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

Development and Synthesis of Novel Organocatalysts

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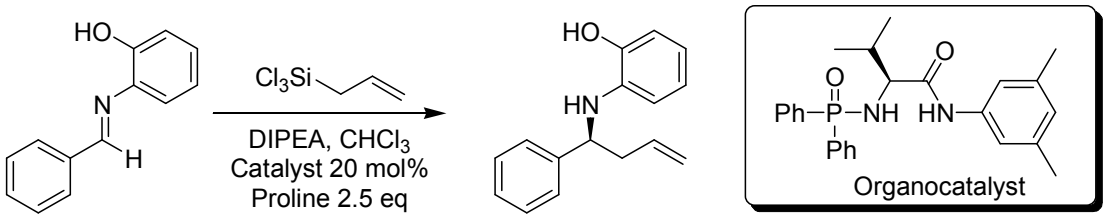
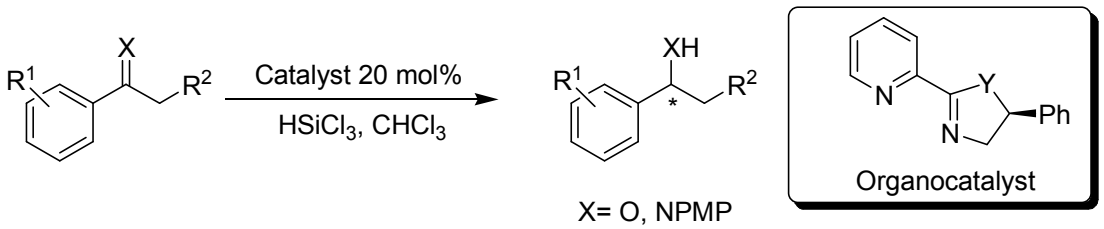
Abstract

The unfavourable use of metal-based catalysts in organic synthesis can be overcome by using small organic molecules; organocatalysts. Herein we report the development and synthesis of a novel range of organocatalysts derived from amino acids incorporating imidazole, thiourea and phosphoramide moieties to confer the capability to act as bifunctional organocatalysts. Our organocatalyst, a phosphoramide derived from valine, showed initial success in the catalytic allylation of aldimine with allyltrichlorosilane, producing 40% ee.



Oxazoline catalysts derived from 2-pyridines have been shown to be effective activators of trichlorosilane for the reduction of ketones and ketimines. The reaction however suffered from chloride promoted ring opening of the catalyst. By replacing the oxygen of the oxazoline moiety with sulphur we were able to successfully avoid this problem. Further expansion of the substrate scope was achieved, heterocyclic imines were reduced in good enantioselectivity, up to 89% ee.



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Contents

Abbreviations

Å	Angstrom
Aq	Aqueous
BINOL	1,1'-Binaphthol
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
bs	broad singlet (NMR spectroscopy)
t-Bu	Tertiary butyl
^{o}C	Degrees centigrade
cat	Catalytic
CI	Chemical ionisation
Cy	Cyclohexyl
d	Doublet (NMR spectroscopy)
DCC	Dicyclohexylcarbodiimide
DCM	Dichloromethane
DEAD	Diethylazodicarboxylate
DIPEA	*N,N*-Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMF	*N,N*-Dimethylformamide
DMSO	Dimethylsulfoxide
EDAC/EDC.HCl	*N*-Ethyl-*N*'-(3-dimrthylaminopropyl)carbodiimide hydrochloride
ee	Enatiomeric excess
EI	Electon impact
Eq/Equiv	Equivalents
FAB	Fast atom bombardment
GC	Gas chromatography
h	Hours
HMPA	Hexamethylphosphoramide
HOBT	1-Hydroxybenzotriazole

HPLC	High Performance Liquid Chromatography
Hz	Hertz
IR	Infrared
LR	Lawesson's reagent
M	Molarity
m	Multiplet (NMR spectroscopy)
Ms/mesyl	Methanesulfonate
min(s)	Minute(s)
MS	Mass Spectroscopy
Naphth	Naphthyl
NMM	*N*-Methylmorpholine
NMR	Nuclear Magnetic Resonance
Phth	Phthalimide
PMA	Polymolybdic acid
PMP	4-Methoxyphenyl
q	Quartet (NMR spectroscopy)
rt	Room temperature
t	Triplet (NMR spectroscopy)
TBDMS	*tert*-Butyldimethylsilane
TLC	Thin Layer Chromatography
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMEDA	Tetramethylenediamine
Ts/Tosyl	4-Toluenesulfonate
UV	Ultraviolet

Preface

Environmentally friendly, selective and high yielding processes are integral to the development and synthesis of new therapeutic reagents and novel compounds. This, coupled with the significance of chirality in nature and, more importantly, the human body, makes the efficient, green, generation of enantiomerically enriched products a key goal in modern organic synthesis.

Generation of single enantiomers of chiral compounds can be achieved in a variety of ways: racemate resolution, chiral pool, chiral auxiliaries and asymmetric catalysis. Racemate resolution is undesirable as the maximum yield is 50% and the unwanted enantiomer must be disposed of. Molecules readily available from the chiral pool (amino acids, terpenes etc.) have limited variation in structure and so multi-step syntheses are required to reach the target molecule. Chiral auxiliaries must be covalently bound to the substrate, this increases the number of steps in a synthesis and the auxiliary must also be recovered or disposed of.

Asymmetric catalysis is advantageous, as it uses achiral starting materials and requires only a catalytic amount of the chiral molecule, which offers the possibility of being recovered at the end of the synthesis. Asymmetric catalysis is widely used in industry due to its advantages over other stoichiometric methods.

Most commonly in industry, transition metal complexes are used as asymmetric catalysts because of their high reactivity and high selectivity; for example ready-made mixtures of some catalytic systems are commercially available, eliminating the need to weigh several compounds. Transition metal catalysis has become so important that in 2001 the Nobel Prize for chemistry was awarded to Knowles, Noyori and Sharpless for their contributions to asymmetric catalysis. However, transition metal catalysis is not free from problems. The metals used are often expensive, toxic and can be difficult to recover from the reaction products. In pharmaceutical products this can prove problematic due to the toxicity, cost of the metal and its recovery. These issues can be resolved by employing organocatalysis.[1]

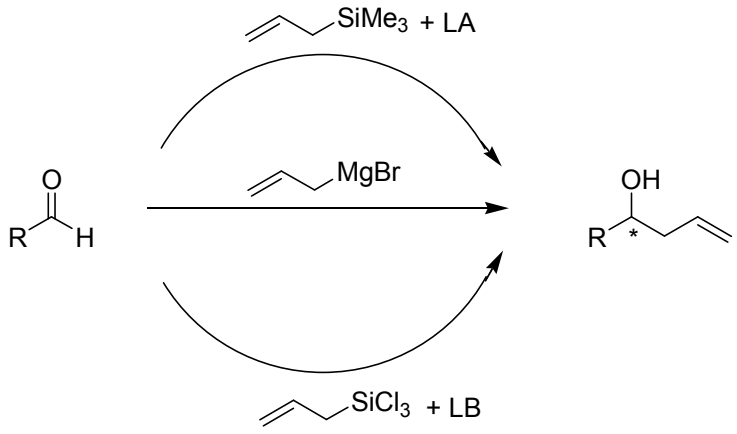
In light of this, the field of organocatalysis has received considerable attention in recent years.[2,3] Although organocatalysis has been known since the early part of the twentieth century at least[4,5], the past decade has seen a vast advancement in the field. There has been large growth in the number of papers published in this area and the number of new organocatalytic systems being discovered.[2,6,7] Organocatalysts are small organic molecules. They offer a favourable alternative to metals as they are less toxic, cheaper and can often be used under an aerobic atmosphere with wet solvents. Small organic molecules also offer the possibility of being recovered and reused, unlike many transition metal catalysts.

Organocatalysts can act by coordination to the substrate to render it more reactive. This is often the case when amines are used as organocatalysts and is typified by enamine activation shown by proline.[8,9] Organocatalysts can also act through weak non-covalent interactions: in this case the substrate or reagent is activated by coordination to the organocatalyst. The activation of organosilicon reagents is one such example; this chapter will focus on the reactions of silicon reagents and the organocatalysts employed in these processes.

1 Introduction

1.1 Lewis Basic Activation of Silicon

Addition of nucleophilic reagents to carbonyl compounds is an area with great importance in organic synthesis. Reactive nucleophiles such as $LiAlH_4$ and Grignard reagents efficiently add to carbonyl compounds, however less reactive nucleophiles such as allyltrichlorosilane and trichlorosilane do not react so readily and additional activation is required. This can be achieved by either adding a Lewis acid to trialkylsilanes or a Lewis base in the case of trichlorosilanes (Scheme **1.1**).



Scheme 1.1: Activation of silanes.

Activation can occur through either Lewis acid coordination to the carbonyl oxygen or through Lewis basic activation of the nucleophilic silane compound. Typically in organocatalysis activation of silanes by Lewis bases is the preferred method.[10] As organosilicon reagents are generally unreactive, only the coordinated silicon species will react. If the activator employed can dissociate from the silicon intermediate at a sufficient rate, it can act as a catalyst rather than a stoichiometric reagent. The use of a chiral Lewis basic catalyst would naturally allow for the preferential formation of a single enantiomer.

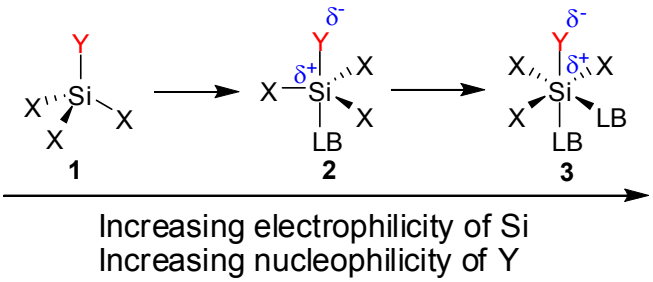


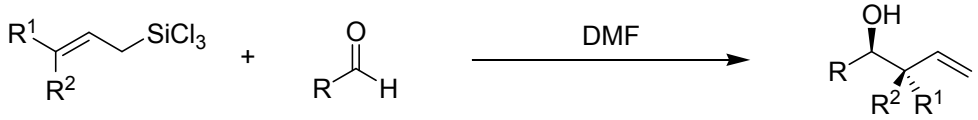
Figure 1.1: Expanding coordination of organosilicon reagents

Coordination of a Lewis base to an organosilicon reagent, **1**, can expand the coordination sphere of silicon resulting in a pentacoordinate, **2**, or hexacoordinate, **3**, species.[11,12] This results in increased positive charge on silicon and increases the negative charge on the ligands (Figure **1.1**).[13,14] If the increased negative charge lies on a ligand which may act as a nucleophile then the hypervalent species can be considered as activated towards nucleophilic attack on an electrophile. In the case of hexacoordinate silicon, **3**, it is possible for a cationic species to be generated by ionisation of an electron-withdrawing ligand, such as a halide. This results in a significant increase in Lewis acidity at silicon and can hence facilitate the activation of an electrophile, such as a carbonyl group, by coordinating to a non-bonding lone-pair of oxygen.[15] Organocatalytic protocols based on silane reagents have taken advantage of the tendency of Lewis bases to activate silane reagents as nucleophiles and enhance the Lewis acidic character of silicon.[16]

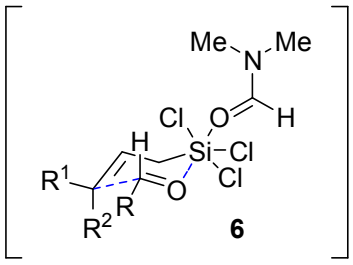
1.2 Allylation Reactions at C=O

The addition of allylsilanes to aldehydes is an important carbon-carbon bond forming reaction that has come under much recent scrutiny.[2,17,18] Part of the reason for the interest in this reaction has been the ability to generate homoallylic alcohols with high enantio- and diastereoselectivity and the synthetic versatility of the end product. Although the reaction is typically carried out by Lewis-acidic (metallic) activation of the carbonyl component or by employing reactive organometallic allyl reagents, the development of Lewis basic activation of allylsilanes has allowed the use of organic molecules as promoters (organocatalysts).

Lewis base promoted allylation of aldehydes with allylsilanes was pioneered by Kobayashi using dimethylformamide as a stoichiometric activator of allyltrichlorosilane, **4.**[19,20] Interestingly, when crotyltrichlorosilanes, **5**, were used, the reaction proceeded stereospecifically suggesting the reaction operates via a closed cyclic transition state, **6** (Scheme **1.2**). Since this initial discovery, a range of further Lewis basic substances that facilitate the allylation reaction have been identified. Typical Lewis basic activators include DMSO[19-22] and HMPA[22,23] as well as compounds with formamide[24,25] and urea[26] structural motifs.



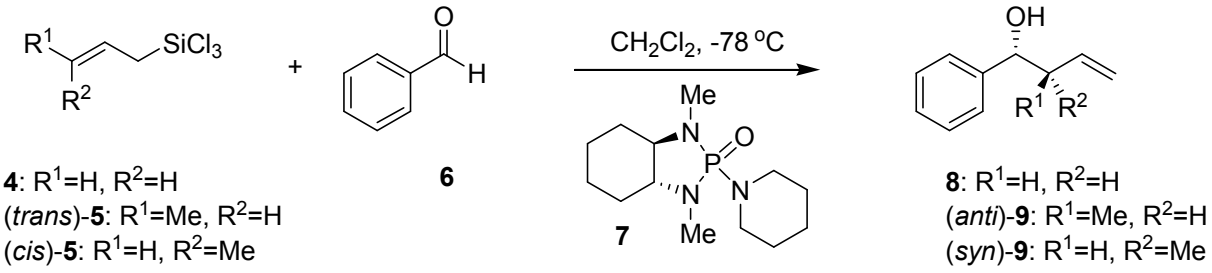
4: R^1=H, R^2=H
(*trans*)-**5**: R^1=Me, R^2=H
(*cis*)-**5**: R^1=H, R^2=Me



Scheme 1.2: Kobayashi closed TS

1.2.1 Phosphoramide Organocatalysed Allylations

The asymmetric Lewis base promoted allylation of aldehydes was pioneered by Denmark who showed that chiral phosphoramides were able to successfully produce enantioenriched homoallylic alcohols,[22] although the phosphoramide catalyst **7** exhibited only modest enantioselectivity. It was shown that the addition of *trans* and *cis* **5** resulted in generation of the anti or syn products respectively, **9**, with high diastereoselectivity (Scheme **1.3**). The transfer of stereochemistry from double bond to product in the crotylation reaction strongly suggests that the reaction proceeds via a closed cyclic transition state, much like that proposed by Kobayashi.



4: R^1=H, R^2=H
(*trans*)-**5**: R^1=Me, R^2=H
(*cis*)-**5**: R^1=H, R^2=Me

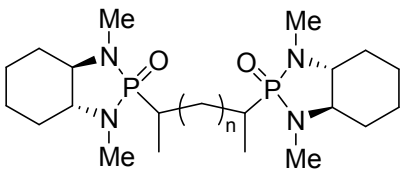
8: R^1=H, R^2=H
(*anti*)-**9**: R^1=Me, R^2=H
(*syn*)-**9**: R^1=H, R^2=Me

silane	cat loading (%)	yield (%)	anti/syn	ee (%)
4	100	80	N.A.	60
(*trans*)-**5**	100	68	98/2	64
(*cis*)-**5**	100	72	2/98	60

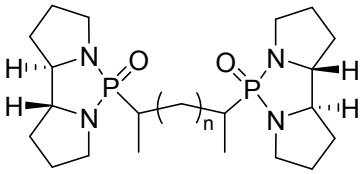
Scheme 1.3: Phosphoramide catalysed allylation of benzaldehyde – Denmark

To further probe the reaction mechanism and dependence of selectivity on catalyst loading, a kinetic study was carried out by Denmark.[27] A non-linear relationship between the enantiopurity of catalyst **7** and product **8** was found, suggesting that two molecules of catalyst are involved in the transition state. It was also proposed that a second, less selective one-catalyst pathway may operate at low phosphoramide levels. In order to reduce the effects of the second, less selective pathway, Denmark designed bisphosphoramide catalysts (Chart **1.1**).[27,28]

Variation of the length of carbon chain linking the phosphoramide units identified a five-methylene tether as the optimum, **10b**. Increased selectivity was observed with the use of organocatalysts **11a-c**, derived from (*R*,*R*)-2,2'-bispyrrolidine. Again, the optimum tether length was determined as five methylene units. Bis-phosphoramide **11b** catalysed allylation of benzaldehyde **6** (loading of 5 mol%) furnishing the allylic alcohol in 85% yield and 87% ee. Catalyst **11b** was also successful in the allylation of a range of aromatic, heteroaromatic and unsaturated aldehydes.[28]



10a: n=4
10b: n=5
10c: n=6



11a: n=4
11b: n=5
11c: n=6

Chart 1.1: Bis-phosphoramide organocatalysts.

In order to further understand the reaction mechanism, Denmark carried out a number of studies involving bis-phosphoramide catalysts **10b** and **11b**.[29] In these studies, complexes of phosphoramides with $SnCl_4$ were synthesised and their properties were studied both in solution and in solid state. Complexes with Sn exhibit similar bonding to those of Si but are also more stable making them easier to study. The similarity in bonding between Si and Sn complexes allows results based on Sn to be extrapolated to the corresponding Si complexes. Based on crystallographic data and ^{31}P and ^{119}Sn NMR studies, Denmark proposed that *trans*-coordination of the silane to the Lewis basic organocatalyst enhances the nucleophilicity of the allyl group. In addition, the aldehyde should preferably coordinate *trans* to the electron-withdrawing chloride group to enhance its anionic character. Coordination of both Lewis basic catalyst and aldehyde to silicon in this fashion generates a chiral pocket, **12**, in which enantioselective allylation can occur (Figure **1.2**).

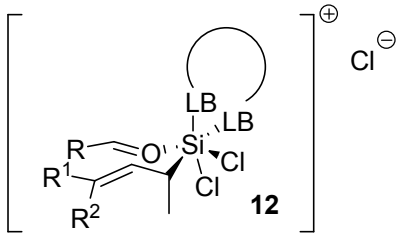
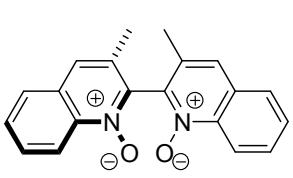
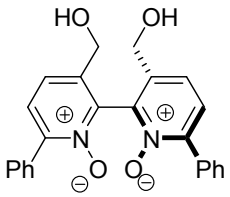


Figure 1.2: Proposed method of allylation promoted by Lewis basic organocatalysts.

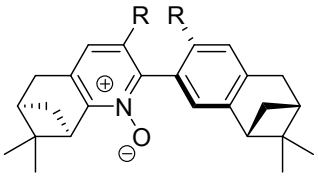
1.2.2 N-Oxide Organocatalysed Allylations



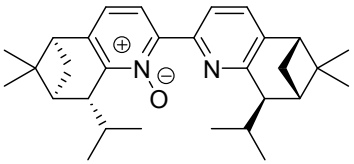
13 Nakajima



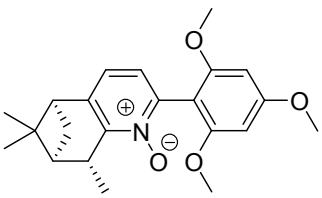
14 Hayashi



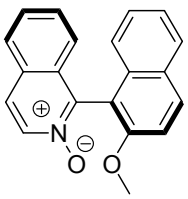
15 R = H; PINDOX
16 R = Me; Me_2PINDOX



17 iso-PINDOX



18 METHOX



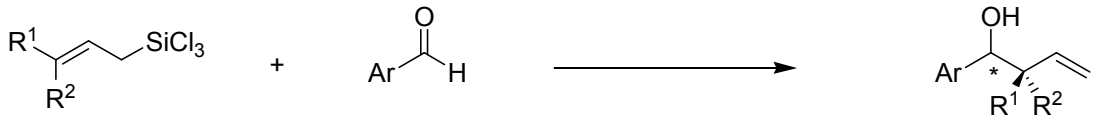
19 QUINOX

Chart 1.2: *N*-oxide based organocatalysts for allylation reactions

Another successful class of organocatalysts for the Lewis-base promoted allylation with allyltrichlorosilanes are *N*-oxides (Chart **1.2**). The use of *N*-oxides was pioneered by Nakajima, who demonstrated that chiral *N,N'*-bisoxide **13** allowed successful transformation in high yield and selectivity (71 – 92% ee) at -78 ^{o}C with a catalyst loading of only 10 mol% (Table **1.1**, entries 1-4).[30] Similar to the phosphoramide catalysed allylation reactions, a six-membered transition state was

proposed due to the high diastereoselectivitiy observed upon the addition of *trans* and *cis* crotylsilanes (Figure **1.2**).

Further to Nakajima's work, a more active *N,N'*-bisoxide **14** was developed by Hayashi.[31] High yields are observed with as little as 0.1 mol% catalyst loading; however enantioselectivity was highly dependent on the electronic nature of the substrate aldehyde (Table **1.1**, entries 5, 6). Electron-deficient aldehydes produced homoallylic alcohols with lower enantioselectivity than that of their electron-rich counterparts. Hayashi suggested that the difference between electron-rich and electron-poor aldehydes could be attributed to π-stacking between the aldehyde and catalyst in the transition state.



4: R^1=H, R^2=H
(*trans*)-**5**: R^1=Me, R^2=H
(*cis*)-**5**: R^1=H, R^2=Me

entry	silane	Ar	catalyst	yield (%)	anti/syn	ee (%)
1	**4**	Ph	**13**	85	NA	88 (*R*)
2	**4**	4-$MeOC_6H_4$	**13**	91	NA	92 (*R*)
3	(*trans*)-**5**	Ph	**13**	68	97/3	86 (*R*)
4	(*cis*)-**5**	Ph	**13**	64	1/99	84 (*R*)
5	**4**	Ph	**14**	95	NA	84 (*S*)
6	**4**	4-$MeOC_6H_4$	**14**	96	NA	94 (*S*)

Table 1.1: Allylation with bis-*N*-oxides **13** and **14**.

Malkov and Kocovsky reported the use of a series of catalysts derived from terpenes; bypyridine *N*-monoxides **15 – 17**.[32,33] *N*-oxide **15**, PINDOX, emerged as an efficient catalyst for the allylation of aromatic and heteroaromatic aldehydes (Table **1.2**, entries 1 - 5). Further studies, however, revealed that Me_2-PINDOX **16** was much more efficient than its analogues PINDOX, **15**, and iso-PINDOX, **17**. It was proposed that the restriction to axial rotation imposed by 3,3'-methyl groups created a favourable chiral environment upon coordination to silicon. Asymmetric

induction is controlled by the configuration of the 2,2'-bipyridyl bond as shown by using both the (+) and (-) atropisomers of Me_2-PINDOX, **16**. Thus, when the (+) atropisomer (10 mol%) was used, the homoallylic alcohol (*S*)-**8** was isolated in 72% yield and 98% ee (Table **1.2**, entry 6); while (-)-**16** results in the formation of the (*R*)-**8** in 82% ee and 67% yield (Table **1.2**, entry 7). To account for the observed results, a bidentate coordination of silicon through both O and N resulting in a hexacoordinate silicon species was proposed.

entry	catalyst	Ar	yield (%)	ee (%)
1	**15**	Ph	78	90 (*S*)
2	**15**	4-$MeOC_6H_4$	68	87 (*S*)
3	**15**	4-$NO_2C_6H_4$	58	65 (*S*)
4	**15**	$PhCH=CH_2$	52	83 (*S*)
5	**15**	2-furyl	63	85 (*S*)
6	(+)-**16**	Ph	72	98 (*S*)
7	(-)-**16**	Ph	67	82 (*R*)
8	**17**	Ph	15	97 (*S*)
9	**17**	4-$MeOC_6H_4$	41	91 (*S*)
10	**17**	$PhCH=CH_2$	25	96 (*S*)

Table 1.2: Allylation of aldehydes with PINDOX and its derivatives.

It was discovered that METHOX, **18**, lacking the second pyridine ring was much more active and achieved the same levels of enantioselectivity as PINDOX analogues, **15** - **17**.[34,35] In light of this Malkov and Kocovsky proposed that aromatic interactions between the catalyst and substrate may play a crucial role in determining the configuration of the transition state, rather than a second coordination point for Si. In addition it was found that METHOX, **18**, remained highly active even at low loadings (1 mol%) and is tolerant of aldehyde electronics (Table **1.3**, entries 1-5).

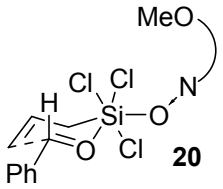
While METHOX exhibited good selectivity regardless of aldehyde electronics, related *N*-oxide catalyst, **19**, QUINOX displays high dependence on the electronics of the substrate aldehyde.[36] Employing QUINOX, **19**, it was found that the reaction of electron-poor aldehydes proceeded with higher rate and selectivity than the

equivalent electron-rich aldehydes (Table **1.3**, entries 6–9). More recent investigations involving computational and kinetic studies by Malkov and co-workers have indicated that the reaction is likely to proceed via an associative reaction mechanism involving one molecule of organocatalyst that generates an octahedral silicon complex, **20** (Figure **1.3**).[37]

entry[a]	catalyst	Ar	loading (%)	solvent	yield (%)	ee (%)
1	**18**	Ph	5	MeCN	95	96 (*S*)
2	**18**	Ph	1	MeCN	68	95 (*S*)
3	**18**	4-CF_3-C_6H_4	5	MeCN	86	93 (*S*)
4	**18**	4-MeO-C_6H_4	5	MeCN	95	96 (*S*)
5	**18**	2-MeO-C_6H_4	5	MeCN	95	89 (*S*)
6	**19**	Ph	5	CH_2Cl_2	60	87 (*R*)
7	**19**	4-MeO-C_6H_4	5	CH_2Cl_2	70	12 (*R*)
8[b]	**19**	4-NO_2-C_6H_4	5	CH_2Cl_2	73	89 (*R*)
9	**19**	4-CF_3-C_6H_4	5	CH_2Cl_2	85	96 (*R*)

[a] All reactions carried out at -40 ^{o}C. [b] Reaction complete after 12h

Table 1.3: Allylation of aldehydes with **18** and **19**.

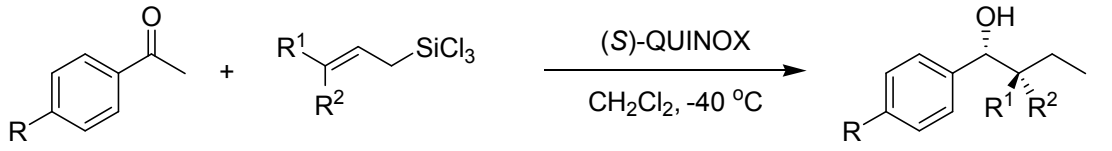


20

Figure 1.3: Proposed TS for allylation of aldehydes with QUINOX **19**.

Crotylation of aldehydes catalysed by PINDOX and its derivatives, **15** - **17**, resulted in the highly diastereoselective formation of homo-allylic alcohols **9**. The transfer of stereochemistry from double bond to alcohol was consistent with the presence of a closed cyclic transition state, i.e. the *trans* alkene produces the *anti* product and *cis* gives the *syn* products. METHOX reacts well with *trans*-**5**, generating *anti*-**9** with very high diastereoselectivity (>99:1) and high ee (95%). The reaction with *cis*-**5** however is slow and not as diastereoselective (6:1).

Crotylation with QUINOX, **19**, as the organocatalyst has been shown to exhibit high diastereoselective control.[36,37] Reaction with *trans* and *cis*-**5** formed the corresponding allylic alcohols with high diastereoselectivity, 95:5 and 1:99 respectively (Table **1.4**). It was again observed that electron-rich aldehydes did not react as well as their electron-poor counterparts. The results indicate that crotylation with QUINOX, **19**, proceeds via a closed chair-like transition state, similar to that proposed by Denmark (Figure **1.4**). Computational studies also suggested that aromatic interactions between catalyst and substrate may play a contributory role in the enantiodifferentiation process.

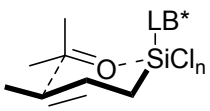


(*trans*)-**5**: R^1=Me, R^2=H
(*cis*)-**5**: R^1=H, R^2=Me

(*anti*)-**9**: R^1=Me, R^2=H
(*syn*)-**9**: R^1=H, R^2=Me

R	Silane	Yield	anti:syn
CF_3	trans	75	96:4
H	trans	65	95:5
MeO	trans	40	83:17
CF_3	cis	85	1:99
H	cis	78	1:99
MeO	cis	50	4:96

Table 1.4: Crotylation of aldehydes with QUINOX



Closed TS
high diastereoselectivity

Figure 1.4: Allylation transition state, LB* = chiral Lewis Base (organocatalyst)

The application of tri-*N*-oxides as Lewis basic activators for this reaction has also been reported by Kwong.[38] Terpene derived pyridine-*N*-oxides **21** – **22** were shown to be effective with loadings of 10 mol% (Chart **1.3**, Table **1.5**). Enantiomeric excess of up to 86% ee was reported however the selectivity proved to be dependent on the electronics of the aldehyde; again; electron-poor aldehydes gave the highest selectivity.

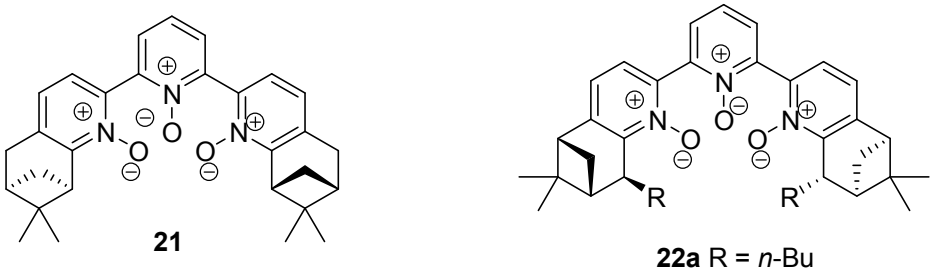
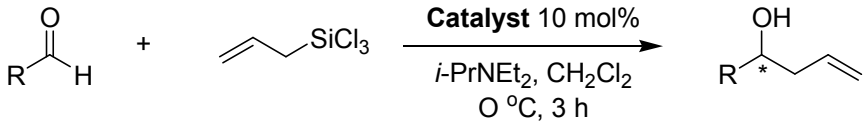


Chart 1.3: Terpene derived *N*-oxide organocatalysts

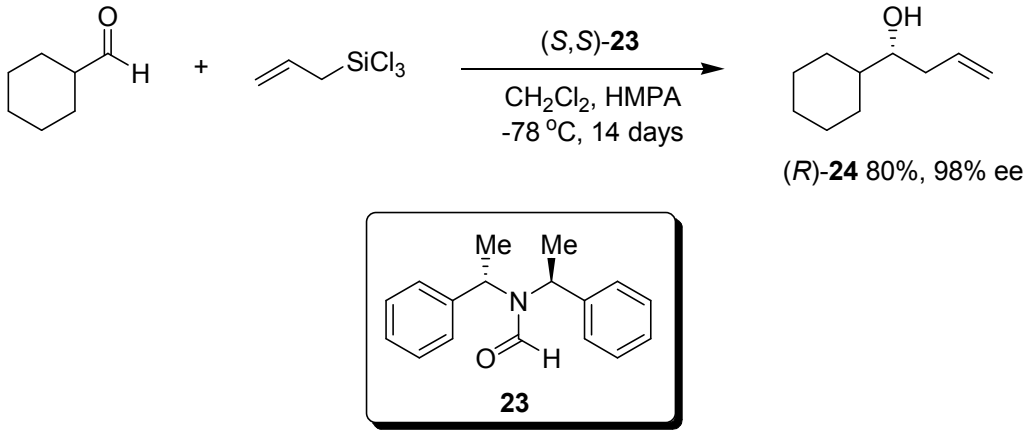


Entry	Catalyst	R	Yield (%)	ee (%)
1	**21**	Ph	85	34 (*R*)
2	**22a**	Ph	87	67 (*R*)
3	**22b**	Ph	89	74 (*R*)
4	**22b**	4-MeO-C_6H_4	94	65 (*S*)
5	**22b**	4-CF_3-C_6H_4	91	86 (*R*)

Table 1.5: Allylation catalysed by tri-*N*-oxides **21** – **22**.

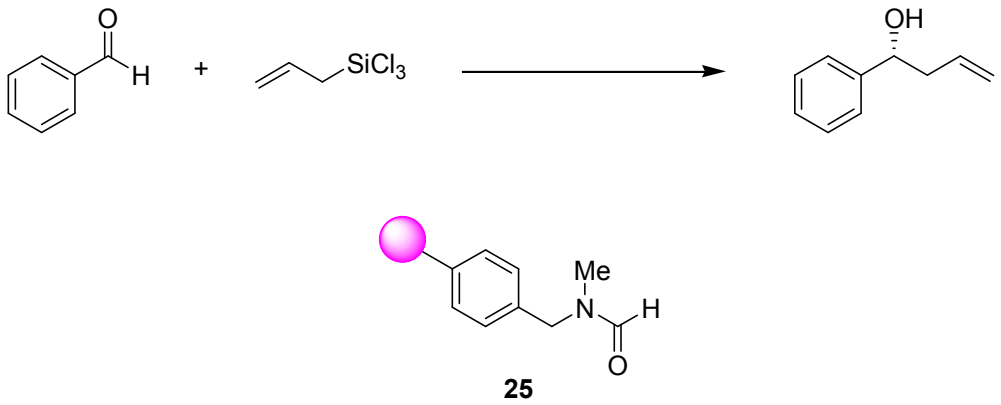
1.2.3 Formamide Organocatalysed Allylations

Chiral formamides have also been employed as organocatalysts for the allylation of aldehydes based upon the work of Kobayashi.[19] Chiral DMF analogues were developed by Iseki and employed in the allylation reaction.[24,25] Formamide **23** was found to be an activator for the reaction however long reaction times at low temperature (7 days at -78 ^{o}C) were required to produce the allylic alcohol **24** in 81% yield and 68% ee (Scheme **1.4**). It was found that the addition of 1.0 equivalents of HMPA was beneficial to the reaction. The product was formed in 80% yield and 98% ee under optimum conditions, 1.0 eq HMPA as an additive, -78 ^{o}C, 14 days. Although **23** operates as a highly selective catalyst, the reaction rate is too sluggish to be considered synthetically useful. It is worth noting, however, that **23** exhibits high selectivity for aliphatic aldehydes (≥ 98% ee) but not with aromatic aldehydes.



Scheme 1.4: Allylation reaction promoted by (*S*,*S*)-**23**.

More recently, Kobayashi described the use of a polymer supported formamide, **25**, which can act as a recyclable promoter for the allylation of aldehydes with silanes (Scheme **1.5**).[39] Allylic alcohol **26** was formed in 91% yield using one equivalent of polymer supported catalyst **25**. It was also found that **25** maintained its activity through several uses.

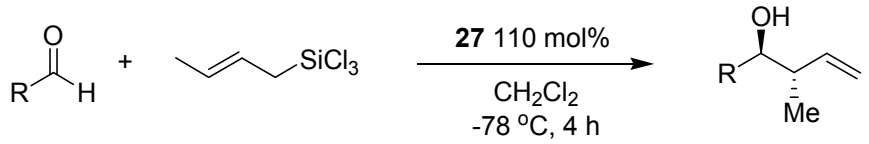


25

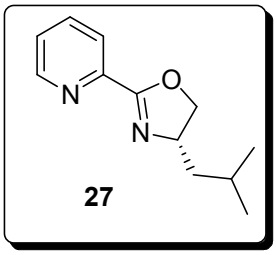
Scheme 1.5: Allylation catalysed by polymer supported formamide.

