenation conditions.[112] This process consisted of a sequence of deprotection, followed by formation and reduction of the imine (Scheme 86).



Scheme 86

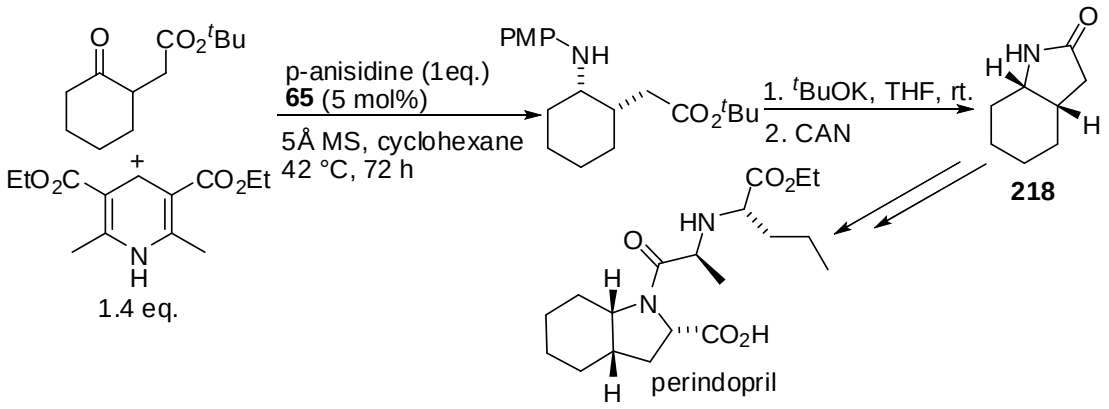
Asymmetric reductive amination of ketones has been investigated using Hantzsch esters as the hydrogen donor with chiral phosphoric acid catalysts. List and co-workers reported that

reductive amination of α-branched aldehydes with *p*-anisidine can give β-branched amines in high yield and enantioselectivity via a dynamic kinetic resolution process (Scheme 87).[113]



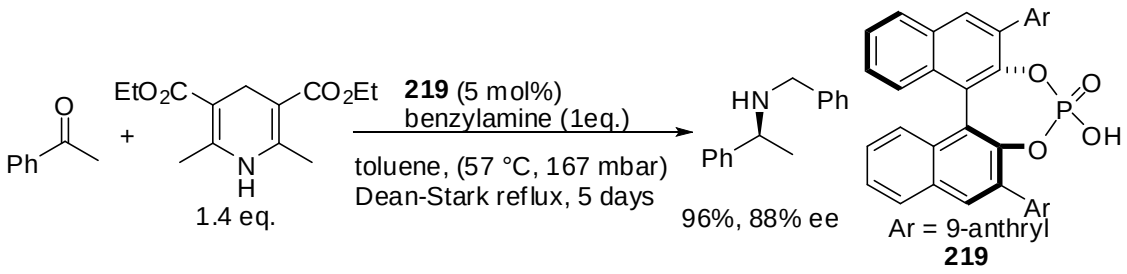
Scheme 87

This process was extended to reductive amination of α-branched cyclic ketones with *p*-anisidine using the same catalyst **65.**[114] The synthesis of a key intermediate lactam **218** for the synthesis of perindopril demonstrated the utility of this transformation (Scheme 88).



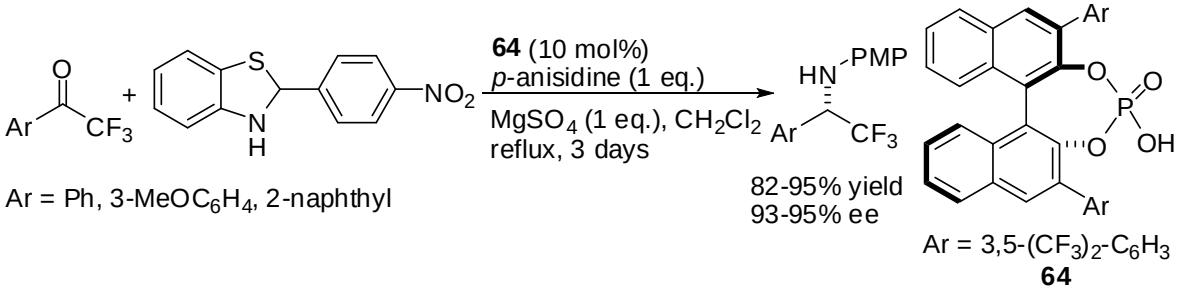
Scheme 88

The same group recently reported the reductive amination of ketones with benzylamine using Dean-Stark conditions by heating at reflux under reduced pressure. For example, acetophenone was transformed in 96% yield and 88% ee using Hanztsch ester with 5 mol% catalyst **219** (Scheme 89).[115]



Scheme 89

Akiyama and co-workers reported that the enantioselective reductive amination of trifluoromethyl ketones with *p*-anisidine using benzothiazolines as the hydride source could be achieved with 10 mol% chiral phosphoric acid catalyst **64** (Scheme 90).[48]



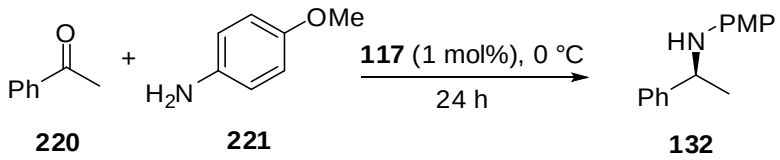
Scheme 90

Limited examples of directed reductive amination of ketones using trichlorosilane as reducing agent catalysed by chiral Lewis bases have been reported by Benaglia (Scheme 46, page 26). In Jones' group, it was found that catalyst **117** only activate trichlorosilane to reduce imines but not ketones. Clearly, this has the potential for reductive amination of ketones.

4.2 Results and discussions

Acetophenone **220** and *p*-anisidine **221** were used as standard substrates for screening optimal conditions with 1 mol% catalyst **117** on a 1 mmol scale (Scheme 91, Table 12). Although the product was obtained in good ee, the yield was unsatisfactory (entry 1). Increasing the equivalents of acetophenone or *p*-anisidine increased the yield slightly (entry 2-3), although increasing the equivalents of trichlorosilane from 2 eq. to 4 eq. gave no benefit (entry 3-5). Using toluene as a solvent gave no significant difference to the reaction in dichloromethane (entry 3 vs 6). In each case, although good enantioselectivities could be

obtained, the yield was unsatisfactory.



Scheme 91

Table 12: Optimization of the reaction conditions for asymmetric reductive amination of ketones

Entry	Molar ratio **220** : **221** : $HSiCl_3$	Additive (eq.)	Solvent (mL)	Yield %	ee %
1	1 : 1.2 : 2	-	CH_2Cl_2 (1)	39	85
2	1 : 2 : 2	-	CH_2Cl_2 (1)	47	84
3	2 : 1: 2	-	CH_2Cl_2 (1)	53	84
4	2 : 1: 3	-	CH_2Cl_2 (1)	52	85
5	2 : 1: 4	-	CH_2Cl_2 (1)	46	86
6	2 : 1: 2	-	Toluene (1)	39	84
7	2 : 1: 2	TMSOTf (0.1)	CH_2Cl_2 (1)	75	77
8	2 : 1: 2	TMSOTf (0.05)	CH_2Cl_2 (1)	58	80
9	2 : 1: 2	TMSOTf (0.1)	Toluene (1)	52	76
10[a]	2 : 1: 2	TMSOTf (0.1)	CH_2Cl_2 (1)	78	77
11	2 : 1: 2	TMSCl (0.1)	CH_2Cl_2 (1)	52	84
12	2 : 1: 2	TMSCl (0.1)	CH_2Cl_2 (1)	40	71
13	2 : 1: 2	-	CH_2Cl_2 (5)	43[b]	79
14	2 : 1: 2	-	CH_2Cl_2 (0.5)	66	84
15	1 : 1.5 : 2	-	CH_2Cl_2 (0.5)	71	84

[a] 0.05 eq. catalyst used; [b] refers to conversion, not yield.

TMSOTf has been successfully used as a catalyst in the three component Strecker reaction for the preparation of α-aminonitriles,[116] and might, in this case, increase the rate of initial imine formation and thus improve the yield. This was indeed the case. Using 0.1 eq. of TMSOTf as additive increased the yield to 75%, but unfortunately the enantioselectivity decreased (entry 7-9), and could not be recovered by increasing catalyst loading from 1 mol% to 5 mol% (entry 10). Using 0.1 eq. of TMSCl as additive also failed to offer any improvements (entry 11-12). Since it appeared that Lewis acid additives promoted formation of the ketimine required for reduction, it was reasoned that increasing the concentration of the substrates and reagents may also lead to a similar effect (entry 13-15), which was indeed the case. Optimum conditions were thus ketone **220**, amine **221** and $HSiCl_3$ in a molar ratio

of 1 : 1.5 : 2, producing the product amine **132** in 71% yield and 84% ee at 1 mol% catalyst loading (entry 15). These conditions offer an order of magnitude difference in catalyst loading, with considerable time savings (24 h vs. 90 h) to deliver a product with almost identical yield and ee to the competitive catalyst system reported by Benaglia (Scheme 46, page 26).[72] Indeed, if one calculates the Asymmetric Catalytic Efficiency (ACE) and Asymmetric Catalytic Efficiency Speed (ACES) that have recently been proposed to compare efficiency of asymmetric transformations, catalyst **117** provides an ACE of 37.5 and ACES of 1.6.[117] These compare very well next to the Benaglia system with an ACE of 5.2 and ACES of 0.1,[72] and illustrate the cost and time savings associated with using the cheap, low molecular weight catalyst **117**.

With the optimal conditions in hand (Table 12, entry 15), the generality of the process was explored (Table 13). Both electronic rich and poor aryl methyl ketones afforded the amine products in good enantioselectivity (70-84% ee, entry 1-7), although slightly lower yields were obtained when using electron-poor aryl methyl ketones as substrates compared to electron-rich ones (entry 4-5). Surprisingly, the asymmetric reductive amination of *o*-methylphenyl methyl ketone afforded amine **226** in low yield, but use of *o*-methoxyphenyl methyl ketone led to a good yield despite a small drop in enantioselectivity (entry 6 *vs.* 7). A similar change in the steric requirements of the substrate adjacent to the reaction site can also been seen when contrasting the 1-naphthyl methyl ketone with 2-naphthyl methyl ketone (entry 8 *vs.* 9). 2-Acetyl thiophene is reasonably well tolerated, while in contrast the furyl analogue is a poor substrate (entry 10 *vs.* 11). Reductive amination of propiophenone afforded the corresponding amine **232** in high enantioselectivity but low yield (entry 12). This illustrates the limitations of this methodology, since ketones with further substitution at the aliphatic centre failed to afford the amine and return only the starting materials after workup (entry 13-14). Dialkyl ketones or cinnamyl methyl ketone provided the products in high yield but low enantioselectivity (entry 15-17).

Reductive amination of α-cyanoacetophenone did not work at all and ketone was recovered after workup. This result could be attributable to the easy enolization of α-

cyanoacetophenone, disfavoring the formation of imine (Figure 9).

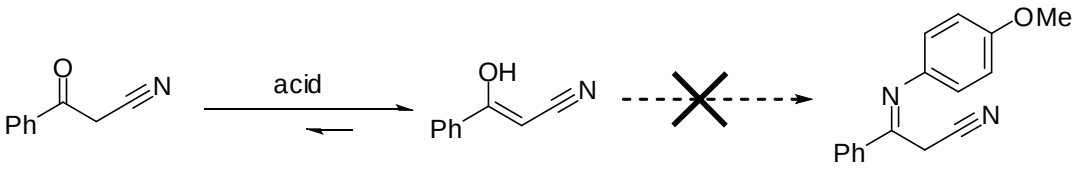
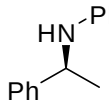
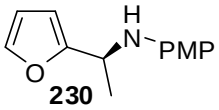
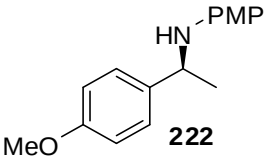
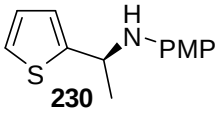
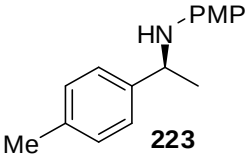
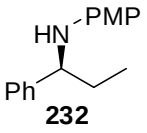
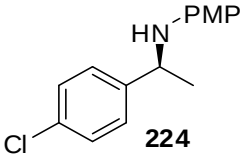
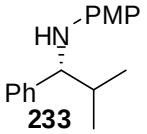
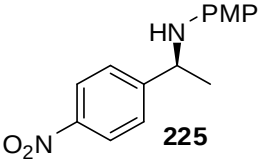
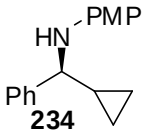
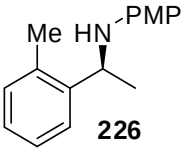
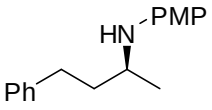
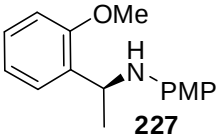
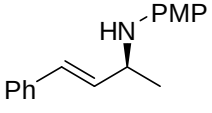
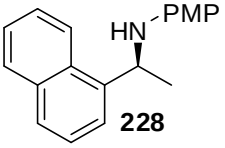
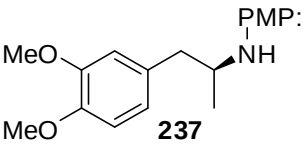
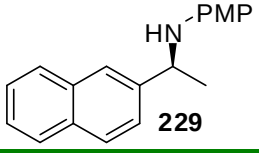


Figure 9

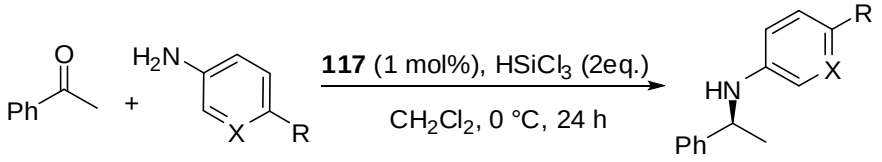
Table 13: Asymmetric reductive amination of ketone substrates[a]

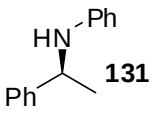
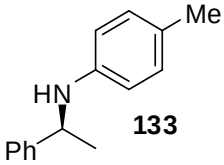
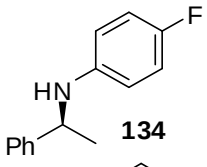
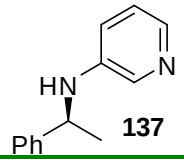
Entry	Amine	Yield (%)	Ee (%)	Entry	Amine	Yield (%)	ee (%)
1	 **132**	71	84	10	 **230**	72	44
2	 **222**	76	81	11	 **230**	61	79
3	 **223**	66	83	12	 **232**	15	85
4	 **224**	61	83	13	 **233**	-[b]	N.A
5	 **225**	46	83	14	 **234**	-[b]	N.A
6	 **226**	12	81	15	 **235**	82	14
7	 **227**	71	70	16	 **236**	77	<2
8	 **228**	11	77	17[c]	 **237**	81	15
9	 **229**	63	85				

[a] A mixture of ketone (1 mmol), *p*-anisidine (1.5 mmol), catalyst **117** (0.01 mmol) and $HSiCl_3$ (2 mmol) in CH_2Cl_2 (0.5 mL) were stirred for 24 h at 0 ºC; [b] No reaction or < 5% conversion; [c] Reaction performed in 1 mL of CH_2Cl_2.

Various aromatic amines can also be used as the amine counterpart for the reductive amination of acetophenone and afforded the product amines in synthetically useful yield and good enantioselectivity (Table 14, entry 1-3). However, reductive amination employing 3-aminopyridine as an amine counterpart gave the product in low enantioselectivity (10% ee), albeit good yield (Table 14, entry 4).

Table 14: Reductive amination of acetophenone **229** with various aromatic amines[a]



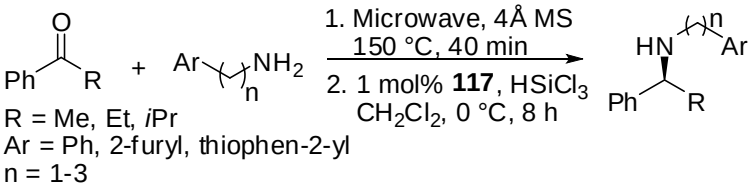
Entry	X	R	Product	Yield %	ee %
1	CH	H	 **131**	56	82
2	CH	Me	 **133**	64	84
3	CH	F	 **134**	65	81
4[b]	N	H	 **137**	58	10

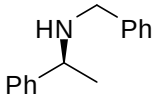
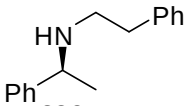
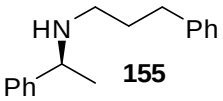
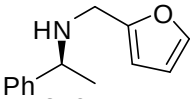
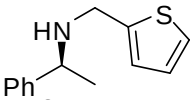
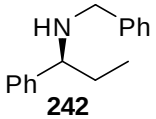
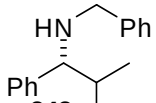
[a] A mixture of acetophenone (1 mmol), amine (1.5 mmol), catalyst **117** (0.01 mmol) and $HSiCl_3$ (2 mmol) in CH_2Cl_2 (0.5 mL) were stirred for 24 h at 0 ºC; [b] Reaction was performed in 2 mL of CH_2Cl_2.

Reductive amination of acetophenone with aliphatic amines provided only recovered starting materials, presumably due to the formation of an initial amino-silane compound that inhibited subsequent reactions. With this in mind, a two-step one-pot procedure was developed by microwave-assisted imine formation immediately prior to reduction. Ketone and aliphatic amine were heated at 150 °C for 40 min in the presence of 4 Å molecular sieves under microwave irradiation and the crude product immediately submitted to standard

reduction conditions. Using this process, several *N*-alkyl amines were successfully obtained in good yield and enantioselectivity (Table 15). It was notable that sterically hindered ketones were also aminated with benzylamine under these conditions (entry 6-7), and that the isopropyl phenyl ketone led to a reversal of the sense of stereoselectivity (entry 7).

Table 15: Reductive amination of ketone with aliphatic amines[a]

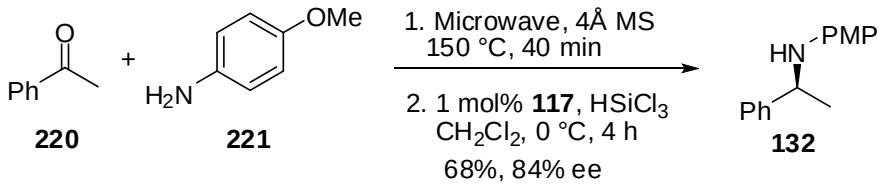


Entry	Product	Yield %	ee %
1	 **238**	63	80
2[b]	 **239**	65	86
3	 **155**	76	84
4	 **240**	65	86
5	 **241**	64	83
6	 **242**	66	73
7	 **243**	62	76

[a] A mixture of ketone (1 mmol), amine (1.5 mmol) and 4Å MS (200 mg) was irradiated under microwave for 40 min at 150 ºC, then cooled to RT. Catalyst **117** (0.01 mmol) and CH_2Cl_2 (0.5 mL) were added, the reaction cooled to 0 ºC, $HSiCl_3$ (2 mmol) added and left to stir for 8 h; [b] Reaction was performed in 2 mL of CH_2Cl_2.

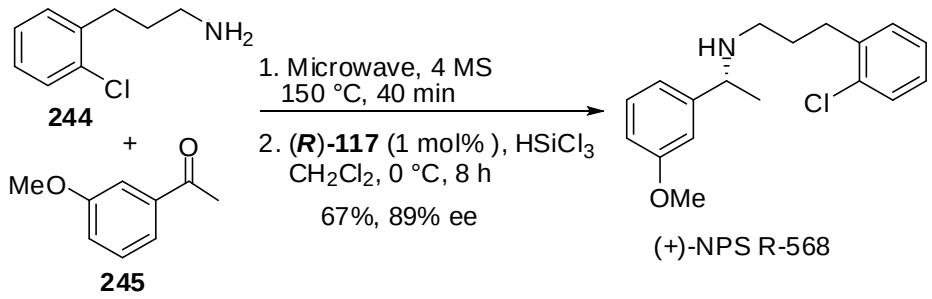
The two-step one-pot procedure can also be used for the reductive amination of acetophenone with aromatic amine **221**. Although the product amine **132** was isolated with approximately the same enantioselectivity and yield compared to the one-pot procedure

(Scheme 92 vs. Table 2, entry 1), the two-step one-pot procedure offers considerable time savings (4 h 40 min *vs*. 24 h), which increased the ACES from 1.6 to 7.6. This also provided amine **132** with a higher yield compared to the standard two-step procedure (52% overall yield) albeit with slightly low ee (84% vs. 90%, Table 1 and Table 2).



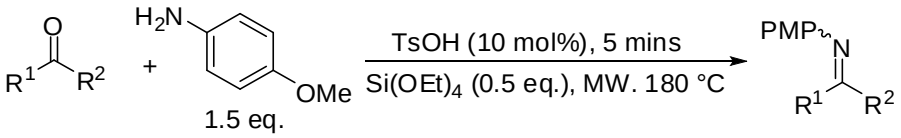
Scheme 92

The synthetic utility of this methodology was demonstrated by synthesis of calcimimetic (*R*)-(+)-NPS R-568 via the two-step one-pot procedure from amine **244** and ketone **245** in 67% yield and 89% ee with 1 mol% catalyst loading of (*R*)-**117** (Scheme 93).



Scheme 93

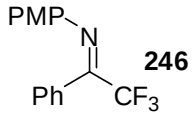
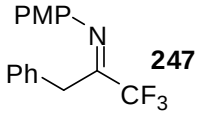
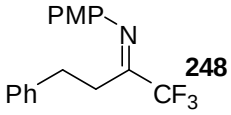
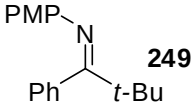
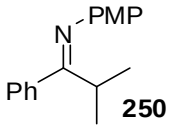
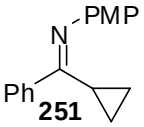
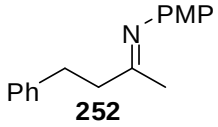
To determine the origins of the reversal of the sense of stereoselectivity in the reductive amination of iso-propyl phenyl ketone, a few sterically bulky imines and trifluoromethyl imines were synthesized. Initially, the synthesis of these substrates proved to be difficult under the traditional conditions. Gratifyingly, a new microwave-assisted method for the preparation of these imine substrates was successfully developed using tetraethoxysilane as a dehydrating reagent (method C). [118] Under optimized conditions, steric bulky and trifluoromethyl imines derived from *p*-anisidine were synthesized in moderate to high yield (Scheme 94, Table 16, entry 1-5). However, under the same conditions, the cyclopropyl phenyl ketone failed to give the corresponding imine **251**, which was prepared under standard Dean-Stark conditions (method B), as was imine **252** (Table 16, entry 6-7).



Scheme 94

Most of the imines were isolated as single isomers, but some of them existed as a mixture of *syn/anti*-imines and enamines. Although it has been shown that the *anti* isomer is the major product formed for aromatic ketimines by ^{1}H NMR experiments,[83] the geometry of trifluoromethyl imines were clearly *syn*-favored according to nOe NMR experiments (see Appendix 2-3).

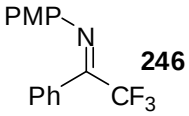
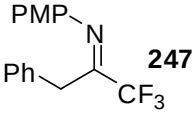
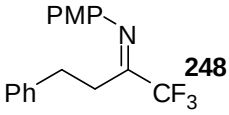
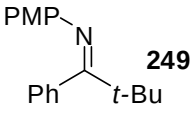
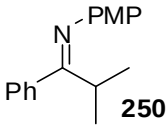
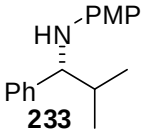
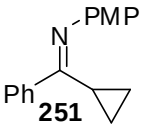
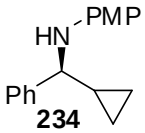
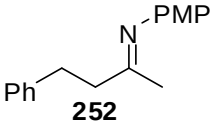
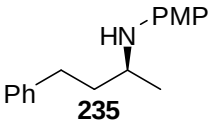
Table 16: Synthesis of sterically bulky imines and trifluoromethyl imines

Entry	Imine	Isomer ratio	Yield (%)
1	 **246**	1:0	85
2	 **247**	1.5:1 (imine/enamine)	78
3	 **248**	1:0	76
4	 **249**	1:0	56
5	 **250**	6:1:1 (ratio of two imine isomers and enamine)	40
6	 **251**	1.6:1	13
7	 **252**	1:0	59

These imines were submitted to the optimized reduction conditions (same conditions as the reductions in Table 2, page 32). The trifluoromethyl imines **246**-**248** were not reduced under these conditions, perhaps due to the reduced basicity of the nitrogen lone pair caused by the strongly electron-withdrawing trifluoromethyl group (Table 17, entry 1-3). Similarly, the

fact that the most sterically bulky imine **249** was unreactive could be due to steric hindrance inhibiting the interaction with an activated silane species (Table 17, entry 4). Both the isopropyl **250** and cyclopropyl imines **251** were reduced in high yield, albeit with much lower enantioselectivity for the reduction of the cyclopropyl imine (Table 17, entry 5-6). Similar to the reductive amination of isopropyl phenyl ketone, a reversal sense of stereoselectivity in the reduction of isopropyl imine **250** was observed, while the reduction of the cyclopropyl imine had a same sense of stereoselectivity. In contrast to trifluoromethyl imine **248**, the corresponding methyl imine **252** can be quantitatively reduced albeit in a racemic fashion (Table 17, entry 7).

Table 17: Reduction of trifluoromethyl imines and sterically bulky imines[a]

Entry	Imine	Product	Yield (%)	Ee (%)
1	 **246**	-	-	-
2	 **247**	-	-	-
3	 **248**	-	-	-
4	 **249**	-	-	-
5	 **250**	 **233**	85	69
6	 **251**	 **234**	98	36
7	 **252**	 **235**	100	3

[a] Conditions were same as in Table 2.

The reasons for the reversal of the sense of stereoselectivity for the reduction of isopropyl phenyl imine might be attributable to the selective reduction of only one geometric isomer of

imine. This, linked with the ability of the imine substrates to interconverted geometry under the reaction conditions can then provide a tentative explanation for these results (Figure 10). In the case of methyl phenyl imine **125**, the interconversion of the *syn* and *anti* imine isomers is relatively fast, with reduction of the *anti*-imine assumed to be faster, affording a majority of (*S*)-isomer as product. In the case of the isopropyl phenyl imine **250**, imine equilibration is still facile, but now steric interaction of the isopropyl group with the PMP group disfavor the *anti* isomer, leading to preferential reduction of the *syn*-isomer. In the case of the cyclopropyl phenyl imine **251**, the imine isomers cannot interconvert, as it would lead to highly strained cyclopropyl enamine. Thus in this case, the ratio of stereoisomers formed should match that of the initial *syn/anti* isomers (1.6:1 or 62:38), which does indeed correlate well with the observed enantioselectivity (68:32), within experimental error.

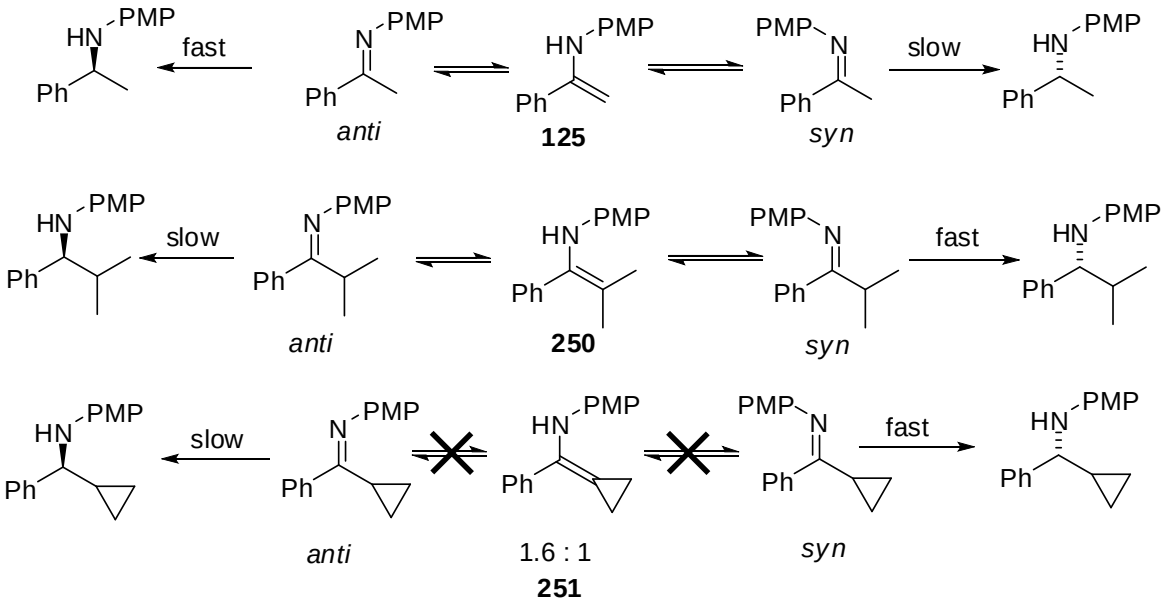


Figure 10

4.3 Conclusions and future work

In conclusion, the asymmetric reductive amination of ketones with both aromatic and aliphatic amines was successfully developed employing an organic catalyst at 1 mol% catalyst loading. Sterically hindered ketones also undergo reductive amination in good yield and enantioselectivity by a two-step one-pot procedure. The asymmetric synthesis of (+)-NPS R-568 using the two-step one-pot procedure was achieved in good yield and high

enantioselectivity. Lewis acidic TMSOTf can improve the yield in the directed reductive amination, but showed a negative effect on the enantioselectivity. Future work will perhaps focus on improving the efficiency of this process by screening some more Lewis acidic additives. An important observation and tentative reaction mechanism has been put forward, linking imine geometry and product selectivity to support the results obtained.

5. Investigation into the mechanism of reduction of imines

5.1 Background

Several models for chiral induction of these Lewis catalysts have been proposed by several research groups. In 2004, Malkov and co-workers proposed a bidentate-activation model for L-valine-derived catalysts (Figure 11, **A**).[64a] In this model, the stacking between the aromatic rings of catalyst and imine is crucial for the enantioselectivity. In 2009, the same group disclosed that low concentrations of acid in commercial trichlorosilane played an important role in the catalytic cycle since proton scavengers were found to slow down the reaction dramatically and also erode the enantioselectivity.[83] According to this observation, a new transition model was proposed (Figure 11, **B**), where the protonated imine coordinated to the catalyst and trichlorosilane was activated by formation of pentacoordinated species.

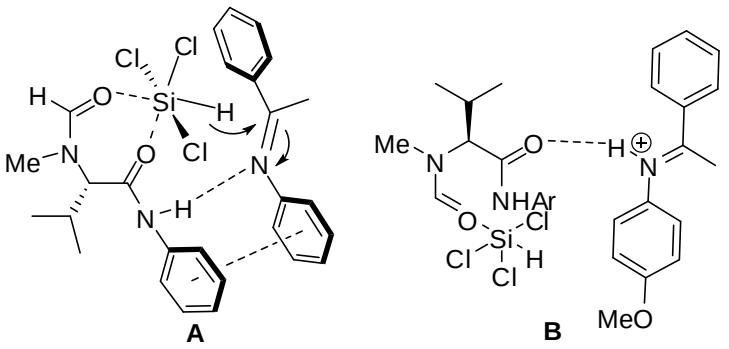


Figure 11

Sun *et al.* proposed bicoordinate-activation transition state models to explain the chiral induction in the reduction of imines based on the structure-activity of catalysts and non-linear study of catalyst ee and product ee.[60,62]

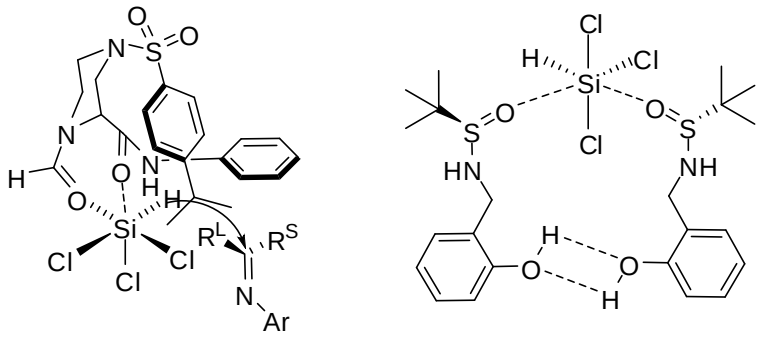


Figure 12

Matsumura *et al*. proposed a transition state model for their catalyst **101** in which both imine and trichlorosilane coordinated with catalyst **101** through hydrogen bonding and noncovalent interactions, respectively (Figure 4, page 25).[70] In this model, trichlorosilane is proposed to be activated by bicoordinate interaction with catalyst **101**, with subsequent hydrogen bonding interactions between the hydroxyl group and the imine used to control stereoselectivity. Similar transition state models involving hydrogen bonding were also used to explain the stereoselectivity of reduction of β-amino esters and imines by Benaglia[72] and Zhang[73] (Figure 13).

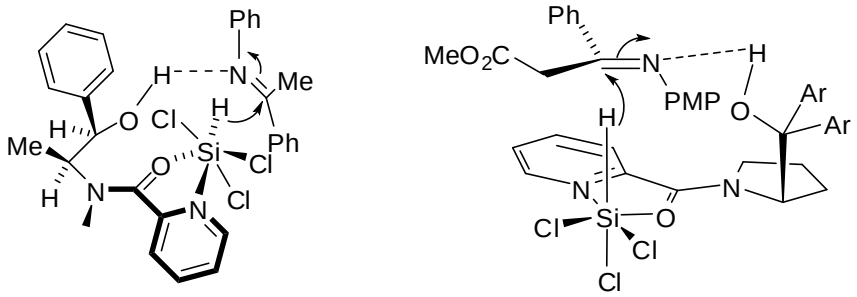


Figure 13

Since these systems strongly resemble the catalyst **117** developed in the Jones group, it is tempting to draw similar transition state models for this system. However, it should be pointed out that all the mechanisms or transition states mentioned above did not elucidate the catalytic cycle and have little supporting evidence. In order to rationalize the design of new catalysts, the focus of this project turned to study the mechanism of reduction of imines with trichlorosilane catalyzed by catalyst **117**.

5.2 Results and discussions

Early studies of the structure and activity of catalysts in Jones' group delivered a similar conclusion to Matsumura's work. In order to get new insights to the mechanism of imine reduction using catalyst **117**, a few more catalysts were prepared as structural probes. The catalysts **255** and **256** were prepared using the same procedure for catalyst **117** by condensation of the corresponding amino alcohols with ethyl 1-methylimidazole-2-carboxylate **123** in toluene in the presence of sodium hydride (Figure 14, page 72). However,

the same method failed to yield the catalysts **257**-**259** and the corresponding oxazolidinones **260**-**262** were formed instead by loss of the imidazole ring (Figure 15).

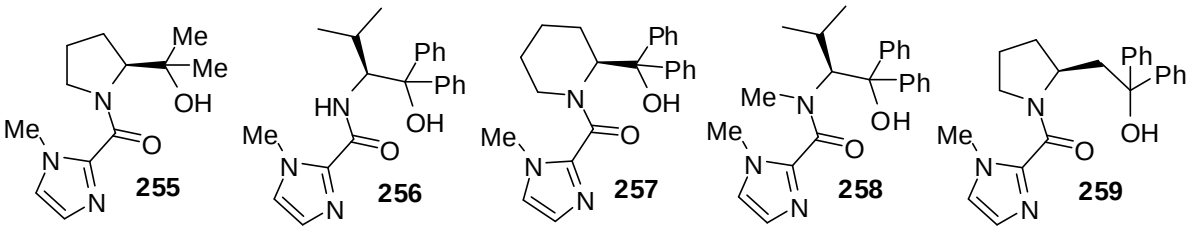


Figure 14

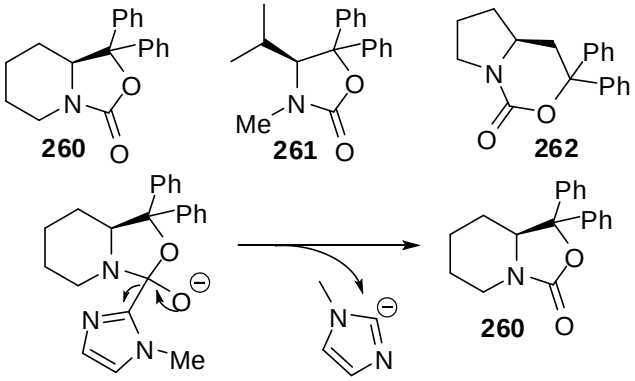
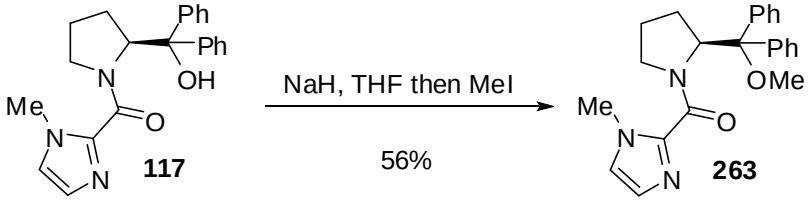


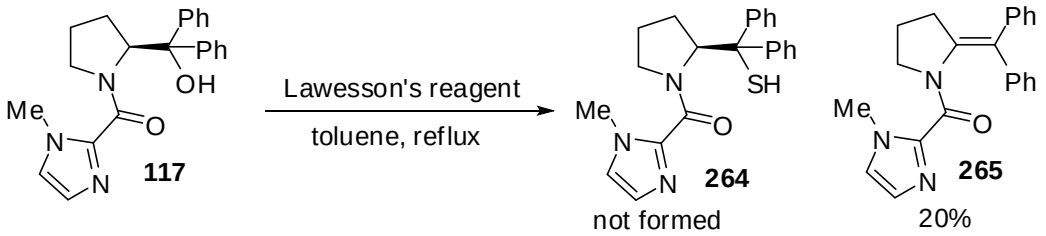
Figure 15

In order to evaluate the role of hydroxyl group in catalyst **117**, attempts were made to synthesize catalysts **263** and **264**. Catalyst **263** was successfully prepared by methylation of catalyst **117** in 56% yield (Scheme 95).



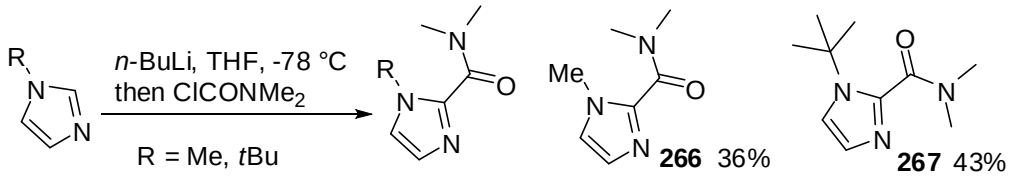
Scheme 95

Treatment of catalyst **117** with Lawesson's reagent in a reflux toluene did not deliver the desired catalyst **264**. Only the dehydrated alkene **265** was isolated in 20% yield (Scheme 96).



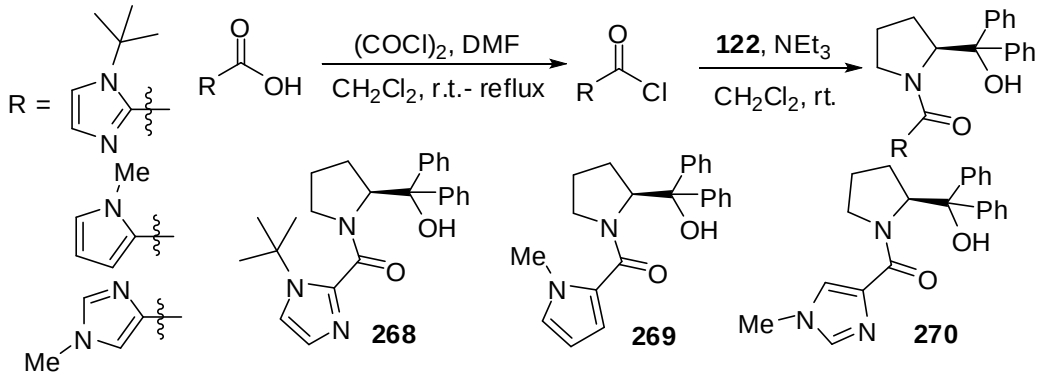
Scheme 96

The synthesis of achiral catalysts **266** and **267** was achieved from the corresponding imidazoles by deprotonation and quenching with dimethylcarbamoyl chloride (Scheme 97).



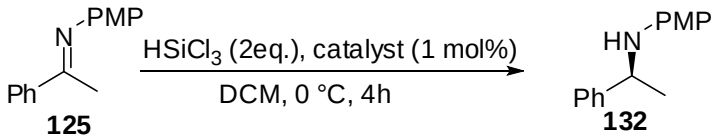
Scheme 97

Another three catalysts **268-270** were synthesized by coupling α,α-diphenylprolinol **122** with the corresponding acid chlorides, which were prepared from carboxylic acids and used directly (Scheme 98).



Scheme 98

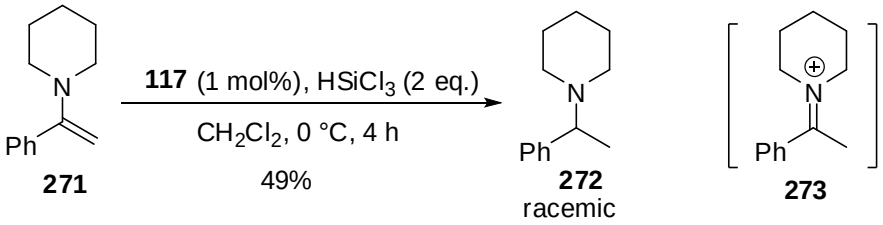
The evaluation of these catalysts was carried out by the reduction of imine **125** using the standard conditions at 1 mol% catalyst loading (Scheme 99).



Scheme 99

Background reaction studies with no catalyst returned the product amine in about 10%

conversion. Given the results discussed earlier with regard to imine/enamine equilibria, it was also important to evaluate the background reaction rate of any transient enamine formed. Thus, model substrate **271** was prepared and subjected to both catalyzed and uncatalysed reaction conditions. The results indicated no difference in conversion of the catalyzed and uncatalysed reactions; however the background reaction appeared to be faster and unselective when compared to those conducted on the imine. Although the substrate is, of course, slightly different to that used in the benchmark reactions, this could mean that any substrate and / or reaction conditions that extend the lifetime of the enamine will lead to erosion of enantioselectivity through reduction of this intermediate. It also implies that reduction of an iminium ion, the proposed reactive intermediate in this reaction, is much faster than that of a neutral imine.



Scheme 100

N-Benzylimidazole and *N*-*t*-butylimidazole exhibited reasonable activities for the reduction of imine **125**, while *N*-methylimidazole had a low activity (Figure 16). This rather unexpected result can perhaps be attributed to the immiscibility of the *N*-methylimidazole (2 mmol) and trichlorosilane (4 mmol) in chloroform (0.5 mL) preventing interaction of the catalyst with the trichlorosilane. In contrast, clear solutions were formed when using *N*-*t*-butylimidazole and *N*-benzylimidazole.

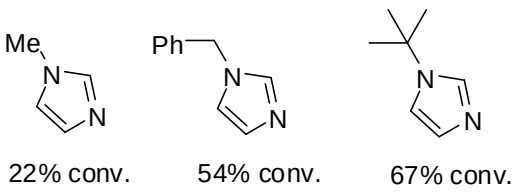


Figure 16: Evaluation of imidazole catalysts

Catalyst **266** was very active but the *N*-*t*-butyl counterpart **267** showed a low catalytic

activity (Figure 17). A possible explanation may come from examination of their reactive conformations. For catalyst **266**, both conformations **266A** and **266B** are reasonably stable and are available to interact with trichlorosilane. In the case of catalyst **267**, severe steric interactions between the *N*-methyl group and the t-butyl group disfavor conformation **267A**, leading to preferred conformation **267B**. If this conformation is the only one available, interaction with trichlorosilane is then slow due to the significant steric hindrance around the carbonyl group. This results in no significant conversion other than the background reaction in the reduction of imine.

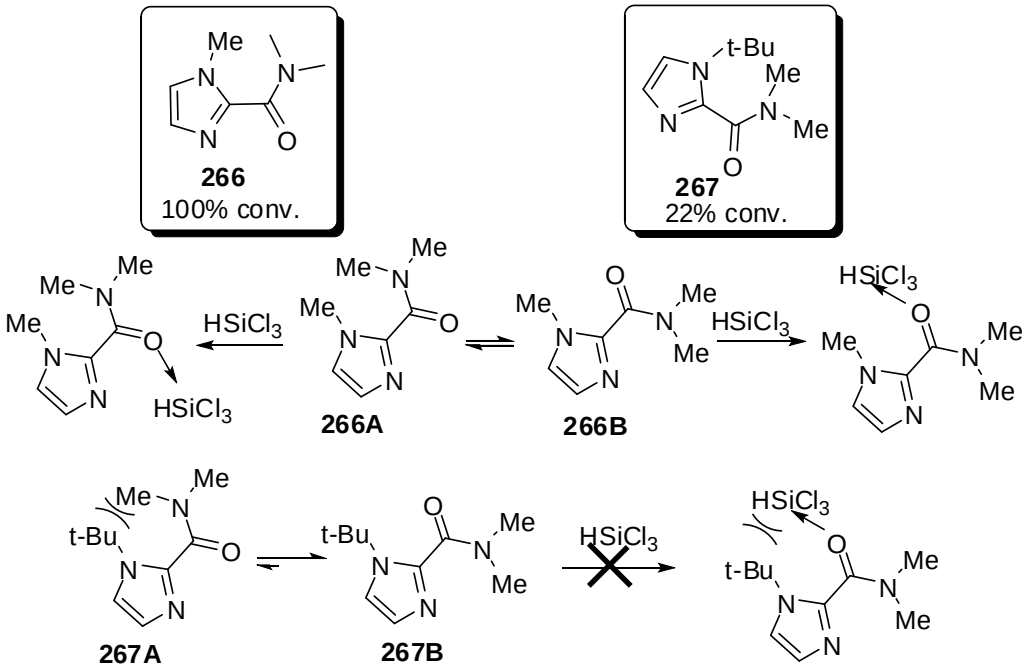


Figure 17: Evaluation and conformation analysis of catalysts **266** and **267**

Catalyst **268** with a *t*-butyl group on the imidazole nitrogen atom showed little catalytic activity (Figure 18). In this case, considering rotamers around the Cα-carbonyl bond, a similar situation arises as with catalyst **267**, this time with steric interactions between the pyrrolidine ring and the *t*-butyl group.

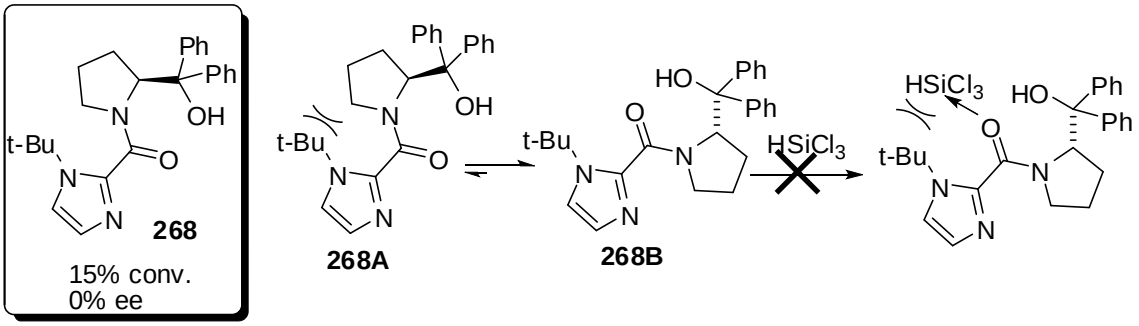


Figure 18: Evaluation and conformation analysis of imidazole catalysts **268**

Catalyst **256** likewise exhibited no catalytic activity. In this case, intramolecular hydrogen bonding could lock conformation **256B**, thus leading again to a conformation where reaction with trichlorosilane is unfavorable (Figure 19).

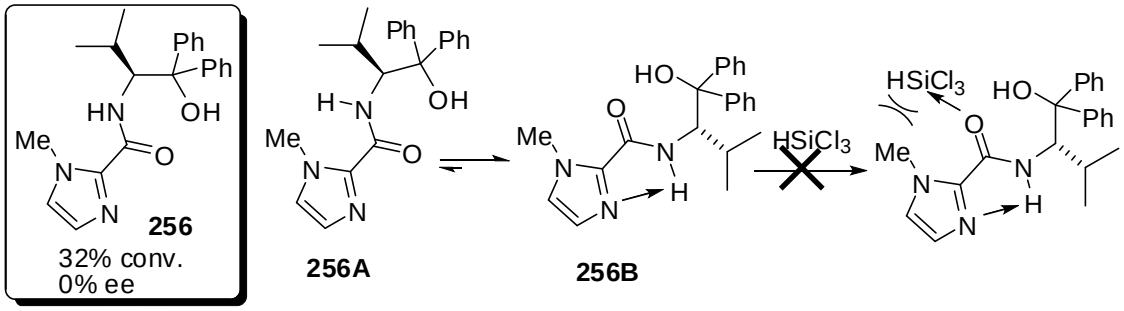


Figure 19: Evaluation and conformation analysis of imidazole catalysts **256**

Similar to catalyst **117**, new catalysts **263** and **255** exhibited very high activity. It is very interesting that catalyst **263** was very active, delivering product with unexpectedly high enantioselectivity. This result is surprising given Matsumura's transition state model, since the hydrogen bonding between the hydroxyl group and the nitrogen atom of the imine cannot exist in this case (Figure 4, page 25). The origins of the low enantioselectivity of catalyst **255** are not clear at this time, but fit in well with previous studies[79] showing a need for steric bulk at the alcohol position in order to maximize enantioselectivity.

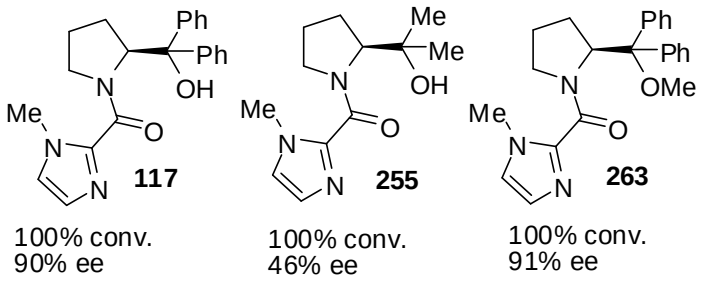


Figure 20: Comparison of activity of catalyst **117** with new catalysts

Catalyst **270** was highly active but led to poor stereoselectivity and a reversal in the sense of absolute stereochemistry (Figure 21). One explanation could be that in this case, steric interactions of the *N*-methyl group with the pyrrolidine ring do not occur, leading to a stable reactive conformation with a coplanar imidazole-amide. The reaction is then able to proceed via a slightly different transition state to that proposed (Figure 30, page 84).

