The University Of Sheffield.

Development of new P(V) catalysts for the asymmetric reduction of ketimines

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of the requirements for the degree of
Doctor of Philosophy

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For Mum and Dad

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Finally I would like to say a huge thank you to my family and friends. Mum and Dad this is for you.

Abstract

The use of Lewis basic P(V) organocatalysts as a means of activating trichlorosilane toward the asymmetric reduction of ketimines has been examined. Screening of a first generation library of catalysts encompassing a diverse range of functionality identified the *P*-chiral scaffold to be the most effective. Examination of the literature however, showed no practical, robust and efficient means for the preparation of such species. As a result studies became centred upon the development of the *N*-phosphinoyl oxazolidinone **178**. Addition of the appropiate aryl or alkyl Grignard reagent to the oxazolidinone **178** afforded the corresponding *P*-chiral phosphine oxide in excellent yield and complete enantiocontrol with studies suggesting an $S_N2(P)$ process in operation. Screening of the second generation library of *P*-chiral phosphine oxide catalysts identified the 2-anisyl species **172** to be the most selective delivering the *N*-PMP amine **107** in >95% yield and 29% ee. Mechanistic studies on the catalyst **172** demonstrated a $[ML_2]$ non-linear effect and led to the hypothesis that a *bis*-*P*-chiral phosphine oxide catalyst would confer higher enantioselectivity. Synthesis of the third generation *bis*-*P*-chiral catalyst **224** through expansion of the *N*-phosphinoyl oxazolidinone chemistry enabled isolation of the amine **107** in 70% conversion and 60% ee after four hours.

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Abbreviations

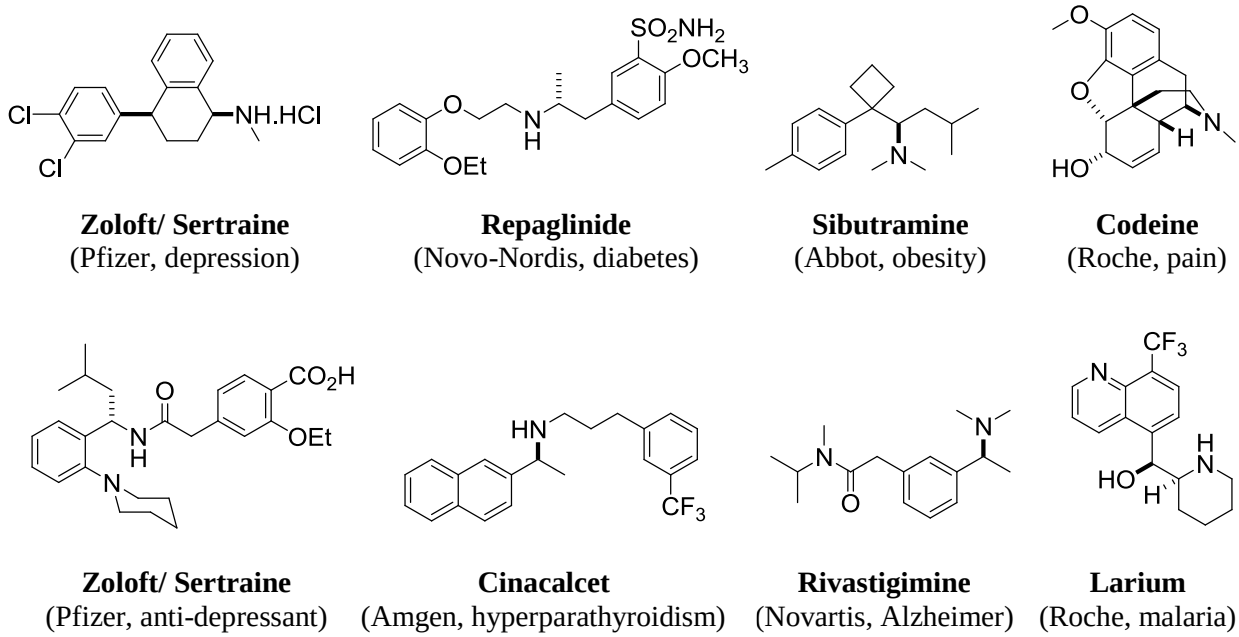
Ac	acetyl
Ar	aryl
ATR	attenuated total reflectance
b.p.	boiling point
Bn	benzyl
c	concentration
cm	centimetre
d	doublet
DCM	dichloromethane
deg	degree
DIOP	[(2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(methylene)]bis(diphenylphosphane)
DiPAMPO	(1*R*,1*R*')-(-)-1,1'-(1,2-Ethanediyl)*bis*[1-(2-methoxyphenyl)-1-phenyl phosphine oxide
DMAP	4-dimethylamino pyridine
DMF	dimethyl formamide
DMPU	1,3-dimethyltetrahydropyrimidin-2(1*H*)-one
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
ee	enantiomeric excess
EI	electron impact
ES	electrospray
Et	ethyl
FT-IR	fourier transformed infrared spectroscopy
GH-II	Grubbs-Hoveyda 2nd generation catalyst
h	hour
HCA	hexachloroacetone
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
Hz	hertz
*i*Pr	*iso*-propyl
J	coupling constant
LC-MS	liquid chromatography mass spectrometry

M	mega
m	multiplet
m.p.	melting point
Me	methyl
mins	minutes
Ms	mesylate
MS	molecular sieves
NMR	nuclear magnetic resonance
Ns	nosyl
Nu	nucleophile
o-tolyl	*ortho*-methyl benzene
Ph	phenyl
PMP	*para*-methoxy phenyl
q	quadruplet
rt	room temperature
s	singlet
SM	starting material
t	triplet
TBAF	*tert*-butyl ammonium fluoride
TBS	*tert*-butyldimethyl silyl
tert	tertiary
Tf	triflate
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethyl silyl
TOF	time of flight
Ts	tosylate
UV	ultra-violet
W	watt

Chapter I
Introduction

1.1 Nucleophilic additions to the carbon-nitrogen double bond

The prevalence of the α-substituted chiral amine motif throughout Nature has led to its development as a powerful pharmacophore for defining new medicines (figure 1). Despite the historical need for and continued interest in the moiety, the synthesis of such species still remains challenging with only a limited number of general, efficient and robust strategies having been reported.[1] Of these strategies, the nucleophilic addition to a carbon-nitrogen double bond represents one of the more practical routes toward the functionality.



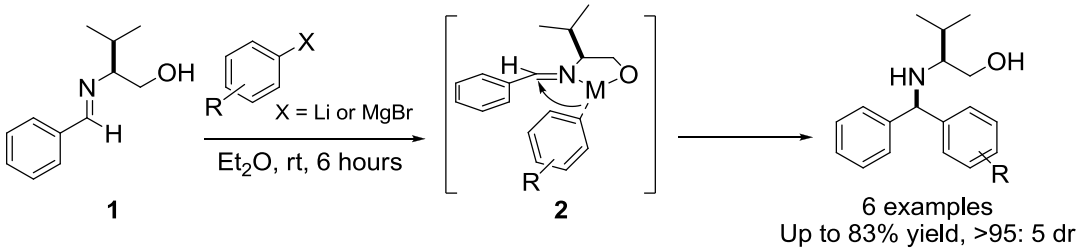
Zoloft/ Sertraine (Pfizer, depression) | **Repaglinide** (Novo-Nordis, diabetes) | **Sibutramine** (Abbot, obesity) | **Codeine** (Roche, pain)

Zoloft/ Sertraine (Pfizer, anti-depressant) | **Cinacalcet** (Amgen, hyperparathyroidism) | **Rivastigimine** (Novartis, Alzheimer) | **Larium** (Roche, malaria)

Figure (1) – Examples of pharmaceutical drugs containing a α-substituted chiral amine.

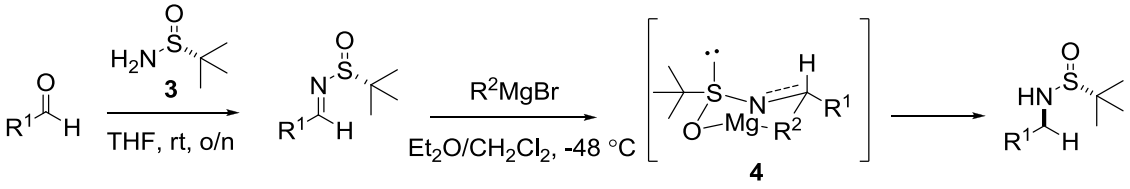
Seminal studies in this field were reliant upon the attachment of a covalently bonded chiral auxiliary to the imine to control the selectivity of the subsequent addition of the organometallic reagent. The structural features of an imine allow for attachment of the auxiliary on either terminus of the double bond and thus enable the use of either a stoichiometric amount of a chiral amine or carbonyl moiety to be employed. Whilst a number of reports on the use of chiral aldehydes or ketones have been disclosed,[2] the majority of investigations have been centred upon the utilisation of a chiral protecting group upon the nitrogen atom.

In 1982, Takahashi reported the highly diastereoselective addition of organometallic reagents to the imine **1** derived from (*S*)-valinol (scheme 1).[3] A range of substituted aromatic organometallic reagents were well tolerated by the reaction conditions and afforded the corresponding amines in excellent diastereoselectivity. Attempts to extend the methodology to aliphatic substrates however, reduced the diastereoselectivity significantly. In order to account for the observed *Si*-facial selectivity, Takahashi hypothesised the existence of the metallo-chelate intermediate **2** in which the large *iso*-propyl group shields the *Re*-face of the imine from attack of the nucleophile.



Scheme (1) – Takahashi's (*S*)-valine derived auxiliary for the addition of organometallic reagents.

Amongst the more popular chiral auxiliaries employed in the preparation of α-substituted chiral amines are those that contain a chiral *N*-sulfinyl imine. Early studies demonstrated that whilst a range of *N*-sulfinyl amines could facilitate the selective addition of a Grignard reagent to a ketimine; the reaction suffered from the disadvantage of competitive organometallic addition to the sulfur atom.[4] To minimise this side reaction, the *N-tert*-butyl sulfonyl auxiliary **3** was developed, in which the steric hindrance of the *tert*-butyl group prevents addition to the sulfur centre.[5] An array of aryl and aliphatic Grignard reagents were shown to add to a variety of aryl and aliphatic *N-tert*-butyl sulfinyl imines in good yield and good to excellent diastereoselectivity (scheme 2, table 1).[6] It is hypothesised that the excellent diastereoselectivity is the result of the reaction proceeding through the chair transition state **4** in which the Lewis acidic magnesium atom is believed to both coordinate to the auxiliary and aid in increasing the reactivity of the imine. The reaction also has the advantage of requiring only mildly acidic conditions to facilitate cleavage of the auxiliary. Subsequent work demonstrated the system to be tolerant to a host of organolithium reagents and arylboronic acids with the latter requiring iridium or rhodium catalysis to facilitate addition.[7-8]



Scheme (2) – The highly selective addition of Grignard reagents to the *N-tert*-butyl sulfinyl imine

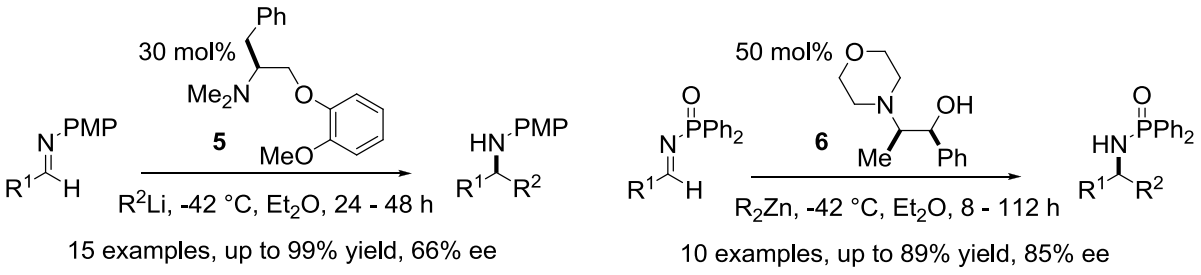
entry	R^1	R^2MgBr	Yield (%)[a]	d.r.[b]
1		PhMgBr	>98	96: 4
2		CH_3MgBr	96	93: 7
3		*i*PrMgBr	97	98: 2
4		EtMgBr	96	92: 8
5		CH_3MgBr	95	97: 3
6		*i*PrMgBr	27	N.D.
7		PhMgBr	97	89: 11
8		CH_3MgBr	98	98: 2
9		VinylMgBr	90	88: 12

[a]Refers to the isolated product; [b] determined by analysis of the crude ^1H NMR spectra.

Table (1) – The scope of the Grignard addition to the *N*-*tert*-butyl sulfinyl imine

The first catalytic asymmetric organometallic addition to an imine was reported by Tomioka in 1990.[9] The group found that the addition of organolithium reagents to a range of *N*-PMP protected imines could be facilitated by the introduction of the chiral ligand **5** in excellent yield and up to 66% ee.[9] The following year, Soai demonstrated that the scope of organometallic reagent employed could be increased to encompass dialkylzinc reagents through altering both the nitrogen protecting group and the chiral ligand **6** employed (scheme 2). The reaction tolerated a range of substrates and enabled the corresponding *N*-phosphinoyl amines to be isolated in up to 85% ee.[10] Both approaches are founded upon the concept that the chiral ligand-organometallic complex displays an increase in reactivity compared to its uncomplexed counterpart.

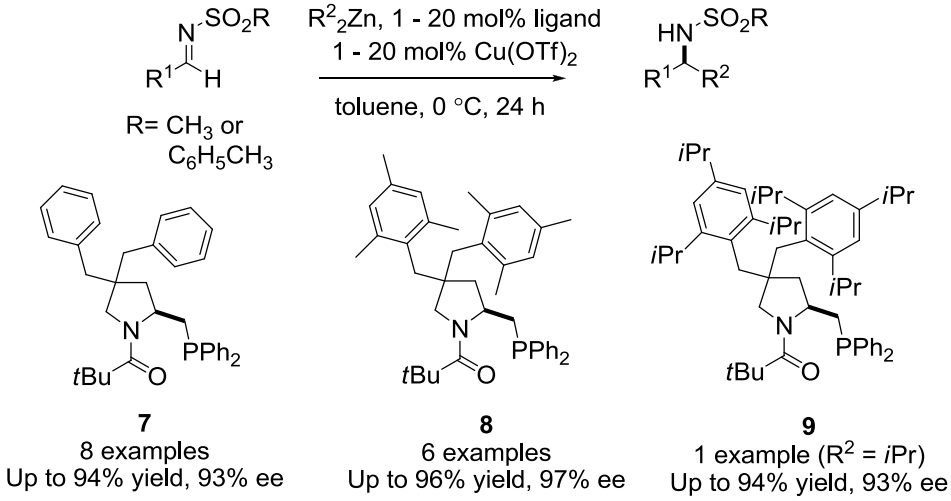
Tomoika (1991) **Soai (1992)**



Scheme (3) – Early approaches toward the catalytic asymmetric addition of organometallic reagents.

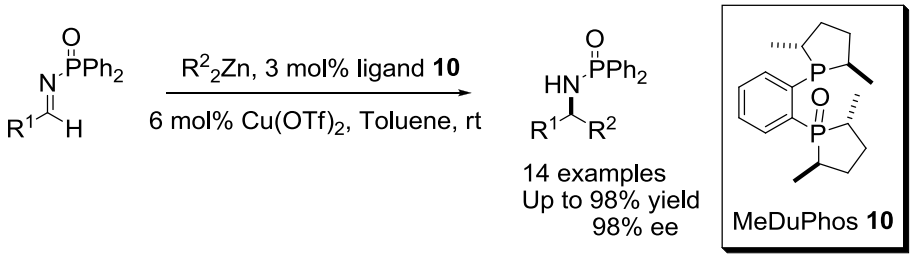
In 2000, Tomioka reported the first copper catalysed addition of dialkylzinc reagents to a range of *N*-tosyl and *N*-mesyl imines (scheme 3).[11] The conditions reported by Feringa and Alexakis for conjugate addition chemistry were very effective in minimising the side reactions traditionally associated with the nucleophilic addition to imines, such as reduction of the imine and attack of the nucleophile at the heteroatom alpha to the nitrogen atom.[12] Pivotal to the

reactivity was the presence of the copper(II) trifluoromethanesulfonamide which was hypothesised to facilitate generation of an alkylcopper(I) compound, the species believed to undergo nucleophilic attack onto the imine. The group screened a range of chiral ligands **7 - 9** derived from (*S*)-proline and demonstrated that high enantioselectivities of up to 97% could be obtained (scheme 4).[13] Interestingly, switching the dialkylzinc reagent from diethylzinc to either dimethyl or di*iso*-propylzinc had a detrimental effect upon the reactivity and selectivity of the addition and thus led to the use higher loadings of both the copper salt and chiral ligand.



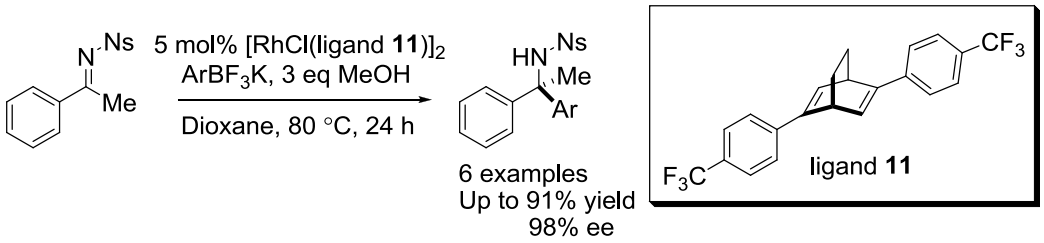
(Scheme 4) – The development of a catalytic asymmetric copper catalysed addition to sulfonyl imines.

A copper catalysed asymmetric addition of dialkylzinc reagents to *N*-phosphinoyl imines was developed by Charette in 2005.[14] The most selective ligand was found to be the Me-DuPHOS monoxide **10**, a hemilabile, bidentate ligand readily prepared in 2 steps.[15] An array of *N*-phosphinoyl imines were well tolerated by the reaction conditions with the resulting amines obtained in high yield and excellent enantioselectivity (scheme 5). The reaction offered the advantage of facile deprotection of the nitrogen protecting group through mild acid hydrolysis, and allowed the substrate scope to be extended toward *N*-phosphinoyl imines derived from enolisable aldehydes, a set of substrates which are known to be prone to degradation.[16]



Scheme (5) – Charette's copper catalysed asymmetric addition to *N*-phosphinoyl imines.

Despite the relatively large number of efficient catalytic systems available for alkyl group transfer from diorganozinc reagents to imines, the analogous reaction employing a diarylzinc reagent is much more convoluted. The major reason for this resides in the fact that aryl group transfer from the diarylzinc reagent to the imine is a far more facile process and thus renders the uncatalysed non-selective background reaction a competitive process.[17] One solution developed to overcome this problem is to utilise an organoboron species, a far more inert organometallic reagent. Hayashi has demonstrated that the synthesis of chiral diarylmethylamines could be readily achieved through the rhodium(I) catalysed addition of organoboron reagents to *N*-tosyl and *N*-nosyl ketimines.[18] Chiral dienes were reported to be highly effective ligands for this process delivering the desired amine products in excellent yield and enantioselectivity. The high activity associated with the ligand is believed to stem from its ability to accelerate the transmetallation between the arylorganoboron reagent and the rhodium metal. A myriad of examples have been reported utilising arylboroxines, arylboronic acids and most recently potassium organotrifluoroborates.[18] One such example disclosed by Hayashi demonstrates that a range of substituted organotrifluoroborates can be readily added to *N*-nosyl ketimines in excellent yield and enantioselectivity (scheme 6).[19] Cleavage of the sulfonyl group to liberate the amine was accomplished in high yield with no erosion of enantioselectivity through treatment with thiophenol and potassium carbonate.



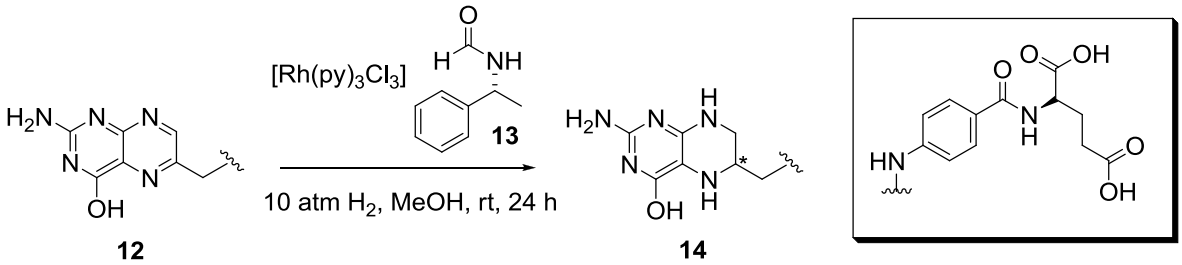
Scheme (6) – Haiyashi rhodium mediated potassium organotrifluoroborates addition to *N*-nosyl imines.

1.2 Metal catalysed asymmetric hydrogenations

The development of a catalytic method of reducing the ketimine functionality has seen substantial interest in recent years. However, progress in the area has been far slower compared to the analogous ketone or olefin moiety. There are several reasons why imines are difficult substrates for hydrogenation. Firstly, the smaller thermodynamic gain from the reduction of the C=N bond relative to a carbon-carbon double bond hinders the hydrogenation process. There is also a less effective orbital overlap and lower affinity for the metal centre due to the η_1-binding mode of an imine compared to the η_2-binding of an olefin. Imines are also readily susceptible to hydrolysis and the resultant amines (including those formed as the product of hydrogenation)

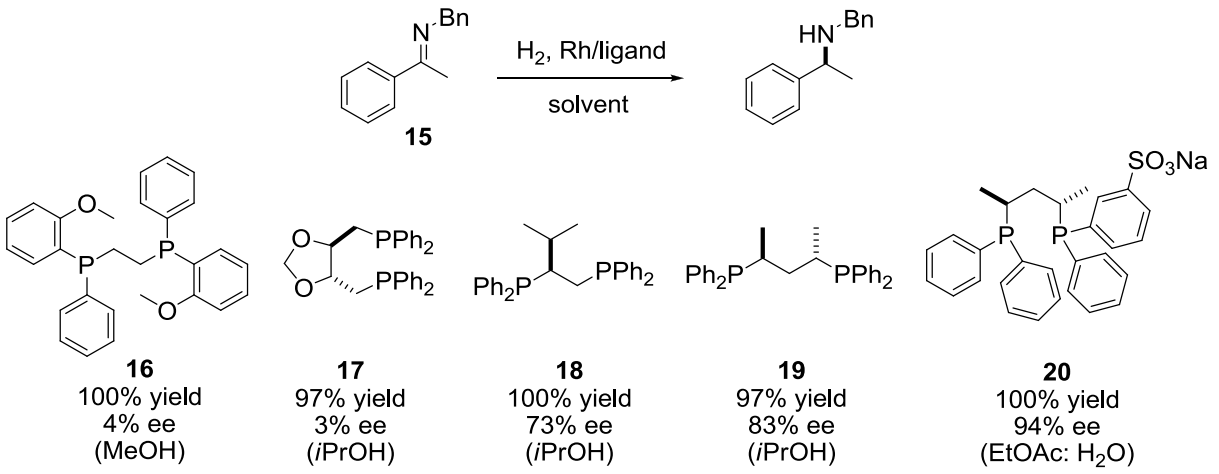
can behave as catalyst poisons, coordinating to the metal centre and thus preventing binding of the desired ligand. Furthermore, increased steric hindrance around the carbon-nitrogen double bond may retard coordination to the metal centre and thus slow down the hydrogenation process, a phenomenon commonly observed amongst olefinic substrates.[22]

The first asymmetric metal-catalysed hydrogenation of a C=N bond was reported by Boyle in 1974. It was found that the reduction of folic acid **12** could occur in the presence of the rhodium catalyst [$Rh(py)_3Cl_3$] and the chiral *N*-formamide **13** (scheme 7).[20] Whilst no indication was given as to the amount of catalyst employed or degree of enantioselectivity, studies demonstrated that the resultant diamine **14** only showed 46% of the biological activity exhibited by an enantiomerically pure sample of tetrahydrofolic acid.



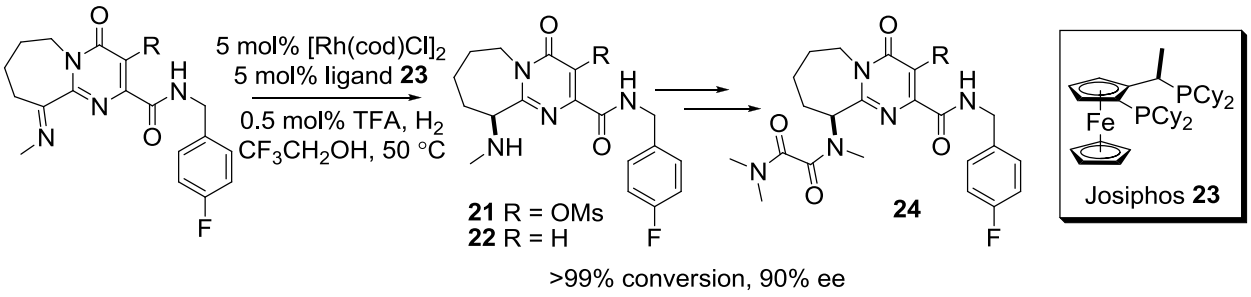
Scheme (7) – Boyle's asymmetric reduction of folic acid

In 1984, Bakos and Marko independently reported the use of chiral *bis*-phosphine species as moderately selective ligands for the asymmetric reduction of the *N*-benzyl ketimine **15** (scheme 8).[21] Both authors noted that the success of the ligands was believed to stem from their ability to allow the metal-ligand complex to adopt a stable five-membered ring complex. The influence of the ligands upon the enantioselectivity of the reduction was also studied, the effects of which suggested a more convoluted process in operation compared to the analogous ketone and olefin hydrogenations. For example, DiPAMP **16**, a *P*-chiral phosphine known to form stable bidentate complexes with rhodium exhibiting no selectivity. Furthermore the ineffectiveness of DIOP **17**, an established chiral ligand for enantioselective olefin and ketone hydrogenations,[22] implies that the ketimine substrate must exert some influence on the selectivity of the reduction. A second generation monosulfonated ligand **20** was disclosed by Bakos five years later and found to be far more selective.[23] A detailed analysis on the effect of polysulfonation upon the aromatic ring indicated that incorporation of a sulfone moiety onto a single site was pivotal for optimum enantioselectivity. No rationale as to the reasoning behind this was reported by the authors.



Scheme (8) – Early examples of the *bis*-phosphine ligands employed in enantioselective imine hydrogenation.

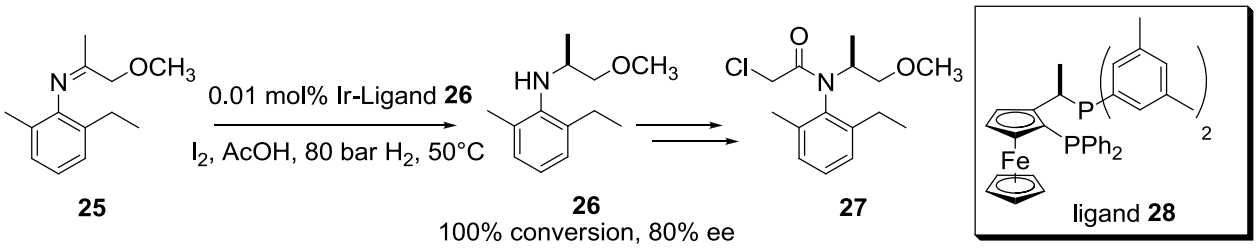
A novel rhodium catalysed hydrogenation was reported by Zhong in 2009 as the key step in the synthesis of the HIV integrase inhibitor **24** (R = OMs) (scheme 9).[24] The reduction occurred under relatively mild conditions with the amine **21** obtained in >99% conversion and 90% ee. A small amount of by-product **22** (R = H) was also isolated, the result of hydrogenolytic cleavage of the mesyl group. Mechanistic studies suggested that the reduction proceeded predominately through the enamine tautomer even though the substrate presided preferentially as the ketimine. Hydrogenation with D_2 gave the product with deuterium incorporation at both the *alpha* and *beta* positions relative to the secondary amine. Further proof for this hypothesis was obtained from analysis of the ^{1}H NMR spectroscopic data which suggested the *cis* delivery of the two deuterium atoms, the result expected should hydrogenation of an enamine be taking place.



Scheme (9) – Zhong's asymmetric hydrogenation toward the synthesis of HIV integrase inhibitor 24.

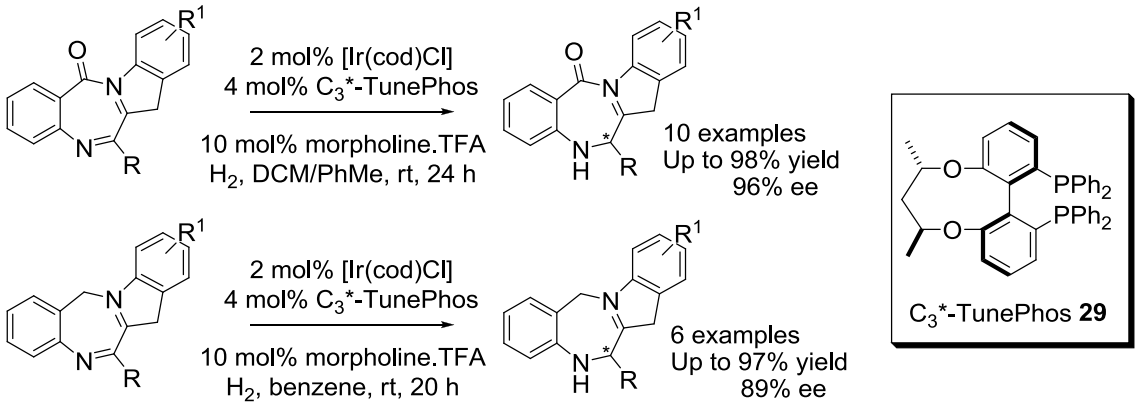
Along with rhodium, chiral iridium complexes have seen a plethora of investigations into their use as catalysts for the asymmetric hydrogenation of ketimines. In 1993, a Novartis group disclosed a new class of iridium-ferrocenyl *bis*-phosphines, which in the presence of iodine and acetic acid facilitated the asymmetric hydrogenation of imine **25** to its corresponding amine **26**, a key precursor to the herbicide Metolachlor **27** (Scheme 10).[25] One of the important features of

the process was the crucial role that both additives exerted upon the reduction; whilst the role of the iodine is not fully understood it is thought that the dramatic rate enhancement observed through introduction of acetic acid stems from the ability of the acid to protonate the amine product and slow its ability to act as a catalyst poison and inhibit the hydrogenation.



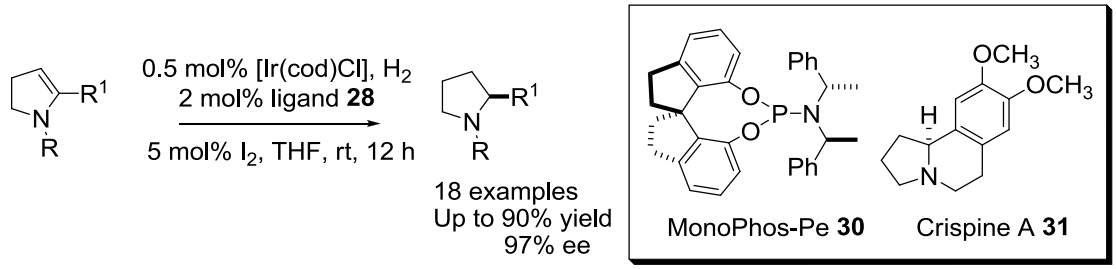
Scheme (10) – The synthesis of (*S*)-Metolachlor, utilising an iridium catalysed asymmetric hydrogenation.

Recently, Zhou has disclosed the iridium catalysed asymmetric hydrogenation of benzodiazepinones and benzodiazepines (scheme 11).[26] Screening of a range of *bis*-phosphine ligands identified the ligand C_3*-TunePhos **27** developed by Zhang, as the most selective ligand toward the reduction.[28] Pivotal to the enantioselectivity was the addition of the salt morpholine.TFA, however, no rationale as to the effect the additive exerts was reported.



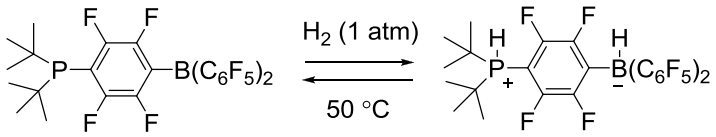
Scheme (11) – The iridium catalysed asymmetric hydrogenation of benzodiazepinones and benzodiazepines

The same group have also reported the first enantioselective hydrogenation of cyclic *N*,*N*-dialkyl enamines using the iridium-MonoPhos-Pe complex **30** (scheme 12).[27] The addition of iodine was found to be fundamental in obtaining full conversion and high enantioselectivity. The authors hypothesised the role of the iodine was to undergo oxidative addition onto the iridium metal and thus facilitate formation of an Ir(III) intermediate, an oxidation state hypothesised to be the key species required for hydrogenation.[28] To exemplify the versatility of the methodology, the group successfully synthesised the isoquinoline alkaloid crispine A **31**.



(Scheme 12) – The iridium catalysed hydrogenation of cyclic *N,N*-dialkyl enamines

In 2006, Stephan reported the non-transition metal mediated activation of molecular hydrogen through the use of a frustrated Lewis pair.[29-30] In such systems, sterically hindered Lewis acids and bases are combined, however, unlike in the adducts traditionally formed, the steric demands of this frustrated Lewis pair prevent such formation and allow the molecule to exhibit both Lewis acid and Lewis base characteristics. The frustrated Lewis pair **32** was shown to facilitate the heterolytic cleavage of molecular hydrogen at atmospheric pressure and room temperature (figure 1). Exposure of this adduct **33** to heat resulted in the regeneration of the frustrated Lewis pair **32** and release of hydrogen gas.



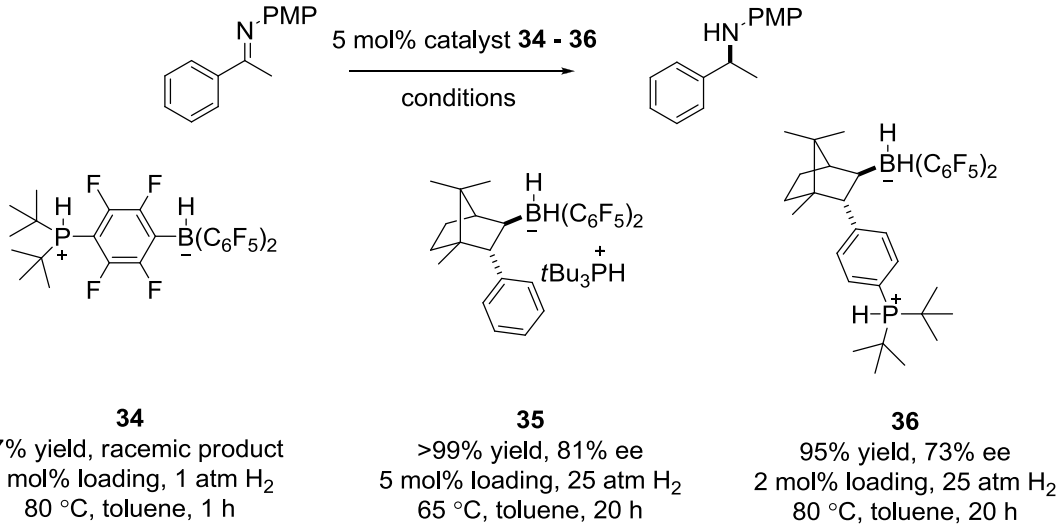
32 **33**

(Figure 1)- The frustrated Lewis pair facilitating reversible heterolytic cleavage of molecular hydrogen.

A year later, the group reported that the activated frustrated Lewis pair **34** could act as a catalyst and activate molecular hydrogen toward the reduction of a range of *N*-aryl substituted imines. [31] It was noted that a key requirement for the imine being reduced was the presence of a sterically demanding substituent upon the nitrogen atom. Reduction of a less hindered ketimine afforded a species capable of binding to the Lewis acidic boron atom of the catalyst precluding further H_2 activation. Mechanistic studies suggested that the reaction proceeds through initial protonation of the imine by the phosphonium centre followed by borohydride attack at the resultant iminium salt.

Klankermayer has recently reported the use of a chiral frustrated Lewis pair **35** as a means of obtaining enantiomerically enriched amines in excellent yield and good enantioselectivity

(scheme 13).[32] An intramolecular second generation frustrated Lewis pair catalyst **36** in which the phosphine unit is attached to the aromatic ring of the molecule showed a dramatic increase in catalytic activity and allowed for catalyst loadings to be lowered to 2 mol% with no significant depreciation in enantioselectivity.[33]



34
97% yield, racemic product
5 mol% loading, 1 atm H_2
80 °C, toluene, 1 h

35
>99% yield, 81% ee
5 mol% loading, 25 atm H_2
65 °C, toluene, 20 h

36
95% yield, 73% ee
2 mol% loading, 25 atm H_2
80 °C, toluene, 20 h

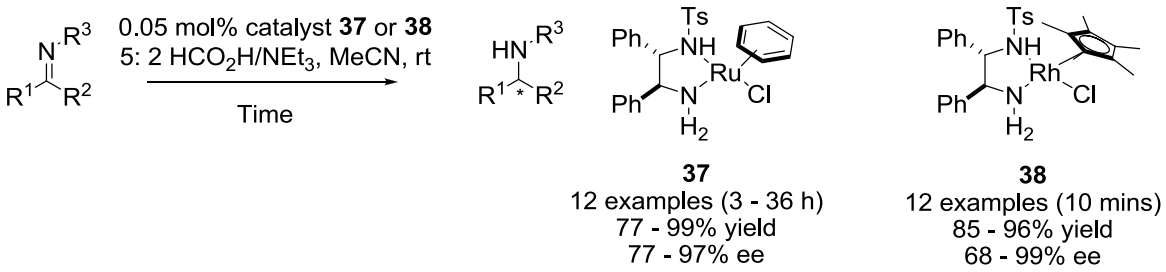
Scheme (13) – A range of achiral and chiral frustrated Lewis pair catalysts recently developed.

1.3 Metal catalysed asymmetric transfer hydrogenation

Transfer hydrogenation is the catalyst mediated reduction of an unsaturated moiety using an equivalent of H_2, which has been abstracted from a donor organic molecule. Molecular H_2 is not involved in the reaction, so transfer hydrogenation is a convenient process for the reduction of an unsaturated bond at atmospheric pressure.[34] Of the hydride transfer reagents employed, formic acid is regarded as the most accessible source of hydrogen as other known reagents are prone to requiring harsher conditions and more active catalysts.[34]

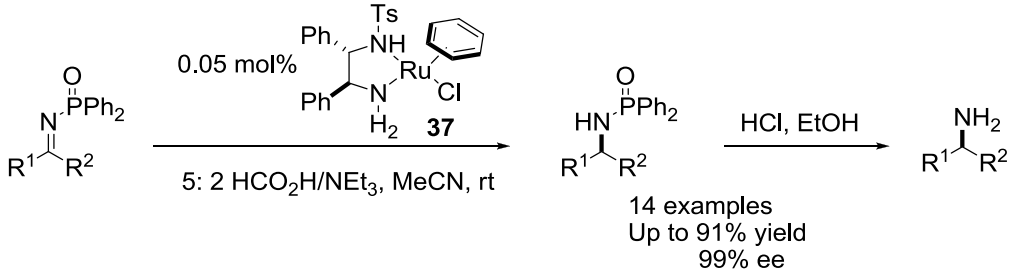
The first example of an asymmetric transfer hydrogenation of a ketimine was disclosed by Noyori in 1996.[35] The ruthenium catalyst **37** initially developed for the reduction of ketones was found to be highly selective toward ketimines (scheme 14). Endocyclic imines were reduced in high yield and excellent enantioselectivity, however, slightly lower selectivity was observed in the case of exocyclic and acyclic substrates. Kinetic studies on the catalyst **37** demonstrated significantly greater reactivity toward ketimines than ketones, a result verified by the observation that quantitative transfer hydrogenation of imine **15** could be performed by catalyst **37** in acetone with only 3% reduction of the solvent to *i*so-propanol observed.

Mao and Baker designed a rhodium analogue of Noyori's catalyst **38** by replacing the arene ligand on the ruthenium metal with a pentamethylcycopentadienyl ligand on the rhodium metal centre (scheme 14).[36] The resulting catalyst **38** was found to be highly selective toward the reduction of 1-aryl-3,4-dihydroisoquinolines however, attempts to expand the scope of ketimine substrates to acyclic variants lowered the enantioselectivity greatly. Subsequent work demonstrated that the activity of both catalysts could be further increased by slow addition of HCO_2H.[37]



Scheme (14) – Ruthenium and rhodium catalysed asymmetric transfer hydrogenation.

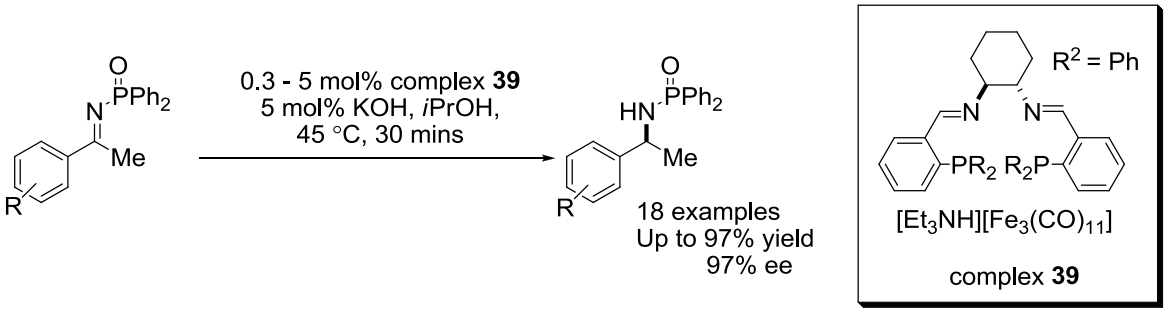
To try and overcome the poor enantioselectivity in the asymmetric transfer hydrogenation of acyclic imines, researchers at Avecia synthesised a range of ketimines bearing a *N*-diphenylphosphoryl protecting group.[38] The steric bulk of the protecting group was hypothesised to enable the acyclic imine to exist as a single geometric isomer and thus prevent poor enantiocontrol during the reduction. Reduction of a range of ketimines using Noyori's catalyst **37** enabled the desired *N*-phosphinoyl protected amines to be isolated in good yield and excellent enantioselectivity (scheme 15). Facile deprotection of the *N*-diphenylphosphinoyl moiety through mild acid hydrolysis afforded the amine with no erosion of enantioselectivity.



Scheme (15) – The asymmetric transfer hydrogenation of acyclic *N*-phosphoryl ketimines.

Recently, Beller has reported the first example of an iron catalysed asymmetric reduction of an imine by means of a transfer hydrogenation. Examination of a variety of chiral nitrogen and phosphine ligands identified the *bis*-phosphine **39**, a ligand previously utilised by Gao for the transfer hydrogenation of ketones, as the most selective species (scheme 16).[39-40] Both electron donating and electron withdrawing substituents on the ketimine were well tolerated by the

reaction. Examination of the impact of the steric hindrance on the ketimine however, demonstrated that the more severely hindered substrates with large substituents on the *ortho* position of the aromatic ring required higher catalyst loadings and prolonged reaction times to achieve results analogous to the less hindered analogues. Attempts at extending the methodology to encompass aliphatic ketimines only sort to have a detrimental impact upon both the yield and enantioselectivity of the reduction.



Scheme (16) – Beller's iron catalysed asymmetric transfer hydrogenation.

1.4 Organocatalysed asymmetric transfer hydrogenations of imines

Organocatalytic hydride transfers are inspired by reduction processes in Nature. In biological systems, C-H stereogenicity is introduced using co-factors that exist as a part of a class of enzyme known as transform specific oxidoreductases.[41] Of the co-factors that exist, the dihydropyridine based nucleotides NADH (reduced nicotinamide adenine dinucleotide) and the closely related NADPH (reduced nicotinamide adenine dinucleotide phosphate) are the two most prevalent and commonly used moieties in biological asymmetric hydride transfer.

From a chemical standpoint, molecules such as NADH exhibit two distinct regions of chemical entity that function synergistically to enable the highly selective delivery of the hydride ion to the electrophile (figure 2). The nucleosidic element of the co-factor enables molecular recognition within a specific enzymatic environment whilst the dihydropyridine ring system, once placed in the correct vicinity has the ability to deliver the hydride ion.

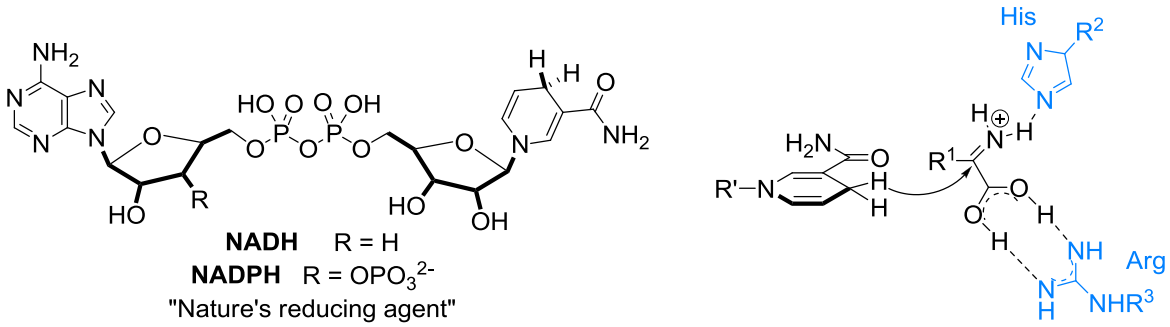
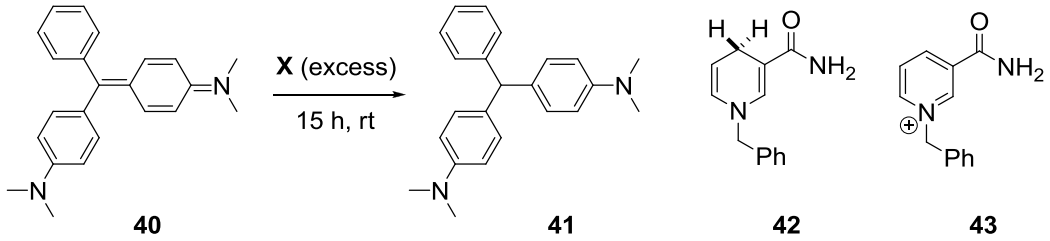


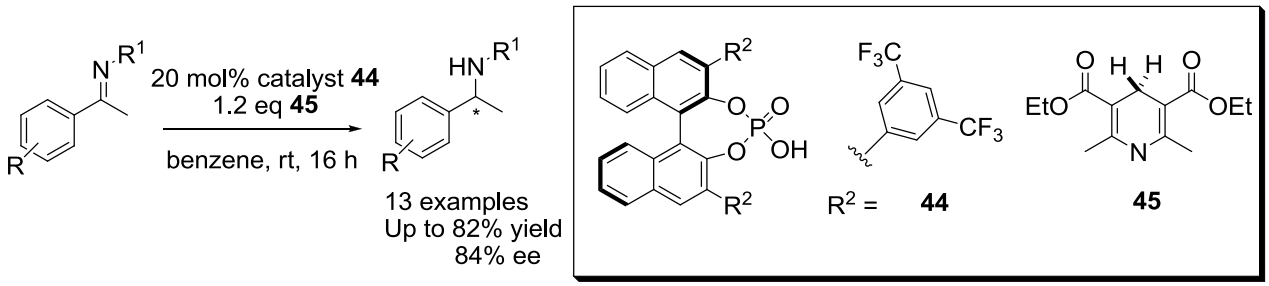
Figure (2) – Organocatalysed reductions in biological systems (Arg: Argenine, His: histidine).

Westheimer and Mauzerall were the first to demonstrate that synthetic dihydropyridine analogues of NADH could facilitate hydrogen transfer.[42-45] The authors reported that 1-benzyldihydronicotinamide **42** reduced the dye **40** to its leuco base **41** with concurrent formation of the pyridinium ion **43** (scheme 17). Deuterium labelling experiments showed that only the 1, 4-dihydropyridine analogue of the reductant transferred deuterium to the product, both the 1,2 and the 1,6 variants exhibited no reductive capabilities.



Scheme (17) - Westheimer and Mauzerall's reduction of the leuco dye X using the Hantschz DHP X.

In 2005, Rueping disclosed the first enantioselective Brønsted acid catalysed reduction of *N*-aryl ketimines using a biaryl phosphoric acid catalyst **44** originating from the Akiyama-Terada family of BINOL-derived organocatalysts (scheme 18).[46-47] Hantschz ester **45** was utilised as the hydrogen source and various 3,3'-aryl substituted phosphoric acids were screened as catalysts for the reduction. Both steric and electronic effects of the substituents on the catalyst were shown to influence the enantioinduction, with the more sterically encumbered electron deficient substituents exhibiting higher enantioselectivity. A strong solvent effect was also observed, with non-polar solvents leading to higher enantioselectivities.



Scheme (18) – The first Brønsted acid catalysed asymmetric transfer hydrogenation of a ketimine

Rueping proposed that the reaction proceeds through initial activation of the ketimine by the Brønsted acid thus generating the chiral ion pair **46**. Subsequent hydride transfer from the Hantschz ester **45** to the iminium ion affords the chiral amine **47** and the pyridinium salt **48** which can undergo a single proton transfer to enable regeneration of the catalyst and completion

of the catalytic cycle. Assignment of the absolute configuration of the amine products by x-ray crystallography led the authors to suggest that the enantioinduction was the result of the complexation of the iminium ion to the phosphoric acid in a manner that allows for the sterically demanding protecting group to protrude toward the less hindered face of the catalyst. Subsequent hydride delivery from the least hindered *Re*-face would correlate with the experimentally observed (*R*)-configured product (figure 3).

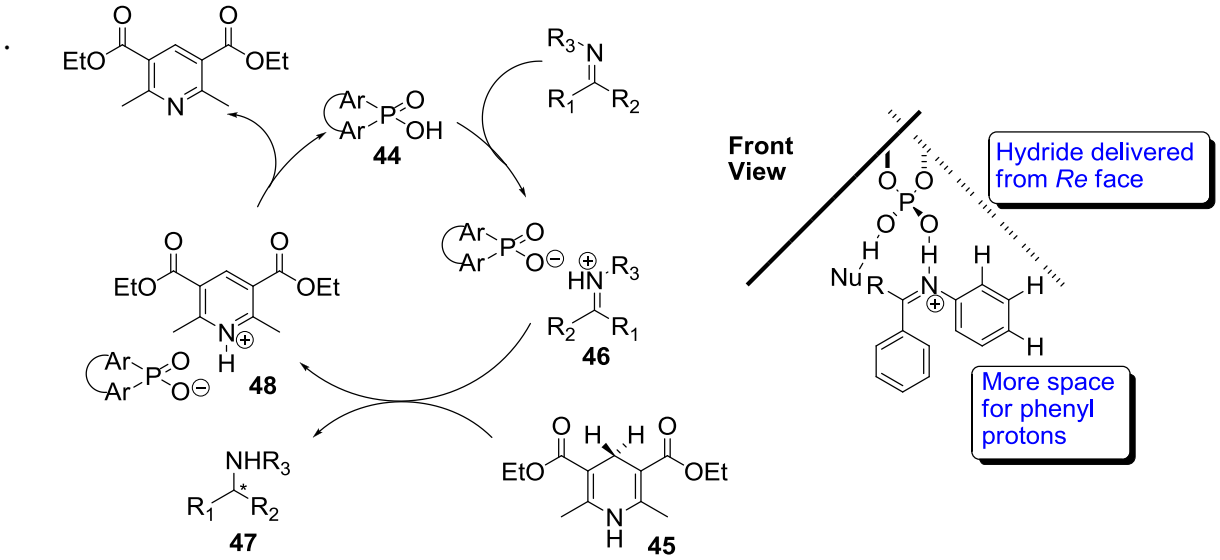
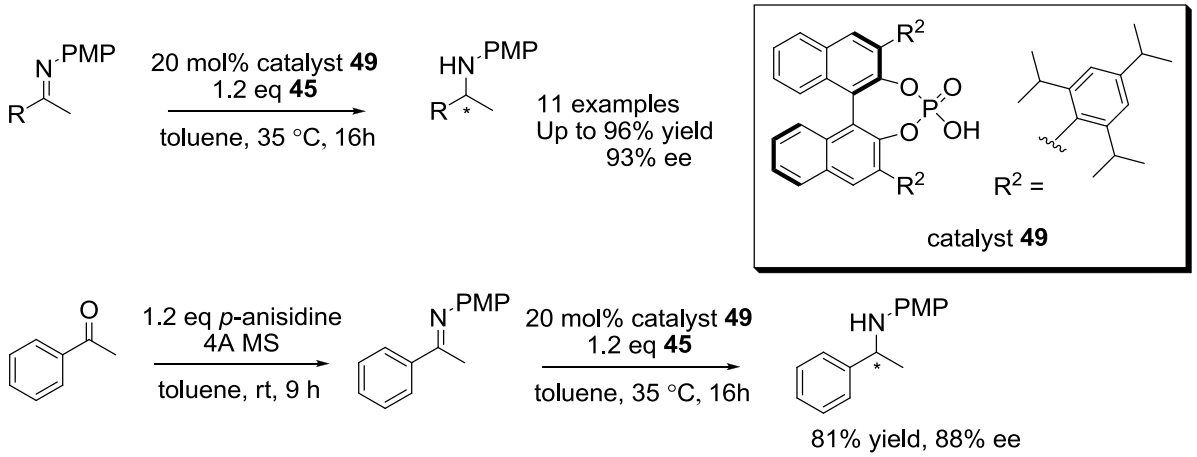


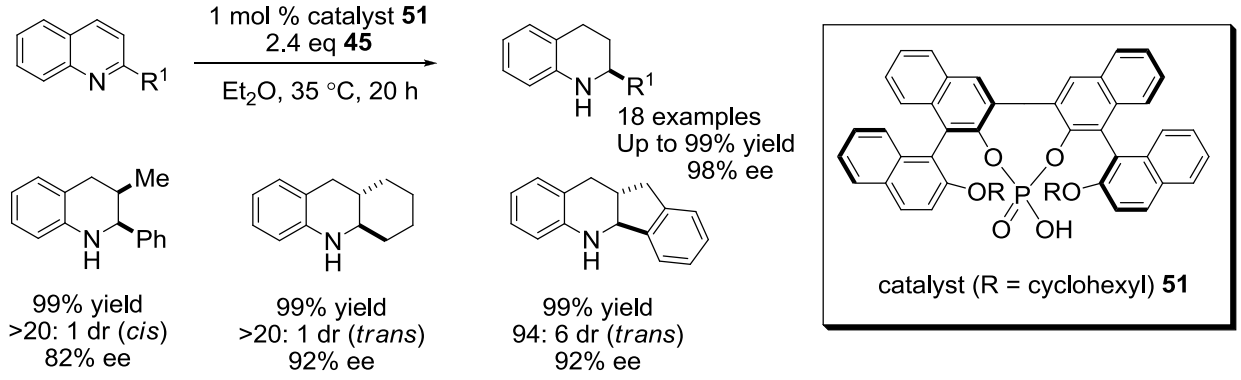
Figure (3) – Rueping's hypothesised catalytic cycle and model to explain the observed stereoinduction.

List independently reported the highly selective reduction of a range of aryl and aliphatic *N*-PMP ketimines using 1 mol% of the (*S*)-BINOL derived phosphoric acid **49** and Hantschz ester **45** as the reductant source.[48] The authors demonstrated for the first time that imine generation could occur *in situ* in the presence of molecular sieves. Deprotection of the *N*-PMP protecting group with CAN afforded the free amine in 81% yield and 88% ee.



Scheme (19) – List's transfer hydrogenation of *N*-PMP ketimines at 1 mol% catalyst loading.

In 2008, Du disclosed a new doubly axial chiral phosphoric acid catalyst **50**. The rationale for the design of the catalyst originated from the observation that substituents in the 3,3' positions of the original BINOL scaffold were pivotal for high enantioinduction.[49] As a result, the authors hypothesised that if the substituents in these positions were to possess sterically hindered substituents that exhibited axial chirality then the size of the chiral pocket that the catalyst exerts would increase and thus allow for higher enantioinduction to be obtained. The doubly axial chiral catalyst **51** was found to be effective for the asymmetric transfer hydrogenation of 2-alkyl and 2-aryl substituted isoquinolines with the corresponding tetrahydroquinolines isolated in excellent yield and enantioselectivity (scheme 20). The increased catalytic activity allowed for the catalyst loading to be reduced to 0.2 mol% without any depreciation in yield or enantioinduction. Du also demonstrated that 2, 3-disubstitutued quinolines could be reduced in excellent diastereo- and enantioselectivity. However, no mechanistic rationale to account for the selectivity was reported by the authors.



Scheme (20) – Du's double axially chiral phosphoric acid catalyst and its application in quinoline reduction

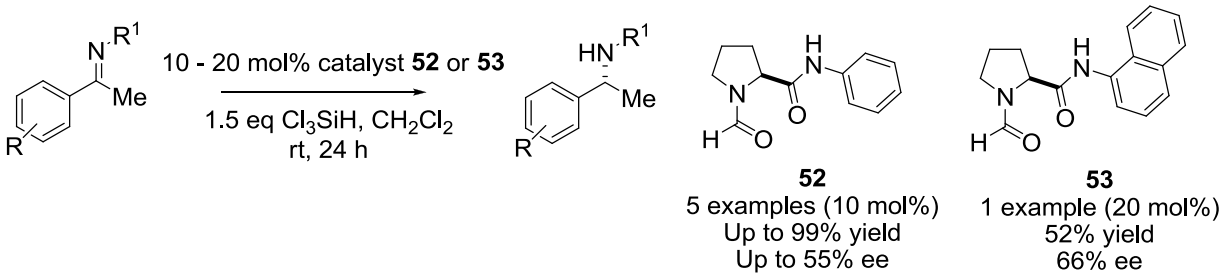
1.5 Trichlorosilane mediated reductions of the C=N bond

The reductive properties of trichlorosilane were first investigated in the 1970s. Seminal studies demonstrated that a solution of trichlorosilane and the Lewis base pyridine formed an isolable but unstable adduct.[50] Early mechanistic NMR and deuterium labelling experiments suggested that coordination of a Lewis base to the silicon atom was vital to induce sufficient hydride characteristics in the silicon-hydrogen bond to enable a reduction to occur.[51]

In 1996, Kobayashi demonstrated that DMF could activate trichlorosilane toward the reduction of a variety of organic substrates.[52] It was noted that the reduction was non-substrate specific and highly chemoselective; aldehydes were reduced at -20 °C, aldimines at 0 °C and ketones at room temperature, with the need however for prolonged reaction times and higher catalyst

loadings. [29]Si NMR spectroscopic studies identified the *in situ* formation of a six coordinate silicon intermediate leading to the hypothesis that the Lewis base was coordinating to trichlorosilane and activating it toward the reduction.

Five years later, the first enantioselective reduction of a ketimine was reported by Matsumura.[53] The proline derived chiral *N*-formamide **52** facilitated the reduction of a range of *N*-aryl and *N*-benzyl protected aryl-methyl ketimines in excellent yield and moderate enantioselectivity (scheme 21). A second catalyst **53** disclosed in the paper containing a 1-naphthyl substituent on the amide bond demonstrated an enhancement in selectivity but marked reduction in catalytic activity.



Scheme (21) – The first trichlorosilane mediated asymmetric reduction of a ketimine.

In order to rationalise the (*R*)-configuration of the resultant amines, Matsumura proposed two transition state models **54** and **55**. It was hypothesised that the adverse steric interactions that exist between the aromatic ring of the ketimine and that of the catalyst disfavours the reaction proceeding through transition state **54** and thus lead to hydride delivery to the less hindered *Re*-face.

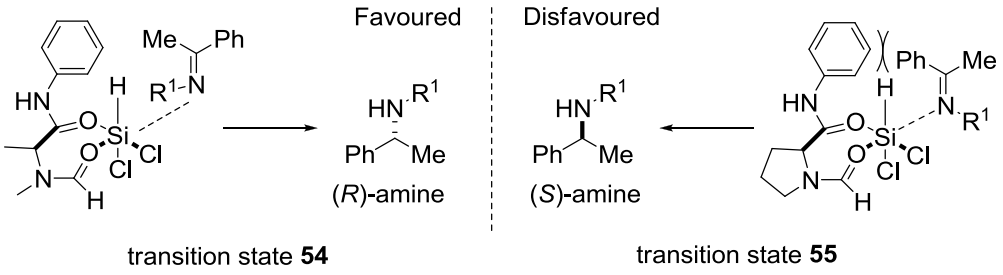
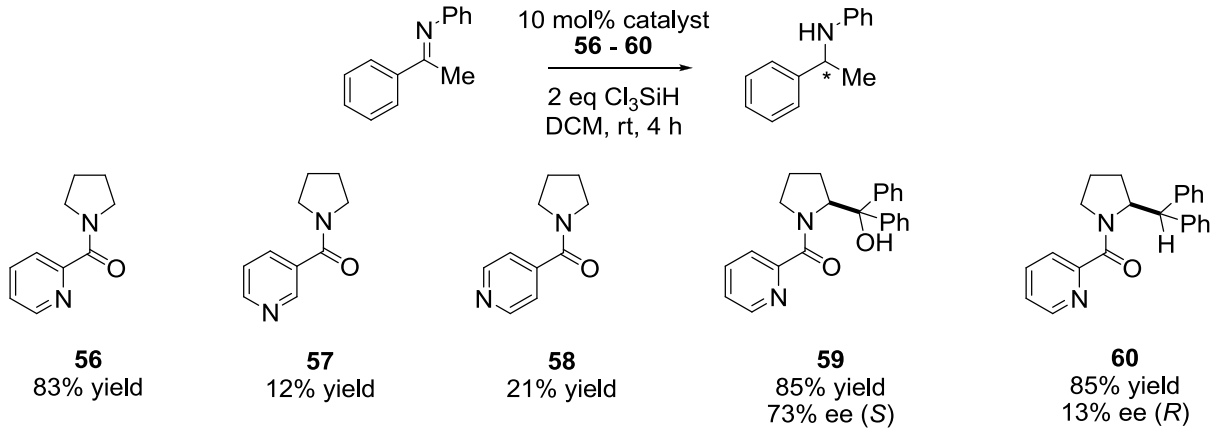


Figure (4) – The two transition states proposed by Matsumura to account for the observed stereoselectivity.

A series of *N*-picolinoyl pyrrolidine modular ligands were reported by the same group in 2006.[54] A detailed structure/activity relationship demonstrated the necessity for the 2-picolinoyl derivative of the catalyst, both the 3 and 4-substituted analogues exhibited a significant depreciation in catalytic activity (scheme 22). The authors also noted that the presence of a hydroxyl group was pivotal for high enantioinduction, as replacement with a hydrogen atom or a

Lewis basic ester or amide moiety resulted in a pronounced loss of selectivity (scheme 22). The catalyst **59** was shown to reduce a range of *N*-aryl acetophenone derived ketimines in excellent yield and good enantioselectivity.



Scheme (22) – Matsumura's structure/activity relationship for the reduction of *N*-phenyl ketimine.

The key requirement of the hydroxyl group to facilitate high enantioinduction led Matsumura to hypothesise the existence of a hydrogen bonding interaction between the tertiary alcohol and ketimine and thus led to the two transition states **61** and **62** (figure 5). It was proposed that the steric clash between the phenyl groups of the catalyst and the protecting group on the ketimine disfavoured the transition state **62** and led to the experimentally observed (*S*)-configured amine.

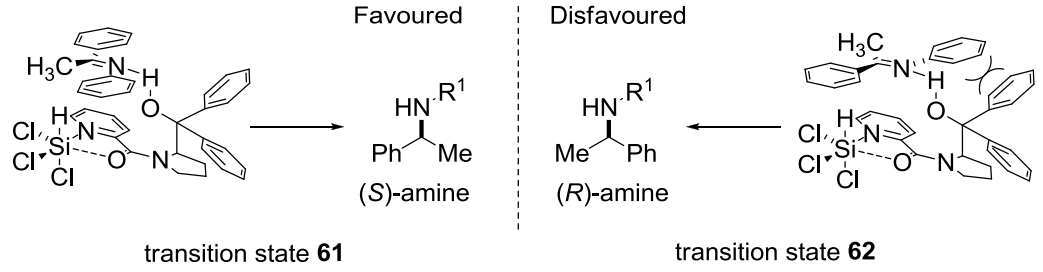
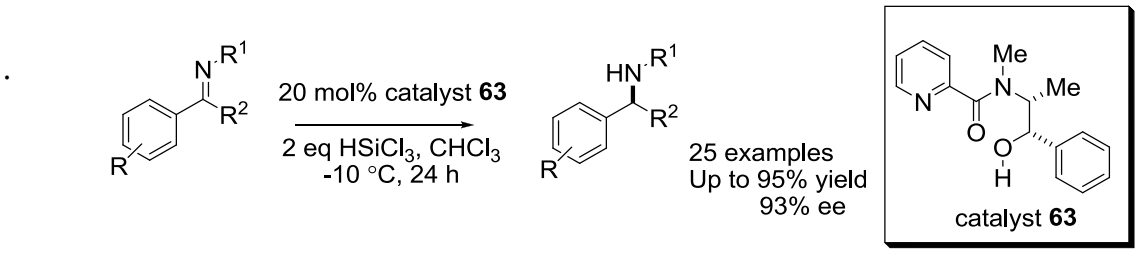


Figure (5) – The two transition states proposed Matsumura to explain the stereoselectivity of catalyst 59

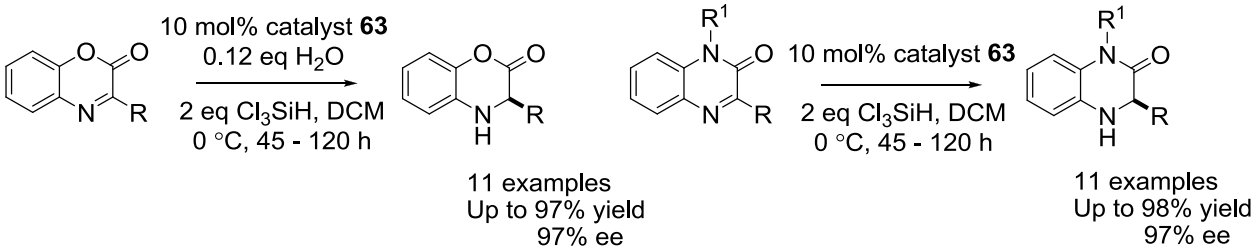
A second generation of catalysts utilising a range of chiral amino-alcohols was reported by Zhang in 2007.[55] Two sets of catalyst were investigated, one with a secondary amide linkage and the other with a tertiary amide appendage. The requirement for either one or two preinstalled stereogenic centres on the amino alcohol was also examined the results of which suggested that the stereogenic centre adjacent to the amide bond was pivotal for reactivity. Zhang also noted the importance of the *N*-methyl group, since this series of catalysts delivered consistently higher enantioselectivities than the series without methylation of the amide nitrogen

atom. Whilst the authors did not comment upon this finding, the increase in selectivity could be due to the existence of a chiral-relay effect, in which the stereogenic centres introduce an additional stereogenic element into the catalyst. Incorporation of a hydroxyl group was also crucial for selectivity and enabled the optimised catalyst **63** to facilitate the reduction of a range of *N*-aryl ketimines in good yield and enantioselectivity (scheme 23).



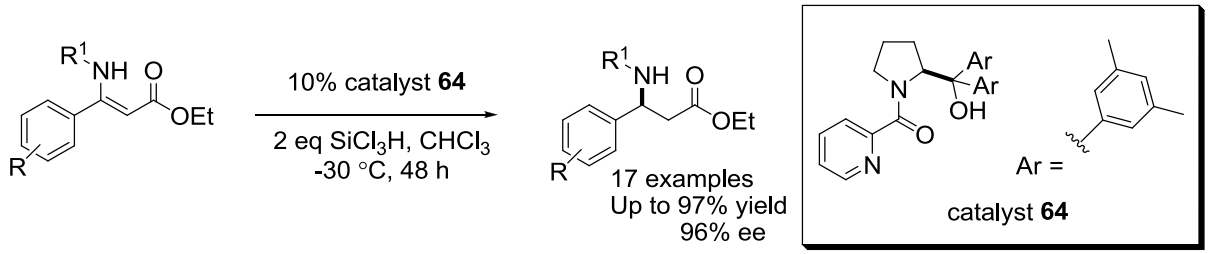
Scheme (23) – Zhang's trichlorosilane mediated reduction of *N*-aryl ketimines using catalyst 63

The catalyst **63** has also been shown to be highly effective toward the reduction of both dihydrobenzooxazinones and dihydroquinoxalinoes.[56] Noteworthy was the observation that the reduction of dihydrobenzooxazinones required the addition of water to facilitate the process, whilst the dihydroquinoxalinoes did not. A range of aryl substituted heteroaromatics were reduced in good yield and excellent enantioselectivity. Attempts at replacing the aryl group with the analogous aliphatic moiety sought to have a dramatic decrease upon the enantioselectivity of the reduction.



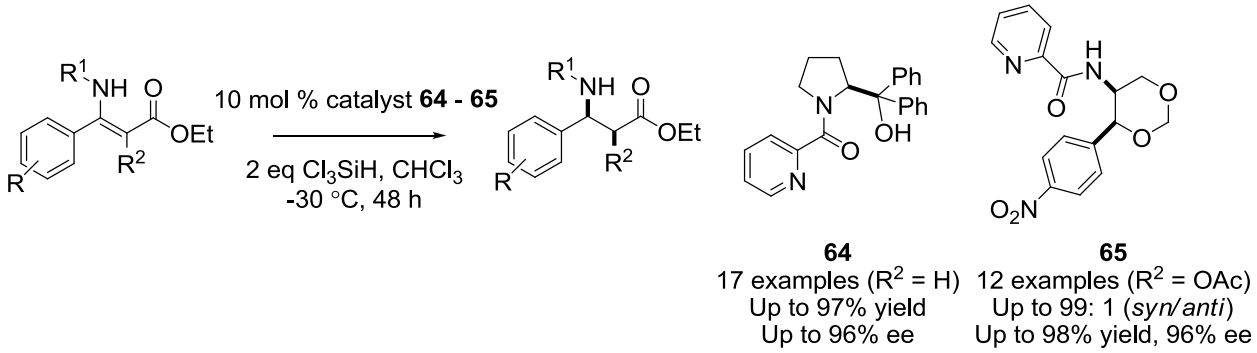
Scheme (24) – The reduction dihydrobenzooxazinones and dihydroquinoxalinoes using Zhang's catalyst 63

The authors were also the first to disclose the enantioselective reduction of β-enamino esters.[57] Studies demonstrated that derivatives of Matsumura's *N*-picolinoyl pyrrolidine **64** were highly effective with the β-amino esters isolated in high yield and excellent enantioselectivity (scheme 25). Interestingly, catalyst **63** was shown to be only moderately effective toward the reduction and also gave the opposing enantiomer of product.



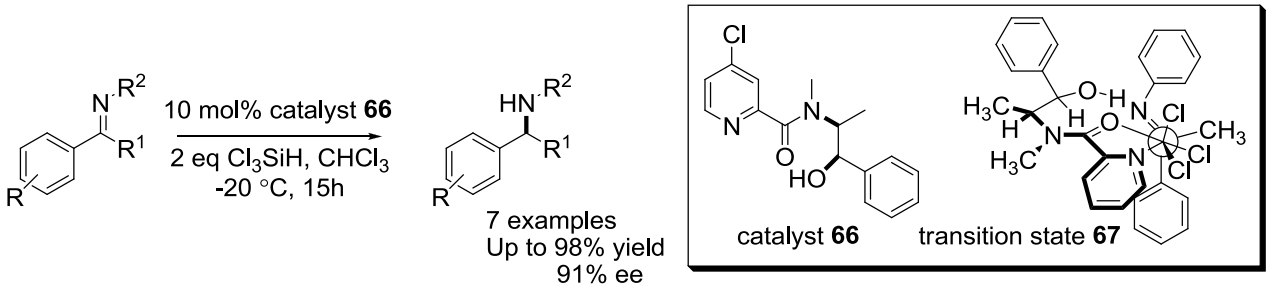
Scheme (25) – The first trichlorosilane mediated reduction of β-enamino esters.

Recent studies from the group have extended the substrate scope of the reduction to encompass α-acetoxy-β-enamino esters.[58] A single catalyst **65** was reported to facilitate the reduction of a range of *N*-aryl β-aryl and β-heteroaryl substrates in good yield and excellent diastereo- and enantioselectivity (scheme 26). No rationale as to the choice of catalyst or whether other catalysts could be employed was reported by the authors. It was noted however, that the reaction proceeded slowly in dehydrated solvent, suggesting that trace quantities of water in un-treated commercial solvents reacted with the trichlorosilane to generate a Brønsted acid that promoted tautomerism of the enamine to the reactive imine tautomer.



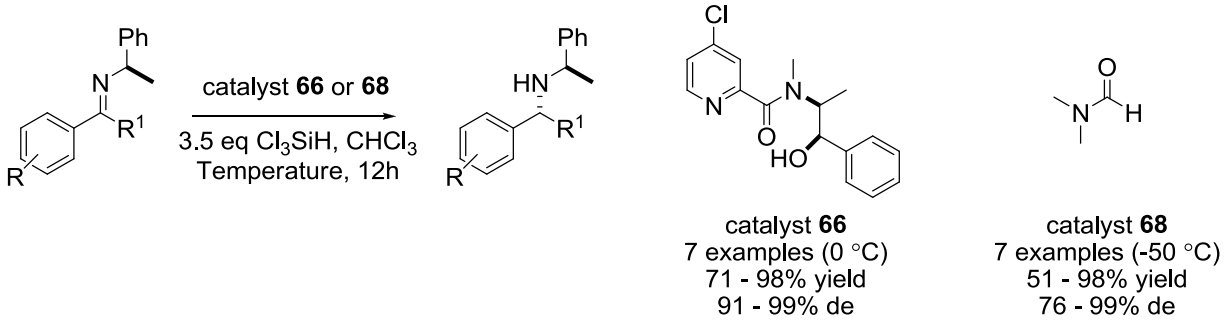
Scheme (26) – Zhang's reduction of β-enamino esters and α-acetoxy-β-enamino esters.

Benalgia has independently reported a third generation *N*-picolinamide **66** that exhibits a marked increase in both enantioselectivity and turnover efficiency.[59] Functionalisation of the pyridine ring identified the 4-chloro analogue **66** capable of reducing a range of *N*-aryl ketimines in good yield and excellent enantioselectivity. One of the important disclosures of the work was the ability of the catalyst **66** to affect the asymmetric reductive amination with unactivated ketones (scheme 27). Three examples were reported and the corresponding amines isolated in comparable yield and selectivity to the analogous two step process.



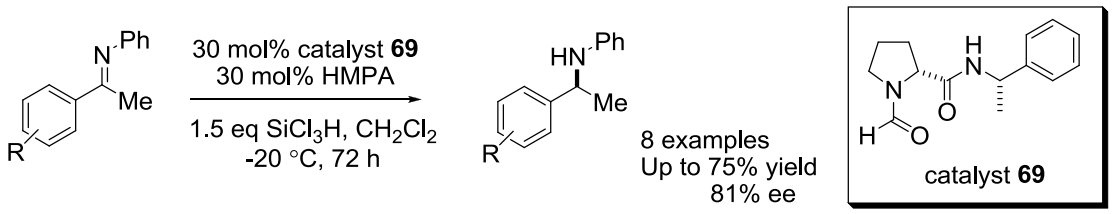
Scheme (27) – Benalgia's third generation *N*-picolinamide 66 catalyst and transition state model to account for the observed stereoselectivity.

To improve upon the selectivity of the reduction further, the hydrosilylation of a diverse range of substrates derived from (*R*)-1-phenylethylamine was reported.[60] The catalyst **66** was found to facilitate the complete diastereoselective reduction of both electron rich and electron poor species. The methodology was successfully extended to incorporate the diastereoselective reduction of dialkyl imines, with the imine derived from *iso*-butyl ketone being reduced in 98% yield and 99% de (scheme 28). Subsequent work demonstrated that analogous results could be achieved through the use of the achiral Lewis base DMF **68** albeit with the need for a large excess of the reagent and lower reaction temperatures.



Scheme (28) – The reduction of a range of ketimines derived from (*R*)-1-phenylethylamine.

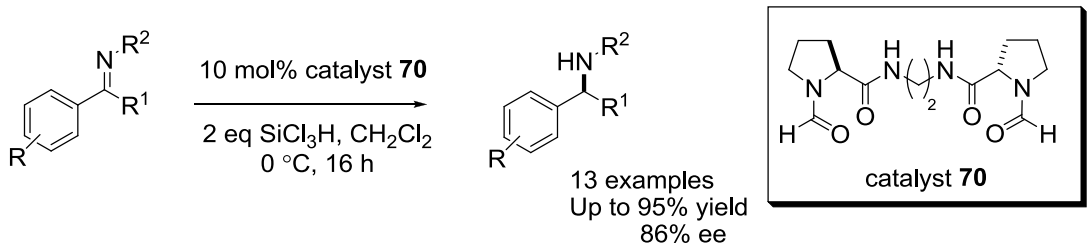
In 2007, Tsogoeva reported the chiral formamide **69** as a moderately selective catalyst for the reduction of a range of *N*-aryl ketimines synthesised from acetophenone derivatives.[61] Pivotal for the selectivity was the high catalyst loading (30 mol%) compared to traditional loadings (10 mol%) utilised. Furthermore, incorporation of an additional stereogenic element onto the catalyst and the use of HMPA as an additive were found to be essential for high enantioinduction. No rationale however, was reported by the authors to account for either observation.



Scheme (29) – Tsogoeva chiral formamide reduction of a range of *N*-aryl ketimines.

In the same year, Sun disclosed the C_2-symmetric chiral tetramide **70** derived from proline to be an effective catalyst for the reduction of a classical set of *N*-aryl ketimines (scheme 30).[62] Crucial for high enantioselectivity was the spacer length between the two diamide units, any deviation significantly sought to lower the enantioinduction capabilities of the catalyst. Whilst no mechanistic data was reported by the authors, Sun proposed two feasible transition states **71**

and **72** with a hexacoordinate silicon atom that explained the synergistic effect of the two diamide moieties (figure 6).



Scheme (30) – Sun's chiral tetramide catalyst for the asymmetric reduction of *N*-aryl ketimines.

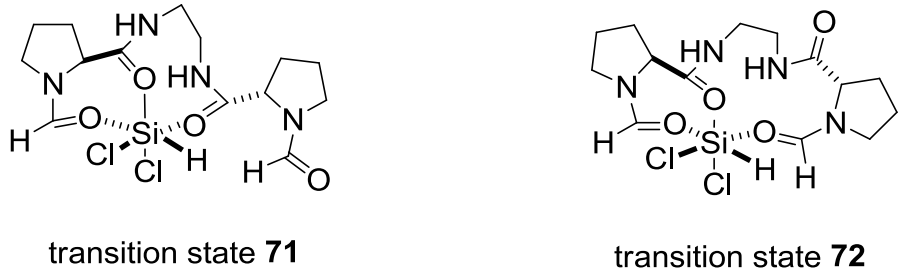
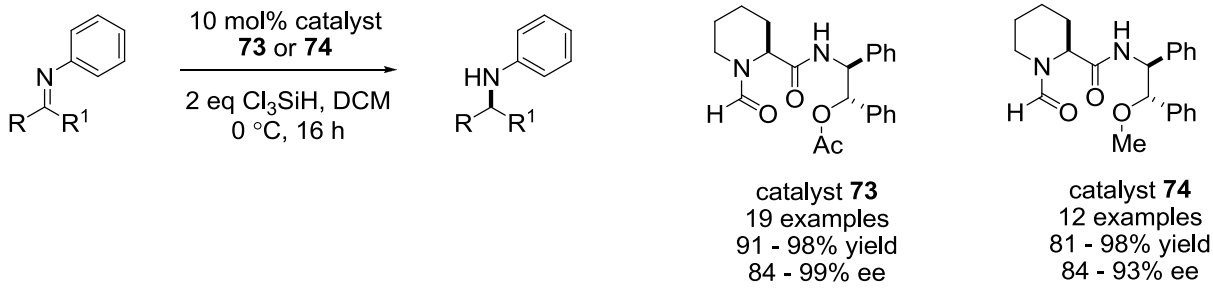


Figure (6) – The two transition states proposed by Sun to account for the selectivity of the chiral tetramide X

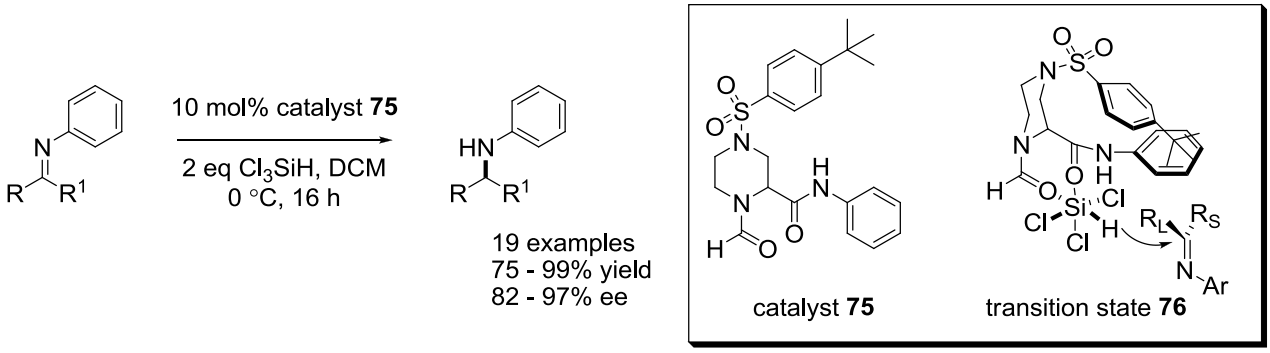
The group were also the first to report the organocatalytic reduction of aliphatic ketimines. Diastereomeric pipecolic acid derivatives containing three stereogenic centres were screened in the reduction with the optimum catalyst **73** providing the resulting amines in excellent yield and enantioselectivity (scheme 31).[63] Sun noted that the stereogenic element at the β-position relative to the amide was found to be crucial for the selectivity of the catalyst. Replacement of the phenyl group with a smaller substituent depreciated the enantioselectivity greatly. Subsequent work also demonstrated that replacing the acetate group with a methyl ether provided a new catalyst **74** with comparable activity and selectivity to the acetate analogue **73**.[64]



Scheme (31) – Sun's reduction of aliphatic ketimines using the diastereomeric pipeliconic acid derivatives

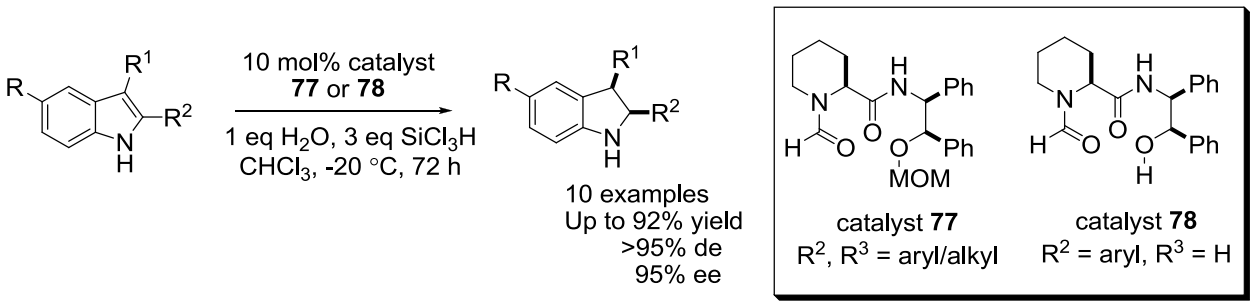
Ensuing work by the authors developed a second generation catalyst based on a piperazine heterocycle.[65] The optimised catalyst **75** was shown to be highly selective toward the reduction

of a range of *N*-phenyl ketimines derived from acetophenone derivatives (scheme 32). It was noted that the catalyst was very sensitive to the nature of the substituent on the nitrogen atom, with both substituted phenyl and benzyl moieties having a deleterious effect upon the enantioselectivity. To account for the stereoselectivity of the reduction Sun hypothesised the transition state **76** in which the large sulfonamide substituent is orientated to ensure that hydride delivery only occurs to one face of the ketimine.



