**A thesis submitted in part fulfilment of the requirements of the degree of Doctor of Philosophy**


UNIVERSITY
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# Organocatalysts for the Asymmetric Reduction of Aromatic Ketimines with Trichlorosilane

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***He who never made a mistake, never made a discovery!***

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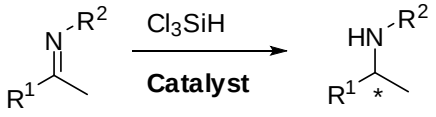
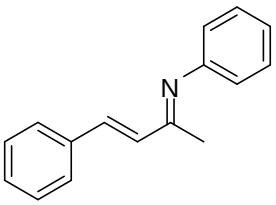
## i. Abstract

Asymmetric reduction of *N*-aryl ketimines **189a-j**, **212**, and **213** with trichlorosilane can be catalyzed by new *N*-methyl L-amino acid-derived Lewis-basic organocatalysts, such as bisamide **197c** (10 mol%), in toluene at room temperature with high enantioselectivity (≤92% ee). The structure-reactivity investigation shows that the product configuration is controlled by the nature of the side chain of the catalyst scaffold (e.g., *i*-Pr vs Me, as in **197c** and **208c**), so that catalysts of the same absolute configuration may induce the formation of the opposite enantiomers of the product. Arene-arene interactions between the catalyst and the incoming imine appear to be the prerequisite for asymmetric induction. This metal-free, organocatalytic protocol is competitive with the traditional, metal-catalyzed methodology.


**189a-j** **190a-j**

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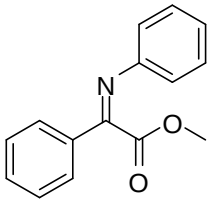


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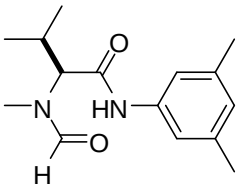
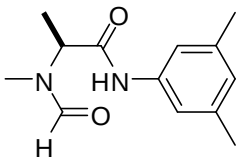



**197c**




**208c**

## ii. Acknowledgements

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Most of all I would like to thank my family and Amanda for all their support and encouragement throughout my research. I couldn't have done it without them!

## iii. Abbreviations

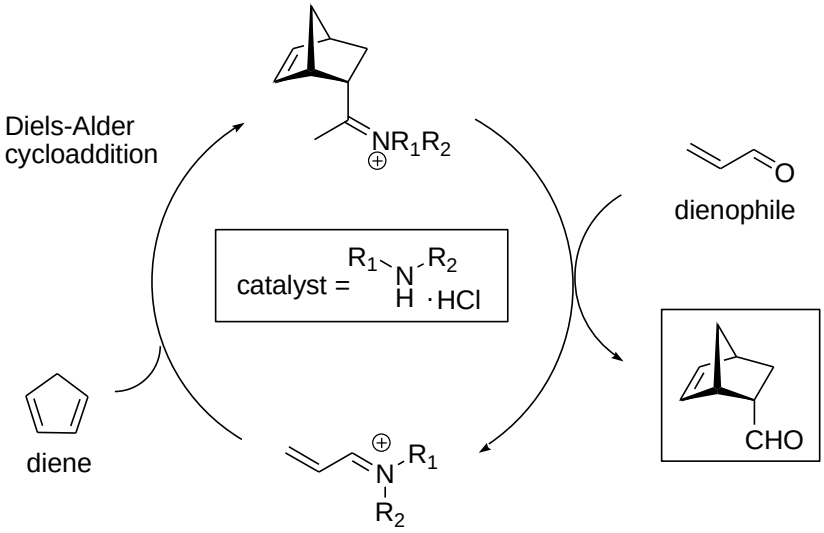
| | |
|---|---|
| Å | Angstrom |
| Aq | Aqueous |
| BINOL | 1,1'-Binaphthol |
| Bn | Benzyl |
| Boc | *tert*-Butoxycarbonyl |
| Bp | Boiling Point |
| *tert*-Bu | Tertiary butyl |
| Bz | Benzoyl |
| $^{o}$C | Degrees centigrade |
| cat | Catalytic |
| CI | Chemical ionisation |
| cm | Centimetre |
| conc | concentrated |
| Cy | Cyclohexyl |
| d | doublet (NMR spectroscopy) |
| DMAP | 4-Dimethylaminopyridine |
| DMF | Dimethylformamide |
| DMSO | Dimethylsulfoxide |
| ee | Enantiomeric excess |
| EI | Electron Impact |
| Equiv | Equivalents |
| GC | Gas Chromatography |
| h | Hours |
| HCN | Hydrogen Cyanide |
| HPLC | High Performance Liquid Chromatography |
| Hz | Hertz |
| IR | Infrared |
| M | Molarity |
| m | Multiplet (NMR spectroscopy) |
| min(s) | Minutes |
| MS | Mass Spectroscopy |
| Naph | Napthyl |
| NMO | *N*-methylmorpholine-*N*-oxide |
| NMR | Nuclear Magnetic Resonance |
| PMP | *para*-Methoxyphenyl |
| q | Quartet (NMR spectroscopy) |
| rt | Room temperature |
| satd | Saturated |
| t | triplet (NMR spectroscopy) |
| TLC | Thin Layer Chromatography |
| UV | Ultraviolet |

# Chapter 1: Introduction

## 1.1 Introduction to Asymmetric Organocatalysis

The area of organocatalysis, although not always known as this, has been around for the past 40 years. In 1998 Professor David MacMillan, then of the University of California, Berkeley became interested in and developed a new concept that was based around small organic catalysts. At this time he had been working on an enantioselective organocatalytic Diels Alder reaction based on iminium-activation [1] (**scheme 1**) and was sure he had developed a new system of catalysis that could be used in many different transformations. He is quoted as saying:

*"I became interested in coining a new name for what was commonly referred to as 'metal-free catalysis'. My motivations for doing so were very simple. I do not like the idea of describing an area of catalysis in terms of what it is not, and I wanted to invent a specific term that would set this field apart from other types of catalysis. The term 'organocatalysis' was born and a field that had existed for at least 40 years acquired a new name"* [2]

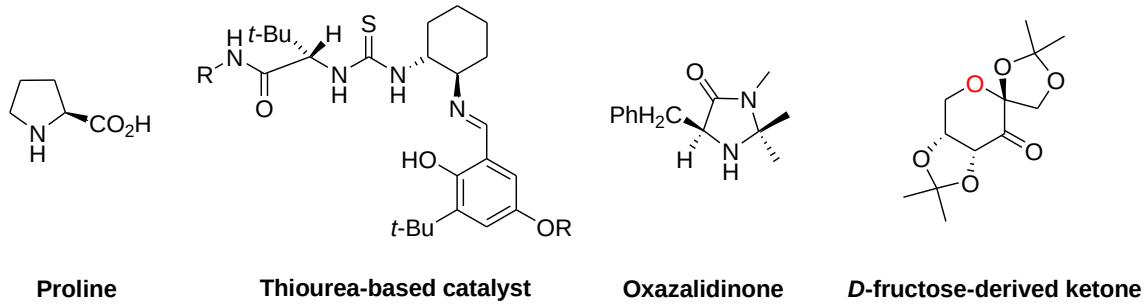



**Scheme 1** Organocatalytic Diels Alder process

Although it has been around for 40 years, organocatalysis is still very much in its developmental stage and as such new organocatalytic processes are appearing in the literature in an almost daily basis. The requirement from the pharmaceutical industry for enantiomerically pure building blocks, free from impurities, has spurred many researchers to begin investigations into new organocatalytic methods. However, competing with the equivalent metal-mediated or enzyme catalysed process is no mean feat and as such much effort and time has been dedicated by investigators to this problem.

It has long been understood that only manufactured transition-metal based catalysts can be used to obtain either one of the two enantiomers of an asymmetric reaction whereas, enzymes are specific only for one enantiomer. Of course, enzymes can be altered by way of mutations but this is not too practical for a synthetic chemist! In between the areas of Organocatalysis could be described as the area of catalysis that utilises only 'organic' molecules made up of, in the main, carbon, hydrogen, nitrogen, sulphur and phosphorus to obtain the enantioselective outcome. Organocatalysts, unlike the organic ligands that are associated with transition metal complexes utilises the intrinsic chirality and low molecular weight that they possess to great effect without the need for metals. The one major advantage of organocatalysts over transition metal derived catalysts and indeed enzymes is cost. Organocatalysts can be produced from inexpensive and readily available starting materials such as amino acids. Also, organocatalytic methods would seem to be of particular interest to the pharmaceutical industry in that it would eliminate the problem of metal leaching in drug compounds.

There are numerous different types of organocatalyst and some are shown in **Figure 1**. Many of these molecules stem from a 'chiral pool' synthesis, where the enantiopure compound is synthesised from a readily available enantiopure substance. The chirality is then preserved in the final compound.[3]



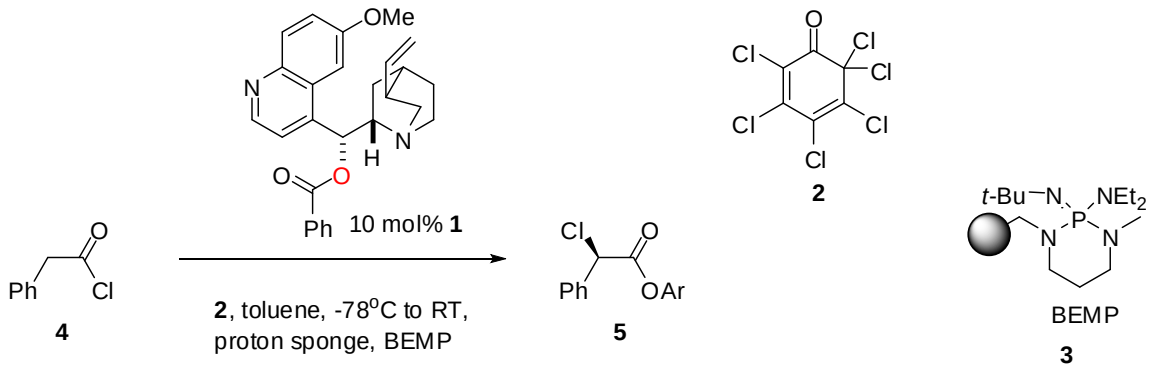

**Proline** **Thiourea-based catalyst** **Oxazalidinone** ***D*-fructose-derived ketone**

**Figure 1** Selection of organocatalyst motifs

Although still in its formative years, the range of asymmetric reactions that can now be carried out organocatalytically is enormous. Reactions such as substitution at aliphatic carbons (i.e. chlorination, bromination), nucleophilic addition to C=N double bonds (i.e. Strecker reaction, Mannich reaction), oxidations (i.e. alcohol oxidation, epoxidation of olefins) and reduction of carbonyl and imine compounds. Some examples of the aforementioned reactions will be described below to give a glimpse of the practical scope of organocatalysis.

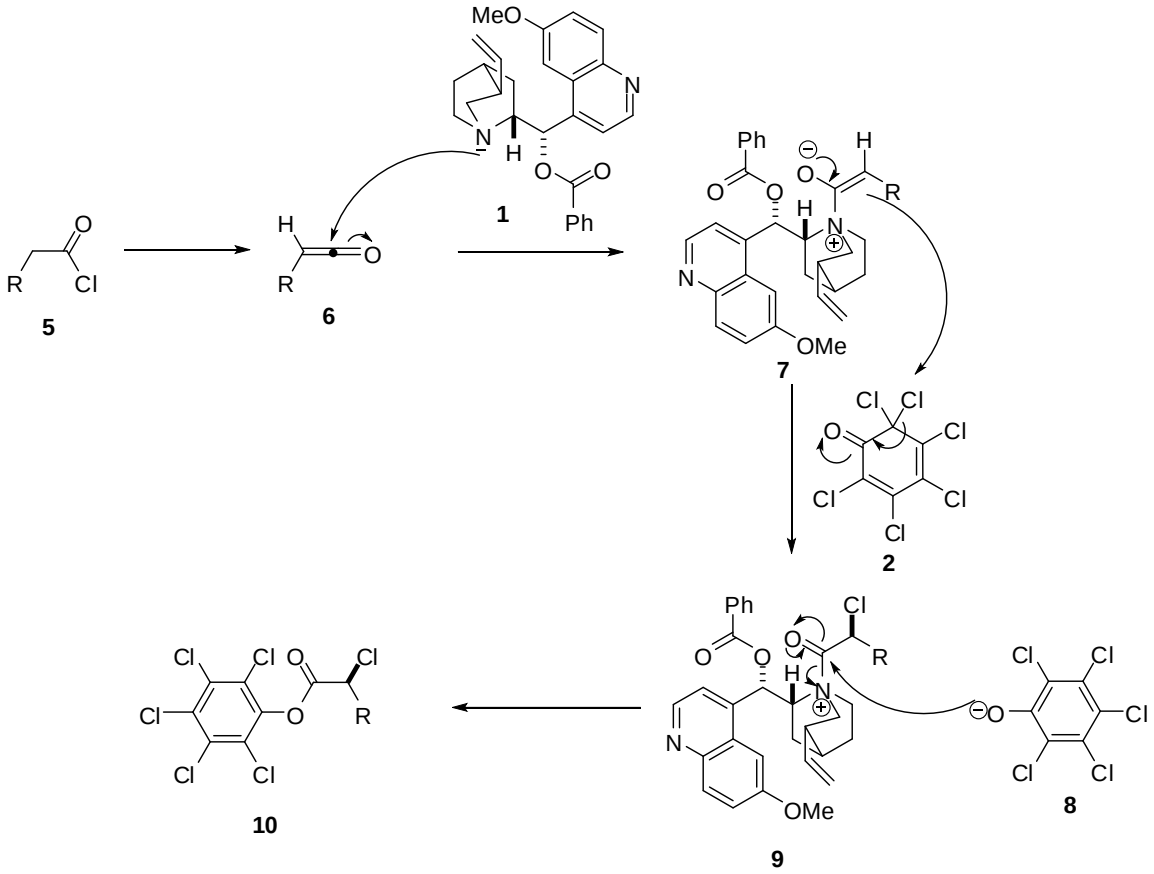
## 1.1.1 Substitution at Aliphatic Carbons

The enantioselective C-Cl bond forming reaction has recently been reported by Leckta *et al*. [4] He has shown that the asymmetric $\alpha$-chlorination of cheap and readily available acid chlorides, mediated by a chinchona alkaloid-derived catalyst **1** can produce highly optically enriched $\alpha$-chloroesters (**scheme 2**). The process occurs by the chiral alkaloid reacting with an *in-situ* generated ketene to form a zwitterionic enolate species. To obtain high yields as well as high enantioselectivity, it was important to generate the ketene via the basic resin-bound BEMP **3**, a highly basic reagent attached to a Merrifield resin. Without this, although enantioselectivities were high, the reactions were low yielding (≤40%). Reaction with an electrophilc halogen **2** then furnishes the desired product. The reaction mechanism is shown in **scheme 3**.



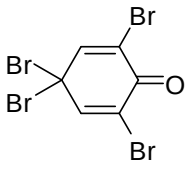

**Scheme 2** General reaction scheme for α-chlorination

The use of benzoylquinine **1** as the chiral alkaloid and the halogenation agent **2** furnished $\alpha$-chloroesters (cf **5**) in yields of ≤81% and *ee*'s of ≤99%. (**Scheme 3**)




**Scheme 3** Mechanism for α-chlorination

This is not limited just to the chlorination reaction but $\alpha$-bromination reactions can also be carried out by simply altering the halogenation agent to effect bromination rather than chlorination **11.**

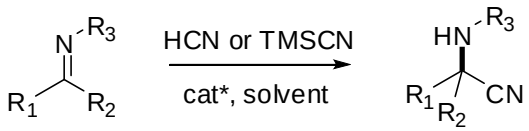



**11**

## 1.1.2 Nucleophilic Addition to C=N Double Bonds

### 1.1.2.1 Strecker Reaction

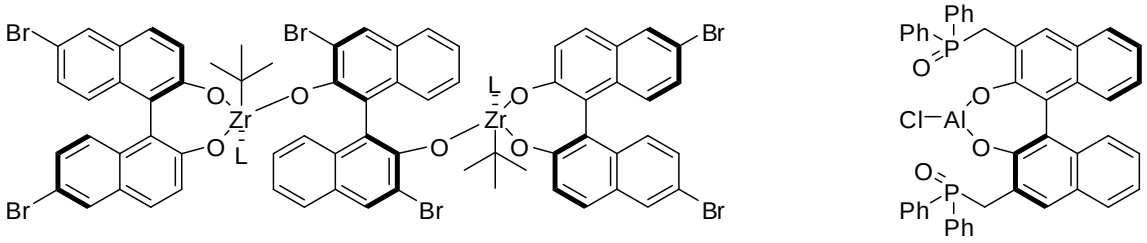
An efficient method for producing α-amino acids is to perform the Strecker reaction. This involves reaction of an aldehyde with ammonia and a cyanide source such as hydrogen cyanide (HCN). However, with regards to an asymmetric version, a more popular method involves the nucleophilic addition of HCN or trimethylsilyl cyanide (TMSCN) to a preformed imine to furnish the amino nitrile (**scheme 4**).




**12** **13**

**Scheme 4** Asymmetric Strecker reaction.

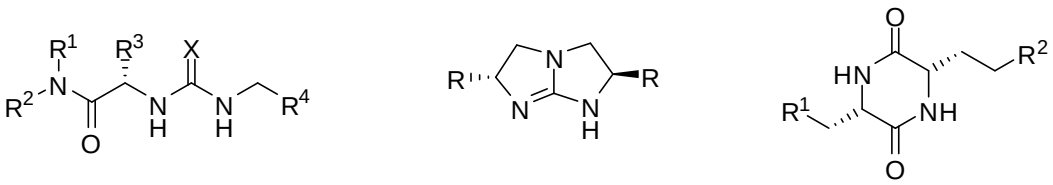
There are various metal-derived catalysts used to effect this transformation (**figure 2**) but more recently a range of organocatalysts have been developed to produce the same result (**figure 2**).



**14** ***Kobayashi*** **15** ***Shibasaki***

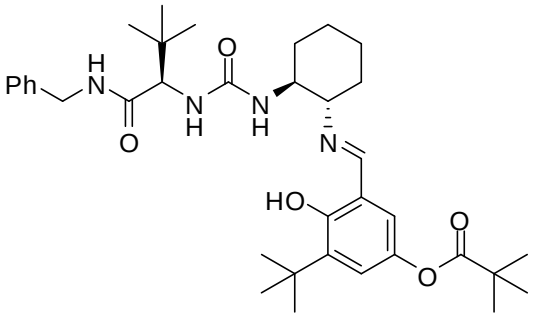
**Figure 2** Examples of metal based catalysts for the asymmetric Strecker reaction [5]

Some examples of organocatalysts that have been developed for this reaction are catalysts based on ureas 1**6**, chiral guanidines 1**7** and diketopiperazines 1**8**.



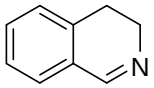
**16** **17** **18**

The chiral ureas are effective over a wide range of substrates (aromatic, aliphatic and cyclic) with enantioselectivities of ≤99% and in excellent yields. Jacobsen *et al* [6] reported a urea catalyst based on phenylalanine and a substituted salicaldehyde 1**9** which could effect the Strecker reaction on a wide range of aromatic and alkyl imines with *ee*'s of ≤99% and yields of ≤99%.



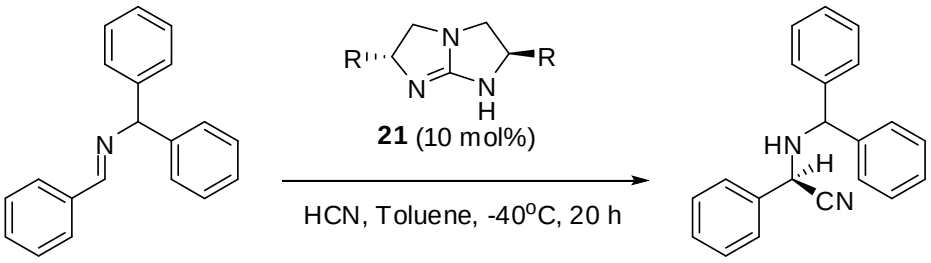
**19**

This catalyst also proved efficient in the cyanation of cyclic imines. Imine **20** was cyanated with **19** in 91% *ee* and 88% yield. [7]



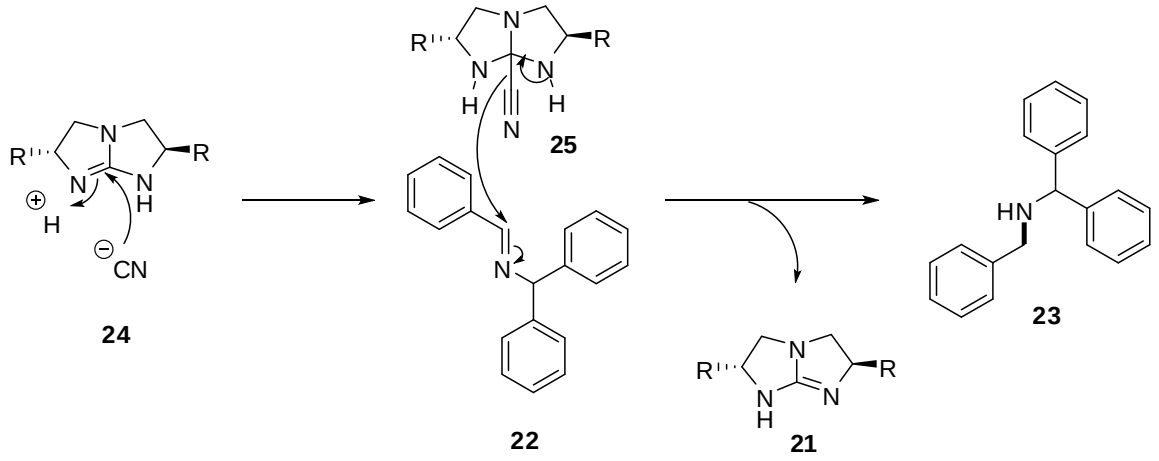
**20**

Corey *et al* [8] in 1999 reported the use of $C_2$-symmetric guanidine derived ligands **7** for the synthesis of chiral $\alpha$-amino nitriles from simple aromatic aldimines. The reaction of a simple benzaldehyde derived aldimines with HCN and in the presence of 10 mol% of guanidine catalyst **21**, afforded the corresponding amino nitrile in 96% yield and in 86% *ee* (**scheme 5**). A proposed reaction mechanism is shown in **scheme 6**.



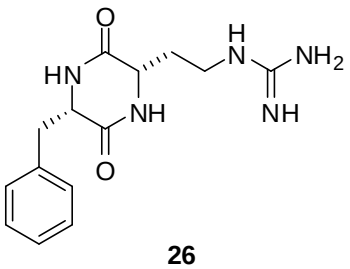

**22** **23**

**Scheme 5** Asymmetric Strecker reaction with chiral guanidine catalyst **21**



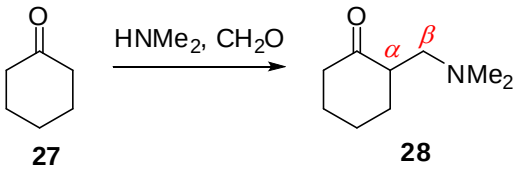

**Scheme 6** Proposed reaction mechanism for the asymmetric Strecker reaction

The Lipton group [9] reported in 1996 the use of a cyclic diketopiperazines **26** as a catalyst in the asymmetric Strecker amino acid synthesis. Using the same substrate as shown in **scheme 5** (Corey), Lipton was able to obtain enantioselectivities in excess of 99% and in almost quantitative yields. He also obtained similar results with a range of other aromatic substrates. It should be noted however, that the system was poor at inducing chirality in heteroaromatic and aliphatic substrates giving enantioselectivities of 32% and 17% respectively.



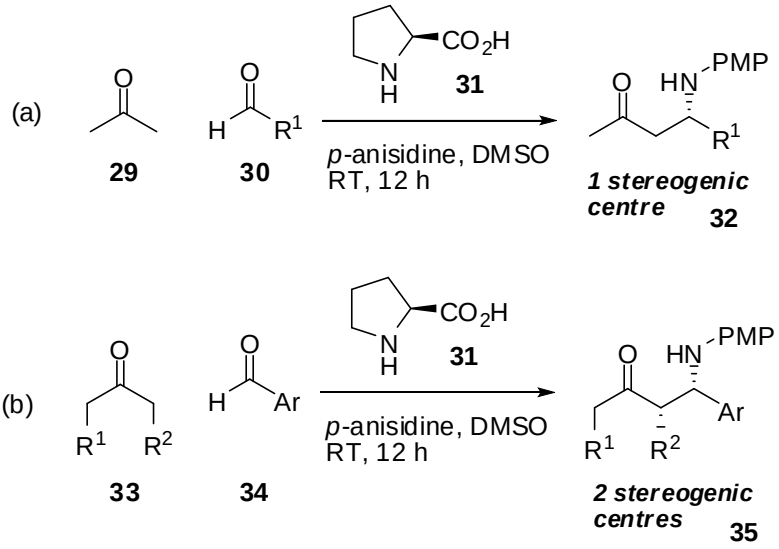

## 1.1.2.2 Mannich Reaction

The Mannich reaction is probably the most popular method for producing *β*-amino carbonyl compounds. It is a three component reaction consisting of an aldehyde, ketone and amine which react in one pot to form the *β*-amino carbonyl compound. The general reaction scheme is shown below (**scheme 8**).



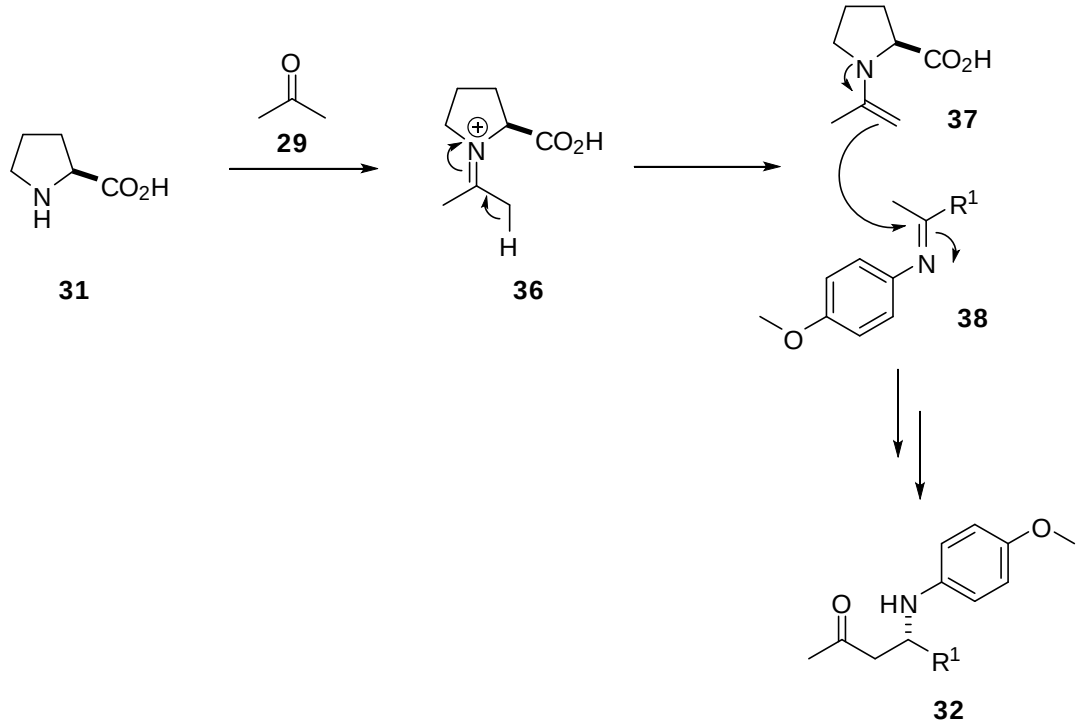

**Scheme 8** General reaction scheme for the Mannich reaction [10]

List *et al* [11] reported the first asymmetric three-component Mannich reaction catalysed by proline. He showed that *β*-amino ketones could be synthesised with either one or two stereogenic centres (**scheme 9**), depending on the starting ketone used with *ee*'s of ≤99% and in excellent yields. Although proline loading was quite high (35 mol%), the low cost and availability of the proline along with the fact that the catalyst could be recovered simply by filtration after the reaction was complete made this an attractive system.



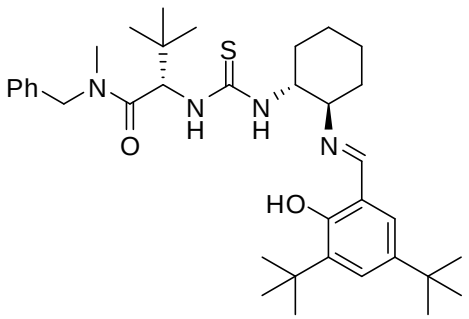

**Scheme 9** Asymmetric proline catalysed Mannich reaction

The above examples represent the direct Mannich reaction (mechanism of (a) shown in **scheme 10**).



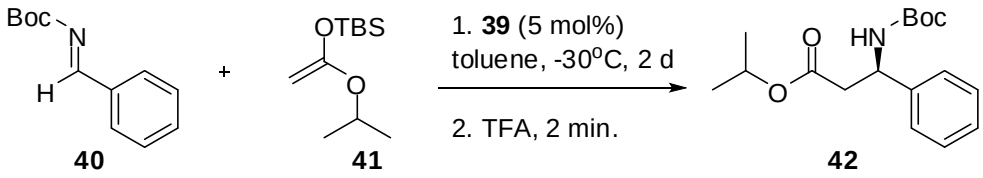

**Scheme 10** Mechanism for asymmetric Mannich reaction

However, there are examples of the indirect Mannich reaction in which the *β*-amino ketones are formed via nucleophilic addition of enolates to preformed imines. Jacobsen *et al* [12] reported the use of a thiourea containing Schiff base **39** to catalyse this process.




**39**

Although he had developed this type of catalyst for the asymmetric Strecker reaction (see section 1.2.1) he found that using 5 mol% of **39** in the asymmetric nucleophilic addition of a silyl ketene acetal to a preformed *N*-Boc-imine could lead to the required *β*-amino ketone in enantioselectivities of ≤97% and yields of up to 95% (**scheme 11**).

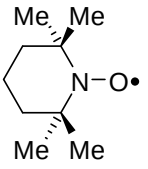



**Scheme 11** Nucleophilic addition of a silyl ketene acetal to a preformed *N*-Boc-imine

## 1.1.3 Oxidations

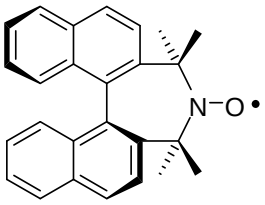
### 1.1.3.1 Alcohol Oxidation

One way of resolving racemic alcohols is *via* kinetic resolution. This is a process by which the differing reaction rates of individual enantiomers with a scalemic reagent are exploited. The reaction, whatever that may be, is carried out to completion on the more reactive enantiomer whilst the less reactive enantiomer remains unchanged. These two products can now be easily separated leaving an enriched enantiomer and some other product. Catalytic oxidation of alcohols with a chiral catalyst is a way of performing kinetic resolution on racemic alcohols. A chiral derivative of a catalyst such as TEMPO **43**, a nitroxyl radical, used alongside hypochlorite or peroxyacetic acid (as the final oxidizing agent) can affect the oxidation of alcohols to carbonyls compounds.




**43**

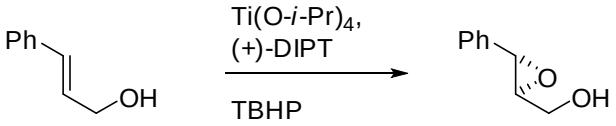
An analogue of TEMPO was developed by Rychnovsky *et al* [13] in 1996. This binapthyl-derived TEMPO **44** analogue was used in the kinetic resolution of a variety of racemic alcohols with *ee*'s of recovered alcohols peaking at 98% (for 1-phenyl ethanol). The reaction was carried out with a catalyst loading of 1 mol% (with 0.6 equivalents of sodium hypochlorite used as the final oxidising agent). This method of kinetic resolution is particularly attractive owing to the low catalyst loadings and use of commercial bleach as the oxidising agent.



**44**

## 1.1.3.2 Epoxidation

The wide use of chiral epoxides in the pharmaceutical industry as intermediates to enantiomerically pure building blocks has prompted researchers to spend much effort in developing more efficient protocols for epoxidation. Sharpless *et al* [14] has found great success in the field of transition-metal catalysed, utilising titanium in the asymmetric epoxidation of allylic alcohols (**scheme 12**). This is however limited to allylic alcohols (and some homoallylic alcohols) and works best for trans-olefins.

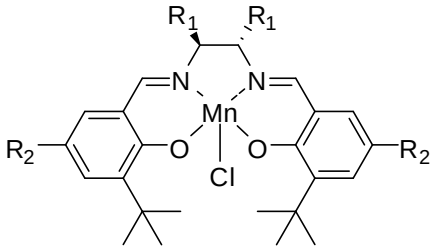



**45** **46**

92% *ee*

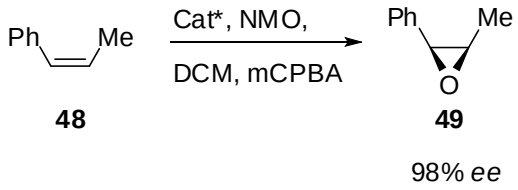
**Scheme 12** Asymmetric epoxidation of allylic alcohols using Titanium (IV). [15]

The epoxidation of unfunctionalised alkenes can also be achieved using (salen)Mn(III) catalysts **47**. Jacobsen *et al* [16] reported the use of the aforementioned catalysts with a variety of alkenes and reaction conditions, with varying enantioselectivities observed (works best for cis-olefins).




**47**

Jacobsen found that when $R_1$ = Ph and $R_2$ = OSi(*i*-Pr)$_3$, the epoxidation of *cis*-β-methylstyrene proceeded with 98% enantioselectivity (**scheme 13**).

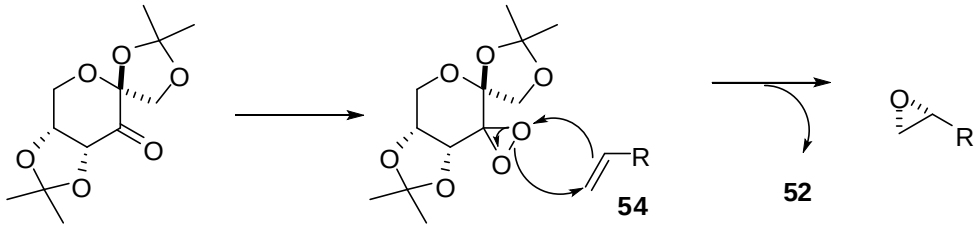



**Scheme 13** Catalytic epoxidation of *cis*-β-methylstyrene with (salen)Mn(III) catalyst.

At present, organocatalytic protocols rely on dioxiranes **50**, generated from chiral ketones **51**, as chiral epoxidising agents.