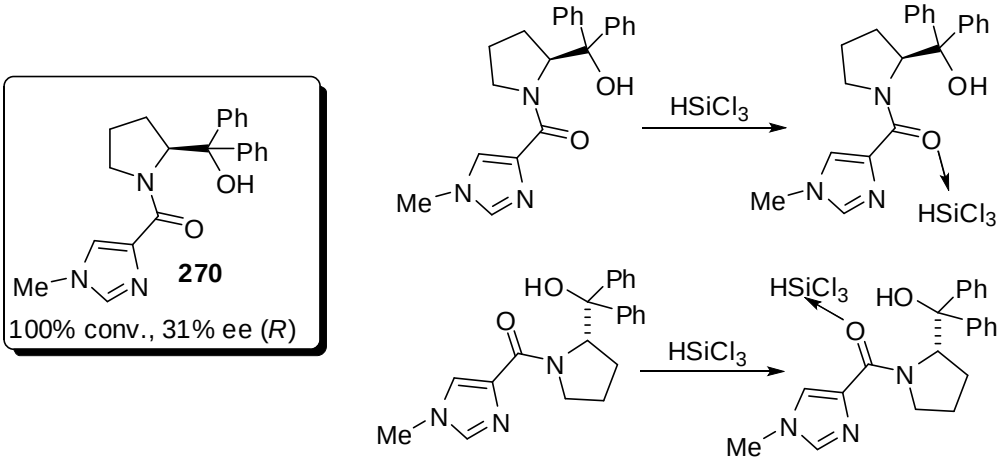
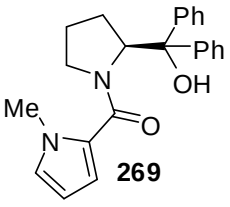


Figure 21: Reversal stereoselectivity of catalyst **270**

The fact that no catalytic activity was observed with catalyst **269** indicates that the nitrogen atom in the imidazole ring plays a crucial role in determining the catalyst activity (Figure 22).

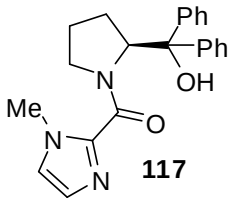
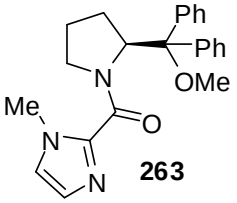
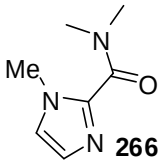
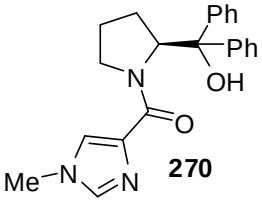


19% conv. 0% ee

Figure 22

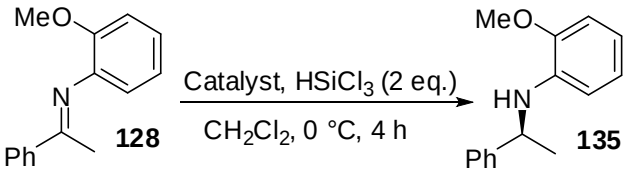
Some of the catalysts tested showed very high activity for the reduction of imine **125** at 1 mol% catalyst loading. In order to compare their activity and the limitation of catalyst loading, the reduction of imine **125** was then performed at a much lower catalyst loading (Table 18). High enantioselectivity still can be obtained at a 0.01 mol% catalyst loading of catalyst **117** or **263**; however, a dramatic decrease in conversion was observed for catalyst **117**, while catalyst **263** was still very active at such low catalyst loading with only a minor decrease in enantioselectivity. Achiral catalyst **266** exhibited a comparable activity with catalyst **263,** while catalyst **270** was less active and showed reversal of absolute stereoselectivity when compared with catalysts **117** and **263**.

Table 18: Evaluation the Limitation of Catalyst Loading

Catalyst	Catalyst loading (%)	Conversion (%)	Ee (%)
 **117**	1	100	90
	0.1	88	87
	0.01	60	80
 **263**	1	100	91
	0.1	100	89
	0.01	96	84
 **266**	1	100	N.R.
	0.1	100	N.R.
	0.01	87	N.R.
 **270**	1%	100%	32 (R)
	0.1%	66%	3 (R)
	0.01%	17%	Untested

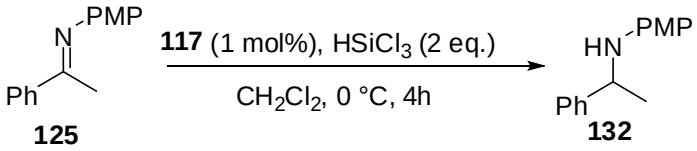
The reduction of imine **128** using 1 mol% catalyst **117** was highly enantioselective but low yielding. With the new most active catalyst **263**, similar results were obtained although high enantioselectivity still can be achieved at a lower catalyst loading than with catalyst **117** (Table 19).

Table 19: Comparison of Activity of Catalysts **117** and **263** by Reduction of imine **128**



Catalyst	Catalyst loading (%)	Conversion (%)	Ee (%)
117	1	35	96
263	1	39	96
263	0.1	39	96

The relationship of product ee and catalyst ee was plotted using imine **125** as a substrate. A clear linear relationship was observed using catalyst **117**, indicating that one catalyst moiety was involved in the catalytically active species.



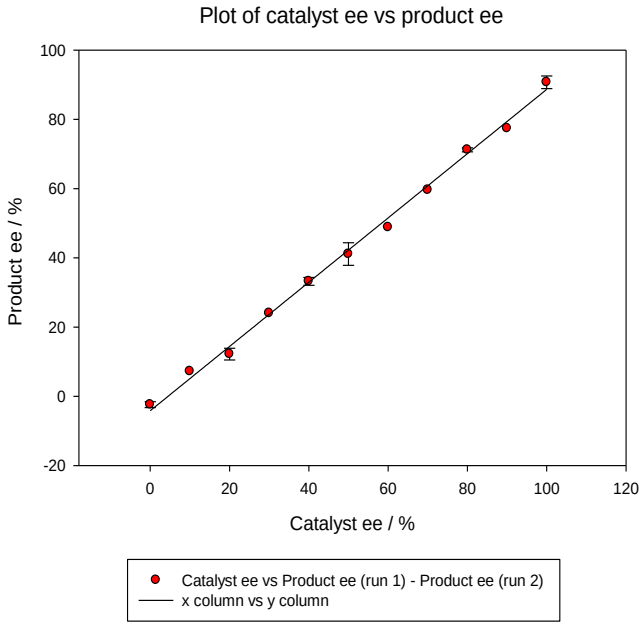


Figure 23

In order to elucidate the mechanism, the intermediates and catalysts used were studied by ^{1}H NMR and ^{29}Si NMR experiments. Firstly, the reduction of imine **125** was performed with trichlorosilane (2 eq.) in $CDCl_3$ with 1 mol% catalyst **117**. After 4 hours, ^{1}H NMR and ^{29}Si NMR spectroscopy disclosed that species from the reduction was intermediate **274** and

tetrachlorosilane was also produced (Figure 24). Intermediate **274** was formed independently by addition of trichlorosilane to the solution of amine **132**.

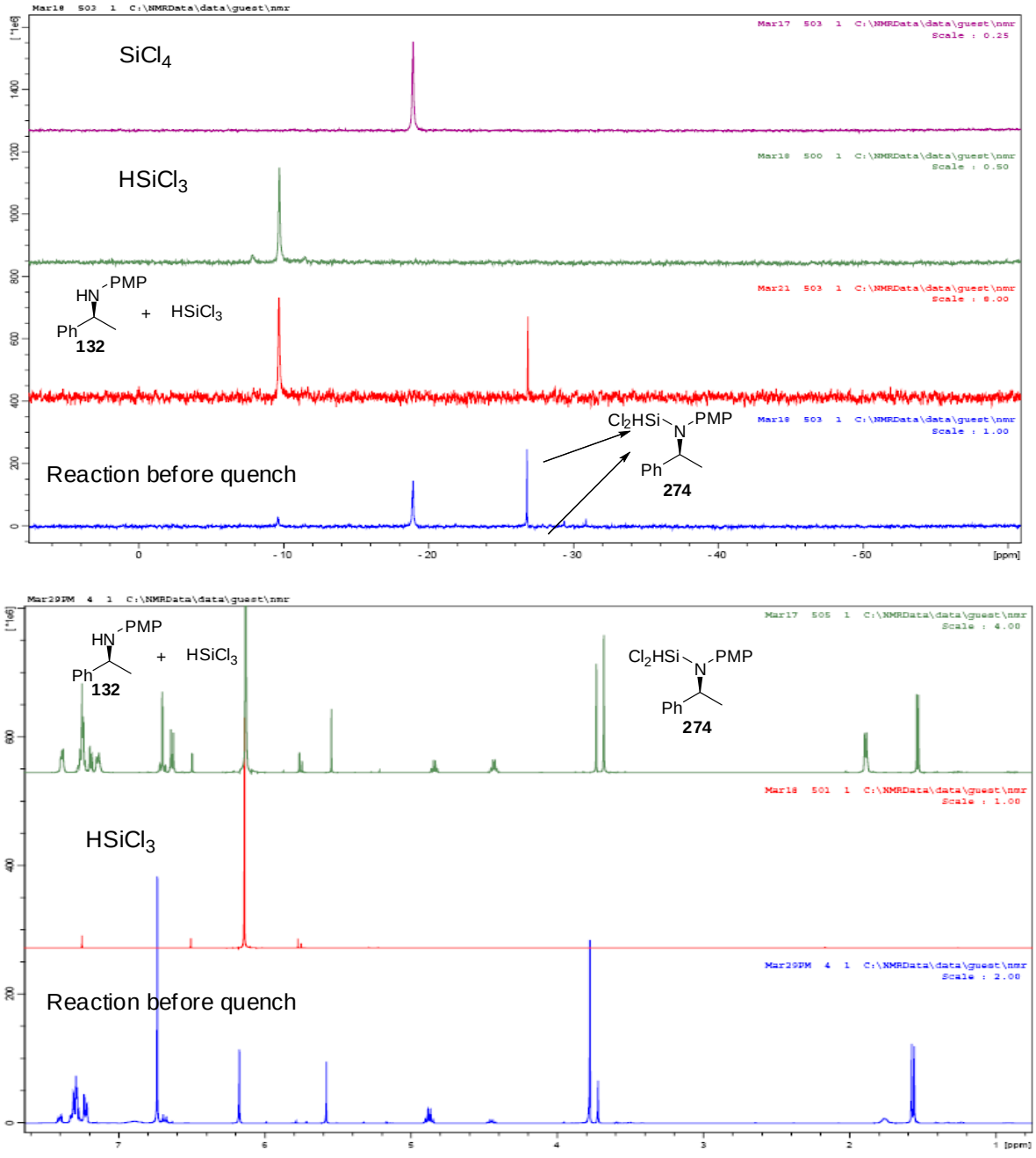


Figure 24: ^{29}Si NMR and ^{1}H NMR study of Active Intermediates

The interaction of the catalysts with trichlorosilane was then investigated. New signals can clearly be observed in the spectra of ^{1}H NMR (4.99 ppm) and ^{29}Si NMR (-33.2 ppm) upon treating catalyst **117** with excess trichlorosilane (1-3 eq.). The signals were attributable to an oxosilane species formed by silylating the hydroxyl group of catalyst **117** confirmed by

comparison of the chemical shifts of related literature signals (Figure 25).[119]

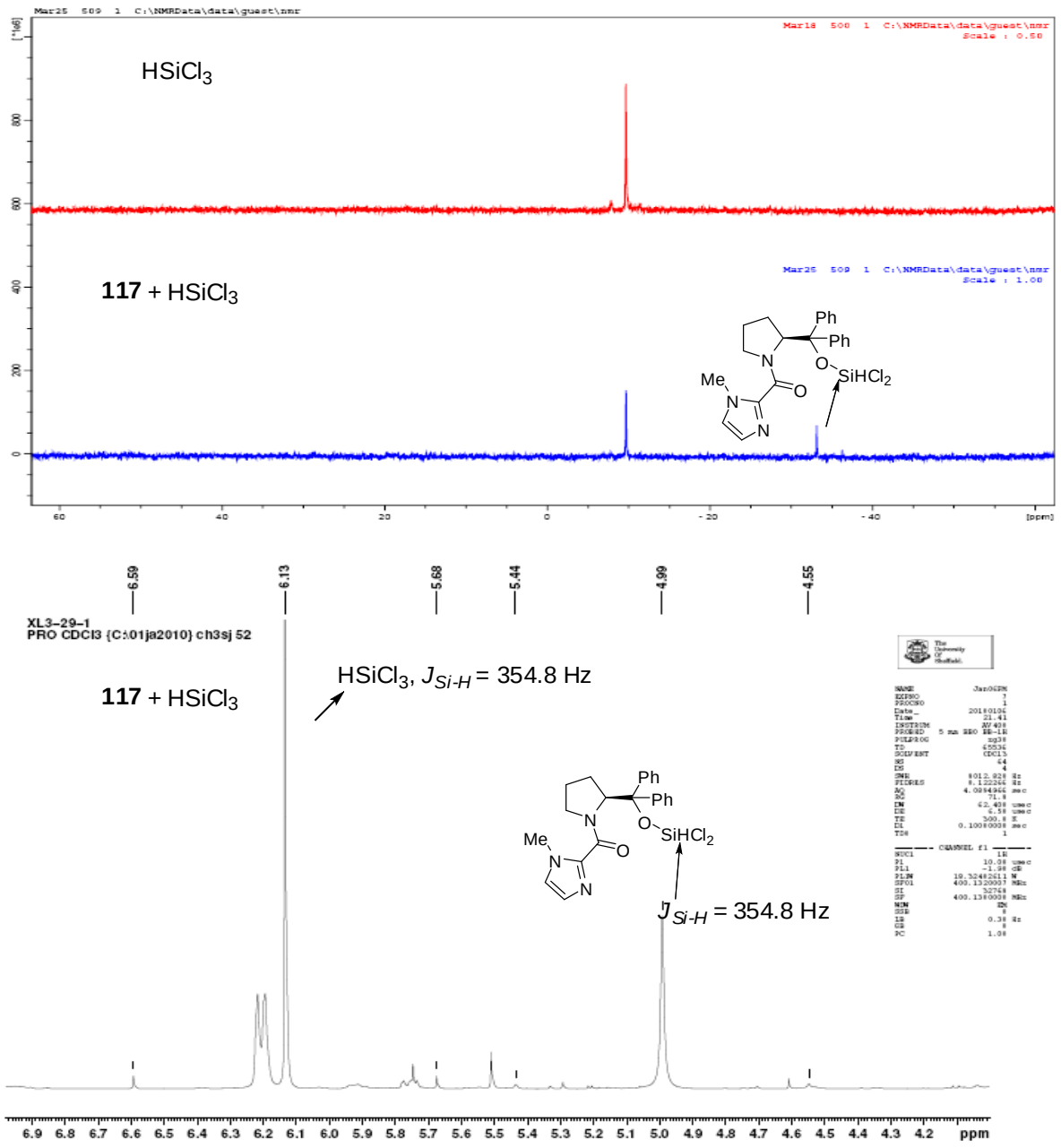


Figure 25: [29]Si NMR and [1]H NMR of Catalyst **117** with $HSiCl_3$

It is then not surprising that no new signals were observed in the [1]H NMR spectrum when catalysts **263** and **266** (with no hydroxyl groups) were treated with trichlorosilane (4 eq.), although the [1]H NMR spectrum of catalyst **263** definitely changed when treated with trichlorosilane (Figure 26). No hexacoordinated silicon species were observed by any of the [29]Si NMR experiments, although these cannot rule out the presence in a very low concentration of such species. An alternative explanation for the changes observed in the [1]H

NMR spectrum could therefore be from the impurities of HCl in the trichlorosilane protonating the imidazole.

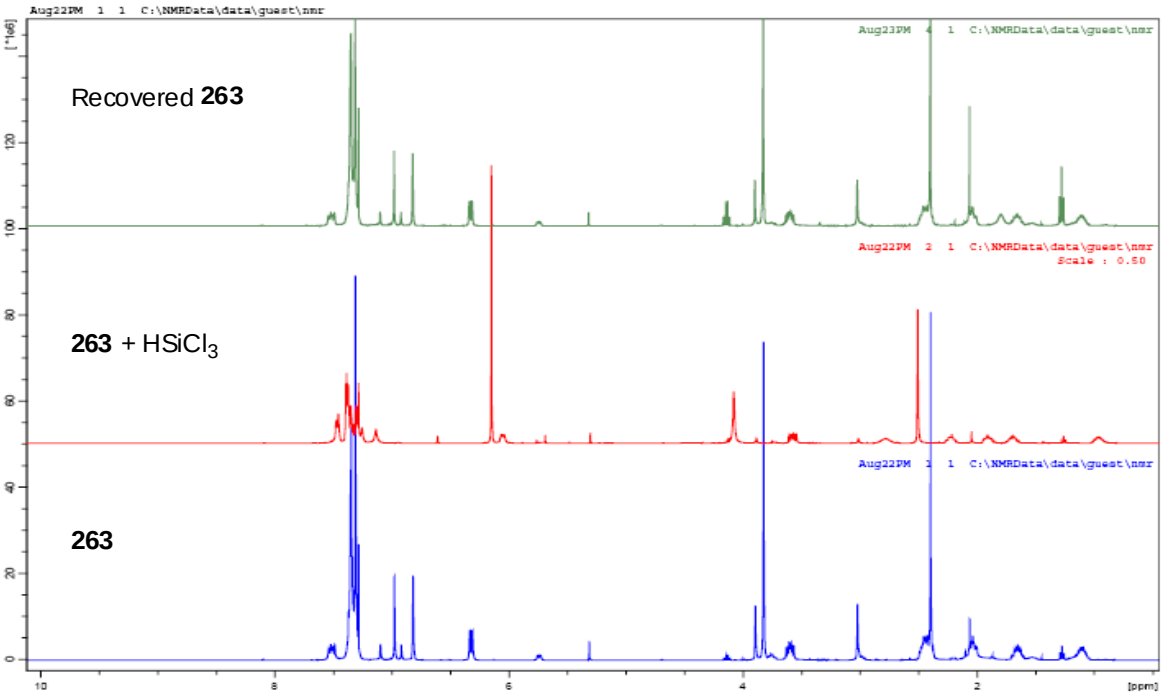


Figure 26: Comparison of ^{1}H NMR of Catalyst **263** Treated with $HSiCl_3$

The catalysts were then studied using *in-situ* ReactIR experiments. The absorption signal of carbonyl group of catalyst **266** in dichloromethane initially appeared at 1635 cm^{-1}; after addition of one equivalent of trichlorosilane, a new signal immediately appeared at 1668 cm^{-1}, while the original signal at 1635 cm^{-1} simultaneously disappeared (Figure 27). This supports the hypothesis that coordination of the trichlorosilane is rapid for this catalyst, leading to a relatively high reaction rate.

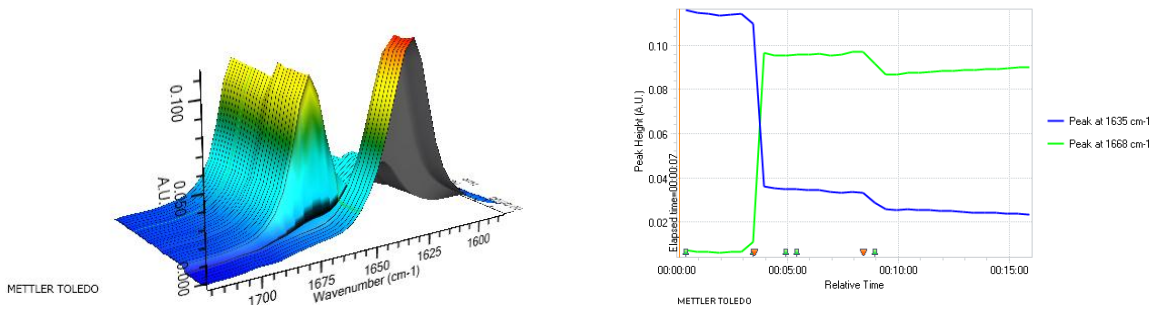


Figure 27: *In-situ* IR Spectrum of Catalyst **266** Treated with Trichlorosilane

A similar observation was made when a solution of catalyst **267** in dichloromethane was treated with one equivalent of trichlorosilane. In this case, the original signal of the carbonyl group was at 1645 cm^{-1} with a smaller new signal at 1671 cm^{-1} once treated with one equivalent of trichlorosilane (Figure 28). It is important to note that in this case the change is not as fast as with catalyst **168** and after the first addition, significant amounts of the un-coordinated catalyst is present. This ratio does not change with time, or when a further equivalent of trichlorosilane is added. This supports the hypothesis that coordination of this catalyst to trichlorosilane is more difficult than in the case of catalyst **266**.

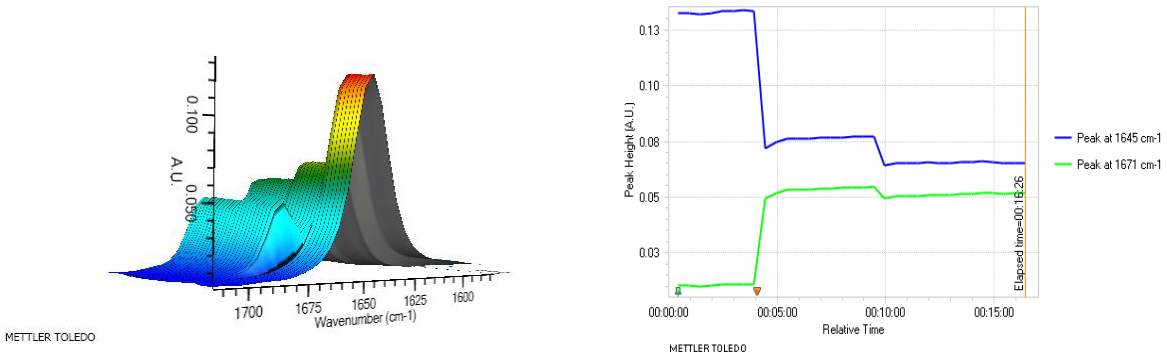


Figure 28: *In-situ* IR Spectrum of Catalyst **267** Treated with Trichlorosilane

The IR absorption signal of chiral catalyst **263** in dichloromethane was at 1623 cm^{-1} and a new signal appeared immediately at 1641 cm^{-1} when being treated with one equivalent of trichlorosilane (Figure 29), but again this was not complete complexation.

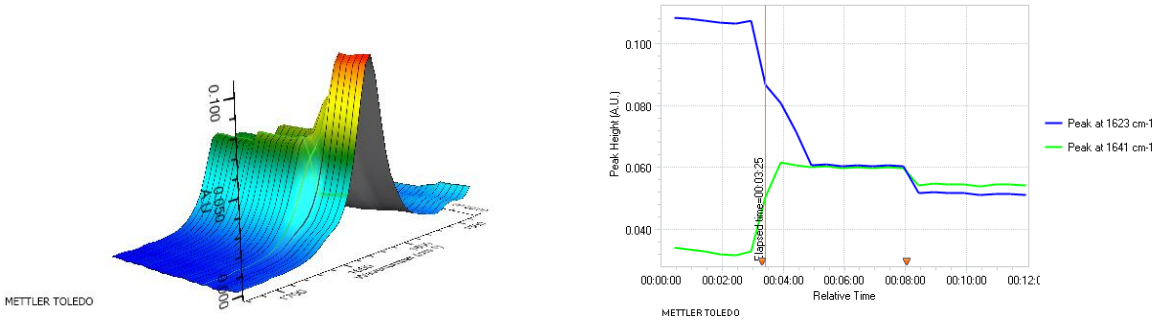


Figure 29: *In-situ* IR Spectrum of Catalyst **263** Treated with Trichlorosilane

These preliminary *in-situ* IR data provide a very useful tool to be able to monitor the species present in the reaction. While insufficient data has been collected at this moment to provide conclusive arguments, it does clearly show that these catalysts do indeed interact with

trichlorosilane, although the puzzle at the moment is that no evidence for a coordinated silane species can be observed in the NMR data.

From related studies, additives such as water (to form HCl *in situ*), acetic acid, and benzoic acid have been successfully used to improve the catalytic activity. Naturally, HCl is also present in commercial unpurified trichlorosilane. Therefore, another possibility that might explain the data accrued so far is that the basic imidazole ring could be protonated once trichlorosilane was added and the protonated catalyst is the real catalytic species involved in the transition state. This would still fit with the proposed conformation models, and also help to explain the reactivity difference between the Matsumura catalyst **101** with a pyridine moiety (pKa 5.21) and ours with an imidazole species (pKa 6.95). A proposed transition state model may well then be as shown in Figure 30. Initial complexation of trichlorosilane must occur via oxygen, based on the NMR data. Next, the *N*-methyl group must be orientated away from the pyrrolidine ring to reduce steric interactions, lying orthogonal to the carbonyl group. In this conformation, it avoids steric interactions with the large siloxane / gem-diaryl group by placing the methyl group on the opposite face. This places the protonated imidazole on the correct face to undergo hydrogen bonding with the imine substrate, holding this in the correct position and activating it to reduction from the pendant silane group, itself activated by interaction with the amide. The difference in reactivity of the hydroxyl catalyst **117** and the methyl ether **263** may then be explained by considering the catalyst turnover-step, since the trichlorosilane cannot form a formal covalent bond with the methyl ether as in the case of the hydroxyl group.

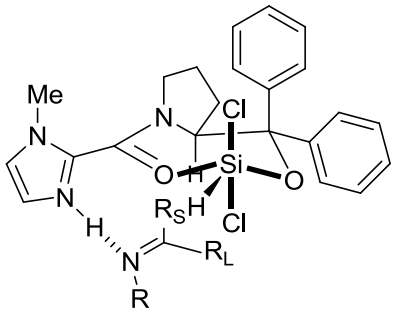


Figure 30

Obviously this model is only tentative at the moment and further experimental mechanistic studies are required to validate it. However, at the moment it appears to be a reasonable working hypothesis that fits much of the data.

5.3 Conclusions and future work

A new highly active catalyst **263** was successfully developed by methylation of the hydroxyl group of the original catalyst **117**. This unexpected discovery has put the Matsumura transition state model into doubt. No evidence was found to support the coordinated silane species by NMR experiments. The preliminary *in-situ* IR experiment did indicate that there are some interactions between the catalyst and trichlorosilane led a red-shift of the absorption of the carbonyl group, although it is yet not clear what they are at the moment. A tentative transition state model was proposed.

Future work will investigate the generality of the new catalyst **263** and validate the tentative transition state model by kinetic study of the reduction employing the advantage of the *in-situ* ReactIR.

6. Conclusions and future work

A chromatography-free process for the synthesis of catalyst **117** has been developed. Asymmetric reduction of both *N*-aryl and *N*-alkyl ketimines can be performed using trichlorosilane catalyzed by **117** at low catalyst loading. The scalability of this process was demonstrated by the reduction of acyclic imine **125** and cyclic imine **141**. These results make the methodology potentially useful to the pharmaceutical industry.

This catalyst can also facilitate the reduction of β-enamino esters with trichlorosilane with good yield and high enantioselectivity albeit with the necessity of high catalyst loading and benzoic acid additive. It is notable that both *N*-aryl and *N*-alkyl substrates are suitable for the reduction with this catalytic system in high enantioselectivity. The results obtained using several different acidic additives identify that the exact additives depend on the catalyst used.

A directed asymmetric reductive amination of ketones with aniline derivatives was demonstrated employing an organic catalyst **117**. For reductive amination of aliphatic amines, a two-step one-pot procedure was developed by microwave-assisted imine formation immediately prior to reduction. Synthetically useful yield and good enantioselectivity were achieved at 1 mol% catalyst loading. Sterically hindered ketones also undergo reductive amination in good yield and enantioselectivity by the two-step one-pot procedure. The asymmetric synthesis of (+)-NPS R-568 was demonstrated in good yield and high enantioselectivity using the two-step one-pot procedure. Lewis acidic TMSOTf can improve the yield in the directed reductive amination, but showed a negative effect on the enantioselectivity.

Initial investigations into the mechanism have resulted in unprecedented discoveries. Both the NMR study of catalyst **117** and the discovery of the new high active catalyst **263** place the Matsumura transition state model into doubt. A new tentative transition state model was proposed according to the study of structure/activity of catalysts and the preliminary *in-situ* IR data.

Considering all the results obtained so far, the generality of the new highly active catalyst

will be investigated in the future. In order to elucidate the mechanism, more structurally related catalysts need be prepared and evaluated. A detailed kinetic study of the reaction is also a good method to justify the tentative transition state model. In this respect, ReactIR provides a powerful tool to accrue this data and as well as identify reactive intermediates. It is very likely that controlling the geometry of imine is crucial to obtaining high selectivity and new experiments will be designed to further confirm this.

7. Experimental

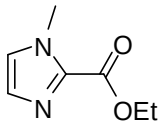
7.1 General information

Unless stated otherwise, all solvents were obtained from a Grubbs dry solvent system and glassware was flame dried and cooled under vacuum before use. All chemicals were used as received without further purification unless otherwise stated. Analytical thin layer chromatography (TLC) was performed using Merck 60 F254 precoated silica gel plates. Subsequent to elution, plates were visualized using UV radiation (254 nm); further visualization was possible by staining with a basic solution of potassium permanganate or silica supported iodine. Flash chromatography was performed using silica gel 40-63μ 60Å (Fluorochem Limited). Columns were typically packed as slurry and equilibrated with the appropriate solvent system prior to use. ^{1}H and ^{13}C NMR spectra were recorded on Bruker 500 MHz, 400 MHz or 250 MHz spectrometer at ambient temperature unless otherwise stated. Chemical shifts for ^{1}H NMR spectra are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-d (δ 7.26, singlet) or DMSO-d_6 (2.50 ppm, quintet). Coupling constants are reported as a *J* value in. Data for ^{13}C NMR are reported as δ in ppm downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-d (δ 77.0, triplet) or DMSO-d_6 (39.7 ppm, quintet). Mass spectra (*m/z*) were recorded on a 'VG'-Autospec for Electron Ionisation (EI) and on a 'Waters'-LCT for Electrospray (ES). Infrared spectra were recorded on a Perkin-Elmer 1600 FT-IR as thin film from a solution in dichloromethane or chloroform. Specific rotations were performed at room temperature on an Optical Activity Ltd. AA-10 automatic polarimeter at 589 nm (Na D-line) and $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. Melting points were measured on a Gallenkamp apparatus and uncorrected. Elemental analysis was performed on a Perkin-Elmer 2400 CHNS/O Series II apparatus. Enantioselectivities were determined by high performance liquid chromatography (HPLC) analysis employing a Gilson HPLC chain with an ABI Analytical Spectroflow 783 UV detector at λ 254 nm unless specified otherwise, using a mixture of hexane and propan-2-ol as mobile phase and Chiralcel OD-H, Chiralcel OJ, Kromasil 3-Cellucoat OD, Phenomenex Lux 3u amylase-2 or Phenomenex Lux 3u

cellulose-1 column as the stationary phase. Mobile phase flow, unless specified otherwise, was 1.0 mL/min. GC was performed using a Perkin Elmer Autosystem XL gas chromatograph fitted with a Supleco fused silica capillary column (Astec Chiraldex B-DM) (30 m × 0.25 mm × 0.12 μm film thickness) using nitrogen as the carrier gas and detection by standard FID. Absolute configuration of the products was determined by comparison with compounds previously published.

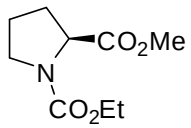
7.2 Procedures for catalyst synthesis

Ethyl 1-methylimidazole-2-carboxylate 123[79]



A solution of 1-methylimidazole (100 mmol, 8.21 g) and triethylamine (25 mL) in acetonitrile (50 mL) was cooled to -30 ºC. A solution of ethyl chloroformate (160 mmol, 15.3 mL) in acetonitrile (25 mL) was added, while maintaining the temperature lower than 10 ºC. The mixture was warmed up to room temperature slowly and stirred overnight. The solid was filtered off and the filtrate was concentrated. The residue was dissolved in water (150 mL), extracted with $CHCl_3$ (2 × 100 mL). The combined organic phases were dried over $MgSO_4$ and filtrated. The filtrate was evaporated under reduced pressure. The resulting yellow oil was purified by chromatography column on silica gel using AcOEt as eluent, yielding a yellow oil (10 g, 65% yield) which crystallised almost immediately upon cooling in fridge, m.p. 43-44 °C (lit.[79] 43-45 ºC); δ_H (250 MHz, $CDCl_3$) 1.42 (t, 3H, *J* 7.2, OCH_2CH_3), 4.00 (s, 3H, NCH_3), 4.39 (q, 2H, *J* 7.2, OCH_2CH_3), 7.02 (app. d, 1H, *J* 1.1, ArC*H*), 7.12 (app. d, 1H, *J* 1.1, ArC*H*); Data was in accordance with the literature.

(*S*)-*N*-Ethoxycarbonylproline methyl ester 121[79]

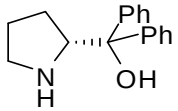


Preparation by the same procedure reported in literature,[79] obtained in quantitative yield as a colourless oil; δ_H (250 MHz, $CDCl_3$, 1:1 mixture of rotamers) 1.20 (t, 3H, rotamer A, *J* 6.9, C_2HCH_3), 1.28 (t, 3H, *J* 6.8, rotamer B, CH_2CH_3), 1.85 - 2.33 (m, 4H, rotamer A, 4 × CH_2),

1.85 - 2.33 (m, 4H, rotamer B, 4 × CH_2), 3.39 - 3.66 (m, 2H, rotamer A, C*H*$_2$N), 3.39 - 3.66 (m, 2H, rotamer B, C*H*$_2$N),3.73 (s, 3H, rotamer A, OC*H*$_3$), 3.75 (s, 3H, rotamer B, OC*H*$_3$), 4.04 - 4.23 (m, 2H, rotamer A, C*H*$_2$CH$_3$), 4.04 - 4.23 (m, 2H, rotamer B, C*H*$_2$CH$_3$), 4.31 (dd, 1H, *J* 8.2, 3.5, rotamer A, C*H*N), 4.38 (dd, 1H, *J* 8.5, 3.5, rotamer B, C*H*N); Data was in accordance with the literature.

(*R*)-*N*-Ethoxycarbonylproline methyl ester **121**[120] was prepared by same procedure starting from D-proline.

(*R*)-α,α-Diphenylprolinol 122[79]

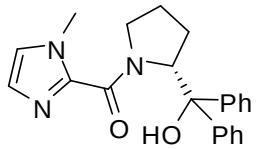


Magnesium turnings (2.74 g, 114 mmol), a catalytic amount of iodine and THF (42 mL) were added into a 250 mL two-necked flask fitted with a dropping funnel under a N_2 atmosphere. Bromobenzene (8.96 g, 57 mmol) and THF (22mL) were introduced into the dropping funnel. The reaction was initiated by heating after addition of *ca*. 5 mL of the solution of bromobenzene in THF, which then was added dropwise at a rate to keep the reaction heated at reflux. After addition was completed, the reaction mixture was stirred at room temperature for 40 mins. This new prepared phenylmagnesium bromide solution was slowly added to an ice cold solution of (*R*)-*N*-ethoxycarbonylproline methyl ester **121** (2.87 g, 14.3 mmol) in THF (40 mL) *via* cannula. The resulting reaction mixture was warmed to room temperature and stirred overnight. After being cooled to 0 °C, the reaction was quenched with saturated aqueous ammonium chloride solution (20 mL). The insoluble solid was filtered off and washed with dichloromethane (100 mL). After the filtrate was concentrated under reduced pressure, the residue was dissolved in water (100 mL) and extracted with chloroform (3 × 60 mL). The combined organic phases were washed with brine (50 mL) and dried over magnesium sulfate. After filtration and evaporation of the solvent, the residue was dissolved in methanol (30 mL) with potassium hydroxide (8.0 g) and refluxed for overnight. After cooling to ambient temperature, the methanol was removed *in vacuo* and the residue was treated with water (50 mL) and extracted with dichloromethane (3 × 50 mL). The combined organic phases were dried over $MgSO_4$. After filtration and

concentration under reduced pressure, the residue was purified by chromatography on silica gel (1 : 1 petroleum ether / ethyl acetate ~ ethyl acetate) to yield the product (1.8 g, 49%) as white solid; m.p. 74-75 °C (lit.[79] 63-65 °C for *S* isomer); $[\alpha]_D$ +58 (*c* 2.0 in MeOH, lit.[121] +59, *c* 2.0 in MeOH); δ_H (250 MHz, $CDCl_3$) 1.55 - 1.82 (m, 4H, 4 × C*H*$_2$), 2.91 - 3.10 (m, 2H, C*H*$_2$N), 4.28 (t, 1H, *J* 7.5, C*H*N), 7.15 - 7.22 (m, 2H, ArC*H*), 7.28 - 7.35 (m, 4H, ArC*H*), 7.50 - 7.62 (m, 4H, ArC*H*); δ_C (63 MHz, $CDCl_3$) 25.6 (*C*H$_2$), 26.3 (*C*H$_2$), 46.8 (*C*H$_2$N), 64.5 (*C*HN), 77.1 (*C*Ph$_2$OH) 125.6 (2 × Ar*C*H), 125.9 (2 × Ar*C*H), 126.4 (Ar*C*H), 126.5 (Ar*C*H), 128.0 (2 × Ar*C*H), 128.3 (2 × Ar*C*H), 145.5 (Ar*C*), 148.3 (Ar*C*). Data was in accordance with the literature.

(*S*)-α,α-Diphenylprolinol **122**[79] was prepared by same procedure starting from (*S*)-*N*-ethoxycarbonylproline methyl ester **121**; white solid, m.p. 65-68 °C (lit.[79] 63-65 °C); $[\alpha]_D$ -57.3 (*c* 2 in MeOH, lit.[121] +59, *c* 2 in MeOH for *R* isomer); Data was in accordance with the literature.

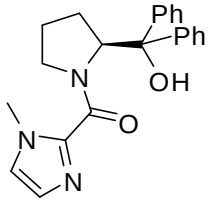
[(2*R*)-2-(Hydroxydiphenylmethyl)-1-pyrrolidinyl](1-methyl-1H-imidazol-2-yl)-methanone 117[79]



(*R*)-α,α-Diphenylprolinol **122** (1.8 g, 7.1 mmol) was dissolved in toluene (8 mL) and NaH (60% dispersion in mineral oil, 371 mg, 9.2 mmol) was added at room temperature. After stirring for 30 mins, ethyl 1-methylimidazole-2-carboxylate **123** (1.31 g, 8.5 mmol) was added. The resulting reaction mixture was slowly warm to 70 °C and stirred for 40 h at the same temperature. The reaction was cooled to room temperature, quenched by addition of water (10 mL) and extracted with dichloromethane (4 × 20 mL). The combined organic extracts were washed with brine (20 mL) and dried over magnesium sulfate. After filtration, the filtrate was evaporated and purified by chromatography on silica gel (50% ethyl acetate in petroleum ether ~ ethyl acetate) to yield the product (1.2 g, 47%) as white solid, m.p. 146-149 °C (from ethyl acetate and petroleum, lit.[79] 143-145 ºC from dichloromethane and petroleum ether 40-60 ºC); (Found: C, 73.07; H, 6.40, N, 11.71. $C_{22}H_{23}N_3O_2$ requires C,

73.11; H, 6.41, N, 11.63); $[\alpha]_D$ +127 (*c* 0.44 in $CHCl_3$, lit.[79] -88, *c* 0.5 in $CHCl_3$ for *S* isomer); δ_H (500 MHz, d_6-DMSO, 102.5 ºC) 1.67 - 1.83 (m, 2H, CH_2), 1.94 - 1.99 (m, 1H, 1 × CH_2), 2.07 - 2.15 (m, 1H, 1 × CH_2), 3.36 (s, 3H, NCH_3), 3.49 (ddd, 1H, *J* 11.5, 8.9, 6.9, CH_2N), 3.93 (ddd, 1H, *J* 11.5, 9.2, 5.2, CH_2N), 5.84 (s, 1H, C*H*N), 6.16 (br, s, 1H, O*H*), 6.86 (app. t, 1H, *J* 0.6, ArC*H*), 6.98 (s, 1H, ArC*H*), 7.05-7.09 (m, 3H, ArC*H*), 7.14 (br, app. d, 2H, *J* 11.0, ArC*H*), 7.21 - 7.25 (m, 1H, ArC*H*), 7.30 - 7.33 (m, 2H, ArC*H*), 7.45 - 7.47 (m, 2H, ArC*H*); δ_C (126 MHz, d_6-DMSO, 102.5 ºC) 22.2 (*C*H_2), 27.2 (*C*H_2), 33.7 (*C*H_2), 47.5 (N*C*H_3), 63.6 (N*C*H), 80.8 (Ph_2*C*OH), 123.2 (Ar*C*H), 125.2 (Ar*C*H), 125.5 (Ar*C*H), 126.08 (2 ×Ar*C*H), 126.1 (3 ×Ar*C*H), 126.5 (2 ×Ar*C*H), 127.1 (2 ×Ar*C*H), 140.1 (Ar*C*), 145.3 (2 × Ar*C*), 158.9 (*C*O); *m*/*z* (TOF ES+) 384.1678 (M^++ Na, $C_{22}H_{23}N_3O_2Na$ requires 384.1688).

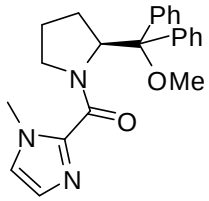
Column free procedure for the synthesis of (*S*)-catalyst 117[79]



Magnesium turnings (4.32 g, 180 mmol), a catalytic amount of iodine and THF (30 mL) were added into a 250 mL three-necked flask fitted with a dropping funnel under a N_2 atmosphere. Bromobenzene (14.13 g, 90 mmol) and THF (100 mL) were introduced into the dropping funnel. The reaction was initiated by heating after addition of *ca*.10 mL of the solution of bromobenzene in THF, which then was added dropwise at a rate to keep the reaction heating at reflux. After complete addition, the reaction mixture was heated to reflux for 30 mins and then cooled to 0 °C. A solution of (*S*)-*N*-ethoxycarbonylproline methyl ester **121** (6.03 g, 30 mmol) in THF (30 mL) was added dropwise. The resulting reaction mixture was warmed to room temperature and stirred overnight. After cooling to 0 °C, the reaction was quenched with saturated aqueous ammonium chloride solution (10 mL). After stirring for 30 mins, the insoluble solid was filtered off and washed with dichloromethane (100 mL). The filtrate was concentrated under reduced pressure, the residue re-dissolved in dichloromethane (200 mL), washed with brine (50 mL) and dried over magnesium sulfate. After filtration and evaporation, the residue was dissolved in methanol (100 mL) with

potassium hydroxide (16.8 g) and refluxed for overnight. After cooling to ambient temperature, methanol was removed *in vacuo* and the residue was treated with water (100 mL). This was extracted with dichloromethane (3 × 100 mL) and the combined organic phases were washed with brine (50 mL) and dried over magnesium sulfate. After filtration, the filtrate was concentrated under reduced pressure to afford mainly prolinol **122** which was used directly for next step. This crude product was dissolved in toluene (30 mL) and NaH (60% dispersion in mineral oil, 1.56 g, 39 mmol) was added at room temperature. After stirring for 30 mins, ethyl 1-methylimidazole-2-carboxylate **123** (5.08 g, 33 mmol) was added. The resulting reaction mixture was slowly warm to 70 °C and stirred for 30 h at the same temperature. After cooling to room temperature, water (30 mL) was added and the mixture was extracted with dichloromethane (4 × 50 mL). The combined organic phases were washed with brine (50 mL) and dried over magnesium sulfate. After filtration, the filtrate was evaporated to give a brown solid that was washed with a mixture of petroleum ether and ethyl acetate. The crude product was purified by recrystallisation from ethyl acetate (2-3 times) to afford the pure product (4.6 g, 42% over 3 steps) as white solid, m.p. 144-146 °C (from ethyl acetate, lit.[79] 143-145 ºC); $[\alpha]_D$ -104 (*c* 0.6 in $CHCl_3$, lit.[79] -88, *c* 0.5 in $CHCl_3$); Data was in accordance with the literature.

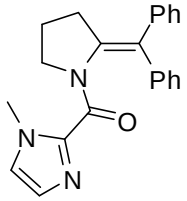
(*S*)-[2-(Methoxydiphenylmethyl)pyrrolidin-1-yl](1-methyl-1H-imidazol-2-yl)methanone 263



NaH (60% dispersion in mineral oil, 44 mg, 1.1 mmol) was added to a solution of (*R*)-**117** (0.361g, 1 mmol) in THF (10 mL). After stirring for 20 min at room temperature, MeI (156 mg, 1.1 mmol) was added dropwise at the same temperature and was then stirred overnight. The resulting mixture was quenched by saturated aqueous NH_4Cl (10 mL). The organic phase was separated and the aqueous phase was extracted with dichloromethane (3 × 10 mL). The combined organic phases were dried over $MgSO_4$. After filtration and concentration, the

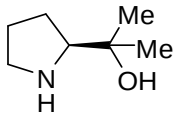
residue was purified by chromatography on silica gel (20% ~ 50% ethyl acetate in petroleum ether) to yield the product as white foam-like solid (0.21 g, 56%); m.p. 93-95 °C; $[\alpha]_D$ -68 (*c* 0.5 in $CHCl_3$); ν_{max} (thin film, cm^{-1}) 2927, 1624, 1463; δ_H (400 MHz, $CDCl_3$, as a 4.6:1 mixture of two rotamers A and B) 1.03 - 1.16 (m, 1H, rotamer A, 1 × C*H*$_2$), 1.03 - 1.16 (m, 1H, rotamer B, 1 × C*H*$_2$), 1.45 - 1.53 (m, 1H, rotamer B, 1 × C*H*$_2$), 1.57 - 1.68 (m, 1H, rotamer A, 1 × C*H*$_2$), 1.98 - 2.05 (m, 1H, rotamer A, 1 × C*H*$_2$) 1.98 - 2.05 (m, 2H, rotamer B, C*H*$_2$), 2.25 - 2.48 (m, 2H, rotamer A, C*H*$_2$), 2.38 (s, 3H, rotamer A, C*H*$_3$), 2.95 - 3.02 (m, 1H, rotamer B, 1 × C*H*$_2$), 3.00 (s, 3H, rotamer B, C*H*$_3$), 3.54 - 3.61 (m, 1H, rotamer A, NC*H*), 3.70 - 3.76 (m, 1H, rotamer B, NC*H*), 3.79 (s, rotamer A, NC*H*$_3$), 3.86 (s, rotamer B, NC*H*$_3$), 5.72 (dd, *J* 8.7, 3.1, 1H, rotamer B, NC*H*), 6.31 (d, *J* 8.9, 1H, rotamer A, NC*H*), 6.79 (d, *J* 0.9, 1H, rotamer A, Ar*H*), 6.89 (s, 1H, rotamer B, Ar*H*), 6.95 (d, *J* 0.9, 1H, rotamer A, Ar*H*), 7.07 (s, 1H, rotamer B, Ar*H*), 7.26 - 7.36 (m, 9H, rotamer A, Ar*H*), 7.26 - 7.36 (m, 10H, rotamer B, Ar*H*), 7.46-7.52 (m, 1H, rotamer A, Ar*H*); δ_C (100 MHz, $CDCl_3$) 21.8 (rotamer A, *C*H_2), 23.9 (rotamer B, *C*H_2), 26.6 (rotamer B, *C*H_2), 29.7 (rotamer A, *C*H_2), 34.2 (rotamer A, N*C*H_3), 35.4 (rotamer B, N*C*H_3), 47.4 (rotamer A, N*C*H_2), 50.7 (rotamer B, N*C*H_2), 51.8 (rotamer A, O*C*H_3), 52.5 (rotamer B, O*C*H_3), 60.4 (rotamer B, N*C*H), 63.5 (rotamer A, N*C*H), 68.8 (rotamer A, *C*OMe), 122.4 (rotamer A, Ar*C*H), 123.9 (rotamer B, Ar*C*H), 126.6 (rotamer A, Ar*C*H), 127.4 (rotamer B, Ar*C*H), 127.5 (rotamer B, Ar*C*H), 127.6 (rotamer A, Ar*C*H), 127.7 (rotamer A, Ar*C*H), 127.8 (rotamer B, Ar*C*H), 129.4 (rotamer A, Ar*C*H), 129.6 (rotamer B, Ar*C*H), 130.0 (rotamer A, Ar*C*H), 138.8 (rotamer A, Ar*C*), 139.7 (rotamer A, Ar*C*), 140.1 (rotamer B, Ar*C*), 141.2 (rotamer B, Ar*C*), 142.6 (rotamer A, Ar*C*), 161.2 (rotamer A, *C*O); *m*/*z* (TOF ES+) 376.2023 (MH^+, $C_{23}H_{26}N_3O_2$ requires 376.2025).

[2-(Diphenylmethylene)pyrrolidin-1-yl](1-methyl-1H-imidazol-2-yl)methanone 265



Lawesson's reagent (0.7 mmol) was added to a solution of (*S*)-**117** (1 mmol) in toluene (5 mL) at room temperature and the resulting mixture was heated at 100 ºC for 15 h. The reaction mixture was then cooled to room temperature and quenched with aqueous NaOH (1 *N*, 20mL). The aqueous phase was extracted with dichloromethane (3 × 30 mL) and the combined organic phases were washed with brine (20 mL) and dried over $MgSO_4$. The desiccant was filtered off and the filtrate was concentrated. The residue was purified by chromatography on silica (50% petroleum in ethyl acetate to 100% ethyl acetate) to afford the product as a light yellow solid (23%); m.p. 169-171 ºC; ν_{max} (thin film, cm^{-1}) 2954, 1633, 1442, 1369; δ_H (500 MHz, 100 ºC, $CDCl_3$) 1.94-2.00 (m, 2H, CH_2), 2.53 (t, 2H, *J* 7.6, CH_2), 3.04 (s, 3H, NCH_3), 3.74 (t, 2H, *J* 7.5, CH_2), 6.69 - 6.71 (m, 2H, Ar*H*), 6.85 - 6.87 (m, 2H, Ar*H*), 7.08 - 7.15 (m, 5H, Ar*H*), 7.19 - 7.22 (m, 1H, Ar*H*), 7.26 - 7.29 (m, 2H, Ar*H*); δ_C (126 MHz, 100 ºC, $CDCl_3$) 20.0 (*C*H_2), 28.9 (*C*H_2), 32.4 (*C*H_3), 45.9 (*C*H_2), 123.1 (Ar*C*H), 125.6 (Ar*C*H), 126.1 (Ar*C*H), 126.3 (Ar*C*H), 126.4 (*C*), 127.1 (2 × Ar*C*H), 127.3 (2 × Ar*C*H), 128.3 (2 × Ar*C*H), 128.9 (2 × Ar*C*H), 137.2 (Ar*C*), 139.7 (*C*), 140.7 (Ar*C*), 141.4 (Ar*C*), 158.6 (*C*O); *m/z* (TOF ES+) 344.1748 (MH^+, $C_{22}H_{22}N_3O$ requires 344.1763).