Scheme (32) – Sun's chiral piperizine sulfonamide catalyst for the reduction of aliphatic ketimines.

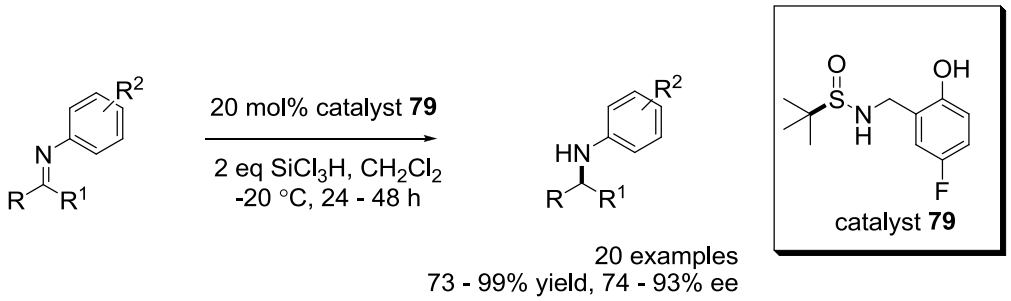
Most recently, the group have reported that the chiral pipecolic acid catalyst **77** can affect the highly diastereo- and enantioselective reduction of 2,3-substituted indoles (scheme 33).[66] Crucial for the high selectivity was the addition of 1 equivalent of water which is thought to react with the trichlorosilane and generate HCl, a species pivotal to aiding in the tautomerisation of the indole to the reactive iminium ion. Interestingly, removal of the MOM group from the catalyst enabled reduction of a range of indoles with sterically encumbered substituents in the 2-position. No rationale to explain the stereochemical outcome of the reductions was reported by the authors.



Scheme (33) – Sun's reduction of 2-substituted and 2,3-disubstituted indoles.

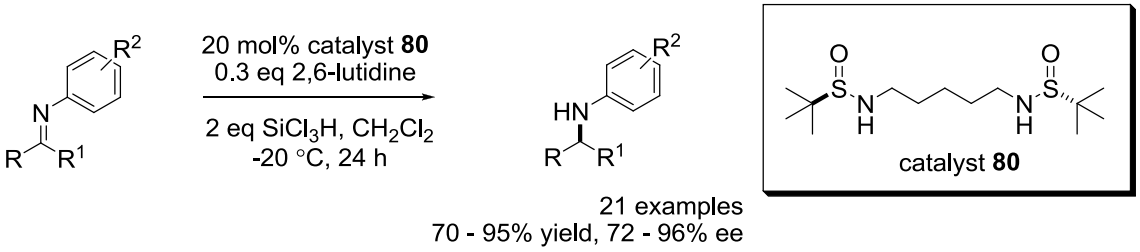
Sun has also synthesised a series of *S*-chiral sulfinamide organocatalysts.[67] A range of catalysts were readily prepared from commercially available (*R*)-*tert*-butylsulfinamide and screened toward the reduction of the *N*-phenyl ketimine derived from acetophenone. Pivotal for high enantioselectivity of the catalyst **79** was the position of the phenol moiety. Movement to either

the *meta* or *para* position of the aromatic ring had a detrimental effect upon the selectivity. The importance of the phenol group was further exemplified by the observation that methylation or acylation of the phenol dramatically decreased the enantioselectivity. Addition of an electron withdrawing group onto the aromatic ring resulted in an increase in catalyst efficacy and led the authors to suggest that the phenol group behaved as a Brønsted acid rather than a site for coordination to trichlorosilane. Mechanistically it was noted that the phenol needed to behave in an intramolecular fashion as any external acid additive failed to exert any influence upon the reaction. A positive non-linear effect was also noted and led to the hypothesis that more than one molecule of catalyst was present in the rate determining step. The optimised catalyst **79** was show to be highly effective toward the reduction of a classical representative set of *N*-aryl aryl-methyl ketimines (scheme 34).



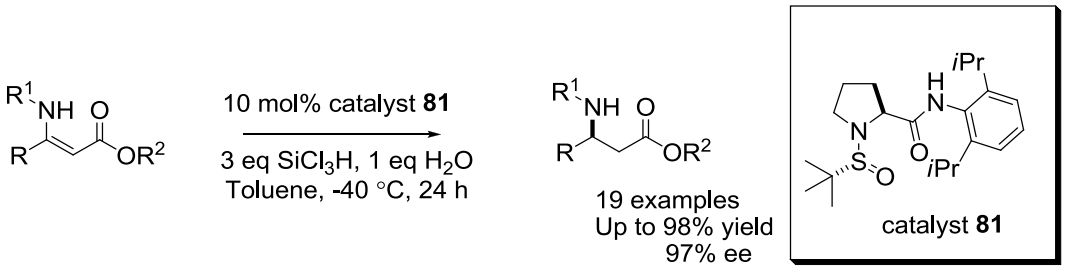
Scheme (34) – Sun's *S*-chiral sulfoxide organocatalyst for the asymmetric reduction of ketimines.

The non-linear effect exhibited by catalyst **79** led to the development of a series of catalysts incorporating two tethered *S*-chiral sulfinamide moieties.[68] Screening of a variety of flexible aliphatic chain lengths as well as more restricted linkers *via* incorporation of a phenyl ring identified the highly selective C_2-symmetric catalyst **80**. The catalyst demonstrated a linear relationship between the enantioselectivity of the product and the enantioselectivity of the catalyst and facilitated the reduction of both aryl and aliphatic ketimines in excellent yield and enantioselectivity (scheme 35). Pivotal to the enantioinduction was the addition of 0.3 equivalents of 2,6-lutidine; any deviation in the amount of additive only sought to have a detrimental effect on the selectivity. No explanation as to the exact nature of the role that the additive exerts was reported by the authors.



Scheme (35) – Sun's dimeric C_2-symmetric sulfoxide catalyst for the asymmetric reduction of ketimines.

Most recently, the *S*-chiral sulfinamide **81** derived from proline has been disclosed as a highly effective catalyst for the reduction of *N*-alkyl-β-enamino esters (scheme 36).[69] As observed with analogous organocatalytic reductions, the role of additives was fundamental for high enantioselectivity. Addition of one equivalent of water was shown to be the optimum additive with its role hypothesised to aid in the generation of HCl, thus facilitating acceleration of the enamine-imine tautomerisation, and increasing the electrophilicity of the imine through protonation of the nitrogen atom.



Scheme (36) – The asymmetric reduction of β-enamino esters using the *S*-chiral sulfoxide 81

In 2004, Kočovský and Malkov reported the *N*-methyl-(*S*)-valine derived formamide **82** as a highly selective catalyst for the reduction of *N*-aryl ketimines synthesised from acetophenone derivatives.[70] The high stereoinducive effects of the catalyst were attributed to arene-arene interactions, hydrogen bonding and a chiral relay effect from the *N*-methyl substituent. The authors proposed a transition state model **84** in which the silicon atom is coordinated by the two carboxamide groups of the ligand (figure 7). A catalyst-substrate hydrogen bonding interaction was also hypothesised which enabled the substrate to be correctly orientated for the stereospecific delivery of the hydride ion.

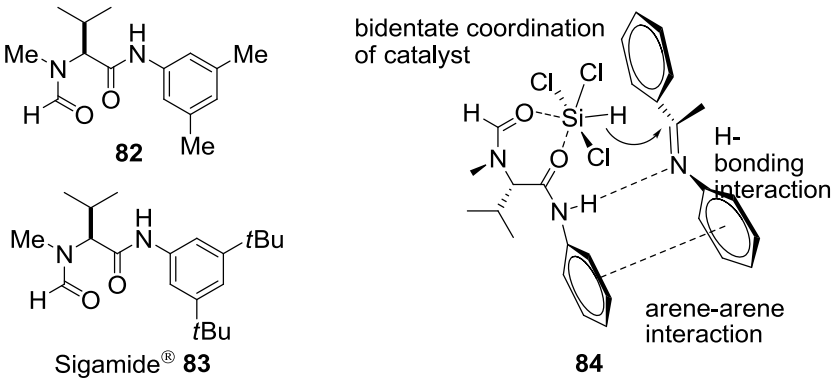
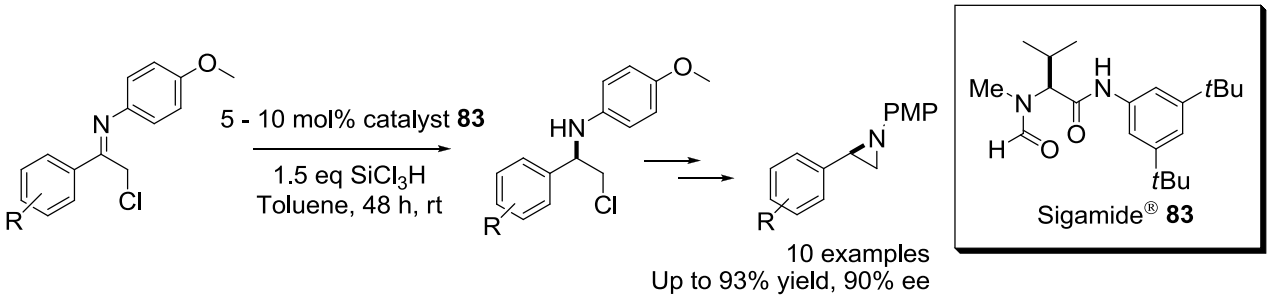


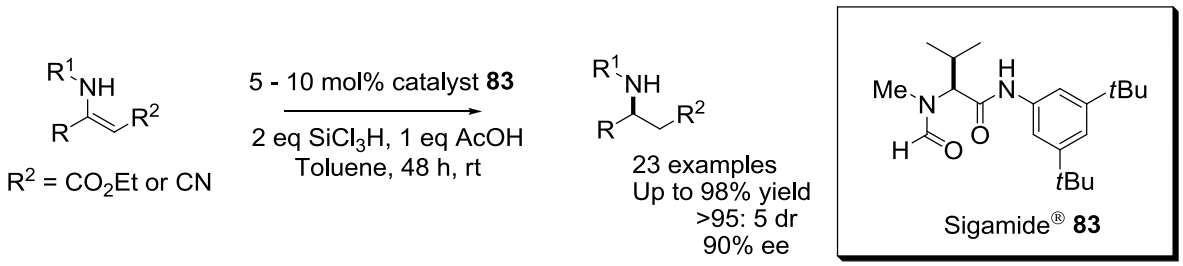
Figure (7) – Malkov and Kočovský 1st generation and Sigamide® catalyst

Replacement of the methyl substituent of the aromatic ring with a *tert*-butyl group led to the development of Sigamide® **83**, a commercially available catalyst.[71] A huge number of ketimines were investigated encompassing aryl, heteroaryl and aliphatic substituents and the corresponding amines isolated in excellent yield and good enantioselectivity. The catalyst **83** was also shown to be highly effective toward the reduction of α-chloro ketimines, the products of which were transformed into enantiomerically enriched aziridines (scheme 37).[72]



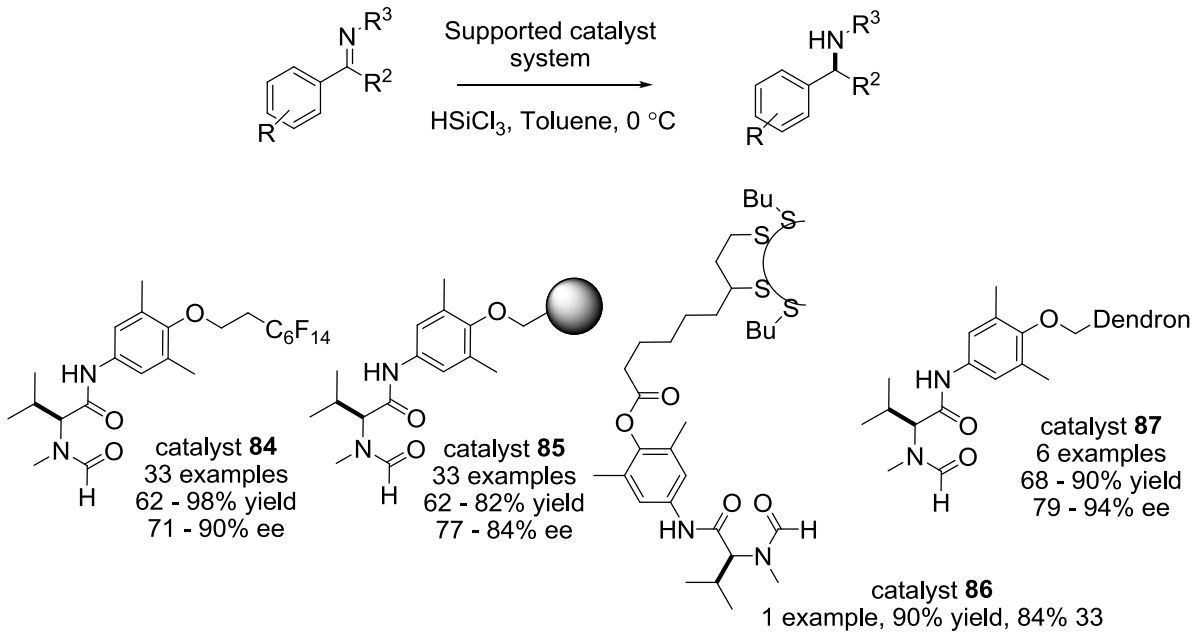
Scheme (37) – The synthesis of enantioenriched aziridines using Sigamide®

Recently, Sigamide® **83** has been shown to be highly effective toward the reduction of β-enamino esters and nitriles (scheme 38).[73] In line with analogous reductions, the addition of an acid additive was crucial for accelerating the rate of tautomerism of the enamine to the reactive iminium ion of the β-enamino ester or nitrile. A range of substrates were well tolerated by the reaction with the corresponding β_2 and $\beta_{2,3}$-amino esters/nitriles isolated in good yield, excellent enantioselectivity and with the latter substrates, complete diastereoselectivity. To account for the formation of a single diastereoisomer, the authors proposed a fast equilibrium between the achiral starting enamine and the reactive ketimine tautomer thus enabling the reaction to proceed *via* dynamic kinetic resolution.



Scheme (38) – The use of Sigamide® for the asymmetric reduction of β-enamino esters and nitriles

To ease with the recovery of the catalyst, the group have developed a perfluoroalkyl tagged **84** and resin supported analogue **85** of Sigamide® which could be recovered by flash column chromatography on fluorous silica or through filtration of the resin, respectively.[74-75] The catalyst gave comparable results to their non-supported counterpart; however, when supported with a polymeric resin an increase in catalyst loading to 25 mol% was required. The Lewis base catalyst has also been attached to gold nanoparticles.[76] The authors noted the methodology enables the reaction to occur under homogenous conditions and facilitate easy recovery and recyclability of the catalyst, through precipitation of the nanoparticles. The nanoparticles displayed excellent solubility in nonpolar solvents and enabled good enantioselectivity (up to 84% ee) to be obtained at room temperature in toluene. Interestingly, recovery experiments demonstrated that whilst the yield remained comparable, the enantioselectivity of the catalyst **86** dropped when recycled for the fourth time. It was hypothesised that this behaviour was due to the partial desorption of the catalyst from the nanoparticles during the work-up and as a result enabled the exposed nanoparticles to catalyse the racemic background reduction.

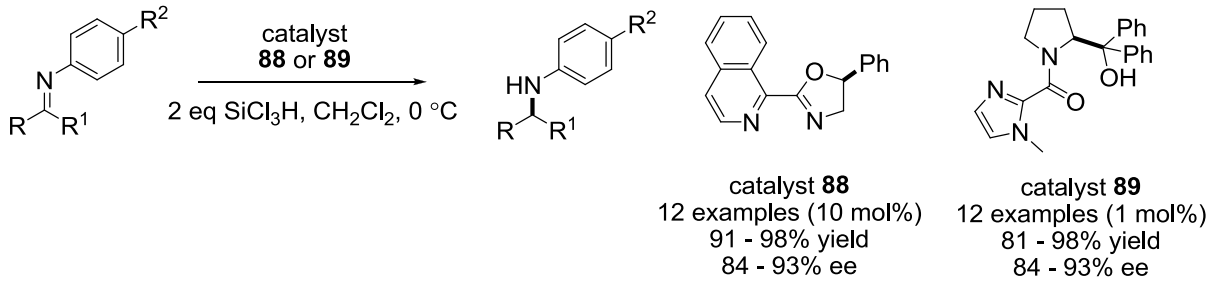


Scheme (39) – The various types of recovery of the Sigamide® catalyst.

Recently, the group have demonstrated that the tethering of Sigamide® to a third generation dendron enabled greater than 95% efficiency in the recyclability of the catalyst.[77] The catalyst also exhibited an improvement in the enantioinduction compared to the other means of recovery. Interestingly, attempts at increasing the scale of the reduction for the dendron catalyst **87** above 0.1 mmol sought to have a detrimental effect upon the activity and selectivity of the catalyst.

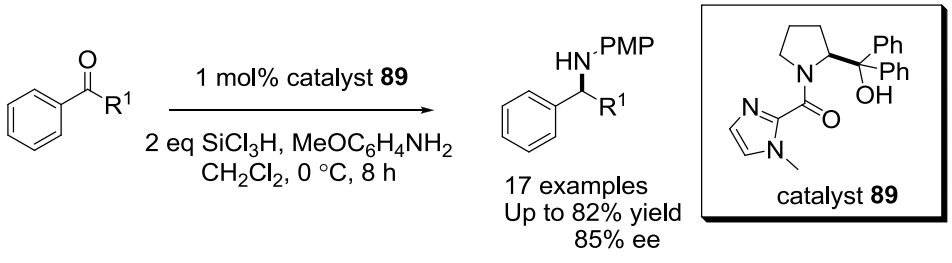
The authors have also disclosed the isoquinoline containing oxazoline **88** as a highly selective catalyst for the asymmetric reduction of ketimines and ketones (scheme 40).[78] A range of classical aryl-methyl derived ketimines were reduced in excellent yield and enantioselectivity. The requirement for a large Lewis basic isoquinoline moiety on the catalyst led the authors to hypothesise that amplification of the steric bulk around the silicon atom upon coordination of the catalyst to trichlorosilane aids in the stereospecific delivery of the hydride ion.

Recently, Jones has identified an *N*-methyl imidazole bifunctional catalyst **89** derived from proline that delivers excellent levels of reactivity and enantioselectivity at 1 mol% catalyst loading (scheme 40).[79] A detailed structure/activity relationship demonstrated that akin to the work of Matsumura, a diaryl tertiary alcohol was pivotal for high enantioinduction. Removal of the carbonyl group adjacent to the *N*-methyl imidazole ring significantly depreciated the reactivity and selectivity of the catalyst. The catalyst **89** was shown to facilitate the reduction of a broad range of electron rich and electron deficient *N*-aryl and *N*-alkyl ketimines.



Scheme (40) – Recently developed organocatalysts for the asymmetric reduction of ketimines.

The catalyst has also been shown to affect the highly selective reductive amination of a diverse range of ketones and aryl and aliphatic amines in good yield and selectivity.[80] Crucial to the success of the protocol was optimising the conditions for the *in situ* formation of the ketimine. Interestingly, the introduction of Lewis acid additives increased the yield of the reduction but had a detrimental effect upon the selectivity. Increasing the concentration of the reaction however, resulted in an increase in the yield with no deleterious effect upon the selectivity.

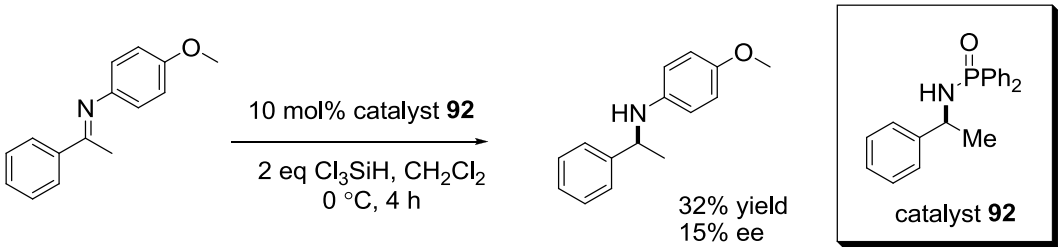


Scheme (41) – The reductive amination of various acetophenone derivatives using Jones' catalyst 89

The work also demonstrated the feasibility of a two step one pot reductive amination strategy in which the ketimine was formed using microwave irridation and then subjected to standard reduction conditions (scheme 41). The authors noted that such a process offered considerable time savings compared to the classical reductive amination strategy and enabled the substrate scope to be extended to *N*-alkyl ketimines, substrates that are notoriously problematic in reductive amination strategies.

1.6 Project aims

During the course of the preliminary studies into the development of the *N*-methyl imidazole catalyst **89**, it was noted that *N*-phosphinyl ketimines were very poor substrates for the reduction. A more detailed analysis identified that the *N*-phosphinyl amine **92**, the product of the reduction was itself acting as a catalyst and activating trichlorosilane toward the reduction. When enantiomerically pure *N*-phosphinoyl amine was employed as the Lewis base catalyst the *N*-PMP amine **107** was isolated in reasonable yield and moderate enantioselectivity (scheme 42).



Scheme (42) – The discovery that the *N*-phosphinyl amine 92 could catalyse the trichlorosilane mediated reduction of ketimines.

The aims of this project therefore are to explore the use of chiral phosphinic amide ligands as a means of activating trichlorosilane toward the enantioselective reduction of aryl and aliphatic ketimine substrates. It is envisaged that a series of first generation catalysts will be synthesised to probe the role of the Lewis basic phosphoryl moiety and examine how altering the phosphinoyl or phosphoryl groups of the catalyst affect the interaction with trichlorosilane. Examination of the substituents on the nitrogen atom will also be undertaken to determine the role of the proton on the nitrogen atom and the spatial requirements at that position. Finally, appraisal of the chiral amine scaffold will identify the requisite for additional motives that can participate in either hydrogen bonding or binding to the trichlorosilane.

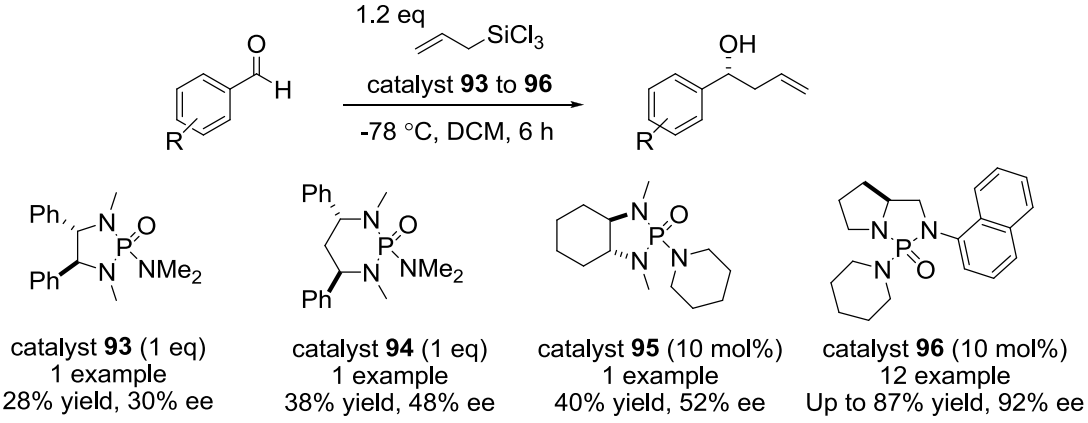
Chapter II

Investigations into the chiral *N*-phosphinic amide scaffold

2.1 Background

The phosphinic amide functionality has found extensive application in organic chemistry. The strong donor properties and Lewis basicity of the moiety make them excellent ligands for transition metal complexes. Furthermore, the nitrogen atoms of the phosphinic amide provide the opportunity for molecular diversification and thus access to structurally and electronically unique analogues.

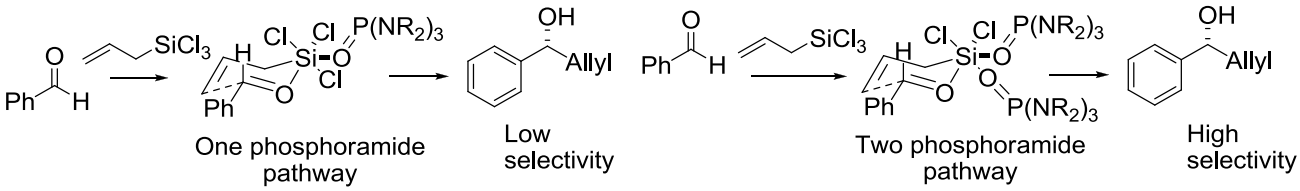
One of the earliest reports into the use of chiral *N*-phosphinic amides as Lewis base catalysts was disclosed by Denmark in 1994.[81] An initial survey of commercially available Lewis bases demonstrated that hexamethylphosphoric triamide (HMPA) could act as an effective promoter for the addition of allyl trichlorosilane to benzaldehyde. Subsequent development of a range of chiral phosphinic amide catalysts **93** - **96** identified the 1-naphthyl analogue **96** derived from proline as a suitable ligand to facilitate the allylation of a range of benzaldehyde derivatives in good yield and enantioselectivity (scheme 43).



Scheme (43) – Denmark's phosphinic amide catalysed addition of allyltrichlorosilane to benzaldehyde

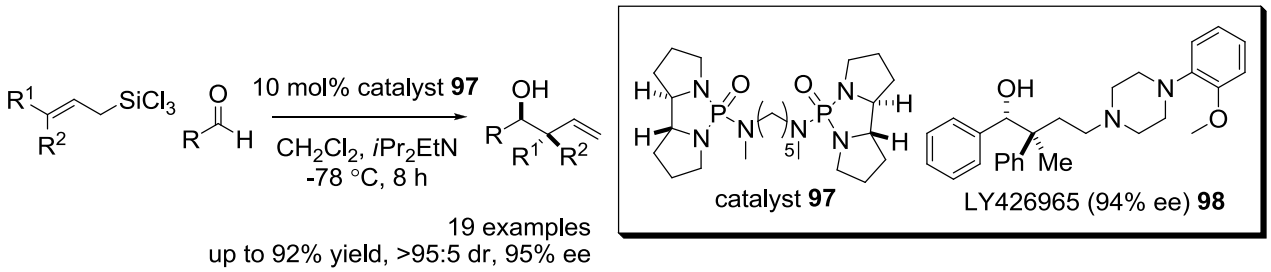
Further studies from the group demonstrated that the enantioselectivity of the allylation was highly dependent on the catalyst loading, with lower loadings leading to lower selectivity.[82] In view of the fact that no kinetically competitive achiral background reaction was present, the authors hypothesised the existence of two catalytic pathways, a lower selective pathway with a single catalyst binding to the silicon atom and a more selective second pathway with two catalysts involved in the rate determining step. To facilitate the reaction preceding through the

higher selective pathway, a series of dimeric *N*-phosphinic amide catalysts were synthesised. The authors noted that the use of a dimeric Lewis base was advantageous as it would allow both Lewis base moieties to act in synergy, disfavour the less selective one phosphinic amide catalysed pathway, and aid in overcoming the entropic disadvantage for the formation of a termolecular transition state with two individual catalytic units.



Scheme (44) – The two catalytic pathways in operation for the allylation of benzaldehyde

A survey of a variety of flexible aliphatic chain lengths, as well as more restricted linkers *via* incorporation of a phenyl ring identified the 2,2'-bispyrrolidine dimeric phosphinic amide **97** as an effective catalyst for the addition of γ and γ,γ'-substituted silanes to an array of aryl aldehydes in good yield, excellent enantioselectivity and in the case of the latter complete diastereoselectivity.[83] As an example of the methodology, the serotonin antagonist LY426965 **98** was successfully synthesised in 94% ee.

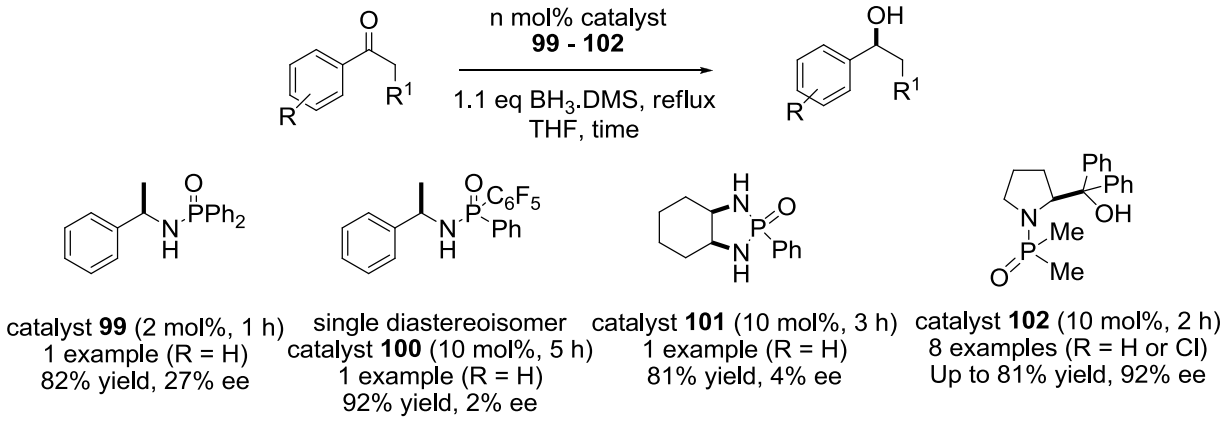


Scheme (45) – The dimeric phosphinic amide 97 catalysed formation of quaternary stereocentres

Wills has also reported a series of modular ligands incorporating the phosphinic amide moiety as catalysts **99 - 102** for the asymmetric reduction of ketones.[84] The effect of the Lewis basicity of the phosphinic amide on the catalyst activity was investigated, the results of which suggested a more convoluted process in operation compared to analogous borane mediated asymmetric reduction of ketones. For example, a Hammett-type study identified the efficacy of the phosphinic amide to be dependent upon the Lewis basicity, with the more Lewis basic catalysts exhibiting pronounced reactivity and selectivity. However, employment of the highly Lewis basic cyclohexadiamine phosphinic amide **101** reduced the yield and enantioselectivity of the catalyst and led the authors to postulate a complex Lewis basic/Brønsted acid mechanism in

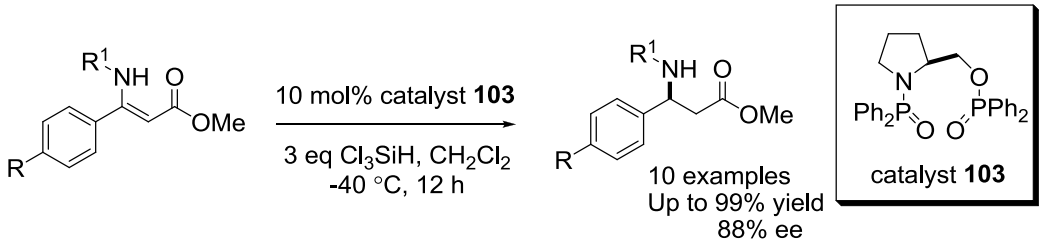
operation, the exact nature of which remains unclear.

A second generation catalyst **102** was disclosed by the group and shown to be highly effective toward the asymmetric reduction of a range of acetophenone derivatives.[85] Pivotal to the selectivity of the catalyst was the replacement of the phenyl substituents around the phosphorus atom with methyl groups, which Wills hypothesised to aid in minimising the steric congestion around the Lewis base upon coordination to the Lewis acid. It was also shown that the presence of a diaryl tertiary alcohol was pivotal for high enantioinduction, as replacement with a hydrogen atom depreciated the enantioselectivity greatly.



Scheme (46) – The reduction of acetophenone derivatives using the *N*-phosphinic amide moiety

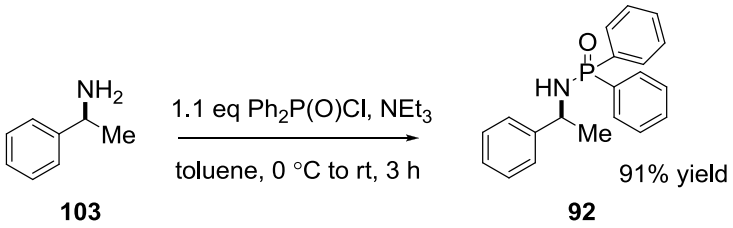
During the course of this PhD study, Benalgia disclosed the potential of a range of chiral phosphinic amides derived from proline to facilitate the hydrosilylation of β-enamino esters.[86] The *bis*-phosphinic amide **103** was shown to reduce an array of electron rich and electron deficient substrates in excellent yield and good selectivity (scheme 47). The selectivity of the process could be improved further by adopting a double stereodifferentiation strategy with incorporation of a chiral α-methylbenzylamine stereodirecting group. No rationale to explain the mechanistic details of the reaction or the stereochemical outcome was reported by the authors.



Scheme (47) – The reduction of β-enamino esters using the *bis*-phosphinic amide 103

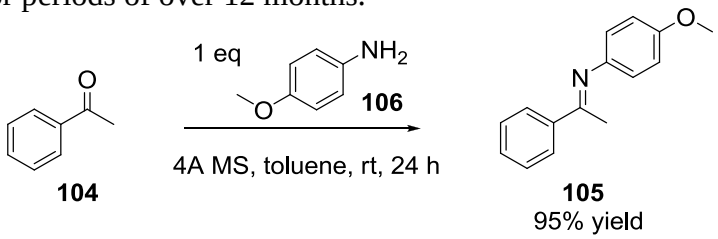
2.2 Investigations into the steric and Lewis basicity requirements of the catalyst

To verify the results previously obtained in this research group, the phosphinic amide **92** was synthesised in its enantiomerically pure form. Treatment of (*S*)-α-methylbenzylamine **103** with diphenyl phosphinic chloride and triethylamine afforded the desired compound in good yield (scheme 48).



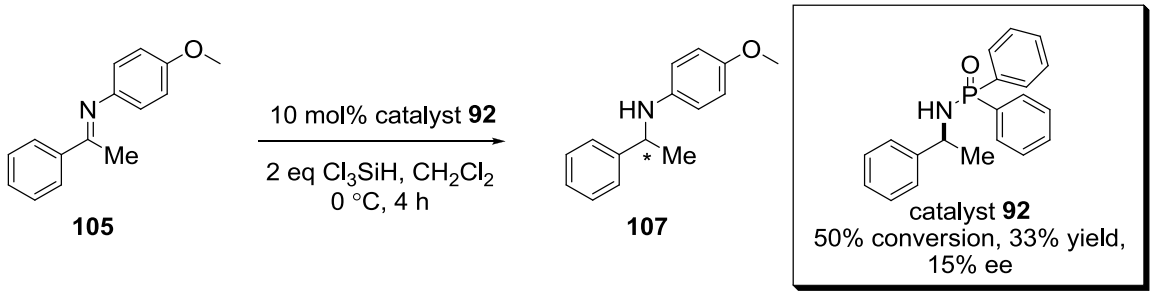
Scheme (48) – The synthesis of the phosphinic amide derived from (*S*)-α-methylbenzylamine

Early studies within the group had utilised the *N*-phenyl protected ketimine as the benchmark substrate for testing catalyst efficacy. Such species, however, were found to be prone to degradation over a 24 hour period. To circumvent this issue, the *N*-PMP ketimine **105** was readily synthesised in excellent yield (scheme 49).[70] Treatment of acetophenone **104** with *p*-anisidine **106** in the presence of 4Å molecular sieves afforded the ketimine **105**, which was found to be stable for periods of over 12 months.



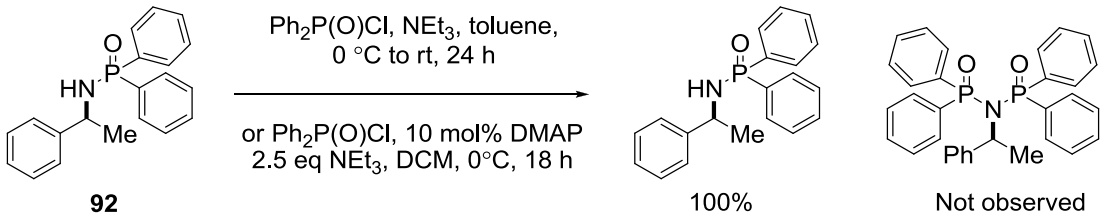
Scheme (49) – The synthesis of the *N*-PMP ketimine from *p*-anisidine and acetophenone

Screening of the catalyst under the standard reduction conditions developed by this group demonstrated that the resultant *N*-PMP amine **107** could be isolated in moderate yield and enantioselectivity (scheme 50).[79] Lowering the catalytic loading to 1 mol% lowered the yield of the amine product **107** but did not change the enantioselectivity, suggesting that the achiral uncatalysed background reaction was not kinetically relevant.



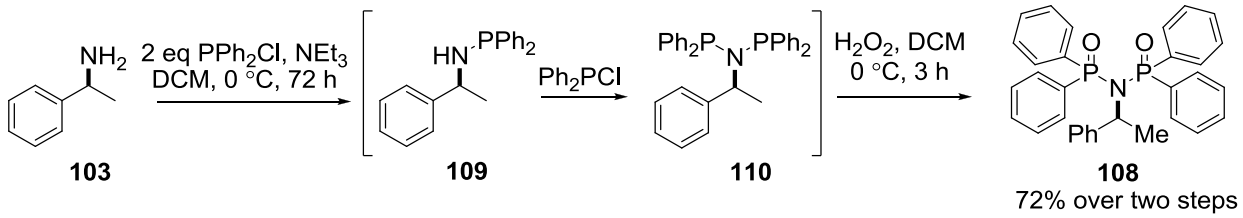
Scheme (50) – The reduction of the *N*-PMP ketimine using the phosphinic amide 92

The limited activity of the original catalyst **92** led to the development of the *bis*-phosphinic amide **108**. It was hypothesised that the presence of two individual Lewis basic moieties may work synergistically in their binding to trichlorosilane and thus facilitate an increase in catalyst efficacy. Initial attempts at synthesising the *bis*-phosphinic amide proved problematic, as treatment of the catalyst **92** with diphenylphosphinic chloride and triethylamine failed to afford any product. Addition of 10 mol% DMAP also failed to assist in product formation suggesting the poor nucleophilicity of the phosphinic amide relative to the analogous amine.



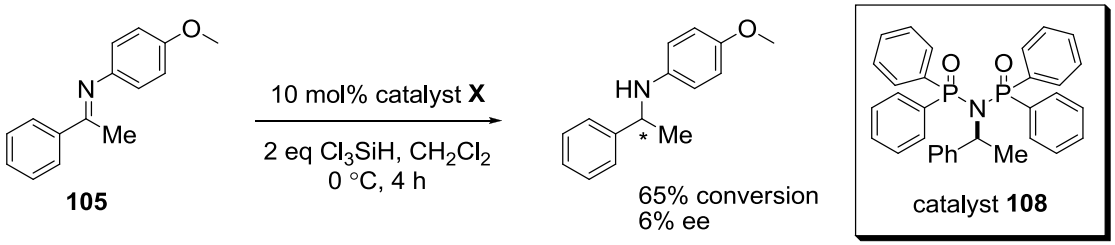
Scheme (51) – Attempted synthesis of the *bis*-phosphinic amide by direct nucleophilic substitution

To circumvent this issue, the enantiomerically pure amine **103** was reacted with two equivalents of the P(III) electrophile, diphenylchlorophosphine. It was envisaged that the intermediary mono-phosphine **109** would exhibit sufficient nucleophilicity to enable addition of a second phosphine moiety and thus generation of the P(III) species **110**. Oxidation of the *bis*-P(III) moiety **110** afforded the target molecule **108** in good yield over two steps (scheme 52).



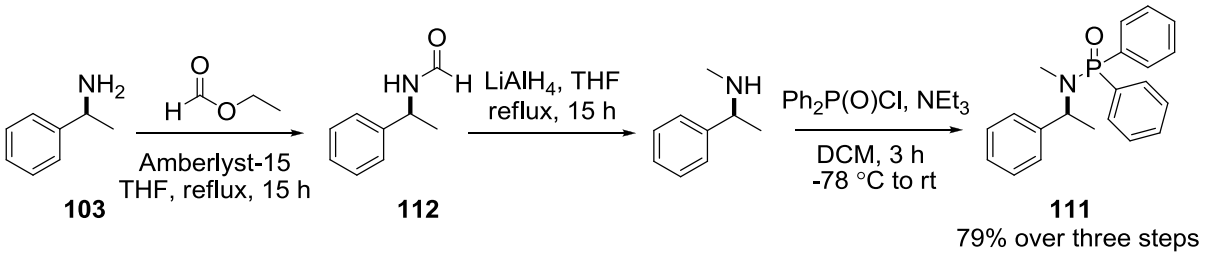
Scheme (52) – The successful synthesis of the *bis*-phosphinic amide 108

Screening of the *bis*-phosphinic amide **108** under the standard reduction conditions showed an increase in conversion to 65% after four hours (scheme 53). The rise in reactivity suggests that the incorporation of a second Lewis basic site onto the catalyst enables the two moieties to synergistically bind to the trichlorosilane and thus facilitate an increase in reactivity. The decline in enantioselectivity however, implies that the NH proton may be crucial for conferring selectivity in the transition state of the reduction.



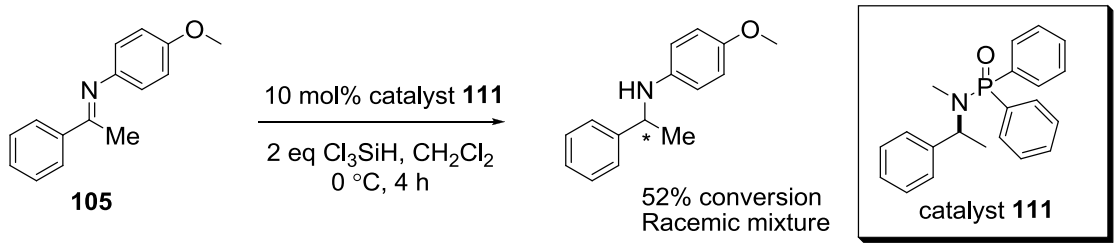
Scheme (53) – Reduction of the *N*-PMP ketimine using the *bis*-phosphinic amide X

To determine the importance of the NH proton on the efficacy of the catalyst, an *N*-methylated phosphinic amide **111** was synthesised.[87] Treatment of (*S*)-α-methylbenzylamine **103** with ethyl formate and the acidic resin Amerlyst-15® yielded the formamide **112** in quantitative yield. Reduction with $LiAlH_4$ and subsequent phosphinic amide formation afforded the target molecule **111** in good yield over three steps (scheme 54).



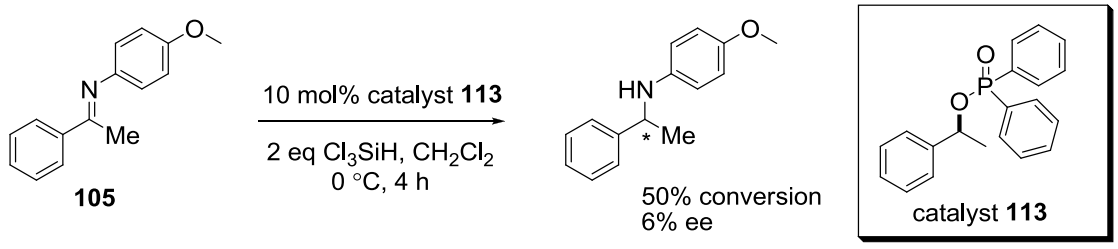
Scheme (54) – The synthesis of the *N*-methylated phosphinic amide 111

Screening of the *N*-methylated phosphinic amide **111** demonstrated a comparable degree of conversion to the original catalyst **92** and suggested that the methyl group did not hinder the interaction between the Lewis base and trichlorosilane. Analysis of the enantioselectivity showed a racemic mixture of the PMP-amine **107** and suggested the importance of the proton on the selectivity of the reduction.



Scheme (55) –Screening of the *N*-methylated phosphinic amide 111

A diphenyl phosphinate catalyst **113** was also synthesised following literature precedent, and shown to reduce the ketimine **105** in 50% conversion and 6% ee after four hours and further confirmed the importance of the NH moiety on the catalyst (scheme 56).[88]



Scheme (56) – Reduction of the *N*-PMP ketimine using the phosphinate catalyst 113

The importance of the amide proton on the catalyst correlated with the work of Malkov and Koĉovský who disclosed that methylation of the amide moiety of their Sigamide® catalyst **83**

resulted in a pronounced depreciation in enantioinduction.[70-72] To rationalise this result the authors hypothesised the formation of a hydrogen bonding interaction between the amidic proton of the catalyst and the nitrogen lone pair of the substrate. This interaction is believed to enable the ketimine to orientate into a single fixed geometry where all steric interactions between the two species are minimised and as a result enables stereospecific delivery of the hydride ion (figure 8).

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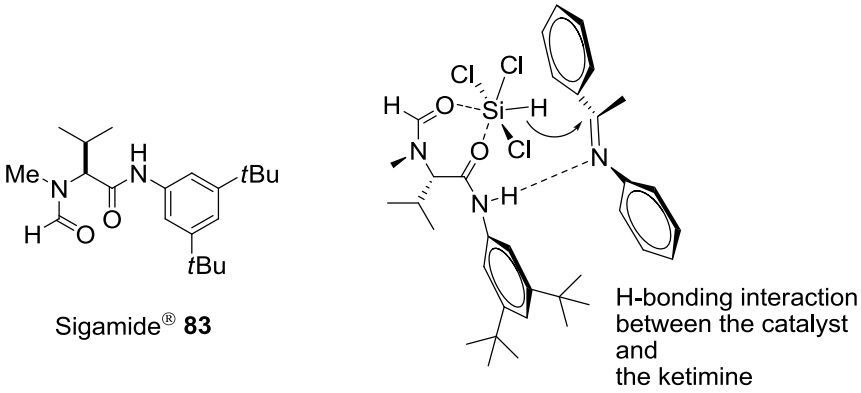
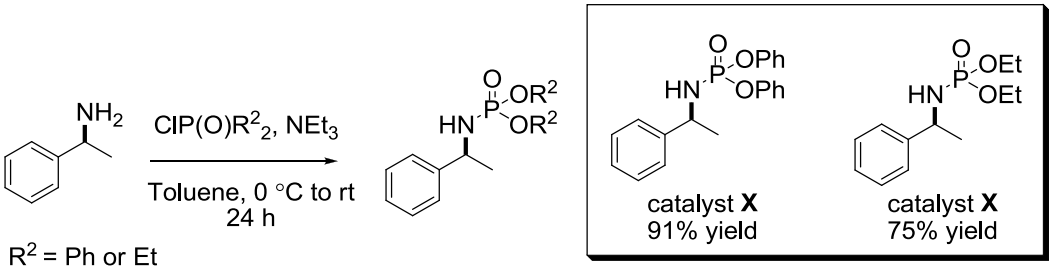


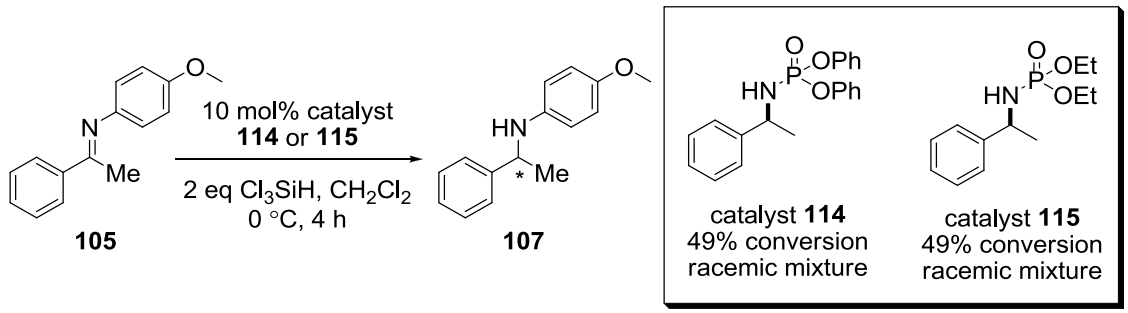
Figure (8) – The transition state proposed by Malkov and Kočovský for the Sigamide® reduction

The limited efficacy of the initial catalysts developed led to investigations into the functionality surrounding the phosphine oxide bond. It was envisaged that the incorporation of a phosphoramidate motif could provide an additional site on the catalyst for binding to the silicon atom as well as alter the shape of the catalyst, thus aiding in the selectivity of the reduction. To probe whether an aryl or aliphatic substituent was the optimum species, two phosphoramidate catalysts **114** and **115** were synthesised in analogous fashion from the appropriate chlorophosphonate (scheme 57).[89-90]



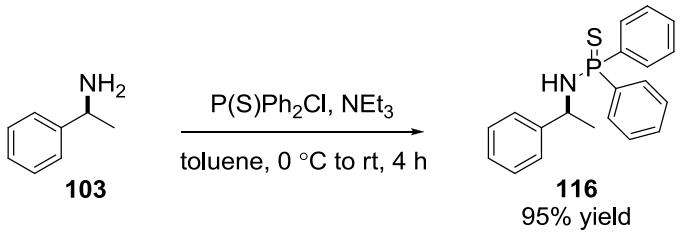
Scheme (57) – The synthesis of the diphenyl and diethyl phosphoramidate catalysts.

Screening of the two catalysts showed comparable activity to the original phosphinic amide **92**, with both exhibiting 49% conversion to the PMP-amine **107** after four hours (scheme 58). Analysis of the enantioselectivity demonstrated that in both cases a racemic mixture of amine was obtained.



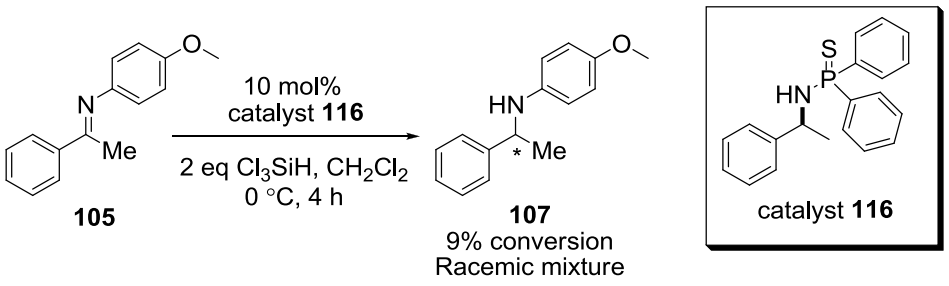
Scheme (58) – Screening of the phosphoramidate catalysts X and X toward the reduction of the ketimine X

The similarities in the activity of the phosphinic amide, phosphinate and phosphoramidate moieties led to efforts to try and improve the activity of the catalyst. The phosphinothioic amide **116** was synthesised with the hypothesis that the larger sulfur atom could confer different binding properties to trichlorosilane and thus result in an increase in reactivity (scheme 59).[91]



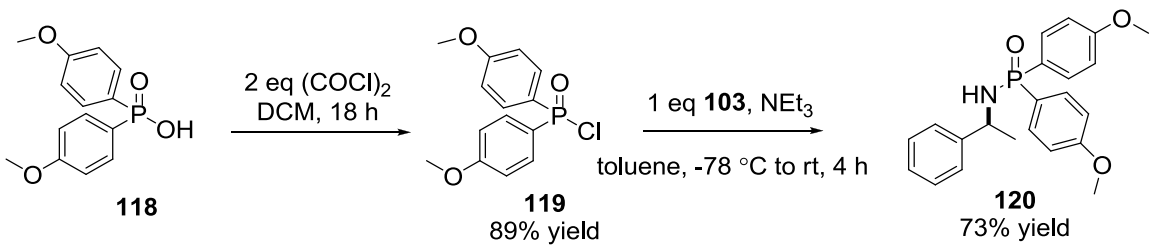
Scheme (59) – The synthesis of the phosphinothioic amide from (*S*)-(-)-methylbenzylamine

Under the standard reduction conditions the catalyst **116** showed a 9% conversion of the ketimine **105** to the PMP-amine **107** (scheme 60). Infrared spectrometry experiments by Laurence have demonstrated the superior Lewis basicity of the phosphine oxide bond over the analogous phosphine sulfide motif. This therefore suggested that the decline in the reactivity of the catalyst was the result of the significant depreciation in the Lewis basicity displayed by the molecule. Analysis of the enantioselectivity of the reduction showed a racemic mixture of the PMP-amine **107**.



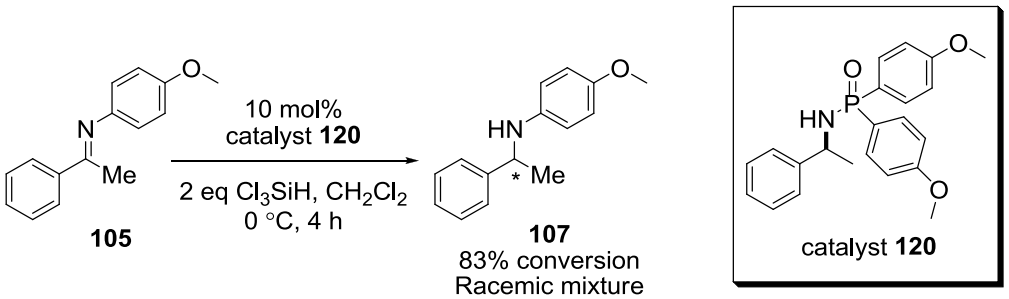
Scheme (60) – Screening of the phosphinothioic amide X toward the reduction of the *N*-PMP ketimine

The observation that a lowering of the Lewis basicity of the catalyst had a detrimental impact upon catalytic activity suggested that the converse, increasing the Lewis basicity of the catalyst, should result in an increase in the proficiency of the phosphinic amide. To probe this hypothesis, the electron rich *para*-methoxy derivative **120** was synthesised. Whilst the *bis*-(4-methoxyphenyl)-phosphinic chloride **119** was not commercially available, it could be readily prepared from the corresponding phosphoric acid **118** in a single step.[92] Addition of the phosphinic chloride to the amine **103** afforded the target molecule in good yield (scheme 61).



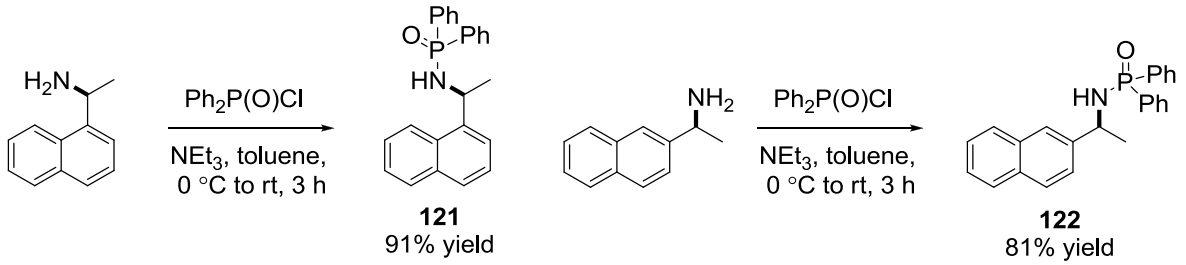
Scheme (61) – The synthesis of the electron rich phosphinic amide 120

Screening of the electron rich catalyst **120** demonstrated an increase in catalyst activity to 83% conversion of the ketimine **105** after 4 hours and demonstrated the need for the catalyst to exhibit high Lewis basicity in order to be effective toward the reduction (scheme 62). Analysis of the enantioselectivity showed a 15% ee, analogous to that of the original catalyst **92**.



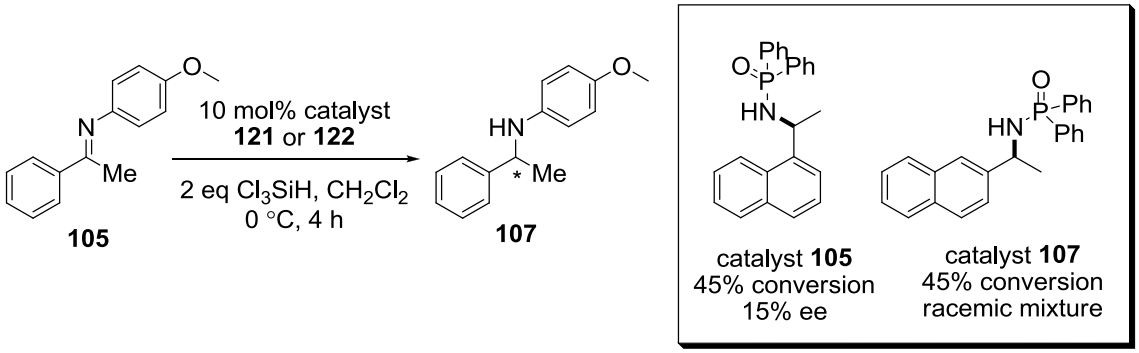
Scheme (62) – Screening of the electron rich phosphinic amide toward the reduction of the ketimine 105

The limited capabilities of the catalysts derived from (*S*)-methylbenzylamine **103** to deliver any appreciative levels of enantioinduction suggested that the chiral scaffold was an inadequate source of chirality. It was thought that the position of the stereogenic centre was too remote in the transition state to exert any stereoselectivity. Denmark had previously shown the necessity for a naphthyl substituent on the phosphinic amide catalyst **96** for high enantioselectivity, and replacement with smaller substituents depreciated the selectivity of the reaction significantly.[81-83] To probe the effect of replacing the phenyl group of the catalyst with a naphthyl derivative, the 1 and 2-substituted naphthyl phosphinic amides **121** and **122** were synthesised according to known literature precedent (scheme 63).[93]



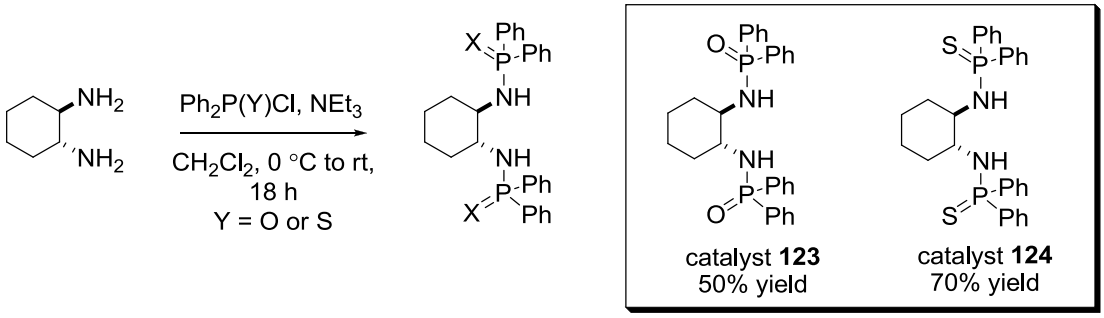
Scheme (63) –The synthesis of the 1 and -2-substituted naphthyl phosphinic amides.

Analysis of the two catalysts showed a comparable level of activity to the original catalyst **92**, with 45% conversion to the PMP-amine **107** after four hours (scheme 64). Determination of the enantioselectivity however, demonstrated that whilst the 1-naphthyl phosphinic amide provided the amine in 15% ee, the analogous 2-substituted analogue **122** delivered the product **107** as a racemic mixture.



Scheme (64) – Screening of the 1-naphthyl and 2-naphthyl phosphinic amide catalysts.

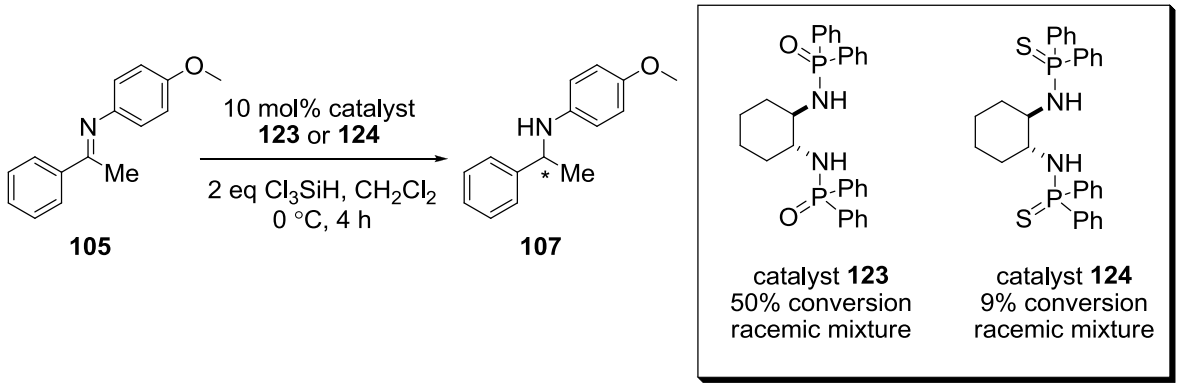
A second series of catalysts were also synthesised from the readily available enantiomerically pure 1,2-cyclohexadiamine scaffold. It was envisaged that the change in the shape of the catalyst and the incorporation of two individual Lewis basic moieties may exhibit a pronounced increase in both reactivity and selectivity. Both the phosphinic amide **123** and analogous sulfur containing catalyst **124** were prepared in good yield in a single step (scheme 65).[94]



Scheme (65) – Preparation of the cyclohexadiamine phosphinic amide and phosphinothioic amide catalysts

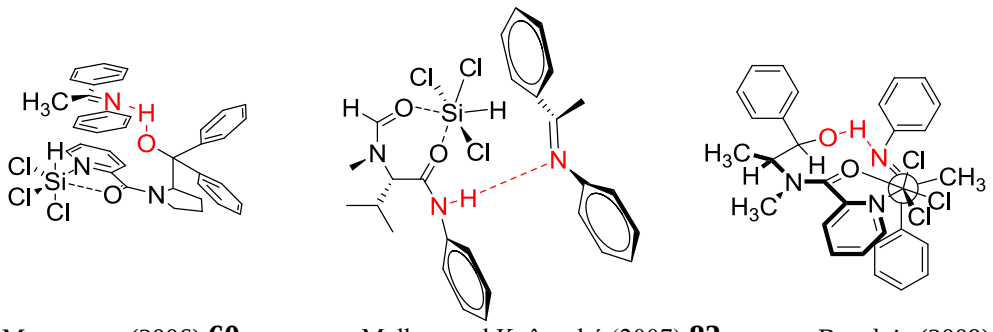
Screening of the two species showed comparative behaviour to the catalysts derived from the (*S*)-methylbenzylamine **103** scaffold. The *bis*-phosphinic amide **123** enabled a 50% conversion

to the PMP-amine **107** after 4 hours, and suggested the two Lewis basic units to be at an incorrect spacer length to enable synergistic bonding to the trichlorosilane (scheme 66). Analysis of the enantioselectivity showed a racemic mixture of amine **107** and supported the work of Wills, who had previously disclosed the unsuitability of the cyclohexadiamine scaffold for the borane mediated asymmetric reduction of ketones.[84-85] The phosphinothioic amide demonstrated a 10% conversion to the PMP-amine and further confirmed the deleterious nature of lowering the Lewis basicity of the catalyst.



Scheme (66) – Screening of the phosphinic amide 123 and phosphinothioic amide 124 catalysts

One of the striking similarities between the catalysts that have been reported to date for the trichlorosilane mediated reduction of ketimines has been the presence of a Brønsted acid (figure 9).[51] The role of the acid is thought to enable the formation of a hydrogen bond between the catalyst and the substrate. The development of this interaction enables the ketimine to adopt a fixed orientation, void of any steric interactions with the catalyst and thus allow for the stereospecific delivery of the hydride ion and high enantioselectivity. Therefore it was envisaged that the incorporation of such functionality onto the phosphinic amide scaffold may enable an increase in the enantioselectivity of the catalyst

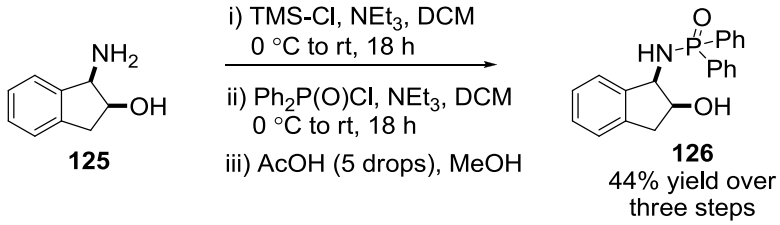


Matsumura (2006) **60** Malkov and Kočovský (2007) **83** Benalgia (2009) **66**

Figure (9)- The key requirement for a Brønsted acidic functionality on the Lewis base catalyst to participate in hydrogen bonding with the ketimine. The hydrogen bonding interaction is marked in red.

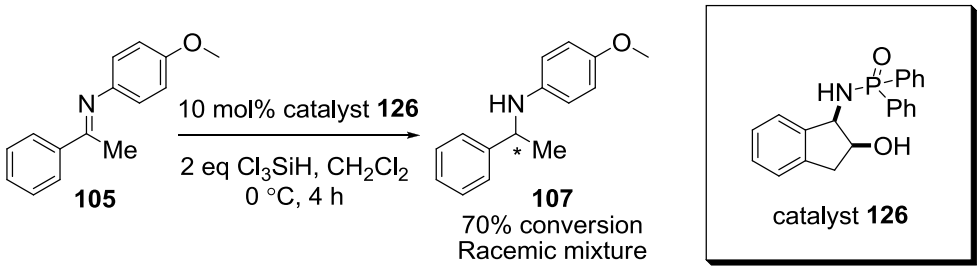
Preliminary investigations centred upon the phosphinic amide derived from amino-indanol **125**.[95] Following known literature precedent the phosphinic amide **126** was synthesised in

moderate yield utilising a one pot three step procedure developed by Wills (scheme 67).[96]



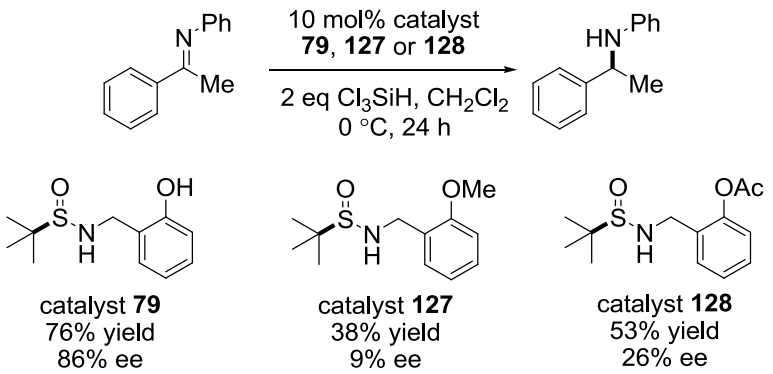
Scheme (67) – The synthesis of the phosphinic amide X derived from amino-indanol

Analysis of the catalyst **126** showed a 70% conversion of the PMP-ketimine **105** after four hours (scheme 68). The increase in reactivity of the catalyst suggested that the hydroxyl group could be working in synergy with the phosphinic amide and acting as a second coordination site to the trichlorosilane. Determination of the enantioselectivity showed a racemic mixture of the PMP-amine **105** and demonstrated the unsuitability of the scaffold to invoke any enantioinduction.



Scheme (68) – The screening of the amino-indanol phosphinic amide 126

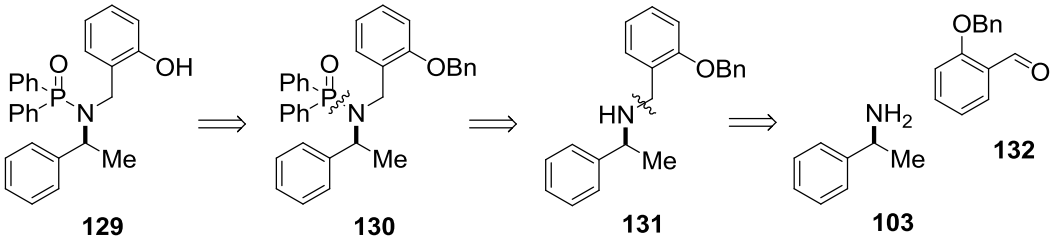
During the development of the chiral sulfoxide catalyst **79**, Sun disclosed the importance of the phenol moiety on the catalyst for high enantioselectivity (scheme 69).[67] The observation that methylation or acylation of the species had a deleterious effect upon the enantioselectivity led the authors to hypothesise the role of the phenol to be as a Brønsted acid and not as a second complimentary site of binding to trichlorosilane. To probe whether an analogous effect could be obtained for the phosphinic amide catalysts, the phenol phosphinic amide **129** was synthesised.



Scheme (69) – Sun's *S*-chiral sulfoxide catalyst and the requirement for the Brønsted acidic phenol moiety

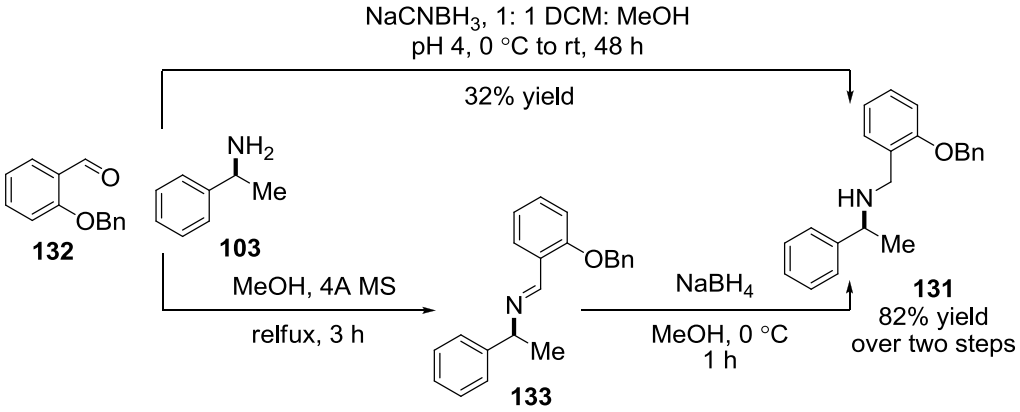
Retrosynthetically, the key secondary amine **131** could be prepared through the reductive

amination of the protected salicylaldehyde **132** and (*S*)-methylbenzylamine **103**, the chiral scaffold that conferred the highest enantioinduction of those tested so far. Subsequent formation of the phosphinic amide **130** and deprotection of the phenol group would enable the preparation of the catalyst **129**.



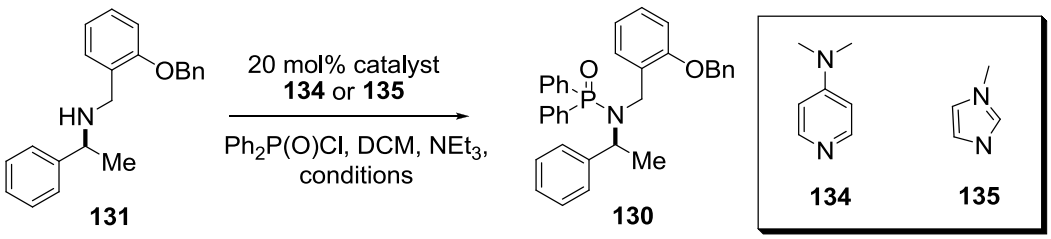
Scheme (70) – The retrosynthetic analysis of the phenol phosphinic amide 129

Reductive amination of the benzyl protected aldehyde **132** with (*S*)-methylbenzylamine **103** and sodium cyanoborohydride afforded the secondary amine **131** in 32% yield. To improve upon the yield, a one pot two step strategy was conducted, in which the ketimine **133** was formed *in situ* and subsequently subjected to reduction with sodium borohydride. Application of this strategy provided the desired amine **131** in excellent yield, and suggested the poor yield of the reductive amination strategy was due to the inferior quality of the reducing agent.



Scheme (71) – The two routes investigated for the formation of the secondary amine 131

Initial attempts at synthesising the phosphinic amide **130** proved problematic, treatment of the secondary amine **131** with diphenylphosphinic chloride and triethylamine failed to afford the desired product with return of the starting amine **103** being the only product observed. Increasing the temperature or leaving the reaction for a prolonged period also failed to induce phosphinic amide formation and suggested that the steric hindrance around the nitrogen atom prevented addition to the electrophile.



Scheme (72) – The synthesis of the desired benzyl protected phosphinic amide X

entry	temperature / °C	time / h	catalyst[a]	conversion to **130** / %[b]	yield of **130** / %[c]
1	rt	24	-	no reaction	-
2	reflux	24	-	no reaction	-
3	reflux	48	-	no reaction	-
4	rt	24	**134**	25	-
5	reflux	24	**135**	65	-
6	reflux	48	**134**	100	81
7	reflux	24	**135**	100	85

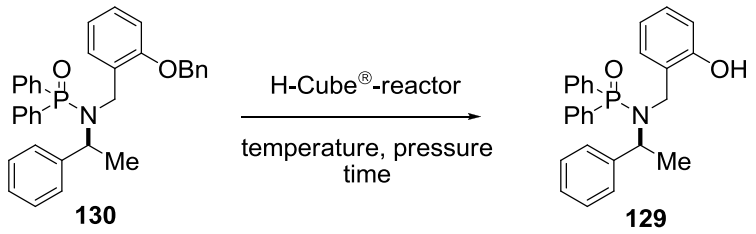
[a] 20 mol% of catalyst; [b] determined by analysis of the crude 1H NMR spectrum; [c] refers to the yield of the isolated product.

Table (1) – Optimisation of the conditions required for phosphinic amide formation

In order to circumvent this issue, 20 mol% of the nucleophilic catalyst DMAP **134** was introduced into the reaction. Analysis of the ^{1}H NMR spectroscopic data showed a 25% conversion to the desired compound **130** after 24 hours at room temperature. Warming the reaction increased the conversion to the phosphinic amide **130** further, however, prolonged reaction periods were still required for complete conversion. Previous work within the group had demonstrated the potential of *N*-methyl imidazole **135** to be a superior nucleophilic catalyst for the phosphorylation of a range of aryl and aliphatic alcohols and it was envisaged that such a species may also aid in the formation of the phosphinic amide **130**.[97] Addition of 20 mol% of *N*-methyl imidazole **135** resulted in complete conversion to the desired compound in 24 hours and isolation of the phosphinic amide **130** in 85% yield.

Deprotection of the phosphinic amide **130** through employment of the H-cube® micro flow reactor fitted with a Pd/C catalyst cartridge failed to afford any of the product **129** (scheme 73, table 2). Manipulation of both the temperature and pressure of the hydrogen gas also failed to induce any debenzylation and suggested that a more reactive source of palladium may be required to remove the sterically encumbered protecting group.[98] Replacement of the Pd/C catalyst with the more reactive $Pd(OH)_2$/C analogue enabled 10% conversion to the desired catalyst **129** after four hours of continuous cycling through the reactor. Further optimisation

identified that the desired phosphinic amide **129** could be obtained in quantitative yield following continuous cycling of the solution through the reactor at 50 °C and 60 atmospheres of hydrogen for 8 hours.



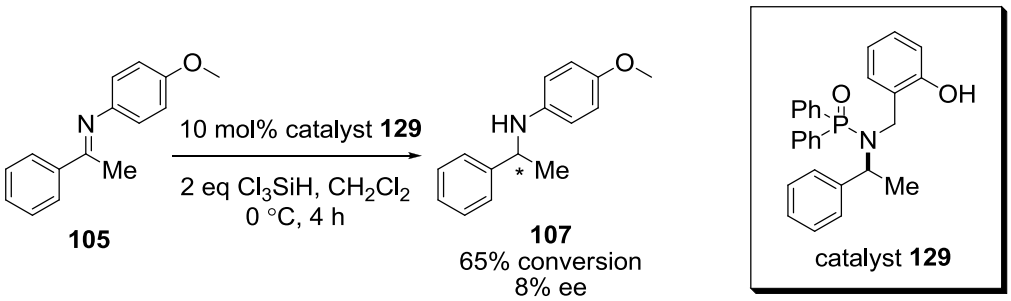
Scheme (73) – Deprotection of the benzyl group to furnish the desired phosphinic amide catalyst 129

entry	catalyst	temperature / °C	time / h	pressure of H_2 / atm	conversion to **129**[a] / %	yield of **129**[b] / %
1	Pd/C	rt	4	1	no reaction	-
2	Pd/C	50	4	1	no reaction	-
3	Pd/C	50	4	50	no reaction	-
4	$Pd(OH)_2/C$	rt	4	1	10	-
5	$Pd(OH)_2/C$	rt	4	50	25	-
6	$Pd(OH)_2/C$	50	8	50	100	95

[a] determined by analysis of the crude 1H NMR spectrum; [b] refers to isolated product

Table (2) – Optimisation of the conditions required for removal of the benzyl group

Analysis of the catalyst **X** showed a 65% conversion of the ketimine **105** to the desired PMP-amine **107** after four hours (scheme X). The increase in catalyst activity compared to the original phosphinic amide **92** suggested the beneficial nature of incorporating a Brønsted acidic site into the catalyst. Determination of the enantioselectivity of the reduction showed an 8% ee in the amine and suggested that the phenol group did not help confer an increase in selectivity.



Scheme (74) – Screening of the 2-phenolic phosphinic amide X catalyst

To identify whether altering the position of the phenol group on the aromatic ring exerted any influence upon the activity and selectivity of the catalyst, the 3- and 4-substituted phosphinic amides **136** and **137** were also synthesised using the previously developed methodology (figure 10).

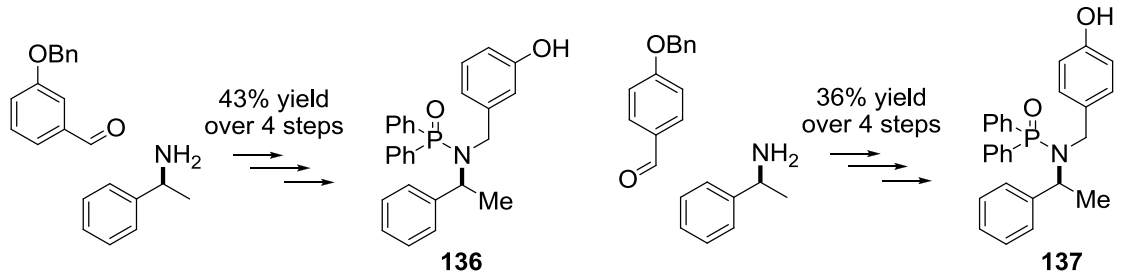
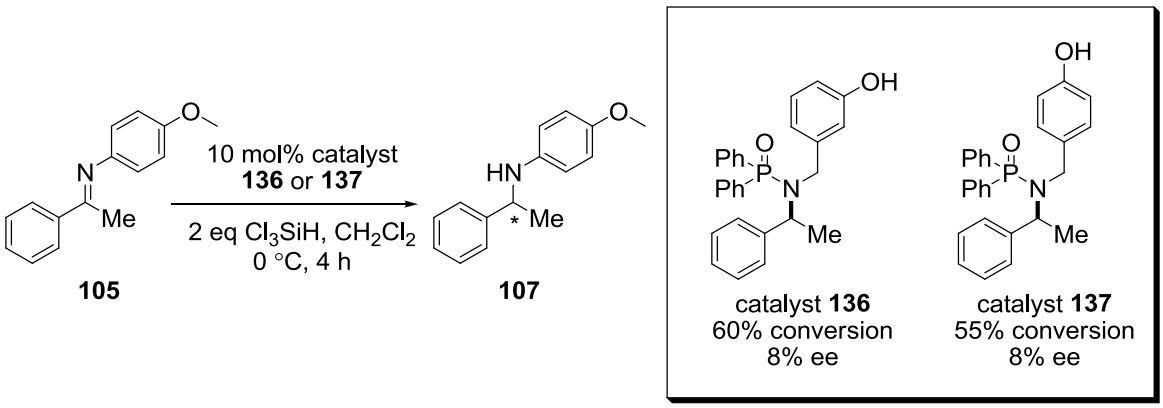


Figure (10) – The 3 and 4-phenolic phosphinic amide catalysts

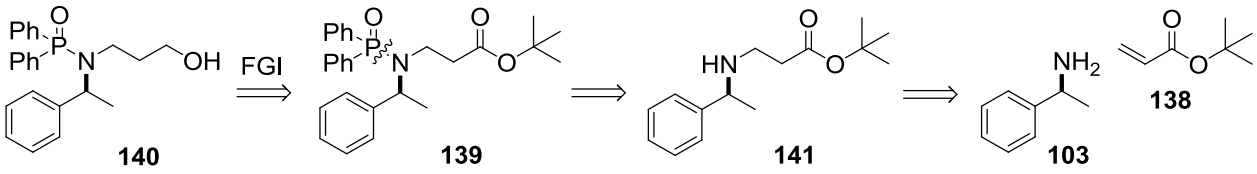
Screening of the 3- and 4-substituted phosphinic amide **136** and **137** showed a 60% and 55% conversion, respectively, to the PMP-amine **107** after four hours (scheme 75). The depreciation in catalyst activity supported the work of Sun who disclosed a deleterious effect on catalyst activity upon moving the site of the phenol group to either the *meta* or *para* positions of the aromatic ring.[67] Determination of the enantioselectivity showed that both catalysts exhibited an 8% ee, the same as the original phenolic-phosphinic amide **92** and thus confirmed that the phenol group was not implicated in the selectivity step.