**50** **51**

One of the most useful chiral ketones available is the Shi ketone **52.**[17] This is an inexpensive ketone prepared from D-Fructose and then functionalised in 2 simple steps (ketalization and then oxidation) to furnish the desired ketone. The dioxiranes **53** are generated *in situ* from Oxone (potassium peroxomonosulfate) and the ketone **x** which then react with the alkene substrate **54** (**scheme 14**). Shi obtained impressive results over a range of alkene substrates with enantioselectivities of >95% achieved.




**52** **53** **54** **52** **55**

**Scheme 14** Epoxidation of an alkene using the Shi ketone

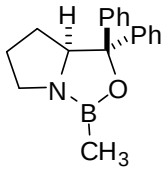
## 1.1.4 Reduction of Carbonyl Compounds

To date, asymmetric hydrogenation, hydrosilylation and borane reductions are the most widely used methods for reducing carbonyl compounds. In industry, hydrogenation is the most favoured method but this is of course not without its problems and limitations, namely associated with metal leaching and catalyst regeneration. Borane reductions, although managing to avoid these problems, have another limitation; cost of the catalyst,

which can be quite high if applying it to a large scale process. Hydrosilylation however, utilises cheap and readily available silane compounds and coupled with a simple chiral activator such as proline [18] or derivatives of quinoline, [19] can produce a very efficient reduction protocol.

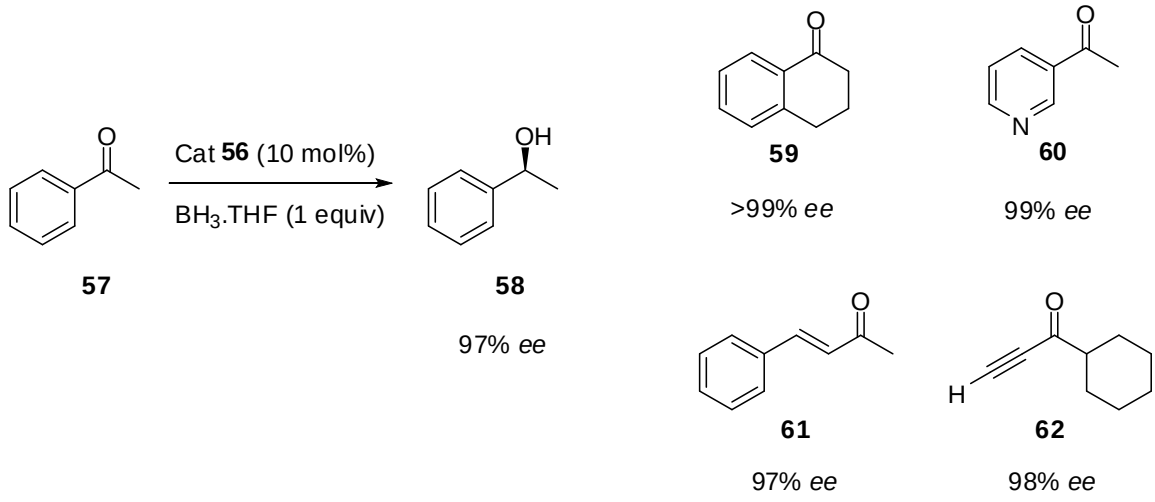
### 1.1.4.1 Borane reduction

Probably the most widely used protocol for the enantioselective reduction of carbonyl compounds is the oxazaborolidine-catalysed borane reduction developed by Corey *et al*. [20] This system utilised the proline-derived bicyclic compound **56.**



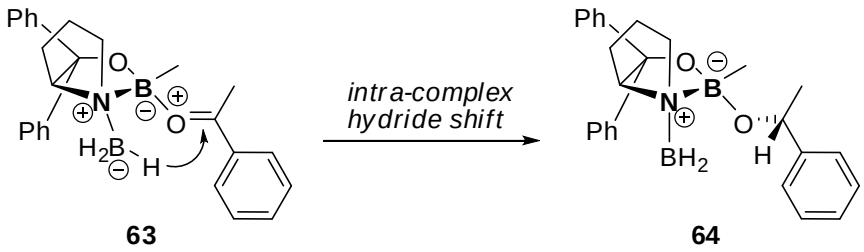

**56**

The reduction of acetophenone (**scheme 15**) with $BH_3$.THF (100 mol%), catalysed with **x** (10 mol%), proceeds smoothly in excellent yield and enantioselectivity (97%). This high level of enantioselectivity was also achieved in a wide range of other ketone substrates (**scheme 15**).




**Scheme 15** Acetophenone reduction mediated by catalyst **56** as well as results for other substrate reductions

The oxaborolidine catalyst **56** is a key example of a bifunctional catalyst, where the ketone and the borane are simultaneously bound to the boron (Lewis-acidic site) and the nitrogen (Lewis-basic site). This results in a complex which allows hydride transfer to the carbonyl to be easily achievable. (**scheme 16**)

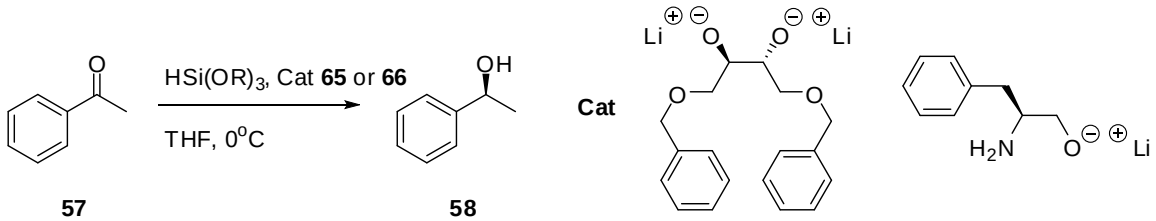



**63** **64**

**Scheme 16** Illustration of how catalyst **x** acts as a bifunctional catalyst

## 1.1.4.2 Hydrosilylation

Hydrosilylation could be described as the addition reaction of silicon hydrides to multiple bonds such as C=C, C=N or C=O. [21] For this reaction to work the silane, such as trichlorosilane, would have to be activated. This could be achieved by using a Lewis base such as DMF. However, as an alternative to this the nucleophilic activator itself could act as a chiral inducer. Hosomi *et al* [22] showed that by using a chiral base as the activator, hydrosilylation, with trialkoxysilanes, of simple aromatic ketones such as acetophenone could be effected in excellent yield and with enantioselectivities of up to 77%. This was achieved by the use of the lithium salts of diolates or amino alcohols (**sheme 17**).




**57** **58** **65** 77% *ee* **66** 44% *ee*

**Scheme 17** Asymmetric reduction of ketones using $Si(OMe)_3$ activated by chiral diolates or amino alcohols

Since then, a plethora of organocatalytic routes to asymmetric ketone reduction has been published within scientific journals. Very recently Malkov-Kocovsky *et al* [19] reported the use of isoquinoline derived organocatalysts **67** for the trichlorosilane mediated reduction of a series of ketones (**figure 3**). As a result, enantioselectivities of ≤ 94% *ee* have been achieved, which is by far the best results obtained for the metal-free hydrosilylation of

ketones to date. With catalyst loadings also as low as 10 mol%, it is also a highly efficient protocol too.

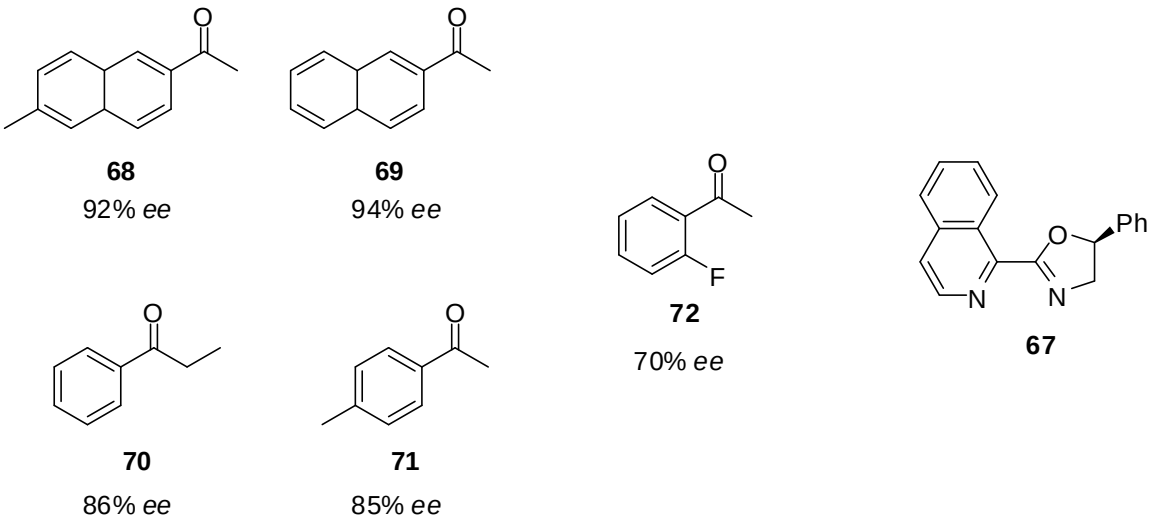



**Figure 3** Reductions of ketones catalysed by catalyst **67**

The mechanism proposed for this system is shown in **figure 4** below.

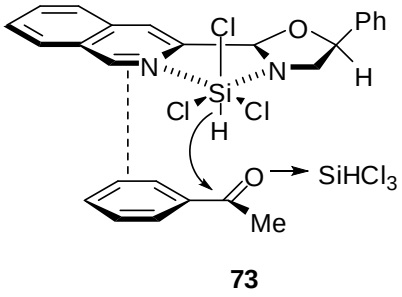


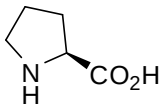

**Figure 4** Proposed mechanism of hydrosilylation

## 1.1.5 Conclusion

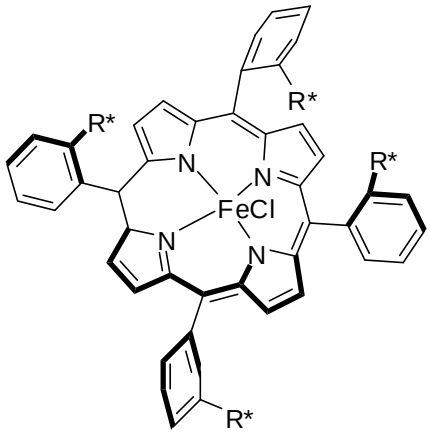
Although organocatalysis is still in its infancy when comparing it to its metal-mediated counterparts, it continues to be one of the most dynamic and expanding areas of organic chemistry. New methods appear almost daily in the literature that hope to compete and better the equivalent metal-based process. Although there will always be a need for metal-mediated catalysis, the pursuit of purely "green" chemistry will no doubt be an ongoing one.

## 1.2 Introduction to Asymmetric Catalysis

Asymmetric catalysis could be described as the process by which an achiral substrate is converted into a chiral product with a preference for one of the enantiomers. This of course is promoted by the use of a chiral catalyst. These catalysts can range from simple organic compounds such as proline **31** to large and elaborate metal-based catalysts such as metalloporphyrin complexes **74**.




**31**




**74**

The demand for chiral compounds and increasingly those of a single enantiomer has risen sharply over the last few years. This has been driven mainly by the pharmaceutical industry since around two thirds of all prescription drugs are chiral, with the vast majority being of a single enantiomer. [23] Classically, chiral compounds were produced by either transforming chemically, compounds from nature's 'chiral pool' or by resolution of a racemic mixture of enantiomers. These of course suffer limitations in that resolution will only yield a maximum of 50% of the required enantiomer and you would also require a stoichiometric amount of substrate from the 'chiral pool' to work with, which of course is not always practical or possible..

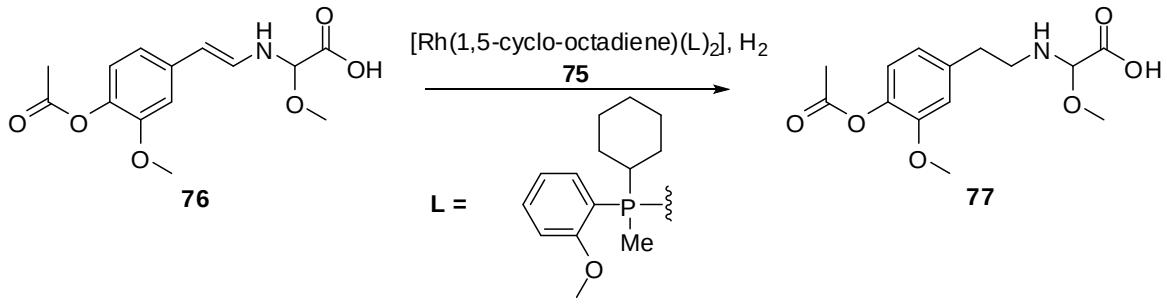
In nature, enzymes carry out asymmetric catalysis smoothly and efficiently and the task of synthetic chemists to compete with nature is a truly daunting one. Today there is a multitude of different methods for asymmetric catalysis spanning across all kinds of synthetic routes and transformations at the disposal of chemists. The ability to produce chiral compounds from simple building blocks, facilitated by a small amount of chiral catalyst makes asymmetric catalysis a very powerful tool in organic chemistry.

This chapter will try and describe the different reactions that can be carried out in this fashion and show the range of different catalysts that can be used.

### 1.2.1 Asymmetric Hydrogenation

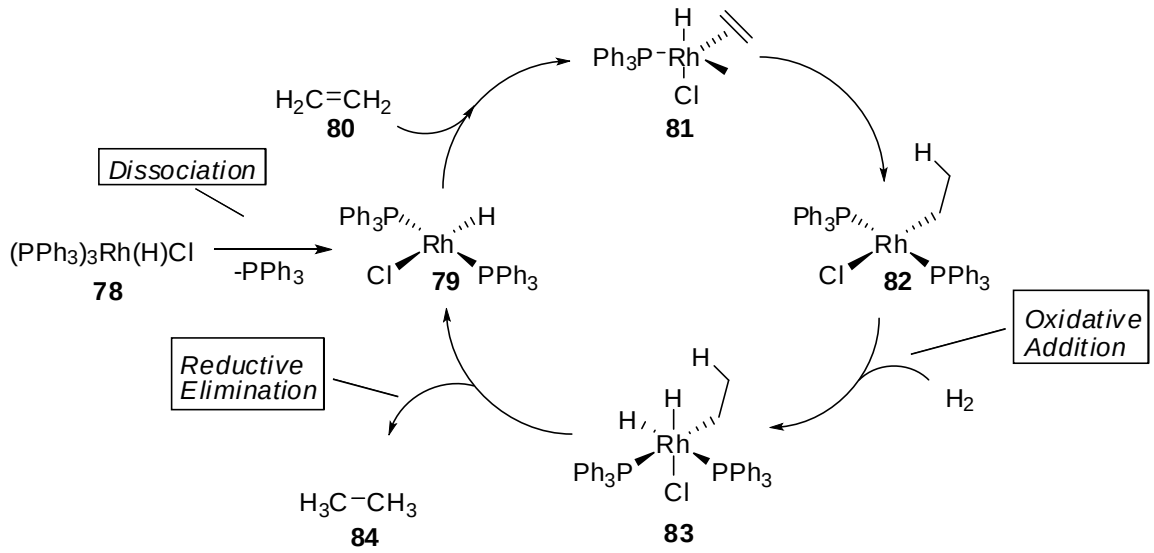
Despite being very simple, dihydrogen is one of the most significant and important molecules in chemistry. On its own, dihydrogen is very stable and won't react with organic compounds, however, when it is activated by transition metals or their complexes then a whole host of reactions can be carried out.

In the early 1970's, Knowles *et al* [24] at the Monsanto Industrial Chemicals Company showed that rhodium complexed with chiral phosphine ligands were able to catalyse the hydrogenation of a range of alkenes with varying degrees of enantioselectivity. Using the crystalline catalyst **75**, the hydrogenation of alkene **76** was achieved in 88% optical purity (**scheme 18**). This was one of the first examples of a synthetic system that could achieve enantioselectivities approaching 100%. This work earned Knowles a share of the 2001 Nobel Prize for chemistry (along with Noyori and Sharpless).



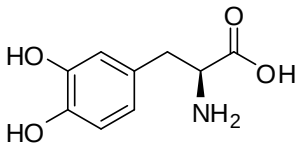

**Scheme 18** Rh-catalysed asymmetric hydrogenation.

The work of Knowles was based upon the non-asymmetric hydrogenation of alkenes developed by Wilkinson *et al*. [25] The mechanism of this process could be visualised in a cyclic manner, incorporating 3 main components: dissociation (of a triphenylphosphine ligand **78 - 79**), oxidative addition (of $H_2$ to the metal **82 - 83**) and reductive elimination (of the alkane product **84**), shown in **scheme 19** below.



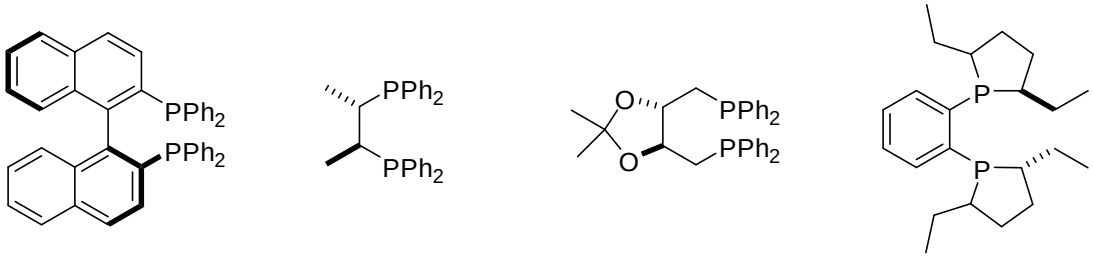

**Scheme 19** Wilkinson catalyst mediated hydrogenation of alkenes

Knowing this process allowed Knowles to deduce that incorporating a chiral ligand onto the metal would furnish a chiral product. Knowles's process was also commercialised to produce the anti-Parkinson drug L-DOPA **85**, followed by the development of other syntheses to produce enantio-enriched compounds.



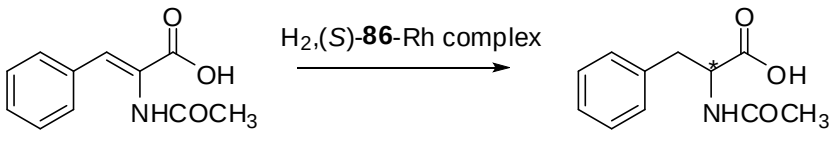

**85**

Having a suitable combination of both metal and chiral ligand is the key to preparing a highly effective catalyst for asymmetric hydrogenation. The development of chiral $C_2$-symmetric diphosphine ligands such as BINAP (**86**), CHIRAPHOS (**87**), DIOP (**88**) and DuPHOS (**89**) presented a great advancement in this area.




**86** **87** **88** **89**

Achieving enantioselectivities of up to 100% with Rhodium complexes (with BINAP) [26], the hydrogenation of functionalised enamides (**scheme 20**) is still one of the most efficient and popular way of synthesising chiral amino acids.



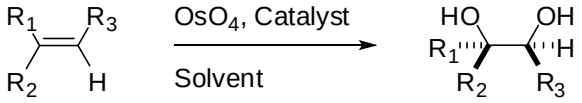

**90** **91**

100% *ee* (*R*)

**Scheme 20** Hydrogenation of functionalised enamide catalysed by (*S*)-BINAP-Rh complex **86**.

## 1.2.2 Asymmetric Dihydroxylation

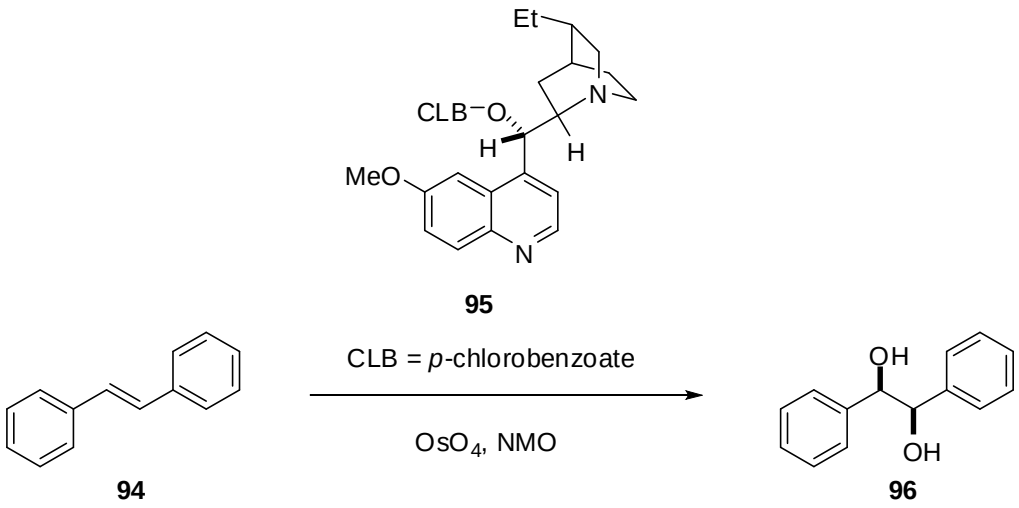
This process is used for the enantioselective synthesis of 1, 2-diols from prochiral alkenes (**scheme 21**).




**92** **93**

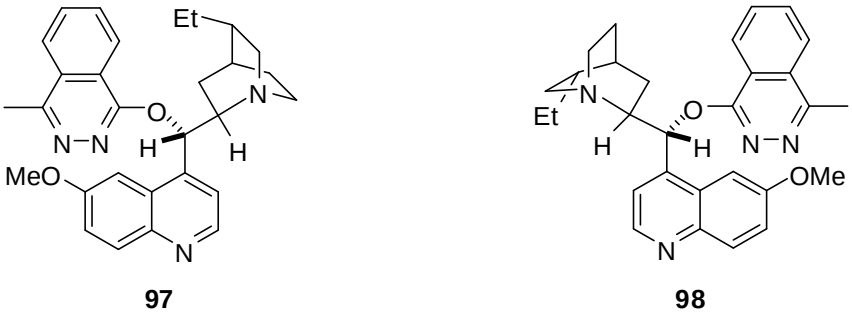
**Scheme 21** General reaction scheme for the asymmetric dihydroxylation

This reaction has been championed by Sharpless since the early 1980s [27] where he used a stoichiometric amount of osmium tetroxide and reacted it with an alkene in pyridine. This was then followed by a reductive hydrolysis with Lithium aluminium hydride (LAH) to furnish the diol. However, Sharpless was able to make this process catalytic by combining it with the Upjohn *N*-oxide based catalytic process.[28] By using *N*-methylmorpholine-*N*-oxide (NMO) as the cooxidant, (*E*)-stilbene, **94** could be dihydroxylated using catalytic amounts of $OsO_4$ and a chiral auxiliary (DHQD-CBL **95**) in 80% yield and 88% *ee* (**scheme 22**). [29]




**Scheme 22** Catalytic asymmetric dihydroxylation of (*E*)-stilbene

The asymmetric dihydroxylation (AD) has undergone major developments since then. One of the most significant has been the introduction of the AD mixes. Since terminal, 1,1-disubstituted and *trans*-substituted olefins could be deemed as 'standard' substrates for AD, then as such they would each require similar reaction conditions. This made it possible to premix all the reagents required ($OsO_2(OH)_4$, which is a non-volatile source of $OsO_4$, $K_2CO_3$, $K_3Fe(CN)_6$, which is used to oxidise the osmate(VI) species and release $OsO_4$ and either $(DHQD)_2PHAL$ **97** (for $\beta$) or $(DHQ)_2PHAL$ **98** (for $\alpha$) as the chiral ligand) for convenience.[30]




The AD mixes could then be employed to effect dihydroxylation and give the added benefit of being able to predict which isomer is formed (ie if AD mix-$\alpha$ gives the *R* isomer, then AD mix-$\beta$ will give the *S* isomer and vice versa). A simple illustration has been designed to show the rationale for enantiofacial selectivity in the AD reaction. (**Figure 5**)

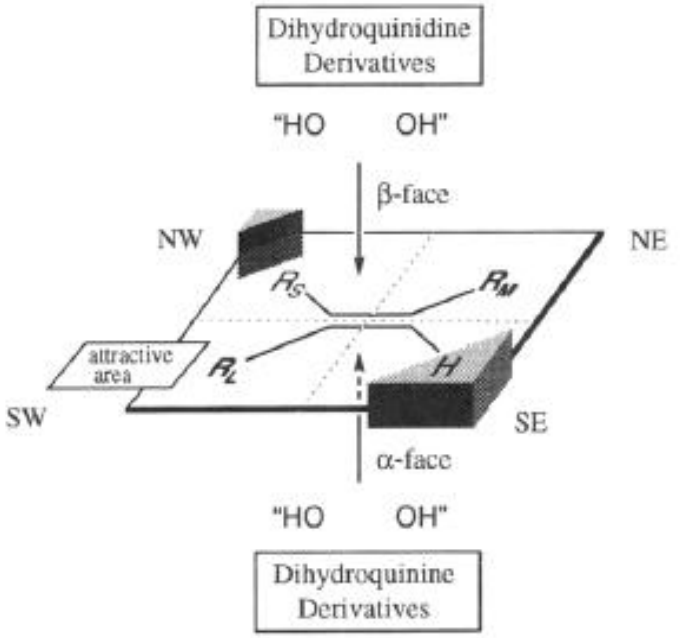
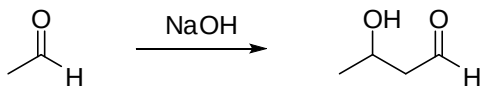



**Figure 5** Rationale for enantiofacial selectivity [30]

This shows that attack can either occur from the $\alpha$ (in the case of DHQ) or $\beta$ (in the case of DHQD) face. The NW and SE areas present steric barriers whereas, the NE area is open to substrates of moderate size and the SW area can accommodate larger substituents. A wide range of olefins can be dihydroxylated using this protocol with enantioselectivities of >99% achieved. The convenience of this protocol along with being able to predict and indeed select which isomer is formed makes this a very powerful and attractive tool for synthetic chemists.

### 1.2.3 Asymmetric Aldol reactions

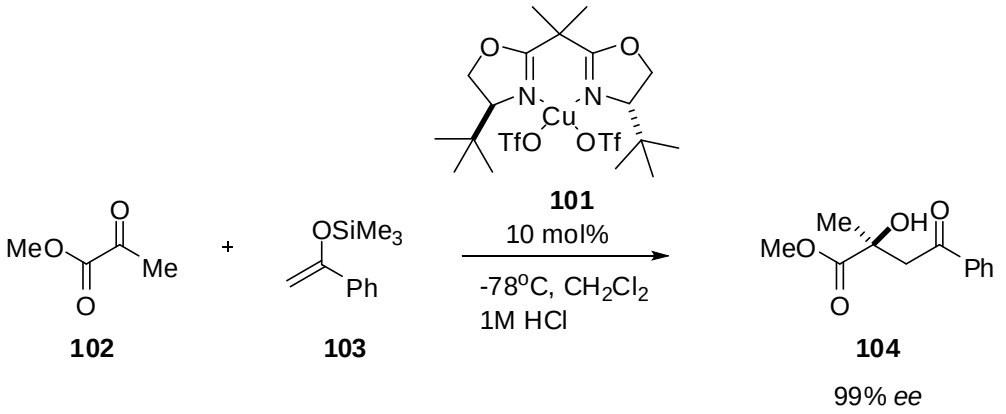
In organic synthesis, the Aldol reaction is one of the most important organic reactions since it is carbon-carbon bond-forming, which can furnish highly functionalised compounds. The asymmetric Aldol reaction has the added benefit of producing two chiral centres. The general reaction scheme is shown below (**scheme 23**).




**99** **100**

**Scheme 23** General base catalysed Aldol reaction [31]

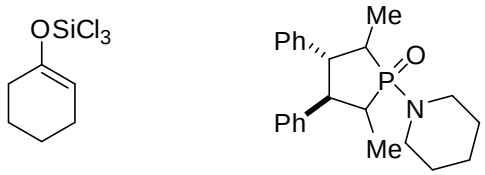
Evans *et al* [32] synthesised and studied Cu(II) complexes prepared from bisoxazoline ligands **101**. He used the ligand complexes in various Aldol addition reactions including methyl pyruvate (**scheme 24**) and benzyloxyacetaldehyde.




**Scheme 24** Asymmetric Aldol addition of methyl pyruvate with silyl enol ether

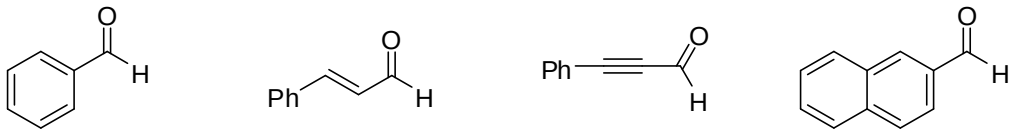
The addition went smoothly furnishing the acetophenone adduct in 99% *ee* using only 10 mol% of ligand complex.

Denmark *et al* [33] described a process that uses trichlorosilyl enolates **105** as the nucleophilic components in the asymmetric Aldol addition reaction. Although these silyl enolates are sufficiently reactive to react with aldehydes, he noted that the addition could be accelerated in the presence of a Lewis basic chiral phosphoramide **106**.




**105** **106**

Over a range of aldehydes, high levels of enantioselectivity was observed (**figure 6**).

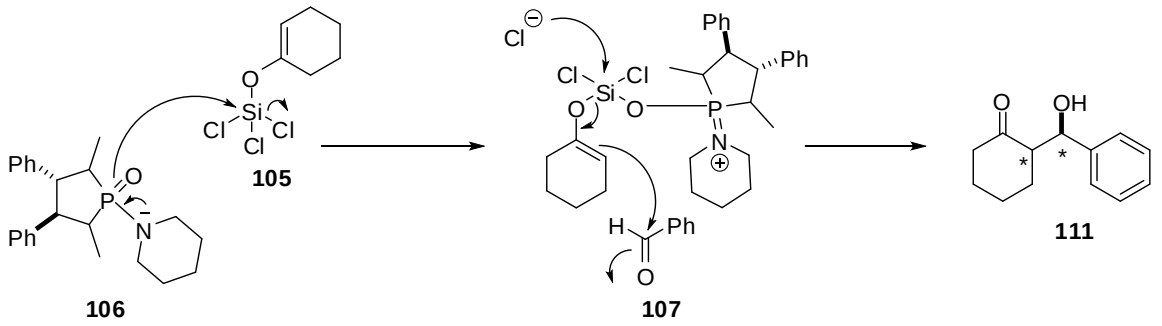



93% *ee* 88% *ee* 82% *ee* 97% *ee*

**107** **108** **109** **110**

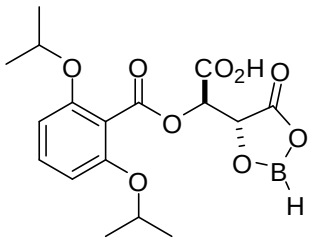
**Figure 6** Substrates used in the Aldol addition with **105** in the presence of **106**.

The proposed mechanism for the transformation of **107** into the *β*-hydroxy ketone **111**, utilising the phosphoramide catalyst **106** and the silyl enolate **105** is shown in **scheme x**.



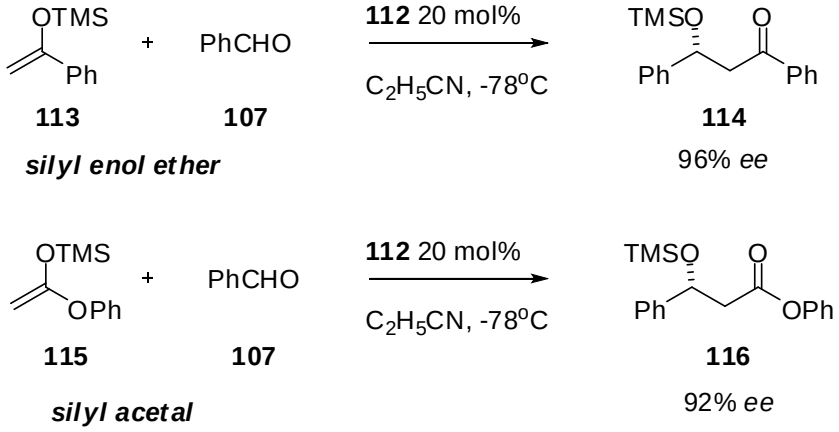

**Scheme 25** Proposed mechanism for the transformation of **107** into the *β*-hydroxy ketone **111**.

Yamamoto *et al* [34] showed that the chiral acyloxyborane complex **112** was a superb catalyst for the asymmetric Mukaiyama condensation of simple silyl enol ethers.




**112**

Using this protocol, the formation of the *syn*-aldol adduct is preferential and in high enantioselectivity. The general scheme is shown below (**scheme 26**). This system is not limited only to simple silyl enol ethers but can be extended to ketene silyl acetals also, again with high enantioselectivities observed (>97% *ee*) (**scheme 26**).




**Scheme 26** Asymmetric Aldol reaction catalysed by complex **112**.

## 1.2.4 Conclusion

From the few examples reported herein, it is clear to see the advances that have occurred within the field of asymmetric catalysis. The use of metal-derived catalysts to facilitate such processes as hydrogenation and Aldol addition, gives the organic chemist access to important and enantiomerically-enriched compounds. Although metal-mediated processes are plagued by high cost catalysts and metal leaching, there will surely always be a requirement for such protocols.

## 1.3 Introduction to imine reduction

From the literature, it is apparent that there are numerous ways in which imines can be reduced into chiral amines. These methods can range from hydrogenation to hydrosilylation and from metal-mediated to organo-catalyst mediated reductions.

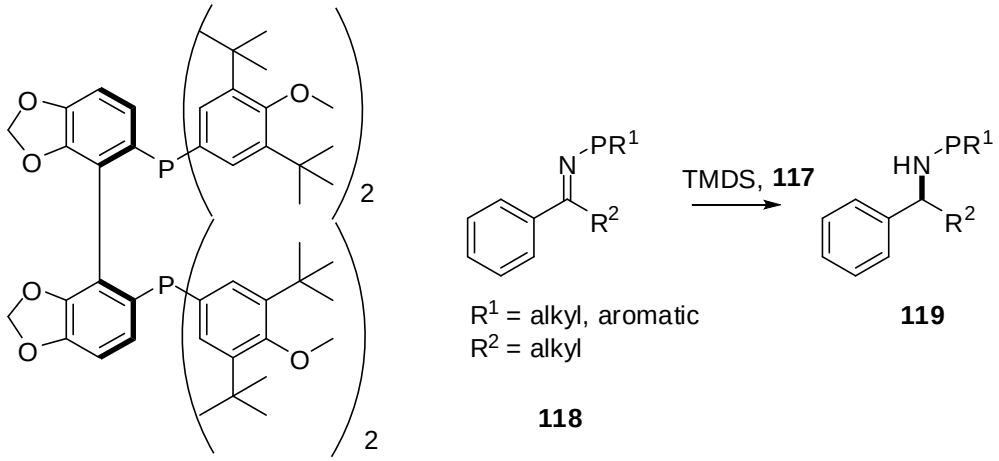
### 1.3.1 Hydrosilylation

Hydrosilylation is described as a process by which Si-H element is added across an unsaturated double bond (C=N in this case) [1].