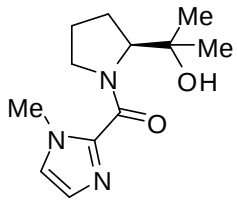
(*S*)-α,α-Dimethyl-2-pyrrolinol[122]



Mg (1.92g, 80 mmol), iodine (one granule) and diethyl ether (20 mL) was added into an oven-dry 3-neck N_2-filled flask. A solution of MeI (4.98 g, 80 mmol) in THF (80 mL) was added dropwise (initiated by heat after about 5-10 mL addition). The mixture was stirred at room temperature for 2 hours and then cooled to 0 °C. A solution of (*S*)-*N*-ethoxycarbonylproline methyl ester **121** (4.02 g, 20 mmol) in diethyl ether (20 mL) was added dropwise. The resulting mixture was stirred at room temperature overnight, cooled to 0 °C and quenched with sat. aqueous ammonium chloride (50 mL). The organic layer was separated and the aqueous layer extracted with diethyl ether (2 × 50 mL). The combined organic extracts were concentrated to afford yellow oil (3.36 g). This residue was treated with KOH (9.3 g), water (60 mL) and ethanol (40 mL), and heated as reflux overnight. The

mixture was cooled to room temperature and ethanol was removed under reduced pressure. The resulting aqueous phase extracted with dichloromethane (2 × 50 mL), the combined extracts were washed with brine (30 mL) and dried over $MgSO_4$. After filtration, the filtrate was concentrated under reduced pressure to afford the title compound as brown low melting solid (1.87 g, 72%); $[\alpha]_D$ -28 (*c* 2 in MeOH, lit.[122] -32.3, *c* 1.84 in MeOH); δ_H (400 MHz, $CDCl_3$) 1.14 (s, 3H, C*H*$_3$), 1.18 (s, 3H, C*H*$_3$), 1.60 - 1.82 (m, 4H, 2 × C*H*$_2$), 2.84 (br s, 2H, N*H* and O*H*), 2.90 - 3.05 (m, 3H, NC*H*$_2$, and NC*H*); δ_C (100 MHz, $CDCl_3$) 25.2 (*C*H_3), 26.1 (*C*H_2), 26.3 (*C*H_2), 28.6 (*C*H_3), 47.0 (N*C*H_2), 67.0 (N*C*H), 70.3 [*C*(*O*H)Me_2); Data was in accordance with the literature.

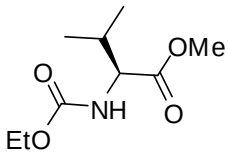
(*S*)-[2-(2-Hydroxypropan-2-yl)pyrrolidin-1-yl](1-methyl-1H-imidazol-2-yl)methanone 256



(*S*)-α,α-Dimethyl-2-pyrrolinol (1.29 g, 10 mmol) was dissolved in toluene (10 mL) and NaH (60% dispersion in mineral oil, 600 mg, 15 mmol) was added at room temperature. After stirring for 30 mins, ethyl 1-methylimidazole-2-carboxylate **123** (1.69 g, 11 mmol) was added. The resulting reaction mixture was slowly warmed to 70 °C and stirred for 40 h at this temperature. The reaction was cooled to room temperature, quenched by addition of water (20 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic phases were dried over $MgSO_4$. After filtration, the filtrate was evaporated and purified by chromatography on silica gel (50% ethyl acetate in petroleum ether ~ ethyl acetate) to yield the product (0.896 g, 39%) as white solid, m.p. 84-86 °C; (Found: C, 60.70; H, 7.98, N, 17.70. $C_{12}H_{19}N_3O_2$ requires C, 60.74; H, 8.07, N, 17.71); ν_{max} (thin film, cm^{-1}) 3353, 2974, 1607, 1455; $[\alpha]_D$ -124 (*c* 1.1 in $CHCl_3$); δ_H (500 MHz, d_6-DMSO, 100 ºC) 1.07 (s, 6H, 2 × C*H*$_3$), 1.65 - 1.70 (m, 1H, 1 × C*H*$_2$), 1.89 - 1.95 (m, 3H, 3 × C*H*$_2$), 3.54 (br, 1H, 1 × NC*H*$_2$), 3.79 (s, 3H, NC*H*$_3$), 4.03 (br, 1H, 1 × C*H*$_2$N), 4.48 (br, 1H, O*H*), 4.71 (br, 1H, NC*H*), 6.95 (s, 1H, ArC*H*), 7.19 (s, 1H, ArC*H*); δ_C (126 MHz, d_6-DMSO, 100 ºC) 23.4 (*C*H_2), 25.6

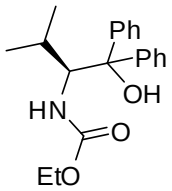
(CH_2), 25.7 (CH_3), 26.9 (CH_3), 33.8 (NCH_3), 48.7 (NCH_2), 65.2 (N*C*H), 72.4 (Me_2*C*OH), 123.5 (Ar*C*H), 126.1 (Ar*C*H), 140.4 (Ar*C*), 160.4 (*C*O); *m*/*z* (TOF ES+) 238.1556 (100%, MH^+, $C_{12}H_{20}N_3O_2$ requires 238.1550), 220.1455 (8).

(*S*)-Methyl 2-(ethoxycarbonylamino)-3-methylbutanoate[123]



The title compound was prepared using the same procedure for the synthesis of (*S*)-*N*-ethoxycarbonylproline methyl ester (**121**). The crude product was obtained colourless oil and used for next step directly without further purification (quantitative yield); δ_H (400 MHz, $CDCl_3$, as a 3.7:1 mixture of two rotamers), major rotamer: 0.91 (d, 3H, *J* 7.8, major rotamer, CH_3), 0.99 (d, 3H, *J* 6.8, major rotamer, CH_3), 1.27 (t, 3H, *J* 7.1, major rotamer, CH_3), 1.33 (t, 3H, minor rotamer, *J* 7.1, CH_3), 2.13 - 2.23 (m, 1H, major rotamer, C*H*), 2.13 - 2.23 (m, 1H, minor rotamer, C*H*), 3.76 (s, 3H, major rotamer, OCH_3), 3.80 (s, 3H, minor rotamer, OCH_3), 4.14 (q, 2H, *J* 7.1, major rotamer, OCH_2), 4.23 (q, 2H, *J* 7.1, minor rotamer, OCH_2), 4.31 (dd, 1H, *J* 8.8, 4.8, major rotamer, NC*H*), 4.57 (dd, 1H, *J* 9.1, 4.8, minor rotamer, NC*H*), 5.17 (d, 1H, *J* 9.2, major rotamer, N*H*), 5.26 (d, 1H, *J* 8.2, minor rotamer, N*H*); ^{1}H NMR data was generally in accordance with the literature, although the minor isomer was not characterised.

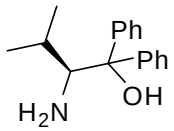
(*S*)-Ethyl 1-hydroxy-3-methyl-1,1-diphenylbutan-2-yl carbamate



Magnesium (4.32 g, 180 mmol), catalytic amount of I_2 (1 granule) and THF (10 mL) was added into a 3-neck flask fitted with a dropping funnel under nitrogen. A solution of bromobenzene (18.84 g, 120 mmol) in THF (110 mL) was introduced into the dropping funnel and added dropwise to keep the reaction mixture heated at gentle reflux (after addition of *c.a.* 10 mL of this solution, if the colour of iodine did not disappear, the reaction

was heated gently to be initiated before addition of the rest bromobenzene solution). The mixture was stirred for 2 h after addition and then cooled to 0 °C. A solution of (*S*)-methyl 2-(ethoxycarbonylamino)-3-methylbutanoate (6.09 g, 30 mmol) in THF (30 mL) was added dropwise, and the resulting mixture was stirred at room temperature for 2 hr. The reaction was cooled to 0 °C and quenched with aqueous saturated ammonium chloride (100 mL). The organic layer was separated and aqueous layer extracted with dichloromethane (2 × 50 mL). The combined organic phase was dried over $MgSO_4$ and filtered. The filtrate was concentrated to afford a solid residue, which was washed with petroleum ether to give pure product (5.4 g, 55 %) as a white solid; m.p. 196-198 °C; (Found: C, 73.27; H, 7.82, N, 4.25. $C_{20}H_{25}NO_3$ requires C, 73.37; H, 7.70, N, 4.28); ν_{max} (thin film, cm^{-1}) 3483, 3359, 1605, 1670, 1545; $[\alpha]_D$ -75.4 (*c* 0.35 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.89 (d, 3H, *J* 6.8, C*H*$_3$), 0.91 (d, 3H, *J* 6.9, C*H*$_3$), 1.15 (t, 3H, *J* 6.9, OCH$_2$C*H*$_3$), 1.82 - 1.87 (m, 1H, C*H*Me$_2$), 2.64 (br, s, 1H, O*H*), 4.05 (q, 2H, *J* 6.9, OC*H*$_2$CH$_3$), 4.67 (d, 1H, *J* 10.3, NC*H*), 7.18 - 7.36 (m, 6H, Ar*H*), 7.46 - 7.53 (m, 4H, Ar*H*); δ_C (100 MHz, $CDCl_3$) 14.6 (*C*H$_3$), 17.4 (*C*H$_3$), 22.7 (*C*H$_3$), 28.9 (*C*HMe$_2$), 59.6 (N*C*H), 60.8 (O*C*H$_2$), 82.3 (*C*Ph$_2$OH), 125.4 (2 × Ar*C*H), 125.7 (2 × Ar*C*H), 126.8 (Ar*C*H), 126.9 (Ar*C*H), 128.3 (2 × Ar*C*H), 128.4 (2 × Ar*C*H), 145.5 (Ar*C*), 146.3 (Ar*C*), 157.1 (*C*O); *m*/*z* (ES+), 310 (100%, MH^+), 282 (10).

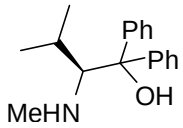
(*S*)-2-Amino-3-methyl-1,1-diphenyl-1-butanol[124]



A solution of (*S*)-ethyl 1-hydroxy-3-methyl-1,1-diphenylbutan-2-yl carbamate (4.3 g, 13.1 mmol) and KOH (7.3 g, 131 mmol) in aqueous 40% EtOH (100 mL) was heated at reflux overnight. The reaction mixture was cooled to room temperature, and a white precipitate formed. Water (40 mL) was added and the solid was collected by filtration to afford the pure product (2.9 g, 85%) as white solid; m.p. 105-107 °C (lit.[124] 96 °C); $[\alpha]_D$ -135 (*c* 0.7 in $CHCl_3$, lit.[124] -127.1, *c* 0.7 in $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 0.91 (d, 3H, *J* 6.8, C*H*$_3$), 0.95 (d, 3H, *J* 7.0, C*H*$_3$), 1.72 - 1.81 (m, 1H, C*H*), 3.87 (d, 1H, *J* 2.1, NC*H*), 7.17 - 7.24 (m, 2H, Ar*H*), 7.27 - 7.36 (m, 4H, Ar*H*), 7.50 - 7.54 (m, 2H, Ar*H*), 7.61 - 7.66 (m, 2H, Ar*H*); δ_C (63

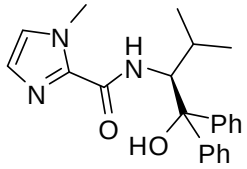
MHz, $CDCl_3$) 16.1 (*C*H_3), 23.0 (*C*H_3), 28.0 (*C*H), 60.2 (N*C*H), 79.7 (*C*OH), 125.5 (2 × Ar*C*H), 125.9 (2 × Ar*C*H), 126.3 (Ar*C*H), 126.6 (Ar*C*H), 128.0 (2 × Ar*C*H), 128.4 (2 × Ar*C*H), 144.9 (Ar*C*), 148.1 (Ar*C*); Data was in accordance with the literature.

(*S*)-3-Methyl-2-(methylamino)-1,1-diphenyl-1-butanol[125]



A solution of (*S*)-ethyl 1-hydroxy-3-methyl-1,1-diphenylbutan-2-yl carbamate (3.27 g, 10 mmol) in THF (20 mL) was added dropwise into a suspension of $LiAlH_4$ (1.52 g, 40 mmol) in THF (20 mL) at 0 °C. The mixture was heated at reflux for 15 h and then cooled to 0 °C. The reaction was carefully quenched with brine (20 mL) and diluted with ethyl acetate (100 mL). The solid was filtered and the filtrate washed with brine (20 mL) and dried over $MgSO_4$. Filtration and evaporation of the solvent afforded the crude product, which was triturated with petroleum ether and filtered. The filtrate was concentrated to afford the pure product as white solid (2.13 g, 79%); m.p. 59-61 °C (lit.[125] 69-71 °C); $[\alpha]_D$ -37.7 (*c* 2.1 in $CHCl_3$, lit.[125] -50.4, *c* 2.1, $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 0.71 (d, 3H, *J* 6.9, C*H*$_3$), 1.07 (d, 3H, *J* 7.1, C*H*$_3$), 1.95 - 2.08 (m, 1H, C*H*), 2.22 (s, NC*H*$_3$), 3.46 (d, 1H, *J* 2.0, NC*H*), 5.19 (br, s, N*H*), 7.16 - 7.36 (m, 6H, Ar*H*), 7.57 - 7.60 (m, 2H, Ar*H*), 7.71 - 7.75 (m, 2H, Ar*H*); δ_C (63 MHz, $CDCl_3$) 15.8 (*C*H_3), 22.9 (*C*H_3), 28.8 (*C*H), 38.1 (N*C*H_3), 70.6 (N*C*H), 78.6 (*C*OH), 125.9 (2 × Ar*C*H), 126.1 (Ar*C*H), 126.2 (2 × Ar*C*H), 126.4 (Ar*C*H), 127.9 (2 × Ar*C*H), 128.0 (2 × Ar*C*H), 145.5 (Ar*C*), 148.9 (Ar*C*); Data was in accordance with the literature.

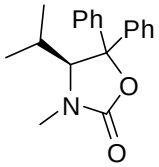
(*S*)-*N*-(1-Hydroxy-3-methyl-1,1-diphenylbutan-2-yl)-1-methyl-1H-imidazole-2-carboxamide 256



(*S*)-2-Amino-3-methyl-1,1-diphenyl-1-butanol (1.27 g, 5 mmol) was dissolved in toluene (10 mL) and NaH (60% dispersion in mineral oil, 0.26 g, 6.5 mmol) was added at room temperature. After stirring for 30 mins, ester **123** (0.847 g, 5.5 mmol) was added. The

resulting reaction mixture was slowly warm to 70 °C and stirred for 48 h at the same temperature. The reaction was cooled to room temperature, quenched by addition of water (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with brine (10 mL) and dried over $MgSO_4$. After filtration, the filtrate was evaporated and the residue was purified by recrystallisation from ethyl acetate/petroleum ether to yield the product (0.7 g, 38%) as white solid, m.p. 199-201 °C; (Found: C, 72.58; H, 6.81, N, 11.50. $C_{22}H_{25}N_3O_2$ requires C, 72.70; H, 6.93, N, 11.56); ν_{max} (thin film, cm^{-1}) 3396, 2960, 1659, 1538, 1503; $[\alpha]_D$ -117.7 (*c* 0.62 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.91 (d, 3H, *J* 6.9, C*H*$_3$), 1.07 (d, 3H, *J* 6.8, C*H*$_3$), 1.95 – 2.03 (m, 1H, C*H*), 4.04 (s, 3H, NC*H*$_3$), 4.47 (s, 1H, O*H*), 5.03 (dd, 1H, *J* 10.2, 2.4, NC*H*), 6.91 (d, 1H, *J* 1.2, Ar*H*), 6.93 (d, 1H, *J* 1.2, Ar*H*), 7.08 - 7.12 (m, 1H, Ar*H*), 7.18 - 7.24 (m, 3H, Ar*H*), 7.32 - 7.35 (m, 2H, Ar*H*), 7.58 - 7.61 (m, 4H, Ar*H*), 8.32 (d, 1H, *J* 10.2, N*H*); δ_C (100 MHz, $CDCl_3$) 18.0 (*C*H$_3$), 23.0 (*C*H$_3$), 29.2 (*C*H), 36.4 (N*C*H$_3$), 59.2 (N*C*H), 82.0 (Ph$_2$*C*OH), 124.4 (Ar*C*H), 125.3 (Ar*C*H), 125.6 (2 × Ar*C*H), 125.7 (2 × Ar*C*H), 126.6 (Ar*C*H), 126.7 (Ar*C*H), 128.1 (2 × Ar*C*H), 128.2 (2 × Ar*C*H), 138.6 (Ar*C*), 146.0 (Ar*C*), 146.8 (Ar*C*), 158.6 (*C*O); *m*/*z* (TOF ES+) 364.2029 (100%, MH^+, $C_{22}H_{26}N_3O_2$ requires 364.2029), 346.1904 (98).

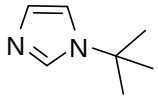
(*S*)-4-Isopropyl-3-methyl-5,5-diphenyloxazolidin-2-one



(*S*)-3-Methyl-2-(methylamino)-1,1-diphenyl-1-butanol (1.28 g, 4.76 mmol) was dissolved in toluene (10 mL) and NaH (60% dispersion in mineral oil, 0.247 g, 6.12 mmol) was added at room temperature. After stirring for 30 mins, ester **123** (0.806 g, 5.23 mmol) was added. The resulting reaction mixture was slowly warm to 70 °C and stirred for 48 h at this temperature. The reaction was cooled to room temperature, quenched by addition of water (30 mL) and extracted with ethyl acetate (3 × 40 mL). The combined organic layers were washed with brine (30 mL) and dried over magnesium sulfate. After filtration, the filtrate was evaporated and the residue was purified by recrystallisation from ethyl acetate/petroleum ether to yield

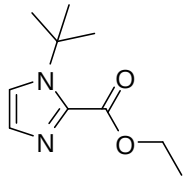
the product (0.71 g, 50%) as white solid, m.p. 208-209 °C; ν_{max} (thin film, cm^{-1}) 1740; $[\alpha]_D$ -275 (*c* 0.57 in $CHCl_3$); δ_H (500 MHz, d_6-DMSO, 100 ºC) 0.61 (d, 3H, *J* 6.8, C*H*$_3$), 1.08 (d, 3H, *J* 6.3, C*H*$_3$), 1.92 - 1.97 (m, 1H, C*H*), 2.91 (s, 1H, NC*H*$_3$), 4.48 (s, 1H, NC*H*), 7.26 - 7.43 (m, 8H, Ar*H*), 7.60 (d, 2H, *J* 8.4, Ar*H*); δ_C (126 MHz, d_6-DMSO, 100 ºC) 14.5 (*C*H$_3$), 21.0 (*C*H$_3$), 28.8 (*C*H), 31.6 (NCH$_3$), 68.5 (N*C*H), 86.4 (Ph$_2$*C*OH), 124.9 (2 × Ar*C*H), 125.5 (2 × Ar*C*H), 126.8 (Ar*C*H), 127.3 (Ar*C*H), 127.4 (2 × Ar*C*H), 127.8 (2 × Ar*C*H), 140.0 (Ar*C*), 144.3 (Ar*C*), 155.7 (*C*O); *m*/*z* (TOF ES+) 296.1662 (MH^+, $C_{19}H_{22}NO_2$ requires 296.1651).

1-*t*-Butylimidazole[126]



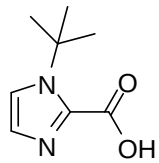
The title compound was prepared using a modified procedure in literature.[126] A 250 mL three-necked flask was equipped with two dropping funnels and a condenser. Distilled water (50 mL) was added to this flask. One dropping funnel was filled with a mixture of 40% aqueous glyoxal (11.5 mL, 0.1 mol) and 37% aqueous formaldehyde (8.1g, 0.1 mol), the other *tert*-butylamine (10.6 mL, 0.1 mol) and 35% aqueous ammonia (4.86 g, 0.1 mol). The water was heated until boiling, and then both solutions were added simultaneously. The resulting mixture turned brown and was stirred for 30 min at reflux after complete addition, and then cooled to room temperature. The mixture was extracted with dichloromethane (3 × 150 mL), the combined organic phases were washed with brine (50 mL) and dried over $MgSO_4$. The desiccant was filtered off and the filtrate was concentrated. The brown residue was purified by via vacuum distillation to give the product as a colourless oil (4.8 g, 39%); δ_H (400 MHz, $CDCl_3$) 1.55 [s, 9H, C(C*H*$_3$)$_3$], 7.03 (s, 1H, Ar*H*), 7.04 (s, 1H, Ar*H*), 7.60 (s, 1H, Ar*H*); δ_C (100 MHz, $CDCl_3$) 30.6 [C(*C*H)$_3$], 54.7 [*C*(CH)$_3$], 116.3 (Ar*C*H), 129.1 (Ar*C*H), 134.3 (Ar*C*H); Data was in accordance with the literature.

Ethyl 1-*t*-butyl-1H-imidazole-2-carboxylate



t-Butylimidazole (4.34 g, 35 mmol) was dissolved in THF (30 mL) and cooled to -78 °C. *n*BuLi (20 mL, 2 M in hexane) was added dropwise by syringe. The resulting mixture was stirred at -78 °C for 2 hours. This solution was added to a solution of ethyl chloroformate (7.56 g, 70 mmol) in THF (20 mL) by cannula at -78 °C and stirred for 1 hour at the same temperature. The reaction mixture was then warmed to room temperature and quenched with saturated aqueous ammonium chloride (50 mL). The resulting mixture was extracted with ethyl acetate (4 × 100 mL), and the combined organic layers were washed with brine (100 mL) and dried over $MgSO_4$. The desiccant was filtered off and the filtrate was concentrated. The residue was purified by chromatography on silica gel (20% ~ 30% ethyl acetate in petroleum ether) to yield the product as a colourless oil (2.50 g, 37%); ν_{max} (thin film, cm^{-1}) 2980, 1721, 1403; δ_H (400 MHz, $CDCl_3$) 1.41 (t, 3H, *J* 7.1, C*H*$_3$), 1.50 [s, 9H, C(C*H*$_3$)$_3$], 4.38 (q, 2H, *J* 7.1, C*H*$_2$), 7.06 (s, 1H, Ar*H*), 7.23 (s, 1H, Ar*H*); δ_C (100 MHz, $CDCl_3$) 14.2 (*C*H$_3$), 30.1 [C(*C*H)$_3$], 58.7 [*C*(CH)$_3$], 61.6 (*C*H$_2$), 122.2 (Ar*C*H), 127.8 (Ar*C*H), 137.4 (Ar*C*), 160.0 (*C*O); *m*/*z* (TOF ES+) 197.1299 (MH^+, $C_{10}H_{17}N_2O_2$ requires 197.1290).

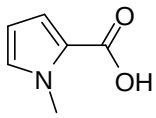
1-*t*-Butyl-1H-imidazole-2-carboxylic acid



Aqueous KOH (20 mL, 2.5 *N*) was added to a solution of ethyl 1-*t*-butyl-1H-imidazole-2-carboxylate (1.29 g, 6.6 mmol) in methanol (20 mL) at room temperature. The reaction mixture was stirred overnight at the same temperature, the methanol was evaporated and the mixture carefully acidified to pH 2 with conc. hydrochloric acid. The resulting mixture was evaporated to give a white solid residue. This residue was treated with methanol (30 mL) and filtered. The filtrate was evaporated to give the crude product in the form of HCl salt as

white solid. The crude product was contaminated a small amount of decarboxylated imidazole (~9%) and was used for next step without further purification; δ_H (400 MHz, MeOD) 1.86 [s, 9H, C(C*H*$_3$)$_3$], 7.71 (d, 1H, *J* 1.8, Ar*H*), 8.02 (d, 1H, *J* 1.8, Ar*H*); δ_C (100 MHz, MeOD) 28.3 [C(*C*H$_3$)$_3$], 63.9 [*C*(CH$_3$)$_3$], 119.1 (Ar*C*H), 124.3 (Ar*C*H), 134.8 (Ar*C*), 154.8 (*C*OOH); *m*/*z* (TOF ES+) 169.0978 (100%, MH^+, $C_8H_{13}N_2O_2$ requires 169.0977), 126.1151 (90); Data for the contaminant *N*-*t*-butylimidazole HCl salt, δ_H (400 MHz, MeOD), 1.72 [s, 9H, C(C*H*$_3$)$_3$], 7.63 (s, 1H, Ar*H*), 7.91 (s, 1H, Ar*H*), 9.10 (s, 1H, Ar*H*).

1-Methyl-2-pyrrolecarboxylic acid[127]



Aqueous KOH (20 mL, 2.5 *N*) was added to a solution of methyl 1-methylpyrrole-2-carboxylate (2.1 g, 6.6 mmol) dissolved in methanol (20 mL) at room temperature and the resulting reaction mixture was stirred overnight at the same temperature. Methanol was evaporated and then carefully acidified to pH 2 with hydrochloric acid (6 *N*). The white precipitate was collected by filtration and washed by water. The precipitate was dissolved in dichloromethane (50 mL) and dried over $MgSO_4$. The desiccant was filtered off and the filtrate was concentrated to give the product as white solid (1.1 g, 57%); m.p.136-138 °C (lit.[127] 135-136 °C); δ_H (400 MHz, $CDCl_3$) 3.96 (s, 3H, C*H*$_3$), 6.18 (dd, 1H, *J* 4.0, 2.1, Ar*H*), 6.87 (t, 1H, *J* 2.1, Ar*H*), 7.13 (dd, 1H, *J* 4.0, 2.1, Ar*H*), 12.2 (br, s, 1H, COO*H*); δ_C (63 MHz, $CDCl_3$) 37.0 (*C*H$_3$), 108.4 (Ar*C*H), 120.1 (Ar*C*H), 121.8 (Ar*C*), 130.8 (Ar*C*H), 166.6 (*C*OOH); Known compound but NMR data was not reported in the literature.

(*S*)-[2-(Hydroxydiphenylmethyl)pyrrolidin-1-yl](1-methyl-1H-pyrrol-2-yl)methanone

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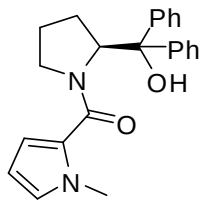
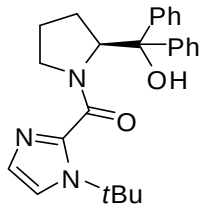


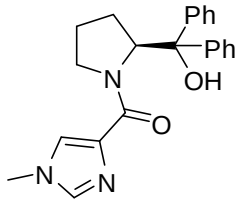
Oxalyl chloride (0.18 mL, 2.1 mmol) was added to a solution of 1-methyl-2-pyrrolecarboxylic acid (131 mg, 1.05 mmol) in dichloromethane (5 mL) at room temperature. One drop of DMF was added and then the reaction mixture was stirred at room temperature for 2 hours. The excess oxalyl chloride and dichloromethane were removed by evaporation under reduced pressure. The residue was dissolved in dichloromethane (5 mL) and this solution was added to a solution of amino alcohol **122** (253 mg, 1 mmol) and triethylamine (0.2 mL, 1.4 mmol) in dichloromethane (5 mL) by pipette. The resulting mixture was stirred at room temperature for 2 hours and then quenched with aqueous saturated $NaHCO_3$ (15 mL). The aqueous phase was extracted with dichloromethane (3× 15 mL), and the combined organic extracts washed with brine (15 mL) and dried over $MgSO_4$. The desiccant was filtered off and the filtrate was concentrated. The residue was purified by chromatography on silica gel (15% ethyl acetate in petroleum ether) to yield the product as a white solid (195 mg, 54%); m.p. 184-186 °C; (Found: C, 76.28; H, 6.64, N, 7.69. $C_{23}H_{24}N_2O_2$ requires C, 76.64; H, 6.71, N, 7.77); ν_{max} (thin film, cm^{-1}) 3246, 2958, 1588, 1435; $[\alpha]_D$ -83.7 (*c* 0.86 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.37 - 1.45 (m, 1H, 1 × C*H*$_2$), 1.55 - 1.67 (m, 1H, 1 × C*H*$_2$), 1.94 - 2.03 (m, 1H, 1 × C*H*$_2$), 2.14 - 2.22 (m, 1H, 1 × C*H*$_2$), 2.89 - 2.96 (m, 1H, 1 × NC*H*$_2$), 3.76 - 3.79 (m, 1H, 1 × NC*H*$_2$), 3.81 (s, 3H, C*H*$_3$), 5.50 (dd, 1H, *J* 8.4, 7.4, NC*H*), 6.08 (dd, 1H, *J* 3.9, 2.0, Ar*H*), 6.23 (dd, 1H, *J* 3.9, 2.0, Ar*H*), 6.70 (app. t, 1H, *J* 2.0, Ar*H*), 6.75 (br, s, O*H*), 7.27 - 7.39 (m, 6H, Ar*H*), 7.48 - 7.50 (m, 2H, Ar*H*), 7.55 - 7.58 (m, 2H, Ar*H*); δ_C (100 MHz, $CDCl_3$) 24.5 (*C*H$_2$), 29.3 (*C*H$_2$), 36.3 (NCH$_3$), 51.6 (*C*H$_2$), 66.8 (N*C*H), 82.7 [*C*Ph$_2$(OH)], 107.1 (Ar*C*H), 114.6 (Ar*C*H), 125.5 (Ar*C*), 127.1 (Ar*C*H), 127.2 (Ar*C*H), 127.3 (Ar*C*H), 127.4 (2 × Ar*C*H), 127.9 (2 × Ar*C*H), 128.0 (2 × Ar*C*H), 128.2 (2 × Ar*C*H), 143.1 (Ar*C*), 145.7 (Ar*C*), 165.5 (*C*O); *m*/*z* (TOF ES+) 361.1913 (90%, MH^+, $C_{23}H_{25}N_2O_2$ requires 361.1916), 343.1794 (100).

(*S*)-(1-*t*-Butyl-1H-imidazol-2-yl)[2-(hydroxydiphenylmethyl)pyrrolidin-1-yl[methanone



The title compound was prepared from the 1-*t*-butyl-1H-imidazole-2-carboxylic acid and amino alcohol **122** using the same procedure for catalyst **269** and purified by chromatography on silica gel (diethyl ether to flush off excess amino alcohol then 50% ethyl acetate in petroleum ether) to yield the product white solid (26%); m.p. 157-159 °C; ν_{max} (thin film, cm^{-1}) 2979, 1618, 1449; $[\alpha]_D$ -153.7 (*c* 0.8 in $CHCl_3$); δ_H (500 MHz, 100 °C, DMSO-d_6) 1.40 (br, s, 1H, 1 × C*H*$_2$), 1.45 [s, 9H, C(C*H*$_3$)$_3$], 1.53 - 1.62 (m, 1H, 1 × C*H*$_2$), 1.93 - 1.99 (m, 1H, 1 × C*H*$_2$), 2.01 - 2.08 (m, 1H, 1 × C*H*$_2$), 3.19 - 3.24 (m, 1H, 1 × C*H*$_2$), 3.46 (br, s, 1H, 1 × C*H*$_2$), 5.41 (dd, 1H, *J* 8.3, 3.3, C*H*), 6.22 (br, s, 1H, O*H*), 6.86 (s, 1H, Ar*H*), 7.13 - 7.16 (m, 1H, Ar*H*), 7.20 - 7.25 (m, 4H, Ar*H*), 7.29 - 7.32 (m, 2H, Ar*H*), 7.42 (d, 2H, *J* 7.5, Ar*H*), 7.48 (d, 2H, *J* 7.7, Ar*H*); δ_C (126 MHz, 100 °C, DMSO-d_6) 22.2 (*C*H$_2$), 27.6 (*C*H$_2$), 29.5 [C(*C*H$_3$)$_3$], 48.6 [*C*(CH$_3$)$_3$] 56.4 (N*C*H$_2$), 64.5 (N*C*H), 80.4 [*C*Ph$_2$(OH)], 118.4 (Ar*C*H), 125.4 (Ar*C*H), 125.8 (Ar*C*H), 126.1 (Ar*C*H), 126.6 (2 × Ar*C*H), 126.7 (4 × Ar*C*H), 126.9 (Ar*C*H), 140.4 (Ar*C*), 144.9 (Ar*C*), 145.8 (Ar*C*), 163.7 (*C*O); *m*/*z* (TOF ES+) 404.2348 (MH^+, $C_{25}H_{30}N_3O_2$ requires 404.2338).

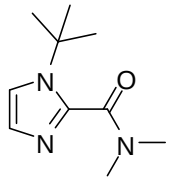
(*S*)-[2-(Hydroxydiphenylmethyl)pyrrolidin-1-yl](1-methyl-1H-imidazol-4-yl)methanone



The title compound was prepared from the 1-*t*-butyl-1H-imidazole-2-carboxylic acid and amino alcohol **122** using the same procedure for catalyst **269** and purified by chromatography on silica gel (diethyl ether to flush off excess amino alcohol then 2% methanol in ethyl acetate) to yield the product white solid (25%); m.p. 68-70 °C; ν_{max} (thin film, cm^{-1}) 2924, 2854, 1587, 1556, 1446, 1434; $[\alpha]_D$ -116.3 (*c* 0.94 in $CHCl_3$); δ_H (500 MHz,

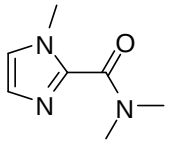
100 °C, DMSO-d_6) 1.30 - 1.39 (m, 1H, 1 × CH_2), 1.51 - 1.60 (m, 1H, 1 × CH_2), 1.88 - 1.94 (m, 1H, 1 × CH_2), 1.99 - 2.07 (m, 1H, 1 × CH_2), 3.28 - 3.34 (m, 1H, 1 × CH_2), 3.63 (s, 3H, NCH_3), 4.08 - 4.13 (m, 1H, 1 × CH_2), 5.67 (s, br, 1H, NC*H*), 6.63 (s, 1H, O*H*), 7.15 - 7.20 (m, 3H, Ar*H*), 7.22 - 7.25 (m, 1H, Ar*H*), 7.28 - 7.36 (m, 5H, Ar*H*), 7.43 - 7.45 (m, 2H, Ar*H*), 7.50 (s, 1H, Ar*H*); δ_C (126 MHz, 100 °C, DMSO-d_6) 22.4 (*C*H_2), 27.6 (*C*H_2), 32.4 (NCH_3), 48.3 (N*C*H_2), 64.3 (N*C*H), 80.8 [*C*Ph_2(OH)], 125.1 (Ar*C*H), 125.7 (Ar*C*H), 126.0 (Ar*C*H), 126.5 (2 × Ar*C*H), 126.7 (2 × Ar*C*H), 126.8 (2 × Ar*C*H), 127.1 (2 × Ar*C*H), 136.4 (Ar*C*H), 136.9 (Ar*C*), 144.6 (Ar*C*), 146.1 (Ar*C*), 163.6 (*C*O); *m*/*z* (TOF ES+) 384.1676 (38%, M+Na^+), 362.1876 (100, M^++1, $C_{22}H_{24}N_3O_2$ requires 362.1869), 344.1771 (50).

1-*t*-Butyl-*N*,*N*-dimethyl-1H-imidazole-2-carboxamide 267



t-Butylimidazole (2.48 g, 20 mmol) was dissolved in THF (20 mL) and cooled to -78 °C. *n*BuLi (12.5 mL, 2 M in hexane) was added dropwise by syringe. The resulting mixture was stirred at -78 °C for 2 hours. This solution was added dropwise to a solution of dimethylcarbamoyl chloride (2.99 g, 28 mmol) in diethyl ether (20 mL) at -78 °C and stirred for 1 hour at the same temperature. The reaction mixture was then warmed to room temperature and quenched with water (50 mL). The organic layer was evaporated and the aqueous was extracted with dichloromethane (3 × 100 mL) and dried over $MgSO_4$. The desiccant was filtered off and the filtrate was concentrated to give the crude residue. Pure product was obtained as white solid after recrystallisation from ethyl acetate; m.p. 146-148 °C; ν_{max} (thin film, cm^{-1}) 3157, 2931, 1638, 1524; δ_H (400 MHz, $CDCl_3$) 1.60 [s, 9H, C(CH_3)$_3$], 2.96 (s, 3H, CH_3), 3.09 (s, 3H, CH_3), 6.97 (d, 1H, *J* 1.2, Ar*H*), 7.05 (d, 1H, *J* 1.2, Ar*H*); δ_C (100 MHz, $CDCl_3$) 30.4 [C(*C*H)$_3$], 35.0 (*C*H_3), 38.6 (*C*H_3), 57.0 [*C*(CH)$_3$], 117.9 (Ar*C*H), 126.8 (Ar*C*H), 140.3 (Ar*C*), 164.5 (*C*O); *m*/*z* (TOF ES+) 196.1442 (MH^+, $C_{10}H_{18}N_3O$ requires 196.1450).

1-Methyl-*N*,*N*-dimethyl-1H-imidazole-2-carboxamide 266[128]



The title compound was prepared using the same procedure for compound **267** and purification by chromatography on silica gel (50% ethyl acetate in petroleum ether ~ ethyl acetate) to yield the product (1.1g, 36%) as colourless oil; δ_H (400 MHz, $CDCl_3$) 3.12 (s, 3H, C*H*$_3$), 3.41 (s, 3H, C*H*$_3$), 3.89 (s, 3H, C*H*$_3$), 6.94 (d, 1H, *J* 1.0, Ar*H*), 7.05 (d, 1H, *J* 1.0, Ar*H*); δ_C (100 MHz, $CDCl_3$) 35.0 (*C*H$_3$), 35.7 (*C*H$_3$), 39.3 (*C*H$_3$), 123.6 (Ar*C*H), 127.3 (Ar*C*H), 140.1 (Ar*C*), 160.9 (*C*O); Data was in accordance with the literature.

7.3 Preparation of imines from their ketone precursor

General procedure A:

Activated 4 Å molecular sieves (20 g), toluene (40 mL), ketone (50 mmol) and amine (60 mmol) were introduced into a 100 mL flask. The mixture was stirred at RT for 24 h and filtered. The imines were purified by distillation or recrystallisation from petroleum ether 40-60 ºC and diethyl ether.

General procedure B:

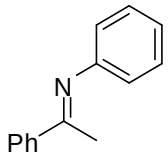
Ketone (10 mmol), amine (1.1~1.3 eq.), *p*-toluene sulfonic acid (0.05 eq.) and toluene (50 mL) were introduced in a round-bottom flask and heated for 24 hours under Dean-Stark conditions. After cooling to room temperature, K_2CO_3 (0.1 eq) was added and then filtered to remove any insoluble solid. The filtrate was concentrated *in vacuo* and the residue was purified by recrystallisation or distillation to afford the imine.

General procedure C:

The mixture of ketone (10 mmol), amine (15 mmol), $Si(OEt)_4$ and *p*-toluene sulfonic acid (1 mmol) was heated at 180 ºC for 5 to 60 mins under microwave irradiation. The resulting mixture was then cooled to room temperature and diluted with diethyl ether (15 mL). After

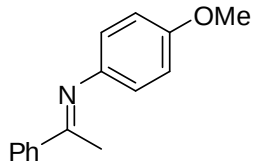
filtering off the insoluble solid, the filtrate was evaporated and the residue was purified by chromatography on silica gel (the silica gel pre-treated overnight with 10% triethylamine in petroleum ether) to afford the product.

_N_-(1-Phenylethylidene)benzenamine 124[79]



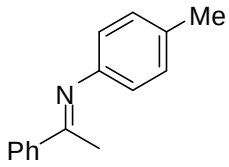
Prepared according to general procedure A and purified by distillation under reduced pressure as pale yellow crystals (52%), m.p. 40-41°C (lit.[79] 42-43 ºC from petroleum ether 40-60 °C); δ_H (250 MHz, $CDCl_3$) 2.26 (3H, s, C*H*$_3$), 6.81 - 6.84 (m, 2H, Ar*H*), 7.08 - 7.15 (m, 1H, Ar*H*), 7.35 - 7.51 (m, 5H, Ar*H*), 7.98-8.01 (m, 2H, Ar*H*); δ_C (63 MHz, $CDCl_3$) 17.4 (*C*H$_3$), 119.4 (2 × Ar*C*H), 123.3 (Ar*C*H), 127.3 (2 × Ar*C*H), 128.4 (2 × Ar*C*H), 129.0 (2 × Ar*C*H), 130.5 (Ar*C*H), 139.6 (Ar*C*), 151.8 (Ar*C*), 164.4 (*C*=N); Data was in accordance with the literature.

4-Methoxy-_N_-(1-phenylethylidene)benzenamine 125[79]



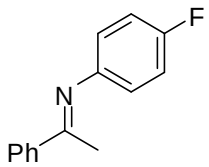
Prepared according to general procedure A and purified by recrystallisation from diethyl ether/petroleum ether as yellow crystals (52%), m.p. 85-86 °C (lit.[79] 86 °C from petroleum 60-80 ºC); δ_H (250 MHz, $CDCl_3$) 2.28 (s, 3H, C*H*$_3$), 3.84 (s, 3H, C*H*$_3$), 6.77 - 6.81 (m, 2H, Ar*H*), 6.91 - 6.96 (m, 2H, Ar*H*), 7.44 - 7.49 (m, 3H, Ar*H*), 7.97 - 8.01 (m, 2H, Ar*H*); δ_C (63 MHz, $CDCl_3$) 17.3 (*C*H$_3$), 55.5 (O*C*H$_3$), 114.3 (2 × Ar*C*H), 120.8 (2 × Ar*C*H), 127.2 (2 × Ar*C*H), 128.4 (2 × Ar*C*H), 130.4 (Ar*C*H), 139.9 (Ar*C*), 144.9 (Ar*C*), 156.0 (Ar*C*), 165.7 (*C*=N). Data was in accordance with the literature.

4-Methyl-_N_-(1-phenylethylidene)benzenamine 126[129]



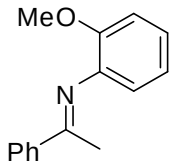
Prepared according to general procedure A and purified by distillation under reduced pressure (72%) as a brown oil; δ_H (400 MHz, $CDCl_3$) 2.27 (3H, s, C*H*$_3$), 2.38 (3H, s, C*H*$_3$), 6.73 (d, 2H, *J* 8.3, Ar*H*), 7.18 (d, 2H, *J* 8.3, Ar*H*), 7.47 - 7.49 (m, 3H, Ar*H*), 7.89 - 8.00 (m, 2H, Ar*H*); δ_C (100 MHz, $CDCl_3$) 17.3 (*C*H$_3$), 20.9 (*C*H$_3$), 119.4 (2 × Ar*C*H), 127.2 (2 × Ar*C*H), 128.4 (2 × Ar*C*H), 129.5 (2 × Ar*C*H), 130.4 (Ar*C*H), 132.6 (Ar*C*), 139.7 (Ar*C*), 149.1 (Ar*C*), 165.5 (*C*=N); Data was in accordance with the literature.

4-Fluoro-*N*-(1-phenylethylidene)benzenamine 127[130]



Prepared according to general procedure A and purified by recrystallisation (46%) as a yellow solid, m.p. 88-89 °C (lit.[130] 86-87 °C); δ_H (400 MHz, $CDCl_3$) 2.27 (s, 3H, C*H*$_3$), 6.75 - 6.80 (m, 2H, Ar*H*), 7.05 - 7.11 (m, 2H, Ar*H*), 7.45 - 7.52 (m, 3H, Ar*H*), 7.97 - 8.01 (m, 2H, Ar*H*); δ_C (100 MHz, $CDCl_3$) 17.4 (*C*H$_3$), 115.6 (d, $^2J_{C\text{-}F}$ 23.0, 2 × Ar*C*H), 120.7 (d, $^3J_{C\text{-}F}$ 7.6, 2 × Ar*C*H), 127.2 (2 × Ar*C*H), 128.4 (2 × Ar*C*H), 130.6 (Ar*C*H), 139.4 (Ar*C*), 147.7 (Ar*C*), 159.2 (d, $^1J_{C\text{-}F}$ 240.8, Ar*C*F), 166.3 (*C*=N); δ_F (235 MHz, $CDCl_3$) -121.3. Data was in accordance with the literature.

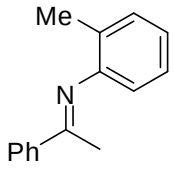
2-Methoxy-*N*-(1-phenylethylidene)benzenamine 128[131]



Prepared according to general procedure A and purified by distillation under reduced pressure as a yellow oil (44%); δ_H (250 MHz, $CDCl_3$) 2.20 (s, 3H, C*H*$_3$), 3.81 (s, 3H, OC*H*$_3$), 6.80 (dd, 1H, *J* 7.5, 1.7, ArC*H*), 6.94 - 7.01 (m, 2H, ArC*H*), 7.07 - 7.14 (m, 1H, ArC*H*), 7.44

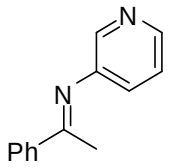
- 7.49 (m, 3H, ArC*H*), 8.01 - 8.05 (m, 2H, ArC*H*); δ_C (63 MHz, $CDCl_3$) 17.8 (*C*H_3), 55.7 (O*C*H_3), 111.8 (Ar*C*H), 120.7 (Ar*C*H), 121.1 (Ar*C*H), 124.3 (Ar*C*H), 127.4 (2 × Ar*C*H), 128.4 (2 × Ar*C*H), 130.5 (Ar*C*H), 139.6 (Ar*C*), 140.8 (Ar*C*), 149.1 (Ar*C*), 167.0 (*C*=N). Data was in accordance with the literature.

2-Methyl-*N*-(1-phenylethylidene)benzenamine 129[132]



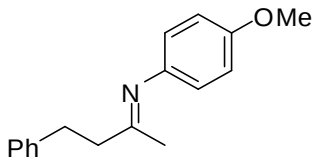
Prepared according to general procedure A and purified by distillation under reduced pressure as a yellow solid (48%), m.p. 49-50 °C (not reported in literature); δ_H (400 MHz, $CDCl_3$) 2.13 (3H, s, C*H*$_3$), 2.20 (3H, s, C*H*$_3$), 6.88 (dd, 1H, *J* 7.8, 1.0, Ar*H*), 7.03 (ddd, 1H, *J* 8.7, 7.6, 1.2, Ar*H*), 7.19 - 7.25 (m, 2H, Ar*H*), 7.46 - 7.51 (m, 3H, Ar*H*), 8.02 - 8.05 (m, 2H, Ar*H*); δ_C (63 MHz, $CDCl_3$) 17.5 (*C*H_3), 17.8 (*C*H_3), 118.5 (Ar*C*H), 123.3 (Ar*C*H), 126.4 (Ar*C*H), 127.2 (2 × Ar*C*H), 128.4 (2 × Ar*C*H), 130.4 (Ar*C*H), 130.5 (Ar*C*H), 139.5 (2 × Ar*C*), 150.4 (Ar*C*), 164.9 (*C*=N). Data was in accordance with the literature.

***N*-(1-Phenylethylidene)pyridin-3-amine 130**



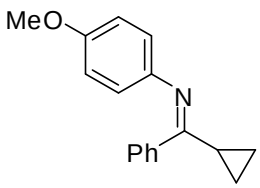
Prepared according to general procedure B, purified by distillation (17%), yellow solid, m.p. 46-48 °C; (Found: C 79.32; H 6.02; N 14.25; $C_{13}H_{12}N_2$ requires C 79.56; H 6.16, N 14.27); ν_{max} (thin film, cm^{-1}) 3406, 3055, 1630, 1578; δ_H (400 MHz, $CDCl_3$) 2.29 (s, 3H, C*H*$_3$), 7.17 - 7.20 (m, 1H, Ar*H*), 7.20 - 7.34 (m, 1H, Ar*H*), 7.46 - 7.53 (m, 3H, Ar*H*), 7.99 - 8.02 (m, 2H, Ar*H*), 8.17 (dd, 1H, *J* 2.7, 0.7, Ar*H*), 8.38 (dd, 1H, *J* 4.9, 1.5, Ar*H*); δ_C (100 MHz, $CDCl_3$) 17.6 (*C*H_3), 123.6 (Ar*C*H), 126.9 (Ar*C*H), 127.3 (2 × Ar*C*H), 128.5 (2 × Ar*C*H), 131.0 (Ar*C*H), 138.7 (Ar*C*), 141.0 (Ar*C*H), 144.7 (Ar*C*H), 147.4 (Ar*C*), 167.3 (*C*=N); *m/z* (EI) 196.0999 (85%, M^+, $C_{13}H_{12}N_2$ requires 196.1000), 181 (100), 119 (20), 78 (75).

4-Methoxy-*N*-(4-phenylbutan-2-ylidene)aniline 252



Prepared according to general procedure B, purified by distillation (isolated as a 3.6:1 isomer mixture, 59%), yellow oil; ν_{max} (thin film, cm^{-1}) 3361, 3027, 1716, 1657, 1512, 1503; δ_H (400 MHz, $CDCl_3$) 1.82 (s, 3H, C*H*$_3$, major isomer), 2.22 (s, 3H, C*H*$_3$, minor isomer), 2.47-2.51 (m, 2H, C*H*$_2$, minor isomer), 2.72-2.76 (m, 2H, C*H*$_2$, major isomer), 2.79-2.83 (m, 2H, C*H*$_2$, minor isomer), 3.02-3.06 (m, 2H, C*H*$_2$, major isomer), 3.81 (s, 3H, OC*H*$_3$, minor isomer), 3.82 (s, 3H, OC*H*$_3$, major isomer), 6.51 - 6.55 (m, 2H, Ar*H*, minor isomer), 6.62 - 6.66 (m, 2H, Ar*H*, major isomer), 6.81 - 6.84 (m, 2H, Ar*H*, minor isomer), 6.85 - 6.89 (m, 2H, Ar*H*, major isomer), 7.05 - 7.07 (m, 2H, Ar*H*, minor isomer), 7.19 - 7.35 (m, 5H, Ar*H*, major isomer), 7.19 - 7.35 (m, 3H, Ar*H*, minor isomer); δ_C (100 MHz, $CDCl_3$) 19.9 (*C*H$_3$, major isomer), 24.2 (*C*H$_3$, minor isomer), 32.5 (*C*H$_2$, major isomer), 33.0 (*C*H$_2$, minor isomer), 35.7 (*C*H$_2$, minor isomer), 43.0 (*C*H$_2$, major isomer), 55.4 (O*C*H$_3$, major isomer), 55.4 (O*C*H$_3$, minor isomer), 114.2 (2 × Ar*C*H, minor), 114.3 (2 × Ar*C*H, major), 120.4 (2 × Ar*C*H, minor), 120.6 (2 × Ar*C*H, major), 126.0 (Ar*C*H, major), 126.3 (Ar*C*H, minor), 128.2 (Ar*C*H, minor), 128.4 (2 × Ar*C*H, major), 128.5 (2 × Ar*C*H, major), 128.5 (2 × Ar*C*H, minor),140.6 (Ar*C*, minor), 141.6 (Ar*C*, major), 144.2 (Ar*C*, minor), 144.8 (Ar*C*, major), 155.7 (Ar*C*, minor), 155.8 (Ar*C*, major), 171.1 (*C*=N, major), 171.7 (*C*=N, minor); *m/z* (TOF ES+) 254.1557 (MH^+ $C_{17}H_{20}N$ requires 154.1545).