1.2.4 Pyridine-oxazoline Organocatalysed Allylations

The use of pyridine-oxazoline derivatives as activators for crotylation of aromatic aldehydes was reported by Barrett.[40] Organic activator **27** derived from leucinol showed the best results for this transformation, giving excellent diastereoselectivity, >99% and moderate-to-good enantioselectivity, 36 – 74% ee (Scheme **1.6**). Formation of the *anti*-allylic alcohol only, indicates the involvement of a hyper-valent silicon species in a closed transition state.



Entry	R	Yield (%)	ee (%)
1	Ph	72	74
2	4-MeO-C_6H_4	79	46
3	4-F-C_6H_4	61	74
4	4-O_2N-C_6H_4	66	36

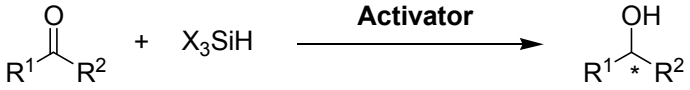


27

Scheme 1.6: Crotylation of aldehydes catalysed by pyridine-oxazolines.

1.3 Reduction of Ketones With Silanes

Silanes are widely accepted as efficient reagents for the reduction of carbonyl functionality. In the case of alkyl silanes, transition metal catalysts are required to activate the reagent[41]; in the case of more Lewis acidic trichloro- and trialkoxysilanes, a metal-free variation can be attained by employing an organic activator (Scheme **1.7)**.

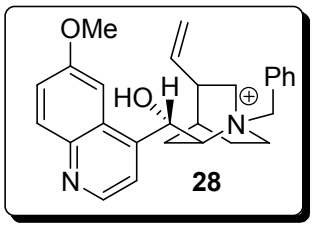


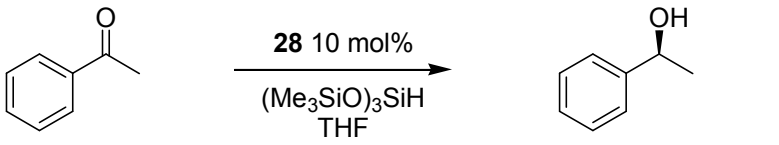
Scheme 1.7: Reduction of ketones with silanes

1.3.1 Anion Promoted Reduction

Trialkoxysilanes were reported as reducing agents for carbonyl compounds by Corriu.[42,43] Although generally unreactive towards carbonyl functionality, triethoxysilane turned into a reactive hypervalent silicon species upon coordination of fluoride anions. A range of carbonyl compounds were reduced by silanes catalysed by alkali metal fluorides.

More recently, Lawrence has reported the use of chiral quinidine fluoride salts as phase-transfer catalysts for an asymmetric variant of this reaction.[44] Activation of trimethoxysilane is again achieved by forming a hypervalent silicon species with fluoride anions. The use of chiral cinchona derived catalyst **28** led to the formation of *sec*-alcohols in up to 78% ee (Scheme **1.8**). It was also found that aromatic *sec*-alcohols were formed with higher levels of enantiodiscrimination than their aliphatic counterparts.



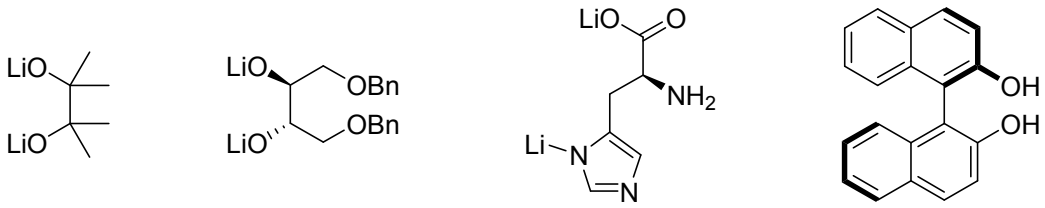


29 (*S*)-**30**, 99%, 78% ee

Scheme 1.8: Reduction of ketones with cinchona derivative **28**

Alkoxides also turned into effective activators of silicon for the reduction of ketones to alcohols with silanes as shown by Hosomi (Chart **1.4**).[45] Lithium alkoxide **31** generated a hypervalent silicon species which converted a range of ketones to the corresponding alcohols in good yield. Hosomi then developed chiral alkoxides as activators of silicon, resulting in an asymmetric transformation.[46] Alkoxide **32** successfully reduced acetophenone, **29**, in 78% yield and 44% ee with a loading of 40 mol%.

Additionally, lithium salts of *L*-Histidine and BINOL have been developed as activators of trialkoxysilanes by Brook[47,48] and Kagan[49] respectively. The lithium salt of *L*-Histidine, **33**, formed (*S*)-phenylethanol, **30**, in 70% yield and only 26% ee; the monolithium salt of BINOL, **34,** formed (*S*)-phenylethanol, **30**, in 92% yield and 70% ee; **34** was also shown to be highly effective for a range of ketones forming the *sec*-alcohol products in good selectivity (up to 93% ee). In both cases the addition of TMEDA was found to be beneficial to the activity of the catalytic system, presumably as it prevents the organolithio compounds from aggregating.

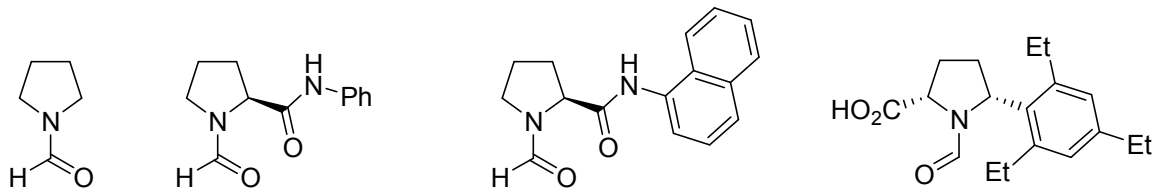


31 **32** **33** **34**

Chart 1.4: Lithium alkoxide activators

1.3.2 Formamide Promoted Reduction

Kobayashi described the reduction of ketones to *sec*-alcohols with the use of a dimethylformamide-trichlorosilane complex.[50] The hypervalent silicon complex thus generated was shown to be an effective reducing agent for ketones, aldehydes and imines. Trichlorosilane proved to be a more desirable reducing agent than trialkoxysilanes as it is less toxic, cheap and easy to handle. Perhaps unsurprisingly, this led to the development of chiral formamide derivatives as activators of trichlorosilane for the reduction of the carbonyl functionality.



35 **36** **37** **38**

Chart 1.5: Formamide activators of Cl_3SiH

Matsumura showed that *N*-formylpyrrolidine derivatives were able to effectively activate trichlorosilane towards reduction in only catalytic quantities (Chart **1.5**).[51] The initial non-enantioselective reduction was carried out with 10 mol% of formamide **35**, resulting in formation of phenylethanol in 92% yield. By employing chiral formamide **36** derived from proline some enantiodiscrimination was observed. Enantioselectivity was increased when formamide **37** was employed, giving the product in 43% ee. Matsumura proposed steric repulsion

between the aryl groups of the catalyst and ketone as a rationale for enantioinduction (Figure **1.5**).

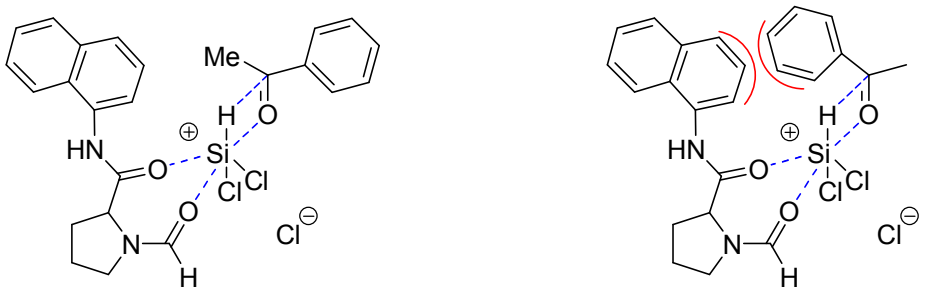
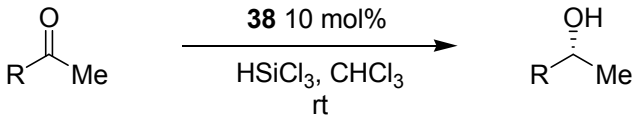


Figure 1.5: Matsumura's proposed transition state.

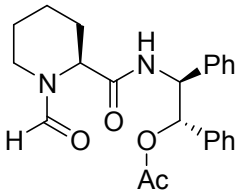
More recently, Matsumura reported the related formamide **38** (Chart **1.5**) as an efficient activator of silanes towards reduction of ketones.[52] Formamide **38** reduced aromatic ketones containing both electron-donating and electron-withdrawing substituents in high selectivity, up to 97% ee (Table **1.6**). Acetyl ferrocene was also successfully reduced by **38** at -60 ^{o}C in 97% yield and 99.7% ee. It was found that the carboxyl group and 2,4,6-triethylphenyl group at the α and α' positions were required for high selectivity and reactivity. This may suggest hydrogen bonding interactions between the catalyst and either ketone or silane. Aromatic interactions between catalyst and substrate may also be suggested as a rationale for selectivity.



Entry	R	Yield (%)	ee (%)
1	Ph	90	95 (*R*)
2	4-NO_2-C_6H_4	93	97 (*R*)
3	4-Cl-C_6H_4	93	97 (*R*)
4	4-F-C_6H_4	91	94 (*R*)

Table 1.6: Reduction of ketones with formamide **38**.

Pipecolinic derived formamides, **39** – **43** (Chart **1.6**), were found to be effective for the reduction of ketones with trichlorosilane by Sun and co-workers.[53] Formamide derivative **43** was found to be the most efficient promoter of the reduction reaction; aromatic ketones were reduced in high yield and enantioselectivity (Table **1.7**, entries 1 – 3). Interestingly, aliphatic ketones were effortlessly reduced in moderate to high selectivity (Table **1.7**, entries 4 and 5).



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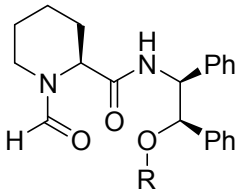
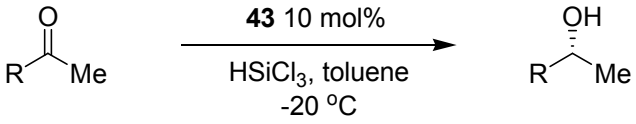


40 R = Ac
41 R = CHO
42 R = Et
43 R = Me

Chart 1.6: Pipecolinic derived formamide organocatalysts.

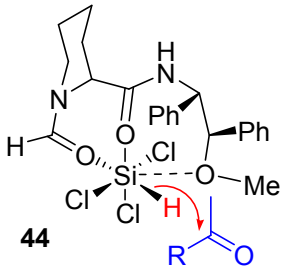


Entry	R	Yield (%)	ee (%)
1	4-CF_3-C_6H_4	92	92 (*R*)
2	4-NO_2-C_6H_4	92	91 (*R*)
3	Ph	94	81 (*R*)
4	*c*-C_6H_{11}	90	88 (*R*)
5	*i*-Pr	81	53 (*R*)

Table 1.7: Reduction of ketones with formamide **43**.

The methoxy substituent at the 2' position was found to be crucial to enantiodifferentiation as replacement of this group results in lower selectivity. Furthermore it was found that reversal of the stereochemistry at C-2' or removal of

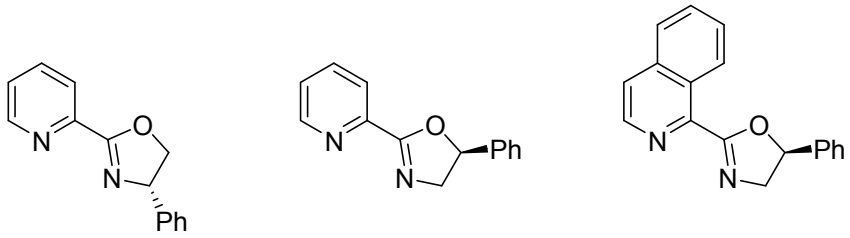
the alkoxy group had a detrimental effect on both selectivity and reactivity. Based on their observed results, Sun *et al* proposed a transition state based on tricoordinate activation of silane by the organocatalyst to generate a heptacoordinate silicon species, **44**, as the active reducing agent (Figure **1.6**).



44

Figure 1.6: Sun proposed transition state for reduction of ketones.

1.3.3 Oxazoline Promoted Reduction



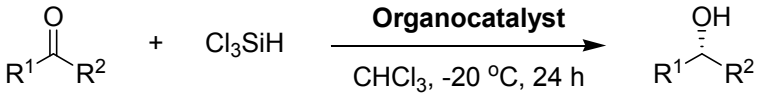
45 **46** **47**

Chart 1.7: Pyridine oxazoline activators of silanes

More recently Malkov and Kocovsky described the use of pyridine oxazolines as highly effective organocatalysts for the reduction of ketones with trichlorosilane (Chart **1.7**).[54] When phenylglycine derived pyridine oxazoline **45** was effectively employed for the hydrosilylation of acetophenone, **29**, the resulting alcohol, **30**, was obtained in low yield and moderate enantioselectivity (Table **1.8**, entry 1). In contrast, the isomeric pyridine oxazoline **46**, obtained from mandelic acid, reduced acetophenone, **29**, in 85% yield and 78% ee (Table **1.8**, entry 2). Steric interactions between the chiral aryl group and the silane ligands, resulting in poor coordination of the silane to **45**, were proposed to account for the difference in selectivity between **45** and **46**. A range of ketones were examined in the

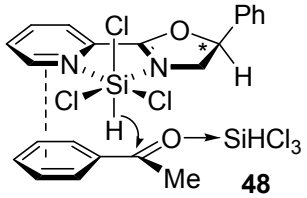
reduction reaction catalysed by **46**, high enantioselectivity was observed only in aromatic ketones (>80% ee), while aliphatic ketones performed rather poorly.

In order to increase activity and selectivity, catalyst **47** derived from 1-isoquinoline and mandelic acid was developed. Catalyst **47** was shown to be much more active over a range of substrates and allowed the catalyst loading to be dropped to 10 mol%. Aromatic ketones were reduced in good yield with high enantioselectivity, >94% (Table **1.8**, entries 3 – 7). Malkov and Kocovsky proposed a transition state accounting for the high selectivity in which the oxazoline catalyst coordinates to trichlorosilane to form a hypervalent silicon species. The ketone, coordinated to a second molecule of trichlorosilane, then approaches from the less hindered face; it was also suggested that aromatic interactions between ketone and catalyst may play a role in stabilising the transition state, **48** (Figure **1.7**).



Entry	Catalyst (mol%)	R^1, R^2	Yield (%)	ee (%)
1	**45** (20)	Ph, Me	29	66
2	**46** (20)	Ph, Me	85	78
3	**47** (10)	Ph, Me	85	84
4	**47** (10)	Ph, Et	55	86
5	**47** (10)	2-MeO-C_6H_4	50	87
6	**47** (10)	2-F-C_6H_4, Me	35	70
7	**47** (10)	2-naphth, Me	93	94

Table 1.8: Organocatalytic reduction of ketones with oxazoline derivatives



48

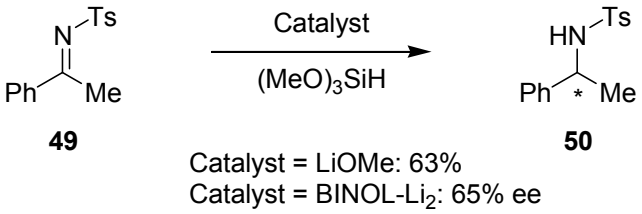
Figure 1.7: Proposed transition state for catalyst **46**.

1.4 Reduction of Imines with Silanes

1.4.1 Anion Promoted Reduction

As an outcome to the activation of trialkoxysilanes for the hydrosilylation of ketones, Hosomi reported the use of lithium methoxide as a catalyst for the reduction of *N*-tosyl imines with trimethoxysilane.[55]

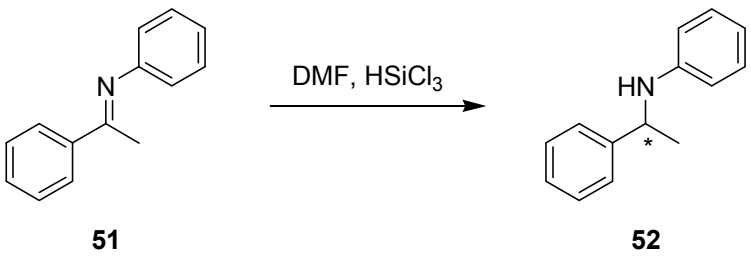
Attempts to render the reaction enantioselective by using lithium salts of various amino alcohols were unsuccessful however.[56] An improvement in selectivity was observed using the dilithium salt of BINOL, **34**. The reduction of **49** to **50** was carried out successfully in 65% enantioselectivity.



Scheme 1.9: Reduction of *N*-tosyl imines

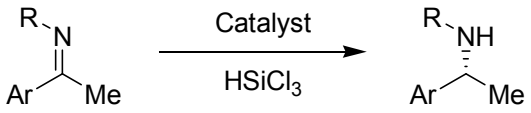
1.4.2 Formamide Promoted Reduction

Analogous to the reduction of ketones, Kobayashi described the generation of a hypervalent dimethylformamide-trichlorosilane complex and its effectiveness as a mild reducing agent for ketimines (Scheme **1.10**).[50]



Scheme 1.10: Reduction of ketimines with DMF-trichlorosilane.

In a similar manner, Matsumura investigated the potential of pyrrolidine derived formamides as catalytic Lewis basic activators for the reduction of prochiral ketimines with trichlorosilane.[57] Formamide **35** was shown to be much more effective than DMF for the achiral reaction, generating amine **52** in 79% yield. By employing enantiomerically pure formamides **36** and **37**, a small range of ketimines were reduced to the corresponding chiral amines in moderate enantioselectivity (Table **1.9**).



Entry	Catalyst	Ar	R	Yield (%)	ee (%)
1	**35**	Ph	Ph	79	NA
2	**36**	Ph	Ph	91	55 (*R*)
3	**37**	Ph	Ph	52	66 (*R*)

Table 1.9: Reduction of ketimines with pyrrolidine derived formamides.

In a modification of the chiral scaffold developed by Matsumura, Malkov and Kocovsky reported valine derived formamides as highly selective organocatalysts for the reduction of ketimines with trichlorosilane (Chart **1.8**).[58] Replacing the rigid cyclic core of the pyrrolidine formamides with a more flexible skeleton resulted in much higher levels of enantiodiscrimination; presumably as the more flexible system allows the catalyst to adopt a more favourable geometry in the transition state. Although both **37** and valine derived formamide **54** have the same absolute configuration, the latter results in formation of the opposite enantiomer.

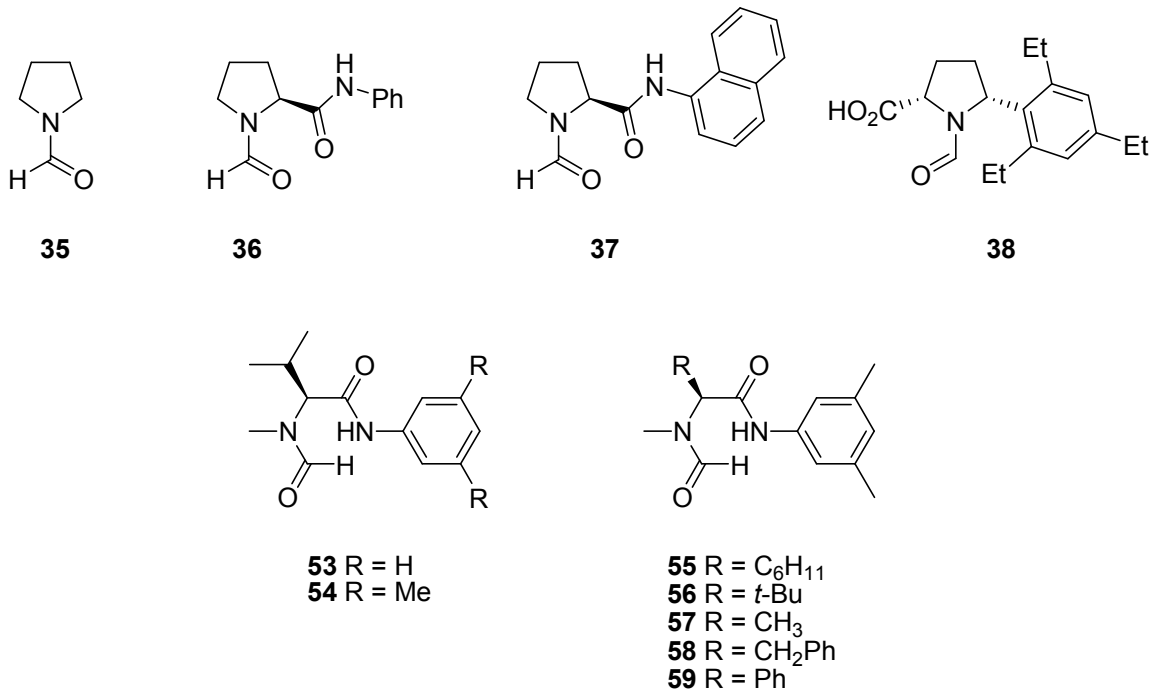
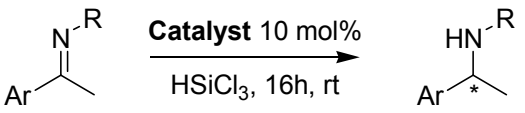


Chart 1.8: Formamide containing organocatalysts for reduction of ketimines

A range of prochiral ketimines were reduced with **53** and **54** as a catalyst (Table **1.10**, entries 1 - 5); tuning the steric properties of the aromatic ring of the catalyst, as in **54**, improved the reactivity. It was found that selectivity was only observed with *N*-aryl imines. In addition, non-polar solvents proved to be superior in terms of reactivity and enantioselectivity, with chloroform and toluene as the optimum. Variation of the amino acid side-chain showed that bulkier groups such as cyclohexyl and *t*-butyl groups, **55** and **56**, exhibited marginally reduced selectivity (Table **1.10**, entries 6 and 7), while catalysts derived from alanine, phenylalanine and phenylglycine, **57**, **58** and **59**, were considerably less selective (Table **1.10**, entries 8 – 10).

It was proposed that activation of trichlorosilane occurs through coordination to the formamide moiety in **54**, it was also conjectured that the amide oxygen may play a role in coordinating silicon. Arene-arene interactions between the catalyst and the *N*-aryl moiety of the imine were suggested as contributing to the enantiodifferentiating process. The chirality of the amino acid side-chain is thought to be transmitted through the *N*-Me moiety of the catalyst.

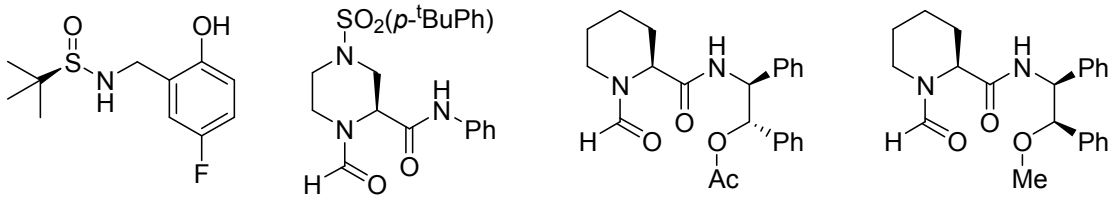


Entry	Catalyst	Ar	R	Solvent	Yield (%)	ee (%)
1	**53**	Ph	Ph	$CHCl_3$	49	92 (*S*)
2[a]	**54**	Ph	Ph	$CHCl_3$	94	92 (*S*)
3	**54**	Ph	Ph	Toluene	81	92 (*S*)
4	**54**	Ph	PMP	Toluene	85	91 (*S*)
5	**54**	Ph	Bn	Toluene	48	8
6	**55**	Ph	PMP	Toluene	95	82 (*R*)
7	**56**	Ph	PMP	Toluene	95	83 (*S*)
8	**57**	4-$CF_3C_6H_4$	Ph	Toluene	92	38 (*R*)
9	**58**	Ph	PMP	Toluene	84	49 (*S*)
10	**59**	Ph	PMP	Toluene	76	0

[a] Reaction carried out at -20 ^{o}C

Table 1.10: Reduction of ketimines with amino acid derived formamides.

A range of formamide derived organocatalysts were developed by Sun, **60** – **63**, and shown to be effective for the reduction of ketimines with trichlorosilane (Chart **1.9**).[53,59-61] The most successful was shown to be **63**, a formamide derivative of L-pipecolinic acid. Similar to the reactivity of ketones (Table **1.7**), formamide **63** effectively reduced not only aromatic ketimines, but aliphatic ketimines as well, in high yield and selectivity (Table **1.11**). Sun suggested that the reaction could not proceed through the analogous transition state as for ketone reduction (Figure **1.6**) due to steric repulsion between the *N*-aryl moiety and catalyst methoxy group. Instead it was suggested that the reduction of ketimines proceeds via a hexacoordinate silicon species (Figure **1.8**).



60 **61** **62** **63**

Chart 1.9: Organocatalysts developed by Sun.

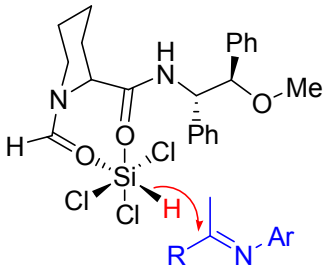
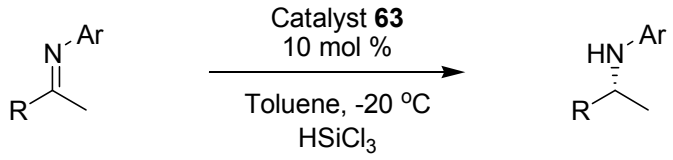


Figure 1.8: Proposed transition state for reduction of ketimines with **63**.

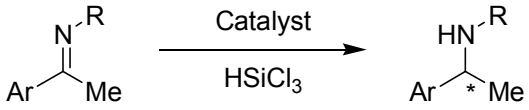


Entry	R	Ar	Yield (%)	ee (%)
1	Ph	Ph	94	93 (*R*)
2	Ph	PMP	93	89 (*R*)
3	4-MeO-C_6H_4	Ph	96	93 (*R*)
4	4-CF_3-C_6H_4	Ph	98	88 (*R*)
5	*c*-C_6H_{11}	Ph	93	92 (*R*)
6	*i*-Pr	Ph	93	89 (*R*)

Table 1.11: Reduction of ketimines with formamide **63**.

1.4.3 Oxazoline Promoted Reduction

In conjunction with their studies of pyridine-oxazoline promoted reduction of ketones, Malkov and Kocovsky described the reduction of ketimines with catalyst **47**.[54] A small range of aromatic ketimines were converted to their corresponding amines in high enantioselectivity (≤87%, Table **1.12**). A similar mechanism to the reduction of ketones was proposed, with the *N*-aryl moiety replacing Cl_3SiH coordinated to oxygen in the transition state (Figure **1.9**).



Entry	Ar	R	Yield (%)	ee (%)
1	Ph	Ph	65	87
2	Ph	PMP	60	85
3	2-naphth	PMP	67	86

Table 1.12: Reduction of ketimines with pyridine-oxazoline **47**.

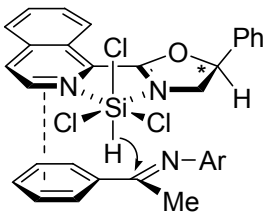


Figure 1.9: Proposed transition state for reduction of ketimines with **47**.

1.5 Conclusions

The past decade has seen considerable advancement in the field of organocatalysis. A vast number of small organic molecules have been reported as catalytic activators of asymmetric organic reactions. A number of these organocatalysts may offer a viable alternative to traditional metal based catalysis due to the reported high yields and high enantioselectivity. Although some organocatalysts may have some foreseeable industrial or commercial applications the field still suffers from several drawbacks.

Many organocatalysts are reaction specific and subtle changes in the catalytic structure can often render the organocatalyst completely inactive. Although general structural motifs can be identified and used as building blocks for new organocatalysts there are few examples of general organocatalysts. Only proline seems to have any great ability to be active for a number of different reactions, however even proline is limited to reactions involving an enamine as the reactive species.

Substrate specificity is another drawback of contemporary organocatalytic reactions. With the exception of formamides **23** and **43**; the organocatalysts reviewed within are dependant on aromatic substrates to obtain good selectivity. In addition high catalytic loadings are often required compared to those used by metal catalysts.

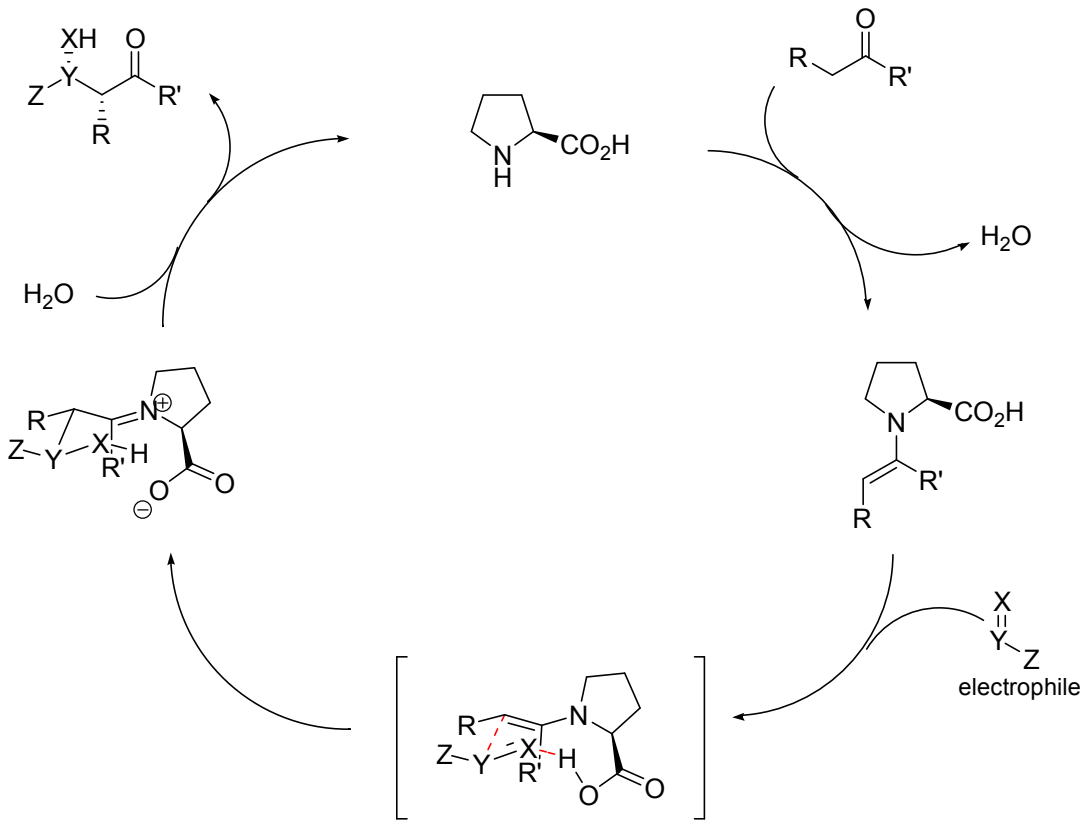
These drawbacks can be capitalised on to improve the field of organocatalysis. By endeavouring to develop more active organocatalysts it may be possible to lower catalyst loadings, improve substrate tolerance and increase crossover between different reactions. In this way it should be possible to make organocatalysis a practicable alternative to metal based catalysis.

2 Bifunctional Organocatalysts

2.1 Introduction

Organocatalysts can act by coordination/activation of substrate or reagent as discussed above. However another class of organocatalysts exists, which may activate both reagent and substrate at the same time. These bifunctional organocatalysts allow the substrate and the reagent to be brought close together and held in a specific geometry, mimicking the closed transition states of intramolecular reactions. In this way, the use of bifunctional organocatalysts often exhibits a greater stereocontrol and an improved reactivity compared to monodentate organocatalysts.

The simple amino acid proline has emerged in recent years as one of the most effective organocatalysts for a wide number of bond forming reactions, in particular at the position α to the carbonyl group in aldehydes and ketones.[9,18,62] It is now widely accepted that proline acts as a bifunctional organocatalyst involving both amine and carboxyl groups in the reaction pathway.[63] The amine group is involved in generation of a nucleophilic enamine intermediate after undergoing condensation with the carbonyl group of the substrate. The electrophile is then activated towards the nucleophilic attack by the enamine by H-bonding to the carboxylic acid group (Scheme **2.1**). In this way, dual activation of both the nucleophile and electrophile by the same molecule has led to the impressive generality of proline catalysis.



Scheme 2.1: Proposed mechanism for proline-catalysed conversions

A similar strategy has also been used in the stereoselective silylation of diols by exploiting the ability of silicon to form hypervalent species.[12,64] Hoyveda and Snapper *et al.* developed a simple amino acid based bifunctional catalyst for selective silylation of diols.[65,66] Lewis basic sites incorporated in the catalyst structure, a secondary amine and amide oxygen, allow the substrate diol to coordinate to the catalyst backbone. Generation of the activated hypervalent silicon species is mediated by the *N*-methylimidazole group integrated into the catalyst framework (Figure **2.1**). This facilitates quasi-intramolecular transfer of the electrophilic silicon moiety to the hydroxyl group.[66]

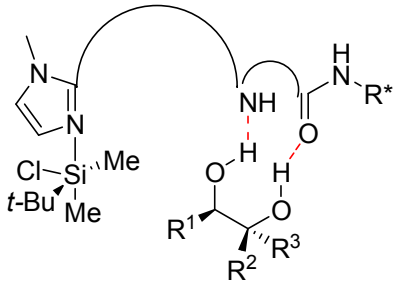
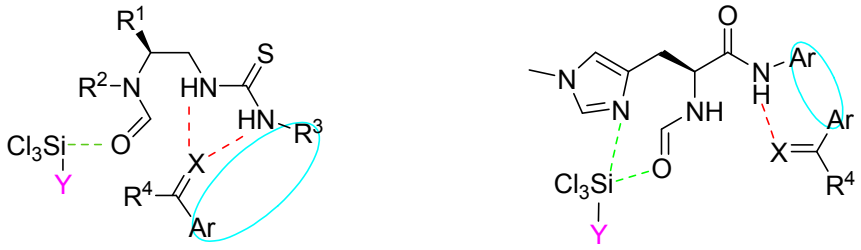


Figure 2.1: Proposed mechanism of catalyst activation of silanes and diols.

Inspired by this we sought to develop a range of novel bifunctional organocatalysts.

2.2 Target Compounds

Amino acids are among the simplest chiral frameworks and as such were chosen as the foundation for the new organocatalysts. The naturally occurring α-amino acids are widely available and are relatively cheap. In addition both enantiomers are easily obtainable and many unnatural analogues are also available. Amino acids lend themselves to synthesis of bifunctional catalysts as they bear both an amino group and a carboxyl group making them easy to derivatise. The chiral core would accommodate a formamide group for coordination of silane reagents. Substrate coordination would be achieved by incorporation of a group capable of hydrogen bonding to oxygen or nitrogen; in our case a thiourea or amide moiety. As we intend to carry out reactions on aromatic ketones or imines, an aromatic group would also be present to aid organisation of the organocatalyst and substrate through possible π-π interactions (Scheme **2.2**).