The identical selectivity exhibited by all three phenolic phosphinic amides suggested that the restriction of the phenol group may hinder the ability of the Brønsted acid to infer an increase in enantioinduction. It was therefore envisaged that replacement of the phenol moiety with an aliphatic alcohol may increase the flexibility of the catalyst sufficiently as to allow for the full effects of the Brønsted acid to be exerted.



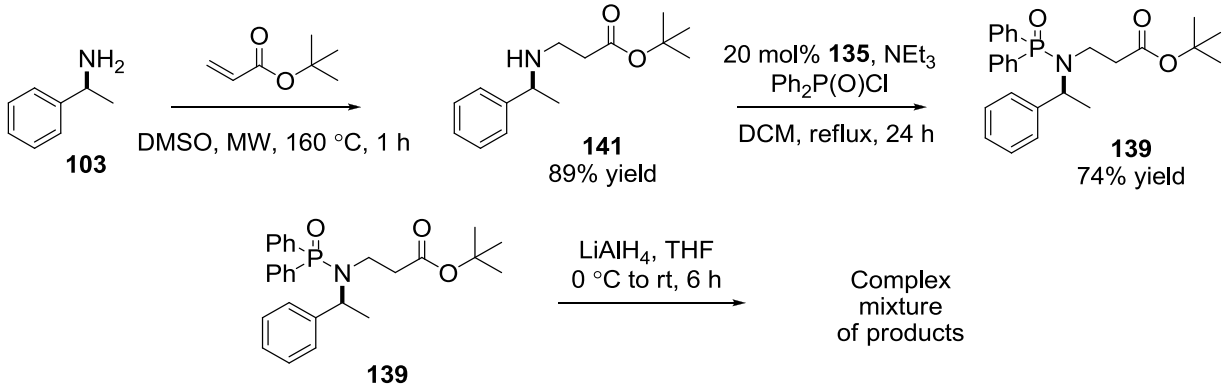
Scheme (75) – Screening of the 3- and 4-substituted phosphinic amide catalysts

Initial studies focused upon the incorporation of a 3-carbon aliphatic alcohol onto the phosphinic amide skeleton. Previous work had demonstrated the formation of phosphinic amides from a secondary amine **131** and thus led to the hypothesis that the amine derived from the Michael addition of (*S*)-methylbenzylamine **103** and *t*-butyl acrylate **138** could be readily phosphorylated. Reduction of the ester to the alcohol **140** would furnish the desired compound.



Scheme (76) – The retrosynthetic analysis of the phosphinic amide 140

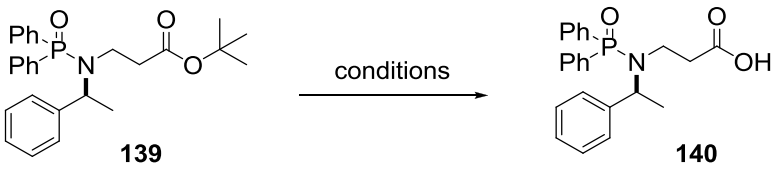
Following literature precedent, (*S*)-methylbenzylamine **103** underwent Michael addition onto *t*-butyl acrylate **138** in excellent yield using microwave irradiation.[99] The analogous thermal addition required prolonged reaction periods and afforded the amine **141** in lower yield. Utilisation of the previously developed phosphorylation conditions afforded the *t*-butyl ester phosphinic amide **139** in good yield. However, reduction of the ester with $LiAlH_4$ resulted in none of the desired alcohol **140**, with analysis of the ^1H crude NMR spectroscopic data indicating the formation of a species containing a P-H bond, the result that would be expected should cleavage of the phosphinic amide functionality have occurred. To circumvent this issue, attempts were made to convert the ester to the carboxylic acid, with the hypothesis that formation of the carboxylic acid would enable the utilisation of a milder borane derived reducing agent and thus prevent cleavage of the phosphinic amide moiety (scheme 77).



Scheme (77) – The synthesis of the *t*-butyl phosphinic amide 77 **and attempted reduction with $LiAlH_4$**

Initial attempts at cleaving the *t*-butyl ester through the use of TFA or H_2SO_4 failed to result in the desired carboxylic acid, with complete cleavage of the phosphinic amide moiety occurring in all cases.[100] Park and Jackson independently reported the use of silica gel as a means of cleaving the *t*-butyl ester functionality, however, neither heating the reaction thermally or by microwave irradiation sought to afford any of the desired acid.[101] Wu and co-workers have also disclosed the use of $ZnBr_2$ as a means of facilitating cleavage of the *t*-butyl ester functionality.[102] The group hypothesised that coordination of the Lewis acid to both oxygen atoms of the ester provided sufficient electrophilicity in the carbonyl group to enable nucleophilic attack of water and formation of the acid. Utilisation of these conditions, along with several other Lewis acids

failed in all cases to induce formation of the carboxylic acid with the starting *t*-butyl ester **139** recovered quantitatively (scheme 78).



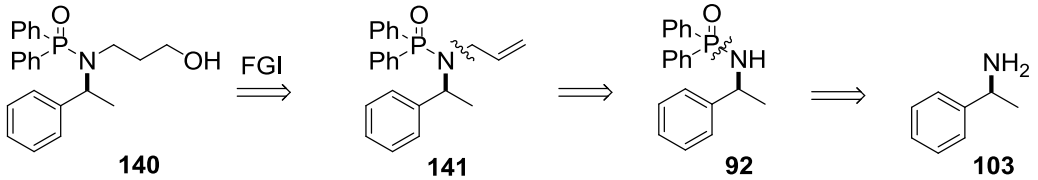
Scheme (78) – Attempted removal of the *t*-butyl ester and formation of the carboxylic acid

entry	conditions	observation[a]
1	5 eq TFA or H_2SO_4, DCM, 0 °C to rt	100% conversion of starting material; complete cleavage of the phosphinic amide observed
2	SiO_2, toluene, reflux, 48 h	Starting material only
3	SiO_2, toluene, MW, 120 °C, 8 h	Starting material only
4	5 eq $ZnBr_2$, DCM 0 °C to rt, 6 h	Starting material only
5	5 eq $Cu(OTf)_2$, DCM 0 °C to rt, 6 h	Starting material only
6	5 eq $CoCl_2$, DCM 0 °C to rt, 6 h	Starting material only

[a] determined by analysis of the ^{1}H crude NMR spectrum.

Table (3) – Conditions attempted for the removal of the *t*-butyl group

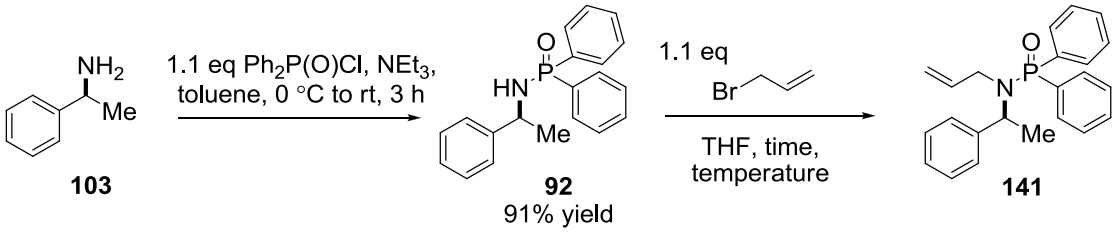
The inability of the *t*-butyl ester to undergo facile reduction or functional group interconversion led to the development of an alternative strategy for the synthesis of the desired catalyst **140**. It was envisaged that the desired alcohol **140** could be revealed through the hydroboration of the allylic phosphinic amide **141.** In spite of previous studies into the synthesis of the *bis*-phosphinic amide **108** demonstrating the severe lack of nucleophilicity of the phosphinic amide nitrogen atom, it was thought that the increased reactivity associated with allyl bromide would enable the desired addition to occur from the original phosphinic amide **92** (Scheme 79).



Scheme (79) – The 2nd generation retrosynthetic analysis for the synthesis of the phosphinic amide X

Preliminary attempts at synthesising the allyl phosphinic amide **141** proved burdensome, treatment of the phosphinic amide **92** with allyl bromide at room temperature failed to result in any of the desired product with analysis of the crude 1H NMR spectroscopic data indication

presence of the starting *N*-phosphinic amide **92** only (Scheme 80, table 4).



Scheme (80) – The optimisation and synthesis of the allylated phosphinic amide 141

entry	time / h	temperature / °C	base	conversion to **X**[b] / %	yield of **X**[c] / %
1	24	rt	-	starting material only	-
2	48	rt	-	starting material only	-
3	24	reflux	-	starting material only	-
4	8	rt	NaH[a]	70	-
5	2	reflux	NaH[a]	100	75

[a] 4 equivalents of base used; [b] determined by analysis of the crude ^{1}H NMR spectrum; [c] refers to the yield of the isolated product.

Table (4) – Optimisation of the allylation conditions

Stirring the reaction for a prolonged period or heating to higher temperatures also failed to afford any of the target molecule with only starting material recovered in all instances (scheme 80, table 4, entries 1, 2 and 3). The use of sodium hydride enabled an increase in the nucleophilicity of the starting material gave 70% conversion to the allyl phosphinic amide **141** after 8 hours (scheme 80, table 4, entry 4). Heating the solution at reflux lowered the reaction time required and enabled the allyl phosphinic amide **141** to be isolated in 75% yield (scheme 80 table 4, entry 5).

Initial attempts at the hydroboration of the alkene proved troublesome with the desired catalyst **140** being formed in 15% yield. TLC analysis of the crude reaction mixture showed complete disappearance of the starting material, and suggested the enhanced stability of the hydroborated intermediate, presumably through interaction of the Lewis basic phosphine oxide with the Lewis acidic boron atom in either an intra- or intermolecular fashion (figure 10). To overcome formation of this intermediate, the hydrolysis conditions were altered; with heating of the mixture at reflux for 24 hours, and as a result enabled formation of the desired catalyst **140** in 49% yield (scheme 81).

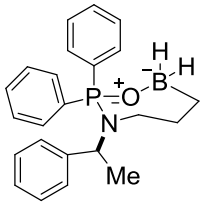
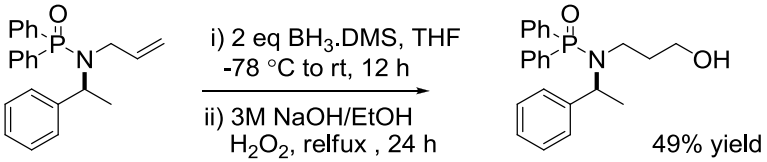
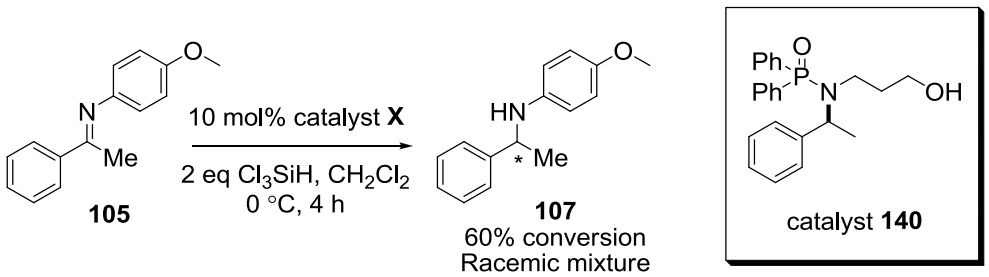


Figure (10) – A possible structure of the intermediate hydroborated phosphinic amide interacting in an intramolecular fashion.



Scheme (81) – The successful hydroboration of the allylated phosphinic amide 140

Screening of the catalyst **140** toward the reduction demonstrated a 60% conversion to the PMP-amine **107** after four hours (scheme 82). Analysis of the enantioselectivity showed a racemic mixture of product and thus suggested that the conformation flexibility of the hydroxyl group exerted no influence upon the selectivity of the reduction.



Scheme (82) – Screening of the conformationally flexible Brønsted acidic catalyst 140

2.3 Summary

The use of the *N*-phosphinic amide functionality as a Lewis base motif for the activation of trichlorosilane has been examined. Initial studies suggested that the phosphinic amide, phosphinate and phosphoramidate functionality all exhibited analogous levels of Lewis basicity and enabled up to 50% conversion of the PMP-ketimine **105** after four hours. Determination of the enantioselectivity that the catalysts exerted however, showed only the phosphinic amide moiety to be capable of inferring any selectivity toward the reduction. The role of the NH proton on the catalyst was also investigated and demonstrated to be pivotal for enantioinduction, replacement of the proton with a methyl substituent led to a comparable degree of activity but

no selectivity toward the reduction of the ketimine **105**.

Further studies on the Lewis basic requirements of the phosphinic amide indicated that an increase in electron density around the catalyst led to a substantial acceleration of catalyst activity. Examination of the electron rich *para*-methoxyphenyl substituted phosphinic amide **120** showed 83% conversion to the PMP-amine **107** compared to 50% conversion for the analogous diphenyl analogue **92**. Additional evidence for this hypothesis was observed when the phosphinothioic amide **117** demonstrated a 9% conversion to the PMP-amine **107**.

To try and increase the efficacy of the methylbenzylamine scaffold a series of catalysts were synthesised incorporating a Brønsted acidic hydroxyl group. Work by Sun had disclosed that the incorporation of a phenol moiety was pivotal to the selectivity of the *S*-chiral sulfoxide **X**, and it was envisaged that incorporation of such functionality onto the phosphinic amide scaffold may enable an analogous result. A series of novel second generation catalyst **129, 136** and **137** were subsequently synthesised, however, in all cases no marked increase in either catalyst activity or selectivity was noted. Interestingly, studies demonstrated that moving the phenol moiety around the aromatic ring had a detrimental impact on catalyst activity only and suggested that the role of the Brønsted acid was to act as a second coordination site to trichlorosilane.

The inability of the hydroxyl group to confer any additional increase in the enantioselectivity led to the hypothesis that the conformationally rigidity of the phenol may be inhibiting its ability to influence the reduction. The *N*-phosphinic amide **140** containing a three carbon flexible aliphatic alcohol was therefore synthesised and screened as a catalyst. Analysis of the catalyst showed a moderate increase in activity compared to the original catalyst **92**. However, examination of the enantioselectivity showed only a racemic mixture of the desired PMP-amine **107**.

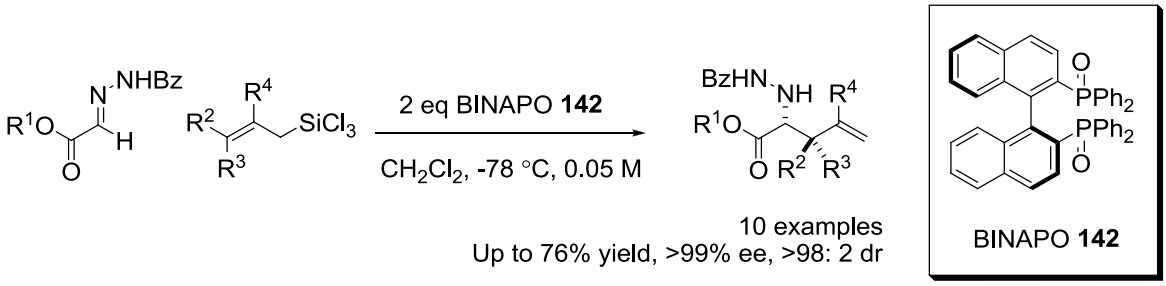
Finally, to examine whether an alternative chiral scaffold could enable the *N*-phosphinic amide moiety to exhibit higher selectivity a series of catalysts incorporating a naphthalene ring or cyclohexadiamine moiety were synthesised. The observation that none of these species exhibited superior reactivity to that of the original phosphinic amide **92**, suggested the limitation of the phosphinic amide functionality as a means of activating trichlorosilane for the reduction of ketimines. Furthermore, the inadequate enantioinduction capabilities of the scaffolds tested, suggested that the stereogenic centre was too remote in all cases to exert any influence upon the stereoselectivity, and suggested that investigations into other non-phosphinic amide scaffolds were warranted.

Chapter III

Investigations into chiral Lewis basic phosphine oxide scaffolds

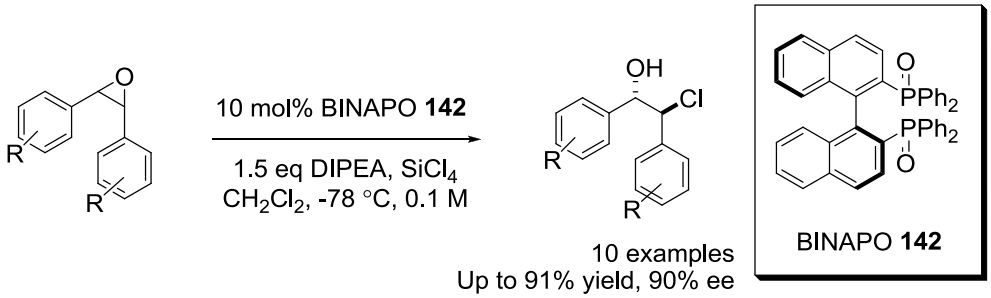
3.1 Background

One of the earliest reports into the use of chiral phosphine oxides was disclosed by Kobayashi in 1994.[103] A survey of commercially available Lewis bases identified BINAPO **142** as an effective promoter for the addition of γ and γ,γ'-substituted silanes to an array of *N*-benzoyl hydrazones in good yield, excellent enantioselectivity, and in the case of the latter, complete diastereoselectivity (scheme 83). Pivotal to the high enantioselectivity of the resultant hydrazines was the use of a greater than stoichiometric amount of the Lewis base. Employment of a catalytic quantity of the phosphine oxide **142** had a detrimental effect on the yield and enantioselectivity of the allylation. No mechanistic rationale to account for this observation was reported by the authors.



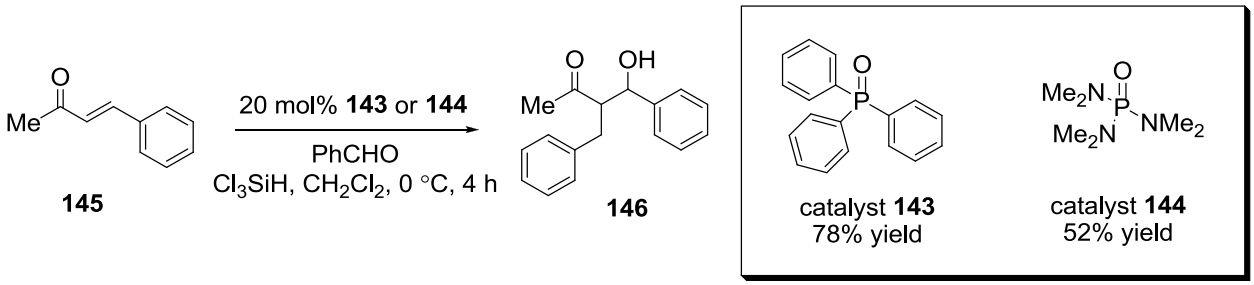
Scheme (83) – The asymmetric allylation of *N*-benzoyl hydrazones catalysed by BINAPO 142

A year later, Nakajima disclosed the first catalytic application of a chiral Lewis basic phosphine oxide. The authors demonstrated the desymmetrisation of a range of diaryl *meso*-epoxides in excellent yield and enantioselectivity.[104] Critical to the selectivity of the process was the employment of DIPEA, as introduction of less sterically encumbered achiral bases resulted in a pronounced depreciation in the enantioselectivity of the chlorohydrin products.



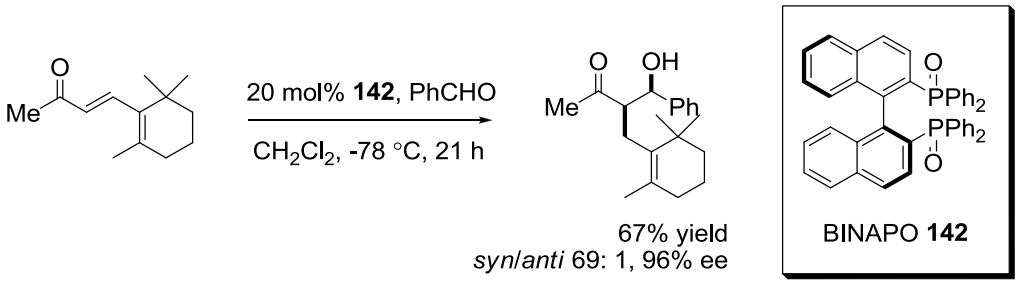
Scheme (84) – Nakajima's BINAPO 142 catalysed *meso*-epoxide desymmetrisation

In 2005, the same authors disclosed the first reductive aldol condensation catalysed by a Lewis basic phosphine oxide. Preliminary studies into an achiral variant of the reaction demonstrated the potential of triphenylphosphine oxide **143** to catalyse the three component coupling of chalcone **145**, benzaldehyde and trichlorosilane. Interestingly replacement of the phosphine oxide with HMPA **144** reduced the yield of the product **146** and suggested the incompatibility of the *N*-phosphinic amides toward the process.[105]



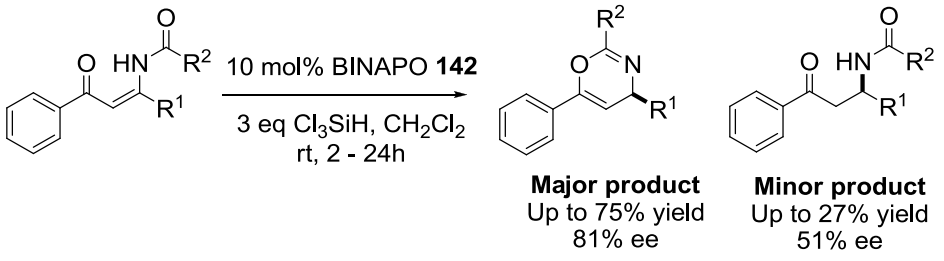
Scheme (85) – Nakajima's reductive aldol reaction of the chalcone 145 with benzaldehyde and trichlorosilane

To demonstrate the potential of an enantioselective process, the group disclosed a single example in which the introduction of 20 mol% of BINAPO **142** facilitated the formation of the β-hydroxy ketone in good yield, excellent enantioselectivity and with complete diastereocontrol (scheme 86).



Scheme (86) – The development of an asymmetric variant of the reductive aldol reaction

Most recently, the authors have disclosed the synthesis of enantioenriched 4*H*-1,3-oxazines through the trichlorosilane mediated reductive cyclisation of *N*-acylated-β-amino enones (scheme 87).[106] Screening of an array of chiral Lewis bases identified BINAPO **142** to be once



Scheme (87) – The novel synthesis of enantioenriched 4*H*-1, 3-oxazines

again the most effective catalyst with the oxazine products isolated in good yield and moderate enantioselectivity (scheme 87). Interestingly, the expected product of the reaction, the uncyclised β-amino ester was isolated in significantly lower yield and enantioselectivity. The difference in the absolute configurations of the cyclised and uncyclised products led the authors to hypothesise the existence of two independent mechanistic pathways. It was envisaged that the major product of the reaction, the cyclised 4*H*-1,3-oxazine, was generated through the conjugate reduction of the *N*-acylated β-amino enone and ensuing cyclisation of the enolate, eliminating $HOSiCl_3$.The uncyclised β-amino ester was believed to originate through the 1, 2-reduction of the *N*-acyl iminium ion generated *via* equilibrium of the enamide (figure 11).

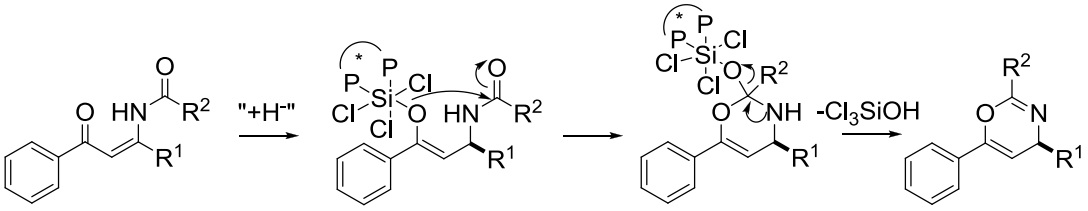
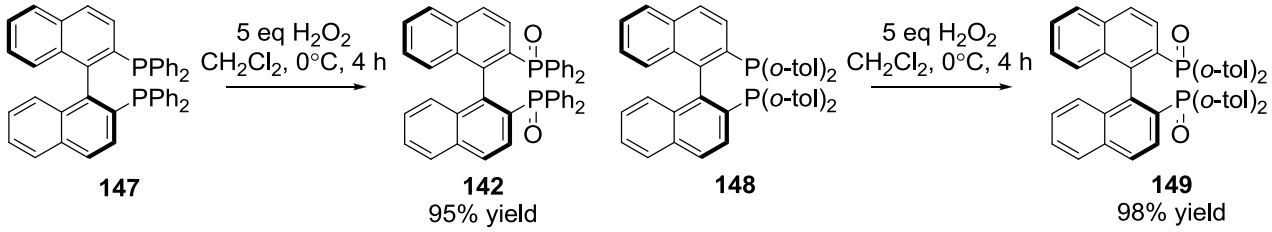


Figure (11) - A postulated mechanism for the formation of the 4*H*-1,3-oxazine

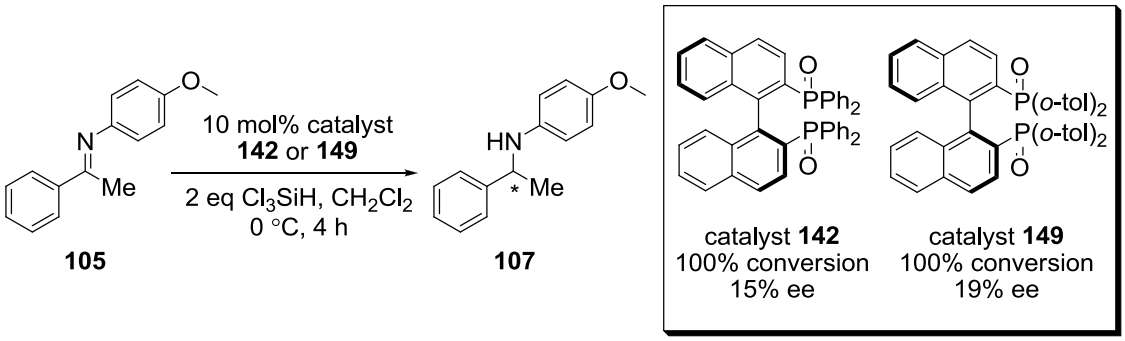
2.2 Investigations into the requirements of the catalyst

The success of BINAPO **142** to facilitate the activation of trichlorosilane toward an array of Lewis base catalysed reactions led studies un this work to screen the species as a catalyst in the reduction of the PMP-ketimine **105**. BINAPO **142** was prepared by treatment of (*S*)-BINAP **147** with hydrogen peroxide afforded the desired P(V) species **142** in quantitative yield (scheme 88).[107] A more substituted TolBINAPO **149** was synthesised in analogous fashion through oxidation of the P(III) precursor **148** (scheme 88).



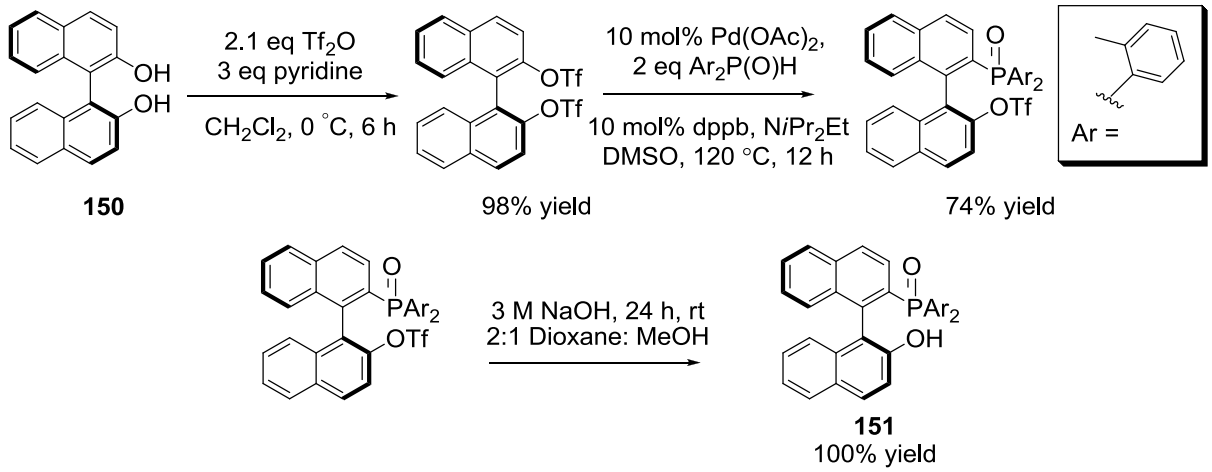
Scheme (88) – The synthesis of BINAPO 142 and TolBINAPO 149 through oxidation of the P(III)-precursors

Analysis of the two catalysts under the standard reduction conditions demonstrated that both catalysts facilitated complete reduction of the PMP-ketimine **107** after four hours (scheme 88). Determination of the enantioselectivity of the reduction showed that (*S*)-BINAPO **142** gave a 15% ee whilst the more hindered (*S*)-TolBINAPO **149** catalyst enabled a 19% ee in the resultant amine **107**.



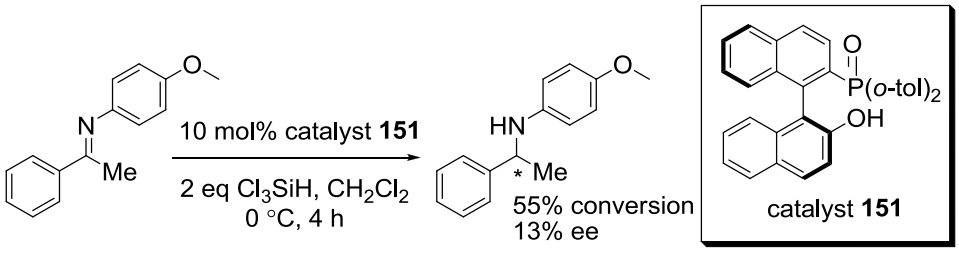
Scheme (89) – Screening of the BINAPO X and TolBINAPO X catalysts toward the reduction

To examine whether the efficacy of the binaphthyl scaffold could be increased, a series of catalysts were synthesised incorporating a Brønsted acidic hydroxyl group. It was envisaged that the presence of the phenol moiety could confer a hydrogen bonding interaction with the ketimine and therefore allow for an increase in the selectivity of the reduction. Following known literature precedent, the mono *ortho*-tolyl catalyst **151** was successfully synthesised in three steps from the commercially available (*S*)-BINOL **150** (scheme 90).[108]



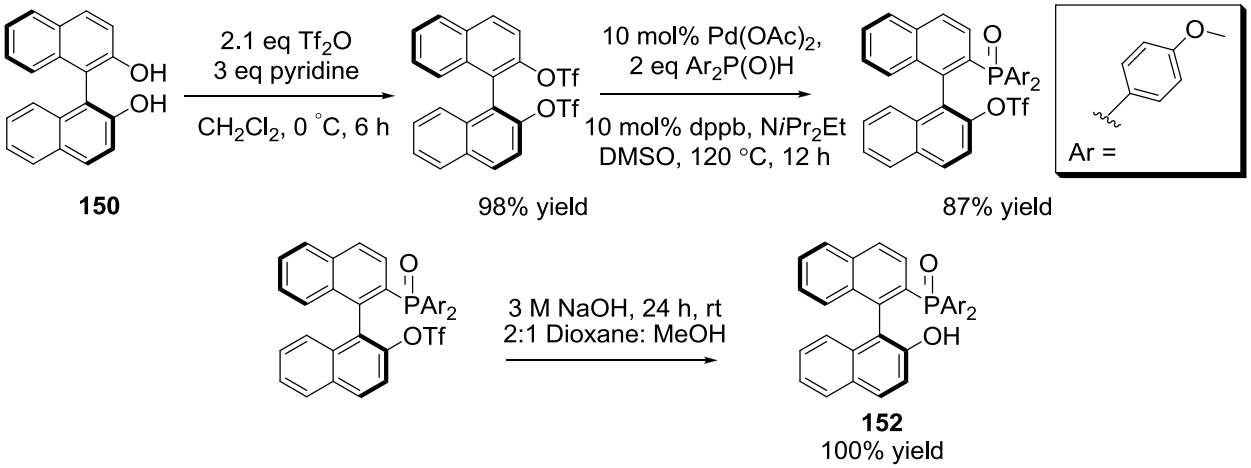
Scheme (90) – The synthesis of the mono *ortho*-tolyl catalyst 151

Screening of the *o*-tolyl catalyst **151** showed a 55% conversion to the PMP-ketimine **107** and 13% ee. To try and increase the activity of the catalyst further, the 2-methyl substituent of the catalyst was replaced with a *para*-methoxyphenyl derivative with the hypothesis that the increase in electron density around the catalyst would confer the substrate to exhibit a higher Lewis basicity and thus a greater activity toward the reduction.[108] Using an analogous procedure

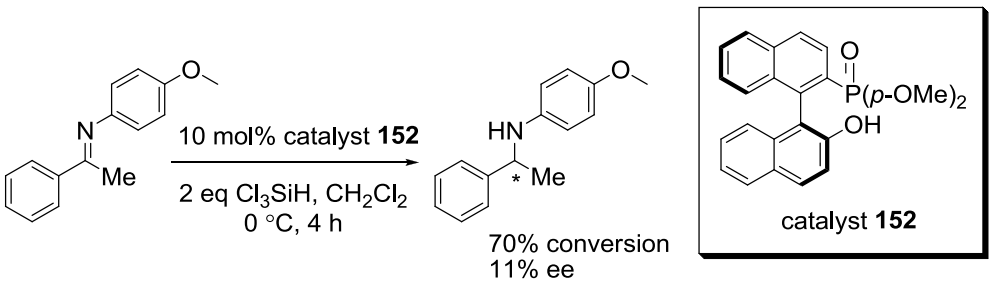


Scheme (91) – Screening of the mono-*ortho*-tolyl catalyst 151 toward the PMP-ketimine 105

the catalyst **152** was synthesised in excellent yield over three steps (scheme 92). Examination of the catalyst **152** showed a 70% conversion to the PMP-amine **107** after four hours and thus confirmed the hypothesis. Determination of the enantioselectivity showed an 11% ee and implied that the hydroxyl group exerted a limited effect upon the selectivity of the catalysts.

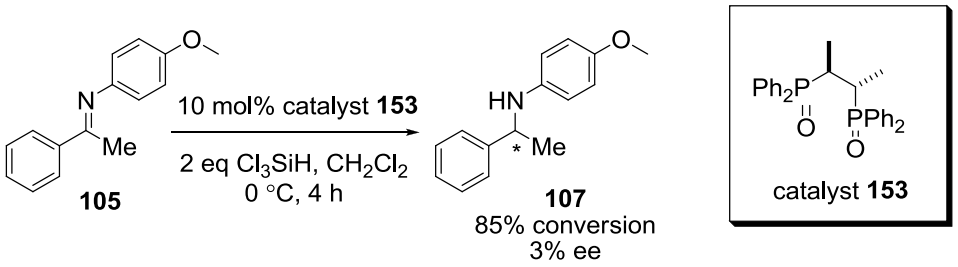


Scheme (92) – The synthesis of the mono *para*-methoxyphenyl catalyst 152



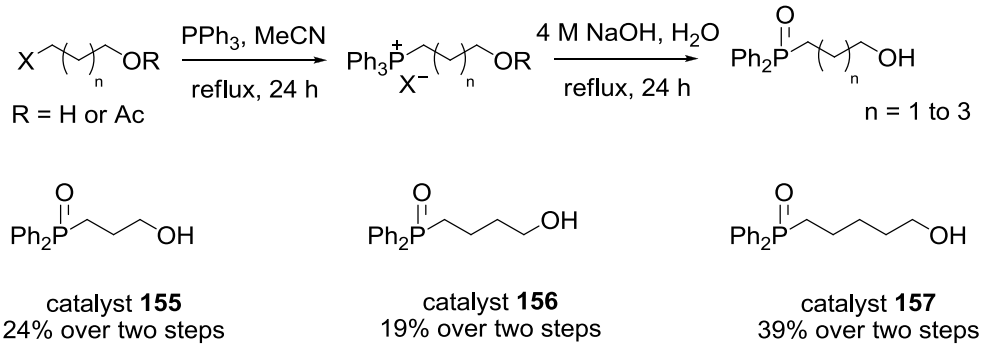
Scheme (93) – Screening of the *para*-methoxyphenyl catalyst toward the reduction of the PMP-ketimine 105

The limitations of the axial scaffold to provide high enantioselectivity suggested that the incorporation of chirality into a flexible aliphatic chain adjacent to the Lewis basic moieties may enable an increase in enantioselectivity. To test this hypothesis, the *bis*-phosphine oxide **153** was readily synthesised in excellent yield following known literature precedent.[109] Analysis of the activity of the catalyst **153** demonstrated 80% conversion to the PMP-amine **107** after 4 hours. Determination of the enantioselectivity showed a 3% ee and implied that the two methyl groups of the ligand did not invoke sufficient steric interactions in the transition state to enable selective delivery of the hydride ion.



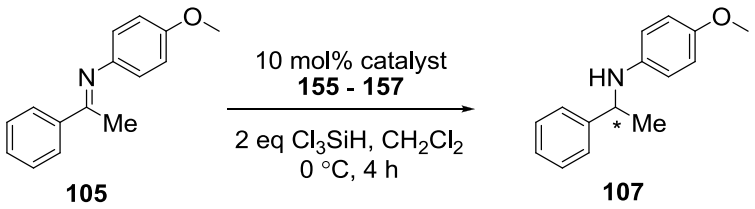
Scheme (94) – The screening of the chiraphoso 153 ligand toward the reduction of the PMP-ketimine 105

A conformationally flexible version of the catalyst **154** was also prepared. In order to determine the optimum spacer length between the Lewis basic phosphine oxide moiety and the Brønsted acid, a series of achiral hydroxyl containing phosphine oxides were prepared.[110] Following literature precedent, the appropriate halohydrin or halo-acetate was reacted initially with triphenylphosphine to afford the phosphonium salt and then subsequently with concentrated sodium hydroxide to induce formation of the desired catalyst.

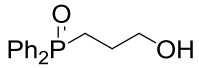
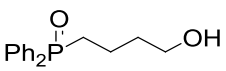
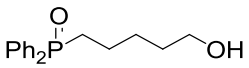


Scheme (95) – The synthesis of the 3 and 5-carbon hydroxyl containing phosphine oxide catalysts

Screening of the achiral catalysts demonstrated that the activity of the phosphine oxide increased slightly upon augmenting the distance between the Lewis base and the Brønsted acid (scheme 96, table 5). As a result, a 5-carbon chain length was chosen as the suitable spacer between the two moieties for the preparation of the chiral analogue **154**.



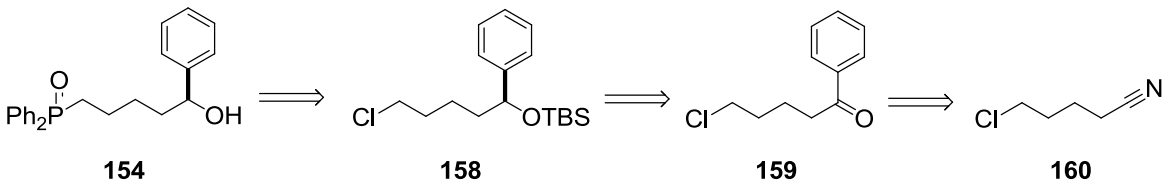
Scheme (96) – The reduction of the PMP-ketimine 105 using the achiral linear phosphine oxide catalysts

entry	catalyst	structure	conversion of PMP-ketimine **105**[a] / %
1	**155**		75
2	**156**		78
3	**157**		81

[a] determined by analysis of the crude ^{1}H NMR spectrum, average result of two runs.

Table (5) – Determination of the optimum chain length between the Lewis base moiety and Brønsted acid

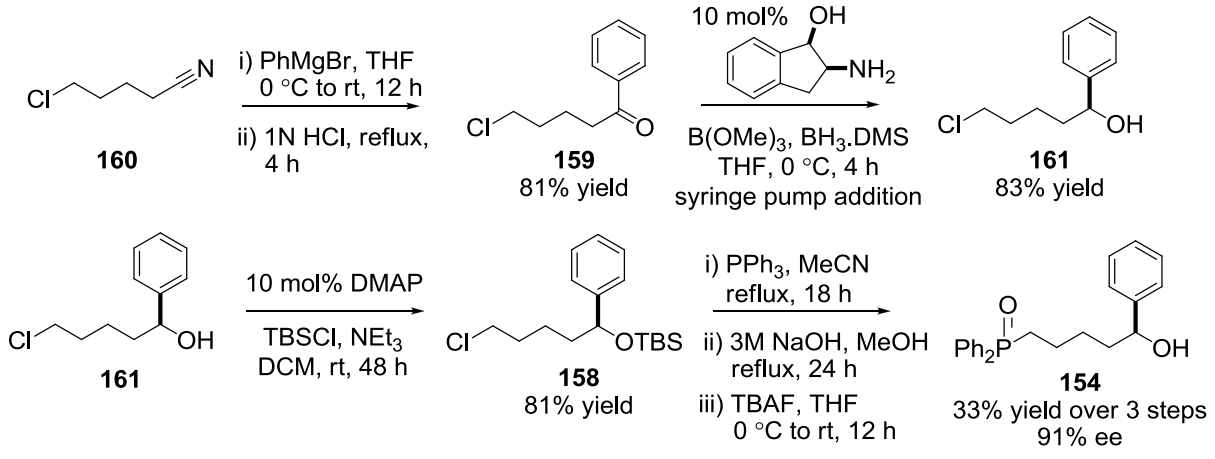
Retrosynthetically, it was envisaged that the incorporation of the chiral Brønsted acidic hydroxyl group could occur through the asymmetric reduction of the phenyl ketone **159** (scheme 97). Previous work within the group had disclosed the oxazaborolidine derived from amino indanol as a highly effective catalyst for the asymmetric reduction of prochiral ketones and it was thought that such a system would form the alcohol in excellent enantioselectivity.[95] Introduction of the phosphine oxide through analogous methodology used to prepare the achiral phosphine oxide species **155** - **157** would afford the desired compound **154**.



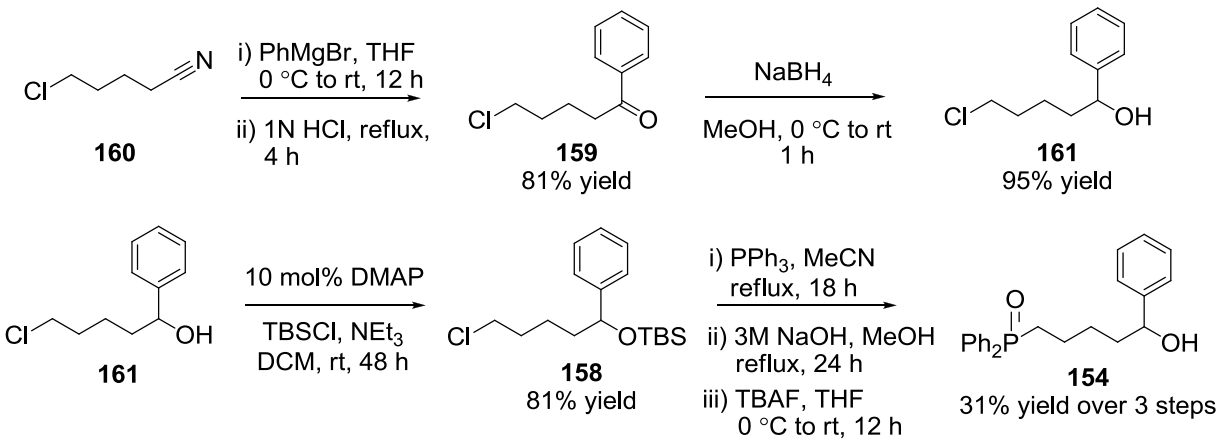
154 **158** **159** **160**

Scheme (97) – The retrosynthetic analysis of the chiral Brønsted acid containing phosphine oxide X

Following literature precedent, the commercially available chloro-nitrile **160** was treated with phenylmagnesium bromide to afford the chloro-ketone **159** in excellent yield (scheme 98).[111] Unpublished work within the group had shown that the efficacy of the oxazaborolidine catalyst could be improved by dropwise addition of the ketone to a solution of the preformed catalyst. [112] The chloro-ketone **159** was therefore added by syringe pump to a solution of (1*R*, 2*S*)-amino indanol and trimethylborate at 0 °C and the resulting alcohol **161** subjected to standard TBS protection. Formation of the phosphonium salt and subsequent oxidation to the phosphine oxide using 3 M NaOH afforded the TBS protected catalyst. Treatment with TBAF enabled formation of the target molecule **154** in six steps (scheme 98).

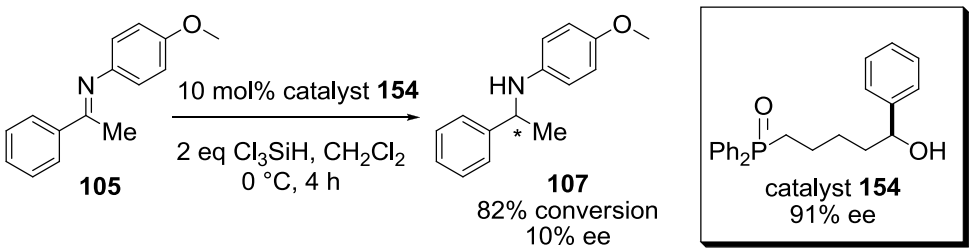


Scheme (98) – The synthesis of the chiral bifunctional phosphine oxide 154



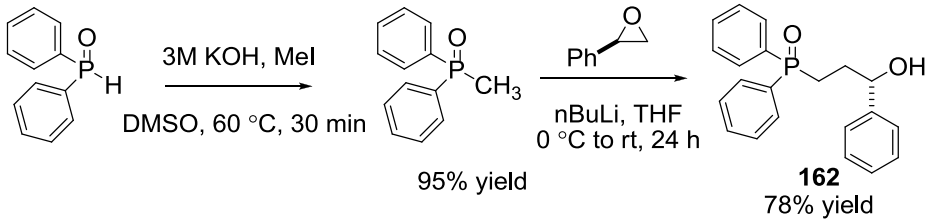
Scheme (99) – The synthesis of the racemic bifunctional phosphine oxide 154

In order to determine the enantioselectivity of the resultant catalyst, a racemic version of the catalyst was synthesised in analogous fashion using the racemic alcohol derived from the sodium borohydride reduction of chloro-ketone **159** (scheme 99). Analysis of the enantioselectivity of the catalyst by chiral HPLC analysis showed a 91% ee, which was sufficient to enable its use. Screening of the phosphine oxide **154** demonstrated an 82% conversion to the PMP-amine **107** after four hours, analogous to that of the achiral linear variant of the catalyst. Determination of the enantioselectivity illustrated a 10% ee in the resultant amine.



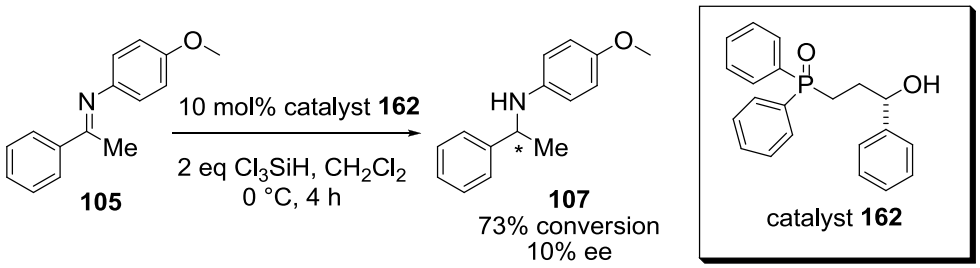
Scheme (100) – Screening of the bifunctional catalyst 154 under the standard reduction conditions

To examine whether the incorporation of a chiral Brønsted acid closer to the Lewis basic phosphine oxide conferred higher selectivity, the 3-carbon catalyst **162** was synthesised through the ring opening of the enantiomerically pure epoxide (scheme X).[110,113]



Scheme (101) – The synthesis of the chiral 3-carbon bifunctional phosphine oxide 162

Screening of the catalyst showed a 73% conversion of the PMP-ketimine **X** after four hours (scheme X). Analysis of the enantioselectivity of the reduction demonstrated a 10% ee and suggested that regardless of the position of the stereogenic centre relative to the phosphine oxide, the use of a chiral Brønsted acid conferred very little influence on the selectivity of the ketimine reduction.



Scheme (102) – Screening of the 3-carbon bifunctional catalyst 162 toward the reduction of the PMP-ketimine 105

3.3 Summary

The use of the Lewis basic phosphine oxide moiety to activate trichlorosilane toward the reduction of the PMP-ketimine **105** has been examined. Initial studies demonstrated that the axial chiral catalysts BINAPO **142** and TolBINAPO **149** enabled the complete reduction of the ketimine **105** after four hours and suggested that the two phosphine oxide units acted in synergy and bound to the trichlorosilane. Analysis of the enantioselectivity, however, showed results analogous to those obtained for the original *N*-phosphinic amide catalyst **92** and suggested that the source of chirality was still unable to confer any selectivity toward the reduction of the ketimine. Attempts at increasing the selectivity of the process through incorporation of a phenol group onto the biaryl scaffold had a detrimental effect upon both the activity and selectivity of the catalysts and confirmed the inferiority of the axial chiral scaffold.

To test whether the introduction of a chiral Brønsted acid could increase the enantioselectivity of the reduction, the bifunctional catalysts **151** and **152** were synthesised and screened toward the reduction. Both catalysts showed comparable activity to their achiral linear analogues **154** and **162** but analysis of the enantioselectivity showed only a 10% ee in both cases and implied that the chiral Brønsted acid had very little effect on the selectivity of the reduction.

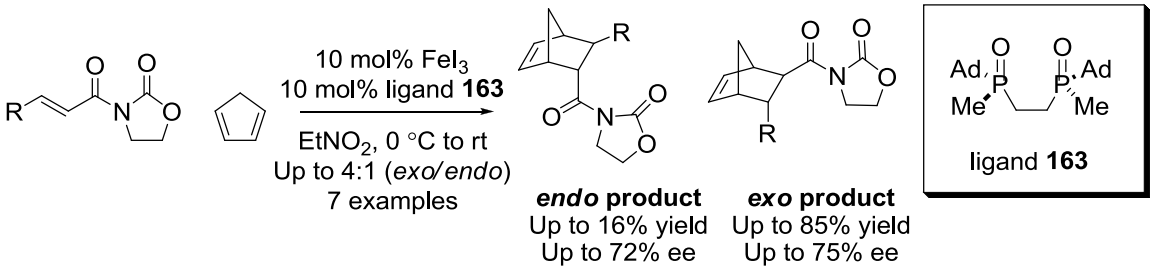
Chapter IV

Investigations into the development of *P*-chiral phosphine oxide catalysts

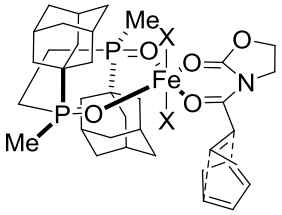
4.1 Background

Non-symmetrically substituted phosphorus compounds are commonplace throughout organic chemistry both as chiral ligands and more recently as organocatalysts.[114-115] Despite their prevalence, the majority of examples that have been reported utilise a *P*-chiral phosphine as the catalytic moiety, very few reports into the application of the analogous *P*-chiral phosphine oxide have been disclosed.

One of the first examples of a reaction catalysed by a *P*-chiral phosphine oxide was reported by Imamoto in 2000.[116] The group demonstrated that the *bis*-phosphine oxide **163** in conjunction with iron(III) iodide could facilitate the Diels-Alder reaction between cyclopentadiene and a range of *N*-crotonoylamide dienophiles in good *exo* selectivity and moderate enantioselectivity (scheme 103). Interestingly, replacement of the iron salt with other transition metals known to catalyse Diels-Alder reactions only sought to promote an achiral variant of the cycloaddition. In order to explain the *exo* selectivity of the cycloaddition the authors proposed the transition state **164**, in which the diene approaches the chelated dienophile in a manner as to avoid any steric interaction with the substituents on the phosphorus ligand (figure 12).



Scheme (103) – Imamoto's asymmetric Diels-Alder reaction using the *bis*-phosphine oxide 163

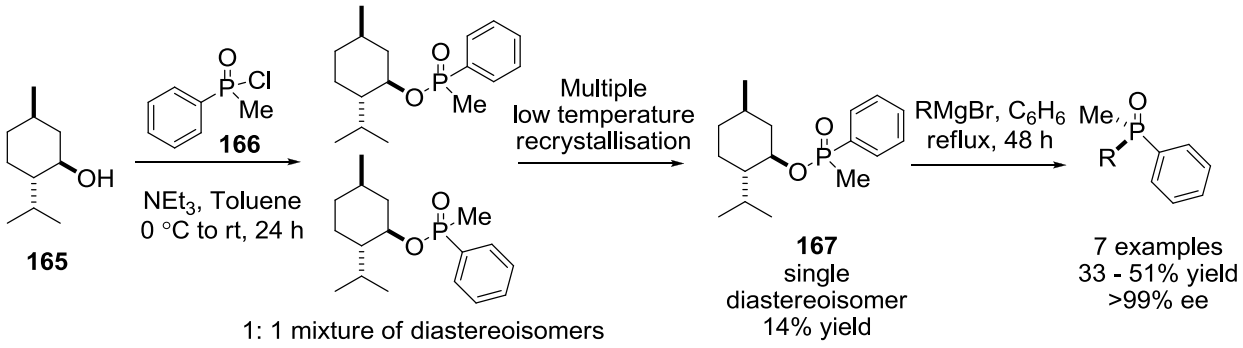


164

Figure (12) – Imamoto's rationale for the observed stereochemical outcome

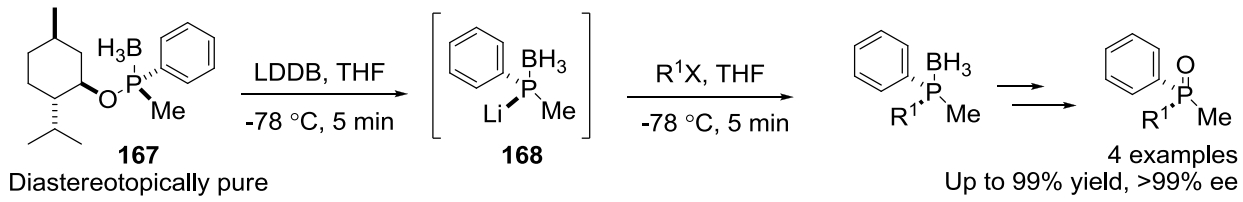
4.2 Preparation of *P*-chiral phosphine oxides

One of the earliest and most widely applicable methods for the preparation of *P*-chiral phosphine oxides was disclosed by Mislow in 1968.[117] The group demonstrated that menthol **165** could act as a chiral auxiliary and react with phenyl(methyl) phosphinic chloride **166** to afford a 1: 1 mixture of two diastereoisomers. Isolation of a single diastereoisomer **167** through multiple low temperature fractional crystallisation, provided the diastereotopically pure auxiliary, that underwent nucleophilic displacement to furnish the desired *P*-chiral phosphine oxide in moderate yield and complete enantiocontrol (scheme 103). Pivotal to the addition of the Grignard reagent was the requirement for elevated temperature and prolonged reaction periods. Any deviation from these parameters resulted in a significant depreciation in the yield of the product. Comparison of the optical rotation values of the resultant *P*-chiral phosphine oxides with enantiomerically pure samples demonstrated an inversion of stereochemical configuration at the phosphorus centre and suggested an $S_N2(P)$ reaction was in operation.



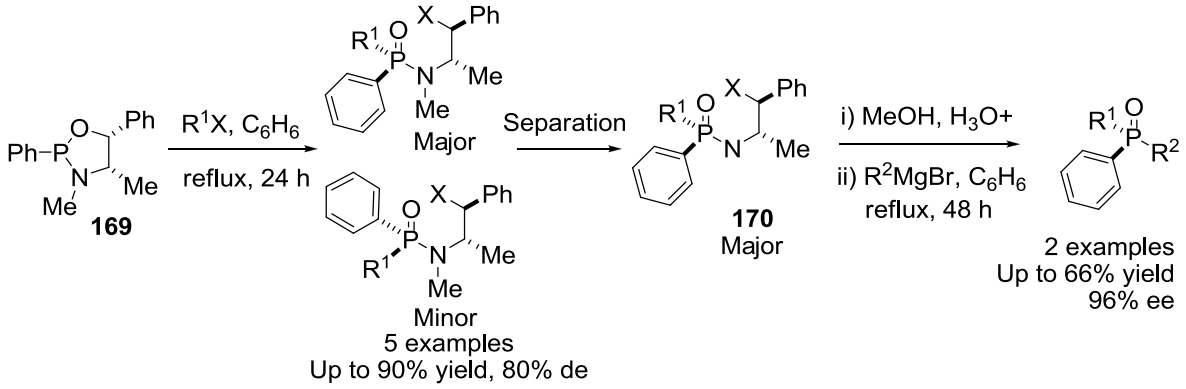
Scheme (103) – Mislow's synthesis of *P*-chiral phosphine oxides using (-)-menthol as a chiral auxiliary

Recently, Imamoto has reported the first stereoselective cleavage of a menthyl phosphinyl borane using the single electron transfer reducing agent LDBB.[118] Pivotal to the configurational stability of the lithiated intermediate **168** was the reaction temperature, as warming above -78 °C resulted in racemisation. Low temperature electrophilic quench with a range of alkyl halides afforded the tertiary phosphine-borane adducts in excellent yield and complete enantiocontrol. Subsequent transformation into the desired *P*-chiral phosphine oxide was readily achieved with no erosion in enantioselectivity (scheme 104).



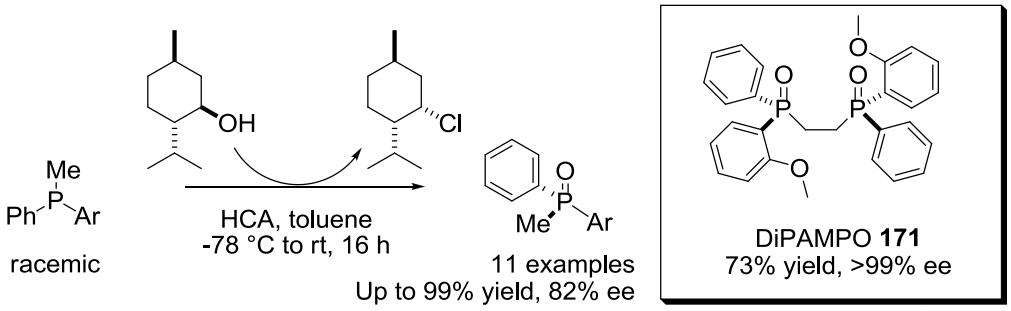
Scheme (104) – Imamoto's stereoselective cleavage of the menthyl group using LDBB

Jugé and Genet reported the preparation of *P*-chiral phosphine oxides by a Michaelis-Arbuzov rearrangement of chiral oxazaphospholidines.[119] Treatment of the diastereotopically pure auxiliary **169** derived from (-)-ephedrine with a range of activated electrophiles afforded the corresponding phosphinic amides in good yield and moderate diastereoselectivity (scheme 105). Analysis of the stereochemical configuration of the major diastereoisomer suggested that the reaction occurred with retention of stereochemistry at the phosphorus atom and was in line with previous reports into the Arbuzov reaction of similar acyclic variants. Isolation of the major diastereoisomer **170**, acidic methanolysis and subsequent treatment with the appropriate Grignard reagent afforded the *P*-chiral phosphine oxide in good yield and excellent enantioselectivity. However, only 2 examples of this transformation were reported by the authors.



Scheme (105) – Jugé and Genet's synthesis of *P*-chiral phosphine oxides *via* a diastereotopic Arbuzov reaction

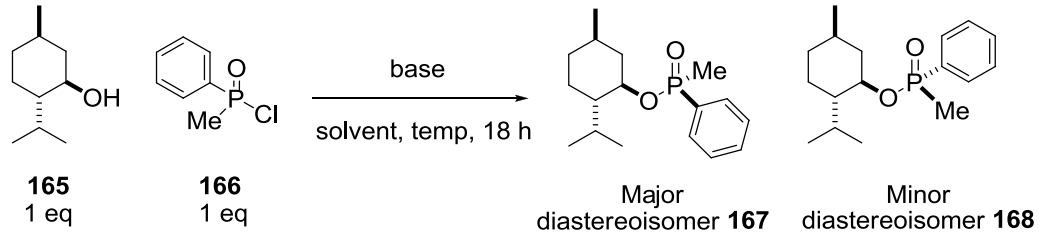
Gilheany and co-workers have recently disclosed the synthesis of a range of diaryl-methyl phosphine oxides using an asymmetric Appel reaction.[120] Both *ortho* and *para* substituted aromatics were well tolerated by the reaction with the resulting *P*-chiral phosphine oxides isolated in excellent yield and moderate to good enantioselectivity (scheme 106). To demonstrate the versatility of the process, the authors reported the synthesis of the *bis*-*P*-chiral phosphine oxide **171**, a precursor to the industrially relevant chiral phosphine DiPAMP in 73% yield and complete enantiocontrol following recrystallisation.



Scheme (106) – Gilheany's asymmetric Appel reaction synthesise scalemic *P*-chiral phosphine oxides

4.3 Investigations toward *P*-chiral phosphine oxide synthesis

To investigate whether moving the location of chirality onto the phosphorus atom would confer a higher enantioselectivity toward the reduction, a series of *P*-chiral phosphine oxides were synthesised. Initially, the method of Mislow was chosen to synthesise such species Phenyl(methyl) phosphinic chloride **166**, readily prepared in three steps, was introduced to a solution of menthol **165** and triethylamine. Analysis of the reaction by ^{1}H NMR spectroscopy demonstrated complete conversion and a 1:1 ratio of the two diastereoisomers **167** and **168** (scheme 107, table 6)**.** Low temperature fractional recrystallisation enabled isolation of the single diastereoisomer **X** in 9% yield and was in line with the results disclosed by Mislow.[117]



Scheme (107) – The synthesis of Mislow's phosphoryl-menthol auxiliary

entry	base	eq. of base	temperature / °C	solvent	conversion to **167** and **168** / %[b]	dr of **167**: **168**[c]	yield of major isomer **167** / %[c]
1	NEt_3	1	0 °C to rt	toluene	100	1: 1	9
2	NEt_3	1	-78 °C	toluene	SM only	-	8
3	NEt_3	1	40 °C	toluene	decomposition	-	-
4	NEt_3	1	0 °C to rt	DCM	100	1: 1	-
5	NEt_3	1	0 °C to rt	Et_2O	100	1: 1	9
6	*i*PrNEt$_2$	1	0 °C to rt	toluene	100	1: 1	6
7	NEt_3	10	0 °C to rt	toluene	100	2: 1	12
8[d]	NEt_3	10	0 °C to rt	toluene	100	3: 1	22
9[d,e]	NEt_3	10	0 °C to rt	toluene	100	3: 1	21

[a] all reactions performed on 1 mmol scale with 2 cm³ of solvent; [b] determined by analysis of the ^{1}H NMR spectroscopic data; [c] refers to isolated yield; [d] ran on 0.05 M dilution; [e] ran on 0.05 M dilution and 5 mmol scale.

Table (6) – Attempts at improving the diastereoselectivity of the addition

Attempts at increasing the diastereoselectivity of the reaction initially proved problematic. Cooling the solution to -78 °C resulted in return of the starting material, whilst warming the mixture to 40 °C led to decomposition (scheme 107, table 6, entries 1, 2 and 3). Changing the solvent and the base utilised also exerted little influence with a 1:1 ratio of both diastereoisomers **167** and **168** in all cases (scheme 107, table 6, entries 4, 5 and 6). Increasing the number of equivalents of triethylamine however, increased in the diastereoselectivity to 2:1

and enabled isolation of the major diastereoisomer **167** in a 12% yield (scheme 107, table 6, entry 7). The diastereoselectivity of the process could be enhanced further by dilution of the reaction mixture and allowed for the auxiliary **167** to be obtained in a 3:1 diastereomeric ratio and 22% yield (scheme 107, table 6, entry 8). Implementation of the optimised conditions on a 5 mmol scale gave analogous results and allowed for the multigram preparation of the compound **167** (scheme 107, table 6, entry 9).

Whilst Mislow failed to comment on the mechanistic details of the reaction, the increase in diastereoselection at high dilution and high concentration of base suggests that the reaction may proceed through a dynamic kinetic resolution, in which the triethylamine promotes interconversion between the two enantiomers of the phosphinic chloride. However, the role of the base could also be to aid in facilitating proton transfer in the trigonal bipyramidal intermediates and allow these species to undergo pseudorotation to lower energy adducts (figure X).

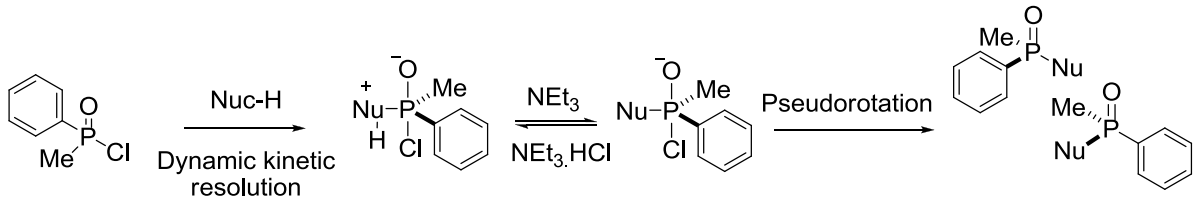
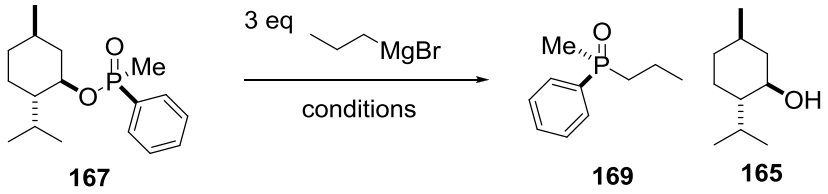


Figure (13) – A generic mechanism to demonstrate the potential processes in operation for the formation of the phosphoryl auxiliaries

With the diastereotopically pure auxiliary **167** in hand, the subsequent nucleophilic displacement with a Grignard reagent was investigated. Originally, Mislow reported five Grignard reagents that undergo reaction with the auxiliary **167** and furnish the desired *P*-chiral phosphine oxides. [117] Crucial to the reactivity was the use of benzene as the solvent and for the reaction mixture to be heated at reflux for 48 hours. In order to try and avoid the use of benzene, a number of reaction parameters were investigated with the addition of *n*-propyl magnesium bromide to the diastereotopically pure auxiliary **167** chosen as the benchmark reaction. Utilisation of Mislow's original conditions afforded the desired *P*-chiral phosphine oxide **169** in poor yield but complete enantiocontrol (scheme 108, table 7, entry 1). Changing the solvent to either THF or diethyl ether failed to afford any of the product, with only starting auxiliary **167** obtained at room temperature (scheme 108, table 7, entries 2 - 8).



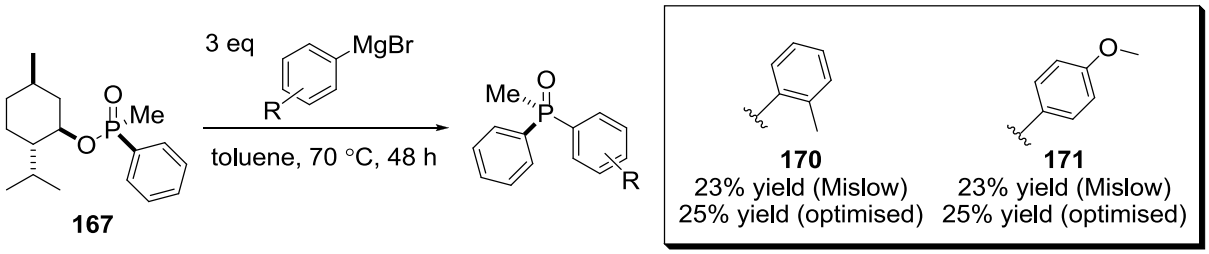
Scheme (108) – Attempted addition of *n*-propyl magnesium bromide to the auxiliary 167

entry[a]	solvent	temperature / °C	time / h	conversion of **167** / %[b]	yield of **169** / %[c]	ee / %[d]
1	benzene	reflux	48	100	21	>99
2	Et_2O	0 °C to rt	48	0	-	-
3	Et_2O	0 °C to rt	96	0	-	-
4	Et_2O	reflux	96	0	-	-
5	THF	0 °C to rt	48	0	-	-
6	THF	0 °C to rt	96	0	-	-
7	THF	reflux	96	0	-	-
8	toluene	0 °C to rt	48	0	-	-
9	toluene	70 °C	48	100	27	>99

[a] all reactions performed on a 0.5 mmol scale with 5 cm³ of solvent; [b] determined by analysis of the ^{1}H NMR spectroscopic data; [c] refers to isolated product following column chromatography; [d] determined by chiral HPLC analysis

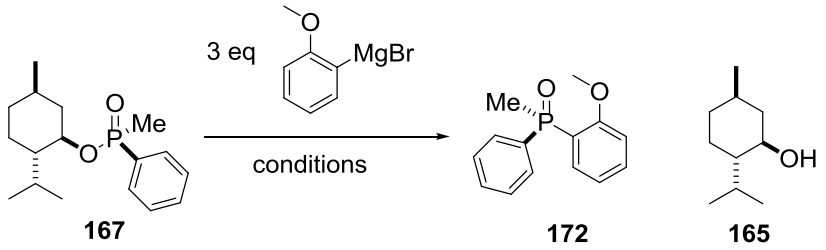
Table (7) – The conditions investigated for the Grignard displacement

Increasing the reaction temperature and prolonging the reaction time also resulted in no reactivity with only the starting auxiliary **167** returned in all cases (scheme 108, table 7, entries 2 - 8). However, switching the solvent to toluene and heating the solution at 70 °C for 48 hours afforded the desired compound **169** in 27% yield. Analysis of the enantioselectivity by comparison of the optical rotation data and chiral HPLC demonstrated a >99% ee. Implementation of the optimised conditions on two Grignard reagents known to successfully add to the auxiliary **167** enabled formation of the 2-tolyl and 4-anisyl *P*-chiral phosphine oxides **170** and **171** in a comparable yield to that obtained under the conditions reported by Mislow (scheme 109).



Scheme (109) – The synthesis of the 2-tolyl and 4-anisyl *P*-chiral phosphine oxides

Analysis of the enantioselectivity by chiral HPLC demonstrated complete enantiocontrol with the desired product isolated in >99% ee. Comparison of the optical rotation value with those in the literature suggested an (*S*)-configuration around the phosphorus atom and was in line with the work of Mislow.[120-121]



167 **172** **165**

Scheme (110) – Attempted addition of 2-anisyl magnesium bromide to the menthol auxiliary 167

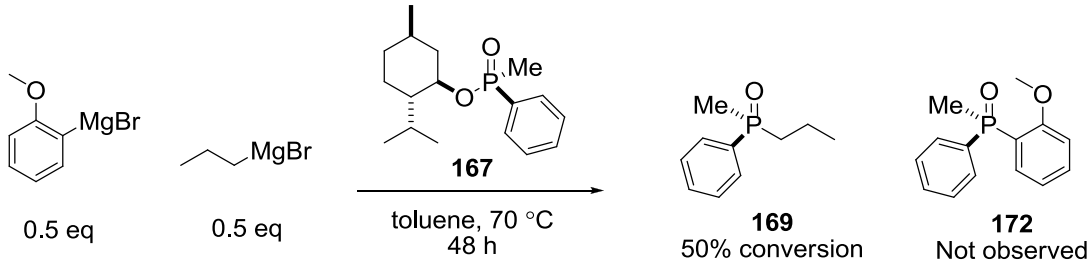
entry[a]	solvent	time / h	temperature / °C	conversion to **X** / %[b]
1	toluene	48	70	0
2	benzene	48	reflux	0
3	toluene	96	70	Decomposition
4	toluene	48	reflux	Decomposition
5[c]	toluene	48	70	Decomposition

[a] all reactions performed on a 0.5 mmol scale using 5 cm³ of solvent; [b] determined by analysis of the ^{1}H NMR spectroscopic data; [c] Grignard formation occurred in diethyl ether followed by addition of toluene and removal of the ether through distillation.

Table (8) – The conditions attempted for the addition of 2-anisylmagnesium bromide

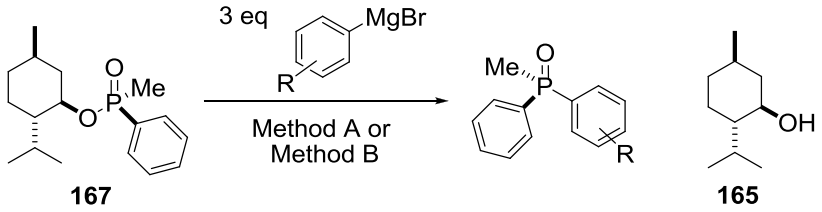
Attempts to expand the scope of Grignard reagent proved troublesome. 2-Anisyl magnesium bromide was chosen as the initial substrate; however, employment of either the optimised conditions or those of Mislow resulted in no formation of the desired *P*-chiral phosphine oxide **172** (scheme 110, table 8)**.** Leaving the reaction for a prolonged period or increasing the temperature of the toluene solution also failed to infer any reactivity with complete degradation of the starting auxiliary **167** observed. The lack of reactivity exerted by the Grignard reagent was hypothesised to be due to its incomplete formation in toluene. In an attempt to circumvent this issue, the desired Grignard reagent was first prepared in diethyl ether, before a solution of anhydrous toluene was added and the ether subsequently removed by distillation. However, once again no reaction occurred. Interestingly, addition of a solution of Grignard reagent prepared in an analogous fashion to a mixture of benzaldehyde and toluene resulted in quantative conversion to the diaryl alcohol and demonstrated that Grignard formation was not the problem. To confirm the incompatibility of the 2-anisyl Grignard reagent with the auxiliary **167**, a competition experiment was performed in which 0.5 equivalents of 2-anisyl magnesium bromide and 0.5 equivalents of *n*-propyl magnesium bromide were added sequentially to the auxiliary. Analysis of the ^{1}H and ^{31}P NMR spectroscopic data showed 50% conversion of the

starting auxiliary **167** to the *n*-propyl *P*-chiral phosphine oxide **169** but no conversion to the analogous 2-anisyl product **172**.

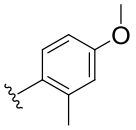
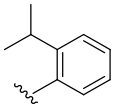
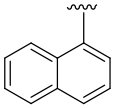
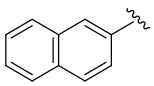


Scheme (111) – Competition experiment to prove the incompatibility of the 2-anisyl Grignard reagent with the Mislow's auxiliary 167

To determine whether other Grignard reagents would be compatible to the transformation, a number of *ortho* and *para* substituted organometallic reagents were screened against both Mislow's and the new optimised conditions (scheme 111, table 9. entries 1 - 8). In all cases no reactivity was observed, with analysis of the ^{1}H NMR spectroscopic data indicating the presence of only the starting regent **167**.



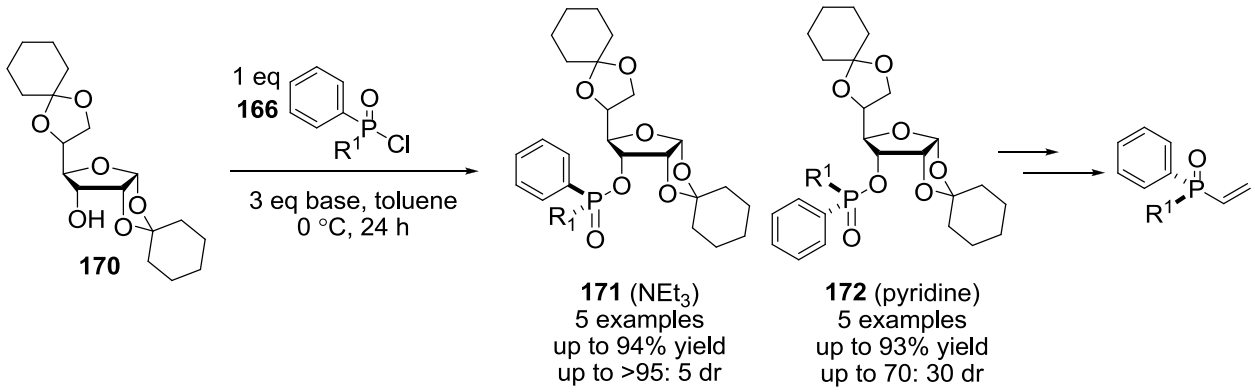
Scheme (112) – Attempted displacement of the Menthol auxiliary using a range of aryl Grignard reagents

entry	Grignard reagent	method[a]	conversion / %[b]
1		A	0
2		B	0
3		A	0
4		B	0
5		A	0
6		B	0
7		A	0
8		B	0

[a] all reactions performed on 0.5 mmol scale and 5 cm³ of solvent. Method A: benzene, reflux, 48 h. Method B: toluene, 70 °C, 48 h; [b] determined by analysis of the ^{1}H NMR spectroscopic data.

Table (9) – The Grignard reagents screened toward the displacement

The lack of reactivity displayed by the menthol phosphinate **167** led to a search for an alternative chiral auxiliary. Recently, Han has reported the use of 1,2:5,6-di-*O*-cyclohexylidene-D-glucofuranose (DCG) **170** as a successful auxiliary for the preparation of a range of *P*-chiral vinyl phosphine oxides.[122] A number of unsymmetrical phosphinic chlorides, readily prepared in 5 steps were found to react with the auxiliary in good to excellent diastereoselectivity (scheme 113). Separation of the two diastereoisomers using flash column chromatography enabled isolation of the diastereotopically pure compound **171** in excellent yield. Interestingly, switching the base from triethylamine to pyridine inversed the diastereoselectivity of the addition, however, no mechanistic rationale to explain this observation was reported by the authors.

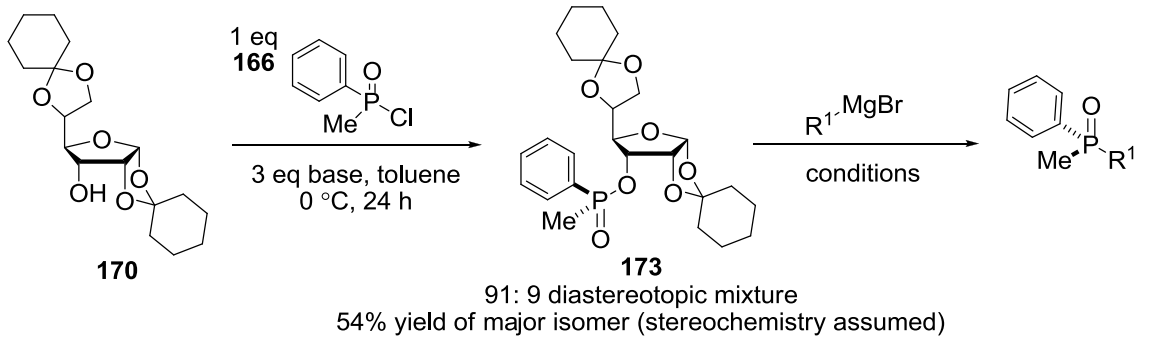


Scheme (113) – The diastereoselective addition of a range of unsymmetrical phosphinic chlorides with DCG

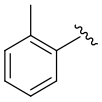
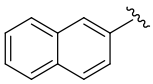
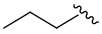
In spite of only a single Grignard reagent being shown to successfully cleave the auxiliary, it was envisaged that the methodology could be expanded to encompass a range of organometallic reagents. Consequently, 1,2:5,6-di-*O*-cyclohexylidene-D-glucofuranose (DCG) **170** was reacted with phenyl(methyl)phosphinic chloride **166** to afford a 91: 9 mixture of the two diastereoisomers **171** and **172** as determined by analysis of the crude ^{1}H NMR spectroscopic data. Separation of the two isomers by flash column chromatography furnished the diastereotopically pure compound **171** in 54% yield. Analogous results were obtained on a 10 mmol scale and enabled multigram preparation of the reagent.