Lipshutz *et al* [35] recently reported the use of TMDS[#] with PMHS (polymethylhydrogensiloxane), at room temperature, in the highly enantioselective

[#] tetramethyl disiloxane

hydrosilylation of a range of aromatic imines. In the presence of (*R*)-(-)-DTBM-SEGPHOS **117**, *N*-phosphonyl imines **118** were reported to be reduced in almost quantitative yields with enantioselectivities peaking at >99% *ee* (**scheme 27**)




**Scheme 27** *N*-phosphonyl imine reduction with **117**

The use of MeOH as an additive, in the presence of NaOMe, drove the reaction almost to completion. Switching from CuH to TMDS, with 1% CuCl as the catalyst had a marked effect on the selectivity: >99% *ee* with TMDS compared with 40% *ee* with CuH. One final observation noted was that when 2-3.3 equivalents of $^{t}$BuOH was added in place of MeOH, the rate of reaction was enhanced, whilst still maintaining the high levels of enantioselectivity. This has proved to be an effective, cost efficient and environmentally sound (since toluene is the solvent of choice) method of reducing imines in a highly enantioselective manner. A suggested transition state for the catalytic cycle is outlined below in **figure 7**.

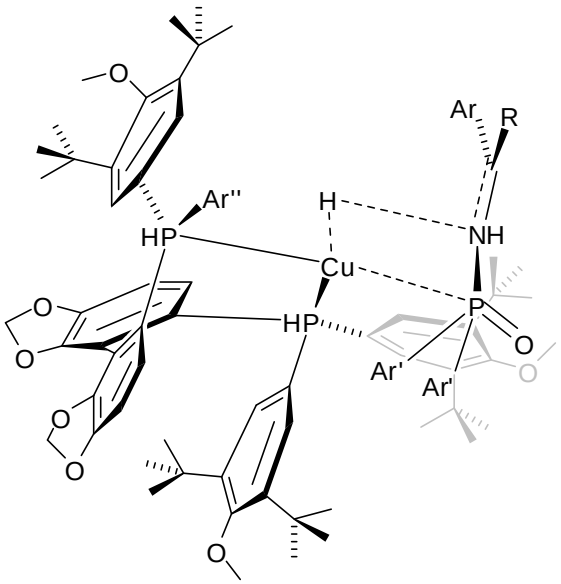
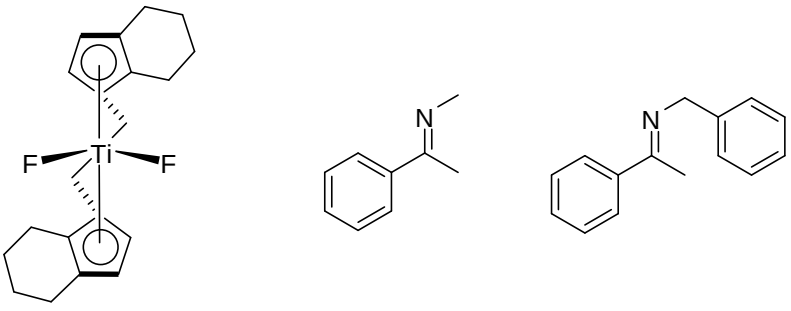



**Figure 7** Suggested transition state for the interaction of (*R*)-(-)-DTBM-SEGPHOS **117** with the active Cu catalyst and imine **118**.

Buchwald *et al* [36] discovered a method by which a range of imines could be reduced in excellent enantioselectivity (>99% *ee*). He utilised a titanium catalyst **120** and when treated with phenylsilane ($PhSiH_3$) at room temperature, in some cases, the imines could be reduced completely within 12 hours, in high selectivity (97% *ee* as in the case of reduction of **121**).

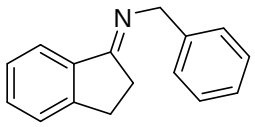



**120** **121** **122**

However, it was observed that this level of enantioselectivity was extremely dependant on the *N*-substituent of the imine since it was postulated that the nitrogen would infact coordinate to the Ti. When the *N*-substituent was switched from methyl **121** to benzyl **122**, and reaction conditions kept the same, it was noted that not only did the enantioselectivity drop significantly (<47% *ee*), but the conversion halved. This would suggest that coordination to the Ti was restricted due to steric factors. Furthermore, if any reaction was to take place at all then the catalyst loading had to be increased 10-fold. The

silane used was then altered. He attempted the reduction of **122** again, only this time using PMHS* as the hydride source, but observed similar disappointing results.

The use of nucleophilic catalysts in organic chemistry to transform intermediates into more reactive species was utilised in an attempt to make the Ti-amido intermediates more reactive. This would allow the system to be more widely applicable to a wider range of imines. A small range of such nucleophilic catalysts was tested alongside PMHS and the titanium ligand **120** on the reduction of **123**.

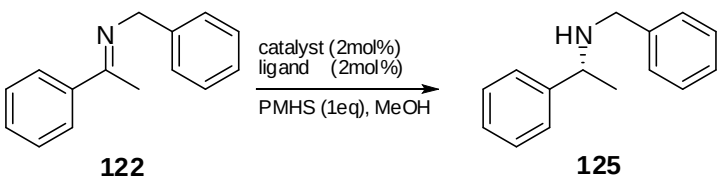


**123**

From his studies, it was noted that bulky nucleophiles such as $^{t}$butylamine and secondary amines such as pyrrolidine were ineffective as nucleophilic catalysts. Isobutylamine proved to be best: furnishing the reduction of **123** with >92% *ee* with 100% conversion. This reaction was also complete in less than 2 hours at 60$^{o}$C. It should be pointed out that loading of **120** was only 1%.

It would therefore appear that this is a protocol that benefits from high selectivity and low reaction times. The use of PMHS is beneficial here in that it is a cheap reagent. The use of **120** however, provides problems due to the high cost of metal-based reagents and also the environmental impacts associated with metals.

Ireland *et al* [37] reported the use of PMHS in the reduction of imines. As with the research of Buchwald [36], Ireland opted to concentrate the asymmetric tests on imine **122**, with the general reduction scheme shown below (**scheme 28**).

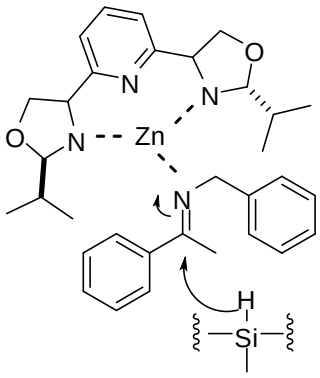



**122** **125**

**Scheme 28** General reduction protocol

* Polymethylhydrosiloxane

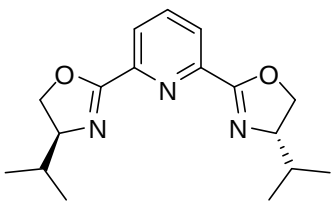
It could be postulated that coordination of the chiral catalyst to the imine, through the metal would block one diastereotopic face and thus result in hydride delivery from one face only. This is shown below (**figure 8**).



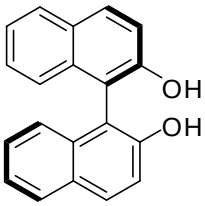

**126**

**Figure 8** Propsed mechanism for the involvement of the chiral catalyst and metal in the hydride delivery

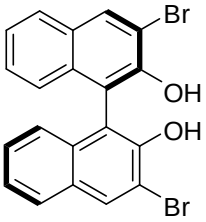
Varieties of metal-based catalysts, as well as a variety of chiral ligands were screened. Without the use of a chiral ligand, it was observed that the catalyst $Zn(OTf)_2$ could be used in only 2 mol% whilst still allowing good conversion. In contrast, the other catalysts ( $Sn(OTf)_2$ , $In(OTf)_3$ , $Cd(CHB)_2$ ) all required 10 mol% loading to achieve comparable conversions. The introduction of a chiral ligand (**figure 9**) did however, allow the catalyst loading to be reduced to 2 mol% across the board.




**127**




**128**




**129**

**Figure 9** Range of chiral catalysts used

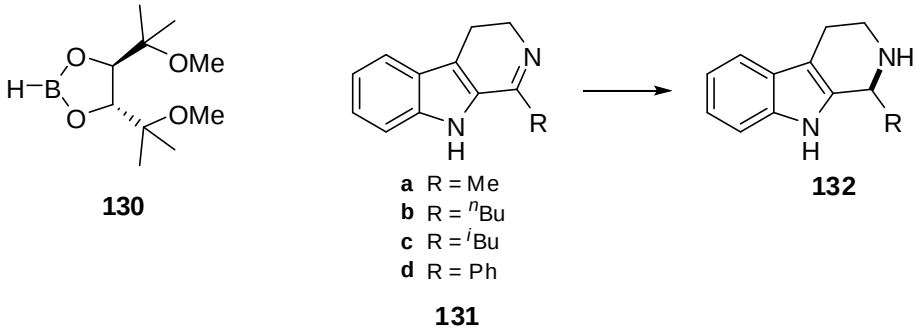
On reduction of **123** using 2 mol% of **128**, PMHS and $Sn(OTf)_2$, conversion was high but enantioselectivity was low (<40%). With such a low value for enantioselectivity, Ireland modified **128** slightly to produce **129**. Using this 3,3'-disubstituted binapthol and entering it into the same reaction conditions as previously used, the conversion remained high, but

most importantly, the selectivity rose to 60% *ee*. Although benefiting from high conversion rates, this system can only afford moderate selectivity.

The use of metals in this system obviously isn't ideal, however, their system does show great resilience in that the reactions can be carried out in air without detriment to the results.

### 1.3.2 Oxazaborolidine/borane-mediated reductions

Nakagawa and co-workers [38], as part of a drive to produce biologically important alkaloids, turned to reducing imines using new chiral borane reagents. Dialkoxyborane **130** was developed and the reduction of a range of β-carbolines (**131a-d**) attempted (**scheme 29**).



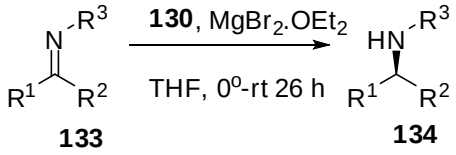

**130** **131** **132**

**Scheme 29** Reduction of **131a-d** with **130**

With the reaction carried out at –78°C in THF, reduction of **131a-c** all occurred within 10 minutes with excellent conversion (98-100%). Enantioselectivities were low however, with **131a-c** obtaining 42, 23 and 23% *ee* respectively. The reduction of **131d** took 7.5 hours to complete but again achieved high conversion (96%). However, as with the others, low selectivity was observed (27% *ee*). These particular imines were selected not only due to their stability, but also because of their potential in the synthesis of indole alkaloids.

With these results at hand, work proc*ee*ded to synthesise and reduce a series of aromatic and alkyl ketimines still using catalyst **130**. However, when an activator ($MgBr_2.OEt_2$) was added to the reaction mixture, a marked rise in the enantioselectivity was observed. Ketimine **133** ($R^1$ Et, $R^2$ Ph, $R^3$ Ph) was reduced to afford **134** in 73% *ee* whilst again

retaining high conversion. Over a range of imines, conversions remained high and the selectivities varied from 65-73% *ee* (**scheme 30**).

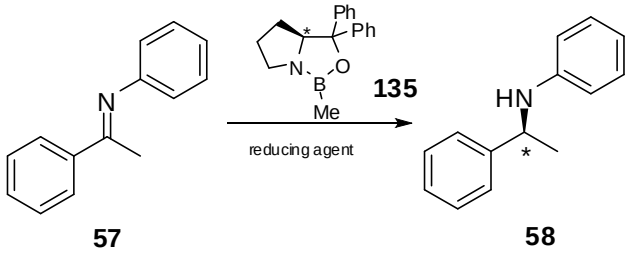



**Scheme 30** Imine reduction catalysed with **130**

The results obtained show excellent potential. With a better understanding of the mechanism of action, the system could be developed to produce higher enantioselectivities.

The use of chiral oxazaborolidines, especially Corey's (*S*)-methyl-CBS-oxazaborolidine **135**, has found a wide range of applications in relation to ketone reduction. However, little investigation has b*ee*n carried out on their potential utility in imine reductions.

Field *et al* [39] had cause to investigate this potential further and began by reducing imine **57** with a reducing agent (borane-THF or catecholborane) in the presence of **135** (**scheme 31**)




**Scheme 31** Ketimine reduction catalysed by **135**

He found that when borane-THF was used, the reduction furnished **58** with decent conversion (69%) and high selectivity (87% *ee*). When catecholborane was used, conversion increased to 98% whereas the selectivity dropped to 47% *ee*. The uncatalysed reactions however, were over in <10 minutes, and conversion in both cases were above 90%. This, as a result, poses a problem for asymmetric reductions since the catalysed reaction would have to be significantly faster than the competing background reaction giving racemic product.

It was noted the absolute configuration of **58** changed when the reducing agents were changed: *R* for borane-THF (see complex **136**) and *S* for catecholborane (see complex **137**). They suggested that this was apparent due to steric effects, and the following transition states (**figure 10**) were proposed

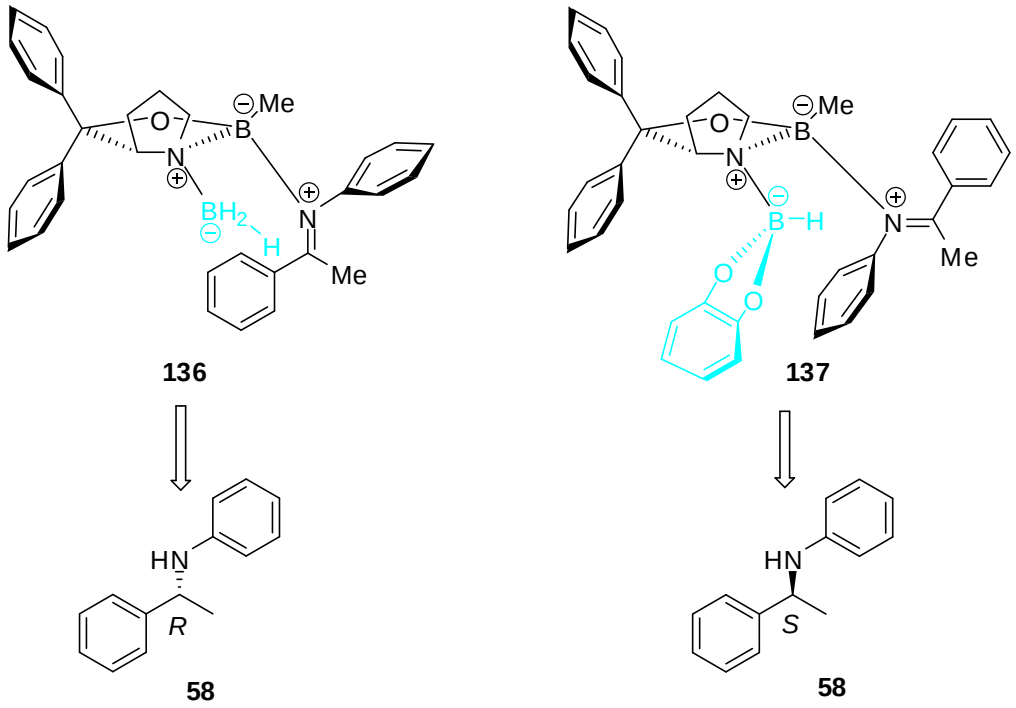
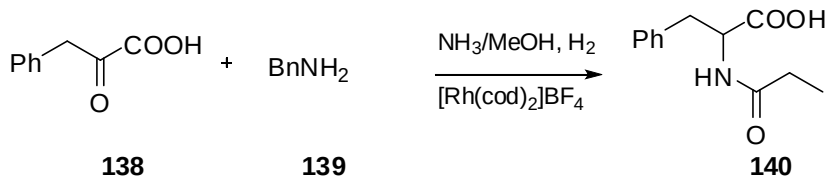



**Figure 10** Proposed transition states

From the models above, it can be s*ee*n that if either were to adopt the opposite conformations, then the steric clashes betw*ee*n the aryl groups would prevent the reductions taking place. This system shows the benefits of not only obtaining high selectivity, but chiral secondary amines can be produced in a predictable configuration. The high costs of the borane reagents are the only limiting factor to this system.

### 1.3.3 Hydrogen-transfer reductions

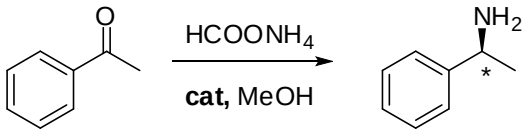
One of the most common methods of preparing amines is the metal-catalysed reductive amination of carbonyl compounds with hydrogen as the reducing agent. [40] Kadyrov *et al* recently developed a highly selective catalytic system for the reductive amination of α-keto acids [41]. This involved reacting a α-keto acid in methanolic ammonia ($NH_3$/MeOH) at 60$^{o}$C in the presence of a rhodium catalyst. This was shown to furnish the corresponding amine smoothly (**scheme 32**).




**138** **139** **140**

**Scheme 32** Reaction of an a-keto acid in the presence of a Rh catalyst

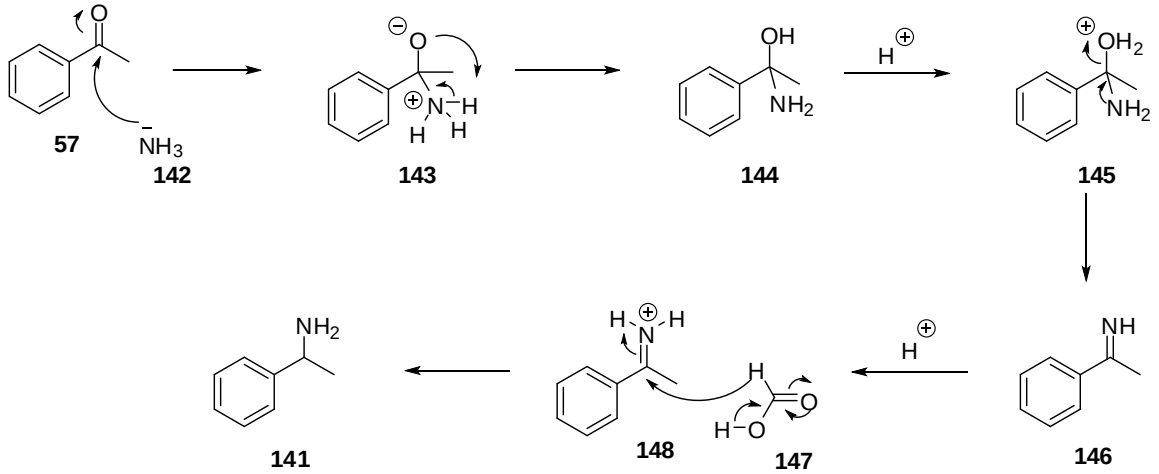
Based on this result, they attempted asymmetric reductive amination, using a chiral catalyst [42]. Under Leuckart-Wallach reaction conditions[#], they used ammonium formate as the hydrogen source, which was shown to work best with a range of metal-based catalysts (**scheme 33**).




**57** **141**

**Scheme 33** Reductive amination under Leuckart-Wallach conditions

The mechanism for this process is suggested below (**scheme 34**).




**Scheme 34** Mechanism for reduction under Leuckart-Wallach conditions.

Initial tests showed that the catalysts [((*S*)-binap)$RuCl_2$] and [(*R*)-tol-binap)$RuCl_2$] proved to be most effective: both affording *ee*'s >90% for the reductive amination of 2-acetylnapthalene. Coordination of the metal to the nitrogen of the imine intermediate would shield one face from attack, leaving the other face open for hydride transfer. Or indeed, coordination to the imine nitrogen and formic acid may align the substrates up in

[#] The reduction of carbonyl compounds with formic acid or formamide

such a way that hydride transfer will occur preferentially to one face of the imine. This would of course be selective for the catalyst used (ie *R* or *S*).

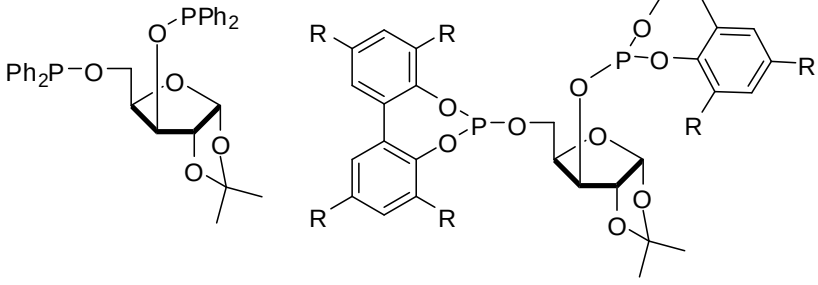
Further tests identified [(*R*)-tol-binap)$RuCl_2$] to be the champion catalyst. When reacted with ammonium formate in $NH_3$/MeOH at 85$^oC$, a series of 12 substrates were reduced in high enantiomeric excesses >91%. Kadyrov and co-workers have developed an admirable system for the synthesis of primary amines. It has also shown high levels of asymmetric induction for aromatic ketones.

## 1.3.4 Hydrogenation

The enantioselective hydrogenation of olefins and ketones using phosphorous ligands in catalytic systems is well documented. However, only a handful of highly selective imine hydrogenations have b*ee*n reported. Spindler [43] reported the reduction of imine **125** with Rh/$bdpp_{sulf}$ occurred with high conversion and optical purity (94% *ee*).

Claver *et al* [44] have recently reported the use of iridium complexes as effective catalysts for the selective hydrogenation of imines. Up until now, iridium-diphosphines were the most effective and commonly used systems for hydrogenation, but little was known about the use of diphosphite or diphosphonites as chelating phosphorus ligands.

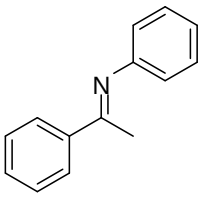
R*ee*tz [45] and Dieguez [46] had recently reported the potential of diphosphite and diphosphonite ligands. A range of alkyl and aromatic olefins had b*ee*n hydrogenated using different rhodium diphosphite ligands with enantioselectivities >98% *ee*. Based on these initial findings, it was decided to apply xylose-based diphosphonite **149** and diphosphite **150**, **151** ligands in the hydrogenation of imine **57**.



**149**

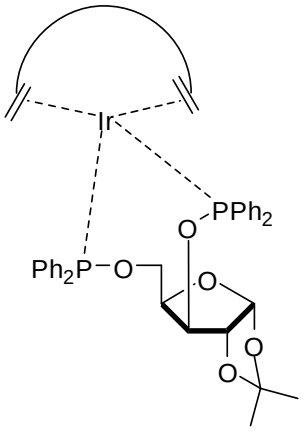


**150** R = H
**151** R = $^t$Bu



**57**

Instead of using rhodium, the use iridium was employed and the corresponding metal complexes of **149** and **152** synthesised.




**152**

Initial hydrogenations of **57** showed promise. Using complex **152**, corresponding amines of **57** could be produced with moderate selectivities of ~57% *ee*. The pressures required for this transformation remained relatively low at 10 bar. The same reaction was again tried, only this time adding $Bu_4NI$ as an additive to observe if it had any effect on the enantioselectivity. Although conversion was high (96%), the additives had a detrimental effect on the enantiomeric excess: lowering it to 15% *ee*.

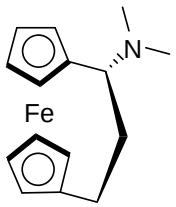
On testing the same hydrogenation using the Ir-complexes of **150** and **151**, without the use of the additive, almost racemic amines were obtained. However, on addition of $Bu_4NI$ or simply $I_2$, selectivity peaked at >46% *ee*.

These results have revealed that diphosphite and diphosphonite ligands can induce moderate selectivity for the hydrogenation of imines. It has also b*ee*n shown that the enantioselectivity obtained is strongly dependant on the structure of the ligand as well on the effect of additives.

### 1.3.5 Other Reactions

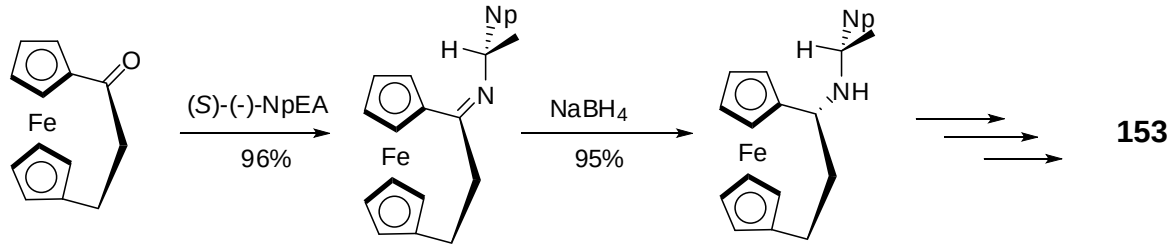
When developing a new system for asymmetric reductions, it is important to obtain the racemic product from the reduction in order to ascertain whether or not the asymmetric results are ind*ee*d valid. To do this, reducing agents such as $NaBH_4$ or $LiAlH_4$ can be used. However, if the substrate being reduced already contains a chiral centre close to the double bond, then the use of $NaBH_4$ can afford highly diastereoselective results.

Weissensteiner *et al* [47] utilised this concept when designing new ferrocene-based ligands. They looked at designing a simple and selective synthesis of amine **153**.




**153**

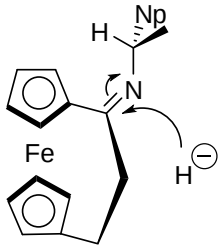
The resolution of this amine was very time consuming, so the ultimate aim here was to find an easier way to make it. Starting from **154**, it only took two easy steps to obtain the correct framework and in the correct configuration (**scheme 35**).




**154** **155** **156**

**Scheme 35** Synthesis of **153**.

The key step in this synthesis was the diastereoselective $NaBH_4$ reduction of imine **155**. Due to the highly selective diastereofacial reduction, **156** was furnished as a single diastereomer and in almost quantitative yield. Thr*ee* more simple steps were performed to afford **153** in an overall yield of 54% with optical purity of >98%*ee*. He postulated that because imine **155** was *syn*, then the $NaBH_4$ reduction could be rationalised by a hydride attack at the C=N bond carbon on the *Si* face **157**. This step then determined the absolute configuration of the final product **153**.

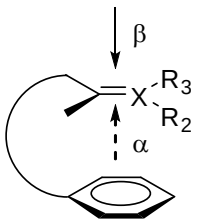



**157**

However, (*S*)-(-)-Np-EA (naphthalene ethylamine) is a rather costly chiral auxiliary, so it was decided to try using the much cheaper (*S*)-(-)-PEA (phenyl ethylamine) instead. It was discovered that use of this auxiliary furnished **151** in 55% yield with an optical purity of >98%. It has b*ee*n shown that the synthesis of **153**, which used to be costly, can now be achieved, without detriment to the purity or yield, at a lower cost.

## 1.4 Introduction to π-π interactions

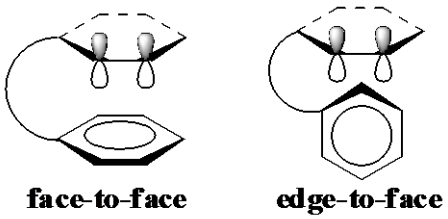
It has been recently shown that π-π interactions can have a distinct impact on the reactivity and enantioselectivity of organocatalytic reactions [48]. The term π-π shielding is used to describe the way that one face of an unsaturated moiety is shielded from attack from an incoming species by an interaction of an aromatic group and is described thoroughly in the 2001 review by Jones. [49] For example, the α-face of an unsaturated compound could be shielded from attack, thus allowing attack to occur exclusively on the β-face **158**.




**158**

This interaction can take two forms; it can be of **steric** origin or of **electronic** origin. The steric origin is how is sounds, merely blocking the approach to the shielded face. The electronic origin however, describes an established stabilising interaction between the two components. However, when an intramolecular distance of 3-4 Å between the two components is observed, then these two forms of interaction are collectively referred to as **π-stacking**, regardless of whether the origin of it is steric or electronic.

π-stacking refers to the interaction of the π-cloud of the unsaturated moiety with the aryl component. This can take the form of a **face-to-face** or **edge-to-face 159** relationship with the aryl component. [50]



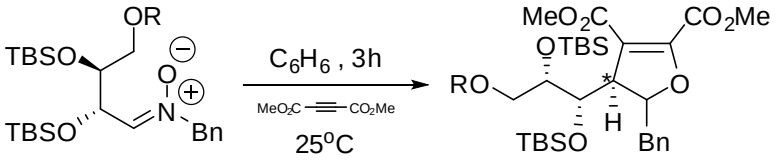

**159**

There are some examples of asymmetric transformations that rely on π–π interactions cited in the literature, as well as examples of yet un-addressed possibilities that may exist for the said systems. To try and quantify what π–π interactions are and how they work in real terms, several asymmetric transformations, namely **cycloadditions**, **conjugate additions**, **alkylations** and π–π interactions related to **artificial receptors** will be described herein.

## 1.4.1 Cycloadditions

In recent years, nitrone-olefin [3+2] cycloadditions, applied in the synthesis of nitrogen-containing natural products have been proving very fashionable. The reason behind this popularity is its ability to add both amino and hydroxyl functionalities to a molecule in chorus as well as lengthening the carbon-chain length by sometimes more than two units: a process fundamentally difficult to achieve.

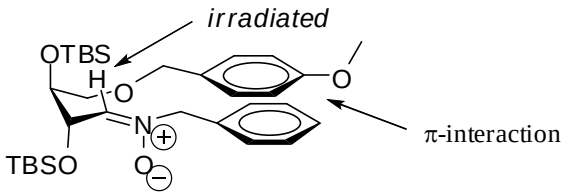
Saito *et al* [51] utilised the concept of facial shielding when designing chiral nitrones for this process. He discovered that when nitrone **160** underwent a [3+2] cycloadditions with DMAD (dimethyl acetylendicarboxylate), adduct **161** was formed exclusively (**scheme 36**).




**160** **161**

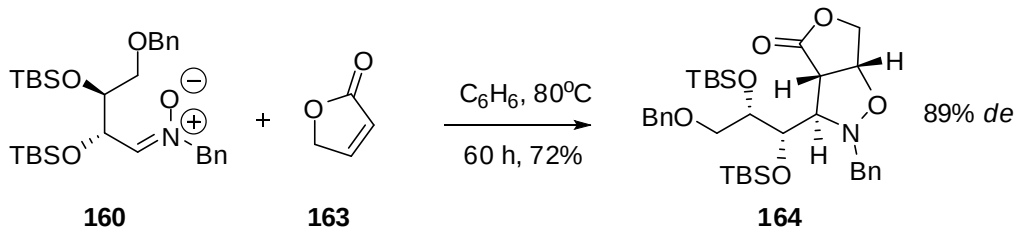
**Scheme 36** [3+2] cycloaddition

It was rationalised this result on the basis that one face of the [C=N] dipole was exclusively shielded, most likely caused by π-interactions between the PMB moiety and Bn group **162.**




**162**

It was proven that this interaction was achievable by showing that the Z-isomer was in fact the exclusive isomer by conducting nOe studies. A nOe of 7.2% was observed on the benzylic protons when the azomethine proton was irradiated. A coupling constant of 3.2 Hz between the two protons on the vicinal protected diol unit also supported this conformation. **160** [R = Bn] was then reacted with γ-butenolide **163** to afford adduct **164** in 89% *de* (**scheme 37)**.

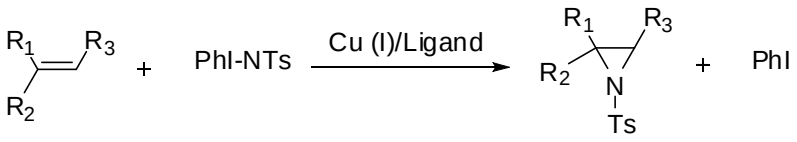



**160** **163** **164**

**Scheme 37** [3+2] cycloaddition.

From this work, the strength of π–π interactions in asymmetric synthesis has been shown. To produce 3 stereogenic centres in a controlled and predictable fashion is no easy feat, and as a result Saito has turned his attention to the problem of how to discriminate the π-[C=C]-face of the olefin. Work on this area continues.

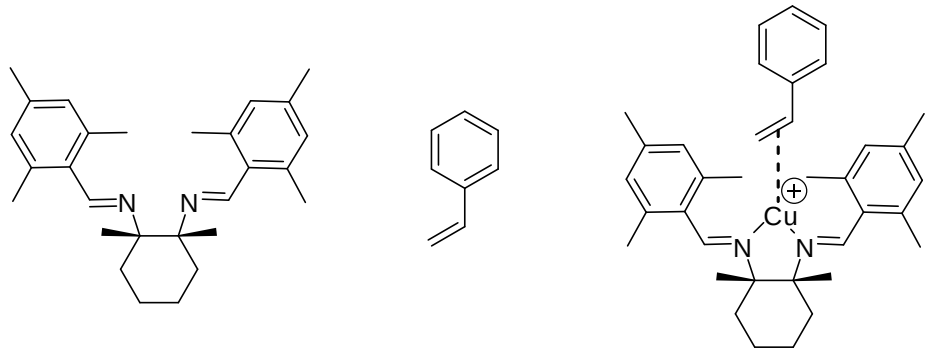
Jacobsen *et al* [52] recently discovered that a $C_2$-symmetric 1,2-diimine could be an effective ligand for the Cu (I)- catalysed aziridination and cycloproponation reactions (**Scheme 38)**.




**165** **166** **167** **168**

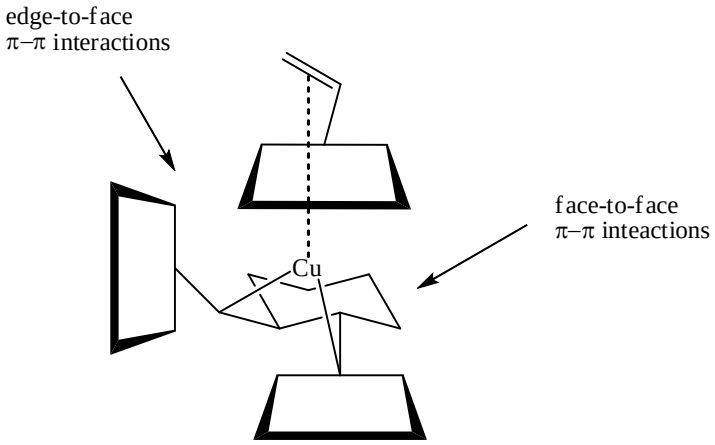
**Scheme 38** Aziridination

The diimine complex **169** [53] was then synthesized and coordinated to styrene **170** and Cu to afford complex **171**.




**169** **170** **171**

He then successfully managed to crystallise complex **171** and as a result, unearthed some unanticipated characteristics. Simultaneous face-to-face and edge-to-face π–π interactions were shown to be occurring within the complex between the substrate and the chiral ligand. This is more clearly shown below **172**.



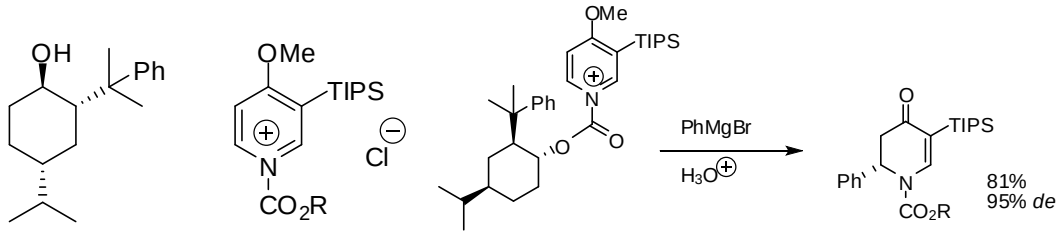

**172**

This type of simultaneous interaction has already been proven to play a crucial role in the enantioselective outcome of the Sharpless asymmetric dihydroxylation reaction [54].