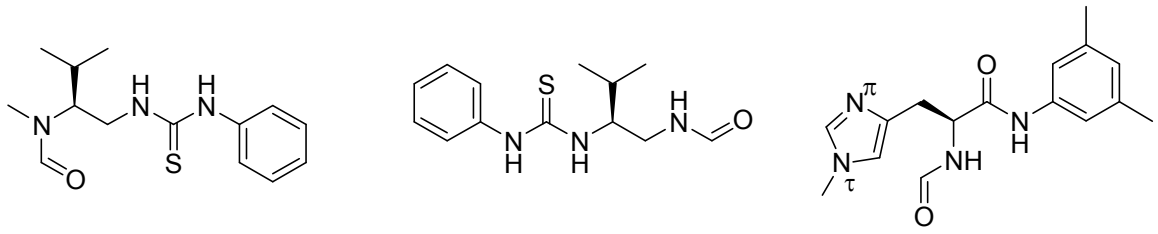


R^1 = Me, iPr, Ph; **R^2** = H, Me;
R^3 = Aromatic; **R^4** = H, Me;
X = O, NAr; **Y** = H, allyl, crotyl etc.

Scheme 2.2: Planned mechanism of action for bifunctional organocatalysts.

2.3 Synthesis

The initial targets were identified as compounds **64** to **66** (Chart **2.1**). The *N*-*α*-methyl group on target **64** is required to transmit the chirality of the amino acid scaffold closer to the reaction centre.[67] In target **65** this methyl group is not required as the formamide moiety is not adjacent to the chiral group. Imidazole is a known activator of silanes[11] and as such, histidine based catalyst **66** offers an additional coordination point for a silicon reagent. Methylation of the imidazole ring proved to be necessary as previous tests demonstrated that *N*-α-Boc-histidine formed an insoluble complex with trichlorosilane.



64 **65** **66**

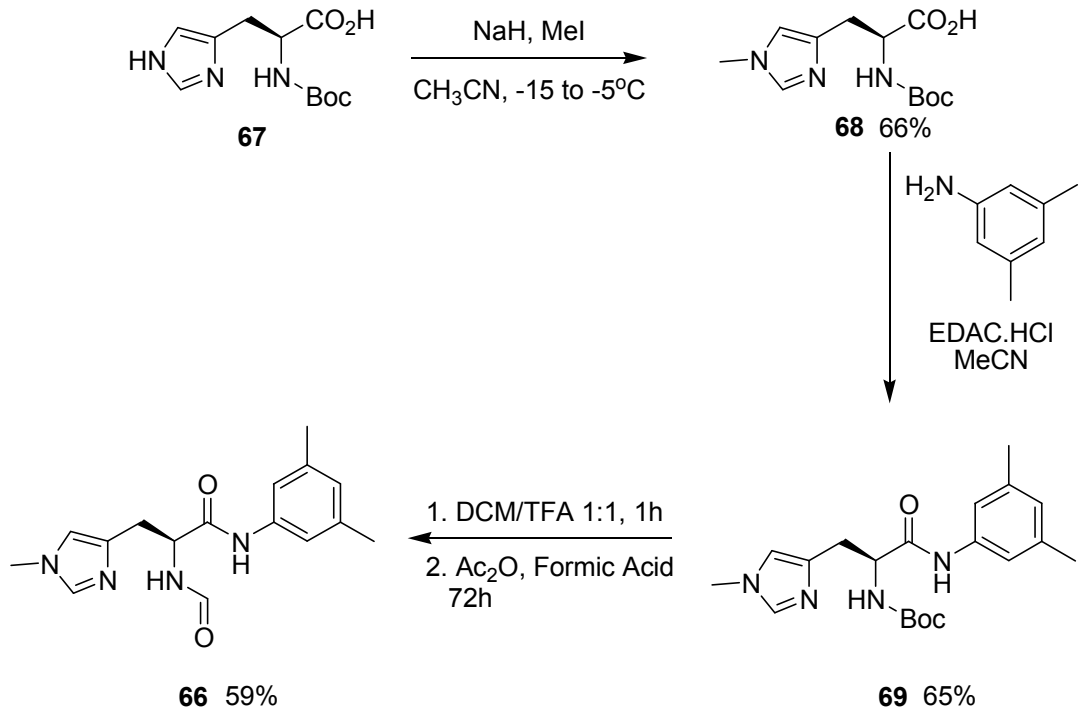
Chart 2.1: Target organocatalysts.

It is known that direct ring alkylation of histidine usually results in a mixture of τ(N-1) and π(N-3) alkylated products.[68] Generally alkylation at the τ(N-1) position is carried out by first protecting the π(N-3) position, as exemplified by Beyerman.[69] A recent report, however, showed that at low temperature *N*-α-Boc-histidine underwent selective deprotonation at the τ-(N-1) position using NaH in DMF,[70] which upon reaction with alkyl halides produced exclusively τ-alkylated products. Following this protocol, *N*-α-Boc-*N*-τ-methyl-histidine was obtained by deprotonation of *N*-α-Boc-histidine, **67**, with NaH in acetonitrile at -15 ^{o}C followed by reaction with methyl iodide. The desired *N*-α-Boc-*N*-τ-methyl-histidine, **68**, was isolated as pale yellow crystals in 66% yield (Scheme **2.3**).

Various coupling methods were tried to convert **68** to amide **69**. Coupling using the mixed anhydride method was unsuccessful. Coupling using DCC under standard conditions resulted in formation of the desired amide, **69**; however **69**

was found to be inseparable from the reaction by-product, DCU. To facilitate separation of the product from the coupling by-products, it was decided to switch to related carbodiimide EDC.HCL. The resulting urea is water soluble and therefore ought to be easily separated from the amide product by extraction. Carrying out the coupling step using EDC.HCL, HOBT and NMM resulted in formation of the desired amide, **69**. Purification was easily accomplished by aqueous extraction of the reaction by-products followed by column chromatography to furnish **69** in 65% yield.

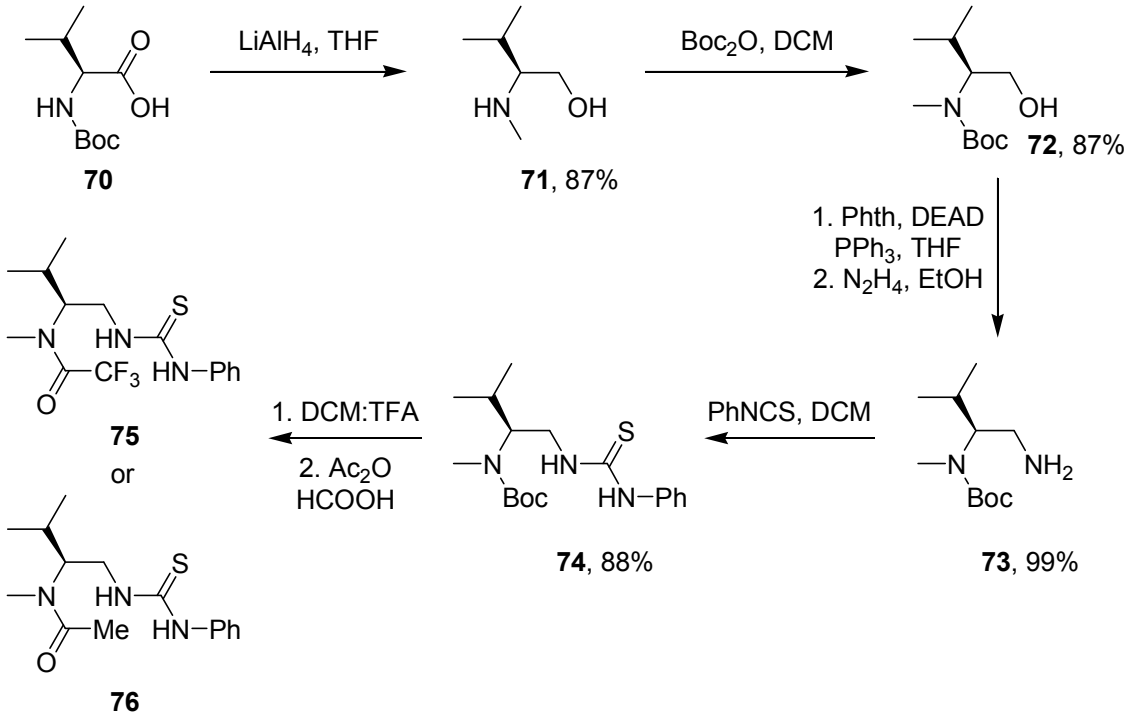
Further investigation showed that EDAC.HCl could be utilized without employing other reagents, such as HOBT and NMM, thus simplifying the reaction procedure. The *N*-Boc group was then removed with TFA in CH_2Cl_2 and converted to the formamide, **66**, using a mixture of acetic anhydride and formic acid. The target catalyst, **66**, was obtained in 59% yield.



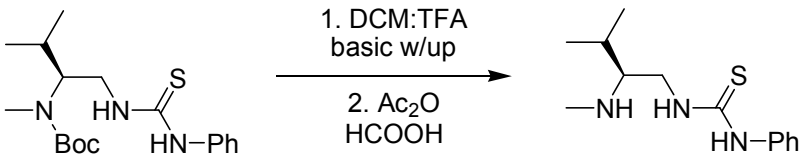
Scheme 2.3: Synthesis of *N*-α-formyl histidine derivative.

Synthesis of thiourea derived catalyst **75** began with reduction of Boc-valine to afford **71**, followed by *N*-Boc protection to generate *N*-Methyl-*N*-Boc valinol, **72**,

in good yield (87%). Conversion of the alcohol to an amine was achieved by introduction of a phthalimide group via the Mitsunobu reaction. This was then easily removed with hydrazine hydrate in ethanol to give the required amine, **73**, in 99% yield over two steps. Treatment of the free amine **73**, with phenyisothiocyanate afforded thiourea **74** in good yield, 88%. Deprotection of the amine was achieved under standard TFA conditions. Formylation with acetic anhydride and formic acid unexpectedly yielded either trifluoroacetamide **75**, or acetamide **76** (Scheme **2.4**). Since the deprotected amine was isolated as the TFA salt it was thought that this was interfering in the formylation reaction. Washing the crude deprotection mixture with a basic solution would remove any TFA and allow formation of the formamide, however when this was attempted only the amine **77** was isolated after 24h (Scheme **2.5**). Attempts to generate the desired compound by treatment with acetic formic anhydride were also unsuccessful.



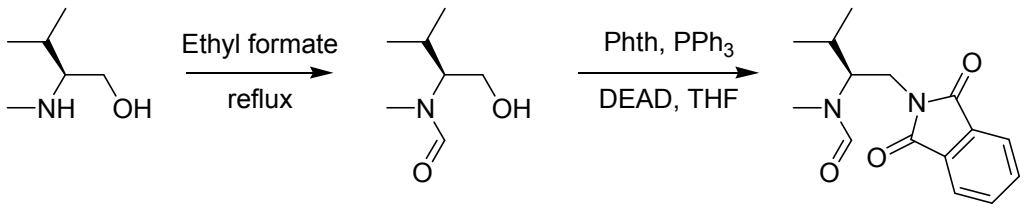
Scheme 2.4: Synthesis of valine-thiourea derivative.



74 **77**

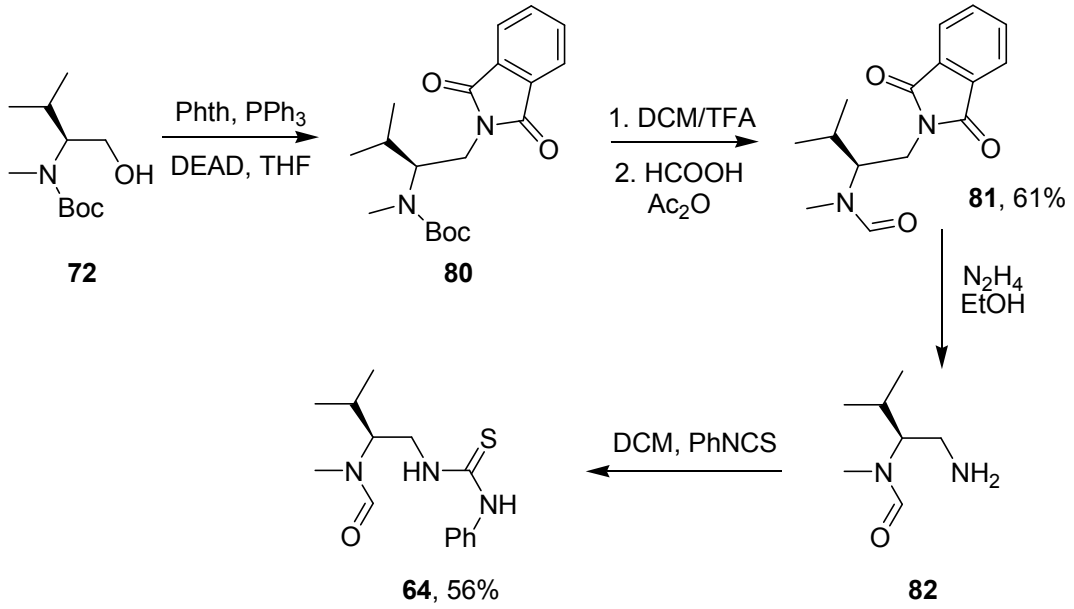
Scheme 2.5: Attempted formylation of **74**.

It was thought that formylation of *N*-methyl valinol instead of Boc protection would circumvent the problems with formylation later in the synthesis (Scheme **2.6**). Formylation of *N*-methyl valinol, **71**, by refluxing overnight in ethyl formate afforded the desired product, **78**, in excellent yield (99%). The phthalimide group was then introduced using the Mitsunobu protocol however it was discovered that **79** was inseparable from the reaction by-products. It was found that to successfully synthesise and isolate the target catalyst **64;** the deprotection/formylation step had to occur between the Mitsunobu and phthalimide removal steps. *N*-Me-*N*-Boc valinol was converted to phthalimide derivative **80** under Mitsunobu conditions. Deprotection of the Boc group and formylation was carried out under standard conditions to afford **81**. Removal of the phthalimide group to reveal the amine **82** was effected with hydrazine in ethanol. Treatment of *N*-Me-*N*-formyl valamine **82** with phenylisothiocyanate yielded the desired compound **64** in 56% yield (Scheme **2.7**).



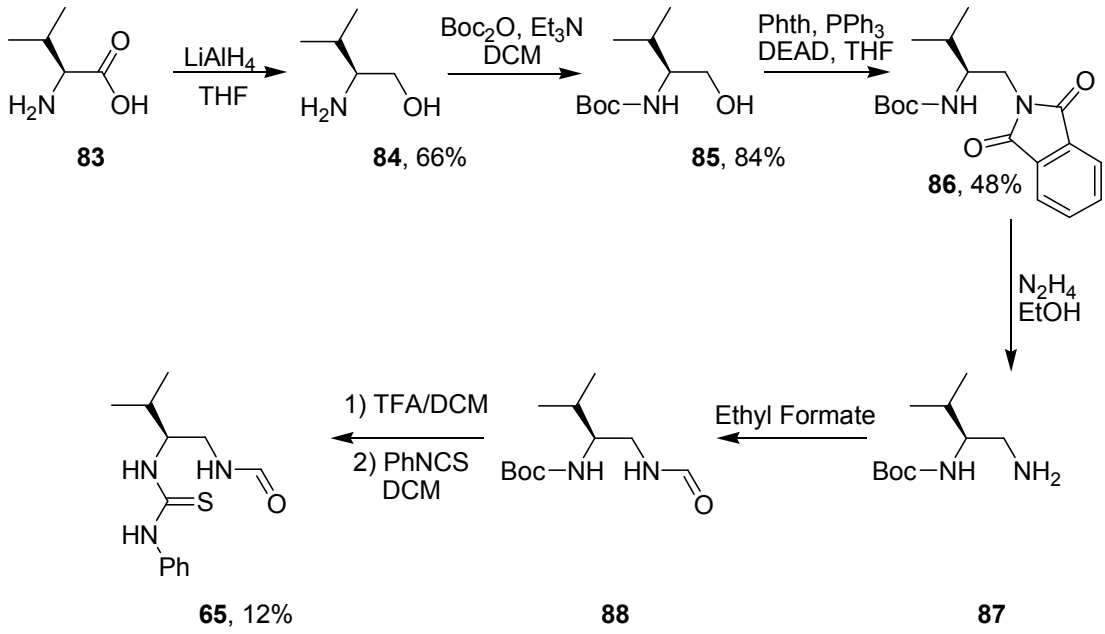
71 **78**, 99% **79**

Scheme 2.6: Alternative formylation protocol.



Scheme 2.7: Synthesis of thiourea derivative **64**.

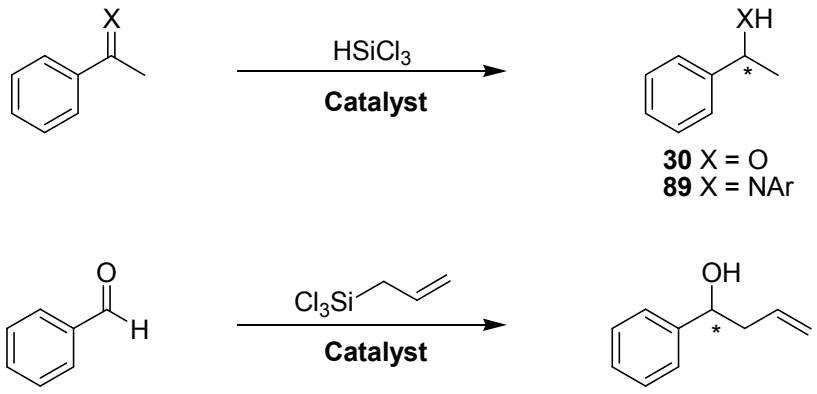
The synthesis of thiourea derivative **65** commenced with reduction of L-valine, **83**, with $LiAlH_4$ (Scheme **2.7**), which afforded L-valinol, **84**, in 66% yield. Protection of the amine was carried out with di-*tert*-butyl dicarbonate in the presence of triethylamine, to afford the protected amino alcohol, **85**, in 84% yield, which was then converted to the phthalimide derivative, **86**, by Mitsunobu reaction in 48% yield. Phthalimide deprotection by hydrazine hydrate in ethanol yielded the mono protected diamine **87**. The formamide derivative, **88**, was obtained by refluxing the mono protected diamine in ethyl formate. The Boc group was then removed with a TFA/DCM mixture (1:2) and the amino formamide treated with phenylisothiocyanate to afford catalyst **65** in 12% yield from **88**.



Scheme 2.8: Synthesis of thiourea derivative **65**.

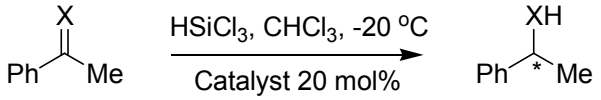
2.4 Application in Model Catalytic Reactions

Allylation of aldehydes and reduction of ketones and imines are reactions that can be carried out using silane reagents.[18] The synthetic versatility of the chiral end-products of these reactions has prompted investigation into an organocatalytic protocol. With this in mind it was proposed that the prospective catalysts would be tested in the reduction of ketones and ketimines with trichlorosilane, and allylation of aldehydes with allyltrichlorosilane respectively (Scheme **2.9**).



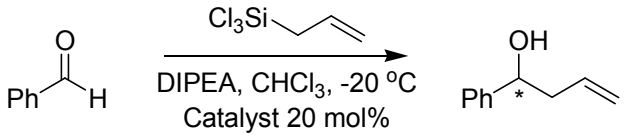
Scheme 2.9: Model catalytic reactions.

Reduction of acetophenone **29** and a simple ketimine with thiourea catalyst **64** (20% catalyst loading) in both cases gave the product in 40% yield, however no enantioselectivity was observed. Catalyst **65** proved to be less reactive in the reduction reactions, the observed yields were 20%, however some selectivity was observed for the reduction of acetophenone, 10% ee, highlighting the importance of having the thiourea moiety next to the stereogenic centre. Reduction using histidine catalyst **66** did not proceed and only starting material was isolated. Disappointingly, none of the catalysts exhibited activity in the allylation of benzaldehyde; only 5% product was isolated for catalysts **64** and **66**.



Entry	X	Catalyst	Yield (%)	ee (%)
1	O	**64**	40	-
2	N-PMP	**64**	40	-
3	O	**65**	20	10
4	N-PMP	**65**	20	-
5	N-PMP	**66**	-	-

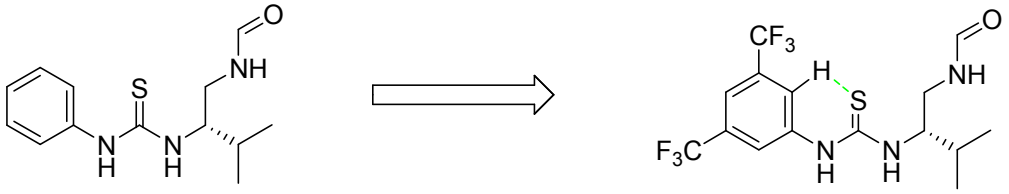
Table 2.1: Reduction test reaction results.



Entry	Catalyst	Yield (%)	ee (%)
1	**64**	5	-
2	**65**	-	-
3	**66**	5	-

Table 2.2: Allylation test reaction results.

Although the thiourea catalysts were equally active for reduction of both ketones and ketimines the conversion was too low to be considered active enough to carry on. It was thought that replacement of the thiourea-phenyl group with a 3,5-trifluoromethylphenyl group would improve reactivity and selectivity through stabilisation of the thiourea conformation. It has been shown that when the *ortho* hydrogen atoms are more positively polarized due to *meta* electron withdrawing groups they form hydrogen bonds to the sulfur atom hindering the rotation of the phenyl group (Scheme **2.10**). This increases the rigidity of the structure and has been shown to increase the binding ability of the thiourea fragment.[71,72] Attempts to introduce the 3,5-bistrifluoromethylphenyl group to the catalyst, as in **90**, did not yield enough material to be used. Histidine derived catalyst **66** was not considered promising enough to be carried on, thus alternative structural motifs were sought.



65 **90**

Scheme 2.10: Attractive S-H interaction

2.5 Phosphoramide Targets

Phosphoramide groups can be used as a coordinating group alternative to formamides for activation of silicon reagents. Our new catalyst design included this as well as an aromatic amide group to promote hydrogen bonding and possibly aromatic interactions between the catalyst and substrate. A selection of intended catalyst structures is shown in Chart **2.2**.

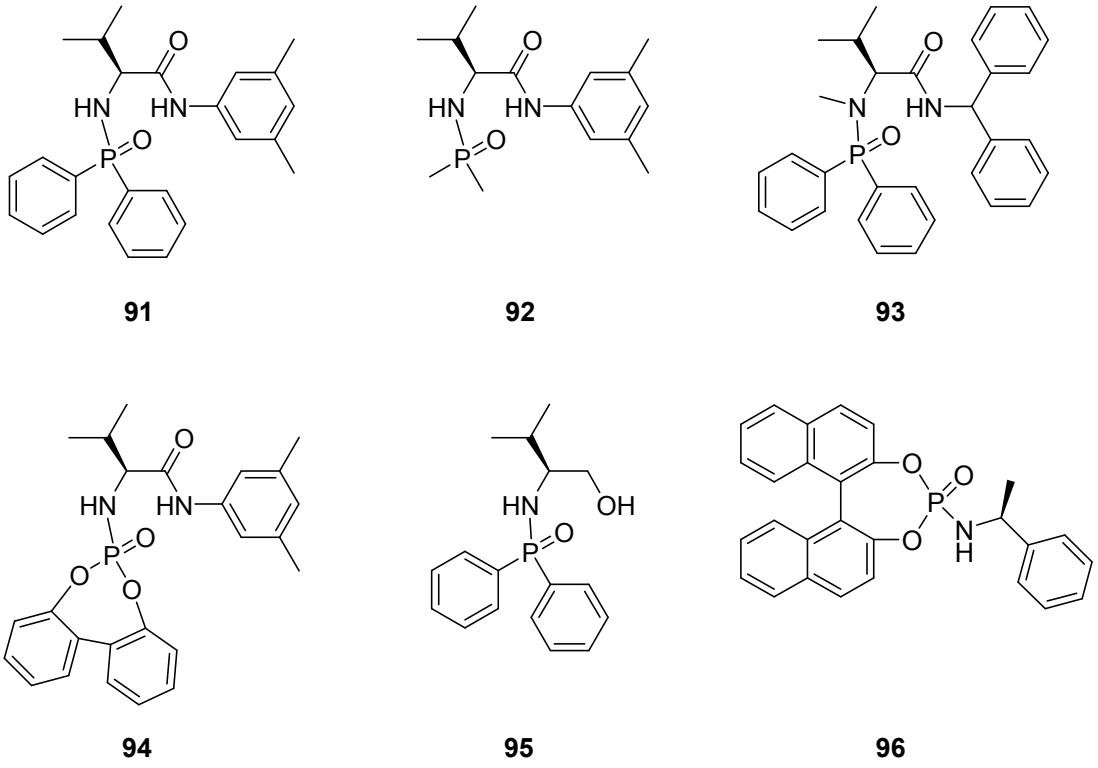
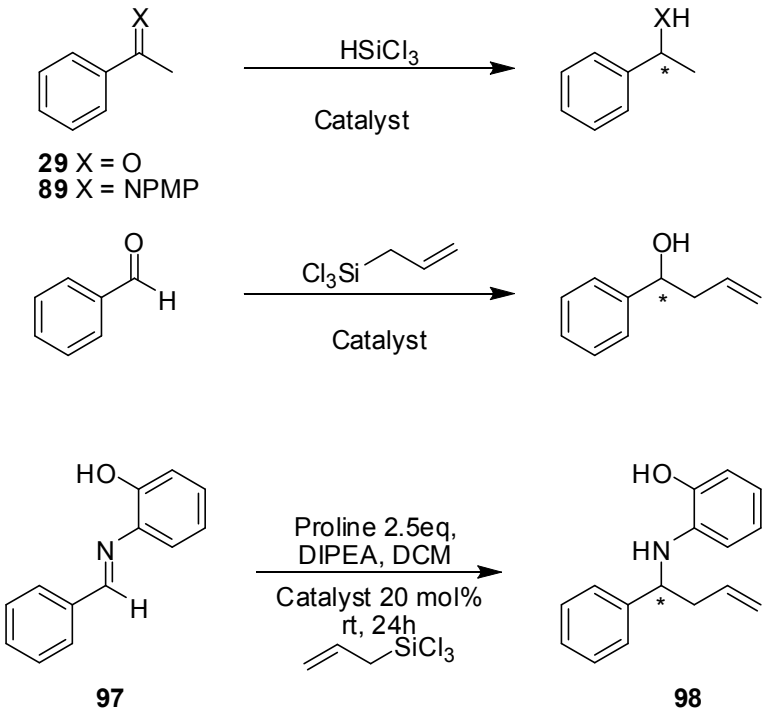


Chart 2.2: Phosphoramide based catalysts.

Initial catalytic tests were carried out using catalyst **91** which was assessed in the reduction of **29** and **89** and the allylation of benzaldehyde **6**. Additionally **91** was also tested in the allylation of 2-hydroxyphenyl imine **97** following the publications by Kobayashi[73] and Tsoegova[74] (Scheme **2.11**).

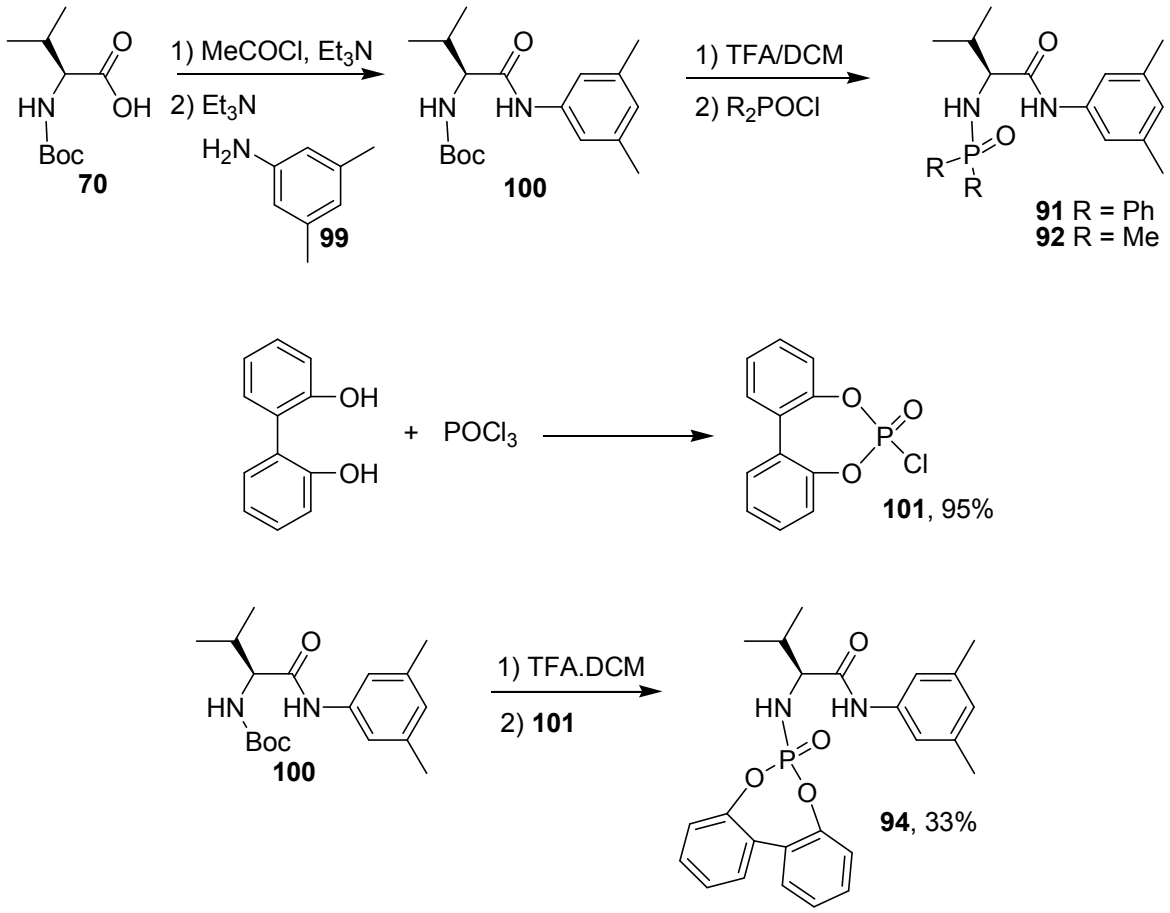


Scheme 2.11: Test reactions for proposed phosphoramide organocatalysts.

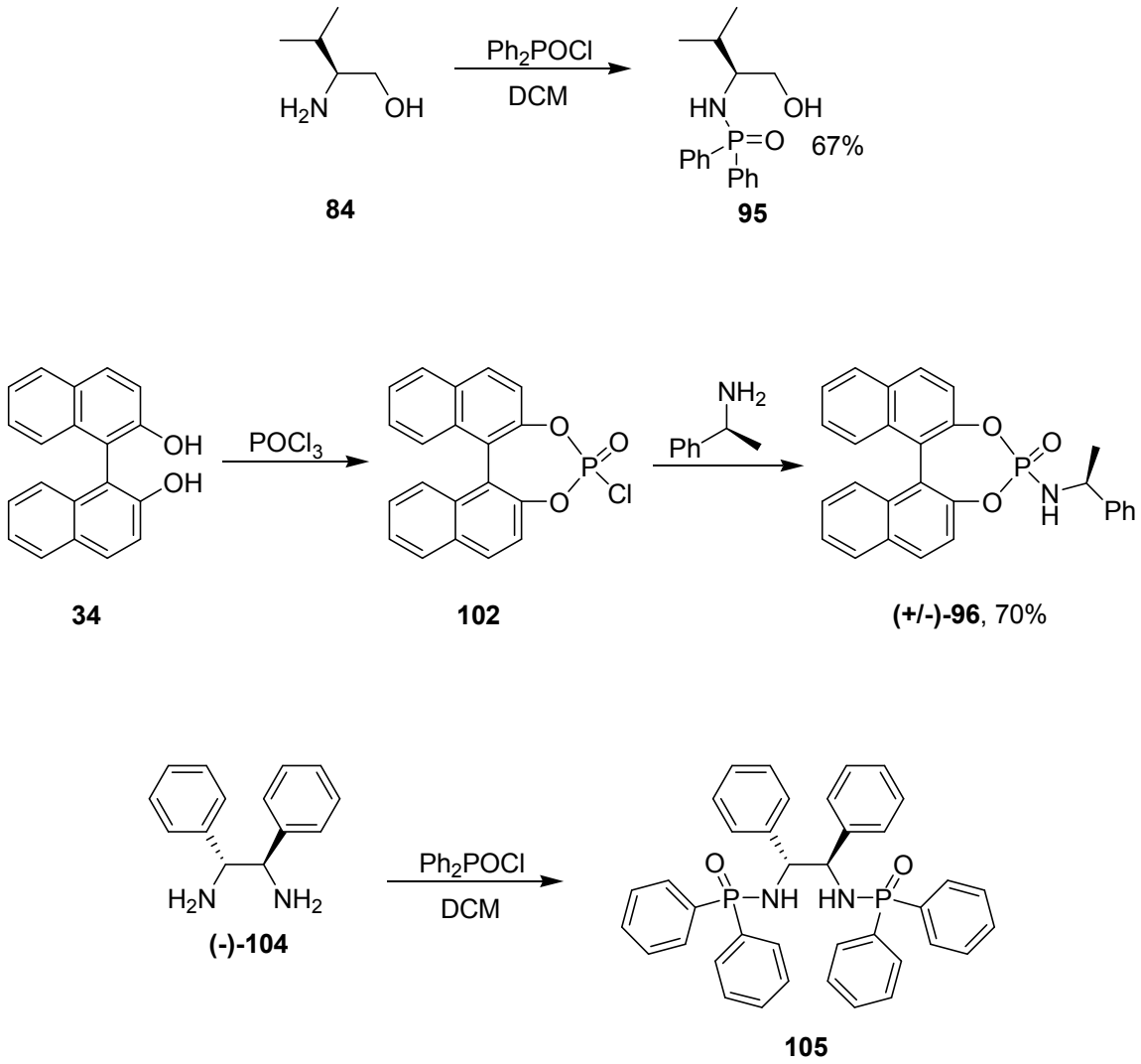
2.6 Synthesis

The synthesis of valine-derived organocatalysts **91** and **92** began with coupling of *N*-Boc valine, **70**, to 3,5-dimethylaniline, **99**, employing the mixed anhydride method to afford amide **100** (Scheme **2.12**). The resulting amide was then treated with TFA in DCM to remove the Boc protecting group. Treatment of the deprotected material with diphenylphosphinic acid chloride and dimethylphosphinic acid chloride yielded **91** and **92** respectively. Ligand **93** was synthesised in an analogous manner with benzhydrylamine, both **92** and **93** were available in our lab. Treatment of 2,2'dihydroxy biphenyl with trichlorophosphine afforded **101**. Ligand **94** was obtained by treating amide **100** with **101** after Boc deprotection (Scheme **2.12**).