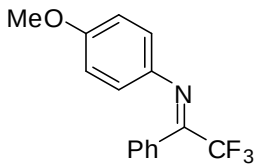
***N*-[Cyclopropyl(phenyl)methylene]-4-methoxyaniline 251[83]**



Prepared according to general procedure B, purified by chromatograph on silica (the silica gel pre-treated overnight with 10% triethylamine in petroleum ether) and further purified by

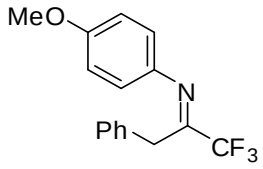
distillation to give the yellow oil product as a 1.6:1 mixture of *cis* and *trans* imines (13%); δ_H (400 MHz, $CDCl_3$) 0.58 - 0.62 (m, 2H, C*H*$_2$, minor isomer), 0.82 - 0.87 (m, 2H, C*H*$_2$, minor isomer), 0.98 - 1.03 (m, 2H, C*H*$_2$, major isomer), 1.15 - 1.19 (m, 2H, C*H*$_2$, major isomer), 1.86 - 1.93 (m, 2H, C*H*, minor isomer), 1.97 - 1.19 (m, 2H, C*H*$_2$, major isomer), 3.72 (s, 3H, OC*H*$_3$, major isomer), 3.85 (s, 3H, OC*H*$_3$, minor isomer), 6.54 [2H, $(AX)_2$, Ar*H*, major isomer], 6.66 [2H, $(AX)_2$, Ar*H*, major isomer], 6.93 [2H, $(AX)_2$, Ar*H*, minor isomer], 6.96 [2H, $(AX)_2$, Ar*H*, minor isomer], 7.16 - 7.18 (m, 2H, Ar*H*, major isomer), 7.23 - 7.25 (m, 3H, Ar*H*, major isomer), 7.41 - 7.43 (m, 3H, Ar*H*, minor isomer), 7.75 - 7.77 (m, 2H, Ar*H*, minor isomer); δ_C (100 MHz, $CDCl_3$) 7.98 (2 × *C*H$_2$, minor isomer), 9.37 (2 × *C*H$_2$, major isomer), 13.9 (*C*H, minor isomer), 20.2 (*C*H, major isomer), 55.3 (O*C*H$_3$, major isomer), 55.4 (O*C*H$_3$, minor isomer), 113.8 (2 × Ar*C*H, major), 114.0 (2 × Ar*C*H, minor), 121.6 (2 × Ar*C*H, minor), 122.2 (2 × Ar*C*H, major), 127.9 (2 × Ar*C*H, minor), 127.97 (2 × Ar*C*H, major), 128.03 (2 × Ar*C*H, minor), 128.1 (2 × Ar*C*H, major), 128.2 (Ar*C*H, major), 129.3 (Ar*C*H, minor), 138.1 (Ar*C*, major), 138.8 (Ar*C*, minor), 144.0 (Ar*C*, minor), 144.2 (Ar*C*, major), 155.4 (Ar*C*, major), 156.0 (Ar*C*, minor), 170.7 (*C*=N, minor), 172.6 (*C*=N, minor). Data was in accordance with the literature.

4-Methoxy-*N*-(2,2,2-trifluoro-1-phenylethylidene)aniline 246[133]



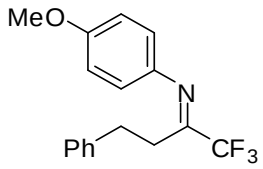
Prepared according to general procedure C heated at 180 ºC for one hour, purified by chromatograph on silica gel (0%~3% diethyl ether in petroleum ether) to afford the product as light yellow oil (85%); δ_H (400 MHz, $CDCl_3$) 3.77 (s, 3H, C*H*$_3$), 6.72 - 6.78 (m, 4H, Ar*H*), 7.25 - 7.28 (m, 2H, Ar*H*), 7.34 - 7.43 (m, 3H, Ar*H*); δ_C (100 MHz, $CDCl_3$) 55.2 (*C*H$_3$), 114.0 (2 × Ar*C*H), 120.2 (q, *J* 278.7, *C*F$_3$), 123.4 (2 × Ar*C*H), 128.6 (2 × Ar*C*H), 128.8 (2 × Ar*C*H), 130.2 (Ar*C*H), 130.7 (Ar*C*), 139.7 (Ar*C*), 155.4 (q, *J* 33.6, *C*=N), 157.9 (Ar*C*); δ_F (235 MHz, $CDCl_3$) -69.93. Data was in accordance with the literature.

4-Methoxy-*N*-(1,1,1-trifluoro-3-phenylpropan-2-ylidene)aniline 247



Prepared according to general procedure C heated at 180 ºC for 5 mins, purified by chromatography on silica gel (0%~5% diethyl ether in petroleum ether) to afford the yellow oil product as a 1.5:1 mixture of imine and enamine (78%); ν_{max} (thin film, cm^{-1}) 3386, 2983, 1731, 1514; δ_H (400 MHz, $CDCl_3$) 3.74 (s, 3H, OC*H*$_3$, enamine), 3.83 (s, 3H, OC*H*$_3$, imine), 3.91 (s, 2H, C*H*$_2$, imine), 5.20 (s, br, 1H, N*H*, enamine), 6.67 [2H, (AX)$_2$, Ar*H*, enamine], 6.72 (s, 1H, C*H*, enamine), 6.73 [2H, (AX)$_2$, Ar*H*, enamine], 6.86 [2H, (AX)$_2$, Ar*H*, imine], 6.94 [2H, (AX)$_2$, Ar*H*, imine], 7.09 (d, 2H, *J* 6.84, Ar*H*, imine), 7.23 - 7.34 (m, 3H, Ar*H*, enamine), 7.23 - 7.34 (m, 3H, Ar*H*, imine), 7.41 - 7.43 (m, 2H, Ar*H*, enamine); δ_C (100 MHz, $CDCl_3$) 34.4 (*C*H$_2$, imine), 55.4 (O*C*H$_3$, imine), 55.5 (O*C*H$_3$, enamine), 114.46 (*C*H), 114.50 (*C*H), 117.5 (*C*H), 120.1 [q, *J* 4.0, enamine, *C*H=C(CF$_3$)NH], 120.5 (*C*H), 122.7 (q, *J* 234.8, *C*F$_3$), 127.1 (*C*H), 128.3 (*C*H), 128.4 (*C*H), 128.7 (*C*H), 128.8 (*C*H), 129.5 (*C*H), 133.0 (*C*), 134.1 (*C*), 135.4 (*C*), 140.3 (*C*), 154.1 (*C*), 157.5 (*C*), 158.2 (q, *J* 32.3, *C*CF$_3$); δ_F (378 MHz, $CDCl_3$) -69.9 (enamine), -70.3 (imine); *m/z* (TOF ES+) 294.1092 (MH^+ $C_{16}H_{15}NOF_3$ requires 294.1106).

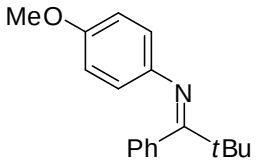
4-Methoxy-*N*-(1,1,1-trifluoro-4-phenylbutan-2-ylidene)aniline 248



Prepared according to general procedure C heated at 180 ºC for 5 mins, purified by chromatography on silica gel (4%~9% diethyl ether in petroleum ether) to afford the yellow oil product as a single isomer (76%); ν_{max} (thin film, cm^{-1}) 3030, 2949, 1678, 1505; δ_H (400 MHz, $CDCl_3$) 2.77 - 2.82 (m, 2H, C*H*$_2$), 2.85 - 2.91 (m, 2H, C*H*$_2$), 3.86 (s, OC*H*$_3$), 6.66 [2H, (AX)$_2$, Ar*H*], 6.93 [2H, (AX)$_2$, Ar*H*], 7.06-7.08 (m, 2H, Ar*H*), 7.23 - 7.32 (m, 2H, Ar*H*); δ_C

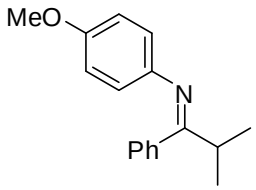
(100 MHz, $CDCl_3$) 30.5 (*C*H_2), 32.5 (*C*H_2), 55.5 (O*C*H_3), 114.4 (2 × Ar*C*H), 121.5 (2 × Ar*C*H), 122.1 (q, *J* 297.7, *C*F_3), 126.7 (Ar*C*H), 128.2 (2 × Ar*C*H), 128.7 (2 × Ar*C*H), 139.6 (Ar*C*), 140.5 (Ar*C*), 157.2 (Ar*C*), 159.9 (q, *J* 32.2, *C*=N); δ_F (235 MHz, $CDCl_3$) -71.4; *m/z* (TOF ES+) 308.1258 (MH^+ $C_{17}H_{17}NOF_3$ requires 308.1262).

_N_-(2,2-Dimethyl-1-phenylpropylidene)-4-methoxyaniline 249[83]



Prepared according to general procedure C heated at 180 ºC for one hour, purified by chromatograph on silica gel (0%~5% diethyl ether in petroleum ether) to afford the product as white solid (56%); m.p. 54-56 ºC (lit.[83] 53-54 ºC); δ_H (400 MHz, $CDCl_3$) 1.29 [s, 9H, C(C*H*$_3$)$_3$], 3.68 (s, 3H, OC*H*$_3$), 6.50 [2H, (AX)$_2$, Ar*H*], 6.60 [2H, (AX)$_2$, Ar*H*], 6.93 - 6.95 (m, 2H, Ar*H*), 7.14 - 7.22 (m, 2H, Ar*H*); δ_C (100 MHz, $CDCl_3$) 28.6 [C(*C*H$_3$)$_3$], 40.4 [*C*(CH$_3$)$_3$], 55.2 (O*C*H$_3$), 113.4 (2 × Ar*C*H), 121.5 (2 × Ar*C*H), 127.1 (Ar*C*H), 127.4 (2 × Ar*C*H), 128.0 (2 × Ar*C*H), 137.5 (Ar*C*), 144.6 (Ar*C*), 155.2 (Ar*C*), 180.1 (*C*=N). Data was in accordance with the literature.

4-Methoxy-_N_-(2-methyl-1-phenylpropylidene)aniline 250[83]



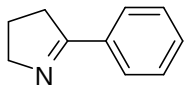
Prepared according to general procedure C heated at 180 ºC for 80 min, purified by chromatograph on silica gel (petroleum ether) and followed by distillation purification to afford the yellow oil product as a 6:1:1 mixture of two imine isomers and one enamine isomer (40%); δ_H (400 MHz, $CDCl_3$) 1.19 [d, 6H, *J* 7.1, CH(C*H*$_3$)$_2$, minor imine isomer], 1.24 [d, 6H, *J* 6.8, CH(C*H*$_3$)$_2$, major imine isomer], 1.84 (s, 3H, C*H*$_3$, enamine isomer), 1.86 (s, 3H, C*H*$_3$, enamine isomer), 2.98 - 3.08 (m, 1H, C*H*, major imine isomer), 3.15 - 3.26 (m,

1H, C*H*, minor imine isomer), 3.71 (s, 3H, OCH_3, major imine isomer), 3.73 (s, 3H, OCH_3, minor imine isomer), 3.84 (s, 3H, OCH_3, enamine isomer), 4.98 (s, br, 1H, N*H*, enamine isomer), 6.56 [2H, $(AX)_2$, Ar*H*, major imine isomer], 6.66 [2H, $(AX)_2$, Ar*H*, major imine isomer], 6.72 [2H, $(AX)_2$, Ar*H*, minor imine isomer], 6.78[2 H, $(AX)_2$, Ar*H*, enamine isomer], 6.93 [2H, $(AX)_2$, Ar*H*, enamine isomer], 7.02 - 7.04 (m, 2H, Ar*H*, major imine isomer), 7.22 - 7.25 (m, 3H, Ar*H*, major imine isomer), 7.28 - 7.32 (m, 3H, Ar*H*, minor imine isomer), 7.36 - 7.39 (m, 2H, Ar*H*, minor imine isomer), 7.42 - 7.44 (m, 3H, Ar*H*, enamine isomer), 7.66 - 7.68 (m, 2H, Ar*H*, major imine isomer); δ_C (100 MHz, $CDCl_3$) major isomer: 20.2 [C(*C*$H_3)_2$], 38.6 (*C*H), 5.3 (OCH_3), 113.7 (2 × Ar*C*H), 122.0 (2 × Ar*C*H), 127.8 (Ar*C*H), 127.86 (2 × Ar*C*H), 127.90 (2 × Ar*C*H), 138.3 (Ar*C*), 144.3 (Ar*C*), 155.5 (Ar*C*), 176.6 (*C*=N); other remaining observable signals: 21.0 [CH(*C*$H_3)_2$, minor imine isomer], 23.4 (*C*H_3, enamine isomer), 28.0 (*C*H_3, enamine isomer), 31.7 (*C*H, minor imine isomer), 55.5 (OCH_3, minor imine isomer), 55.7 (OCH_3, enamine isomer), 114.3 (Ar*C*H), 114.6 (Ar*C*H), 115.8 (Ar*C*H), 120.0 (Ar*C*H), 122.7 (Ar*C*H), 128.9 (Ar*C*H), 127.0 (Ar*C*H), 129.4 (Ar*C*H). Data was in general accordance with the literature – the enamine isomer was not assigned in literature 83.

General procedure D:

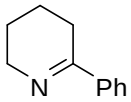
The procedure of preparations of imines **122**, **123** and **130** was same with the procedure reported by Coindet *et al*.[82]

2-Phenyl-1-pyrroline 141[134]



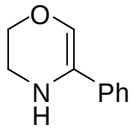
Prepared by general procedure D in a 22% yield as a white melting solid; δ_H (400 MHz, $CDCl_3$) 1.97 - 2.06 (m, 2H, CH_2), 2.90 - 2.95 (m, 2H, CH_2), 4.04 - 4.09 (m, 2H, CH_2), 7.37 - 7.42 (m, 3H, Ar*H*), 7.83 - 7.86 (m, 2H, Ar*H*); δ_C (100 MHz, $CDCl_3$) 22.7 (*C*H_2), 34.9 (*C*H_2), 61.5 (*C*H_2), 127.6 (2 × Ar*C*H), 128.4 (2 × Ar*C*H), 130.3 (Ar*C*H), 134.6 (Ar*C*), 173.2 (*C*=N). Data was in accordance with the literature.

2,3,4,5-Tetrahydro-6-phenylpyridine 142[134]



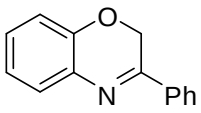
Prepared by general procedure D in a 20% yield as a light yellow oil; δ_H (250 MHz, $CDCl_3$) 1.65 - 1.74 (m, 2H, C*H*$_2$), 1.81 - 1.91 (m, 2H, C*H*$_2$), 2.62 - 2.69 (m, 2H, C*H*$_2$), 3.82 - 3.89 (m, 2H, C*H*$_2$), 7.37 - 7.41 (m, 3H, ArC*H*), 7.76 - 7.80 (m, 2H, ArC*H*); δ_C (63 MHz, $CDCl_3$) 19.8 (*C*H$_2$), 21.9 (*C*H$_2$), 27.0 (*C*H$_2$), 49.9 (*C*H$_2$), 125.9 (2 × Ar*C*H), 128.2 (2 × Ar*C*H), 129.5 (Ar*C*H), 140.2 (Ar*C*), 165.6 (*C*=N). Data was in accordance with the literature.

5-Phenyl-3,4-dihydro-2H-1,4-oxazine 149



Prepared by general procedure D in a 3% yield as a yellow solid, m.p. 54-56 ºC; δ_H (250 MHz, $CDCl_3$) 3.69 - 3.76 (m, NC*H*$_2$), 4.35 (app. t, 2H, *J* 5.3, OC*H*$_2$), 6.88 (br, s, 1H, N*H*), 7.28 - 7.52 (m, 3H, Ar*H*), 7.76 - 7.80 (m, 2H, Ar*H*), 8.06 (s, 1H, C=C*H*); δ_C (100 MHz, $CDCl_3$) 39.1 (N*C*H$_2$), 62.8 (O*C*H$_2$), 127.0 (2 × Ar*C*H), 128.6 (2 × Ar*C*H), 131.6 (Ar*C*H), 134.1 (Ar*C*), 161.0 (N*C*=CHO), 167.8 (NC=*C*HO). Further analysis could not be performed due to quantity of available material.

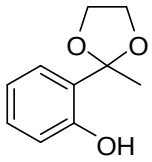
3-Phenyl-2H-benzo[b][1,4]oxazine 138[135]



A mixture of 2-hydroxyaniline (2.18 g, 20 mmol), 2-bromoacetophenone (3.98 g, 20 mmol) and K_2CO_3 (3.6 g, 26 mmol) in toluene (80 mL) was refluxed for 10 h. The reaction mixture was cooled to room temperature, and the solid was filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by chromatography (petroleum ether/ethyl acetate, 50:1). Further purification by recrystallisation from petroleum and ether

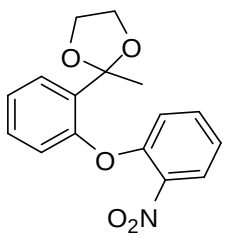
afforded the product as colorless needle-like crystals (2.5g, 60% yield), m.p. 111-112 °C (lit.[135] 113 ºC from ethanol); δ_H (250 MHz, $CDCl_3$) 5.10 (s, 2H), 6.94 (dd, 1H, *J* 7.9, 1.3, Ar*H*), 7.05 (dt, 1H, *J* 7.5, 1.3, ArH), 7.18 (dt, 1H, *J* 7.5, 1.6, ArH), 7.45-7.54 (m, 4H, ArH), 7.93-7.97 (m, 2H, ArH); δ_C (63 MHz, $CDCl_3$) 62.9 (*C*H_2), 115.6 (Ar*C*H), 122.4 (Ar*C*H), 126.5 (2 × Ar*C*H), 127.9 (Ar*C*H), 128.7 (Ar*C*H), 128.8 (2 × Ar*C*H), 131.2 (Ar*C*H), 133.9 (Ar*C*), 135.5 (Ar*C*), 146.4 (Ar*C*), 158.7 (*C*=N). Data was in accordance with the literature.

2-(2-Methyl-1,3-dioxolan-2-yl)phenol[136]



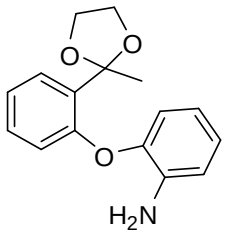
2′-Hydroxyacetophenone (6.12 g, 45 mmol), glycol (5.58 g, 90 mmol), p-TsOH·H_2O (100 mg) and benzene (60 mL) were introduced into a single-necked round bottom flask (100 mL). The mixture was heated at reflux under Dean-Stark conditions for 40 h. After the mixture was cooled to RT and the solvent was evaporated *in vacuo*. The residue was purified by recrystallisation from petroleum to afford the product (4.0g, 49 % yield) as white solid, m.p. 66-69 ºC (lit.[136]135 61.5-63.5 ºC); (Found: C 66.60, H 6.73; $C_{10}H_{12}O_3$ requires C 66.65, H 6.71); ν_{max} (thin film, cm^{-1}) 3324, 2996, 2899, 1613, 1579, 1482; δ_H (250 MHz, $CDCl_3$) 1.71 (s, 3H, C*H*$_3$), 3.83 - 3.97 (m, 2H, C*H*$_2$), 4.06-4.20 (m, 2H, C*H*$_2$), 6.85-6.92 (m, 2H, Ar*H*), 7.19 - 7.26 (m, 1H, Ar*H*), 7.32 (dd, 1H, *J* 7.9, 1.9, Ar*H*); δ_C (63 MHz, $CDCl_3$) 26.6 (*C*H_3), 64.4 (2 × *C*H_2), 110.0 (*C*CH_3), 117.1 (Ar*C*H), 120.0 (Ar*C*H), 126.2 (Ar*C*), 126.5 (Ar*C*H), 129.9 (Ar*C*H), 154.4 (Ar*C*OH); *m/z* (EI) 180 (M^+, 50), 165 (68), 121 (100). Data was in accordance with the literature.

2-Methyl-2-[2-(2-nitrophenoxy)phenyl]-1,3-dioxolane



Sodium hydride (60 % dispersion in mineral oil, 788mg, 19.6 mmol) was added to a solution of 2-(2-methyl-1,3-dioxolan-2-yl)phenol (3.54 g, 19.6 mmol) in DMF (30 mL) at RT. The mixture was stirred for 20 min at RT and a precipitate formed. A solution of 2-chloronitrobenzene (2.82 g, 17.8 mmol) in DMF (10 mL) was added at RT. The resulting mixture was stirred for 30 min at RT and for 20 h at 105 °C. After cooling to RT, water (50 mL) was added and extracted with ethyl acetate (3 × 50 mL). The combined organic phases were dried over $MgSO_4$ and filtered. The filtrate was concentrated and purified by chromatography (petroleum/ethyl acetate, 20:1~10:1) to afford the desired product (4.5 g, yield 84%) as white solid, mp 103-105 ºC; ν_{max} (thin film, cm^{-1}) 2936, 2890, 1610, 1578, 1531; δ_H (250 MHz, $CDCl_3$) 1.84 (s, 3H, C*H*$_3$), 3.68 - 3.82 (m, 2H, C*H*$_2$), 3.90-4.00 (m, 2H, C*H*$_2$), 6.81 (dd, 1H, *J* 8.5, 1.3, Ar*H*), 6.98 (dd, 1H, *J* 7.9, 1.3, Ar*H*), 7.13 (ddd, 1H, *J* 8.2, 7.5, 1.3, Ar*H*), 7.22 (dt, 1H, *J* 7.5, 1.3, Ar*H*), 7.35 (dt, 1H, *J* 7.5, 1.6, Ar*H*), 7.45 (ddd, 1H, *J* 8.2, 7.5, 1.6, Ar*H*), 7.66 (dd, 1H, *J* 7.5, 1.6, Ar*H*), 7.99 (dd, 1H, *J* 8.2, 1.6, Ar*H*); δ_C (63 MHz, $CDCl_3$) 25.9 (*C*H$_3$), 64.5 (2 × *C*H$_2$), 108.0 (*C*CH$_3$), 118.7 (Ar*C*H), 121.6 (Ar*C*H), 121.9 (Ar*C*H), 124.9 (Ar*C*H), 125.7 (Ar*C*H), 127.8 (Ar*C*H), 129.9 (Ar*C*H), 133.9 (Ar*C*H), 134.8 (Ar*C*), 140.4 (Ar*C*), 152.1 (Ar*C*), 152.2 (Ar*C*); *m/z* (EI) 301.0940 (<5%, M^+, $C_{16}H_{15}NO_5$ requires 301.0950), 286 (100), 196 (33).

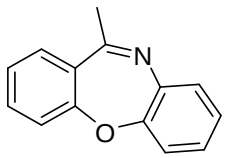
2-Methyl-2-[2-(2-aminophenoxy)phenyl]-1,3-dioxolane



A solution of 2-methyl-2-[2-(2-nitrophenoxy)phenyl]-1,3-dioxolane (3.22 g, 13.3 mmol) in EtOAc (120 mL) was passed through a Pd/C Catcart on H-cube apparatus (30 bar H_2, 40 °C). The solvent was evaporated under reduced pressure to afford the product as white solid (2.87 g, 99%), m.p. 71-73 °C; (Found: C 70.54, H 6.30, N 5.08; $C_{16}H_{15}NO_5$ requires C 70.83, H 6.32, N 5.16); ν_{max} (thin film, cm^{-1}) 3456, 3354, 2983, 2886; 1622, 1501; δ_H (250 MHz,

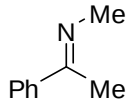
$CDCl_3$) 1.92 (s, 3H, C*H*$_3$), 3.88 - 3.94 (m, 2H, 2 × C*H*$_2$), 4.04 (br, s, 2H, N*H*$_2$), 4.08 - 4.10 (m, 2H, 2 × C*H*$_2$), 6.71 - 6.78 (m, 1H, Ar*H*), 6.82 - 6.85 (m, 2H, Ar*H*), 6.94 - 7.06 (m, 3H, Ar*H*), 7.21 (ddd, 1H, *J* 9.4, 7.5, 1.9, Ar*H*), 7.59 (dd, 1H, *J* 7.5, 1.6, Ar*H*); δ_C (63 MHz, $CDCl_3$) 25.8 (*C*H$_3$), 64.7 (2 × *C*H$_2$), 108.7 (*C*CH$_3$), 116.4 (Ar*C*H), 116. 5 (Ar*C*H), 118.2 (Ar*C*H), 121.2 (Ar*C*H), 122.0 (Ar*C*H), 125.1 (Ar*C*H), 126.9 (Ar*C*H), 129.5 (Ar*C*H), 131.5 (Ar*C*), 139.4 (Ar*C*), 142.8 (Ar*C*), 155.1 (Ar*C*); m/z (EI) 271.1215 (55%, M^+, $C_{16}H_{17}NO_3$ requires 271.1208), 210 (100), 209 (92).

11-Methyldibenz[b,f][1,4]oxazepine 139



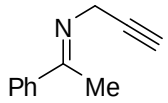
The solution of 2-methyl-2-[2-(2-aminophenoxy)phenyl]-1,3-dioxolane (4.1 g, 15.1 mmol) and *p*-TsOH·H_2O (143 mg, 0.75 mmol) in toluene (60 mL) and water (1 mL) was stirred for 4 h at 100 °C. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (100 mL) and washed with brine (60 mL). The organic layer was dried over magnesium sulfate. After filtration, the solvent was evaporated to afford the crude product. Pure product (3.1 g, 98%) was obtained by recrystallisation from ethyl acetate and petroleum ether as a light yellow solid, m.p. 84-85 °C; ν_{max} (thin film, cm^{-1}) 3051, 1618, 1599, 1474, 1440; δ_H (250 MHz, $CDCl_3$) 2.67 (s, 3H, C*H*$_3$), 7.16-7.33 (m, 6H, Ar*H*), 7.42-7.49 (m, 2H, Ar*H*); δ_C (63 MHz, $CDCl_3$) 27.6 (*C*H$_3$), 120.7 (Ar*C*H), 120.8 (Ar*C*H), 126.1 (Ar*C*H), 125.6 (Ar*C*H), 127.2 (Ar*C*H), 127.7 (Ar*C*H), 128.5 (Ar*C*H), 129.1 (Ar*C*), 133.0 (Ar*C*H), 140.7 (Ar*C*), 152.5 (Ar*C*), 160.9 (Ar*C*), 167.3 (*C*=N); *m/z* (EI) 209.0837 (100%, M^+ $C_{14}H_{11}NO$ requires 209.0841), 194 (15), 180 (54).

***N*-(1-Phenylethylidene)methanamine 153**[137]



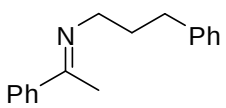
The mixture of acetophenone (2.4 g, 20 mmol), 4Å molecular sieves (4 g) and methylamine (33% wt in ethanol, 15 mL) was stirred for 48 h at room temperature. After filtration, the solvent was evaporated and the residue was purified by distillation (2.05 g, 77%, isomer ratio=16:1), colourless oil; δ_H (400 MHz, $CDCl_3$, isomer ratio, 16:1) 2.27 (q, 3H, *J* 0.7, C*H*$_3$, major), 2.32 (q, 3H, *J* 1.4, C*H*$_3$, minor), 3.09 (q, 3H, *J* 1.4, NC*H*$_3$, minor), 3.38 (q, 3H, *J* 0.72, NC*H*$_3$, major), 7.39 - 7.42 (m, 3H, ArH, major), 7.76 - 7.78 (m, 2H, ArH, major); δ_C (100 MHz, $CDCl_3$, major isomer) 15.1 (*C*H$_3$), 39.5 (*C*H$_3$), 126.4 (2 × Ar*C*H), 128.2 (2 × Ar*C*H), 129.4 (Ar*C*H), 141.2 (Ar*C*), 167.0 (*C*=N). Data was in accordance with the literature.

_N_-(1-Phenylethylidene)prop-2-yn-1-amine 154



Prepared according to general procedure A and purified by distillation (45%, isomer ratio 3:1) as a yellow oil; ν_{max} (thin film, cm^{-1}) 3293, 3058, 2219, 1683, 1631, 1447; δ_H (400 MHz, $CDCl_3$, isomer ratio, 10:1) 2.30 (t, 1H, *J* 2.5, CC*H*, major), 2.35 (app. t, 3H, *J* 0.6, C*H*$_3$, major), 2.39 (app. t, 4H, *J* 1.3, CC*H* and C*H*$_3$, minor), 3.99-4.01 (m, 2H, NC*H*$_2$, minor), 4.33 (app. dd, 2H, *J* 2.5, 0.6, NC*H*$_2$, major), 7.38 - 7.44 (m, 3H, Ar*H*), 7.83 - 7.85 (m, 2H, Ar*H*); δ_C (100 MHz, $CDCl_3$) 16.4 (*C*H$_3$, major), 29.6 (*C*H$_3$, minor), 41.4 (*C*H$_2$, major), 43.0 (*C*H$_2$, minor), 71.3 (C*C*H, major), 71.5 (C*C*H, minor), 81.8 (C*C*H, major), 126.3 (2 × Ar*C*H, minor), 127.2 (2 × Ar*C*H, major), 128.7 (2 × Ar*C*H, major), 129.2 (2 × Ar*C*H, minor), 130.4 (Ar*C*H, major), 140.9 (Ar*C*, major), 169.4 (*C*=N, major); *m/z* (EI) 157.0884 (70%, M^+, $C_{11}H_{11}N$ requires 157.0891), 156 (100) 142 (96), 115 (52), 77 (50).

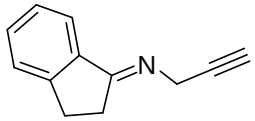
3-Phenyl-_N_-(1-phenylethylidene)propan-1-amine 155



Prepared according to general procedure B and purified by distillation (17 %, isomer

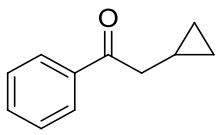
ratio=15:1) as a brown oil; ν_{max} (thin film, cm^{-1}) 3024, 2934, 2858, 1634; 1495, 1446; δ_H (400 MHz, $CDCl_3$, major isomer) 2.14-2.21 (m, 2H, C*H*$_2$), 2.25 (s, 3H, C*H*$_3$), 2.87 (t, 2H, *J* 7.4, C*H*$_2$), 3.55 (t, 2H, *J* 6.8, C*H*$_2$), 7.15 - 7.46 (m, 8H, ArC*H*), 7.85 - 7.87 (m, 2H, ArC*H*); δ_C (63 MHz, $CDCl_3$, major isomer) 15.6 (*C*H$_3$), 32.5 (*C*H$_2$), 33.8 (*C*H$_2$), 51.4 (*C*H$_2$), 125.8 (Ar*C*H), 126.6 (2 × Ar*C*H), 128.3 (2 × Ar*C*H), 128.4 (2 × Ar*C*H), 128.6 (2 × Ar*C*H), 129.4 (Ar*C*H), 141.5 (Ar*C*), 143.4 (Ar*C*), 165.2 (*C*=N); δ_H (400 MHz, $CDCl_3$, selected signals of minor isomer): 2.36 (s, 3H, C*H*$_3$), 2.66 (t, 2H, *J* 7.8, C*H*$_2$), 3.32 (t, 2H, *J* 7.1, C*H*$_2$); δ_C (63 MHz, $CDCl_3$, minor isomer) 29.2 (*C*H$_3$, minor), 32.7 (*C*H$_2$, minor), 33.7 (*C*H$_2$, minor), 52.8 (*C*H$_2$, minor); *m/z* (EI) 237.1522 (5%, M^+, $C_{17}H_{19}N$, requires 237.1517), 132 (100), 91 (86), 77 (26).

_N_-(2,3-Dihydro-1H-inden-1-ylidene)prop-2-yn-1-amine 156



Prepared according to general procedure A and purified by recrystallization from ether/petroleum (47 %), obtained as a single isomer of an off-white solid, m.p. 82-83 ºC; ν_{max} (thin film, cm^{-1}) 3266, 3220, 2924, 1652, 1604; δ_H (250 MHz, $CDCl_3$) 2.30 (t, 1H, *J* 2.5, CC*H*), 2.80 - 2.82 (m, 2H, C*H*$_2$), 3.11 - 3.16 (m, 2H, C*H*$_2$), 4.28 (app. 2H, *J* 2.5, 1.3, NC*H*$_2$), 7.28 - 7.46 (m, 3H, Ar*H*), 7.88 (d, 1H, *J* 7.6, Ar*H*); δ_C (63 MHz, $CDCl_3$) 28.1 (*C*H), 28.2 (*C*H$_2$), 42.1 (*C*H$_2$), 70.9 (C*C*H), 81.3 (*C*CH), 122.6 (Ar*C*H), 125.6 (Ar*C*H), 127.0 (Ar*C*H), 131.6 (Ar*C*H), 139.3 (Ar*C*), 149.9 (Ar*C*), 177.7 (*C*=N); *m/z* (EI) 169.0886 (83%, M^+, $C_{12}H_{11}N$, requires 169.0891), 168 (100), 115 (52), 77 (30).

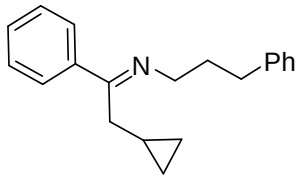
2-Cyclopropyl-1-phenyl-ethanone[138]



Magnesium (1.92g, 80 mmol), catalytic amount iodine and diethyl ether (30 mL) was placed into a oven-dried 2-necked flask under N_2 atmosphere. Bromobenzene (12.56 g, 80 mmol) in

diethyl ether (60 mL) was added dropwise at a rate to keep the reaction mixture at gently reflux. After addition was complete, the reaction mixture was heated at reflux for another 30 mins. A solution of cyclopropylacetonitrile (6.4 g, 79 mmol) in diethyl ether (60 mL) was added dropwise. At the end of addition, a precipitate was formed and after addition complete, the mixture was heated at reflux for another 1 h. The reaction mixture was allowed to stand at room temperature overnight. The ice-cooled reaction mixture was decomposed carefully by a mixture of water (40 mL) and conc. HCl (25 mL). The ether was removed by rotary evaporation. The aqueous phase was heated for 1 h to ensure hydrolysis of ketimine. This was extracted with diethyl ether (3 × 60mL), and the combined ether layers were washed with brine (50 mL) and dried over magnesium sulfate. After filtration, the filtrate was concentrated and the residue was purified by chromatography (petroleum ether/ethyl acetate, 20:1) to give the ketone as light oil (8.85 g, 70% yield). δ_H (400 MHz, $CDCl_3$) 0.20 - 0.23 (m, 2H, C*H*$_2$), 0.60 - 0.65 (m, 2H, C*H*$_2$), 1.14-1.24 (m, 1H, C*H*), 2.91 (d, 2H, *J* 6.8, C*H*$_2$), 7.46 - 7.51 (m, 2H, ArC*H*), 7.56 - 7.60 (m, 1H, ArC*H*), 7.96 - 7.99 (m, 2H, ArC*H*); δ_C (100 MHz, $CDCl_3$) 4.6 (*C*H$_2$), 6.7 (*C*H), 43.8 (*C*H$_2$), 128.1 (2 × Ar*C*H), 128.5 (2 ×Ar*C*H), 132.9 (Ar*C*H), 137.0 (Ar*C*), 200.0 (*C*=O). Data was in accordance with the literature.

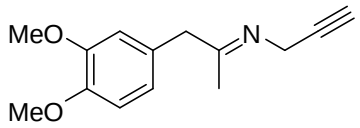
***N*-(2-Cyclopropyl-1-phenylethylidene)-3-phenylpropan-1-amine 157**



Prepared according to general procedure A and purified by distillation under reduced pressure as a yellow oil (25%); ν_{max} (thin film, cm^{-1}) 3025, 2936, 1686, 1631, 1495, 1453; δ_H (250 MHz, $CDCl_3$, isomer ratio 2:1) 0.08 - 0.16 (m, 2H, C*H*$_2$), 0.36 - 0.49 (m, 2H, C*H*$_2$), 0.74 - 0.88 (m, 1H, C*H*), 1.87 - 1.99 (m, 2H, C*H*$_2$, minor), 2.05 - 2.17 (m, 2H, C*H*$_2$, major), 2.48 (d, 2H, *J* 6.9, *o*-PrC*H*$_2$, minor), (d, 2H, *J* 6.6, *o*-PrC*H*$_2$, major), 2.62 (app. t, 2H, *J* 7.9, C*H*$_2$, minor), 2.82 (app. t, 2H, *J* 7.7, C*H*$_2$, major), 3.25 (t, 2H, *J* 6.9, C*H*$_2$, minor), 3.57 (t, 2H, *J* 6.9, C*H*$_2$, major), 7.10 - 7.43 (m, 13H, Ar*H*, major and minor), 7.77 - 7.81 (m, 2H, Ar*H*,

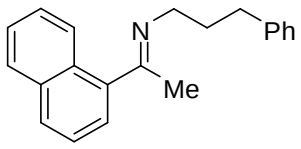
major); δ_C (63 MHz, $CDCl_3$) 4.6 (*C*H_2, minor), 5.2 (*C*H_2, major), 8.6 (*C*H, minor), 8.7 (*C*H, major), 32.8 (*C*H_2), 33.7 (*C*H_2, minor), 38.8 (*C*H_2, major), 47.2 (*C*H_2), 51.1 (*C*H_2), 52.5 (*C*H_2), 125.7 (Ar*C*H), 126.5 (Ar*C*H), 127.1 (Ar*C*H), 127.9 (Ar*C*H), 128.3 (Ar*C*H), 128.5 (Ar*C*H), 128.6 (Ar*C*H), 129.2 (Ar*C*H), 139.0 (Ar*C*), 141.1 (Ar*C*), 142.4 (2 × Ar*C*), 168.5 (*C*=N, major), 172.2 (*C*=N, minor); *m/z* (EI) 277.1821 (4%, M^+ $C_{20}H_{23}N$ requires 277.1830), 222 (45), 105 (100), 91 (75), 77 (68).

_N_-[1-(3,4-Dimethoxyphenyl)propan-2-ylidene]prop-2-yn-1-amine 158



Prepared according to general procedure A and purified by distillation (100 %, isomer ratio = 5:1) as a brown oil; ν_{max} (thin film, cm^{-1}) 2936, 2835, 1708; 1655, 1516; δ_H (400 MHz, $CDCl_3$) 1.86 (s, 3H, C*H*$_3$), 2.18 (s, 3H, C*H*$_3$, minor), 2.02 (t, 1H, *J* 1.2, CC*H*, minor), 2.27 (t, 1H, *J* 2.7, CC*H*), 3.56 (s, 2H, C*H*$_2$), 3.88 (s, 3H, OC*H*$_3$), 3.89 (s, 3H, OC*H*$_3$), 4.09-4.10 (m, 2H, NC*H*$_2$), 4.22-4.23 (m, 2H, NC*H*$_2$, minor), 6.72-6.87 (m, 3H, Ar*H*); δ_C (100 MHz, $CDCl_3$) 16.8 (*C*H_3, major), 27.3 (*C*H_3, minor), 38.0 (*C*H_2, minor), 40.3 (*C*H_2, major), 48.9 (*C*H_2, major), 50.5 (*C*H_2, minor), 55.8 (O*C*H_3, major), 70.6 (C*C*H, major), 81.3 (*C*CH, major), 111.2 (Ar*C*H, major), 112.0 (Ar*C*H, major), 121.2 (Ar*C*H, major), 129.4 (Ar*C*, major), 147.9 (Ar*C*, major), 149.0 (Ar*C*, major), 172.3 (*C*=N, minor), 173.1 (*C*=N, major); *m.z* (EI) 231.1257 (15%, M^+, $C_{14}H_{17}NO_2$, requires 231.1259), 194 (40), 151 (100).

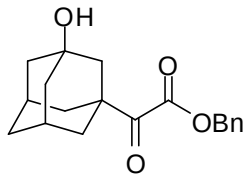
3-Phenyl-_N_-(1-naphthylethylidene)propan-1-amine 159



Prepared according to general procedure B and purified by distillation (47 %, isomer ratio = 3:1) to give a yellow sticky oil; ν_{max} (thin film, cm^{-1}) 3024, 2934, 2858, 1634; 1495, 1446; δ_H (400 MHz, $CDCl_3$) 1.89 - 1.97 (m, 2H, C*H*$_2$, major), 2.18 - 2.26 (m, 2H, C*H*$_2$, minor), 2.33 (s, 3H, C*H*$_3$, minor), 2.46 (s, 3H, C*H*$_3$, major), 2.57 (t, 2H, *J* 7.9, C*H*$_2$, major), 2.88 (t, 2H, *J* 7.7,

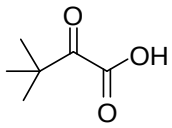
CH_2, minor), 3.03 - 3.17 (m, 2H, CH_2, major), 3.63 (t, 2H, *J* 7.0, CH_2, minor), 7.10-8.09 (m, 12H, ArC*H*); δ_C (63 MHz, $CDCl_3$) 29.6 (*C*H_3, major), 31.3 (*C*H_3, minor), 32.4 (*C*H_2, minor), 32.6 (*C*H_2, major), 33.8 (*C*H_2, major), 34.1 (*C*H_2, minor), 51.8 (*C*H_2, minor), 53.3 (*C*H_2, major), 123.1 (Ar*C*H), 124.7 (Ar*C*H), 124.9 (Ar*C*H), 125.4 (Ar*C*H), 125.5 (Ar*C*H), 125.7 (Ar*C*H), 125.9 (Ar*C*H), 126.4 (Ar*C*H), 126.9 (Ar*C*H), 128.2 (Ar*C*H), 128.3 (Ar*C*H), 128.7 (Ar*C*H), 128.8 (Ar*C*H), 133.6 (Ar*C*, major), 134.1 (Ar*C*, minor), 138.3 (Ar*C*, major), 141.6 (Ar*C*, minor), 142.3 (Ar*C*, major), 168.3 (*C*=N, minor), 168.8 (*C*=N, major); *m/z* (EI) 287.1686 (45%, M^+, $C_{21}H_{21}N$, requires 287.1674), 272 (25), 182 (100), 127 (60).

Benzyl tricyclo[3.3.1.13,7]decane-1-oxoacetate



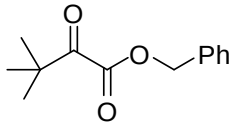
The mixture of hydroxyadamantane keto-acid (6.72 g, 30 mmol), benzyl bromide (5.64 g, 33 mmol), KI (150 mg) and K_2CO_3 (4.55 g, 33 mmol) in acetone (100 mL) was heated at reflux for 24 h. The solvent was evaporated, the residue dissolved in water (50 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic phases were washed with brine (50 mL) and dried over magnesium sulfate. Filtration and concentration afforded the crude product (5.0 g, 53%) as a light yellow solid, which was used directly without further purification. An analytically pure sample was obtained after purification by chromatography column on silica gel as white solid, mp 52-54 ºC; (Found: C 72.60, H 6.95; $C_{19}H_{22}O_4$ requires C 72.59, H 7.05); ν_{max} (thin film, cm^{-1}) 3385, 2921, 1734, 1711, 1455; δ_H (400 MHz, $CDCl_3$) 1.60 (s, 2H), 1.66 - 1.85 (m, 11H), 1.97 (s, br, 1H, O*H*), 2.29 (s, 2H), 5.38 (s, 2H, OCH_2Ph), 7.37 - 7.40 (m, 5H, ArH); δ_C (100 MHz, $CDCl_3$) 30.0 (*C*H), 34.8 (*C*H_2), 36.1 (*C*H_2), 44.2 (*C*H_2), 44.5 (*C*H_2), 48.4 (*C*H_2), 67.3 (O*C*H_2Ph), 68.1 (*C*OH), 128.6 (2 × Ar*C*H), 128.7 (Ar*C*H), 128.8 (2 × Ar*C*H), 134.5 (Ar*C*), 163.5 (CO), 199.6 (COOBn); *m/z* (ES) 337.1404 (MNa^+ $C_{19}H_{22}O_4Na$ requires 337.1416), 251 (100).

3,3-Dimethyl-2-oxobutanoic Acid[139]



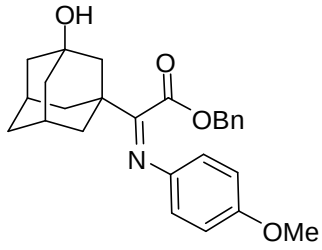
Preparation by the same procedure reported in the literature,[139] gave a light yellow oil (75% yield); δ_H (400 MHz, $CDCl_3$) 1.36 (s, 9H); Data was in accordance with the literature.

Benzyl 3,3-dimethyl-2-oxobutanoate



The mixture of keto-acid (5.0 g, 38 mmol), benzyl bromide (6.6 g, 38 mmol) and K_2CO_3 (5.8 g, 42 mmol) in acetone (80 mL) was refluxed for 48 h. The solid was filtered off and the filtrate was concentrated under reduced pressure to give the crude product (5.0 g, 60%) as a colorless oil, which was used directly for next step without further purification; δ_H (400 MHz, $CDCl_3$) 1.25 [s, 9H, C(C*H*$_3$)$_3$], 5.30 (s, 2H, C*H*$_2$), 7.36-7.40 (m, 5H, ArH).

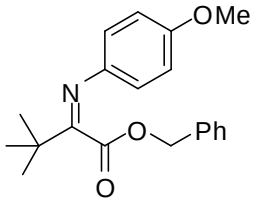
Benzyl tricyclo[3.3.1.13,7]decane-1-(4-methoxyphenylimino)acetate 167



Prepared by general procedure B and purified by chromatography on silica gel (29%) to provide colorless crystals (isomer ratio, 9:1); m.p. 82-85 ºC; (Found: C 74.42, H 6.87, N 3.21; $C_{26}H_{29}O_4$ requires C 74.44, H 6.97, N 3.34); ν_{max} (thin film, cm^{-1}) 3376, 2911, 2854, 1727, 1643, 1503; δ_H (400 MHz, $CDCl_3$, major isomer) 1.63 (t, 2H *J* 2.7Hz, 2 × C*H*$_2$), 1.70 - 1.90 (m, 12H, 12 × C*H*$_2$), 2.32 (s, 2H, 2 × C*H*$_2$), 3.79 (s, 3H, OC*H*$_3$), 4.98 (s, 2H, OC*H*$_2$), 6.74 - 6.77 (m, 4H, Ar*H*), 7.01 - 7.03 (m, 2H, Ar*H*), 7.25 - 7.12 (m, 3H, Ar*H*); δ_H (400 MHz, $CDCl_3$, selected peaks for minor isomer) 5.30 (s, 2H, OC*H*$_2$), 6.82 [2 H, (AX)$_2$, Ar*H*], 6.94 [2 H, (AX)$_2$, Ar*H*]; δ_C (100 MHz, $CDCl_3$, major isomer) 30.0 (*C*H), 35.0 (*C*H$_2$), 38.2 (*C*H$_2$), 43.8 (*C*H$_2$), 44.3 (*C*H$_2$), 46.8 (*C*H$_2$), 55.3 (O*C*H$_3$), 66.6 (O*C*H$_2$), 68.6 (*C*OH), 114.0 (2 ×

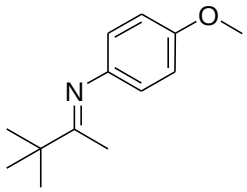
Ar*C*H), 120.8 (2 × Ar*C*H), 128.3 (Ar*C*H), 128.4 (Ar*C*H), 128.6 (Ar*C*H), 134.6 (Ar*C*), 143.0 (Ar*C*), 156.7 (Ar*C*), 165.1 (*C*O), 169.7 (*C*OOBn); *m/z* (EI) 419 (M^+, 56), 284 (100).

Benzyl 2-(4-methoxyphenylimino)-3,3-dimethylbutanoate 169



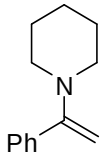
Prepared by general procedure B and purified by chromatography on silica gel (petroleum ether/ethyl acetate, 50:1~20:1) and further by recrystallisation from petroleum ether and diethyl ether to afford the product as a white solid (82%, isomer ratio, 11.5: 1); m.p. 53-55 ºC; (Found: C 73.91, H 7.16, N 4.20; $C_{20}H_{23}NO_3$ requires C 73.82, H 7.12, N 4.30); v (thin film, cm^{-1}) 2951, 1730, 1641, 1501; δ_H (400 MHz, $CDCl_3$, isomer ratio, 11.5:1) 1.25 [s, 9H, C(C*H*$_3$)$_3$, minor)], 1.30 [s, 9H, C(C*H*$_3$)$_3$, major)], 3.79 (s, 3H, OC*H*$_3$, major), 3.81 (s, 3H, OC*H*$_3$, minor), 4.98 (s, 2H, OC*H*$_2$Ph, major), 5.30 (s, 3H, OC*H*$_2$Ph, minor), 6.73 - 6.78 (m, 4H, Ar*H*), 7.02 - 7.05 (m, 2H, Ar*H*), 7.25 - 7.31 (m, 3H, Ar*H*); *m/z* (EI) 325 (M^+, 50%), 192 (98), 130 (100).

***N*-(3,3-Dimethylbutan-2-ylidene)-4-methoxybenzenamine 171[83]**



Prepared according to general procedure A, purified by distillation to give the product as a yellow oil (24%); δ_H (250 MHz, $CDCl_3$) 1.24 [s, 9H, C(C*H*$_3$)], 1.78 (s, 3H, C*H*$_3$), 3.80 (s, 3H, OC*H*$_3$), 6.59 - 6.62 (m, 2H, ArC*H*), 6.84 - 6.89 (m, 2H, ArC*H*); δ_C (63 MHz, $CDCl_3$) 15.1 (*C*H$_3$), 27.9 [C(*C*H$_3$)], 40.2 [*C*(CH$_3$)], 55.4 (O*C*H$_3$), 114.2 (2 × Ar*C*H), 120.1 (2 × Ar*C*H), 145.5 (Ar*C*), 155.5 (Ar*C*), 177.8 (*C*=N). Data was in accordance with the literature.

1-(1-Phenylvinyl)piperidine 271[140]



The reactions were carried out under argon. A three-necked flask containing a magnetic stirrer was charged with anhydrous pentane (150 mL), acetophenone (3 g, 24.9 mmol) and piperidine (6.38 g, 74.9 mmol). The mixture was stirred at r.t. for 1 h, then was cooled to 0 °C, $TiCl_4$ (2.37 g, 12.5 mmol) was added dropwise over 5 min. The mixture was stirred for 1 h, then allowed to warm to r.t. and stirred for another 5 h. After filtration, the filtrate was concentrated and the residue was purified by distillation to afford the desired product as light yellow oil (1 g, 21%); δ_H (250 MHz, $CDCl_3$) 1.55 - 1.70 (m, 6H, 6 × C*H*$_2$), 2.82-2.86 (m, 4H, 4 × C*H*$_2$), 4.19 (s, 1H, 1 × C=C*H*$_2$), 4.29 (s, 1H, 1 × C=C*H*$_2$), 7.31-7.40 (m, 3H, Ar*H*), 7.48 - 7.53 (m, 2H, Ar*H*); δ_C (63 MHz, $CDCl_3$) 24.6 (*C*H$_2$), 26.0 (2 × *C*H$_2$), 50.5 (2 × *C*H$_2$), 90.1 (C=*C*H$_2$), 127.7 (Ar*C*H), 127.8 (Ar*C*H), 128.1 (Ar*C*H), 140.4 (Ar*C*), 158.1 (*C*=CH$_2$). Data was in accordance with the literature.