It has been revealed that attractive edge-to-face and face-to-face π–π interactions can play an influential role in the enantiofacial selectivity in the binding of prochiral substrates to this class of chiral catalyst. He has shown that complex **171** can be formed with an enantiofacial selectivity of >98:2 (or >96% de).

### 1.4.2 Conjugate Additions

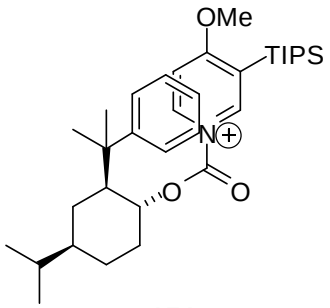
The synthesis of synthetically useful dihydropyridones by addition of Grignard reagents to acylpyridinium salts can pave the way to synthesis of alkaloids in an enantioselective manner. Comins *et al* [55] have recently been working on just that. By exploring different cyclohexyl-based chiral auxiliaries of the 8-phenylmenthol type, he found that Grignard addition to an acylpyridinium ion could give access to a dihydropyridones in up to 95% *de*. It was found that the CPC auxiliary **172** (cyclohexyl based auxiliary of the 8-phenylmenthol) type was best and when coupled to a pyridinium ion of type **173**, **175** could be formed in >95% *de* after alkyl addition, with the dihydropyridones unlocked after hydrolysis (**scheme 39**).




**172** **173** **174** **175**

**Scheme 39** Conjugate addition of PhMgBr to **173.**

This high selectivity was most probably explained by π–π interactions. The overlap of the phenyl group with the pyridinium ion could be reasonably assumed, thus resulting in the top face becoming shielded and only lower face attack occurring **174**.

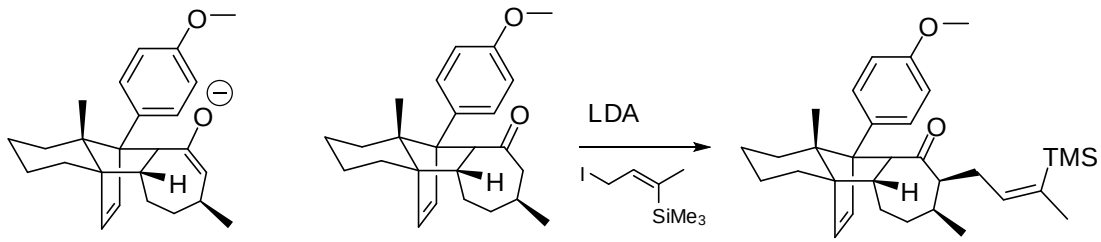



**174**

This particular auxiliary proved most effective but the contribution of the $^{i}$Pr group is not easily explained, but may influence rotamer populations and thus provide the optimum π–π overlap. This work carried out by Comins further shows the effect that π–π interactions have on asymmetric synthesis when producing enantioselectively, synthetically useful compounds.

## 1.4.3 Alkylations

Winterfeldt *et al* [56] utilised the concept of π-shielding with a diastereoselective alkylation in part of the synthesis of Clavularin A. The enolate **176** of **177** underwent a clean alkylation with the allylic iodide **178** to give selectively the *cis*-product **179 (scheme 40**).

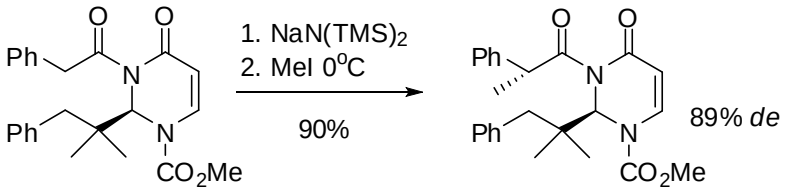



**176** **177** **178** **179**

**Scheme 40** Alkylation of **177** with **178**.

This observation was rationalised by predicting that there was a remote π–π interaction with the aryl group shielding the α-face of the [C=C] of the enolate. This resulted in the β or syn-product being formed exclusively. The role of the *p*-methoxy group, if any, could not be ascertained with any great clarity.

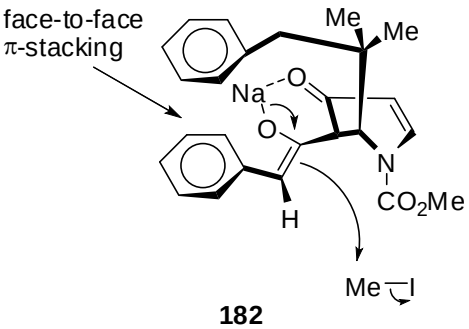
Negrete *et al* [57] also studied the stereoselective alkylation of enolates, but in a bid to study the influence of intramolecular π–π interactions, he synthesized the sodium enolates of a range of aryl pyrimidinones including **180.** This was alkylated simply using methyl iodide and the stereochemistry of **181** determined (**scheme 41**).




**180** **181**

**Scheme 41** Alkylation of aryl pyrimidinone **180**

In this case **181** was formed in decent diastereoselectivity with high conversion also. With this result in mind, it was postulated that π-stacking (face-to-face) between the two aryl groups resulted in the upper face becoming blocked and allowing almost selective attack at the lower face (see **figure 11**).

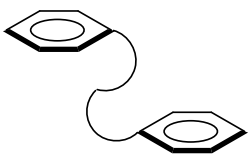



**182**

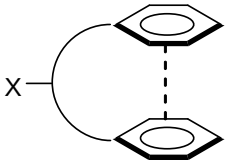
**Figure 11** Role of arene-arene interactions in selective alkylations

## 1.4.4 Artificial Receptors

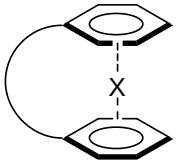
In recent years there has been a growing interest in the development of synthetic receptors where diaryl compounds **183** can interact in unexpected ways. These compounds can adopt π–π-orientated conformations that will allow substrates to interact with receptor framework in a manner external **184** or internal **185** to it.



**183**

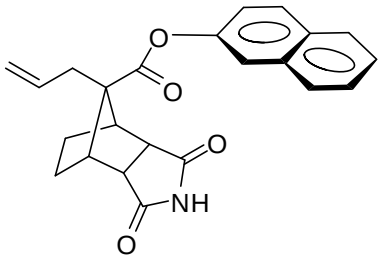



**184**



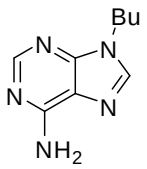

**185**

Deslongchamps and co-workers [58] developed an example of a synthetic receptor **185**. The compound was designed to specifically probe the stacking interactions in Adenine: Thymine base pair mimics.

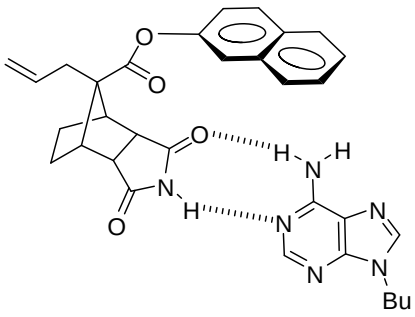



**185**

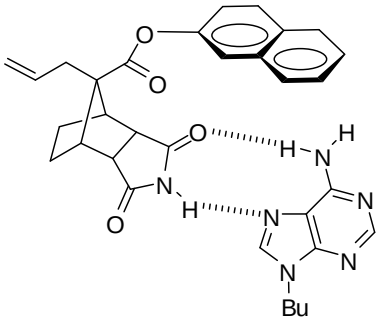
When the receptor was reacted with 9-butyladenine **186**, NMR analysis of the complex showed there to be evidence of both Watson-Crick **187** and Hoogsteen **188** complexes, so the participation of π-stacking interactions were confirmed.




**186**




**187**




**188**

## 1.4.5 Conclusion

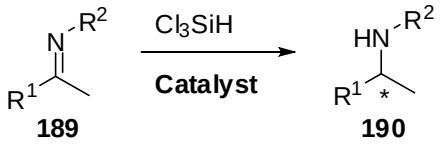
The concepts of π–π interactions (π-shielding and π-stacking) continue to be used to explain the outcome of numerous regio- and stereochemical processes. As the concept of π–π interactions is still in its infancy, evidence reported herein would suggest that with a proper and full understanding, it may be possible to unlock and harness its full potential.

# Chapter 2: Results and Discussion

## 2. Results and Discussion

### 2.1 Introduction

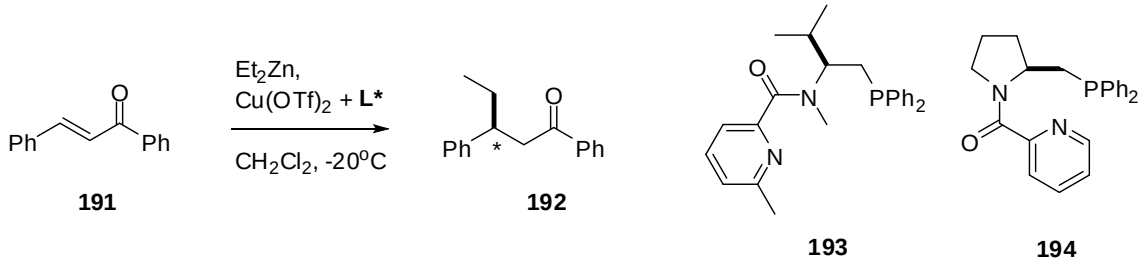
To date, the asymmetric reduction of ketones, both stoichiometric and catalytic is well known and well developed.[59] However, the corresponding ketimine reductions have a much more limited portfolio of protocols and applications.[59-61] These protocols rely heavily on transition metal catalysis with the most successful being high pressure hydrogenation,[59,60] hydrosilylation[58,60] and transfer hydrogenation.[60,42] These classical approaches (**Scheme 42**), although effective, suffer from the problems of metal leaching and catalyst regeneration. The metal leaching can be a considerable problem if the protocol is being used in the manufacture of pharmaceuticals and due to the high cost of the catalysts, not being able to regenerate them can have significant economic implications for users. So for these reasons, the development of an organocatalytic approach would seem to be very attractive.




**189** **190**

**Scheme 42** General scheme for the reduction of ketimines

In general, to develop a new catalytic protocol involves a fine balancing act between various factors, such as catalyst structure, loading, solvent and temperature. Often even an insignificant change in any of these factors can result in a very significant change in the stereochemical outcome of the reaction and not always for the better.[59,62] There are many approaches that can be used to help design a catalyst but one which is gaining strength is the chiral relay effect.[63] This is designed to enhance enantioselectivity through structural variations by carefully placing a conformationally flexible group in such a way that the chiral information from the catalyst can be passed onto the reaction centre.[63] This was shown effectively by the Kocovsky-Malkov group.[64] For the Cu(I)-catalysed conjugate addition of $Et_2Zn$ to α,β-enones (**Scheme 43**) it was shown that the *N*-methylamino acid-derived amidophosphine ligands derived from *N*-methylvaline **193** (83% *ee*) were far superior to those derived from proline **194** (7% *ee*). This showed that the rigid, cyclic framework of proline did not always provide an advantage over the flexible framework of valine.




**Scheme 43** Conjugate addition showing the benefit to using flexible catalysts over rigid catalysts

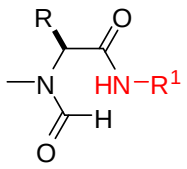
Herein, it will be shown that these principles can be utilised in the area of organocatalysis and can be used to affect a powerful protocol for the catalytic asymmetric reduction of ketimines to chiral amines.

## 2.2 Ligand Synthesis and Initial Investigation

Since it is known that $Cl_3SiH$ can be activated by Lewis bases such as DMF, MeCN, $R_3N$ etc, to effect the hydrosilylation of imines we set about designing a chiral Lewis-basic ligand, based on *N*-methylvaline, that could be viewed as a chiral analogue of DMF **195**. Designing these analogues made use of amino acids as the chiral scaffold with the α–amino group converted into the formamide moiety **196**. The analogue of DMF would then be completed by the inclusion of a chiral moiety in place of one of the methyl groups **196**.


R = aliphatic or aromatic

To increase the scope for the ligand we intended to functionalise the amino acid carboxyl into another amide group and thus create the possibility for bidentate coordination using either an aliphatic or aromatic amine **197.** With this in mind, the initial synthesis was carried out. Valine was utilised as the starting amino acid due to its low cost and availability. It was thought that the α-isopropyl group would provide a sterically hindered enough group whilst the *N*-methyl group was thought essential to invoke the chiral relay effect.

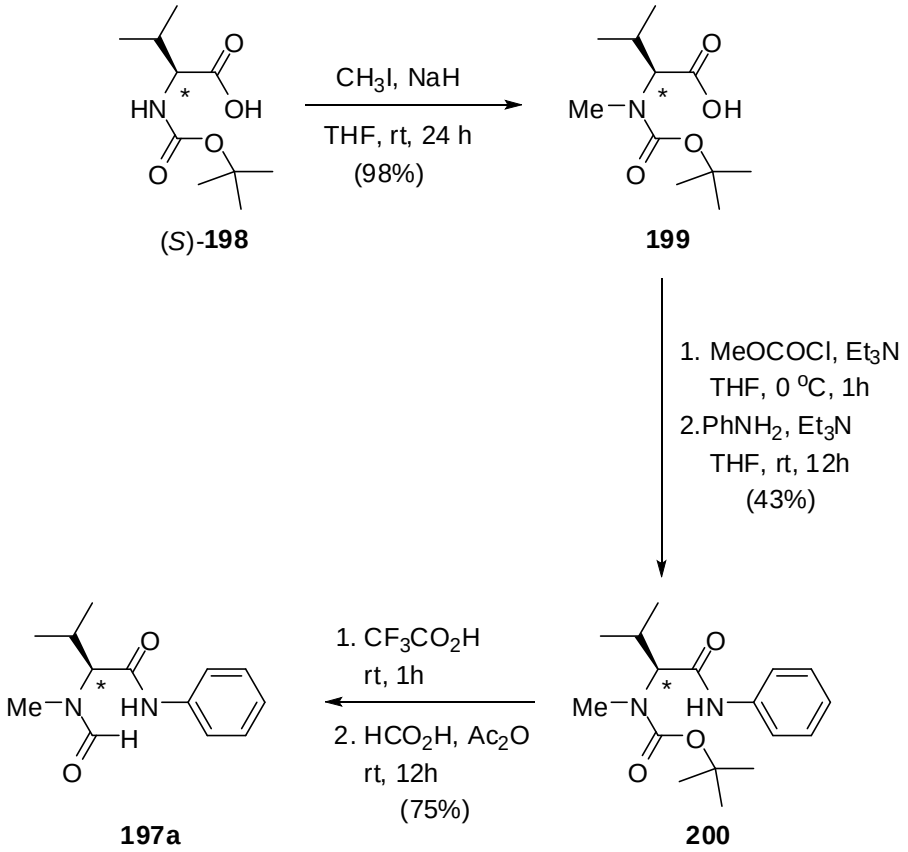



**197**

$R^1$ = aliphatic or aromatic

The synthesis was started with the *N*-methylation of the $^t$BOC-protected L-valine **198** with MeI in the presence of NaH (**Scheme 44**), which furnished the $^t$BOC protected *N*-methyl valine in almost quantitative yield **199**. This reaction was not trivial however. Logic would suggest that deprotonation of the N-H should be carried out first with sodium hydride, followed by the addition of the methyl iodide. This however, proved not to be the case and in fact, the sodium hydride had to be added portion-wise to a solution of amino acid and methyl iodide otherwise the reaction would become very sluggish. Another problem arising from this protocol was the addition of the hydride which involves the evolution of hydrogen which required careful venting. In addition to this, if the hydride was not added portion-wise over a certain time-scale (~1h) then the reaction did not work.

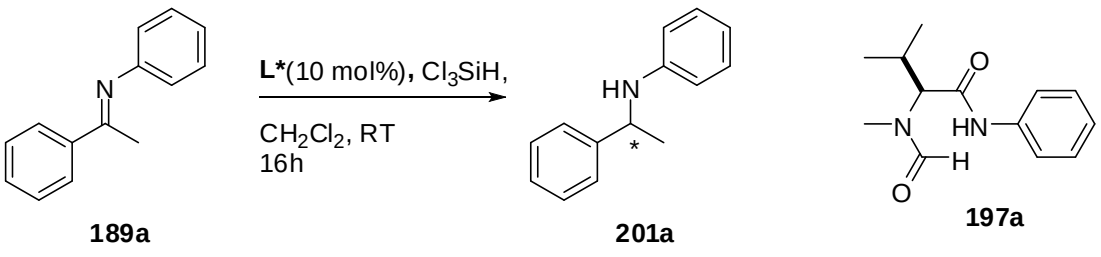
The use of dimethyl sufide as a *N*-alkylating reagent, in the presence of sodium hydride, had literature precedence [65] however, when the *N*-methylation of $^t$BOC-valine **198** was attempted, it was discovered that alkylation had occurred preferentially at the carboxyl end. This method was therefore abandoned in favour of the alkylation with methyl iodide which produced tertiary amide **199** in 98% yield.




**Scheme 44** Synthesis of the parent ligand **197a**

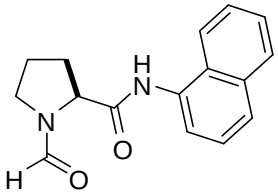
Amide **100** was then converted into bis-amide **101** using the mixed anhydride method for amine coupling. The mixed anhydride was formed *in situ* from **199** and methyl chloroformate and then reacted with aniline to furnish **200**. Deprotection of the $^{t}$BOC group was then carried out with TFA in $CH_2Cl_2$ to afford the TFA salt which was subsequently formylated *via* a mixed anhydride, generated *in situ* from formic acid and acetic anhydride to furnish the ligand **197a**.

An initial asymmetric reduction was carried out using **102** and a simple acetophenone based imine **189a** (**Scheme 45**). The result proved very promising giving the corresponding secondary amine **201a** in 79% *ee*.

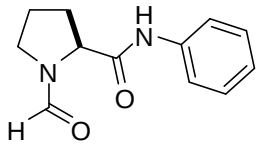



**Scheme 45** Initial asymmetric reduction

Whilst the initial investigation was underway, Matsumura *et al* [66] reported the same reduction catalysed by the L-proline derived formamide (S)-**202** with enantioselectivities of ≤ 66%. This provided credence that the flexible nature of the valine skeleton was more beneficial than that of the rigid, cyclic skeleton of proline. However, one interesting observation was that although both the valine (**197a**) and proline (**202a, b**) ligands were the same configuration, (*S*), the amines generated from the two asymmetric reductions were in fact opposite enantiomers! This suggested that the enantiodifferentiating mechanisms for valine- and proline-derived ligands are significantly different and would require a thorough investigation into the structural effects of both the ligand and substrate.

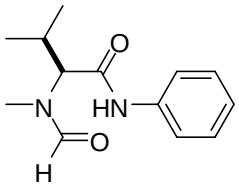


**202a**

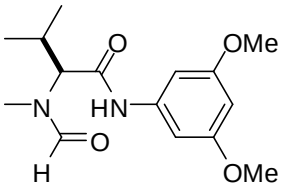


**202b**

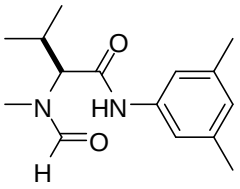
The investigation started with the variation of the amide functionality on the ligand. This was carried out simply by altering the amine used at the coupling stage and as a result a series of ligands **197a-e, 203a,b**, containing both aromatic and aliphatic moieties were realised.



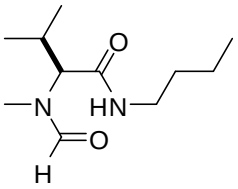
**197a**



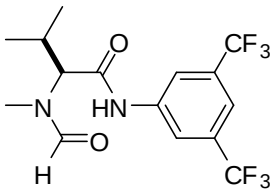
**197b**



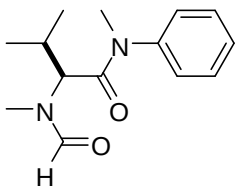
**197c**



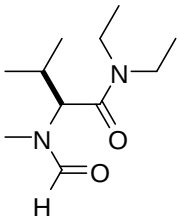
**197d**



**197e**



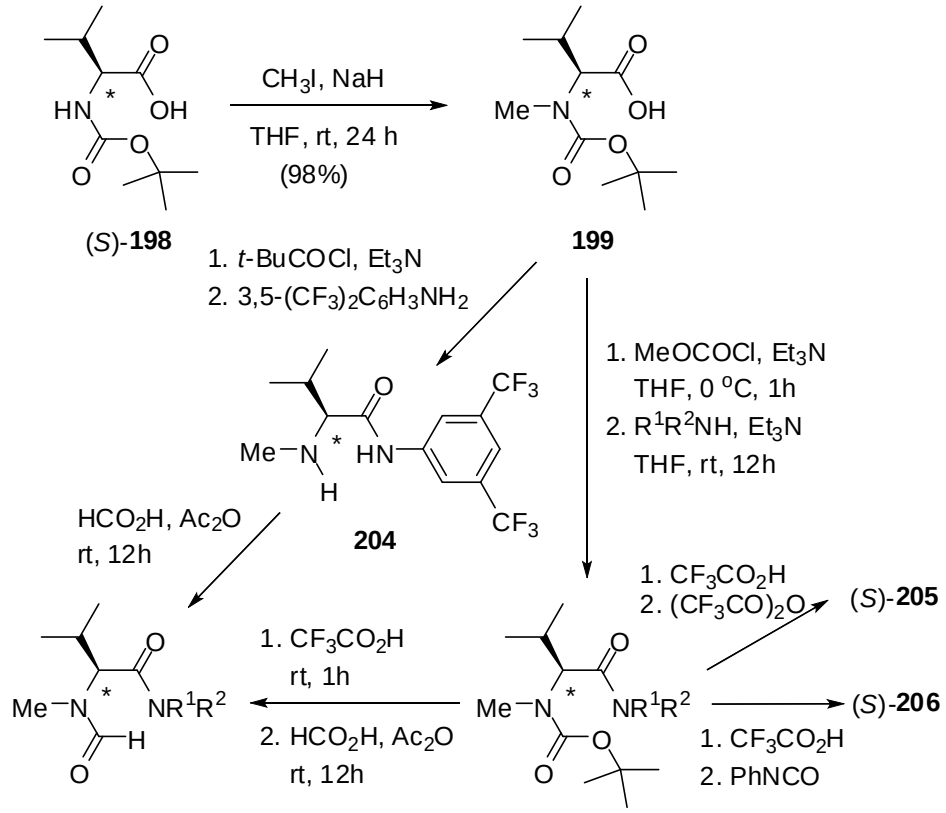
**203a**



**203b**

The synthesis of this series of ligands was carried out in the same way as described. In one case however, the synthesis failed when trying to attach 3,5-bis-(trifluoromethyl)aniline, **204**. Due to the electron withdrawing nature of the trifluoromethyl groups, the nitrogen is far less nucleophilic, therefore pivaloyl chloride was employed here to generate the mixed anhydride. This procedure worked well to furnish the desired amide, but as a consequence

of the more acidic conditions, the $^{t}$BOC group was also removed. The formylation step was then carried out to furnish **197e** (**Scheme 46**).

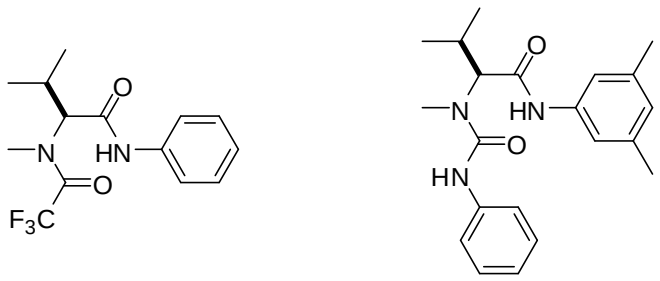



**197a**, $R^1$ = Ph, $R^2$ = H
**197b**, $R^1$ = 3,5-$(MeO)_2C_6H_3$, $R^2$ = H
**197c**, $R^1$ = 3,5-$Me_2C_6H_3$, $R^2$ = H
**197d**, $R^1$ = *n*-Bu, $R^2$ = H
**197e**, $R^1$ = 3,5-$(CF_3)_2C_6H_3$, $R^2$ = H
**203a**, $R^1$ = Ph, $R^2$ = Me
**203b**, $R^1$ = Et, $R^2$ = Et

**200a**, $R^1$ = Ph, $R^2$ = H
**200b**, $R^1$ = 3,5-$(MeO)_2C_6H_3$, $R^2$ = H
**200c**, $R^1$ = 3,5-$Me_2C_6H_3$, $R^2$ = H
**200d**, $R^1$ = *n*-Bu, $R^2$ = H
**200e**, $R^1$ = Ph, $R^2$ = Me
**200f**, $R^1$ = Et, $R^2$ = Et

**Scheme 46** Synthesis of *N*-methyl valine-derived ligands.

The remaining valine-derived analogues, **205** and **206** were then synthesised.

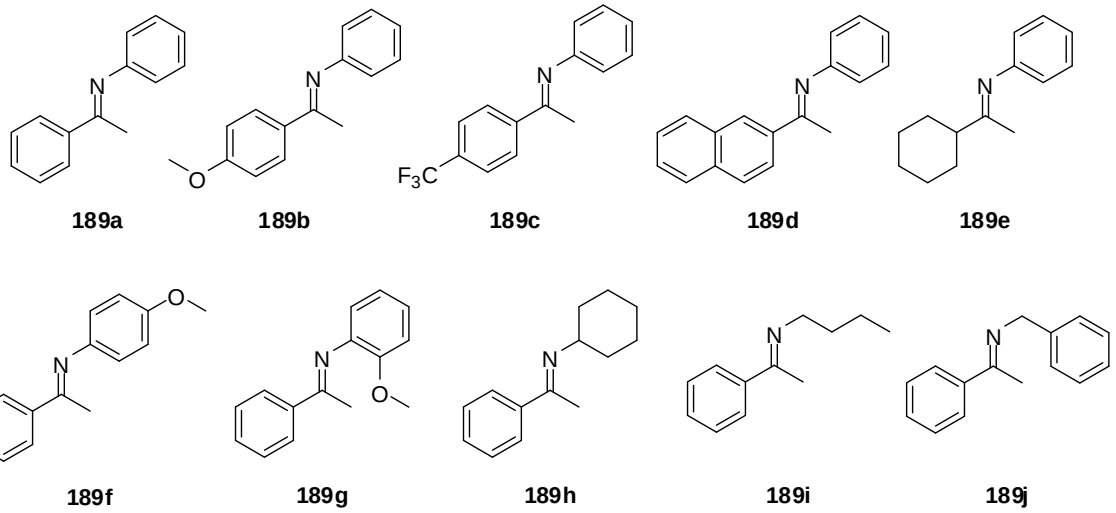


**205** **206**

The trifluoroacetamide **205** was obtained from **200b** *via* deprotection of the $^{t}$BOC group followed by acylation with trifluoroacetic anhydride. The urea derivative **206** was formed from **200c** by deprotection followed by treatment with phenylisocyanate.

## 2.3 Asymmetric Reduction

Initial work was carried out using ligand **197a** and a range of imines based on the acetophenone motif **189a-j**. Each reduction was carried out with a catalyst loading of 10mol% and in the first instance, performed in $CH_2Cl_2$. As mentioned previously, early results were promising with the reduction of **189a** furnishing the corresponding amine in good yield and with 79% *ee*. By simply altering the solvent to $CHCl_3$, an increase in yield was observed as well as in increase in enantioselectivity to 86% *ee*. Lowering the reaction temperature to -20$^{o}$C also gave a marked rise in enantioselectivity (92% *ee*) but at the detriment to the reaction rate. Changing the solvent once more to MeCN showed a large reduction in both yield and enantioselectivity.




**189a** **189b** **189c** **189d** **189e**

**189f** **189g** **189h** **189i** **189j**

Previous work within the Kocovsky-Malkov group had shown the powerful impact that arene-arene interactions could have on organocatalysis.[67] The effect of changing the solvent system seemed to substantiate the idea that non-covalent interactions were involved in the reduction, since it had been shown that $CHCl_3$ was the solvent that would most strongly stabilise arene-arene interactions. [68] This was further examined by altering the structure of the imines and indeed at the same time explore the scope of the reductive system. By comparison of the electron-rich and electron-deficient imines (**189b** and **189c** respectively) it was noted that the electronic effect on both reactivity and enantioselectivity was minimal (**table 1**). Removing the aromatic ring on the ketone

portion of the imine (**189e**) resulted in a marked reduction in enantioselectivity (37% *ee*) (**table 1**, entry 10) but lowering the reaction temperature to -20°C increased this to 59% *ee* (see **table 1**, entry 11). This would suggest that there is a fast, non-catalytic background reaction in play which is suppressed by cooling the reaction. Inclusion of a 2-naphthyl group (**189d**) had little effect on the reduction, with similar reactivity and enantioselectivity as shown in the reduction of **189a**.

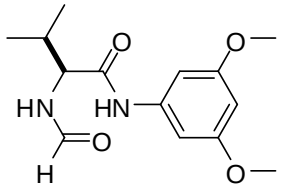
**Table 1** Reduction of imines **189a-j** with ligand **197a** and **203a,b.**[a]

| entry | imine | cat | solvent | yield (%)[b] | **amine**, % ee[c] (config)[d] |
|---|---|---|---|---|---|
| 1 | **189a** | **197a** | $CH_2Cl_2$ | 68 | 79 (*S*) |
| 2 | **189a** | **197a** | $CHCl_3$ | 79 | 86 (*S*) |
| 3[e] | **189a** | **197a** | $CHCl_3$ | 49 | 92 (*S*) |
| 4 | **189a** | **197a** | MeCN | 65 | 30 (*S*) |
| 5 | **189a** | **203a** | $CH_2Cl_2$ | 91 | 55 (*R*)[f] |
| 6 | **189a** | **203b** | $CH_2Cl_2$ | 52 | 66 (*R*)[f] |
| 7 | **189b** | **197a** | $CHCl_3$ | 57 | 80 (*S*) |
| 8 | **189c** | **197a** | $CHCl_3$ | 43 | 87 (*S*) |
| 9 | **189d** | **197a** | $CHCl_3$ | 60 | 87 (*S*) |
| 10 | **189e** | **197a** | $CHCl_3$ | 80 | 37 (*S*) |
| 11[e] | **189e** | **197a** | $CHCl_3$ | 53 | 59 (*S*) |
| 12 | **189f** | **197a** | $CHCl_3$ | 96 | 85 (*S*) |
| 13 | **189g** | **197a** | $CH_2Cl_2$ | 36 | 22 (*S*) |
| 14 | **189h** | **197a** | $CHCl_3$ | 50 | <5 |
| 15 | **189i** | **197a** | $CHCl_3$ | 60 | <5 |
| 16 | **189j** | **197a** | $CHCl_3$ | 46 | 8 |

[a]The reaction was carried out at 0.5 mmol scale with 1.5 equiv of $Cl_3SiH$ and 10 mol% of the catalyst at room temperature for 16 h. [b]Isolated yield. [c]Determined by chiral HPLC or GC. [d]Established from the optical rotation (measured in $CHCl_3$) by comparison with the literature data (see the Experimental section) and/or by HPLC/GC via comparison with authentic samples. [e]The reaction was carried out at –20 °C. [f]Ref 9

The alteration of the *N*-substituent on the imine had a much more marked effect. It was shown that steric effects must play a part in the reductive mechanism since the *p*-methoxy imine gave high conversion (96%) and high enantioselectivity (85% *ee*) (**table 1**, entry 12), whilst the corresponding *o*-methoxy isomer was much more sluggish, with both low conversion (36%) and low enantioselectivity (22% *ee*) (**table 1**, entry 13). Removal of the aromatic substituent altogether (**189h, i**) or by moving it one carbon further away from the nitrogen centre (**189j**) resulted in poor conversion and almost racemic product (see **table 1**, entries 14-16), showing that the *N*-aryl moiety is essential for chiral induction.

The role of the aromatic functionality of the catalyst was probed using catalysts **197a-b** and **203a-b** (**Table 2**). Reduction of imine **189a** with the 3,5-dimethoxy catalyst **102b** proved to be less efficient than the same reduction with **197a**, showing that the inclusion of donor groups on the aryl ring was detrimental. Reduction of **189a** with the 3,5-bis(trifluoromethyl) catalyst **197e** gave a similar result indicating that electronic effects are not too important. Conversely, reduction with the 3,5-dimethyl catalyst **197c** actually showed an increase in both conversion and enantioselectivity over the reduction with the parent formamide **197a**, demonstrating the importance of steric factors. Removing the aromatics completely and replacing it with an *n*-butyl moiety **197d** resulted in no reaction whatsoever, proving the importance of the aromatic moiety. The diethylamide **203b** as expected proved ineffective, further strengthening the premise that the aromatic system is vital. The tertiary amide **203a** also showed itself to be ineffective which may indicate that hydrogen bonding between the catalyst and imine is an important feature of the transition state.




**207**

Furthermore, removing the *N*-methyl group from the formamide, **207**, reduced the efficiency of the catalyst. This would further strengthen the argument that the *N*-methyl group is vital for the chiral relay.[63]

**Table 2** Reduction of imines **189a, c** and **f** with ligand **197b-e** and **203a, b** and **207.**[a]

| entry | imine | cat | solvent | temp ($^oC$) | yield (%)[b] | amine, % ee[c] (config)[d] |
|---|---|---|---|---|---|---|
| 1 | **189a** | (*S*)-**197b** | $CHCl_3$ | ambient | 81 | 82 (*S*) |
| 2 | **189c** | (*S*)-**197b** | $CHCl_3$ | ambient | 94 | 77 (*S*) |
| 3 | **189f** | (*S*)-**197b** | $CHCl_3$ | ambient | 82 | 79 (S) |
| 4 | **189a** | (*S*)-**197c** | $CHCl_3$ | ambient | 70 | 89 (*S*) |
| 5 | **189a** | (*S*)-**197c** | $CHCl_3$ | –20 | 94 | 92 (*S*) |
| 6 | **189a** | (*S*)-**197d** | $CHCl_3$ | ambient | 0 | – |
| 7 | **189c** | (*S*)-**197e** | $CHCl_3$ | ambient | 92 | 69 (*S*) |
| 8 | **189a** | (*S*)-**197e** | $CHCl_3$ | ambient | 88 | 53 (*S*) |
| 9 | **189a** | (*S*)-**203a** | $CHCl_3$ | ambient | 23 | 7 (*S*) |
| 10 | **189a** | (*S*)-**203b** | $CHCl_3$ | ambient | 0 | – |
| 11 | **189c** | (*S*)-**207** | $CHCl_3$ | ambient | 84 | 35 (*S*) |

[a]The reaction was carried out at 0.5 mmol scale with 1.5 equiv of $Cl_3SiH$ and 10 mol% of the catalyst for 16 h. [b]Isolated yield. [c]Determined by chiral HPLC or GC. [d]Established from the optical rotation (measured in $CHCl_3$) by comparison with the literature data (see the Experimental) and/or by HPLC/GC via comparison with authentic samples.