To confirm the viability of the Grignard displacement, the DCG adduct **173** was reacted with vinyl magnesium bromide under the conditions reported by Han. Analysis of the crude ^{1}H and ^{31}P NMR data showed no conversion to the desired *P*-chiral oxide with only the starting material recovered. Increasing the number of equivalents of Grignard reagent used or changing the solvent in which the displacement took place also resulted in no formation of the desired phosphine oxide with only starting auxiliary **173** returned in all cases (scheme 114, table 10, entries 1 - 8). Altering the reaction temperature had little effect. Warming to 0 °C or room

temperature resulted in no reaction, whilst heating to temperatures above 40 °C caused complete decomposition of the staring material. To confirm the limited reactivity of the substrate **173**, a number of Grignard reagents other than vinyl magnesium bromide were screened toward the displacement. In all cases, no reactivity was observed, with analysis of the ^{1}H and ^{31}P NMR spectroscopic data indicating the presence of only the starting material.



Scheme (114) – The formation of the DCG auxiliary X and attempts at the nucleophilic displacement

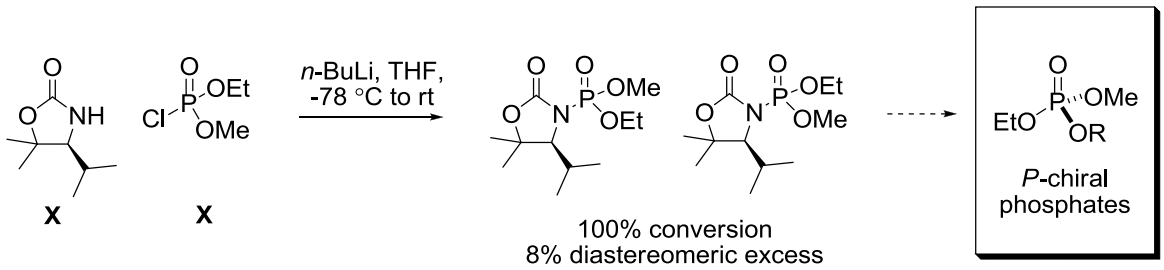
entry	R^1	number of equivalents[a]	solvent	temperature / °C	conversion to **X** / %[b]	recovery of auxiliary **X** / %[b]
1		2	THF	-78 to -40	-	>95
2		6	THF	-78 to -40	-	>95
3		2	Et_2O	-78 to -40	-	>95
4		2	toluene	-78 to -40	-	>95
5		2	THF	-20 to rt	-	>95
6		2	THF	0	-	>95
7		2	THF	rt	-	>95
8[c]		2	THF	40	0	0
9		2	THF	-78 to -40	-	>95
10		2	THF	-78 to -40	-	>95
11		2	THF	-78 to -40	-	>95

[a] all reactions performed on a 1 mmol scale and 5 cm³ of solvent, Grignard reagent added dropwise to a solution of the auxiliary **167** in the appropriate solvent; [b] determined by analysis of the crude ^{1}H and ^{31}P NMR spectroscopic date;

Table (10) – Attempted cleavage of the DCG auxiliary

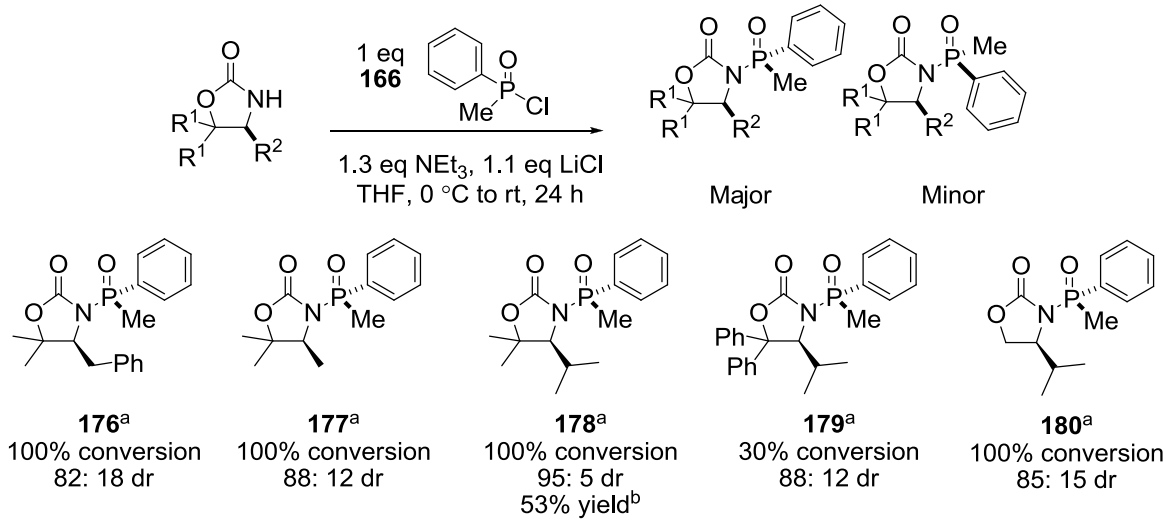
The failure of the DCG adduct **173** to undergo nucleophilic displacement led to an alternative strategy for the synthesis of *P*-chiral phosphine oxides to be sought. Work from this research

group has demonstrated the potential of the SuperQuat® auxiliary, originally pioneered by Davies, to invoke diastereoselectivity in its addition to an unsymmetrical phosphoryl chloride **175** (scheme 115).[123] In spite the single example demonstrating poor diastereoselectivity, the work provided a foundation for subsequent investigations into the addition of the analogous phosphinic chlorides.



Scheme (115) – Previous studies by the group into the synthesis of *P*-chiral phosphonates

Research undertaken by a fourth year undergraduate student during the course of this PhD study demonstrated that the addition of methyl(phenyl)phosphinic chloride **166** to a SuperQuat® auxiliary could occur in excellent diastereoselectivity and moderate yield. Screening of a range of oxazolidinones identified the dimethyl oxazolidinone **174** derived from valine as the most selective auxiliary (scheme 116).[124]



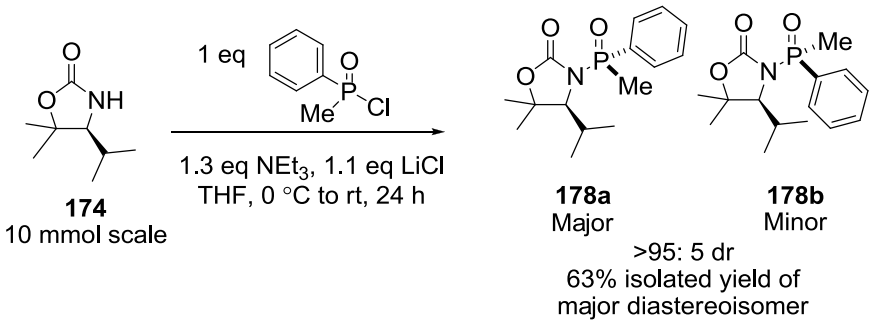
[a]determined by analysis of the crude ^{1}H and ^{31}P NMR spectroscopic data, major isomer is depicted in all cases; [b] refers to isolated yield of diastereotopically pure *N*-phosphoryl oxazolidinone **178**.

Scheme (116) – Investigations into the formation of a range of *N*-phosphoryl oxazolidinones

Pivotal to the high diastereoselectivity was the base combination of triethylamine and lithium chloride, conditions that were initially developed by Mathre for the addition of acyl chlorides to Evans-type auxiliaries.[125] The use of stronger lithiated and magnesium metalled bases resulted in a decrease in both the yield and the diastereoselectivity of the addition. Analogous to the formation of the menthol auxiliary **167** it is thought that the reaction proceeds through a

pseudorotation at the phosphorus centre, with the role of the triethylamine envisaged to be to aid in facilitating proton transfer in the reaction intermediates (figure 13).[117] Whilst it is feasible that the reaction may proceed through a dynamic kinetic resolution, the poor nucleophilicity of triethylamine and the observation that altering the concentration of base failed to infer a change in the diastereomeric ratio of the *N*-phosphoryl oxazolidinone suggests this not to be the case.

Using this methodology, the *N*-phosphoryl oxazolidinone **178** was readily prepared from the SuperQuat **174** and the phosphinic chloride **166** in moderate yield and excellent diastereoselectivity (scheme 117). Increasing the scale of the reaction to 10 mmol gave analogous results and enabled the multigram preparation of the auxiliary. Attempts at separating the two diastereoisomers by recrystallisation proved troublesome and led to the requirement of flash column chromatography for isolation of the diastereotopically pure *N*-phosphoryl oxazolidinone **178**.



Scheme (117) – The synthesis of the *N*-phosphoryl oxazolidinone 178a and 178b

A crystal structure of the major diastereoisomer **178** was obtained to determine the absolute stereochemistry around the phosphorus atom (figure 14). In line with both the Evans and SuperQuat *N*-acyl auxiliaries, the two double bonds of the molecule lie in an opposite orientation to one and other, in order to minimise the dipole moment.[126] Determination of the stereochemical configuration at the phosphorus atom showed an (R_P)-centre, with the large phenyl ring protruding away from the *iso*-propyl group to minimise any steric interaction within the molecule.

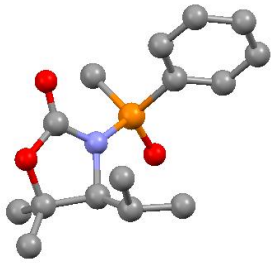
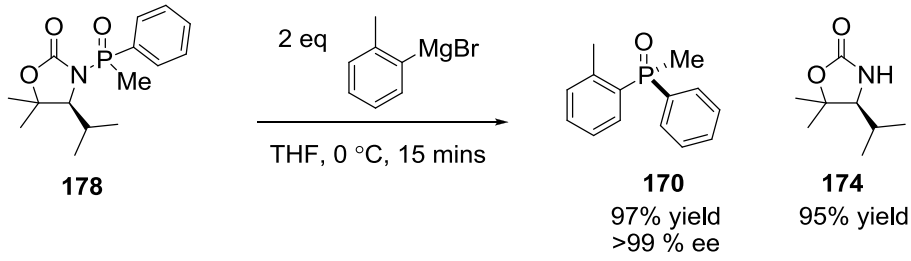


Figure (14) – X-ray crystal structure of the major diastereoisomer of the *N*-phosphoryl oxazolidinone X, the hydrogen atoms have been removed for clarity

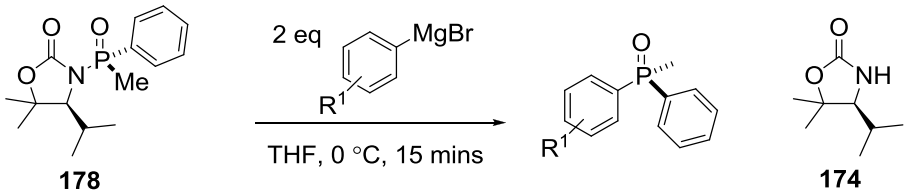
It was envisaged that introduction of the appropriate Grignard reagent would allow cleavage of the auxiliary and furnish the desired *P*-chiral phosphine oxide. To test this hypothesis, the diastereotopically pure *N*-phosphoryl oxazolidinone **178** was treated with two equivalents of *ortho*-tolyl magnesium bromide in THF at 0 °C. Analysis of the ^{1}H and ^{31}P NMR spectroscopic data after two hours showed complete cleavage of the auxiliary **178** and formation of the SuperQuat **174** and the desired *P*-chiral phosphine oxide **170** in >99% ee as determined by chiral HPLC analysis (scheme 118). Monitoring of the reaction by LC-MS enabled the reaction time to be reduced to 15 minutes with no depreciation in either the yield or enantioselectivity of the displacement. The significant difference in polarity between the phosphine oxide **170** and the SuperQuat auxiliary **174** allowed facile separation of the two moieties by flash column chromatography and isolation of the *P*-chiral phosphine oxide **170** in 83% yield and recovery of the SuperQuat auxiliary **174** in 95% yield. Comparison of the optical rotation value with those in the literature demonstrated an inversion of stereochemistry at the phosphorus centre and suggested that the reaction proceeded *via* an $S_N2(P)$ process.[117,121]



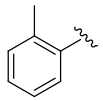
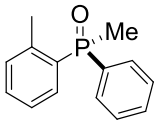
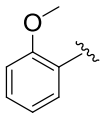
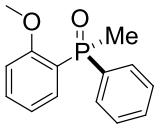
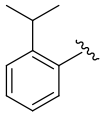
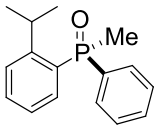
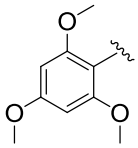
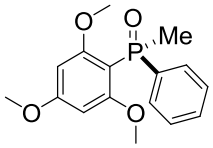
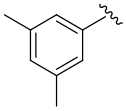
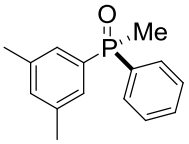
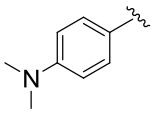
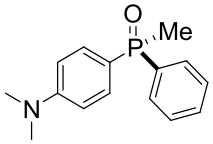
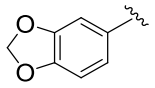
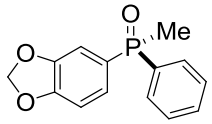
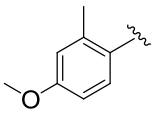
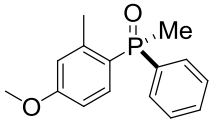
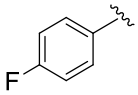
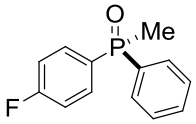
Scheme (118) – Initial results for the cleavage of the *N*-phosphoryl oxazolidinone

Having determined an optimal set of conditions for the cleavage of the *N*-phosphinoyl oxazolidinone **178**, the scope of aryl Grignard reagent was examined. An array of both electron rich and electron poor Grignard reagents were well tolerated by the reaction with the corresponding *P*-chiral phosphine oxides isolated in moderate to excellent yield (scheme 119, table 11). Interestingly, both *meta* and *para* substituted reagents gave a higher yield of the phosphine oxide than the analogous *ortho* substituted compounds and suggested that the increase in steric amplitude around the organometallic reagent hindered its ability to undergo nucleophilic displacement at the phosphorus centre. For example, 4-*tert*-butylphenyl magnesium bromide afforded the corresponding phosphine oxide in 99% yield, whilst the analogous 2-*tert*-butylphenyl species failed to deliver the corresponding *P*-chiral phosphine oxide being isolated (scheme 119, table 11, entries 13 and 14). Further support for this hypothesis was ascertained by the limited reactivity of 1-naphthyl magnesium bromide compared to the 2-substituted reagent (scheme 119, table 11, entries 15 and 16). Analysis of the products by both chiral HPLC and where present within the literature, optical rotation analysis demonstrated a greater than 99% ee

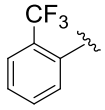
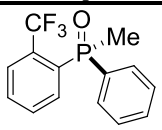
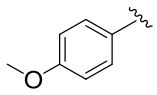
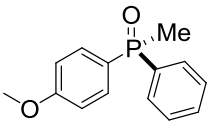
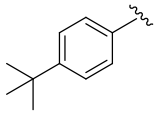
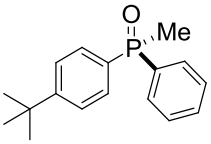
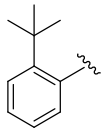
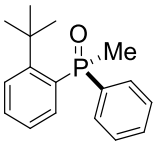
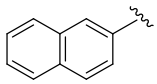
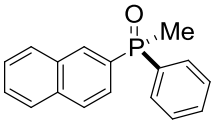
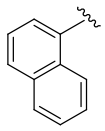
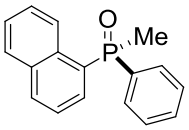
and inversion of stereochemistry at the phosphorus centre.



Scheme (119) – Diversifying the scope of aryl Grignard reagent able to undergo the displacement

entry	R^1	*P*-chiral product[a]	yield of **X** / %[b]	yield of **X** / %[b]	ee of **X**/ %[c]
1			83	95	>99[d]
2			85	95	>99[d]
3			42	91	>99[d]
4			53	86	>99[e]
5			91	91	>99[e]
6			93	95	>99[e]
7			86	91	>99[e]
8			78	94	>99[e]
9			95	93	>99[d]

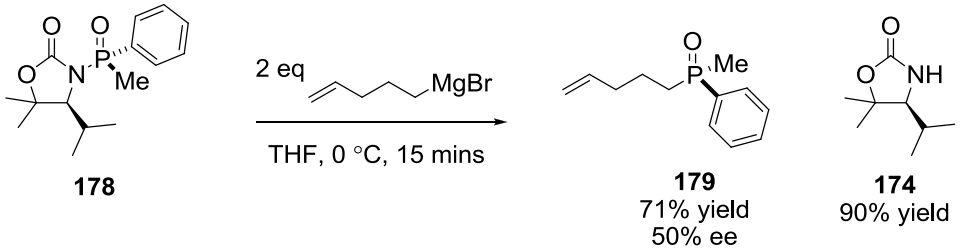
[a] all reactions run on 1 mmol scale using 5 cm³ of solvent, where the appropriate Grignard reagent was not commercially available, the reagent was prepared from the corresponding aryl bromide and magnesium in anhydrous THF; [b] refers to yield of isolated product; [c] determined by chiral HPLC analysis; [d] (S_P)-configuration confirmed by comparison of optical rotation value with literature value; [e] compound not present in the literature therefore configuration is defined tentatively as (S_P) in line with other known products

entry	R^1	*P*-chiral product[a]	yield of **X** / %[b]	yield of **X** / %[b]	ee of **X** / %[c]
11			56	89	>99[d]
12			95	92	>99[d]
13			99	93	>99[e]
14			-[f]	-	-
15			41	91	>99[d]
16			<10[g]	-	N.D.

[a] all reactions run on 1 mmol scale using 5 cm³ of solvent, where the appropriate Grignard reagent was not commercially available, the reagent was prepared from the corresponding aryl bromide and magnesium in anhydrous THF; [b] refers to yield of isolated product; [c] determined by chiral HPLC analysis; [d] (S_P)-configuration confirmed by comparison of optical rotation value with literature value; [e] compound not present in the literature therefore configuration is defined tentatively as (S_P) in line with other known products; [f] no reaction observed, only *N*-phosphoryl oxazolidinone recovered; [g] refers to conversion based on analysis of the crude ^{1}H and ^{31}P NMR spectroscopic data; N.D. not determined.

(Table 11) – The scope of aryl Grignard reagent addition to the *N*-phosphoryl oxazolidinone 178

Attempts at expanding the scope of the reaction to aliphatic Grignard reagents initially proved troublesome. Pent-4-enyl magnesium bromide was chosen as the benchmark substrate for the displacement; however, implementation of the conditions required for the addition of aryl organometallic reagents afforded the desired *P*-chiral phosphine oxide **179** in 71% yield and 50% ee. To try and increase the enantioselectivity of the displacement, a range of reaction parameters were investigated. Cooling the temperature of the reaction solution resulted in prolonged periods



Scheme (120) – Initial attempts at expanding the Grignard displacement to aliphatic moieties

of reactivity being required, however, no increase in enantioinduction (scheme 121, table 12, entries 1, 2 and 3). Changing the solvent from THF to either toluene or diethyl ether also had little effect on the enantioselectivity, with the phosphine oxide isolated in 51% ee in both cases (scheme 121, table 12, entries 5, 6, 7 and 8).

Recently, Liu has reported the use of an Evans auxiliary to synthesise a range of enantioenriched polyfluoroalkylsufinamides.[127] During their preliminary studies, the authors noted that cleavage of the *N*-sulfinyl auxiliary **181** and **182** with LiHMDS depreciated the enantioselectivity of the resultant polyfluoroalkylsufinamide. To explain this observation, Liu hypothesised that the by-product of the reaction, the lithiated Evans auxiliary **180**, could undergo nucleophilic attack on the *N*-sulfinyl auxiliary **181** and thus invert the absolute configuration of the sulfur atom (figure 15). Subsequent S_N2 nucleophilic displacement with LiHMDS would afford the opposite enantiomer of the polyfluoroalkylsufinamide and thus account for the depreciation in enantioselectivity.

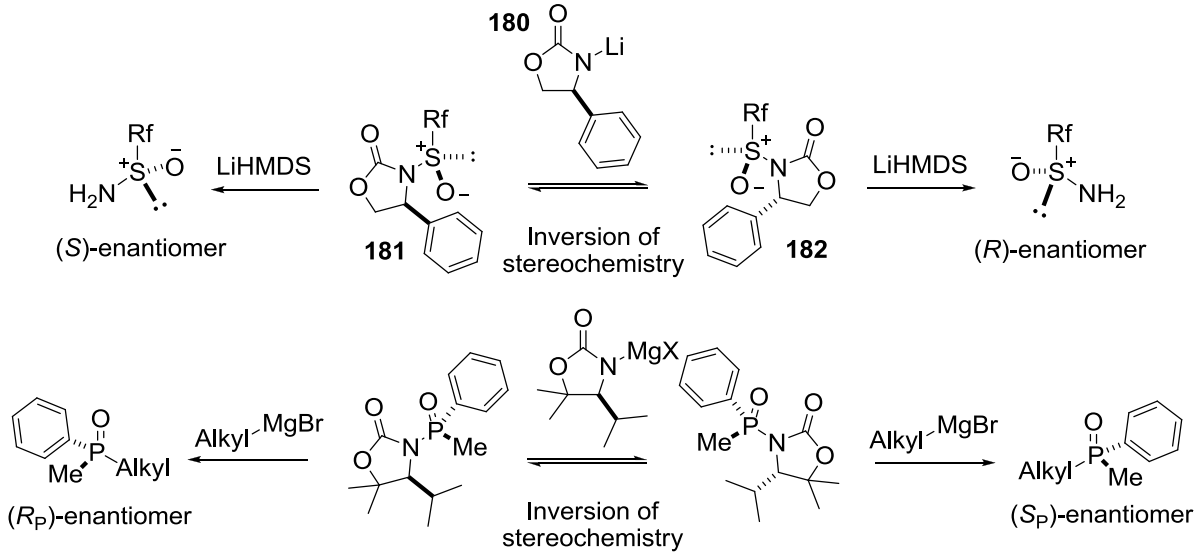
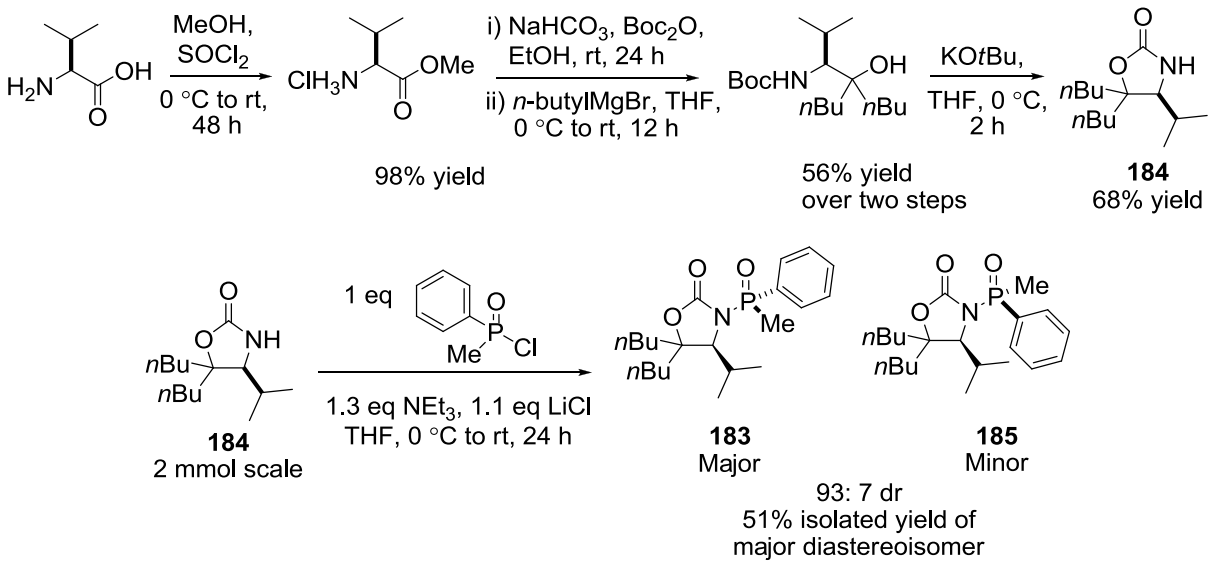


Figure (15) – Liu's mechanism for the racemisation of the perfluoroalkyl sulfinamides and the proposed analogous pathway of racemisation for the *N*-phosphoryl oxazolidinone chemistry

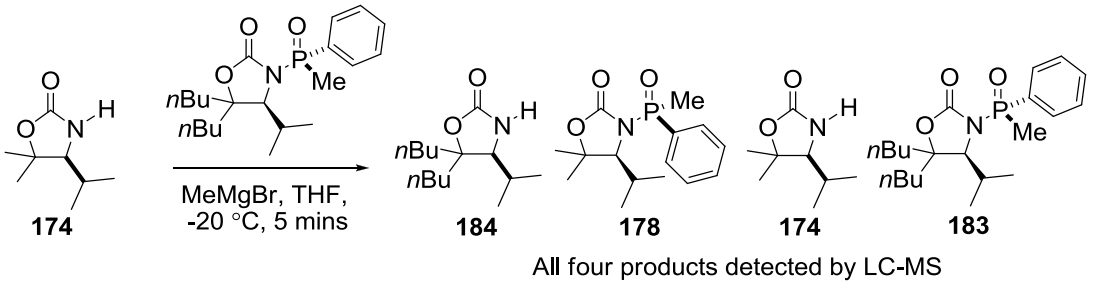
To try and verify whether an analogous process was in operation for the addition of the aliphatic Grignard reagent to the auxiliary **178**, the *N*-phosphorylated oxazolidinone **183** was synthesised. It was envisaged that the differing molecular weights of the two auxiliaries would enable the use of LC-MS to examine the feasibility of the dimethyl oxazolidinone **174** to undergo nucleophilic attack on the *n*-butyl auxiliary **183** and furnish the expected crossover products, the original *N*-phosphoryl oxazolidinone **178** and the *n*-butyl oxazolidinone **184**. Following literature precedent for the preparation of similar species, the *n*-butyl oxazolidinone **184** was synthesised in 4 steps

from L-valine (scheme 121).[128] The *N*-phosphoryl oxazolidinone **183** was prepared in moderate yield and excellent diastereoselectivity using the methods described earlier.



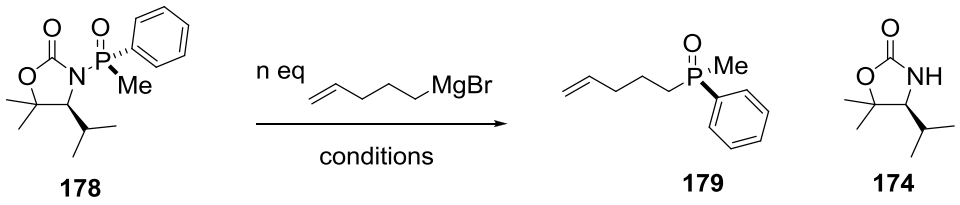
Scheme (121) – The synthesis of the *n*-butyl *N*-phosphoryl oxazolidinone 183

Deprotonation of the oxazolidinone **174** using methyl magnesium bromide and subsequent introduction of the *n*-butyl auxiliary **184** afforded the expected crossover products as observed by LC-MS, and suggested the presence of a racemisation pathway similar to that observed by Liu (scheme 122).



Scheme (122) – The result of the crossover experiment, determined by LC-MS

To circumvent this issue, the auxiliary **178** was introduced *via* syringe pump to a solution of the Grignard reagent with the hypothesis that minimising the concentration of the metallated oxazolidinone would inhibit the racemisation pathway and allow for complete enantiocontrol. Analysis of the enantioselectivity showed a >99% ee in the resultant *P*-chiral phosphine oxide and enabled isolation of the enantiopure species in 99% yield (scheme 123, table 12, entry 9).



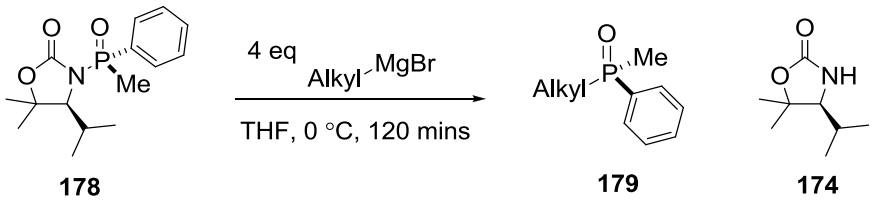
Scheme (123) – The displacement of the *N*-phosphoryl oxazolidinone using pent-4-enyl magnesium bromide

entry	number of equivalents	solvent	temperature / °C	time / mins[b]	yield of **179** / %[c]	yield of **174** / %[c]	ee of **179** / %[d]
1	2	THF	0 to rt	20	90	98	50
2	2	THF	-20	40	88	94	51
3	2	THF	-40	60	79	89	49
4	2	THF	-78	180	88	98	50
5	2	Et_2O	0 to rt	20	84	98	50
6	2	Et_2O	-20	40	82	94	49
7	2	toluene	0 to rt	20	86	93	48
8	2	toluene	-20	40	83	95	50
9[e]	4	THF	0	120	92	99	>99

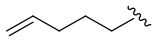
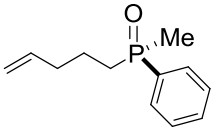
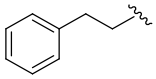
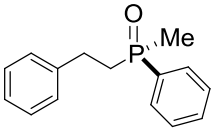
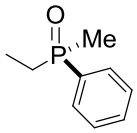
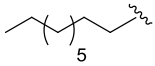
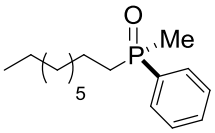
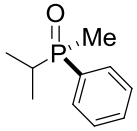
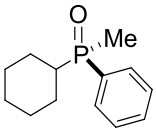
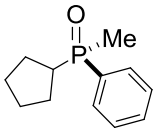
[a] all reactions performed on 0.5 mmol scale in 5 cm³ of solvent; [b] time taken for reaction to be complete as determined by TLC analysis; [c] refers to the yield of the isolated product; [d] determined by chiral HPLC analysis; [e] syringe pump (1 cm³ / hr) addition of a solution of auxiliary **179** in THF (2 cm³) to Grignard reagent.

Table (12) – The conditions utilised for the Grignard addition

Having identified an optimised set of reaction conditions, the scope of aliphatic Grignard addition was examined (scheme 124, table 13). A range of primary Grignard reagents were shown to afford the corresponding *P*-chiral phosphine oxides **186** – **192** in excellent yield and complete enantiocontrol as determined by chiral HPLC analysis. The significant difference in polarity between the *P*-chiral phosphine oxide and the SuperQuat® auxiliary **174** enabled the facile separation of the two species and excellent recovery of the oxazolidinone in all cases. Comparison of the optical rotation value of the ethyl substituted product **188** with that of the literature, confirmed inversion of stereochemical configuration at the phosphorus centre and suggested that an $S_N2(P)$ reaction was in effect. Attempts to expand the scope of aliphatic Grignard reagent to secondary organometallic moieties proved more troublesome, with only the *iso*-propyl Grignard reacting with the auxiliary **178** to produce the *P*-chiral phosphine oxide **190** in poor yield and >99% ee. (scheme 124, table 13, entry 5). Both the cyclohexyl and cyclopentyl Grignard reagents failed to undergo nucleophilic displacement with return of the starting auxiliary **178** the only product observed (scheme 124, table 13, entry 6 and 7).



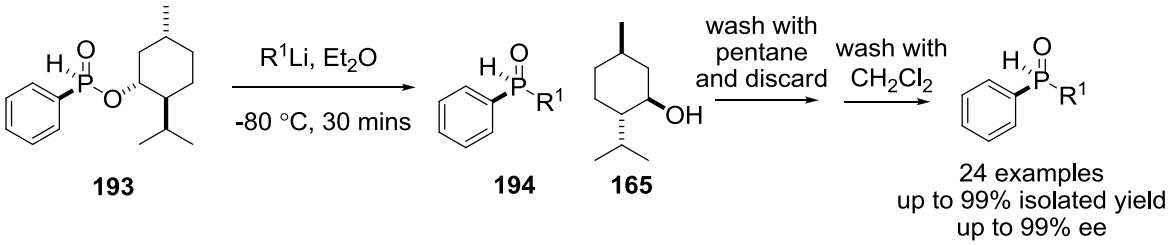
Scheme (124) – Expanding the scope of aliphatic Grignard reagent

entry	Alkyl group	*P*-chiral product[a]	yield of **179** / %[b]	yield of **174** / %[b]	ee of **179** / %[c]
1			99	94	>99[fe]
2			99	92	>99[e]
3			65	92	>99[d]
4			76	88	>99[e]
5			31	25	>99[e]
6			<5[g]	-	-
7			<5[g]	-	-

[a] all reactions performed on 1 mmol scale with the auxiliary diluted in 2 cm³ of THF and added *via* syringe pump (1 cm³ / h) to a solution of Grignard reagent, where the appropriate Grignard reagent was not commercially available the reagent was prepared from the corresponding aryl bromide and magnesium in anhydrous THF; [b] refers to the yield of the isolated product; [c] determined by chiral HPLC analysis; [d] (R_P)-configuration confirmed by comparison of optical rotation value with literature value; [e] compound not present in the literature therefore configuration is defined tentatively as (S_P) in line with other known products; [f] refers to conversion based on analysis of the crude ^{1}H and ^{31}P NMR spectroscopic data.

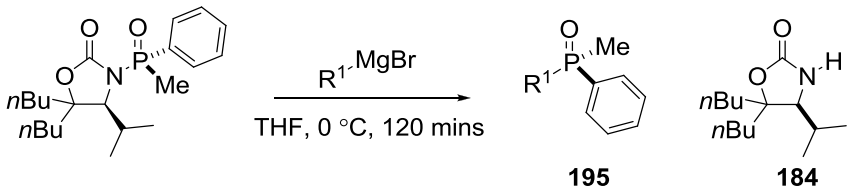
Table (13) – The scope of aliphatic Grignard addition to the *N*-phosphoryl oxazolidinone 178

Throughout the preparation of the *P*-chiral phosphine oxides it was apparent that the desired products had partial solubility in water. A similar observation was noted by Han and co-workers during the synthesis of optically pure *H*-phosphinates **194** and enabled the group to avoid the use of flash column chromatography in order to isolate the desired products.[129] The authors disclosed that sequential washing of the reaction medium with petroleum ether to extract the menthol auxiliary **165** and then subsequently with chloroform enabled isolation of the *P*-chiral species in good yield and excellent enantioselectivity (scheme 125).

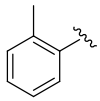
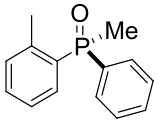
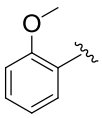
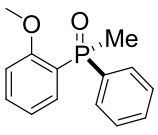


Scheme (125) – Han's synthesis of enantioenriched *H*-phosphinates

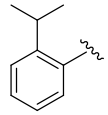
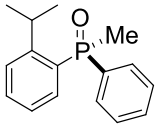
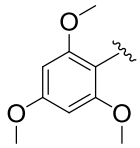
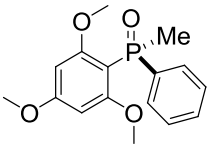
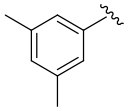
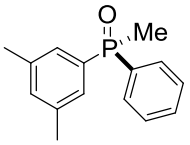
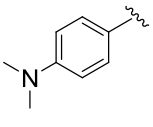
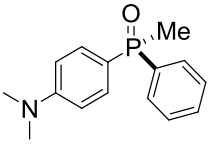
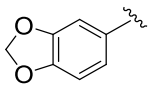
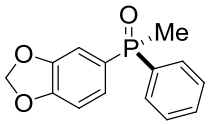
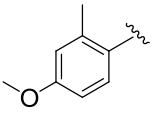
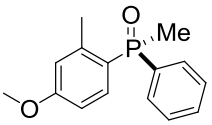
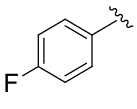
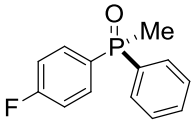
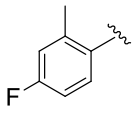
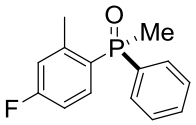
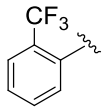
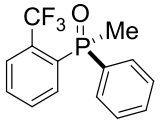
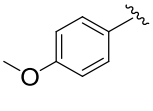
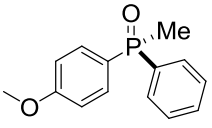
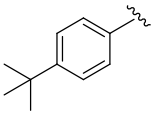
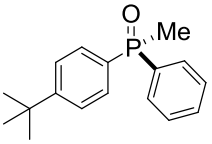
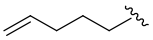
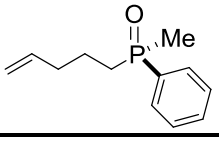
Despite the original dimethyl oxazolidinone **174** being poorly soluble in pentane, the analogous *n*-butyl species **184** showed far greater solubility and it was envisaged that the use of the corresponding *N*-phosphoryl oxazolidinone **183** may enable the isolation of the *P*-chiral phosphine oxide through sequential washing of the reaction solution. To test this hypothesis, the *N*-phosphoryl auxiliary **183**, was introduced *via* syringe pump to a solution of *ortho*-tolyl magnesium bromide. Sequential washings of the reaction mixture with first pentane to remove the *n*-butyl oxazolidinone **184** and then with chloroform enabled isolation of the desired *P*-chiral phosphine oxide **195** in 86% yield, >99% ee and >90% purity as confirmed by ^{1}H NMR spectroscopy (scheme 126, table 14, entry 1).



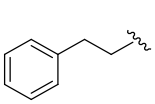
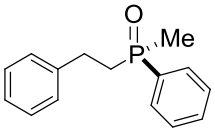
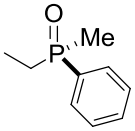
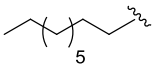
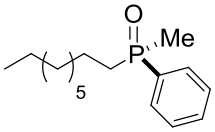
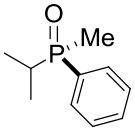
Scheme (126) – The use of the lipophillic *N*-phosphoryl oxazolidinone

entry	R^1	*P*-chiral product	yield **195** / %[a]	yield **184** /%[a]	ee **195** / %[c]	yield of **195** / %[b]	yield of **174** / %[b]	ee **195** / %[c]
1			83	95	>99	84	93	>99
2			85	95	>99	95	91	>99

all reactions performed on 0.5 mmol scale with the auxiliary diluted in 2 cm³ of THF and added *via* syringe pump (1 cm³ / h) to a solution of Grignard reagent, where the appropriate Grignard reagent was not commercially available the reagent was prepared from the corresponding aryl bromide and magnesium in anhydrous THF; [a] isolated from *N*-phosphoryl auxiliary **178** using flash column chromatography; [b] isolated from *N*-phosphoryl auxiliary **184** by sequential washing with pentane to isolate auxiliary **183** and then with chloroform to isolate phosphine oxide **195**, in all cases purity >90% as determined by ^{1}H NMR spectroscopic data; [d] determined by chiral HPLC analysis.

entry	R^1	*P*-chiral product	yield **195** / %[a]	yield **184** /%[a]	ee **195** / %[c]	yield **195** / %[b]	yield **174** / %[b]	ee **195** / %[c]
3			42	91	>99	39	88	>99
4			53	86	>99	48	95	>99
5			91	91	>99	89	94	>99
6			93	95	>99	92	92	>99
7			86	91	>99	88	91	>99
8			78	94	>99	72	89	>99
9			95	93	>99	95	95	>99
10			80	97	>99	71	93	>99
11			56	89	>99	49	96	>99
12			95	92	>99	93	95	>99
13			99	93	>99	93	91	>99
14			99	94	>99	91	94	>99

all reactions performed on 0.5 mmol scale with the auxiliary diluted in 2 cm³ of THF and added *via* syringe pump (1 cm³ / h) to a solution of Grignard reagent, where the appropriate Grignard reagent was not commercially available the reagent was prepared from the corresponding aryl bromide and magnesium in anhydrous THF; [a] isolated from *N*-phosphoryl auxiliary **178** using flash column chromatography; [b] isolated from *N*-phosphoryl auxiliary **183** by sequential washing with pentane to isolate auxiliary and then with chloroform to isolate phosphine oxide **184**, in all cases purity >90% as determined by ^{1}H NMR spectroscopic data; [d] determined by chiral HPLC.

entry	R^1	*P*-chiral product	yield **195** / %[a]	yield **184** /%[a]	ee **195** / %[c]	yield **195** / %[b]	yield **174** / %[b]	ee **195** / %[c]
15			99	92	>99	90	92	>99
16			65	92	>99[d]	71	91	>99
17			76	88	>99[e]	80	98	>99
18			31	25	>99[e]	<10[e]	-	N.D.

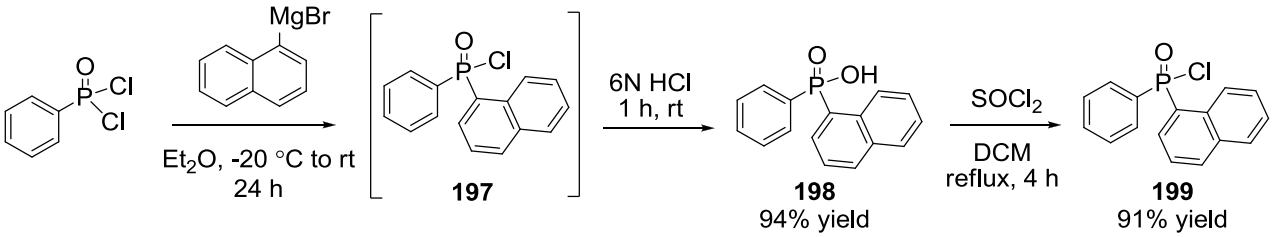
all reactions performed on 0.5 mmol scale with the auxiliary diluted in 2 cm³ of THF and added *via* syringe pump (1 cm³ / h) to a solution of Grignard reagent, where the appropriate Grignard reagent was not commercially available the reagent was prepared from the corresponding aryl bromide and magnesium in anhydrous THF; [a] isolated from *N*-phosphoryl auxiliary **178** using flash column chromatography; [b] isolated from *N*-phosphoryl auxiliary **184** by sequential washing with pentane to isolate auxiliary **183** and then with chloroform to isolate phosphine oxide **195**, in all cases purity >90% as determined by ^{1}H and NMR spectroscopic data; [d] determined by chiral HPLC analysis; [e] refers to conversion based on analysis of the crude ^{1}H and ^{31}P NMR spectroscopic data; N.D. not determined

Table (14) – The scope of Grignard reagent available to the displacement

Having identified a suitable set of conditions, the scope of Grignard reagent was once again examined. Both aryl and aliphatic Grignard reagents were well tolerated by the reaction, with the corresponding *P*-chiral phosphine oxides isolated in excellent yield, >99% ee and greater than >90% purity as determined by chiral HPLC and analysis of the ^{1}H NMR spectroscopic data respectively. Comparison of the optical rotation values with those previously obtained confirmed an inversion of stereochemistry at the phosphorus centre and suggested a $S_N2(P)$ reaction to be in effect. In the majority of cases the yields obtained through the new procedure were similar to those obtained *via* column chromatography. Interestingly, the ethyl phosphine oxide **188** was obtained in a higher yield through the use of the new sequential washing procedure than with the previous methodology and suggested the potential of this method as a means of synthesising more challenging substrates. In line with previous results, the *meta* and *para* substituted aryl Grignard reagents gave a higher yield of the resultant phosphine oxides when compared to the analogous *ortho* substituted species and suggested that the increase in steric interactions around the organometallic reagent hindered the ability to undergo nucleophilic displacement at the phosphorus centre. Attempts to expand the methodology to encompass secondary aliphatic Grignard reagents proved problematic. For example, *iso*-propyl magnesium bromide which had been shown to exhibit moderate reactivity toward the original

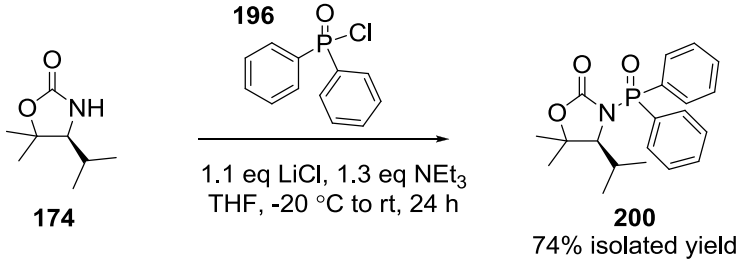
auxiliary **178**, failed to undergo nucleophilic displacement with the *N*-phosphoryl oxazolidinone **183**, only resulting in return of the starting material.

The success of the *N*-phosphoryl oxazolidinone **178** led to attempts at diversifying the phosphinic chloride used in the reaction. Initially, the 1-naphthyl(phenyl) phosphinic chloride **197** was chosen as the benchmark substrate. Whilst the synthesis of such species had been shown to be feasible in 5 steps, it was found that addition of phenylphosphonic dichloride **196** to an equivalent of 1-naphthyl magnesium bromide and subsequent acidic hydrolysis could afford the corresponding phosphoric acid **198** in excellent yield (scheme 127). [120,122] Treatment of the acid **198** with thionyl chloride enabled the synthesis of the desired compound **199** as an off white solid in two steps.



Scheme (127) – An improved synthesis of the 1-naphthyl(phenyl) phosphinic chloride 199

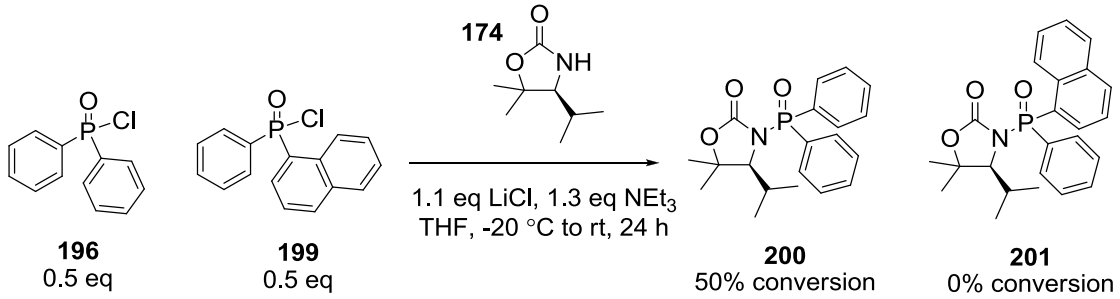
Addition of the phosphinic chloride **199** to a solution of the oxazolidinone **174**, lithium chloride and triethylamine in THF failed to afford any of the *N*-phosphorylated oxazolidinone, with only starting material and the phosphoric acid **198** identified by ^{1}H and ^{31}P NMR spectroscopy. The lack of reactivity displayed by the phosphinic chloride **199** was hypothesised to be the result of the increase in the size of the reactant. To examine whether this observation was true of analogous diaryl species, the commercially available diphenyl phosphinic chloride was used in the reaction. Analysis of the ^{1}H NMR spectroscopic data showed 100% conversion to the *N*-phosphoryl oxazolidinone **200** and enabled isolation of the product in 74% yield (scheme 128).



Scheme (128) – Attempted synthesis of the 1-naphthyl(phenyl) *N*-phosphoryl oxazolidinone

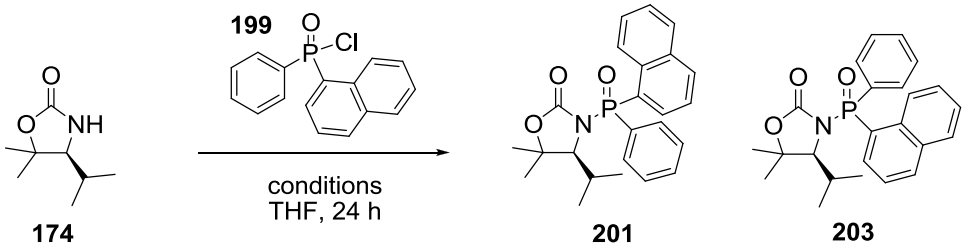
A subsequent competition experiment using 0.5 equivalents of both the diphenyl and 1-naphthyl(phenyl)phosphinic chlorides **196** and **199** demonstrated 50% conversion to the diphenyl *N*-phosphoryl oxazolidinone **200** but no conversion to the analogous 1-

naphthyl(phenyl) species **201** and confirmed the 1-naphthyl phosphinic chloride to be too sterically encumbered to react under these conditions (scheme 129).



Scheme (129) – Competition experiment to demonstrate the lack of reactivity of the oxazolidinone toward the 1-naphthyl phosphinic chloride 201

In order to try and increase the reactivity of the oxazolidinone **174**, a number of lithiated and magnesium metallated bases were introduced into the reaction with the premise that formal deprotonation of the oxazolidinone may confer increased reactivity toward sterically encumbered electrophiles.



Scheme (130) – The attempted synthesis of the *N*-phosphorylated oxazolidinone

entry	base[a]	temperature / °C	conversion to **201** and **203** / %[b]	dr of **201**: **203**[b]	isolated yield of **201**/ %[c]
1	*n*BuLi	-78 to 0	<10	N.D.	-
2	*n*BuLi	0 to rt	<10	N.D.	-
3	LDA	-78 to 0	<10	N.D.	-
4	LDA	0 to rt	<10	N.D.	-
5	LHMDS	-78 to 0	<10	N.D.	-
6	LHMDS	0 to rt	30	N.D.	-
7	LiTMP	-78 to 0	<10	N.D.	-
8	LiTMP	0 to rt	<10	N.D.	-
9	MeMgBr	-78 to 0	<10	N.D.	-
10	MeMgBr	0 to rt	100	3: 1	47

[a] all reactions performed on 1 mmol scale using 5 cm³ of solvent, the base was added to a solution of the oxazolidinone 1 hour before addition of the phosphinic chloride occurred; [b] determined by analysis of the crude ^{1}H NMR spectroscopic data; [c] following purification by flash column chromatography; N.D. not determined

Table (15) – Conditions investigated for the synthesis of the *N*-phosphoryl oxazolidinone

In line with the results obtained for the formation of the original *N*-phosphoryl oxazolidinone **178**, the use of lithiated bases gave limited reactivity. *n*-Butyllithium, LDA and LiTMP all

failed to afford any of the desired product **201** and **203** at either -78 °C or 0 °C with only the starting oxazolidinone **174** recovered in all instances. Interestingly, the use of LiHMDS at 0 °C enabled a 30% conversion to the desired product **201** in a 2:1 diastereoselectivity as determined by analysis of the ^{1}H NMR spectroscopic data. Switching the base to methyl magnesium bromide however, afforded complete conversion to the *N*-phosphoryl oxazolidinone in a 3:1 diastereoisomeric ratio and 47% isolated yield of the major diastereoisomer **201**. The scale of the reaction could be increased to a 5 mmol scale with no depreciation in either the yield or the diastereoselectivity of the addition and enabled the multigram preparation of the auxiliary **201**.

To ascertain the stereochemical configuration around the phosphorus atom, a crystal structure of the major diastereoisomer **201** was obtained. In line with the original auxiliary **178**, the molecule adopts a solid state conformation in which the two double bonds orientate in opposite direction to one and other in order to minimise the dipole moment.[126] Once again the major diastereoisomer was shown to exhibit an (R_P)-configuration in which the larger of the substituents, the 1-naphthyl ring is located in a position to protrude away from the *iso*-propyl moiety of the oxazolidinone **174** and thus minimise any steric interaction.

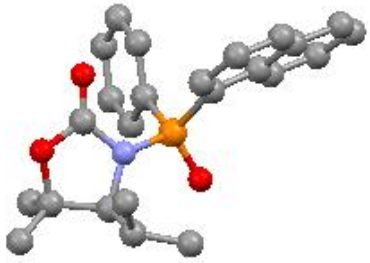
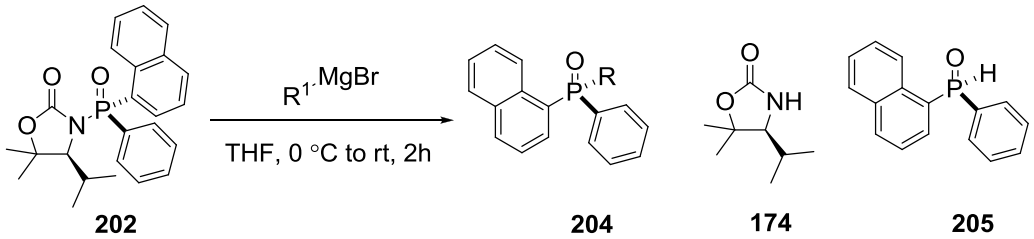


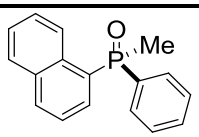
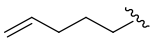
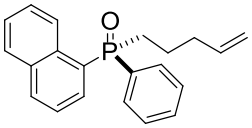
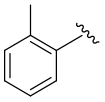
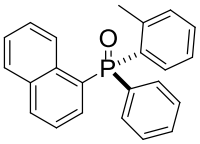
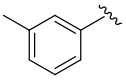
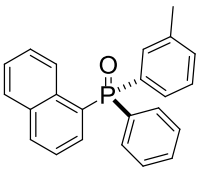
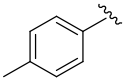
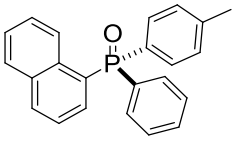
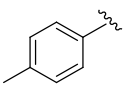
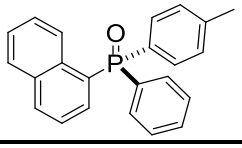
Figure (16) – X-ray crystal structure of the major diastereoisomer of the *N*-phosphinoyl oxazolidinone 201, the hydrogen atoms have been removed for clarity

To test whether the auxiliary **201** could undergo nucleophilic displacement, the *N*-phosphinoyl oxazolidinone was added *via* syringe pump to a solution of methylmagnesium bromide at 0 °C. Analysis of the crude reaction mixture by both ^{1}H NMR spectroscopy and LC-MS indicated formation of the desired *P*-chiral phosphine oxide **204** and recovery of the SuperQuat® auxiliary **174** in excellent yield. Determination of the enantioselectivity showed a greater than 99% ee in favour of the (S_P)-enantiomer and suggested that an S_N2(P) reaction was in effect. Attempts to expand the scope of Grignard reagent capable of undergoing the nucleophilic displacement proved problematic. Neither aryl nor aliphatic organometallic reagents afforded the corresponding *P*-chiral phosphine oxides with starting auxiliary recovered in all instances and suggested that the steric bulk of the naphthyl substituent prevents the nucleophile from

approaching the phosphorus atom in the correct geometry for nucleophilic attack (scheme 131, table 16, entries 2, 3, 4 and 5). Interestingly, attempts to conduct the reaction under Barbier conditions resulted in reductive cleavage of the *N*-phosphoryl oxazolidinone **202** and formation of the secondary phosphine oxide **205**. However, determination of the enantioselectivity showed formation of a racemic mixture (scheme 126, table 16, entry 6).



Scheme (131) – The attempted Grignard displacement of the *N*-phosphoryl oxazolidinone 202

entry	R^1	*P*-chiral species[a]	yield of **204** / %[b]	yield of **174** / %[b]	yield of **205** / %[b]	ee of **204** / %[c]	ee of **205** / %[c]
1			61	94	-	>99[d]	-
2			<5[e]	-	-	N.D.	-
3			<5[e]	-	-	N.D.	-
4			<5[e]	-	-	N.D.	-
5			<5[e]	-	-	N.D.	-
6[f]			-	92	81	-	0

[a] all reactions performed on 0.5 mmol scale with the auxiliary diluted in 2 cm³ of THF and added *via* syringe pump (1 cm³ / h) to a solution of Grignard reagent;;[b] refers to isolated yield; [c] determined by chiral HPLC analysis; [d]assigned as (S_P) through comparison ofoptical rotation value with that of literature; [e] refers to conversion based on analysis of the crude ^{1}H and ^{31}P NMR spectroscopic data; [f] reaction performed by dropwise addition of auxiliary to a solution of Grignard reagent in excess magnesium; N.D. not determined.

Table (16) – The scope of Grignard reagent examined for the nucleophilic displacement

The inability of the oxazolidinone **178** to react with sterically encumbered phosphinic chlorides led to investigations into the use of the analogous P(III) chlorophosphine species. It was envisaged that this approach would have two advantages; firstly, the use of a P(III) electrophile should confer a greater reactivity and thus require milder conditions for the formation of the *N*-phosphoryl auxiliary **206**. Furthermore, the potential of quenching the reaction mixture with either Oxone®, elemental sulfur or a source of borane would enable the corresponding phosphine oxide **207**, phosphine sulfide **208** and phosphine borane **209** compounds to be readily synthesised from a single precursor **206** (figure 16).

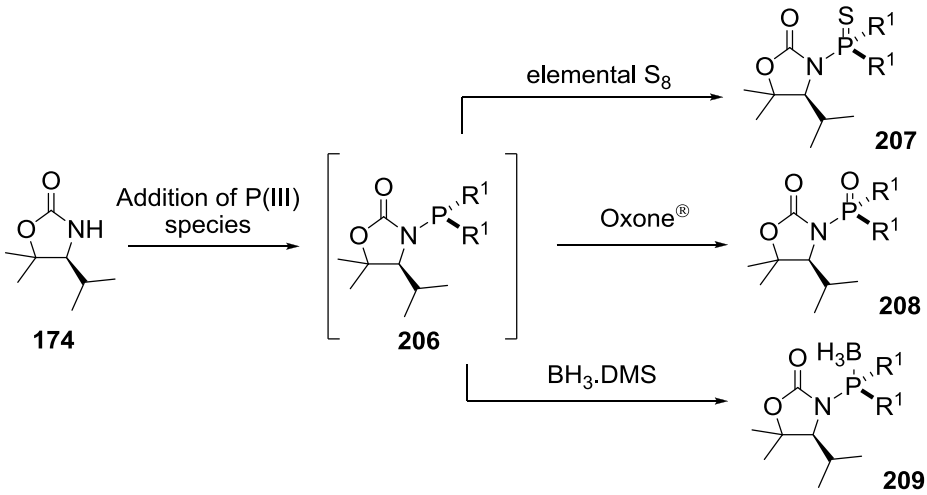
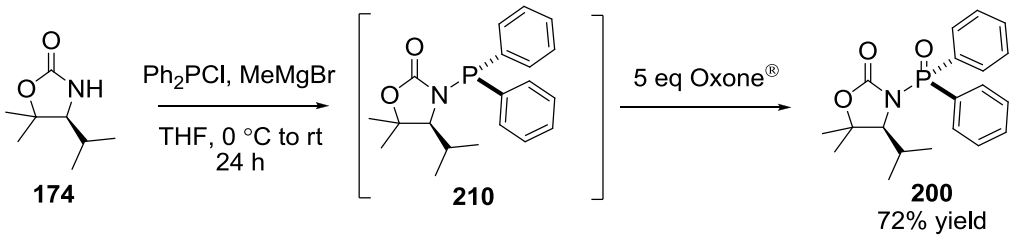


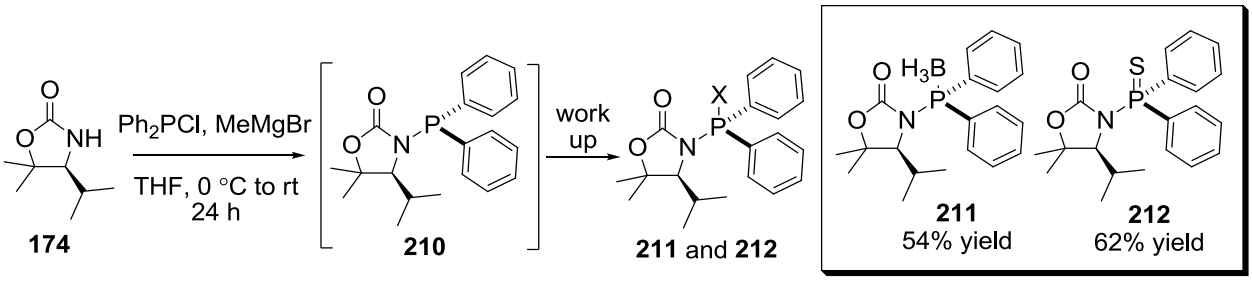
Figure (16) – The proposed route into phosphine oxides, phosphine sulfides and phosphine boranes from the single precursor 206

To test this hypothesis, diphenylchlorophosphine was added to a solution of oxazolidinone **174**, triethylamine and lithium chloride in THF. Analysis of the crude reaction mixture showed only the starting auxiliary **174** and the secondary phosphine oxide, the result of nucleophilic attack of water onto the chlorophosphine and suggested stronger basic conditions would be required for auxiliary formation. Utilisation of the reaction conditions required for the synthesis of the 1-naphthyl oxazolidinone **202** enabled the synthesis of the P(III)-auxiliary **210** as determined by ^{1}H and ^{31}P NMR spectroscopy (scheme 132). Quenching of the reaction mixture with an excess of Oxone® yielded the diphenyl *N*-phosphinyl species **200** in 72% yield (scheme 132).



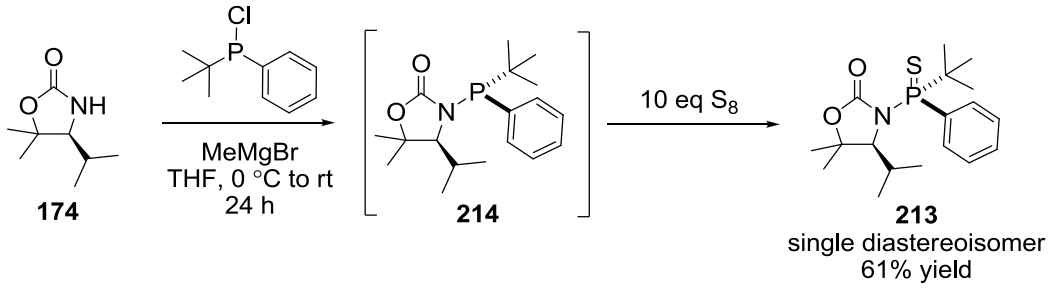
Scheme (132) – The synthesis of the *N*-phosphoryl oxazolidinone 200 through the oxidation of the P(III)-precursor 210

Addition of either BH_3.DMS or elemental sulfur to the *in situ* P(III) auxiliary **210** enabled the synthesis of the corresponding phosphine-borane **211** and phosphine-sulfide **212** oxazolidinones in good yield (scheme 133).



Scheme (133) – The synthesis of the *N*-phosphine sulfide and *N*-phosphine borane oxazolidinones 211 and 212

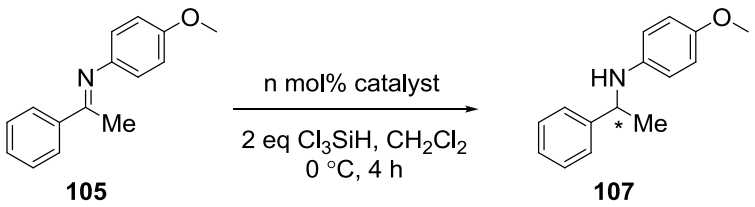
Having established a route into the three diphenyl analogues, the use of an unsymmetrical P(III) chlorophosphine was investigated. The phosphine-sulfide was chosen as the benchmark substrate due to its ease of workup and purification. Utilisation of the commercially available chlorophosphine and elemental sulfur workup enabled the synthesis of the phosphine sulfide **213**. Due to the presence of excess elemental sulfur in the reaction it was not plausible to assay the diastereoselectivity of the crude reaction mixture. Purification of the crude reaction mixture by flash column chromatography afforded the desired oxazolidinone **213** in 61% yield and as a single diastereoisomer. This result in conjunction with the observation that only a single spot was observable by thin layer chromatography suggested that the reaction proceeded with high diastereoselectivity. *In situ* analysis of the P(III) intermediate **214** was not conducted so no influence in the stereospecificity of the sulfurisation could be construed. Attempts at ascertain x-ray crystallographic data proved problematic, therefore the stereochemistry of the auxiliary **213** was tentatively assigned as (S_P) with the large *tert*-butyl group protruding away from the *iso*-propyl of the oxazolidine to minimise any steric interaction.



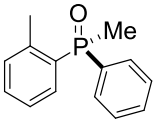
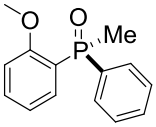
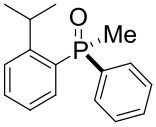
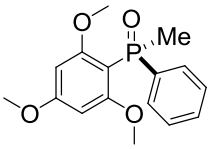
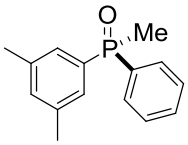
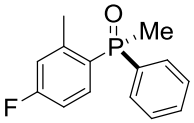
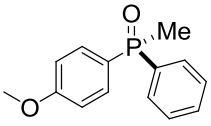
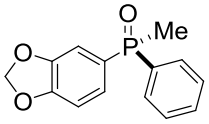
Scheme (134) – The synthesis of the diastereotopically pure *N*-phosphine sulfide auxiliary

4.4 Screening of the *P*-chiral phosphine oxides as catalysts

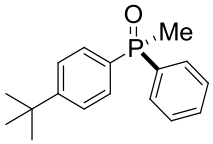
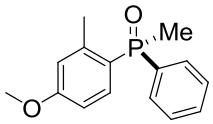
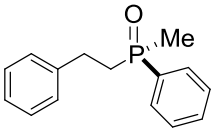
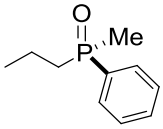
With a range of diaryl and dialkyl *P*-chiral phosphine oxides in hand, their potential as catalysts for the asymmetric reduction of the *N*-PMP ketimine **105** was investigated (scheme 135, table 17).



Scheme (135) – The reduction of the *N*-PMP ketimine 105

entry	catalyst[a]	10 mol% loading conversion to **107** / %[a]	yield / %[b]	ee of **107**/ %[c]	1 mol% loading conversion to **107** / %[a]	yield / %[b]	ee of **107**/ %[c]
1		100	91	22	73	41	21
2		100	90	29	78	43	28
3		100	87	16	64	39	17
4		100	94	28	81	48	27
5		100	81	12	68	39	10
6		100	88	20	72	41	18
7		100	92	7	77	37	7
8		100	85	11	79	41	10

[a] all reactions performed on 1 mmol scale using 1 cm³ of DCM with either 1 or 10 mol% loading of catalyst; [b] determined by analysis of the crude ^{1}H NMR spectroscopic data; [c] refers to yield of isolated product; [d] determined by chiral HPLC analysis;

entry	catalyst[a]	10 mol% loading conversion to **107** / %[a]	yield / %[b]	ee of **107**/ %[c]	1 mol% loading conversion to **107** / %[a]	yield / %[b]	ee of **107**/ %[c]
9		100	88	10	77	39	11
10		100	91	23	74	35	21
11		100	90	19	75	41	19
12		100	95	22	78	42	21

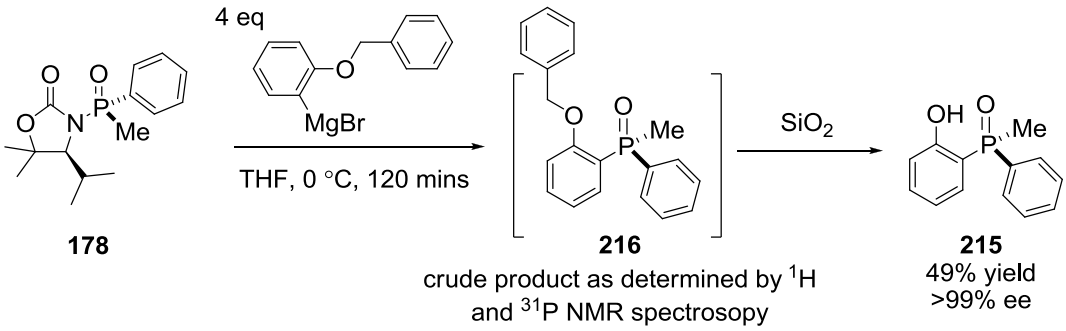
[a] all reactions performed on 1 mmol scale using 1 cm³ of DCM with either 1 or 10 mol% loading of catalyst; [b] determined by analysis of the crude ^{1}H NMR spectroscopic data; [c] refers to yield of isolated product; [d] determined by chiral HPLC analysis;

Table (17) – The catalysts screened toward the reduction of the *N*-PMP ketimine 105

In all cases, the *P*-chiral phosphine oxides displayed excellent reactivity at 10 mol% loading with each catalyst screened toward the reduction enabling complete conversion to the *N*-PMP amine **107** after four hours (scheme 135, table 17, entry 1 - 12). In line with previous results, reduction of the catalyst loading to 1 mol% conferred a decrease in reactivity and resulted in the product **107** being isolated in a lower yield. Interestingly, the introduction of electron rich substituents onto the catalyst enabled such species to exhibit a higher reactivity toward the reduction (scheme 135, table 17, entries 4, 7, 8 and 10).

Analysis of the enantioselectivities of the diaryl phosphine oxide catalysts showed the *ortho*-substituted species to display the highest selectivity toward the reduction of the *N*-PMP ketimine **105**. For example, the 2-anisyl phosphine oxide gave a 29% ee in the resultant amine **107** whilst the 4-substituted species exhibited only a 7% ee and suggested that an increase in steric hindrance around the Lewis base conferred a higher selectivity. This effect however appears to be a very subtle one as the introduction of a large *ortho iso*-propyl unit resulted in a depreciation in enantioselectivity to 16% ee. Replacement of the anisyl group with the corresponding tolyl moiety once again reduced the enantioselectivity and suggested that the oxygen atom may be a key component of the catalyst. Analysis of the dialkyl *P*-chiral phosphine oxides showed similar selectivity to the diaryl species with both the ethylphenyl and *n*-propyl catalysts enabling a 19 and 21% ee respectively.

In order to further probe the role of the anisyl group, the 2-phenol catalyst **215** was synthesised (scheme 136). Addition of the *N*-phosphoryl oxazolidinone **178** *via* syringe pump to a solution of the benzylated Grignard reagent afforded the phosphine oxide as determined by analysis of the crude ^{1}H and ^{31}P NMR spectroscopy.[130] Attempts to purify the species **216** by flash column chromatography resulted in spontaneous debenzylation and formation of the desired phenol **215** in moderate yield and >99% ee as determined by chiral HPLC analysis.



Scheme (136) – The synthesis of the 2-phenol *P*-chiral phosphine oxide 215

Screening of the phenol catalyst **215** showed a 60% conversion to the *N*-PMP amine after four hours. The marked decrease in reactivity suggests that the phenol could be binding to the trichlorosilane and inhibiting the ability of the Lewis base to catalyse the reduction. However, attempts to ascertain evidence for the formation of this bond by ^{29}Si NMR analysis proved unsuccessful. Analysis of the enantioselectivity of the reduction showed a 6% ee in the resulting amine **107** and suggested the detrimental nature of replacing the anisyl group with a phenol moiety.

In order to gain an understanding into the mechanistic details of the reduction, the relationship between the enantioselectivity of the 2-anisyl catalyst **172** and that of the resultant *N*-PMP amine **107** was plotted (figure 17). Analogous to the *S*-chiral sulfoxide **79** developed by Sun, the catalyst **172** exhibited a negative non-linear relationship.[65] Non-linear relationships arise when more than one molecule of catalyst is present in the transition state of the reaction.[131] In such systems, the presence of both enantiomers of the ligand at lower catalyst enantioselectivity enables formation of both the homochiral and *meso* diastereotopic complexes and thus formation of either the chiral or racemic product respectively. Should the rate of reaction of these complexes differ, then the relative amounts of the chiral and racemic product produced will also alter and as a result cause a non-linear effect to be observed. Mathematical models proposed by Kagan tentatively suggest that in accordance with Sun's *S*-chiral sulfoxide **79**, the 2-anisyl catalyst **172** fits a negative [ML_2] non-linear system in which two ligands are required

in the stereoselective step of the reduction.[131] To utilise this effect, Sun developed a second generation *bis*-*S*-chiral sulfoxide **80** that delivered consistently higher reactivity and selectivity, and it was hypothesised that an analogous result could be conferred through the introduction of two *P*-chiral Lewis basic units onto the catalyst scaffold. [67]

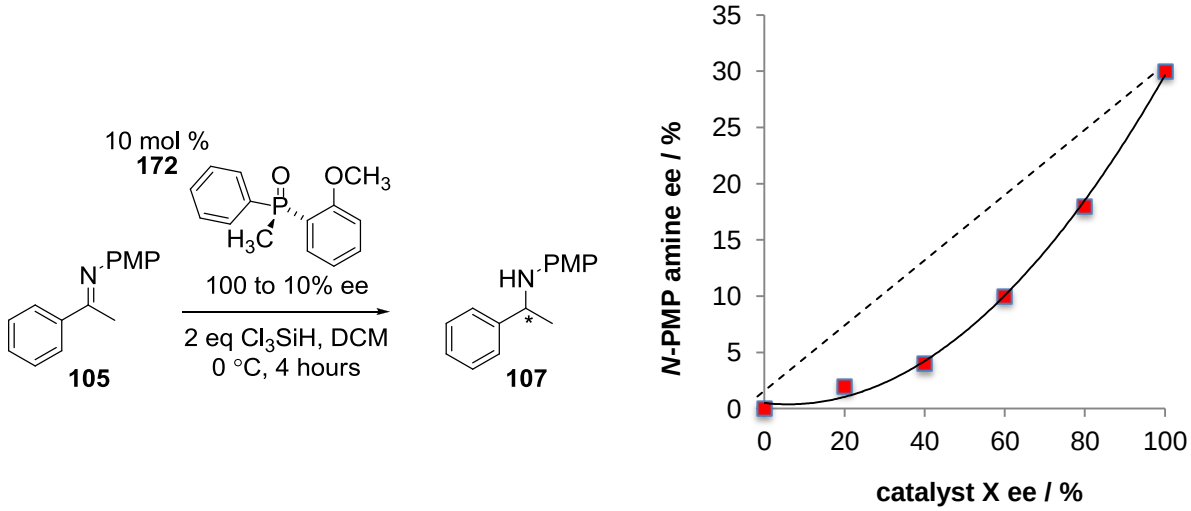
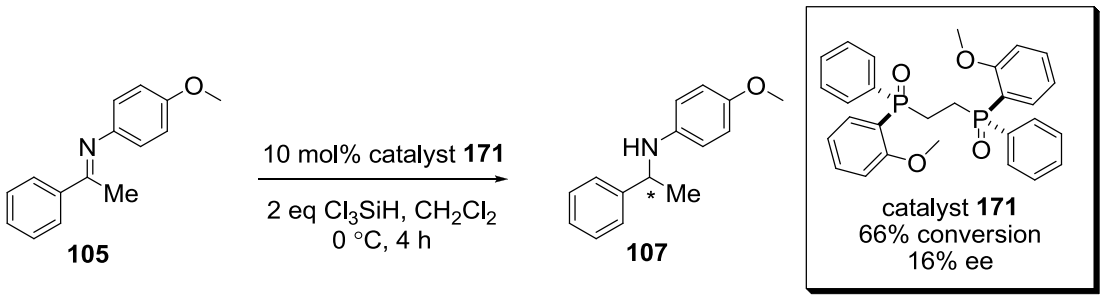


Figure (17) – The non-linear relationship of the *P*-chiral phosphine oxide 172

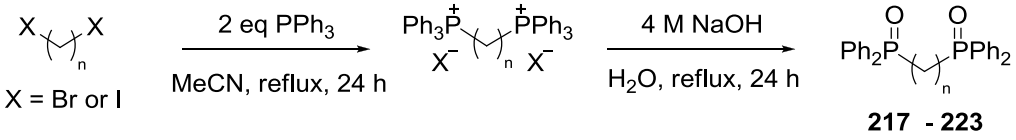
To test this hypothesis, the *bis*-*P*-chiral phosphine oxide DiPAMPO **171** was readily synthesised following known literature precedent from the commercially available phosphine.[132] The catalyst showed a 66% conversion to the *N*-PMP amine **107** after four hours. Determination of the enantioselectivity demonstrated a 16% ee and suggested that the two carbon linker between the two *P*-chiral phosphine oxides was not at a sufficient distance to confer a high selectivity (scheme 137).



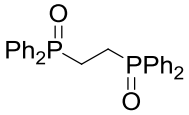
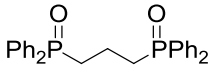
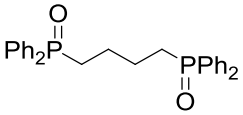
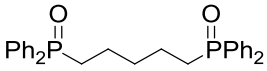
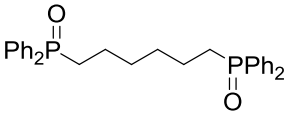
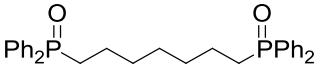
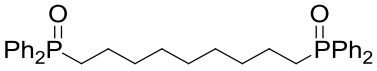
Scheme (137) – Screening of the DiPAMPO 171 catalyst toward the reduction of the *N*-PMP ketimine 105

In order to determine the optimum spacer length between the two phosphine oxide moieties, a number of achiral diphenyl *bis*-phosphine oxide catalysts **217 - 223** were synthesised with chain lengths varying from two to nine carbon atoms.[133] Following known literature precedent, the appropiate alkyldihalide was treated with triphenylphosphine to form the *bis*-phosphonium salt

and then subsequently with concentrated sodium hydroxide to afford the desired catalysts in excellent yield (scheme 138, table 18).



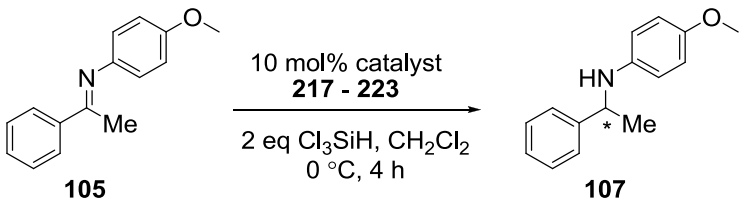
Scheme (138) – The synthesis of the achiral diphenyl *bis*-phosphine oxide catalysts

entry	X	n	catalyst[a]	structure	yield / %[b]
1	Br	2	**217**		95
2	Br	3	**218**		72
3	Br	4	**219**		80
4	Br	5	**220**		67
5	I	6	**221**		64
6	Br	7	**222**		80
7	Br	9	**223**		70

[a] all reactions performed on 5 mmol scale, where the appropiate alkyldihalide was not commercially available it was prepared from the corresponding diol;
[a] refers to the yield of the isolated product following recrystallisation.

Table (18) – The achiral diphenyl *bis*-phosphine oxide catalysts synthesised

Screening of the achiral catalysts **217** - **223** demonstrated the six carbon spacer length to be optimum for catalyst activity (scheme 139, table 19). Any deviation to either longer or shorter carbon linkers resulted in a depreciation in catalyst activity and a lower yield of the resultant *N*-PMP amine **107**.



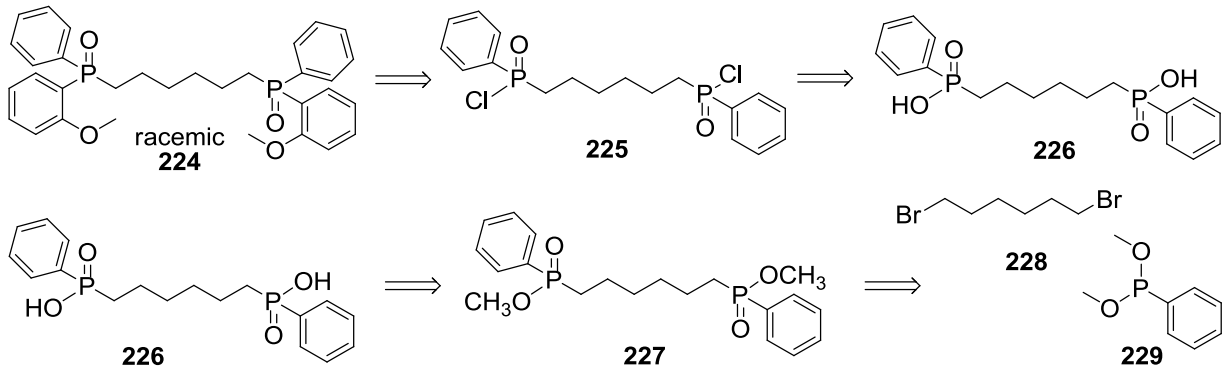
Scheme (139) – The reduction of the *N*-PMP ketimine 105

		run 1		run 2	
entry	catalyst[a]	conversion to **107** / %[b]	yield of **107** / %[b]	conversion to **107** / %[b]	yield of **107** / %[b]
1	**217**	40	12	38	16
2	**218**	55	24	54	21
3	**219**	59	29	62	42
4	**220**	65	35	68	49
5	**221**	81	68	83	71
6	**222**	74	31	74	54
7	**223**	63	28	61	29

A all reactions performed on 1 mmol scale using 1 cm^3 of solvent; [b] determined by analysis of the crude ^1H NMR spectroscopic data; [c] refers to yield of isolated product

Table (19) – The activity of the *bis*-phosphine oxide catalysts 217 – 223

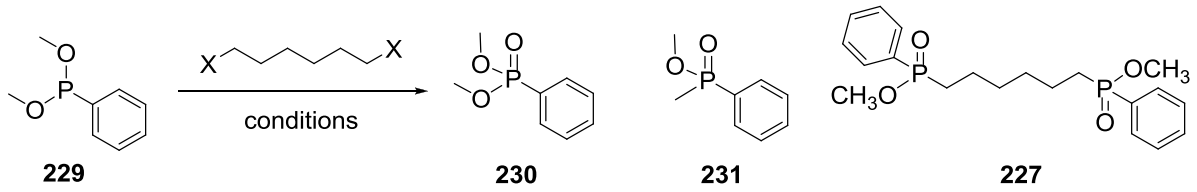
As a result, initial studies were centred upon the preparation of a racemic variant of the desired catalyst **224**. Retrosynthetically, the preparation of such species was envisaged to occur through treatment of the phosphinic chloride **225** with 2-anisyl magnesium bromide. Despite the synthesis of the phosphinic chloride being previously unknown, it was thought that the compound could be readily prepared through from the *bis*-phosphonate **227**, a species which in turn could be ascertained *via* the double Arbuzov reaction of the phosphonite **229** and 1,6-dibromohexane **228**.