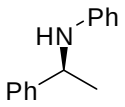
7.4 Asymmetric reduction of imines

General procedure E

Imine (1 mmol), catalyst and dry CH_2Cl_2 (0.5 mL or 1mL) were introduced into an oven-dried 25 mL two-necked flask or an oven-dried carousel tube. The mixture was stirred until complete dissolution, then cooled to 0 ºC and trichlorosilane (2 mmol, 0.2 mL) was added by syringe over five to ten seconds. The reaction was left to stir for the desired time. Hydrochloric acid (1 M, *ca.* 2 mL) was added, which led to gas evolution and precipitation, followed by CH_2Cl_2 (20 mL) and aqueous sodium hydroxide (1 M, 20 mL). This mixture was stirred until the precipitate was completely dissolved. The organic phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 20mL). The combined organic phases were washed with brine (20mL) and dried over $MgSO_4$. Filtration and concentration gave the product that could be purified by chromatography column on silica gel using 2% ~ 10% solution of diethyl ether or ethyl acetate in petroleum ether. Racemic

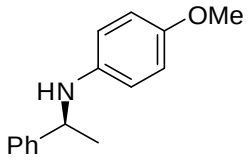
samples of compound were obtained by this procedure, using *N*-formylpyrrolidine (10%) as catalyst.

(*S*)-*N*-(1-Phenylethyl)-aniline 131[79]



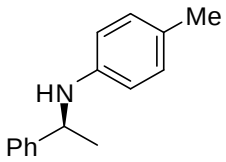
Prepared according to general procedure E (96%, 85% ee) as a yellow oil; $[\alpha]_D$ +16 (85% ee from HPLC, *c* 1.0 in MeOH, lit.[79] $[\alpha]_D$ +13.9, *c* 1.0 in MeOH，86% ee); δ_H (250 MHz, $CDCl_3$) 1.55 (d, 3H, *J* 6.6, C*H*$_3$), 4.05 (br, 1H, N*H*), 4.51 (q, 1H, *J* 6.6, C*H*), 6.51 - 6.55 (m, 2H, Ar*H*), 6.63 - 6.70 (m, 1H, Ar*H*), 7.08 - 7.14 (m, 2H, Ar*H*), 7.21 - 7.42 (m, 5H, Ar*H*), δ_C ($CDCl_3$, 63MHz) 25.1 (*C*H$_3$), 53.5 (N*C*H), 113.4 (2 × Ar*C*H), 117.4 (Ar*C*H), 126.0 (2 × Ar*C*H), 127.0 (Ar*C*H), 128.8 (2 × Ar*C*H), 129.2 (2 × Ar*C*H), 145.4 (Ar*C*), 147.4 (Ar*C*); Enantiomeric excess was determined by chiral phase HPLC (Kromasil 3-Cellucoat OD-H), 5% ipa in hexane @ 1 mL min^{-1}, t_R = 5.0 min (major), 5.9 min (minor). Data was in accordance with the literature.

(*S*)-4-Methoxy-*N*-(1-phenylethyl)aniline 132[79]



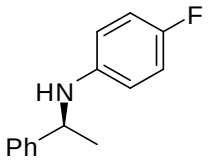
Prepared according to general procedure E (100%, 90% ee) as a brown oil; $[\alpha]_D$ -2.65 (88% ee from HPLC, *c* 3.4 in $CHCl_3$, Lit.[79] $[\alpha]_D$ -5.6, *c* 0.54 in $CHCl_3$, 87% ee); δ_H (400 MHz, $CDCl_3$) 1.52 (d, 3H, *J* 6.8, C*H*$_3$), 3.72 (s, 3H, OC*H*$_3$), 3.81 (br, 1H, N*H*), 4.43 (q, 1H, *J* 6.8, NC*H*), 6.49 [2H, $(AX)_2$, Ar*H*], 6.71 [2H, $(AX)_2$, Ar*H*], 7.23 - 7.40 (m, 5H, Ar*H*); δ_C ($CDCl_3$, 100 MHz) 25.2 (*C*H$_3$), 54.3 (N*C*H), 55.8 (*C*H$_3$O), 114.6 (2 × Ar*C*H), 114.8 (2 × Ar*C*H), 125.9 (2 × Ar*C*H), 126.9 (Ar*C*H), 128.6 (2 × Ar*C*H), 141.6 (Ar*C*), 145.5 (Ar*C*), 151.9 (Ar*C*); Enantiomeric excess was determined by chiral phase HPLC (Phenomenex Lux 3 µm Cellulose-1) 2 % ipa in hexane @ 1 mL min^{-1}, t_R= 16.5 min (minor), 19.2 min (major). Data was in accordance with the literature.

(*S*)-4-Methyl-*N*-(1-phenylethyl)aniline 133[62a]



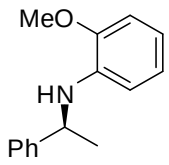
Prepared according to general procedure E (100 %, 87% ee) as a yellow solid, mp 75-76 °C (lit.[141] 70 °C); $[\alpha]_D$ +31.6 (87% ee from HPLC, *c* 1.25 in ethyl acetate, lit.[62a] $[\alpha]_D$ +27.3, *c* 0.7 in ethyl acetate, 91% ee); δ_H (400 MHz, $CDCl_3$) 1.54 (d, 3H, *J* 6.6, C*H*$_3$), 2.22 (s, 3H, ArC*H*$_3$), 3.95 (s, br, 1H, N*H*), 4.49 (q, 1H, *J* 6.6, NC*H*), 6.47 [2H, $(AX)_2$, Ar*H*], 6.94 [2H, $(AX)_2$, Ar*H*], 7.24 - 7.42 (m, 5H, Ar*H*); δ_C (100 MHz, $CDCl_3$) 20.5 (Ar*C*H$_3$), 25.2 (*C*H$_3$), 53.8 (N*C*H), 111.5 (2 × Ar*C*H), 126.0 (2 × Ar*C*H), 126.4 (Ar*C*), 126.9 (Ar*C*H), 128.7 (2 × Ar*C*H), 129.7 (2 × Ar*C*H), 145.1 (Ar*C*), 145.6 (Ar*C*); Enantiomeric excess was determined by chiral phase HPLC (Kromasil 3-Cellucoat OD-H), 1% ipa in hexane @ 1 mL min^{-1}, t_R = 7.2 min (minor), 8.0 min (major). Data was in accordance with the literature.

(*S*)-4-Fluoro-*N*-(1-phenylethyl)aniline 134[130]



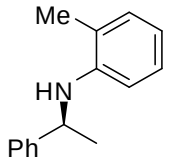
Prepared according to general procedure E (95%, 88% ee) as a yellow oil; $[\alpha]_D$ +23.8 (88% ee from HPLC, *c* 1.05 in $CHCl_3$, lit.[130] $[\alpha]_D$ -16.8, *c* 1.0 $CHCl_3$, 84% ee *R* isomer); δ_H (400 MHz, $CDCl_3$) 1.53 (d, 3H, *J* 6.6, C*H*$_3$), 3.95 (br, 1H, N*H*), 4.44 (q, 1H, *J* 6.6, C*H*), 6.43 - 6.47 (m, 2H, Ar*H*), 6.79 - 6.84 (m, 2H, Ar*H*), 7.23 - 7.28 (m, 1H, Ar*H*), 7.32 - 7.38 (m, 4H, Ar*H*); δ_C (100 MHz, $CDCl_3$) 25.1 (*C*H$_3$), 54.1 (*C*H), 114.1 (d, $^3J_{C\text{-}F}$ 6.9, 2 × Ar*C*H), 115.5 (d, $^2J_{C\text{-}F}$ 22.2, 2 × Ar*C*H), 125.9 (2 × Ar*C*H), 127.0 (Ar*C*H), 128.8 (2 × Ar*C*H), 143.7 (Ar*C*), 145.1 (Ar*C*), 155.5 ($^1J_{C\text{-}F}$ 234.6, Ar*C*F); δ_F (235 MHz, $CDCl_3$) -128.4; Enantiomeric excess was determined by chiral phase HPLC (Kromasil 3-Cellucoat OD-H), 2% ipa in hexane @ 1 mL min^{-1}, t_R = 6.9 min (minor), 7.8 min (major). Data was in accordance with the literature.

(*S*)-2-Methoxy-*N*-(1-phenylethyl)aniline 135[62a]



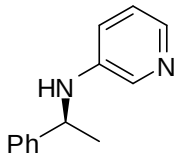
Prepared according to general procedure E (35%, 95% ee) as a white solid, mp 78-80 ºC (not reported in literature); $[\alpha]_D$ +78.3 (95% ee from HPLC, *c* 0.6 in ethyl acetate, lit.[62a] +76.4, *c* 0.5 in ethyl acetate 88% ee); δ_H (400 MHz, $CDCl_3$) 1.57 (d, 3H, *J* 6.8, C*H*$_3$), 3.91 (s, 3H, OC*H*$_3$), 4.49 (q, 1H, *J* 6.8, NC*H*), 4.68 (br, 1H, N*H*), 6.36 (dd, 1H, *J* 7.6, 1.6, Ar*H*), 6.63 (dt, 1H, *J* 7.6, 1.9, Ar*H*), 6.70 (dt, 1H, *J* 7.5, 1.6, Ar*H*), 6.77 (dd, 1H, *J* 7.8, 1.9, Ar*H*), 7.20 - 7.41 (m, 5H, Ar*H*); δ_C ($CDCl_3$, 100 MHz) 25.3(*C*H$_3$), 54.3 (N*C*H), 55.5(*C*H$_3$O), 109.4 (Ar*C*H), 111.2 (Ar*C*H), 116.4 (Ar*C*H), 121.3 (Ar*C*H), 126.0 (2 × Ar*C*H), 126.9 (Ar*C*H), 128.7 (2 × Ar*C*H), 137.3 (Ar*C*), 145.6 (Ar*C*), 1146.7 (Ar*C*); Enantiomeric excess was determined by chiral phase HPLC (Kromasil 3-Cellucoat OD-H), 0.2% ipa in hexane @ 1 mL min^{-1}, t_R = 7.5 min (major), 10.6 min (minor). Data was in accordance with the literature.

(*S*)-2-Methyl-*N*-(1-phenylethyl)aniline 136[142]



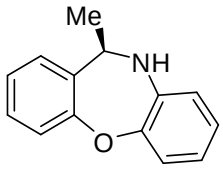
Prepared according to general procedure E (64%, 97% ee) as a white solid, mp 42-44 ºC (not reported in literature); $[\alpha]_D$ +60.8 (97% ee from HPLC, *c* 1.09 in $CHCl_3$, lit.[142] $[\alpha]_D$ +14, *c* 0.5 in $CHCl_3$, 16% ee); δ_H (400 MHz, $CDCl_3$) 1.59 (d, 3H, *J* 6.7, C*H*$_3$), 2.26 (s, 3H, ArC*H*$_3$), 3.88 (s, br, 1H, N*H*), 4.56 (q, 1H, *J* 6.7, NC*H*), 6.39 (d, 1H, *J* 8.1, ArH), 6.33 (t, 1H, *J* 7.2, Ar*H*), 6.98 (t, 1H, *J* 7.7, Ar*H*), 7.01 (d, 1H, *J* 7.2, Ar*H*), 7.25 (t, 1H, *J* 7.1, Ar*H*), 7.33 - 7.40 (m, 4H, Ar*H*); δ_C (100MHz, $CDCl_3$) 17.7(Ar*C*H$_3$), 25.1 (*C*H$_3$), 53.4 (N*C*H), 111.1 (Ar*C*H), 116.9 (Ar*C*H), 121.6 (Ar*C*), 125.9 (2 × Ar*C*H), 126.9 (Ar*C*H), 127.1 (Ar*C*H), 128.7 (2 × Ar*C*H), 130.1 (Ar*C*H), 145.2 (Ar*C*), 145.4 (Ar*C*); Enantiomeric excess was determined by chiral phase HPLC (Kromasil 3-Cellucoat OD-H), 3% ipa in hexane @ 1 mL min^{-1}, t_R = 4.1 min (major), 7.0 min (minor). Data was in accordance with the literature.

(*S*)-*N*-(1-Phenylethyl)pyridin-3-amine 137[143]



Prepared according to the general procedure E (44%, 60% ee) as a white solid; m.p. 88-90 ºC (not reported in literature); $[\alpha]_D$ +0.9 (*c* 1.05 in $CHCl_3$, 60% ee from HPLC, not reported in literature); δ_H (400 MHz, $CDCl_3$) 1.55 (d, 3H, *J* 6.6, C*H*$_3$), 4.33 (s, br, 1H, N*H*), 4.49 (q, 1H, *J* 6.6, C*H*), 6.72 (ddd, 1H, *J* 8.3, 2.7, 1.2, ArC*H*), 6.97 (dd, 1H, *J* 8.3, 1.2, ArC*H*), 7.23 - 7.38 (m, 5H, ArC*H*), 7.91 (d, 1H, *J* 4.2, ArC*H*), 8.02 (d, 1H, *J* 2.2, ArC*H*); δ_C (100 MHz, $CDCl_3$) 24.9 (CH_3), 53.3 (*C*H), 119.0 (Ar*C*H), 123.6 (Ar*C*H), 125.8 (Ar*C*H), 127.2 (Ar*C*H), 128.8 (2 × Ar*C*H), 136.6 (Ar*C*H), 138.5 (2 × Ar*C*H), 143.3 (Ar*C*), 144.3 (Ar*C*); Enantiomeric excess was determined by chiral phase HPLC (Phenomenex Lux 3 um Cellulose-1), 8% ipa in hexane @ 1 mL min^{-1}, t_R = 21.4 min (major), 48.3 min (minor). Data was in accordance with the literature.

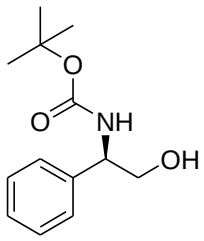
(*S*)-10, 11-Dihydro-11-methyl-dibenz[b, f]oxazepine 143



Prepared according to general procedure E (86% conversion, 99% ee) as a yellow oil; $[\alpha]_D$ = -21 (*c* 1.05 in MeOH, 99% ee from HPLC); (Found: C 79.50; H 6.15; N 6.70; $C_{14}H_{13}NO$ requires C 79.59; H 6.20; N 6.63); ν_{max} (thin film, cm^{-1}) 3386, 3058, 2970, 1609, 1494; δ_H (400 MHz, $CDCl_3$) 1.66 (d, 3H, *J* 6.7, C*H*$_3$), 3.25 (s, br, 1H, N*H*), 5.10 (q, 1H, *J* 6.7, NC*H*), 6.60 (dd, 1H, *J* 7.8, 1.6, Ar*H*), 6.71 (ddd, 1H, *J* 8.4, 7.2, 5.6, Ar*H*), 6.88 (dt, 1H, *J* 8.4, 1.5, Ar*H*), 7.10-7.31 (m, 5H, Ar*H*); δ_C (100 MHz, $CDCl_3$) 20.0 (*C*H$_3$), 50.5 (N*C*H), 119.1 (Ar*C*H), 120.0 (Ar*C*H), 120.9 (Ar*C*H), 121.8 (Ar*C*H), 124.5 (Ar*C*H), 124.6 (Ar*C*H), 125.7 (Ar*C*H), 128.9 (Ar*C*H), 134.4 (Ar*C*), 137.0 (Ar*C*), 145.0 (Ar*C*), 157.3 (Ar*C*); *m/z* (EI) 211.1006 (45%, M^+ $C_{14}H_{13}NO$ requires 211.0997), 196(100); Enantiomeric excess was

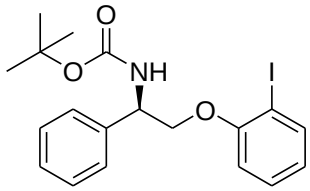
determined by chiral phase HPLC (Kromasil 3-cellucoat OD-H), 1% ipa in hexane @ 1 $mLmin^{-1}$, t_R = 12.6 min (minor), 13.4 min (major).

(*R*)-*t*-Butyl 2-hydroxy-1-phenylethylcarbamate[144]



A solution of $(Boc)_2O$ (2.4 g, 11 mmol) in THF (5mL) was added dropwise to a solution of triethylamine (1.1 g, 11 mmol) and (*R*)-2-phenylglycinol (1.37 g, 10 mmol) in THF (15 mL) at 0 °C. The reaction mixture was stirred at room temperature overnight. Diethyl ether (40 mL) was added and the resulting mixture was washed by brine (2 × 30 mL). The organic layer was dried over $MgSO_4$, filtrated and evaporated to afford the desired product as a white solid (2.0 g, 84 % yield), m.p. 136-137 ºC (lit.[144] 136-137 ºC); $[\alpha]_D$ -40 (*c* 1.0 in $CHCl_3$, lit.[144] +38.7, *c* 1.0 in $CHCl_3$, *S* isomer); δ_H ($CDCl_3$, 400 MHz) 1.46 [s, 9H, $C(CH_3)_3$], 1.87 (br, 1H, O*H*), 3.87 (d, 2H, *J* 4.4, OCH_2), 4.80 (br s, 1H), 5.25 (br s, 1H), 7.28 - 7.40 (m, 5H, ArC*H*). Data was in accordance with the literature.

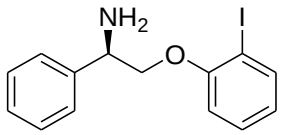
(*R*)-*t*-Butyl 2-(2-iodophenoxy)-1-phenylethylcarbamate



(*R*)-*t*-Butyl 2-hydroxy-1-phenylethylcarbamate (1.64 g, 6.91 mmol), 2-iodophenol (1.52 g, 6.91mmol) and PPh_3 (2.35 g, 8.98 mmol) were introduced into a 2-necked flask. The flask was evacuated and backfilled with N_2 three times. Dried THF (60mL) was added by syringe. The mixture was cooled to 0 °C and DIAD (1.8 mL, 8.98 mmol) was added dropwise. The resulting mixture was stirred at RT for 36 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (petroleum ether

/ ethyl acetate, 20 : 1 to 10 : 1) to afford the desired product as a white solid (1.85 g, 61 % yield), m.p. 109-110 ºC (from petroleum ether / diethyl ether); $[\alpha]_D$ -36.6 (*c* 0.9 in $CHCl_3$). (Found: C 52.13; H 4.89, N 2.88; $C_{19}H_{22}INO_3$ requires C 51.95; H 5.05; N 3.19); ν_{max} (thin film, cm^{-1}) 3426, 3351, 2931, 1712, 1448; δ_H (400 MHz, $CDCl_3$) 1.46 [s, 9H, C(C*H*$_3$)$_3$], 4.19 - 4.25 (m, 1H, 1 × OC*H*$_2$), 4.29 (dd, 1H, *J* 9.1, 4.4, 1 × OC*H*$_2$), 5.13 (br, s, 1H), 5.61 (br, s, 1H), 6.72 - 6.79 (m, 2H, ArC*H*), 7.26 - 7.33 (m, 2H, ArC*H*), 7.36 - 7.41 (m, 2H, ArC*H*), 7.51 (d, 2H, *J* 7.3, ArC*H*), 7.77 (dd, 1H, *J* 7.8, 1.4, ArC*H*); δ_C (100 MHz, $CDCl_3$) 28.4 [C(*C*H$_3$)$_3$], 53.8 (N*C*H), 72.1 (O*C*H$_2$), 79.8 [*C*(CH$_3$)$_3$], 86.7 (Ar*C*I), 112.3 (Ar*C*H), 123.1 (Ar*C*H), 127.1 (2 × Ar*C*H), 127.7 (Ar*C*H), 128.6 (2 × Ar*C*H), 129.5 (Ar*C*H), 139.4 (Ar*C*H), 139.7 (Ar*C*), 155.3 (Ar*C*), 156.8 (*C*O); *m/z* (EI) 440 (3%, MH^+), 439 (10, M^+), 150 (100).

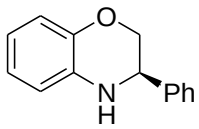
(*R*)-2-(2-Iodophenoxy)-1-phenylethanamine



Trifluoroacetic acid (2.54 g, 22 mmol) was added dropwise to an ice-cooled solution of (*R*)-*t*-butyl 2-(2-iodophenoxy)-1-phenylethylcarbamate (1.63 g, 3.7 mmol) in DCM (10 mL). The mixture was stirred at room temperature for 12 h, then neutralized with 1 *N* aqueous NaOH and the aqueous phase was exacted with dichloromethane (3 × 30 mL). The combined organic phases were dried over $MgSO_4$, the solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel (petroleum ether / ethyl acetate, 5:1~1:1) to afford the title compound as a colourless oil (1.2 g, 96 % yield); $[\alpha]_D$ -63 (*c* 1 in $CHCl_3$); (Found: C 49.22; H 3.97; N 3.90; $C_{14}H_{14}INO$ requires C 49.58; H 4.16; N 4.13); ν_{max} (thin film, cm^{-1}) 3381, 3049, 2923, 2854, 1579, 1472; δ_H (400 MHz, $CDCl_3$) 2.09 (s, br, 2H, N*H*$_2$), 3.96 (t, 1H, *J* 8.8, C*H*NH$_2$), 4.18 (dd, 1H, *J* 8.8, 3.4, 1 × C*H*$_2$O), 4.54 (dd, 1H, *J* 8.8, 3.4, 1 × C*H*$_2$O), 6.72 - 6.80 (m, 2H, Ar*H*), 7.26 - 7.36 (m, 2H, Ar*H*), 7.38 - 7.43 (m, 2H, Ar*H*), 7.51 - 7.54 (m, 2H, Ar*H*), 7.79 (dd, 1H, *J* 7.5, 1.5, Ar*H*); δ_C (100 MHz, $CDCl_3$) 55.2 (NH$_2$*C*H), 75.2 (O*C*H$_2$), 86.7 (Ar*C*I), 112.3 (Ar*C*H), 122.8 (Ar*C*H), 127.1 (2 × Ar*C*H),

127.8 (Ar*C*H), 128.6 (2 × Ar*C*H), 129.5 (Ar*C*H), 139.4 (Ar*C*H), 141.5 (Ar*C*), 157.1 (Ar*C)*; *m*/*z* (EI) 339 (3%, M^+), 212 (3), 106 (100).

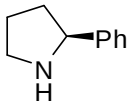
(*R*)-3-Phenyl-3,4-dihydro-2*H*-1,4-benzoxazine 143[145]



(*R*)-2-(2-Iodophenoxy)-1-phenylethanamine (169.5 mg, 0.5 mmol), BINAP (31 mg, 0.05mmol), $Pd_2(dba)_3$ (14.4 mg, 0.025mmol) and *t*-BuONa (62.4 mg, 0.65 mmol) were introduced into a 2-necked flask, which was evacuated and refilled with nitrogen three times. Dry toluene (5 mL) was added and the resulting mixture was stirred at 95 °C for 16 h. After cooling to room temperature, AcOEt (10 mL) and saturated aqueous NH_4Cl (20 mL) were added. The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine (30 mL), and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel (petroleum ether/ethyl acetate, 30:1) to afford the title compound as a yellow oil (95 mg, 90 % yield); $[\alpha]_D$ -140 (*c* 0.95 in $CHCl_3$, lit.[145] -118.1, *c* 1.0 in $CHCl_3$, 98% ee *R* isomer); δ_H (400 MHz, $CDCl_3$) 4.10 (dd, 1H, *J* 8.8, 10.8, 1 × OC*H*$_2$), 4.34 (dd, 1H, *J* 3.0, 10.8, 1 × OC*H*$_2$), 4.55 (dd, 1H, *J* 8.8, 3.0, NC*H*), 6.71 - 6.91 (m, 4H, ArC*H*), 7.37 - 7.48 (m, 5H, ArC*H*); δ_C (100MHz, $CDCl_3$) 54.3 (N*C*H), 71.0 (O*C*H_2), 115.5 (Ar*C*H), 116.7 (Ar*C*H), 119.1 (Ar*C*H), 121.6 (Ar*C*H), 127.2 (2 × Ar*C*H), 128.4 (Ar*C*H), 128.9 (2 × Ar*C*H), 133.9 (Ar*C*), 139.2 (Ar*C*), 143.6 (Ar*C*). Data was in accordance with the literature.

(*S*)-**128** was prepared according to general procedure E (26% conversion, 21% ee); Enantiomeric excess was determined by chiral phase HPLC (Kromasil 3-cellucoat OD-H), 5% ipa in hexane @ 1 $mLmin^{-1}$, t_R = 10.7 min (minor), 14.8 min (major).

(*S*)-2-Phenylpyrrolidine 145[146]

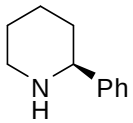


Prepared according to the general procedure E (27%, 89% ee); yellow oil; $[\alpha]_D$ -31.6 (89% ee from GC, *c* 0.95 in MeOH, lit.[147] -22, *c* 1.0 in MeOH, >98% ee); δ_H (250 MHz, $CDCl_3$) 1.62 - 2.03 (m, 3H, 3 × CH_2), 2.14 - 2.27 (m, 1H, 1 × CH_2), 2.56 (s, 1H, N*H*), 2.96 - 3.06 (m, 1H, 1 × CH_2), 3.16 - 3.26 (m, 1H, 1 × CH_2), 4.12 (t, 1H, *J* 7.6, NC*H*), 7.21 - 7.41 (m, 5H, Ar*H*); δ_C (63 MHz, $CDCl_3$) 25.6 (*C*H_2), 34.3 (*C*H_2), 46.9 (N*C*H_2), 62.6 (N*C*H), 126.6 (2 × Ar*C*H), 126.8 (Ar*C*H), 128.4 (2 × Ar*C*H), 144.6 (Ar*C*); Enantiomeric excess was determined by GC analysis of its trifluoromethyl-acetyl derivative on Astec Chiraldex B-DM at 140 ºC, t_R = 8.35 min (major), 8.91 min (minor). Data was in accordance with the literature.

The sample for GC analysis was prepared as below:

Trifluoromethyl acetic anhydride (0.2 mL) was added into a solution of amine **145** (20 mg) and triethylamine (0.2 mL) in dichloromethane (3 mL) at room temperature and then stirring for 1 hour. The volatile material was evaporated under reduced pressure and the residue was directed used for GC analysis.

(*S*)-2-Phenylpiperidine 146[148]

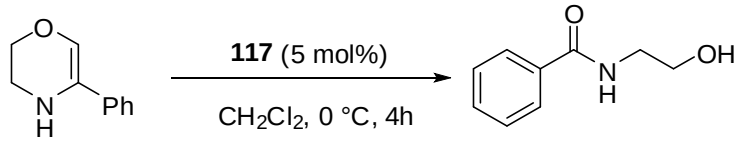


Prepared according to general procedure E (53%, 73% ee); light yellow oil; $[\alpha]_D$ -41 (89% ee from GC, *c* 0.5 in $CHCl_3$, lit.[148] -63.8, *c* 0.5 in $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 1.46 - 1.93 (m, 6H, 3 × CH_2), 2.13 (br, s, 1H, N*H*), 2.81 (td, 1H, *J* 11.5, 3.1, 1 × NCH_2), 3.21 (app. dq, 1H, 11.5, 1.2, 1 × NCH_2), 3.61 (app. dd, 1H, *J* 10.5, 2.5, NCH), 7.22 - 7.41 (m, 5H, Ar*H*); δ_C (63 MHz, $CDCl_3$) 25.4 (*C*H_2), 25.8 (*C*H_2), 34.9 (*C*H_2), 47.8 (N*C*H_2), 62.3 (N*C*H), 126.7 (2 × Ar*C*H), 127.1 (Ar*C*H), 128.4 (2 × Ar*C*H), 145.3 (Ar*C*); Enantiomeric excess was determined by GC analysis of its trifluoromethyl-acetyl derivative on Astec Chiraldex B-DM at 130 ºC, t_R = 16.3 min (major), 17.3 min (minor). Data was in accordance with the literature.

The sample for GC analysis was prepared as below:

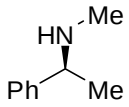
Trifluoromethyl acetic anhydride (0.2 mL) was added into a solution of amine **146** (20 mg) and triethylamine (0.2 mL) in dichloromethane (3 mL) at room temperature and then stirring for 1 hour. The volatile material was evaporated under reduced pressure and the residue was directed used for GC analysis.

***N*-(2-Hydroxyethyl)benzamide 150**[149]



Prepared according to the general procedure E as a white solid (66%); δ_H (400 MHz, $CDCl_3$) 3.03 (t, 1H, *J* 4.9, CH_2OH), 3.62-3.66 (m, 2H, NCH_2), 3.85 (q, 2H, *J* 4.9, CH_2OH), 6.81 (br, s, 1H, N*H*), 7.41-7.46 (m, 2H, Ar*H*), 7.50-7.54 (m, 1H, Ar*H*), 7.78-7.81 (m, 2H, Ar*H*); δ_C (100 MHz, $CDCl_3$) 42.8 (NCH_2), 62.0 (OCH_2), 127.0 (2 × Ar*C*H), 128.6 (2 × Ar*C*H), 131.7 (Ar*C*H), 134.1 (Ar*C*), 168.7 (*C*O); Data was in accordance with the literature.

(*S*)-*N*-Methyl-1-phenylethanamine 160[150]



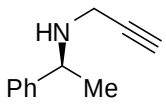
Prepared according to general procedure E (89%, 77% ee) as colourless oil; $[\alpha]_D$ -64.7 (77% ee from GC, *c* 1.05 in $CHCl_3$, lit.[150] $[\alpha]_D$ +77.7, *c* 1.0 $CHCl_3$, pure *R* isomer); δ_H (250 MHz, $CDCl_3$) 1.38 (d, 3H, *J* 6.6, CH_3), 2.33 (s, 3H, NCH_3), 3.66 (q, 1H, *J* 6.6, NC*H*), 7.22 - 7.39 (m, 5H, Ar*H*); Enantiomeric excess was determined by GC analysis of its trifluoromethyl-acetyl derivative on Astec Chiraldex B-DM at 100 ºC, t_R = 15.4 min (major), 16.3 min (minor). Data was in accordance with the literature.

The sample for GC analysis was prepared as below:

Trifluoromethyl acetic anhydride (0.2 mL) was added into a solution of amine **160** (20 mg) and triethylamine (0.2 mL) in dichloromethane (3 mL) at room temperature and then stirring

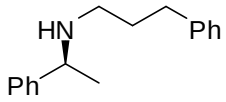
for 1 hour. The volatile material was evaporated under reduced pressure and the residue was directed used for GC analysis.

(*S*)-*N*-2-Propyn-1-yl- phenylethanamine 161[151]



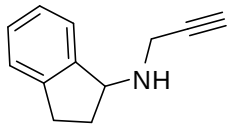
Prepared according to general procedure E (60%, 90% ee) as colourless oil; $[\alpha]_D$ -161 (*c* 1.0 in $CHCl_3$, 90% ee from HPLC, lit.[151] +169.6, *c* 0.1 $CHCl_3$, *R* isomer); δ_H (400 MHz, $CDCl_3$) 1.39 (d, 3H, *J* 6.2, C*H*$_3$), 2.24 (t, 1H, *J* 2.4, CC*H*), 3.18 (dd, 1H, *J* 17.1, 2.4, 1 × C*H*$_2$), 3.38 (dd, 1H, *J* 17.1, 2.4, 1 × C*H*$_2$), 3.99 (q, 1H, *J* 6.2, C*H*), 7.25 - 7.30 (m, 1H, ArC*H*), 7.33 - 7.38 (m, 4H, ArC*H*); δ_C (100 MHz, $CDCl_3$) 24.6 (*C*H$_3$), 36.3 (*C*H$_2$), 56.7 (N*C*H), 71.7 (C*C*H), 82.7 (*C*CH), 127.3 (2 × Ar*C*H), 127.6 (Ar*C*H), 128.9 (2 × Ar*C*H), 144.8 (Ar*C*); Enantiomeric excess was determined by chiral phase HPLC (Phenomenex Lux 3 um Cellulose-1), 1% ipa in hexane @ 1 mL min^{-1} (λ 210nm), t_R = 6.2 min (major), 6.6 min (minor). Data was in accordance with the literature.

(*S*)-*N*-(3-Phenylpropyl)-1-phenylethylamine 162[152]



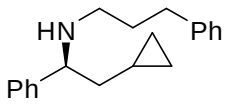
Prepared according to general procedure E as colourless oil; $[\alpha]_D$ -41 (*c* 1.0 in $CHCl_3$, 80% ee from HPLC, $[\alpha]_D$ not reported in literature); δ_H (250 MHz, $CDCl_3$) 1.30 (s, br, 1H, N*H*), 1.37 (d, 3H, *J* 6.6, C*H*$_3$), 1.75 - 1.87 (m, 2H, C*H*$_2$), 2.45 - 2.74 (m, 4H, 4 × C*H*$_2$), 3.77 (q, 3H, *J* 6.6, C*H*$_3$), 7.16 - 7.39 (m, 10H, ArC*H*); δ_C (63 MHz, $CDCl_3$) 24.4 (*C*H$_3$), 32.0 (*C*H$_2$), 33.8 (*C*H$_2$), 47.4 (N*C*H$_2$), 58.4 (N*C*H), 125.8 (Ar*C*H), 126.6 (Ar*C*H), 126.9 (Ar*C*H), 128.4 (3 × Ar*C*H), 128.5 (2 × Ar*C*H), 142.3 (Ar*C*), 146.0 (Ar*C*); Enantiomeric excess was determined by chiral phase HPLC (Phenomenex Lux 3 um Cellulose-1), 1% ipa in hexane @ 1 mL min^{-1} (λ 210nm), t_R = 9.0 min (minor), 9.7 min (major). Data was in accordance with the literature.

(*S*)-Indan-1-yl-prop-2-ynyl-amine 163[153]



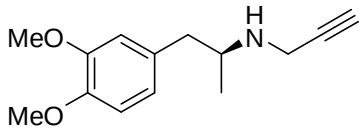
Prepared according to general procedure E as yellow oil (44%, 88% ee); $[\alpha]_D$ -20.6 (*c* 1.7 in $CHCl_3$, 88% ee from HPLC, lit.[153] $[\alpha]_D$ +18.8, *c* 1.7 $CHCl_3$, *R* isomer); δ_H (400 MHz, $CDCl_3$) 1.86 - 1.94 (m, 1H, CH_2), 2.30 (t, 1H, *J* 2.5, CC*H*), 2.39 - 2.48 (m, 1H, 1 × CH_2), 2.82 - 2.90 (m, 1H, 1 × CH_2), 3.04 - 3.11 (m, 1H, 1 × CH_2), 3.56 (t, 2H, *J* 2.5, NCH_2), 4.45 (t, 1H, *J* 6.4, NC*H*), 7.21 - 7.30 (m, 3H, Ar*H*), 7.37 - 7.39 (m, 1H, Ar*H*); δ_C (100 MHz, $CDCl_3$) 30.5 (*C*H_2), 33.4 (*C*H_2), 36.2 (*C*H_2), 61.9 (N*C*H), 71.4 (C*C*H), 82.5 (*C*CH), 124.2 (Ar*C*H), 124.9 (Ar*C*H), 126.3 (Ar*C*H), 127.7 (Ar*C*H), 143.8 (Ar*C*), 144.6 (Ar*C*); Enantiomeric excess was determined by chiral phase HPLC (Phenomenex Lux 3 um Cellulose-1), 1% ipa in hexane @ 1 mL min^{-1} (λ 214nm), t_R = 21.4 min (major), 48.3 min (minor). Data was in accordance with the literature.

(*S*)-*N*-(2-Cyclopropyl-1-phenylethyl)-3-phenylpropan-1-amine 164



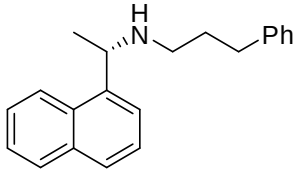
Prepared according to general procedure E as colourless oil (68%, 57% ee); $[\alpha]_D$ -14 (*c* 1.5 $CHCl_3$, 57% ee from HPLC); ν_{max} (thin film, cm^{-1}) 3062, 3025, 2921, 1603, 1495, 1454; δ_H (250 MHz, $CDCl_3$) 0.06 - 0.15 (m, 2H, 2 × CH_2), 0.30 - 0.62 (m, 2H, 2 × CH_2), 1.39 - 1.50 (m, 2H, 2 × CH_2), 1.63 - 1.86 (m, 3H, 3 × CH_2), 2.48 - 2.73 (m, 4H, 4 × CH_2), 3.70 (t, 1H, *J* 6.9, NC*H*), 7.15 - 7.34 (m, 10H, Ar*H*); δ_C (63 MHz, $CDCl_3$) 4.3 (*C*H_2), 4.8 (*C*H_2), 8.4 (*C*H), 32.0 (*C*H_2), 33.7 (*C*H_2), 43.7 (*C*H_2), 47.3 (*C*H_2), 64.1 (N*C*H), 125.8 (Ar*C*H), 126.9 (Ar*C*H), 127.3 (2 × Ar*C*H), 128.4 (4 × Ar*C*H), 128.5 (2 × Ar*C*H), 142.4 (Ar*C*), 144.9 (Ar*C*); *m/z* (ES+) 280.2064 (MH^+, $C_{20}H_{26}N$ requires 280.2065); Enantiomeric excess was determined by chiral phase HPLC (Phenomenex Lux 3 um Cellulose-1), 1% ipa in hexane @ 1 mL min^{-1} (λ 214nm), t_R = 6.6 min (major), 7.7 min (minor). Data was in accordance with the literature.

(*S*)-*N*-(1-(3,4-dimethoxyphenyl)propan-2-yl)prop-2-yn-1-amine 165



Prepared according to general procedure E as colourless oil (77%, 53% ee); $[\alpha]_D$ -3.2 (*c* 1.9 in $CHCl_3$, 53% ee from HPLC); ν_{max} (thin film, cm^{-1}) 3285, 2961, 2932, 1607, 1516, 1464; δ_H (250 MHz, $CDCl_3$) 1.09 (d, 3H, *J* 7.0, C*H*$_3$), 2.18 (t, 1H, *J* 2.4, CCH), 2.56 - 2.71 (m, 2H, C*H*$_2$), 3.09 - 3.22 (m, 1H, NC*H*), 3.40 (dd, 1H, *J* 17.3, 2.5, NC*H*$_2$C), 3.49 (dd, 1H, *J* 17.3, 2.5, NC*H*$_2$), 3.88 (s, 3H, OC*H*$_3$), 3.89 (s, 3H, OC*H*$_3$), 6.74 - 6.84 (m, 3H, Ar*H*); δ_C (63 MHz, $CDCl_3$) 19.6 (*C*H$_3$), 35.5 (*C*H$_2$), 48.1 (*C*H$_2$), 52.4 (O*C*H$_3$), 55.8 (O*C*H$_3$), 71.2 (C*C*H), 82.0 (*C*CH$_2$), 111.3 (Ar*C*H), 112.4 (Ar*C*H), 121.2 (Ar*C*H), 131.5 (Ar*C*), 147.5 (Ar*C*), 148.9 (Ar*C*); *m/z* (ES+) 234.1483 (MH^+, $C_{14}H_{20}NO_2$ requires 234.1494); Enantiomeric excess was determined by chiral phase HPLC (Phenomenex Lux 3 um Cellulose-1), 5% ipa in hexane @ 0.8 mL min^{-1} (λ 214nm), t_R = 22.1 min (major), 25.6 min (minor).

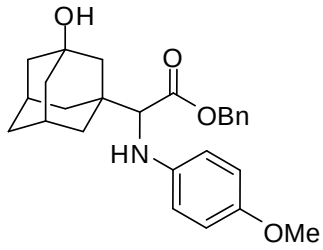
(*S*)-*N*-[1-(naphthalen-1-yl)ethyl]-3-phenylpropan-1-amine 166[152]



Prepared according to general procedure E as colourless oil (40%, 50% ee); $[\alpha]_D$ +17.5 (*c* 1.2 $CHCl_3$, 50% ee from HPLC); δ_H (250 MHz, $CDCl_3$) 1.52 (d, 3H, *J* 6.6, C*H*$_3$), 1.82 - 1.93 (m, 2H, C*H*$_2$), 2.58 - 2.77 (m, 2H, 2 × C*H*$_2$), 4.65 (q, 1H, *J* 6.6, NC*H*), 7.17 - 7.32 (m, 5H, Ar*H*), 7.47 - 7.58 (m, 3H, Ar*H*), 7.68 (app. dd, 1H, *J* 6.9, 0.9, Ar*H*), 7.78 (d, 1H, *J* 8.2, Ar*H*), 7.89 - 7.92 (m, 1H, Ar*H*), 8.20 - 8.24 (m, 1H, Ar*H*) ; δ_C (63 MHz, $CDCl_3$) 23.8 (*C*H$_3$), 32.2 (*C*H$_2$), 33.8 (*C*H$_2$), 47.7 (*C*H$_2$), 53.8 (N*C*H), 122.8 (Ar*C*H), 123.1 (Ar*C*H), 125.4 (Ar*C*H), 125.9 (2 × Ar*C*H), 127.3 (Ar*C*H), 128.4 (2 × Ar*C*H), 128.5 (Ar*C*H), 129.1 (Ar*C*H), 131.5 (Ar*C*), 134.1 (Ar*C*), 141.5 (Ar*C*), 142.3 (Ar*C*); Enantiomeric excess was determined by

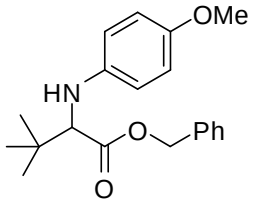
chiral phase HPLC (Phenomenex Lux 3 um Cellulose-1), 1% ipa in hexane @ 1 mL min^{-1} (λ 214nm), t_R = 12.5 min (major), 13.4 min (minor). Data was in accordance with the literature.

Benzyl tricyclo[3.3.1.13,7]decane-1-(4-methoxyphenylamino)acetate 168



Prepared according to general procedure E (23%, 0% ee) as a yellow oil; ν_{max} (thin film, cm^{-1}) 2909, 2852, 1728, 1513; δ_H (400MHz, $CDCl_3$) 1.46 - 1.78 (m, 13H), 2.24 (s, 2H), 3.70 (s, 1H, N*H*), 3.76 (s, 3H, OCH_3), 5.13 (s, 2H, OCH_2), 6.64 [2H, $(AX)_2$, ArC*H*], 6.76 [2H, $(AX)_2$, ArC*H*], 7.26 - 7.30 (m, 2H, Ar*H*), 7.33 - 7.35 (m, 3H, Ar*H*); δ_C (100 MHz, $CDCl_3$) 30.4 (2 × *C*H), 35.3 (*C*H_2), 37.7 (*C*H_2), 37.8 (*C*H_2), 39.8 (*C*H_2), 44.5 (*C*H_2), 44.6 (*C*H_2), 46.7 (*C*H_2), 55.7 (O*C*H_3), 66.5 (O*C*H_2), 67.4 (N*C*H), 68.7 (*C*OH), 114.8 (2 × Ar*C*H), 115.9 (2 × Ar*C*H), 128.4 (Ar*C*H), 128.5 (4 × Ar*C*H), 135.5 (Ar*C*), 141.6 (Ar*C*), 153.0 (Ar*C*), 172.9 (*C*O); *m/z* (EI) 421.2236 (M^+ $C_{26}H_{31}NO_4$ requires 421.2253), 286 (100); Enantiomeric excess was determined by chiral phase HPLC (Phenomenex Lux 3 um Cellulose-1), 10% ipa in hexane @ 1 mL min^{-1}, t_R = 27.4 min, 30.7 min.

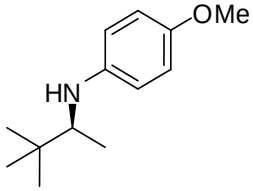
Benzyl 2-(4-methoxyphenylamino)-3,3-dimethylbutanoate 170



Prepared according to general procedure E (21%, 0% ee) as a white solid, mp 62-64 °C; (Found: C 73.35, H 7.74, N 4.26; $C_{20}H_{25}NO_3$ requires C 73.37, H 7.70, N 4.28); ν_{max} (thin film, cm^{-1}) 3390, 2951, 1725, 1510; δ (400 MHz, $CDCl_3$) 1.07 [s, 9H, C(CH_3)$_3$], 3.75 (s, 1H, N*H*), 3.76 (s, br, 1H, NC*H*), 3.77 (s, 3H, OCH_3), 5.11 (s, 2H, OCH_2Ph), 6.65 [2H, $(AX)_2$, ArC*H*], 6.76 [2H, $(AX)_2$, ArC*H*], 7.26 - 7.35 (m, 5H, ArH); δ_C (100 MHz, $CDCl_3$) 26.8

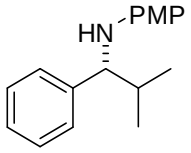
[C(*C*H_3)$_3$], 34.4 [*C*(CH$_3$)$_3$], 55.7 (O*C*H_3), 66.5 (O*C*H_2Ph), 67.2 (N*C*H), 114.9 (2 × Ar*C*H), 115.8 (2 × Ar*C*H), 128.3 (Ar*C*H), 128.4 (2 × Ar*C*H), 128.5 (2 × Ar*C*H) 135.6 (Ar*C*), 141.7 (Ar*C*), 152.9 (Ar*C*), 173.7(*C*O); m/z (EI) 327 (M^+, 56), 270 (55), 192 (75), 91 (100); Enantiomeric excess was determined by chiral phase HPLC (Phenomenex Lux 3 um Cellulose-1), 2% ipa in hexane @ 1 mL min^{-1}, t_R = 10.8 min, 13.4 min.

(*S*)-*N*-(3,3-dimethylbutan-2-yl)-4-methoxyaniline 172



Prepared according to general procedure E (74%) as colorless oil; $[\alpha]_D$ +18.4 (33% ee from HPLC, *c* 1.3 in $CHCl_3$); ν_{max} (thin film, cm^{-1}) 3390, 2951, 1510; δ_H (400 MHz, $CDCl_3$) 1.00 [s, 9H, C(C*H*$_3$)], 1.11 (d, 3H, *J* 6.4, C*H*$_3$), 3.15 (q, 1H, *J* 6.4, NC*H*), 3.78 (s, 3H, OC*H*$_3$), 6.61 [2H, (AX)$_2$, ArC*H*], 6.81 [2H, (AX)$_2$, ArC*H*]; δ_C (100 MHz, $CDCl_3$) 15.8 (*C*H$_3$), 16.6 [(C(*C*H$_3$)], 34.7 [(*C*(CH$_3$)], 55.9 (O*C*H$_3$), 58.7 (N*C*H), 114.6 (2 × Ar*C*H), 115.0 (2 × Ar*C*H), 142.9 (Ar*C*), 151.6 (Ar*C*); *m*/*z* (EI) 207.1621 (M^+, $C_{13}H_{21}NO$ requires 207.1623), 192 (8), 150 (100); Enantiomeric excess was determined by chiral phase HPLC (Phenomenex Lux 3 um Cellulose-1), 2% ipa in hexane @ 1 mL min^{-1}, t_R = 4.5 min (minor), 5.2 min (major).

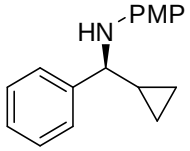
(*R*)-4-Methoxy-*N*-(2-methyl-1-phenylpropyl)aniline 253[83]



Prepared according to general procedure E as yellow oil (85% yield, 69% ee); $[\alpha]_D$ +18.5 (*c* 1.08 in $CHCl_3$, 69% ee; lit.[83] -22, *c* 1.0 in $CHCl_3$, 97% ee for *S* isomer); δ_H (400 MHz, $CDCl_3$) 0.93 (d, 3H, *J* 6.8, C*H*$_3$), 1.00 (d, 3H, *J* 6.8, C*H*$_3$), 2.00 - 2.08 (m, 1H, C*H*), 3.70 (s, 3H, OC*H*$_3$), 3.89 (br, s, 1H, N*H*), 4.07 (d, 1H, *J* 5.6, C*H*), 6.48 [(AX)$_2$, 2H, Ar*H*], 6.70 [(AX)$_2$, 2H, Ar*H*], 7.21 - 7.25 (m, 1H, Ar*H*), 7.27 - 7.32 (m, 4H, Ar*H*); δ_C (100 MHz,

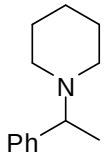
$CDCl_3$) 18.7 (*C*H_3), 19.8 (*C*H_3), 35.0 (*C*H), 55.8 (O*C*H_3), 64.7 (*C*H), 114.4 (2 × Ar*C*H), 114.8 (2 × Ar*C*H), 126.8 (2 × Ar*C*H), 127.3 (Ar*C*H), 128.2 (2 × Ar*C*H), 142.1 (Ar*C*), 142.8 (Ar*C*), 151.7 (Ar*C*); Enantiomeric excess was determined by chiral phase HPLC (Chiralpak IA) 1 % ipa in hexane @ 1 mL min^{-1}, t_R = 8.6 min (major), 9.4 min (minor). Data was in accordance with the literature.

(*S*)-*N*-(Cyclopropyl(phenyl)methyl)-4-methoxyaniline 254[83]



Prepared according to general procedure E as yellow oil (98% yield, 36% ee); $[\alpha]_D$ +24 (*c* 1.9 in $CHCl_3$, 36% ee; lit.[83] +66, *c* 1.0 in $CHCl_3$, 95% ee); δ_H (400 MHz, $CDCl_3$) 0.38 - 0.44 (m, 1H, 1 × C*H*$_2$), 0.47 - 0.53 (m, 1H, 1 × C*H*$_2$), 0.54 - 0.59 (m, 1H, 1 × C*H*$_2$), 0.61 - 0.68 (m, 1H, 1 × C*H*$_2$), 1.16 - 1.25 (m, 1H, 1 × C*H*$_2$), 3.59 (d, *J* 8.4, 1H, NC*H*), 3.71 (s, 3H, OC*H*$_3$), 4.15 (s, br, 1H, N*H*), 6.46 [$(AX)_2$, 2H, Ar*H*], 6.70 [$(AX)_2$, 2H, Ar*H*], 7.26 - 7.29 (m, 1H, Ar*H*), 7.36 (app. t. 2H, *J* 7.6, Ar*H*), 7.44 (app. d, 2H, *J* 7.7, Ar*H*); δ_C (100 MHz, $CDCl_3$) 3.49 (*C*H_2), 4.25 (*C*H_2), 19.9 (*C*H), 55.8 (O*C*H_3), 63.9 (*C*H), 114.6 (2 × Ar*C*H), 114.7 (2 × Ar*C*H), 126.5 (2 × Ar*C*H), 127.0 (Ar*C*H), 128.5 (2 × Ar*C*H), 142.0 (Ar*C*), 143.6 (Ar*C*), 151.9 (Ar*C*); Enantiomeric excess was determined by chiral phase HPLC (Phenomenex Lux 3 um Cellulose-1) 1 % ipa in hexane @ 1 mL min^{-1}, t_R = 12.4 min (minor), 17.1 min (major). Data was in accordance with the literature.