The reductions to this point had been carried out mainly in chlorinated solvents, with $CHCl_3$ proving best. MeCN proved to be ineffective for this protocol suggesting that a non-polar solvent was important. Since neither $CHCl_3$ nor $CH_2Cl_2$ are deemed to be environmentally friendly, another non-polar solvent, toluene, was investigated and was quickly found to be the solvent of choice. In fact, the reduction of **189a** with catalyst **197c** in toluene, at room temperature actually matched the same reduction in $CHCl_3$ at –20 $^oC$ with catalyst **197a** in terms of enantioselectivity but in much better yield. Since catalyst **197c** appeared to be best, more reductions were carried out in toluene to investigate its efficiency (see **Table 3**).

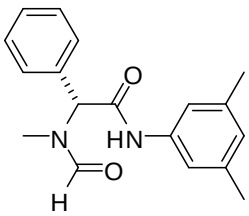
**Table 3** Reduction of imines **189a-c, f** and **k** with ligand **197c.** [a]

| entry | imine | cat | solvent | temp ($^oC$) | yield (%)[b] | **amine**, % ee[c] (config)[d] |
|---|---|---|---|---|---|---|
| 1 | **189a** | (*S*)-**197c** | Tol | ambient | 81 | 92 (*S*) |
| 2 | **189a** | (*S*)-**197c** | Tol | –20 | 54 | 92 (*S*) |
| 3 | **189b** | (*S*)-**197c** | Tol | ambient | 86 | 85 (*S*) |
| 4 | **189c** | (*S*)-**197c** | Tol | ambient | 86 | 89 (*S*) |
| 5 | **189c** | (*S*)-**197c** | Tol | –20 | 80 | 89 (*S*) |
| 6 | **189f** | (*S*)-**197c** | Tol | ambient | 85 | 91 (*S*) |
| 7 | **189f** | (*S*)-**197c** | Tol | –20 | 46 | 93 (*S*) |
| 8 | **189k** | (*S*)-**197c** | Tol | ambient | 90 | 92 (*S*)[e] |

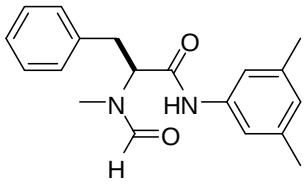
[a]The reaction was carried out at 0.5 mmol scale with 1.5 equiv of $Cl_3SiH$ and 10 mol% of the catalyst for 16 h. [b]Isolated yield. [c]Determined by chiral HPLC or GC. [d]Established from the optical rotation (measured in $CHCl_3$) by comparison with the literature data (see the Experimental) and/or by HPLC/GC via comparison with authentic samples. [e]Configuration is assumed to be (*S*) in analogy with the rest of the series.

With the exception of the reduction of **189f**, which showed a marginal increase in enantioselectivity, there was no further improvement in carrying out the reductions at -20$^o$C (**table 3**, entry 6-7).

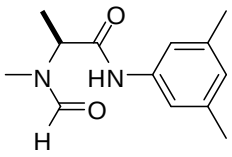
Modification of the amino acid side chain was investigated next. This was achieved simply by varying the amino acid used in the catalyst synthesis. Four differing amino acids were chosen as suitably different to valine but not so much that the overall structure would change dramatically (in terms of sterics etc).



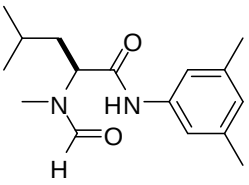

**208a**




**208b**

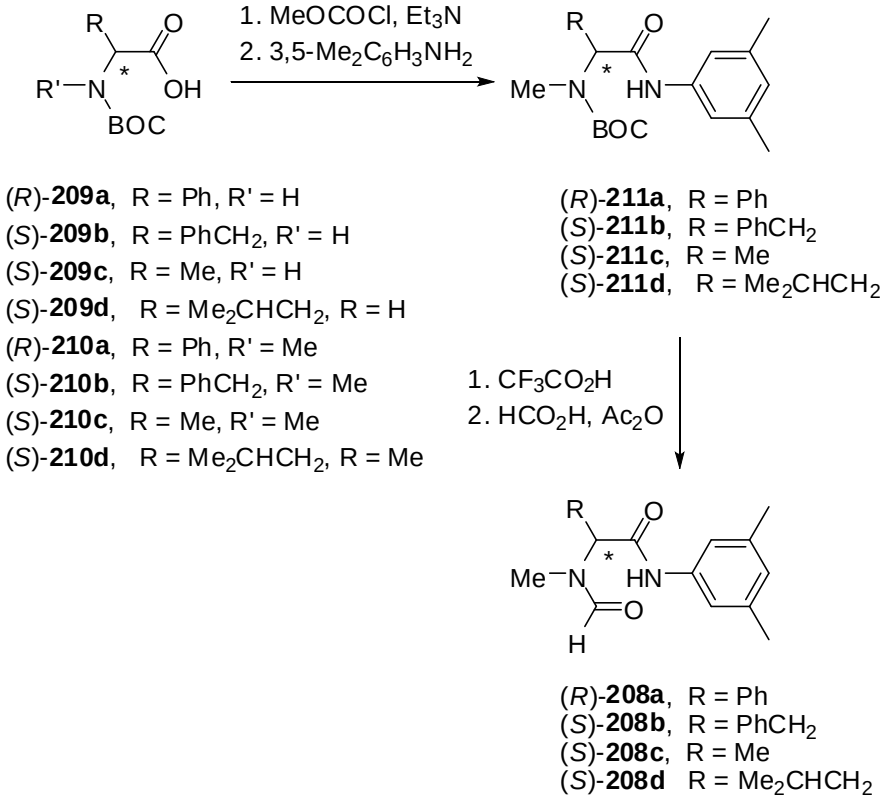



**208c**




**208d**

The catalysts were synthesised from phenylglycine **208a**, phenylalanine **208b**, alanine **208c** and leucine **208d** following the same protocol as previously (see **scheme 47**)




**Scheme 47** Synthesis of alternative *N*-methyl amino acid catalysts

Reductions of various imines were carried out, catalysed by **208a-d** in toluene at room temperature (see **Table 3.3.4**). The reduction of **103c** with the leucine-derived catalyst **112d** showed excellent reactivity (89%) but very low chiral induction (10% *ee*) (**table 4**, entry 7). The alanine-derived catalyst **208c** showed moderate enantioselectivity (38% *ee*) (**table 4**, entry 6) the reduction of imine **189c** but interestingly induced the opposite enantiomer of the amine preferentially. The phenylalanine-derived catalyst **208b** also showed low enantioselectivity (26% *ee*) (**table 4**, entry 4) but surprisingly the phenylglycine-derived catalyst **208a** gave rise to a completely racemic mixture

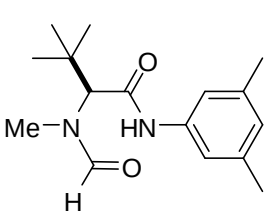
**Table 4** Reduction of imines **189c** and **f** with ligand **205- 206** and **208a-d**[a]

| entry | imine | cat | solvent | yield (%)[b] | **amine**, % ee[c] (config)[d] |
|---|---|---|---|---|---|
| 1[e] | **189a** | (*R*)-**208a** | Tol | 84 | 0 |
| 2[e] | **189c** | (*R*)-**208a** | Tol | 70 | 0 |
| 3[e] | **189f** | (*R*)-**208a** | Tol | 76 | 0 |
| 4 | **189c** | (*S*)-**208b** | Tol | 85 | 26 (*S*) |
| 5 | **189f** | (*S*)-**208b** | Tol | 84 | 49 (*S*) |
| 6 | **189c** | (*S*)-**208c** | Tol | 92 | 38 (*R*) |
| 7 | **189c** | (*S*)-**208d** | Tol | 89 | 10 (*S*) |
| 8 | **189a** | (*S*)-**205** | $CH_2Cl_2$ | <10 | 0 |
| 9 | **189c** | (*S*)-**206** | Tol | 70 | 0 |

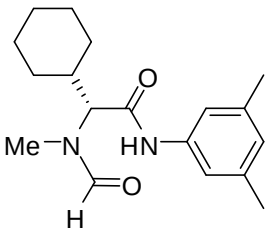
[a] The reaction was carried out at 0.5 mmol scale with 1.5 equiv of $Cl_3SiH$ and 10 mol% of the catalyst for 16 h. [b]Isolated yield. [c]Determined by chiral HPLC or GC. [d]Established from the optical rotation (measured in $CHCl_3$) by comparison with the literature data (see the Experimental) and/or by HPLC/GC via comparison with authentic samples. [e]Note the (*R*) configuration of the catalyst.

To probe the importance of the formamide moiety on the catalyst activity, the valine-derivatives that had the formamide portion replaced by a trifluoroacetamide group **205** and a urea group **206** were tested. The much less Lewis-basic trifluoroacetamide proved to be totally inefficient, having no effect on the reduction whatsoever. The urea derivative did however catalyse the reduction but afforded only racemic product. This gave strength to the opinion that the formamide portion is crucial for its catalytic activity.

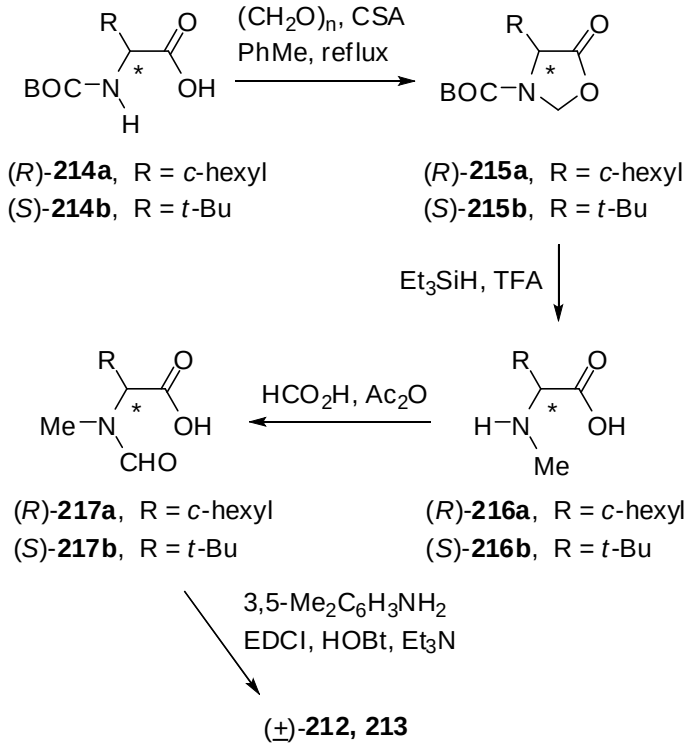
In terms of efficiency and enantioselective outcome, the 3,5-dimethylphenylamide catalyst is undoubtedly the best. Work carried out within the Kocovsky-Malkov group [69] at the same time investigated the use of two other amino acid catalyst derived from cyclohexylglycine **212** and *tert*-leucine **213**, the synthesis of which are shown in **scheme 48**.




**212**



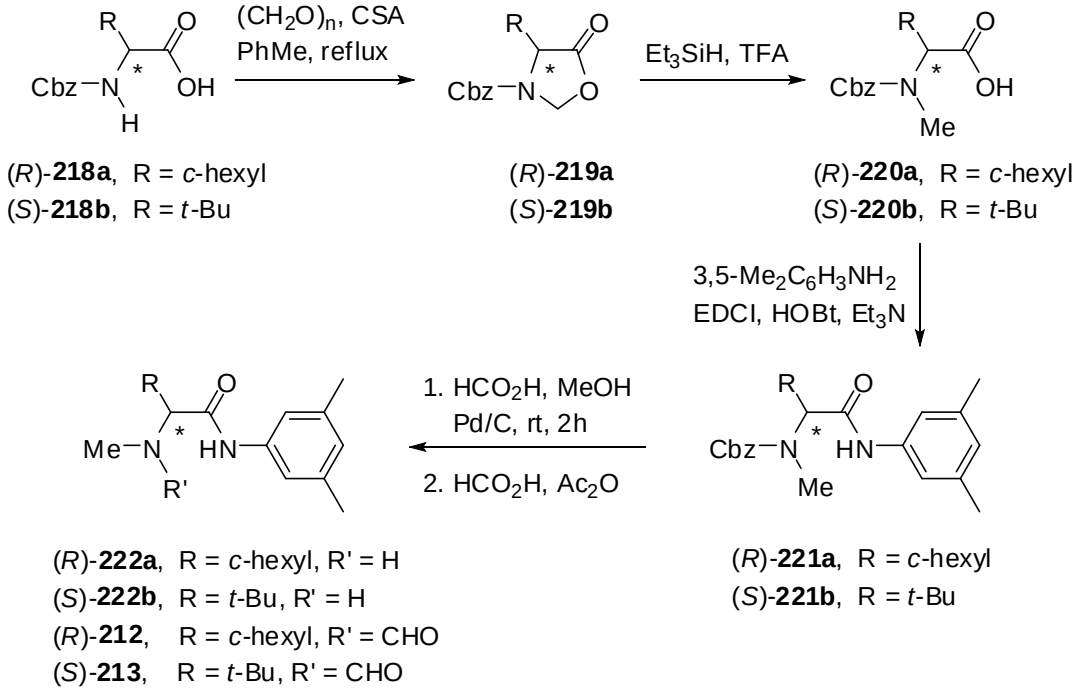

**213**




**Scheme 48** Attempted synthesis of catalysts **212** and **213**

The synthesis of both these catalysts (**212** and **213**) was extremely problematic. The first main problem encountered was the solubility of cyclohexylglycine, with heating required for complete dissolution. However, the $^{t}$BOC derivative went into solution with relative ease. Methylation of both then proved to be the most complicated. Standard methods using methyliodide and sodium hydride proved to be ineffective. Heating the reaction mixture to reflux also had no bearing. Alkylation with dimethyl sulphide also proved fruitless, giving exclusively the methyl ester. An alternative approach using Nosyl-protected derivatives [70] in the presence of methyl iodide, base and carried out in acetonitrile also proved a failure. In a dramatically different approach [71], the $^{t}$BOC derivatives were first converted into the respective oxazolidinones (as in **215a,b**) (**scheme 48**). The oxazolidinones were then treated with $Et_3SiH$ and trifluoroacetic acid to give both cleavage of the C-O bond and removal of the $^{t}$BOC group, leaving the *N*-methyl amino acid. Formylation was then carried out under standard methods and formation of the amide with 3, 5-dimethyl aniline completed using the carbodiimide method (as in **217** to **212, 213**). However, the resulting catalysts **212** and **213** were found to be racemic, due to racemisation in the final step. The mixed anhydride method also proved ineffective. An alternative was then used utilising the Cbz-protecting group. [72] This proceeded well, forming the oxazolidinone as previously. However, cleavage of the C-O bond proved very slow (~7 days at room temperature) furnishing the *N*-methyl amino acid **220a,b** in

low yield. Subsequent amide coupling using the carbodiimide method produced **221a** in moderate yield with **222b** being formed as an inseparable mixture with **219b**. The deprotection and formylation was carried out without issue to furnish **212** and **213** in good yield.




(*R*)-**218a**, R = *c*-hexyl
(*S*)-**218b**, R = *t*-Bu

(*R*)-**219a**
(*S*)-**219b**

(*R*)-**220a**, R = *c*-hexyl
(*S*)-**220b**, R = *t*-Bu

(*R*)-**221a**, R = *c*-hexyl
(*S*)-**221b**, R = *t*-Bu

(*R*)-**222a**, R = *c*-hexyl, R' = H
(*S*)-**222b**, R = *t*-Bu, R' = H
(*R*)-**212**, R = *c*-hexyl, R' = CHO
(*S*)-**213**, R = *t*-Bu, R' = CHO

**Scheme 49** Synthesis of catalysts **212** and **213**

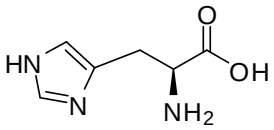
Both of these catalysts performed well with **212** showing similar enantioselectivities to the valine-derived counterpart (see **table 5**). The cyclohexyl analogue **212** showed to be only slightly less efficient that its isopropyl analogue (see **table 5**) however, although exhibiting very similar activity to the valine-derived catalyst **197c**, neither **212** nor **213** were as attractive as **197c** due to the cumbersome and inefficient synthesis.

**Table 5** Reduction of imines **189c** and **f** with ligand **212**and **213.**[a]

| entry | imine | cat | solvent | yield (%)[b] | **amine**, % ee[c] (config)[d] |
|---|---|---|---|---|---|
| 1[e] | **189c** | (*R*)-**212** | Tol | 74 | 89 (*R*) |
| 2[e] | **189f** | (*R*)-**212** | Tol | 95 | 82 (*R*) |
| 3 | **189c** | (*S*)-**213** | Tol | 84 | 82 (*S*) |
| 4 | **189f** | (*S*)-**213** | Tol | 95 | 83 (*S*) |

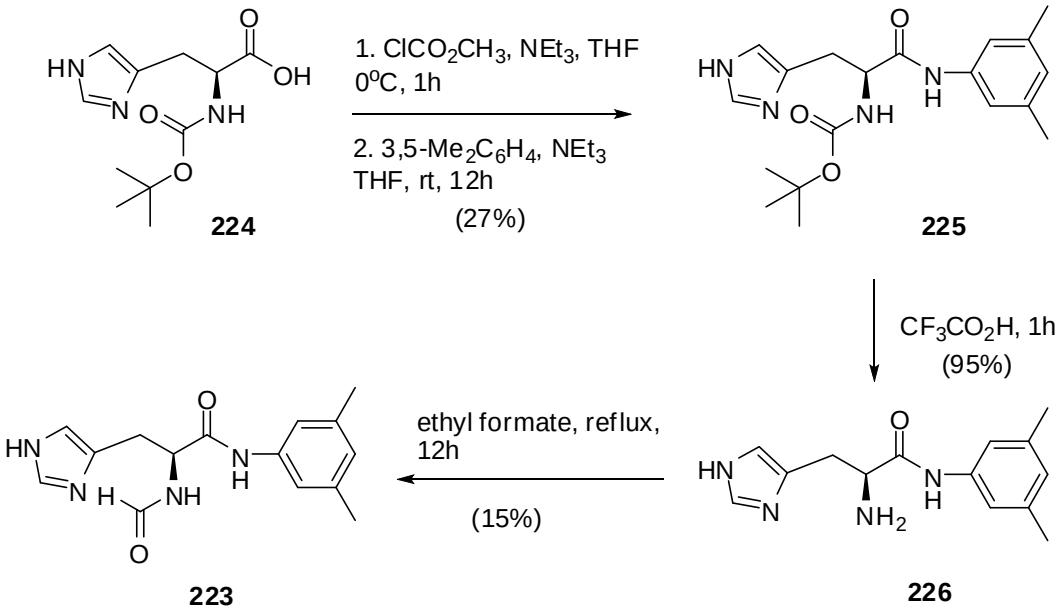
[a] The reaction was carried out at 0.5 mmol scale with 1.5 equiv of $Cl_3SiH$ and 10 mol% of the catalyst for 16 h. [b]Isolated yield. [c]Determined by chiral HPLC or GC. [d]Established from the optical rotation (measured in $CHCl_3$) by comparison with the literature data (see the Experimental) and/or by HPLC/GC via comparison with authentic samples. [e]Note the (*R*) configuration of the catalyst.

Another variation in the side chain was achieved by introducing an imidazole ring, starting from the amino acid histidine **223**.




**223**

The imidazole moiety would hopefully provide another coordination point for the system and in turn improve enantioselectivity. The synthesis proved bothersome due to the basicity of the nitrogens on the imidazole ring, it was not possible to selectively alkylate the primary amine over the ring nitrogen. Protection of the ring nitrogen with $^t$BOC or Cbz, as well as mono-protection of the primary amine functionality also resulted in no alkylation. Various methods of methylation were employed (described earlier, section **2.2**) but all were fruitless. It was therefore decided that the synthesis would be carried forward without *N*-alkylation (**scheme 50**).

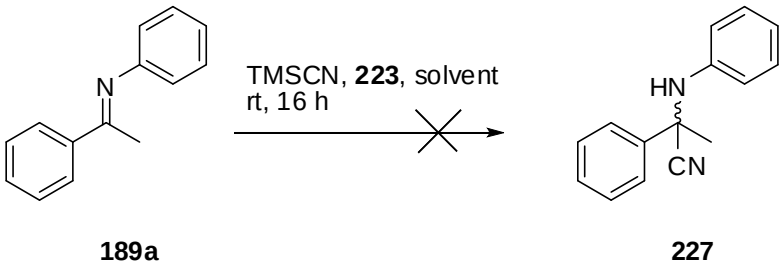



**Scheme 50** Synthesis of catalyst **223** from commercially available **224**

The coupling of the aniline to furnish **225** was carried out using the same mixed anhydride procedure as used previously. The *N*-$^{t}$BOC group was then removed with trifluoroacetic acid and formylation completed by refluxing the free amine with ethyl formate. Refluxing was essential in this case due to the insoluble nature of the compound. The final compound was then purified by crystallisation from methanol. Only a small amount was isolated (>85mg) however.

## 2.4 Imidazole Catalyst Investigations

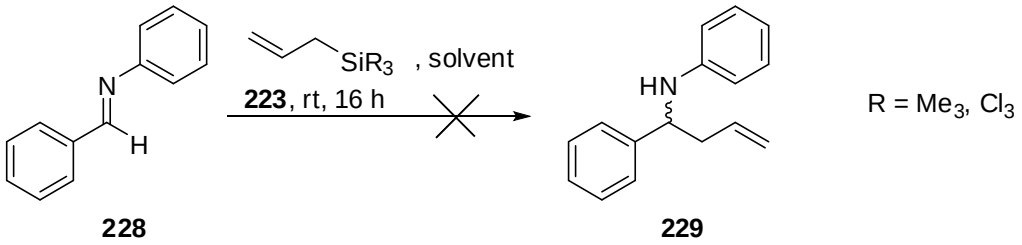
Turning briefly away from ketimine reductions, it was decided that **223** would be used to try and facilitate the Strecker type cyanation (**scheme 51**)




**Scheme 51** Strecker type cyanation with catalyst **223**

The reaction was firstly carried out in toluene however, no reaction was observed. The solvent was then switched to chloroform but as before, no reaction was observed. An

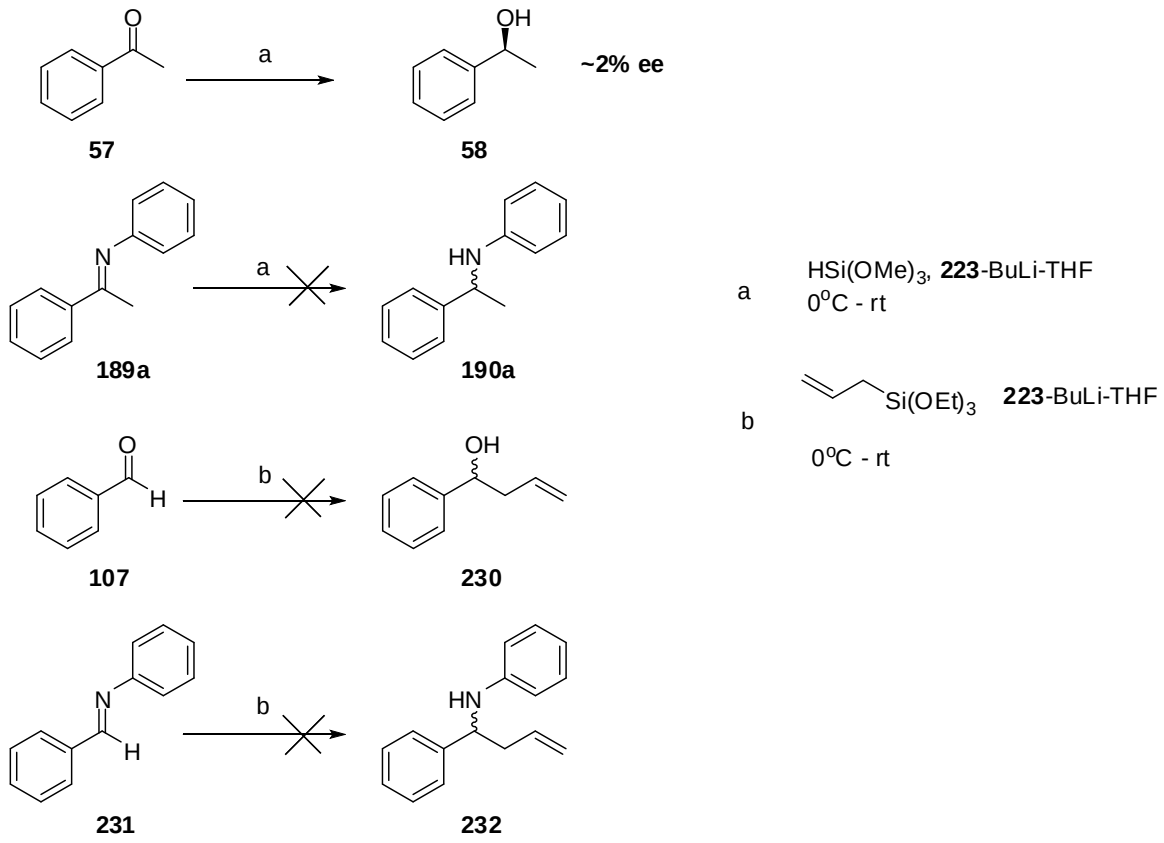
allylation (Sakurai type) on the aldimine **228** was then attempted (**Scheme 52**) which also resulted in no reaction.




**228** **229**

**Scheme 52** Allylation of aldimines **228**

These results were, of course very disappointing as it was expected that the reactions would proceed irrespective of whether or not chirality was induced. However, we believed that the lack of catalysis was due to the insolubility of the catalyst itself. Work carried out by Brook and co-workers [73] on ketone reduction using extracoordinate silicon showed that using neutral imidazole derivatives could not trigger reduction of ketones with alkoxysilanes. However, the corresponding imidalozide anions were shown to activate the said reductions. This concept was utilised, not only to aid reactivity, but the formation of the imidalozide anion in catalyst **223** could assist dissolution. A series of reductions and allylations were attempted using this model as shown in **scheme 53**.




**Scheme 53** Reduction and allylation with **223** using the Brooks model

As can be seen from **scheme 53**, the reduction of **189a** and the allylation of **107** and **231** did not proceed at all. In contrast, the reduction of acetophenone **57** did give the resulting alcohol but in poor enantioselectivity (2% *ee*). The reaction itself was also very sluggish as indicated by TLC. It is clear that further development of this catalyst will be required to address the solubility issue as well as trying to make it a more efficient catalyst. [69]

## 2.5 Mechanistic Observations

The experiments carried out so far indicate key points in both the catalyst and substrate that are essential for the protocol to work (see **fig. 12**).

The catalyst requires two amide functionalities for an effect to be realised. One must be of the formamide type and the other an anilide. Without either the formamide or the anilide, chiral induction will not occur (in the case of **206**) and in some cases will not even catalyse the reduction (in the case of **197d** and **208b**). These are assumed to be required as donors for coordination to $HSiCl_3$. NMR investigation strengthened this assumption. The $^{13}C$ NMR spectrum of a 1:1 mixture of **197c** and $HSiCl_3$ indicated that the carbonyls of the formamide and anilide shifted by ~0.1 and 0.2 ppm respectively in relation to the

free catalyst and indeed, the methyl groups on the aromatic ring became non-equivalent. In the free catalyst, the two methyl groups show as a single peak at 21.71 ppm but in the mixture they split in to two peaks showing at 21.69 and 21.76 ppm. This suggests a weak coordination that may restrict rotation around the N-aromatic bond.

Having the correct balance of steric and electronic properties on the *N*-aromatic ring also plays a major part. Keeping the formamide portion constant and altering the aromatic ring gave insight into how changing the ring donor properties affected catalysis. By adding electron-withdrawing (**197e**) and electron-donating (**197b**) groups, it was shown that efficiency was decreased in both cases compared to that of the parent catalyst (**197a**). Inclusion of the withdrawing groups however, led to a greater degree of inefficiency suggesting that it did not coordinate well. The 3,5-dimethyl catalyst **197c** appears to contain the correct balance of steric and electronic properties.

The tertiary *versus* secondary anilide question was also investigated. It was shown that the secondary anilides (**197a-c,e**) were efficient catalysts whilst the tertiary anilides (**203a-b**) were not. It would appear that the N-H bond plays a key role in the catalyst activity, whether through hydrogen bonding or indeed just allowing the amide bond to rotate more freely. However, as mentioned previously, the amide must be aromatic since replacing the aromatic moiety with an aliphatic one (**197d**) rendered the catalyst ineffective.

The tertiary formamide portion also appears to be vital to catalyst activity. There are two requirements for the formamide group however. It must be adequately Lewis-basic and must be suitably small. Catalyst **205** demonstrates the first provision. The electron-withdrawing trifluoromethyl group makes the formamide much less Lewis-basic and as a result renders the catalyst ineffective. The phenylglycine-derived catalyst **208a** is also ineffective in producing chiral induction. On comparison to the parent catalyst **197a**, it is apparent that the added bulk around the amide portion is a limiting factor. This is also evident in the urea derivative **206**, which again is shown to be ineffective.

The *N*-methyl moiety is also important in terms of enantioselectivity. The synthesis of catalyst **207**, lacking the *N*-methyl group proved to be effective at catalysing the reduction but was poor at inducing chirality (comparing the reductions with **197b** and **207**). It is apparent that the methyl group helps to provide the correct conformation of the formamide

to convey the chiral information from the chiral centre. Without it, chiral induction is more sluggish.

The side chain of the amino acid provided the most interesting observation. Larger substituents such as isopropyl (**197a-e**, **203a-b** and **207**) from valine, cyclohexyl (**212**), *tert*-butyl (**213**), benzyl (**208b**) and *iso*-butyl (**208d**) all functioned to form the same configuration of amine. However, the single methyl group (**208c**) from alanine induced the formation of the opposite enantiomer of amine. This was also noticed, as mentioned previously, when the proline-derived catalysts (**202a-b**) were used. [9] We believe that there is no conformational bias created between the *N*-alkyl group and the alkyl group $\alpha$ to the nitrogen of the catalyst. This allows the two groups to remain close to each other, and not be forced away as in the more bulky catalysts. This would account for the opposite configuration of the amine product. At the borderline lies the phenylglycine derivative (**208a**). Use of this catalyst gave racemic product. It is clear that the phenyl group at the $\alpha$-position provides too much steric bulk for the catalyst to induce any stereocontrol. The side chain appears therefore, to be directly involved in determining enantiodifferentiation. By altering the side chain, subtle changes in the conformation of the catalyst can result in differing enantiomers of product.

The structure of the substrate ketimine also plays an important role. The $R^1$ group (see **scheme 42**) should be aromatic preferably (**189a-d**) which gives better results in terms of conversion and enantioselectivity. However, non-aromatic groups (**189e**) can be employed here but at the cost of lower enantioselectivity. The aromatic groups can also endure electron-withdrawing (**189c**) and donating (**189b**) substituents well, with the former performing slightly better. With respect to the $R^2$ substituents, the inclusion of an aromatic group attached directly to the N was crucial. Examination of imines **189a,f**,**g** showed that whilst **189a** (containing a *N*-phenyl moiety) and **189f** (containing a *N*-*p*-methoxyphenyl moiety) gave comparable, high enantioselectivities on reduction, **189g** (with a *N*-*o*-methoxyphenyl moiety) gave considerably lower enantioselectivities and reaction rate (**table 1**, entries 2, 12, 13). This would indicate that steric congestion around the N is not favourable and should be avoided. The high enantioselectivities obtained with the *p*-methoxypheny ketimine **189f** is of even greater importance since electron-rich *N*-aromatic groups such as *p*-methoxyphenyl can be removed by oxidative methods (using CAN).[74] This gives the opportunity to extend the protocol to the production of primary amines.

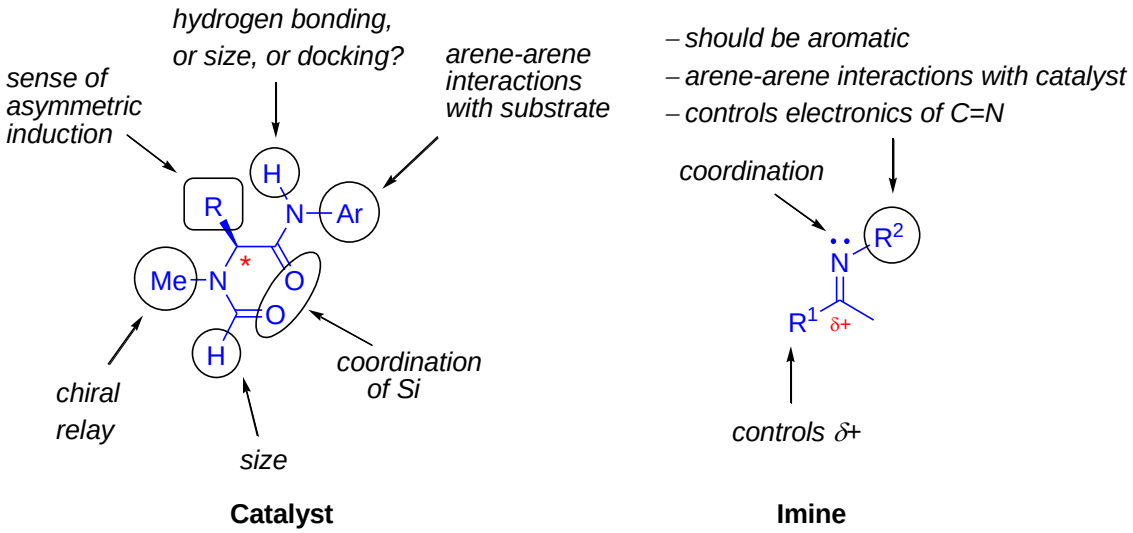
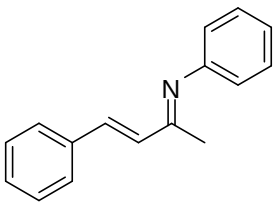
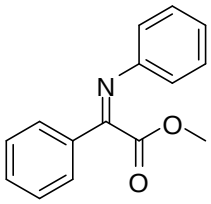



**Figure 12** Key features of the catalyst and imine

Since clearly the 3,5-dimethylanilide catalyst **197c** had performed best both in terms of reactivity and ability to induce chirality into a substrate, its scope was briefly investigated using a chalcone-based imine **233** and a phenylglycine-based imine **234**.




**233**




**234**

The reasons for the choice of these two substrates were that in the case of **233** we could further look at the effect of changing $R^1$ (**scheme 42**) to include conjugation. Also if the conjugated olefin remained intact then that could pave the way for more chemistries to be carried out (epoxidation, hydroxylation etc.). For **234**, if the reduction was successful then deprotection of the *N*-aryl moiety could give access to chiral α-amino acids. The imines were reduced using the standard reduction protocol and the results shown in **table 6**. With the chalcone derivative **233**, the reduction proceeded smoothly at ambient temperature but with reduced enantioselectivity (74% *ee*). However, lowering the temperature to -20°C had the effect of increasing the enantioselectivity to 81% *ee* (**table 6**, entries 1, 2). Most interesting was that the olefin remained intact. The reduction of the phenylglycine derivative **234** was not as effective. Reduction at room temperature gave poor enantioselectivity (30% *ee*) but good reactivity (68% after 16h). Lowering the

temperature to -20°C did increase the enantioselectivity almost two-fold (59% *ee*) (**table 3.3.**6, entries 3, 4) but this was to the detriment of reactivity (69% after 24h).