Catalyst **95** was obtained in 67% yield by treating valinol, **84**, with diphenylphosphinyl chloride (Scheme **2.13**). The synthesis of catalyst **96** commenced with conversion of racemic binol to the corresponding phosphoryl chloride **102**. Treatment of **102** with (*S*)-methylbenzylamine, **103**, generated the phosphoramide **96** in 70% overall yield. Resolution of the diastereomers was carried out by recrystallisation from ethanol. Finally, ligand **105** was synthesised from enantiopure diamine **104** and diphenylphosphinylchloride; recrystallisation from toluene afforded the pure phosphoramide in 72% yield (Scheme **2.13**).



Scheme 2.12: Synthesis of Phosphorous containing ligands.

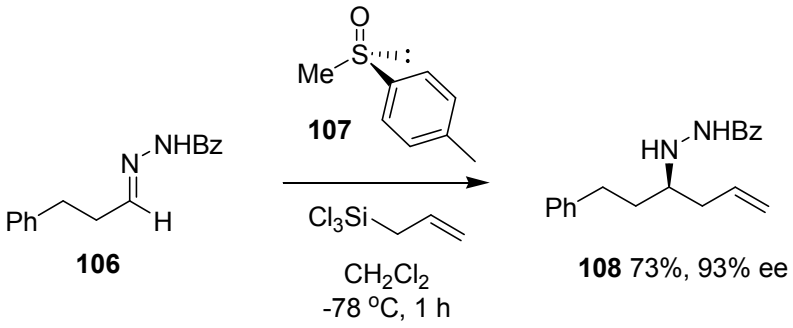


Scheme 2.13: Synthesis of diastereomeric phosphorous ligands.

2.7 Allylation at C=N

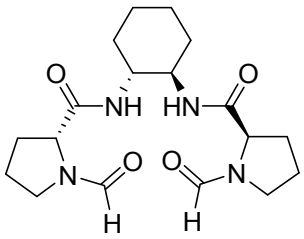
Allylation of imines is an important C-C bond forming reaction as it leads to the generation of chiral amines which represent synthetically useful intermediates for many applications.[75,76] However, it is one of the few reactions that has remained solely in the realm of transition metal catalysis and to date there has been no publication of a true organocatalytic reaction for the allylation of aldimines.[2,18] Recent advances are pushing closer to development of an organocatalytic protocol for this elusive reaction.[39,74] Although not purely catalytic, some organic molecules have emerged as good activators of allylsilanes when employed in stoichiometric quantities.[2,18,39,74]

Work carried out by Kobayashi showed that allylation of acylhydrazones derived from aldehydes with allyltrichlorosilane could be achieved in the presence of neutral coordinate organocatalysts (NCOs). It was shown that NCOs such as DMF and HMPA were able to efficiently promote the racemic reaction when used as solvent.[39] Further development identified sulfoxides as another NCO capable of promoting the reaction; in particular the use of a chiral sulfoxide resulted in an asymmetric reaction taking place.[73] By using chiral sulfoxide **107** at a loading of 300 mol%, chiral amine derivative **108** was obtained in 73% yield and 93% ee (Scheme **2.14**). While *N*-acylhydrazones showed good reactivity in the allylation reaction, simple aldimines remained unreactive towards allyltrichlorosilanes.

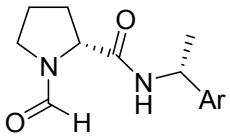


Scheme 2.14: Asymmetric addition of allylsilanes to acylhydrazones with NCO's.

More recently a chiral bisformamide **109**, (Chart **2.3**) has emerged as a stoichiometric activator for the allylation of simple aldimines.[74] Tsogoeva *et al* showed that aldimines derived from benzaldehyde and 2-aminophenol could be successfully converted to allylic amines by using allyltrichlorosilane in the presence of bisformamide **109** in conjunction with L-proline. Homoallylic amines were formed in good yield (>89%) and high selectivity (≤85%), however 2 equivalents each of bisformamide **109** and L-proline are required (Table **2.3**, entries 1 – 4). It was suggested that proline forms a chiral silane reagent in situ, **113**. This silane complex is then able to coordinate both the imine through the aromatic hydroxyl group and bisformamide **109** to generate the chiral transition state (Figure **2.2**). In the absence of the 2-hydroxyl group no reaction occurs, supporting the interaction with silicon. Further studies with monoformamides **110** (Chart **2.3**) showed that the second formamide group is integral to the selectivity observed with **109**[77]. Based on these results, Tsogoeva proposed a transition state involving a hexacoordinate silicon species. It was suggested that the imine was activated by forming a bond with silicon through the *ortho*-hydroxy group; coordination of a formamide moiety to silicon results in a hypervalent silicon species with enhanced nucleophilicity (Figure **2.2**).

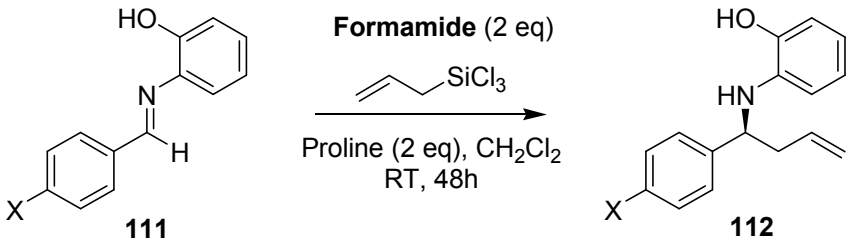


109



110a Ar = Ph
110b Ar = naphth

Chart 2.3: Formamide catalysts developed by Tsogoeva.



Entry	X	Yield (%)	ee (%)
1	NO_2	94	85
2	CF_3	91	81
3	Cl	89	85
4	OMe	94	68

Table 2.3: Allylation of imines with allyltrichlorosilane and bis-formamide activator.

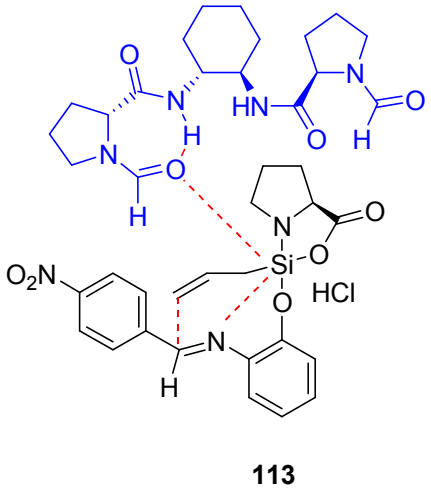
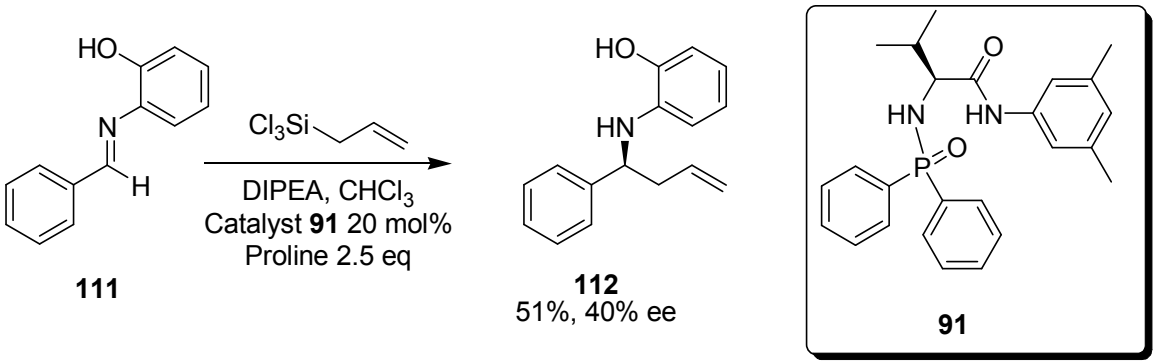


Figure 2.2: Transition state proposed by Tsogoeva

2.8 Applications in Model Catalytic Reactions

Phosphoramide **91** showed some promise in the allylation of aldimine **111** with allyltrichlorosilane, forming the chiral amine in 51% yield and 40% ee with catalyst loading 20 mol% (Scheme **2.15**). Unfortunately, the catalyst **91** turned out to be inactive in the allylation of aldehydes or reduction of ketones and ketimines.



Scheme 2.15: Organocatalytic allylation reactions with **91** as organocatalyst.

Variation in the temperature of the reaction identified room temperature as the optimum (Table **2.4**). Surprisingly, when the reaction mixture was cooled, selectivity also dropped. It may be that at lower temperatures an uncatalysed reaction mechanism may be favoured over the more selective pathway. The additive was found to be required for enantiodiscrimination (Table **2.5**, entry 1). A range of additives other than (L)-proline were also examined (Table **2.5**). In the presence of *N*-methyl imidazole, *iso*-propanol and dimethylaminopyridine the desired *sec*-amine was formed in moderate yields however the enantioselectivity was much lower than that observed for proline (Table **2.5**, entries 2-4). In the case of (D)-proline (Table **2.5**, entry 5), the opposite enantiomer of *sec*-amine **112** was formed in good yield (61%) and similar selectivity (38%), indicating that proline is involved in the enantiodifferentiation process in the transition state. Additionally the allylation of **111** did not proceed in the absence of di-isopropylethylamine.

Entry	Temperature (°C)	Yield (%)	ee (%)
1	-20	N.A.	N.A.
2	0	44	20 (*S*)
3	rt	51	40 (*S*)

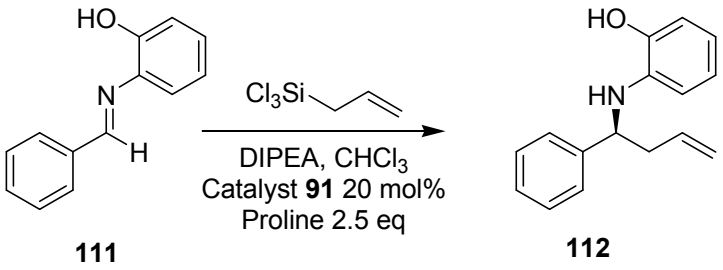
Table 2.4: Effects of temperature on catalytic allylation reaction.

entry	catalyst	activator	yield (%)	ee (%)
1	**91**	none	44	0
2	**91**	NMI	58	13 (*S*)
3	**91**	^{i}PrOH	59	11 (*S*)
4	**91**	(D)-proline	61	38 (*R*)
5	**91**	DMAP	20	0

Table 2.5: Activators for allylation reaction.

After identifying a set of optimum conditions a range of other chiral nitrogen-phosphorous ligands were tested in the allylation of aldimine **111** (Table **2.6**).

A number of structural changes were made to the parent catalyst **91** (Chart **2.2**). Posphinamide **92** where Ph_2P moiety was replaced with Me_2P resulted in a significant decrease in selectivity. Likewise, phosphate derivative **93** was active, however not as selective as **91**. The important role of the aromatic amide moiety present in **91** was demonstrated by the reduced selectivity observed with catalyst **95**, which produced only racemic product. Attempts to tune selectivity by replacing the phenyl group with a larger aromatic moiety **93** were unsuccessful, resulting in a marginal drop in enantiodifferentiation. Diastereomeric phosphoramides **96**, derived from BINOL and **105,** did not succeed in the formation of **112**, identifying **91** as the superlative phosphoramide organocatalyst tested.



111 **112**

Entry	Catalyst	Yield (%)	ee (%)
1	**91**	51	40 (*S*)
2	**92**	70	7 (*S*)
3	**93**	54	30 (*S*)
4	**94**	0	0
5	**95**	0	0
6	**96**	0	0
7	**105**	0	0

Table 2.6: Effects of catalyst structure variation on catalytic allylation reaction.

2.9 Summary

Design and synthesis of a number of potential bifunctional organocatalysts incorporating imidazole, thiourea and phosphoramide moieties was successfully achieved. The organocatalysts were tested in the allylation and reduction reactions of carbonyl compounds and imines.

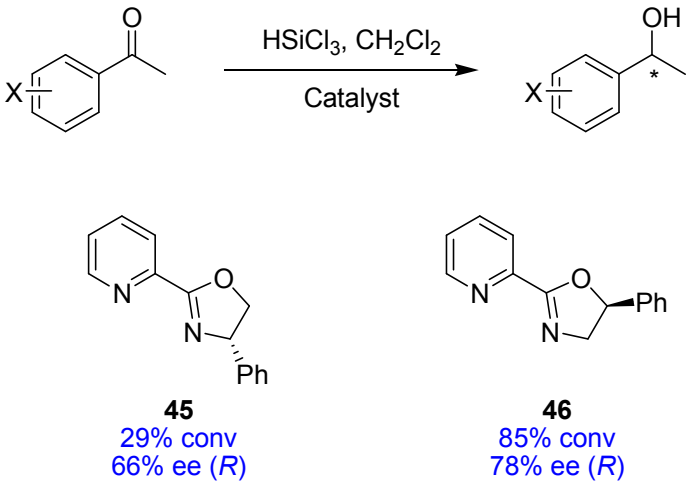
The greatest success was achieved by valine derived phosphoramide **91** which catalysed the allylation of imine **111** to homoallylic amine **112** in 40% ee with a loading of 20 mol%, the reaction hitherto reported only with the use of stoichiometric activators. Our other bifunctional ligands did not show much promise in the model test reactions, however they may still find use in other catalytic processes, so further testing to reveal potential applications is required.

3 Quinoline Derived Organocatalysts

3.1 Introduction and Target Compounds

Reduction of prochiral ketones and imines is most commonly carried out in industry via asymmetric hydrogenation. However this method is not free from problems, namely those associated with metal leaching, high pressure, and the cost of the catalyst and its regeneration. The alternative metal-free protocols are rare, however high selectivity has been attained with the use of formamide derivatives and trichlorosilane.[58]

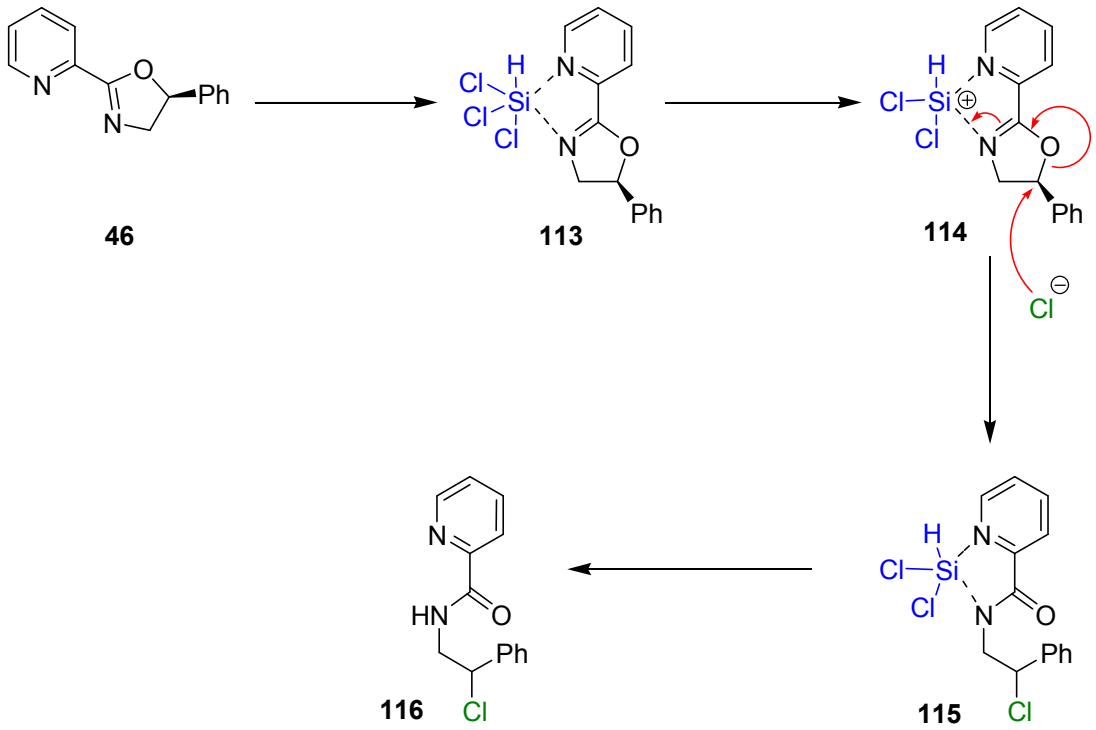
As part of our group's focus into Lewis-basic activators for silanes, (2-pyridyl) oxazolines were identified as an efficient class of catalysts for the reduction of ketones with trichlorosilane. A range of ketones were successfully converted to the corresponding secondary alcohols with high selectivity.[54] The initial results also showed the catalysts **45** and **46** were effective for the reduction of a small range of aromatic ketimines (Scheme **3.1**).



Scheme 3.1: Reduction of ketones with 2-pyridyl oxazolines.

Although catalyst **46** successfully reduced aromatic ketones and ketimines with high selectivity, in some cases it suffered from low conversion. Subsequent studies showed that the catalyst decomposed under the reaction conditions.

Bidentate coordination of the catalyst to trichlorosilane generates a hexacoordinate silicon species, **113**; a chloride can then dissociate to form a stable pentacoordinate silicon species, **114**. In this species, the Lewis acidic silicon activates the oxazoline towards nucleophilic attack. The dissociated chloride is able to attack at the benzylic position and leads to opening of the oxazoline ring, **115** (Scheme **3.2**).



Scheme 3.2: Decomposition of oxazoline derived catalyst.

Amide **116** was isolated from the reaction mixture and its structure was confirmed by spectroscopic data. The susceptibility of the oxazoline 5-position to nucleophilic attack is due in part to the electronegativity of oxygen. It was proposed that replacing the oxazoline moiety with thiazoline would prevent chloride promoted ring-opening as the decreased electronegativity of sulfur should reduce the propensity for nucleophilic attack at the benzylic position. Further, it was considered that replacement of oxygen with either an *N*-methyl group or a CH_2 group could also prevent ring-opening.

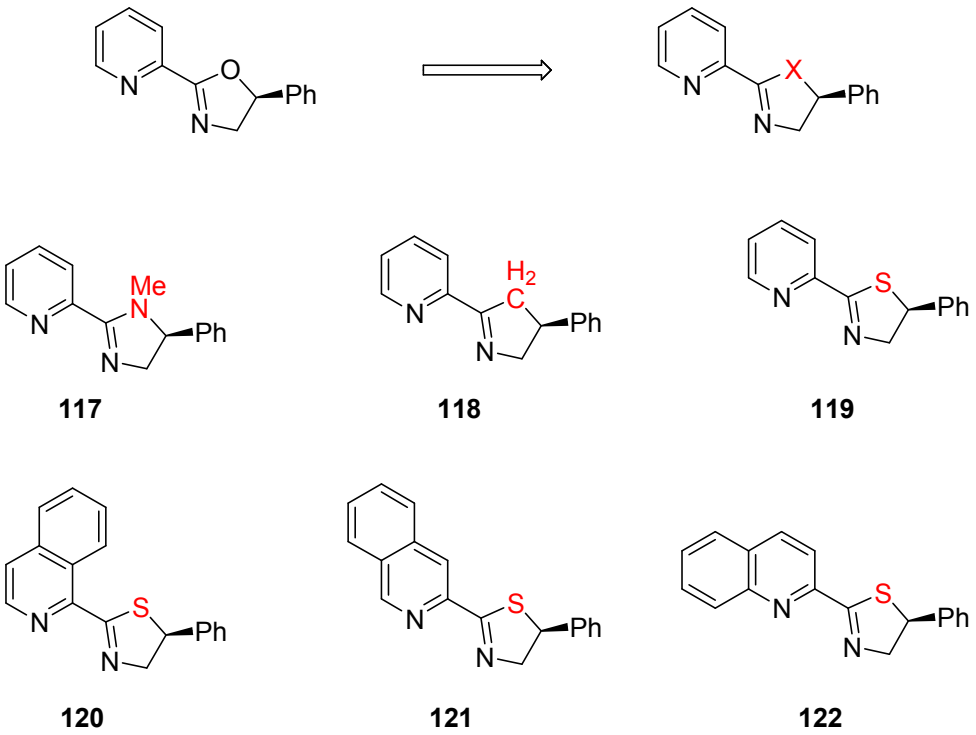
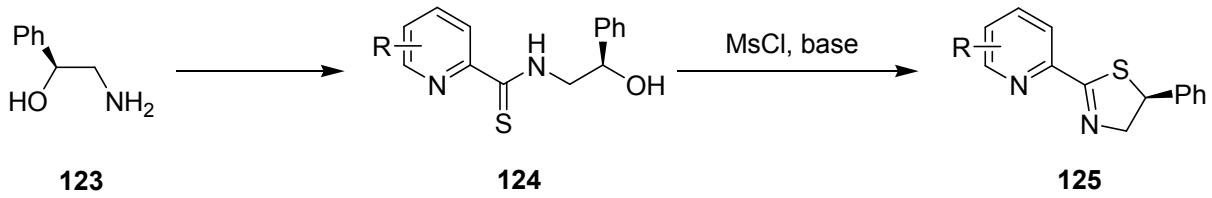


Chart 3.1: Alternatives to the oxazoline moiety for prevention of ring-opening.

To this end, we identified structures **117** to **122** as alternatives to **46** that would not be as susceptible to ring opening (Chart **3.1**). Pyridine imidazoline **117** was synthesized in our group and shown to be inferior to **46** as a promoter for the reduction of ketones. Reduction of acetophenone **29** with **117** afforded alcohol **30** in 17% conversion and 34% ee, compared with 40% conversion, 64% ee for the corresponding oxazoline under the same conditions.

3.2 Synthesis

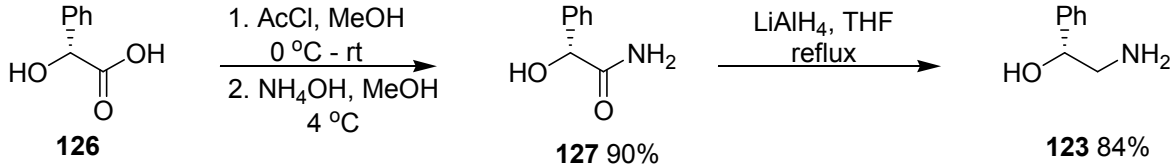
The synthesis of (2-pyridyl) thiazoline derivatives **119** to **122** was based on generation of the general thioamide **124** through coupling with mandelic acid derivative **123** followed by cyclisation with mesyl chloride (Scheme **3.3**).



123 **124** **125**

Scheme 3.3: General method for formation of thiazoline via cyclisation.

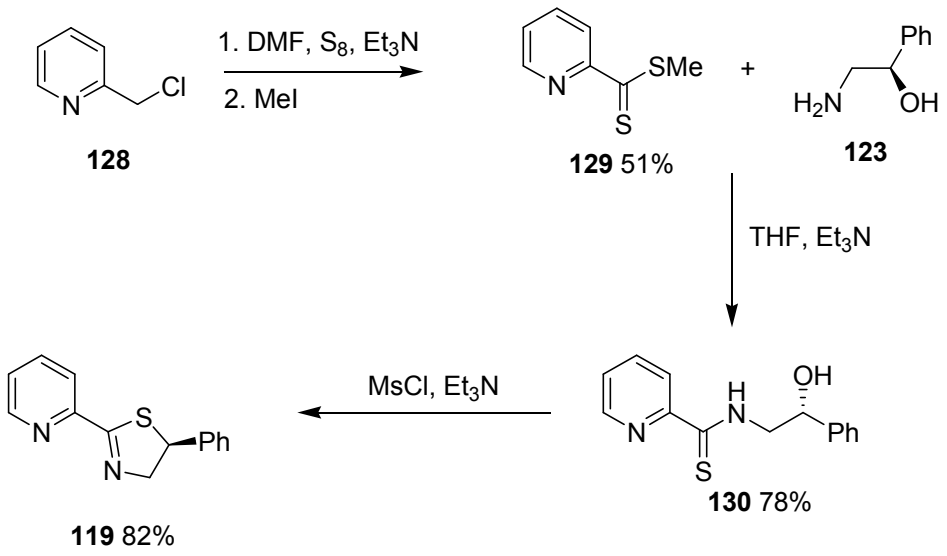
Amino alcohol **123** was generated from mandelic acid in a two-step process, according to the protocol developed by Brunner.[78] First, mandelic acid, **126**, was converted to mandelamide **127** in 90% yield. The resulting amide **127** was then reduced with lithium aluminium hydride in refluxing tetrahydrofuran to produce amino alcohol **123** in 84% yield (Scheme **3.4**).



126 **127** 90% **123** 84%

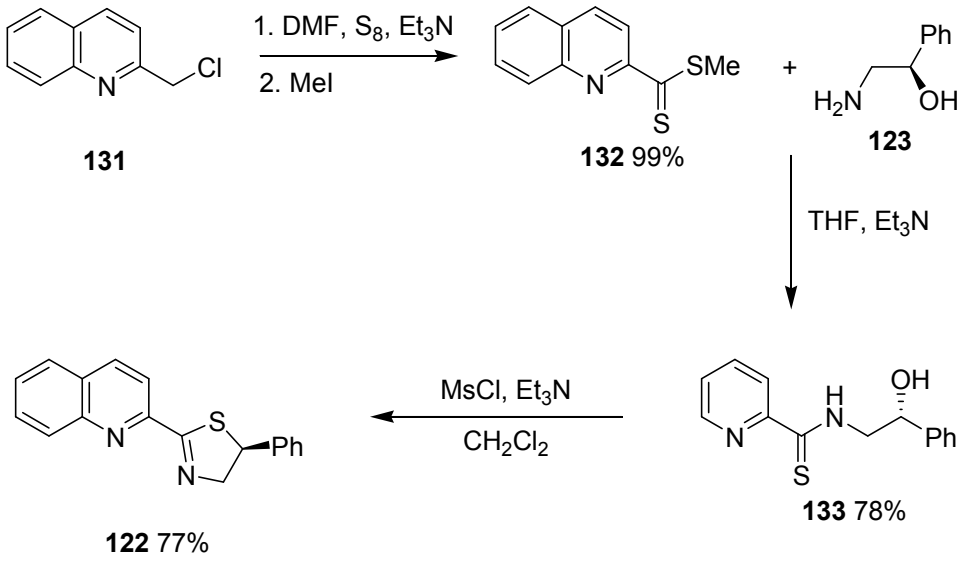
Scheme 3.4: Synthesis of mandelic acid derived amino alcohol.

Synthesis of pyridyl-thiazoline derivative **119** began with generation of thioester **129** from 2-chloromethylpyridine, **128**, sulfur and methyl iodide in 51% yield. The resulting thioester was then coupled with amino alcohol **123** in THF in the presence of triethylamine. Thioamide **130** was isolated in 78% yield. Cyclisation was then achieved by treating thioamide **130** with mesyl chloride, furnishing pyridine-thiazoline **119** in 82% yield as a white crystalline solid (Scheme **3.5**).



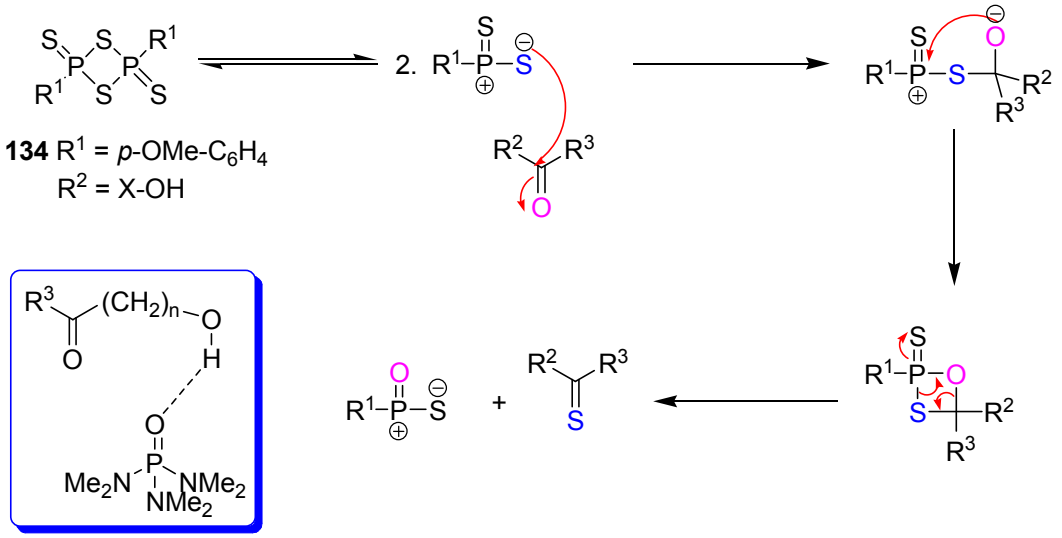
Scheme 3.5: Synthesis of 2-pyridyl thiazoline

Synthesis of (2-quinolyl) thiazoline **122** was carried out in analogous manner to **119**, beginning with generation of thioester **132** from 2-chloromethyl quinoline, **131** (99%). Thioester **132** was then coupled with amino alcohol **123** to yield thioamide **133** in 78% yield. Cyclisation was again achieved by treating thioamide **133** with mesyl chloride, furnishing 2-quinoline-thiazoline **122** as a black oil which yielded black crystals on recrystallisation from ethanol (77%, Scheme **3.6**).



Scheme 3.6: Synthesis of 2-quinolinyl thiazoline

Taking into account that 1-chloromethylisoquinoline is not readily available; 1-isoquinoline carboxylic acid, **135**, was identified as an alternative starting material. It was thought that coupling of the acid with amino alcohol **123** followed by thionation would result in the desired thioamide **136**. Lawesson's reagent, **134**, was chosen because it was shown to be superior to P_2S_5 for conversion of carbonyl groups to thiocarbonyl groups (Scheme **3.7**).[79,80] Lawesson also showed that HMPA could act as a non-covalent protecting group to prevent thionation of alcohols, thus preventing an additional two steps being carried out to prevent undesired thionation of the hydroxyl group.

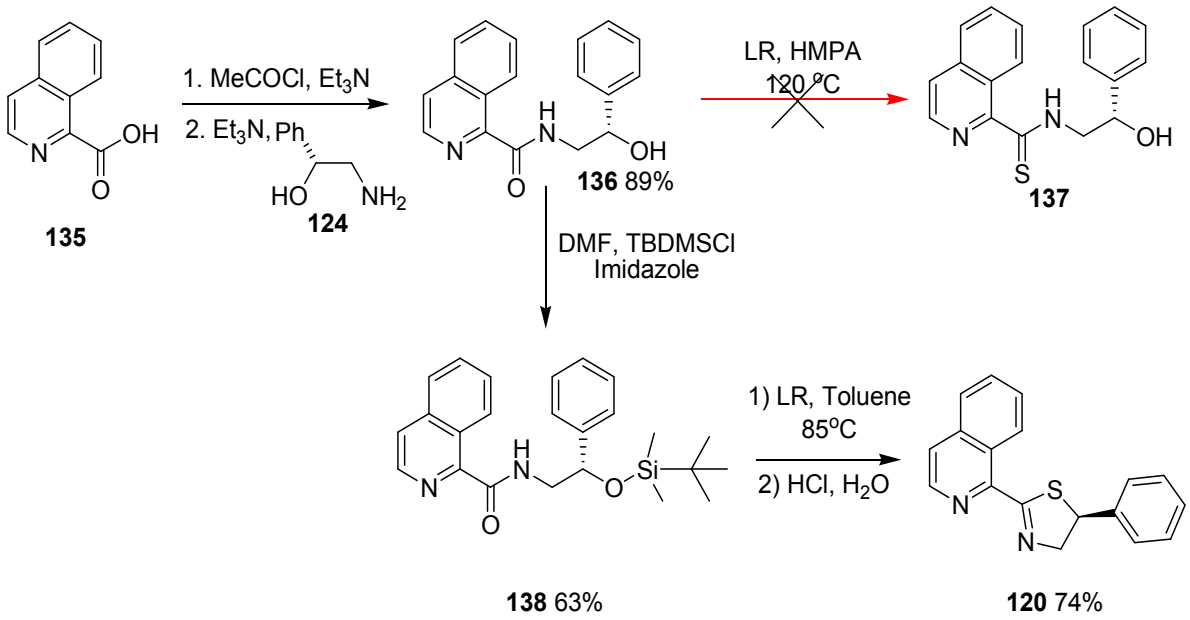


Scheme 3.7: Mechanism of action of Lawesson's reagent

Coupling of 1-isoquinoline carboxylic acid, **135**, with amino alcohol **123** was carried out using the mixed anhydride method and produced the amide **136** in 89% yield (Scheme **3.8**). Thionation of the amide with Lawesson's reagent was carried out in HMPA; however conversion to the desired thioamide **137** was very low, furthermore it could not be isolated from the crude reaction mixture. It is known that thionation with Lawesson's reagent is very sensitive to solvent and depends on the substrate therefore it was decided to investigate influence of different solvents.

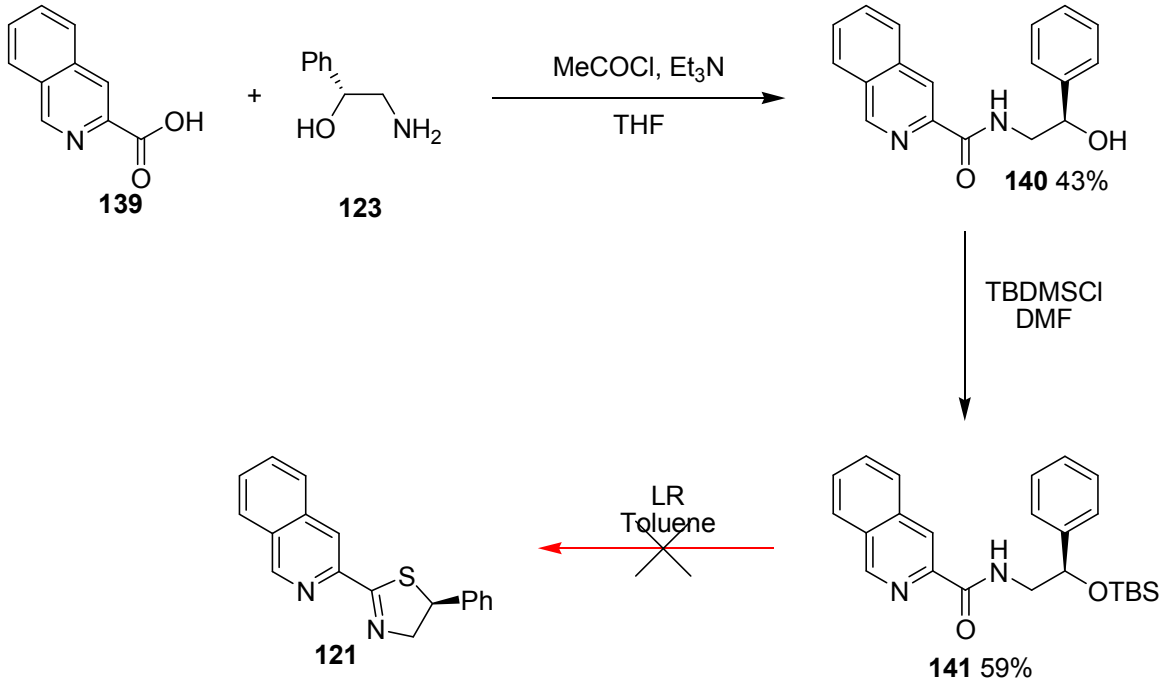
Toluene is known to be an efficient solvent for thionation using Lawesson's reagent and so was chosen as a starting point for solvent investigations. As HMPA would not be employed, the hydroxyl was protected with a TBS ether to afford **138**

(63%). The silylated compound was then subjected to Lawesson's reagent in refluxing toluene overnight after which successful thionation was observed. Treatment of the crude reaction mixture with acid followed by column chromatography led to the isolation of desired catalyst **120** in 74% yield (Scheme **3.8**).