(±)1-(1-Phenylethyl)piperidine 272[154]



Prepared according to general procedure E as colourless oil (49% yield, 0% ee); δ_H (400 MHz, $CDCl_3$) 1.37 - 1.43 (m, 2H, 2 × C*H*$_2$), 1.39 (d, 3H, *J* 6.8, C*H*$_3$), 1.54 - 1.60 (m, 4H, 4 × C*H*$_2$), 2.31 - 2.45 (m, 4H, 4 × C*H*$_2$), 3.41 (q, 1H, *J* 6.8, NC*H*), 7.23-7.33 (m, 5H, Ar*H*); δ_C (100 MHz, $CDCl_3$) 19.4 (*C*H_3) , 24.6 (*C*H_2), 26.3 (2 × *C*H_2), 51.5 (2 × *C*H_2), 65.2 (N*C*H),

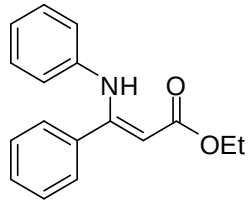
126.7 (Ar*C*H), 127.8 (2 × Ar*C*H), 128.0 (2 × Ar*C*H), 144.0 (Ar*C*); Enantiomeric excess was determined by GC analysis on Astec Chiraldex B-DM at 140 ºC, t_R = 43.2 min, 45.3 min. Data was in accordance with the literature.

7.5 Asymmetric reduction of β-enamino esters

General procedure F for the synthesis of β-enamino esters

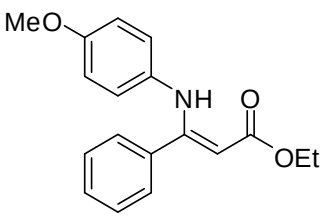
A mixture of β-ketoester (10 mmol), amine (1.1~1.3 eq.) and *p*-TsOH (0.1 mmol) in ethanol was heated at reflux for overnight. The mixture was then cooled to room temperature and the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel to give the β-enamino ester.

(*Z*)-Ethyl 3-phenyl-3-(phenylamino)acrylate 183[155]



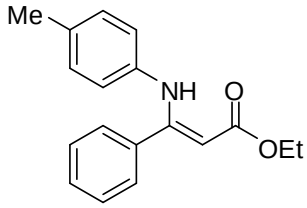
Obtained by general procedure F as a white solid (34%); m.p. 72-74 ºC (lit.[155] 65-66 °C); δ_H (250 MHz, $CDCl_3$) 1.34 (t, 3H, *J* 7.2, CH_3), 4.22 (q, 2H, *J* 7.2, OCH_2), 5.01 (s, 1H, C*H*), 6.65 - 6.70 (m, 2H, Ar*H*), 6.89 - 6.96 (m, 1H, Ar*H*), 7.07 - 7.13 (m, 2H, Ar*H*), 7.26 - 7.38 (m, 5H, Ar*H*), 10.32 (s, br, 1H, N*H*); δ_C (63 MHz, $CDCl_3$) 14.6 (*C*H_3), 59.3 (O*C*H_2), 91.3 (*C*H), 122.2 (2 × Ar*C*H), 123.0 (2 × Ar*C*H), 128.3 (2 × Ar*C*H), 128.4 (2 × Ar*C*H), 128.6 (Ar*C*H), 129.4 (Ar*C*H), 136.1 (Ar*C*), 140.1(Ar*C*), 159.1 (*C*=CH), 170.1 (*C*O). Data was in accordance with the literature.

(*Z*)-Ethyl 3-(4-methoxyphenylamino)-3-phenylacrylate 184[67]



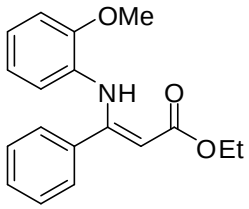
Obtained by general procedure F as a yellow solid (60%); m.p. 102-105 ºC (lit.[67] 96-98 ºC); δ_H (250 MHz, $CDCl_3$) 1.33 (t, 3H, *J* 7.1, C*H*$_3$), 3.72 (s, 3H, OC*H*$_3$), 4.22 (q, 2H, *J* 7.1, OC*H*$_2$), 4.95 (s, 1H, C*H*), 6.65 (s, 4H, Ar*H*), 7.24 - 7.37 (m, 5H, Ar*H*), 10.25 (s, br, 1H, N*H*); δ_C (63 MHz, $CDCl_3$) 14.6 (*C*H$_3$), 55.3 (O*C*H$_3$), 59.2 (O*C*H$_2$), 89.6 (*C*H), 113.9 (2 × Ar*C*H), 124.3 (2 × Ar*C*H), 128.3 (2 × Ar*C*H), 128.4 (2 × Ar*C*H), 129.2 (Ar*C*H), 133.6 (Ar*C*), 136.1 (Ar*C*), 155.9 (Ar*C*), 159.9 (*C*=CH), 170.3 (*C*O). Data was in accordance with the literature.

(*Z*)-Ethyl 3-phenyl-3-(p-tolylamino)acrylate 185



Obtained by general procedure F as a white solid (53% yield); m.p. 72-74 ºC; (Found C 76.71, H 6.77, N 4.87; requires $C_{18}H_{19}NO_2$ C 76.84, H 6.81, N 4.98); ν_{max} (thin film, cm^{-1}) 3259, 2979, 1657, 1598; δ_H (400 MHz, $CDCl_3$) 1.34 (t, 3H, *J* 7.1, C*H*$_3$), 2.23 (s, 3H, C*H*$_3$), 4.23 (q, 2H, *J* 7.1, OC*H*$_2$), 4.98 (s, 1H, C*H*), 6.59 [(AX)$_2$, 2H, Ar*H*], 6.90 [(AX)$_2$, 2H, Ar*H*], 7.28 - 7.38 (m, 5H, Ar*H*), 10.28 (s, br, 1H, N*H*); δ_C (100 MHz, $CDCl_3$) 14.6 (*C*H$_3$), 20.7 (*C*H$_3$), 59.2 (O*C*H$_2$), 90.4 (*C*H), 122.4 (2 × Ar*C*H), 128.3 (2 × Ar*C*H), 128.4 (2 × Ar*C*H), 129.2 (Ar*C*H), 129.3 (2 × Ar*C*H), 132.6 (Ar*C*), 136.2 (Ar*C*), 137.8 (Ar*C*), 159.4 (*C*=CH), 170.2 (*C*O); *m/z* (TOF ES+) 282 (100%, MH^+), 236 (8).

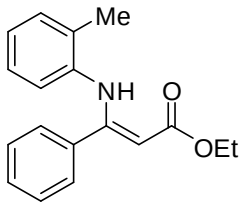
(*Z*)-Ethyl 3-(2-methoxyphenylamino)-3-phenylacrylate 186[156]



Obtained by general procedure F as a yellow crystal (60%); m.p. 90-91 ºC (lit.[156] 105 °C); δ_H (400 MHz, $CDCl_3$) 1.34 (t, 3H, *J* 7.1, C*H*$_3$), 3.93 (s, 3H, OC*H*$_3$), 4.24 (q, 2H, *J* 7.1, OC*H*$_2$), 5.02 (s, 1H, C*H*), 6.21 - 6.24 (m, 1H, Ar*H*), 6.52 - 6.56 (m, 1H, Ar*H*), 6.84 - 6.91 (m, 2H, Ar*H*), 7.28 - 7.40 (m, 5H, Ar*H*), 10.29 (s, br, 1H, N*H*); δ_C (100 MHz, $CDCl_3$) 14.6 (*C*H$_3$), 55.7 (O*C*H$_3$), 59.3 (O*C*H$_2$), 91.6 (*C*H), 110.5 (Ar*C*H), 120.0 (Ar*C*H), 121.8 (Ar*C*H), 122.9

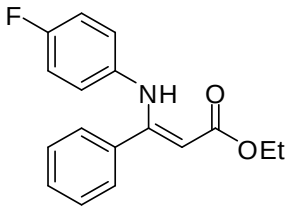
(Ar*C*H), 128.0 (2 × Ar*C*H), 128.4 (2 × Ar*C*H), 129.4 (Ar*C*H), 129.6 (Ar*C*), 136.4 (Ar*C*), 150.5 (Ar*C*), 158.4 (*C*=CH), 169.9 (*C*O). Data was in accordance with the literature.

(*Z*)-Ethyl 3-phenyl-3-(*o*-tolylamino)acrylate 187



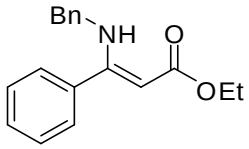
Obtained by general procedure F as a light yellow solid (41%); m.p. 103-105 ºC; (Found C 76.73, H 6.83, N 4.91; requires $C_{18}H_{19}NO_2$ C 76.84, H 6.81, N 4.98); ν_{max} (thin film, cm^{-1}) 3253, 2978, 1655, 1617, 1595; δ_H (400 MHz, $CDCl_3$) 1.35 (t, 3H, *J* 7.1, C*H*$_3$), 2.45 (s, 3H, C*H*$_3$), 4.24 (q, 2H, *J* 7.1, OC*H*$_2$), 5.06 (s, 1H, C*H*), 6.35 (d, 1H, *J* 7.8, Ar*H*), 6.83 (td, 1H, *J* 7.8, 1.2, Ar*H*), 6.88 (td, 1H, *J* 7.4, 1.0, Ar*H*), 7.16 (d, 1H, *J* 7.4, Ar*H*), 7.26 - 7.35 (m, 5H, Ar*H*), 10.17 (s, br, 1H, N*H*); δ_C (100 MHz, $CDCl_3$) 14.6 (*C*H$_3$), 18.2 (*C*H$_3$), 59.3 (O*C*H$_2$), 90.8 (*C*H), 123.5 (Ar*C*H), 123.9 (Ar*C*H), 125.8 (Ar*C*H), 128.1 (2 × Ar*C*H), 128.3 (2 × Ar*C*H), 129.4 (Ar*C*H), 130.2 (Ar*C*), 130.4 (Ar*C*H), 136.2 (Ar*C*), 139.0 (Ar*C*), 159.8 (*C*=CH), 170.3 (*C*O); *m/z* (TOF ES+) 282.1 (100%, MH^+), 236 (10).

(*Z*)-Ethyl 3-(4-fluorophenylamino)-3-phenylacrylate 188[157]



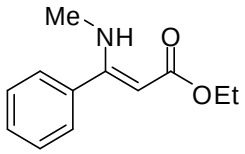
Obtained by general procedure F as a white solid (59% yield); m.p. 75-77 ºC (not reported in literature); δ_H (400 MHz, $CDCl_3$) 1.34 (t, 3H, *J* 7.1, C*H*$_3$), 4.23 (q, 2H, *J* 7.1, OC*H*$_2$), 5.02 (s, 1H, C*H*), 6.64 - 6.68 (m, 2H, Ar*H*), 6.78 - 6.82 (m, 2H, Ar*H*), 7.28 - 7.38 (m, 5H, Ar*H*); δ_C (100 MHz, $CDCl_3$) 14.5 (*C*H$_3$), 59.3 (O*C*H$_2$), 91.0 (*C*H), 115.3 (d, $^2J_{C\text{-}F}$ 22.7, 2 × Ar*C*H), 124.0 (d, $^3J_{C\text{-}F}$ 7.9, 2 × Ar*C*H), 128.3 (2 × Ar*C*H), 128.5 (2 × Ar*C*H), 129.5 (Ar*C*H), 135.7 (Ar*C*), 136.5 (Ar*C*), 159.0 (d, $^3J_{C\text{-}F}$ 242.8, Ar*C*H), 159.3 (*C*=CH), 170.2 (*C*O); δ_F (235 MHz, $CDCl_3$) -119.9. Data was in accordance with the literature, although ^{19}F NMR not reported.

(*Z*)-Ethyl 3-(benzylamino)-3-phenylacrylate 189[63]



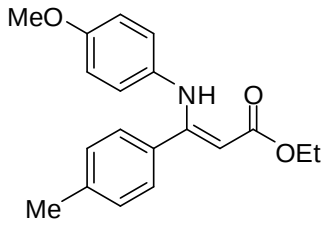
Obtained by general procedure F as a white solid (42% yield); m.p. 71-72 ºC (lit.[63] 66-67 ºC); δ_H (400 MHz, $CDCl_3$) 1.33 (t, 3H, *J* 7.1, C*H*$_3$), 4.21 (q, 2H, *J* 7.1, OC*H*$_2$), 4.32 (d, 2H, *J* 6.5, NC*H*$_2$), 4.75 (s, 1H, C*H*), 7.22 - 7.44 (m, 10H, Ar*H*), 9.00 (s, br, 1H, N*H*); δ_C (100 MHz, $CDCl_3$) 14.7 (*C*H$_3$), 48.4 (NCH$_2$), 58.8 (OCH$_2$), 86.6 (*C*H), 126.9 (2 × Ar*C*H), 127.3 (Ar*C*H), 127.9 (2 × Ar*C*H), 128.5 (2 × Ar*C*H), 128.7 (2 × Ar*C*H), 129.3 (Ar*C*H), 136.1 (Ar*C*), 139.4 (Ar*C*), 164.7 (*C*=CH), 170.4 (*C*O). Data was in accordance with the literature.

(*Z*)-Ethyl 3-(methylamino)-3-phenylacrylate 190



Obtained by general procedure F as light yellow oil except using methanaminium acetate instead of methylamine (55%); ν_{max} (thin film, cm^{-1}) 3296, 2978, 1650, 1613, 1595, 1574; δ_H (400 MHz, $CDCl_3$) 1.30 (t, 3H, *J* 7.1, C*H*$_3$), 2.79 (d, 3H, *J* 5.2, NC*H*$_3$), 4.16 (q, 2H, *J* 7.1, C*H*$_2$), 4.62 (s, 1H, C*H*), 7.28 - 7.43 (m, 5H, Ar*H*), 8.52 (s, br, 1H, N*H*); δ_C (100 MHz, $CDCl_3$) 14.6 (*C*H$_3$), 31.4 (*C*H$_3$), 58.6 (OCH$_2$), 84.8 (CH), 127.8 (2 × Ar*C*H), 128.3 (2 × Ar*C*H), 129.1 (Ar*C*H), 135.9 (Ar*C*), 165.6 (*C*=CH), 170.6 (C=O); *m/z* (TOF ES+) 206.1172 (MH$^+$, $C_{12}H_{16}NO_2$ requires 206.1181).

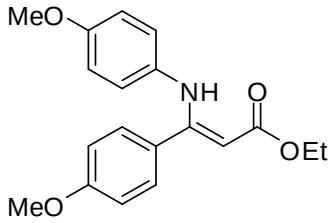
(*Z*)-Ethyl 3-(4-methoxyphenylamino)-3-*p*-tolylacrylate 191



Obtained by general procedure F as yellow crystals (41% yield); mp 78-80 ºC; (Found C 73.24, H 6.62, N 4.43; requires $C_{19}H_{21}NO_3$ C 73.29, H 6.80, N 4.50); ν_{max} (thin film, cm^{-1}) 3251, 2978, 1653, 1615, 1513; δ_H (400 MHz, $CDCl_3$) 1.34 (t, 3H, *J* 7.1, C*H*$_3$), 2.34 (s, 3H, C*H*$_3$), 3.73 (s, 3H, OC*H*$_3$), 4.22 (q, 2H, *J* 7.1, C*H*$_2$), 4.94 (s, 1H, C*H*), 6.65 - 6.69 (m, 4H,

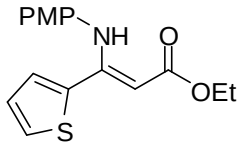
Ar*H*), 7.09 [$(AX)_2$, 2H, Ar*H*], 7.23 [$(AX)_2$, 2H, Ar*H*], 10.23 (s, br, 1H, N*H*); δ_C (100 MHz, $CDCl_3$) 14.6 (*C*H_3), 21.3 (*C*H_3), 55.3 (O*C*H_3), 59.1 (O*C*H_2), 89.3 (*C*H), 113.9 (2 × Ar*C*H), 124.2 (2 × Ar*C*H), 128.3 (2 × Ar*C*H), 129.0 (2 × Ar*C*H), 133.1 (Ar*C*), 133.7 (Ar*C*), 139.3 (Ar*C*), 155.8 (Ar*C*), 160.0 (*C*=CH), 170.4 (*C*O); *m/z* (TOF ES+) 312 (100, MH+), 266 (10).

(*Z*)-Ethyl 3-(4-methoxyphenyl)-3-(4-methoxyphenylamino)acrylate 192[67]



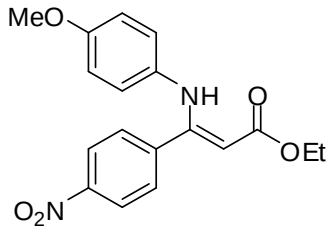
Obtained by general procedure F as brown sticky oil (50% yield); δ_H (400 MHz, $CDCl_3$) 1.33 (t, 3H, *J* 7.1, C*H*$_3$), 3.74 (s, 3H, OC*H*$_3$), 3.83 (s, 3H, OC*H*$_3$), 4.20 (q, 2H, *J* 7.1, OC*H*$_2$), 4.93 (s, 1H, C*H*), 6.65 - 6.69 (m, 4H, Ar*H*), 6.80 [$(AX)_2$, 2H, Ar*H*], 7.26 [$(AX)_2$, 2H, Ar*H*], 10.21 (s, br, 1H, N*H*); δ_C (100 MHz, $CDCl_3$) 14.6 (*C*H_3), 55.3 (O*C*H_3), 55.3 (O*C*H_3), 59.1 (O*C*H_2), 88.9 (*C*H), 113.8 (2 × Ar*C*H), 113.9 (2 × Ar*C*H), 124.3 (2 × Ar*C*H), 128.2 (Ar*C*), 129.8 (2 × Ar*C*H), 133.8 (Ar*C*), 155.7 (Ar*C*), 159.7 (Ar*C*), 160.4 (*C*=CH), 170.4 (*C*O). Data was in accordance with the literature.

(*Z*)-Ethyl 3-(4-methoxyphenylamino)-3- (thiophen-2-yl)acrylate 193[83]



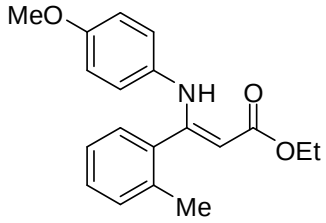
Obtained by general procedure F as yellow crystals (45% yield); m.p. 54-56 ºC (lit.[83] 52-53 ºC); δ_H (400 MHz, $CDCl_3$) 1.34 (t, 3H, *J* 7.1, C*H*$_3$), 3.77 (s, 3H, OC*H*$_3$), 4.22 (q, 2H, *J* 7.1, C*H*$_3$), 5.15 (s, 1H, C*H*), 6.73 [$(AX)_2$, 2H, Ar*H*], 6.83 [$(AX)_2$, 2H, Ar*H*], 6.92 (dd, 1H, *J* 5.0, 3.7, Ar*H*), 7.01 (dd, 1H, *J* 3.7, 1.2, Ar*H*), 7.30 (dd, 1H, *J* 5.0, 1.2, Ar*H*); δ_C (100 MHz, $CDCl_3$) 14.6 (*C*H_3), 55.4 (O*C*H_3), 59.3 (O*C*H_2), 89.5 (*C*H), 114.0 (2 × Ar*C*H), 125.3 (3 × Ar*C*H), 127.1 (Ar*C*H), 127.6 (Ar*C*H), 129.0 (Ar*C*H), 133.5 (Ar*C*), 137.6 (Ar*C*), 153.0 (Ar*C*), 156.5 (*C*=CH), 170.1 (*C*O). Data was in accordance with the literature.

(*Z*)-Ethyl 3-(4-methoxyphenylamino)-3-(4-nitrophenyl)acrylate 194



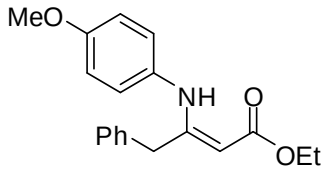
Obtained by general procedure F as yellow needle-like crystals (82% yield); m.p. 126-128 ºC; (Found C 63.29, H 5.26, N 8.17; requires $C_{18}H_{18}N_2O_5$ C 63.15, H 5.30, N 8.18); ν_{max} (thin film, cm^{-1}) 3258, 2979, 1658, 1615, 1591, 1514; δ_H (400 MHz, $CDCl_3$) 1.35 (t, 3H, *J* 7.1, CH_2CH_3), 3.73 (s, 3H, OCH_3), 4.24 (q, 2H, *J* 7.1, CH_2CH_3), 5.00 (s, 1H, C*H*), 6.64-6.69 (m, 4H, Ar*H*), 7.51 [$(AX)_2$, 2H, Ar*H*], 8.14 [$(AX)_2$, 2H, Ar*H*], 10.17 (s, br, 1H, N*H*); δ_C (100 MHz, $CDCl_3$) 14.5 (CH_3), 55.3 (OCH_3), 59.5 (OCH_2), 91.3 (*C*H), 114.2 (2 × Ar*C*H), 123.6 (2 × Ar*C*H), 124.8 (2 × Ar*C*H), 129.3 (2 × Ar*C*H), 132.7 (Ar*C*), 142.7 (Ar*C*), 148.0 (Ar*C*), 156.4 (Ar*C*), 157.2 (*C*=CH), 169.8 (*C*O); m/z (TOF ES+) 343.1290 (MH^+, $C_{18}H_{19}N_2O_5$ requires 343.1294).

(*Z*)-Ethyl 3-(4-methoxyphenylamino)-3-*o*-tolylacrylate 195[67]



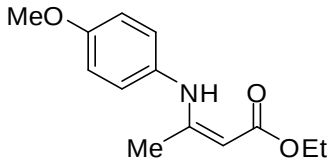
Obtained by general procedure F as a white solid (11%); m.p. 58-61 ºC (lit.[67] 51-53 ºC); δ_H (400 MHz, $CDCl_3$) 1.34 (t, 3H, *J* 7.1, CH_2CH_3), 2.13 (s, 3H, CH_3), 3.71 (s, 3H, OCH_3), 4.22 (q, 2H, *J* 7.1, CH_2CH_3), 4.72 (s, 1H, C*H*), 6.57 - 6.62 (m, 4H, Ar*H*), 7.08 (d, 1H, *J* 7.4, Ar*H*), 7.20 (td, 1H, *J* 7.4, 0.7, Ar*H*), 7.26 (td, 1H, *J* 7.4, 1.6, Ar*H*), 7.32 (dd, *J* 7.4, 1.5, 1H, Ar*H*), 10.51 (s, br, 1H, N*H*); δ_C (100 MHz, $CDCl_3$) 14.6 (CH_3), 19.5 (CH_3), 55.3 (OCH_3), 59.1 (OCH_2), 88.1 (*C*H), 113.9 (2 × Ar*C*H), 122.9 (2 × Ar*C*H), 125.8 (Ar*C*H), 129.0 (Ar*C*H), 130.3 (2 × Ar*C*H), 133.1 (Ar*C*), 135.5 (Ar*C*), 135.9 (Ar*C*), 155.8 (Ar*C*), 160.2 (*C*=CH), 170.5 (*C*O). Data was in accordance with the literature.

(*Z*)-Ethyl 3-(4-methoxyphenylamino)-4-phenylbut-2-enoate 196



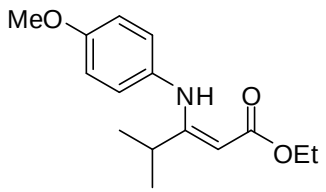
Obtained by general procedure F as white needle-like crystals (56% yield), m.p. 70-72 ºC; (Found C 73.52, H 6.78, N 4.47; requires $C_{19}H_{21}NO_3$ C 73.29, H 6.80, N 4.50); ν_{max} (thin film, cm^{-1}) 3252, 1651, 1613, 1514; δ_H (400 MHz, $CDCl_3$) 1.30 (t, 3H, *J* 7.1, CH_2CH_3), 3.52 (s, 2H, CH_2), 3.81 (s, 3H, OCH_3), 4.16 (q, 2H, *J* 7.1, OCH_2), 4.62 (s, 1H, C*H*), 6.81 [$(AX)_2$, 2H, Ar*H*], 6.96 [$(AX)_2$, 2H, Ar*H*], 7.03-7.06 (m, 2H, Ar*H*), 7.18-7.26 (m, 3H, Ar*H*), 10.15 (s, br, N*H*); δ_C (100 MHz, $CDCl_3$) 14.6 (CH_3), 38.7 (CH_2), 55.4 (OCH_3), 58.8 (OCH_2), 86.1 (*C*H), 114.1 (2 × Ar*C*H), 126.6 (Ar*C*H), 127.8 (2 × Ar*C*H), 128.4 (2 × Ar*C*H), 128.9 (2 × Ar*C*H), 131.8 (Ar*C*), 137.0 (Ar*C*), 157.8 (Ar*C*), 162.4 (*C*=CH), 170.7 (*C*O); *m/z* (TOF ES+) 312.1610 (MH^+, $C_{18}H_{22}NO_3$ requires 312.1600).

(*Z*)-Ethyl 3-(4-methoxyphenylamino)but-2-enoate 197[155]



Obtained by general procedure F as white needle-like crystals (66% yield), m.p. 42-44 ºC (lit.[155] 43-44 ºC); δ_H (400 MHz, $CDCl_3$) 1.31 (t, 3H, *J* 7.2, CH_3), 1.91 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3), 4.17 (q, 2H, *J* 7.2, CH_2), 4.67 (s, 1H, CH), 6.69 [$(AX)_2$, 2H, Ar*H*], 7.05 [$(AX)_2$, 2H, Ar*H*], 10.17 (s, br, 1H, N*H*); δ_C (100 MHz, $CDCl_3$) 14.6 (CH_3), 20.1 (CH_3), 55.4 (OCH_3), 58.6 (OCH_2), 84.7 (*C*H), 114.2 (2 × Ar*C*H), 126.8 (2 × Ar*C*H), 132.1 (Ar*C*), 157.5 (Ar*C*), 160.0 (*C*=CH), 170.5 (*C*O). Data was in accordance with the literature.

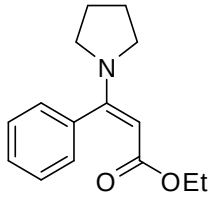
(*Z*)-Ethyl 3-(4-methoxyphenylamino)-4-methylpent-2-enoate 198[67]



Obtained by general procedure F as a white solid (42% yield); m.p. 37-39 ºC (lit.[67] 36 -39 ºC); δ_H (400 MHz, $CDCl_3$) 1.08 [d, 6H, *J* 6.8, $CH(CH_3)_2$], 1.32 (t, 3H, *J* 7.1, CH_3), 2.68-2.78 (sept, 1H, *J* 6.8, C*H*), 3.83 (s, 3H, CH_3), 4.17 (q, 2H, *J* 7.1, CH_2), 4.73 (s, 1H, CH), 6.89

[(ArX)$_2$, 2H, Ar*H*], 7.05 [(ArX)$_2$, 2H, Ar*H*], 10.19 (s, br, 1H, N*H*); δ_C (100 MHz, $CDCl_3$) 14.6 (*C*H$_3$), 22.0 (2 × *C*H$_3$), 28.4 (CH), 55.4 (O*C*H$_3$), 58.7 (O*C*H$_2$), 80.3 (*C*H), 114.3 (2 × Ar*C*H), 127.8 (2 × Ar*C*H), 131.8 (Ar*C*), 157.7 (Ar*C*), 171.1 (*C*=CH), 171.3 (*C*O). Data was in accordance with the literature.

(*E*)-Ethyl 3-phenyl-3-(pyrrolidin-1-yl)acrylate 215[158]



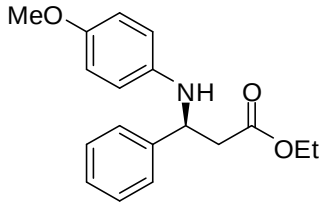
A mixture of ketoester (1.92 g, 10 mmol), pyrrolidine (1.07 g, 15 mmol) and Zn(OAc)$_2$ (91.5 mg, 0.5 mmol) was stirred for 20 hours at 50 ºC. The mixture was cooled to room temperature and purified by chromatography on alumina (petroleum ether / ethyl acetate, 20:1~5:1) to afford the product as yellow oil (69%); δ_H (400 MHz, $CDCl_3$) 1.09 (t, 3H, *J* 7.1, C*H*$_3$), 1.84 - 1.97 (m, 4H, 4 × C*H*$_2$), 3.02 - 3.29 (m, 4H, 4 × C*H*$_2$), 3.93 (q, 2H, *J* 7.1, OC*H*$_2$), 4.70 (s, 1H, C*H*), 7.23 - 7.25 (m, 2H, Ar*H*), 7.38 - 7.45 (m, 3H, Ar*H*); δ_C (100 MHz, $CDCl_3$) 14.4 (*C*H$_3$), 25.3 (2 × *C*H$_2$), 58.2 (2 × *C*H$_2$), 85.2 (*C*H), 127.4 (2 × Ar*C*H), 128.0 (Ar*C*H), 128.2 (2 × Ar*C*H), 137.8 (Ar*C*), 160.9 (*C*=CH), 168.0 (*C*O). Data was in accordance with the literature.

General procedure G

β-Ketoester (0.5 mmol), catalyst **117** (0.1 mmol), benzoic acid (0.05 mmol) and dry dichloromethane (1 mL) were added into a 20 mL Schlenk tube. The mixture was stirred until complete dissolution, then cooled to 0 ºC and trichlorosilane (0.2 mmol) was added by syringe. The resulting mixture was left to stir for 10 hours at 0 ºC. The reaction was diluted by CH_2Cl_2 (20 mL), quenched by water (2 mL) and followed by addition of aqueous sodium hydroxide (1 M, 20 mL). This mixture was stirred until the precipitate was completely dissolved and no gas was evolved. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic phases were washed with brine (20 mL) and dried over $MgSO_4$. Filtration and concentration gave crude product,

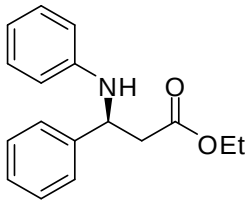
which was purified by chromatography on silica gel using 2% ~ 20% solution of diethyl ether in petroleum ether.

(*S*)-Ethyl 3-(4-methoxyphenylamino)-3-phenylpropanoate 199[67]



Obtained by general procedure G as a white solid (76% yield, 91% ee); m.p. 68-70 ºC (lit.[67] 51-53 ºC); $[\alpha]_D$ -5.7 (*c* 0.7 in $CHCl_3$, 91% ee; lit.[67] -5.6, *c* 1.0 in $CHCl_3$, 92.3% ee); δ_H (400 MHz, $CDCl_3$) 1.22 (t, 3H, *J* 7.1, C*H*$_3$), 2.75 - 2.85 (m, 2H, C*H*$_2$), 3.72 (s, 3H, OC*H*$_3$), 4.09 - 4.16 (m, 2H, OC*H*$_2$), 4.33 (s, br. 1H, N*H*), 4.77 (t, 1H, *J* 6.7, NC*H*), 6.55 [$(AX_2)_2$, 2H, Ar*H*], 6.72 [$(AX)_2$, 2H, Ar*H*], 7.24 - 7.28 (m, 1H, Ar*H*), 7.32 - 7.40 (m, 4H, Ar*H*); δ_C (100 MHz, $CDCl_3$) 14.2 (*C*H$_3$), 43.0 (*C*H$_2$), 55.7 (N*C*H), 56.0 (O*C*H$_3$), 60.8 (O*C*H$_2$), 114.8 (2 × Ar*C*H), 115.2 (2 × Ar*C*H), 126.3 (2 × Ar*C*H), 127.4 (Ar*C*H), 128.7 (2 × Ar*C*H), 141.0 (Ar*C*), 142.5 (Ar*C*), 152.3 (Ar*C*), 171.3 (*C*O); Enantiomeric excess was determined by chiral phase HPLC (Phenomenex Lux 3 um Cellulose-1) 5 % ipa in hexane @ 1 mL min^{-1}, t_R = 13.3 min (minor), 17.7 min (major). Data was in accordance with the literature.

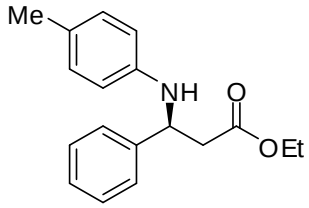
(*S*)-Ethyl 3-phenyl-3-(phenylamino)propanoate 200[159]



Obtained by general procedure G as a white solid (64% yield, 85% ee); m.p. 74-76 ºC (lit.[159] 77-79 ºC); $[\alpha]_D$ 0 (*c* 1.0 in $CHCl_3$, 85% ee; lit.[101] -1.3, *c* 1.0 in $CHCl_3$, 92.3% ee); δ_H (400 MHz, $CDCl_3$) 1.22 (t, 3H, *J* 7.2, C*H*$_3$), 2.81 (dd, 1H, *J* 14.8, 7.5, 1 × C*H*$_2$), 2.85 (dd, 1H, *J* 14.8, 5.9, 1 × C*H*$_2$), 4.07 - 4.19 (m, 2H, C*H*$_2$), 4.65 (s, br, 1H, N*H*), 4.86 (app. t, *J* 6.5, NC*H*), 6.58 - 6.60 (m, 2H, Ar*H*), 6.68 - 6.72 (m, 1H, Ar*H*), 7.11 - 7.15 (m, 2H, Ar*H*), 7.23 - 7.29 (m, 1H, Ar*H*), 7.33 - 7.37 (m, 2H, Ar*H*), 7.40 - 7.42 (m, 2H, Ar*H*); δ_C (100 MHz, $CDCl_3$) 14.2 (*C*H$_3$), 42.9 (*C*H$_2$), 55.0 (N*C*H), 60.8 (O*C*H$_2$), 113.7 (2 × Ar*C*H), 117.8

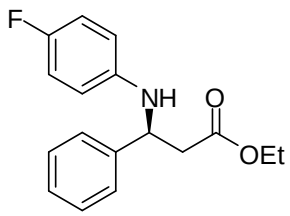
(Ar*C*H), 126.3 (2 × Ar*C*H), 127.5 (Ar*C*H), 128.8 (2 × Ar*C*H), 129.2 (2 × Ar*C*H), 142.2 (Ar*C*), 146.8 (Ar*C*), 171.1 (*C*O); Enantiomeric excess was determined by chiral phase HPLC (Phenomenex Lux 3 um Cellulose-1) 5 % ipa in hexane @ 1 mL min^{-1}, t_R = 12.2 min (major), 12.8 min (minor). Data was in accordance with the literature.

(*S*)-Ethyl 3-phenyl-3-(4-methylphenylamino)propanoate 201



Obtained by general procedure G as a white solid (68% yield, 87% ee); m.p. 58-60 ºC; $[\alpha]_D$ -5.7 (*c* 0.7 in $CHCl_3$, 87% ee); (Found C 76.09, H 7.38, N 4.72; requires $C_{18}H_{21}NO_2$ C 76.29, H 7.47, N 4.94); ν_{max} (thin film, cm^{-1}) 3392, 2981, 1728, 1618, 1520; δ_H (400 MHz, $CDCl_3$) 1.22 (t, 3H, *J* 7.2, C*H*$_3$), 2.22 (s, 3H, C*H*$_3$), 2.80 (dd, 1H, *J* 14.7, 7.5, 1 × C*H*$_2$), 2.84 (dd, 1H, *J* 14.7, 6.0, 1 × C*H*$_2$), 4.08 - 4.19 (m, 2H, C*H*$_2$), 4.48 (s, br, 1H, N*H*), 4.83 (t, *J* 6.5, NC*H*), 6.52 [$(AX)_2$, 2H, Ar*H*], 6.95 [$(AX)_2$, 2H, Ar*H*], 7.25-7.29 (m, 1H, Ar*H*), 7.33-7.37 (m, 2H, Ar*H*), 7.40-7.42 (m, 2H, Ar*H*); δ_C (100 MHz, $CDCl_3$) 14.2 (*C*H_3), 20.4 (*C*H_3), 43.0 (*C*H_2), 55.3 (N*C*H), 60.8 (O*C*H_2), 113.9 (2 × Ar*C*H), 126.3 (2 × Ar*C*H), 127.0 (Ar*C*H), 127.4 (Ar*C*), 128.8 (2 × Ar*C*H), 129.7 (2 × Ar*C*H), 142.5 (Ar*C*), 144.6 (Ar*C*), 171.2 (*C*O); m/z (TOF ES+) 284 (MH^+, 100); Enantiomeric excess was determined by chiral phase HPLC (Phenomenex Lux 3 um Cellulose-1) 5 % ipa in hexane @ 1 mL min^{-1}, t_R = 9.5 min (minor), 11.7 min (major).

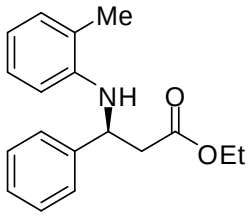
(*S*)-Ethyl 3-phenyl-3-(4-fluorophenylamino)propanoate 202



Obtained by general procedure G as a white solid (59% yield, 71% ee); m.p. 50-52 ºC; $[\alpha]_D$ +10 (*c* 1.2 in $CHCl_3$, 71% ee); (Found C 70.75, H 6.29, N 4.77; requires $C_{19}H_{23}NO_3$ C 71.06, H 6.31, N 4.87); ν_{max} (thin film, cm^{-1}) 3393, 2982, 1727, 1510; δ_H (400 MHz, $CDCl_3$) 1.22

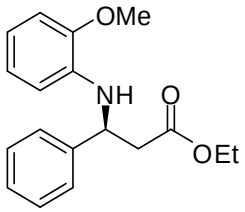
(t, 3H, *J* 7.2, C*H*$_3$), 2.78 (dd, 1H, *J* 14.8, 7.9, 1 × C*H*$_2$), 2.83 (dd, 1H, *J* 14.8, 5.5, 1 × C*H*$_2$), 4.10 - 4.17 (m, 2H, C*H*$_2$), 4.51 (s, br, 1H, N*H*), 4.75 - 4.79 (m, 1H, NC*H*), 6.49 - 6.52 (m, 2H, Ar*H*), 6.80 - 6.84 (m, 2H, Ar*H*), 7.25 - 7.39 (m, 5H, Ar*H*); δ_C (100 MHz, $CDCl_3$) 14.1 (*C*H$_3$), 42.9 (*C*H$_2$), 55.7 (N*C*H) 60.8 (O*C*H$_2$), 114.6 (d, $^3J_{C\text{-}F}$ 7.5, 2 × Ar*C*H), 115.6 (d, $^2J_{C\text{-}F}$ 22.3, 2 × Ar*C*H), 126.3 (2 × Ar*C*H), 127.5 (Ar*C*H), 128.8 (2 × Ar*C*H), 142.1 (Ar*C*), 143.2 (Ar*C*), 156.0 (d, $^1J_{C\text{-}F}$ 235.4, Ar*C*F), 171.2 (*C*O); δ_F (235 MHz, $CDCl_3$) -127.6; m/z (TOF ES+) 288.1393 (MH^+, $C_{17}H_{19}NO_2F$ requires 288.1400); Enantiomeric excess was determined by chiral phase HPLC (Phenomenex Lux 3 um Cellulose-1) 5 % ipa in hexane @ 1 mL min^{-1}, t_R = 9.4 min (minor), 11.7 min (major).

(*S*)-Ethyl 3-(2-methylphenylamino)-3-phenylpropanoate 203



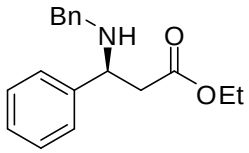
Obtained by general procedure G as a colourless oil (contaminated by ketoester and failed to isolate the pure product; 53% yield, 86% ee); ν_{max} (thin film, cm^{-1}) 3419, 2980, 1728, 1606, 1588; δ_H (400 MHz, $CDCl_3$) 1.23 (t, 3H, *J* 7.1, C*H*$_3$), 2.28 (s, 3H, C*H*$_3$), 2.84 (dd, 1H, *J* 14.5, 7.7, 1 × C*H*$_2$), 2.89 (dd, 1H, *J* 14.5, 5.5, 1 × C*H*$_2$), 4.11 - 4.17 (m, 2H, C*H*$_2$), 4.65 (s, br, 1H, N*H*), 4.88 (dd, *J* 7.7, 5.5, NC*H*), 6.41 (d, 1H, *J* 8.0, Ar*H*), 6.65 (br, t, 1H, *J* 7.3, Ar*H*), 6.99 (br. t, 1H, *J* 8.0, Ar*H*), 7.08 (br. d, 1H, *J* 7.3, Ar*H*), 7.25-7.29 (m, 1H, Ar*H*), 7.33-7.42 (m, 4H, Ar*H*); δ_C (100 MHz, $CDCl_3$) 14.2 (*C*H$_3$), 17.6 (*C*H$_3$), 43.2 (*C*H$_2$), 55.0 (N*C*H), 60.9 (O*C*H$_2$), 111.2 (Ar*C*H), 117.3 (Ar*C*H), 122.3 (Ar*C*), 126.2 (2 × Ar*C*H), 127.0 (Ar*C*H), 127.4 (Ar*C*H), 128.8 (2 × Ar*C*H), 130.1 (Ar*C*H), 142.3 (Ar*C*), 144.8 (Ar*C*), 171.3 (*C*O); *m/z* (TOF ES+) 284.1644 (MH^+, $C_{18}H_{22}NO_2$ requires 284.1651); Enantiomeric excess was determined by chiral phase HPLC (Phenomenex Lux 3 um Cellulose-1) 5 % ipa in hexane @ 1 mL min^{-1}, t_R = 10.1 min (major), 13.8 min (minor).

(*S*)-Ethyl 3-(2-methoxyphenylamino)-3-phenylpropanoate 204[160]



Obtained by general procedure G as a colourless oil (41% yield, 13% ee); $[\alpha]_D$ +3.0 (*c* 2.3 in $CHCl_3$, 13% ee; lit.[160] -19, *c* 1.2 in $CHCl_3$, 83% ee for *R* isomer); δ_H (400 MHz, $CDCl_3$) 1.22 (t, 3H, *J* 7.2, C*H*$_3$), 2.83 (dd, 1H, *J* 14.6, 6.0, 1 × C*H*$_2$), 2.88 (dd, 1H, *J* 14.6, 7.7, 1 × C*H*$_2$), 3.90 (s, 3H, OC*H*$_3$), 4.07 - 4.19 (m, 2H, C*H*$_2$), 4.87 (app. q, 1H, *J* 6.8, NC*H*), 5.10 (d, 1H, *J* 6.2, N*H*), 6.65 (td, 1H, *J* 7.7, 1.5, Ar*H*), 6.74 (td, 1H, *J* 7.7, 1.4, Ar*H*), 6.79 (dd, 1H, *J* 7.8, 1.2, Ar*H*), 7.24 - 7.28 (m, 1H, Ar*H*), 7.73 - 7.36 (m, 2H, Ar*H*), 7.40 - 7.42 (m, 2H, Ar*H*); δ_C (100 MHz, $CDCl_3$) 14.1 (*C*H$_3$), 43.3 (*C*H$_2$), 54.9 (N*C*H), 55.5 (OCH$_3$), 60.7 (OCH$_2$), 109.5 (Ar*C*H), 111.2 (Ar*C*H), 116.9 (Ar*C*H), 121.2 (Ar*C*H), 126.3 (2 × Ar*C*H), 127.4 (Ar*C*H), 128.7 (2 × Ar*C*H), 136.8 (Ar*C*), 142.5 (Ar*C*), 146.9 (Ar*C*), 171.0 (*C*O); Enantiomeric excess was determined by chiral phase HPLC (Phenomenex Lux 3 um Cellulose-1) 5 % ipa in hexane @ 1 mL min^{-1}, t_R = 15.3 min (minor), 19.3 min (major). Data was in accordance with the literature.

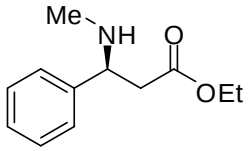
(*S*)-Ethyl 3-(benzylamino)-3-phenylpropanoate 205[161]



Obtained by general procedure G as a colourless oil (57% yield, 93% ee); $[\alpha]_D$ -41 (*c* 1.5 in acetone, 93% ee; lit.[162] -5.7, *c* 0.5, 40% ee); δ_H (400 MHz, $CDCl_3$) 1.21 (t, 3H, *J* 7.1, C*H*$_3$), 2.12 (s, br. 1H, N*H*), 2.64 (dd, 1H, *J* 15.5, 5.2, 1 × C*H*$_2$), 2.74 (dd, 1H, *J* 15.5, 8.8, 1 × C*H*$_2$), 3.57 (d, 1H, *J* 13.2, 1 × NC*H*$_2$), 3.67 (d, *J* 13.2, 1 × NC*H*$_2$), 4.09 - 4.15 (m, 3H, NC*H* and OC*H*$_2$), 7.23-7.40 (m, 10H, ArC*H*); δ_C (100 MHz, $CDCl_3$) 14.2 (*C*H$_3$), 43.2 (*C*H$_2$), 51.4 (NCH$_2$), 58.9 (N*C*H), 60.5 (OCH$_2$), 126.9 (Ar*C*H), 127.2 (2 × Ar*C*H), 127.5 (Ar*C*H), 128.3 (2 × Ar*C*H), 128.4 (2 × Ar*C*H), 128.6 (2 × Ar*C*H), 140.3 (Ar*C*), 142.6 (Ar*C*), 171.8 (*C*O); Enantiomeric excess was determined by chiral phase HPLC (Phenomenex Lux 3 um

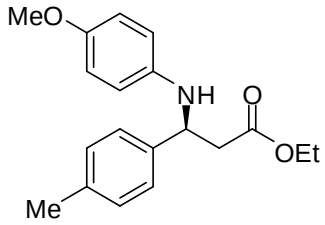
Cellulose-1) 5 % ipa in hexane @ 1 mL min^{-1} at λ 210nm, t_R = 6.8 min (minor), 9.6 min (major). Data was in accordance with the literature.

(*S*)-Ethyl 3-(methylamino)-3-phenylpropanoate 206



Obtained by general procedure G as a colourless oil (59% yield, 94% ee); $[\alpha]_D$ -25 (*c* 1.3 in $CHCl_3$, 94% ee); ν_{max} (thin film, cm^{-1}) 3345, 2978, 1731, 1453; δ_H (400 MHz, $CDCl_3$) 1.22 (t, 3H, *J* 7.1, CH_2CH_3), 1.70 (br, s, 1H, N*H*), 2.29 (s, 3H, NCH_3), 2.63 (dd, 1H, *J* 15.5, 5.4, 1 × CH_2), 2.73 (dd, 1H, *J* 15.5, 8.5, 1 × CH_2), 3.98 (dd, *J* 8.5, 5.4, NC*H*), 4.12 (q, 2H, *J* 7.1, OCH_2), 7.28 - 7.36 (m, 5H, Ar*H*); δ_C (100 MHz, $CDCl_3$) 14.1 (CH_3), 34.4 (CH_3), 42.8 (CH_2), 60.5 (OCH_2), 61.5 (N*C*H), 127.1 (2 × Ar*C*H), 127.4 (Ar*C*H), 128.5 (2 × Ar*C*H), 142.4 (Ar*C*), 171.9 (CO); *m/z* (TOF ES+) 208.1345 (MH^+, $C_{12}H_{18}NO_2$ requires 208.1338); Enantiomeric excess was determined by comparison of the integrals in the ^1H NMR spectrum in $CDCl_3$ of the diastereomeric salts formed by addition of excess L-mandelic acid.

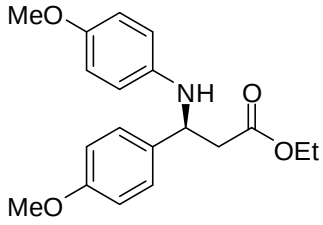
(*S*)-Ethyl 3-(4-methoxyphenylamino)-3-(4-methylphenyl)propanoate 207



Obtained by general procedure G as a colourless oil (75%, yield, 92% ee); $[\alpha]_D$ -19.4 (*c* 0.62 in $CHCl_3$, 92% ee); (Found C 72.94, H 7.75, N 4.43; requires $C_{19}H_{23}NO_3$ C 72.82, H 7.40, N 4.47); ν_{max} (thin film, cm^{-1}) 3386, 2983, 1731, 1513, 1239; δ_H (400 MHz, $CDCl_3$) 1.22 (t, 3H, *J* 7.1, CH_3), 2.23 (s, 3H, CH_3), 2.78 (d, 2H, *J* 6.8, CH_2), 3.72 (s, 3H, OCH_3), 4.07 - 4.18 (m, 2H, OCH_2), 4.28 (s, br, 1H, N*H*), 4.74 (t, 1H, *J* 6.8, NC*H*), 6.54 [$(AX)_2$, 2H, Ar*H*], 6.72 [$(AX)_2$, 2H, Ar*H*], 7.14 [$(AX)_2$, 2H, Ar*H*], 7.27 [$(AX)_2$, 2H, Ar*H*]; δ_C (100 MHz, $CDCl_3$) 14.2 (CH_3), 21.1 (CH_3) 43.0 (CH_2), 55.7 (N*C*H), 60.7 (OCH_2), 114.8 (2 × Ar*C*H), 115.2 (2 × Ar*C*H), 126.2 (2 × Ar*C*H), 129.4 (2 × Ar*C*H), 137.0 (Ar*C*), 139.5 (Ar*C*), 141.2 (Ar*C*), 152.3 (Ar*C*), 171.3 (*C*O); *m/z* (TOF ES+) 314.1750 (MH^+, $C_{19}H_{24}NO_3$ requires 314.1756);

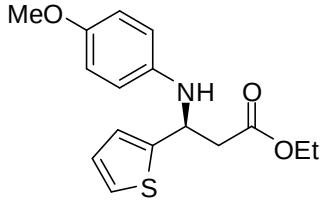
Enantiomeric excess was determined by chiral phase HPLC (Phenomenex Lux 3 um Cellulose-1) 5 % ipa in hexane @ 1 mL min^{-1}, t_R = 11.6 min (minor), 12.8 min (major).

(*S*)-Ethyl 3-(4-methoxyphenylamino)-3-(4-methoxyphenyl)propanoate 208[67]



Obtained by general procedure G as a colourless oil (70% yield, 91% ee); (Phenomenex Lux 3 um Cellulose-1, flow rate 1 ml/min, 90:10 hexane/2-propanol); $[\alpha]_D$ -20 (*c* 1.0 in $CHCl_3$, 91% ee; lit.[67] -17.9, *c* 1.0 in $CHCl_3$, 88% ee); δ_H (400 MHz, $CDCl_3$) 1.22 (t, 3H, *J* 7.1, C*H*$_3$), 2.74 - 2.83 (m, 2H, C*H*$_2$), 3.72 (s, 3H, OC*H*$_3$), 3.80 (s, 3H, OC*H*$_3$), 4.09 - 4.17 (m, 2H, OC*H*$_2$), 4.28 (s, br, 1H, N*H*), 4.73 (t, 1H, *J* 6.8, NC*H*), 6.55 [$(AX)_2$, 2H, Ar*H*], 6.73 [$(AX)_2$, 2H, Ar*H*], 6.88 [$(AX)_2$, 2H, Ar*H*], 7.30 [$(AX)_2$, 2H, Ar*H*]; δ_C (100 MHz, $CDCl_3$) 14.2 (*C*H$_3$), 43.0 (*C*H$_2$), 55.2 (N*C*H), 55.4 (O*C*H$_3$), 55.7 (O*C*H$_3$), 60.7 (O*C*H$_2$), 114.1 (2 × Ar*C*H), 114.8 (2 × Ar*C*H), 115.2 (2 × Ar*C*H), 127.4 (2 × Ar*C*H), 134.5 (Ar*C*), 141.1 (Ar*C*), 152.3 (Ar*C*), 158.8 (Ar*C*), 171.3 (*C*O); Enantiomeric excess was determined by chiral phase HPLC (Phenomenex Lux 3 um Cellulose-1) 5 % ipa in hexane @ 1 mL min^{-1}, t_R = 12.9 min (minor), 14.1 min (major). Data was in accordance with the literature.