**Table 6** Reduction of imines **233** and **234** with catalyst **197c.** [a]

| entry | imine | temp (°C) | yield (%)[b] | % ee[c] (config)[d] |
|---|---|---|---|---|
| 1 | **233** | ambient | 59 | 74 (*S*) |
| 2 | **233** | –20 | 64 | 81 (*S*) |
| 3 | **234** | ambient | 68 | 30 (*R*)[e] |
| 4 | **234** | –20 | 69 | 59 (*R*)[e,f] |

[a]The reaction was carried out at 0.5 mmol scale with 1.5 equiv of $Cl_3SiH$ and 10 mol% of the catalyst in toluene for 16 h. [b]Isolated yield. [c]Determined by chiral HPLC or GC. [d]Established from the optical rotation (measured in $CHCl_3$) by comparison with the literature data (see the Experimental) and/or by HPLC/GC via comparison with authentic samples. [e]Note the change of substituent priorities in the CIP nomenclature. [f]The reaction was run for 24 h.

The result of the chalcone derivative **233** also shows that although when the imine substituent $R^1$ (**scheme 31**) is non-aromatic and enantioselectivities decrease, extending the conjugation has the effect of increasing the enantioselectivity back up to acceptable levels, showing that conjugation is valuable.

## 2.6 Nonlinear effect (NLE) investigation

Until about twenty years ago, no organic chemist would have thought that a chiral catalyst/auxiliary with a low enantiopurity could induce chirality into a substrate higher than its own or indeed to the same level as if an enantiopure catalyst was used! This phenomenon whereby the relationship between the *ee* of the catalyst and the *ee* of the product deviates from linearity has given rise to what is now called nonlinear effects (NLEs). This effect reflects the complexity of molecular interactions and reaction mechanisms. However, it can be used to generate products with high *ee*'s from enantiomerically impure catalysts. Most importantly, NLEs can be used as a probe to obtain details on mechanisms that are involved in creating chirality.

Kagan *et al* [75] challenged the assumption that the maximum *ee* of a product could only be obtained if an enantiopure catalyst was used. Kagan showed that this was not always the case and the linear relationship between the catalyst *ee* and the substrate *ee* could in fact be deviated from. From data collected from various experiments, it was concluded that

deviations from linearity would result in either a plain curve either above ((+)-NLE) or below ((-)-NLE) the straight line (**figure 13**)

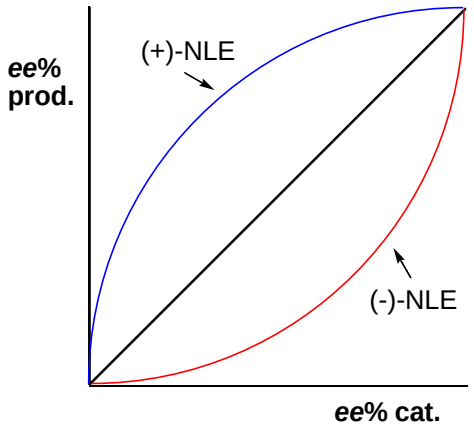
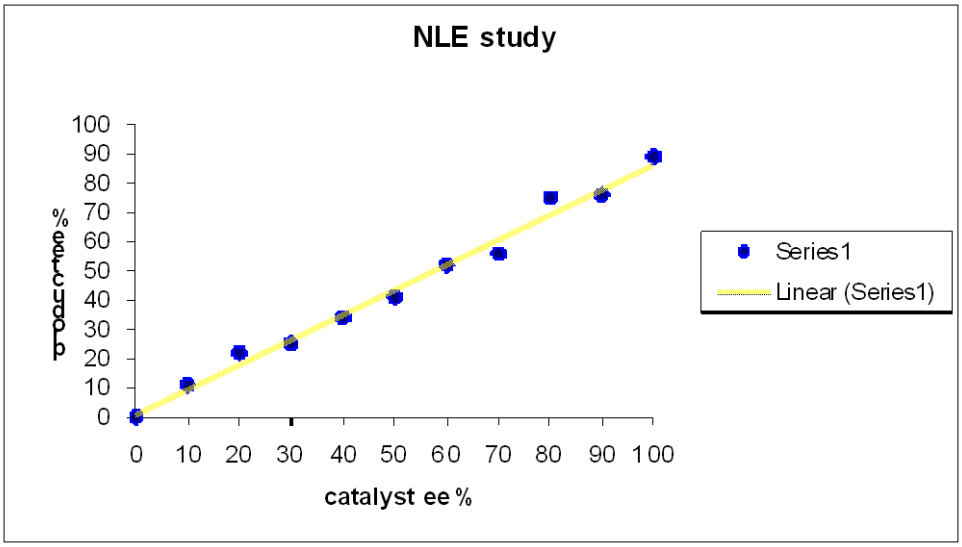



**Figure 13** Curves showing typical (+) and (-)-nonlinear effects

Of course, the curves shown are simplified and more complicated examples exist that don't follow the clear-cut positive and negative curves. However, **figure 13** gives a good illustration of the power of the nonlinear effect. For example, if a system could be designed that follows a (+)-NLE then an enantiomerically impure catalyst could be used to furnish a product in high enantioselectivity. Of course, the opposite could be found if a (-)-NLE was in play. A NLE an also give insight into the mechanism of how a reaction proceeds. If a linear correlation is found then it suggests that only one molecule of catalyst is involved in the enantiodifferentiating process. For this reason it was decided that an NLE study on our system would be beneficial and help provide some more insight to our catalytic system.

The NLE investigation was carried out using the reduction of **189c** as the model reaction. Catalyst **197c**, at varying degrees of enantiopurity[1] (100-0% *ee*), was then used to catalyse the reduction under the standard protocol and the results plotted in a scatter graph (see **graph 1**).

[1] Assuming **197c** is 100% enantiopure, mixing with racemic **197c** at various ratios will lower the *ee* of the catalyst (100%-0 at intervals of 10%)

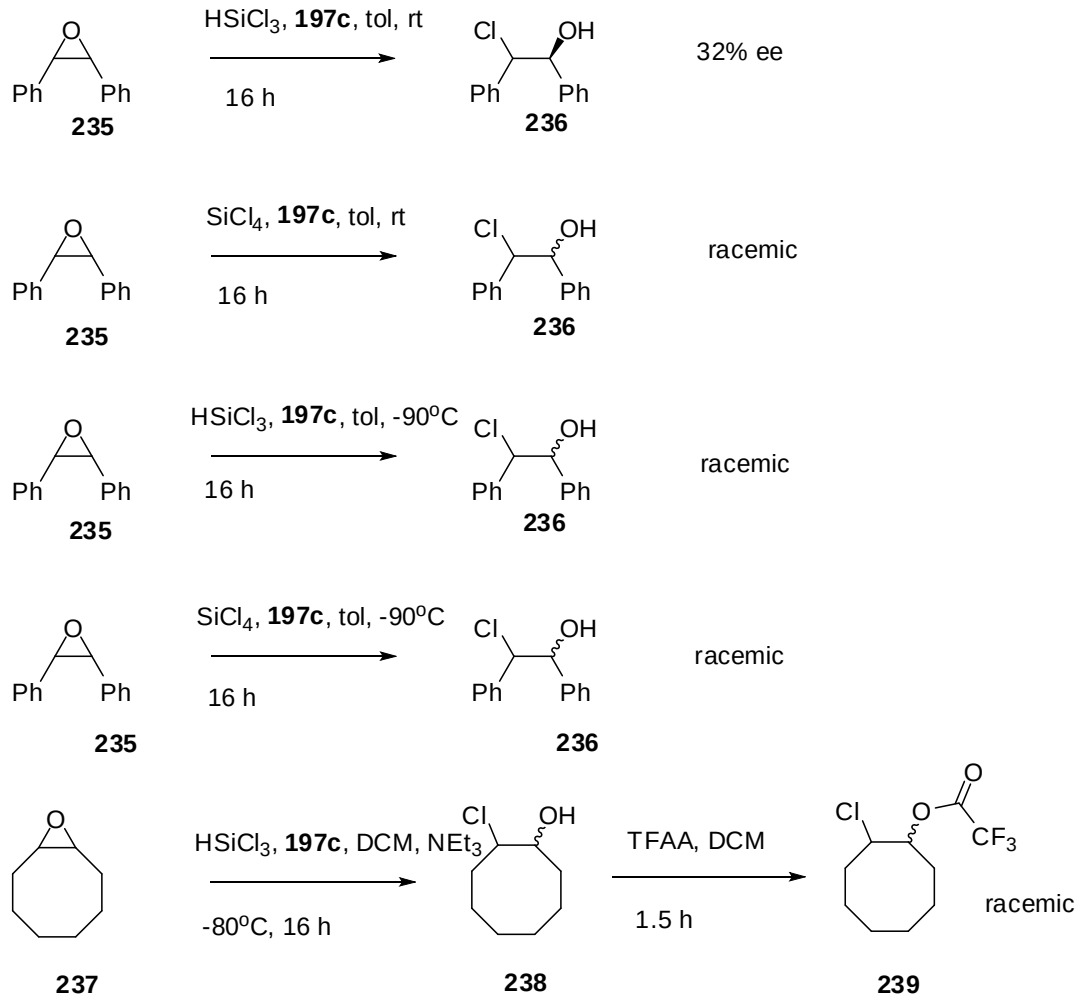



**Graph 1** Results of NLE study using **197c**

From the results obtained, a linear correlation between product *ee* and catalyst *ee* was evident. This, as stated previously suggests that only one molecule of **102c** is involved in the enantiodifferentiating process. (It should be noted that the points deviating from the straight line are most likely due to experimental error during the preparation of the catalyst ratios).

## 2.7 Further investigation into protocol scope

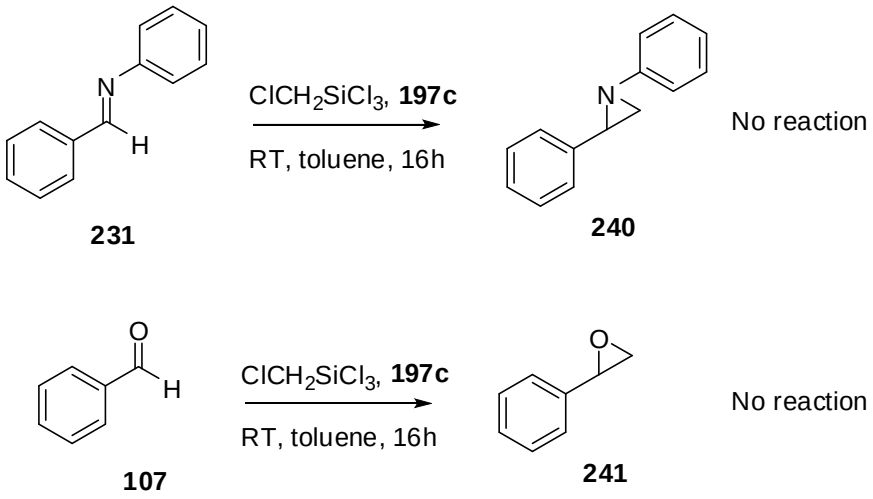
To investigate further uses of catalyst **197c**, a series of epoxide ring opening reactions were attempted. Using both $HSiCl_3$ and $SiCl_4$ , ring openings on *cis*-stilbene oxide **235** and cyclooctene oxide **237** were carried out (see **scheme 54**).




**Scheme 54** Epoxide ring-opening reactions

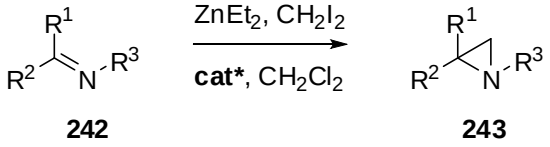
Although mostly racemic products were obtained, the ring opening of *cis*-stilbene oxide with $HSiCl_3$ in toluene at room temperature showed promise (giving product in 32% *ee*) and with further catalyst development, it may be possible to increase this further yet.

A series of aziridinations and epoxidations were carried out in order to determine whether or not catalyst **197c** could facilitate these transformations. [76] The reactions carried out are shown in **Scheme 55**.



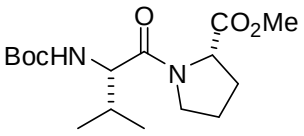

**Scheme 55** Aziridination and epoxidation facilitated by catalyst **197c**

Use of trichloro(chloromethyl)silane in the presence of catalyst **197c** proved friutless. This was also the case when carried out at -20$^{o}$C. An alternative strategy was then employed. Utilising the asymmetric Simmons-Smith cyclopropanation protocol (**Scheme 56**)[77] using diethyl zinc and diiodomethane, in the presence of **197c** the aziridination of aldimines **242** was attempted.



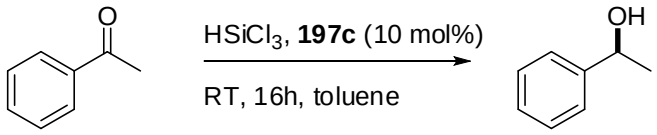

**Scheme 56** Asymmetric Simmons-Smith cyclopropanation

It was postulated that this protocol would suit our catalytic system since Shi *et al* had shown that a simple didpeptide **244,** on treatment with $ZnEt_2$ and $CH_2I_2$ could facilitate the cyclopropanation of unfunctionalised olefins in high enantioselectivity. This catalyst had a similar framework to our catalyst **197c** and it was therefore assumed that it might behave in a similar manner. However, this proved not to be the case. Indeed, in the presence of our catalyst, the reaction failed to proceed at all. This line of investigation was taken no further.




**244**

On-going work within the group [67] on ketone reduction (**scheme 57)** prompted us to consider the use of **102c** in the said reduction. The reaction, on acetophenone was carried out in the same way as the ketimine reductions ($HSiCl_3$, 10mol% **197c**).



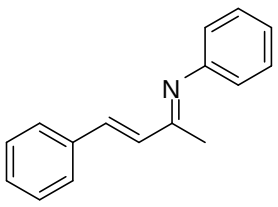

**57** **58**

**Scheme 57** Asymmetric ketone reduction with catalyst **197c**

Results from work carried out during an undergraduate project on ketone reduction (using **197a**) suggested that the reduction would not proceed. However, since our champion catalyst had not been used it was thought prudent that this should be attempted. The reduction proceeded well, furnishing the alcohol **58** in modest enantioselectivity (41% *ee*).

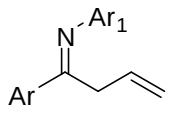
As a final exploration into the variety of different asymmetric transformations that could be facilitated, the Strecker-type cyanation was attempted. Ketimine **189a** was subjected to similar reaction conditions as previously used and although the reaction proceeded to completion, the resulting cyano-compound was found to be racemic. No further investigation into the Strecker-type cyanation was carried out.

Owing to the successful reduction of the α,β-unsaturated imine **233** whilst leaving the unsaturated double bond intact, it was decided that a range of imines containing an unsaturated double bond would be synthesised and subsequently tested.

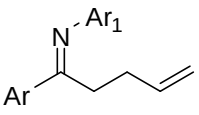



**233**

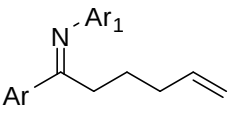
Beginning with the homoallylic framework (cf. **245**), the following series of imines were hoped to be produced (**245, 246** and **247**).




**245**

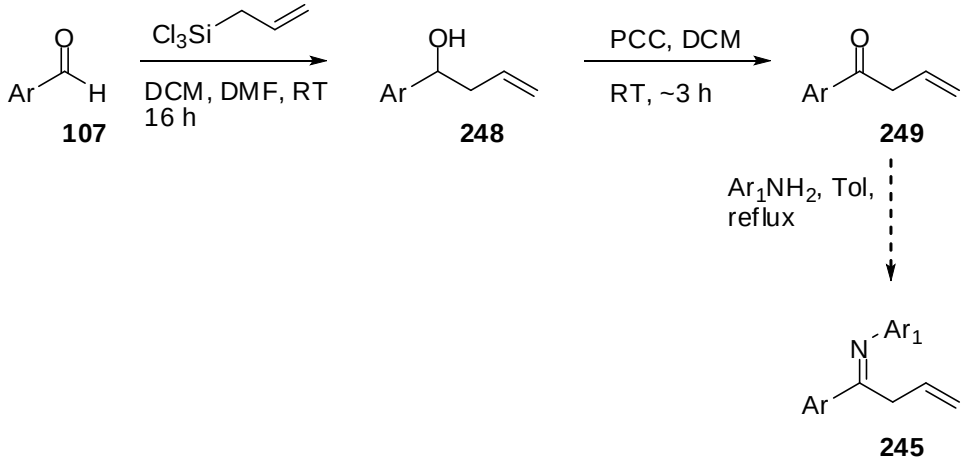



**246**



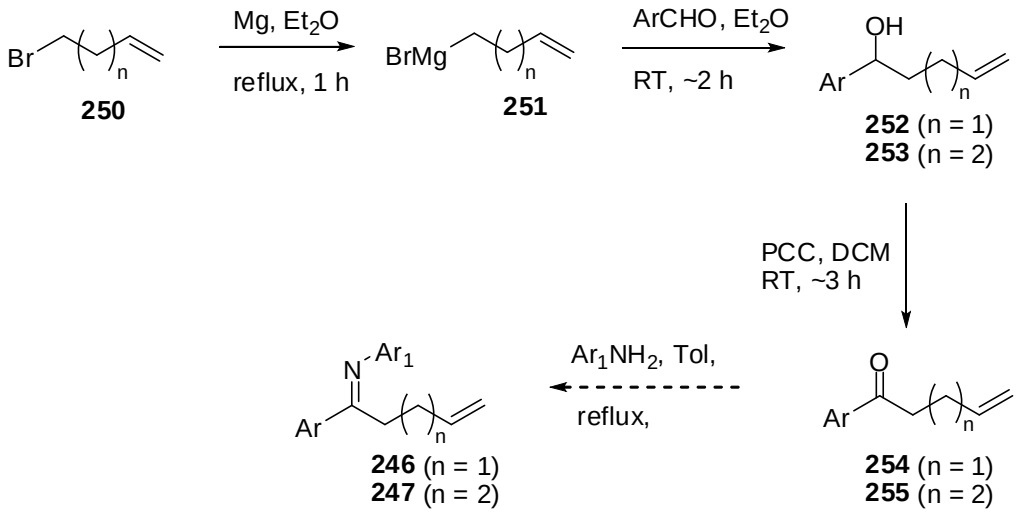

**247**

For the homoallylic series, the synthesis began with the allylation of the corresponding aldehyde under Lewis basic allylation conditions.[78] Using DMF as the Lewis base, allylation of the aldehyde with allyltrichlorosilane afforded the corresponding homoallylic alcohol in moderate yields. The oxidation to the ketone proved troublesome at first with methods such as PDC oxidation, Swern, Oppenhauer [79] and oxidation with calcium hypochlorite [80] all giving inferior results. Literature precedence of oxidations of similar alcohols with PCC [81] prompted us to try this method and subsequently the oxidations were successful, with excellent yields and reaction times of ≤3 hours. A representative synthetic scheme is shown below (**Scheme 58**).




**Scheme 58.** Representative synthesis of homoallylic imines **245**

The synthesis of frameworks **246** and **247** were slightly different in that the alkyl chain was incorporated on to the aldehyde via a Grignard reaction. [82] Using the appropriate bromo alkene (4-bromobut-1-ene for **246** and 5-bromopent-1-ene for **246**) and magnesium turnings, the Grignard reagent was synthesised and to this was added the aldehyde to furnish the corresponding alcohols with moderate yields in ~3.5 hours. The oxidation step used was as in **Scheme 58**. The representative scheme for the synthesis of frameworks **246** and **247** is shown in **Scheme 59**.

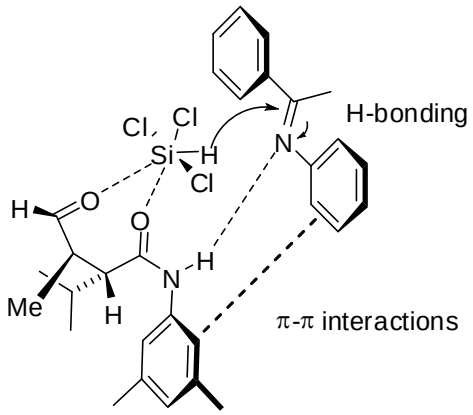



**Scheme 59.** Representative synthesis of **246** and **247**

The imine synthesis to date has proven difficult. With the simpler acetophenone based imines the transformation was complete and almost quantitative in ≤ 12 hours. However, with the allylic ketones and longer chain ketones the imine synthesis has proved sluggish with ~50% conversion achieved in 2 days. Different strategies have been employed in an attempt to remedy this with differing results. The Dean and Stark protocol, which involves azeotropic removal of water afforded no product. The imine has also proved difficult to separate from the starting ketone as both starting material and product have similar $R_f$ values on TLC. Owing to time constraints, unfortunately this could not be continued.

## 2.8 Conclusion

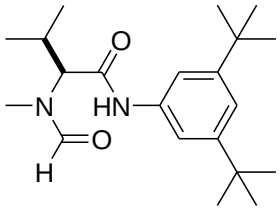
We have designed new amino acid derived organocatalysts **197** that are capable of catalysing the reduction of a range of aromatic imines to the corresponding secondary amines by way of hydrosilylation of *N*-aryl ketimines with $HSiCl_3$. A proposed transition state for this is shown below in **figure 14**.




**256**

**Figure 14** Proposed transition state for catalyst interaction with imine and $HSiCl_3$.

We have achieved enantioselectivities of ≤93% *ee* which match and indeed surpass some well established metal-mediated protocols.[2] The valine-derived formamide **197c** performed best with toluene as the solvent of choice. With the system being metal free and the solvent being environmentally sound, we have developed an efficient and workable alternative to metal-mediated ketimine reduction. Further development has continued with the synthesis of catalyst **213**, the 3,5-di-*tert*-butyl anilide derivative of **197**.[83] This has been utilised successfully in the aziridination of α-chloroketones, *via* reductive amination. This again shows the strength and depth of our protocol.



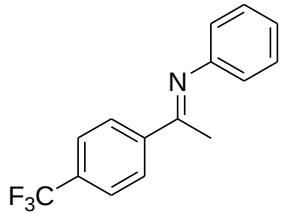

**x**

The synthesis of catalyst **197c** is now also being scaled up to the multi-gram level and is in the process of being made available commercially. When this project was embarked on, the aim was to provide an environmentally friendly alternative to metal-mediated ketimine reduction that could be utilised in an industrial setting. Perhaps we are almost there!

# Chapter 3: Experimental

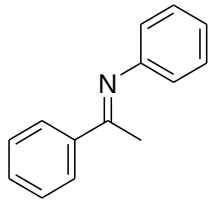
## 3. Experimental Section

**General Methods.** Melting points were determined on a Kofler block and are uncorrected. Optical rotations were recorded in $CHCl_3$ at 25 °C unless otherwise indicated, with an error of ≤±0.1. The $[\alpha]_D$ values are given in $10^{-1}$ deg $cm^3$ $g^{-1}$. The NMR spectra were recorded in $CDCl_3$, $^1H$ at 400 MHz and $^{13}C$ at 100.6 MHz with chloroform-$d_1$ (δ 7.26, $^1H$; δ 77.0, $^{13}C$) as internal standard unless otherwise indicated. Various 2D-techniques and DEPT experiments were used to establish the structures and to assign the signals. The IR spectra were recorded for $CHCl_3$ solutions unless otherwise indicated. The mass spectra (EI and/or CI) were measured on a dual sector mass spectrometer using direct inlet and the lowest temperature enabling evaporation. All reactions were performed under an atmosphere of dry, oxygen-free nitrogen in oven-dried glassware, twice evacuated and filled with inert gas. Solvents and solutions were transferred by syringe-septum and cannula techniques. All solvents for the reactions were of reagent grade and were dried and distilled immediately before use (dichloromethane from calcium hydride). Petroleum ether refers to the fraction boiling in the range of 60-80 $^oC$. Yields are given for isolated products showing one spot on a TLC plate and no impurities detectable in the NMR spectrum. The identity of the products prepared by different methods was checked by comparison of their NMR, IR, and MS data and by the TLC behaviour. The chiral GC and HPLC methods were calibrated with the corresponding racemic mixtures. The imines are known compounds and were prepared according to the procedure shown for **103c**, the only new member of this series. Amines are all know compounds and their absolute configuration was established in reference to the literature data.

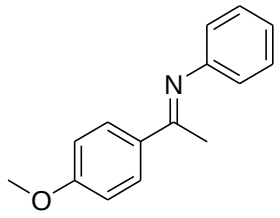



***N*-(1-(4-(trifluoromethyl)phenyl)ethylidene)benzenamine 189c** A mixture of $NaHCO_3$ (2.2 g, 26 mmol), aniline (0.48 mL, 5.3 mmol), *p*-trifluoromethylacetophenone (1.0 g, 5.3 mmol), and activated molecular sieves (4 g, 4 Å) in anhydrous toluene (5 mL) was heated at 80 $^oC$ for 12 h under an argon atmosphere. The mixture was filtered through celite and the celite washed with $CH_2Cl_2$. The filtrate was evaporated *in vacuo* and the product was

crystallized from petroleum ether at 5 $^{o}$C to give pure **189c** (0.67 g, 48%): mp 74-77 $^{o}$C; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 2.17 (s, 3H), 6.71 (d, *J* = 8.0 Hz, 2H), 7.03 (t, *J* = 8.0 Hz, 1H), 7.30 (t, *J* = 8.0, 2H), 7.61 (d, *J* = 8.2 Hz, 2H), 7.99 (d *J* = 8.2, 2H); $^{13}$C NMR δ 17.80 ($CH_3$), 119.57 (CH), 124.04 (CH), 125.72 (CH), 127.92 (CH), 129.44 (CH), 132.31 ($CF_3$), 143 (C), 151.51 (C), 164.69 (C); IR (NaCl) ν 1643 cm$^{-1}$; MS *m/z* (%) 263.1 ($M^+$, 61%) 248.1 (100), 244.1 (7), 152.1 (4), 181.1 (16), 77.1 (71); HRMS (EI): 263.0922 ($C_{15}H_{12}N_2F_3$ requires 263.0921).



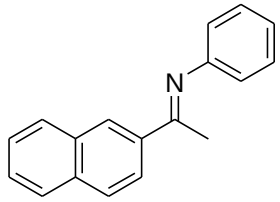

**General procedure for the synthesis of imines: Phenyl-(1-phenyl-ethylidene)-amine (189a).** In a typical experiment $NaHCO_3$ (8.2 g, 98 mmol), aniline (1.82 mL, 20 mmol), acetophenone (2.34 mL, 20 mmol), activated molecular sieves (14 g, 4 Å) and anhydrous toluene were heated at 80 $^{o}$C under an argon atmosphere. The mixture of reaction was filtered through celite and the celite washed with DCM. The filtrate was evaporated in vacuo and the product **189a** was crystallised in petroleum ether at –20 $^{o}$C; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 2.26 (s, 3H), 6.81 (d, *J*= 8.1Hz, 2H), 7.12 (t, *J*= 7.1Hz, 1H), 7.39 (t, *J*= 7.3Hz, 2H), 7.45 (m, 3H), 8.0 (d, *J*= 8.1Hz, 2H) in agreement with literature values. [84]




**[1-(4-Methoxy-phenyl)-ethylidene]-phenyl-amine (189b)**. Prepared according to the general procedure.

- $NaHCO_3$ (8.2 g, 98 mmol);
- aniline (1.82 mL, 20 mmol);
- (4-methoxy)-acetophenone (3.0 g, 20 mmol);
- toluene (8 mL);
- MS 4 A (14 g)

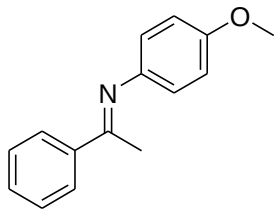
The mixture of reaction was filtered through celite and the celite washed with DCM. The filtrate was evaporated in vacuo and the product **189b** was crystallised in petroleum ether at 5 $^{o}$C; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 2.22 (s, 3H), 3.90 (s, 3H), 6.80 (d, *J*= 7.1Hz, 2H), 6.98 (d, *J*= 6.9Hz, 2H), 7.09 (t, *J*= 7.4Hz, 1H), 7.34 (t, *J*= 7.2Hz, 2H), 7.97 (d, *J*= 7.9Hz, 2H) in agreement with literature values. [60]




**(1-Naphthalen-2-yl-ethylidene)-phenyl-amine (189d)**. Prepared according to the general procedure.

- $NaHCO_3$ (8.2 g, 98 mmol);
- aniline (1.82 mL, 20 mmol)
- 2-acetophanone (3.4 g, 20 mmol);
- toluene (8 mL);
- MS 4 A (14 g)

The mixture of reaction was filtered through celite and the celite washed with DCM. The filtrate was evaporated in vacuo and the product **189d** was crystallised in petroleum ether at room temperature; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 2.38 (s, 3H), 6.86 (d, *J*= 8.1Hz, 2H), 7.13 (t, *J*= 7.4Hz, 1H), 7.42 (t, *J*= 7.3Hz, 2H), 7.53 (m, 2H), 7.92 (m, 3H), 8.22 (d, *J*= 7.9Hz, 1H) in agreement with literature values. [60]

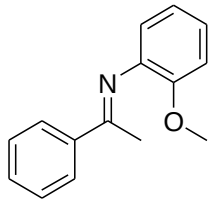



**(4-Methoxy-phenyl)-(1-phenyl-ethylidene)-amine (189f)**. Prepared according to the general procedure.

- $NaHCO_3$ (8.2 g, 98 mmol);
- *p*-anisidine (2.46 g, 20 mmol);

- acetophenone (2.34 mL, 20 mmol);
- toluene (8 mL);
- MS 4 A (14 g)

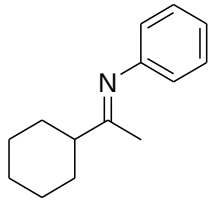
The mixture of reaction was filtered through celite and the celite washed with DCM. The filtrate was evaporated in vacuo and the product **189f** was crystallised in petroleum ether and ethyl acetate at room temperature; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 2.28 (s, 3H), 3.84 (s, 3H), 6.77 (d, *J*= 7.9Hz, 2H), 6.94 (d, *J*= 7.8Hz, 2H), 7.47 (m, 3H), 7.98 (d, *J*= 7.4, 2H) in agreement with literature values. [85]




**(2-Methoxy-phenyl)-(1-phenyl-ethylidene)-amine (189g)**. Prepared according to the general procedure.

- $NaHCO_3$ (8.2 g, 98 mmol);
- *o*-anisidine (2.26 mL, 20 mmol);
- acetophenone (2.34 mL, 20 mmol);
- toluene (8 mL);
- MS 4 A (14 g)

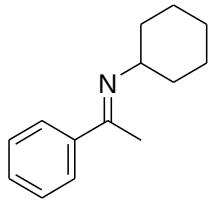
The mixture of reaction was filtered through celite and the celite washed with DCM. The filtrate was evaporated in vacuo and the product **189g** was distilled under reduced pressure. [85]



**(1-Cyclohexyl-ethylidene)-phenyl-amine (189e)**. Prepared according to the general procedure.

- $NaHCO_3$ (8.2 g, 98 mmol);
- aniline (1.82 mL, 20 mmol);
- 1-cyclohexyl-ethanone (2.75 mL, 20 mmol);
- toluene (8 mL);
- MS 4 A (14 g)

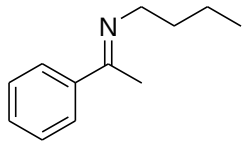
The mixture of reaction was filtered through celite and the celite washed with DCM. The filtrate was evaporated in vacuo and the product **189e** was distilled under reduced pressure. $^1$H NMR (400 MHz, $CDCl_3$) δ 1.05-2.40 (m, 11H), 1.72 (s, 3H), 6.69 (d, *J*= 8.4Hz, 2H), 7.05 (t, *J*= 8.8Hz, 1H), 7.29 (t, *J*= 10.0Hz, 2H) in agreement with literature values. [60]



**Cyclohexyl-(1-phenyl-ethylidene)-amine (189h)**. Prepared according to the general procedure.

- $NaHCO_3$ (8.2 g, 98 mmol);
- cyclohexylamine (2.28 mL, 20 mmol);
- acetophenone (2.34 mL, 20 mmol);
- toluene (8 mL);
- MS 4 A (14 g)

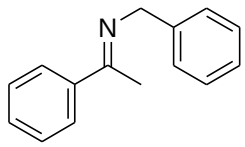
The mixture of reaction was filtered through celite and the celite washed with DCM. The filtrate was evaporated in vacuo and the product **189h** was distilled under reduced pressure. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 1.25-1.91 (m, 10H), 2.27 (s, 3H), 3.51 (m, 1H), 7.40 (m,3H), 7.78 (t, *J*= 7.6Hz, 2H) in agreement with literature values. [60]



**Butyl-(1-phenyl-ethylidene)-amine (189i)**. Prepared according to the general procedure.

- $NaHCO_3$ (8.2 g, 98 mmol);
- Butylamine (2.0 mL, 20 mmol);
- acetophenone (2.34 mL, 20 mmol);
- toluene (8 mL);
- MS 4 A (14 g)

The mixture of reaction was filtered through celite and the celite washed with DCM. The filtrate was evaporated in vacuo and the product **189i** was distilled under reduced pressure; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 0.85 (t, *J*= 7.8Hz, 3H), 1.45 (m, 2H), 1.74 (m, 2H), 2.26 (s, 3H), 3.50 (t, *J*= 7.2Hz, 2H), 7.39 (m, 3H), 7.78 (m, 2H) in agreement with literature values. [84]

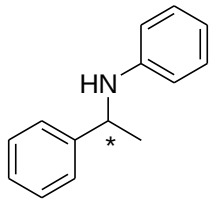


**Benzyl-(1-phenyl-ethylidene)-amine (189j)**. Prepared according to the general procedure.

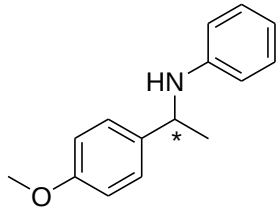
- $NaHCO_3$ (8.2 g, 98 mmol);
- benzylamine (2.2 mL, 20 mmol);
- acetophenone (2.34 mL, 20 mmol);
- toluene (8 mL);
- MS 4 A (14 g)

The mixture of reaction was filtered through celite and the celite washed with DCM. The filtrate was evaporated in vacuo and the product **189j** was distilled under reduced pressure; $^1$H NMR (400 MHz, $CDCl_3$) δ 2.39 (s, 3H), 4.81 (s, 2H), 7.28 (t, *J*= 7.67Hz, 2H), 7.38 (d, *J*=7.3Hz, 2H), 7.41 (t, *J*= 7.6Hz, 4H), 7.48 (d, *J*= 7.5Hz, 2H) in agreement with literature values. [60]

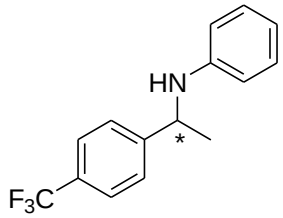
**Protocol A: General Procedure for the Catalytic Hydrosilylation of Imines.** Trichlorosilane (77 μL, 0.77 mmol) was added dropwise to a stirred solution of the imine (0.51 mmol) and the catalyst (0.051 mmol) and in anhydrous $CH_2Cl_2$ (or $CHCl_3$ or MeCN or toluene; see **tables 1-5**) at 0 $^oC$ (or at -20 $^oC$), and the mixture was allowed to stir overnight at room temperature (or at -20 $^oC$) under an argon atmosphere. The reaction was quenched with a saturated solution of $NaHCO_3$ (10 mL) and the product was extracted with ethyl acetate (100 mL). The extract was washed with brine and dried over anhydrous $MgSO_4$ and the solvent was evaporated. Purification using column chromatography on silica gel with a petroleum ether-ethyl acetate mixture (24:1) afforded the product as an oil. The yields and ee are given in Tables 1-4.