Scheme (140) – The retrosynthetic analysis for the preparation of the racemic *bis*-phosphine oxide 224

Following known literature precedent, dichlorophenylphosphine was treated with methanol to afford the phosphonite **229** in excellent yield .[122] Attempts at undertaking the subsequent double Arbuzov reaction proved problematic. Treatment of the phosphonite **229** with 1,6-dibromohexane resulted in no conversion to the desired *bis*-phosphinate **227** after 24 hours with the phosphonate **230**, derived through *in* situ oxidation of the phosphonite **229**, the only product observed by analysis of the crude ^1H and ^{31}P NMR spectroscopic data. Heating the reaction to higher temperature also delivered the phosphonate **230** and suggested the poor electrophilicity of the dibromoalkane **228** in the Arbuzov reaction. Replacing the electrophile with the more

reactive 1,6-diiodohexane gave a 30% conversion to the desired *bis*-phosphinate **227** after 18 hours. Analysis of the crude ^{1}H and ^{31}P NMR spectroscopic data suggested that the major product of the reaction was the methyl phosphinate **231**, derived through the Arbuzov reaction of methyl iodide generated *in situ* and the phosphonite **229** (scheme 141, table 20). Attempts to separate the two species through either vacuum distillation or flash column chromatography were unsuccessful and suggested an alternative starting material was needed.



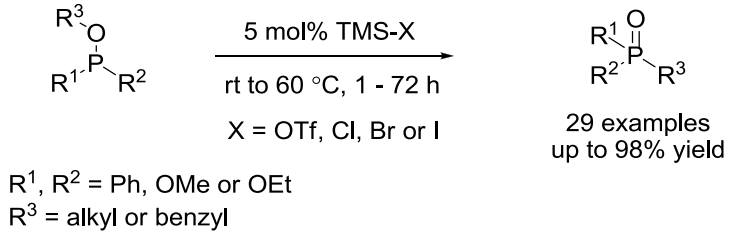
Scheme (141) – The attempted Arbuzov reaction of the phosphinate 229 with alkyldihalides.

entry	X	solvent	temperature / °C	time / h	conversion to **230** / %	conversion to **231** / %	conversion to **227** / %
1	Br	hexane	0 to rt	24	100	-	-
2	Br	neat	rt	24	100	-	-
3	Br	neat	80	24	100	-	-
4	Br	neat	140	24	100	-	-
5[d]	I	neat	140	18	-	80	20

[a] reactions performed on a 5 mmol scale; [b] 10 cm^3 of hexane used as solvent; c determined by [a] analysis of the crude ^{1}H and ^{31}P NMR spectroscopic data; [d] unseparable by either flash column chromatography or vacuum distillation.

Table (20) – The conditions examined for the attempted Arbuzov reaction

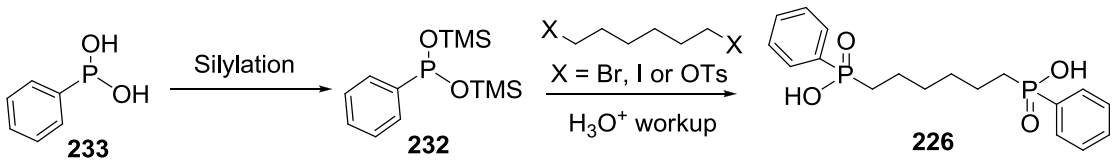
Recently, Renard has reported the Michaelis-Arbuzov reaction of phenyl phosphonites catalysed by an array of oxophilic Lewis acids (scheme 142).[134] A key advantage of the process was the ability to allow the transformation to occur at temperatures and times significantly lower than those traditionally associated with the Arbuzov reaction.



Scheme (142) – Renard's Lewis acid catalysed Arbuzov reaction

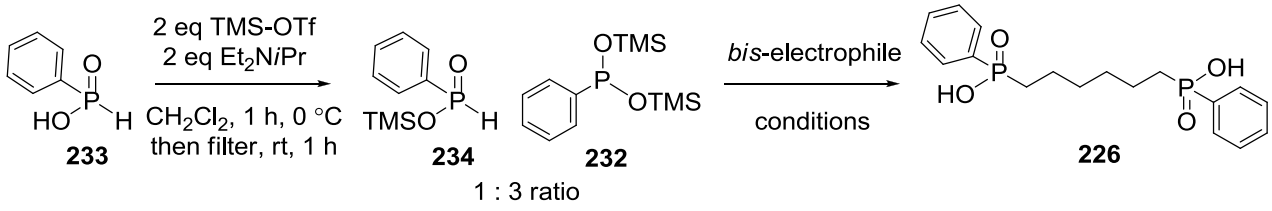
Despite the paper failing to describe an intermolecular variant of the reaction using an alkyl halide electrophile, it was thought that the introduction of an oxophilic Lewis acid could generate a reactive silyl protected phosphonite **232** which would undergo the Michaelis-

Arbuzov reaction and form the desired *bis*-phosphonate **227** (scheme 143).[135]

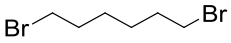
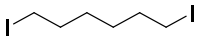
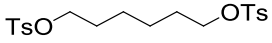
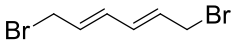
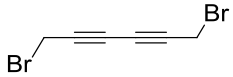


Scheme (143) – The hypothesised route to the *bis*-phosphoric acid X through a Lewis acid catalysed Michaelis-Arbuzov reaction

The commercially available phenylphosphinic acid **233** was chosen as the starting material as it was envisaged that should the more reactive 1,6-diiodohexane be required for the Arbuzov reaction then the problematic methyl phosphinate **231** side product would be avoided. Treatment of the acid **233** with 2 equivalents of TMS-OTf and Hunigs base in chloroform at 0 °C afforded a 1:1 mixture of the mono and *bis*-silylated phosphonites **234** and **232** as detected by analysis of the crude ^{1}H and ^{31}P NMR spectroscopic data. Optimisation of the reaction conditions gave an increase in the ratio of the *bis*-silylated phosphonite **232** to 3:1. Initial attempts at utilising this species in the Arbuzov reaction proved problematic. Addition of 1,6-dibromohexane **228** to the 3:1 solution of the *bis*-silylated phosphonite at 0 °C failed to afford the desired *bis*-phosphoric acid **226** with only recovery of the phosphinic acid **233** being observed (scheme 144, table 21, entry 1). Warming the reaction above 80 °C gave complete degradation of the starting material whilst lowering the temperature failed to confer any reactivity, with only quantative recovery of the starting acid **X** observed (scheme 144, table 21, entries 2 – 5). Switching the electrophile to either 1,6-diiodohexane **235** or the *bis*-tosylate **236** also failed to afford the desired acid **226** with return of the starting material at room temperature and degradation of the reactants at higher temperature. Attempts to increase the electrophilicity of the Arbuzov partner, through utilisation of the *bis*-allylic and propargylic bromides led to degradation of the starting material (scheme 144, table 21, entries 12 - 13).



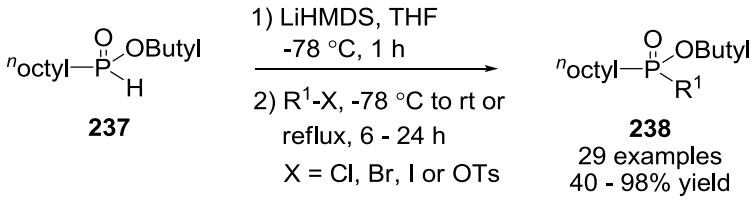
Scheme (144) – The attempted Arbuzov reaction using the mono and *bis*-silylated phosphonites 234 and 232

entry[a]	electrophile	temperature / °C	time / h	conversion to **226** / %[b]
1		0 to rt	24	0
2		40	24	0
3		80	24	degradation
4		-40	24	0
5		-78	24	0
6		0 to rt	18	0
7		80	18	degradation
8		-78	18	0
9		0 to rt	18	0
10		80	18	degradation
11		-78	18	0
12		0 to rt	24	degradation
13		0 to rt	24	degradation

[a] all reactions performed on 1 mmol scale, with addition of the electrophile to the solution of the mono and *bis*-silylated phosphonites **234** and **232**. In all cases the ratio of the mono to *bis*-silylated phosphonite was 1: 3 as determined by ^{31}P NMR spectroscopic analysis; b determined by analysis of the ^{1}H and ^{31}P NMR spectroscopic data.

Table (21) – The electrophiles and conditions examined toward the double Arbuzov reaction

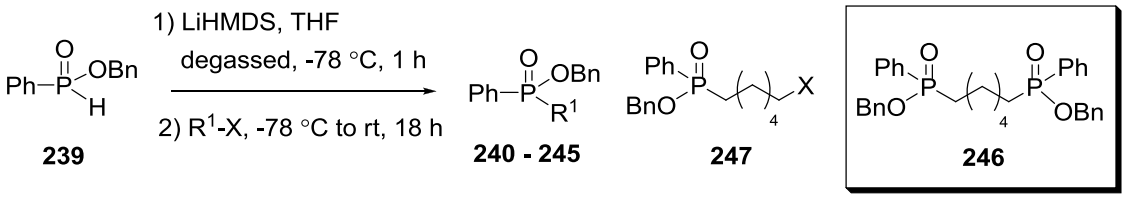
The incompatibility of the double Arbuzov reaction toward led to an alternative strategy to be sought. Recently, Montchomp has reported the alkylation of the *H*-phosphinate ester **237** under basic conditions.[136] Screening of a number of metallated bases identified LiHMDS to be the most potent, with the *H*-phosphinate **237** alkylated in good to excellent yield using a variety of primary and secondary alkyl iodides, bromides and tosylates (scheme 145). The authors also noted that the reaction tolerated the use of alkyl chlorides as the source of electrophile; however, prolonged reaction times and high temperatures were required compared to the other electrophiles utilised by the authors.



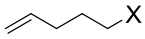
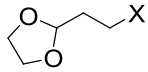
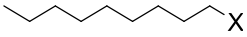
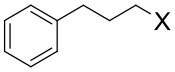
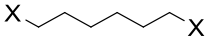
Scheme (145) – Montchomp's alkylation of the *H*-Phosphinate 237 with various electrophiles

Despite the methodology solely demonstrating the alkylation of the commercially available *H*-phosphinate **237**, it was thought that if the alkylation strategy was extended toward the benzyl *H*-phosphinate **239,** then subsequent hydrogenation of the benzyl group would reveal the corresponding phosphoric acid. To test this hypothesis, the benzyl *H*-phosphinate **239** readily prepared from benzyl chloroformate and the phosphinic acid **233** was deprotonated with

LiHMDS at -78 °C.[137] Addition of methyl iodide enabled isolation of the corresponding phosphinate **240** in 41% yield (scheme 146, table 22, entry 1). Throughout their studies, Montchomp had noted the importance of deoxygenated solvent on the yield of the phosphinate with the authors noting that failure to degas the solvent resulting in a pronounced depreciation in the yield of the product.[136] It was hypothesised that the reason for this was due to the capability of the lithiated intermediate to react with the oxygenated solvent and thus hinder the nucleophilicity of the substrate. Applying this degassing procedure afforded the desired phosphinate **240** in an improved yield of 87% yield (scheme 146, table 22, entry 2). To examine the scope of the electrophile available, a range of primary and secondary alkyl halides were screened toward the alkylation. In line with the work of Montchomp, both primary alkyl bromide and alkyl iodide electrophiles reacted readily and afforded the corresponding benzyl phosphinate **241 - 246** in good to excellent yield, with the alkyl iodides giving a slightly higher yield in all cases (scheme 146, table 22). Interestingly, with the secondary *iso*-propyl electrophile, only the corresponding alkyl iodide was reactive, with the use of the less reactive alkyl bromide only afforded the starting phosphinic acid **233**. The use of either primary or secondary alkyl chlorides or alkyl tosylates also failed to afford the desired product with only the starting material observed in all cases. Extending the scope of the methodology toward dihaloalkanes proved successful with the addition of 1,6-diiodohexane affording the desired *bis*-phosphinate **246** in good yield. A small amount of the mono phosphinate **247** was also observed, however, the difference in polarity between the two products led to facile separation of the compounds by flash column chromatography. Analogous results for the alkylation were obtained on a 5 mmol scale and enabled the multigram preparation of the *bis*-phosphinate **246**.



Scheme (146) – Expanding the methodology toward the alkylation of the benzyl *H*-phosphinate 239

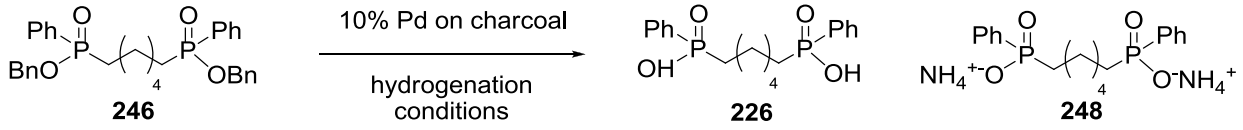
entry[a]	electrophile[b]	X	yield of **240 - 245** / %[d]	yield of **247** / %[d]	yield of **246** / %[d]
1		I[c]	41	-	-
2		I	87	-	-
3		I	63	-	-
4		Br	42	-	-
5		Cl	0[f]	-	-
6		OTs	0[f]	-	-
7		I	71	-	-
8		Br	0[f]	-	-
9		Cl	0[f]	-	-
10		Br	55	-	-
11		I	65	-	-
12		Br	51	-	-
13		Cl	0[f]	-	-
14		OTs	0[f]	-	-
14		I	85	-	-
15[e]		I	-	12	66
16[e]		Br	-	19	51

[a] all reactions performed on a 1 mmol scale using 5 cm³ of solvent and 1 equivalent of electrophile. The solvent was degassed for 90 minutes before being cooled to -78 °C; [b] the alkyl halides used were all commercially available, the alkyl tosylates were prepared according to literature precedent; [c] solvent was not degassed; [d] refers to isolated yield; [e] 0.5 equivalents of electrophile used; [f] benzyl *H*-phosphinate **239** was recovered in all cases.

Table (22) – The scope of the alkylation of the benzyl *H*-phosphinate 239

The hydrogenation of the *bis*-phosphinate **246** was next examined. Previous work had shown the H-cube micro flow reactor as a means of debenzylating the *N*-phosphinic amide **130**.[98] Utilisation of similar conditions enabled the complete removal of the benzyl protecting group and formation of the desired *bis*-phosphoric acid **226** as a crystalline solid that precipitated from the reaction medium. The precipitation of the product however, was found to be problematic as it caused the tubing of the flow reactor to become blocked. An alternate means of removing the benzyl group was therefore investigated by treatment of the *bis*-phosphinate **246** with one atmosphere of hydrogen and 20% Pd on charcoal, but this failed to afford the acid **226** and only returned the starting material (scheme 147, table 23, entry 2). Increasing the temperature of the hydrogenation also failed to afford the desired product with return of the phosphinate **246** the only product observed. Use of the conditions reported by Ram for the ammonium formate mediated transfer hydrogenation enabled complete conversion of the phosphinate **246** after 14 hours (scheme 147, table 23, entry 4).[138] Analysis of the ^{1}H NMR spectroscopic data however, suggested the product to be the *bis*-ammonium salt **248**. To avoid the formation of such species, the source of hydrogen was changed to 1,3-cyclohexadiene, and as a result enabled isolation of

the acid **226** in 81% yield (scheme 147, table 23, entry 5 and 6).[139]



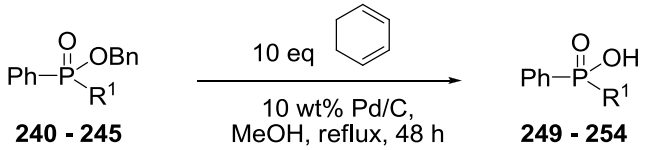
Scheme (147) – The hydrogenation conditions examined for formation of the *bis*-phosphoric acid 226

entry[a]	source of H_2	solvent	time / h	temperature / °C	conversion of **246** / %[b]	yield of **226** / %[c]	yield of **248** / %[c]
1[d]	10 atmospheres of H_2 gas	EtOH	2	rt	100	21	-
2[e]	1 atmosphere of H_2 gas	EtOH	24	rt	0[f]	-	-
3[e]	1 atmosphere of H_2 gas	EtOH	24	50	0[f]	-	-
4[g]	NH_4CO_2	MeOH	48	reflux	100	-	85
5[g,h,i]	1,3-cyclohexadiene	MeOH	48	reflux	100	81	-
6[g,h,i]	1,3-cyclohexadiene	MeOH	48	reflux	100	75	-

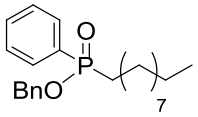
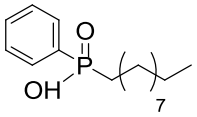
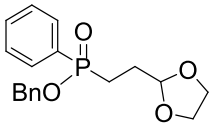
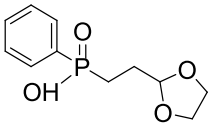
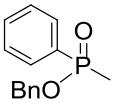
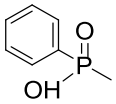
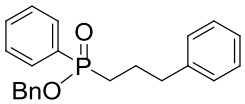
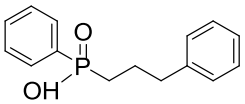
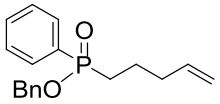
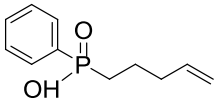
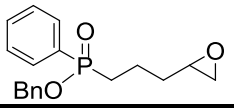
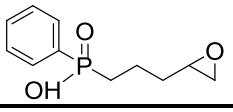
[a] all reactions performed on a 0.5 mmol at a concentration of 0.05 M using 20 wt% of Pd/C catalyst; [b] determined by analysis of the crude ^1H and ^{31}P NMR spectroscopic data; [c] refers to yield of isolated product; [d] reaction performed using the Thalesnano H-Cube micro flow reactor using a 10% Pd/C Catcart; [e] reaction performed using a hydrogen balloon; [f] only the starting *bis*-phosphinate **246** recovered; [g] reaction performed under a nitrogen atmosphere; [h] 10 equivalents of the hydrogen source used; [i] reaction performed on a 1 mmol scale.

Table (23) – The hydrogenation conditions examined for the debenzylation of the *bis*-phosphinate 246

In order to examine the versatility of the debenzylation strategy, a number of the benzyl phosphinates were deprotected to the corresponding phosphoric acids **249** - **252** in excellent yield (scheme 148, table 24, entries 1 - 4).[120] Interestingly, attempts to utilise the transfer hydrogenation conditions toward the alkene phosphinate **241** resulted in complete degradation of the starting material (scheme 148, table 24 entry 5). To try and circumvent this issue, the alkene **253** was transformed into the epoxide using *m*-CPBA and subsequently subjected to the transfer hydrogenation. Analysis of the ^1H and ^{31}P NMR spectroscopic data however, showed only degradation of the starting material (scheme 147, table 22, entry 6).



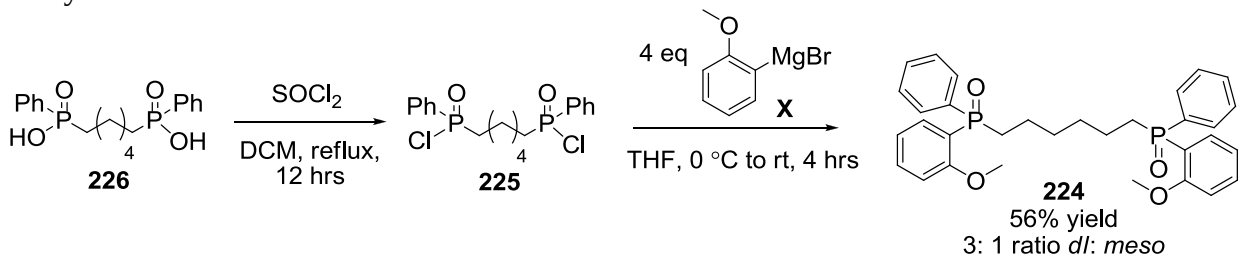
Scheme (148) – The debenzylation of a range of benzyl phosphinates

entry[a]	benzyl phosphinate	structure	phosphoric acid	structure	yield / %[b]
1	**244**		**249**		83
2	**243**		**250**		66
3	**240**		**251**		91
4	**245**		**252**		83
5	**241**		**253**		0
6[c]	**254a**		**254b**		0

[a] all reactions performed on 0.6 mmol scale using 5 cm³ of ethanol and 10 wt% of Pd/C; [b] refers to yield of the isolated product; [c] the epoxide **254a** was synthesised through *m*-CPBA epoxidation of the alkene phosphinate **241** under standard conditions; [d] complete degradation of starting material observed.

Table (24) – The scope of the phosphoric acids synthesised

With the *bis*-phosphoric acid **226** in hand, the transformation into the desired catalyst **224** was investigated. Treatment of the acid **226** with excess thionyl chloride at reflux afforded the desired phosphinic chloride **225** in excellent yield (scheme 149). Addition of the phosphinic chloride **225** to a solution of 4 equivalents of 2-anisyl magnesium bromide yielded the catalyst **224** in moderate yield. Attempts to lower the amount of Grignard reagent required proved troublesome with lower yields obtained in all instances. Analogous results for the two step procedures were obtained on a 5 mmol scale and enabled the multigram preparation of the catalyst **224**.

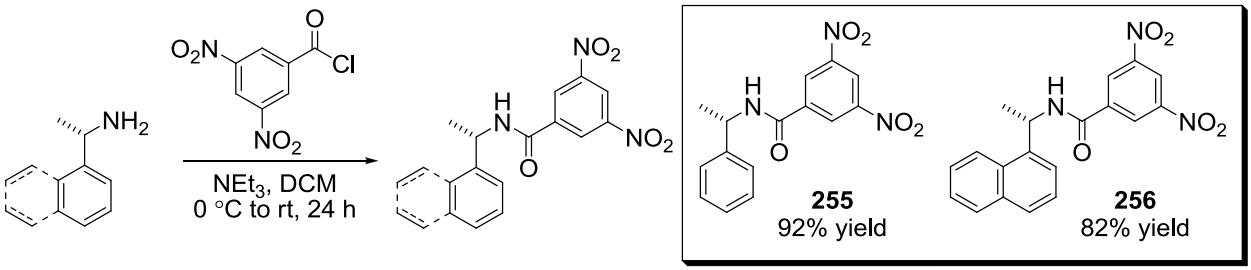


Scheme (149) – The synthesis of the *bis*-*P*-chiral phosphine oxide

Having established a route to the racemic *bis*-phosphine oxide **224**, the optical resolution of the species was attempted. Throughout the literature, a number of chiral resolving agents have been utilised to resolve a range of both *P*-chiral and more recently atropisomeric phosphine oxides.[140]

However, no reports into the resolution of the corresponding *bis*-*P*-chiral phosphine oxides have been reported.

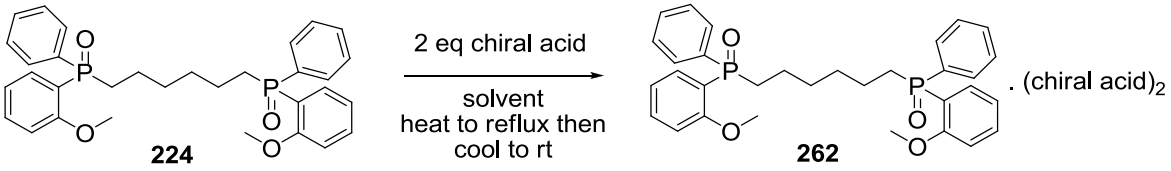
In order to determine the success of the resolution, attempts were made to separate two enantiomers and the *meso* variant of the catalyst **224** by chiral HPLC. Screening of the chiral columns available within the department, however, failed to separate the species and meant that an alternate means of analysing the resolution was needed. Work by Kagan has demonstrated the potential of the chiral amides **255** and **256** derived from 3,5-dinitrobenzoylchloride and the commercially available enantiopure amines **103** and **257** to determine the enantiomeric excess of a number of *P*-chiral phosphine oxides and *S*-chiral sulfoxides (scheme 150).[141] It is thought that the chiral solvating agent enables association with the substrate through non-covalent interactions and thus renders the two enantiomers and *meso* form of the catalyst **224** diastereotopic and distinguishable by ^{1}H and ^{31}P NMR spectroscopy. Despite the phenyl derived amide **255** failing to confer any separation of the three forms of the catalyst by ^{1}H or ^{31}P NMR spectroscopy, the analogous 1-naphthyl derived amide **256** enabled all three forms of the catalyst to be observed by ^{1}H NMR spectroscopy and demonstrated the racemic catalyst to be a 3:1 mixture of the *dl*: *meso* forms of the *bis*-phosphine oxide.



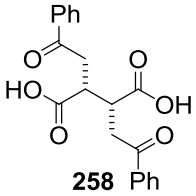
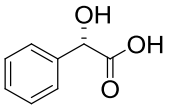
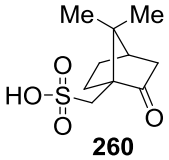
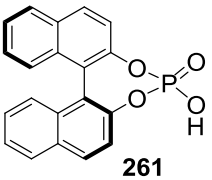
Scheme (150) – The synthesis of the two Kagan's amide

Attempts to resolve the racemic catalyst by addition of a range of chiral acids proved problematic. Introduction of dibenzoyl-*L*-tartaric acid **258** or mandelic acid **259** to a solution of the catalyst in ethyl acetate failed to precipitate the diastereotopic inclusion complex (scheme 151, table 25). Changing the solvent utilised also exerted little effect with no precipitation of the complex observed in all cases. However, introduction of camphorsulfonic acid **260** to a solution of the catalyst **224** in ethyl acetate precipitated the inclusion complex in a moderate yield of 38%. Analysis of the resolution using Kagan's NMR resolving agent **256** however, showed two sets of phosphorus environments, which were tentatively assigned as the two enantiomers of the catalyst **224**. Changing either the solvent or the stoichiometry of the chiral acid **260** conferred analogous results with no resolution of the catalyst in all instances. Utilisation of the chiral

phosphoric acid **261** derived from BINOL **150** also failed to afford the inclusion complex and suggested the incompatibility of the acid with the resolution (scheme 151, table 25).[142] Attempts to change the stoichiometry of the phosphoric acid **261** or the solvent in which the resolution took place also gave no precipitation of the complex **262**.



Scheme (151) – Attempted resolution of the racemic *bis*-phosphine oxide 224

entry[a]	resolving agent[b]	solvent	precipitation observed	yield of **262** / %[d]
1	 **258**	CH_3Cl	No	-
2		CH_3Cl:EtOAc[c]	No	-
3		EtOAc	No	-
4	 **259**	CH_3Cl	No	-
5		CH_3Cl:EtOAc[c]	No	-
6		EtOAc	No	-
7	 **260**	EtOAc	Yes	29[c]
8		EtOAc	Yes	31[c]
9		EtOAc	Yes	36[e]
10	 **261**	EtOAc	No	-
11		EtOAc[f]	No	-
12		$CHCl_3$[g]	No	-

[a] all reactions performed on 1 mmol scale using 1 cm³ of solvent; [b] 2 eq of the acid used; [c] 0.5 cm³ of each solvent used; [d] refers to yield of isolated product; [e] no resolution observed; [f] 4 eq of the acid used; [g] 8 eq of the acid used.

Table (25) – The chiral acids used in the attempted resolution of the *bis* phosphine oxide X

The failure to resolve the racemic catalyst **224** required an alternate means of synthesising the *bis*-*P*-chiral phosphine oxide. A number of research groups have successfully reported the deprotonation alpha to a phosphine oxide and subsequent quench with an activated electrophile.[110,113,143] With this in mind, it was thought that the chiral catalyst **224** could be obtained through a cross metathesis and subsequent hydrogenation of the *P*-chiral phosphine oxide **263**. Despite the deprotonation of the 2-anisylphenylmethyl phosphine oxide **264** being unknown, it was envisaged that deprotonation and addition of ally bromide to the *P*-chiral phosphine oxide **172** would enable preparation of the key precursor **264** (figure 18).

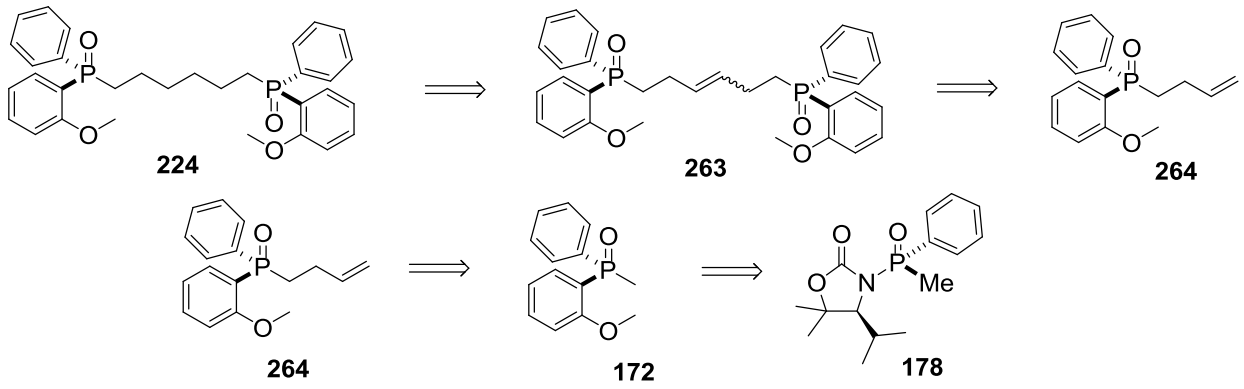
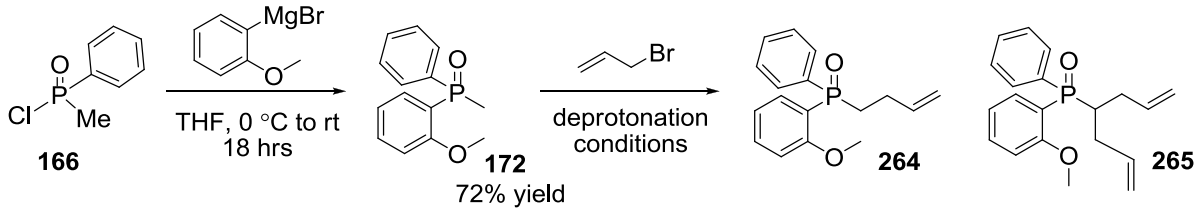


Figure (18) – The retrosynthetic analysis of the *bis*-phosphine oxide *via* the deprotonation of the *P*-chiral phosphine oxide 172

To test the feasibility of the deprotonation, initial studies focused upon screening a number of lithiated and magnesium metallated bases toward the deprotonation of the racemic 2-anisyl phosphine oxide **172**, a species prepared through addition of 2-anisyl magnesium bromide to the phosphinic chloride **166** (scheme 152, table 26). Both methyl magnesium bromide and LiHMDS failed to deprotonate the starting material (scheme 152, table 26, entries 1 - 7). Introduction of *n*-butyl lithium also failed to afford any of the desired product **264** at -78 °C. However, warming the temperature of the reaction mixture to 0 °C gave complete conversion of the starting material to a complex mixture of products as determined by analysis of the crude ^{1}H and ^{31}P NMR spectroscopic data. Purification of the crude mixture by flash column chromatography gave the desired compound **264** in 8% yield and also isolation of the *bis*-allylated species **265** in 5% yield (scheme 152, table 26, entry 9). Addition of HMPA or DMPU failed to aid formation of the allylated phosphine oxide with both the mono **264** and *bis*-allylated species **265** isolated in a similar yield (scheme 152, table 26, entries 10 and 11). To confirm the incompatibility of the phosphine oxide **172** toward the deprotonation, a competition experiment was undertaken. Introduction of 0.5 equivalents of the achiral diphenyl phosphine oxide **266** and 0.5 equivalents of the 2-anisyl species **172** were subjected to the deprotonation conditions. Analysis of the ^{1}H and ^{31}P NMR spectroscopic data following addition of an excess of allyl bromide showed 50% conversion to the diphenyl product **266** but less than 10% conversion to the corresponding 2-anisyl species **264** (scheme 153).

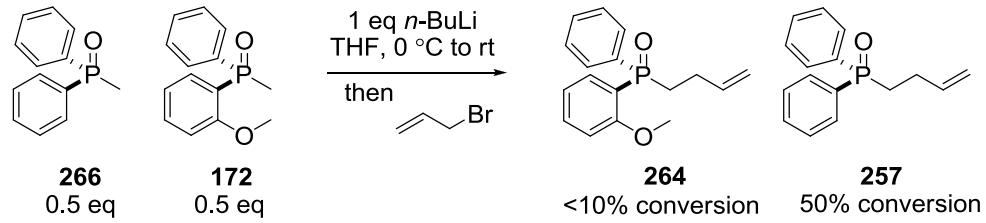


Scheme (152) – The attempted deprotonation of the methyl phosphine oxide 172

entry[a]	base	solvent	temperature / °C	conversion of **172** /%[b]	yield of **264** / %[c]	yield of **265** / %[c]
1	MeMgBr	THF	-78 to rt	0	-	-
2		THF	-40 to rt	0	-	-
3		THF	0 to rt	0	-	-
4	LiHMDS	Et_2O	-78 to rt	0	-	-
5		THF	-78 to rt	0	-	-
6		THF	-40 to rt	0	-	-
7		THF	0 to rt	0	-	-
8		Et_2O	-78 to rt	0	-	-
9	*n*BuLi	THF	0 to rt	100	8	4
10[d]		THF	0 to rt	100	5	3
11[e]		THF	0 to rt	100	7	6
12[f]		THF	0 to rt	100	9	5

[A] all reactions performed on 1 mmol scale using 5 cm³ of the appropiate solvent; [b] determined by analysis of the crude ^{1}H and ^{31}P NMR spectroscopic data; [c] refers to yield of the isolated product; [d] 1 equivalent of HMPA used; [e] 1 equivalent of DMPU used; [f] 10 equivalents of DMPU used.

Table (26) – The conditions screened toward the deprotonation of the phosphine oxide 172



Scheme (153) – Competition experiment to confirm the incompatibility of the 2-anisyl phosphine oxide toward the deprotonation

The inability to deprotonate the 2-anisyl phosphine oxide **172** led to development of a second generation route toward the desired *P*-chiral phosphine oxide **264**. It was envisaged that use of the *N*-phosphoryl oxazolidinone **268** would enable addition of the Grignard reagent derived from 1-bromobutene and thus the synthesis of the key precursor **264** (figure 19). Despite the required phosphinic chloride being known within the literature, the only reported synthesis

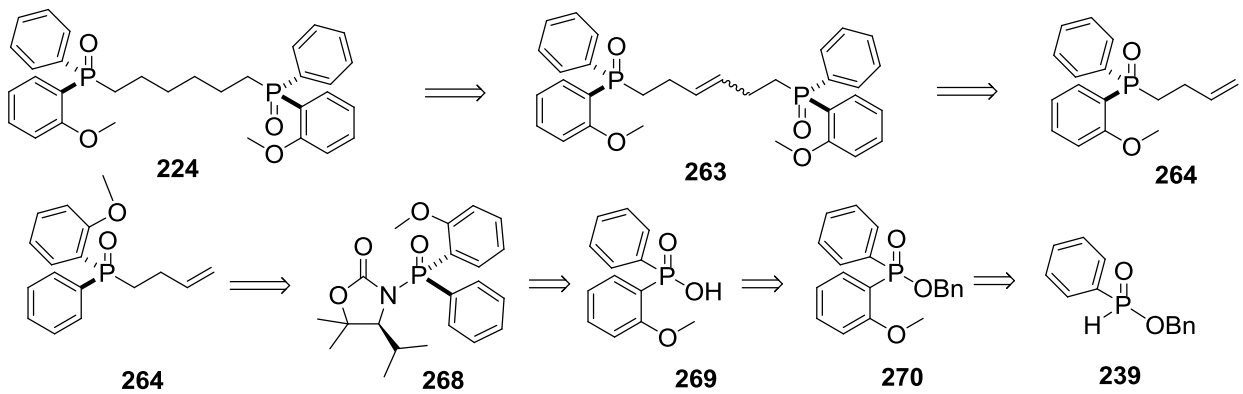
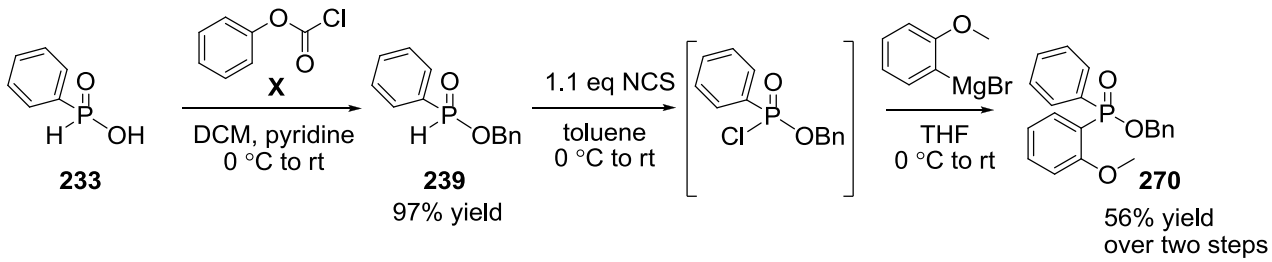


Figure (19) – The 2nd generation retrosynthetic analysis of the *bis*-*P*-chiral phosphine oxide 224

disclosed by Han required six steps and manipulation of air sensitive and pyrophoric intermediates.[122] To circumvent this issue, it was hypothesised that the phosphinic chloride could be synthesised in a single step from the benzyl phosphinate **270** through direct chlorination using NCS. To test this hypothesis, the benzyl phosphinate **270**, readily prepared from benzyl chloroformate and phenyl phosphinic acid **233** was introduced to a solution of NCS in toluene at -20 °C. Analysis of the reaction solution by ^{31}P NMR spectroscopy showed complete consumption of the starting material after 90 minutes. Filtration of the solution to remove the precipitated succinimide and introduction to a solution of excess 2-anisyl magnesium bromide enabled formation of the desired diaryl benzyl phosphinate **270** in 56% yield (scheme 154). However, it was found that this two step procedure was very precarious and difficult to reproduce with varying yields of the product obtained, and thus led to an alternate means of synthesising the species **270**.



Scheme (154) – The synthesis of the 2-anisyl benzyl phosphinate 270

Previous work on the preparation of the hydroxy containing phosphine oxide **151** derived from BINOL demonstrated the potential of a palladium catalysed cross coupling of a secondary phosphine oxide with an aryl triflate.[107-108] It was thought that if this methodology were to be extended toward the benzyl phosphinate **239** then the desired diaryl species **270** could be readily prepared in a single step (figure 20). Initially, the conditions previously used for formation of the phosphine oxide **151** were applied in the cross coupling of the benzyl phosphinate **239** and 2-iodoanisole. Analysis of the crude ^{1}H and ^{31}P NMR spectroscopic data showed 20% conversion to the desired species after 16 hours (scheme 155, table 27, entry 1).

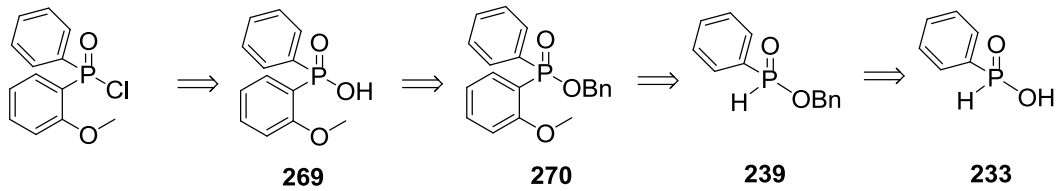
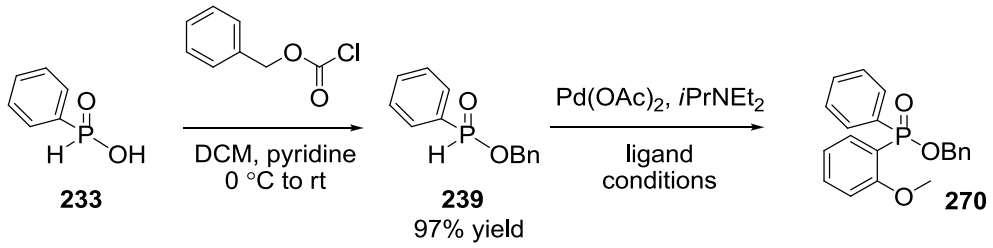


Figure (20) – The second generation retrosynthetic analysis toward the benzyl phosphinate 270



Scheme (155) – A palladium catalysed cross coupling strategy for the synthesis of the benzyl phosphinate X

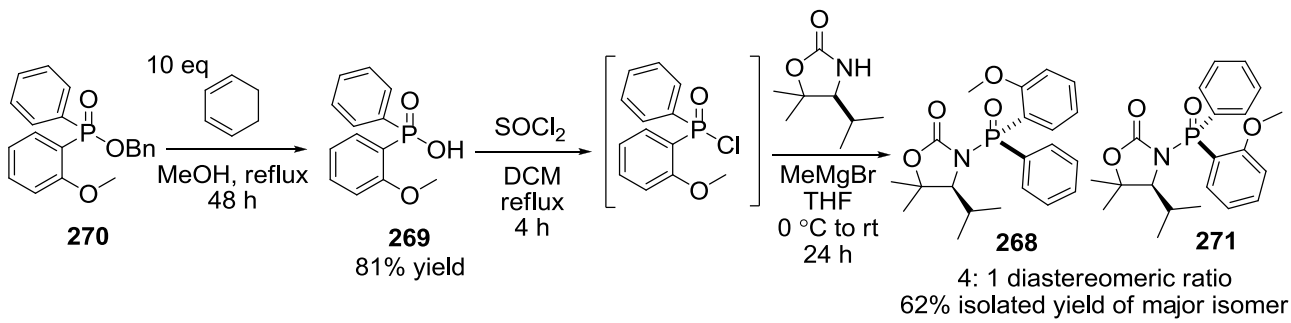
entry[a]	ligand	solvent	time / h	temperature / °C	conversion of **239** / %[b]	yield of **270** / %[c]
1	dppb	DMSO	12	120	20	-
2	dppb	MeCN	24	70	65	-
3	dppp	MeCN	24	70	58	-
4	dppe	MeCN	24	70	47	-
5	BINAP	MeCN	24	70	60	-
6	PPh_3	MeCN	24	70	30	-
7	$P(o\text{-tol})_3$	MeCN	24	70	35	-
8[d]	dppb	MeCN	48	70	100	71

[a] all reactions performed on a 1 mmol scale using 5 cm³ of solvent, 4 equivalents of base, 10 mol% loading of palladium and 10 mol% of the ligand in the dark; [b] determined by analysis of the crude ^1H and ^{31}P NMR spectroscopic data; [c] refers to yield of the isolated product; [d] 20 mol% loading of both palladium and the phosphine ligand utilised.

Table (27) – The conditions investigated for the palladium catalysed cross coupling

Changing the solvent from DMSO to acetonitrile and increasing the reaction time to 24 hours gave an increase in conversion to 65%. Screening of a range of mono and *bis*-phosphine ligands other than dppb failed to increase the degree of conversion and suggested the original ligand to be the best species. Increasing the amount of both the palladium source and the phosphine ligand however, enabled complete conversion to the diaryl benzyl phosphinate **270** after 48 hours and isolation of the compound in 71% yield after column chromatography (scheme 155, table 27, entry 8).

Use of the previously developed transfer hydrogenation conditions afforded the phosphoric acid **269**, which in turn was transformed into the phosphinic chloride in excellent yield over two steps (scheme 156). Addition of the phosphinic chloride to a solution of the SuperQuat® **174** pre-treated with one equivalent of methyl magnesium bromide afforded the *N*-phosphinyl oxazolidinone **268** and **271** in a 4:1 diastereotopic ratio and a 62% isolated yield of the major isomer (scheme 156). Interestingly, attempts to use the lithium chloride and triethylamine conditions, shown to be successful for other phosphinic chlorides, failed to afford the desired compound **268** and **271** and suggested the substituent in the 2-position of the aromatic ring provided sufficient hindrance to prevent addition to the SuperQuat® **174**.



Scheme (156) – The synthesis of the diaryl *N*-phosphinyl oxazolidinones 268 and 271

A crystal structure of the major diastereoisomer **268** showed an (R_P)-configuration around the phosphorus centre with the larger 2-anisyl ring protruding away from the *iso*-propyl group of the oxazolidinone to minimise any steric interaction (figure 21).

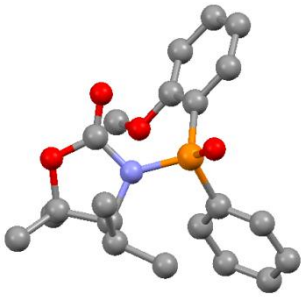
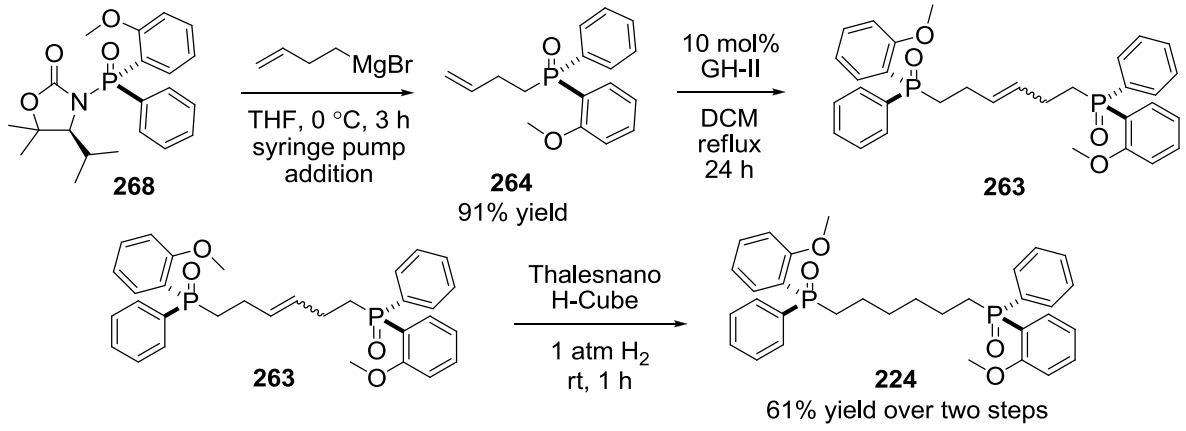


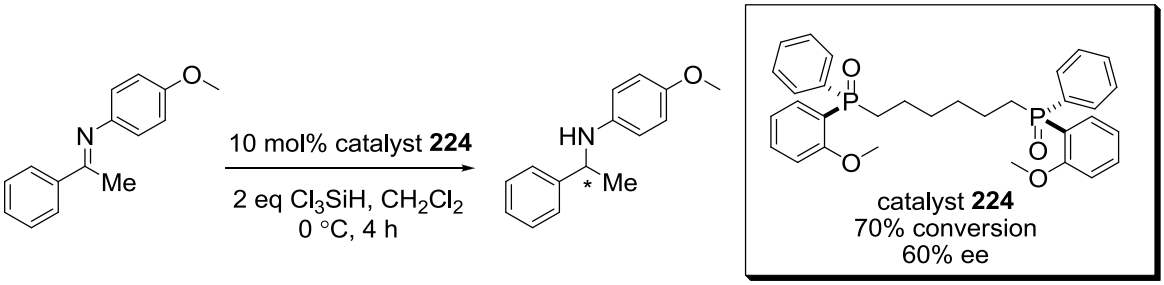
Figure (21) – The crystal structure of the major diastereoisomer of the *N*-phosphinoyl auxiliary 268

Dropwise addition of the oxazolidinone **268** to a solution of but-3-enylmagenisum bromide enabled the desired *P*-chiral phosphine oxide **264** to be obtained in excellent yield and >99% ee as determined by chiral HPLC analysis (scheme 157). Treatment of the phosphine oxide **264** with 10 mol% of Grubbs-Hoveyda second generation catalyst in DCM at reflux yielded the *bis*-*P*-chiral phosphine oxide **263** which was immediately hydrogenated using the Thalesnano H-Cube micro reactor to afford the desired catalyst **224** in good yield over the two steps.[144]



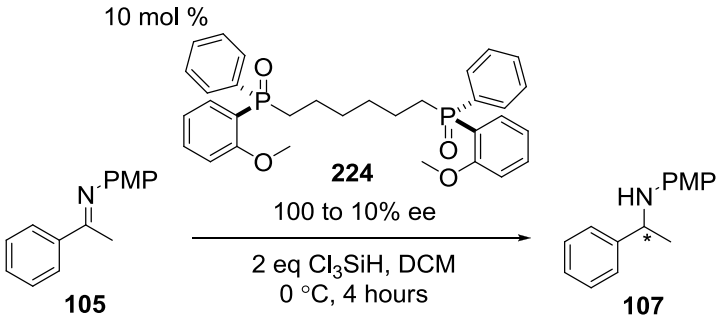
(Scheme 157) – The end game synthesis of the *P*-chiral *bis*-phosphine oxide 224

Screening of the catalyst **224** under the standard reduction conditions enabled an 88% conversion to the *N*-PMP amine **107** after four hours (scheme 158). Analysis of the enantioselectivity of the reduction showed a 60% ee and confirmed the hypothesis that two phosphine oxide moieties were required to enable high enantiocontrol.

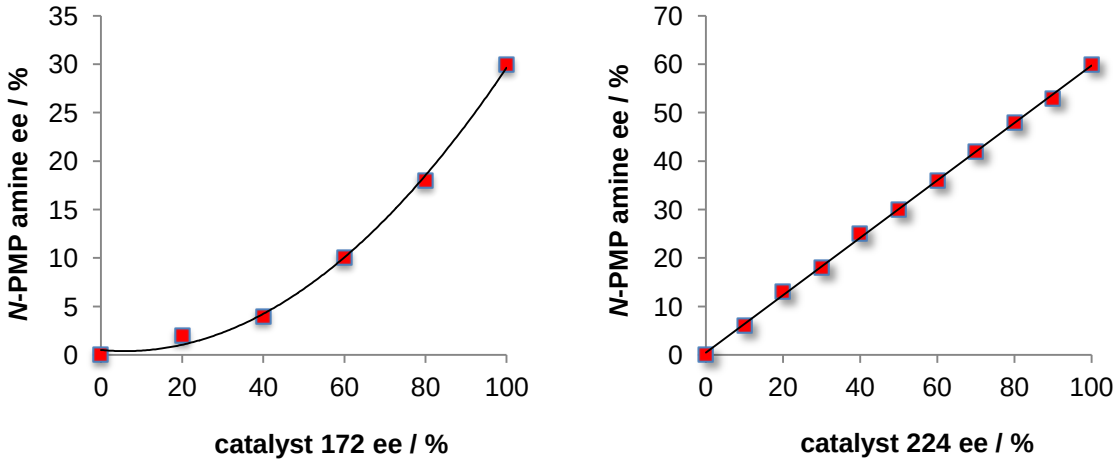


Scheme (160) – Screening of the *P*-chiral *bis*-phosphine oxide 224

To confirm the need for the two *P*-chiral phosphine oxide units, a non-linear relationship was undertaken on the catalyst **224** (scheme 159, figure 22). The observation of a direct linear relationship between the enantioselectivity of the catalyst and the enantioselectivity of the resultant *N*-PMP amine **107** confirmed that the reaction now proceeded through a pathway in which only a single molecule of the catalyst **224** was present in the transition state.



Scheme (159) – Non-linear effect study on the *bis*-*P*-chiral phosphine oxide catalyst



2-anisyl *P*-chiral catalyst **172** *bis P*-chiral catalyst **224**

Figure (22) – Non-linear effect studies on the mono and *bis*-*P*-chiral phosphine oxide catalysts

4.4 Summary

The use of a *P*-chiral phosphine oxide as a Lewis base catalyst for the enantioselective reduction of the *N*-PMP ketimine **105** has been examined. Initial studies focused upon using the work of Mislow to synthesise a library of *P*-chiral phosphine oxides. Despite being able to increase the diastereoselection of the menthyl phosphinate **167** from a 1:1 to a 3:1 diastereotopic ratio, the subsequent displacement with the Grignard reagent failed to afford the expected *P*-chiral phosphine oxide and led to an alternative auxiliary to be sought.

Han and co-workers had shown the potential of the DCG auxiliary **171** to synthesise an array of *P*-chiral vinyl phosphine oxides; however, attempts to utilise such methodology proved irreproducible. To circumvent this issue, the *N*-phosphoryl oxazolidinone **178** was developed and as a consequence enabled a range of diaryl *P*-chiral phosphine oxides to be synthesised in excellent yield and complete enantiocontrol as determined by chiral HPLC. Analysis of the optical rotation values of the phosphine oxides with those of the literature indicated an inversion of stereochemistry and suggested that the reaction proceeded through an $S_N2(P)$ mechanism.

Attempts to extend the methodology toward the addition of aliphatic Grignard reagents initially proved troublesome, with use of the conditions for aryl Grignard addition resulting in a depreciation in the enantioselectivity of the resultant *P*-chiral phosphine oxide. Development of an alternate procedure in which the oxazolidinone **178** was introduced by syringe pump to the Grignard reagent enabled the dialiphatic phosphine oxides to be isolated in good yield and >99% ee. To remove the necessity of flash column chromatography, the lipophillic oxazolidinone **183** was developed. Sequential washing of the crude reaction solution with first petroleum ether 40 – 60 °C to remove the auxiliary **184**, and then with CH_2Cl_2 enabled isolation of the *P*-chiral phosphine oxide in excellent yield and complete enantiocontrol.

Screening of the *P*-chiral phosphine oxides as catalysts identified the ortho substituted species to be the most enantioselective, with the most selective substrate identified as the 2-anisyl species **172**. Mechanistic studies on the catalyst **172** demonstrated the presence of a non-linear effect and suggested that more than one molecule of the catalyst was present in the transition state of the reduction. To try and increase the enantioselectivity of the reduction, the *bis*-*P*-chiral phosphine oxide **224** was synthesised and screened toward the reaction. Analysis of the catalyst showed an 70% conversion and 60% ee in the resultant amine and suggested the *bis*-*P*-chiral phosphine oxide to be the most superior catalytic scaffold developed toward the reduction so far.

Chapter V
Conclusions and future work

The development of new P(V) organocatalysts for the asymmetric reduction of ketimines has been examined. Screening of a range of functionality identified the *P*-chiral phosphine scaffold to be the most reactive and selective toward the reduction and suggested the requirement for the source of chirality to be in close proximity to the Lewis base. Further support for this hypothesis was obtained with the observation that catalysts bearing axial chirality or those synthesised from (*S*)-(-)-α-methylbenzylamine consistently delivered poorer enantioselectivity.

Despite a number of research groups reporting the preparation of *P*-chiral phosphine oxides, attempts to use such methodology proved problematic, with minimal substrate scope, irreproducible results and poor yields of the *P*-chiral products observed in all cases. To circumvent this issue, the readily prepared *N*-phosphinoyl oxazolidinone **178** was synthesised. Treatment of the oxazolidinone **178** with the appropiate Grignard reagent afforded the *P*-chiral phosphine oxide in excellent yield and complete enantiocontrol and represented a marked improvement in any methodology previously reported for the synthesis of such species. The incompatibility of sterically encumbered *ortho*-substituted Grignard reagents toward the transformation however, suggested a limit to the size of the substituents that the phosphorus atom could accommodate during the nucleophilic attack. Further support for this hypothesis was obtained by the observation that only methyl magnesium bromide could undergo nucleophilic attack onto the oxazolidinone **202** derived from 1-naphthyl(phenyl)phosphinic chloride **199**.

Mechanistic studies on the most selective first generation 2-anisyl catalyst **172** identified the catalyst to exhibit a non-linear effect and led to the hypothesis that more than one molecule of the catalyst was present in the transition state of the reduction. A similar observation had been noted by Sun during the development of the *S*-chiral sulfoxide **79** and as a result had led the authors to develop a second generation *bis*-*S*-chiral sulfoxide **80**, a species that delivered consistently higher reactivity and selectivity. To examine whether a similar effect could be obtained for the *P*-chiral catalyst **172**, the *bis* species **224** was prepared through expansion of the *N*-phosphinyl oxazolidinone chemistry. Evaluation of the catalyst **224** showed a 60% ee in the resultant *N*-PMP amine **107** and suggested the *bis*-*P*-chiral phosphine oxide to be the most prolific scaffold developed toward the reduction thus far. A non-linear effect study on the catalyst demonstrated a linear relationship between the enantioselectivity of the catalyst and the

enantioselectivity of the *N*-PMP amine **107** and implied that only a single molecule of the species was present in the transition state of the reduction.

Recent unpublished work in the laboratory on the trichlorosilane mediated asymmetric reduction of ketimines has identified the requirements of the catalyst to exhibit 'dual activation' and contain both a Lewis basic site for activation of the trichlorosilane and an additional basic site capable of reacting with the HCl present in the trichlorosilane solution. Mapping of these requirements onto successful catalysts reported in the literature show such species to exhibit the desired requirements. For example, Sun's *bis*-*S*-chiral sulfoxide **80** fits this criteria with the complex **273** and a more plausible catalytic species **272** that fits the propensity of the OH groups to react with trichlorosilane is depicted for the mono-sulfoxide **79** (figure 23).

With this hypothesis in mind, future work would be concerned with examining the role of the second basic site of the *P*-chiral phosphine oxide. Hybrid second generation catalysts containing either an alcohol or an imidazole or pyridine heterocycle would be envisaged to react more readily with HCl and fulfil the dual requirements of the catalyst in a more facile manner.

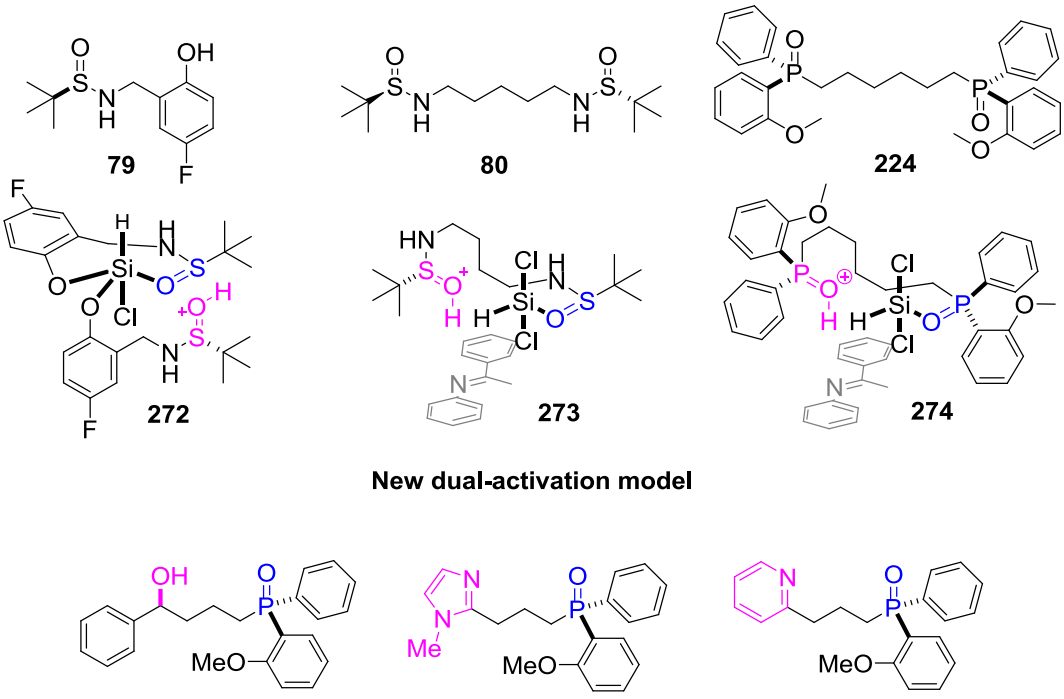


Figure (23) – The proposed 'dual activation' mode and the hypothesised 2nd generation catalysts. The Lewis basic site is marked in blue and the proposed protonated site is marked in pink

Chapter VI
Experimental

6.1 General procedure

All reactions were performed under a nitrogen atmosphere using acetone washed, flame dried glassware with magnetic stirring and if required heated through the use of Dry Syn™ blocks.
All reagents used were supplied or, as indicated prepared in the laboratory. 4Å Molecular sieves were purchased from Lancaster as 1-2 mm beads and activated by flame-drying under vacuum. Reactions that were performed at 0 °C and -78 °C used water/ice baths and acetone/dry ice baths, respectively. All solvents used in the course of the project were obtained from the departmental Grubbs solvent system and stored under a positive pressure of nitrogen. All microwave reactions were performed on a CEM Focused Microwave^{TM} synthesis system coupled with an explorer hybrid automated delivery system operating at 17 bar of pressure and 200W. Reagents that were susceptible to air were titrated against a standard solution of menthol to determine the concentration of the reagent. Phenanthroline was present as an indicator in all cases.

Analytical thin layer chromatography (TLC) was carried out utilising aluminium backed Merck TLC plates (silica gel 60 F254) and visualised with UV light (254 nm) or basic $KMnO_4$ solution. Flash column chromatography was performed using Fluorochem Limited Silica Gel 40-63μ 60Å as the stationery phase. Columns were typically packed as a slurry, and the eluent used for a particular purification noted within the individual experimental details for each reaction.

All ^{1}H, ^{13}C, ^{19}F and ^{31}P spectra were obtained using either a Bruker AC 250 or AC 400 spectrometer. Unless specifically stated, all samples were ran at 20 °C using deuteriated chloroform as the solvent. Chemical shifts are expressed in parts per million (ppm) downfield from tetramethylsilane (TMS). For ^{1}H analysis the sweep range was 12ppm whilst for ^{13}C analyses, JMODulation experiments were undertaken using a 250ppm sweep. All coupling constants given are in Hz.

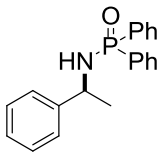
High resolution mass spectrometry (HRMS) was performed on either a MicroMass LCT spectrometer operating in electrospray mode or a MicroMass Prospec system operating in

electron impact mode**.** Infrared spectra were recorded on a Perkin-Elmer 1600 FT-IR. Specific rotations were performed on an Optical Activity Ltd. AA-10 automatic polarimeter at 589 nm (Na D-line) and $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. Melting points were measured on a Gallenkamp apparatus and are uncorrected. Elemental analysis was performed on a Perkin-Elmer 2400 CHNS/O Series II apparatus.

Determination of the enantiomeric excess of the PMP-amine and the *P*-chiral phosphine oxides were performed using a Gilson HPLC chain with an ABI Analytical Spectroflow 783 UV detector. The chiral column used for each compound and the wavelength at which the detector was set is as described in the individual experimental details. In all cases, a mixture of hexane and propan-2-ol were used as the mobile phase, the exact ratio of which is described in the individual experimental details. Mobile phase flow, unless specified otherwise, was 1.0 cm^3 min^1. Absolute configuration of the products was determined by comparison with compounds previously published.

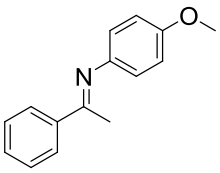
6.2 Synthesis

P,*P*-Diphenyl-*N*-[(*S*)-Phenylethyl]phosphinic amide **92**[145]



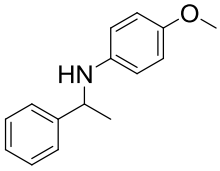
(*S*)-(-)-Methylbenzylamine (1.90 g, 2.0 cm³, 15.2 mmol) was added to a solution of freshly distilled triethylamine (3.80 g, 5.2 cm³, 45.6 mmol) in toluene (20 cm³) and the mixture cooled to -78 °C. Diphenylphosphinic chloride (3.60 g, 2.9 cm³, 15.2 mmol) was added and the solution warmed to room temperature and stirred for 90 minutes. The reaction was poured over ice water (30.0 g) and the organic layer separated. The aqueous phase was extracted with ethyl acetate (3 × 30 cm³) and the combined organic phases washed with 1M NaOH solution (10 cm³) and dried over magnesium sulfate. Removal of the solvent *in vacuo* afforded a yellow solid. Trituration of the crude material from diethyl ether furnished the title compound as a white crystalline solid (4.42 g, 91%). m.p. 187 – 188 °C (lit.[145] 187 °C); $[\alpha]_D^{25}$ -32.0 [*c* 1.0 in $CHCl_3$, lit.[145] +32.0 *c* 1.0 in $CHCl_3$ for the (*R*)-enantiomer]; δ_H (400 MHz, $CDCl_3$) 1.56 (2H, d, *J* 6.6, C*H*$_3$), 3.19 – 3.23 (1H, dd, *J* 9.8, 6.6, N*H*), 4.32 – 4.42 (1H, tq, *J* 9.8, 6.6, PhC*H*CH_3), 7.23 – 7.58 (11H, m, ArC*H*), 7.78 – 7.92 (4H, m, ArC*H*); δ_P (121 MHz, $CDCl_3$) 22.4. All data is in accordance with the literature.

4-Methoxy-*N*-(1-phenylethylideneamine) **105**[79]



Acetophenone (2.10 g, 2.0 cm³, 5 mmol) dissolved in toluene (5.0 cm³) was added in a single portion to a solution of *p*-anisidine (0.62 g, 5 mmol) and activated 4Å molecular sieves (4.50 g) in toluene (15 cm³). The solution was stirred at room temperature for 24 hours, filtered and the solvent removed *in vacuo* to afford an orange solid. Recrystallisation of the crude material from diethyl ether furnished the title compound as a yellow crystalline solid (1.11 g, 95 %). m.p. 86 °C (lit.[79] 86 °C); δ_H (400 MHz, $CDCl_3$) 2.25 (3H, s, C*H*$_3$), 3.81 (3H, s, OC*H*$_3$), 6.77 [2H, $(AX)_2$, ArC*H*], 6.92 [2H, $(AX)_2$, ArC*H*], 7.39 – 7.47 (3H, m, Ar*C*H), 7.94 – 7.99 (2H, m, ArC*H*). All data was in accordance with the literature.

N-(4-Methoxyphenyl)-1-phenylethanamine **107**[79]

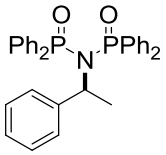


The PMP-ketimine **105** (213 mg, 1 mmol) was dissolved in methanol (2.0 cm³) and the mixture cooled to 0 °C. Sodium borohydride (76 mg, 2 mmol) was added in a single portion and the solution warmed to room temperature and stirred for 2 hours. Dichloromethane (5.0 cm³) and a 1*N* HCl solution (2.0 cm³) were added sequentially and the reaction mixture basified with a 1M NaOH solution (10 cm³). The organic phase was separated, and the aqueous phase extracted with DCM (3 × 5.0 cm³). The combined organic layers were washed with brine (10 cm³) and dried over magnesium sulfate. Removal of the solvent *in vacuo* yielded the crude material. Purification of the crude product by flash column chromatography on silica gel using an eluent of 10 % ethyl acetate : petroleum ether 40 – 60 °C afforded the title compound as a golden yellow crystalline material (212 mg, 99%). m.p. 64 °C (lit.[79] 65 °C); δ_H (400 MHz, $CDCl_3$) 1.52 (3H, d, *J* 6.7, C*H*$_3$CHN), 3.80 (3H, s, OC*H*$_3$), 3.83 (1H, bs, NH), 4.42 (1H, q, *J* 6.7, CH$_3$C*H*N), 6.48 [2H, $(AX)_2$, ArC*H*], 6.70 (2H, $(AX)_2$, ArC*H*], 7.20 – 7.25 (5H, m, ArC*H*). All data is in accordance with the literature.

General procedure A for the asymmetric reduction of the PMP-ketimine 105.

The PMP-ketimine **105** (213 mg, 1 mmol) and catalyst (0.1 mmol) were dissolved in DCM (0.5 cm³) and the solution cooled to 0 °C. Trichlorosilane (0.2 cm³, 2 mmol) was added dropwise and the reaction mixture stirred for 4 hours. The reaction solution was quenched through addition of 1N HCl solution (2.0 cm³), diluted with DCM (5.0 cm³) and basified with 1M NaOH solution (10 cm³). The organic phase was separated, and the aqueous phase extracted with DCM (3 × 5 cm³). The combined organic layers were washed with brine (10 cm³) and dried over magnesium sulfate. Removal of the solvent *in vacuo* yielded the crude material. Purification of the crude product by flash column chromatography on silica gel using an eluent of 10 % ethyl acetate: petroleum ether 40 – 60 °C afforded the desired amine **107** as a golden yellow solid.

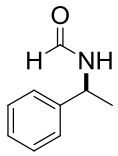
N-(Diphenylphosphino)-*P*,*P*-diphenyl-*N*-[(1*S*)-1-phenylethyl]-phosphinic amide **108**



Chlorodiphenylphosphine (4.00 g, 3.0 cm³, 20 mmol) was added dropwise to a solution of (*S*)-(-)-methylbenzyl amine (1.00 g, 1.0 cm³, 8 mmol) and freshly distilled triethylamine (3.00 g, 5.0 cm³, 33 mmol) in chloroform (20 cm³) and the mixture stirred at room temperature for 72 hours. The solution was poured over ice water (100 g) and the organic phase separated. The aqueous phase was extracted with diethyl ether (3 × 30 cm³), washed with 1M NaOH solution (20 cm³) and dried over magnesium sulfate. Removal of the solvent *in vacuo* yielded a crude yellow oil. The crude material was dissolved in anhydrous dichloromethane (20 cm³) and hydrogen peroxide solution (35%, 0.5 cm³) added. The reaction mixture was stirred for five hours before being poured into water (10 cm³). The organic phase was separated and the aqueous layer extracted with dichloromethane (3 × 10 cm³). The organic layers were combined, washed with a saturated solution of sodium sulfite (15 cm³) and dried over magnesium sulfate. Removal of the solvent *in vacuo* afforded a white solid that required no further purification (3.15 g, 72%); m.p. 143 °C; $[\alpha_D]_D^{25}$ - 38.3 (*c* 1.0 in $CHCl_3$); υ_{max} (ATR) / cm^{-1} 3269, 2960, 1546, 1431; (Found C, 73.83; H, 5.30; N, 2.56; $C_{32}H_{30}NO_2P_2$ requires C, 73.70; H, 5.60; N, 2.69%); δ_H (400 MHz, $CDCl_3$) 1.71 (3H, d, *J* 7.2, C*H*$_3$), 4.95 (1H, tq, *J* 17.4 7.2, C*H*), 7.11 – 7.42 (17H, m, ArC*H*), 7.71 – 7.83 (8H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 20.6 (*C*H3), 57.8 (*C*H), 127.1 (ArCH), 127.5 (ArCH), 127.6 (ArCH), 127.75 (ArCH), 127.78 (ArCH), 127.9 (ArCH), 128.7 (ArCH), 131.1 (ArC), 132.8 (ArCH), 132.9 (ArCH), 132.96 (ArCH), 133.1 (ArCH), 133.4 (ArC), 141.2 (Ar*C*);

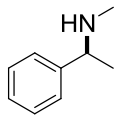
δ_P (121 MHz, $CDCl_3$) 27.8; *m/z* (TOF ES^+) 522.1757 (100%, MH^+, $C_{32}H_{30}NO_2P_2$ requires 522.1752). The presence of carbon-phosphorus splitting means that the values listed for the ^{13}C NMR spectroscopic data represent each individual signal from the spectrum.

(*S*)-(-)-α-Methylbenzyl formamide **112**[87]



(*S*)-(-)-Methylbenzylamine (1.90 g, 2.0 cm³, 15.2 mmol) was added to a solution of THF (50 cm³) and Amberlyst-15 (100 mg) at 50 °C and the mixture stirred for 15 minutes. Ethyl formate (8.80 g, 10 cm³, 119 mmol) was added dropwise and the solution heated to reflux for 24 hours. The reaction mixture was cooled to room temperature and diethyl ether added (25 cm³). The solution was filtered through a pad of Celite and the solvent removed *in vacuo* to afford the title compound as an orange oil which required no further purification (2.22 g, 100%). $[\alpha]_D^{25}$ -167 [*c* 1.0 in $CHCl_3$, lit.[87] + 167 *c* 1.0 in $CHCl_3$ for the (*R*)-enantiomer]; δ_H (400 MHz, $CDCl_3$) 1.51 (2.4H, d, *J* 6.9, C*H*$_3$ major rotamer), 1.56 (0.6H, d, *J* 6.9, C*H*$_3$ minor rotamer), 4.67 (0.2H, quintet, *J* 6.9, C*H* minor rotamer), 5.20 (0.8H, quintet, *J* 6.9, C*H* major rotamer), 6.30 (0.8H, br s, N*H* major rotamer), 6.70 (0.2H, br s, N*H* minor rotamer), 7.25 – 7.41 (5H, m, ArC*H*), 8.04 (0.2H, s, CHO minor rotamer), 8.14 (0.8H, s, C*H*O major rotamer). All data is in accordance with the literature.

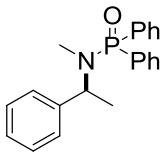
(*S*)-(-)-*N*-Methyl-α-methylbenzylamine **275**[87]



Formamide **112** (2.00 g, 13 mmol) was added to a solution of lithium aluminium hydride (2.05 g, 52 mmol) in THF (30 cm³) and the mixture heated at reflux for 18 hours. The solution was cooled to 0 °C and the excess $LiAlH_4$ destroyed through dropwise addition of water (10 cm³). Diethyl ether (50 cm³) was added and the suspension filtered through a pad of Celite. The organic phase was separated and the aqueous phase extracted with diethyl ether (3 × 20 cm³). The organic phases were combined, dried over magnesium sulfate and the solvent removed *in vacuo* to afford the title compound as a yellow oil that required no further purification (1.73 g, 94%). $[\alpha]_D^{25}$ -77.0 [*c* 1.0 in $CHCl_3$, lit.[87] + 77.0 *c* 1.0 in $CHCl_3$ for (*R*)-enantiomer]; δ_H (400

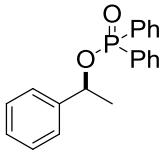
MHz, $CDCl_3$) 1.37 (3H, d, *J* 6.9, C*H*$_3$), 2.24 (3H, s, NC*H*$_3$), 3.57 (1H, q, *J* 6.9, C*H*NH), 7.16 – 7.27 (5H, m, ArC*H*). All data is in accordance with the literature.

(*S*)-*N*-Methyl-*P*,*P*-diphenyl-*N*-(1-phenylethyl)phosphinic amide **111**[87]



(*S*)-(-)-*N*-methyl-α-methylbenzylamine **275** (200 mg, 2 mmol) was added to a solution of freshly distilled triethylamine (0.5 cm³, 3 mmol) and dichloromethane (10 cm³) and the mixture cooled to 0 °C. Diphenylphosphinic chloride (0.4 cm³, 2 mmol) was added dropwise and the solution warmed to room temperature and stirred for 24 hours. The mixture was poured into water (5.0 cm³) and the organic layer separated. The aqueous phase was extracted with dichloromethane (3 × 10 cm³) and the combined organic layers washed with a saturated solution of ammonium chloride (10 cm³) and dried over magnesium sulfate. Removal of the solvent *in vacuo* afforded a yellow oil. Purification of the crude material by flash column chromatography on silica gel using an eluent of 50% ethyl acetate: petroleum ether 40 – 60 °C afforded the title compound as a white crystalline solid (220 mg, 44%). m.p. 82 °C (lit.[87] 82 - 83 °C); $[\alpha]_D^{25}$ -50.1 [*c* 1.0 in $CHCl_3$, lit.[87] + 50.3 *c* 1.0 in $CHCl_3$ for the (*R*)-enantiomer]; δ_H (400 MHz, $CDCl_3$) 1.61 (3H, d, *J* 7.1, C*H*$_3$), 2.38 (3H, d, $J_{H\text{-}P}$ 11.0, NC*H*$_3$), 4.74 (1H, app. quint, *J* 7.1, C*H*NCH_3), 7.26 – 7.30 (1H, m, Ar*H*), 7.36 – 7.39 (2H, m, Ar*H*), 7.44 – 7.53 (8H, m, Ar*H*), 7.88 – 7.96 (4H, m, Ar*H*); δ_P (121 MHz, $CDCl_3$) 30.8. All data is in accordance with the literature.

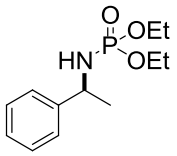
(*S*)-1-Phenylethyl diphenylphosphinate **114**[89]



(*S*)-(-)-Phenylethanol (200 mg, 0.2 cm³, 2 mmol) was added to a solution of freshly distilled pyridine (0.4 cm³, 5 mmol) and anhydrous dichloromethane (10 cm³) at -10 °C. Diphenylphosphinic chloride (580 mg, 0.5 cm³, 3 mmol) was added dropwise and the solution stirred for 30 minutes before being warmed to room temperature. The reaction mixture was stirred for a further 90 minutes before being quenched with water (5.0 cm³). The organic phase was separated and the aqueous layer extracted with diethyl ether (3 × 10 cm³). The organic phases were combined, washed with a 1M NaOH solution (10 cm³) and dried over magnesium

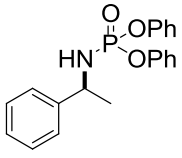
sulfate. Removal of the solvent *in vacuo* yielded a crude yellow oil. Purification of the crude material by flash column chromatography on silica gel using an eluent of 30% methanol: *n*-hexane afforded the title compound as a white crystalline solid (246 mg, 50%). m.p. 81 - 82°C (lit.[89] 81 – 81.5 °C); $[\alpha]_D^{25}$ -38.0 (*c* 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.66 (3H, d, *J* 6.6, C*H*$_3$), 5.53 (1H, dq, *J* 9.1 6.6, C*H*$_3$), 7.27 – 7.36 (7H, m, Ar*H*), 7.41 – 7.56 (4H, m, ArC*H*), 7.63 – 7.74 (2H, m, ArC*H*), 7.82 – 7.92 (2H, m, ArC*H*); δ_P (121 MHz, $CDCl_3$) 31.7. No optical rotation value is reported within the literature, otherwise all other data is in accordance.

P,*P*-Diethylester-*N*-[(*1S*)-Phenylethyl]phosphoramidate **115**[90]



(*S*)-(-)-Methylbenzylamine (3.0 cm³, 20 mmol) was added to a solution of freshly distilled triethylamine (4.0 cm³, 30 mmol) and dichloromethane (20 cm³) at 0 °C. Diethyl chlorophosphate (3.0 cm³, 20 mmol) was added dropwise and the reaction mixture warmed to room temperature and stirred for 8 hours. The reaction solution was quenched through addition of water (10 cm³) and the organic layer separated. The aqueous phase was extracted with diethyl ether (3 × 15 cm³) and the combined organic phases washed with a saturated aqueous solution of $NaHCO_3$ (10 cm³) and dried over magnesium sulfate. Removal of the solvent *in vacuo* yielded a crude yellow oil. Purification of the crude material by vacuum distillation afforded the title compound as a colourless oil (3.40 g, 75%). b.p. 132 °C / 0.06 mmHg (lit.[90] 140 °C / 0.08 mmHg); $[\alpha]_D^{25}$ - 40.1 [*c* 1.0 in acetone, lit.[90] + 40.6 *c* 1.0 in acetone for the (*R*)-enantiomer]; δ_H (250 MHz, $CDCl_3$) 1.11 [3H, t, *J* 7.1, 1 × $(OCH_2CH_3)_2$], 1.29 [3H, t, *J* 7.1, 1 × $(OCH_2CH_3)_2$], 1.13 (3H, d, *J* 6.8 0.7, C*H*$_3$), 3.13 (1H, t, *J* 9.7, N*H*), 3.65 – 3.81 [1H, m, 1 × $(OCHHCH_3)_2$], 3.90 – 4.13 [3H, m, 3 × $(OCHHCH_3)_2$], 4.23 – 4.27 (1H, m, C*H*), 7.20 – 7.29 (5H, m, ArC*H*); δ_P (121 MHz, $CDCl_3$) 7.40. All data is in accordance with that of the literature.

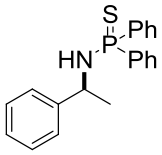
P,*P*-Diphenylester-*N*-[(*1S*)-Phenylethyl]phosphoramidate **114**[89]



Diphenylphosphoryl chloride (4.00 g, 3.0 cm³, 15 mmol) was added dropwise to a solution of freshly distilled triethylamine (4.00 g, 5.0 cm³, 46 mmol) and (*S*)-(-)-methylbenzylamine (2.00 g, 2.0 cm³, 15 mmol) in toluene (20 cm³) at 0 °C. The reaction mixture was stirred for 2 hours

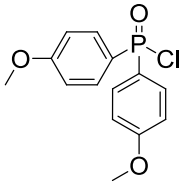
before being poured into ice water (100 cm³). The organic layer was separated and the aqueous phase extracted with dichloromethane (3 × 30 cm³). The organic layers were combined, washed with a saturated aqueous solution of $NaHCO_3$ (10 cm³) and dried over magnesium sulfate. Removal of the solvent *in vacuo* yielded a crude yellow solid. Trituration of the crude material with diethyl ether afforded the title compound as a white crystalline solid (4.7 g, 91%). m.p. 104 – 105 °C (lit.[89] 104 – 106 °C); $[\alpha]_D^{25}$- 34.2 (*c* 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.49 (3H, d, *J* 6.8, CHC*H*$_3$), 3.87 – 4.04 (1H, m, N*H*), 4.56 - 4.65 (1H, m, C*H*CH_3), 7.02 – 7.34 (15H, m, ArC*H*); δ_P (121 MHz, $CDCl_3$) -0.01. No optical rotation value is stated within the literature, otherwise all other data is in accordance.