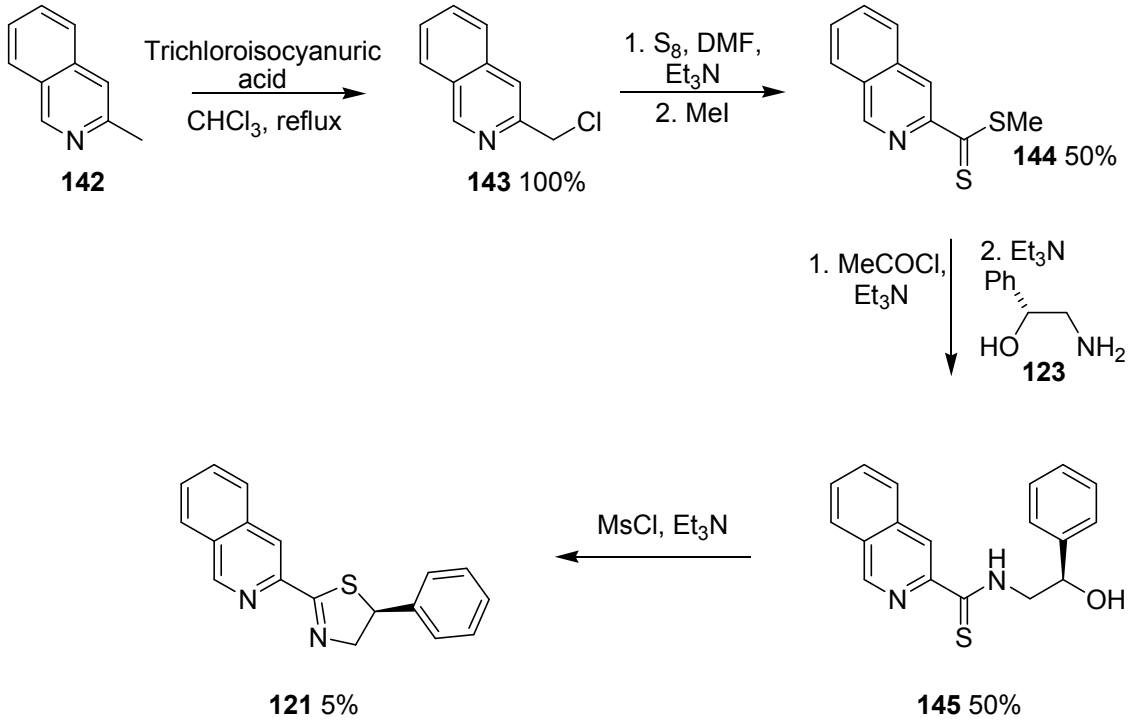
Scheme 3.8: Synthesis of 1-isoquinoline thiazoline

Synthesis of catalyst **121** was first attempted employing the same method used for 1-isoquinoline derivative **120**. Coupling of 3-isoquinoline carboxylic acid **139** to mandelamine **123** was achieved using the mixed anhydride method and the target molecule, **140**, was isolated in 43% yield. Protection of the hydroxyl group was then carried out with TBDMSCl furnishing the protected compound **141** in 59% yield. On treatment with Lawesson's reagent in refluxing toluene however, the only material recovered was amide **140** (Scheme **3.9**).



Scheme 3.9: Synthesis of 3-isoquinoline thiazoline, strategy 1.

An alternative strategy beginning with 3-methyl isoquinoline **142** as a precursor was employed (Scheme **3.10**). Conversion of 3-methyl isoquinoline, **142**, to thioester **144** was achieved by chlorination with trichlorisocyanuric acid in refluxing chloroform followed by treatment with sulphur and methyl iodide. Thioester **144** was then coupled to mandelamine **123** to produce thioamide **145** in 50% yield. Thioamide **145** was then treated with mesyl chloride in the presence of triethylamine to affect cyclisation. The cyclisation did not proceed as well as anticipated, however enough of the target thiazoline **121** (5%) was isolated to allow catalytic screening (Scheme **3.10**).



142

143 100%

144 50%

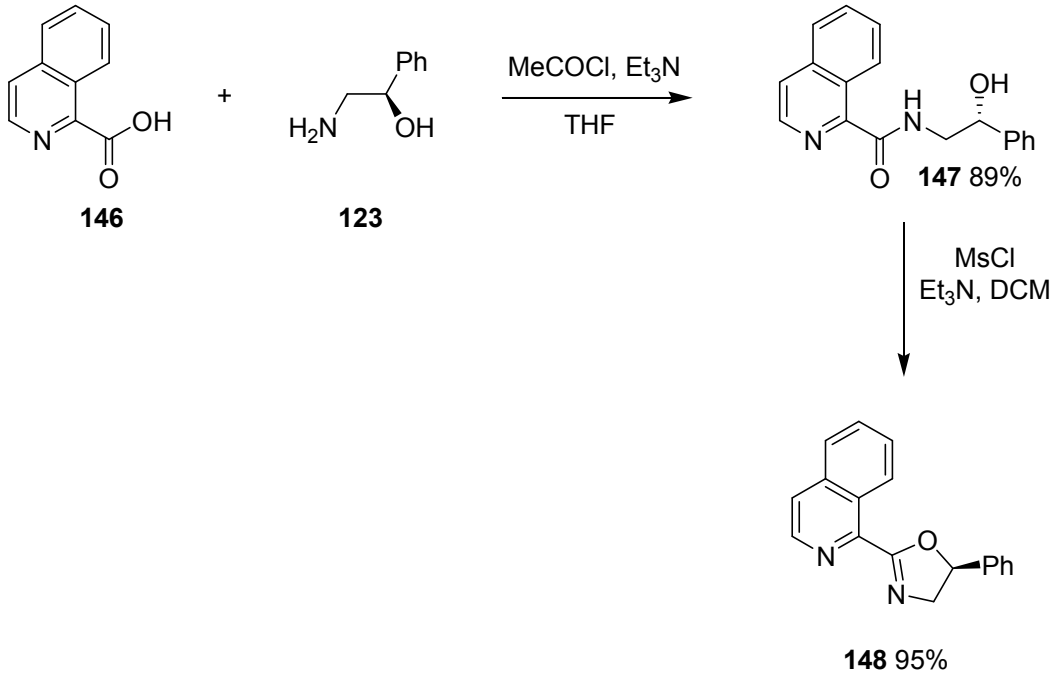
123

145 50%

121 5%

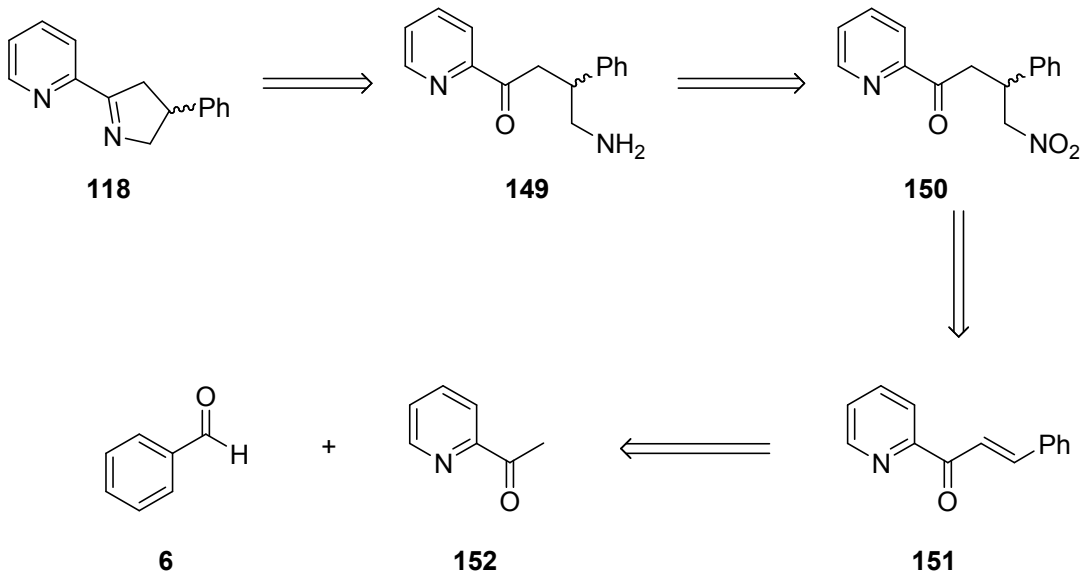
Scheme 3.10: Synthesis of 3-isoquinoline thiazoline, strategy 2.

To allow comparison with thiazoline catalyst, an oxazoline analogue **148** was prepared.[54] Synthesis of 1-isoquinoline oxazoline, **148**, commenced with coupling of 1-isoquinoline carboxylic acid **146** to mandelamine **123** using the mixed anhydride method. The resulting amide **147** was formed in 89% yield and isolated as a white crystalline solid. Amide **147** was then treated with mesyl chloride in the presence of triethylamine to affect cyclisation. The desired 1-isoquinoline oxazoline **148** was recrystallised from ethanol and isolated as a white solid in 95% yield (Scheme **3.11**).



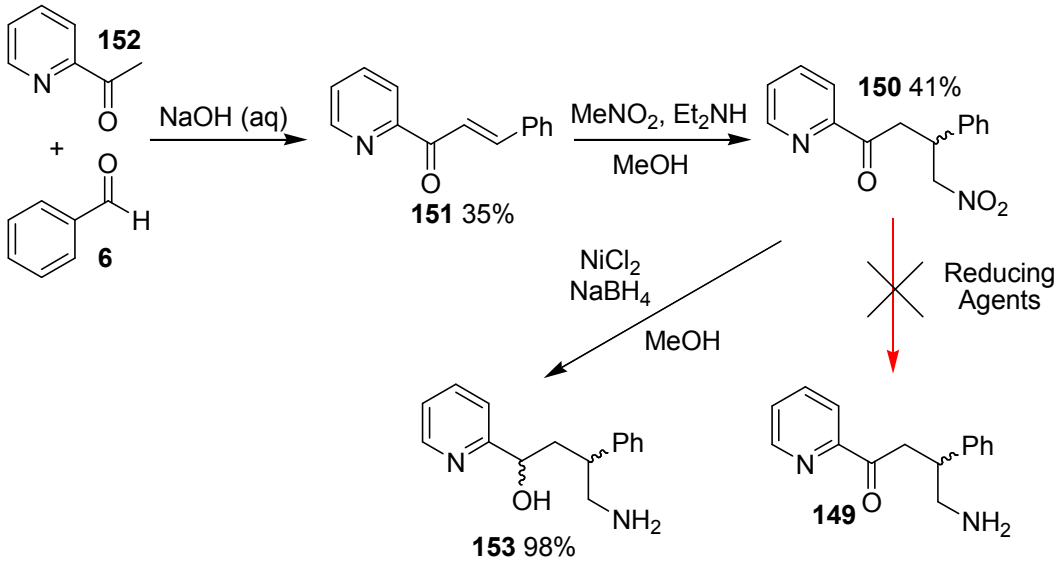
Scheme 3.11: Synthesis of 1-isoquinoline oxazoline.

Finally, synthesis of pyrroline catalyst **118** was attempted. It was proposed that intramolecular condensation of 1,4-amino-ketone **149** would yield the desired pyrroline **118**. Aldol condensation of 2-acetyl pyridine, **152**, and benzaldehyde, **6**, to generate **151**, followed by Michael addition of nitromethane, would form a suitable starting material for formation of 1,4-amino-ketone **149** (Scheme **3.12**).



Scheme 3.12: Retrosynthetic analysis of 2-pyridine pyrroline.

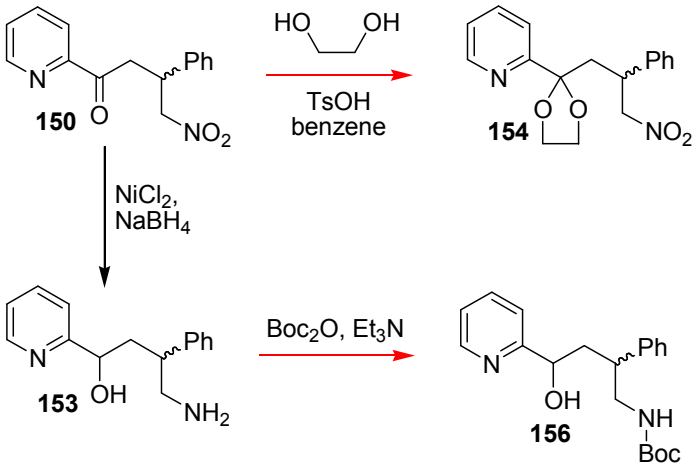
Synthesis of 2-pyridine pyrroline **118** commenced with aldol condensation of acetyl pyridine, **152**, and benzaldehyde, **6**, in aqueous sodium hydroxide to afford **151** in 35% yield (Scheme **3.13**). Michael addition of nitromethane to **151** in methanol resulted in the nitro compound **150** (41%). Reduction of the nitro group had to be carried out selectively to prevent unwanted reduction of the ketone group. Initial reduction of the nitro group with $SnCl_2$ did not result in formation of **149** and only starting material was isolated. Attempts to reduce **150** with $NaBH_4$ or by hydrogenation were equally unsuccessful. Further attempts at reduction with the more reactive species $NiCl_2/NaBH_4$ resulted in over-reduction to amino alcohol **153**. Although **153** was formed in 98% yield, re-oxidation to the ketone was unsuccessful.



Scheme 3.13: Synthesis of 2-pyridine pyrroline

It was believed that protection of the ketone before treatment with $NaBH_4/NiCl_2$ would prevent over-reduction; however attempts to form the protected ketone **154** were unsuccessful (Scheme **3.14**). We then attempted to re-oxidise the fully reduced amino alcohol **153**, first protecting the amino group. Attempts to protect the amino functionality with a Boc group, **156**, in order to allow

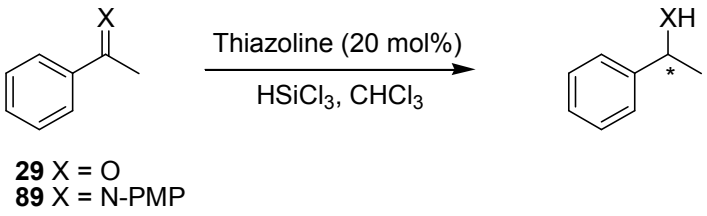
oxidation of the alcohol to ketone however, did not produce the desired products (Scheme **3.14**). At this point the synthesis of **118** was discontinued.



Scheme 3.14: Protection of ketone and amino groups.

3.3 Applications in Organocatalytic Reduction Reactions

Prospective thiazoline activators **119** to **122** were tested in the organocatalytic reduction of acetophenone **29** and simple ketimine **89** (Scheme **3.15**). After completion the reaction mixtures were analysed by chiral GC and NMR to evaluate enantioselectivity and catalyst degradation.

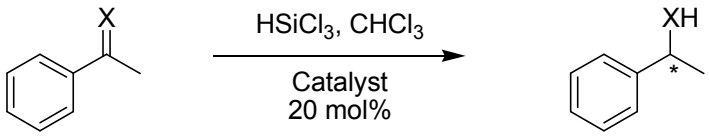


Scheme 3.15: Model catalytic reactions.

Pyridine derived thiazoline **119** showed promising initial results; phenylethanol, **30**, was obtained in 25% yield and 64% ee. Chiral amine **89** was also isolated in reasonable yield, 29%, and selectivity of 28% ee (Table **3.1**, entries 1 and 2). Analysis of the reaction mixture after work up by ^{1}H NMR showed that the thiazoline catalyst **119** had remained intact and was not degraded. However, the reactivity of the thiazoline catalyst was considerably reduced compared to the related oxazoline, **46**.

The addition of further steric constraints from the quinoline and isoquinoline fragments reduced the activity of the thiazoline derived organocatalysts even further. Thiazolines **120** and **122** derived from 1-isoquinoline and 2-quinoline were unsuccessful in the reduction of both ketones and ketimines. Thiazoline **121** obtained from 3-isoquinoline showed some activity in the reduction of acetophenone (~5% conversion), however was inactive in the reduction of ketimines (Table **3.1**). Oxazoline catalyst **148** however performed well in the reduction of both acetophenone **29** and ketimines (Table **3.1**, entries 9 and 10) although some degradation product was observed. It may be that **120** does not allow efficient coordination of the silane due to the extra aromatic steric constraints while the increased size of sulfur compared to oxygen, forced the rings out of plane

in the case of **122**. Thiazoline **121** may allow weak coordination to the silane however apparently it remains insufficient to successfully activate trichlorosilane towards reduction.



Entry	Catalyst	X	Yield (%)	ee (%)
1	**119**	O	25	64
2	**119**	N-PMP	29	28
3	**120**	O	0	N.A.
4	**120**	N-PMP	0	N.A.
5	**121**	O	0	N.A.
6	**121**	N-PMP	0	N.A.
7	**122**	O	0	N.A.
8	**122**	N-PMP	0	N.A.
9	**148**	O	96[a]	81[b]
10	**148**	N-PMP	60	85[b]

[a]Conversion determined by GC after standard reaction work-up; [b]previously reported results[54]

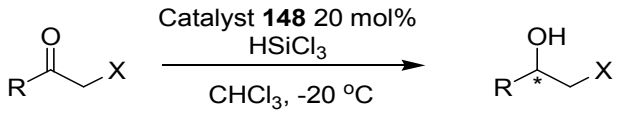
Table 3.1: Reduction with ligands **119 –122, 148**.

Based on these results it is believed that catalysts **120** and **122** do not permit favourable coordination of the silane whereas 3-isoquinoline derived catalyst **121** was not sufficiently active to promote reduction of ketones and ketimines. Pyridine thiazoline **119**, although successful, proved to be too sluggish to be further investigated. The initial results, however, show that 1-isoquinoline oxazoline **148** is a superior organocatalyst for the reduction of ketones and ketimines. It was decided to carry out further studies with organocatalyst **148** in order to expand the substrate range and investigate the scope of the reaction.

A range of α-chloro and heterocyclic ketones and ketimines were subjected to reduction with trichlorosilane in the presence of oxazoline **148** (Table **3.2**).

Ketones and imines derived from α-chloro acetophenone after reduction to the corresponding alcohols and amines can be cyclised into the corresponding epoxides and aziridines. Reduction of heterocyclic ketones or imines allows easy generation of chiral alcohols and amines finding application as chiral building blocks and synthetic intermediates in target synthesis.

Reduction of a range of ketones was carried out with 20 mol% of oxazoline catalyst **148** in $CHCl_3$ using $HSiCl_3$ as the reducing agent. Only 2-acetylthiophene and 2-methyl-5-acetylfuran exhibited reasonable reactivity, although the resulting alcohols were found to be racemic (Table **3.2**, entries 1 and 2). Unfortunately, no product was formed with other ketones tried (Table **3.2**, entries 3 – 8). It is possible that the Lewis basic heteroatom in the tested heterocyclic ketones coordinates to silane interfering with the catalytic process and preventing reduction from occurring.



Entry	R	X	Conversion (%)	ee (%)
1	2-thiophene	H	70	0
2	2-methyl-5-furan	H	50	0
3	Ph	Cl	-	-
4	2-pyridine	H	-	-
5	4-pyridine	H	-	-
6	2-thiazole	H	-	-
7	2,5-dimethyl-3-furan	H	-	-
8	1-(benzofuran-2-yl)	H	-	-
9[a]	2-MeO-C_6H_4	H	50	87
10[a]	2-F-C_6H_4	H	35	70
11[a]	Ph	H	85	84

[a]Previously reported results[54]

Table 3.2: Reduction of prochiral ketones with thiazoline **148**.

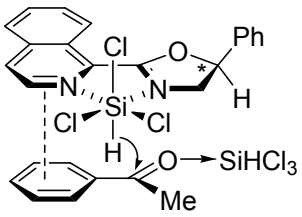


Figure 3.1: Proposed transition state for catalysts **119** – **122**, **148**

Reduction of prochiral imines was more successful. It was carried out in $CHCl_3$ with 20 mol% of oxazoline catalyst **148** using $HSiCl_3$ as the reducing agent. Propiophenone was reduced in 90% yield and 79% ee (Table **3.3**, entry1). Chiral α-chloro amines were obtained in 88 to 89% ee and good yield; 47% to 90% (Table **3.3**, entries 2-4). Furan and thiophene derived imines were successfully reduced in 73% yield, 55% ee and 77% yield, 60% ee respectively (Table **3.3**, entries 5 and 6). Even imine derived from pyridine was successfully transformed to its corresponding amine in 41% yield and 82% ee (Table **3.3**, entry 7). The results obtained are consistent with our current theory of enantiodifferentiation (Figure **3.2**).[54]

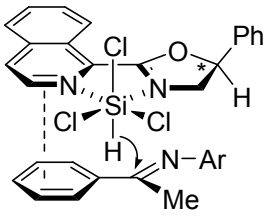
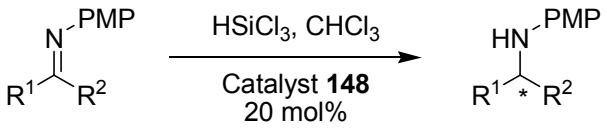


Figure 3.2: Proposed transition state for reduction of ketimines with **148**.



Entry	R^1	R^2	Yield (%)	ee (%)
1	phenyl	Et	90	79
2	phenyl	CH_2Cl	90	88
3	1-chloro-4-benzene	CH_2Cl	47	88
4	1-fluoro-4-benzene	CH_2Cl	70	89
5	2-furan	Me	73	55
6	2-thiophene	Me	77	60
7	4-pyridine	Me	41	82
8	2-pyridine	Me	88	75

Table 3.3: Reduction of prochiral ketimines with oxazoline **148**.

3.4 Summary

Thiazoline catalysts derived from 2-pyridines have been shown to be effective activators of trichlorosilane for the reduction of ketones and ketimines. The problem of chloride promoted ring opening of the catalyst can be successfully avoided however at the cost of catalyst activity and selectivity.

Due to the lower reactivity of the thiazoline catalysts, further investigation was carried out with oxazoline catalyst **148**. Catalyst **148** was shown to be an efficient organocatalyst for the reduction of a range of ketimines with a large substrate scope. The reactivity observed was in line with our previous mechanistic proposals.

4 Experimental

General Methods

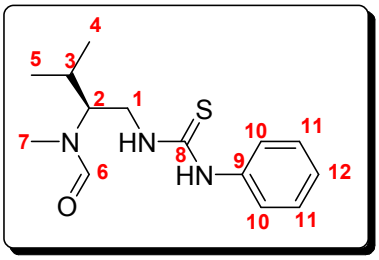
All reactions were carried out under an inert atmosphere in oven-dried glassware unless otherwise stated. Room temperature refers to ambient room temperature (20-22 ^{o}C); 0 ^{o}C refers to an ice slush bath. Heated experiments were conducted using thermostatically controlled oil baths. Reactions were monitored by Thin Layer Chromatography using aluminium backed silica gel 60 (F_{254}) plates, visualised using $UV_{254/286\ nm}$ and PMA, Dragendorf, Platinum and Ninhydrin dips as appropriate. Flash chromatography was carried out using 60 Å silica gel as the stationary phase.

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 $CDCl_3$, ^{1}H at 400 MHz and ^{13}C at 100.6 MHz on a Bruker Spectrospin 400 (400 MHz) spectrometer. Chemical shifts are reported in δ units, parts per million with chloroform-d_1 (δ 7.26, ^{1}H; δ 77.0, ^{13}C) as internal standard unless otherwise indicated. Coupling constants (*J*) are measured in Hz and are unadjusted; therefore due to limits in resolution, in some cases there are small differences (<1 Hz) in the measured *J* value of some coupling constants. The IR spectra were recorded on a JASCO FT-IR spectrophotometer for a thin film between NaCl plates. The mass spectra (EI, CI and/or FAB) were measured on a Joel JMS700 spectrometer.

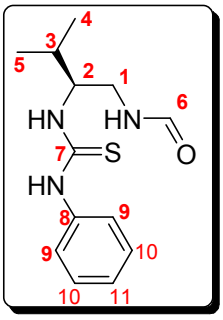
Enantiomeric excess was determined by chiral GC analysis (using a Hewlett Packard 6890 Series GC system, Hewlett Packard 3395 integrator and Supelco α-Dex™ or Supelco β-Dex™ column) or by chiral HPLC analysis (using a Hewlett Packard Agilent 1100 Series quarternary pump, vacuum degasser, diode array detector, manual injector and Hewlett Packard ChemStation). The chiral GC and HPLC methods were calibrated with the corresponding racemic mixtures.

Imines used for catalytic reduction reactions were available in the laboratory and were synthesised using known methods.

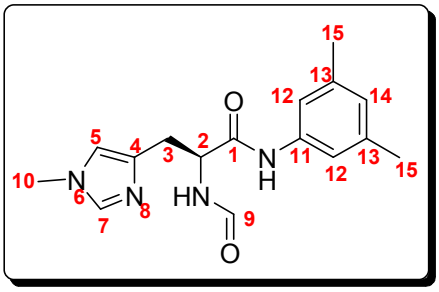
Bifunctional Organocatalysts



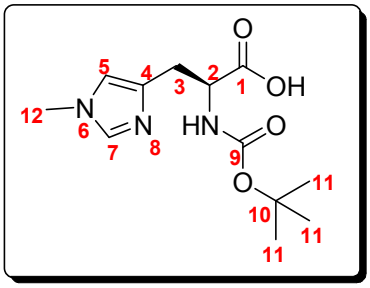
(S)-(-)-*N*-Methyl-*N*-[2-methyl-1-[(3-phenyl-thioureido)-methyl]-propyl]-formamide (64): To a solution of *N*-(1-Aminomethyl-2-methyl-propyl)-*N*-methyl-formamide (524 mg, 1.88 mmol) in CH_2Cl_2 was slowly added phenylisothiocyanate (0.26 mL, 2.0 mmol). The reaction mixture was allowed to stir at room temperature overnight. The solvent was then removed in vacuo. The crude mixture was then purified on a column of silica gel with a CH_2Cl_2-MeOH mixture (5:1) to afford **64** as a colourless oil (56%): **$[\alpha]_D$** -65.20 (*c* = 0.75, $CHCl_3$/MeOH, 3:1); **^{1}H NMR** (400MHz, $CDCl_3$) δ_H 0.78 (3H, d, $J_{3\text{-H},4\text{-H}}$ = 6.4 Hz, 4-H), 0.93 (3H, d, $J_{3\text{-H},5\text{-H}}$ = 6.2 Hz, 5-H), 1.65 – 1.74 (1H, m, 3-H), 2.61 (3H, s, 7-H), 3.63 - 3.70 (2H, m, 1-H), 4.10 – 4.17 (1H, m, 2-H), 7.08 – 7.14 (2H, m), 7.29 – 7.45 (2H, m), 7.54 (1H, bs); **^{13}C NMR** (100MHz, $CDCl_3$) δ_C 16.7 (CH_3, 4-C), 19.0 (CH_3, 5-C), 27.7 (CH, 3-C), 32.5 (CH_3, 7-C), 42.7 (CH_2, 1-C), 64.9 (2-C), 124.8 (CH), 126.6 (CH), 129.4 (CH), 137.2 (C, 9-C), 175.9 (CH, 6-C), 182.2 (C, 8-C); **MS CI** *m/z* (%) 280.3 (100, M+H), 246.3 (44), 218.3 (18), 163.1 (38), 145.2 (30); **HRMS** (CI) 280.1484 ($C_{14}H_{22}N_3OS$ requires 280.1483.



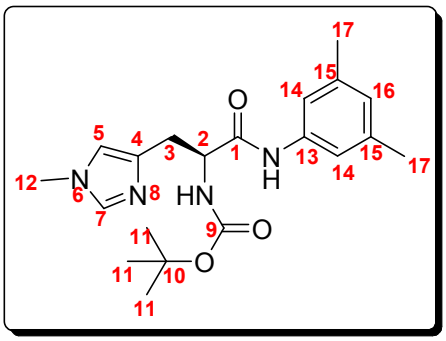
(*S*)-(-)-*N*-[3-Methyl-2-(3-phenyl-thioureido)-butyl] formamide (*S*)-(-)-65: **(*S*)-88** (736 mg, 3.2 mmol) was dissolved in a CH_2Cl_2-TFA (2:1) mixture (15 mL) and stirred at room temperature for 1 h. The reaction mixture was then poured into saturated $NaHCO_3$ solution (25 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The aqueous layer was then evaporated to dryness and the resulting solid extracted three times with CH_2Cl_2. The organic layer was concentrated *in vacuo* and the residue dissolved in dry CH_2Cl_2 to which was added phenyl isothiocyanate (0.4 mL, 3.3 mmol) and the reaction was allowed to stir at room temperature overnight. The solvent was then removed *in vacuo* and the crude residue purified on a column of silica gel with a Petrol – EtOAc mixture (3:2). The product was then recrystallised from hexane/EtOAc to afford **(*S*)-(-)-65** as an off white solid (100 mg, 12%): **$[\alpha]_D$** -96.6 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.81 (d, $J_{4\text{-H},3\text{-H}}$ = 7.1 Hz, 3H, 4-H), 0.88 (d, $J_{5\text{-H},3\text{-H}}$ = 6.8 Hz, 3H, 5-H), 1.75 – 1.81 (m, 1H, 3-H), 3.18 – 3.23 (m, 1H, 1α-H), 3.45 – 3.49 (m, 1H, 1β-H), 4.06 – 4.22 (m, 1H, 2-H), 5.99 (d, *J* = 9.1 Hz, 1H, 2-NH), 6.52 (bs, 1H, 1-NH), 7.16 (d, *J* = 8.3 Hz, 2H), 7.24 – 7.35 (m, 1H), 7.37 – 7.42 (m, 1H), 8.12 (s, 1H, 6-H); **^{13}C NMR** (100MHz, $CDCl_3$) δ_C 18.3 (CH_3, 4-C), 19.3 (CH_3, 5-C), 30.8 (CH, 3-C), 41.5 (CH_2, 1-C), 59.5 (CH, 2-C), 125.7 (CH), 127.9 (CH), 130.3 (8-C), 130.4 (CH), 161.9 (6-C), 181.69 (7-C).



(*S*)-*N*-(3,5-Dimethyl-phenyl)-2-formylamino-3-(τ-methyl-1*H*-imidazol-4-yl)-propionamide (*S*)-66: A solution of **(*S*)-69** and trifluoroacetic acid (5 mL) in dichloromethane (5 mL) was stirred at room temperature for 1 h. The solvent was evaporated in vacuo and the crude TFA salt was dissolved in formic acid (5 mL). Acetic anhydride (2.5 mL) was added and the solution was allowed to stir at room temperature for 72 h. The mixture was then evaporated to dryness and the crude product was purified by chromatography on a column of silica gel (60g) with a CH_2Cl_2–MeOH mixture (5:1) to afford **(*S*)-66** (100 mg, 59%) as an orange solid: **$[\alpha]_D$** 0.0 (*c* 1.0, $CHCl_3$)[81]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 2.21 (6H, s, 15-H), 2.94 (1H, dd, $J_{3\alpha\text{-H},\ 3\beta\text{-H}}$ = 15.2 Hz, $J_{3\alpha\text{-H},\ 2\text{-H}}$ = 7.2 Hz, 3α-H), 3.11 (1H, dd, $J_{3\alpha\text{-H},\ 3\beta\text{-H}}$ = 15.2 Hz, $J_{3\beta\text{-H},\ 2\text{-H}}$ = 4.0 Hz, 3β-H), 3.59, (3H, s, 10-H), 4.77 (1H, bd, $J_{3\beta\text{-H},\ 2\text{-H}}$ = 4.0 Hz, 2-H), 6.66 (1H, s, 5-H), 6.73 (1H, s, 7-H), 7.10 (2H, s, 12-H), 7.39 (1H, s, 14-H), 7.64 (1H, bs, 2-NH), 8.24 (1H, s, 1-NH), 9.83 (1H, bs, 9-H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 21.4 (CH_3, 15-C), 29.7 (CH_2, 3-C), 33.7 (CH_3, 10-C), 52.5 (CH, 2-C), 117.6 (CH, 5-C), 118.3 (CH, 7-C), 126.0 (CH), 138.6 (C), 161.4 (CH), 168.82 (9-C); **IR** (NaCl) ν 3019, 2399, 1215 cm^{-1}; **MS** (CI) *m/z* (%) 318.29 (100, M + NH_4).



(*S*)-(+)-*N*-τ-Me-*N*-α-Boc-Histidine (*S*)-(+)-68[70]: Sodium hydride (705 mg, 29.4 mmol) was placed in a two-neck flask, flushed with Ar, washed 3× with petroleum ether, and dried under vacuum. The dry NaH was then added slowly to a suspension of *N*-α-Boc-histidine **67** (2.5 g, 9.8 mmol) in CH_3CN at –15 °C and stirred for 30 min. Methyl iodide (1.53 g, 10.7 mmol) was added and the reaction mixture was then heated to –5 °C and allowed to stir overnight at this temperature. The reaction was quenched with excess MeOH and the solvent was removed on a rotary evaporator. The resulting solid was then extracted with $CHCl_3$ (3 × 50 mL), the solvent was evaporated and the resulting solid was purified by chromatography on a column of silica gel (50g), with a CH_2Cl_2–MeOH mixture (5:1), to give *N*-τ-Me-*N*-α-Boc-Histidine **(*S*)-(+)-68** as a pale yellow solid (1.64 g, 66%): **mp** (decomposition) 166-168 °C; **$[\alpha]_D^{25}$** +29.5 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, DMSO-d_6) δ_H 1.36 (9H, s, 11-H) 2.82 (2H, d, *J* = 4.8 Hz, 3-H) 3.56 (3H, s, 12-H) 3.91 (1H, bs, 2-H) 6.17 (1H, d, *J* = 5.6 Hz, 5-H), 6.77 (1H, s, 7-H) 7.49 (1H, s, NH) in accordance with literature.[70]



(*S*)-(+)-[1-(3,5-Dimethyl-phenylcarbamoyl)-2-(1-methyl-1*H*-imidazol-4-yl)-ethyl]-carbamic acid *tert*-butyl ester (*S*)-(+)-69:

Mixed anhydride method:

N-τ-Me-*N*-α-Boc-Histidine **(*S*)-(+)-68** (600mg, 2.3 mmol) and triethylamine (0.38 mL, 2.8 mmol) were dissolved in THF and cooled to 0^{o}C. Methylchloroformate (0.27 mL, 2.8mmol) was then added drop wise and the reaction allowed to stir for 1 hour. The precipitate was then filtered off. Triethylamine (0.38 ml, 2.8 mmol) and 3,5-dimethylaniline (0.35 ml, 2.8 mmol) were added and the reaction mixture left to stir overnight. No product was observed.

DCC Coupling Method:

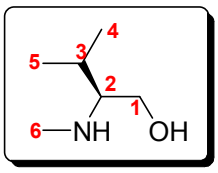
N-τ-Me-*N*-α-Boc-Histidine **(*S*)-(+)-68** (200 mg, 0.76 mmol) was dissolved in CH_2Cl_2 and a solution of DCC (190 mg, 0.92 mmol) in CH_2CL_2 (2 mL) was added. 3,5-dimethylaniline (130 mg, 1.07 mmol) was slowly added and the reaction mixture was left to stir overnight. Although formation of the desired product was observed, it was found to be inseparable from DCU, the reaction by-product.