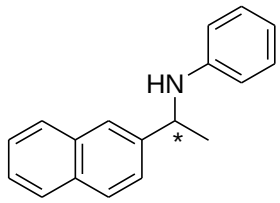

**(*S*)-(+)-*N*-(1-phenylethyl)benzenamine 190a.** $[\alpha]_D$ +16.8 (*c* 0.5, MeOH); $^1$H NMR (400 MHz, $CDCl_3$) δ 1.41 (d, *J* = 7.1 Hz, 3H), 3.94 (br s, 1H), 4.41 (q, *J* = 6.7 Hz, 1H), 6.44 (d, *J* = 8.6 Hz, 2H), 6.57 (t, *J* = 7.3 Hz, 1H), 7.01 (t, *J* = 7.5 Hz, 2H), 7.13 (t, *J* = 6.8 Hz, 1H), 7.27 (t, *J* = 7.3 Hz, 2H), 7.30 (d, *J* = 7.3 Hz, 2H) in agreement with the literature data;[86] chiral HPLC (Chiralcel OD-H, hexane/2-propanol 15:1 + 0.1% $NEt_3$, 0.5 mL/min) showed 92% ee ($t_S$ = 15.1 min, $t_R$ = 17.7 min).



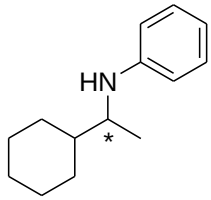
**(*S*)-(+)-*N*-(1-(4-methoxyphenyl)ethyl)benzenamine 190b.** $[\alpha]_D$ +4.45 (*c* 0.5, MeOH); $^1$H NMR (400 MHz, $CDCl_3$) δ 1.38 (d, *J* = 7.2 Hz, 3H), 3.68 (s, 3H), 3.90 (br s, 1H), 4.35 (q, *J* = 6.6 Hz, 1H), 6.41 (d, *J* = 8.5 Hz, 2H), 6.55 (t, *J* = 7.31 Hz, 1H), 6.77 (d, *J* = 7.2 Hz, 2H), 6.97 (t, *J* = 6.5 Hz, 2H), 7.14 (d, *J* = 7.2 Hz, 2H) in agreement with the literature data;[60,84] chiral HPLC (Chiralcel OD-H, hexane/2-propanol 15:1 + 0.1% $NEt_3$ 0.5 mL/min) showed 80% ee ($t_S$ = 19.3 min, $t_R$ = 22.7 min).



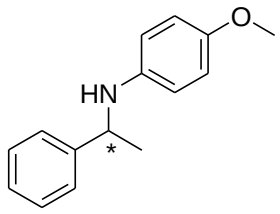

**(*S*)-(+)-*N*-(1-(4-(trifluoromethyl)phenyl)ethyl)benzenamine 190c.** $[\alpha]_D$ +20.0 (*c* 0.5, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 1.46 (d, *J* = 7.1 Hz, 3H), 3.97 (br s, 1H), 4.46 (q, *J* = 6.7 Hz, 1H), 6.38 (d, *J* = 7.6 Hz, 2H), 6.59 (t, *J* = 7.4 Hz, 1H), 7.02 (t, *J* = 7.3 Hz, 2H), 7.41 (d, *J* = 8.2 Hz, 2H), 7.51 (d, *J* = 8.2 Hz, 2H) in agreement with the literature data;[86] chiral GC (Supelco β-DEX 120 column, oven: 125 $^o$C for 2 min, then 1 $^o$C/min to 200 $^o$C, 10 min at that temperature) showed ee of 89% ($t_S$ = 42.8 min, $t_R$ = 43.2 min).



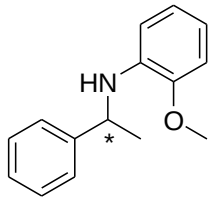

**(*S*)-(+)-*N*-(1-(naphthalen-2-yl)ethyl)benzenamine 190d.** $[\alpha]_D$ +16.2 (*c* 1.0, MeOH); $^1$H NMR (400 MHz, $CDCl_3$) δ 1.49 (d, *J* = 7.1 Hz, 3H), 4.03 (br s, 1H), 4.54 (q, *J* = 6.7 Hz, 1H), 6.45 (d, *J* = 8.0 Hz, 2H), 6.56 (t, *J* = 7.5 Hz, 1H), 6.98 (t, *J* = 7.6 Hz, 2H), 7.30 (t, *J* = 7.8 Hz, 2H), 7.36 (d, *J* = 7.2 Hz, 2H), 7.69 (d, *J* = 7.8 Hz, 2H), 7.70 (s, 1H) in agreement with the literature data;[86,87] chiral HPLC (Chiralcel OD-H, hexane/2-propanol 15:1 + 0.1% $NEt_3$, 0.5 mL/min) showed 88% ee ($t_S$ = 18.7 min, $t_R$ = 21.2 min).



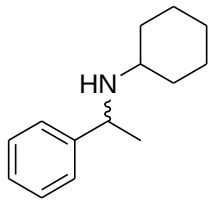

**(*S*)-(+)-*N*-(1-cyclohexylethyl)benzenamine 190e.** $[\alpha]_D$ +6.1 (*c* 1.0, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) δ 0.91-1.80 (m, 11H), 1.05 (d, *J* = 6.7 Hz, 3H), 3.2 (q, *J* = 8.0 Hz, 1H), 3.38 (br s, 1H), 6.49 (d, *J* = 8.0 Hz, 2H), 6.55 (t, *J* = 8.0 Hz, 1H), 7.07 (t, *J* = 10.0 Hz, 2H) in agreement with the literature data;[61] chiral HPLC (Chiralcel OD-H, hexane/2-propanol 99:1, 0.75 mL/min) showed 37% ee ($t_R$ = 8.2 min, $t_S$ = 8.7 min).



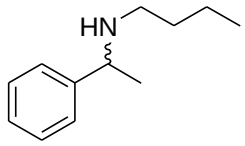

**(*S*)-(+)-4-methoxy-*N*-(1-phenylethyl)benzenamine 190f.** $[\alpha]_D$ +2.5 (*c* 1.0, MeOH); $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.40 (d, *J* = 7.0 Hz, 3H), 3.60 (s, 3H), 4.32 (q, *J* = 6.4 Hz, 1H), 6.37 (d, *J* = 8.1 Hz, 2H), 6.61 (d, *J* = 7.6 Hz, 2H), 7.15 (t, *J* = 7.4 Hz, 1H), 7.22 (t, *J* = 7.4 Hz, 2H), 7.28 (d, *J* = 7.6 Hz, 2H) in agreement with the literature data;[86,88]. chiral HPLC (Chiralcel OD-H, hexane/2-propanol 99:1, 0.75 mL/min) showed 85% ee ($t_R$ = 15.5 min, $t_S$ = 18.6 min).



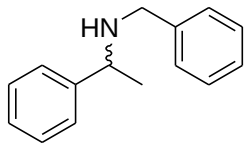

**(*S*)-(+)-2-methoxy-*N*-(1-phenylethyl)benzenamine 190g.** $[\alpha]_D$ +9.2 (*c* 0.5, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.44 (d, *J* = 7.1 Hz, 3H), 3.80 (s, 3H), 4.38 (q, *J* = 6.8 Hz, 1H), 4.54 (br s, 1H), 6.25 (d, *J* = 8.0 Hz, 1H), 6.52 (t, *J* = 6.9 Hz, 1H), 6.61 (t, *J* = 7.2 Hz, 1H), 6.69 (d, *J* = 7.1 Hz, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 7.24 (t, *J* = 7.2 Hz, 2H), 7.33 (d, *J* = 7.2 Hz, 2H) in agreement with the literature data;[89] chiral HPLC (Chiralcel OD-H, hexane/2-propanol 99:1, 0.75 mL/min) showed 22% ee ($t_S$ = 7.1 min, $t_R$ = 8.1 min).



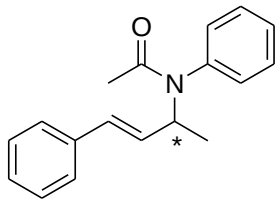

**(±)-*N*-(1-phenylethyl)cyclohexanamine 190h** $^1$H NMR (400 MHz, $CDCl_3$) δ 0.91-2.29 (m, 11H), 1.34 (d, *J* = 6.8 Hz, 3H), 3.93 (q, *J* = 6.8 Hz, 1H), 7.16-7.29 (m, 5H) in agreement with the literature data.[90] The racemic nature was confirmed by running the NMR spectrum in the presence of mandelic acid (2 equiv).




**(±)-*N*-(1-phenylethyl)butan-1-amine 190i.** $^1$H NMR (400 MHz, $CDCl_3$) δ 0.79 (t, *J* = 7.3 Hz, 3H), 1.19 (m, 2H), 1.32 (d, *J* = 7.2 Hz, 3H), 1.36 (m, 2H), 2.40 (m, 2H), 3.73 (q, *J* = 6.6 Hz, 1H), 7.1-7.3 (arom, 5H) in agreement with the literature data.[84] The racemic nature was confirmed by running the NMR spectrum in the presence of mandelic acid (2 equiv).

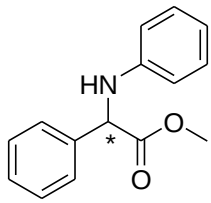



***N*-benzyl-1-phenylethanamine 190j.** $^1$H NMR (400 MHz, $CDCl_3$) δ 1.30 (d, *J* = 7.1 Hz, 3H), 2.13 (br s, 1H), 3.53 (m, 2H), 3.73 (q, *J* = 5.5 Hz, 1H), 7.1-7.3 (arom, 10H) in agreement with the literature data.[60,89] The almost racemic nature was confirmed by running the NMR spectrum in the presence of mandelic acid (2 equiv).




**(*S*)-(–)-*N*-phenyl-N-(4-phenylbut-3-en-2-yl)acetamide 233a.** $[\alpha]_D$ -17.4 (*c* 1.0, $CHCl_3$) [lit.[91] gives +4.4 (*c* 1.0, $CHCl_3$) for the (*R*)-enantiomer]; $^1$H NMR (400 MHz, $CDCl_3$) δ

1.32 (d, $J$ = 6.64 Hz, 3H), 3.63 (br s, 1H), 4.05 (m, 1H), 6.13 (dd, $J$ = 5.80 Hz, $J$ = 15.96 Hz, 1H), 6.50 (d, $J$ = 15.96 Hz, 1H), 6.56-7.28 (m, 10H) in agreement with the literature data;[91,92,] For the ee determination, amine **233** was converted into the acetyl derivative by heating at reflux with acetyl chloride (3 equiv), triethylamine (3 equiv) and DMAP (cat.) in $CHCl_3$ for 30 min. Aqueous work up followed by purification using column chromatography on silica gel with a petroleum ether-ethyl acetate mixture (2:1) afforded the acetamide derivative as an oil: $^1$H NMR (400 MHz, $CDCl_3$) δ 1.16 (d, $J$ = 6.5 Hz, 3H), 1.72 (s, 3H), 5.55 (q, $J$ = 6.7 Hz, 1H), 6.04 (dd, $J$ = 5.8, 15.9 Hz, 1H), 6.40 (d, $J$ = 15.9 Hz, 1H) 7.03-7.34 (m, 10H); chiral HPLC (Chiralcel OD-H, hexane/2-propanol 85:15, 1.0 mL/min) showed 74% ee ($t_S$ = 17.5 min, $t_R$ = 36.8 min).

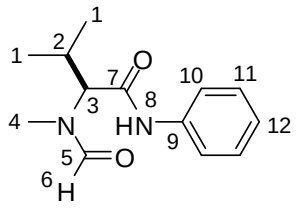



**(*R*)-(–)-methyl-2-phenyl-2-(phenylamino)acetate 234a.** $[\alpha]_D$ -20.2 (*c* 1.0, $CHCl_3$), -13.2 (*c* 1.0, THF) [lit.[93] gives +68.3 (*c* 0.32, THF) for the (*S*)-enantiomer]; $^1$H NMR (400 MHz, $CDCl_3$) δ 3.66 (s, 3H), 4.87 (br s, 1H), 5.01 (d, $J$ = 5.6 Hz, 1H), 6.47 (d, $J$ = 8.4 Hz, 2H), 6.62 (t, $J$ = 6.8 Hz, 1H), 7.05 (t, $J$ = 7.6 Hz, 2H), 7.24-7.31 (m, 3H), 7.43 (d, $J$ = 7.6 Hz, 2H) in agreement with the literature data;[93] chiral HPLC (Chiralcel OD-H, hexane/2-propanol 99:1, 1 mL/min) showed 30% ee ($t_S$ = 19.5 min, $t_R$ = 23.1 min).

**Protocol B: General Procedure for the Synthesis of Formamides:** The BOC derivative (1.03 mmol) was dissolved in trifluoroacetic acid (2.0 mL) at room temperature. After 1 hour the reaction mixture was evaporated in vacuo, the residue (the free amine) was dissolved in formic acid (1.5 mL) and the resulting solution was cooled to 0 $^o$C. Acetic anhydride (0.68 mL, 7.21 mmol) was added dropwise and the mixture was allowed to stir at room temperature overnight. The volatiles were then removed by reduced pressure. Purification using column chromatography on silica gel with a petroleum ether-ethyl acetate mixture (2:1) afforded the desired product; the yields are give below. Formylation of amine **204** (1.03 mmol) in the same fashion (skipping the deprotection step) furnished **197e**.

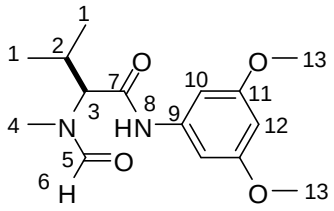
**Protocol C: General Procedure for the Synthesis of *N*-Methyl BOC-Protected Amino Acids** Sodium hydride (60% dispersion in mineral oil; 3.0 g, 138 mmol) was added in small portions to a stirred solution of the respective BOC-protected amino acid (13.8 mmol) and methyl iodide (19.6 g, 138 mmol) in anhydrous THF (60 mL) at 0 $^{o}$C. The mixture was allowed to stir at room temperature for 24 h under an argon atmosphere, the reaction was then quenched with water (15 mL), ethyl acetate (10 mL) was added and the mixture was evaporated in vacuo. The concentrate was diluted with water (300 mL) and washed with ethyl acetate (150 mL). The aqueous solution was acidified to pH 3.5 with a solution of 5% citric acid and extracted with ethyl acetate (200 mL). The extract was washed with brine, dried over anhydrous $MgSO_4$, and evaporated *in vacuo* to give the desired product; the yields are given below.

**Protocol D: General Procedure for the Synthesis of Amides.** Methyl chloroformate (0.55 mL, 7.15 mmol) was added dropwise to a stirred solution of (*S*)-**100** (1.40 g, 6.05 mmol) and triethylamine (1.0 mL, 7.15 mmol) in anhydrous THF (30 mL) at 0 $^{o}$C under an argon atmosphere and the mixture was stirred at that temperature for 2 h. The precipitate was removed by suction filtration and the filtrate was added dropwise to a solution of the corresponding amine (8.5 mmol) and triethylamine (1.0 mL, 7.15 mmol) in anhydrous THF (30 mL) at 0 $^{o}$C. The mixture was allowed to stir at room temperature overnight under an argon atmosphere and the solvent was then removed under reduced pressure. The residue was purified using column chromatography on silica gel with a petroleum ether-ethyl acetate mixture (4:1) to afford the desired product; the yields are given below.

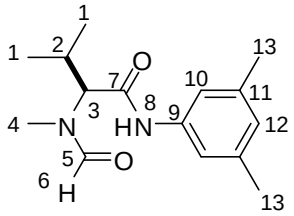



**(*S*)-(–)-3-methyl-2-(*N*-methylformamido)-*N*-phenylbutanamide 197a.** Obtained from (*S*)-**200a** using protocol B (oil, 180 mg, 75%): $[\alpha]_D$ -187.0 (*c* 1.0, $CHCl_3$); $^{1}$H NMR (400 MHz, $CDCl_3$) δ 0.85 (H-1, d, *J* = 6.6 Hz, 3H), 0.99 (H-1, d, *J* = 6.7 Hz, 3H), 2.40 (H-2, m, 1H), 2.92 (H-4, s, 3H), 4.41 (H-3, d, *J* = 10.3 Hz, 1H), 7.0 (Ar-H, t, *J* = 7.4 Hz, 1H), 7.22 (Ar-H, t, *J* = 7.8 Hz, 2H), 7.46 (Ar-H, d, *J* = 7.7 Hz, 2H), 8.09 (H-6, s, 1H), 8.50 (H-8, br s, 1H); $^{13}$C NMR δ 17.59 (C-1, $CH_3$), 17.78 (C-1, $CH_3$), 18.49 (C-4, $CH_3$), 24.47 (C-2, CH), 30.60 (C-3, CH), 118.95 (Ar-C, CH), 123.39 (Ar-C, CH), 127.92 (Ar-C, CH) 136.80

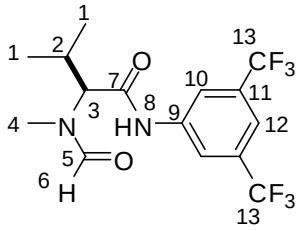
(Ar-C, C), (CHO), 166.31 (CO); IR (Golden Gate) ν 3274 (NH), 1650 (CO) $cm^{-1}$; MS *m/z* (%) 234 ($M^{\bullet+}$, 8), 142 (20), 114 (35), 85 (65), 47 (15); HRMS (EI) 234.1368 ($C_{13}H_{18}O_2N_2$ requires 234.1367).



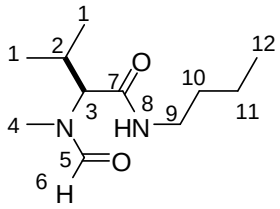
**(*S*)-(–)-*N*-(3,5-dimethoxyphenyl)-3-methyl-2-(*N*-methylformamido)butanamide 197b.** Obtained from (*S*)-**200b** using protocol B (oil, 131 mg, 26%): $[\alpha]_D$ –137.5 (*c* 1.0, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ 0.94 (H-1, d, *J* = 6.7 Hz, 3H), 1.04 (H-1, d, *J* = 6.8 Hz, 3H), 2.49 (H-2, m, 1H), 3.02 (H-4, s, 3H), 3.79 (H-13, s, 6H), 4.38 (H-3, d, *J* = 11.2 Hz, 1H), 6.25 (Ar-H, s, 1H), 6.78 (Ar-H, s, 2H), 8.04 (H-8, br s, 1H), 8.17 (H-6, s, 1H); $^{13}$C NMR δ 18.89 (C-1, $CH_3$), 19.95 (C-1, $CH_3$), 25.57 (C-4, $CH_3$), 32.04 (C-2, CH), 55.79 (C-3, CH), 97.5 (C-13, $CH_3$), 98.37 (C-13, $CH_3$), 139.73 (Ar-C, CH), 161.42 (COMe), 164.50 (CHO), 167.52 (CO); IR (NaCl) ν 3293 (NH), 1655 (CO) $cm^{-1}$; MS *m/z* (%) 294 ($M^{\bullet+}$, 4), 280 (41), 220 (3), 192 (11), 153 (100), 100 (40), 55 (19); HRMS (EI) 294.1580 ($C_{15}H_{22}O_4N_2$ requires 294.1582).



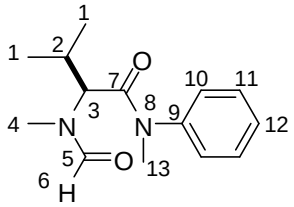
**(*S*)-(–)-*N*-(3,5-dimethylphenyl)-3-methyl-2-(*N*-methylformamido)butanamide 197c.** Obtained from (*S*)-**200c** using protocol B (142 mg, 82%): mp 83-86 °C; $[\alpha]_D$ -19.2 (*c* 1.0, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 0.84 (H-1, d, *J* = 6.6 Hz, 3H), 0.99 (H-1, d, *J* = 6.5 Hz, 3H), 2.20 (H-13, s, 6H), 2.39 (H-2, m, 1H), 2.95 (H-4, s, 3H), 4.35 (H-3, d, *J* = 11.2 Hz, 1H), 6.67 (Ar-H, s, 1H), 7.09 (Ar-H, d, *J* = 8.3 Hz, 2H), 8.07 (H-6, s, 1H), 8.18 (H-8, br s, 1H); $^{13}$C NMR δ 18.97 (C-1, $CH_3$), 19.92 (C-13, $CH_3$), 21.71 (C-4, $CH_3$), 25.74 (C-2, CH), 63.47 (C-3, CH), 118.21 (Ar-C, CH), 126.56 (Ar-C, CH), 137.92 (C), 139.13 (C), 164.35 (CHO), 167.61 (CO); IR (Golden Gate) ν 3284 (NH), 1650 (CO) $cm^{-1}$; MS *m/z* (%) 262 ($M^{\bullet+}$, 29), 160 (7), 142 (43), 114 (100), 86 (21), 83 (19), 42 (7); HRMS (EI) 262.1681 ($C_{15}H_{22}O_2N_2$ requires 262.1680).



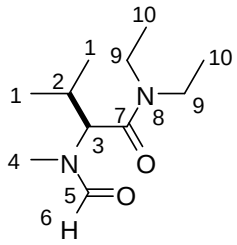
**(*S*)-(–)-*N*-(3,5-bis(trifluoromethyl)phenyl)-3-methyl-2-(*N*-methylformamido)butanamide 197e.** Obtained using protocol B from the free amine (*S*)-**204** so that no BOC deprotection was required prior to the formylation (189 mg, 95%): mp 152-154 $^{o}$C; $[\alpha]_D$ –81.5 (*c* 1.5, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ 0.89 (H-1, d, *J* = 6.6 Hz, 3H), 1.03 (H-1, d, *J* = 6.6 Hz, 3H), 2.45 (H-2, m, 1H), 2.96 (H-4, s, 3H), 4.34 (H-3, d, *J* = 11.3 Hz, 1H), 7.52 (Ar-H, s, 1H), 7.95 (Ar-H, s, 2H), 8.10 (H-6, s, 1H), 8.90 (H-8, br s, 1H); $^{13}$C NMR δ 19.06 (C-1, $CH_3$), 19.85 (C-1, $CH_3$), 26.02 (C-4, $CH_3$), 32.29 (C-2, CH), 63.67 (C-3, CH), 117.80 (Ar-C, CH), 119.94 (Ar-C, CH), 139.84 (C), 164.51 (CHO), 168.35 (CO); IR (NaCl) ν 3233 (NH), 1648 (CO) cm$^{-1}$; MS *m/z* (%) 370 ($M^{\bullet+}$, 24), 351 (65), 299 (16), 256 (15), 228 (26), 188 (8); HRMS 370.1118 ($C_{15}H_{16}O_2N_2F_6$ requires 370.1116).



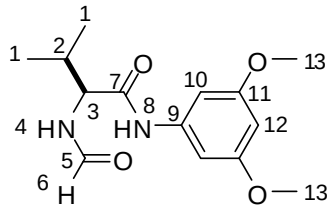
**(*S*)-(–)-*N*-butyl-3-methyl-2-(*N*-methylformamido)butanamide 197d.** Obtained from (*S*)-**200d** using protocol B; purification using column chromatography on silica gel with an ethyl acetate-methanol mixture (9:1) afforded the product as an oil (357 mg, 51%); $[\alpha]_D$ -8.10 (*c* 1.5, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 0.91 (H-1 and H-12, m, 9H), 1.32 (H-11, m, 2H), 1.49 (H-10, m, 2H), 2.41 (H-2, m, 1H), 3.00 (H-4, s, 3H), 3.21 (H-9, m, 2H), 4.24 (H-3, d, *J* = 11.2 Hz, 1H), 6.14 (H-8, br s, 1H), 8.15 (H-6, s, 1H); $^{13}$C NMR δ 14.00 (C-1, $CH_3$), 18.87 (C-1, $CH_3$), 19.86 (C-12, $CH_3$), 20.21 (C-11, $CH_2$), 25.68 (C-2, CH), 27.88 (C-4, $CH_3$) 31.68 (C-10, $CH_2$), 39.51 (C-9, $CH_2$), 164.41 (CHO), 169.38 (CO); IR (NaCl) ν 3318 (NH), 1653 (CO), 1558 cm$^{-1}$; MS *m/z* (%) 215 ($M^{\bullet+}$, 100), 201 (5), 132 (8), 114 (6), 79 (4); HRMS (EI): 215.1760 ($C_{11}H_{23}O_2N_2$ requires 215.1760).



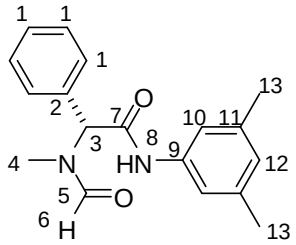
**(*S*)-(–)-*N*-3-dimethyl-2-(N-methylformamido)-*N*-phenylbutanamide 203a.** Obtained from (*S*)-**200e** using protocol B (oil, 20 mg, 37%): $[\alpha]_D$ -104.0 (*c* 0.5, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 0.61 (H-1, d, *J* = 6.7 Hz, 3H), 0.86 (H-1, d, *J* = 6.5, 3H), 2.37 (H-2, m, 1H), 2.76 (H-4, s, 3H), 3.20 (H-13, s, 3H), 4.54 (H-3, d, *J* = 10.9 Hz, 1H), 7.05 (Ar-H, t, *J* = 7.6 Hz, 1H), 7.30 (Ar-H, t, *J* = 7.8 Hz, 2H), 7.33 (Ar-H, d, *J* = 7.7 Hz, 2H), 7.84 (H-6, s, 1H); $^{13}$C NMR δ 18.50 ($CH_3$), 18.77 (C-1, $CH_3$), 27.29 (C-2, CH), 31.39 (C-4, $CH_3$), 38.01 (C-13, $CH_3$), 64.21 (C-3, CH), 128.11 (Ar-C, CH), 129.16 (Ar-C, CH), 130.65 (Ar-C, CH), 142.98 (C), 163.44 (CHO), 169.77 (CO); IR (Golden Gate) ν 1658 (CO) cm$^{-1}$; MS *m/z* (%) 248 ($M^{\bullet+}$, 3), 142 (21), 114 (53), 83 (100), 77 (5), 47 (16); HRMS 248.1526 ($C_{14}H_{20}O_2N_2$ requires 248.1525).



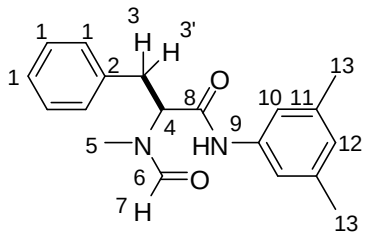
**(*S*)-(–)-*N*,*N*-diethyl-3-methyl-2-(*N*-methylformamido)butanamide 203b.** Obtained from (*S*)-**200f** using protocol B (oil, 75 mg, 83%): $[\alpha]_D$ -11.6 (*c* 1.5, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 0.77 (H-1, d, *J* = 6.7 Hz, 3H), 0.85 (H-1, d, *J* = 6.8 Hz, 3H), 1.09 (H-10, m, 3H), 1.11 (H-10, m, 3H), 2.36 (H-2, m, 1H), 2.85 (H-4, s, 3H), 3.20 (H-9, m, 2H), 3.33 (H-9, m, 2H), 4.76 (H-3, d, *J* = 10.7 Hz, 1H), 8.02 (H-6, br s, 1H); $^{13}$C NMR δ 13.23 (C-1, $CH_3$), 15.51 (C-1, $CH_3$), 18.51 (C-10, $CH_3$), 19.87 (C-10, $CH_3$), 26.77 (C-2, CH), 31.26 (C-4, $CH_3$), 40.87 (C-9, $CH_2$), 42.06 (C-9, $CH_2$), 63.79 (C-3, CH), 163.23 (CHO), 168.43 (CO); MS *m/z* (%) 215 ($M^{\bullet+}$, 100), 187 (4), 142 (10), 114 (8), 81 (19); HRMS (EI): 215.1760 ($C_{11}H_{23}O_2N_2$ requires 215.1761).



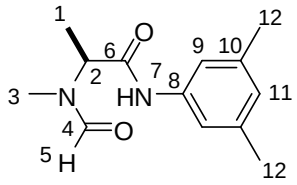
**(*S*)-(+)-*N*-(3,5-dimethoxyphenyl)-2-formamido-3-methylbutanamide 207.** Obtained from (*S*)-**100** using protocol B (191 mg, 60%): mp 151-153 $^{o}$C; $[\alpha]_D$ +1.2 (*c* 1.0, MeOH); $^{1}$H NMR (400 MHz, $CDCl_3$) δ 0.96 (H-1, d, *J* = 6.8 Hz, 3H), 0.98 (H-1, d, *J* = 6.7 Hz, 3H), 2.12 (H-2, m, 1H), 3.69 (H-13, s, 6H), 4.50 (H-3, t, *J* = 7.8 Hz, 1H), 6.16 (Ar-H, s, 1H), 6.70 (Ar-H, s, 2H), 8.21 (H-6, s, 1H), 8.37 (br s, 1H); $^{13}$C NMR δ 18.76 (C-1, $CH_3$), 19.67 (C-1, $CH_3$), 31.83 (C-2, CH), 55.72 (C-13, $CH_3$), 58.44 (C-3, CH), 97.4 (Ar-C, CH), 98.58 (Ar-C, CH), 139.73 (C), 161.36 (C), 161.74 (CHO), 169.79 (CO); IR (NaCl) ν 3272 (NH), 1645 (CO) cm$^{-1}$; MS (CI) *m/z* (%) 281 ([MH]$^{\bullet+}$, 100), 263 (2), 192 (3); HRMS (CI) 281.1501 ($C_{14}H_{21}O_4N_2$ requires 281.1501).



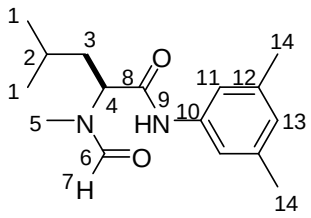
**(*R*)-(+)-*N*-(3,5-dimethylphenyl)-2-(*N*-methylformamido)-2-phenylacetamide 208a.** Obtained from (*R*)-**211a** using protocol B (solid, 292 mg, 34%): mp 149-150 $^{o}$C; $[\alpha]_D$ +8.9 (*c* 1.0, $CHCl_3$); $^{1}$H NMR (400 MHz, $CDCl_3$) δ 2.23 (H-13, s, 6H), 2.94 (H-4, s, 3H), 6.22 (H-3, s, 1H), 6.80 (Ar-H, s, 1H), 7.16 (Ar-H, s, 2H), 7.43-7.47 (H-1, m, 5H), 8.26 (H-6, s, 1H); $^{13}$C NMR δ 21.04 (C-13, $CH_3$), 28.81 (C-4, $CH_3$), 58.34 (C-3, CH), 117.00-128.87 (Ar-C, CH), 134.65-138.45 (Ar-C, C), 167.52 (CO), 168.35 (CHO); IR (KBr) ν 3275 (NH), 1653 (CO) cm$^{-1}$; MS *m/z* (%) 296 (M$^{\bullet+}$, 24), 274 (5), 210 (1), 175 (33), 148 (100), 120 (50), 77 (14), 42 (24); HRMS (EI) 296.1525 ($C_{18}H_{20}O_2N_2$ requires 296.1524).



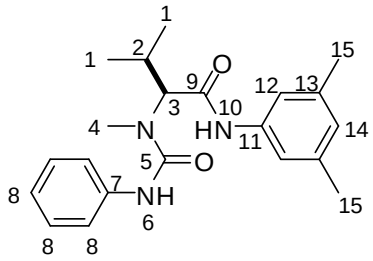
**(*S*)-(–)-*N*-(3,5-dimethylphenyl)-2-(*N*-methylformamido)-3-phenylpropanamide 208b.** Obtained from (*S*)-**211b** using protocol B (solid, 1.50 g, 78%): mp 81-85 $^{o}$C; $[\alpha]_D$ –87.8 (*c* 1.0, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$, a mixture of rotamers in ca. 4:1 ratio; the signals for the minor rotamer are marked by *) δ 2.29 (H-13, s, 6H), 2.94* (s, 0.6H), 2.98 (H-5, s, 2.4H), 3.01* (H-3, dd, *J* = 14.4 and 1.4 Hz, 0.2H), 3.12 (H-3, dd, *J* = 14.4 and 8.4 Hz, 0.8H), 3.43 (H-3', dd, *J* = 14.4 and 7.6 Hz, 0.8H), 3.56* (H-3', dd, *J* = 14.8 and 4.4 Hz, 0.2H), 5.25 (H-4, t, *J* = 8.0 Hz, 1H), 6.76 (Ar-H, s, 0.8H), 6.85* (Ar-H, s, 0.2H), 7.13 (Ar-H, s, 1.6H), 7.18* (Ar-H, s, 0.4H), 7.28-7.36 (Ar-H, m, 5H), 8.06 (br s, 0.8H), 8.08 (s, 0.8H), 8.37* (s, 0.2H), 8.66* (s, 0.2H); $^{13}$C NMR δ 20.94 (C-13, $CH_3$), 26.62 (C-5, $CH_3$), 34.78 (C-3, $CH_2$), 62.26 (C-4, CH), 115.15-126.52 (a set of signals, Ar,-C, CH), 128.29-138.54 (a set of signals, C), 159.42-168.36 (a set of signals, CO); IR (KBr) ν 3308 (NH), 1703 (CO) cm$^{-1}$; MS *m/z* (%) 310 ($M^{\bullet+}$, 50), 251 (10), 190 (39), 162 (100), 134 (85), 91 (29), 42 (15); HRMS (EI) 310.1681 ($C_{19}H_{22}O_2N_2$ requires 310.1682).



**(*S*)-(–)-*N*-(3,5-dimethylphenyl)-2-(*N*-methylformamido)propanamide 208c.** Obtained from (*S*)-**211c** using protocol B (oil, 916 mg, 78%): $[\alpha]_D$ –222.6 (*c* 1.0, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 1.46 (H-1, d, *J* = 7.2 Hz, 3H), 2.30 (H-12, s, 6H), 2.97 (H-3, s, 3H), 5.08 (H-2, q, *J* = 7.2 Hz, 1H), 6.76 (Ar-H, s, 1H), 7.01 (Ar-H, s, 2H), 8.16 (H-5, s, 1H); $^{13}$C NMR δ 12.64 (C-1, $CH_3$), 21.35 (C-12, $CH_3$), 30.98 (C-3, $CH_3$), 51.29 (C-2, CH), 117.83 (Ar-C, CH), 126.15 (Ar-C, CH), 137.50 (C), 138.01 (C), 163.87 (CHO), 168.04 (CO); IR (NaCl) ν 3289 (NH), 1644 (CO) cm$^{-1}$; MS *m/z* (%) 234 ($M^{\bullet+}$, 33), 199 (5), 147 (6), 113 (31), 82 (100), 58 (37), 49 (39); HRMS (EI) 234.1371 ($C_{13}H_{18}O_2N_2$ requires 234.1368).