(*S*)-*P*, *P*-Diphenyl-*N*-(1-phenylethyl)phosphinothioic amide **117**[91]



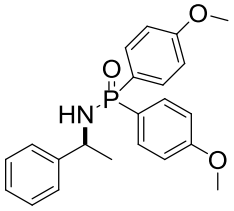
Diphenylphosphinothioic chloride (3.5 cm³, 15.2 mmol) was added dropwise to a solution of (*S*)-(-)-methylbenzylamine (2.0 cm³, 15.2 mmol) and freshly distilled triethylamine (5.2 cm³, 45.6 mmol) in dichloromethane (15 cm³) at 0 °C. The reaction mixture was stirred for 3 hours before being poured into ice water (100 cm³). The organic phase was separated and the aqueous layer extracted with ethyl acetate (3 × 20 cm³). The organic layers were combined, washed with brine (10 cm³) and dried over magnesium sulfate. Removal of the solvent *in vacuo* afforded a yellow solid. Trituration of the crude material from diethyl ether furnished the title compound as a white crystalline solid (4.43 g, 95%). m.p. 174 °C; $[\alpha]_D^{25}$ - 22.0 (*c* 1.0 in $CHCl_3$); (Found C, 71.53; H, 5.82; N, 3.91; $C_{20}H_{20}NPS$ requires C, 71.19; H, 5.97; N, 4.15%); υ_{max} (ATR) / cm^{-1} 3272, 2971, 1818, 1586, 1493; δ_H (400 MHz, $CDCl_3$) 1.55 (3H, d, *J* 6.9, C*H*$_3$), 2.86 (1H, dd, *J* 8.4 4.8, N*H*), 4.55 – 4.65 (1H, m, C*H*), 7.23 – 7.51 (11H, m, ArC*H*), 7.87 – 7.93 (2H, m, ArC*H*), 8.04 – 8.09 (2H, m, ArC*H*); δ_P (101 MHz, $CDCl_3$) 58.6; *m/z* (TOF ES^+) 338.1117 (100%, MH^+, $C_{20}H_{21}NPS$ requires 338.1132). No mass spectrometry, infra red, optical rotation or melting point data is reported within the literature. All other data is in accordance.

bis-(4-Methoxyphenyl) phosphinic chloride **119**[92]



bis-(4-Methoxyphenyl) phosphoric acid (5.00 g, 18 mmol) was dissolved in dichloromethane (100 cm³) and the solution cooled to 0 °C. Oxalyl chloride (9.0 cm³, 45 mmol) was added dropwise over a period of 60 minutes and the reaction mixture warmed to room temperature and stirred at room temperature for 18 hours. The solvent was removed *in vacuo* to afford the title compound as a yellow oil that required no further purification (4.4 g, 89%). δ_H (250 MHz, $CDCl_3$) 3.88 (6H, s, OC*H*$_3$), 6.97 – 7.04 (4H, m, ArC*H*), 7.74 – 7.84 (4H, m, ArC*H*); δ_P (101 MHz, $CDCl_3$) 45.0. All data is in accordance with the literature.

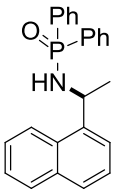
(*S*)-(-)-*P*,*P*-*bis*(4-Methoxyphenyl)-*N*-(1-phenylethyl)phosphinamide **120**



bis-(4-Methoxyphenyl) phosphoric acid chloride **119** (1.00 g, 4 mmol) was added dropwise to a solution of (*S*)-(-)-methylbenzylamine (0.40 g, 0.4 cm³, 3 mmol) and freshly distilled triethylamine (0.50 g, 0.7 cm³, 6 mmol) in dichloromethane (10 cm³) at 0 °C. The mixture was warmed to room temperature and stirred for 6 hours before being poured over ice water (100 g). The organic phase was separated and the aqueous phase extracted with diethyl ether (3 × 15 cm³). The organic layers were combined, washed with a 1M NaOH solution (15 cm³), brine (10 cm³) and dried over magnesium sulfate. Removal of the solvent *in vacuo* furnished a yellow oil. Purification of the crude material by flash column chromatography on silica gel using an eluent of 60% ethyl acetate: petroleum ether 40 – 60 °C afforded the title compound as a white crystalline material (840 mg, 73%). m.p. 171 °C; $[\alpha]_D^{25}$ + 28.0 (*c* 0.5 in $CHCl_3$); (Found C, 69.05; H, 6.14; N, 3.68; $C_{22}H_{24}NO_3P$ requires C, 69.28; H, 6.34; N, 3.67%); υ_{max} (ATR) / cm^{-1} 3123, 3089, 1599, 1576, 1457, 1227; δ_H (400 MHz, $CDCl_3$) 1.58 (3H, d, *J* 6.6, C*H*$_3$), 3.12 (1H, dd, *J* 9.8 4.9, N*H*), 3.81 (3H, s, OC*H*$_3$), 3.83 (3H, s, OC*H*$_3$), 4.37 (1H, tq, *J* 9.8 6.6, C*H*), 6.87 (2H, dd, *J* 8.8 2.5, ArC*H*), 6.94 (2H, dd, *J* 8.8 2.5, ArC*H*), 7.24 – 7.35 (5H, m, ArC*H*), 7.74 (2H, dd, *J* 11.5 8.8, ArC*H*), 7.82 (2H, dd, *J* 11.5 8.8, ArC*H*); δ_C (100 MHz, $CDCl_3$) 26.1 (d, $J_{C\text{-}P}$ 4.0, *C*H$_3$), 50.9 (*C*H), 55.3 (O*C*H$_3$), 55.4 (O*C*H$_3$), 113.8 (d, $J_{C\text{-}P}$ 5.3, 2 × Ar*C*H), 114.0 (d, $J_{C\text{-}P}$ 5.3, 2

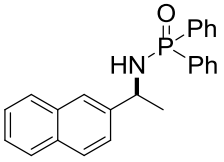
× Ar*C*H), 123.6 (d, $J_{C\text{-}P}$ 121.2, Ar*C*), 125.0 (d, $J_{C\text{-}P}$ 119.7, Ar*C*), 126.0 (2 × Ar*C*H), 127.0 (Ar*C*H), 128.6 (2 × Ar*C*H), 133.6 (d, $J_{C\text{-}P}$ 10.7, 2 × Ar*C*H), 134.2 (d, $J_{C\text{-}P}$ 10.7, 2 × Ar*C*H), 145.2 (d, $J_{C\text{-}P}$ 6.4, Ar*C*), 162.3 (2 × Ar*C*); δ_P (101 MHz, $CDCl_3$) 22.7; *m/z* (TOF ES^+) 382.1563 (100%, MH^+, $C_{22}H_{25}NO_3P$ requires 382.1572).

(*S*)-*N*-[1-(Naphthalen-1-yl)ethyl]-*P*,*P*-diphenylphosphinamide **121**[92]



(*S*)-1-(Naphthalen-1-yl)ethanamine (0.30 g, 2 mmol) was dissolved in a solution of triethylamine (0.30 g, 0.4 cm³, 3 mmol) and dichloromethane (10 cm³) and the mixture cooled to 0 °C. Diphenylphosphinic chloride (0.4 cm³, 2 mmol) was added dropwise and the solution warmed to room temperature and stirred for 18 hours. The reaction mixture was poured into ice water (50 g) and the organic layer separated. The aqueous phase was extracted with dichloromethane (3 × 10 cm³) and the combined organic layers washed with brine (10 cm³) and dried over magnesium sulfate. Removal of the solvent *in vacuo* yielded a yellow solid. Recrystallisation of the crude material from diethyl ether afforded the title compound as a white crystalline solid (500 mg, 91%). m.p. 133 °C; $[\alpha]_D^{25}$ - 27.0 (*c* 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.71 (3H, d, *J* 6.7, CH_3), 3.40 (1H, dd, *J* 8.3 6.7, N*H*), 5.17 – 5.32 (1H, m, C*H*), 7.24 – 7.54 (9H, m, ArC*H*), 7.63 – 7.65 (1H, m, ArC*H*), 7.74 – 7.98 (7H, m, ArC*H*); δ_P (121 MHz, $CDCl_3$) 22.9. No melting point or optical rotation data is reported within the literature, otherwise all other data is in accordance.

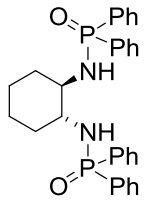
(*S*)-*N*-[1-(Naphthalen-2-yl)ethyl]-*P*,*P*-diphenylphosphinamide **122**[92,93]



(*S*)-1-(Naphthalen-2-yl)ethanamine (342 mg, 2 mmol) was dissolved in a solution of triethylamine (0.4 cm³, 3 mmol) and dichloromethane (10 cm³) and the mixture cooled to 0 °C. Diphenylphosphinic chloride (0.4 cm³, 2 mmol) was added dropwise and the reaction solution warmed to room temperature and stirred for 18 hours. The reaction mixture was poured into ice water (50 g) and the organic layer separated. The aqueous phase was extracted with dichloromethane (3 × 10 cm³) and the combined organic layers washed with brine (10 cm³) and

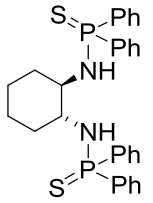
dried over magnesium sulfate. Removal of the solvent *in vacuo* yielded a yellow solid. Trituration of the crude material from diethyl ether afforded the title compound as a white crystalline solid (450 mg, 81%). m.p. 148 °C; $[\alpha]_D^{25}$ - 51.0 (*c* 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.68 (3H, d, *J* 6.8, C*H*$_3$), 3.31 – 3.35 (1H, m, N*H*), 4.54 – 4.62 (1H, m, C*H*), 7.28 (9H, m, ArC*H*), 7.67 (1H, app s, ArC*H*), 7.78 – 7.98 (7H, m, Ar*C*H); δ_P (121 MHz, $CDCl_3$) 22.7. No melting point or optical rotation data is reported within the literature, otherwise all other data is in accordance.

N,*N*'-[(1*R*,2*R*)-Cyclohexane-1,2-diyl]-*bis*(*P*,*P*-diphenylphosphinamide) **123**[94]



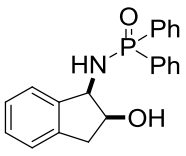
(1*R*,2*R*)-1,2-Cyclohexanediamine (1.05 g, 10 mmol) was added to a solution of freshly distilled triethylamine (6.0 cm³, 40 mmol) and dichloromethane (20 cm³) and the mixture cooled to 0 °C. Diphenylphosphinic chloride (4.0 cm³, 22 mmol) was added dropwise over a period of 15 minutes and the solution warmed to room temperature and stirred for 18 hours. The mixture was poured into ice water (50 g) and the organic phase separated. The aqueous layer was extracted with ethyl acetate (3 × 25 cm³) and the combined organic phases washed with brine (15 cm³) and dried over magnesium sulfate. Removal of the solvent *in vacuo* yielded a yellow oil. Purification of the crude material by flash column chromatography on silica gel using an eluent of 50% ethyl acetate: petroleum ether 40 – 60 °C afforded the title compound as a colourless oil (2.60 g, 50%). $[\alpha]_D^{25}$ + 22.0 (*c* 1.0 in $CHCl_3$); δ_H ($CDCl_3$, 400 MHz) 1.03 – 1.14 (2H, m, 2 × C*H*H), 1.25 – 1.29 (2H, m, 2 × C*H*H), 1.53 – 1.55 (2H, m, 2 × C*H*H), 2.00 – 2.06 (2H, m, 2 × C*H*H), 4.25 (2H, app. t, *J* 7.3, 2 × C*H*N), 7.32 – 7.36 (4H, m, Ar*C*H), 7.44 – 7.54 (8H, m, ArC*H*), 7.78 – 7.82 (4H, m, ArC*H*), 7.97 – 8.02 (4H, m, ArC*H*); δ_P ($CDCl_3$, 101 MHz) 25.3. No optical rotation value is reported within the literature, all other data is in accordance with the literature.

N,*N'*-[(1*R*,2*R*)-Cyclohexane-1,2-diyl]-*bis*(*P*,*P*-diphenylphosphinothioic amide) **124**



(1*R*,2*R*)-Cyclohexanediamine (1.00 g, 10 mmol) was added to a solution of freshly distilled triethylamine (6.0 cm³, 40 mmol) and dichloromethane (20 cm³) and the mixture cooled to 0 °C. Diphenylphosphinothioic chloride (4.0 cm³, 22 mmol) was added dropwise over a period of 15 minutes and the solution warmed to room temperature and stirred for 18 hours. The mixture was poured into ice water (100 g) and the organic layer separated. The aqueous phase was extracted with ethyl acetate (3 × 25 cm³) and the combined organic layers washed with brine (15 cm³) and dried over magnesium sulfate. Removal of the solvent *in vacuo* yielded a yellow oil. Purification of the crude material by flash column chromatography on silica gel using an eluent of 10% ethyl acetate: petroleum ether 40 – 60 °C afforded the title compound as a white solid (3.80 g, 70%). m.p. 121 °C; $[\alpha]_D^{25}$ + 20.0 (*c* 1.0 in $CHCl_3$); υ_{max} / cm^{-1} (ATR) 3207, 3054, 2935, 1437; δ_H ($CDCl_3$, 400 MHz) 1.08 – 1.14 (2H, m, 2 × C*H*H), 1.28 – 1.39 (2H, m, 2 × C*H*H), 1.51 – 1.56 (2H, m, 2 × C*H*H), 1.86 – 1.91 (2H, m, 2 × C*H*H), 3.28 – 3.41 (2H, m, 2 × N*H*), 4.05 (2H, app. t, *J* 5.9, C*H*N), 7.33 – 7.52 (12H, m, ArC*H*), 7.80 – 7.87 (4H, m, Ar*C*H), 8.06 – 8.11 (4H, m, Ar*C*H); δ_C ($CDCl_3$, 100 MHz) 25.0 (2 × CH_2), 35.7 (2 × CH_2), 55.6 (d, $J_{C\text{-}P}$ 5.0, 2 × *C*HN), 128.2 (d, $J_{C\text{-}P}$ 11.4, 4 × Ar*C*H), 128.3 (d, $J_{C\text{-}P}$ 10.7, 4 × Ar*C*H), 131.2 (d, $J_{C\text{-}P}$ 11.4, 4 × Ar*C*H), 131.5 (d, $J_{C\text{-}P}$ 3.0, 2 × Ar*C*H) 131.6 (d, $J_{C\text{-}P}$ 3.0, 2 × Ar*C*H), 132.3 (d, $J_{C\text{-}P}$ 11.4, 4 × Ar*C*H), 134.0 (d, $J_{C\text{-}P}$ 74.7, 2 × Ar*C*), 135.1 (d, $J_{C\text{-}P}$ 76.9, 2 × Ar*C*); δ_P ($CDCl_3$, 101 MHz) 60.6; *m/z* (TOF ES^+) 547.1558 (100%, MH^+, $C_{30}H_{33}N_2P_2S_2$ requires 547.1561).

N-[(1*R*,2*S*)-2-Hydroxy-2,3-dihydro-1*H*-inden-1-yl]-*P*,*P*-diphenylphosphinamide **126**[96]



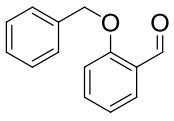
Trimethylsilyl chloride (0.70 g, 0.8 cm³, 7 mmol) was added dropwise to a solution of (1*R*, 2*S*)-Aminoindan-2-ol **125** (1.00 g, 6 mmol) and freshly distilled triethylamine (1 cm³, 7 mmol) in dichloromethane (10 cm³) at 0 °C and the mixture stirred for 18 hours. The mixture was cooled to 0 °C and triethylamine (1.00 g, 2.0 cm³, 13 mmol) and diphenylphosphinic chloride (2.00 g, 1.0 cm³, 6 mmol) added sequentially. The solution was warmed to room temperature and stirred for a further 18 hours. The reaction was poured into ice water (50 cm³) and the organic phase

separated. The aqueous layer was extracted with dichloromethane (3 × 10 cm³) and the combined organic phases washed with a saturated solution of NH_4Cl solution (10 cm³), water (10 cm³), brine (10 cm³) and dried over magnesium sulfate. Removal of the solvent *in vacuo* afforded the silyl protected product as a colourless oil. The TMS-protected product was dissolved in methanol (15 cm³) and acetic acid (15 – 20 drops) added. The solution was stirred overnight and the solvent removed *in vacuo* to yield a crude yellow oil. The crude material was purified by flash column chromatography on silica gel using an eluent of 10% methanol: dichloromethane to furnish the title compound as a colourless oil (1.05 g, 44%). $[\alpha]_D^{25}$ + 17.0 (*c* 1.0 in $CHCl_3$); δ_H ($CDCl_3$, 400 MHz) 2.99 (1H, dd, *J* 16.8, 2.1, 1 × C*H*H), 3.09 (1H, dd, *J* 16.8, 5.7, 1 × C*H*H), 3.72 (1H, dd, *J* 5.7, 2.8, N*H*), 4.30 (1H, br. s, O*H*), 4.48 (1H, quint, *J* 5.7, C*H*N), 4.59 (1H, td, *J* 5.7, 2.1, C*H*OH) 7.22 – 7.29 (3H, m, Ar*C*H), 7.30 – 7.44 (7H, m, Ar*C*H), 7.93 – 7.99 (2H, m, Ar*C*H), 8.06 – 8.13 (2H, m, Ar*C*H); δ_P ($CDCl_3$, 101 MHz) 25.7. No optical rotation value is reported within the literature, all other data is in accordance.

General procedure B for the benzyl protection of the salicylaldehyde derivatives

Potassium carbonate (11.00 g, 82 mmol) was added in a single portion to a solution of the hydroxy-benzaldehyde in DMF (20 cm³). Benzyl bromide (6.0 cm³, 50 mmol) was added dropwise and the reaction mixture heated at 60 °C for 12 hours. The solution was cooled to room temperature and diluted with ethyl acetate (100 cm³) and water (50 cm³). The organic phase was separated, washed once with a saturated solution of ammonium chloride (50 cm³), twice with brine (2 × 50 cm³) and dried over magnesium sulfate. Removal of the solvent *in vacuo* yielded the crude material. Purification of the crude material occurred as described in the individual experimental details.

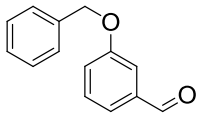
2-(Benzyloxy)-benzaldehyde **132**[146]



Prepared according to general procedure **B** using 2-hydroxybenzaldehyde (5.00 g, 41 mmol). Removal of the solvent *in vacuo* yielded a yellow oil. Purification of the crude material by flash column chromatography on silica gel using an eluent of 2% ethyl acetate: petroleum ether 40-60 °C afforded the title compound as a colourless oil (7.10 g, 82%). δ_H (400 MHz, $CDCl_3$) 5.22 (2H, s, OCH_2), 7.05 – 7.09 (2H, m, ArC*H*), 7.36 – 7.49 (5H, m, ArC*H*), 7.54 – 7.58 (1H, m,

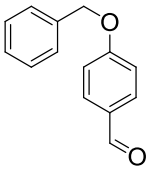
ArC*H*), 7.88 (1H, dd, *J* 7.9, 1.8, ArC*H*), 10.60 (1H, s, C*H*O). All data is in accordance with the literature.

3-(Benzyloxy)benzaldehyde **276**[147]



Prepared according to general procedure **B** using 3-hydroxybenzaldehyde (5.00 g, 41 mmol). Removal of the solvent *in vacuo* yielded a yellow solid. Recrystallisation of the crude material from ethanol afforded the title compound as a white crystalline solid (6.20 g, 71%). m.p. 57 - 58 °C (lit.[147] 58 °C); δ_H (400 MHz, $CDCl_3$) 5.14 (2H, s, OCH_2), 7.29 (1H, dt, *J* 7.4, 2.4, ArC*H*), 7.36 – 7.52 (8H, m, ArC*H*), 9.99 (1H, s, C*H*O). All data is in accordance with the literature.

4-(Benzyloxy)benzaldehyde **277**[147]



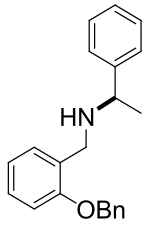
Prepared according to general procedure **B** using 4-hydroxybenzaldehyde (5.00 g, 41 mmol). Removal of the solvent *in vacuo* afforded a crude yellow solid. Recrystallisation of the crude material from ethanol afforded the title compound as a white crystalline solid (6.40 g, 73%). m.p. 72 °C (lit.[147] 72 °C); δ_H (400 MHz, $CDCl_3$) 5.16 (2H, s, OCH_2), 7.10 (2H, app. d, *J* 8.5, ArC*H*), 7.36 – 7.48 (5H, m, ArC*H*), 7.86 (2H, app. d, *J* 8.8, ArC*H*), 9.90 (1H, s, C*H*O). All data is in accordance with the literature.

General procedure C for the reductive amination of the benzyl protected salicylaldehyde derivatives and (*S*)-(-)-methylbenzylamine

The benzyl protected hydroxybenzaldehyde was added to a solution of methanol (20 cm³), (*S*)-methylbenzylamine (2.0 cm³, 14 mmol) and 4 Å molecular sieves (2.00 g) and the solution heated at reflux for 18 hours. The reaction mixture was cooled to 0 °C and sodium borohydride (1.90 g, 50 mmol) added portionwise over a period of 30 minutes. The solution was returned to room temperature and stirred for 90 minutes. The reaction mixture was quenched through addition of saturated ammonium chloride solution (15 cm³) and basified with an aqueous solution of 1M NaOH (30 cm³). The aqueous phase was extracted with dichloromethane (3 × 30 cm³) and the combined organic layers washed with brine (10 cm³) and dried over magnesium

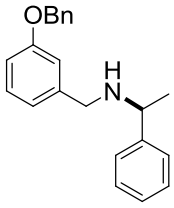
sulfate. Removal of the solvent *in vacuo* afforded the crude material. Purification of the crude material occurred as described in the individual experimental details.

(*S*)-*N*-[2-(Benzyloxy)benzyl)-1-phenylethanamine] **131**



Prepared according to general procedure **C** using 2-(benzyloxyl)-benzaldehyde **132** (3.00 g, 14 mmol). Purification of the crude material by flash column chromatography on silica gel using an eluent of 30% ethyl acetate: petroleum ether 40 – 60 °C afforded the title compound as a colourless oil (3.60 g, 82%). $[\alpha]_D^{25}$ - 21.0 (*c* 1.0 in $CHCl_3$); (Found C, 83.54; H, 7.01; N, 4.33; $C_{22}H_{23}NO$ requires C, 83.24; H, 7.30; N, 4.41%); υ_{max} (ATR) / cm^{-1} 3029, 2924, 1601, 1492, 1451; δ_H (400 MHz, $CDCl_3$) 1.33 (3H, d, *J* 6.6, C*H*$_3$), 3.60 (1H, d, *J* 13.2, C*H*H), 3.75 – 3.80 (2H, m, C*H*H and C*H*CH_3), 5.08 (1H, *J* 7.1, OC*H*H), 5.14 (1H, *J* 7.1, OC*H*H), 6.92 – 6.97 (2H , m, ArC*H*), 7.19 – 7.43 (12H, m, ArC*H*); δ_C (100 MHz, $CDCl_3$) 24.5 (*C*H_3), 47.7 (*C*H_2NH), 57.3 (*C*HNH), 70.0 (O*C*H_2), 111.6 (Ar*C*H), 120.7 (Ar*C*H), 126.7 (Ar*C*H), 126.8 (2 × Ar*C*H), 127.4 (2 × Ar*C*H), 127.9 (Ar*C*H), 128.2 (Ar*C*H), 128.4 (2 × Ar*C*H), 128.6 (2 × Ar*C*H), 128.9 (Ar*C*), 130.3 (Ar*C*H), 137.1 (Ar*C*), 145.7 (Ar*C*), 156.9 (Ar*C*); *m/z* (TOF ES^+) 318.1852 (100%, MH^+, $C_{22}H_{24}NO$ requires 318.1858).

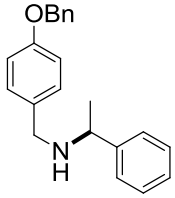
(*S*)-*N*-[3-(Benzyloxy)benzyl)-1-phenylethanamine] **278**



Prepared according to general procedure **C** using 3-(benzyloxyl)-benzaldehyde **276** (3.00 g, 14 mmol). Purification of the crude material by flash column chromatography on silica gel using an eluent of 30% ethyl acetate: petroleum ether 40 - 60 °C afforded the title compound as a colourless oil (3.20 g, 72%). $[\alpha]_D^{25}$- 23.0 (*c* 1.0 in $CHCl_3$); (C, 83.48, H, 7.49, N, 4.25; $C_{22}H_{23}NO$ requires C, 83.24, H, 7.30, N, 4.41%); ν_{max} (ATR) / cm^{-1} 3029, 1610, 1510, 1380; δ_H (400 MHz, $CDCl_3$) 1.38 (3H, d, *J* 6.6, C*H*$_3$), 1.62 (1H, br. s, N*H*), 3.59 (1H, d, *J* 13.2, C*H*H), 3.63 (1H, d, *J* 13.2, C*H*H), 3.82 (1H, q, *J* 6.6, C*H*$_3$), 5.08 (2H, s, OC*H*$_2$), 6.87 – 6.91 (2H, m,

ArC*H*), 6.97 (1H, app. s, ArC*H*), 7.23 – 7.36 (11H, m, ArC*H*); δ_C (100 MHz, $CDCl_3$) 24.5 (*C*H_3), 51.5 (*C*H_2), 57.4 (*C*H), 69.9 (O*C*H_2), 113.2 (Ar*C*H), 114.6 (Ar*C*H), 120.7 (Ar*C*H), 126.7 (2 × Ar*C*H), 126.9 (Ar*C*H), 127.5 (2 × Ar*C*H), 127.9 (Ar*C*H), 128.4 (2 × Ar*C*H), 128.6 (2 × Ar*C*H), 129.4 (Ar*C*H), 137.1 (Ar*C*), 145.5 (Ar*C*), 158.9 (Ar*C*), 171.5 (Ar*C*); *m/z* (TOF ES^+) 318.1854 (100%, MH^+, $C_{22}H_{24}NO$ requires 318.1858).

(*S*)-*N*-[4-(Benzyloxy)benzyl]-1-phenylethanamine **279**

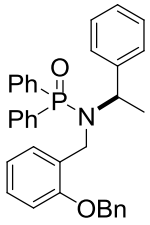


Prepared according to general procedure **C** using 4-(benzyloxyl)-benzaldehyde **277** (3.00 g, 14 mmol). Removal of the solvent *in vacuo* yielded an orange oil. Purification of the crude material by flash column chromatography on silica gel using an eluent of 30% ethyl acetate: petroleum ether 40 – 60 °C afforded the title compound as a colourless oil (2.50 g, 62%). $[\alpha]_D^{25}$- 4.0 (*c* 0.1 in $CHCl_3$); (C, 83.44, H, 7.46, N, 4.27; $C_{22}H_{23}NO$ requires C, 83.24, H, 7.30, N, 4.41%) υ_{max} (ATR)/ cm^{-1} 3029, 1610, 1510, 1453, 1241; δ_H (400 MHz, $CDCl_3$); 1.38 (3H, d, *J* 6.4, C*H*$_3$), 3.52 (1H, d, *J* 12.7, C*H*H), 3.56 (1H, d, *J* 12.7, C*H*H) 3.83 (1H, q, *J* 6.4, C*H*), 5.08 (2H, s, OC*H*$_2$), 6.95 (2H, d, *J* 8.6, ArC*H*), 7.21 – 7.48 (12H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 24.5 (*C*H_3), 51.1 (*C*H_2), 57.4 (*C*H), 70.1 (O*C*H_2), 114.7 (2 × Ar*C*H), 126.7 (2 × Ar*C*H), 126.9 (Ar*C*H), 127.5 (2 × Ar*C*H), 127.9 (Ar*C*H), 128.5 (2 × Ar*C*H), 128.6 (2 × Ar*C*H), 129.3 (2 × Ar*C*H), 133.1 (Ar*C*), 137.2 (Ar*C*), 145.6 (Ar*C*), 157.8 (Ar*C*); *m/z* (TOF ES^+) 318.1865 (100%, MH^+, $C_{22}H_{24}NO$ requires 318.1858).

General procedure D for the formation of the phosphinic amide from the benzyl protected secondary amines

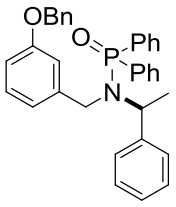
The secondary amine was added to a solution of freshly distilled triethylamine (2.0 cm^3, 14 mmol) and *N*-methyl imidazole (0.05 cm^3, 52 mg, 0.6 mmol) in DCM (10 cm^3) and the mixture cooled to 0 °C. Diphenylphosphinic chloride (1.0 cm^3, 5 mmol) was added dropwise and the solution heated at reflux for 24 hours. The mixture was poured into ice water (100 g) and the organic phase separated. The aqueous layer was extracted with dichloromethane (3 × 15 cm^3) and the combined organic phases washed with brine (10 cm^3) and dried over magnesium sulfate. Removal of the solvent *in vacuo* yielded the crude material. Purification of the crude material occurred as described in the individual experimental details

(*S*)-*N*-[2-(benzyloxy)benzyl]-*P*,*P*-diphenyl-*N*-(1-phenylethyl)phosphinamide **130**



Prepared according to general procedure **D** using the secondary amine **131** (1.00 g, 3 mmol). Purification of the crude material by flash column chromatography on silica gel using an eluent of 50% ethyl acetate: petroleum ether 40 -60 °C afforded the title compound as a colourless oil (1.40 g, 85%). $[\alpha]_D^{25}$ - 12.0 (*c* 1.0 in $CHCl_3$); (Found C, 78.92; H, 6.31; P, 2.73; $C_{34}H_{32}NO$ requires C, 78.90; H, 6.23; N, 2.71%); υ_{max} (ATR)/ cm^{-1} 3052, 2931, 1515; δ_H (400 MHz, $CDCl_3$) 1.55 (3H, d, *J* 7.1, C*H*$_3$), 4.22 (1H, dd, *J* 17.1, 12.2, C*H*H), 4.35 (1H, dd, *J* 17.1, 12.2, C*H*H), 4.78 – 4.89 (3H, m, C*H* and OCH_2), 6.65 (1H, dd, *J* 7.3 0.7, ArC*H*), 6.80 (1H, td, *J* 7.5, 0.9, ArC*H*), 7.05 (1H, td, *J* 7.9, 1.4, ArC*H*), 7.16 – 7.45 (17H, m, ArC*H*), 7.82 – 7.95 (4H, m, ArC*H*); δ_C (100 MHz, $CDCl_3$) 20.1 (*C*H_3), 41.4 (d, $J_{C\text{-}P}$ 4.0, *C*H_2N), 55.8 (d, $J_{C\text{-}P}$ 5.0, *C*H), 70.1 (O*C*H_2), 111.3 (Ar*C*H), 120.7 (Ar*C*H), 127.6 (Ar*C*H), 127.8 (Ar*C*H), 128.41 (Ar*C*H), 128.42 (Ar*C*H), 128.5 (Ar*C*H), 128.57 (Ar*C*H), 128.7 (Ar*C*H), 128.8 (Ar*C*H), 128.9 (Ar*C*H), 129.0 (Ar*C*H), 130.1 (Ar*C*H), 131.8 (d, $J_{C\text{-}P}$ 8.3, Ar*C*H), 132.3 (d, $J_{C\text{-}P}$ 13.7, Ar*C*), 132.9 (Ar*C*H), 133.0 (Ar*C*H), 133.1 (Ar*C*H), 133.5 (d, $J_{C\text{-}P}$ 16.7, Ar*C*), 137.5 (Ar*C*), 141.7 (Ar*C*), 141.8 (Ar*C*), 155.9 (Ar*C*); δ_P (121 MHz, $CDCl_3$) 31.2; *m/z* (TOF ES^+) 518.2249 (100%, MH^+, $C_{34}H_{33}NOP$ requires 518.2249). The complexity of carbon-phosphorus splitting means that the values listed for the ^{13}C NMR spectroscopic data represent each individual signal from the spectrum.

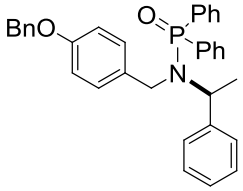
(*S*)-*N*-[3-(Benzyloxy)benzyl]-*P*,*P*-diphenyl-*N*-(1-phenylethyl)phosphinamide **280**



Prepared according to general procedure **D** using (*S*)-*N*-[3-(benzyloxy)benzyl)-1-phenylethanamine] **278** (1.00 g, 3 mmol). Purification of the crude material by flash column chromatography on silica gel using an eluent of 50% ethyl acetate: petroleum ether 40 -60 °C afforded the title compound as a colourless oil (1.40 g, 85%). $[\alpha]_D^{25}$ - 11.0 (c 1.0 in $CHCl_3$); υ_{max} (ATR)/ cm^{-1} 3058, 2931, 1510, 1438; δ_H (400 MHz, $CDCl_3$) 1.46 (3H, d, *J* 7.1, C*H*$_3$), 3.93 (1H, dd, *J* 16.0, 11.6, C*H*H), 4.22 (1H, dd, *J* 16.0, 12.1, C*H*H), 4.83 (1H, dq, *J* 9.8, 7.1, C*H*),

4.96 (2H, s, OC*H*$_2$), 6.64 (1H, d, *J* 7.3, ArC*H*), 6.75 (1H, s, ArC*H*), 6.79 (1H, dd, *J* 8.1, 2.2, ArC*H*), 7.07 (1H, t, *J* 7.8, ArC*H*), 7.27 – 7.50 (17H, m, ArC*H*), 7.92 – 8.01 (4H, m, ArC*H*); δ_C (100 MHz, $CDCl_3$) 19.8 (d, $J_{C\text{-}P}$ 2.0, *C*H$_3$), 47.4 (d, $J_{C\text{-}P}$ 3.0, *C*H$_2$), 55.4 (d, $J_{C\text{-}P}$ 4.0, C*H*), 69.7 (O*C*H$_2$), 114.0 (Ar*C*H), 114.2 (Ar*C*H), 120.8 (Ar*C*H), 127.4 (Ar*C*H), 127.9 (Ar*C*H), 128.2 (Ar*C*H), 128.3 (Ar*C*H), 128.40 (Ar*C*H), 128.48 (Ar*C*H), 128.52 (Ar*C*H), 128.6 (Ar*C*H), 128.65 (Ar*C*H), 128.9 (Ar*C*H), 131.7 (Ar*C*H), 131.8 (Ar*C*), 132.6 (Ar*C*H), 132.7 (Ar*C*H), 133.0 (d, $J_{C\text{-}P}$ 7.0, Ar*C*), 137.3 (Ar*C*), 141.0 (d, $J_{C\text{-}P}$ 4.0, Ar*C*), 141.4 (d, $J_{C\text{-}P}$ 3.0, Ar*C*), 158.6 (Ar*C*); δ_P (101 MHz, $CDCl_3$) 30.9; *m/z* (TOF ES$^+$) 518.2254 (100%, MH$^+$ $C_{34}H_{33}NO_2P$ requires 518.2249). The complexity of carbon-phosphorus splitting means that the values listed for the ^{13}C NMR spectroscopic data represent each individual signal from the spectrum.

(*S*)-*N*-[4-(Benzyloxy)benzyl]-*P*,*P*-diphenyl-*N*-(1-phenylethyl)phosphinamide **281**

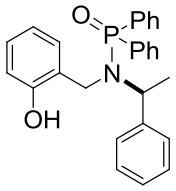


Prepared according to general procedure **D** using (*S*)-*N*-[4-(Benzyloxy)benzyl)-1-phenylethanamine] **279** (1.00 g, 3 mmol). Purification of the crude material by flash column chromatography on silica gel using an eluent of 50% ethyl acetate: petroleum ether 40 - 60 °C afforded the title compound as a colourless oil (1.50 g, 89%). $[\alpha]_D^{25}$ - 12.0 (c 1.0 in $CHCl_3$); (Found C, 78.92; H,6.31; P, 2.73; $C_{34}H_{32}NO$ requires C, 78.90; H, 6.23; N, 2.71%); υ_{max} (ATR)/ cm^{-1} 3058, 2932, 1510, 1438; δ_H (400 MHz, $CDCl_3$) 1.44 (3H, d, *J* 7.1, C*H*$_3$), 3.86 (1H, dd, *J* 15.6, 11.2, 1 × C*H*H), 4.18 (1H, dd, *J* 15.6, 11.6, 1 × C*H*H), 4.82 (1H, dq, *J* 9.8 7.1, C*H*N), 5.04 (2H, s, OC*H*$_2$), 6.77 – 6.79 (2H, m, ArC*H*), 6.96 – 6.99 (2H, m, ArC*H*), 7.22 – 7.50 (17H, m, ArC*H*), 7.92 – 7.99 (4H, m, ArC*H*); δ_C (100 MHz, $CDCl_3$) 19.9 (d, $J_{C\text{-}P}$ 2.0, *C*H$_3$), 47.0 (d, $J_{C\text{-}P}$ 3.0, *C*H$_2$), 55.2 (d, $J_{C\text{-}P}$ 4.0, C*H*N), 69.9 (O*C*H$_2$), 114.3 (Ar*C*H), 127.3 (Ar*C*H), 127.5 (Ar*C*H), 127.9 (Ar*C*H), 128.2 (Ar*C*H), 128.3 (Ar*C*H), 128.4 (Ar*C*H), 128.5 (Ar*C*H), 128.53 (Ar*C*H), 128.6 (Ar*C*H), 129.6 (Ar*C*H), 131.6 (Ar*C*H), 131.8 (d, $J_{C\text{-}P}$ 3.8, Ar*C*),132.5 (Ar*C*H), 132.64 (Ar*C*H), 132.68 (Ar*C*H), 132.73 (Ar*C*H) 133.1 (Ar*C*), 137.1 (Ar*C*), 140.9 (ArC), 141.0 (Ar*C*), 157.7 (Ar*C*); δ_P (101 MHz, $CDCl_3$) 30.9; *m/z* (EI) 518.2264 (100%, MH$^+$, $C_{34}H_{33}NO_2P$ requires 518.2249). The complexity of carbon-phosphorus splitting means that the values listed for the ^{13}C NMR spectroscopic data represent each individual signal from the spectrum.

General procedure E for the removal of the benzyl protecting group from the secondary phosphinic amides

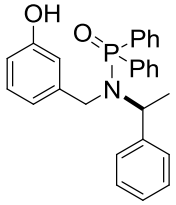
The benzyl protected phosphinic amide was dissolved in ethanol (10 cm^3) and subjected to continuous cycling through a $Pd(OH)_2/C$ Thalesnano Catcart H-Cube™ for 8 hours under 50 atmospheres of H_2 at 50 °C. Removal of the solvent *in vacuo* afforded the title compound which required no further purification.

(*S*)-*N*-(2-Hydroxybenzyl)-*P*,*P*-diphenyl-*N*-(1-phenylethyl)phosphinic amide **129**



Prepared according to general procedure **E** from the benzyl phosphinic amide **130** (300 mg, 0.6 mmol). Removal of the solvent *in vacuo* afforded a colourless oil that required no further purification (250 mg, 95%). $[\alpha]_D^{25}$ – 4.0 (*c* 0.2 in $CHCl_3$); υ_{max} (ATR) / cm^{-1} 3344, 3048, 2971, 1428; δ_H (400 MHz, $CDCl_3$) 1.34 (3H, d, *J* 7.1, C*H*$_3$), 3.97 (1H, dd, *J* 15.3, 10.9, 1 × C*H*H), 4.41 – 4.51 (2H, m, C*H* and 1 × C*H*H), 6.66 – 6.68 (2H, m, ArC*H*), 6.91 – 6.93 (1H, m, ArC*H*), 7.14 – 7.21 (3H, m, ArC*H*), 7.29 – 7.35 (3H, m, ArC*H*), 7.47 – 7.57 (6H, m, ArC*H*), 7.81 – 7.91 (4H, m, ArC*H*), 10.55 (1H, s, O*H*); δ_C (101 MHz, $CDCl_3$) 19.7 (*C*H_3), 45.7 (d, $J_{C\text{-}P}$ 4.0, *C*H_2), 55.8 (d, $J_{C\text{-}P}$ 6.0, *C*H), 119.1 (Ar*C*H), 119.3 (Ar*C*H), 127.8 (Ar*C*H), 128.4 (2 × Ar*C*H), 128.7 (2 × Ar*C*H), 129.1 (d, $J_{C\text{-}P}$ 9.0, 2 × Ar*C*H), 129.2 (d, $J_{C\text{-}P}$ 9.0, 2 × Ar*C*H), 130.2 (Ar*C*H), 130.7 (d, $J_{C\text{-}P}$ 63.0, Ar*C*), 131.7 (d, $J_{C\text{-}P}$ 63.0, Ar*C*), 132.2 (Ar*C*H), 132.6 (d, $J_{C\text{-}P}$ 2.6, Ar*C*H), 132.7 (d, $J_{C\text{-}P}$ 2.6, Ar*C*H), 132.8 (d, $J_{C\text{-}P}$ 9.8, 2 × Ar*C*H), 133.2 (d, $J_{C\text{-}P}$ 9.9.2 × Ar*C*H), 140.5 (d, $J_{C\text{-}P}$ 6.0, Ar*C*), 157.7 (*C*OH); δ_P (101 MHz, $CDCl_3$) 38.3; *m/z* (TOF ES^+) 428.1777 (100%, MH^+, $C_{27}H_{27}NO_2P$ requires 428.1779).

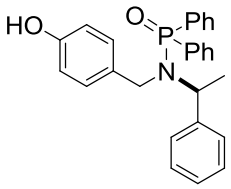
(*S*)-*N*-(3-Hydroxybenzyl)-*P*,*P*-diphenyl-*N*-(1-phenylethyl)phosphinic amide **136**



Prepared according to general procedure **E** from the benzyl protected phosphinamide **280** (300 mg, 0.6 mmol). Removal of the solvent *in vacuo* afforded a colourless oil that required no

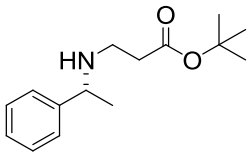
further purification (256 mg, 100%). $[\alpha]_D^{25}$ - 3.0 (*c* 0.2 in $CHCl_3$); (Found C, 75.81; H, 6.17; N, 3.25; $C_{27}H_{26}NO_2P$ requires C, 75.86; H, 6.13; N, 3.28%); υ_{max} (ATR) / cm^{-1} 3059, 2978, 1590, 1438, 1175; δ_H (400 MHz, $CDCl_3$) 1.45 (3H, d, *J* 7.1, C*H*$_3$), 3.87 (1H, dd, *J* 16.0 13.1, C*H*H), 4.16 (1H, dd, *J* 16.0 11.9, C*H*H), 4.70 – 4.78 (1H, m, C*H*), 6.51 (1H, d, *J* 7.6, ArC*H*), 6.81 (1H, app. dd, *J* 8.0 1.9, ArC*H*), 7.00 – 7.06 (2H, m, ArC*H*), 7.21 – 7.40 (5H, m, ArC*H*), 7.40 – 7.50 (6H, m, ArC*H*), 7.97 – 8.01 (4H, m, ArC*H*), 8.78 (1H, s, O*H*); δ_C (100 MHz, $CDCl_3$) 20.1 (*C*H$_3$), 47.9 (d, $J_{C\text{-}P}$ 3.0, *C*H), 55.7 (d, $J_{C\text{-}P}$ 4.0, *C*H$_2$), 114.2 (Ar*C*H), 115.7 (Ar*C*H), 119.2 (Ar*C*H), 127.4 (Ar*C*H), 128.1 (Ar*C*H), 128.4 (Ar*C*H), 128.5 (Ar*C*H), 128.6 (Ar*C*H), 129.0 (Ar*C*H), 131.1 (d, $J_{C\text{-}P}$ 10.7, Ar*C*), 131.9 (Ar*C*H), 132.4 (d, $J_{C\text{-}P}$ 9.9, Ar*C*), 132.5 (Ar*C*H), 132.6 (Ar*C*H), 132.7 (Ar*C*H), 140.6 (d, $J_{C\text{-}P}$ 4.6, Ar*C*), 141.0 (d, $J_{C\text{-}P}$ 2.3, Ar*C*), 156.9 (Ar*C*); δ_P (101 MHz, $CDCl_3$) 31.2; *m/z* (TOF ES^+) 428.1772 (100%, MH^+, $C_{27}H_{27}NO_2P$ requires 428.1779). The complexity of carbon-phosphorus splitting means that the values listed for the ^{13}C NMR spectroscopic data represent each individual signal from the spectrum.

(*S*)-*N*-(4-Hydroxybenzyl)-*P*,*P*-diphenyl-*N*-(1-phenylethyl)phosphinic amide **137**



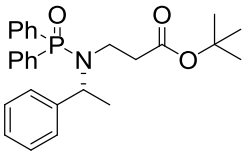
Prepared according to general procedure **E** from the benzyl protected phosphinamide **281** (300 mg, 0.6 mmol)**.** Removal of the solvent *in vacuo* afforded a colourless oil that required no further purification (234 mg, 91%). $[\alpha]_D^{25}$ - 3.3 (*c* 0.2 in $CHCl_3$); (Found C, 75.89; H, 6.12; N, 3.28; $C_{27}H_{26}NO_2P$ requires C, 75.86; H, 6.13; N, 3.28%); υ_{max} (ATR) / cm^{-1} 3292, 2939, 1438; δ_H (400 MHz, $CDCl_3$) 1.43 (3H, d, *J* 7.1, C*H*$_3$), 3.92 (1H, app. t, *J* 15.2, C*H*H), 4.23 (1H, dd, *J* 15.2 12.2, C*H*H), 4.67 (1H, quint., *J* 7.1, C*H*), 6.94 (2H, app. d, *J* 8.6, ArC*H*), 7.06 (2H, app. d, *J* 8.6, ArC*H*), 7.27 – 7.38 (5H, m, ArC*H*), 7.44 – 7.53 (6H, m, ArC*H*), 7.98 – 8.06 (4H, m, ArC*H*), 9.88 (1H, br. s, O*H*); δ_C (100 MHz, $CDCl_3$) 20.0 (*C*H$_3$), 48.2 (d, $J_{C\text{-}P}$ 3.0, *C*H), 55.4 (d, $J_{C\text{-}P}$ 5.0, *C*H$_2$), 115.4 (2 × Ar*C*H), 127.3 (Ar*C*H), 128.2 (2 × Ar*C*H), 128.3 (2 × Ar*C*H), 128.6 (2 × Ar*C*H), 128.7 (2 × Ar*C*H), 129.2 (Ar*C*), 130.0 (2 × Ar*C*H), 131.2 (Ar*C*), 131.7 (d, $J_{C\text{-}P}$ 3.1, Ar*C*H), 131.8 (Ar*C*H), 132.5 (Ar*C*), 132.6 (d, $J_{C\text{-}P}$ 9.1, Ar*C*H), 132.7 (d, $J_{C\text{-}P}$ 9.1, Ar*C*H), 140.9 (d, $J_{C\text{-}P}$ 6.0, Ar*C*), 156.9 (Ar*C*O); δ_P (101 MHz, $CDCl_3$) 30.7; *m/z* (TOF ES^+) 428.1781 (100%, MH^+, $C_{27}H_{27}NO_2P$ requires 427.1779).

(*R*)-(+)-*tert*-Butyl 3-(1-phenylethylamino)propanoate **141**[99]



tert-Butyl acrylate (2.0 cm³, 14 mmol) and (*R*)-(+)-methylbenzylamine (2.0 cm³, 15 mmol) were dissolved in DMSO (2.0 cm³) and transferred to a microwave vial. The solution was irradiated in the microwave at 160 °C for 30 minutes. The reaction mixture was cooled to room temperature and water (5.0 cm³) added. The aqueous phase was extracted with ethyl acetate (3 × 5.0 cm³) and dried over magnesium sulfate. Removal of the solvent *in vacuo* afforded a colourless oil that required no further purification (3.05 g, 89%). $[\alpha]_D^{25}$ + 29.0 [*c* 0.66 in $CHCl_3$, lit.[99] - 28.9 *c* 0.66 in $CHCl_3$ for the (*S*)-enantiomer]; δ_H (400 MHz, $CDCl_3$) 1.36 (3H, d, *J* 6.6, C*H*$_3$), 1.46 [9H, s, C(C*H*$_3$)$_3$], 1.68 (1H, br. s, N*H*), 2.38 – 2.42 (2H, m, C*H*$_2$), 2.64 – 2.77 (2H, m, C*H*$_2$), 3.78 (1H, q, *J* 6.6, C*H*), 7.22 – 7.37 (5H, m, ArC*H*). All data is in accordance with the literature.

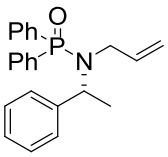
(*R*)-(+)-*tert*-Butyl 3-[(diphenylphosphinyl)-1-phenylethyl-amino]propanoate **139**



(*R*)-(+)-*tert*-Butyl 3-(1-phenylethylamino)propanoate **141** (0.60 g, 3 mmol) was added to a solution of *N*-methyl imidazole (0.04 cm³, 0.5 mmol) and triethylamine (1.0 cm³, 6 mmol) in dichloromethane (15 cm³) and the mixture cooled to 0 °C. Diphenylphosphinic chloride (0.6 cm³, 3 mmol) was added dropwise and the solution heated at reflux for 24 hours. Upon cooling to room temperature the mixture was poured into ice water (50 g) and the organic phase separated. The aqueous layer was extracted with dichloromethane (3 × 10 cm³) and the organic phases combined, washed with brine (10 cm³) and dried over magnesium sulfate. Removal of the solvent *in vacuo* yielded a yellow oil. Purification of the crude material by flash column chromatography on silica gel using an eluent of 100% ethyl acetate afforded the title compound as a colourless oil that solidified upon standing (0.83 g, 74%). m.p. 86 °C; $[\alpha]_D^{25}$ + 12.0 (*c* 1.0 in $CHCl_3$); (Found C, 72.07; H, 7.18; N, 3.01; $C_{27}H_{32}NO_3P$ requires C, 72.14; H, 7.18; N, 3.12%); υ_{max} / cm^{-1} (ATR) 3059, 2973, 2931, 1724, 1368; δ_H (400 MHz, $CDCl_3$) 1.26 [9H, s, C(C*H*$_3$)$_3$], 1.62 (3H, d, *J* 7.1, C*H*$_3$), 1.80 (1H, tt, *J* 11.0, 4.9, C*H*H), 2.13 (1H, tt, *J* 11.0, 4.9, C*H*H), 3.07 – 3.30 (2H, m, C*H*$_2$), 4.77 (1H, dq, *J* 8.8 7.2, C*H*), 7.24 – 7.28 (1H, m, ArC*H*), 7.32 – 7.36 (2H, m, ArC*H*), 7.43 – 7.90 (12H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 18.8 (d, $J_{C\text{-}P}$ 3.0, *C*H_3), 27.9

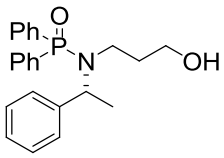
[C(*C*H$_3$)$_3$], 37.2 (d, $J_{C\text{-}P}$ 2.0, *C*H$_2$), 38.8 (d, $J_{C\text{-}P}$ 4.0, *C*H$_2$), 54.0 (d, $J_{C\text{-}P}$ 3.0, *C*H), 80.2 [*C*(CH$_3$)$_3$], 127.4 (Ar*C*H), 127.9 (2 × Ar*C*H), 128.4 (2 × Ar*C*H), 128.5 (Ar*C*H), 128.6 (Ar*C*H), 131.6 (d, $J_{C\text{-}P}$ 14.0, Ar*C*), 131.7 (2 × Ar*C*H), 131.8 (2 × Ar*C*H), 132.3 (d, $J_{C\text{-}P}$ 3.8, 2 × Ar*C*H), 132.5 (d, $J_{C\text{-}P}$ 3.8, 2 × Ar*C*H), 132.9 (d, $J_{C\text{-}P}$ 14.0, Ar*C*), 141.6 (d, $J_{C\text{-}P}$ 5.0, Ar*C*), 170.8 (*C*O); δ_P (121 MHz, $CDCl_3$) 30.2; *m/z* (TOF ES$^+$) 450.2194 (100%, MH$^+$, $C_{27}H_{33}NO_3P$ requires 450.2198). No data is reported within the literature.

(*R*)-(+)-*N*-Allyl-*P*,*P*-diphenyl-*N*-(1-phenylethyl)phosphinic amide **141**



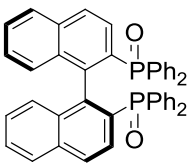
P,*P*-Diphenyl-*N*-[(*R*)-phenylethyl]phosphinic amide **92** (500 mg, 1.6 mmol) was added in a single portion to pre-washed sodium hydride (150 mg, 6.2 mmol) in anhydrous THF (10 cm³) at 0 °C and the resulting suspension stirred for 60 minutes. Allyl bromide (0.15 cm³, 209 mg, 1.6 mmol) was added dropwise and the solution heated at reflux for 4 hours. The reaction was cooled and quenched through dropwise addition of saturated ammonium chloride solution (10 cm³). The organic phase was extracted with diethyl ether (3 × 15 cm³), washed with a 1M NaOH solution (10 cm³), brine (10 cm³) and dried with magnesium sulfate. The solvent was removed *in vacuo* to yield a yellow oil. The crude material was purified *via* flash column chromatography on silica gel using an eluent of 10% methanol: ethyl acetate to afford a colourless oil that slowly solidified upon standing (434 mg, 75%). m.p. 128 °C; $[\alpha]_D^{25}$ + 30.0 (*c* 1.0 in $CHCl_3$); (Found C, 76.04; H, 6.20; N, 3.88; $C_{23}H_{24}NOP$ requires C, 76.43; H, 6.69; N, 3.88%); υ_{max} (ATR) / cm^{-1} 3201, 3113, 3079, 1614, 1213, 1021; δ_H (400 MHz, $CDCl_3$) 1.64 (3H, d, *J* 6.8, C*H*$_3$), 3.33 – 3.39 (1H, m, NC*H*H), 3.50 – 3.60 (1H, m, NC*H*H), 4.61 (1H, dd, *J* 17.2 1.4, CH=C*H*H), 4.74 – 4.82 (2H, m, CH=C*H*H and C*H*), 5.62 (1H, dddd, *J* 17.2 10.1 7.3 5.5, C*H*=CH$_2$), 7.27 – 7.29 (1H, m, ArC*H*), 7.34 – 7.38 (2H, m, ArC*H*), 7.44 – 7.54 (8H, m, ArC*H*), 7.91 – 7.99 (4H, m, ArC*H*); δ_C (100 MHz, $CDCl_3$) 19.5 (d, $J_{C\text{-}P}$ 3.0, *C*H$_3$), 46.5 (d, $J_{C\text{-}P}$ 4.0 , *C*H$_2$), 54.5 (*C*H, d, $J_{C\text{-}P}$ 3.0, *C*H), 115.5 (CH=*C*H$_2$), 127.2 (Ar*C*H), 128.2 (Ar*C*H), 128.4 (Ar*C*H), 128.5 (Ar*C*H), 131.7 (*C*H=CH$_2$), 131.8 (d, $J_{C\text{-}P}$ 13.0, Ar*C*), 132.5 (d, $J_{C\text{-}P}$ 2.3, Ar*C*H), 132.6 (d, $J_{C\text{-}P}$ 2.3, Ar*C*H), 133.1 (d, $J_{C\text{-}P}$ 13.0, Ar*C*), 137.7 (Ar*C*H), 137.8 (Ar*C*H), 141.3 (d, $J_{C\text{-}P}$ 4.6, Ar*C*); δ_P (101 MHz, $CDCl_3$) 30.4; *m/z* (TOF ES$^+$) 362.1691 (M$^+$, 100%, $C_{23}H_{25}NOP$ requires 362.1674). The complexity of carbon-phosphorus splitting means that the values listed for the ^{13}C NMR spectroscopic data represent each individual signal from the spectrum.

(*R*)-(+)-*N*-(3-Hydroxypropyl)-*P*,*P*-diphenyl-*N*-(1-phenylethyl)phosphinic amide **140**



The allylated phosphinic amide **141** (2.00 g, 6 mmol) was dissolved in THF (10 cm³) and the reaction mixture cooled to -78 °C. BH_3.DMS (1.0 cm³, 12 mmol) was added dropwise and the solution warmed to room temperature and stirred overnight. Ethanol (16 cm³), 3M NaOH solution (8 cm³) and hydrogen peroxide (35%, 8 cm³) were added sequentially to the reaction mixture and the solution heated at reflux for 18 hours behind a blast shield. The reaction mixture was poured into water (10 cm³) and the aqueous phase extracted with dichloromethane (3 × 15 cm³). The organic layers were combined, washed with a saturated solution of sodium sulfite (15 cm³) and dried over magnesium sulfate. Removal of the solvent *in vacuo* yielded a yellow oil. Purification of the crude material *via* flash column chromatography on silica gel using an eluent of 70% ethyl acetate: petroleum ether 40 – 60 °C afforded a white solid (1.03 g, 49%). m.p. 106 °C; $[\alpha]_D^{25}$ - 41.0 (*c* 1.0 in $CHCl_3$); (Found C, 72.54; H, 6.59; N, 3.48; $C_{23}H_{26}NO_2P$ requires C, 72.81; H, 6.91; N, 3.69%); υ_{max} (ATR) / cm-1 3382, 3063, 1638, 1438; δ_H (400 MHz, $CDCl_3$) 1.32 – 1.47 (2H, m, C*H*$_2$), 1.59 (3H, d, *J* 7.0, C*H*$_3$), 3.00 – 3.09 (1H, m, C*H*H), 3.13 - 3.23 (1H, m, C*H*H), 3.35 – 3.45 (2H, m, C*H*$_2$OH), 3.52 (1H, s, O*H*), 4.56 – 4.64 (1H, m, C*H*), 7.29 – 7.52 (11H, m, ArC*H*), 7.83 – 7.90 (4H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 19.7 (*C*H$_3$), 34.3 (*C*H$_2$), 40.4 (d, $J_{C\text{-}P}$ 4.0, *C*H$_2$), 54.9 (d, $J_{C\text{-}P}$ 5.0, *C*H), 59.7 (*C*H$_2$OH), 127.9 (Ar*C*H), 128.4 (2 × Ar*C*H), 128.7 (2 × Ar*C*H), 128.9 (d, $J_{C\text{-}P}$ 6.0, 2 × Ar*C*H), 129.0 (d, $J_{C\text{-}P}$ 5.0, 2 × ArCH), 131.8 (d, $J_{C\text{-}P}$ 6.0, Ar*C*), 132.3 (2 × Ar*C*H), 132.8 (Ar*C*H), 132.9 (2 × Ar*C*H), 133.0 (Ar*C*H), 133.1 (d, $J_{C\text{-}P}$ 6.0, Ar*C*), 141.7 (d, $J_{C\text{-}P}$ 5.0, Ar*C*); δ_P (121 MHz, $CDCl_3$) 32.6; *m/z* (TOF ES$^+$) 380.1785 (100%, MH$^+$, $C_{23}H_{27}NO_2P$ requires 380.1779).

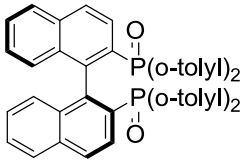
(*S*)-2,2'-*Bis*-(Diphenylphosphinoyl)-1,1'-binaphthyl **142**[107]



(*S*)-2,2'-*bis*-(Diphenylphosphino)-1,1'-binaphthyl **147** (300 mg, 0.5 mmol) was added to dichloromethane (10 cm³) and the solution cooled to 0 °C. Hydrogen peroxide (35 wt.%, 0.2 cm³) was added dropwise and the mixture stirred for 18 hours. The solution was poured into water (10 cm³) and the organic phase separated. The aqueous layer was extracted with diethyl ether (3 × 15 cm³) and the combined organic phases washed with a saturated aqueous solution of

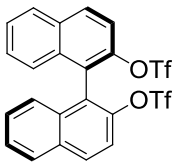
sodium sulfite (10 cm³) and dried over magnesium sulfate. Removal of the solvent *in vacuo* afforded a white crystalline solid that required no further purification (290 mg, 95%). m.p. 261 °C (lit.[107] 260.5 °C – 261.5 °C); $[\alpha]_D^{25}$ - 390 (*c* 1.0 in C_6H_6, lit.[107] -391.2 *c* 1.0 in C_6H_6); δ_H (250 MHz, $CDCl_3$) 6.78 – 6.85 (4H, m, ArC*H*), 7.26 – 7.51 (20H, m, ArC*H*), 7.69 – 7.77 (4H, m, ArC*H*), 7.82 – 7.89 (4H, m, ArC*H*); δ_P (250 MHz, $CDCl_3$) 28.3. All data is in accordance with the literature.

(*S*)-2,2'-*bis*(di-*o*-Tolylphosphinoyl)-1,1'-binaphthyl **149**[107]



(*S*)-(−)-2,2′-*bis*(di-*o*-Tolylphosphino)-1,1′-binaphthyl **148** (100 mg, 0.1 mmol) was dissolved in dichloromethane (5 cm³) and the solution cooled to 0 °C. Hydrogen peroxide (35 wt. %, 0.2 cm³) was added dropwise and the reaction mixture stirred for 18 hours. The solution was poured into water (10 cm³) and the organic layer separated. The aqueous layer was extracted with diethyl ether (3 × 15 cm³) and the combined organic phases washed with a saturated solution of sodium sulfite (10 cm³) and dried over magnesium sulfate. Removal of the solvent *in vacuo* afforded the title compound as a white crystalline solid that required no further purification (100 mg, 98%). m.p. 268 °C; $[\alpha]_D^{25}$ - 421 (*c* 1.0 in C_6H_6, lit.[107] - 419.2 *c* 1.0 in C_6H_6); δ_H (400 MHz, $CDCl_3$) 2.33 (12H, d, $J_{P\text{-}H}$ 23.4, 4 × C*H*$_3$), 6.89 – 6.94 (4H, m, ArC*H*), 6.98 – 7.00 (4H, m, ArC*H*), 7.06 – 7.09 (4H, m, ArC*H*), 7.30 – 7.39 (4H, m, ArC*H*), 7.40 (2H, ddd, *J* 8.1, 4.9, 3.2, 2 × ArC*H*), 7.44 – 7.54 (6H, m, 6 × ArC*H*), 7.82 – 7.85 (4H, m, 4 × ArC*H*); δ_P (121 MHz, $CDCl_3$) 28.4. No melting point is reported within the literature, otherwise all other data is in accordance.

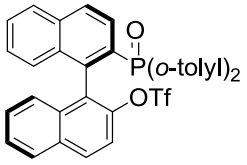
(*R*)-1,1'-Binaphthyl-2,2'-diyl *bis*(trifluoromethanesulfonate) **282**[107]



(*R*)-BINOL **150** (1.00 g, 4 mmol) was dissolved in a solution of dichloromethane (20 cm³) and freshly distilled pyridine (1.0 cm³, 13 mmol) and the mixture cooled to 0 °C. Triflic anhydride (3.00 g, 2.0 cm³, 12 mmol) was added dropwise over a period of 30 minutes and the mixture warmed to room temperature and stirred for six hours. The solution was diluted with ethyl acetate (50 cm³) and the organic phase was separated. The aqueous phase was extracted with

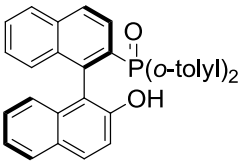
ethyl acetate (3 × 10 cm³) and the combined organic layers washed sequentially with an aqueous solution of 5% HCl (20 cm³), aqueous saturated sodium hydrogen carbonate solution (20 cm³) and brine (20 cm³). The organic phase was dried over sodium sulfate and the solvent removed *in vacuo* to yield an orange oil. Purification of the crude material by column chromatography on silica gel using an eluent of 5% ethyl acetate: petroleum ether 40 – 60 °C furnished the title compound as a white crystalline solid (3.03 g, 100%). m.p. 75 °C (lit.[107] 74 – 76 °C); $[\alpha]_D^{25}$ + 146.2 (*c* 1.0 in $CHCl_3$, lit.[107] + 145.0 *c* 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.27 – 7.29 (2H, m, ArC*H*), 7.41 – 7.46 (2H, m, ArC*H*), 7.59 – 7.65 (4H, m, ArC*H*), 8.03 (2H, d, *J* 8.0, ArC*H*), 8.17 (2H, d, *J* 9.0, ArC*H*); δ_F (235 MHz, $CDCl_3$) -74.57 (2 × CF_3). All data is in accordance with that of the literature.

(*R*)-2-[*bis*-(*o*-Tolylphosphinyl)]- 2'-[(trifluoromethanesulfonoyl)oxy]-1,1'-binaphthyl **283**[107]



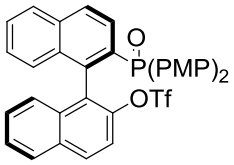
(*R*)-1,1'-Binaphthyl-2,2'-diyl-*bis*-trifluoromethanesulfonate **282** (0.60 g, 1 mmol) was added to a stirred solution of bis-(2-methylphenyl)-phosphine oxide (0.60 g, 3 mmol), palladium acetate (0.06 g, 0.3 mmol) and diphenylphosphoryl butane (0.10 g, 0.3 mmol) under an atmosphere of argon. *N*,*N*-Diisopropylethylamine (0.70 g, 1.0 cm³, 6 mmol) was added dropwise and the reaction mixture heated to 120 °C for 12 hours. Upon cooling to room temperature, the solution was diluted with ethyl acetate (50 cm³) and washed successively with water (3 × 20 cm³), 1*N* HCl (20 cm³) and an aqueous saturated solution of $NaHCO_3$ (20 cm³). The organic layer was dried over magnesium sulfate and the solvent removed *in vacuo* to yield an orange oil. Purification of the crude material by flash column chromatography on silica gel using an eluent of 40% ethyl acetate: petroleum ether 40 – 60 °C afforded the title compound as a white crystalline solid (630 mg, 74%). m.p. 78 °C; $[\alpha]_D^{25}$ + 62.2 (*c* 0.5 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.15 (3H, s, CH_3), 2.48 (3H, s, CH_3), 6.90 – 7.13 (7H, m, ArC*H*), 7.25 – 7.31 (3H, m, ArC*H*), 7.35 – 7.45 (5H, m, ArC*H*), 7.61 (1H, app. t, *J* 7.1, ArC*H*), 7.87 (1H, app. d, *J* 8.1, ArC*H*), 7.97 – 8.01 (3H, m, ArC*H*); δ_F (235 MHz, $CDCl_3$) -74.9; δ_P (101 MHz, $CDCl_3$) 33.9. No melting point or optical rotation value is stated within the literature, otherwise all other data is in accordance.

(*R*)-2'-[*bis*-(*o*-Tolylphosphinoyl]-[1,1'-binapthalen]-2-ol **151**[107]



(*R*)-2-[*bis*-(*o*-Tolylphosphinyl)]- 2'-[(trifluoromethanesulfonoyl)oxy]-1,1'-binaphthyl **283** (0.30 g, 0.4 mmol) was added to a solution of dioxane (10 cm³) and methanol (5.0 cm³) at room temperature. A 3M solution of NaOH (3.0 cm³) was introduced in a single portion and the solution stirred at room temperature for 24 hours. The reaction was acidified to pH 1 using concentrated HCl (5.0 cm³) and the aqueous phase extracted with ethyl acetate (3 × 10 cm³). The organic phases were combined, washed with brine (10 cm³) and dried over magnesium sulfate. Removal of the solvent *in vacuo* yielded a yellow oil. Purification of the crude material by flash column chromatography on silica gel using an eluent of 50% ethyl acetate: petroleum ether 40 – 60 °C afforded the title compound as a white crystalline solid (210 mg, 96%). m.p. 162 °C; $[\alpha]_D^{25}$ + 135.0 [*c* 0.7 in $CHCl_3$, lit. [107] - 136.0 *c* 0.7 in $CHCl_3$ for the (*S*)-enantiomer]; δ_H (400 MHz, $CDCl_3$) 2.03 (3H, s, C*H*$_3$), 2.72 (3H, s, C*H*$_3$), 6.21 (1H, d, *J* 8.5, ArC*H*), 6.52 – 6.63 (2H, m, ArC*H*), 6.74 – 6.81 (2H, m, ArC*H*), 7.03 – 7.25 (6H, m, ArC*H*), 7.47 – 7.52 (6H, m, ArC*H*), 7.70 (1H, d, *J* 8.5, ArC*H*), 7.91 – 8.00 (2H, m, ArC*H*), 9.33 (1H, s, O*H*); δ_P (121 MHz, $CDCl_3$) 37.2. No melting point data is reported within the literature, all other data is in accordance.

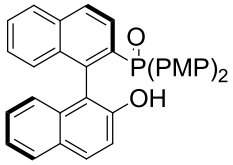
(*R*)-2-[*bis*-(4-Methoxyphenyl)phosphinoyl]-2'-[(trifluoromethanesulfonyl)oxy]-1,1'-binaphthyl **284**[107]



(*R*)-1,1'-Binaphthyl-2,2'-diyl-*bis*-trifluoromethanesulfonate **282** (0.60 g, 1 mmol) was added to a stirred solution of *bis*(4-methoxyphenyl)phosphine oxide (0.60 g, 3 mmol), palladium acetate (0.06 g, 0.3 mmol) and 1,4-*bis*(diphenylphosphino)butane (0.10 g, 0.3 mmol) under an atmosphere of argon. *N*,*N*-Diisopropylethylamine (0.70 g, 1.0 cm³, 6 mmol) was added dropwise and the reaction mixture heated to 120 °C for 12 hours. Upon cooling, the solution was diluted with ethyl acetate (50 cm³) and washed successively with water (3 × 20 cm³), 1N HCl (20 cm³) and a 1M aqueous solution of $NaHCO_3$ (20 cm³). The organic layer was dried over magnesium sulfate and the solvent removed *in vacuo* to yield an orange oil. Purification of the crude material by flash column chromatography on silica gel using an eluent of 40% ethyl

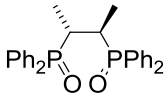
acetate: petroleum ether 40 – 60 °C afforded the title compound as a white crystalline solid (700 mg, 87%). m.p. 81 °C (lit. **[107]** 80 – 81 °C); $[\alpha]_D^{25}$ + 66.1 (*c* 0.7 in $CHCl_3$, lit. **[107]** + 66.3 *c* 0.7 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 3.79 (3H, s, OC*H*$_3$), 3.81 (3H, s, OC*H*$_3$), 6.66 – 6.69 (2H, m, ArC*H*), 6.77 – 6.80 (2H, m, ArC*H*), 7.01 (1H, d, *J* 8.6, ArC*H*), 7.12 (1H, d, *J* 8.6, ArC*H*), 7.18 – 7.23 (1H, m, ArC*H*), 7.30 – 7.39 (6H, m, ArC*H*), 7.45 (1H, ddd, *J* 8.2, 6.9, 1.2, ArC*H*), 7.56 – 7.60 (1H, m, ArC*H*), 7.78 (1H, dd, *J* 11.4, 8.6, ArC*H*), 7.84 (1H, d, *J* 8.3, ArC*H*), 7.90 (1H, d, *J* 9.0, ArC*H*), 7.96 (1H, d, *J* 8.3, ArC*H*), 8.04 (1H, dd, *J* 8.8, 2.2, ArC*H*); δ_F (235 MHz, $CDCl_3$) -75.0; δ_P (101 MHz, $CDCl_3$) 27.9. All spectroscopic data is in accordance with the literature.

(*R*)-2'-[*bis*-(4-Methoxyphenyl)phosphinoyl]-[1,1'-binapthalen]-2-ol **152**



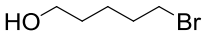
(*R*)-2-[*bis*(4-Methoxyphenyl)phosphinyl]-2'-[(trifluoromethanesulfonyl)oxy]-1,1'-binaphthyl **284** (0.30 g, 0.4 mmol) was added to a solution of dioxane (10 cm³) and methanol (5.0 cm³) at room temperature. A 3M solution of NaOH (3.0 cm³) was introduced in one portion and the solution stirred at room temperature for 24 hours. The reaction was acidified to pH 1 using concentrated HCl (5.0 cm³) and the aqueous phase extracted with ethyl acetate (3 × 10 cm³). The organic phases were combined, washed with brine (10 cm³) and dried over magnesium sulfate. Removal of the solvent *in vacuo* yielded a yellow oil. Purification of the crude material by flash column chromatography on silica gel using an eluent of 50% ethyl acetate: petroleum ether 40 – 60 °C afforded the title compound as a white crystalline solid (215 mg, 100%). m.p. 178 °C; $[\alpha]_D^{25}$ -126.0 [*c* 0.7 in $CHCl_3$, lit.[107] + 126.3 *c* 0.7 in $CHCl_3$ for the (*S*)-enantiomer]; δ_H (400 MHz, $CDCl_3$) 3.55 (3H, s, OC*H*$_3$), 3.89 (3H, s, OC*H*$_3$), 6.21 – 6.24 (2H, m, ArC*H*), 6.43 (1H, app. d, *J* 8.6, ArC*H*), 6.92 – 6.96 (1H, m, ArC*H*), 7.05 (2H, app. dd, *J* 8.6, 2.3, ArC*H*), 7.10 – 7.16 (4H, m, ArC*H*), 7.20 – 7.24 (1H, m, ArC*H*), 7.38 – 7.45 (2H, m, ArC*H*), 7.50 – 7.56 (2H, m, ArC*H*), 7.67 (1H, app. d, *J* 8.6, ArC*H*), 7.81 – 7.92 (4H, m, ArC*H*) 9.40 (1H, s, O*H*); δ_P (121 MHz, $CDCl_3$) 31.25. No melting point data is reported within the literature, all other data is in accordance.

(2*R*,3*R*)-(+)- 2,3-*bis*(Diphenylphosphinoyl)butane **153**[109]



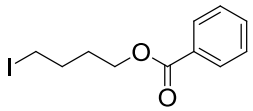
(2*R*,3*R*)-(+)-*bis*(Diphenylphosphino)butane (200 mg, 0.5 mmol) was dissolved in DCM (10 cm³) and the reaction solution cooled to 0 °C. Hydrogen peroxide (35 wt. %, 0.5 cm³) was added dropwise and the reaction mixture stirred for 18 hours. The solution was poured into water (10 cm³) and the organic phase separated. The aqueous layer was extracted with dichloromethane (3 × 10 cm³) and the organic phases combined, washed with a saturated aqueous solution of sodium sulfite (15 cm³) and dried over magnesium sulfate. Removal of the solvent *in vacuo* afforded the title compound as a white crystalline solid that required no further purification (203 mg, 94%). m.p. 183 °C (lit.[109] 183 – 184 °C); $[\alpha]_D^{25}$ + 39.0 (*c* 2.0 in CH_2Cl_2, lit.[109] + 39.0 *c* 2.0 in CH_2Cl_2); δ_H (250 MHz, $CDCl_3$) 1.29 – 1.39 (6H, m, 2 × C*H*$_3$), 2.87 (2H, qd, *J* 7.1, 5.1, 2 × C*H*), 7.28 – 7.81 (20H, m, ArC*H*); δ_P (101 MHz, $CDCl_3$) 36.7. All data is in accordance with the literature.

5-Bromopropan-1-ol **285**[148]



Boron tribromide (24 cm³, 24 mmol, 1M in hexanes) was added dropwise to an anhydrous solution of tetrahydropyran (7 cm³, 72 mmol) and dichloromethane (20 cm³) at 0 °C. The resulting solution was heated at reflux for 24 hours. Upon cooling to room temperature, the solvent was removed *in vacuo* and the crude residue dissolved in methanol (20 cm³) and heated at reflux for 3 hours. The solution was filtered through a small silica plug eluting with ethyl acetate (50 cm³). Removal of the solvent *in vacuo* yielded a crude yellow oil. Purification of the crude material by flash column chromatography on silica gel using an eluent of 2% ethyl acetate: petroleum ether 40 – 60 °C afforded the title compound as a colourless oil (8.50 g, 71%). δ_H (400 MHz, $CDCl_3$) 1.48 – 1.64 (5H, m, 2 × C*H*$_2$ and O*H*), 1.86 – 1.92 (2H, m, C*H*$_2$), 3.41 – 3.45 (2H, m, C*H*$_2$OH), 3.64 – 3.69 (2H, m, C*H*$_2$Br). All data is in accordance with the literature.

4-Iodobutyl benzoate **286**[149]



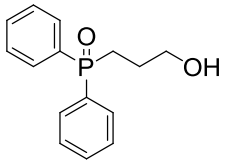
Benzoyl chloride (4.0 cm³, 37 mmol) was added dropwise to a solution of sodium iodide (6.00 g, 37 mmol) and THF (3.0 cm³, 37 mmol) in acetonitrile (10 cm³) at 0 °C. The mixture was

stirred in the dark for 18 hours before being poured into water (25 cm³). The organic phase was separated and the aqueous phase extracted with dichloromethane (3 × 15 cm³). The organic phases were combined, washed with brine (15 cm³) and dried over magnesium sulfate. Removal of the solvent *in vacuo* yielded a yellow oil. Purification of the crude material by flash column chromatography on silica gel using an eluent of 15% ethyl acetate: petroleum ether 40 – 60 °C afforded the title compound as a colourless oil (8.00 g, 73%). δ_H (400 MHz, $CDCl_3$) 1.89 – 1.95 (2H, m, C*H*$_2$), 1.96 – 2.07 (2H, m, C*H*$_2$), 3.28 (2H, t, *J* 6.6, C*H*$_2$I), 4.37 (2H, t, *J* 6.4, C*H*$_2$O), 7.45 – 7.50 (2H, m, ArC*H*), 7.57 – 7.61 (1H, m, ArC*H*), 8.05 – 8.07 (2H, m, ArC*H*). All data is in accordance with the literature.

General procedure F for the formation of the diphenylphosphine oxide moiety from the halogenated alcohol or ester

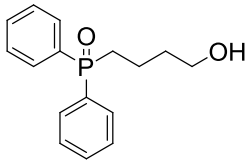
The halogenated alcohol or ester (7 mmol) was added dropwise to a suspension of sodium iodide (1.00 g, 7 mmol) and triphenylphosphine (2.00 g, 7.0 mmol) in acetonitrile (20 cm³) and the reaction mixture heated at reflux for 24 hours. The solution was cooled to room temperature and the solvent removed *in vacuo* to yield the phosphonium salt. The salt was dissolved in a 30% aqueous solution of NaOH (20 cm³) and methanol (10 cm³) and heated at reflux for 12 hours. The reaction mixture was poured into a saturated solution of ammonium chloride (20 cm³) and the aqueous phase extracted with dichloromethane (3 × 30 cm³). The organic layers were combined, washed with brine (10 cm³) and dried over magnesium sulfate. Removal of the solvent *in vacuo* afforded the crude material. Purification of the crude material occurred as described in the individual experimental details.

3-(Diphenylphosphinoyl)-1-propanol **155**[110,113]



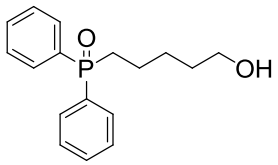
Prepared in accordance to general procedure **F** using 3-chloro-propan-1-ol (0.7 cm³, 7 mmol). Trituration of the crude material from diethyl ether (20 cm³) gave the title compound as a white crystalline solid (0.60 g, 24%). m.p. 95 °C (lit.[110,113] 95 – 96 °C); δ_H (400 MHz, $CDCl_3$) 1.83 – 1.93 (2H, m, C*H*$_2$), 2.42 (2H, dt, *J* 11.5 7.3, PC*H*$_2$), 3.69 - 3.72 (2H, m, C*H*$_2$OH), 4.23 (1H, br. s, O*H*), 7.45 – 7.55 (6H, m, ArC*H*), 7.72 – 7.77 (4H, m, ArC*H*); δ_P (101 MHz, $CDCl_3$) 34.7. All data is in accordance with the literature.

4-(Diphenylphosphinoyl)butan-1-ol **156**[110,113]



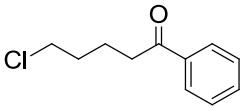
Prepared according to general procedure **F** using 4-iodobutyl benzoate **286** (2.00 g, 7 mmol). Purification of the crude material by flash column chromatography on silica gel using an eluent of 100% ethyl acetate afforded the title compound as a colourless oil (270 mg, 19%). δ_H (400 MHz, $CDCl_3$) 1.65 – 1.79 (4H, m, C*H*$_2$), 2.28 – 2.38 (2H, m, C*H*$_2$), 2.90 (1H, br.s, O*H*), 3.65 (2H, t, *J* 5.8, C*H*$_2$OH), 7.28 – 7.55 (6H, m, ArC*H*), 7.67 – 7.78 (4H, m, ArC*H*); δ_P (101 MHz, $CDCl_3$) 33.7. All data is in accordance with that of the literature.

5-(Diphenylphosphinoyl)pentan-1-ol **157**[110,113]



Prepared according to general procedure **F** using 5-bromopentan-1-ol **285** (1.00 g, 7 mmol). Purification of the crude material by flash column chromatography on silica gel using an eluent of 100% ethyl acetate afforded the title compound as a colourless oil (700 mg, 39%). δ_H (400 MHz, $CDCl_3$) 1.43 – 1.75 (6H, m, 3 × C*H*$_2$), 1.95 (1H, br. s, O*H*), 2.21 – 2.34 (2H, m, C*H*$_2$), 3.61 (2H, t, *J* 6.3, C*H*$_2$OH), 7.42 – 7.54 (6H, m, ArC*H*), 7.70 – 7.78 (4H, m, ArC*H*); δ_H (101 MHz, $CDCl_3$) 32.7. All data is in accordance with that of the literature.

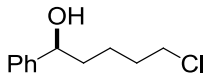
5-Chloro-1-phenyl-pentan-1-one **159**[111]



5-Chlorovaleronitrile (5.00 g, 5.0 cm³, 43 mmol) was added to THF (20 cm³) and the solution cooled to 0 °C. Phenyl magnesium bromide (29.0 cm³, 3M in THF, 86 mmol) was added dropwise over a period of 90 minutes and the reaction mixture warmed to room temperature and stirred overnight. A 10% aqueous solution of HCl (25 cm³) was added and the resulting suspension heated at reflux for 3 hours. The mixture was cooled to room temperature and the aqueous phase extracted with dichloromethane (3 × 30 cm³). The organic layers were combined, washed with 1M NaOH solution (20 cm³) and dried over magnesium sulfate. Removal of the solvent *in vacuo* yielded a yellow solid. Recrystallisation of the crude material from *n*-hexane

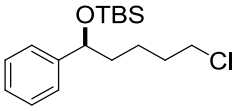
afforded the title compound as a white crystalline material (7.05 g, 81%); m.p. 50 – 51 °C (lit. 51 °C); δ_H (400 MHz, $CDCl_3$) 1.90 – 1.93 (4H, m, C*H*$_2$), 3.03 (2H, t, *J* 6.8, C*H*$_2$CO), 3.60 (2H, t, *J* 6.1, C*H*$_2$Cl), 7.48 (2H, app. t, *J* 7.8, ArC*H*), 7.58 (2H, app. t, *J* 5.3, ArC*H*), 7.96 – 7.98 (1H, m, ArC*H*). All data is in accordance with that of the literature.