EDC.HCL Coupling Method:

Prepared by modification of the procedure developed by Rosenberg.[82] 3,5-dimethylaniline (95 mg, 0.79 mmol) was dissolved in DMF (5 mL). *N*-τ-Me-*N*-α-Boc-Histidine **(*S*)-(+)-68** (200 mg, 0.76 mmol), 1-hydroxybenzotriazole hydrate (233 mg, 1.7 mmol) and 4-methylmorpholine (96 mg, 0.91 mmol) were added sequentially. The reaction mixture was then cooled to –23 ^{o}C, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (226 mg, 1.14 mmol) added and the reaction allowed to stir for two hours. The reaction was then heated to room temperature and left to stir overnight. The reaction mixture was then poured into saturated $NaHCO_3$ solution and extracted 3x with EtOAc. The organic layer was then washed with water and brine and dried over $MgSO_4$. The solvent was removed and the crude mixture purified by column chromatography (PE:EtOAc 5:1). The product **(*S*)-(+)-69** was obtained as yellow crystals in 65% yield.

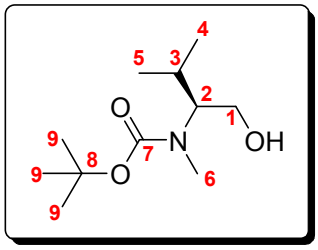
EDAC Coupling Method:

3,5-Dimethylaniline, (472 mg, 3.9 mmol) was added to a solution of *N*-τ-Me-*N*-α-Boc-Histidine **(*S*)-(+)-68** (1.0 g, 3.9 mmol), in dry MeCN. The solution was cooled to 0 ^{o}C and EDAC.HCl (910 mg, 4.7 mmol) was added and the reaction mixture was allowed to stir at room temperature for 48 h. The mixture was then poured into saturated $NaHCO_3$ solution and extracted 3× with EtOAc. The organic layer was washed with water and brine and dried over $MgSO_4$. The solvent was evaporated in vacuo and the crude product was purified by chromatography on a column of silica gel (75g) with a CH_2Cl_2–MeOH mixture (5:1) to afford **(*S*)-(+)-69** as a pale orange solid (896mg, 60%): **[α]$_D$** +53 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 1.38 (9H, s, 11-H), 2.20 (6H, s, 17-H), 2.91 (1H, dd, $J_{3\alpha\text{-H},\ 3\beta\text{-H}}$ = 15.6 Hz, $J_{3\alpha\text{-H},\ 2\text{-H}}$ = 6.4 Hz, 3α-H), 3.05 (d, $J_{3\alpha\text{-H},\ 3\beta\text{-H}}$ = 15.6 Hz, $J_{3\beta\text{-H},\ 2\text{-H}}$ = 2H), 3.64 (3H, s, 12-H), 4.46 (1H, s, 2-H), 6.23 (1H, s,), 6.65 (1H, s, 5-H), 6.67 (1H, s, 7-H), 7.19 (2H, s, 14-H), 7.37 (1H, s, 16-H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 21.4 (CH_3, 17-C), 28.3 (CH_3, 11-C), 30.7 (CH_2, 3-C), 33.4 (CH_3, 12-C), 50.4 (CH, 2-C), 80.0 (10-C), 117.6 (CH, 5-C), 118.6 (CH, 7-C), 125.9 (CH, 16-C), 137.2 (CH, 14-C), 138.5 (15-C), 155.1 (9-C), 170.2 (1-C).

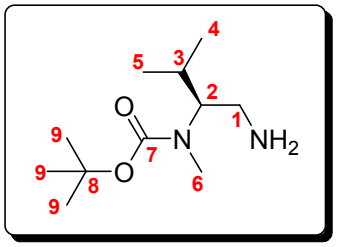


(*S*)-*N*-methyl valinol (*S*)-71: To a suspension of $LiAlH_4$ (3.8 g, 0.1 mol) in THF (60 mL) at 0 ^{o}C was slowly added *N*-Boc valine (5.0 g, 23.0 mmol) The reaction was allowed to stir at this temperature for 2h and was then heated overnight at 70 ^{o}C. The mixture was then cooled to 0 ^{o}C, $NaSO_4.10H_2O$ was added to remove excess $LiAlH_4$ and the mixture was then filtered through Celite. The solvent was then removed in vacuo to afford *N*-methyl valinol as a colourless oil (2.36 g, 87%): **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.82 (3H, d, $J_{4\text{-H},5\text{-H}}$ = 6.8 Hz, 4-H), 0.89 (3H, d, $J_{4\text{-H},5\text{-H}}$ = 6.8 Hz, 5-H), 2.35 (3H, s, 6-H), 3.26 (1H, dd, *J* = 7.2 Hz, $J_{1\alpha\text{-H},1\beta\text{-H}}$ = 10.8 Hz, 1α-H), 3.55 (1H, dd, *J* = 4.4

Hz, $J_{1\alpha\text{-H},1\beta\text{-H}}$ = 10.8 Hz, 1β-H), 3.69 (1H, t, *J* = 6.8 Hz, 2-H) in agreement with literature.[83]

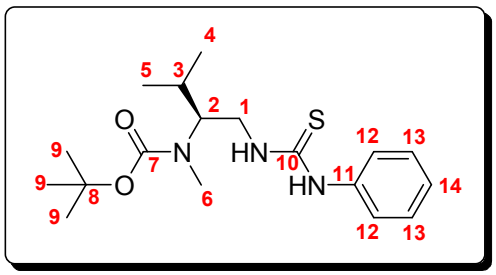


(*S*)-(-)-*N*-methyl-*N*-*tert*-butoxycarbonyl valinol (*S*)-72: To a solution of di-*tert*-butyl-dicarbonate in CH_2Cl_2 (25 mL) at 0 ^oC was added *N*-methyl valinol (2.36 g, 20.1 mmol) and triethylamine (6.2 mL, 44.22 mmol). The reaction mixture was allowed to warm to room temperature and left to stir overnight. The reaction mixture was then acidified to pH 5 with 1M citric acid and extracted with CH_2Cl_2 (3 x 25 mL). The organic phase was then dried over $MgSO_4$ and evaporated to dryness. The crude mixture was then purified on a column of silica gel with a Pet Ether-EtOAc mixture (2:1) to afford (*S*)-N-methyl-*N*-*tert*-butoxycarbonyl valinol as a colourless oil (3.8 g, 87%): **$[\alpha]_D$** -25.00 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.81 (3H, d, $J_{4\text{-H},5\text{-H}}$ = 6.8 Hz, 4-H), 0.90 (3H, d, $J_{4\text{-H},5\text{-H}}$ = 6.8 Hz, 5-H), 1.47 (9H, s, 9-H), 1.8 (1H, m, 3-H), 2.69 (3H, s, 6-H), 3.40 – 3.48 (1H, m), 3.60 – 3.69 (1H, m), 3.91 – 4.23 (1H, m); **CI MS** *m/z* (%) 218.2 (20, M+H), 162.1 (100), 118.2 (18); **HRMS** (CI+) 218.1756 ($C_{11}H_{24}O_3N$ requires 218.1758).



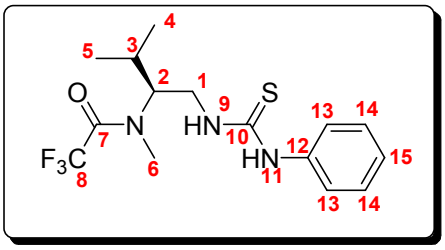
(*S*)-(1-Aminomethyl-2-methyl-propyl)-methyl-carbamic acid tert-butyl ester (*S*)-73: To a dry round bottomed flask was added phthalimide (2.04 g, 13.88 mmol), THF (25 mL), triphenylphosphine (7.28 g, 27.75 mmol) and *N*-methyl-*N*-*tert*-butoxycarbonyl valinol (2.0 g, 9.25 mmol) in that order. The mixture was cooled to 0^{o}C and diethylazodicarboxylate (4.02 g, 23.12 mmol) added. The reaction mixture was warmed to rt and allowed to stir overnight. The solvent was then removed in vacuo and the residue passed through a column of silica gel with a Pet Ether-EtOAc mixture (5:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.78 – 1.19 (m, 15H), 1.72 (bs, 1H), 2.55 (s, 3H), 3.61 – 3.72 (m, 2H), 3.95 (m, 1H), 7.52 – 7.61 (m, 2H), 7.70 – 7.80 (m, 2H).

To a solution of the crude material in EtOH (5 mL) was added hydrazine hydrate (1.44 g, 45.0 mmol). The reaction mixture was allowed to stir overnight at room temperature. The reaction mixture was then filtered and washed with Et_2O, the solvent was removed in vacuo to afford (1-Aminomethyl-2-methyl-propyl)-methyl-carbamic acid tert-butyl ester as an off white solid (99%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.85 (3H, dd, *J* = 2.0 Hz, *J* = 6.4 Hz, 4-H), 0.99 (3H, dd, *J* = 6.0 Hz, *J* = 6.8 Hz, 5-H), 1.49 (9H, s, 9-H), 1.65 (1H, m, 3-H), 2.73, 2.80 (2 x s, 2 x 3H), 2.93 (1H, dd, *J* = 4.4 Hz, *J* = 12.4 Hz, 1α-H), 2.98 (1H, dd, *J* = 3.6 Hz, *J* = 13.6 Hz, 1β-H), 3.78 (1H, m, 2-H).

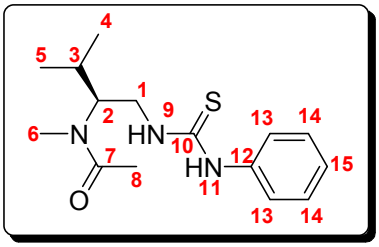


(*S*)-(-)-Methyl-[2-methyl-1-[(3-phenyl-thioureido)-methyl]-propyl]-carbamic acid tert-butyl ester (*S*)-74: To a solution of (1-Aminomethyl-2-methyl-propyl)-methyl-

carbamic acid tert-butyl ester **(*S*)-73** (1.61 g, 4.60 mmol) in Et_2O was slowly added phenylisothiocyanate (676 mg, 5.0 mmol). The reaction mixture was allowed to stir at room temperature overnight. The solvent was then removed in vacuo and the crude product purified purified on a column of silica gel with a Pet Ether-EtOAc mixture (2:1) to afford **(*S*)-74** (1.43 g, 88%) as a white solid: **$[\alpha]_D$** -29.9 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.75 (3H, d, $J_{4\text{-}H,\ 3\text{-}H}$ = 6.8 Hz, 4-H), 0.95 (3H, d, $J_{5\text{-}H,\ 3\text{-}H}$ = 6.8 Hz, 5-H), 1.27 (9H, s, 9-H), 1.70 (1H, m, 3-H), 2.62 (3H, s, 6-H), 3.72 (2H, m, 1-H), 4.02 (1H, m, 2-H), 7.08 – 7.12 (2H, m, 12-H), 7.20 - 7.33 (3H, m, 13-H, 14-H); **CI MS** *m/z* (%) 352.3 (82, M+H), 218.3 (100); **HRMS** (CI) 352.2059 ($C_{18}H_{30}N_3O_2S$ requires 352.2061).

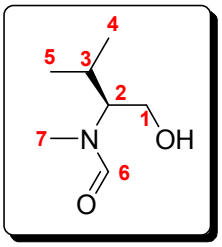


(*S*)-2,2,2-Trifluoro-*N*-methyl-*N*-[2-methyl-1-[(3-phenyl-thioureido)-methyl]-propyl]-acetamide (*S*)-75: Methyl-[2-methyl-1-[(3-phenyl-thioureido)-methyl]-propyl]-carbamic acid tert-butyl ester **(*S*)-74** (98 mg, 0.28 mmol) was dissolved in a CH_2Cl_2-TFA (2:1) mixture (5 mL) and stirred at room temperature for 1 hour. The solvent was then removed in vacuo. The crude TFA salt was dissolved in formic acid (1 mL) and acetic anhydride (224 mg, 2.2 mmol) added and the reaction mixture was allowed to stir for 16h. The solvent was then removed in vacuo and the crude residue purified on a column of silica gel with a Pet Ether – EtOAc mixture (2:1) to afford **(*S*)-75** as a white solid (62 mg, 64%): **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.96 (3H, d, $J_{4\text{-}H,\ 3\text{-}H}$ = 6.8 Hz, 4-H), 1.05 (3H, d, $J_{5\text{-}H,\ 3\text{-}H}$ = 6.8 Hz), 2.05 (1H, m, 3-H), 2.56 (3H, s, 6-H), 3.41 (1H, m, 1α-H), 3.51 (1H, m, 1β-H), 4.10 (1H, m, 2-H), 7.07 – 7.26 (5H, m), 7.79 (1H, bs, 9-NH), 8.63 (1H, bs, 11-NH); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 16.8 (CH_3, 4-C), 19.1 (CH_3, 5-C), 27.7 (CH, 3-C), 32.4 (CH_3, 6-C), 42.6 (CH_2, 1-C), 64.9 (CH, 2-C), 124.8 (CH), 126.5 (CH), 129.3 (CH), 137.3 (C), 162.5 (C, 7-C), 182.2 (C, 10-C).

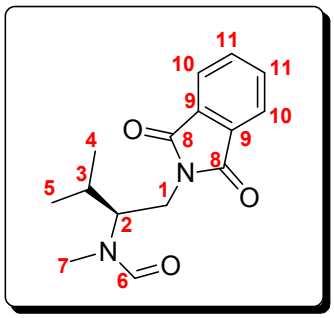


(*S*)-*N*-Methyl-*N*-[2-methyl-1-[(3-phenyl-thioureido)-methyl]-propyl]-acetamide

(*S*)-76: Methyl-[2-methyl-1-[(3-phenyl-thioureido)-methyl]-propyl]-carbamic acid tert-butyl ester **(*S*)-74** (1.43 g, 4.07 mmol) was dissolved in a CH_2Cl_2-TFA (2:1) mixture (10 mL) and stirred at room temperature for 1 hour. The solvent was then removed in vacuo. The crude TFA salt was dissolved in formic acid (10 mL) and acetic anhydride (3.32 g, 32.6 mmol) added and the reaction mixture was allowed to stir for 16h. The solvent was then removed in vacuo and the crude residue purified on a column of silica gel with a Pet Ether – EtOAc mixture (5:1) to afford *N*-Methyl-*N*-[2-methyl-1-[(3-phenyl-thioureido)-methyl]-propyl]-acetamide as a yellow oil: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 1.05 (3H, d, $J_{4\text{-}H,\ 3\text{-}H}$ = 6.8 Hz, 4-H), 1.12 (3H, d, $J_{5\text{-}H,\ 3\text{-}H}$ = 6.8 Hz, 5-H), 1.99 (3H, s, 8-H), 2.11 (1H, m, 3-H), 2.18 (3H, s, 6-H), 3.44 (1H, bs, 1α-H), 3.62 (2H, m, 1β-H, 2-H), 7.17 – 7.41 (m, 5H), 8.29 (1H, bs, 9-NH), 8.61 (1H, bs, 11-NH); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 16.7 (CH_3, 4-C), 18.9 (CH_3, 5-C), 20.8 (CH_3, 8-C), 27.7 (CH, 3-C), 32.5 (CH_3, 6-C), 42.7 (CH_2, 1-C), 64.9 (CH, 2-C), 124.8 (CH), 126.6 (CH), 129.4 (CH), 137.2 (C, 12-C), 175.9 (C, 7-C), 182.2 (C, 10-C); **CI MS** *m/z* (%) 280.3 (100, M+H), 246.3 (43), 218.3 (28), 163.1 (38), 145.2 (30); **HRMS** (EI) 279.1405 ($C_{14}H_{21}ON_3S$ requires 279.1404).



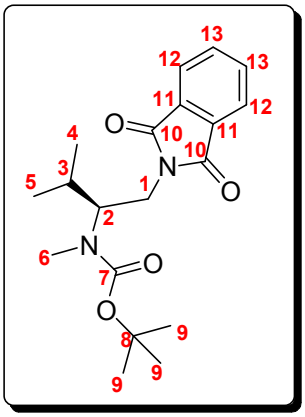
(*S*)-(-)-*N*-Methyl-*N*-formyl valinol (*S*)-(-)-78: *N*-Methyl valinol (1.64 g, 13.9 mmol) was dissolved in ethyl formate (10 mL) and allowed to reflux for 16h. The solvent was then removed in vacuo to afford *N*-Methyl-*N*-formyl valinol as a yellow oil (99%), which was carried on without purification: $[\alpha]_D$ -16.80 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (400MHz, $CDCl_3$) δ_H 0.88 (3H, d, $J_{3\text{-H},4\text{-H}}$ = 6.4 Hz, 4-H), 1.00 (3H, d, $J_{3\text{-H},5\text{-H}}$ = 6.4 Hz, 5-H), 1.83 – 1.87 (1H, m, 3-H), 2.79 (3H, s, 7-H), 3.02 – 3.07 (1H, m, 2-H), 3.78 – 3.82 (2H, m, 1-H), 8.03 (1H, s, 6-H).



(*S*)-*N*-[1-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-methyl-propyl]-*N*-methyl-formamide (*S*)-79:

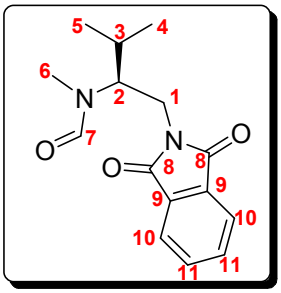
Method A: To a dry round bottomed flask were added phthalimide (3.07 g, 41.7 mmol), THF (25 mL), triphenylphosphine (10.94 g, 20.85 mmol) and *N*-Methyl-*N*-formyl valinol (3.81 g, 13.9 mmol) in that order. The mixture was cooled to 0^{o}C and diethylazodicarboxylate (6.05 g, 34.75 mmol) added. The reaction mixture was warmed to rt and allowed to stir overnight. The reaction mixture could not be purified.

Method B: [1-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-methyl-propyl]-methyl-carbamic acid tert-butyl ester (2.16 g, 6.26 mmol) was dissolved in a mixture of CH_2Cl_2-TFA (2:1, 10 mL) and stirred at room temperature for 1h. The solvent was then removed in vacuo and the residue dissolved in CH_2Cl_2 (20 mL) and washed with sat. $NaHCO_3$ (2 x 10 mL). The organic phase was dried over $MgSO_4$ and concentrated in vacuo. The resulting solid was then dissolved in formic acid (10 mL) and acetic anhydride (5 mL, 50 mmol) added. The reaction mixture was allowed to stir at room temperature overnight. The solvent was then removed in vacuo and the residue purified on a column of silica gel with a Pet Ether-EtOAc mixture (2:1) to afford *N*-[1-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-methyl-propyl]-*N*-methyl-formamide **(*S*)-79** as a white solid (1.03 g, 60%): **^{1}H NMR** (400MHz, $CDCl_3$) δ_H 0.94 (d, *J* = 6.8 Hz, 3H), 1.19 (d, *J* = 6.4 Hz, 3H) 1.97 (m, 1H), 2.71, 2.93 (2 x s, 2 x 3H), 3.54 (dt, *J* = 3.6 and 10.8 Hz, 1H), 3.7 – 3.9 (m, 2H), 7.58 – 7.82 (m, 5H).

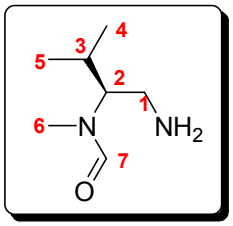


(*S*)-[1-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-methyl-propyl]-methyl-carbamic acid tert-butyl ester (*S*)-80: To a dry round bottomed flask was added phthalimide (2.04 g, 13.88 mmol), THF (25 mL), triphenylphosphine (7.28 g, 27.75 mmol) and *N*-methyl-*N*-*tert*-butoxycarbonyl valinol (2.0 g, 9.25 mmol) in that order. The mixture was cooled to 0^{o}C and diethylazodicarboxylate (4.02 g, 23.12 mmol) added. The reaction mixture was warmed to rt and allowed to stir overnight. The solvent was then removed in vacuo and the residue purified on a column of silica

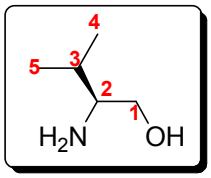
gel with a Pet Ether-EtOAc mixture (5:1). After column chromatography the product was not pure however further attempts at purification were not successful. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.78 – 1.19 (15H, m, 4-H, 5-H, 9-H), 1.72 (1H, bs, 3-H), 2.55 (3H, s, 6-H), 3.61 – 3.72 (2H, m, 1-H), 3.95 (1H, m, 2-H), 7.52 – 7.61 (2H, m, 13-H), 7.70 – 7.80 (2H, m, 12-H).



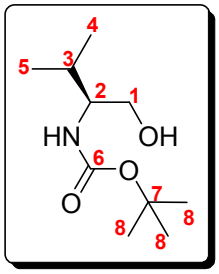
(*S*)-*N*-[1-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-methyl-propyl]-*N*-methyl-formamide (*S*)-81: **(*S*)-80** (2.16 g, 6.26 mmol) was dissolved in a mixture of CH_2Cl_2-TFA (2:1, 10 mL) and stirred at room temperature for 1h. The solvent was then removed in vacuo and the residue dissolved in CH_2Cl_2 (20 mL) and washed with sat. $NaHCO_3$ (2 x 10 mL). The organic phase was dried over $MgSO_4$ and concentrated in vacuo. The resulting solid was then dissolved in formic acid (10 mL) and acetic anhydride (5 mL, 50 mmol) added. The reaction mixture was allowed to stir at room temperature overnight. The solvent was then removed in vacuo and the residue purified on a column of silica gel with a Pet Ether-EtOAc mixture (2:1) to afford *N*-[1-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-methyl-propyl]-*N*-methyl-formamide **(*S*)-81** as a white solid (1.03 g, 60%): ^{1}H NMR (400MHz, $CDCl_3$) δ 0.94 (3H, d, *J* = 6.8 Hz, 4-H), 1.19 (3H, d, *J* = 6.4 Hz, 5-H) 1.95 – 1.98 (1H, m, 3-H), 2.71, 2.93 (2 x 3H, 2 x s, 6-H), 3.54 (1H, dt, *J* = 3.6 and 10.8 Hz, 2-H), 3.7 – 3.9 (2H, m, 1-H), 7.58 – 7.82 (4H, m, 10-H, 11-H).



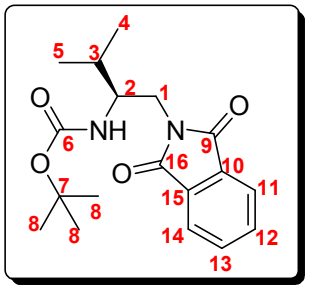
(*S*)-*N*-(1-Aminomethyl-2-methyl-propyl)-*N*-methyl-formamide (*S*)-82: (*S*)-81 (516 mg, 1.88 mmol) was dissolved in EtOH and hydrazine hydrate (302 mg, 9.45 mmol) added. The reaction mixture was allowed to stir at room temperature overnight. The mixture was then filtered and the precipitate washed with Et_2O. The solvent was removed and the crude mixture carried on without purification.



(*S*)-Valinol (*S*)-84: To a suspension of valine **83** (10.04 g, 85.7 mmol) in THF (100 mL) at 0 ^{o}C was slowly added $LiAlH_4$ (6.7g, 0.18 mol). The reaction was allowed to stir at this temperature or 2h and was then heated overnight at 70 ^{o}C. The mixture was then cooled to 0 ^{o}C, $NaSO_4.10H_2O$ was added to remove excess $LiAlH_4$ and the mixture was then filtered through Celite. The solvent was then removed in vacuo to afford (*S*)-valinol (5.81 g, 66%) as a pale yellow oil: **^{1}H NMR** (400MHz, $CDCl_3$) δ_H 0.98 (3H, d, $J_{4\text{-H},5\text{-H}}$ = 4.1 Hz, 4-H), 1.01 (3H, d, $J_{4\text{-H},5\text{-H}}$ = 6.5 Hz, 5-H), 1.59 – 1.61 (1H, m,), 1.86 (3H, br s,), 2.54 – 2.57 (1H, m,), 3.32 (1H, m,), 3.66 (1H, dd, *J* = 3.95, 10.44 Hz,) in accordance with literature.[84]

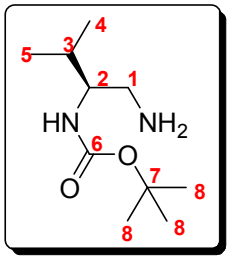


(*S*)-(-)-*N*-*tert*-butoxycarbonyl valinol (*S*)-(-)-85: To a solution of valinol **(*S*)-84** (5.0 g, 48.5 mmol) in CH_2Cl_2 (50 mL) at 0 ^oC was added di-*tert*-butyl dicarbonate (12.7 g, 58.15 mmol) and triethylamine (13.5 mL, 96.9 mmol) and the reaction mixture allowed to stir at room temperature for 16 h. The reaction mixture was then acidified to pH 5 with 2 M HCl and extracted with CH_2Cl_2 (3 x 25 mL). The organic layer was then dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford *N*-*tert*-butoxycarbonyl valinol **(*S*)-(-)-85** (8.32 g, 84%) as a yellow oil; **$[\alpha]_D$** -15.0 (*c* = 2.0, $CHCl_3$); **^{1}H NMR** (400MHz, $CDCl_3$) δ_H 0.84 (3H, d, $J_{3\text{-}H,4\text{-}H}$ = 7.6 Hz, 4-H), 0.90 (3H, d, $J_{3\text{-}H,5\text{-}H}$ = 7.1 Hz, 5-H), 1.38 (9H, s, 8-H), 1.77 (1H, m, 3-H), 3.35 (1H, m, 2-H), 3.55 (1H, m, 1α-H), 3.63 (1H, m, 1β-H), 4.58 (1H, bs, NH); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 18.6 (CH_3, 4-H), 19.5 (CH_3, 5-H), 28.4 (CH_3, 8-C), 29.4 (CH, 3-C), 46.2 (CH_2, 1-C), 58.1 (CH, 2-C), 85.2 (C, 7-C), 156.9 (C, 6-C) in agreement with literature values.[85]

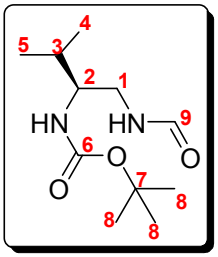


(*S*)-[1-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-methyl-propyl]carbamic acid *tert*-butyl ester (*S*)-86: To a dry round bottomed flask was added phthalimide (4.51 g, 30.68 mmol), THF (100 mL), triphenylphosphine (16.08 g, 61.3 mmol) and *N*-*tert*-butoxycarbonyl valinol **(*S*)-85** (4.15 g, 20.45 mmol) in that order. The mixture was cooled to 0 ^oC and diethylazodicarboxylate (8.04 mL, 51.0 mmol) added. The

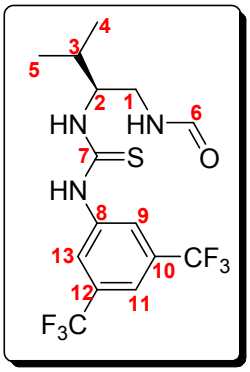
reaction mixture was warmed to room temperature and allowed to stir overnight. The solvent was then removed *in vacuo* and the residue purified on a column of silica gel with a Petrol-EtOAc mixture (5:1). After column chromatography **(*S*)-86** was isolated (48%) but was not pure and further attempts at purification were not successful. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.93 (3H, d, $J_{3\text{-H},4\text{-H}}$ = 6.8, 4-H), 0.95 (3H, d, $J_{3\text{-H},5\text{-H}}$ = 6.8, 5-H) 1.10 (9H, s, 8-H), 1.81 – 1.89 (1H, m, 3-H), 3.67 -3.74 (1H, m, 2-H), 3.85 – 3.93 (2H, m, 1-H), 4.70 (1H, d, *J* = 9.8 Hz, NH), 7.67 – 7.77 (2H, m), 7.78 – 7.91 (2H, m); **MS CI** *m/z* (%) 333.3 (M+H, 27), 277.2 (100), 233.2 (55), 172.3 (31).



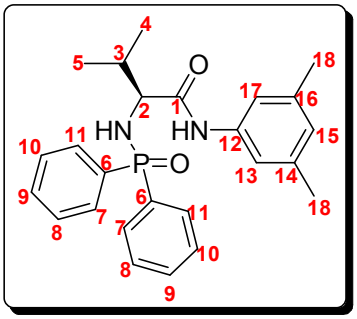
(*S*)-1-amino-2-*tert*-butyl carbamate-3-methyl butane (*S*)-87: To a solution of crude **(*S*)-86** in EtOH (10 mL) was added hydrazine hydrate (2.88 g, 90.0 mmol). The reaction mixture was allowed to stir overnight at room temperature. The reaction mixture was then filtered and washed with Et_2O, the solvent was removed *in vacuo* to afford **(*S*)-87** as an off white solid: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.83 (3H, d, $J_{3\text{-H},4\text{-H}}$ = 6.8 Hz, 4-H), 0.86 (3H, d, $J_{3\text{-H},5\text{-H}}$ = 6.8 Hz, 5-H), 1.38 (9H, s, 8-H), 1.67 (1H, m, 3-H), 2.54 (1H, dd, $J_{1\alpha\text{-H},1\beta\text{-H}}$ = 13.1 Hz, $J_{1\alpha\text{-H},2\text{-H}}$ = 7.8 Hz, 1α-H), 2.73 (1H, dd, $J_{1\alpha\text{-H},1\beta\text{-H}}$ = 13.1 Hz, $J_{1\beta\text{-H},2\text{-H}}$ = 4.0 Hz, 1β-H), 3.30 – 3.35 (1H, m, 2-H), 4.50 (1H, d, *J* = 10.1 Hz, NH); **^{13}C NMR** (100MHz, $CDCl_3$) δ_C 17.5 (CH_3, 4-C), 18.5 (CH_3, 5-C), 28.3 (CH_3, 8-C), 30.3 (CH, 3-C), 43.8 (CH_2, 1-C), 79.0 (C, 7-C), 156.5 (C, 6-C).



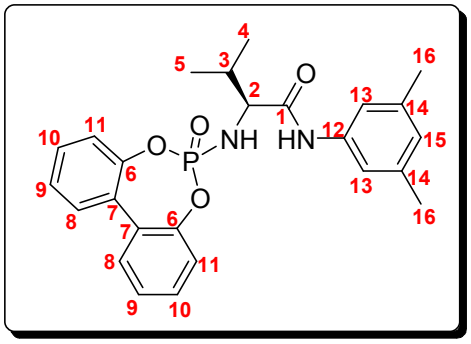
(*S*)-1-formylamino-2-*tert*-butyl carbamate-3-methyl butane (*S*)-88: Crude **(*S*)-87** was dissolved in ethyl formate (50 mL) and stirred at reflux for 24 h after which the solvent was removed to afford **(*S*)-88** as an off white solid: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.88 (3H, d, $J_{3\text{-}H,4\text{-}H}$ = 7.6 Hz, 4-H), 0.89 (3H, d, $J_{3\text{-}H,5\text{-}H}$ = 7.1 Hz, 5-H), 1.37 (9H, s, 8-H), 1.71 (1H, m, 3-H), 3.29 (2H, m, 1-H), 3.48 (1H, m, 2-H), 4.57 (1H, d, *J* = 8.6 Hz, NH), 8.11 (1H, s, 9-H).



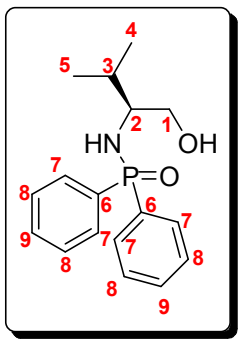
(*S*)-*N*-[2-[3-(3,5-Bis-trifluoromethyl-phenyl)-thioureido]-3-methyl-butyl]-formamide (*S*)-90: Reaction performed on 3.2 mmol scale utilising the same procedure for the preparation of **(*S*)-65**. 3,5-Bis(trifluoromethyl)phenyl isothiocyanate (0.5 mL, 3.3 mmol) was substituted for phenyl isothiocyanate. **(*S*)-90** was purified on a column of silica gel using a Petrol – EtOAc mixture (1:2). The product was then recrystallised from EtOAc/Hexane but was still impure; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.96 (6H, m, 4-H, 5-H), 1.67 (1H, m, 3-H), 3.15 (1H, m), 3.34 – 3.59 (2H, m), 4.72 (1H, bs, NH), 6.27 (1H, bs, NH), 6.61 (1H, bs, NH), 7.56 (2H, s, 9-H and 13-H), 8.05 (1H, s, 11-H), 8.16 (1H, s, 6-H).



(*S*)-(-)-1-(3,5-dimethylphenylcarbamoyl)-2-methylpropyldiphenyl phosphoramide (*S*)-(-)-91: (*S*)-*tert*-butyl-1-(3,5-dimethylphenylcarbamoyl)-2-methylpropylcarbamate **(*S*)-100** (1.21 g, 3.7 mmol) was dissolved in a TFA/DCM (1:2) mixture and stirred at room temperature for 1h. To the mixture was added saturated $NaHCO_3$ until pH = 7 and the resulting mixture was then extracted with CH_2Cl_2 (3 x 25 mL). The organic layer was dried over $MgSO_4$ and the solvent removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (25 mL) and diphenylphosphinic acid chloride (0.73 mL, 3.8 mmol) and triethylamine (1.03 mL, 7.4 mmol) were added. The mixture was allowed to stir at room temperature overnight after which the solvent was removed. The residue was then dissolved in EtOAc (10 mL) and washed with sat. $NaHCO_3$ solution (10 mL), 1M HCl (10 mL) and brine (10 mL). The organic phase was dried over $MgSO_4$ and the solvent removed under reduced pressure. The residue was then recrystallised from ethanol to afford **(*S*)-(-)-91** as an off white solid 80%; **mp** 184 – 187 ^{o}C **$[\alpha]_D$** = -158.4 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (400MHz, $CDCl_3$) δ_H 0.80 (3H, d, $J_{3\text{-}H,4\text{-}H}$ = 6.4 Hz, 4-H), 0.98 (3H, d, $J_{3\text{-}H,5\text{-}H}$ = 6.4 Hz, 5-H), 2.11 (1H, m, 3-H), 2.14 (6H, s, 18-H), 3.98 (2H, m, 2-H), 6.65 (1H, s, 1-NH), 6.93 – 7.36 (8H, m), 7.47 (2H, m), 8.89 (1H, s, 2-NH); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 17.9 (CH_3, 4-C), 18.5 (CH_3, 5-C), 21.4 (CH_3, 18-C), 29.7 (CH, 3-C), 61.9 (CH, 2-C), 117.7 (CH), 121.6 (CH), 121.8 (CH), 126.0 (CH), 126.4 (CH), 128.4 (C), 129.7 (CH), 129.9 (CH), 130.1 (CH), 130.2 (CH), 137.8 (C), 138.5 (C), 147.7 (C), 170.3 (1-C); **EI MS** *m/z* (%) **HRMS** 450.1708 ($C_{25}H_{27}O_4N_2P$ requires 450.1708); **Anal. Calcd.** for $C_{25}H_{29}N_2O_2P$: C 71.87 H 7.19 N 6.45. Found C 71.61 H 6.86 N 6.43.