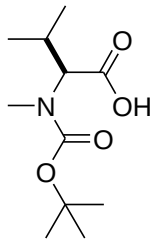


**(*S*)-(–)-*N*-(3,5-dimethylphenyl)-4-methyl-2-(N-methylformamido)pentanamide 208d.** Obtained from (*S*)-**211d** using protocol B (oil, 1.13 g, 84%): $[\alpha]_D$ –191.1 (*c* 1.0, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 0.98 (H-1, d, *J* = 6.6 Hz, 3H), 1.01 (H-1, d, *J* = 6.6 Hz, 3H), 1.59 (H-2, hept, *J* = 6.6 Hz, 1H), 1.72 (H-3, ddd, *J* = 14.0, 8.0 and 6.0 Hz, 1H), 1.87-1.94 (H-3, m, 1H), 2.30 (H-14, s, 6H), 2.90 (H-5, s, 3H), 4.99 (H-4, t, *J* = 8.0 Hz, 1H), 6.76 (Ar-H, s, 1H), 7.16 (Ar-H, s, 2H), 8.03 (H-9, br s, 1H), 8.16 (H-7, s, 1H); $^{13}$C NMR δ 21.37 (C-1, $CH_3$), 22.83 (C-14, $CH_3$), 24.77 (C-2, CH), 31.28 (C-5, $CH_3$), 35.61 (C-3, $CH_2$), 54.07 (C-4, CH), 117.90 (Ar-C, CH), 126.31 (Ar-C, CH), 137.24 (C), 138.71 (C), 164.12 (CHO), 167.88 (CO); IR (NaCl) ν 3299 (NH), 1681 (CO); MS *m/z* (%) 276 ($M^{\bullet+}$, 36), 220 (5), 176 (4), 156 (30), 128 (100), 86 (23), 58 (16); HRMS (EI) 276.1840 ($C_{16}H_{24}O_2N_2$ requires 276.1838).

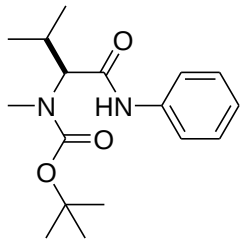


**(*S*)-(–)-1-(1-(3,5-dimethylphenylamino)-3-methyl-1-oxobutan-2-yl)-1-methyl-3-phenylurea 206.** The BOC derivative (*S*)-**200c** (504 mg, 1.5 mmol) was dissolved in trifluoroacetic acid (2.0 mL) at room temperature. After 1 hour the reaction mixture was evaporated in vacuo, the residue was dissolved in cold, dry $Et_2O$ (50 mL) and the reaction stirred at room temperature, under argon, for 90 minutes. Phenylisocyanate (0.22 mL, 20.9 mmol) was then added dropwise to the solution and then allowed to stir over night at room temperature. The solvent was then removed *in vacuo*. Purification using column chromatography on silica gel with a petroleum ether-ethyl acetate mixture (1:1) afforded (*S*)-**206** as a solid (292 mg, 55%): mp 131-133 $^o$C; $[\alpha]_D$ -158.1 (*c* 1.0, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 0.87 (H-1, d, *J* = 6.4 Hz, 2H), 0.98 (H-1, d, *J* = 6.4 Hz, 2H), 2.21 (H-15, s, 6H), 2.34 (H-2, m, 1H), 2.98 (H-4, s, 3H), 4.33 (H-3, d, *J* = 11.6 Hz, 1H), 6.66 (Ar-H, s, 1H), 7.01 (Ar-H, t, *J* = 7.4 Hz, 1H), 7.07 (Ar-H, s, 2H), 7.32(Ar-H, t, *J* = 5.6 Hz, 2H), 7.34 (Ar-H, d, *J* = 7.6 Hz, 2H), 8.15 (H-10, br s, 1H); $^{13}$C NMR δ 18.82 (C-1, $CH_3$),

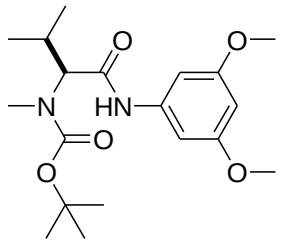
19.87 (C-15, $CH_3$), 21.38 (C-4, $CH_3$), 26.33 (C-2, CH), 117.52 (Ar-C, CH), 120.32 (Ar-C, CH), 121.26 (Ar-C, CH), 123.75 (Ar-C, CH), 124.41 (Ar-C, CH), 125.99 (Ar-C, CH), 129.04 (Ar-C, CH), 129.39 (Ar-C, CH), 137.74 (C), 138.60 (C), 138.74 (C), 156.91 (CO), 168.87 (CO); IR (KBr) ν 3272 (NH), 1644 (CO); MS *m/z* (%) 353 ($M^{\bullet+}$, 10), 232 (33), 205 (19), 160 (5), 121 (48), 86 (100), 84 (18), 49 (17); HRMS (EI) 353.2106 ($C_{21}H_{27}O_2N_3$ requires 353.2103).



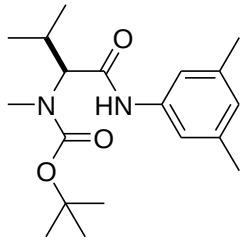

**(*S*)-2-(*tert*-Butoxycarbonyl-methyl-amino)-3-methyl-butyric Acid (*S*)-199.** Obtained from (*S*)-**198** as an oil (3.15 g, 13.6 mmol, 98%) using protocol C; this product was used in the following step without further purification: $^1$H NMR (400 MHz, $CDCl_3$) δ 0.93 (d, *J* = 6.7 Hz, 3H), 1.05 (d, *J* = 6.6 Hz, 3H), 1.49 (s, 9H), 2.39 (m, 1H), 2.90 (s, 3H), 4.01 (d, *J* = 10.4 Hz, 1H), in agreement with literature.[94]



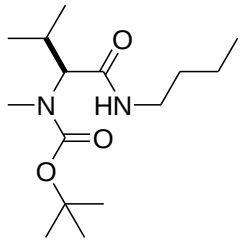

**(*S*)-*tert*-butylmethyl(3-methyl-1-oxo-1-(phenylamino)butan-2-yl)carbamate 200a.** Obtained from (*S*)-**199**, using protocol D (oil, 803 mg, 43%): $^1$H NMR (400 MHz, $CDCl_3$) δ 0.85 (d, *J* = 6.7 Hz, 3H), 0.97 (d, *J* = 6.4 Hz, 3H), 1.43 (s, 9H), 2.32 (m, 1H), 2.75 (s, 3H), 4.03 (d, *J* = 10.2 Hz, 1H), 6.98 (t, *J* = 7.4 Hz, 1H), 7.22 (t, *J* = 7.8 Hz, 2H), 7.44 (d, *J* = 7.8 Hz, 2H), 8.19 (br s, 1H); $^{13}$C NMR δ 18.99 ($CH_3$), 20.30 ($CH_3$), 26.24 ($CH_3$), 28.76 ($CH_3$), 30.94 ($CH_3$), 66.70 (C), 81.10 (C), 120.06 (CH), 124.48 (CH), 129.37 (CH), 138.45 (C), 169.18 (CO); IR (Golden Gate) ν 3311 (NH), 1658 (CO) $cm^{-1}$; MS *m/z* (%) 306 ($M^+$, 6%) 214 (7), 186 (14), 130 (71), 83 (100), 57 (39), 47 (17); HRMS (EI): 306.1943 ($C_{17}H_{26}O_3N_2$ requires 306.1943).



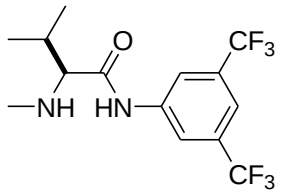
**(*S*)-*tert*-butyl-1-(3,5-dimethoxyphenylamino)-3-methyl-1-oxobutan-2-yl(methyl)carbamate 200b.** Obtained from (*S*)-**199**, using protocol D (oil, 451 mg, 29%): $^1$H NMR (400 MHz, $CDCl_3$) δ 0.82 (d, *J* = 6.8 Hz, 3H), 0.96 (d, *J* = 6.7 Hz, 3H), 1.39 (s, 9H), 2.95 (m, 1H), 2.75 (s, 3H), 3.70 (s, 6H), 4.00 (m, 1H), 6.15 (s, 1H), 6.68 (s, 2H), 8.18 (br s, 1H).



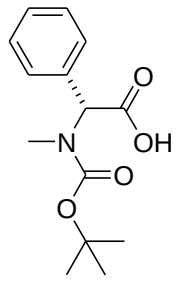
**(*S*)-*tert*-butyl-1-(3,5-dimethylphenylamino)-3-methyl-1-oxobutan-2-yl(methyl)carbamate 200c.** Obtained from (*S*)-**199**, using protocol D; purification by column chromatography on silica gel with a petroleum ether-ethyl acetate mixture (24:1) afforded pure product as an oil (240 mg, 70%): $^1$H NMR (400 MHz, $CDCl_3$) δ 0.77 (d, *J* = 6.5 Hz, 3H), 0.88 (d, *J* = 6.5 Hz, 3H), 1.38 (s, 9H), 2.17 (s, 6H), 2.25 (m, 1H), 2.76 (s, 3H), 4.08 (d, *J* = 10.8 Hz, 1H), 6.62 (s, 1H), 7.07 (s, 2H), 8.24 (br s, 1H).



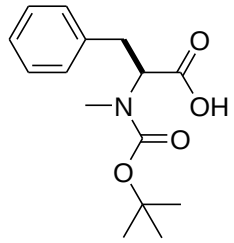
**(*S*)-*tert*-butyl-1-(butylamino)-3-methyl-1-oxobutan-2-yl(methyl)carbamate 200d.** Obtained from (*S*)-**199**, using protocol D; purification by column chromatography on silica gel with a petroleum ether-ethyl acetate mixture (3:1) afforded a pure product as an oil (928 mg, 61%): $^1$H NMR (400 MHz, $CDCl_3$) δ 0.80 (m, 9H), 1.29 (m, 2H), 1.39 (s, 9H), 2.20 (m, 1H), 2.73 (s, 3H), 3.17 (m, 2H), 3.90 (d, *J* = 10.9 Hz, 1H), 6.04 (br s, 1H).



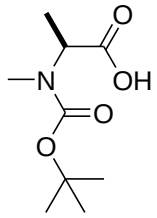

**(*S*)-*N*-(3,5-bis(trifluoromethyl)phenyl)-3-methyl-2-(methylamino)butanamide 204.** Following a literature protocol,[95] a solution of pivaloyl chloride (1.1 mL, 8.6 mmol) in anhydrous THF (8 mL) was added dropwise to a stirred solution of (*S*)-**199** (2.0 g, 8.6 mmol) and triethylamine (1.2 mL, 8.6 mmol) in anhydrous THF (16 mL) at –15 $^{o}$C. The solution was then warmed to 0 $^{o}$C and allowed to stir at this temperature for 5 min. The solution was then cooled again to –15 $^{o}$C and a solution of 3,5-bis(trifluoromethyl)-aniline (1.34 mL) in anhydrous THF (8 mL) was added dropwise and the mixture was stirred at 0 $^{o}$C for 1 h. The mixture was then warmed to room temperature and stirring was continued for 27 h under an argon atmosphere. The solvent was then removed under reduced pressure, the residue was diluted with water (20 mL) and then extracted with ethyl acetate (20 mL). The extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification using column chromatography on silica gel with a petroleum ether-ethyl acetate mixture (1:1) afforded (*S*)-**204** as an oil (185 mg, 7%): $^{1}$H NMR (400 MHz, $CDCl_3$) δ 0.87 (d, *J* = 6.9 Hz, 3H), 0.99 (d, *J* = 7.0 Hz, 3H), 2.15 (m, 1H), 2.42 (s, 3H), 2.87 (d, *J* = 4.24Hz, 1H), 7.50 (s, 1H), 8.05 (s, 2H), 9.69 (br s, 1H).



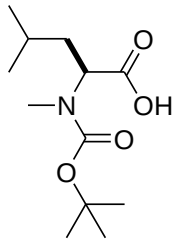

**(*R*)-2-(*tert*-butoxycarbonyl)-2-phenylacetic acid 210a.** Obtained from (*R*)-**209a** as an oil (2.33 g, 78%) using protocol C; this product was used in the following step without further purification: $^{1}$H NMR (400 MHz, $CDCl_3$) δ 1.42 (s, 9H), 2.62 (s, 3H), 7.21-7.45 (m, 5H).



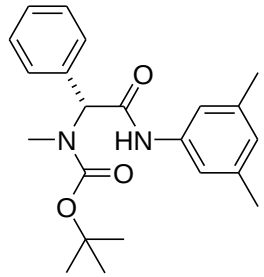
**(*S*)-2-(*tert*-butoxycarbonyl)-3-phenylpropanoic acid 210b.** Obtained from (*S*)-**209a** as an oil (2.38 g, 71%) using protocol C; this product was used in the following step without further purification: $^1$H NMR (400 MHz, $CDCl_3$ a mixture of rotamers in ca 1:1 ratio) δ 1.23 (s, 4.5H), 1.33 (s, 4.5H), 2.52 (s, 1.5H), 2.59 (s, 1.5H), 2.90 (m, 1H), 3.11 (m, 1H), 4.44 (dd, *J* = 4.0 and 10.4 Hz, 0.5H), 4.65 (dd, *J* = 5.2 and 10.8 Hz, 0.5H), 7.01-7.21 (m, 5H).



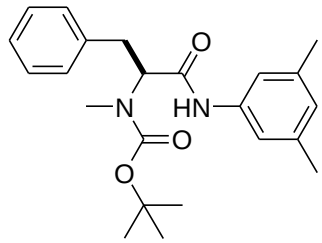
**(*S*)-2-(*tert*-butoxycarbonyl)propanoic acid 210c.** Obtained from (*S*)-**209c** as an oil (4.90 g, 98%) using protocol C; this product was used in the following step without further purification: $^1$H NMR (400 MHz, $CDCl_3$) δ 1.37 (d, *J* = 6.7 Hz, 3H), 1.40 (s, 9H), 2.89 (s, 3H), 4.19 (m, 1H).



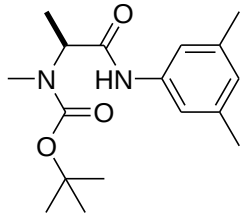
**(*S*)-2-(*tert*-butoxycarbonyl)-4-methylpentanoic acid 210d.** Obtained from (*S*)-**209d** as an oil (2.60 g, 72%) using protocol C; this product was used in the following step without further purification: $^1$H NMR (400 MHz, $CDCl_3$) δ 0.87 (d, *J* = 6.8 Hz, 3H), 0.89 (d, *J* = 6.8 Hz, 3H), 1.39 (s, 9H), 1.49 (m, 1H), 1.66 (m, 1H), 2.73 (s, 3H), 4.73 (m, 1H).



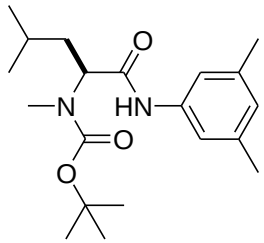
***(R)*-*tert*-butyl-2-(3,5-dimethylphenylamino)-2-oxo-1-phenylethyl(methyl)carbamate 211a.** Obtained from (*R*)-**210a**, using protocol D; purification by column chromatography on silica gel with a petroleum ether-ethyl acetate mixture (1:1) afforded a pure product as an oil (2.01g, 56%): $^1$H NMR (400 MHz, $CDCl_3$) δ 1.42 (s, 9H), 2.22 (s, 6H), 2.72 (s, 3H), 5.88 (br s, 1H), 6.69 (s, 1H), 7.09 (s, 2H), 7.23-7.46 (m, 5H).



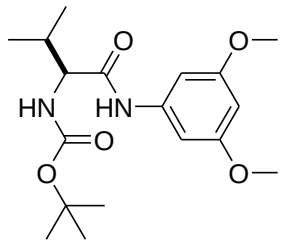
**(*S*)-*tert*-butyl-1-(3,5-dimethylphenylamino)-1-oxo-3-phenylpropan-2-yl(methyl)carbamate 211b.** Obtained from (*S*)-**210b**, using protocol D; purification by column chromatography on silica gel with a petroleum ether-ethyl acetate mixture (1:1) afforded a pure product as an oil (2.38g, 94%): $^1$H NMR (400 MHz, $CDCl_3$) δ 1.42 (s, 9H), 2.22 (s, 6H), 2.80 (s, 3H), 3.10 (dd, *J* = 14 and 8.2 Hz, 1H), 3.38 (dd, *J* = 14 and 6.8 Hz, 1H), 4.98-5.01 (m, 1H), 6.74 (s, 1H), 7.12 (s, 2H), 7.15-7.32 (m, 5H), 8.11 (br s, 1H).



**(*S*)-*tert*-butyl-1-(3,5-dimethylphenylamino)-1-oxopropan-2-yl(methyl)carbamate 210c.** Obtained from (*S*)-**211c**, using protocol D; purification by column chromatography on silica gel with a petroleum ether-ethyl acetate mixture (2:1) afforded a pure product as an oil (1.54 g, 93%): $^1$H NMR (400 MHz, $CDCl_3$) δ 1.32 (d, *J* = 7.2 Hz, 3H), 1.43 (s, 9H), 2.26 (s, 6H), 2.74 (s, 3H), 4.75 (bs, 1H), 6.67 (s, 1H), 7.07 (s, 2H), 8.12 (br s, 1H).



**(*S*)-*tert*-butyl-1-(3,5-dimethylphenylamino)-4-methyl-1-oxopentan-2-yl(methyl)carbamate 210d.** Obtained from (*S*)-**211d**, using protocol H; purification by column chromatography on silica gel with a petroleum ether-ethyl acetate mixture (2:1) afforded a pure product as an oil (1.70 g, 75%): $^1$H NMR (400 MHz, $CDCl_3$) δ 0.88 (d, *J* = 6.4 Hz, 3H), 0.91 (d, *J* = 6.4 Hz, 3H), 1.43 (s, 9H), 1.46-1.54 (m, 1H), 1.56-1.64 (1H, m), 1.69-1.82 (m, 1H), 2.26 (s, 6H), 2.71 (s, 3H), 4.66 (br s, 1H), 6.67 (s, 1H), 7.06 (s, 2H), 8.05 (br s, 1H).

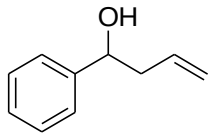


**(*S*)-*tert*-butyl-1-(3,5-dimethoxyphenylamino)-3-methyl-1-oxobutan-2-ylcarbamate 200b.** Obtained from (*S*)-**198**, using protocol D; purification by column chromatography on silica gel with a petroleum ether-ethyl acetate mixture (1:1) afforded a pure product as an oil (309 mg, 19%): $^1$H NMR (400 MHz, $CDCl_3$) δ 0.84 (d, *J* = 6.8 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 3H), 1.39 (s, 9H), 2.90 (m, 1H), 3.70 (s, 6H), 3.90 (t, *J* = 6.4 Hz, 1H), 4.98 (br s, 1H), 6.16 (s, 1H), 6.69 (s, 2H), 7.78 (br s, 1H).

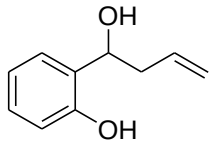
**General Procedure for the Allylation of Aldehydes**

Allyltrichlorosilane (11.8 mmol) was added drop wise to a stirred solution of aldehyde (9.4 mmol), anhydrous DMF (6 mL) in anhydrous $CH_2Cl_2$ (30 mL) at 0 $^oC$, and the mixture allowed to stir overnight at room temperature under an atmosphere of nitrogen. The reaction was then quenched with a saturated aqueous solution of $NaHCO_3$ (10 mL) and the product extracted with ethyl acetate (50 mL). The extract was washed with brine and dried over anhydrous $MgSO_4$ and the solvent removed *in vacuo*. Purification using

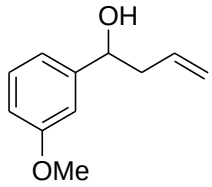
column chromatography on silica gel with a petroleum ether-ethyl acetate mixture (5:1) afforded the product as an oil. [96]



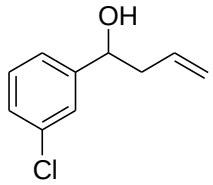

**1-phenylbut-3-en-1-ol 248a**: (89%, oil) $^1$H NMR (400 MHz, $CDCl_3$) δ 2.08 (s, 1H), 2.37-2.49 (m, 2H), 4.62-4.66 (m, 1H), 5.05-5.15 (m, 2H), 5.68-5.78 (m, 1H), 7.17-7.29 (m, 5H); MS *m/z* (%) 148 ($M^{\bullet+}$, 2), 128 (3), 107 (99), 79 (80), 51 (12) in agreement with literature data. [97]




**2-(1-hydroxybut-3-enyl)phenol 248b**: (10%, oil) $^1$H NMR (400 MHz, $CDCl_3$) δ 2.58-2.69 (m, 2H), 2.66 (bs, 1H), 4.89-4.93 (m, 1H), 5.24-5.30 (m, 2H), 5.81-5.94 (m, 1H), 6.83-6.91 (m, 2H), 7.01 (dd, *J* = 7.56, 1.56 Hz, 1H), 7.19-7.25 (m, 1H), 8.04 (bs, 1H); MS *m/z* (%) 164 ($M^{\bullet+}$, 10), 145 (11), 123 (99), 95 (33), 77 (41), 39 (15) in agreement with literature data [98]



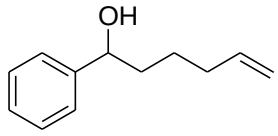

**1-(3-methoxyphenyl)but-3-en-1-ol 248c**: (25%, oil) $^1$H NMR (400 MHz, $CDCl_3$) δ 2.06 (bs, 1H), 2.46-2.59 (m, 2H), 3.88 (s, 3H), 4.73-4.76 (m, 1H), 5.16-5.23 (m, 2H), 5.79-5.89 (m, 1H), 6.82-6.85 (m, 1H), 6.95-6.97 (m, 2H), 7.21-7.33 (m, 1H); MS *m/z* (%) 178 ($M^{\bullet+}$, 10), 152 (1), 137 (91), 109 (99), 94 (29), 77 (32), 28 (12) in agreement with literature data [99]



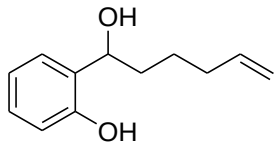

**1-(3-chlorophenyl)but-3-en-1-ol 248d**: (49%, oil) $^1$H NMR (400 MHz, $CDCl_3$) δ 2.02 (bs, 1H), 2.44-2.58 (m, 2H), 4.74-4.77 (m, 1H), 5.18-5.23 (m, 2H), 5.76-5.87 (m, 1H), 7.30-7.36 (m, 4H); MS *m/z* (%) 182 ($M^{\bullet+}$, 1), 178 (1), 141 (99), 139 (9), 113 (20), 77 (72), 28 (18) in agreement with literature data [100]

**General Procedure for Grignard Reaction:**

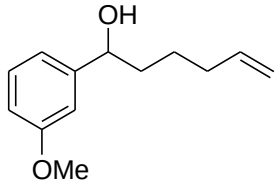
To a suspension of magnesium turnings (16.3 mmol) in anhydrous $Et_2O$ (5 mL) was added a solution of 5-bromopent-1-ene (or 4-bromobut-1-ene) (14.8 mmol) in anhydrous $Et_2O$ (50 mL) and the resulting solution refluxed for 1 hour. The mixture was then cooled to -10 $^oC$ and too this was added aldehyde (15.5 mmol) drop wise, keeping the temperature below -5 $^oC$. The reaction mixture was then slowly brought to room temperature and then poured into ice (100 g) and $H_2SO_4$ (15 mL). This was extracted with $Et_2O$ (2 x 50 mL) and the organic layers dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Purification using column chromatography on silica gel with a petroleum ether-ethyl acetate mixture (8:1) afforded the product as an oil. [101]



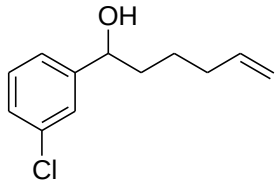

**1-phenylhex-5-en-1-ol 253a**: (67%, oil) $^1$H NMR (400 MHz, $CDCl_3$) δ 1.32-1.49 (m, 1H), 1.51-1.62 (m, 1H), 1.71-1.90 (m, 2H), 2.04-2.15 (m, 2H), 4.69-4.73 (m, 1H), 4.96-5.05 (m, 2H), 5.78-5.87 (m, 1H), 7.29-7.47 (m, 5H); MS *m/z* (%) 178 ($M^{\bullet+}$, 2), 133 (20), 107 (99), 105 (15), 79 (61), 41 (9), 28 (17) in agreement with literature data [102]



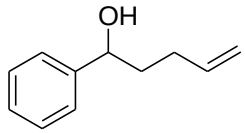

**2-(1-hydroxyhex-5-enyl)phenol 253b**: (8%, oil) $^{1}$H NMR (400 MHz, $CDCl_3$) δ 1.01-1.10 (m, 1H), 1.12-1.24 (m, 1H), 1.29-1.38 (m, 1H), 1.42-1.56 (m, 1H), 1.69-1.80 (m, 1H), 1.81-1.92 (m, 1H), 2.50 (bs, 1H), 4.72-4.78 (m, 1H), 4.84-4.98 (m, 2H), 5.66-5.88 (m, 1H), 6.72-7.09 (m, 4H), 7.81 (bs, 1H); MS *m/z* (%) 194 ($M^{\bullet+}$, 1), 192 (35), 174 (73), 145 (32), 123 (99), 95 (64), 65 (22), 27 (12) in agreement with literature data [103]



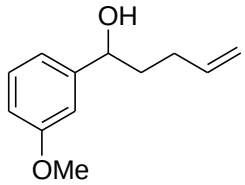

**1-(3-methoxyphenyl)hex-5-en-1-ol 253c**: (45%, oil) $^{1}$H NMR (400 MHz, $CDCl_3$) δ 1.37-1.48 (m, 1H), 1.52-1.61 (m, 1H), 1.71-1.87 (m, 3H), 2.07-2.13 (m, 2H), 3.85 (s, 3H), 4.67-4.70 (m, 1H), 4.95-5.05 (m, 2H), 5.76-5.87 (m, 1H), 6.83-6.86 (m, 1H), 6.93-6.96 (m, 2H), 7.27-7.31 (m, 1H); MS *m/z* (%) 208 ($M^{\bullet+}$, 2), 175 (4), 163 (22), 137 (81), 109 (99), 77 (29), 65 (10), 28 (21) in agreement with literature data [104]




**1-(3-chlorophenyl)hex-5-en-1-ol 253d**: (68%, oil) $^{1}$H NMR (400 MHz, $CDCl_3$) δ 1.38-1.47 (m, 1H), 1.49-1.61 (m, 1H), 1.67-1.83 (m, 2H), 1.89 (bs, 1H), 2.05-2.11 (m, 2H), 4.67-4.71 (m, 1H), 4.94-5.05 (m, 2H), 5.76-5.86 (m, 1H), 7.20-7.36 (m, 4H); $^{13}$C NMR δ 24.92 ($CH_2$), 33.68 ($CH_2$), 38.63 ($CH_2$), 73.91 (CH), 114.46 ($CH_2$), 124.50 (CH), 126.39 (CH), 128.31 (CH), 129.69 (CH), 134.46 (C), 138.35 (CH), 147.04 (C); IR (NaCl) ν 3439 (OH), 997 ($RHC=CH_2$); MS *m/z* (%) 210 ($M^{\bullet+}$, 13), 192 (3), 167 (48), 141 (99), 139 (23), 113 (68), 75 (10), 41 (21), 39 (18); HRMS (EI) 210.0812 ($C_{12}H_{15}OCl$ requires 210.0811).



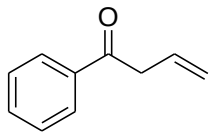

**1-phenylpent-4-en-1-ol 252a**: (19%, oil) $^{1}$H NMR (400 MHz, $CDCl_3$) δ 1.78-1.98 (m, 2H), 2.07-2.25 (m, 2H), 4.71-4.75 (m, 1H), 4.99-5.10 (m, 2H), 5.81-5.92 (m, 1H), 7.18-7.47 (m, 5H); MS *m/z* (%) 162 ($M^{\bullet+}$, 3), 144 (7), 120 (21), 107 (69), 105 (12), 79 (47), 77 (30), 51 (8) in agreement with literature data [105]




**1-(3-methoxyphenyl)pent-4-en-1-ol 252c**: (64%, oil) $^{1}$H NMR (400 MHz, $CDCl_3$) δ 1.67-1.86 (m, 3H), 1.95-2.13 (m, 2H), 3.75 (s, 3H), 4.59-4.63 (m, 1H), 4.84-4.98 (m, 2H), 5.69-5.83 (m, 1H), 6.73-7.75 (m, 1H), 6.84-6.87 (m, 2H), 7.15-7.18 (m, 1H); MS *m/z* (%) 192 ($M^{\bullet+}$, 27), 163 (3), 137 (96), 109 (99), 77 (44), 65 (15), 39 (15) in agreement with literature data [10]

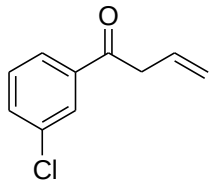
**General Procedure for PCC[*] Oxidation:**

To a solution of alcohol (3.48 mmol) in $CH_2Cl_2$ (30 mL) was added PCC (7.31 mmol) and the mixture allowed to stir, at room temperature for ~3 hours. $Et_2O$ (15 mL) was then added and stirred for a further 15 minutes. The reaction mixture was then filtered through a short pad of silica, washed with $Et_2O$ (~15 mL) and concentrated *in vacuo* to afford the corresponding ketone as an oil (unless otherwise stated). No further purification was required. [107]

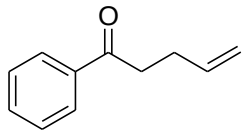



**1-phenylbut-3-en-1-one 249a**: (42%, oil) $^{1}$H NMR (400 MHz, $CDCl_3$) δ 3.69-3.71 (m, 2H), 5.13-5.19 (m, 2H), 5.97-6.08 (m, 1H), 7.36-7.42 (m, 2H), 7.55-7.59 (m, 1H), 7.89-7.92 (m, 2H) in agreement with literature data. [108]

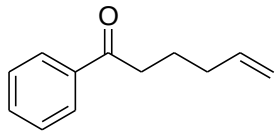
[*] Pyridinium Chlorochromate



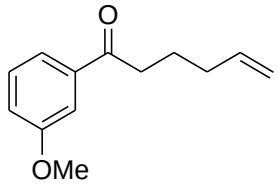

**1-(3-chlorophenyl)but-3-en-1-one 249d**: (70%, oil) $^{1}$H NMR (400 MHz, $CDCl_3$) δ 3.75-3.78 (m, 2H), 5.22-5.29 (m, 2H), 6.05-6.15 (m, 1H), 7.46-7.49 (m, 2H), 7.92-7.96 (m, 2H); $^{13}$C NMR δ 43.43 ($CH_2$), 119.04 ($CH_2$), 128.86 (CH x2), 129.95 (CH), 130.93 (CH), 134.67 (C), 139.67 (C), 196.82 (CO); IR (KBr) ν 1682 (C=O), 921 (RCH=$CH_2$); MS *m/z* (%) 180 ($M^{\bullet+}$, 18), 139 (98), 111 (52), 83 (39), 75 (40), 49 (61), 39 (17); HRMS (EI) 180.0348 ($C_{10}H_9OCl$ requires 180.0342).




**1-phenylpent-4-en-1-one 254a**: (71%, oil) $^{1}$H NMR (400 MHz, $CDCl_3$) δ 2.50-2.56 (m, 2H), 3.09-3.13 (m, 2H), 5.03-5.33 (m, 2H), 5.89-5.99 (m, 1H), 7.49-7.51 (m, 2H), 7.57-7.61 (m, 1H), 7.99-8.12 (m, 2H); MS *m/z* (%) 160 ($M^{\bullet+}$, 4), 145 (2), 129 (2), 105 (99), 82 (55), 77 (41), 51 (12), 46 (15). in agreement with literature data [109]

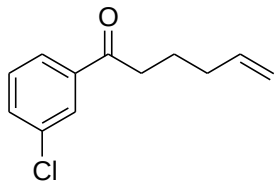



**1-phenylhex-5-en-1-one 255a**: (54%, oil) $^{1}$H NMR (400 MHz, $CDCl_3$) δ 1.73-1.82 (m, 2H), 2.05-2.11 (m, 2H), 2.89-2.93 (m, 2H), 4.90-4.99 (m, 2H), 5.72-5.81 (m, 1H), 7.35-7.41 (m, 2H), 7.43-7.51 (m, 1H), 7.86-7.90 (m, 2H); MS *m/z* (%) 174 ($M^{\bullet+}$, 10), 133 (4), 105 (99), 77 (52), 51 (15), 28 (19) in agreement with literature data. [110]




**1-(3-methoxyphenyl)hex-5-en-1-one 255c**: (91%, oil) $^{1}$H NMR (400 MHz, $CDCl_3$) δ 1.84-1.91 (m, 2H), 2.16-2.21 (m, 2H), 2.97-3.01 (m, 2H), 3.89 (s, 3H), 5.02-5.06 (m, 2H),

5.80-5.90 (m, 1H), 7.13 (dd, *J* = 2.0, 8.4 Hz, 1H), 7.37-7.41 (m, 1H), 7.51-7.52 (m, 1H), 7.55-7.57 (m, 1H); MS *m/z* (%) 204 ($M^{\bullet+}$, 23), 175 (1), 150 (99), 135 (81), 107 (40), 77 (37), 64 (12), 28 (28); HRMS (EI) 204.1151 ($C_{13}H_{16}O_2$ requires 204.1150). in agreement with literature data [104]




**1-(3-chlorophenyl)hex-5-en-1-one 255d**: (72%, oil) $^1$H NMR (400 MHz, $CDCl_3$) δ 1.84-1.91 (m, 2H), 2.16-2.21 (m, 2H), 2.96-3.00 (m, 2H), 5.02-5.11 (m, 2H), 5.79-5.89 (m, 1H), 7.41-7.45 (m, 1H), 7.52-7.57 (m, 1H), 7.85-7.87 (m, 1H), 7.94-7.95 (m, 1H); $^{13}$C NMR δ 23.11 ($CH_2$), 33.10 ($CH_2$), 37.80 ($CH_2$), 115.49 ($CH_2$), 126.12 (CH), 128.19 (CH), 129.94 (CH), 132.88 (CH), 134.93 (C), 137.90 (CH), 138.60 (C), 198.89 (CO); IR (NaCl) ν 1690 (C=O), 913 (RCH=$CH_2$); MS *m/z* (%) 209/211 (M+H, 51/19), 193 (8), 157 (8), 125 (6), 113 (32), 85 (45), 73 (99); HRMS (EI) 209.0733 ($C_{12}H_{14}OCl$ requires 209.0734).

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# Chapter 5: Appendix