(*S*)-5-Chloro-1-phenyl-pentan-1-ol **161**[150]



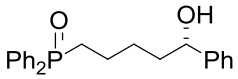
Trimethyl borate (0.1 cm³, 0.5 mmol) was added dropwise to a solution of (1*R*, 2*S*)-(+)-1-amino-2-indanol (0.80 g, 0.5 mmol) in THF (2.0 cm³) at 0 °C and the mixture stirred for 30 minutes. BH_3.DMS (0.50 cm³, 5 mmol) was added dropwise and stirring continued for a further 45 minutes. The ketone **159** (900 mg, 4 mmol) dissolved in THF (5 cm³) was introduced by syringe pump (1.8 cm³ / hr) at 0 °C and the mixture warmed to room temperature and stirred for a further 90 minutes following complete addition of the ketone **159**. Methanol (5.0 cm³) was added in a single portion and the aqueous phase extracted with dichloromethane (3 × 15 cm³). The organic layers were combined, washed with 1M HCl (10 cm³), brine (10 cm³) and dried over magnesium sulfate. Removal of the solvent *in vacuo* yielded a yellow oil. Purification of the crude material by flash column chromatography on silica gel using an eluent of 3% ethyl acetate: petroleum ether 40 – 60 °C afforded the title compound as a white fluffy solid (800 mg, 83%). A racemic version of the alcohol **161** was prepared through treatment of the ketone **159** with sodium borohydride. m.p. 37 °C (lit.[150] 37 – 38 °C); $[\alpha]_D^{25}$ – 17.4 [*c* 1.0 in benzene, lit.[150] -18.0 *c* 1.0 in benzene, 98% ee for (*S*)-isomer]; δ_H (400 MHz, $CDCl_3$) 1.40 – 1.51 (1H, m, C*H*H), 1.51 – 1.57 (1H, m, C*H*H), 1.70 – 1.87 (5H, m, 2 × C*H*$_2$ and O*H*), 3.54 (2H, t, *J* 6.8, C*H*$_2$Cl), 4.70 (1H, t, *J* 6.8, C*H*OH), 7.28 – 7.41 (5H, m, ArC*H*); δ_C (100 MHz, $CDCl_3$) 23.3 (C*H*$_2$), 32.5 (*C*H$_2$), 38.2 (*C*H$_2$), 44.9 (*C*H$_2$Cl), 74.4 (CHOH), 125.8 (2 × Ar*C*H), 127.7 (2 × Ar*C*H), 128.6 (Ar*C*H), 144.6 (Ar*C*). No ^{13}C NMR data is reported within the literature, otherwise all other data is in accordance. The enantioselectivity of this compound could not be assayed.

(*S*)-*tert*-Butyl(5-chloro-1-phenylpentyloxy)dimethylsilane **158**



(*S*)-5-Chloro-1-phenyl-pentan-1-ol **161** (1.00 g, 5 mmol) was added to a solution of 4-diaminomethylpyridine (0.20 g, 2 mmol) and triethylamine (2.00 g, 2.0 cm³, 15 mmol) in dichloromethane (20 cm³). The solution was cooled to 0 °C and *tert*-butyl(chloro)dimethylsilane (2.00 g, 10 mmol) added in a single portion. The reaction mixture was stirred for 18 hours before being poured into water (10 cm³). The organic phase was separated and aqueous layer extracted with diethyl ether (3 × 15 cm³). The organic layers were combined, washed with 1M NaOH (10 cm³), brine (10 cm³) and dried over magnesium sulfate. Removal of the solvent *in vacuo* yielded a yellow oil. Purification of the crude material by flash column chromatography on silica gel using an eluent of 10% ethyl acetate: petroleum ether 40 – 60 °C afforded the title compound as a colourless oil (936 mg, 60%). A racemic version of the molecule was prepared in analogous fashion from the racemic alcohol **161**. $[\alpha]_D^{25}$ - 33.0 (c 0.5 in $CHCl_3$); υ_{max} (ATR)/ cm^{-1} 3121, 3061, 1515; δ_H (400 MHz, $CDCl_3$) -0.12 (3H, s, SiC*H*$_3$), 0.05 (3H, s, SiC*H*$_3$), 0.91 [9H, s, (C*H*$_3$)$_3$], 1.37 – 1.55 [6H, m,(C*H*$_2$)$_3$], 3.52 (2H, t, *J* 6.9, C*H*$_2$Cl), 4.66 (1H, dd, *J* 7.5 4.8, C*H*), 7.22 – 7.34 (5H, m, ArC*H*); δ_C (100 MHz, $CDCl_3$) -4.9 (Si*C*H$_3$), -4.6 (Si*C*H$_3$), 18.3 (*C*[CH$_3$]$_3$), 23.0 (*C*H$_2$), 25.8 (3 × *C*H$_3$), 32.6 (*C*H$_2$), 40.1 (*C*H$_2$), 44.9 (*C*H$_2$), 74.8 (*C*H), 125.8 (2 × Ar*C*H), 126.9 (2 × Ar*C*H), 128.0 (Ar*C*H), 145.5 (Ar*C*); *m/z* (TOF) 317.1751 (100%, MH^+, $C_{17}H_{29}{}^{35}ClOSi$ requires 313.1754).

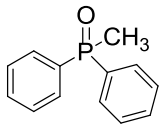
(*S*)-5-(Diphenylphosphoryl)-1-phenylpentan-1-ol **154**



(*S*)-t*ert*-Butyl(5-chloro-1-phenylpentyloxy)dimethylsilane **158** (0.10 g, 0.4 mmol) was added to a stirred suspension of triphenylphosphine (0.10 g, 0.4 mmol) and sodium iodide (0.06 g, 0.4 mmol) in acetonitrile (5.0 cm³) and the solution heated to reflux for 18 hours. The solvent was removed *in vacuo* to afford the crude phosphonium salt that was immediately dissolved in a 30% NaOH solution (10 cm³) and heated to reflux for a further 24 hours. The aqueous phase was extracted with dichloromethane (3 × 10 cm³), washed with an aqueous solution of $NaHCO_3$ (10 cm³) and dried over magnesium sulfate. Removal of the solvent *in vacuo* yielded a yellow oil. The crude material was dissolved in THF (10 cm³) and cooled to 0 °C. TBAF (1.5 cm³, 1M in THF, 0.8 mmol) was added dropwise and the solution warmed to room temperature and stirred for 24 hours. The reaction mixture was poured into water (5.0 cm³) and ethyl acetate (10

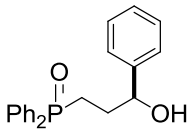
cm³) and the organic layer separated. The aqueous phase was extracted with ethyl acetate (3 × 10 cm³) and the organic layers combined, washed with 1M NaOH (10 cm³), brine (10 cm³) and dried over magnesium sulfate. Removal of the solvent *in vacuo* yielded a yellow oil. Purification of the crude material by flash column chromatography on silica gel using an eluent of 50% ethyl acetate: petroleum ether 40 – 60 °C afforded the title compound as a colourless oil (45 mg, 33%). A racemic version of the catalyst **154** was prepared in analogous fashion from the TBS protected alcohol **158**; t_R 10.5 min (*S* isomer) and 13.2 min (*R* isomer) (Celluose-1, 1: 1 hexane: propan-2-ol); $[\alpha]_D^{25}$ – 4.0 (91% ee from HPLC, *c* 0.2 in $CHCl_3$); υ_{max} (ATR) / cm^{-1} 3430, 1641, 1515; δ_H (400 MHz, $CDCl_3$) 1.41 – 1.85 (5H, m, C*H*$_2$), 2.18 – 2.30 (3H, m, C*H*$_2$), 4.64 – 4.67 (1H, m, C*H*OH), 7.26 – 7.36 (4H, m, ArC*H*), 7.46 – 7.56 (6H, m, ArC*H*), 7.71 – 7.75 (4H, m, ArC*H*); δ_C (100 MHz, $CDCl_3$) 21.3 (d, $J_{C\text{-}P}$ 4.0, *C*H_2), 27.0 (d, $J_{C\text{-}P}$ 14.0, *C*H_2), 29.5 (d, $J_{C\text{-}P}$ 71.0, *C*H_2), 38.6 (*C*H_2P), 73.7 (*C*HOH), 125.9 (2 × Ar*C*H), 127.1 (Ar*C*H), 128.2 (2 × Ar*C*H), 128.5 (2 × Ar*C*H), 128.7 (2 × ArCH), 130.6 (d, $J_{C\text{-}P}$ 4.0, 2 × Ar*C*H), 130.7 (d, $J_{C\text{-}P}$ 4.0, 2 × Ar*C*H), 131.65 (Ar*C*H), 131.68 (Ar*C*H), 132.3 (d, $J_{C\text{-}P}$ 8.4, Ar*C*), 133.4 (d, $J_{C\text{-}P}$ 8.4, Ar*C*), 145.2 (Ar*C*); δ_P (121 MHz, $CDCl_3$) 32.4; *m/z* (TOF ES^+) 365.1671 (100%, MH^+, $C_{23}H_{26}O_2P$ requires 365.1670), 347 (35, M^+-H_2O).

Methyl diphenylphosphine oxide **256**[109]



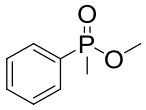
Diphenylphosphine oxide (1.00 g, 12 mmol) was dissolved in DMSO (15 cm³) and the reaction cooled to 0 °C. 1M potassium hydroxide solution (12 cm³) and methyl iodide (0.8 cm³, 14 mmol) were added sequentially and the solution heated to 80 °C for 1 hour. The reaction mixture was diluted with water (25 cm³) and the aqueous phase extracted with dichloromethane (3 × 20 cm³). The organic layers were combined, washed with brine (15 cm³) and dried over magnesium sulfate. The solvent was removed *in vacuo* to yield a white crystalline solid that required no further purification (2.60 g, 95%). m.p. 110 °C (lit.[109] 110 – 111 °C); δ_H ($CDCl_3$, 400 MHz) 2.02 (3H, d, $J_{C\text{-}P}$ 12.9, C*H*$_3$), 7.45 – 7.55 (6H, m, ArC*H*), 7.70 – 7.76 (4H, m, ArC*H*); δ_P ($CDCl_3$, 101 MHz) 29.8. All data is in accordance with that of the literature.

(*S*)-3-(Diphenylphosphoryl)-1-phenylpropan-1-ol **162**[113]



Methyldiphenylphosphine oxide **X** (0.50 g, 2 mmol) was dissolved in anhydrous THF (10 cm³) and the solution cooled to 0 °C. *n*-Butyl lithium (2.0 cm³, 2M in hexanes, 4 mmol) was added dropwise and the reaction mixture stirred for 90 minutes. (*S*)-2-Phenyloxirane (0.3 cm³, 2.5 mmol) was introduced and the solution warmed to room temperature and stirred overnight. The mixture was poured into a saturated ammonium chloride solution (10 cm³) and the aqueous phase extracted with diethyl ether (3 × 15 cm³). The organic layers were combined, washed with brine (15 cm³) and dried over magnesium sulfate. Removal of the solvent *in vacuo* afforded a yellow oil. Purification of the crude material by flash column chromatography on silica gel using an eluent of 10% methanol: ethyl acetate afforded the title compound as a white solid (604 mg, 78%). m.p. 127 °C (lit.**[113]** 127 – 129 °C); $[\alpha]_D^{25}$ - 11.5 [*c* 0.7 in $CHCl_3$, lit.**[113]**- 11.7 *c* 1.0 in $CHCl_3$]; δ_H ($CDCl_3$, 400 MHz) 1.99 – 2.20 (2H, m, C*H*$_2$), 2.33 – 2.50 (2H, m, C*H*$_2$), 2.65 (1H, br. s, O*H*), 4.86 (1H, dd, *J* 7.3, 4.2, C*H*), 7.25 – 7.35 (5H, m, ArC*H*), 7.46 – 7.57 (6H, m, ArC*H*), 7.70 – 7.77 (4H, m, ArC*H*); δ_P ($CDCl_3$, 101 MHz) 32.7. All data is in accordance with the literature.

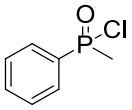
Methyl methyl(phenyl)phosphinate **277**[120]



Dichlorophenyl phosphine (9.00 g , 8 cm³, 55 mmol) was added dropwise to a solution of hexane (200 cm³) and freshly distilled pyridine (9 cm³, 110 mmol) at -10 °C and the mixture stirred for 20 minutes. Anhydrous methanol (6.0 cm³, 110 mmol) was introduced and the solution warmed to room temperature and stirred for a further 5 hours. The suspension was filtered and the filtrate removed *in vacuo* to afford dimethylphenylphosphonite as a colourless oil that required no further purification. The phosphonate (8.00 g, 55 mmol) was added dropwise to a two neck round bottom flask containing methyl iodide (0.1 cm³, 1.6 mmol) at a rate to maintain a steady reflux. The reaction mixture was stirred for a further 18 hours before being purified by vacuum distillation to afford the title compound as a colourless oil (8.05 g, 82%). bp 82-84 °C / 0.03 mmHg. (lit.[120] 80-85 °C / 0.4 mmHg); δ_H (400 MHz, $CDCl_3$) 1.69 (3H, d, $J_{P\text{-}H}$

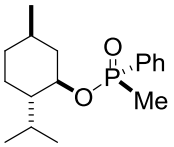
14.8, PC*H*$_3$), 3.63 (3H, d, $J_{P\text{-}H}$ 11.3, OC*H*$_3$), 7.47 – 7.62 (3H, m, ArC*H*), 7.76 – 7.85 (2H, m, ArC*H*); δ_P (101 MHz, $CDCl_3$) 44.0. All data is in accordance with the literature.

Methyl(phenyl)phosphinic chloride **166**[120]



Methyl methyl(phenyl)phosphinate **277** (6.00 g, 35 mmol) was dissolved in 1,2-dichloroethane (30 cm³) and the solution warmed to 40 °C. Phosphorus pentachloride (7.00 g, 35 mmol) was added in 1 g portions over a period of 45 minutes. The mixture was stirred for 18 hours and the solvent removed *in vacuo* to yield a yellow oil. Purification of the crude material by vacuum distillation afforded the title compound as a colourless oil (4.03 g, 71%). b.p. 117 °C / 0.6 mmHg (lit.**[120]** 122 °C / 0.5 mmHg); δ_H (250 MHz, $CDCl_3$) 2.18 (d, $J_{P\text{-}H}$ 15.0, PC*H*$_3$), 7.46 – 7.62 (3H, m, ArC*H*), 7.79- 7.88 (2H, m, ArC*H*); δ_P (121 MHz, $CDCl_3$) 51.6. All data is in accordance with that of the literature.

(*S*)-[(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl]methyl(phenyl)phosphinate **167**[117]



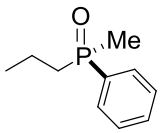
Methyl(phenyl)phosphinic chloride **166** (1.00 g, 5 mmol) was dissolved in anhydrous toluene (100 cm³) and the solution cooled to 0 °C. Triethylamine (1.0 cm³, 15 mmol) was added dropwise and the reaction mixture stirred for 10 minutes. (1*R*, 2*S*, 5*R*)-menthol (3.00 g, 17 mmol) dissolved in anhydrous toluene (10 cm³) was added in a single portion and the solution stirred for 8 hours. The reaction was filtered and the solvent removed *in vacuo* to afford a yellow oil as a 3:1 ratio of the two diastereoisomers. Purification of the crude material by flash column chromatography on silica gel using an eluent of 50% ethyl acetate: petroleum ether 40 – 60 °C yielded a white solid. Repeated recrystallisations of the purified material from hexane afforded the diastereotopically pure compound as a white crystalline material (900 mg, 21%). m.p. 79 °C (lit.**[117]** 79 – 80 °C); $[\alpha]_D^{25}$ - 94.2 (*c* 1.0 in C_6H_6, lit.**[117]** - 95.0 *c* 1.0 in C_6H_6); δ_H (400 MHz, $CDCl_3$) 0.31 (3H, d, *J* 6.8, C*H*$_3$), 0.80 [3H, d, *J* 7.2, 1 × CH(C*H*$_3$)$_2$], 0.82 – 0.93 (2H, m, C*H*$_2$), 0.95 [3H, d, *J* 7.2, 1 × CH(C*H*$_3$)$_2$], 1.20 – 1.47 (3H, m, C*H*), 1.54 – 1.58 (2H, m, C*H*), 1.72 (3H, d, $J_{P\text{-}H}$ 14.7, PC*H*$_3$), 1.96 – 2.31 (1H, m, C*H*), 2.31 – 2.41 (1H, m, C*H*), 3.96 (1H, dddd, *J* 14.9 7.8 6.1 4.4, C*H*OP), 7.46 – 7.56 (3H, m, ArC*H*), 7.79 – 7.85 (2H, m, ArC*H*); δ_C

(100 MHz, $CDCl_3$) 15.2 (*C*H_3), 16.5 (d, $J_{C\text{-}P}$ 102.0, P*C*H_3), 21.1 (*C*H_3), 21.9 (*C*H_3), 22.7 (*C*H_2), 25.4 (*C*H), 31.6 (*C*H), 34.1 (*C*H_2), 43.9 (*C*H_2), 48.7 (d, $J_{C\text{-}P}$ 7.0, *C*H), 76.7 (OC*H*), 128.4 (d, $J_{C\text{-}P}$ 13.0, 2 × Ar*C*H), 131.1 (d, $J_{C\text{-}P}$ 10.0, 2 × Ar*C*H), 131.8 (d, $J_{C\text{-}P}$ 19.0, Ar*C*H), 132.0 (d, $J_{C\text{-}P}$ 105.0, Ar*C*); δ_P (101 MHz, $CDCl_3$) 40.4. No carbon NMR data is reported within the literature, otherwise all other data is in accordance.

General procedure G for the preparation of *P*-chiral phosphine oxides from the menthyl phosphonate 167.

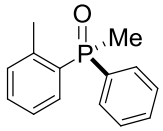
Menthyl phosphinate **167** (300 mg, 1 mmol) was added in a single portion to a solution of the appropiate Grignard reagent (3 mmol) in anhydrous toluene (10 cm³) at 70 °C and the mixture stirred for 18 hours. Upon cooling to room temperature, the solution was poured into water (50 cm³) and the organic phase separated. The aqueous layer was extracted with ethyl acetate (3 × 20 cm³) and the organic layers were combined, washed with brine (20 cm³) and dried over magnesium sulfate. Removal of the solvent *in vacuo* yielded the crude phosphine oxide which was purified as described in the individual experimental details. Racemic samples of the phosphine oxide were prepared from addition of the Grignard reagent to the phosphinic chloride **166**.

(R_P)-(+)-Methylphenylpropyl phosphine oxide **169**[117]



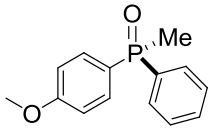
Prepared according to general procedure **G** from *n*-propylmagnesium bromide (3.0 cm³, 1M in toluene , 3 mmol). Purification of the crude material by flash column chromatography on silica gel using an eluent of 5% methanol: dichloromethane afforded the title compound as a colourless oil (0.05 g, 27%). t_R 17.1 (minor isomer) and 27.2 (major isomer) (Celluose-2, 90: 10 hexane: propan-2-ol, 210nm); $[\alpha]_D^{25}$ + 16.0 (>99% ee, *c* 1.0 in CH_3OH, lit.[117]+ 14.8 *c* 1.0 in CH_3OH, >95% ee); δ_H (400 MHz, $CDCl_3$) 0.94 (3H, t, *J* 7.3, C*H*$_3$CH$_2$), 1.42 – 1.61 (2H, m, C*H*$_2$), 1.64 (3H, d, $J_{P\text{-}H}$ 12.7, PC*H*$_3$), 1.77 – 1.96 (2H, m, C*H*$_2$); 7.41 – 7.49 (3H, m, ArC*H*), 7.63 – 7.69 (2H, m, ArC*H*); δ_C (100 MHz, $CDCl_3$) 15.3 (d, $J_{C\text{-}P}$ 3.8, CH_3CH_2); 15.5 (d, $J_{C\text{-}P}$ 17.5, P*C*H_3), 16.4 (*C*H_3), 33.8 (d, $J_{C\text{-}P}$ 70.1, *C*H_2), 128.6 (d, $J_{C\text{-}P}$ 10.7, Ar*C*H), 129.9 (d, $J_{C\text{-}P}$ 9.2, 2 × Ar*C*H), 131.5 (d, $J_{C\text{-}P}$ 3.1, 2 × Ar*C*H), 133.6 (d, $J_{C\text{-}P}$ 94.5, Ar*C*); δ_P (121 MHz, $CDCl_3$) 37.0. No ^{13}C NMR data is reported within the literature, otherwise all other data is in accordance.

(S_P)-(-)-Methylphenyl-*o*-tolyl phosphine oxide **170**[151]



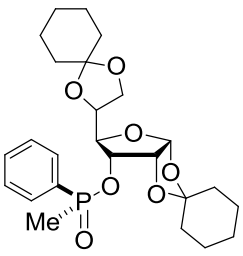
Prepared according to general procedure **G** from 2-tolylmagnesium bromide (6.0 cm³ 0.5M in toluene, 3 mmol). Purification of the crude material by flash column chromatography on silica gel using an eluent of 5% methanol: dichloromethane afforded the title compound as a colourless oil (53 mg, 25%). t_R 16.3 (major isomer) and 23.9 (minor isomer) (Chiralpak-IA, 90: 10 hexane: propan-2-ol, 254 nm); $[\alpha]_D^{25}$ - 28.0 [>99% ee, *c* 1.0 in $CHCl_3$, lit.[151] + 16.1 for the (*R*)-enantiomer, 62% ee]; δ_H (250 MHz, $CDCl_3$) 2.03 (3H, d, J_{P-H} 13.3, PCH_3); 2.38 (3H, s, CH_3), 7.20 – 7.33 (2H, m, ArC*H*), 7.40 – 7.53 (4H, m, ArC*H*), 7.61 – 7.72 (3H, m, ArC*H*); δ_P (101 MHz, $CDCl_3$) 31.4. All data is in accordance with the literature.

(S_P)-(-)-Methylphenyl-*p*-anisyl phosphine oxide **171**[117]



Prepared according to general procedure **G** from 4-anisylmagnesium bromide (3 cm³, 1M in toluene, 3 mmol). Purification of the crude material by flash column chromatography on silica gel using an eluent of 5% methanol: dichloromethane afforded the title compound as a white crystalline solid (62 mg, 25%). m.p. 120 °C (lit.[117] 120 – 121 °C); $[\alpha]_D^{25}$ + 8.0 [>99% ee, *c* 1.0 in CH_3OH, lit.[117] – 8.0 *c* 1.0 in CH_3OH for the (*S*)-enantiomer, >95% ee]; δ_H (250 MHz, $CDCl_3$) 1.94 (3H, d, J_{P-H} 13.2, PCH_3), 3.79 (3H, s, OCH_3), 6.90 – 6.96 (2H, m, ArC*H*), 7.37 – 7.47 (3H, m, ArC*H*), 7.57 – 7.66 (4H, m, ArC*H*); δ_P (121 MHz, $CDCl_3$) 29.6. All data is in accordance with the literature.

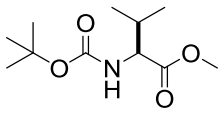
Dicyclohexylidene-*D*-glucose-(*S*)-methylphenyl phosphinate ester **173**[122]



Triethylamine (2.0 cm³, 15 mmol) was added dropwise to a solution of methylphenylphosphinic chloride **166** (880 mg, 5 mmol) in anhydrous toluene (20 cm³) at 0 °C. The suspension was stirred for 30 minutes before di-*o*-cyclohexylidene-α-D-glucofuranose **X** (2.00 g, 6 mmol)

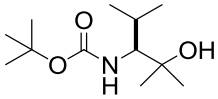
dissolved in anhydrous toluene (10 cm³) was introduced over a period of 20 minutes. The reaction was warmed to room temperature, filtered and the solvent removed *in vacuo* to afford an orange oil as a 91:9 diastereotopic mixture as determined by analysis of the ^{1}H crude NMR spectra. Purification and isolation of the major diastereoisomer by flash column chromatography on silica gel using an eluent of 100% diethyl ether afforded a diastereotopically pure white crystalline solid (2.74 g, 54%). m.p. 49 – 50 °C (lit.[122] 49 – 51 °C); $[\alpha]_D^{25}$ - 58.0 (*c* 1.0 in $CHCl_3$, lit.[122] - 58.6 *c* 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.36 – 1.67 (20H, m, C*H*$_2$), 1.73 (3H, d, $J_{P\text{-}H}$ 23.6, PC*H*$_3$) 3.99 – 4.08 (2H, m, C*H*$_2$), 4.14 (1H, dd, *J* 8.0 6.6, C*H*), 4.31 (1H, ddd, *J* 8.0 5.9 4.6, C*H*), 4.45 (1H, dd, *J* 6.9 2.5, C*H*), 5.12 (1H, d, *J* 3.8, C*H*), 5.97 (1H, d, *J* 3.8, C*H*), 7.46 – 7.55 (2H, m, ArC*H*), 7.57 – 7.65 (1H, m, ArC*H*), 7.91 – 7.99 (2H, m, ArC*H*); δ_P (121 MHz, $CDCl_3$) 45.1. All data is in accordance with that of the literature

(*S*)-Methyl 2-(tert-butoxycarbonylamino)-3-methylbutanoate **278**[128]



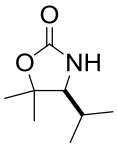
L-Valine (5.00 g, 43 mmol) was added in a single portion to methanol (200 cm³) and the resulting suspension cooled to 0 °C. Thionyl chloride (5.0 cm³, 65 mmol) was added dropwise over a period of 60 minutes. The solution was warmed to room temperature and stirred for 36 hours. The solvent was removed *in vacuo* to afford L-Valine methyl ester hydrochloride as a white solid which was used without further purification. The methyl ester (7.00 g, 43 mmol) was added in a single portion to a suspension of sodium hydrogen carbonate (11 g, 128 mmol) in ethanol (100 cm³) at 0 °C and stirred for 30 minutes. Di-*tert*-butyl dicarbonate (9.78 g, 44.8 mmol) was introduced in a single portion and the suspension warmed to room temperature and stirred for 24 hours. The reaction mixture was filtered and the solvent removed *in vacuo* to afford the title compound as a colourless oil that required no further purification (8.50 g, 85%); $[\alpha]_D^{25}$ + 11.4 (*c* 2.5 in $CHCl_3$, lit.[128] + 11.2 *c* 2.5 in $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 0.78 (3H, d, *J* 6.9, C*H*$_3$), 0.85 (3H, d, *J* 6.9, C*H*$_3$), 1.33 [9H, s, C(C*H*$_3$)$_3$], 1.93 – 2.11 [1H, m, C*H*(CH$_3$)$_2$], 3.62 (3H, s, OC*H*$_3$), 4.10 (1H, dd, *J* 9.1 5.0, C*H*), 5.07 (1H, d, *J* 9.1, N*H*). All data is in accordance with the literature.

(*S*)-*tert*-Butyl 2-hydroxy-2,4-dimethylpentan-3-yl-carbamate **279**[128]



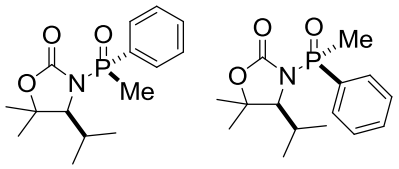
The *N*-boc protected ester **278** (5.00 g, 22 mmol) was dissolved in THF (30 cm³) and the solution cooled to 0 °C. Methyl magnesium bromide (29.0 cm³, 3M in Et_2O, 86 mmol) was added dropwise and the mixture warmed to room temperature and stirred for 18 hours. A saturated solution of ammonium chloride (20 cm³) was added dropwise and the aqueous phase extracted with ethyl acetate (3 × 50 cm³). The organic layers were combined, washed with brine (30 cm³) and dried over magnesium sulfate. Removal of the solvent *in vacuo* yielded a crude yellow oil. Purification of the crude material by flash column chromatography on silica gel using an eluent of 10% ethyl acetate: petroleum ether 40 – 60 °C afforded the title compound as a colourless oil (5.08 g, 96%). $[\alpha]_D^{25}$ - 6.0 (*c* 1.0 in $CHCl_3$, lit.**[128]** - 6.0 *c* 1.0 in $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 0.88 [6H, app. t, *J* 7.3, CH(C*H*$_3$)$_2$], 1.18 [3H, s, 1 × C(C*H*$_3$)$_2$OH], 1.22 [3H, s, 1 × C(C*H*$_3$)$_2$OH], 1.44 [9H, s, C(C*H*$_3$)$_3$], 2.07 [1H, septd, *J* 6.8, 2.6, C*H*(CH$_3$)$_2$], 2.25 (1H, s, O*H*), 3.33 (1H, dd, *J* 10.4, 2.6, C*H*), 4.92 (1H, d, *J* 10.4, N*H*). All data is in accordance with the literature.

(4*S*)-5,5-Dimethyl-4-isopropyloxazolidin-2-one **174**[128]



(*S*)-Methyl-2-(*tert*-butoxycarbonylamino)-3-methylbutanoate **279** (4.90 g, 22 mmol) was dissolved in anhydrous THF (10 cm³) and the solution cooled to 0 °C. Potassium *tert*-butoxide (2.70 g, 26.4 mmol) was added in a single portion and the mixture stirred for 4 hours. The solvent was evaporated and the residue taken up in ethyl acetate (50 cm³), washed with brine (20 cm³) and dried over magnesium sulfate. Removal of the solvent *in vacuo* afforded a yellow solid which was recrystallised from petroleum ether 40 – 60 °C to afford the title compound as a white crystalline material (2.40 g, 68%). m.p. 86 °C (lit.[128] 87 °C); $[\alpha]_D^{25}$ + 24.0 [*c* 1.0 in $CHCl_3$, lit.[128] -24.2 *c* 1.0 in $CHCl_3$ for the (*R*)-enantiomer]; δ_H (400 MHz, $CDCl_3$) 0.93 [3H, s, 1 × CH(C*H*$_3$)$_2$], 1.01 [3H, s, 1 × CH(C*H*$_3$)$_2$], 1.40 (3H, d, *J* 6.6, C*H*$_3$), 1.50 (3H, d, *J* 6.6, C*H*$_3$), 1.83 [1H, dhept, *J* 8.6 6.6, C*H*(CH$_3$)$_2$], 3.20 (1H, d, *J* 8.6, C*H*NH), 6.41 (1H, s, N*H*). All data is in accordance with the literature.

(*S*)-4-Isopropyl-5,5-dimethyl-3-[(*R*)-methyl(phenyl)phosphinyl]oxazolidin-2-one **178a** and (*S*)-4-isopropyl-5,5-dimethyl-3-[(*S*)-methyl(phenyl)phosphinyl]oxazolidin-2-one **178b**



178a **178b**

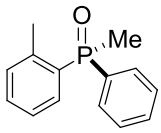
Oxazolidinone **174** (1.20 g, 7 mmol) was added in a single portion to a solution of freshly distilled triethylamine (1.5 cm³, 10 mmol) and lithium chloride (350 mg, 8.4 mmol) in anhydrous THF (10 cm³). The suspension was cooled to -20 °C and methyl(phenyl)phosphinic chloride **166** (1.30 g, 7 mmol) added dropwise over a period of 10 minutes. The mixture was warmed to room temperature and stirred for 24 hours before being quenched through addition of 1N HCl (10 cm³). The aqueous phase was extracted with ethyl acetate (3 × 20 cm³), washed with brine (10 cm³) and dried over magnesium sulfate. Removal of the solvent *in vacuo* afforded a yellow oil of 95: 5 diastereoselectivity as determined by analysis of the crude ^{1}H NMR data. Purification and separation of the diastereotopic mixture by flash column chromatography on silica gel using an eluent of 75% ethyl acetate: petroleum ether 40 – 60 °C afforded a diastereotopically pure white crystalline solid **178a** as the major diastereoisomer (1.40 g, 63%) and compound **178b** as the minor diastereoisomer (50 mg, 2.5%). *major diastereoisomer* **178a** m.p. 129 - 130 °C; $[\alpha]_D^{25}$ + 50.0 (*c* 1.0 in $CHCl_3$); υ_{max} (ATR) / cm^{-1} 2986, 2969, 2928, 1741; (Found C, 61.00; H, 7.67; N, 4.63; $C_{15}H_{22}NO_3P$ requires C, 61.01; H, 7.51; N, 4.74%); δ_H (400 MHz, $CDCl_3$) 0.72 (3H, d, *J* 6.9, C*H*$_3$), 0.76 (3H, d, *J* 6.9, C*H*$_3$), 1.49 (3H, s, C*H*$_3$), 1.51 (3H, s, C*H*$_3$), 1.97 [1H, heptd, *J* 6.9, 2.0, C*H*$(CH_3)_2$], 2.08 (3H, d, *J* 14.4, PC*H*$_3$), 3.98 (1H, dd, *J* 3.3, 2.0, C*H*N), 7.47 – 7.59 (3H, m, ArC*H*), 8.08 – 8.12 (2H, m, ArC*H*); δ_C (100 MHz, $CDCl_3$) 16.5 (*C*H_3), 16.7 (d, $J_{C\text{-}P}$ 87.0, P*C*H_3), 20.2 (*C*H_3), 21.5 (*C*H_3). 28.9 (*C*H_3), 29.8 (*C*H_3), 68.7 (*C*HN), 84.6 [d, $J_{C\text{-}P}$ 6.0, O*C*$(CH_3)_2$], 128.5 (d, $J_{C\text{-}P}$ 13.7, 2 × Ar*C*H), 131.0 (d, $J_{C\text{-}P}$ 11.4, 2 × Ar*C*H), 132.5 (d, $J_{C\text{-}P}$ 2.3, Ar*C*H), 132.9 (d, $J_{C\text{-}P}$ 121.9, Ar*C*), 157.0 (d, $J_{C\text{-}P}$ 8.0, *C*O); δ_P (121 MHz, $CDCl_3$) 34.3; *m/z* (TOF ES$^+$) 296.1402 (MH^+, 100%, $C_{15}H_{23}NO_3P$ requires 296.1416). *minor diastereoisomer* **178b** m.p. 116 - 118 °C; $[\alpha]_D^{25}$ + 21.0 (*c* 1.0 in $CHCl_3$); υ_{max} (FTR)/ cm^{-1} 2969, 2928, 1741; δ_H (400 MHz, $CDCl_3$) 1.06 (3H, d, *J* 6.9, C*H*$_3$), 1.11 (3H, s, C*H*$_3$), 1.16 (3H, d, *J* 6.9, C*H*$_3$), 1.45 (3H, s, C*H*$_3$), 2.16 [1H, heptd, *J* 6.9 2.0, C*H*$(CH_3)_2$], 2.23 (3H, d, $J_{P\text{-}H}$ 14.8, PC*H*$_3$), 3.77 (1H, dd, *J* 3.4 2.0, C*H*N), 7.47 – 7.59 (3H, m, ArC*H*), 7.89 – 7.95 (2H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 15.9 (d, $J_{C\text{-}P}$ 89.3, P*C*H_3), 17.1 (*C*H_3), 20.4 (*C*H_3), 21.5 (*C*H_3), 28.8 (*C*H_3), 30.2 (*C*H_3), 68.5 (*C*HN), 84.2 [d, $J_{C\text{-}P}$ 5.3, O*C*$(CH_3)_2$], 128.4 (d, $J_{C\text{-}P}$ 13.7, 2 × Ar*C*H), 130.9 (d, $J_{C\text{-}P}$ 9.9, 2 × Ar*C*H), 132.2 (Ar*C*), 132.7 (d, $J_{C\text{-}P}$ 2.3, Ar*C*H), 156.3 (d, $J_{C\text{-}P}$ 7.6, *C*O); δ_P

(121 MHz, $CDCl_3$) 34.2; *m/z* (TOF ES^+) 296.1402 (MH^+, 100%, $C_{15}H_{23}NO_3P$ requires 296.1416).

General procedure H for the preparation of diaryl methyl *P*-chiral phosphine oxides from the *N*-phosphinoyl oxazolidinone 178

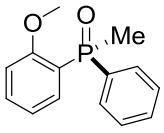
N-phosphinoyl oxazolidinone **178** (297 mg, 1 mmol) was dissolved in anhydrous THF (5 cm^3) and the solution cooled to 0 °C. The Grignard reagent (2 mmol) was added dropwise and the reaction mixture warmed to room temperature and stirred for 45 minutes. 1*N* HCl solution (5 cm^3) was added dropwise and the aqueous phase extracted with dichloromethane (3 × 10 cm^3). The organic phases were combined, washed with brine (10 cm^3) and dried over magnesium sulfate. Removal of the solvent *in vacuo* yielded the crude phosphine oxide. Purification of the crude material occurred as described in the individual experimental details. Racemic samples of the phosphine oxide were prepared from addition of the Grignard reagent to the phosphinic chloride **166**. Characterisation of the chiral phosphine oxides were made from the racemic samples.

(S_P)-(-)-Methylphenyl-*o*-tolyl phosphine oxide **170**[150]



Prepared according to general procedure **H** using 2-tolylmagnesium bromide (4.0 cm^3, 0.5M in THF, 2 mmol). Purification of the crude material by flash column chromatography on silica gel using a gradient eluent of 75% ethyl acetate: petroleum ether 40 – 60 °C to 5% methanol: dichloromethane afforded the oxazolidinone **174** as a yellow solid (144 mg, 95%) and the phosphine oxide as a white crystalline material (191 mg, 83%). All data was consistent with the previous synthesis of the species from general procedure **G**.

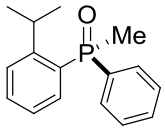
(S_P)-2-*o*-Methoxyphenylmethylphenyl phosphine oxide **172**[152]



Prepared according to general procedure **H** using 2-anisylmagnesium bromide (2.0 cm^3, 1M in THF, 2 mmol). Purification of the crude material by flash column chromatography on silica gel using a gradient eluent of 75% ethyl acetate: petroleum ether 40 – 60 °C to 5% methanol:

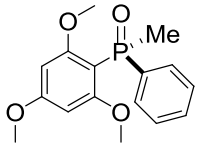
dichloromethane afforded the oxazolidinone **174** as a yellow solid (144 mg, 95%) and the phosphine oxide as a white crystalline material (209 mg, 85%). t_R 24.7 (minor isomer) and 27.6 (major isomer) (Celluose-1, 90:10 hexane: propan-2-ol, 210 nm); m.p. 129 °C (lit.[152]128 – 131 °C); $[\alpha]_D^{25}$ – 23.0 (>99% ee, *c* 1.0 in $CHCl_3$, lit. [152] - 25.5 *c* 1.0 in MeOH, >99% ee); δ_H (400 MHz, $CDCl_3$) 2.10 (3H, d, $J_{P\text{-}H}$ 13.9, PCH_3), 3.75 (3H, s, OCH_3), 6.90 (1H, dd, *J* 8.3, 5.4, ArC*H*), 7.12 (1H, t, *J* 7.4, ArC*H*), 7.42 – 7.55 (4H, m, ArC*H*), 7.74 – 7.79 (2H, m, ArC*H*), 7.99 (1H, ddd, *J* 13.0, 7.5, 1.8, ArC*H*); δ_P (101 MHz, $CDCl_3$) 28.6. All data is in accordance with the literature

(S_P)-2-*iso*-Propylphenylmethylphenyl phosphine oxide **289**[120]



Prepared according to general procedure **H** using *iso*-propylphenylmagnesium bromide (2 cm³, 1M in THF, 2 mmol). Purification of the crude material by flash column chromatography using a gradient eluent of 75% ethyl acetate: petroleum ether 40 – 60 °C to 5% methanol: dichloromethane afforded the oxazolidinone **174** as a yellow crystalline material (143 mg, 91%) and the phosphine oxide as a white solid (108 mg, 42%). t_R 39.4 (minor isomer) and 48.2 (major isomer) (CHIRALPAK-AS, 95: 5 hexane: propan-2-ol, 254 nm); m.p. 141 °C; $[\alpha]_D^{25}$ - 34.0 (>99% ee, *c* 1.0 in $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 0.85 [3H, d, *J* 6.8, 1 × CH(CH_3)$_2$), 1.14 [3H, d, *J* 6.8, 1 × CH(CH_3)$_2$], 2.06 (3H, d, $J_{P\text{-}H}$ 13.0, PCH_3), 3.48 [1H, heptet, *J* 6.8, C*H*(CH_3)$_2$], 7.27 – 7.76 (9H, m, ArC*H*); δ_P (121 MHz, $CDCl_3$) 31.2. No melting point data or optical rotation value is reported within the literature, otherwise all data is in accordance.

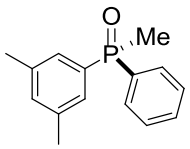
(S_P)-2, 4, 6-trimethoxyphenylmethylphenyl phosphine oxide **290**



Prepared according to general procedure **H** using 2, 4, 6-trimethoxyphenylmagnesium bromide (4 cm³, 0.5M in THF, 2 mmol). Purification of the crude material by flash column chromatography on silica gel using a gradient eluent of 75% ethyl acetate: petroleum ether 40 – 60 °C to 5% methanol: dichloromethane afforded the oxazolidinone **X** as a yellow crystalline material (133 mg, 86%) and the phosphine oxide as a white solid (162 mg, 53%). t_R 33.3 (minor isomer) and 49.6 (major isomer) (Celluose-1, 90:10 hexane: propan-2-ol, 210 nm); m.p. 133 °C;

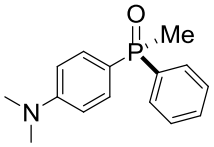
$[\alpha]_D^{25}$ - 28.1 (>99% ee, *c* 1.0 in $CHCl_3$); υ_{max} (ATR) / cm^{-1} 3201, 1599, 1577, 1229; δ_H (400 MHz, $CDCl_3$) 1.98 (3H, d, J_{P-H} 14.0, PC*H*$_3$), 3.58 (6H, s, 2 × OC*H*$_3$), 3.82 (3H, s, OC*H*$_3$), 6.06 (2H, d, *J* 3.6, 2 × ArC*H*), 7.35 – 7.41 (3H, m, ArC*H*), 7.64 – 7.67 (2H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 21.8 (d, J_{C-P} 76.0, P*C*H$_3$), 55.4 (O*C*H$_3$), 55.5 (2 × O*C*H$_3$), 91.0 (Ar*C*H), 91.1 (Ar*C*H), 127.8 (d, J_{C-P} 13.0, 2 × Ar*C*H), 129.2 (d, J_{C-P} 10.0, 2 × Ar*C*H), 130.0 (d, J_{C-P} 3.0, Ar*C*H), 138.9 (d, J_{C-P} 107.0, Ar*C*), 164.0 (2 × Ar*C*OCH$_3$), 165.0 (Ar*C*OCH$_3$); δ_P (121 MHz, $CDCl_3$) 27.1; *m/z* (TOF ES^+) 307.1105 (MH^+, 100%, $C_{16}H_{20}O_4P$ requires 307.1099). No data is reported within the literature.

(S_P)-3,5-Dimethylphenylmethylphenyl phosphine oxide **291**



Prepared according to general procedure **H** using 3,5-dimethylphenylmagnesium bromide (1.0 cm³, 2M in THF, 2 mmol). Purification of the crude material by flash column chromatography on silica gel using a gradient eluent of 75% ethyl acetate: petroleum ether 40 – 60 °C to 5% methanol: dichloromethane afforded the oxazolidinone **174** as a yellow crystalline material (143 mg, 91%) and the phosphine oxide as a white solid (222 mg, 91%). t_R 87.2 (minor isomer) and 96.3 (major isomer) (CHIRALPAK-IA, 90: 10 hexane: propan-2-ol, 254 nm); m.p. 82 °C; $[\alpha]_D^{25}$ - 8.0 (>99% ee, *c* 0.5 in $CHCl_3$); υ_{max} (ATR) / cm^{-1} 2976, 1600, 1441; (Found C, 73.58; H, 7.04; $C_{15}H_{17}OP$ requires C, 73.76; H, 7.01%); δ_H (400 MHz, $CDCl_3$) 1.99 (3H, d, J_{P-H} 13.2, PC*H*$_3$), 2.33 (6H, s, 2 × C*H*$_3$), 7.13 (1H, s, ArC*H*), 7.32 (2H, d, *J* 12.2, 2 × ArC*H*), 7.42 – 7.52 (3H, m, ArC*H*), 7.69 – 7.73 (2H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 16.5 (d, J_{C-P} 73.5, P*C*H$_3$), 21.3 (2 × *C*H$_3$), 128.1 (d, J_{C-P} 9.7, 2 × Ar*C*H), 128.6 (d, J_{C-P} 11.9, 2 × Ar*C*H), 130.5 (d, J_{C-P} 9.8, 2 × Ar*C*H), 131.5 (d, J_{C-P} 2.4, Ar*C*H), 133.4 (d, J_{C-P} 2.4, Ar*C*H), 133.6 (d, J_{C-P} 76.0, Ar*C*), 134.6 (d, J_{C-P} 76.0, Ar*C*), 138.3 (d, J_{C-P} 12.4, 2 × Ar*C*); δ_P (101 MHz, $CDCl_3$) 29.9; *m/z* (TOF ES^+) 245.1093 (100%, MH^+, $C_{15}H_{18}OP$ requires 245.1095).

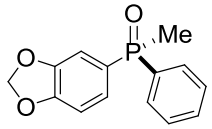
(S_P)-4-Dimethylaminophenylmethylphenyl phosphine oxide **292**



Prepared according to general procedure **H** using 4-dimethylaminophenylmagenesium bromide (4.0 cm³, 0.5M in THF, 2 mmol). Purification of the crude material by flash column chromatography using a gradient eluent of 75% ethyl acetate: petroleum ether 40 – 60 °C to 5%

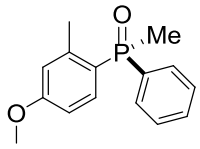
methanol: dichloromethane afforded the oxazolidinone **174** as a yellow crystalline material (149 mg, 95%) and the phosphine oxide as a white solid (241 mg, 93%). t_R 31.6 min (minor isomer) and 36.9 (major isomer) (Celluose-1, 90: 10 hexane: propan-2-ol, 285 nm); m.p. 134 – 136 °C; $[\alpha]_D^{25}$ - 22.0 (97% ee, *c* 0.5 in $CHCl_3$); υ_{max} (ATR) / cm^{-1} 2975, 1603, 1520, 1442; (Found C, 69.86; H, 6.95; N, 5.40; $C_{15}H_{18}NOP$ requires C, 69.48; H, 7.00; N, 5.40%); δ_H (400 MHz, $CDCl_3$) 1.97 (3H, d, *J* 13.1, PC*H*$_3$), 3.03 (6H, s, 2 × NC*H*$_3$), 6.73 (2H, dd, *J* 8.9, 2.2, 2 × ArC*H*), 7.44 – 7.52 (3H, m, ArC*H*), 7.56 (2H, dd, *J* 11.4, 8.9, 2 × ArC*H*), 7.70 – 7.75 (2H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 16.8 (d, $J_{C\text{-}P}$ 73.5, P*C*H$_3$), 39.9 (2 × N*C*H$_3$), 111.4 (d, $J_{C\text{-}P}$ 12.5, 2 × Ar*C*H), 118.4 (d, $J_{C\text{-}P}$ 111.8, Ar*C*), 128.4 (d, $J_{C\text{-}P}$ 11.6, 2 × Ar*C*H), 130.5 (d, $J_{C\text{-}P}$ 9.9, 2 × Ar*C*H), 131.2 (d, $J_{C\text{-}P}$ 2.4, Ar*C*H), 131.9 (d, $J_{C\text{-}P}$ 10.9, 2 × Ar*C*H), 135.3 (d, $J_{C\text{-}P}$ 100.6, Ar*C*), 152.3 (d, $J_{C\text{-}P}$ 2.1, Ar*C*); δ_P (101 MHz, $CDCl_3$) 29.8; *m/z* (TOF ES^+) 260.1204 (100%, MH^+, $C_{15}H_{19}NOP$ requires 260.1204).

(S_P)-Benzo[1,3]dioxolephenylmethyl phosphine oxide **292**



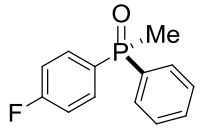
Prepared according to general procedure **H** using benzo[1,3]dioxol-5-ylmagnesium bromide (0.9 cm^3, 2.2 M in THF, 2 mmol). Purification of the crude material by flash column chromatography on silica gel using a gradient eluent of 75% ethyl acetate: petroleum ether 40 – 60 °C to 5% methanol: dichloromethane afforded the oxazolidinone **174** (143 mg, 91%) and the phosphine oxide as a white solid (223 mg, 86%). t_R 27.0 min (minor isomer) and 30.6 min (major isomer) (Celluose-1, 90: 10 hexane: propan-2-ol, 254 nm); m.p. 122 – 123 °C; $[\alpha]_D^{25}$ - 8.0 (97% ee, *c* 1.0 in $CHCl_3$); υ_{max} (ATR) / cm^{-1} 2943, 1483, 1400; (Found C, 64.41; H, 4.87; $C_{14}H_{13}O_3P$ requires C, 64.62; H, 5.04%); δ_H (400 MHz, $CDCl_3$) 1.96 (3H, d, $J_{P\text{-}H}$ 13.2, PC*H*$_3$), 5.98 (2H, s, C*H*$_2$), 6.86 (1H, dd, *J* 7.9, 2.3, ArC*H*), 7.09 (1H, dd, *J* 11.4, 1.4, ArC*H*), 7.25 (1H, ddd, *J* 12.5, 7.9, 1.4, ArC*H*), 7.42 – 7.50 (3H, m, ArC*H*), 7.66 – 7.72 (2H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 16.7 (d, $J_{C\text{-}P}$ 73.7, P*C*H$_3$), 101.6 (*C*H$_2$), 108.7 (d, $J_{C\text{-}P}$ 14.7, Ar*C*H), 110.1 (d, $J_{C\text{-}P}$ 13.0, Ar*C*H), 125.7 (d, $J_{C\text{-}P}$ 10.7, Ar*C*H), 127.2 (d, $J_{C\text{-}P}$ 104.4, Ar*C*), 128.6 (d, $J_{C\text{-}P}$ 11.8, 2 Ar*C*H), 130.4 (d, $J_{C\text{-}P}$ 9.8, 2 × Ar*C*H), 131.6 (d, $J_{C\text{-}P}$ 2.5, Ar*C*H), 134.2 (d, $J_{C\text{-}P}$ 101.2 × Ar*C*), 148.0 (d, $J_{C\text{-}P}$ 17.9, Ar*C*), 150.6 (d, $J_{C\text{-}P}$ 2.7, Ar*C*); δ_P (101 MHz, $CDCl_3$) 29.8; *m/z* (TOF ES^+) 261.0671 (100%, MH^+, $C_{14}H_{14}O_3P$ requires 261.0681).

(S_P)-2-Methyl-4-methoxyphenylmethylphenyl phosphine oxide **294**



Prepared according to general procedure **H** from 2-methyl-4-methoxyphenyl magnesium bromide (2.0 cm³, 1 M in THF, 2 mmol). Purification of the crude material by flash column chromatography on silica gel using a gradient eluent of 75% ethyl acetate: petroleum ether 40 – 60 °C to 5% methanol: dichloromethane afforded the oxazolidinone **174** (148 mg, 94%) and the phosphine oxide as a white solid (203 mg, 78%). t_R 13.0 (minor isomer) and 19.3 (major isomer) (Celluose-1, 95: 5 hexane: propan-2-ol, 210 nm); m.p. 119 - 120 °C; $[\alpha]_D^{25}$ - 22.0 (*c* 1.0 in $CHCl_3$); υ_{max} (ATR) / cm^{-1} 3021, 1493, 1441; δ_H (400 MHz, $CDCl_3$) 2.00 (3H, d, J_{P-H} 13.1, PC*H*$_3$), 2.32 (3H, s, C*H*$_3$), 3.81 (3H, s, OC*H*$_3$), 6.72 – 6.82 (2H, m, ArC*H*), 7.39 – 7.51 (3H, m, ArC*H*), 7.57 – 7.67 (3H, m, ArC*H*); δ_C (100 MHz, $CDCl_3$) 17.4 (d, J_{C-P} 74.0, P*C*H$_3$), 21.5 (d, J_{C-P} 4.0, *C*H$_3$), 55.2 (O*C*H$_3$), 110.5 (d, J_{C-P} 13.1, ArC*H*), 117.4 (d, J_{C-P} 11.0, Ar*C*H), 123.0 (d, J_{C-P} 105.0, Ar*C*), 128.5 (d, J_{C-P} 11.8, 2 × Ar*C*H), 130.3 (d, J_{C-P} 9.9, 2 × Ar*C*H), 131.3 (d, J_{C-P} 2.3, Ar*C*H), 133.4 (d, J_{C-P} 12.7, Ar*C*H), 135.2 (d, J_{C-P} 99.7, Ar*C*), 144.2 (d, J_{C-P} 9.4, Ar*C*), 162.3 (d, J_{C-P} 3.0, Ar*C*); δ_P (101 MHz, $CDCl_3$) 29.1; *m/z* (TOF ES^+) 261.1041 (MH^+, 100%, $C_{15}H_{18}O_2P$ requires 261.1044).

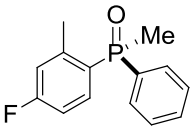
(S_P)-4-Fluorophenylmethylphenyl phosphine oxide **294**



Prepared according to general procedure **H** using 4-fluorophenyl magnesium bromide (1.5 cm³, 1.3 M in THF, 2 mmol). Purification of the crude material by flash column chromatography on silica gel using a gradient eluent of 75% ethyl acetate: petroleum ether 40 – 60 °C to 5% methanol: dichloromethane afforded the oxazolidinone **174** (145 mg, 93%) as a white solid and the phosphine oxide as a white solid (222 mg, 95%). t_R 14.5 (minor isomer) and 15.8 (major isomer) (Celluose-1, 90:10 hexane: propan-2-ol, 260 nm); m.p. 106 °C; $[\alpha]_D^{25}$ - 3.0 (>99% ee, *c* 1.0 in $CHCl_3$); υ_{max} (ATR) /cm^{-1} 2954, 1621, 1417; (Found C, 66.27; H, 5.16; $C_{13}H_{12}FOP$ requires C, 66.67; H, 5.16%); δ_H (400 MHz, $CDCl_3$) 2.00 (3H, d, J_{P-H} 13.2, PC*H*$_3$), 7.11 (2H, ddd, *J* 10.7, 4.7, 2.0, 2 × ArC*H*), 7.41 – 7.51 (3H, m, ArC*H*), 7.65 – 7.72 (4H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 16.6 (d, J_{C-P} 75.0, P*C*H$_3$), 115.5 (dd, *J* 21.2, 12.9, Ar*C*F), 128.7 (d, J_{C-P} 12.1, 2 × Ar*C*H), 130.0 (dd, *J* 104.0, 3.8, Ar*C*), 130.4 (d, J_{C-P} 10.0, 2 × Ar*C*H), 131.4 (d, J_{C-P} 3.1,

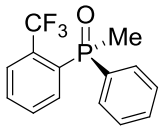
ArC*H*), 132.9 (d, $J_{C\text{-}P}$ 9.2, 2 × Ar*C*H), 133.1 (d, $J_{C\text{-}P}$ 9.2, 2 × Ar*C*H), 133.8 (d, $J_{C\text{-}P}$ 102.1, Ar*C*), 164.9 (dd, $J_{C\text{-}F}$ 253.5, $J_{C\text{-}P}$ 4.0, Ar*C*); δ_P (101 MHz, $CDCl_3$) 29.1; δ_F (235 MHz, $CDCl_3$) -106.4; *m/z* (TOF ES^+) 235.0677 (100%, MH+, $C_{13}H_{13}FOP$ requires 235.0688). No data is reported within the literature.

(S_P)-2-methyl-4-fluorophenylmethylphenyl phosphine oxide **296**[120]



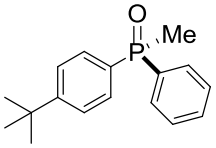
Prepared according to general procedure X from 2-methyl-4-fluorophenyl magnesium bromide (1.7 cm³, 1.4 M in THF, 2 mmol). Purification of the crude material by flash column chromatography on silica gel using a gradient eluent of 75% ethyl acetate: petroleum ether 40 – 60 °C to 5% methanol: dichloromethane afforded the oxazolidinone **174** (150 mg, 97%) as a white solid and the phosphine oxide as a white solid (200 mg, 80%); t_R 14.4 (minor isomer) and 16.4 (major isomer) (CHIRALPAK-OD, 95: 5 hexane: propan-2-ol, 254 nm); m.p. 134 °C; $[\alpha_D]$ -24.0 (>99% ee, *c* 1.0 in $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 2.04 (3H, d, $J_{P\text{-}H}$ 13.1, PCH_3), 2.38 (3H, s, CH_3), 6.91 -7.05 (2H, m, ArC*H*), 7.42 – 7.75 (6H, m, ArC*H*); δ_P (101 MHz, $CDCl_3$) 30.6; δ_F (250 MHz, $CDCl_3$) -107.9. No melting point data or optical rotation value is reported within the literature, otherwise all data is in accordance.

(*S*)-2-Trifluoromethylphenylmethylphenyl phosphine oxide **297**[120]



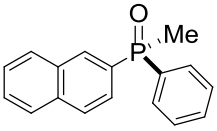
Prepared according to general procedure **H** from 2-trifluoromethylphenylmagnesium bromide (2.0 cm³, 1 M in THF, 2 mmol). Purification of the crude material by flash column chromatography on silica gel using a gradient eluent of 75% ethyl acetate: petroleum ether 40 – 60 °C to 5% methanol: dichloromethane afforded the oxazolidinone **X** (140 mg, 89%) as a white solid and the phosphine oxide as a white solid (159 mg, 56%); t_R 17.0 (minor isomer) and 21.0 (major isomer) (CHIRALPAK-OD, 95: 5 hexane: propan-2-ol, 254 nm); m.p. 68 °C (lit.[120] 67 – 68 °C); $[\alpha]_D^{25}$ - 10.0 (>99% ee, *c* 1.0 in MeOH, lit.[120] >99% ee, - 9.4 *c* 1.0 in MeOH); δ_H (250 MHz, CDCl3) 2.18 (3H, d, $J_{P\text{-}H}$ 13.5, PCH_3), 7.41 – 7.85 (8H, m, ArC*H*), 8.32 – 8.43 (1H, m, ArC*H*); δ_F (235 MHz, $CDCl_3$) -56.3; δ_P (101 MHz, $CDCl_3$) 30.7. All data is in accordance with the literature.

(S_P)-4-*tert*-Butylphenylmethylphenyl phosphine oxide **298**



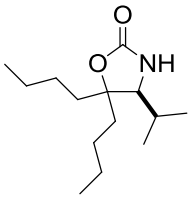
Prepared according to general procedure **H** from 4-*tert*-butyl magnesium bromide (1.7 cm³, 1.4 M in THF, 2 mmol). Purification of the crude material by flash column chromatography on silica gel using a gradient eluent of 75% ethyl acetate: petroleum ether 40 – 60 °C to 5% methanol: dichloromethane afforded the oxazolidinone **174** (145 mg, 93%) as a white solid and the phosphine oxide as a white solid (206 mg, 99%). t_R 11.5 (minor isomer) and 12.8 (major isomer) (Celluose-1, 90: 10 hexane: propan-2-ol, 225 nm); m.p. 130 – 131 °C; $[\alpha]_D^{25}$ - 24.0 (>99% ee, *c* 1.0 in $CHCl_3$); υ_{max} (ATR) /cm^{-1} 2957, 1598, 1437; δ_H (400 MHz, $CDCl_3$) 1.33 [9H, s, C(C*H*$_3$)$_3$], 2.01 (3H, d, J_{P-H} 13.2, PC*H*$_3$), 7.48 – 7.51 (5H, m, ArC*H*), 7.64 – 7.69 (2H, m, ArC*H*), 7.73 – 7.78 (2H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 16.8 (d. J_{C-P} 73.0, P*C*H$_3$), 31.1 [CH(*C*H$_3$)$_3$], 34.9 [*C*H(CH$_3$)$_3$], 125.5 (d, J_{C-P} 11.9, 2 × Ar*C*H), 128.5 (d, J_{C-P} 11.6, 2 × Ar*C*H), 130.3 (d, J_{C-P} 10.3, 2 × Ar*C*H), 130.5 (d, J_{C-P} 9.8, 2 × Ar*C*H), 131.5 (d, J_{C-P} 2.3, Ar*C*H), 131.6 (d, J_{C-P} 98.3, Ar*C*), 134.4 (d, J_{C-P} 100.3, Ar*C*), 155.2 (d, J_{C-P} 2.0, Ar*C*); δ_P (121 MHz, $CDCl_3$) 29.4; *m/z* (TOF ES^+) 273.1405 (100%, MH^+, $C_{17}H_{22}OP$ requires 273.1408).

(S_P)-(2-Naphthyl)phenylmethyl phosphine oxide **299**[153]



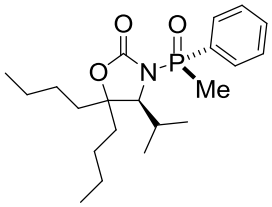
Prepared according to general procedure **H** from 4-*tert*-butyl magnesium bromide (1.7 cm³, 1.4 M in THF, 2.0 mmol). Purification of the crude material by flash column chromatography on silica gel using a gradient eluent of 75% ethyl acetate: petroleum ether 40 – 60 °C to 5% methanol: dichloromethane afforded the oxazolidinone **174** (140 mg, 91%) as a white solid and the phosphine oxide as a white solid (109 mg, 41%). t_R 10.2 (minor isomer) and 13.1 (major isomer) (Celluose-1, 90: 10 hexane: propan-2-ol, 225 nm); $[\alpha]_D^{25}$ - 22.0 [>99% ee, *c* 2.0 in MeOH, lit.[153] + 21.0 *c* 2.0 in MeOH for the (*R*)-enantiomer, >99% ee]; m.p. 141 °C (lit.[153] 140 – 142 °C); δ_H (250 MHz, $CDCl_3$) 2.15 (3H, d, J_{P-H} 13.3, C*H*$_3$), 7.38 – 7.59 (7H, m, ArC*H*), 7.68 – 7.79 (2H, m, ArC*H*), 7.85 – 7.98 (2H, m, ArC*H*), 8.02 – 8.05 (1H, m, ArC*H*), 8.39 – 8.47 (1H, m, ArC*H*). δ_P (101 MHz, $CDCl_3$) 39.1. All data is in accordance with the literature.

(*S*)-4-*iso*-propyl-5,5-dibutyl-2-oxazolidinone **184**



The *N*-boc protected ester **288** (1.70 g, 7.5 mmol) was dissolved in THF (30 cm³) and the solution cooled to 0 °C. *n*-Butyl magnesium bromide (13.6 cm³, 2.2 M in THF, 30 mmol,) was added dropwise and the mixture warmed to room temperature and stirred for 18 hours. A saturated solution of ammonium chloride (20 cm³) was added dropwise and the aqueous phase extracted with ethyl acetate (3 × 50 cm³). The organic layers were combined, washed with brine (30 cm³) and dried over magnesium sulfate. Removal of the solvent *in vacuo* yielded a crude yellow oil. The residue was dissolved in THF (100 cm³) and cooled to 0 °C. Potassium *tert*-butoxide (0.9 g, 8.3 mmol) was added in a single portion and the reaction warmed to room temperature and stirred for 6 hours. The reaction mixture was poured into water (100 cm³) and the aqueous phase extracted with ethyl acetate (3 × 40 cm³). The organic layers were combined, washed with brine (20 cm³) and dried over magnesium sulfate. Removal of the solvent *in vacuo* yielded the oxazolidinone as an orange oil. Purification of the crude material by flash column chromatography on silica gel using an eluent of 35% ethyl acetate: petroleum ether 40 – 60 °C afforded the title compound as a yellow solid (1.2 g, 68%). m.p. 47 – 49 °C; $[\alpha]_D^{25}$ + 5.0 (*c* 1.0 in $CHCl_3$); (Found C, 69.66; H, 11.27; N, 5.80; $C_{14}H_{27}NO_2$ requires C, 69.42; H, 11.67; N, 5.71%); υ_{max} (ATR) / cm^{-1} 2956, 2872, 1742; δ_H (400 MHz, $CDCl_3$) 0.91 – 0.94 (9H, m, 3 × C*H*$_3$), 1.00 (3H, d, *J* 6.5, C*H*$_3$), 1.30 – 1.41 (7H, m, C*H*$_2$), 1.46 – 1.66 (3H, m, C*H*$_2$), 1.76 – 1.85 (2H, m, C*H*$_2$), 1.91 [1H, m, C*H*$(CH_3)_2$], 3.34 (1H, d, *J* 7.2, C*H*), 6.79 (1H, s, N*H*); δ_C (101 MHz, $CDCl_3$) 13.9 (2 × *C*H_3), 19.5 (*C*H_3), 20.6 (*C*H_3) , 22.9 (*C*H_2), 23.3 (*C*H_2), 25.4 (*C*H_2), 25.5 (*C*H_2), 28.0 (*C*H), 32.7 (*C*H_2), 37.1 (*C*H_2), 65.3 (*C*HN), 87.6 (*C*HO), 159.7 (*CO*); *m/z* (TOF ES^+) 242.2110 (100%, MH^+, $C_{19}H_{39}NO_2$ requires 242.2120). No data is reported within the literature.

(*S*)-4-*iso*-Propyl-5,5,-dibutyl-3-[(R_P)-methyl(phenyl)phosphinyl] oxazolidinone **183**



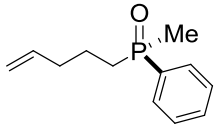
Oxazolidinone **184** (241 mg, 1 mmol) was added in a single portion to a solution of freshly distilled triethylamine (131 mg, 0.2 cm³, 1 mmol) and lithium chloride (46 mg, 1 mmol) in anhydrous THF (5 cm³). The suspension was cooled to -20 °C and methyl(phenyl)phosphinic chloride **166** (191 mg, 1 mmol) added dropwise over a period of 10 minutes. The mixture was warmed to room temperature and stirred for 24 hours before being quenched through addition of 1N HCl (10 cm³). The aqueous phase was extracted with ethyl acetate (3 × 20 cm³), washed with brine (10 cm³) and dried over magnesium sulfate. Removal of the solvent *in vacuo* afforded a yellow oil of 93:7 diastereoselectivity as determined by analysis of the crude ^{1}H NMR spectroscopic data. Purification and separation of the diastereotopic mixture by flash column chromatography on silica gel using an eluent of 60% ethyl acetate: petroleum ether 40 – 60 °C afforded the title compound as a diastereotopically pure colourless oil that solidified slowly upon standing (220 mg, 51%). m.p. 84 °C; $[\alpha]_D^{25}$ + 23.0 (*c* 0.5 in $CHCl_3$); (Found C, 66.65; H, 9.24; N, 3.53; $C_{21}H_{34}NO_3P$ requires C, 66.47; H, 9.03; N, 3.69%); υ_{max} (ATR) / cm^{-1} 2961, 2934, 1738, 1221; δ_H (400 MHz, $CDCl_3$) 0.65 (3H, d, *J* 6.9, C*H*$_3$), 0.75 (3H, d, *J* 7.1, C*H*$_3$), 0.88 – 0.95 (6H, m, C*H*$_2$), 1.26 – 1.39 (8H, m, C*H*$_3$ and C*H*$_2$), 1.62 – 1.90 [5H, m, 2 × C*H*$_2$ and C*H*(CH$_3$)$_2$], 2.02 (3H, d, J_{P-H} 14.5, PC*H*$_3$), 4.00 (1H, dd, *J* 3.7, 1.4, C*H*N), 7.42 – 7.56 (3H, m, ArC*H*), 8.06 – 8.12 (2H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 13.8 (*C*H$_3$), 13.9 (*C*H$_3$), 16.5 (*C*H$_3$), 16.6 (d, J_{C-P} 87.4, P*C*H$_3$), 21.1 (*C*H$_3$), 22.9 (*C*H$_2$), 23.0 (*C*H$_2$), 25.5 (*C*H$_2$), 25.9 (*C*H$_2$), 28.9 (*C*H), 30.7 (*C*H$_2$), 36.4 (*C*H$_2$), 67.2 (CH*C*O), 89.0 (d, J_{C-P} 5.3, *C*HN) 128.4 (d, J_{C-P} 13.4, 2 × Ar*C*H), 131.0 (d, J_{C-P} 11.1, 2 × Ar*C*H), 132.3 (d, J_{C-P} 2.4, Ar*C*H), 133.7 (Ar*C*), 157.2 (d, J_{C-P} 7.5, *C*O); δ_P (121 MHz, $CDCl_3$) 34.2; *m/z* (TOF ES$^+$) 380.2352 (100%, MH$^+$, $C_{21}H_{35}NO_3P$ requires 380.2355).

General procedure I for the preparation of the dialiphatic phenyl *P*-chiral phosphine oxides from the *N*-phosphinyl oxazolidinone 178

The *N*-phosphinyl oxazolidinone **183** (297 mg, 1 mmol) was dissolved in anhydrous THF (2.0 cm³) and added *via* syringe pump (1 cm³ / h) to a solution of the appropiate Grignard reagent (4 eq) in THF (5.0 cm³) at 0 °C. Following complete addition of the oxazolidinone **174**, the

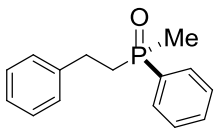
reaction was warmed to room temperature and stirred for a further 20 minutes. The solution was poured into water (10 cm³) and the aqueous phase extracted with dichloromethane (3 × 10 cm³). The organic layers were combined, washed with brine (10 cm³) and dried over magnesium sulfate. Removal of the solvent *in vacuo* yielded the crude phosphine oxide. Purification of the crude material occurred as described in the individual experimental details. Racemic samples of the phosphine oxide were prepared from addition of the Grignard reagent to the phosphinic chloride **166**.

(R_P)-(Pent-1-ene)methylphenyl phosphine oxide **179**



Prepared according to general procedure **I** using pent-1-enemagnesium bromide (4 cm³, 1M in THF, 4 mmol,). Purification of the crude material by flash column chromatography on silica gel using a gradient eluent of 75% ethyl acetate: petroleum ether 40 – 60 °C to 5% methanol: dichloromethane afforded the oxazolidinone **174** (145 mg, 94%) as a white solid and the phosphine oxide (206 mg, 99%) as a colourless oil. t_R 27.8 (minor isomer) and 38.2 (major isomer) (Celluose-2, 90: 10 hexane: propan-2-ol, 210nm); $[\alpha]_D^{25}$ + 6.0 (>99% ee, *c* 1.0 in $CHCl_3$), υ_{max} (ATR) /cm^{-1} 2933, 1440, 1163; δ_H (400 MHz, $CDCl_3$) 1.53 – 1.64 (1H, m, C*H*H), 1.70 (3H, d, J_{P-H} 12.6, PC*H*$_3$), 1.71 – 1.80 (1H, m, C*H*H), 1.83 – 2.00 (2H, m, C*H*$_2$), 2.09 – 2.14 (2H, m, C*H*$_2$), 4.96 – 5.00 (2H, m, CH=C*H*$_2$), 5.67 – 5.72 (1H, m, C*H*=CH$_2$); 7.48 – 7.54 (3H, m, ArC*H*), 7.69 – 7.73 (2H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 16.1 (d, J_{C-P} 69.5, P*C*H$_3$), 20.8 (d, J_{C-P} 3.5, *C*H$_2$), 31.0 (d, J_{C-P} 70.5, *C*H$_2$), 34.6 (d, J_{C-P} 14.8, *C*H$_2$), 115.7 (CH=*C*H$_2$), 128.6 (d, J_{C-P} 11.4, 2 × Ar*C*H), 130.0 (d, J_{C-P} 9.2, 2 × Ar*C*H), 131.5 (d, J_{C-P} 2.5, Ar*C*H), 133.6 (d, J_{C-P} 95.3, Ar*C*), 137.2 (*C*H=CH$_2$); δ_P (121 MHz, $CDCl_3$) 37.3; *m/z* (TOF ES$^+$) 209.1093 (100%, MH$^+$, $C_{12}H_{17}OP$ requires 209.1095).

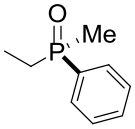
(R_P)-(Phenylethyl)methylphenyl phosphine oxide **187**



Prepared according to general procedure **I** using phenylethylmagnesium bromide (2.0 cm³, 2M in THF, 4 mmol). Purification of the crude material by flash column chromatography on silica gel using a gradient eluent of 75% ethyl acetate: petroleum ether 40 – 60 °C to 5% methanol: dichloromethane afforded the oxazolidinone **174** (144 mg, 92%) as a white solid and the

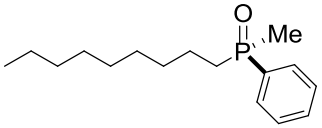
phosphine oxide (244 mg, 99%) as a colourless oil. t_R 41.5 (minor isomer) and 66.0 (major isomer) (Celluose-2, 90: 10 hexane: propan-2-ol, 210nm); $[\alpha]_D^{25}$ - 19.0 (>99% ee, *c* 1.0 in $CHCl_3$); υ_{max} (ATR) /cm^{-1} 3002, 1427, 1143 δ_H (400 MHz, $CDCl_3$) 1.72 (3H, d, J_{P-H} 12.8, PC*H*$_3$), 2.11 – 2.37 (2H, m, C*H*$_2$), 2.73 – 2.83 (1H, m, C*H*), 2.95 – 3.03 (1H, m, C*H*), 7.15 – 7.21 (3H, m, ArC*H*), 7.26 – 7.31 (2H, m, ArC*H*), 7.49 – 7.58 (3H, m, ArC*H*), 7.73 – 7.78 (2H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 16.2 (d, J_{C-P} 70.0, P*C*H$_3$), 27.6 (d, J_{C-P} 4.0, *C*H$_2$), 33.6 (d, J_{C-P} 68.0, *C*H$_2$), 126.4 (2 × Ar*C*H), 128.0 (2 × Ar*C*H), 128.8 (d, J_{C-P} 11.5, 2 × Ar*C*H), 130.0 (d, J_{C-P} 9.2, 2 × Ar*C*H), 131.7 (d, J_{C-P} 2.3, Ar*C*H), 133.4 (d, J_{C-P} 95.8, Ar*C*), 141.0 (d, J_{C-P} 14.0, Ar*C*); δ_P (121 MHz, $CDCl_3$) 36.3; *m/z* 245.1093 (100%, MH^+, $C_{15}H_{18}OP$ requires 245.1095).

(R_P)-Ethylmethylphenyl phosphine oxide **188**[154]



Prepared according to general procedure **I** using ethylmagnesium bromide (4 cm³, 1M in Et_2O, 4 mmol). Purification of the crude material by flash column chromatography on silica gel using a gradient eluent of 75% ethyl acetate: petroleum ether 40 – 60 °C to 5% methanol: dichloromethane afforded the oxazolidinone **174** (142 mg, 92%) as a white solid and the phosphine oxide (110 mg, 65%) as a colourless oil. t_R 39.2 (minor isomer) and 47.0 (major isomer) (Celluose-2, 90: 10 hexane: propan-2-ol, 210 nm); $[\alpha]_D^{25}$ - 24.0 [>99% ee, *c* 2.0 in CH_3OH, lit.[154] + 24.4 *c* 2.0 in CH_3OH for the (S_P)-enantiomer, 98% ee]; δ_H (400 MHz, $CDCl_3$) 1.12 (3H, dt, *J* 17.8 7.6, CH_2CH_3), 1.69 (3H, d, J_{P-H} 12.6, PC*H*$_3$), 1.83 – 2.03 (2H, m, C*H*$_2$CH$_3$); δ_P (121 MHz, $CDCl_3$) 38.9. All data is in accordance with the literature.

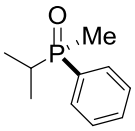
(R_P)-Nonylmethylphenyl phosphine oxide **189**



Prepared according to general procedure **I** using nonylmagnesium bromide (2 cm³, 2M in THF, 4 mmol). Purification of the crude material by flash column chromatography on silica gel using a gradient eluent of 75% ethyl acetate: petroleum ether 40 – 60 °C to 5% methanol: dichloromethane afforded the oxazolidinone **174** (138 mg, 88%) as a white solid and the phosphine oxide (202 mg, 76%) as a white solid. m.p. 66 - 67 °C; t_R 19.7 (minor isomer) and 29.3 (major isomer) (Celluose-2, 90: 10 hexane: propan-2-ol, 210 nm); $[\alpha]_D^{25}$ + 11.0 (>99% ee, *c* 1.0 in $CHCl_3$); υ_{max} (ATR) /cm^{-1} 2916, 1469, 1167; δ_H (400 MHz, $CDCl_3$) 0.79 (3H, t, *J* 6.8,

C*H*$_3$), 1.15 – 1.61 (14H, m, C*H*$_2$), 1.66 (3H, d, $J_{P\text{-}H}$ 17.1, PC*H*$_3$), 1.83 – 1.95 (2H, m, C*H*$_2$), 7.41 – 7.44 (3H, m, ArC*H*), 7.62 – 7.67 (2H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 13.9 (*C*H$_3$), 15.9 (d, $J_{C\text{-}P}$ 69.0, P*C*H$_3$), 21.5 (d, $J_{C\text{-}P}$ 3.9, *C*H$_2$), 22.5 (*C*H$_2$), 29.0 (d, $J_{C\text{-}P}$ 11.4, *C*H$_2$), 29.2 (*C*H$_2$), 30.8 (d, $J_{C\text{-}P}$ 14.1, *C*H$_2$), 31.4 (*C*H$_2$), 31.7 (*C*H$_2$), 32.1 (*C*H$_2$), 128.5 (d, $J_{C\text{-}P}$ 11.4, 2 × Ar*C*H), 129.9 (d, $J_{C\text{-}P}$ 9.1, 2 × Ar*C*H), 131.4 (d, $J_{C\text{-}P}$ 2.4, Ar*C*H), 133.8 (d, $J_{C\text{-}P}$ 94.6, Ar*C*); δ_P (121 MHz, $CDCl_3$) 37.3; *m/z* (TOF ES$^+$) 267.1881 (100%, MH$^+$, $C_{16}H_{28}OP$ requires 267.1878).

(R_P)-*iso*-Propylmethylphenyl phosphine oxide **190**[155]



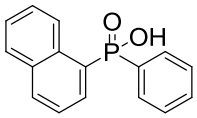
Prepared according to general procedure **I** using *iso*-propylmagnesium bromide (3 cm³, 1.5M in Et_2O, 4 mmol). Purification of the crude material by flash column chromatography on silica gel using a gradient eluent of 75% ethyl acetate: petroleum ether 40 – 60 °C to 5% methanol: dichloromethane afforded the oxazolidinone **174** (39 mg, 25%) as a white solid and the phosphine oxide as a colourless oil that solidified upon standing at room temperature (56 mg, 31%); t_R 14.0 (minor isomer) and 18.0 (major isomer) (Celluose-2, 95: 5 hexane: propan-2-ol, 210 nm); $[\alpha]_D^{25}$ + 25.0 [>99% ee, *c* 1.0 in MeOH, lit.[155] -25.4 >99% ee, *c* 1.0 in MeOH for the (S_P) enantiomer]; m.p. 58 °C (lit.[155] 58 – 60 °C); δ_H (250 MHz, $CDCl_3$) 1.08 [3H, dd, $J_{P\text{-}H}$ 16.4, $J_{H\text{-}H}$ 7.2, 1 × CH(C*H*$_3$)$_2$], 1.21 [3H, dd, $J_{P\text{-}H}$ 16.4, $J_{H\text{-}H}$ 7.2, 1 × CH(C*H*$_3$)$_2$], 1.70 (3H, d, $J_{P\text{-}H}$ 12.3, PC*H*$_3$), 1.92 – 2.14 [1H, m, C*H*(CH$_3$)$_2$], 7.44 – 7.58 (3H, m, ArC*H*), 7.66 – 7.76 (2H, m, ArC*H*); δ_P (121 MHz, $CDCl_3$) 42.9. All data is in accordance with the literature.

General procedure J for the preparation of the *P*-chiral phosphine oxides from the *N*-phosphinoyl oxazolidinone 183

The *N*-phosphinoyl oxazolidinone **183** (380 mg, 1 mmol) was dissolved in anhydrous THF (2.0 cm³) and added *via* syringe pump (1.0 cm³ / h) to a solution of the appropiate Grignard reagent (4 eq) in THF (5.0 cm³) at 0 °C. Following complete addition of the oxazolidinone **183**, the reaction was warmed to room temperature and stirred for a further 20 minutes. The solution was poured into water (10 cm³) and the aqueous phase extracted with *n*-pentane (10 cm³) to remove the auxiliary **184** and then with chloroform (3 × 10 cm³). The chloroform extracts were combined, washed with brine and dried over magnesium sulfate. Removal of the solvent *in vacuo* afforded the *P*-chiral phosphine oxide in >90% purity as determined by analysis of the ^{1}H NMR spectroscopic data. The analytical data and retention times of the products were in direct

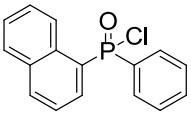
correlation with those of obtained through general procedures **H** and **I**.

Naphthalen-1-yl(phenyl)phosphoric acid **198**[122]



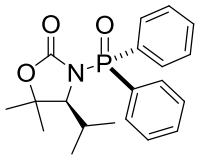
Magnesium turnings (2.00 g, 75 mmol) and anhydrous THF (25 cm³) were introduced into a 250 cm³ three neck round bottom flask fitted with a reflux condenser and dropping funnel. The dropping funnel was charged with a solution of 1-bromonaphthalene (4.0 cm³, 26 mmol) and anhydrous THF (30 cm³) and added dropwise to the flask over a period of 30 minutes. The resulting Grignard reagent was transferred by cannula into a solution of phenylphosphonic dichloride (5.00 g, 4.0 cm³, 26 mmol) in THF (10 cm³) and the solution stirred for 16 hours. The reaction mixture was quenched with concentrated hydrochloric acid (15 cm³) and stirred for 1 hour. The aqueous layer was extracted with dichloromethane (3 × 30 cm³) and the combined organic phases were dried over magnesium sulfate. Removal of the solvent *in vacuo* yielded a crude yellow oil. Trituration of the oil with ethanol (20 cm³) afforded the title compound as a white crystalline solid (6.02 g, 94%) m.p. 186 °C (lit.[122] 185 – 187 °C); δ_H (400 MHz, d^6-DMSO) 7.38 – 7.66 (6H, m, ArC*H*), 7.72 – 7.82 (2H, m, ArC*H*), 7.94 – 8.00 (1H, m, ArC*H*), 8.09 – 8.24 (2H, m, ArC*H*), 8.63 – 8.68 (1H, m, ArC*H*), 11.00 (1H, s, O*H*); δ_P (101 MHz, d^6-DMSO) 24.1. All data is in accordance with that of the literature.