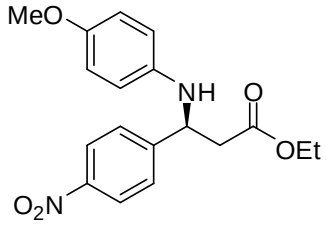
(*S*)-Ethyl 3-(4-methoxyphenylamino)-3-(thiophen-2-yl)propanoate 209[67]



Obtained by general procedure G as a colourless oil (66% yield, 90% ee); $[\alpha]_D$ -15 (*c* 1.0 in $CHCl_3$, 90% ee; lit.[67] -9.1, *c* 1.0, 70% ee); δ_H (400 MHz, $CDCl_3$) 1.25 (t, 3H, *J* 7.1, C*H*$_3$), 2.88 - 3.00 (m, 2H, C*H*$_2$), 3.75 (s, 3H, OC*H*$_3$), 4.16 (q, 2H, *J* 7.1, OC*H*$_2$), 4.23 (s, br. N*H*), 5.09 (t, 1H, *J* 6.5, NC*H*), 6.67 [$(ArX)_2$, 2H, Ar*H*], 6.78 [$(AX)_2$, 2H, Ar*H*], 6.94-7.19 (m, 2H, Ar*H*), 7.20 (dd, 1H, *J* 5.0, 1.2, Ar*H*); δ_C (100 MHz, $CDCl_3$) 14.2 (*C*H$_3$), 42.6 (*C*H$_2$), 52.3 (N*C*H), 55.7 (O*C*H$_3$), 60.8 (O*C*H$_2$), 114.8 (2 × Ar*C*H), 115.8 (2 × Ar*C*H), 123.8 (Ar*C*H),

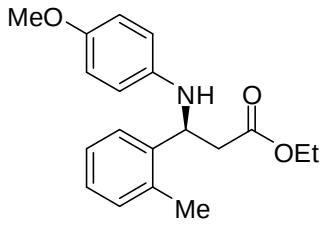
124.2 (Ar*C*H), 126.8 (Ar*C*H), 140.6 (Ar*C*), 147.3 (Ar*C*), 152.9 (Ar*C*), 170.9 (*C*O); Enantiomeric excess was determined by chiral phase HPLC (Phenomenex Lux 3 um Cellulose-1) 10 % ipa in hexane @ 1 mL min^{-1}, t_R = 10.6 min (minor), 13.0 min (major). Data was in accordance with the literature.

(*S*)-Ethyl 3-(4-methoxyphenylamino)-3-(4-nitrophenyl)propanoate 210



Obtained by general procedure G as an orange oil (50% yield, 82% ee); $[\alpha]_D$ -23 (*c* 0.8 in $CHCl_3$, 82% ee); ν_{max} (thin film, cm^{-1}) 3386, 2983, 1730, 1514; δ_H (400 MHz, $CDCl_3$) 1.22 (t, 3H, *J* 7.2, C*H*$_3$), 2.78 - 2.88 (m, 2H, C*H*$_2$), 3.71 (s, 3H, OC*H*$_3$), 4.14 (q, 2H, *J* 7.2, OC*H*$_2$), 4.48 (s, br, 1H, N*H*), 4.86 (t, 1H, *J* 6.2, NC*H*), 6.49 [(AX)$_2$, 2H, Ar*H*], 6.72 [(AX)$_2$, 2H, Ar*H*], 7.58 [(AX)$_2$, 2H, Ar*H*], 8.19 [(AX)$_2$, 2H, Ar*H*]; δ_C (100 MHz, $CDCl_3$) 14.1 (*C*H$_3$), 42.3 (*C*H$_2$), 55.5 (N*C*H), 55.6 (O*C*H$_3$), 61.1 (O*C*H$_2$), 114.9 (2× Ar*C*H), 115.2 (2 × Ar*C*H), 124.0 (2× Ar*C*H), 127.4 (2× Ar*C*H), 140.2 (Ar*C*), 147.3 (Ar*C*), 150.3 (Ar*C*), 152.7 (Ar*C*), 170.6 (*C*O); *m/z* (TOF ES+) 345.1435 (MH^+, $C_{18}H_{21}N_2O_5$ requires 345.1450); Enantiomeric excess was determined by chiral phase HPLC (Chiralpak IA) 10 % ipa in hexane @ 1 mL min^{-1}, t_R = 27.9 min (minor), 30.5 min (major).

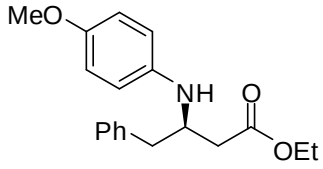
(*S*)-Ethyl 3-(4-methoxyphenylamino)-3-(2-methylphenyl)propanoate 211



Obtained by general procedure G as a light yellow oil (27% yield, 3% ee); $[\alpha]_D$ 0 (*c* 1.0 in $CHCl_3$, 3% ee; lit.[67] +1.4, *c* 1.0 in $CHCl_3$, 79% ee); δ_H (400 MHz, $CDCl_3$) 1.23 (t, 3H, *J* 7.2, C*H*$_3$), 2.48 (s, 3H, C*H*$_3$), 2.68 (dd, 1H, *J* 14.8, 8.4, 1 × C*H*$_2$), 2.77 (dd, 1H, *J* 14.8, 5.1, 1 × C*H*$_2$), 3.72 (s, 3H, OC*H*$_3$), 4.08 - 4.19 (m, 2H, OC*H*$_2$), 4.27 (s, br, 1H, N*H*), 4.96 (dd, 1H, *J*

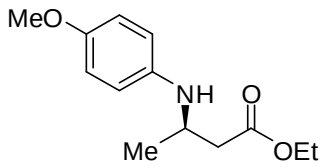
8.4, 5.1, NC*H*), 6.48 [$(AX)_2$, 2H, Ar*H*], 6.72 [$(AX)_2$, 2H, Ar*H*], 7.15 - 7.21 (m, 3H, Ar*H*), 7.40 - 7.44 (m, 1H, Ar*H*); δ_C (100 MHz, $CDCl_3$) 14.2 (*C*H_3), 19.1 (*C*H_3), 41.3 (*C*H_2), 52.4 (N*C*H), 55.7 (O*C*H_3), 60.8 (O*C*H_2), 114.8 (2 × Ar*C*H), 114.9 (2 × Ar*C*H), 125.2 (Ar*C*H), 126.6 (Ar*C*H), 127.2 (Ar*C*H), 130.8 (Ar*C*H), 135.0 (Ar*C*), 140.2 (Ar*C*), 141.1 (Ar*C*), 152.3 (Ar*C*), 171.3 (*C*O); Enantiomeric excess was determined by chiral phase HPLC (Phenomenex Lux 3 um Cellulose-1) 5 % ipa in hexane @ 1 mL min^{-1}, t_R = 10.2 min (minor), 15.6 min (major). Data was in accordance with the literature.

(*S*)-Ethyl 3-(4-methoxyphenylamino)-4-phenylbutanoate 223



Obtained by general procedure G as a light yellow oil (56% yield, 30% ee); $[\alpha]_D$ +2.3 (*c* 1.3 in $CHCl_3$, 30% ee); ν_{max} (thin film, cm^{-1}) 3371, 2981, 2934, 1728, 1512; δ_H (400 MHz, $CDCl_3$) 1.26 (t, 3H, *J* 7.1, C*H*$_3$), 2.44 (dd, 1H, *J* 15.3, 6.3, 1 × C*H*$_2$), 2.51 (dd, 1H, *J* 15.3, 6.0, 1 × CH_2), 2.87 (dd, 1H, *J* 13.6, 7.2, 1 × C*H*$_2$), 2.97 (dd, 1H, *J* 13.6, 5.1, 1 × C*H*$_2$), 3.64 (s, br, 1H, N*H*), 3.78 (s, 3H, OC*H*$_3$), 4.01 - 4.07 (m, 1H, NC*H*), 4.14 (q, 2H, *J* 7.1, OC*H*$_2$), 6.66 [$(AX)_2$, 2H, Ar*H*], 6.82 [$(AX)_2$, 2H, Ar*H*], 7.19 - 7.33 (m, 5H, Ar*H*); δ_C (100 MHz, $CDCl_3$) 14.2 (*C*H_3), 38.3 (*C*H_2), 40.0 (*C*H_2), 52.6 (N*C*H), 55.8 (O*C*H_3), 60.5 (O*C*H_2), 115.0 (2× Ar*C*H), 115.5 (2× Ar*C*H), 126.6 (Ar*C*H), 128.5 (2 × Ar*C*H), 129.5 (2 × Ar*C*H), 137.9 (Ar*C*), 140.9 (Ar*C*), 152.5 (Ar*C*), 172.0 (*C*O); m/z (TOF ES+) 314.1749 (MH^+, $C_{19}H_{24}NO_3$ requires 314.1756); Enantiomeric excess was determined by chiral phase HPLC (Phenomenex Lux 3 um Cellulose-1) 10 % ipa in hexane @ 1 mL min^{-1}, t_R = 8.7 min (major), 9.8 min (minor).

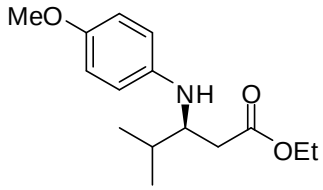
(*S*)-Ethyl 3-(4-methoxyphenylamino)butanoate 224[101]



Obtained by general procedure G as a light yellow oil (63% yield, 20% ee); $[\alpha]_D$ 0 (*c* 1.0 in $CHCl_3$, 20% ee; lit.[101] -4, *c* 0.5 in MeOH, 94% ee); δ_H (400 MHz, $CDCl_3$) 1.27 (d, 3H, *J* 6.4,

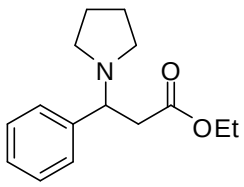
C*H*$_3$), 1.28 (t, 3H, *J* 7.2, C*H*$_3$), 2.42 (dd, 1H, *J* 15.0, 6.8, 1 × C*H*$_2$), 2.62 (dd, 1H, *J* 15.0, 6.8, 1 × C*H*$_2$), 3.51 (s, br, 1H, N*H*), 3.37 (s, 3H, OC*H*$_3$), 3.83 - 3.91 (m, 1H, NC*H*), 4.16 (q, 2H, *J* 7.2, OC*H*$_2$), 6.64 [(AX)$_2$, 2H, Ar*H*], 6.80 [(AX)$_2$, 2H, Ar*H*]; δ_C (100 MHz, $CDCl_3$) 14.2 (*C*H$_3$), 20.6 (*C*H$_3$), 41.0 (*C*H$_2$), 47.3(N*C*H), 55.7 (O*C*H$_3$), 60.4 (O*C*H$_2$), 114.9 (2 × Ar*C*H), 115.5 (2 × Ar*C*H), 141.0 (Ar*C*), 152.4 (Ar*C*), 172.0 (*C*O); Enantiomeric excess was determined by chiral phase HPLC (Phenomenex Lux 3 um Cellulose-1) 5 % ipa in hexane @ 1 mL min^{-1}, t_R = 10.2 min (minor), 10.9 min (major). Data was in accordance with the literature.

Ethyl 3-(4-methoxyphenylamino)-4-methylpentanoate 225[67]



Obtained by general procedure G as a light yellow oil (44% yield, 56% ee); $[\alpha]_D$ +20 (*c* 1.0 in $CHCl_3$, 56% ee; lit[67] +21.3, *c* 1.0 in $CHCl_3$, 59% ee); δ_H (400 MHz, $CDCl_3$) 0.95 (d, 3H, *J* 6.8, C*H*$_3$), 1.00 (d, 3H, *J* 6.8, C*H*$_3$), 1.23 (t, 3H, *J* 7.1, C*H*$_3$), 1.86 - 1.98 (m, 1H, C*H*), 2.43 (dd, 1H, *J* 14.8, 7.3, 1 × C*H*$_2$), 2.52 (dd, 1H, *J* 14.8, 5.3, 1 × C*H*$_2$), 3.46 (s, br, 1H, N*H*), 3.61 - 3.65 (m, 1H, NC*H*), 3.76 (s, 3H, OC*H*$_3$), 4.10 (q, 2H, *J* 7.1, OC*H*$_2$), 6.63 [(AX)$_2$, 2H, Ar*H*], 6.78 [(AX)$_2$, 2H, Ar*H*]; δ_C (100 MHz, $CDCl_3$) 14.2 (*C*H$_3$), 18.6 (*C*H$_3$), 18.7 (*C*H$_3$), 31.7 (*C*H), 36.9 (*C*H$_2$), 55.8 (O*C*H$_3$), 57.2 (N*C*H), 60.4 (O*C*H$_2$), 114.9 (2 × Ar*C*H), 115.0 (2 × Ar*C*H), 141.9 (Ar*C*), 152.1 (Ar*C*), 172.4 (*C*O); Enantiomeric excess was determined by chiral phase HPLC (Phenomenex Lux 3 um Cellulose-1) 5 % ipa in hexane @ 1 mL min^{-1}, t_R = 9.1 min (minor), 9.9 min (major). Data was in accordance with the literature.

(±)-Ethyl 3-phenyl-3-(pyrrolidin-1-yl)propanoate 216[163]



Obtained by general procedure G as a yellow oil (62%, 0% ee); δ_H (400 MHz, $CDCl_3$) 1.08 (t, 3H, *J* 7.1, C*H*$_3$), 1.72 - 1.82 (m, 4H, 4 × C*H*$_2$), 2.37 - 2.46 (m, 2H, 2 × C*H*$_2$), 2.51 - 2.60 (m, 2H, 2 × C*H*$_2$), 2.71 (dd, 1H, *J* 14.6, 9.1, 1 × C*H*$_2$), 3.00 (dd, 1H, *J* 14.6, 5.7, 1 × C*H*$_2$), 3.70 (dd, 1H, *J* 9.1, 5.7, 1 × C*H*$_2$), 3.98 (q, 2H, *J* 7.1, OC*H*$_2$), 7.23 - 7.36 (m, 5H, Ar*H*); δ_C (100 MHz, $CDCl_3$) 14.01 (*C*H$_3$), 23.3 (2 × *C*H$_2$), 41.7 (*C*H$_2$), 52.2 (2 × *C*H$_2$), 60.2 (*C*H$_2$), 66.5 (*C*H), 85.2 (*C*H), 127.4 (Ar*C*H), 128.0 (2 × Ar*C*H), 128.2 (2 × Ar*C*H), 141.7 (Ar*C*), 171.6 (*C*O); Enantiomeric excess was determined by chiral phase HPLC (Chiralcel OD-H) 5 % ipa in hexane @ 1 mL min^{-1} and at λ 205 nm, t_R = 4.1 min, 5.3 min (major). Data was in general accordance with the literature, although ^{1}H NMR data has missed the signals of the eight protons on the pyrrolidinyl ring in reference 163.

7.6 Asymmetric reductive amination of ketones

General procedure H

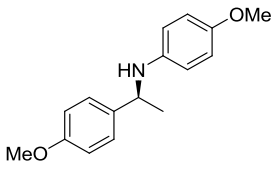
Ketone (1 mmol), amine (1.5 mmol), catalyst **117** (0.01 mmol) and dry CH_2Cl_2 (0.5mL) were introduced into an oven-dried 25mL two-necked flask or an oven-dried carousel tube. The mixture was stirred until complete dissolution, then cooled to 0 ºC and trichlorosilane (2 mmol, 0.2 mL) was added by syringe. A suspension was formed immediately upon addition of trichlorosilane. The resulting reaction mixture was left to stir for 24 h at 0 ºC. The reaction was diluted by CH_2Cl_2 (20 mL), quenched by water (2 mL) and followed by addition of aqueous sodium hydroxide (1 M, 20 mL). This mixture was stirred until the precipitate was completely dissolved and no gas was evolved. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic phase was wash with brine (20 mL) and dried over $MgSO_4$. Filtration and concentration gave crude product, which was purified by chromatography on silica gel using 2% ~ 10% solution of diethyl ether in petroleum ether.

General procedure I

Ketone (1 mmol), amine (1.5 mmol),and 4 Å molecular sieves (200 mg) was introduced into a microwave tube (10 mL) and the mixture was heated at 150 °C for 40 min under

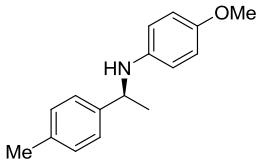
microwave irradiation. After the reaction mixture was cooled to room temperature, catalyst **117** (0.01 mmol) and dry CH_2Cl_2 (0.5mL or as mentioned) were added, the vessel cooled to 0 ºC and trichlorosilane (2 mmol, 0.2 mL) added by syringe. The resulting reaction mixture was left to stir at 0 ºC for 8 h. The reaction was diluted by CH_2Cl_2 (20 mL), quenched by water (2 mL) and followed by addition of aqueous sodium hydroxide (1 M, 20 mL). This mixture was stirred until the precipitate was completely dissolved and no gas was evolved. The organic phases were separated and the aqueous phases were extracted with CH_2Cl_2 (2 × 20 mL). The combined organic phase was wash with brine (20 mL) and dried over $MgSO_4$. Filtration and concentration gave crude product, which was purified by chromatography on silica gel using 2% ~ 20% solution of diethyl ether in petroleum ether.

(*S*)-*N*-[1-(4'-Methoxyphenyl)ethyl]-4-methoxyaniline 222[79]



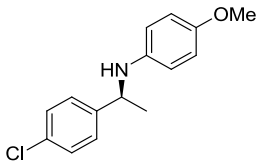
Obtained using general procedure H as a white solid (76% yield, 81% ee); m.p. 93-95 ºC (not reported in literature); $[\alpha]_D$ -14.5 (*c* 0.96 in $CHCl_3$, 81% ee, lit.[79] -15.5, *c* 1.1 in $CHCl_3$, 85% ee); δ_H (250 MHz, $CDCl_3$) 1.49 (d, 3H, *J* 6.6, C*H*$_3$), 3.72 (s, 3H, OC*H*$_3$), 3.76 (s, br, 1H, N*H*), 3.80 (s, 3H, OC*H*$_3$), 4.39 (q, 1H, *J* 6.6, NC*H*), 6.49 [$(AX)_2$, 2H, ArC*H*], 6.71 [$(AX)_2$, 2H, ArC*H*], 6.87 [$(AX)_2$, 2H, ArC*H*], 7.29 [$(AX)_2$, 2H, ArC*H*]; δ_C (63 MHz, $CDCl_3$) 25.1 (*C*H$_3$), 53.7 (N*C*H), 55.3 (O*C*H$_3$), 55.8 (O*C*H$_3$), 114.0 (2 × Ar*C*H), 114.6 (2 × Ar*C*H), 114.8 (2 × Ar*C*H), 127.0 (2 × Ar*C*H), 137.6 (Ar*C*), 141.7 (Ar*C*), 151.9 (Ar*C*), 158.5 (Ar*C*); Enantiomeric excess was determined by chiral phase HPLC (Phenomenex Lux 3 um Cellulose-1) 10 % ipa in hexane @ 1 mL min^{-1}, t_R = 9.1 min (minor), t_R = 10.1 min (major). Data was in accordance with the literature.

(*S*)- (*N*-[1-(4'-Methylphenyl)ethyl]-4-methoxyaniline 224[164]



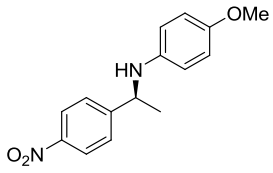
Obtained using general procedure H as a yellow solid (66% yield, 83% ee); mp 50-52 ºC (not reported in literature); $[\alpha]_D$ -17.8 (*c* 1.05 in $CHCl_3$, 83% ee, lit.[164] +13.3, *c* 2 in $CHCl_3$, 79% ee); δ_H (250 MHz, $CDCl_3$) 1.50 (d, 3H, *J* 6.6, C*H*$_3$), 2.34 (s, 3H, C*H*$_3$), 3.72 (s, 3H, OC*H*$_3$), 3.78 (s, br, 1H, N*H*), 4.41 (q, 1H, *J* 6.6, NC*H*), 6.49 [$(AX)_2$, 2H, ArC*H*], 6.71 [$(AX)_2$, 2H, ArC*H*], 7.13 - 7.16 (m, 2H, Ar*H*), 7.26 - 7.29 (m, 2H, Ar*H*); δ_C (63 MHz, $CDCl_3$) 21.2 (*C*H$_3$), 25.2 (*C*H$_3$), 54.0 (N*C*H), 55.8 (O*C*H$_3$), 114.7 (2 × Ar*C*H), 114.9 (2 × Ar*C*H), 125.9 (2 × Ar*C*H), 129.4 (2 × Ar*C*H), 136.4 (Ar*C*), 141.8 (Ar*C*), 142.6 (Ar*C*), 152.0 (Ar*C*); Enantiomeric excess was determined by chiral phase HPLC (Chiralcel OD-H) 5% ipa in hexane @ 1 mL min^{-1}, t_R = 7.5 min (minor), t_R = 8.6 min (major). Data was in accordance with the literature.

(*S*)-*N*-[1-(4'-Chlorophenyl)ethyl]-4-methoxyaniline 224[47b]



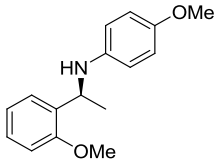
Obtained using general procedure H as a yellow oil (61% yield, 83% ee); $[\alpha]_D$ -10.9 (*c* 1.1 in $CHCl_3$, 83% ee, lit.[47b] +8.9, *c* 1.16 in $CHCl_3$, 97% ee, *R* isomer); δ_H (400 MHz, $CDCl_3$) 11.50 (d, 3H, *J* 6.6, C*H*$_3$), 3.73 (s, 3H, OC*H*$_3$), 3.81 (s, br, 1H, N*H*), 4.41 (q, 1H, *J* 6.6, NC*H*), 6.47 [$(AX)_2$, 2H, ArC*H*], 6.73 [$(AX)_2$, 2H, ArC*H*], 7.28 - 7.35 (m, 4H, Ar*H*); δ_C (100 MHz, $CDCl_3$) 25.2 (*C*H$_3$), 53.8 (N*C*H), 55.8 (O*C*H$_3$), 114.6 (2 × Ar*C*H), 114.9 (2 × Ar*C*H), 127.4 (2 × Ar*C*H), 128.8 (2 × Ar*C*H), 132.4 (Ar*C*), 141.4 (Ar*C*), 144.2 (Ar*C*), 152.1 (Ar*C*); Enantiomeric excess was determined by chiral phase HPLC (Phenomenex Lux 3 µm Cellulose-1) 8% ipa in hexane @ 1 mL min^{-1}, t_R = 10.6 min (minor), t_R = 12.6 min (major). Data was in accordance with the literature.

(*S*)-*N*-[1-(4'-Nitrophenyl)ethyl]-4-methoxyaniline 225[79]



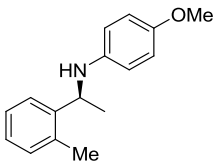
Obtained using general procedure H as a brown oil (46% yield, 83% ee); $[\alpha]_D$ -30.8 (*c* 1.0 in $CHCl_3$, 83% ee, lit.[79] -25.9, *c* 0.54 in $CHCl_3$, 86% ee); δ_H (400 MHz, $CDCl_3$) 1.55 (d, 3H, *J* 6.8, C*H*$_3$), 3.72 (s, 3H, OC*H*$_3$), 3.93 (br s, 1H, N*H*), 4.53 (q, 1H, *J* 6.8, NC*H*), 6.43 [$(AX)_2$, 2H, Ar*H*], 6.72 [$(AX)_2$, 2H, Ar*H*], 7.57 [$(AX)_2$, 2H, Ar*H*], 8.20 [$(AX)_2$, 2H, Ar*H*]; δ_C (100 MHz, $CDCl_3$) 25.0 (*C*H$_3$), 54.0 (N*C*H), 55.7 (O*C*H$_3$), 114.5 (2 × Ar*C*H), 114.8 (2 × Ar*C*H), 124.1 (2 × Ar*C*H), 126.8 (2 × Ar*C*H), 140.7 (Ar*C*), 147.0 (Ar*C*), 152.3 (Ar*C*), 153.6 (Ar*C*); Enantiomeric excess was determined by chiral phase HPLC (Phenomenex Lux 3 µm Cellulose-1) 10% ipa in hexane @ 1 mL min^{-1}, t_R = 28.3 min (minor), t_R = 34.8 min (major); Data was in accordance with the literature.

(*S*)-*N*-[1-(2'-Methoxyphenyl)ethyl]-4-methoxyaniline 227[38]



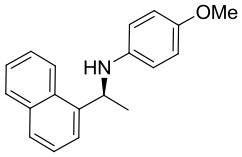
Obtained using general procedure H as a light yellow solid (71% yield, 70% ee), mp 56 – 58 °C (not reported in literature); $[\alpha]_D$ +11.8 (*c* 1.5 in $CHCl_3$, 70% ee, lit.[38] +14.0 *c* 0.25 in $CDCl_3$, 90% ee, absolute configuration assumed to be *S*); δ_H (250 MHz, $CDCl_3$) 1.58 (d, 3H, *J* 6.6, C*H*$_3$), 3.77 (s, 3H, OC*H*$_3$), 3.96 (s, 3H, OC*H*$_3$), 4.04 (s, br, 1H, N*H*), 4.90 (q, 1H, *J* 6.6, NC*H*), 6.59 [$(AX)_2$, 2H, Ar*H*], 6.80 [$(AX)_2$, 2H, Ar*H*], 6.99 (t, 2H, *J* 7.4, Ar*H*), 7.29 (td, 1H, *J* 7.4, 1.6, Ar*H*), 7.42 (dd, 1H, *J* 7.4, 1.6, Ar*H*); δ_C (63 MHz, $CDCl_3$) 23.0 (*C*H$_3$), 49.0 (N*C*H), 55.4 (O*C*H$_3$), 55.8 (O*C*H$_3$), 110.6 (Ar*C*H), 114.7 (2 × Ar*C*H), 114.9 (2 × Ar*C*H), 120.9 (Ar*C*H), 126.6 (Ar*C*H), 127.7 (Ar*C*H), 133.1 (Ar*C*), 141.9 (Ar*C*), 151.9 (Ar*C*), 156.9 (Ar*C*); Enantiomeric excess was determined by chiral phase HPLC (Chiralcel OD-H) 5% ipa in hexane @ 1 mL min^{-1}, t_R = 7.9 min (minor), t_R = 9.2 min (major); Data was in accordance with the literature.

(*S*)-*N*-[1-(2'-Methylphenyl)ethyl]-4-methoxyaniline 226[44b]



Obtained using general procedure H as a yellow oil (12% yield, 81% ee); $[\alpha]_D$ +35.4 (*c* 0.48 in MeOH, 81% ee, lit.[44b] -33.5, *c* 2.2 in MeOH, 78% ee, *R* isomer); δ_H (250 MHz, $CDCl_3$) 1.50 (d, 3H, *J* 6.6, C*H*$_3$), 2.49 (s, 3H, C*H*$_3$), 3.74 (s, 3H, OC*H*$_3$), 4.65 (q, 1H, *J* 6.6, NC*H*), 6.45 [$(AX)_2$, 2H, Ar*H*], 6.74 [$(AX)_2$, 2H, Ar*H*], 7.17 - 7.25 (m, 3H, Ar*H*), 7.46 - 7.50 (m, 1H, Ar*H*); δ_H (63 MHz, $CDCl_3$) 19.0 (*C*H$_3$), 23.2 (*C*H$_3$), 50.5 (N*C*H), 55.8 (O*C*H$_3$), 114.3 (2 × Ar*C*H), 114.9 (2 × Ar*C*H), 124.7 (Ar*C*H), 126.6 (2 × Ar*C*H), 130.6 (Ar*C*H), 134.6 (Ar*C*), 141.7 (Ar*C*), 143.1 (Ar*C*), 151.9 (Ar*C*); Enantiomeric excess was determined by chiral phase HPLC (Phenomenex Lux 3 µm Cellulose-1) 10% ipa in hexane @ 1 mL min^{-1}, t_R = 6.3 min (minor), t_R = 7.7 min (major); Data was in accordance with the literature.

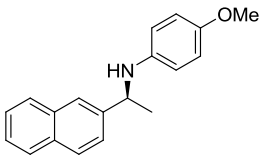
(*S*)-*N*-[1-(Naphthalen-1-yl)ethyl]-4-methoxyaniline 228[79]



Obtained using general procedure H as a yellow solid (11% yield, 77% ee), m.p. 88-89 °C (lit.[79] 61 ºC); $[\alpha]_D$ +135 (*c* 0.4 in $CHCl_3$, 77% ee, lit.[79] +123.8, *c* 0.44 in $CHCl_3$, 74% ee); δ_H (400 MHz, $CDCl_3$) 1.70 (d, *J* 6.6, 3H, C*H*$_3$), 3.73 (s, 3H, OC*H*$_3$), 4.00 (s, br, 1H, N*H*), 5.28 (q, 1H, *J* 6.6, NC*H*), 6.50 [$(AX)_2$, 2H, Ar*H*], 6.73 [$(AX)_2$, 2H, Ar*H*], 7.48 (t, 1H, *J* 7.6, Ar*H*), 7.56 - 7.65 (m, 2H, Ar*H*), 7.73 (d, 1H, *J* 7.1, Ar*H*), 7.81 (d, 1H, *J* 8.1, Ar*H*), 7.97 (d, 1H, *J* 8.1, Ar*H*), 8.24 (d, 1H, *J* 8.3, Ar*H*); δ_H (100 MHz, $CDCl_3$) 23.9 (*C*H$_3$), 50.2 (N*C*H), 55.8 (O*C*H$_3$), 114.4 (2 × Ar*C*H), 114.9 (2 × Ar*C*H), 122.4 (Ar*C*H), 122.7 (Ar*C*H), 125.5 (Ar*C*H), 126.0 (Ar*C*H), 126.1 (Ar*C*H), 127.5 (Ar*C*H), 129.2 (Ar*C*H), 130.9 (Ar*C*), 134.2 (Ar*C*), 140.3 (Ar*C*), 141.5 (Ar*C*), 151.9 (Ar*C*); Enantiomeric excess was determined by chiral phase HPLC (Phenomenex Lux 3 µm Cellulose-1) 5% ipa in hexane @ 1 mL min^{-1}, t_R = 12.9 min

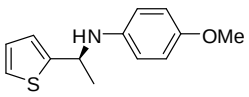
(minor), t_R = 19.0 min (major); Data was in accordance with literature.

(*S*)-*N*-[1-(Naphthalen-2-yl)ethyl]-4-methoxyaniline 229[79]



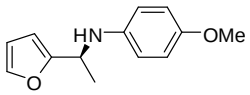
Obtained using general procedure H as a light yellow solid (63% yield, 85% ee), mp 96 – 98 °C (lit.[79] 95 – 96 ºC); $[\alpha]_D$ -24 (*c* 1.0 in $CHCl_3$, 85% ee, lit.[79] -26.0, *c* 1.0 in $CHCl_3$, 86% ee); δ_H (250 MHz, $CDCl_3$) 1.59 (d, 3H, *J* 6.9, C*H*$_3$), 3.70 (s, 3H, OC*H*$_3$), 3.90 (s, br, 1H, N*H*), 4.59 (q, 1H, *J* 6.9, NC*H*), 6.53 [$(AX)_2$, 2H, Ar*H*], 6.71 [$(AX)_2$, 2H, Ar*H*], 7.42 - 7.55 (m, 3H, Ar*H*), 7.80 - 7.86 (m, 4H, Ar*H*); δ_C (63 MHz, $CDCl_3$) 25.2 (*C*H$_3$), 54.6 (N*C*H), 55.8 (O*C*H$_3$), 114.7 (2 × Ar*C*H), 114.8 (2 × Ar*C*H), 124.4 (Ar*C*H), 124.5 (Ar*C*H), 125.5 (Ar*C*H), 126.0 (Ar*C*H), 127.7 (Ar*C*H), 127.9 (Ar*C*H), 128.5 (Ar*C*H), 132.8 (Ar*C*), 133.7 (Ar*C*), 141.7 (Ar*C*), 143.1 (Ar*C*), 152.0 (Ar*C*); Enantiomeric excess was determined by chiral phase HPLC (Phenomenex Lux 3 µm Cellulose-1) 10% ipa in hexane @ 1 mL min^{-1}, t_R = 10.1 min (minor), t_R = 12.0 min (major); Data was in accordance with the literature.

(*S*)-*N*-[1-(Thiophen-2-yl)ethyl]-4-methoxyaniline 231[83]



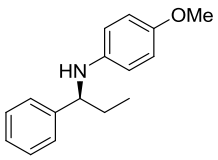
Obtained using general procedure H as a yellow oil (61% yield, 79% ee); $[\alpha]_D$ -8.0 (*c* 1.0 in $CHCl_3$, 79% ee, lit.[83] -9.0, *c* 1.0 in $CHCl_3$, 89% ee); δ_H (250 MHz, $CDCl_3$) 1.63 (d, 3H, *J* 6.6, C*H*$_3$), 3.75 (s, 3H, OC*H*$_3$), 4.76 (q, 1H, *J* 6.6, NC*H*), 6.62 [$(AX)_2$, 2H, Ar*H*], 6.75 [$(AX)_2$, 2H, Ar*H*], 6.94 - 6.98 (m, 2H, Ar*H*), 7.18 (dd, 1H, *J* 4.7, 1.6, Ar*H*); δ_C (63 MHz, $CDCl_3$) 24.8 (*C*H$_3$), 50.6 (N*C*H), 55.8 (O*C*H$_3$), 114.9 (2 × Ar*C*H), 115.2 (2 × Ar*C*H), 123.0 (Ar*C*H), 123.6 (Ar*C*H), 126.7 (Ar*C*H), 141.2 (Ar*C*), 150.6 (Ar*C*), 152.5 (Ar*C*); Enantiomeric excess was determined by chiral phase HPLC (Phenomenex Lux 3µm Cellullose-1) 2% ipa in hexane @ 1 mL min^{-1}, t_R = 15.1 min (minor), t_R = 17.3 min (major); Data was in accordance with the literature.

(*S*)-*N*-[1-(Furan-2-yl)ethyl]-4-methoxyaniline 230[165]



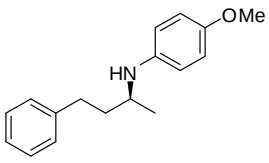
Obtained using general procedure H as a yellow oil (72% yield, 44% ee); $[\alpha]_D$ -46 (*c* 1.0 in $CHCl_3$, 44% ee, lit.[83] -48, *c* 1.0 in $CHCl_3$, 62% ee); δ_H (250 MHz, $CDCl_3$) 1.57 (d, 3H, *J* 6.6, C*H*$_3$), 3.63 (br, s, 1H, N*H*), 3.76 (s, 3H, OC*H*$_3$), 4.58 (q, 1H, *J* 6.6, NC*H*), 6.18 (app. d, 1H, *J* 3.2, Ar*H*), 6.32 (dd, 1H, *J* 3.2, 1.8 Ar*H*), 6.63 [$(AX)_2$, 2H, Ar*H*], 6.79 [$(AX)_2$, 2H, Ar*H*], 7.36 (app. s, 1H, Ar*H*); δ_C (63 MHz, $CDCl_3$) 21.0 (*C*H$_3$), 48.4 (N*C*H), 55.7 (OCH$_3$), 105.1 (Ar*C*H), 110.1 (Ar*C*H), 114.8 (2 × Ar*C*H), 115.2 (2 × Ar*C*H), 141.2 (Ar*C*), 141.4 (Ar*C*H), 152.5 (Ar*C*), 157.6 (Ar*C*); Enantiomeric excess was determined by chiral phase HPLC (Chiralcel OJ) 10% ipa in hexane @ 1 mL min^{-1}, t_R = 45.1 min (major), t_R = 56.4 min (minor); Data was in accordance with the literature.

(*S*)-*N*-(1-Phenylpropyl)-4-methoxyaniline 232[79]



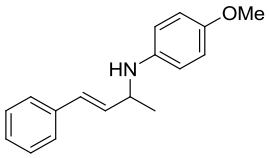
Obtained using general procedure H as a yellow oil (15% yield, 85% ee); $[\alpha]_D$ -22 (*c* 1.0 in $CHCl_3$, 85% ee, lit.[79] -26.9, *c* 1.0, $CHCl_3$, 84% ee); δ_H (250 MHz, $CDCl_3$) 0.96 (t, 3H, *J* 7.2, C*H*$_3$), 1.74-1.90 (m, 2H, C*H*$_2$), 3.71 (s, 3H, OC*H*$_3$), 3.85 (s, br, 1H, N*H*), 4.17 (t, 1H, *J* 6.6, NC*H*), 6.58 [$(AX)_2$, 2H, Ar*H*], 6.72 [$(AX)_2$, 2H, Ar*H*], 7.20 - 7.37 (m, 5H, Ar*H*); δ_C (63 MHz, $CDCl_3$) 11.0 (CH_2CH_3), 31.8 (CH_2CH_3), 55.8 (OCH$_3$), 60.7 (N*C*H), 114.6 (2 × Ar*C*H), 114.9 (2 × Ar*C*H), 126.7 (2 × Ar*C*H), 127.0 (Ar*C*H), 128.6 (2 × Ar*C*H), 142.0 (Ar*C*), 144.3 (Ar*C*), 152.0 (Ar*C*); Enantiomeric excess was determined by chiral phase HPLC (Chiralcel OD-H) 5% ipa in hexane @ 1 mL min^{-1}, t_R = 7.0 min (minor), t_R = 7.7 min (major); Data was in accordance with the literature.

(*S*)-*N*-[2-(4'-Phenylbutyl)]-4-methoxyaniline 235[166]



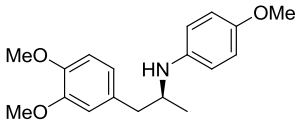
Obtained using general procedure H as light yellow oil (82% yield, 14% ee); $[\alpha]_D$ +0.7 (*c* 5.1 in $CHCl_3$, 14% ee, lit.[166] -4.0, *c* 2.06 in $CHCl_3$, 91% ee, *R* isomer); δ_H (250 MHz, $CDCl_3$) 1.25 (d, 3H, *J* 6.3, C*H*$_3$), 1.72 - 2.00 (m, 2H, C*H*$_2$), 2.78 (t, 2H, *J* 7.8, C*H*$_2$), 3.17 (br, s, 1H, N*H*), 3.46 (m, 1H, NC*H*), 3.80 (s, 3H, OCH_3), 6.57 [$(AX)_2$, 2H, Ar*H*], 6.83 [$(AX)_2$, 2H, Ar*H*], 7.22 - 7.37 (m, 5H, Ar*H*); δ_C (63 MHz, $CDCl_3$) 20.9 (*C*H_3), 32.6 (*C*H_2), 38.9 (*C*H_2), 49.0 (N*C*H), 55.9 (O*C*H_3), 114.8 (2 × Ar*C*H), 115.0 (2 × Ar*C*H), 125.9 (Ar*C*H), 128.4 (2 × Ar*C*H), 128.5 (2 × Ar*C*H), 141.9 (Ar*C*), 142.2 (Ar*C*), 151.9 (Ar*C*); Enantiomeric excess was determined by chiral phase HPLC (Chiralcel OD-H) 5% ipa in hexane @ 1 mL min^{-1}, t_R = 10.7 min (minor), t_R = 11.8 min (major); Data was in accordance with the literature.

(±)-(*E*)-*N*-(4-Phenylbut-3-en-2-yl)-4-methoxyaniline 236[65]



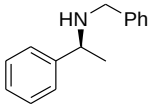
Obtained using general procedure H as yellow oil (77% yield, 0% ee); δ_H (250 MHz, $CDCl_3$) 1.41 (d, 3H, *J* 7.6, C*H*$_3$), 3.45 (s, br, 1H, N*H*), 3.76 (s, OCH_3), 4.04 - 4.14 (m, 1H, NC*H*), 6.24 (dd, 1H, *J* 16.0, 6.0, C*H*CH), 6.55 - 6.68 (m, 3H, 2 ×Ar*H* and CH=C*H*), 6.76 - 6.81 (m, 2H, Ar*H*), 7.20 - 7.40 (m, 5H, Ar*H*); δ_C (63 MHz, $CDCl_3$) 22.2 (*C*H_3), 51.9 (N*C*H), 55.8 (O*C*H_3), 115.0 (2 × Ar*C*H), 115.1 (2 × Ar*C*H), 126.5 (2 × Ar*C*H), 127.4 (Ar*C*H), 128.6 (2 × Ar*C*H), 129.4 (*C*H), 133.7 (*C*H), 137.2 (Ar*C*), 141.8 (Ar*C*), 152.2 (Ar*C*); Enantiomeric excess was determined by chiral phase HPLC (Kromasil 3-Cellucoat OD-H) 5% ipa in hexane @ 1 mL min^{-1}, t_R = 10.2 min, t_R = 11.9 min; Data was in accordance with the literature.

(*S*)-*N*-[2-(3',4'-Dimethoxyphenylpropyl)]-4-methoxyaniline 237[167]



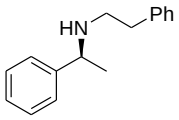
Obtained using general procedure H as light yellow oil (81% yield); $[\alpha]_D$ +4.5 (*c* 1.0 in $CHCl_3$, 15% ee, lit.[167] -3.5, *c* 0.3 in $CHCl_3$, 66% ee *R* isomer); δ_H (250 MHz, $CDCl_3$) 1.15 (d, 3H, *J* 6.3Hz , C*H*$_3$), 2.70 (dd, 1H, *J* 13.5, 6.9, C*H*$_2$), 2.84 (dd, 1H, *J* 13.5, 4.7, C*H*$_2$), 3.27 (s, br, 1H, N*H*), 3.62 - 3.72 (m, 1H, NC*H*), 3.72 (s, 3H, OC*H*$_3$), 3.86 (s, 3H, OC*H*$_3$), 3.88 (s, 3H, OC*H*$_3$), 6.60 - 6.84 (m, 7H, Ar*H*); δ_H (63 MHz, $CDCl_3$) 20.3 (*C*H$_3$), 41.7 (*C*H$_2$), 50.3 (N*C*H), 55.8 (O*C*H$_3$), 55.9 (2 × O*C*H$_3$), 111.3 (Ar*C*H), 113.0 (Ar*C*H), 115.0 (4 × Ar*C*H), 121.6 (Ar*C*H), 131.2 (Ar*C*), 141.6 (Ar*C*), 147.6 (Ar*C*), 148.8 (Ar*C*), 152.1 (Ar*C*); Enantiomeric excess was determined by chiral phase HPLC (Phenomenex Lux Cellulose-2) 5% ipa in hexane @ 1 mL min^{-1}, t_R = 29.4 min (minor), t_R = 34.9 min (major); Data was in accordance with the literature.

(*S*)-*N*-Benzyl-1-phenylethylamine 238[168]



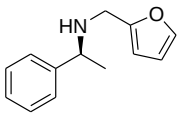
Obtained using general procedure I as a colourless oil (63% yield); $[\alpha]_D$ -44.3 (*c* 0.7 in EtOH, 80% ee, lit.[168] -41.1, *c* 0.6 in EtOH, 91% ee) δ_H (250 MHz, $CDCl_3$) 1.39 (d, 3H, *J* 6.6, C*H*$_3$), 1.59 (br s, 1H, N*H*), 3.60 (d, 1H, *J* 13.1, 1 × PhC*H*$_2$), 3.68 (d, 1H, *J* 13.1, 1 × PhC*H*$_2$), 3.84 (q, 1H, *J* 6.6, NC*H*), 7.23 - 7.41 (m, 10H, Ar*H*); δ_C (63 MHz, $CDCl_3$) 24.5 (*C*H$_3$), 51.7 (NCH$_2$), 57.6 (N*C*H), 126.8 (2 × Ar*C*H), 126.9 (2 × Ar*C*H), 127.0 (Ar*C*H), 128.2 (Ar*C*H), 128.4 (2 × Ar*C*H), 128.5 (2 × Ar*C*H), 140.7 (Ar*C*), 145.7 (Ar*C*); Enantiomeric excess was determined by comparison of the integrals in the ^{1}H NMR spectrum in $CDCl_3$ of the diastereomeric salts formed by addition of excess L-mandelic acid. Data was in accordance with the literature.

(*S*)-*N*-(2-Phenylethyl)-1-phenylethylamine 239[154]



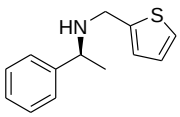
Obtained using general procedure I as a light yellow oil (65% yield); $[\alpha]_D$ -47.8 (*c* 1.1 in $CHCl_3$, 86% ee, lit.[154] +54.2, *c* 2.84 in $CHCl_3$, 97% ee *R*-isomer); δ_H (250 MHz, $CDCl_3$) 1.34 (d, 3H, *J* 6.6, C*H*$_3$), 2.70 - 2.84 (m, 4H, C*H*$_2$C*H*$_2$), 3.81 (q, 1H, *J* 6.6, NC*H*), 7.16-7.36 (m, 10H, Ar*H*); δ_C (63 MHz, $CDCl_3$) 24.3 (*C*H$_3$), 36.5 (*C*H$_2$Ph), 48.9 (N*C*H$_2$), 58.2 (N*C*H), 126.1 (Ar*C*H), 126.6 (2 × Ar*C*H), 126.9 (Ar*C*H), 128.4 (4 × Ar*C*H), 128.7 (2 × Ar*C*H), 140.1 (Ar*C*), 145.7 (Ar*C*); Enantiomeric excess was determined by comparison of the integrals in the ^{1}H NMR spectrum in $CDCl_3$ of the diastereomeric salts formed by addition of excess L-mandelic acid; Data was in general accordance with the literature – the signal at δ 145.7 ppm is missing in the reported ^{13}C NMR data in reference 154.

(*S*)-*N*-(Furan-2-ylmethyl)-1-phenylethylamine 240[169]



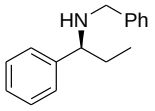
Obtained using general procedure I as a colourless oil (65% yield); $[\alpha]_D$ -78 (*c* 0.4 in $CHCl_3$, 86% ee, $[\alpha]_D$ not reported in literature); δ_H (250 MHz) 1.38 (d, 3H, *J* 6.6, C*H*$_3$), 1.66 (s, br, 1H, N*H*), 3.59 (d, 1H, *J* 14.4, 2 × NC*H*$_2$), 3.69 (d, 1H, *J* 14.4, 2 × NC*H*$_2$), 3.80 (q, 1H, *J* 6.6, NC*H*), 6.12 (dd, 1H, *J* 0.4, 3.1, Ar*H*), 6.32 (dd, 1H, *J* 1.8, 3.1, Ar*H*), 7.23 - 7.40 (m, 6H, Ar*H*); δ_C (63 MHz, $CDCl_3$) 24.3 (*C*H$_3$), 44.0 (N*C*H$_2$), 57.1(N*C*H), 106.8 (Ar*C*H), 110.1 (Ar*C*H), 126.8 (2 × Ar*C*H), 127.0 (Ar*C*H), 128.5 (2 × Ar*C*H), 141.7 (Ar*C*H), 145.1 (Ar*C*), 154.1 (Ar*C*); Enantiomeric excess was determined by comparison of the integrals in the ^{1}H NMR spectrum in $CDCl_3$ of the diastereomeric salts formed by addition of excess L-mandelic acid; Data was in accordance with the literature.

(*S*)-*N*-(Thiophen-2-ylmethyl)-1-phenylethylamine 241



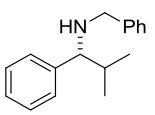
Obtained using general procedure I as a yellow oil (64% yield); $[\alpha]_D$ -42.5 (*c* 0.8 in $CHCl_3$, 83% ee); ν_{max} (ATR) / cm^{-1} 2963, 1492, 1451; δ_H (400 MHz, $CDCl_3$) 1.40 (d, 3H, *J* 6.6, C*H*$_3$), 1.65 (br s, 1H, N*H*), 3.81 - 3.89 (m, 2H, C*H*$_2$), 3.88 (q, 1H, *J* 6.6, NC*H*), 6.88 - 6.89 (m, 1H, Ar*H*), 6.96 (dd, 1H, *J* 3.4, 5.1, Ar*H*), 7.23 (dd, 1H, *J* 1.2, 5.1, Ar*H*), 7.26 - 7.31 (m, 1H, Ar*H*), 7.35 - 7.39 (m, 4H, Ar*H*); δ_C (100 MHz, $CDCl_3$) 24.4 (*C*H$_3$), 46.1 (NCH$_2$), 57.1 (N*C*H), 124.3 (Ar*C*H), 124.7 (Ar*C*H), 126.6 (Ar*C*H), 126.8 (2 × Ar*C*H), 127.1 (Ar*C*H), 128.5 (2 × Ar*C*H), 144.5 (Ar*C*), 145.2 (Ar*C*); *m/z* (EI^+) 217.0923 (4%, M^+, $C_{13}H_{15}NS$ requires 217.0925), 202 (60), 97 (100); Enantiomeric excess was determined by comparison of the integrals in the ^{1}H NMR spectrum in $CDCl_3$ of the diastereomeric salts formed by addition of excess L-mandelic acid.

(*S*)-*N*-Benzyl-1-phenylpropylamine 142[84]



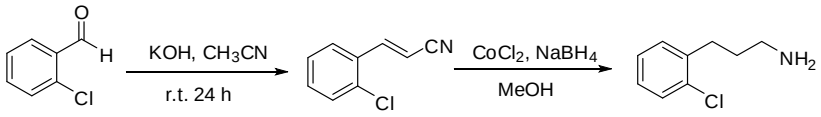
Obtained using general procedure I as a colourless oil (66% yield); $[\alpha]_D$ -37 (*c* 1.0 in $CHCl_3$, 73% ee, lit.[84] +32, *c* 0.2 in $CHCl_3$, 89% ee for *R*-isomer); δ_H (400 MHz, $CDCl_3$) 0.86 (t, 3H, *J* 7.4, C*H*$_3$), 1.65 - 1.87 (m, 3H, C*H*$_2$ and N*H*), 3.57 - 3.61 (m, 2H, NC*H* and 2 × NC*H*$_2$), 3.71 (d, 1H, *J* 13.2, 2 × NC*H*$_2$), 7.27 - 7.42 (m, 10H, Ar*H*); δ_C (100 MHz, $CDCl_3$) 10.8 (*C*H$_3$), 31.2 (*C*H$_2$), 51.6 (NCH$_2$), 64.2 (N*C*H), 126.8 (Ar*C*H), 126.9 (Ar*C*H), 127.5 (2 × Ar*C*H), 128.2 (2 × Ar*C*H), 128.3 (4 × Ar*C*H), 140.8 (Ar*C*), 144.1 (Ar*C*); Enantiomeric excess was determined by comparison of the integrals in the ^{1}H NMR spectrum in $CDCl_3$ of the diastereomeric salts formed by addition of excess L-mandelic acid; Data was in accordance with the literature.