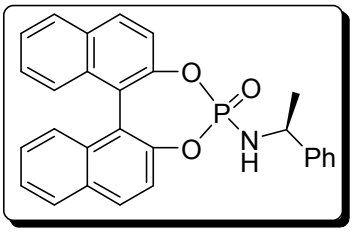


(*S*)-94: Reaction carried out on 3.92 mmol scale utilising the same procedure as for **(*S*)-91**. **(*S*)-94** was isolated by crystallisation form EtOH in 33% yield: **mp** 218 – 221 ^{o}C; **^{1}H NMR** (400MHz, $CDCl_3$) δ_H 0.80 (3H, d, $J_{3\text{-}H,4\text{-}H}$ = 6.4 Hz, 4-H), 0.98 (3H, d, $J_{3\text{-}H,5\text{-}H}$ = 6.4 Hz, 5-H), 2.06 (1H, m, 3-H), 2.14 (6H, s, 16-H), 4.01 (1H, m, 2-H), 6.65 (1H, s, 1-NH), 7.13 (2H, s, Ar-H), 7.35 (4H, m, Ar-H), 7.48 (2H, m, Ar-H), 8.89 (1H, s, 2-NH); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 17.9 (CH_3, 4-C), 18.5 (CH_3, 5-C), 21.4 (CH_3, 16-C), 29.7 (CH, 3-C), 61.9 (CH, 2-C), 117.7 (CH), 121.6 (CH), 121.8 (CH), 126.0 (CH), 126.4 (CH), 128.4 (C), 129.7 (CH), 129.9 (CH), 130.1 (CH), 130.2 (CH), 137.8 (C), 138.5 (C), 147.7 (C), 170.3 (C, 1-C); **MS EI** *m/z* (%) 450.1 (19, M), 302.1 (100); **HRMS** (EI) 450.1708 ($C_{25}H_{27}N_2O_4P$ requires 450.1705).

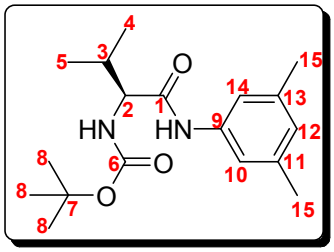


(*S*)-*N*-(diphenylphosphine oxide)-valinol (*S*)-95: To a solution of valinol (1.0 g, 9.69 mmol) in CH_2Cl_2 (20 mL) at 0 ^{o}C was added triethylamine (3.23 mL, 23.2 mmol) and diphenylphosphinic acid chloride (2.22 mL, 11.69 mmol). The mixture was then allowed to reach room temperature and stirred for 16 h. The reaction mixture was then diluted with 1M HCl until neutral and extracted with CH_2Cl_2 (3 x 25 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent removed under

reduced pressure. The residue was purified on a column of silica gel with a Pet Ether-EtOAc mixture (4:1) and then recrystallised from hexane/ethyl acetate to afford a white solid (67%) which was identified as a mixture of cis/trans isomers of **(*S*)-95**; **mp** 84 – 86 ^{o}C and 95 – 101 ^{o}C; **^{1}H NMR** (400MHz, $CDCl_3$) δ_H 0.62 (d, *J* = 6.8 Hz, 4-H), 0.81 (d, *J* = 6.8 Hz, 5-H), 0.87 (d, *J* = 6.8 Hz, 4-H), 0.95 (d, *J* = 6.8 Hz, 5-H), 1.45 (m,), 1.91 (m,), 2.40 (m,), 2.99 (m,), 7.42 (6H, m), 7.87 (4H, m).

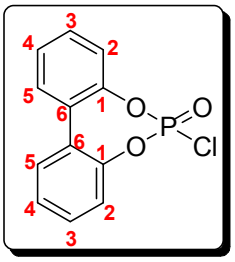


(*R,*S)-(+)-1,1'-Binaphthyl-2,2'diyl-*N*-(α-(*S*)-methylbenzyl) phosphoramidate (*R,*S)-(+)-96: Prepared by modification of the protocol developed by Hu[86]. The crude phosphoric acid chloride **101** was dissolved in CH_2Cl_2 (10 mL) and cooled in a salt-ice bath. A solution of (*S*)-methylbenzylamine (1.4 mL, 10.5 mmol) and triethylamine (1.67 mL, 12.08 mmol) in CH_2Cl_2 (10 mL) was added. The mixture was left to stir for 30 minutes then allowed to reach room temperature and left to stir for 36 hours. The solution was then washed with 0.5M HCl (20 mL) and brine (25 mL), dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude mixture (70%) of diastereomers was dissolved in refluxing ethanol (50 mL) and left to recrystallise over 48 hours to afford **(*R,*S)-(+)-96** as yellow crystals; **$[\alpha]_D$** = +316^{o}; **^{1}H NMR** (400MHz, $CDCl_3$) δ_H 1.48 (3H, d, *J* = 6.8 Hz,), 3.31 (1H, t, *J* = 10.4 Hz, NH), 4.42 (1H, m,), 6.69 – 7.50 (12H, m), 7.53 (1H, d, *J* = 4.8 Hz), 7.77 (1H, d, *J* = 9.2 Hz), 7.85 (2H, dd, *J* = 2.8 Hz, *J* = 8.4 Hz), 7.93 (1H, d, *J* = 8.8 Hz); **^{31}P NMR** (160 MHz, $CDCl_3$) δ_P 12.30 in agreement with the literature.[86]



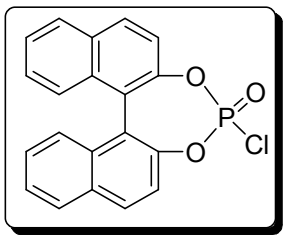
(*S*)-(-)-*tert*-butyl-1-(3,5-dimethylphenylcarbamoyl)-2-methylpropylcarbamate

(*S*)-(-)-100: Methyl chloroformate (0.55 mL, 7.15 mmol) was added dropwise to a stirred solution of **(*S*)-70** (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 (*S*)-*tert*-butyl-1-(3,5-dimethylphenylcarbamoyl)-2-methylpropylcarbamate **(*S*)-(-)-100** as a white solid; **mp** 137 – 140 ^{o}C; **[α]$_{D}$** -12.0 (*c* = 0.5, $CHCl_3$); **^{1}H NMR** (400MHz, $CDCl_3$) δ_H 0.75 (6H, d, *J* = 6.8 Hz, 4-H, 5-H), 1.37 (9H, s, 8-H), 2.20 (6H, s, 15-H), 2.24 (1H, m, 3-H), 4.04 (2H, m, 2-H), 5.36 (1H, d, *J* = 8.4 Hz, 2-NH), 6.59 (1H, s, 12-H), 7.18 (2H, s, 10-H, 14-H), 8.46 (1H, bs, 1-NH); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 17.6 (CH_3, 4-C), 18.3 (CH_3, 5-C), 20.2 (CH_3, 13-C), 27.3 (CH_3, 8-C), 30.2 (CH, 3-C), 59.9 (CH, 2-C), 78.9 (C, 7-C), 116.7 (CH, 10-C), 124.7 (CH, 12-C), 136.6 (C, 9-C), 137.3 (C, 11-C), 155.5 (C, 6-C), 169.9 (C, 1-C); **MS EI** *m/z* (%) 320.1 (100, M), 121.1 (100), 72.1 (88), 57.1 (73); **HRMS** (EI) 320.2100 ($C_{18}H_{28}N_2O_3$ requires 320.2099); **Anal. Calcd.** for $C_{18}H_{28}N_2O_3$: C 66.79 H 7.56 N 10.16. Found C 66.49 H 8.78 N 9.03.

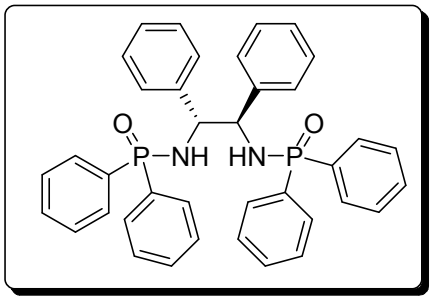


Biphenyl-2,2'-chlorophosphate 101: 2,2'-biphenol (2,00 g, 10.7 mmol) was dissolved in toluene (25 mL) and cooled to 0 ^{o}C. To the reaction mixture, a solution of $POCl_3$ (2.40 mL, 16.0 mmol) and Et_3N (4.5 mL, 32.0 mmol) was added slowly. The reaction mixture was then allowed to warm to room temperature and stirred for 36 h after which the solid residue was removed via vacuum filtration and the solution concentrated *in vacuo* to afford **101** as a yellow oil 95%: **^{1}H NMR** (400MHz, $CDCl_3$) δ_H

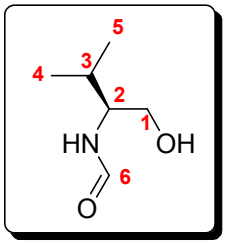
^{13}C NMR (100 MHz, $CDCl_3$) δ_C 120.7 (CH), 126.7 (CH), 127.3 (6-C), 129.4 (CH), 129.7 (CH), 146.7 (1-C); **^{31}P NMR** (160 MHz, $CDCl_3$) δ_P 10.17; **EI MS** *m/z* (%) 266.0 (100, M)**,** 168.1 (76), 139.1 (24), 82.9 (48); **HRMS** (EI) 265.9900 ($C_{12}H_8O_3ClP$ requires 265.9902) in agreement with literature.[87]



Phosphoric acid chloride 102: Prepared following the protocol developed by Hu[86]. Racemic Binol (3 g, 10.5 mmol) was slurried in CH_2Cl_2 (100 mL) and $POCl_3$ (2.25 g, 14.7 mmol) was added followed by slow addition with stirring of triethylamine (2.6 g, 25.5 mmol) so as to maintain gentle reflux. After 1h the reaction mixture was washed with water (25 mL) and evaporated to afford the crude acid chloride **102** which was carried on without purification.

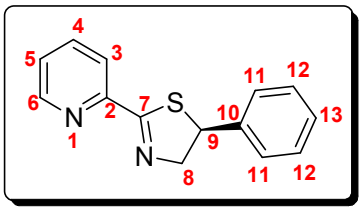


(*R*),(*R*)-105: Diamine **(-)-104** (50 mg, 0.24 mmol) was dissolved in CH_2Cl_2 (2 mL) and diphenylphosphinic acid chloride (110 mg, 0.50 mmol) and triethylamine (0.14 mL, 0.60 mmol) were added. The mixture was allowed to stir at room temperature overnight after which the solvent was removed. The residue was then dissolved in EtOAc (10 mL) and washed with sat. $NaHCO_3$ solution (10 mL), 1M HCl (10 mL) and brine (10 mL). The organic phase was dried over $MgSO_4$ and the solvent removed under reduced pressure. The residue was then recrystallised from toluene to afford **(*R*),(*R*)-105** as an off white solid (72%): **^{1}H NMR** (400MHz, $CDCl_3$) δ_H 4.19 (2H, m, 1-H), 5.81 (2H, m, NH), 6.77 (4H, m, Ar-H), 7.04 (6H, m, Ar-H), 7.15 (6H, m, Ar-H), 7.32 (8H, m, Ar-H), 7.43 (2H, m, Ar-H), 7.58 (4H, m, Ar-H), 7.71 (4H, m, Ar-H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 61.7 (CH), 126.9 (CH), 127.4 (CH), 128.0 (CH), 128.1 (CH), 128.3 (CH), 128.4 (CH), 128.5 (CH), 131.0 (C), 131.5 (CH), 131.6 (CH), 131.6 (CH), 131.8 (C), 131.9 (C), 131.9 (CH), 133.0 (CH), 141.9 (C), 142.0 (C); **MS FAB** *m/z* (%) 613.1 (77, M+H), 396.1 (48), 306.1 (86), 201.5 (100), 107.7 (41); **HRMS** (FAB) 613.2174 ($C_{38}H_{35}N_2O_2P_2$ requires 613.2179).

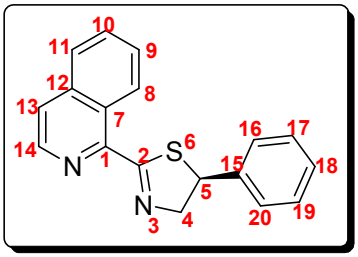


(*S*)-(-)-*N*-Formyl-valinol: Valinol (4.64 g, 44.9 mmol) was dissolved in ethyl formate (20 mL) and allowed to reflux for 16h. The solvent was removed in vacuo to afford *N*-Formyl-valinol as a yellow oil which was carried on without purification; **$[\alpha]_D$** -32.9 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (400MHz, $CDCl_3$) δ_H 0.90 (3H, d, $J_{4\text{-}H,3\text{-}H}$ = 6.8 Hz, 4-H), 0.98 (3H, d, $J_{5\text{-}H,3\text{-}H}$ = 6.8 Hz, 5-H), 1.85 (1H, m, 3-H) 2.29 (1H, m, 2-H), 3.34 (1H, dd, $J_{1\alpha\text{-}H,1\beta\text{-}H}$, $J_{1\alpha\text{-}H,2\text{-}H}$ = 10.4 Hz, 1α-H), 3.64 (1H, dd, $J_{1\alpha\text{-}H,1\beta\text{-}H}$ = 6.4 Hz, $J_{1\beta\text{-}H,2\text{-}H}$ = 4.0 Hz, 1β-H), 8.19 (1H, s, 6-H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 18.6 (CH, 4-C), 19.3 (CH, 5-C), 29.3 (CH, 3-C), 55.9 (CH, 2-C), 63.3 (CH_2, 1-C), 165.7 (C, 6-C); **CI MS** *m/z* (%) 132.2 (100, M+H), 114.2 (45), 104.2 (22); **HRMS** (CI) 132.1025 ($C_6H_{14}NO_2$ requires 132.1022); **Anal. Calcd.** for $C_7H_{15}NO_2$: C 57.90 H 10.41N 9.65. Found: C 57.87 H 10.36 N 9.47 in agreement with literature values.[88]

Quinoline Derived Organocatalysts



(*S*)-(-)-2-(5-Phenyl-4,5-dihydro-thiazol-2-yl)-pyridine (*S*)-(-)-119: To a solution of **(*S*)-130** (1.29 g, 4.99 mmol) in THF (15 mL) at 0°C was added mesyl chloride (0.57 mL, 7.01 mmol) and triethylamine (2.15 mL, 14.3 mmol). The reaction was then allowed to stir at room temperature for 48h. Water (10 mL) was then added and the mixture extracted with DCM (3 x 20 mL). The organic layer was dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude solid was then purified on a column of silica gel (20 g) with a Pet Ether-EtOAc mixture (1:1) to afford an off white solid which was recrystallised from EtOH to afford 2-(5-Phenyl-4,5-dihydro-thiazol-2-yl)-pyridine **(*S*)-(-)-119** as a white crystalline solid (0.98 g, 82%); **mp** 105 – 106 °C; **$[\alpha]_D$** –77.50 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.60 (1H, dd, $J_{8\alpha\text{-H},8\beta\text{-H}}$ = 16.4 Hz, $J_{9\text{-H},8\alpha\text{-H}}$ = 5.8 Hz, 8α-H), 4.82 (1H, dd, $J_{8\alpha\text{-H},8\beta\text{-H}}$ = 16.4 Hz, $J_{9\text{-H},\beta\text{-H}}$ = 9.1 Hz, 8β-H), 4.99 (1H, dd, $J_{9\text{-H},8\alpha\text{-H}}$ = 5.8 Hz, $J_{9\text{-H},\beta\text{-H}}$ = 9.1 Hz, 9-H), 7.17 – 7.33 (6H, m), 7.73 (1H, dt, *J* = 7.8 Hz, *J* = 1.8 Hz), 8.05 (1H, dt, *J* = 7.8 Hz, *J* = 1.0 Hz), 8.60 (1H, ddd, *J* = 4.8 Hz, *J* = 1.0 Hz, *J* = 0.8 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 53.5 (CH, 9-C), 73.9 (CH_2, 8-C), 121.6 (CH), 125.5 (CH), 127.2 (CH), 127.7 (CH), 128.9 (CH), 136.6 (CH), 142.2 (C, 2-C), 149.4 (CH), 151.2 (C, 9-C), 170.2 (C, 7-C); **MS EI+** *m/z* (%) 240.1 (M+, 100), 118.0 (49), 78.0 (74), 51.0 (20); **HRMS** (EI) 240.0721 ($C_{14}H_{12}N_2S$ requires 240.0718).

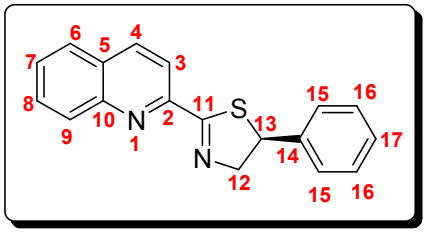


(*S*)-(-)-1-(5-Phenyl-4,5-dihydro-thiazol-2-yl) isoquinoline (*S*)-(-)-120:

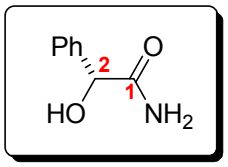
Method A: (*R*)-(-)-*N*-(2-hydroxy-2-phenylethyl)isoquinoline-1-carboxyamide **(*R*)-136** (100 mg, 0.34 mmol) and Lawesson's reagent (165 mg, 0.41 mmol) were dissolved in HMPA (2.0 mL) and heated at 120 ^{o}C overnight. The reaction mixture was then allowed to cool down and acidified to pH = 3 with 2M HCl and the precipitate filtered off. The filtrate was then extracted with CH_2Cl_2 (3 x 30 mL) and the organic layer washed with water (3 x 15 ml). The organic layer was dried over $MgSO_4$, filtered and the solvent removed. The crude residue was then purified on a column of silica gel with a Petrol – EtOAc mixture (5:1) to afford **(*S*)-(-)-120** as a brown oil (7 mg, 7%).

Method B: (*R*)-138 (253 mg, 0.71 mmol) and Lawesson's reagent (344 mg, 0.85 mmol) were dissolved in toluene (20 mL) and heated at 85 ^{o}C overnight. The reaction mixture was then allowed to cool down and acidified to pH = 3 with 2M HCl and the precipitate filtered off. The filtrate was then extracted with CH_2Cl_2 (3 x 30 mL) and the organic layer washed with water (3 x 15 ml). The organic layer was then dried over $MgSO_4$, filtered and the solvent removed. The crude residue was then purified on a column of silica gel with a Pet Ether – EtOAc mixture (5:1) to afford **(*S*)-(-)-120** as a yellow oil (74%): **$[\alpha]_D$** = -22.9^{o} (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (400MHz, $CDCl_3$) δ_H 4.78 (1H, dd, *J* = 4.3, 15.2 Hz, 2-H), 4.83 – 4.89 (1H, m, 1α-H), 5.02 – 5.06 (1H, m, 1β-H), 7.17 (m, 1H), 7.21 – 7.25 (m, 2H), 7.33 – 7.35 (m, 2H), 7.59 – 7.66 (m, 3H), 7.89 - 7.97 (m, 1H), 8.52 (d, *J* = 5.6 Hz, 1H), 9.42 (dd, *J* = 1.5, 7.8 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 52.2 (CH, C-2), 75.2 (CH_2, C-1), 123.2 (CH), 126.4 (C-3), 127.0 (CH), 127.2 (CH), 127.5 (CH), 127.6 (CH), 128.9 (CH), 130.4 (CH), 136.9 (C-14), 141.5 (CH), 142.4 (CH), 149.2 (C-9), 168.1 (C-8), 170.9 (C-7); **MS EI** *m/z*

(%) 290.1 (M+, 100), 186.0 (44), 128.0 (92), 91.0 (28); **HRMS** EI 290.0878 ($C_{18}H_{14}N_2S$ requires 290.0879).

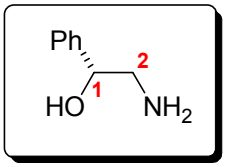


(*S*)-(+)-2-(5-Phenyl-4,5-dihydro-thiazol-2-yl)-quinoline (*S*)-(+)-122: Reaction carried out on a 3.66 mmol scale utilising the same procedure as for **(*S*)-(-)-119**. After recrystallisation from EtOH **(*S*)-(+)-122** was isolated as black crystals (77%); **mp** 118 – 120 °C; **$[\alpha]_D$** +126.6 ($CHCl_3$, *c* = 0.25); **^{1}H NMR** (400MHz, $CDCl_3$) δ_H 4.66 (1H, dd, $J_{12\alpha\text{-}13}$ = 6.0 Hz, $J_{12\alpha\text{-}12\beta}$ = 16.4 Hz, 12α-H), 4.87 (1H, dd, $J_{12\beta\text{-}13}$ = 9.2 Hz, $J_{12\alpha\text{-}12\beta}$ = 16.8 Hz, 12β-H), 5.02 (1H, dd, $J_{12\alpha\text{-}13}$ = 6.0 Hz, $J_{12\beta\text{-}13}$ = 9.2 Hz, 13-H), 7.20 (1H, m, Ar-H), 7.25 (2H, m, Ar-H), 7.32 (2H, m, Ar-H), 7.53 (1H, m, Ar-H), 7.67 (1H, m, Ar-H), 7.78 (1H, m, Ar-H), 8.15 (3H, m, Ar-H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 53.4 (CH, 12-C), 74.1 (CH_2, 13-C), 118.7 (CH), 127.3 (CH), 127.6, (CH), 127.7 (CH), 127.9 (CH), 128.9 (CH), 128.9 (C), 130.0 (CH), 130.1 (CH), 136.6 (CH), 142.3 (C), 147.6 (C), 151.1 (C), 171.0 (C); **MS CI** *m/z* (%) 291.2 (100, M+H); **HRMS** (CI) 291.0956 ($C_{18}H_{15}N_2S$ requires 291.0953).

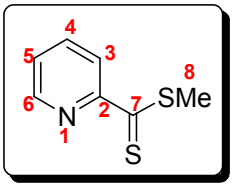


(*R*)-(-)-2-Hydroxy-2-phenyl acetamide (*R*)-(-)-127: Prepared according to the protocol of Brunner[78], acetyl chloride (4.4 mL) was added to a solution of (*R*)-mandelic acid (8.4 g, 54.6 mmol) in methanol (200 mL) at 0 °C. The reaction was then allowed to reach room temperature and stirred overnight. The solvent was then removed and the solid residue dissolved in a mixture of methanol (150 mL) and aqueous ammonium hydroxide (28%, 445 mL) and stored in the fridge

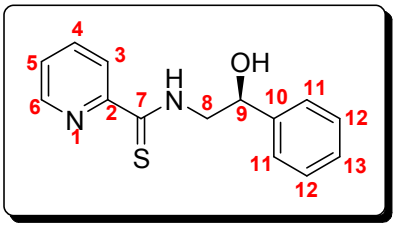
overnight. The solvent was then removed and the solid residue recrystallised from toluene to give pure amide (90%) as a white solid: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 2.19 (1H, bs, OH), 5.11 (1H, s, 2-H), 5.59 (1H, bs, NH), 6.02 (1H, bs, NH), 7.36-7.47 (5H, m, Ar) in agreement with the literature.[78]



(*R*)-(-)-2amino-1-phenyl ethanol (*R*)-(-)-124: Prepared according to the protocol developed by Brunner[78], to a suspension of (*R*)-(-)-2-Hydroxy-2-phenyl-acetamide **(*R*)-(-)-127** (1.88 g, 12.4 mmol) in THF (100 mL) at 0 ^oC was slowly added $LiAlH_4$ (1.2 g, 31.03 mmol). The reaction was allowed to stir at this temperature for 2 h and was then heated overnight at 70 ^oC. The mixture was then cooled to 0 ^oC, $NaSO_4.10H_2O$ was added to remove excess $LiAlH_4$ and the mixture was then filtered through Celite. The solvent was then removed *in vacuo* to afford (*R*)-(-)-2-amino-1-phenyl ethanol as a yellow oil (84%); **$[\alpha]_D$** -26.6 (*c* = 0.5, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 1.78 (bs, 3H), 2.74 (1H, dd, $J_{2\alpha,2\beta}$ = 12.8 Hz, $J_{1,2\alpha}$ = 7.8 Hz, 2α-H), 2.93 (1H, dd, $J_{2\alpha,2\beta}$ = 12.8 Hz, $J_{1,2\beta}$ = 4.0 Hz, 2β-H), 4.56 (1H, dd, $J_{1,2\alpha}$ = 7.8 Hz, $J_{1,2\beta}$ = 4.0 Hz, 1-H), 7.19-7.36 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 49.2 (CH_2, 2-C), 68.0 (CH, 1-C), 126.0 (CH), 127.7 (CH), 128.5 (CH), 142.6 (C); **MS CI** *m/z* (%) 138.2 (100, M+H), 120.2 (70); **HRMS** (CI) 138.0919 ($C_8H_{12}NO$ requires 138.0918) in accordance with the literature.[78]

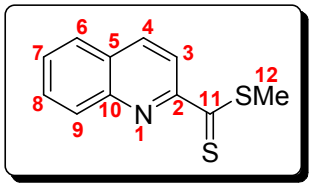


Methyl 2-pyridylthiocarboxylate 129: Prepared according to the protocol developed by Metzner *et al*.[89] To a mixture of 2-picolylchloride hydrochloride (2.0 g, 12.2 mmol) in DCM (5.0 mL) and H_2O (5.0 mL), was added a saturated aqueous solution of $NaHCO_3$ until neutralisation. The mixture was then extracted with DCM and the organic layer dried over $MgSO_4$. The solvent was removed to afford the free amine. Sulfur (1.18 mg, 34.5 mmol), DMF (6.0 mL) and triethylamine (5.0 mL, 34.5 mmol) were added to the free amine and the mixture was allowed to stir for 18h. The reaction mixture was then cooled to 0 ^{o}C and methyl iodide (6.8 mL, 109 mmol) was added dropwise. The reaction mixture was then stirred at room temperature for 20 minutes after which ether was added until the mixture was homogeneous. The reation mixture was then washed with brine (20 mL) and the red aqueous layer extrated with ether until it became yellow. The organic layer was then dried over $MgSO_4$ and the solvent removed *in vacuo*. The residue was then purified on a column of silica gel (25 g) with a Pet Ether-EtOAc mixture (1:1) to afford methyl 2-pyridylthiocarboxylate as deep red crystals (1.05 g, 51%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 2.68 (3H, s, 8-H), 7.41 (1H, ddd, *J* = 7.6 Hz, *J* = 4.8 Hz, *J* = 1.2 Hz), 7.72 (1H, dt, *J* = 7.8 Hz, *J* = 1.8 Hz), 8.26 (1H, dt, *J* = 8.1 Hz, *J* = 1.0 Hz), 8.56 (1H, ddd, *J* = 1.0 Hz, *J* = 4.8 Hz, *J* = 1.8 Hz) in agreement with literature.[89]

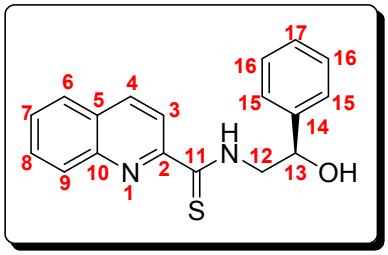


N-((*S*)-2-hydroxy-2-phenylethyl)pyridine-2-carbothioamide (*S*)-130: Prepared by modification of the protocol developed by Masson[90]. To a solution of thioester

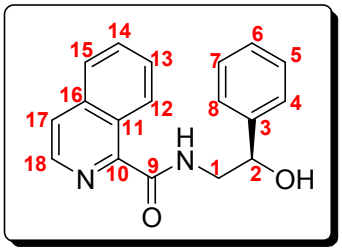
129 (1.05 g, 6.4 mmol) in THF was added amino alcohol (1.20 g, 8.5 mmol) and triethylamine (1.12 mL, 8.5 mmol). The reaction mixture was allowed to stir at room temperature for 18h after which the solvent was removed *in vacuo*. The residue was then purified on a column of silica gel (35 g) wlth a Pet Ether-EtOAc mixture (1:1) to afford Pyridine-2-carbothioic acid (2-hydroxy-2-phenyl-ethyl)-amide as a colourless oil (1.289 g, 78%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.82 (1H, ddd, *J* = 10.1 Hz, *J* = 8.8 Hz, *J* = 4.8 Hz, 8α-H) 4.35 (1H, ddd, *J* = 13.9 Hz, *J* = 7.1 Hz, *J* = 3.3 Hz, 8β-H) 5.11 (1H, dd, *J* = 8.8 Hz, *J* = 3.3 Hz, 9-H), 7.24 – 7.42 (6H, m), 7.77 (1H, dt, *J* = 7.8 Hz, *J* = 1.7 Hz), 8.42 (1H, ddd, *J* = 4.8 Hz, *J* = 1.8 Hz, *J* = 1.0 Hz), 8.63 (1H, dt, 8.1 Hz, *J* = 1.0 Hz), 10.50 (1H, bs, *N*-H).



Methyl 2-quinolinylldithiocarboxylate 132: Reaction carried out on a 4.67 mmol scale utilising the same procedure as for **129**[89]. The residue was purified on a column of silica gel (25 g) with a Pet Ether-EtOAc mixture (1:1) to afford **132** as a deep pink solid (1.02 g, 100%); **mp** 98 – 101 ^{o}C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 2.73 (3H, s, 12-H), 7.57 (1H, ddd, *J* = 1.3 Hz, *J* = 7.1 Hz, *J* = 8.1 Hz), 7.72 (1H, ddd, *J* = 1.3 Hz, *J* = 6.8 Hz, *J* = 8.3 Hz), 7.79 (1H, dd, *J* = 1.0 Hz, *J* = 8.3 Hz), 8.16 (2H, dd, *J* = 3.0 Hz, *J* = 8.6 Hz), 8.37 (1H, d, *J* = 8.6 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 20.2 (CH_3, 12-C), 119.5 (C, 5-C), 127.6 (CH), 128.4 (CH), 129.5 (C, 10-C), 130.4 (CH), 130.6 (CH), 136.6 (CH), 146.3 (C, 2-C), 228.7 (C, 11-C); **MS FAB** *m/z* (%) 220.3 (M+H, 100), 172.8 (69), 154.9 (40), 137.2 (46), 129.3 (38); **HRMS** (FAB) 220.0255 ($C_{11}H_{10}NS_2$ requires 220.0252).

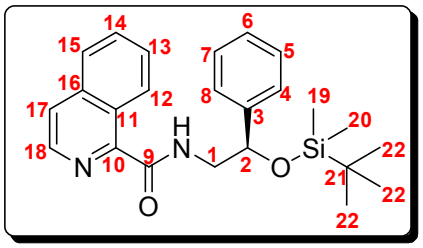


(*R*)-Quinoline-2-carbothioic acid (2-hydroxy-2-phenyl-ethyl)-amide (*R*)-133: Reaction carried out on a 4.67 mmol scale utilising the same procedure as for **130**[90]. **133** was isolated as a yellow/orange oil (1.13 g, 78%); **^{1}H NMR** (400MHz, $CDCl_3$) δ_H 3.91 (1H, ddd, *J* = 4.8 Hz, *J* = 8.6 Hz, $J_{12\alpha\text{-H,NH}}$ = 13.6 Hz, 12α-H), 4.41 (1H, ddd, *J* = 3.5 Hz, *J* = 7.1 Hz, $J_{12\beta\text{-H,NH}}$ = 13.9 Hz, 12β-H), 5.18 (1H, dd, *J* = 3.5 Hz, *J* = 8.8 Hz, 13-H), 7.27 – 7.30 (1H, m), 7.34 – 7.38 (2H, m), 7.43 – 7.48 (2H, m), 7.56 (1H, ddd, *J* = 1.3 Hz, *J* = 7.1 Hz, *J* = 8.1 Hz), 7.70 (1H, ddd, *J* = 1.3 Hz, *J* = 6.8 Hz, *J* = 8.3 Hz), 7.80 (1H, d, *J* = 7.8 Hz), 8.02 (1H, d, *J* = 8.6 Hz), 8.21 (1H, d, *J* = 8.6 Hz), 8.77 (1H, d, *J* = 8.6 Hz), 10.70 (1H, bs, NH); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 52.9 (CH_2, 12-C), 72.6 (CH, 13-C), 121.4 (CH), 125.9 (CH), 127.7 (CH), 128.1 (CH), 128.3 (CH), 128.8 (CH), 129.2 (C, 14-C), 129.9 (CH), 130.4 (CH), 137.0 (CH), 141.5 (C, 5-C), 145.5 (C, 10-C), 150.2 (C, 2-C), 192.1 (C, 11-C).



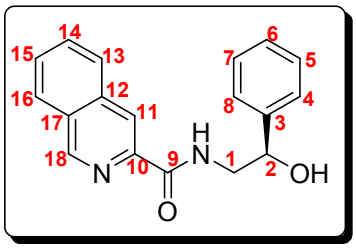
(*R*)-(-)-*N*-(2-hydroxy-2-phenylethyl)isoquinoline-1-carboxyamide (*R*)-(-)-136: Methylchloroformate (0.68 mL, 8.79 mmol) was added dropwise to a solution of 1-isoquinoline carboxylic acid, **135** (1.17 g, 7.33 mmol) and triethylamine (1.23 mL, 8.79 mmol) in THF (30 mL) at 0 ^{o}C and stirred at that temperature for 1 h. The precipitate was removed by filtration *in vacuo* and the filtrate added to a solution of (*R*)-2-amino-1-phenyl-ethanol, **124** , (1.19 g, 8.79 mmol) and triethylamine (1.23

mL, 8.79 mmol) in THF (30 mL) at 0 °C and the mixture allowed to reach room temperature and stirred overnight. The solvent was then removed and the residue purified on a column of silica gel with a Petrol – EtOAc mixture (1:1) to afford **(*R*)-(-)-136** as a white solid (89%); **[α]$_D$** -78.6 (*c* = 0.5, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.48 (1H, ddd, $J_{1\alpha,1\beta}$ = 13.9 Hz, $J_{1\alpha,2}$ = 8.6 Hz, $J_{1\alpha,NH}$ = 5.3 Hz, 1α-H), 3.85 (1H, ddd, $J_{1\alpha,1\beta}$ = 13.9 Hz, $J_{1\beta,NH}$ = 7.1 Hz, , $J_{1\beta,2}$ = 3.3 Hz, 1β-H), 5.08 (1H, dd, $J_{1\alpha,2}$ = 8.6 Hz, $J_{1\beta,2}$ = 3.3 Hz, 2-H), 7.15-7.26 (3H, m), 7.37 (2H, d, *J* = 7.1 Hz,), 7.49-7.57 (2H, m), 7.59 (d, *J* = 5.3 Hz, 2H), 7.70 (1H, d, *J* = 7.6 Hz,), 8.17 (1H, d, *J* = 5.6 Hz,), 8.67 (1H, t, *J* = 5.8 Hz, 18-H), 9.30 (1H, d, *J* = 8.6 Hz, 12-H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 47.9 (CH, 1-C), 74.2 (CH_2, 2-C), 124.6 (CH), 125.9 (CH), 126.9 (CH), 127.1 (C, 3-C), 127.7 (CH), 127.9 (CH), 128.6 (CH), 128.8 (CH), 130.6 (CH), 137.4 (C, 11-C), 140.28 (CH), 141.9 (C, 16-C), 147.9 (C, 10-C), 167.5 (C, 9-C) **CI MS** *m/z* (%) 293 ([M+H]$^+$, 100), 275 (15), 186 (7), 173 (5), 123 (4), 107 (5); **HRMS** (CI) 293.1288 ($C_{18}H_{17}N_2O_2$ requires 293.1290).