(*R*)-*N*-Benzyl-2-methyl-1-phenylpropylamine 243[170]



Obtained using general procedure I as a colourless oil (62% yield); $[\alpha]_D$ +56 (*c* 1.05 in $CHCl_3$, 76% ee, lit.[170] +63.1, *c* 1.4 in $CHCl_3$ 94% ee for *R* isomer); δ_H (400 MHz, $CDCl_3$) 0.77 (d, 3H, *J* 6.8, C*H*$_3$), 1.00 (d, 3H, *J* 6.6, C*H*$_3$), 1.61 (br s, 1H, N*H*), 1.86 - 1.92 (m, 1H, C*H*), 3.37 (d, 1H, *J* 9.0, NC*H*), 3.49 (d, 1H, *J* 13.3, 2 × NC*H*$_2$), 3.67 (d, 1H, *J* 13.3, 2 × NC*H*$_2$), 7.24 - 7.38 (m, 10H, Ar*H*); δ_C (100 MHz, $CDCl_3$) 19.5 (*C*H$_3$), 19.7 (*C*H$_3$), 34.5 (*C*H), 51.8 (N*C*H$_2$), 68.8 (N*C*H), 126.8 (2 × Ar*C*H), 128.0 (2 × Ar*C*H), 128.2 (4 × Ar*C*H), 128.3 (2 × Ar*C*H), 141.0 (Ar*C*), 142.9 (Ar*C*); Enantiomeric excess was determined by comparison of the integrals in the ^{1}H NMR spectrum in $CDCl_3$ of the diastereomeric salts formed by addition of excess L-mandelic acid; Data was in accordance with the literature.

3-(2-Chlorophenyl)-propylamine

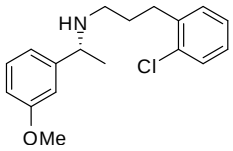


KOH powder (2 g, 36.1 mmol) and 2-chlorobenzaldehyde (5.07 g, 36.1 mmol) were stirred in acetonitrile (300 mL) at room temperature for 24 h and then poured into a 1:1 mixture of ice-water (300 g). The mixture was extracted with dichloromethane (3 × 150 mL), the combined extracts washed with brine (50 mL) and dried over $MgSO_4$. After filtration, the filtrate was concentrated and the residue was purified by chromatography on silica gel (5% ~ 17% ethyl acetate in petroleum ether) to give 1.57 g 2-chloro-cinnamonitrile as white solid; mp 35-37 ºC (not reported in literature); δ_H (250 MHz, $CDCl_3$) 5.92 (d, 1H, *J* 16.6, C*H*), 7.28 - 7.48 (m, 3H, Ar*H*), 7.56 (dd, 1H, *J* 1.9, 7.5, Ar*H*), 7.51 (d, 1H, *J* 16.6, C*H*); δ_C (63 MHz, $CDCl_3$) 99.0 (*C*H), 117.8 (*C*N), 127.0 (*C*H), 127.4 (*C*H), 130.3 (*C*H), 131.6 (*C*), 132.1 (*C*H), 134.4 (*C*), 146.3 (*C*H); ^{13}C NMR not reported in the literature, while reported ^{1}H NMR data is at much lower resolution.[171]

A suspension of 2-chloro-cinnamonitrile (1.57 g, 9.6 mmol) and $CoCl_2$ (2.42 g, 18.6 mmol) in MeOH (60 mL) was cooled to 0 ºC under N_2 atmosphere. $NaBH_4$ (3.5 g, 93 mmol) was added portionwise over 30 min. The resulting mixture was allowed to warm to room temperature and stirred overnight. 6*N* HCl (20 mL) was added, and the reaction carefully

basified with 2*N* aqueous NaOH to pH 11. The resulting mixture was extracted with diethyl ether (3 × 150 mL), the combined organic phases washed with brine (50 mL) and dried over $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure to afford the desired amine (1.2 g) as light brown oil; δ_H (250 MHz, $CDCl_3$) 1.14 (br s, 2H, N*H*$_2$), 1.73 - 1.85 (m, 2H, C*H*$_2$), 2.70 - 2.82 (m, 4H, 2 × C*H*$_2$), 7.11 - 7.37 (m, 4H, Ar*H*); δ_C (63 MHz, $CDCl_3$) 30.9 (*C*H$_2$), 33.9 (*C*H$_2$), 41.9 (*C*H$_2$), 126.7 (Ar*C*H), 127.3 (Ar*C*H), 129.5 (Ar*C*H), 130.3 (Ar*C*H), 139.7 (Ar*C*H); Data was in general accordance with the literature, although one signal in the ^{13}C NMR was ambiguous due to the low concentration of the sample.[152]

(*R*)-3-(2-Chlorophenyl)-*N*-(1-(3-methoxyphenyl)ethyl)propan-1-amine 6 [(+)-NPS R-56][172]



Obtained using general procedure I as a light brown oil, except 2 mL of CH_2Cl_2 was used with 1 mol% of (*R*)-**117** as catalyst (67% yield); $[\alpha]_D$ +41.2 (*c* 0.8 in $CHCl_3$, 89% ee; lit.[172] +41.9, *c* 1.1 in $CHCl_3$ assumed to be 100% ee); δ_H (250 MHz, $CDCl_3$) 1.37 (d, 3H, *J* 6.6, C*H*$_3$), 1.74 - 1.89 (m, 2H, C*H*$_2$), 2.47 - 2.65 (m, 2H, C*H*$_2$), 2.68 - 2.86 (m, 2H, C*H*$_2$), 3.77 (q, 1H, *J* 6.6, NC*H*), 3.84 (s, 3H, OC*H*$_3$), 6.80 (ddd, 1H, *J* 1.0, 2.4, 8.3, Ar*H*), 6.91 - 6.93 (m, 2H, Ar*H*), 7.09 - 7.35 (m, 5H, Ar*H*); δ_H (63 MHz, $CDCl_3$) 24.3 (*C*H$_3$), 30.2 (*C*H$_2$), 31.3 (*C*H$_2$), 47.3 (*C*H$_2$), 55.2 (O*C*H$_3$), 58.3 (N*C*H), 112.1 (Ar*C*H), 112.2 (Ar*C*H), 119.0 (Ar*C*H), 126.7 (Ar*C*H), 127.2 (Ar*C*H), 129.4 (2 × Ar*C*H), 130.3 (Ar*C*H), 133.9 (Ar*C*), 139.8 (Ar*C*), 147.7 (Ar*C*), 159.8 (Ar*C*); Enantiomeric excess was determined by comparison of the integrals in the ^{1}H NMR spectrum in $CDCl_3$ of the diastereomeric salts formed by addition of excess L-mandelic acid; Data was in general agreement with the literature, although ^{13}C NMR data in reference 172 has an additional signal and data has been mis-assigned.

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Appendix 1 Crystal structure of the salt of amine **144**

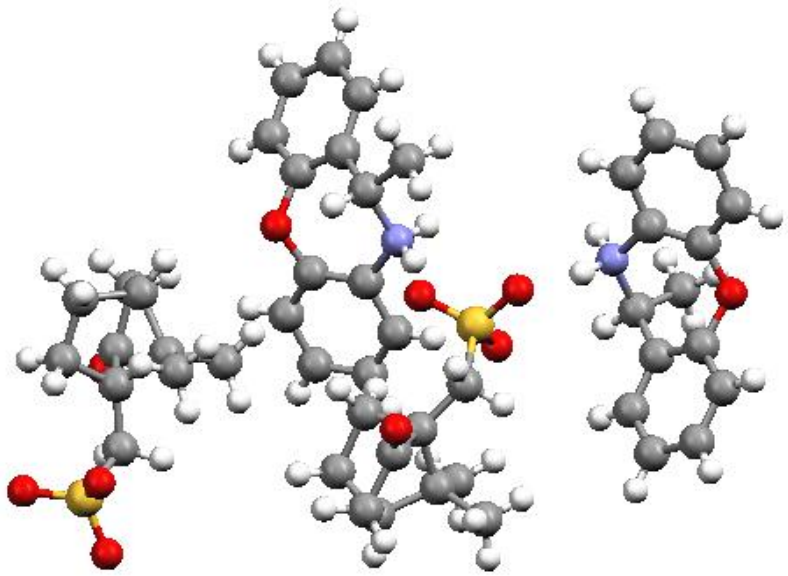


Table 1. Crystal data and structure refinement for OSJ230P1.

Identification code	osj230p1	
Empirical formula	C24 H29 N O5 S	
Formula weight	443.54	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P1	
Unit cell dimensions	a = 7.4795(2) Å	α= 93.8720(10)°.
	b = 11.7976(4) Å	β= 95.2810(10)°.
	c = 13.1065(4) Å	γ = 104.7550(10)°.
Volume	1108.65(6) $Å^3$	
Z	2	
Density (calculated)	1.329 Mg/m^3	
Absorption coefficient	0.182 mm^{-1}	
F(000)	472	
Crystal size	0.42 x 0.38 x 0.32 mm^3	
Theta range for data collection	2.83 to 27.57°.	
Index ranges	-9<=h<=9, -15<=k<=15, -16<=l<=17	

Reflections collected	14299
Independent reflections	5102 [R(int) = 0.0174]
Completeness to theta = 27.57°	99.3 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9441 and 0.9275
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5102 / 3 / 565
Goodness-of-fit on F^2	0.961
Final R indices [I>2sigma(I)]	R1 = 0.0282, wR2 = 0.0763
R indices (all data)	R1 = 0.0285, wR2 = 0.0767
Absolute structure parameter	?
Largest diff. peak and hole	0.354 and -0.254 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for OSJ230P1. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S(1)	5652(1)	6332(1)	4249(1)	22(1)
S(2)	4080(1)	3429(1)	11167(1)	22(1)
N(1)	6250(2)	6652(1)	1593(1)	18(1)
N(2)	2566(2)	3352(1)	3825(1)	21(1)
O(1)	8916(2)	8618(1)	631(1)	24(1)
O(2)	396(2)	1488(2)	5044(1)	33(1)
O(3)	5240(2)	7073(1)	3446(1)	28(1)
O(4)	6858(2)	5609(1)	3939(1)	29(1)
O(5)	3965(2)	5640(1)	4619(1)	30(1)
O(6)	6057(2)	3585(2)	11424(1)	36(1)
O(7)	3610(2)	4557(1)	11081(1)	26(1)
O(8)	2921(2)	2702(1)	11845(1)	33(1)
C(1)	5757(2)	7486(2)	906(1)	19(1)
C(2)	3849(3)	7353(2)	684(2)	26(1)
C(3)	3189(3)	8079(2)	38(2)	32(1)
C(4)	4428(3)	8941(2)	-399(2)	32(1)
C(5)	6322(3)	9090(2)	-165(2)	28(1)
C(6)	7007(3)	8384(2)	500(1)	20(1)
C(7)	9857(2)	8635(2)	1603(1)	20(1)
C(8)	11173(3)	9670(2)	1977(2)	25(1)
C(9)	12237(3)	9705(2)	2913(2)	28(1)
C(10)	11987(3)	8720(2)	3452(2)	28(1)
C(11)	10645(3)	7689(2)	3073(2)	23(1)
C(12)	9572(2)	7631(2)	2130(1)	19(1)
C(13)	8195(2)	6496(2)	1687(1)	19(1)
C(14)	8610(3)	5970(2)	667(2)	25(1)
C(15)	3352(3)	2634(2)	4525(1)	21(1)
C(16)	5289(3)	2882(2)	4651(2)	26(1)
C(17)	6181(3)	2259(2)	5290(2)	30(1)
C(18)	5137(3)	1360(2)	5796(2)	32(1)
C(19)	3219(3)	1113(2)	5669(2)	30(1)
C(20)	2310(3)	1753(2)	5048(2)	25(1)
C(21)	-698(3)	1234(2)	4100(2)	26(1)

C(22)	-1911(3)	122(2)	3874(2)	35(1)
C(23)	-3118(3)	-114(2)	2980(2)	38(1)
C(24)	-3122(3)	746(2)	2317(2)	34(1)
C(25)	-1904(3)	1862(2)	2545(2)	27(1)
C(26)	-685(2)	2120(2)	3451(2)	22(1)
C(27)	539(3)	3338(2)	3798(2)	21(1)
C(28)	219(3)	4288(2)	3126(2)	28(1)
C(29)	6869(3)	7385(2)	5268(1)	22(1)
C(30)	7420(3)	6998(2)	6309(1)	20(1)
C(31)	6216(3)	5838(2)	6670(2)	27(1)
C(32)	7454(3)	5603(2)	7611(2)	33(1)
C(33)	9171(3)	6659(2)	7717(2)	29(1)
C(34)	8519(4)	7722(2)	8114(2)	34(1)
C(35)	7353(3)	7931(2)	7168(2)	26(1)
O(10)	6519(3)	8685(1)	7101(1)	36(1)
C(38)	10936(3)	8014(2)	6474(2)	41(1)
C(39)	9899(4)	5857(2)	5969(2)	39(1)
C(40)	3547(3)	2627(2)	9927(2)	22(1)
C(41)	1663(2)	2492(2)	9312(1)	19(1)
C(42)	-42(3)	2546(2)	9899(2)	31(1)
C(43)	-1521(3)	2705(2)	9053(2)	40(1)
C(44)	-565(3)	2669(2)	8074(2)	34(1)
C(48)	-497(3)	1395(2)	7830(2)	29(1)
C(49)	995(3)	1293(2)	8666(2)	26(1)
O(9)	1539(3)	436(1)	8804(2)	47(1)
C(45)	1499(3)	3314(2)	8448(2)	28(1)
C(46)	1823(4)	4609(2)	8813(2)	41(1)
C(47)	2840(4)	3245(2)	7635(2)	44(1)
C(37)	9443(3)	6881(2)	6581(2)	26(1)

Table 3. Bond lengths [Å] and angles [°] for OSJ230P1.

S(1)-O(4)	1.4558(15)
S(1)-O(5)	1.4604(15)
S(1)-O(3)	1.4726(15)
S(1)-C(29)	1.7703(19)
S(2)-O(6)	1.4470(16)
S(2)-O(8)	1.4638(15)
S(2)-O(7)	1.4686(15)
S(2)-C(40)	1.783(2)
N(1)-C(1)	1.470(2)
N(1)-C(13)	1.507(2)
N(1)-H(1A)	0.9200
N(1)-H(1B)	0.9200
N(2)-C(15)	1.471(2)
N(2)-C(27)	1.509(2)
N(2)-H(2A)	0.9200
N(2)-H(2B)	0.9200
O(1)-C(6)	1.375(2)
O(1)-C(7)	1.394(2)
O(2)-C(20)	1.385(2)
O(2)-C(21)	1.390(3)
C(1)-C(6)	1.394(3)
C(1)-C(2)	1.396(2)
C(2)-C(3)	1.389(3)
C(2)-H(2)	0.9500
C(3)-C(4)	1.386(3)
C(3)-H(3)	0.9500
C(4)-C(5)	1.385(3)
C(4)-H(4)	0.9500
C(5)-C(6)	1.395(3)
C(5)-H(5)	0.9500
C(7)-C(8)	1.385(2)
C(7)-C(12)	1.390(2)
C(8)-C(9)	1.391(3)
C(8)-H(8)	0.9500
C(9)-C(10)	1.383(3)
C(9)-H(9)	0.9500

C(10)-C(11)	1.392(3)
C(10)-H(10)	0.9500
C(11)-C(12)	1.398(3)
C(11)-H(11)	0.9500
C(12)-C(13)	1.508(2)
C(13)-C(14)	1.527(2)
C(13)-H(13)	1.0000
C(14)-H(14A)	0.9800
C(14)-H(14B)	0.9800
C(14)-H(14C)	0.9800
C(15)-C(20)	1.392(3)
C(15)-C(16)	1.394(3)
C(16)-C(17)	1.385(3)
C(16)-H(16)	0.9500
C(17)-C(18)	1.394(3)
C(17)-H(17)	0.9500
C(18)-C(19)	1.381(3)
C(18)-H(18)	0.9500
C(19)-C(20)	1.392(3)
C(19)-H(19)	0.9500
C(21)-C(22)	1.386(3)
C(21)-C(26)	1.390(3)
C(22)-C(23)	1.377(4)
C(22)-H(22)	0.9500
C(23)-C(24)	1.381(4)
C(23)-H(23)	0.9500
C(24)-C(25)	1.392(3)
C(24)-H(24)	0.9500
C(25)-C(26)	1.394(3)
C(25)-H(25)	0.9500
C(26)-C(27)	1.508(2)
C(27)-C(28)	1.523(3)
C(27)-H(27)	1.0000
C(28)-H(28A)	0.9800
C(28)-H(28B)	0.9800
C(28)-H(28C)	0.9800
C(29)-C(30)	1.523(2)
C(29)-H(29A)	0.9900

C(29)-H(29B)	0.9900
C(30)-C(35)	1.534(3)
C(30)-C(37)	1.565(3)
C(30)-C(31)	1.564(3)
C(31)-C(32)	1.556(3)
C(31)-H(31A)	0.9900
C(31)-H(31B)	0.9900
C(32)-C(33)	1.533(3)
C(32)-H(32A)	0.9900
C(32)-H(32B)	0.9900
C(33)-C(34)	1.534(3)
C(33)-C(37)	1.552(3)
C(33)-H(33)	1.0000
C(34)-C(35)	1.521(3)
C(34)-H(34A)	0.9900
C(34)-H(34B)	0.9900
C(35)-O(10)	1.213(3)
C(38)-C(37)	1.533(3)
C(38)-H(38A)	0.9800
C(38)-H(38B)	0.9800
C(38)-H(38C)	0.9800
C(39)-C(37)	1.532(3)
C(39)-H(39A)	0.9800
C(39)-H(39B)	0.9800
C(39)-H(39C)	0.9800
C(40)-C(41)	1.523(2)
C(40)-H(40A)	0.9900
C(40)-H(40B)	0.9900
C(41)-C(49)	1.539(2)
C(41)-C(45)	1.555(2)
C(41)-C(42)	1.561(3)
C(42)-C(43)	1.548(3)
C(42)-H(42A)	0.9900
C(42)-H(42B)	0.9900
C(43)-C(44)	1.529(4)
C(43)-H(43A)	0.9900
C(43)-H(43B)	0.9900
C(44)-C(48)	1.530(3)

C(44)-C(45)	1.554(3)
C(44)-H(44)	1.0000
C(48)-C(49)	1.524(3)
C(48)-H(48A)	0.9900
C(48)-H(48B)	0.9900
C(49)-O(9)	1.201(3)
C(45)-C(46)	1.521(3)
C(45)-C(47)	1.542(3)
C(46)-H(46A)	0.9800
C(46)-H(46B)	0.9800
C(46)-H(46C)	0.9800
C(47)-H(47A)	0.9800
C(47)-H(47B)	0.9800
C(47)-H(47C)	0.9800

O(4)-S(1)-O(5)	112.35(9)
O(4)-S(1)-O(3)	112.64(9)
O(5)-S(1)-O(3)	112.21(9)
O(4)-S(1)-C(29)	108.92(9)
O(5)-S(1)-C(29)	107.52(9)
O(3)-S(1)-C(29)	102.58(8)
O(6)-S(2)-O(8)	114.01(10)
O(6)-S(2)-O(7)	112.14(9)
O(8)-S(2)-O(7)	111.44(10)
O(6)-S(2)-C(40)	104.84(10)
O(8)-S(2)-C(40)	105.95(9)
O(7)-S(2)-C(40)	107.85(9)
C(1)-N(1)-C(13)	119.86(13)
C(1)-N(1)-H(1A)	107.4
C(13)-N(1)-H(1A)	107.4
C(1)-N(1)-H(1B)	107.4
C(13)-N(1)-H(1B)	107.4
H(1A)-N(1)-H(1B)	106.9
C(15)-N(2)-C(27)	119.89(14)
C(15)-N(2)-H(2A)	107.3
C(27)-N(2)-H(2A)	107.3
C(15)-N(2)-H(2B)	107.3
C(27)-N(2)-H(2B)	107.3

H(2A)-N(2)-H(2B)	106.9
C(6)-O(1)-C(7)	120.42(14)
C(20)-O(2)-C(21)	118.14(16)
C(6)-C(1)-C(2)	119.31(17)
C(6)-C(1)-N(1)	125.94(15)
C(2)-C(1)-N(1)	114.73(16)
C(3)-C(2)-C(1)	120.77(19)
C(3)-C(2)-H(2)	119.6
C(1)-C(2)-H(2)	119.6
C(2)-C(3)-C(4)	119.99(18)
C(2)-C(3)-H(3)	120.0
C(4)-C(3)-H(3)	120.0
C(5)-C(4)-C(3)	119.33(19)
C(5)-C(4)-H(4)	120.3
C(3)-C(4)-H(4)	120.3
C(4)-C(5)-C(6)	121.35(19)
C(4)-C(5)-H(5)	119.3
C(6)-C(5)-H(5)	119.3
O(1)-C(6)-C(5)	114.33(17)
O(1)-C(6)-C(1)	126.37(16)
C(5)-C(6)-C(1)	119.16(17)
C(8)-C(7)-C(12)	122.13(17)
C(8)-C(7)-O(1)	116.61(17)
C(12)-C(7)-O(1)	121.10(16)
C(7)-C(8)-C(9)	118.80(18)
C(7)-C(8)-H(8)	120.6
C(9)-C(8)-H(8)	120.6
C(10)-C(9)-C(8)	120.32(18)
C(10)-C(9)-H(9)	119.8
C(8)-C(9)-H(9)	119.8
C(9)-C(10)-C(11)	120.29(18)
C(9)-C(10)-H(10)	119.9
C(11)-C(10)-H(10)	119.9
C(10)-C(11)-C(12)	120.29(18)
C(10)-C(11)-H(11)	119.9
C(12)-C(11)-H(11)	119.9
C(7)-C(12)-C(11)	118.15(16)
C(7)-C(12)-C(13)	121.33(16)

C(11)-C(12)-C(13)	120.49(16)
C(12)-C(13)-N(1)	110.16(14)
C(12)-C(13)-C(14)	115.11(15)
N(1)-C(13)-C(14)	110.62(14)
C(12)-C(13)-H(13)	106.8
N(1)-C(13)-H(13)	106.8
C(14)-C(13)-H(13)	106.8
C(13)-C(14)-H(14A)	109.5
C(13)-C(14)-H(14B)	109.5
H(14A)-C(14)-H(14B)	109.5
C(13)-C(14)-H(14C)	109.5
H(14A)-C(14)-H(14C)	109.5
H(14B)-C(14)-H(14C)	109.5
C(20)-C(15)-C(16)	119.64(17)
C(20)-C(15)-N(2)	124.86(17)
C(16)-C(15)-N(2)	115.50(16)
C(17)-C(16)-C(15)	120.50(19)
C(17)-C(16)-H(16)	119.7
C(15)-C(16)-H(16)	119.7
C(16)-C(17)-C(18)	119.84(19)
C(16)-C(17)-H(17)	120.1
C(18)-C(17)-H(17)	120.1
C(19)-C(18)-C(17)	119.58(19)
C(19)-C(18)-H(18)	120.2
C(17)-C(18)-H(18)	120.2
C(18)-C(19)-C(20)	121.02(19)
C(18)-C(19)-H(19)	119.5
C(20)-C(19)-H(19)	119.5
O(2)-C(20)-C(19)	115.76(18)
O(2)-C(20)-C(15)	124.78(17)
C(19)-C(20)-C(15)	119.38(19)
C(22)-C(21)-C(26)	121.6(2)
C(22)-C(21)-O(2)	118.44(19)
C(26)-C(21)-O(2)	119.70(18)
C(23)-C(22)-C(21)	119.2(2)
C(23)-C(22)-H(22)	120.4
C(21)-C(22)-H(22)	120.4
C(22)-C(23)-C(24)	120.44(19)

C(22)-C(23)-H(23)	119.8
C(24)-C(23)-H(23)	119.8
C(23)-C(24)-C(25)	120.2(2)
C(23)-C(24)-H(24)	119.9
C(25)-C(24)-H(24)	119.9
C(24)-C(25)-C(26)	120.2(2)
C(24)-C(25)-H(25)	119.9
C(26)-C(25)-H(25)	119.9
C(21)-C(26)-C(25)	118.37(18)
C(21)-C(26)-C(27)	118.49(18)
C(25)-C(26)-C(27)	122.97(17)
C(26)-C(27)-N(2)	110.55(14)
C(26)-C(27)-C(28)	114.51(16)
N(2)-C(27)-C(28)	107.35(15)
C(26)-C(27)-H(27)	108.1
N(2)-C(27)-H(27)	108.1
C(28)-C(27)-H(27)	108.1
C(27)-C(28)-H(28A)	109.5
C(27)-C(28)-H(28B)	109.5
H(28A)-C(28)-H(28B)	109.5
C(27)-C(28)-H(28C)	109.5
H(28A)-C(28)-H(28C)	109.5
H(28B)-C(28)-H(28C)	109.5
C(30)-C(29)-S(1)	120.47(13)
C(30)-C(29)-H(29A)	107.2
S(1)-C(29)-H(29A)	107.2
C(30)-C(29)-H(29B)	107.2
S(1)-C(29)-H(29B)	107.2
H(29A)-C(29)-H(29B)	106.8
C(29)-C(30)-C(35)	109.67(15)
C(29)-C(30)-C(37)	119.80(16)
C(35)-C(30)-C(37)	100.19(15)
C(29)-C(30)-C(31)	119.54(16)
C(35)-C(30)-C(31)	102.77(15)
C(37)-C(30)-C(31)	102.01(15)
C(32)-C(31)-C(30)	103.58(16)
C(32)-C(31)-H(31A)	111.0
C(30)-C(31)-H(31A)	111.0

C(32)-C(31)-H(31B)	111.0
C(30)-C(31)-H(31B)	111.0
H(31A)-C(31)-H(31B)	109.0
C(33)-C(32)-C(31)	103.42(16)
C(33)-C(32)-H(32A)	111.1
C(31)-C(32)-H(32A)	111.1
C(33)-C(32)-H(32B)	111.1
C(31)-C(32)-H(32B)	111.1
H(32A)-C(32)-H(32B)	109.0
C(32)-C(33)-C(34)	105.8(2)
C(32)-C(33)-C(37)	102.81(16)
C(34)-C(33)-C(37)	103.08(16)
C(32)-C(33)-H(33)	114.6
C(34)-C(33)-H(33)	114.6
C(37)-C(33)-H(33)	114.6
C(35)-C(34)-C(33)	101.86(16)
C(35)-C(34)-H(34A)	111.4
C(33)-C(34)-H(34A)	111.4
C(35)-C(34)-H(34B)	111.4
C(33)-C(34)-H(34B)	111.4
H(34A)-C(34)-H(34B)	109.3
O(10)-C(35)-C(34)	126.83(18)
O(10)-C(35)-C(30)	126.34(18)
C(34)-C(35)-C(30)	106.83(16)
C(37)-C(38)-H(38A)	109.5
C(37)-C(38)-H(38B)	109.5
H(38A)-C(38)-H(38B)	109.5
C(37)-C(38)-H(38C)	109.5
H(38A)-C(38)-H(38C)	109.5
H(38B)-C(38)-H(38C)	109.5
C(37)-C(39)-H(39A)	109.5
C(37)-C(39)-H(39B)	109.5
H(39A)-C(39)-H(39B)	109.5
C(37)-C(39)-H(39C)	109.5
H(39A)-C(39)-H(39C)	109.5
H(39B)-C(39)-H(39C)	109.5
C(41)-C(40)-S(2)	120.01(13)
C(41)-C(40)-H(40A)	107.3

S(2)-C(40)-H(40A)	107.3
C(41)-C(40)-H(40B)	107.3
S(2)-C(40)-H(40B)	107.3
H(40A)-C(40)-H(40B)	106.9
C(40)-C(41)-C(49)	111.27(14)
C(40)-C(41)-C(45)	119.28(16)
C(49)-C(41)-C(45)	99.31(14)
C(40)-C(41)-C(42)	119.04(15)
C(49)-C(41)-C(42)	103.06(15)
C(45)-C(41)-C(42)	102.02(16)
C(43)-C(42)-C(41)	104.17(17)
C(43)-C(42)-H(42A)	110.9
C(41)-C(42)-H(42A)	110.9
C(43)-C(42)-H(42B)	110.9
C(41)-C(42)-H(42B)	110.9
H(42A)-C(42)-H(42B)	108.9
C(44)-C(43)-C(42)	103.02(17)
C(44)-C(43)-H(43A)	111.2
C(42)-C(43)-H(43A)	111.2
C(44)-C(43)-H(43B)	111.2
C(42)-C(43)-H(43B)	111.2
H(43A)-C(43)-H(43B)	109.1
C(43)-C(44)-C(48)	106.9(2)
C(43)-C(44)-C(45)	103.08(17)
C(48)-C(44)-C(45)	102.90(17)
C(43)-C(44)-H(44)	114.2
C(48)-C(44)-H(44)	114.2
C(45)-C(44)-H(44)	114.2
C(49)-C(48)-C(44)	101.19(16)
C(49)-C(48)-H(48A)	111.5
C(44)-C(48)-H(48A)	111.5
C(49)-C(48)-H(48B)	111.5
C(44)-C(48)-H(48B)	111.5
H(48A)-C(48)-H(48B)	109.3
O(9)-C(49)-C(48)	126.58(19)
O(9)-C(49)-C(41)	126.23(19)
C(48)-C(49)-C(41)	107.19(16)
C(46)-C(45)-C(47)	107.0(2)

C(46)-C(45)-C(44)	114.24(19)
C(47)-C(45)-C(44)	113.76(18)
C(46)-C(45)-C(41)	115.39(16)
C(47)-C(45)-C(41)	112.31(18)
C(44)-C(45)-C(41)	94.08(16)
C(45)-C(46)-H(46A)	109.5
C(45)-C(46)-H(46B)	109.5
H(46A)-C(46)-H(46B)	109.5
C(45)-C(46)-H(46C)	109.5
H(46A)-C(46)-H(46C)	109.5
H(46B)-C(46)-H(46C)	109.5
C(45)-C(47)-H(47A)	109.5
C(45)-C(47)-H(47B)	109.5
H(47A)-C(47)-H(47B)	109.5
C(45)-C(47)-H(47C)	109.5
H(47A)-C(47)-H(47C)	109.5
H(47B)-C(47)-H(47C)	109.5
C(39)-C(37)-C(38)	108.6(2)
C(39)-C(37)-C(33)	113.30(18)
C(38)-C(37)-C(33)	113.11(18)
C(39)-C(37)-C(30)	114.58(17)
C(38)-C(37)-C(30)	112.78(17)
C(33)-C(37)-C(30)	94.07(15)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for OSJ230P1. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	27(1)	20(1)	16(1)	0(1)	1(1)	2(1)
S(2)	21(1)	20(1)	21(1)	4(1)	-3(1)	-1(1)
N(1)	17(1)	18(1)	17(1)	1(1)	2(1)	1(1)
N(2)	21(1)	17(1)	23(1)	6(1)	1(1)	2(1)
O(1)	18(1)	30(1)	24(1)	10(1)	3(1)	2(1)
O(2)	26(1)	40(1)	35(1)	19(1)	9(1)	8(1)
O(3)	37(1)	32(1)	18(1)	2(1)	1(1)	14(1)
O(4)	39(1)	24(1)	26(1)	1(1)	6(1)	11(1)
O(5)	28(1)	31(1)	26(1)	-2(1)	3(1)	-2(1)
O(6)	25(1)	34(1)	43(1)	8(1)	-12(1)	1(1)
O(7)	26(1)	19(1)	26(1)	-2(1)	-1(1)	0(1)
O(8)	41(1)	28(1)	22(1)	4(1)	1(1)	-6(1)
C(1)	19(1)	20(1)	17(1)	-1(1)	2(1)	5(1)
C(2)	19(1)	32(1)	25(1)	0(1)	2(1)	6(1)
C(3)	24(1)	43(1)	30(1)	-1(1)	-1(1)	15(1)
C(4)	36(1)	38(1)	26(1)	5(1)	0(1)	20(1)
C(5)	33(1)	29(1)	24(1)	8(1)	3(1)	11(1)
C(6)	20(1)	23(1)	18(1)	2(1)	2(1)	6(1)
C(7)	15(1)	21(1)	23(1)	2(1)	2(1)	5(1)
C(8)	18(1)	17(1)	38(1)	1(1)	8(1)	3(1)
C(9)	15(1)	26(1)	38(1)	-9(1)	3(1)	2(1)
C(10)	20(1)	34(1)	29(1)	-6(1)	-3(1)	8(1)
C(11)	22(1)	24(1)	24(1)	1(1)	0(1)	9(1)
C(12)	17(1)	18(1)	21(1)	0(1)	2(1)	4(1)
C(13)	17(1)	17(1)	21(1)	2(1)	1(1)	3(1)
C(14)	25(1)	23(1)	25(1)	-3(1)	6(1)	3(1)
C(15)	24(1)	20(1)	21(1)	3(1)	2(1)	7(1)
C(16)	25(1)	26(1)	27(1)	2(1)	5(1)	8(1)
C(17)	26(1)	38(1)	29(1)	2(1)	2(1)	14(1)
C(18)	38(1)	36(1)	26(1)	6(1)	0(1)	20(1)
C(19)	39(1)	29(1)	26(1)	10(1)	7(1)	12(1)
C(20)	26(1)	26(1)	24(1)	6(1)	4(1)	8(1)
C(21)	22(1)	22(1)	37(1)	9(1)	9(1)	7(1)

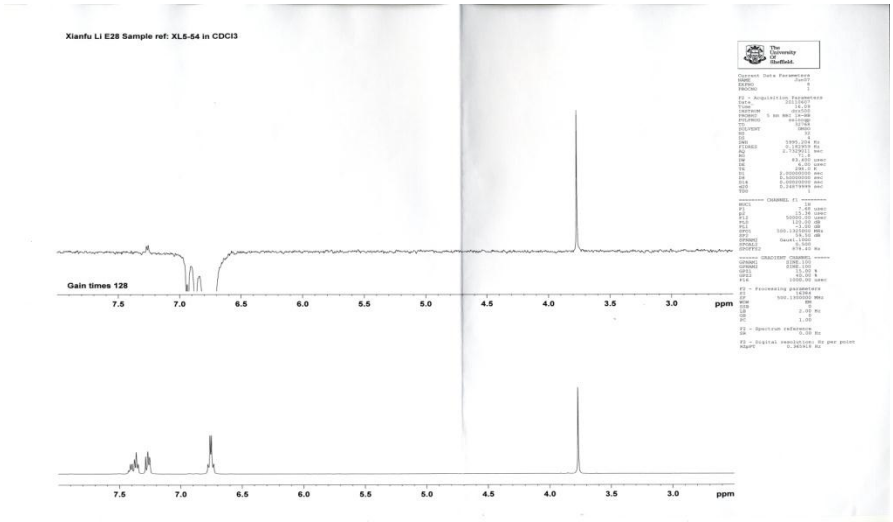
C(22)	25(1)	20(1)	66(2)	13(1)	16(1)	8(1)
C(23)	21(1)	21(1)	68(2)	-7(1)	13(1)	1(1)
C(24)	22(1)	32(1)	44(1)	-11(1)	3(1)	4(1)
C(25)	22(1)	26(1)	32(1)	-1(1)	3(1)	6(1)
C(26)	19(1)	16(1)	30(1)	2(1)	5(1)	5(1)
C(27)	22(1)	17(1)	26(1)	2(1)	3(1)	5(1)
C(28)	27(1)	19(1)	39(1)	6(1)	0(1)	8(1)
C(29)	31(1)	16(1)	18(1)	2(1)	-1(1)	3(1)
C(30)	25(1)	17(1)	19(1)	2(1)	1(1)	4(1)
C(31)	32(1)	20(1)	25(1)	7(1)	2(1)	0(1)
C(32)	42(1)	24(1)	30(1)	9(1)	-1(1)	5(1)
C(33)	36(1)	25(1)	24(1)	2(1)	-6(1)	7(1)
C(34)	50(1)	30(1)	21(1)	-4(1)	-6(1)	12(1)
C(35)	35(1)	22(1)	21(1)	-1(1)	1(1)	5(1)
O(10)	50(1)	30(1)	31(1)	-4(1)	-1(1)	19(1)
C(38)	28(1)	45(1)	44(1)	12(1)	-1(1)	-2(1)
C(39)	43(1)	49(1)	32(1)	0(1)	2(1)	27(1)
C(40)	20(1)	23(1)	24(1)	-1(1)	1(1)	7(1)
C(41)	20(1)	18(1)	19(1)	0(1)	2(1)	6(1)
C(42)	21(1)	45(1)	27(1)	-4(1)	2(1)	8(1)
C(43)	25(1)	52(1)	43(1)	-14(1)	-7(1)	18(1)
C(44)	41(1)	32(1)	30(1)	-6(1)	-14(1)	18(1)
C(48)	34(1)	25(1)	25(1)	-4(1)	-5(1)	6(1)
C(49)	24(1)	19(1)	32(1)	-3(1)	-1(1)	5(1)
O(9)	44(1)	22(1)	71(1)	-10(1)	-20(1)	13(1)
C(45)	41(1)	18(1)	22(1)	2(1)	-5(1)	8(1)
C(46)	60(2)	22(1)	38(1)	0(1)	-12(1)	12(1)
C(47)	56(2)	42(1)	24(1)	2(1)	8(1)	-4(1)
C(37)	26(1)	27(1)	26(1)	3(1)	-1(1)	8(1)

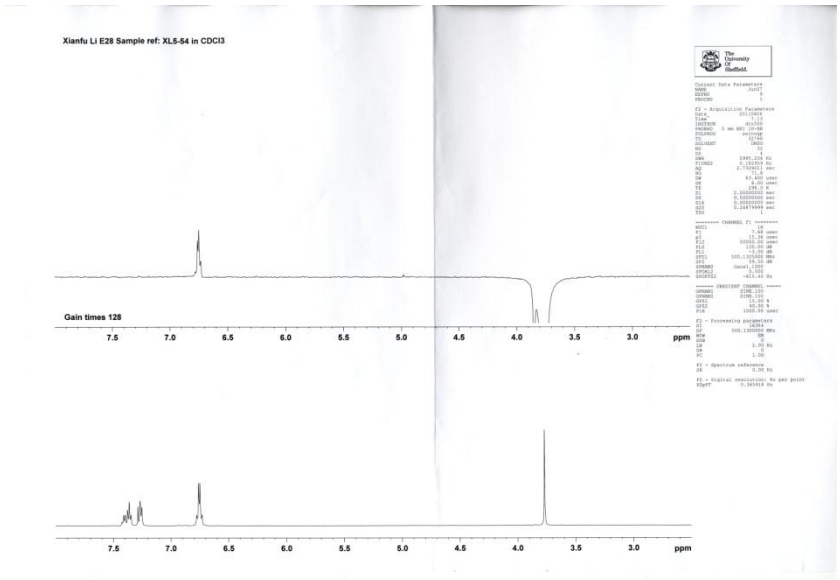
Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for OSJ230P1.

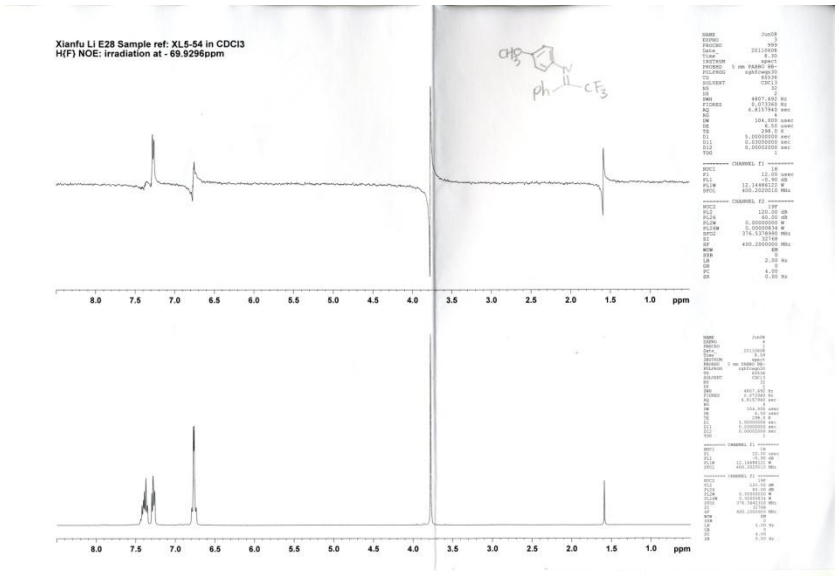
	x	y	z	U(eq)
H(1A)	5446	5924	1387	22
H(1B)	6008	6871	2243	22
H(2A)	2766	3127	3169	25
H(2B)	3251	4121	3982	25
H(2)	2993	6760	978	31
H(3)	1887	7984	-103	38
H(4)	3983	9426	-856	38
H(5)	7171	9684	-462	33
H(8)	11345	10343	1602	30
H(9)	13139	10410	3182	33
H(10)	12734	8746	4085	34
H(11)	10459	7021	3456	27
H(13)	8236	5908	2197	23
H(14A)	8646	6538	153	38
H(14B)	7634	5248	430	38
H(14C)	9816	5785	764	38
H(16)	6002	3484	4296	31
H(17)	7501	2443	5383	36
H(18)	5741	920	6226	38
H(19)	2509	497	6011	36
H(22)	-1910	-470	4331	42
H(23)	-3952	-873	2820	45
H(24)	-3960	576	1702	41
H(25)	-1902	2448	2083	32
H(27)	296	3558	4512	26
H(28A)	-1078	4322	3112	42
H(28B)	484	4101	2424	42
H(28C)	1046	5052	3408	42
H(29A)	8024	7839	5019	27
H(29B)	6100	7941	5389	27
H(31A)	5022	5945	6873	32
H(31B)	5954	5181	6120	32

H(32A)	6808	5574	8239	39
H(32B)	7798	4854	7481	39
H(33)	10289	6542	8132	35
H(34A)	7764	7537	8693	41
H(34B)	9586	8413	8338	41
H(38A)	12143	7957	6794	62
H(38B)	10610	8686	6818	62
H(38C)	11009	8125	5743	62
H(39A)	8929	5130	6008	58
H(39B)	11103	5764	6260	58
H(39C)	9958	6021	5248	58
H(40A)	4514	3003	9498	27
H(40B)	3686	1826	10011	27
H(42A)	-501	1810	10225	37
H(42B)	289	3219	10437	37
H(43A)	-2676	2059	9009	48
H(43B)	-1825	3467	9184	48
H(44)	-1124	3013	7487	41
H(48A)	-1707	832	7887	35
H(48B)	-128	1268	7133	35
H(46A)	3112	4926	9126	62
H(46B)	974	4692	9323	62
H(46C)	1593	5044	8225	62
H(47A)	4108	3680	7916	65
H(47B)	2461	3592	7019	65
H(47C)	2804	2420	7452	65

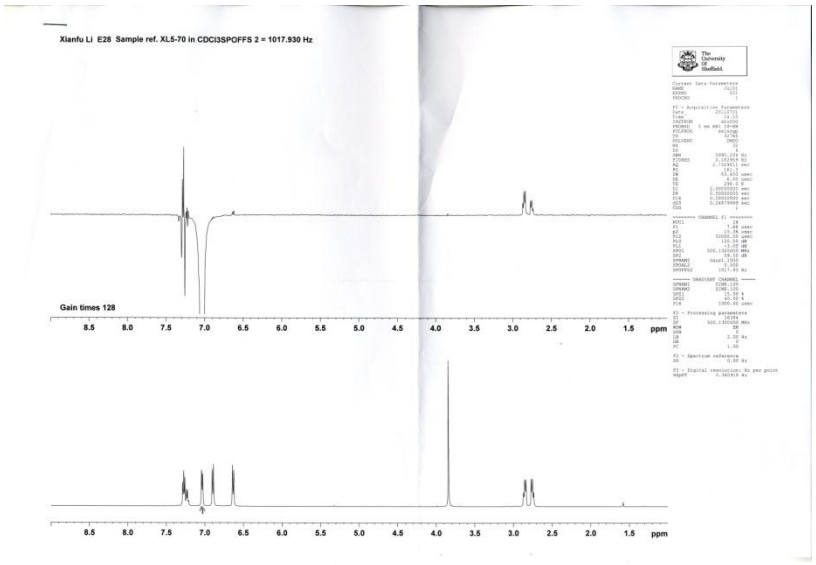
Appendix 2 nOe experiments of imine **246**

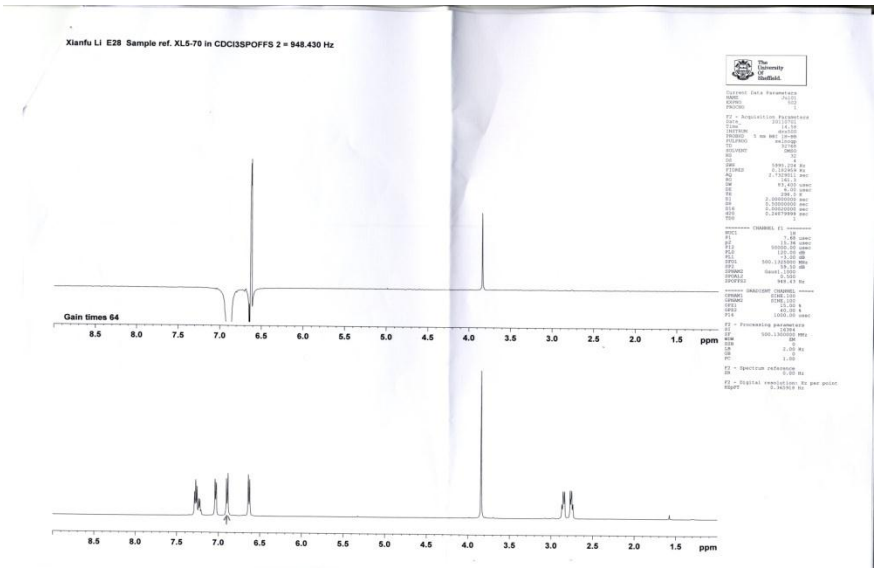


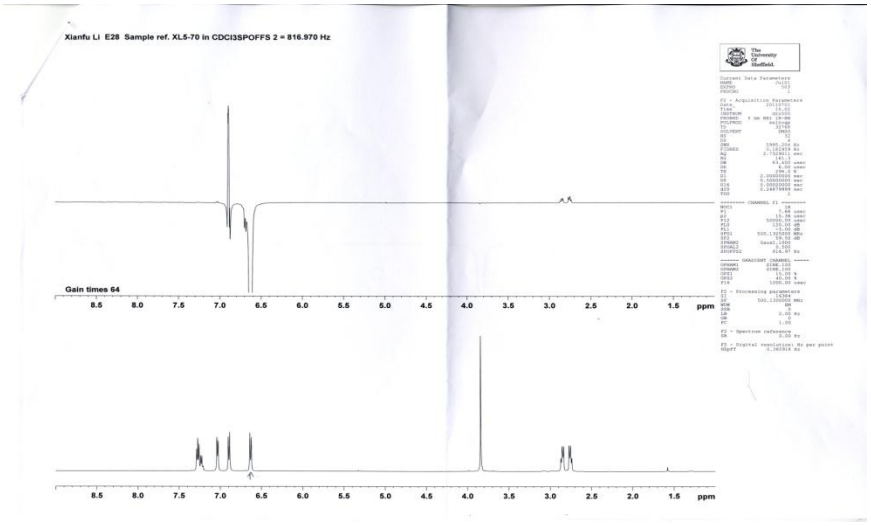


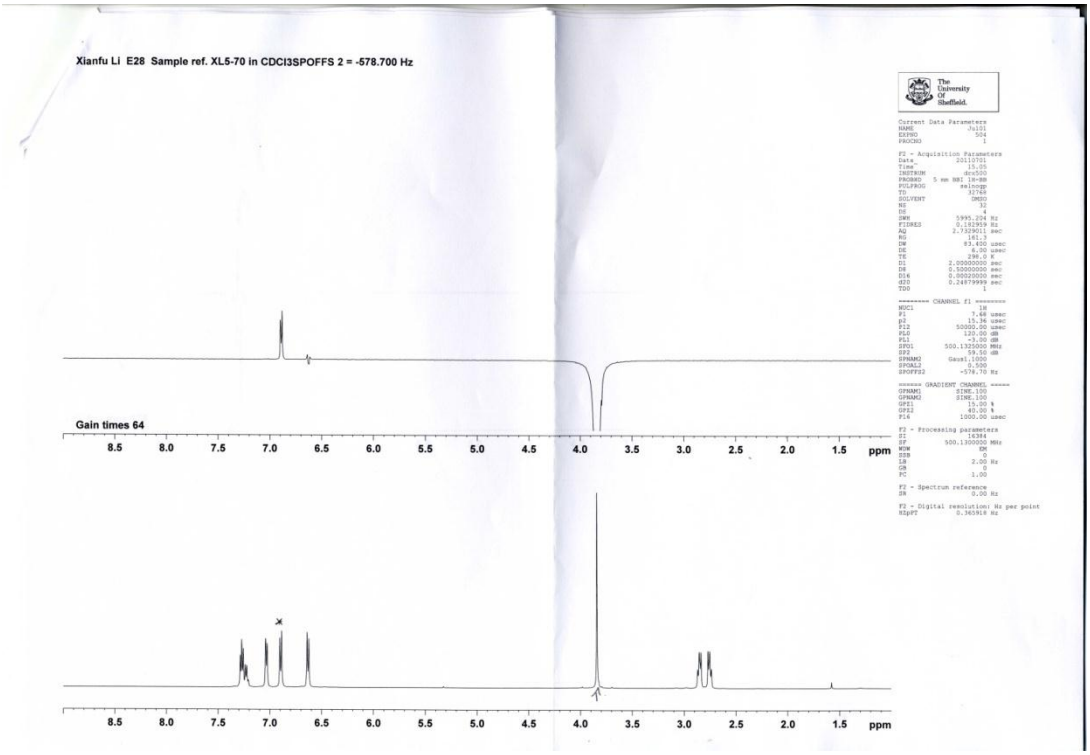


Appendix 3 nOe experiments of imine **248**








Xianfu Li E28 Sample ref. XL5-70 in CDCl3SPOFFS 2 = -578.700 Hz
Gain times 64
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 ppm
The University Of Sheffield.
Current Data Parameters
NAME Julio
EXPNO 504
PROCNO 1
F2 - Acquisition Parameters
Date_ 20110701
Time 15.05
INSTRUM drx500
PROBHD 5 mm NMI 1H-BB
PULPROG zg30zgp
TD 32768
SOLVENT DMSO
NS 32
DS 4
SWH 5995.204 Hz
FIDRES 0.182959 Hz
AQ 2.7329011 sec
RG 161.3
DW 83.400 usec
DE 6.50 usec
TE 298.0 K
D1 2.00000000 sec
D8 0.50000000 sec
D16 0.00020000 sec
dES 0.24979999 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 7.48 usec
p2 15.36 usec
P12 50000.00 usec
PL1 120.00 dB
PL2 0.00 dB
SFO1 500.1325000 MHz
SF2 59.50 dB
SPNAM2 Gaus1.1000
SPOAL2 0.500
SPOFF2 -578.70 Hz
====== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPNAM2 SINE.100
GPZ1 15.00 %
GPZ2 40.00 %
P16 1000.00 usec
F2 - Processing parameters
SI 16384
SF 500.1300000 MHz
WDW EM
SSB 0
LB 2.00 Hz
GB 0
PC 1.00
F2 - Spectrum reference
SR 0.00 Hz
F2 - Digital resolution(Hz per point
RESPT 0.365918 Hz