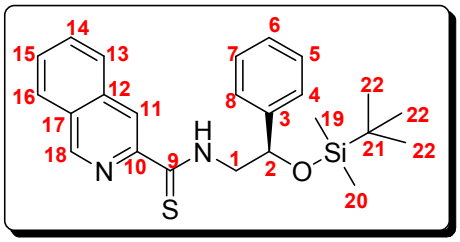


(*R*)-(-)-*N*-(2-*tert*-butyldimethylsilanoxy-2-phenylethyl)isoquinoline-1-carboxyamide (*R*)-(-)-138: **(*R*)-136** (500 mg, 1.71 mmol), *tert*-butyldimethylsilyl chloride (309 mg, 2.05 mmol) and imidazole (291 mg, 4.28 mmol) were dissolved in DMF (5 mL) and allowed to stir at room temperature overnight. The mixture was then diluted with aqueous NH_4Cl and extracted with CH_2Cl_2. The organic phase was washed with brine (3 x 25 mL) dried over $MgSO_4$ and the solvent removed under reduced pressure to afford **(*R*)-(-)-138** as a colourless oil (63%); **[α]$_D$** -23.70 (*c* = 1.00, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.01 (6H, s, 19-H, 20-H), 0.82 (9H, s, 22-H), 3.36 (1H, ddd, *J* = 13.89 Hz, *J* = 8.4 Hz, *J* = 4.8 Hz, 1α-H), 3.90 (1H, ddd, *J* = 13.6 Hz, *J* = 8.0 Hz, *J* = 4.0 Hz, 1β-H), 4.90 (1H, dd, *J* = 8.4 Hz, *J* = 4.0 Hz, 2-H), 7.31 – 7.41 (5H, m), 7.65 – 7.84 (3H, m), 8.44 (1H, d, *J* = 5.6 Hz), 8.62 (1H, bs), 9.61 (1H, d, *J* = 5.2 Hz);

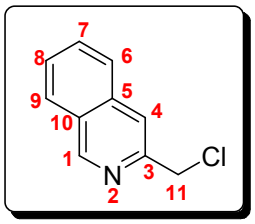
^{13}C NMR (100 MHz, $CDCl_3$) δ_C -4.6 (CH_3, C-19), -3.6 (CH_3, C-20), 18.2 (C-21), 25.7 (CH_3, C-22), 47.9 (CH_2, C-1), 74.0 (CH, C-2); **MS EI** *m/z* (%) 406.14 (M+, 5), 349.11 (42), 221.1 (100), 185.1 (35), 128.0 (54), 73.0 (60); **HRMS** 406.2077 ($C_{24}H_{30}O_2N_2Si$ requires 406.2076); **Anal. Calcd.** for $C_{24}H_{30}N_2O_2Si$: C 70.90 H 7.44 N 6.89. Found C 70.81 H 7.44 N 6.69.



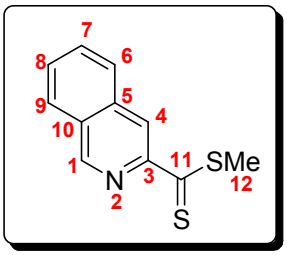
***N*-((*R*)-2-hydroxy-2-phenylethyl)isoquinoline-3-carboxamide (*R*)-140:** Reaction carried out on 2.89 mmol scale utilising the same procedure for **(*R*)-136**. **(*R*)-140** was purified on a column of silica gel with a Petrol – EtOAc mixture (1:1) to afford the product as a white solid (43%); **mp** 104 – 105 ^{o}C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.86 (1H, t, *J* = 10.6 Hz, 1α-H), 4.21 (1H, dd, $J_{1\beta,2}$ = 5.6 Hz, $J_{1\alpha,1\beta}$ = 10.6 Hz, 1β-H), 5.05 (1H, dd, $J_{1\beta,2}$ = 5.6 Hz, $J_{1\alpha,2}$ = 10.4 Hz, 2-H), 7.23 – 7.38 (6H, m), 7.59 (1H, dt, *J* = 1.26 Hz, *J* = 6.8 Hz), 7.66 (1H, dt, *J* = 1.3 Hz, *J* = 6.8 Hz), 7.84 (1H, d, *J* = 8.3 Hz), 7.90 (1H, d, *J* = 8.3 Hz), 8.22 (1H, s), 9.07 (1H, s); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 55.7 (CH_2, 1-C), 76.8 (CH, 2-C), 121.7 (CH), 126.4 (CH), 126.6 (CH), 127.5 (CH), 127.7 (CH), 128.5 (CH), 128.5 (CH), 128.6 (CH), 128.9 (C), 130.9 (CH), 135.9 (C), 137.7 (C), 148.4 (C), 150.8 (CH), 164.7 (9-C); **CI+ MS** *m/z* (%) 293.3 (M+H, 100), 275.3 (15), 107.2 (72), 85.2 (88); **HRMS** (CI+) 293.1290 ($C_{18}H_{17}N_2O_2$ requires 293.1288).



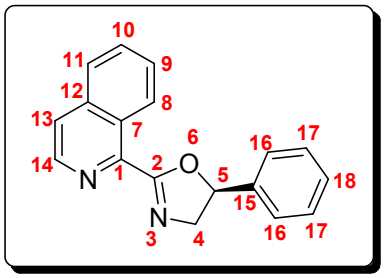
***N*-((*R*)-2-*tert* butyldimethylsilyloxy-2-phenylethyl)isoquinoline-3-carboxamide (*R*)-141:** Reaction carried out on 1.26 mmol scale utilising the same procedure for **(*R*)-138**. **(*R*)-141** was isolated as a colourless oil (59%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.01 (6H, s, 19-H, 20-H), 0.84 (9H, s, 22-H), 3.84 (1H, t, *J* = 10.6 Hz, 1α-H), 4.20 (1H, dd, $J_{1\alpha,1\beta}$ = 10.8 Hz, $J_{1\beta,2}$ = 5.3 Hz, 1β-H), 5.04 (1H, dd, $J_{1\alpha,2}$ = 10.4 Hz, $J_{1\beta,2}$ = 5.6 Hz, 2-H), 7.22 – 7.37 (6H, m), 7.58 (1H, dt, *J* = 1.26 Hz, *J* = 6.8 Hz), 7.65 (1H, dt, *J* = 1.3 Hz, *J* = 6.8 Hz), 7.83 (1H, d, *J* = 8.3 Hz), 7.87 (1H, d, *J* = 8.3 Hz), 8.20 (1H, s), 9.06 (1H, s); **CI MS** *m/z* (%) 423.3 (100, M+H), 155.2 (54); **HRMS** (CI) 423.1926 ($C_{24}H_{31}N_2OSiS$ requires 423.1923).



Chloromethyl-3-isoquinoline 143: Prepared according to a literature procedure[91]. Methyl-3-isoquinoline (250 mg, 1.75 mmol) and trichloroisocyanuric acid (162 mg, 0.7 mmol) were refluxed in $CHCl_3$ (10 mL) overnight, the mixture was then cooled to room temperature and filtered. The filtrate was diluted with CH_2Cl_2 (20 mL) and washed with NaOH (2M, 2 x 15 mL) and brine (2 x 15 mL). The organic phase was then dried over $MgSO_4$, filtered and evaporated to afford **143** as a colourless oil (311 mg, 100%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.01 (2H, s, 11-H), 7.65 (1H, ddd, *J* = 1.3 Hz, *J* = 7.1 Hz, *J* = 8.1 Hz), 7.78 (1H, m), 7.94 (1H, m), 8.19 (1H, m), 9.11 (1H, d, *J* = 6.6 Hz) in agreement with literature values.[91]

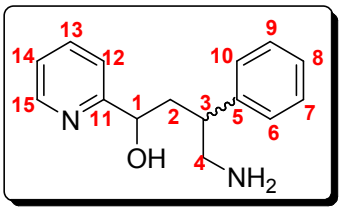


Methyl-3-isoquinolinylthiocarboxylate 144: Prepared by modification of the protocol of Metzner *et al*[89] To a solution of **143** (311 mg, 1.75 mmol) in DMF (6.0 mL) was added sulfur (169 mg, 4.95 mmol) and triethylamine (0.69 mL, 4.95 mmol) were added and the mixture was allowed to stir for 18h. The reaction mixture was then cooled to 0°C and methyl iodide (0.97 mL, 15.6 mmol) was added dropwise. The reaction mixture was then stirred at room temperature for 20 minutes after which ether was added until the mixture was homogeneous. The reaction mixture was then washed with brine (20 mL) and the red aqueous layer extracted with ether until it became yellow. The organic layer was then dried over $MgSO_4$ and the solvent removed *in vacuo*. The residue was then purified on a column of silica gel (25 g) with a Pet Ether-EtOAc mixture (1:1) to afford **144** as brown solid (50%); **mp** 91-93 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 2.81 (3H, s, 12-H), 7.66 (1H, ddd, *J* = 1.0 Hz, *J* = 7.1 Hz, *J* = 8.1 Hz), 7.81 (1H, ddd, *J* 1.3 = Hz, *J* = 6.8 Hz, *J* = 8.3 Hz), 7.98 (1H, d, *J* = 8.3 Hz), 8.27 (1H, d, *J* = 8.6 Hz), 9.1 (1H, s); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 19.2 (CH_3, 12-C), 123.2 (CH), 126.3 (CH), 126.8 (CH), 127.7 (CH), 130.4 (C), 131.1 (CH), 133.3 (C), 149.2 (CH), 151.1 (C), 226.9 (C, 11-C).



(*S*)-(+)-1-(5-phenyl-4,5-dihydro-1,3-oxazol-2-yl)isoquinoline (*S*)-(+)-148. Triethylamine (2.2 mL, 15.6 mmol) was added to a solution of **(*R*)-136** (1.65 g, 5.6

mmol) in CH_2Cl_2 (65 mL). The reaction was then cooled to 0 ˚C and mesyl chloride (0.65 mL, 8.25 mmol) was added dropwise over 15 min. The reaction vessel was then allowed to attain room temperature and stirred overnight. The reaction mixture was washed with water (3 × 40 mL) and the organic layer was dried over $MgSO_4$. Concentration *in vacuo* afforded a residue which was purified *via* column chromatography on silica gel (petroleum ether-ethyl acetate, 1:1) to give an oil which solidified on standing. Recrystallisation from ether gave **(*S*)-(+)-148** (1.2 g, 78%) as a white solid: **mp** 78-80 °C (Et_2O); **$[\alpha]_D$** +83.5 (*c* 0.5, $CHCl_3$); **IR** (KBr) 700, 759, 838 (aryl), 1645 (C=N), 2866, 2931 (CH/CH_2), 3064 (aryl-H) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.19 (1H, dd, $J_{4\alpha\text{-H},4\beta\text{-H}}$ = 15.2 Hz, $J_{4\alpha\text{-H},5\text{-H}}$ = 8.0 Hz, 4α-H), 4.64 (1H, dd, $J_{4\alpha\text{-H},4\beta\text{-H}}$ = 15.2 Hz, $J_{4\beta\text{-H},5\text{-H}}$ = 10.4 Hz, 4β-H), 5.75 (1H, dd, $J_{4\beta\text{-H},5\text{-H}}$ = 10.4 Hz, $J_{4\alpha\text{-H},5\text{-H}}$ = 8.4 Hz, 5-H), 7.27 - 7.39 (m, 5H), 7.61-7.70 (m, 2H), 7.73 (1H, d, *J* = 5.2 Hz), 7.83 (1H, d, *J* = 7.2 Hz), 8.61 (1H, d, *J* = 5.6 Hz), 9.18 (1H, d, *J* = 8.4 Hz); **^{13}C NMR** (100MHz, $CDCl_3$) δ_C 63.9 (CH_2), 80.7 (CH), 123.5 (CH), 126.1 (CH), 127.2 (CH), 127.3 (CH), 127.4 (C), 128.4 (CH), 128.6 (CH), 128.9 (CH), 130.5 (CH), 136.8 (C), 140.7 (C), 141.9 (CH), 146.3 (C), 162.7 (C); **EI MS** *m/z* (%) 274 ($M^{+\bullet}$, 65), 168 (70), 128 (100), 101 (15), 82 (35), 77 (10), 47 (5); **HRMS** (EI) 274.1105 ($C_{18}H_{14}N_2O$ requires 274.1106).

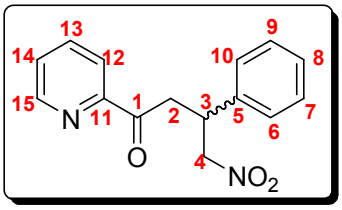


(±)-4-Amino-3-phenyl-1-pyridin-2-yl-butan-1-ol (±)-149:

Method A: $SnCl_2.2H_2O$ (391 mg, 1.74 mmol) and **150** (158 mg, 0.58 mmol) were dissolved in anhydrous EtOH and heated to reflux overnight. The reaction mixture was then allowed to reach room temperature and sat. $NaHCO_3$ was added until pH = 8. The mixture was then extracted with EtOAc (3 x 20 mL), the organic phase was dried over $MgSO_4$, filtered and the solvent removed. Only starting material was isolated.

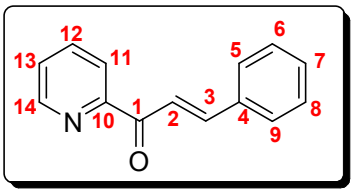
Method B: A solution of **150** (310 mg, 0.57 mmol) in EtOH (5 mL) was added to a round bottomed flask containing Pd/C (50 mg, 30%). The flask was evacuated and filled with hydrogen three times. The mixture was then stirred vigorously overnight at room temperature. The reaction mixture was then filtered, the precipitate washed thoroughly with EtOH and the solvent removed *in vacuo*. Only starting material was isolated.

Method C: To a solution of anhydrous nickel (II) chloride (91 mg, 0.7 mmol) in MeOH (5 mL) at 0 ^{o}C was added $NaBH_4$ (133 mg, 3.5 mmol). The mixture was allowed to stir for 15 min. after which **150** (190 mg, 0.7 mmol) and $NaBH_4$ (266 mg, 7.0mmol) were added. The reaction mixture was then allowed to reach room temperature and allowed to stir for a further 45 min. The mixture was then acidified with 2M HCl and extracted with ethyl acetate (3 x 20 mL). The aqueous phase was then treated with ammonia solution and extracted with CH_2Cl_2 (3 x 20 mL). The CH_2Cl_2 phase was dried over $MgSO_4$ and the solvent removed to give **149** (98%) as a brown oil: **^{1}H NMR (400MHz, $CDCl_3$) δ_H** 2.12 (m, 1H), 2.62 (m, 1H), 2.87 (m, 3H), 4.62 (m, 1H) 7.03 – 7.26 (m, 7H), 7.54 (m, 1H), 8.43 (m, 1H).



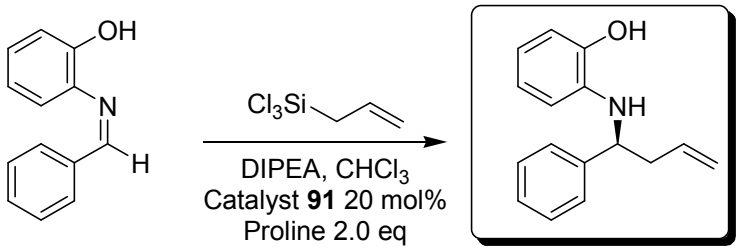
(±)-4-Nitro-3-phenyl-1-pyridin-2-yl-butan-1-one (±)-150: Diethylamine (0.26 mL, 2.5 mmol) and **151** (100 mg, 0.5 mmol) were dissolved in anhydrous methanol (2 mL). Nitromethane (0.14 mL, 2.5 mmol) was added and the mixture heated at reflux overnight. The mixture was then acidified with 2M HCl and extracted with DCM (3 x 20 mL). The organic phase was then dried over $MgSO_4$ and the solvent removed to afford **150** as a brown oil (41%): **^{1}H NMR (400MHz, $CDCl_3$) δ_H** 3.60 (1H, dd, $J_{4\alpha,4\beta}$ = 18.4 Hz, $J_{3,4\alpha}$ = 7.1 Hz, 4α-H), 3.72 (dd, $J_{4\alpha,4\beta}$ = 18.4 Hz, $J_{3,4\beta}$ = 7.1 Hz, 1H, 4β-H), 4.18 (m, 1H), 4.61 (1H, dd, $J_{2\alpha,2\beta}$ = 12.1 Hz, $J_{2\alpha,3}$ = 8.1 Hz, 2α-H), 4.71 (1H, d,

$J_{2\alpha,2\beta}$ = 12.1 Hz, $J_{2\beta,3}$ = 6.6 Hz, 2β-H), 7.22 (m, 5H), 7.41 (t, *J* = 6.3 Hz, 1H), 7.75 (t, *J* = 7.6 Hz, 1H), 7.92 (d, *J* = 7.8 Hz, 1H), 8.59 (1H, d, *J* = 4.3 Hz, 15-H).



3-Phenyl-1-pyridin-2-yl-propenone 151: Adapting the method of Engberts[92] acetyl pyridine (2.06 g, 17.0 mmol) and benzaldehyde (1.85 g, 16.5 mmol) were mixed in water (100 mL) at 4 ^{o}C, 10% aqueous NaOH (10 ml) was added and the mixture stored in the fridge overnight. The mixture was then shaken and filtered and the resulting solid recrystallised from ethanol to give 3-phenyl-1-pyridin-2-yl-propenone **151** as yellow crystals (35%): **^{1}H NMR** (400MHz, $CDCl_3$) δ_H 7.31 – 7.37 (3H, m), 7.43 (1H, ddd, *J* = 7.6, 4.8, 1.3 Hz), 7.67 (2H, m), 7.81 (1H, dt, *J* = 7.8, 1.8 Hz), 7.88 (1H, d, $J_{2,3}$ = 16.2 Hz, 2-H), 8.13 (1H, dt, *J* = 1.0, 8.1 Hz), 8.24 (1H, d, $J_{2,3}$ = 16.2 Hz, 3-H), 8.64 – 8.67 (1H, m); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 120.9 (CH), 121.8 (CH), 122.9 (CH), 126.6 (CH), 126.9 (CH), 128.4 (CH), 130.6 (CH), 135.2 (C), 136.8 (CH), 137.1 (CH), 144.8 (CH), 148.8 (CH), 189.5 (C=O), 200.1 (C); **IR (NaCl)** *v* 1700 (C=0), 1620 (C=C) cm^{-1}; **MS EI HRMS** (EI+) 209.0841 ($C_{14}H_{11}NO$ requires 209.0843) in agreement with the literature.[92]

Organocatalytic Reactions

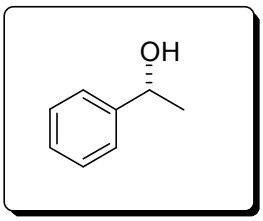


General procedure for the asymmetric allylation of aldimine 111 with allyltrichlorosilane:

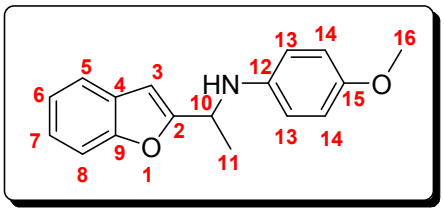
Aldimine **111** (49 mg, 0.25 mmol), proline (57 mg, 0.50 mmol), DIPEA (0.11mL, 0.63 mmol) and catalyst **(*S*)-91** (22 mg, 0.05 mmol) were dissolved in CH_2Cl_2 (2 mL). The solution was allowed to stir at room temperature for 20 minutes after which allyltrichlorosilane (54 µL, 0.37 mmol) was added. The reaction mixture was left to stir for 24 h after which saturated aqueous $NaHCO_3$ (3 mL) was added to quench the reaction. The mixture was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic fractions were dried over $MgSO_4$. Concentration *in vacuo* followed by chromatography on a column of silica gel with a Petrol – EtOAc mixture (4:1) afforded **112** as a slightly yellow oil; **^{1}H NMR** (400MHz, $CDCl_3$) δ_H 2.44 – 2.59 (2H, m), 4.28 – 4.39 (1H, m), 5.05 – 5.11 (2H, m), 5.67 – 5.77 (1H, m), 6.31 (1H, dd, *J* = 8.0 Hz, *J* = 1.6 Hz), 6.48 – 6.51 (1H, m), 6.58 – 6.64 (2H, m), 7.10 – 7.19 (2H, m), 7.24 – 7.87 (4H, m).

General procedure for the asymmetric reduction of ketones and ketimines:

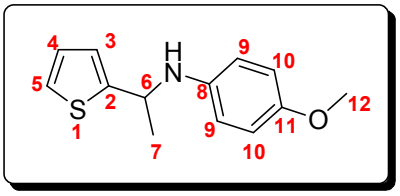
Trichlorosilane (86 µL, 0.84 mmol) was slowly added dropwise to a solution of catalyst (22 mg, 0.08 mmol) and the corresponding ketone (0.40 mmol) in $CHCl_3$ (2 mL) at –20 ˚C. The reaction mixture was stirred for 24 h at -20 ˚C, after which saturated aqueous $NaHCO_3$ (1 mL) was added to quench the reaction. The mixture was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic fractions were dried over $MgSO_4$. Concentration *in vacuo* followed by flash chromatography on silica gel (3 × 15 cm) with CH_2Cl_2 afforded *sec*-alcohol **30**.



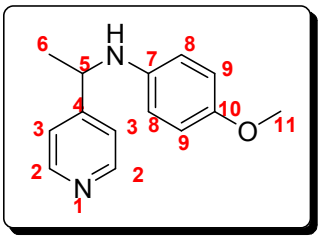
(*R*)-(+)-1-Phenylethanol (*R*)-(+)-30: Isolated as a slightly yellow oil: **$[\alpha]_D$** +45.2 (*c* 0.93, $CHCl_3$, 64% *ee*)[93], gives $[\alpha]_D$ +49.0 (*c* 1.0, $CHCl_3$, 98% *ee*)]; **^{1}H NMR** (400MHz, $CDCl_3$) δ_H 1.52 (d, *J* = 6.4 Hz, 3H), 2.21 (bd, 1H), 4.92 (q, *J* = 6.4 Hz, 1H), 7.28-7.50 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 25.2 (CH_3), 70.4 (CH), 125.4 (CH), 127.5 (CH), 128.5 (CH), 145.9 (C); Chiral GC (Supelco β-DEX^{TM}), carrier gas: He (flow 2 mL/min), injection temp: 220 ˚C; column temp: initial temp, 80 ˚C for 2 min; rate, 1.5 ˚C/min; final temperature 160 ˚C (t_R = 23.31 min; t_S = 24.21 min).



(+)-*N*-(1-(benzofuran-2-yl)ethyl)-4-methoxybenzenamine: 77% yield, purified on a column of silica gel with a Petrol – EtOAc mixture (95:5) to give a colourless oil, Chiral HPLC (Chiracel OJ-H) Hexane:^{i}PrOH 80:20 0.75 mL min^{-1} (t_{major} = 21.27 min, t_{minor} = 24.56 min) showed 75% ee; **$[\alpha]_D$** +181 (*c* = 0.2, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 1.56 (3H, d, $J_{11\text{-H},10\text{-H}}$ = 6.8 Hz, 11-H), 3.65 (3H, s, 16-H), 4.58 (1H, q, $J_{11\text{-H},10\text{-H}}$ = 6.8 Hz, 10-H), 6.45 (1H, s, 3-H), 6.55 (2H, m, 14-H), 6.67 (2H, m, 13-H), 7.12 (2H, m), 7.40 (2H, m); **EI MS** *m/z* (%) 267 (M^+, 65), 145 (100), 123 (44), 115 (42); **HRMS** (EI) 267.1259 ($C_{17}H_{17}N_2O$ requires 267.1261).

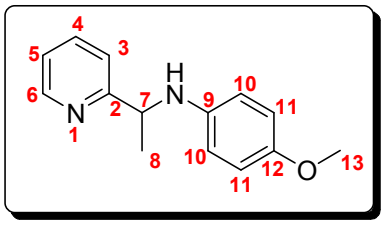


(+)-4-methoxy-*N*-(1-(thiophen-2-yl)ethyl)benzenamine: 77%, yield purified on a column of silica gel with a Petrol – EtOAc mixture (95:5) to give a yellow oil, Chiral HPLC (Chiracel OJ-H) Hexane:^{i}PrOH 80:20 0.75 mL min^{-1} (t_{major} = 24.25 min, t_{minor} = 26.89 min) showed 60% ee; **[α]$_D$** +5.5 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 1.52 (3H, d, $J_{7\text{-H},6\text{-H}}$ = 6.8 Hz, 7-H), 3.65 (3H, s, 12-H), 4.66 (1H, q, $J_{7\text{-H},6\text{-H}}$ = 6.8 Hz, 6-H) 6.52 (2H, m, 8-H), 6.67 (2H, m, 9-H), 6.88 (2H, m, 3-H, 4-H), 7.17 (1H, m, 5-H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 20.5 (CH_3, 7-C), 50.6 (CH, 6-C), 55.7 (CH_3, 12-C), 114.8 (CH), 115.2 (CH), 122.9 (CH), 123.7 (CH), 128.7 (CH), 141.0 (C, 8-C), 150.5 (C, 2-C), 152.5 (C, 11-C); **EI MS** *m/z* (%) 233 (M^+, 39), 216 (54), 123 (37), 111 (92), 83 (100); **HRMS** (EI) 233.0874 ($C_{13}H_{15}NOS$ requires 233.0873).

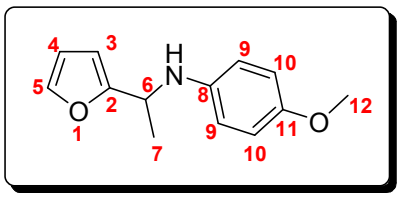


(-)-4-methoxy-*N*-(1-(pyridin-4-yl)ethyl)benzenamine: 70% yield, purified on a column of silica gel with a Petrol – EtOAc mixture (7:3) to give an off-white solid, Chiral HPLC (Chiracel OJ-H) Hexane:^{i}PrOH 80:20 0.75 mL min^{-1} (t_{minor} = 27.89 min, t_{major} = 38.29 min) showed 82% ee; **[α]$_D$** -19.0 (*c* = 1.0, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 1.43 (3H, d, $J_{6\text{-H},5\text{-H}}$ = 6.8 Hz, 6-H), 3.63 (3H, s, 11-H), 4.31 (1H, q, $J_{6\text{-H},5\text{-H}}$ = 6.8 Hz, 5-H), 6.33 (2H, d, $J_{8\text{-H},\ 9\text{-H}}$ = 3.6 Hz, 9-H), 6.61 (2H, d, $J_{8\text{-H},\ 9\text{-H}}$ = 3.6 Hz, 8-H), 7.22 (2H, d, $J_{2\text{-H},\ 3\text{-H}}$ = 2.4 Hz, 3-H), 8.46 (2H, d, $J_{2\text{-H},\ 3\text{-H}}$ = 2.8 Hz, 2-H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 24.6 (CH_3, 6-C), 53.5 (CH, 5-H), 55.7 (CH_3, 11-H), 114.5 (CH), 114.8 (CH), 121.3 (CH), 140.8 (C, 7-C), 149.9 (CH), 152.3 (C, 10-C), 154.9 (C, 4-C); **CI MS** *m/z* (%)

229 (M^+, 100), 213 (8), 123 (15), 108 (12), 71 (15); **HRMS** (CI) 229.1341 ($C_{14}H_{17}N_2O$ requires 229.1342).

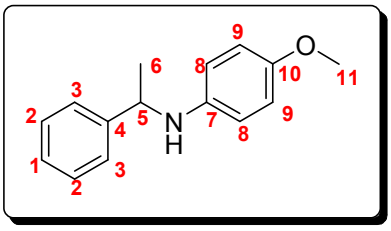


(-)-4-methoxy-N-(1-(pyridin-2-yl)ethyl)benzenamine: purified on a column of silica gel with a Petrol – EtOAc mixture (7:3) to give an off-white solid, Chiral HPLC (Chiracel OJ-H) Hexane:^{i}PrOH 80:20 0.75 mL min^{-1} (t_{minor} = 27.89 min, t_{major} = 38.29 min) showed 79% ee; **[α]$_D$** -15.0 (*c* = 0.1, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 1.45 (3H, d, $J_{8\text{-H},7\text{-H}}$ = 6.8 Hz, 8-H), 3.62 (3H, s, 13-H), 4.47 (1H, q, $J_{8\text{-H},7\text{-H}}$ = 6.8 Hz, 7-H), 6.45 (2H, d, *J* , 10-H), 6.62 (2H, d, 11-H), 7.06 (1H, dd, *J* = 7.2 Hz, *J* = 5.2 Hz, 5-H), 7.27 (1H, d, *J* = 8.0 Hz, 3-H), 7.53 (1H, dt, *J* = 1.6 Hz, *J* = 7.6 Hz, 4-H), 8.50 (d, *J* = 4.98 Hz, 6-H); **EI MS** *m/z* (%) 228 (M^+, 100), 213 (98), 169 (37), 150 (97), 122 (90), 106 (97); **HRMS** (EI) 228.1263 ($C_{14}H_{16}N_2O$ requires 228.1265) in agreement with literature values.[94]

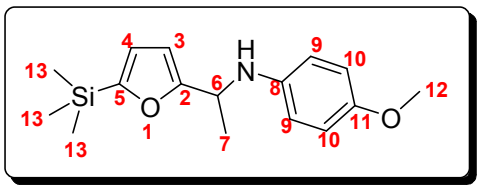


***N*-(1-(furan-2-yl)ethyl)-4-methoxybenzenamine:** 70% yield, purified on a column of silica gel with a Petrol – EtOAc mixture 94:6, , Chiral HPLC (Chiracel OJ-H) Hexane:^{i}PrOH 80:20 0.75 mL min^{-1} (t_{minor} = 41.51 min, t_{major} = 49.19 min) showed 55% ee; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 1.46 (3H, d, $J_{7\text{-H},6\text{-H}}$ = 6.8 Hz, 7-H), 3.66 (3H, s, 12-H), 4.47 (1H, q, $J_{7\text{-H},6\text{-H}}$ = 6.8 Hz, 6-H), 6.06 (1H, d, $J_{3\text{-H},\ 4\text{-H}}$ = 2.4 Hz, 3-H), 6.21 (1H, d, $J_{3\text{-H},\ 4\text{-H}}$ = 2.4 Hz, 4-H), 6.52 (2H, d, $J_{9\text{-H},\ 10\text{-H}}$ = 3.6 Hz, 9-H), 6.67 (2H, d, $J_{9\text{-H},\ 10\text{-H}}$ = 3.6

Hz, 10-H), 7.24 (1H, s, 5-H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 20.9 (CH_3, 7-C), 48.5 (CH, 6-C), 55.7 (CH_3, 12-C), 105.1 (CH, 3-C), 110.1 (CH, 4-C), 114.8 (CH, 9-C), 115.3 (CH, 10-C), 141.0 (C, 8-C), 152.5 (C, 11-C), 157.4 (C, 2-C); **EI MS** *m/z* (%) 217 (M^+, 55), 202 (37), 123 (42), 95 (100); **HRMS** (EI) 217.1103 ($C_{13}H_{15}N_2O$ requires 217.1101) in agreement with literature values.[95]

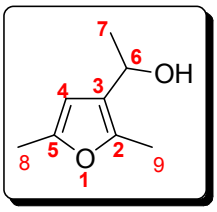


4-methoxy-*N*-(1-phenylethyl)benzenamine: Isolated as a slightly yellow oil, Chiral HPLC (Chiracel OJ-H) Hexane:^{i}PrOH 99:1 0.75 mL min^{-1} (t_{major} = 13.12 min, t_{minor} = 14.36 min) showed 79% ee; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.87 (3H, t, $J_{7\text{-H},6\text{-H}}$ = 7.8 Hz, 7-H), 1.73 (2H, m, 6-H), 3.56 (3H, s, 12-H), 4.08 (1H, t, $J_{6\text{-H},5\text{-H}}$ = 6.8 Hz, 5-H), 6.40 (2H, d, 9-H), 6.59 (2H, d, 10-H), 7.22 (5H, m, 1-H, 2-H, 3-H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 10.9 (CH_3, 7-C), 31.7 (CH_2, 6-C), 55.8 (CH, 5-C), 60.6 (CH_3, 12-C), 114.5 (CH), 114.8 (CH), 126.6 (CH), 126.9 (CH), 128.5 (CH), 141.9 (C, 8-C), 144.2 (C, 4-C), 151.9 (C, 11-C); **EI MS** *m/z* (%) 241 (M^+, 57), 212 (100), 91 (67); **HRMS** (EI) 241.1467 ($C_{16}H_{19}ON$ requires 241.1469) in agreement with literature.[96]

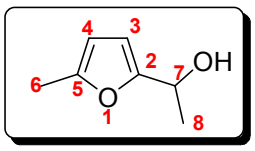


(+)-4-methoxy-*N*-(1-(5-(trimethylsilyl)furan-2-yl)ethyl)benzenamine: Isolated as a colourless oil, **$[\alpha]_D$** +13.4 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.05 (9H, s, 13-H), 1.35 (3H, d, $J_{7\text{-H},6\text{-H}}$ = 6.8 Hz, 7-H), 3.55 (3H, s, 12-H), 4.38 (1H, q, $J_{7\text{-H},6\text{-H}}$ = 6.8 Hz, 6-H), 5.96 (1H, d, $J_{3\text{-H},4\text{-H}}$ = 4.6 Hz, 3-H), 6.31 (1H, d, $J_{3\text{-H},4\text{-H}}$ = 4.8 Hz, 4-H), 6.43

(2H, d, 9-H), 6.57 (2H, d, 10-H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 0.00 (CH_3, 13-C), 22.5 (CH_3, 7-C), 50.2 (CH, 6-C), 57.3 (CH_3, 12-C), 106.5 (CH, 3-C), 116.3 (CH, 4-C), 116.8 (CH, 9-C), 121.7 (CH, 10-C), 142.9 (C, 8-C), 153.9 (C, 11-C), 160.7 (C, 2-C), 163.5 (C, 5-C); **EI MS** *m/z* (%) 289 (M^+, 20), 167 (70), 123 (15), 83 (99), 75 (30), 49 (100); **HRMS** (EI) 289.1498 ($C_{16}H_{23}NO_2Si$ requires 289.1495).



1-(2,5-dimethylfuran-3-yl)ethanol: Isolated as a colourless oil, **^{1}H NMR** (400MHz, $CDCl_3$) δ_H 1.35 (3H, d, *J* = 6.3 Hz, 7-H), 2.16 (3H, s, 8-H), 2.17 (3H, s, 9-H), 4.71 (1H, q, *J* = 6.3 Hz), 5.93 (1H, s, 4-H); Chiral GC (Supelco β-DEX^{TM}), carrier gas: He (flow 2 mL/min), injection temp: 220 ˚C; column temp: initial temp, 80 ˚C for 7 min; rate, 3.0 ˚C/min; final temperature 200 ˚C (t_1 = 29.90 min; t_2 = 30.08 min).



1-(5-methylfuran-2-yl)ethanol: **^{1}H NMR** (400MHz, $CDCl_3$) δ_H 1.55 (3H, d, $J_{7\text{-H},8\text{-H}}$ = 6.6 Hz, 8-H), 2.31 (3H, s, 6-H), 4.85 (1H, dq, *J* = 1.5 Hz, $J_{7\text{-h},8\text{-H}}$ = 6.6 Hz, 7-H), 5.93 (1H, dq, $J_{3\text{-H},4\text{-H}}$ = 3.0 Hz, *J* = 1.0 Hz), 6.13 (1H, d, *J* = 3.0 Hz); Chiral GC (Supelco β-DEX^{TM}), carrier gas: He (flow 2 mL/min), injection temp: 220 ˚C; column temp: initial temp, 80 ˚C for 5 min; rate, 2.0 ˚C/min; final temperature 200 ˚C (t_1 = 12.32 min; t_2 = 12.65 min).

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