Naphthalen-1-yl(phenyl)phosphinic chloride **199**[122]



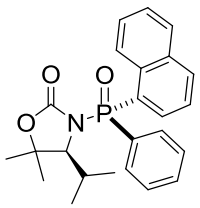
Phosphoric acid **198** (2.00 g, 7.4 mmol) was suspended in anhydrous dichloromethane (25 cm³) and cooled to 0 °C. Thionyl chloride (10 cm³, 13.7 mmol) was added dropwise over a period of 10 minutes and the solution heated at reflux for 3 hours. The solvent and excess thionyl chloride were removed *in vacuo* to afford the title compound as a yellow oil that required no further purification (1.90 g, 91%). δ_H ($CDCl_3$, 250 MHz) 7.51 – 7.68 (6H, m, ArC*H*), 7.88 – 8.12 (5H, m, ArC*H*), 8.53 – 8.59 (1H, m, ArC*H*); δ_P ($CDCl_3$, 101 MHz) 45.9 (s). All data is in accordance with the literature.

(*S*)-3-(Diphenylphosphoryl)-4-*iso*-propyl-5,5-dimethyloxazolidin-2-one **200**



Oxazolidinone **174** (157 mg, 1 mmol) was added in a single portion to a solution of freshly distilled triethylamine (0.3 cm³, 2 mmol) and lithium chloride (46 mg, 1 mmol) in THF (5.0 cm³). The reaction mixture was cooled to -20 °C and diphenylphosphinic chloride (0.2 cm³, 1 mmol) added dropwise over a period of 10 minutes. The solution was warmed to room temperature and stirred for 24 hours before being poured into a saturated aqueous solution of ammonium chloride (10 cm³). The aqueous phase was extracted with dichloromethane (3 × 10 cm³) and the organic layers combined, washed with brine (10 cm³) and dried over magnesium sulfate. Removal of the solvent *in vacuo* yielded a crude orange oil. Purification of the crude material by flash column chromatography on silica gel using an eluent of 50% ethyl acetate: petroleum ether 40 – 60 °C afforded the title compound as a white solid (253 mg, 75%). m.p. 125 °C; $[\alpha]_D^{25}$ + 16.0 (*c* 1.0 in $CHCl_3$); υ_{max} / cm^{-1} (ATR) 2989, 2974, 1745, 1270; δ_H (400 MHz, $CDCl_3$) 0.90 [6H, app. t, *J* 7.5, CH(C*H*$_3$)$_2$], 1.48 (3H, s, C*H*$_3$), 1.51 (3H, s, C*H*$_3$), 2.03 – 2.10 [1H, m, C*H*(CH$_3$)$_2$], 4.18 (1H, dd, *J* 3.4 2.0, C*H*N), 7.38 – 7.47 (2H, m, ArC*H*), 7.52 – 7.60 (3H, m, ArC*H*), 7.62 – 7.68 (1H, m, ArC*H*), 7.70 – 7.79 (2H, m, ArC*H*), 8.15 – 8.24 (2H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 16.7 (*C*H$_3$), 20.7 [*C*H(CH$_3$)$_2$], 21.6 (*C*H$_3$), 29.3 (*C*H$_3$), 30.2 (*C*H$_3$), 69.0 (*C*H), 84.7 [d, $J_{C\text{-}P}$ 5.0, *C*(CH$_3$)$_2$], 128.2 (d, $J_{C\text{-}P}$ 14.0, 2 ×Ar*C*H), 128.6 (d, $J_{C\text{-}P}$ 13.0, 2 × Ar*C*H), 129.9 (d, $J_{C\text{-}P}$ 70.0, Ar*C*), 131.2 (d, $J_{C\text{-}P}$ 70.0, Ar*C*), 132.0 (d, $J_{C\text{-}P}$ 9.0, 2 × Ar*C*H), 132.4 (d, $J_{C\text{-}P}$ 11.0, 2 × Ar*C*H), 132.6 (d, $J_{C\text{-}P}$ 2.0, Ar*C*H), 132.8 (d, $J_{C\text{-}P}$ 2.0, Ar*C*H), 156.6 (d, $J_{C\text{-}P}$ 7.0, *C*O); δ_P (101 MHz, $CDCl_3$) 27.4; *m/z* (TOF ES$^+$) 358.1573 (100%, MH$^+$, $C_{20}H_{25}NO_3P$ requires 358.1572).

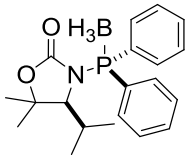
(*S*)-4-iso-Propyl-5,5-dimethyl-3-[(*R*$_P$)-naphthalen-1-yl(phenyl)phosphoryl]oxazolidin-2-one **201**



Oxazolidinone **174** (157 mg, 1 mmol) was dissolved in THF (5.0 cm³) and the solution cooled to 0 °C. Methylmagnesium bromide (1.0 cm³, 1M in Et_2O, 1 mmol) was added dropwise and the reaction mixture stirred for 90 minutes. Naphthalen-1-yl(phenyl)phosphinic chloride **199** (286

mg, 1 mmol) was introduced and the solution warmed to room temperature and stirred for 24 hours. The reaction mixture was quenched through addition of a saturated aqueous solution of ammonium chloride (10 cm³) and dichloromethane (15 cm³) added. The organic phase was separated and the aqueous layer extracted with dichloromethane (2 × 15 cm³). The organic phases were combined, washed with brine (20 cm³) and dried over magnesium sulfate. Removal of the solvent *in vacuo* yielded the title compound as a 3:1 mixture of diastereoisomers as determined by analysis of the crude ^{1}H NMR spectroscopic data. Purification and isolation of the major isomer by flash column chromatography on silica gel using an eluent of 50% ethyl acetate: petroleum ether 40 – 60 °C afforded the diastereotopically pure compound as a white solid (210 mg, 47%). m.p. 141 °C; $[\alpha]_D^{25}$ + 60.0 (*c* 1.0 in $CHCl_3$); υ_{max} / cm^{-1} (ATR) 2990, 1735, 1220; δ_H (400 MHz, $CDCl_3$) 0.98 [3H, d, *J* 7.0, 1 × CH(C*H*$_3$)$_2$] 1.16 [3H, d, *J* 7.0, 1 × CH(C*H*$_3$)$_2$], 1.43 (3H, s, C*H*$_3$), 1.57 (3H, s, C*H*$_3$), 2.09 – 2.20 [1H, m, C*H*(CH$_3$)$_2$], 4.38 (1H, dd, *J* 4.8 2.7, C*H*N), 7.35 – 7.55 (5H, m, ArC*H*), 7.66 – 7.77 (3H, m, ArC*H*), 7.93 (1H, d, *J* 8.2, ArC*H*), 8.14 (1H, d, *J* 8.2, ArC*H*), 8.48 – 8.55 (2H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 17.2 (*C*H$_3$), 21.1 (*C*H$_3$), 21.5 (*C*H), 29.3 (*C*H$_3$), 30.3 (*C*H$_3$), 68.7 (*C*HN), 84.7 [d, $J_{C\text{-}P}$ 5.0, *C*(CH$_3$)$_2$], 124.3 (d, $J_{C\text{-}P}$ 15.3, Ar*C*H), 125.5 (d, $J_{C\text{-}P}$ 129.4, Ar*C*), 126.5 (Ar*C*H), 126.8 (d, $J_{C\text{-}P}$ 6.0, Ar*C*H), 127.6 (Ar*C*H), 128.1 (d, $J_{C\text{-}P}$ 13.8, 2 × Ar*C*H), 128.9 (Ar*C*H), 131.0 (d, $J_{C\text{-}P}$ 121.8, Ar*C*), 132.2 (d, $J_{C\text{-}P}$ 11.5, 2 × Ar*C*H), 132.7 (d, $J_{C\text{-}P}$ 2.4, Ar*C*H), 133.4 (d, $J_{C\text{-}P}$ 13.0, Ar*C*), 133.7 (Ar*C*), 133.9 (d, $J_{C\text{-}P}$ 3.0, Ar*C*H), 156.5 (d, $J_{C\text{-}P}$ 6.0, *C*O); δ_P (101 MHz, $CDCl_3$) 30.9; *m/z* (TOF ES+) 408.4495 (100%, MH^+, $C_{24}H_{27}NO_3P$ requires 408.4498).

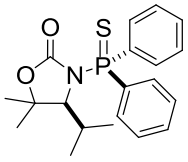
(*S*)-3-(Diphenylphosphinoborane)-4-*iso*-propyl-5,5-dimethyloxazolidin-2-one **211**



Oxazolidinone **174** (157 mg, 1 mmol) was dissolved in anhydrous THF (3.0 cm³) and the solution cooled to 0 °C. Methyl magnesium bromide (1 cm³, 1M in Et_2O, 1 mmol) was added dropwise and the reaction mixture stirred for 1 hour. Chlorodiphenylphosphine (0.2 cm³, 1 mmol) was introduced in a single portion and the solution warmed to room temperature and stirred for 24 hours. The mixture was cooled to 0 °C and borane dimethyl sulfide complex (0.1 cm³, 1 mmol) added and stirring continued for a further hour. A saturated aqueous solution of ammonium chloride (5.0 cm³) was added and the solution diluted with dichloromethane (10 cm³). The organic phase was separated and the aqueous layer was extracted with dichloromethane (2 × 5.0 cm³). The organic phases were combined, washed with brine (5.0 cm³)

and dried over magnesium sulfate. Removal of the solvent *in vacuo* yielded a yellow oil. Purification of the crude material by flash column chromatography on silica gel using an eluent of 10% ethyl acetate: petroleum ether 40 – 60 °C afforded the title compound as a white solid (205 mg, 54%). m.p. 124 °C; $[\alpha]_D^{25}$ + 17.0 (*c* 1.0 in $CHCl_3$); (Found C, 67.58; H, 7.62; N, 3.90; $C_{20}H_{27}BNO_2$ requires C, 67.62; H, 7.66; N, 3.94%); υ_{max} (ATR) / cm^{-1} 3021, 1732, 1208; δ_H (400 MHz, $CDCl_3$) 0.81 (3H, d, *J* 7.2, C*H*$_3$), 0.93 (3H, d, *J* 6.9, C*H*$_3$), 1.54 (3H, s, C*H*$_3$), 1.57 (3H, s, C*H*$_3$), 2.07 [1H, heptd, *J* 7.0 2.4, C*H*$(CH_3)_2$], 4.13 (1H, dd, *J* 4.2 2.4, C*H*), 7.39 – 7.46 (2H, m, ArC*H*), 7.48 – 7.52 (1H, m, ArC*H*), 7.62 – 7.68 (5H, m, ArC*H*), 8.16 (2H, m, ArC*H*); δ_C (100 MHz, $CDCl_3$) 17.3 [*C*H$(CH_3)_2$], 21.8 [2 × CH$(CH_3)_2$], 29.1 (*C*H_3), 30.9 (*C*H_3), 70.2 (d, $J_{C\text{-}P}$ 4.0, *C*HN), 84.6 [d, $J_{C\text{-}P}$ 6.0, *C*$(CH_3)_2$] , 128.1 (Ar*C*), 128.3 (d, $J_{C\text{-}P}$ 11.0, 2 × Ar*C*H), 28.7 (Ar*C*), 128.8 (d, $J_{C\text{-}P}$ 11.4, 2 × Ar*C*H), 131.7 (d, $J_{C\text{-}P}$ 1.3, Ar*C*H), 132.4 (d, $J_{C\text{-}P}$ 11.2, 2 × Ar*C*H), 132.6 (d, $J_{C\text{-}P}$ 2.1, Ar*C*H), 133.7 (d, $J_{C\text{-}P}$ 11.7, 2 × Ar*C*H), 156.6 (d, $J_{C\text{-}P}$ 4.0, *C*O); δ_P (101 MHz, $CDCl_3$) 59.5; *m/z* (TOF ES^+) 356.1955 (MH^+, 100%, $C_{20}H_{28}B^{10}NO_2$ requires 356.1951).

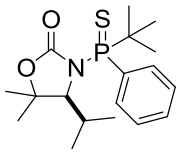
(*S*)-3-(Diphenylphosphorothioyl)-4-*iso*-propyl-5,5-dimethyloxazolidin-2-one **212**



Oxazolidinone **174** (157 mg, 1 mmol) was dissolved in THF (5.0 cm^3) and the solution cooled to 0 °C. Methyl magnesium bromide (0.5 cm^3, 2M in Et_2O, 1 mmol) was added dropwise and the reaction mixture stirred for 90 minutes. Chlorodiphenylphosphine (0.2 cm^3, 1 mmol) was introduced and the solution warmed to room temperature and stirred for 24 hours. Elemental sulfur (256 mg, 1 mmol) was added in a single portion and the reaction mixture stirred for four hours before being quenched through addition of a saturated aqueous solution of ammonium chloride (5 cm^3). The aqueous phase was extracted with dichloromethane (3 × 10 cm^3) and the organic layers combined, washed with brine (10 cm^3) and dried over magnesium sulfate. Removal of the solvent *in vacuo* yielded a yellow solid. Purification of the crude material by flash column chromatography on silica gel using an eluent of 10% ethyl acetate: petroleum ether 40 – 60 °C afforded the title compound as a white solid (220 mg, 62%). m.p. 52 °C; $[\alpha]_D^{25}$ + 14.0 (*c* 1.0 in $CHCl_3$); υ_{max} / cm^{-1} (ATR) 3057, 2869, 1756, 1437; δ_H (400 MHz, $CDCl_3$) 0.78 [3H, d, *J* 7.1, 1 × CH(C*H*$_3$)$_2$], 0.89 [3H, d, *J* 7.1, 1 × CH(C*H*$_3$)$_2$], 1.53 (3H, s, C*H*$_3$), 1.57 (3H, s, C*H*$_3$), 1.99 – 2.13 [1H, m, *J* 7.1, 1 × C*H*$(CH_3)_2$], 4.50 (1H, dd, *J* 6.5 1.6, C*H*N), 7.38 – 7.52 (4H, m, ArC*H*), 7.59 – 7.71 (5H, m, ArC*H*), 8.34 (1H, dd, *J* 14.5 7.3, ArC*H*); δ_C (101 MHz, $CDCl_3$) 16.9 [1 × CH(*C*H$_3$)$_2$], 20.1 [*C*H$(CH_3)_2$], 21.7 [1 × CH(*C*H$_3$)$_2$], 29.0 (*C*H_3), 30.4 (*C*H_3), 69.3 (d,

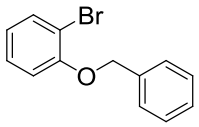
$J_{C\text{-}P}$ 1.0, *C*HN), 84.4 [d, $J_{C\text{-}P}$ 7.0, *C*$(CH_3)_2$], 128.2 (d, $J_{C\text{-}P}$ 14.1, 2 × Ar*C*H), 128.5 (d, $J_{C\text{-}P}$ 14.1. 2 × Ar*C*H), 131.0 (d, $J_{C\text{-}P}$ 105.4, Ar*C*), 131.5 (d, $J_{C\text{-}P}$ 12.2, 2 × Ar*C*H), 131.9 (d, $J_{C\text{-}P}$ 2.9, Ar*C*H), 132.6 (d, $J_{C\text{-}P}$ 2.9, Ar*C*H), 133.1 (d, $J_{C\text{-}P}$ 97.4, Ar*C*), 133.2 (d, $J_{C\text{-}P}$ 11.9, 2 × Ar*C*H), 155.9 (*C*O); δ_P (101 MHz, $CDCl_3$) 62.7; *m/z* (TOF ES^+) 374.4562 (100%, MH^+, $C_{20}H_{25}NO_2PS$ requires 374.4567).

(*S*)-4-Isopropyl-5,5-dimethyl-3-[(R_P)-*tert*-butyl(phenyl)phosphorothioyl]oxazolidin-2-one **213**



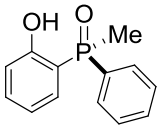
Oxazolidinone **174** (157 mg, 1 mmol) was dissolved in THF (5 cm³) and the solution cooled to 0 °C. Methyl magnesium bromide (1cm³, 1 mmol, 1M in Et_2O) was added dropwise and the reaction mixture stirred for 90 minutes. Chloro(*tert*-butyl)phenylphosphine (0.2 cm³, 1 mmol) was introduced and the solution warmed to room temperature and stirred for 24 hours. Elemental sulfur (256 mg, 1 mmol) was added and the reaction mixture stirred for four hours before being quenched through addition of a saturated aqueous solution of ammonium chloride (5 cm³). The aqueous phase was extracted with dichloromethane (3 × 10 cm³) and the organic layers combined, washed with brine (10 cm³) and dried over magnesium sulfate. Removal of the solvent *in vacuo* yielded a yellow solid of unknown diastereoselectivity. Purification of the crude material by flash column chromatography on silica gel using an eluent of 10% ethyl acetate: petroleum ether 40 – 60 °C afforded the title compound as a white solid (200 mg, 57%). m.p. 131 °C; $[\alpha]_D^{25}$ + 31.0 (*c* 1.0 in $CHCl_3$); υ_{max} / cm^{-1} (ATR) 3051, 2948, 1769, 1431; δ_H (400 MHz, $CDCl_3$) 0.67 [3H, d, *J* 7.1, 1 × CH(C*H*$_3$)$_2$], 0.85 [3H, d, *J* 7.1, 1 × CH(C*H*$_3$)$_2$], 1.39 (9H, d, *J* 18.6, C*H*$_3$), 1.51 (3H, s, C*H*$_3$), 1.54 (3H, s, C*H*$_3$), 1.95 [3H, d, *J* 7.1, 1 × CH(C*H*$_3$)$_2$], 4.58 (1H, dd, *J* 5.2 2.1, C*H*), 7.41 – 7.57 (3H, m, ArC*H*), 8.21 – 8.30 (2H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 17.4 [CH(*C*H_3)$_2$], 22.1 [2 × *C*H(CH$_3$)$_2$], 27.5 [d, $J_{C\text{-}P}$ 2.0, C(*C*H_3)$_3$], 28.8 (*C*H_3), 30.7 (*C*H_3), 40.4 [d, $J_{C\text{-}P}$ 56.0, C(*C*H_3)$_3$], 71.3 (C*H*N), 84.2 [d, $J_{C\text{-}P}$ 6.0, *C*$(CH_3)_2$], 128.0 (d, $J_{C\text{-}P}$ 13.0, 2 × Ar*C*H), 131.5 (d, $J_{C\text{-}P}$ 85.0, Ar*C*), 132.0 (d, $J_{C\text{-}P}$ 4.0, ArC*H*), 133.1 (d, $J_{C\text{-}P}$ 11.0, 2 × Ar*C*H), 156.8 (d, $J_{C\text{-}P}$ 3.0, *C*O); δ_P (101 MHz, $CDCl_3$) 62.7. *m/z* (TOF ES^+) 354.1562 (100%, MH^+, $C_{18}H_{29}NO_2PS$ requires 354.1657).

1-(Benzyloxy)-2-bromobenzene **300**[156]



2-Bromophenol (1.0 cm³, 11 mmol) was added to a suspension of potassium carbonate (4.00 g, 25 mmol) and sodium iodide (2.00 g, 15 mmol) in DMF (12 cm³). Benzyl bromide (1.0 cm³, 12 mmol) was introduced and the reaction mixture heated to 60 °C for 4 hours. Upon cooling to room temperature the solution was diluted with ethyl acetate (20 cm³), washed with water (8 × 20 cm³) and dried over magnesium sulfate. Removal of the solvent *in vacuo* afforded the title compound as an orange oil (2.11 g, 68%). δ_H (400 MHz, $CDCl_3$) 5.17 (2H, s, C*H*$_2$), 6.87 (1H, td, *J* 7.7 1.4, ArC*H*), 8.3 1.4, ArC*H*), 7.24 – 7.28 (2H, m, ArC*H*), 7.32 – 7.39 (1H, m, ArC*H*), 7.41 – 7.44 (2H, m, ArC*H*), 7.50 – 7.52 (2H, m, ArC*H*), 7.59 (1H, dd, *J* 7.7 1.4, ArC*H*). All data is in accordance with the literature.

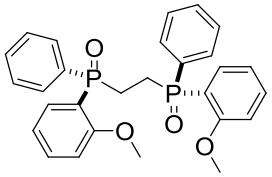
(S_P)-2-[Methyl(phenyl)phosphoryl]phenol **215**



N-phosphinoyl oxazolidinone **178** (297 mg, 1 mmol) was dissolved in anhydrous THF (2.0 cm³) and added *via* syringe pump (1.0 cm³ / h) to a solution of (2-benzyloxy)phenylmagnesium bromide (8 cm³, 4.0 mmol, 0.5M in THF) at 0 °C. Following complete addition of the oxazolidinone, the reaction mixture was warmed to room temperature and stirred for a further 20 minutes. The solution was poured into water (10 cm³) and the aqueous phase extracted with dichloromethane (3 × 10 cm³). The organic layers were combined, washed with brine and dried over magnesium sulfate. Removal of the solvent *in vacuo* yielded the benzyl protected phosphine oxide. Purification of the crude material by flash column chromatography on silica gel using an eluent of 75% ethyl acetate: petroleum ether 40 – 60 °C resulted in spontaneous debenzylation and formation of the title compound as a white solid (115 mg, 49%). t_R 14.0 (minor isomer) and 17.1 (major isomer) (Celluose-1, 90: 10 hexane: propan-2-ol, 210 nm); m.p. 117 °C; $[\alpha]_D^{25}$ + 22 (*c* 1.0 in $CHCl_3$); υ_{max} / cm^{-1} (ATR) 3822, 3022, 2858, 1443; δ_H (400 MHz, $CDCl_3$) 2.08 (3H, d, $J_{P\text{-}H}$ 13.5, PC*H*$_3$), 6.85 – 6.89 (1H, m, ArC*H*), 6.94 (1H, dd, *J* 8.4 4.6, ArC*H*), 7.15 (1H, ddd, *J* 13.4 7.6 1.6, ArC*H*), 7.36 – 7.40 (1H, m, ArC*H*), 7.45 – 7.57 (3H, m, ArC*H*), 7.74 – 7.81 (2H, m, ArC*H*), 11.10 (1H, s, O*H*); δ_C (101 MHz, $CDCl_3$) 16.9 (d, $J_{C\text{-}P}$ 73.0, P*C*H$_3$), 113.0 (d, $J_{C\text{-}P}$ 101.0, Ar*C*), 118.3 (d, $J_{C\text{-}P}$ 7.0, Ar*C*H), 119.4 (d, $J_{C\text{-}P}$ 12.0, Ar*C*H), 128.9 (d, $J_{C\text{-}P}$ 12.0, 2 × Ar*C*H), 130.1 (d, $J_{C\text{-}P}$ 10.0, 2 × Ar*C*H), 130.6 (d, $J_{C\text{-}P}$ 10.0, Ar*C*H), 132.3 (d,

$J_{C\text{-}P}$ 2.0, Ar*C*H), 133.6 (d, $J_{C\text{-}P}$ 101.0, Ar*C*), 134.2 (d, $J_{C\text{-}P}$ 1.0, Ar*C*H), 162.8 (d, $J_{C\text{-}P}$ 3.0, Ar*C*); δ_P (101 MHz, $CDCl_3$) 41.4; *m/z* (TOF ES^+) 233.0726 (100%, MH^+, $C_{13}H_{14}O_2P$ requires 233.0731). No data is reported within the literature.

(1*R*,1*R*')-(-)-1,1'-(1,2-Ethanediyl)*bis*[1-(2-methoxyphenyl)-1-phenyl-phosphine oxide **171**[132]

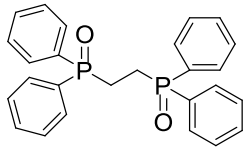


(1*R*,1*R*')-(-)-*bis*[(2-Methoxyphenyl)phenylphosphino]ethane (100 mg, 0.2 mmol) was dissolved in anhydrous dichloromethane (5.0 cm³) and the solution cooled to 0 °C. Hydrogen peroxide (35 wt. %, 0.1 cm³) was added dropwise and the solution warmed to room temperature and stirred for 12 hours. The reaction was poured into water (3.0 cm³) and the organic phase separated. The aqueous layer was extracted with dichloromethane (3 × 10 cm³), and the organic phases combined, washed with a saturated solution of sodium bisulfite (10 cm³) and dried with magnesium sulfate. Removal of the solvent *in vacuo* afforded a white crystalline solid as the title compound which required no further purification (100 mg, 96%). m.p. 206 °C (lit.**[132]** 205 – 207 °C); $[\alpha]_D^{25}$ - 44.5 (*c* 1.0 in MeOH, lit.[132] - 44.9 *c* 1.0 in MeOH); δ_H (400 MHz, $CDCl_3$) 2.57 – 2.74 (4H, m, 2 × CH_2), 3.57 (6H, s, 2 × OCH_3), 6.79 – 6.82 (2H, m, ArC*H*), 7.08 (2H, t, *J* 7.3, ArC*H*), 7.37 – 7.49 (8H, m, ArC*H*), 7.72 – 7.77 (2H, m, ArC*H*), 7.97 – 7.99 (4H, m, ArC*H*); δ_P (121 MHz, $CDCl_3$) 32.2. All data is in accordance with that of the literature.

General procedure K for the preparation of the achiral *bis*-phosphine oxide catalysts

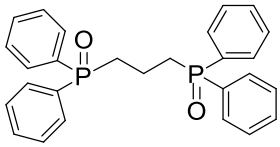
The dibromoalkane (5 mmol) and triphenyl phosphine (2.60 g, 10 mmol) were dissolved in acetonitrile (20 cm³) and the solution heated to reflux for 18 hours. Upon cooling to room temperature the solvent was removed *in vacuo* to afford the crude phosphonium salt. The phosphonium salt was redissolved in a solution of methanol (10 cm³) and aqueous 6N KOH solution (10 cm³) and heated at reflux for a further 24 hours. The solvent was removed *in vacuo* to afford the crude *bis*-phosphine oxide. Purification of the crude material occurred as described within the individual experimental details.

1,2-*bis*(Diphenylphosphinoyl)ethane **217**[133]



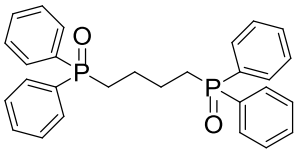
Prepared according to general procedure **K** from 1,2-dibromoethane (0.4 cm³, 5 mmol). Recrystallisation of the crude compound from methanol: ethyl acetate afforded the title compound as a white crystalline solid (2.02 g, 95%). m.p. 273 – 274 °C (lit.[133]273 -276 °C); δ_H (400 MHz, $CDCl_3$) 2.51 (4H, d, $J_{P\text{-}H}$ 1.8, 2 × CH_2), 7.41 – 7.53 (12H, m, ArC*H*), 7.66 – 7.73 (8H, m, ArC*H*); δ_P (101 MHz, $CDCl_3$) 32.5. All data is in accordance with that of the literature.

1,3-*bis*(Diphenylphosphinoyl)propane **218**[133]



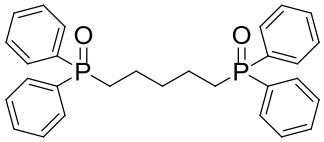
Prepared according to general procedure **K** from 1,3-dibromopropane (0.5 cm³, 5 mmol). Recrystallisation of the crude material from methanol: ethyl acetate afforded the title compound as a white solid (1.61 g, 72%). m.p. 140 – 141 °C (lit. [133] 139 – 140 °C); δ_H (400 MHz, $CDCl_3$) 1.92 – 2.08 (2H, m, CH_2), 2.45 – 2.56 (4H, m, 2 × CH_2), 7.39 – 7.52 (12H, m, ArC*H*), 7.65 – 7.72 (8H, m, ArC*H*); δ_P (101 MHz, $CDCl_3$) 32.2. All data is in accordance with the literature.

1,4-*bis*(Diphenylphosphinoyl)butane **219**[133]



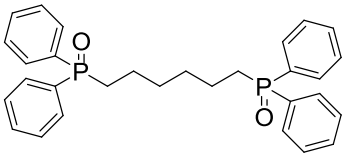
Prepared according to general procedure **K** from 1,4-dibromobutane (0.6 cm³, 5 mmol). Recrystallisation of the crude material from methanol: ethyl acetate afforded the title compound as a white crystalline solid (1.81 g, 80%). m.p. 267 -268 °C (lit.[133] 267 - 269 °C); δ_H (400 MHz, $CDCl_3$) 1.67 – 1.79 (4H, m, 2 × CH_2), 2.21 – 2.28 (4H, m, 2 × CH_2), 7.42 – 7.53 (12H, m, ArC*H*), 7.66 – 7.73 (8H, m, ArC*H*); δ_P (101 MHz, $CDCl_3$) 32.2. All data is in accordance with the literature.

1,5-*bis*(Diphenylphosphinoyl)pentane **220**[133]



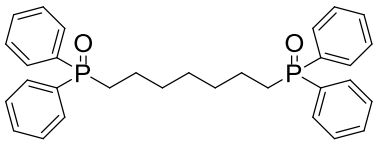
Prepared according to general procedure **K** from 1,5-dibromopentane (0.7 cm³, 5 mmol). Recrystallisation of the crude material from methanol: ethyl acetate afforded the title compound as a white crystalline solid (1.64 g, 67%). m.p. 119 - 120 °C (lit.[133] 119 - 120 °C); δ_H (400 MHz, $CDCl_3$) 1.55 – 1.69 (6H, m, 3 × CH_2), 2.15 – 2.26 (4H, m, 2 × CH_2), 7.44 – 7.48 (12H, m, ArC*H*), 7.66 – 7.74 (8H, m, ArC*H*); δ_P (101 MHz, $CDCl_3$) 32.2. All data is in accordance with the literature.

1,6-*bis*(Diphenylphosphinoyl)hexane **221**[133]



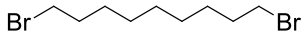
Prepared according to general procedure **K** from 1,6-dibromohexane (0.8 cm³, 5 mmol). Recrystallisation of the crude material from methanol: ethyl acetate afforded the title compound as a white crystalline solid (1.53 g, 64%). m.p. 196 – 197 °C (lit.[133] 197 °C); δ_H (400 MHz, $CDCl_3$) 1.35 – 1.42 (4H, m, 2 × CH_2), 1.54 – 1.65 (4H, m, 2 × CH_2), 2.19 – 2.26 (4H, m, 2 × CH_2), 7.44 – 7.56 (12H, m, ArC*H*), 7.69 – 7.76 (8H, m, ArC*H*); δ_P (101 MHz, $CDCl_3$) 32.1. All data is in accordance with that of the literature.

1,7-*bis*(Diphenylphosphinoyl)heptane **222**[133]



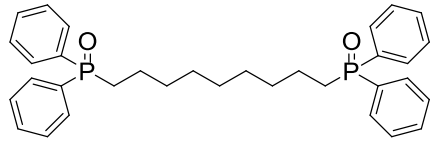
Prepared according to general procedure **K** from 1,7-dibromoheptane (0.9 cm³, 5 mmol). Recrystallisation of the crude material from methanol: ethyl acetate afforded the title compound as a white crystalline solid (2.01 g, 80%). m.p. 90 – 91 °C (lit.[133] 90 - 91 °C); δ_H (250 MHz, $CDCl_3$) 0.84 – 0.92 (2H, m, CH_2), 1.23 – 1.43 (4H, m, 2 × CH_2), 1.50 – 1.67 (4H, m, 2 × CH_2), 2.17 – 2.30 (4H, m, 2 × CH_2), 7.42 – 7.58 (12H, m, ArC*H*), 7.68 – 7.78 (8H, m, ArC*H*); δ_P (101 MHz, $CDCl_3$) 32.3. All data is in accordance with the literature.

Dibromononane **301**[157]



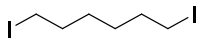
48% HBr solution in water (41 cm³, 157 mmol) was added dropwise to a mixture of 1,9-nonanediol (9.60 g, 60 mmol) in toluene (100 cm³) and the solution heated at reflux under Dean Stark conditions for 18 hours. The solution was cooled to room temperature and neutralised through addition of solid sodium hydrogen carbonate (12 g). The suspension was filtered and the solvent removed *in vacuo* to afford a crude orange oil. Purification of the crude material by flash column chromatography on silica gel using an eluent of 100% petroleum ether 40-60 °C afforded the title compound as a colourless oil (16 g, 92%). δ_H (400 MHz, $CDCl_3$) 1.28 – 1.34 (6H, m, 3 × CH_2), 1.38 – 1.47 (4H, m, 2 × CH_2), 1.86 (4H, quintet, *J* 7.1, 2 × CH_2CH_2Br), 3.41 (4H, t, *J* 7.1, 2 × CH_2Br). All data is in accordance with that of the literature.

1,9-*bis*(Diphenylphosphoryl)nonane **223**[133]



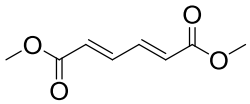
Prepared according to general procedure **K** from 1,9-dibromononane **301** (2.62 g, 5 mmol). Recrystallisation of the crude compound from methanol: ethyl acetate afforded the title compound as a white crystalline solid (1.80 g, 70%). m.p. 123 -125 °C (lit.[133] 123 - 125 °C); δ_H (250 MHz, $CDCl_3$) 1.10 – 1.38 (10H, m, 5 × CH_2), 1.52 – 1.68 (4H, m, 2 × CH_2), 2.19 – 2.30 (4H, m, 2 × CH_2), 7.43 – 7.56 (12H, m, ArC*H*), 7.70 – 7.78 (8H, m, ArC*H*); δ_P (101 MHz, $CDCl_3$) 32.4. All data is in accordance with the literature.

1,6- Diiodohexane **302**[158]



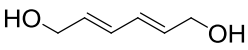
1,6-Dibromohexane (4 cm³, 25 mmol) and sodium iodide (15 g, 100 mmol) were dissolved in acetone (50 cm³) and the mixture heated at reflux for 6 hours. Upon cooling to room temperature, the solvent was removed *in vacuo* to afford a white solid. Diethyl ether (50 cm³) was added and the solution decanted to remove the sodium iodide. Removal of the solvent *in vacuo* afforded the title compound as a colourless oil that was stored under nitrogen and in the dark to prevent degradation (8.00 g, 95%). δ_H (400 MHz, $CDCl_3$) 1.39 – 1.78 (4H, m, 2 × CH_2), 1.79 – 1.85 (4H, m, 2 × CH_2), 3.17 (4H, t, *J* 7.0, 2 × CH_2I).

(2*E*,4*E*)-Dimethylhexa-2,4-dienedioate **303**[159]



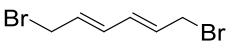
Thionyl chloride (5.0 cm³, 68 mmol) was added dropwise to a suspension of (2*E*,4*E*)-hexa-2,4-dienedioic acid (3.01 g, 21 mmol) in a solvent mixture of chloroform (10 cm³) and methanol (10cm³). The solution was heated at reflux for 2 hours to enable complete dissolution of the solid. Removal of the solvent *in vacuo* afforded the title compound as an off white solid (3 g, 91%). m.p. 164 °C (lit.[159] 164 °C); δ_H (250 MHz, $CDCl_3$) 3.80 (6H, s, OC*H*$_3$), 6.21 [2H, $(AX)_2$, C*H*=CHCO$_2$Me], 7.35 [2H, $(AX)_2$, CH=C*H*CO$_2$Me]. All data is in accordance with the literature.

(2*E*,4*E*)-Hexa-2,4-diene-1,6-diol **304**[160]



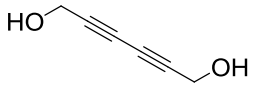
Methyl ester **303** (2.82 g, 16 mmol) was dissolved in dichloromethane (10 cm³) and the solution cooled to 0 °C. DIBAL-H (66 cm³, 1M in hexanes, 66 mmol) was added dropwise and the reaction mixture slowly warmed to room temperature and stirred for 18 hours. Methanol (30 cm³) was added dropwise to the solution until effervescence seized and the resulting mixture filtered through a celite plug. The plug was washed with methanol (3 × 20 cm³) and the filtrate removed *in vacuo* to afford the title compound as a white solid (1.70 g, 94%). m.p. 104 °C (lit. [160]104 – 106 °C); δ_H (400 MHz, MeOD) 4.10 (4H, d, *J* 10.3, 2 × C*H*$_2$), 5.77 – 5.86 (2H, m, 2 × C*H*=CHCH$_2$OH), 6.25 – 6.35 (2H, m, 2 × CH=C*H*CH$_2$OH). All data is in accordance with the literature.

(2*E*,4*E*)-1,6-Dibromohexa-2,4-diene **305**[161]



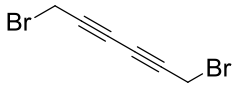
(2*E*,4*E*)-Hexa-2,4-diene-1,6-diol **304** (800 mg, 7 mmol) was dissolved in diethyl ether (30 cm³) and the solution cooled to 0 °C. Phosphorus tribromide (0.5 cm³, 4.6 mmol) was added dropwise and the mixture warmed to room temperature and stirred for 6 hours. The solvent was removed *in vacuo* and the residue filtered through a short silica plug eluting with diethyl ether (100 cm³). Removal of the solvent *in vacuo* afforded the title compound as a golden yellow solid which required no further purification (3.05 g, 85%). m.p. 85 – 86 °C (lit.[161] 85 °C); δ_H (400 MHz, $CDCl_3$) 4.04 (4H, d, *J* 7.6, 2 × C*H*$_2$Br); 5.90 – 6.01 (2H, m, C*H*=CHCH$_2$), 6.26 – 6.34 (2H, m, CH=C*H*CH$_2$). All data is in accordance with that of the literature.

Hexa-2,4-diyne-1,6-diol **306**[162]



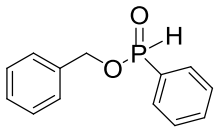
Prop-2-yn-1-ol (0.6 cm³, 10 mmol), copper iodide (190 mg, 1 mmol) and sodium acetate (820 mg, 10 mmol) were dissolved in DMF (10 cm³). The solution was heated to 90 °C and stirred vigorously for 14 hours. Upon cooling to room temperature, the mixture was diluted with ethyl acetate (30 cm³) and the organic phase separated. The organic layer was washed with water (8 × 10 cm³) and dried over magnesium sulfate. Removal of the solvent *in vacuo* afforded the title compound as a colourless oil (590 mg, 54%). δ_H (400 MHz, d_6-DMSO) 4.17 (4H, s, 2 × C*H*$_2$), 5.41 (2H, s, 2 × O*H*). All data was in accordance with the literature.

1,6-Dibromohexa-2,4-diyne **307**[163]



Bromine (0.1 cm³, 4 mmol) was added dropwise to a solution of hexa-2,4-diyne-1,6-diol **306** (200 mg, 2 mmol) and triphenylphosphine (1.00 g, 4 mmol) in anhydrous dichloromethane (10 cm³) at 0 °C. The solution was stirred for 1 hour before being warmed to room temperature and stirred for a further hour. The reaction was quenched through addition of water (10 cm³) and the organic phase separated and dried over magnesium sulfate. Removal of the solvent *in vacuo* yielded a colourless oil. Petroleum ether 40 - 60 °C (10 cm³) was added and the resulting white solid filtered. Removal of the filtrate *in vacuo* afforded the title compound as a colourless oil (235 mg, 56%). δ_H (400 MHz, $CDCl_3$) 3.99 (4H, s, 2 × C*H2*). All data is in accordance with the literature.

Benzyl phenylphosphonate **239**[137]



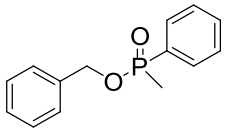
Phenylphosphinic acid (1.00 g, 7 mmol) was added in a single portion to a solution of benzyl chloroformate (0.6 cm³, 7 mmol) and dichloromethane (15 cm³) and the mixture cooled to 0 °C. Pyridine (1.0 cm³, 7 mmol) was added dropwise and the solution stirred until effervescence ceased. The organic phase was washed with an aqueous 0.1*N* HCl solution (10 cm³), brine (2 × 10 cm³) and dried over magnesium sulfate. Removal of the solvent *in vacuo* afforded the title compound as a pale yellow oil (1.52 g, 91%). δ_H (250 MHz, $CDCl_3$) 5.03 – 5.25 [2H, $(AX)_2$,

C*H*$_2$], 7.31 – 7.44 (5H, m, ArC*H*), 7.47 – 7.68 (3H, m, ArC*H*), 7.72 (1H, d, $J_{P\text{-}H}$ 566.5, P*H*), *7*.75 – 7.87 (2H, m, ArC*H*). All data is in accordance with the literature.

General procedure L for the alkylation of benzyl phenylphosphonate 239

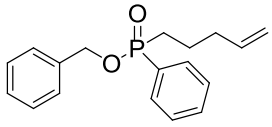
Secondary phosphinate **239** (242 mg, 1 mmol) was dissolved in degassed THF (2.0 cm³) and the reaction cooled to -78 °C. LiHMDS (1.0 cm³, 1 mmol, 1M in THF) was added dropwise and the reaction mixture stirred for 1 hour before addition of the appropiate electrophile (1 mmol). Upon warming to room temperature the reaction solution was stirred for 8 hours before being quenched through addition of a1*N* HCl solution (5.0 cm³). The organic phase was extracted with ethyl acetate (3 × 10 cm³), washed with brine (10 cm³) and dried over magnesium sulfate to afford the crude alkylated phosphinate. Purification of the crude material occurred as described in the individual experimental details.

Benzyl methyl(phenyl)phosphinate **240**



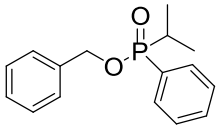
Prepared according to general procedure **L** using methyl iodide (0.1 cm³, 1 mmol) as the electrophile. Purification of the crude material by flash column chromatography using a gradient eluent of 100% ethyl acetate to 5% methanol: dichloromethane afforded the title compound as a yellow oil (165 mg, 87%). υ_{max} / cm^{-1} 3062, 3034, 1641, 1439; δ_H (400 MHz, $CDCl_3$) 1.69 (3H, d, $J_{P\text{-}H}$ 14.6, PC*H*$_3$), 4.73 (1H, dd, *J* 11.7 7.3, C*H*H), 5.06 (1H, dd, *J* 11.7 7.3, C*H*H), 7.25 – 7.35 (5H, m, ArC*H*), 7.43 – 7.50 (2H, m, ArC*H*), 7.52 – 7.58 (1H, m, ArC*H*), 7.76 – 7.85 (2H, m, ArC*H*); δ_C (101MHz, $CDCl_3$) 15.9 (d, $J_{C\text{-}P}$ 102.4, P*C*H$_3$), 65.9 (d, $J_{C\text{-}P}$ 5.7, O*C*H$_2$), 127.9 (2 × Ar*C*H), 128.3 (Ar*C*H), 128.5 (2 × Ar*C*H), 128.7 (d, $J_{C\text{-}P}$ 12.6, 2 × Ar*C*H), 131.2 (d, $J_{C\text{-}P}$ 10.3, 2 × Ar*C*H), 131.4 (d, $J_{C\text{-}P}$ 126.7, Ar*C*), 132.4 (d, $J_{C\text{-}P}$ 2.6, Ar*C*H), 136.3 (d, $J_{C\text{-}P}$ 7.4, Ar*C*); δ_P (101 MHz, $CDCl_3$) 43.3; *m/z* (TOF ES$^+$) 247.0886 (100%, MH$^+$, $C_{14}H_{16}O_2P$ requires 247.0888).

Benzyl pent-4-enyl(phenyl)phosphinate **241**



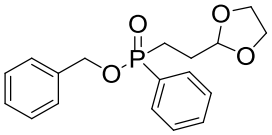
Prepared according to general procedure **L** using 5-iodo-pent-1-ene (0.1 cm³, 1 mmol) as the electrophile. Purification of the crude material by flash column chromatography on silica gel using an eluent of 50% ethyl acetate: petroleum ether 40 – 60 °C afforded the title compound as a yellow oil (145 mg, 63%). (Found C, 71.80; H, 7.03; $C_{18}H_{21}O_2P$ requires C, 71.98; H, 7.05); υ_{max} (ATR) / cm^{-1} 3063, 2928, 1591, 1438; δ_H (400 MHz, $CDCl_3$) 1.57 – 1.80 (2H, m, CH_2), 1.85 – 2.13 (4H, m, 2 × CH_2), 4.75 (1H, dd, *J* 11.8 6.8, C*H*H), 4.94 – 4.99 (2H, m, CH=CH_2), 5.10 (1H, dd, *J* 11.8 6.8, CH*H*), 5.64 – 5.74 (1H, m, C*H*=CH_2), 7.28 – 7.38 (5H, m, ArC*H*), 7.46 – 7.52 (2H, m, ArC*H*), 7.54 – 7.59 (1H, m, ArC*H*), 7.77 – 7.84 (2H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 20.9 (d, $J_{C\text{-}P}$ 3.0, *C*H_2), 29.2 (d, $J_{C\text{-}P}$ 100.0, *C*H_2), 34.4 (d, $J_{C\text{-}P}$ 16.0, *C*H_2), 65.8 (d, $J_{C\text{-}P}$ 6.0, O*C*H_2), 115.7 (CH=*C*H_2), 127.9 (2 × Ar*C*H), 128.2 (*C*H=CH_2), 128.5 (2 × Ar*C*H), 128.7 (d, $J_{C\text{-}P}$ 12.3, 2 × Ar*C*H), 130.6 (d, $J_{C\text{-}P}$ 122.0, Ar*C*), 131.7 (d, $J_{C\text{-}P}$ 9.9, 2 ×Ar*C*H), 132.3 (d, $J_{C\text{-}P}$ 2.2, Ar*C*H), 136.5 (d, $J_{C\text{-}P}$ 7.1, Ar*C*), 137.3 (Ar*C*H); δ_P (121 MHz, $CDCl_3$) 46.1; *m/z* (TOF ES^+) 301.1366 (100%, MH^+, $C_{18}H_{22}O_2P$ requires 301.1357).

Benzyl *iso*-propyl(phenyl)phosphinate **242**



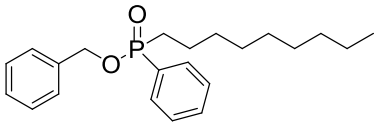
Prepared according to general procedure **L** using 2-iodopropane (0.1 cm³, 1 mmol) as the electrophile. Purification of the crude material by flash column chromatography on silica gel using an eluent of 50% ethyl acetate: petroleum ether 40 – 60 °C afforded the title compound as a yellow oil (194 mg, 71%). υ_{max} / cm^{-1} 3065, 3045, 1684, 1421; δ_H (400 MHz, $CDCl_3$) 1.10 [3H, dd, *J* 18.1 7.1, 1 × CH(CH_3)$_2$], 1.23 [3H, dd, *J* 18.1 7.1, 1 × CH(CH_3)$_2$], 2.09 – 2.20 [1H, m, C*H*(CH_3)$_2$], 4.80 (1H, dd, *J* 11.8 6.4, C*H*H), 5.14 (1H, dd, *J* 11.8 6.4, C*H*H), 7.31 – 7.39 (5H, m, ArC*H*), 7.54 – 7.56 (2H, m, ArC*H*), 7.61 – 7.77 (1H, m, ArC*H*), 7.77 – 7.84 (2H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 15.2 [d, $J_{C\text{-}P}$ 3.0, 1 × CH(*C*H_3)$_2$], 15.6 [1 × CH(*C*H_3)$_2$], 28.5 (d, $J_{C\text{-}P}$ 101.0, *C*H(CH_3)$_2$], 65.9 (d, $J_{C\text{-}P}$ 6.0, O*C*H_2), 127.7 (2 × Ar*C*H), 128.2 (Ar*C*H), 128.5 (2 × Ar*C*H), 128.6 (d, $J_{C\text{-}P}$ 11.0, 2 × Ar*C*H), 129.8 (Ar*C*), 132.3 (2 × Ar*C*H), 132.4 (Ar*C*H), 136.7 (d, $J_{C\text{-}P}$ 7.0, Ar*C*); δ_P (400 MHz, $CDCl_3$) 49.9; *m/z* (TOF ES^+) 275.3021 (100%, MH^+, $C_{16}H_{20}O_2P$ requires 275.3026).

Benzyl 2-(1,3-dioxolan-2-yl)ethyl(phenyl)phosphinate **243**



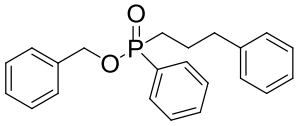
Prepared according to general procedure **L** from 2-(2-bromoethyl)-1,3-dioxolane (0.1 cm³, 1 mmol) as the electrophile. Purification of the crude material by flash column chromatography on silica gel using an eluent of 50% ethyl acetate: petroleum ether 40 – 60 °C afforded the title compound as an orange oil (182 mg, 55%). υ_{max} / cm^{-1} 2964, 2923, 2884, 1650; δ_H (400 MHz, $CDCl_3$) 1.73 – 2.17 (4H, m, 2 × C*H*$_2$), 3.74 – 3.89 (4H, m, 2 × *C*H$_2$), 4.75 (1H, dd, *J* 11.7 6.9, C*H*H), 4.84 – 4.89 (1H, m, C*H*), 5.07 (1H, dd, *J* 11.7 6.9, C*H*H), 7.24 – 7.34 (5H, m, ArC*H*), 7.41 – 7.56 (3H, m, ArC*H*), 7.72 – 7.81 (2H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 23.5 (d, $J_{C\text{-}P}$ 102.4, *C*H$_2$), 26.1 (d, $J_{C\text{-}P}$ 2.3, *C*H$_2$), 65.0 (2 × *C*H$_2$), 65.9 (d, $J_{C\text{-}P}$ 6.0, O*C*H$_2$), 103.2 (d, $J_{C\text{-}P}$ 16.0, *C*H), 127.8 (2 × Ar*C*H), 128.2 (Ar*C*H), 128.5 (2 × Ar*C*H), 128.7 (d, $J_{C\text{-}P}$ 12.4, 2 × Ar*C*H), 130.2 (d, $J_{C\text{-}P}$ 124.0, Ar*C*), 131.7 (d, $J_{C\text{-}P}$ 9.9, 2 × Ar*C*H), 132.4 (d, $J_{C\text{-}P}$ 2.4, Ar*C*H), 136.4 (d, $J_{C\text{-}P}$ 8.0, Ar*C*); δ_P (101 MHz, $CDCl_3$) 45.6; *m/z* (TOF ES^+) 333.1259 (100%, MH^+, 333.1256).

Benzyl nonyl(phenyl)phosphinate **244**



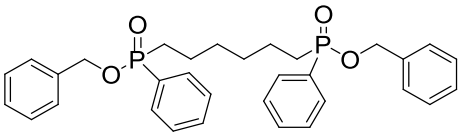
Prepared according to general procedure **L** using 1-nonyliodide (0.2 cm³, 1 mmol) as the electrophile. Purification of the crude material by flash column chromatography on silica gel using an eluent of 75% ethyl acetate: petroleum ether 40 – 60 °C afforded the title compound as an orange oil (221 mg, 65%). υ_{max} / cm^{-1} 3085, 2987, 1688, 1421; δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, *J* 8.0, C*H*$_3$), 1.16 – 1.41 (12H, m, 6 × C*H*$_2$), 1.47 – 1.68 (2H, m, C*H*$_2$), 1.85 – 2.06 (2H, m, C*H*$_2$), 4.77 (1H, dd, *J* 11.8 6.8, C*H*H), 5.10 (1H, dd, *J* 11.8 6.8, C*H*H), 7.30 – 7.41 (5H, m, ArC*H*), 7.41 – 7.53 (2H, m, ArC*H*), 7.54 – 7.60 (1H, m, ArC*H*), 7.77 – 7.85 (2H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 14.1 (*C*H$_3$), 21.6 (d, $J_{C\text{-}P}$ 4.0, *C*H$_2$), 22.6 (*C*H$_2$), 29.0 (*C*H$_2$), 29.2 (*C*H$_2$), 29.3 (*C*H$_2$), 30.3 (*C*H$_2$), 30.7 (d, $J_{C\text{-}P}$ 46.0, *C*H$_2$), 31.8 (*C*H$_2$), 65.8 (d, $J_{C\text{-}P}$ 7.0, O*C*H$_2$), 127.8 (2 × Ar*C*H), 128.2 (Ar*C*H), 128.4 (2 × Ar*C*H), 128.6 (d, $J_{C\text{-}P}$ 13.0, 2 × Ar*C*H), 130.8 (d, $J_{C\text{-}P}$ 121.7, Ar*C*), 131.7 (d, $J_{C\text{-}P}$ 9.8, 2 × Ar*C*H), 132.2 (d, $J_{C\text{-}P}$ 2.0, Ar*C*H), 136.6 (d, $J_{C\text{-}P}$ 7.0, Ar*C*); δ_P (101 MHz, $CDCl_3$) 46.1; *m/z* (TOF ES^+) 359.2146 (100%, MH^+, $C_{22}H_{32}O_2P$ requires 359.2140). No data is reported within the literature.

Benzyl phenyl(3-phenylpropyl)phosphinate **245**



Prepared according to general procedure **L** using (3-iodoproyl)benzene (0.2 cm³, 1 mmol) as the electrophile. Purification of the crude material by flash column chromatography on silica gel using an eluent of 50% ethyl acetate: petroleum ether 40 – 60 °C afforded the title compound as a yellow oil (284 mg, 85%). υ_{max} / cm^{-1} 3120, 2998, 1629, 1431; δ_H (400 MHz, $CDCl_3$) 1.80 – 2.08 (4H, m, C*H*$_2$), 2.61 – 2.72 (2H, m, C*H*$_2$), 4.76 (1H, dd, *J* 11.8 6.9, C*H*H), 5.10 (1H, dd, *J* 11.8 6.9, C*H*H), 7.08 – 7.13 (2H, m, ArC*H*), 7.16 (1H, m, ArC*H*), 7.24 – 7.29 (2H, m, ArC*H*), 7.30 – 7.38 (5H, m, ArC*H*), 7.46 – 7.52 (2H, m, ArC*H*), 7.54 – 7.60 (1H, m, ArC*H*), 7.75 – 7.84 (2H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 23.3 (d, $J_{C\text{-}P}$ 3.0, *C*H$_2$), 29.1 (d, $J_{C\text{-}P}$ 99.0, *C*H$_2$), 36.5 (d, $J_{C\text{-}P}$ 16.0, *C*H), 65.9 (d, $J_{C\text{-}P}$ 6.0, O*C*H$_2$), 126.1 (2 × Ar*C*H), 127.9 (2 × Ar*C*H), 128.3 (Ar*C*H), 128.5 (d, $J_{C\text{-}P}$ 8.4, 2 × Ar*C*H), 128.6 (2 × Ar*C*H), 128.7 (d, $J_{C\text{-}P}$ 12.0, 2 × Ar*C*H), 130.5 (d, $J_{C\text{-}P}$ 122.1, Ar*C*), 131.7 (d, $J_{C\text{-}P}$ 10.0, 2 × Ar*C*H), 132.4 (Ar*C*H), 136.5 (d, $J_{C\text{-}P}$ 7.0, Ar*C*), 140.9 (Ar*C*); δ_P (101 MHz, $CDCl_3$) 45.7; *m/z* (TOF ES^+) 351.3990 (100%, MH^+, $C_{22}H_{24}O_2P$ requires 351.3985).

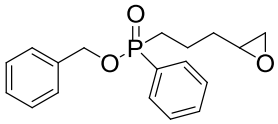
Benzyl hexane-1,6-diyl*bis*(phenylphosphinate) **246**



Prepared according to general procedure **L** using 1,6-diiodohexane **302** (0.05 cm³, 0.5 mmol) as the electrophile. Removal of the solvent *in vacuo* yielded a crude orange oil as a 1: 5 mixture of the *mono* and *bis*-phosphinates as determined by the crude ^{1}H NMR spectroscopy. Purification and isolation of the *bis*-phosphinate by flash column chromatography on silica gel using a gradient eluent of 100% ethyl acetate to 5% methanol: dichloromethane afforded the title compound as a pale yellow oil (290 mg, 66%). υ_{max} / cm-1 3060, 2938, 1638, 1438; δ_H (400 MHz, $CDCl_3$) 1.21 – 1.62 (8H, m, 4 × C*H*$_2$), 1.72 – 2.03 4H, m, 2 × C*H*$_2$), 4.73 (2H, dd, *J* 11.7 6.9, 2 × C*H*H), 5.06 (2H, dd, *J* 11.7 6.9, 2 × C*H*H), 7.25 – 7.36 (10H, m, ArC*H*), 7.43 – 7.57 (6H, m, ArC*H*), 7.73 – 7.81 (4H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 21.5 (d, $J_{C\text{-}P}$ 3.4, 2 × *C*H$_2$), 29.6 (d, $J_{C\text{-}P}$ 99.8, 2 × *C*H$_2$), 30.1 (d, $J_{C\text{-}P}$ 16.0, 2 × *C*H$_2$), 65.8 (d, $J_{C\text{-}P}$ 6.0, 2 × O*C*H$_2$), 127.9 (4 × Ar*C*H), 128.2 (2 × Ar*C*H), 128.5 (4 × Ar*C*H), 128.7 (d, $J_{C\text{-}P}$ 12.3, 4 × Ar*C*H), 130.6 (d, $J_{C\text{-}P}$

121.8, 2 × Ar*C*), 131.7 (d, $J_{C\text{-}P}$ 9.8, 4 × Ar*C*H), 132.3 (d, $J_{C\text{-}P}$ 2.2, 2 × Ar*C*H), 136.5 (d, $J_{C\text{-}P}$ 7.0, 2 × Ar*C*); δ_P (101 MHz, $CDCl_3$) 45.7; *m/z* (TOF ES+) 547.2151 (100%, MH^+, 547.2167).

Benzyl 3-(oxiran-2-yl)propyl(phenyl)phosphinate **255**

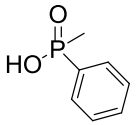


Benzyl phosphinate **241** (200 mg, 0.6 mmol) was dissolved in dichloromethane (5 cm³) and the solution cooled to 0 °C. *m*-CPBA (108 mg, 0.6 mmol) was added in a single portion and the reaction mixture warmed to room temperature and stirred for 12 hours. Dichloromethane (10 cm³) and a saturated aqueous solution of $NaHCO_3$ (10 cm³) were added and the organic phase separated. The aqueous layer was extracted with dichloromethane (2 × 10 cm³) and the organic phases combined, washed with a saturated aqueous solution of $NaHCO_3$ (3 × 10 cm³) and dried over magnesium sulfate. Removal of the solvent *in vacuo* afforded the title compound as a colourless oil (142 mg, 75%). υ_{max} / cm^{-1} 3071, 3012, 2945, 1642; δ_H (400 MHz, $CDCl_3$) 1.45 – 1.57 (1H, m, C*H*H), 1.59 – 1.86 (3H, m, C*H2* and C*H*H), 1.88 – 2.13 (2H, m, CH_2), 2.38 – 2.41 (1H, m, C*H*), 2.68 – 2.70 (1H, m, C*H*), 2.81 – 2.87 (1H, m, C*H*), 4.76 (1H, ddd, *J* 11.7 7.0 0.7, C*H*H), 5.08 (1H, ddd, *J* 11.7 7.0 0.7, C*H*H), 7.27 – 7.37 (5H, m, ArC*H*), 7.45 – 7.52 (1H, m, ArC*H*), 7.53 – 7.59 (2H, m, ArC*H*), 7.76 – 7.84 (2H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 18.6 (dd, $J_{C\text{-}P}$ 10.2 3 .2, CH_2), 29.5 (d, $J_{C\text{-}P}$ 97.0, CH_2), 33.2 (dd, $J_{C\text{-}P}$ 15.4 11.2, CH_2), 46.7 (CH_2), 51.6 (d, $J_{C\text{-}P}$ 4.8, *C*H), 65.9 (d, $J_{C\text{-}P}$ 6.1, *C*H2), 129.7 (2 × Ar*C*H), 128.3 (Ar*C*H), 128.5 (2 × Ar*C*H), 128.7 (d, $J_{C\text{-}P}$ 12.3, 2 × Ar*C*H), 129.6 (dd, $J_{C\text{-}P}$ 122.4 5.0, Ar*C*), 131.7 (d, $J_{C\text{-}P}$ 9.8, 2 × Ar*C*H), 132.4 (d, $J_{C\text{-}P}$ 2.0, Ar*C*H), 136.4 (d, $J_{C\text{-}P}$ 7.1, Ar*C*); δ_P (101 MHz, $CDCl_3$) 45.2; *m/z* (TOF ES^+) 317.1297 (100%, MH^+, $C_{18}H_{22}O_3P$ requires 317.1307).

General procedure M for the debenzylation of the benzyl phosphinates 240 - 246

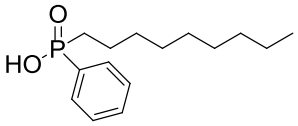
Benzyl phosphinate (0.6 mmol) was dissolved in ethanol (1 cm³) and added to a suspension of 10% Pd on carbon (20 mg) in ethanol (5 cm³). 1,3-Cyclohexadiene (0.2 ml, 2 mmol) was introduced and the reaction heated at reflux for 48 hours. Upon cooling to room temperature the suspension was filtered through cotton wool and the filtrate removed *in vacuo* to afford the desired phosphoric acid.

Phenyl(methyl)phosphoric acid **251**[164]



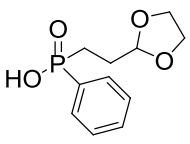
Prepared according to general procedure **M** using benzyl phosphonate **240** (94 mg, 0.6 mmol). Removal of the solvent *in vacuo* afforded the title compound as a white solid (85 mg, 91%). m.p. 132 – 133 °C (lit.[REF] 133 °C); δ_H (400 MHz, *d*$_6$-DMSO) 1.51 (3H, d, $J_{P\text{-}H}$ 14.4, PC*H*$_3$), 7.47 – 7.57 (3H, m, ArC*H*), 7.72 – 7.77 (2H, m, ArC*H*), 10.60 (1H, s, O*H*); δ_C (101 MHz, *d*$_6$-DMSO) 16.9 (d, $J_{C\text{-}P}$ 99.0, C*H*$_3$), 128.8 (d, $J_{C\text{-}P}$ 12.3, 2 × Ar*C*H), 130.8 (d, $J_{C\text{-}P}$ 10.2, 2 × Ar*C*H), 131.8 (d, $J_{C\text{-}P}$ 2.2, Ar*C*H), 135.8 (d, $J_{C\text{-}P}$ 127.6, Ar*C*); δ_P (101 MHz, *d*$_6$-DMSO) 34.6. No ^{13}C data is reported within the literature, otherwise all other data is in accordance.

Nonyl(phenyl)phosphoric acid **249**



Prepared according to general procedure **M** from benzyl phosphonate **244** (215 mg, 0.6 mmol). Removal of the solvent *in vacuo* afforded the title compound as a yellow oil (134 mg, 83%). υ_{max} / cm^{-1} 3220, 3051, 2969, 1668; δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, *J* 8.0, C*H*$_3$), 1.16 – 1.33 (12H, m, 6 × *C*H$_2$), 1.38 – 1.52 (2H, m, *C*H$_2$), 1.71 – 1.89 (2H, m, C*H*$_2$), 7.34 – 7.53 (3H, m, Ar*C*H), 7.67 – 7.82 (2H, m, Ar*C*H), 11.8 (1H, s, O*H*); δ_C (400 MHz, $CDCl_3$) 14.1 (*C*H$_3$), 21.8 (*C*H$_2$), 22.7 (*C*H$_2$), 29.1 (*C*H$_2$), 29.2 (*C*H$_2$), 29.3 (*C*H$_2$), 30.5 (d, $J_{C\text{-}P}$ 101.0, *C*H$_2$), 30.7 (d, $J_{C\text{-}P}$ 15.0, *C*H$_2$), 31.8 (*C*H$_2$), 128.3 (d, $J_{C\text{-}P}$ 12.1, 2 × Ar*C*H), 131.1 (d, $J_{C\text{-}P}$ 9.4, 2 × Ar*C*H), 131.7 (Ar*C*H), 131.7 (d, $J_{C\text{-}P}$ 134.4, Ar*C*); δ_P (101 MHz, $CDCl_3$) 47.5; *m/z* (TOF ES$^+$) 269.3391 (MH$^+$, 100%, $C_{15}H_{26}O_2P$ requires 269.3395).

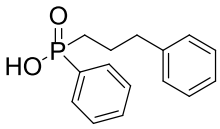
2-(1,3-dioxolan-2-yl)ethyl(phenyl)phosphoric acid **250**



Prepared according to general procedure **M** using benzyl phosphinate **243** (199 mg, 0.6 mmol). Removal of the solvent *in vacuo* afforded a colourless oil (96 mg, 66%). υ_{max} / cm^{-1} 3221, 3051, 2912, 1669; δ_H (400 MHz, $CDCl_3$) 1.69 – 1.99 (4H, m, 2 × C*H*$_2$), 3.69 – 3.94 (4H, m, 2 × C*H*$_2$), 4.71 – 4.91 (1H, m, C*H*), 7.13 – 7.53 (3H, m, ArC*H*), 7.67 – 7.83 (2H, m, ArC*H*), 9.34 (1H, s, O*H*); δ_C (101 MHz, $CDCl_3$) 24.5 (d, $J_{C\text{-}P}$ 99.0, *C*H$_2$), 26.3 (*C*H$_2$), 65.0 (2 × *C*H$_2$), 103.5 (*C*H),

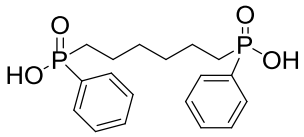
128.4 (d, $J_{C\text{-}P}$ 11.0, 2 × Ar*C*H), 131.1 (d, $J_{C\text{-}P}$ 8.0, 2 × Ar*C*H), 131.9 (Ar*C*); δ_P (101 MHz, $CDCl_3$) 44.4; *m/z* (TOF ES^+) 243.0786 (100%, MH^+, $C_{11}H_{16}O_4P$ requires 243.0777). No data is reported within the literature.

Phenyl(3-phenylpropyl)phosphoric acid **252**



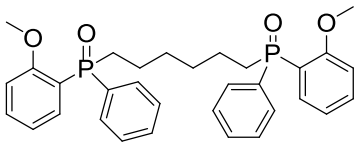
Prepared according to general procedure **M** using benzyl phosphinate **245** (210 mg, 0.6 mmol). Removal of the solvent *in vacuo* afforded the title compound as a white solid (130 mg, 83%). m.p. 97 °C; υ_{max} / cm^{-1} 3240, 3058, 2939, 1673; δ_H (400 MHz, d_6-DMSO) 1.53 – 1.84 (4H, m, 2 × CH_2), 2.47 – 2.64 (2H, m, CH_2), 7.07 – 7.19 (3H, m, ArC*H*), 7.21 – 7.28 (2H, m, ArC*H*), 7.43 – 7.58 (3H, m, ArC*H*), 7.63 – 7.77 (2H, m, ArC*H*); δ_C (101 MHz, d_6-DMSO) 24.5 (CH_2), 30.1 (d, $J_{C\text{-}P}$ 100.0, CH_2), 36.2 (d, $J_{C\text{-}P}$ 15.0, CH_2), 126.3 (2 × Ar*C*H), 128.7 (2 × Ar*C*H), 128.8 (2 × Ar*C*H), 131.2 (Ar*C*H), 131.3 (Ar*C*H), 131.8 (2 × Ar*C*H), 134.9 (d, $J_{C\text{-}P}$ 121.0, Ar*C*), 141.9 (Ar*C*); δ_P (400 MHz, d_6-DMSO) 36.4; *m/z* (TOF ES^+) 261.1037 (100%, MH^+, $C_{15}H_{18}O_2P$ requires 261.1044). No data is reported within the literature.

Hexane-1,6-diyl-*bis*-(phenylphosphoric acid) **226**



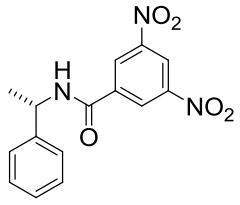
Benzyl phosphinate **246** (0.15 g, 0.27 mmol) was dissolved in a suspension of 10% palladium on charcoal (0.05 g) and ethanol (5 cm^3). 1,3-Cyclohexadiene (0.1 cm^3, 1 mmol) was added and the mixture heated at reflux for 18 hours. The suspension was filtered through cotton wool and the solvent removed *in vacuo* to afford the title compound as a white crystalline solid (0.11 g, 81%). m.p 158 °C; υ_{max} / cm^{-1} 3600, 3060, 2928, 1705; δ_H (400 MHz, d_6-DMSO) 1.15 – 1.30 (8H, m, 4 × CH_2), 1.61 – 1.76 (4H, m, 2 × CH_2), 7.45 – 7.56 (6H, m, ArC*H*), 7.68 – 7.71 (4H, m, ArC*H*), 9.87 (2H, s, 2 × O*H*); δ_C (101 MHz, d_6-DMSO) 22.0 (d, *J* 3.0, 2 × CH_2), 29.9 (2 × CH_2), 30.4 (d, $J_{C\text{-}P}$ 83.0, 2 × CH_2), 128.7 (d, $J_{C\text{-}P}$ 11.9, 4 × Ar*C*H), 131.2 (d, $J_{C\text{-}P}$ 9.6, 4 × Ar*C*H), 131.8 (d, $J_{C\text{-}P}$ 1.8, 2 × Ar*C*H), 134.8 (d, $J_{C\text{-}P}$ 123.0, Ar*C*); δ_P (101 MHz, d_6-DMSO) 37.1; *m/z* (TOF ES^+) 367.1232 (100%, MH^+, $C_{18}H_{25}O_4P_2$ requires 367.1228).

1,6-*bis*[(2-Methoxyphenyl)(phenyl)phosphinoyl]hexane **224**



Phosphoric acid **X** (366 mg, 1 mmol) was suspended in dichloromethane (10 cm³) and thionyl chloride (0.4 cm³, 5 mmol) added dropwise. The mixture was heated at reflux for 6 hours before being cooled to room temperature and the volatiles removed *in vacuo* to yield the *bis*-phosphinic chloride. The phosphinic chloride (382 mg, 0.9 mmol) was added to a solution of 2-anisyl magnesium bromide (3 cm³, 1M in THF, 3 mmol) in THF (10 cm³) at 0 °C and the mixture stirred for 8 hours. An aqueous saturated solution of ammonium chloride (10 cm³) was added dropwise to destroy the excess Grignard reagent and the solution diluted through addition of dichloromethane (30 cm³). The organic phase was separated and the aqueous layer extracted with dichloromethane (2 × 15 cm³). The organic phases were combined, washed with brine (30 cm³) and dried over magnesium sulfate. Removal of the solvent *in vacuo* yielded a crude yellow oil. Purification of the crude material by flash column chromatography on silica gel using an eluent of 5% methanol: dichloromethane afforded the title compound as a white solid (350 mg, 56%). m.p. 143 - 144 °C; υ_{max} / cm^{-1} 3062, 2929, 1923, 1588; δ_H (400 MHz, $CDCl_3$) 1.30 – 1.67 (8H, m, 4 × C*H*$_2$), 2.24 – 2.46 (4H, m, 2 × C*H*$_2$), 3.74 (6H, s, 2 × OC*H*$_3$), 6.88 (2H, dd, *J* 7.6 5.5, 2 × ArC*H*), 7.08 (2H, t, *J* 7.6, 2 × ArC*H*), 7.40 – 7.50 (8H, m, ArC*H*), 7.74 (4H, dd, *J* 11.2 7.6, 4 × ArC*H*), 7.98 (2H, dd, *J* 12.6 7.6, 2 × ArC*H*); δ_C (100 MHz, $CDCl_3$) 21.4 (d, $J_{C\text{-}P}$ 3.7, 2 × *C*H_2), 29.0 (d, $J_{C\text{-}P}$ 73.1, 2 × *C*H_2), 30.5 (d, $J_{C\text{-}P}$ 15.1, 2 × *C*H_2), 55.3 (2 × O*C*H_3), 110.8 (d, $J_{C\text{-}P}$ 6.6, 2 × Ar*C*H), 120.4 (d, $J_{C\text{-}P}$ 95.9, 2 × Ar*C*), 121.1 (d, $J_{C\text{-}P}$ 10.6, 2 × Ar*C*H), 128.2 (d, $J_{C\text{-}P}$ 11.7, 4 × Ar*C*H), 130.6 (d, $J_{C\text{-}P}$ 9.6, 4 × Ar*C*H), 131.2 (2 × Ar*C*H), 133.8 (2 × Ar*C*H), 134.0 (d, $J_{C\text{-}P}$ 80.4, 2 × Ar*C*), 134.4 (2 × Ar*C*H), 159.9 (d, $J_{C\text{-}P}$ 4.2, 2 × Ar*C*); δ_P (101 MHz, $CDCl_3$) 32.0; *m/z* (TOF ES^+) 547.2190 (100%, MH^+, $C_{32}H_{37}O_4P_2$ requires 547.2167).

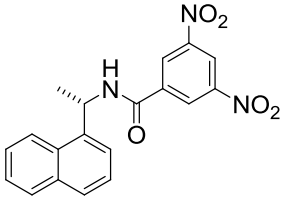
(*S*)-(-)-*N*-(3, 5-Dinitrobenzoyl)-1-phenylethylamine **255**[141]



(*S*)-(-)-1-phenylethylamine **103** (1.00 g, 8 mmol) was added to a solution of triethylamine (1.0 cm³, 8 mmol) in dichloromethane (10 cm³) and the reaction mixture cooled to 0 °C. 3, 5-Dinitrobenzoyl chloride (3.00 g, 8 mmol) was added in a single portion and the solution warmed

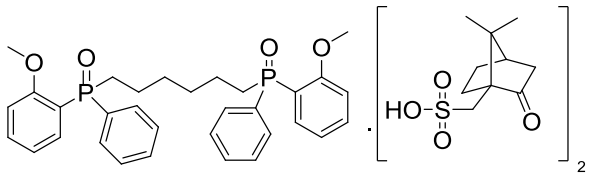
to room temperature and stirred overnight. 1*N* HCl (10 cm³) was added and the organic phase separated, washed with a saturated aqueous solution of $NaHCO_3$ (10 cm³), brine (10 cm³) and dried over magnesium sulfate. Removal of the solvent *in vacuo* yielded a crude orange oil. The oil was dissolved in diethyl ether (20 cm³) and filtered through a small neutral alumina plug to afford the title compound as a pale yellow solid (2.05 g, 91%). m.p 159 °C (lit.[141] 158 – 160 °C); $[\alpha]_D^{25}$ - 17.0 [*c* 0.9 in acetone, lit.[141] + 17.5 *c* 0.9 for the (*R*)-enantiomer]; δ_H (250 MHz, $CDCl_3$) 1.66 (3H, d, *J* 7.1, C*H*$_3$), 5.32 (1H, quintet, *J* 7.1, C*H*), 6.96 (1H, d, *J* 7.1, N*H*), 7.24 – 7.41 (5H, m, ArC*H*), 8.95 (2H, d, *J* 2.1, 2 × ArC*H*), 9.14 (1H, t, *J* 2.1, ArC*H*). All data is in accordance with that of the literature.

(*S*)-(-)-*N*-(3, 5-Dinitrobenzoyl)-1-(1-napthyl)ethylamine **245**[141]



(*S*)-(-)-1-(1-Naphthyl)ethylamine (0.4 cm³, 3 mmol) was added to a solution of triethylamine (0.4 cm³, 3 mmol) and dichloromethane (10 cm³) and the reaction mixture cooled to 0 °C. 3,5-Dinitrobenzoyl chloride (0.9 g, 3 mmol) was added in a single portion and the solution warmed to room temperature and stirred overnight. 1*N* HCl (10 cm³) was added and the organic phase separated, washed with a saturated aqueous solution of $NaHCO_3$ (10 cm³), brine (10 cm³) and dried over magnesium sulfate. Removal of the solvent *in vacuo* yielded a crude orange oil. The oil was dissolved in diethyl ether (20 cm³) and filtered through a small neutral alumina plug to afford the title compound as a pale yellow solid (1.05 g, 82%). m.p. 227 - 228 °C (lit.[141] 228 °C); $[\alpha]_D^{25}$ - 9.0 [*c* 2.0 in EtOH, lit.[141] + 9.2 *c* 2.0 in EtOH for the (*R*)-enantiomer]; δ_H (400 MHz, $CDCl_3$) 1.84 (3H, d, *J* 7.1, C*H*$_3$), 6.14 (1H, quintet, *J* 7.1, C*H*), 6.61 (1H, d, *J* 7.1, N*H*), 7.50 -7.65 (4H, m, ArC*H*), 7.86 – 7.93 (2H, m, ArC*H*), 8.08 (1H, d, *J* 8.3, ArC*H*), 8.90 (2H, d, *J* 2.1, 2 × ArC*H*), 9.14 (1H, t, *J* 2.1, ArC*H*). All data is in accordance with that of the literature.

(±)-1,6-*bis*[(2-Methoxyphenyl)(phenyl)phosphoryl]hexane-*di*-(*S*)-camphorsulfonic acid salt **262**



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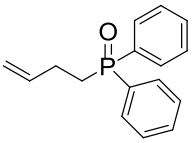
(±)-1,6-*bis*[(2Methoxyphenyl)(phenyl)phosphoryl]hexane **224** (100 mg, 0.18 mmol) was added to ethyl acetate (3 cm³) and the solution heated at reflux until complete dissolution was observed. (*S*)-Camphorsulfonic acid (20 mg, 0.09 mmol) was introduced in a single portion and the mixture cooled slowly to room temperature. The resulting crystals were filtered, washed with cold ethyl acetate (3 cm³) and dried to afford the title compound as a white crystalline solid (25 mg, 36%). m.p. 156 - 157 °C; υ_{max} (ATR) / cm^{-1} 3463, 2956, 1740, 1589; δ_H (400 MHz, $CDCl_3$) 0.85 (6H, s, C*H*$_3$), 1.11 (6H, s, 2 × C*H*$_3$), 1.32 – 1.53 (8H, m, 4 × C*H*$_2$), 1.53 – 1.72 (4H, m, 2 × C*H*$_2$), 1.91 (2H, d, *J* 18.4, 2 × C*H*), 1.95 – 2.09 (4H, m, 4 × C*H*), 2.36 (2H, app. dt, *J* 18.4 3.9, 2 × C*H*), 2.48 – 2.68 (6H, m, 6 × C*H*), 2.92 (2H, d, *J* 15.0, 2 × C*H*), 3.47 (2H, d, *J* 15.0, 2 × C*H*), 3.80 (6H, s, 2 × OC*H*$_3$), 6.95 (2H, dd, *J* 8.1 6.1, 2 × ArC*H*), 7.15 (2H, app. t, *J* 7.4, 2 × ArC*H*), 7.45 – 7.52 (4H, m, 4 × ArC*H*), 7.52 – 7.60 (4H, m, 4 × ArC*H*), 7.78 (4H, dd, *J* 12.4 7.4, 4 × ArC*H*), 7.90 – 7.99 (2H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 19.8 (2 × *C*H$_3$), 20.0 (2 × *C*H$_3$), 21.0 (d, $J_{C\text{-}P}$ 4.1, 2 × *C*H$_2$), 25.1 (2 × *C*H$_2$), 26.8 (2 × *C*H$_2$), 26.9 (2 × *C*H$_2$), 27.5 (2 × *C*H$_2$), 29.7 (d, $J_{C\text{-}P}$ 15.5, 2 × *C*H$_2$), 42.7 [2 × *C*(CH$_3$)$_2$], 42.8 (2 × *C*H$_2$), 48.0 (2 × *C*H), 55.7 (2 × O*C*H$_3$), 58.4 (2 × *C*H$_2$SO$_2$H), 111.2 (d, $J_{C\text{-}P}$ 7.1, 2 × Ar*C*H), 115.7 (d, $J_{C\text{-}P}$ 102.6, 2 × Ar*C*), 121.6 (d, $J_{C\text{-}P}$ 11.2, 2 × Ar*C*H), 128.6 (d, $J_{C\text{-}P}$ 12.5, 4 × Ar*C*H), 129.8 (d, $J_{C\text{-}P}$ 102.0, 2 × Ar*C*), 130.8 (d, $J_{C\text{-}P}$ 10.6, 4 × Ar*C*H), 132.5 (2 × Ar*C*H), 134.2 (d, $J_{C\text{-}P}$ 4.9, 2 × Ar*C*H), 135.2 (2 × Ar*C*), 160.1 (d, $J_{C\text{-}P}$ 6.0, 2 × Ar*C*), 216.8 (2 × *C*O); δ_P (121 MHz, $CDCl_3$) 44.8; *m/z* (TOF ES^+) 233.0839 (MH^+, 100%, $C_{10}H_{17}O_4S$ requires 233.0848) and 547.2169 (MH^+, 100%, $C_{32}H_{37}O_4P_2$ requires 547.2167).

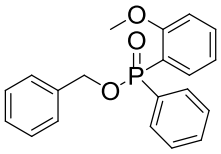
3-Butenyldiphenylphosphine oxide **267**



Diphenyl(methyl) phosphine oxide (216 mg, 1 mmol) was dissolved in THF (5.0 cm³) and the reaction mixture cooled to 0 °C. *n*-Butyllithium (0.7 cm³, 1 mmol, 1.5M in *n*-hexanes) was added dropwise and the solution stirred for 90 minutes. Allyl bromide (0.7 cm³, 8 mmol) was added and the solution warmed to room temperature and stirred for 12 hours. The reaction

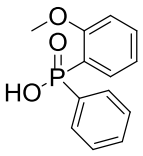
mixture was quenched through addition of an aqueous solution of 1 *N* HCl (10 cm³) and the organic phase extracted with ethyl acetate (3 × 10 cm³). The organic layers were combined, washed with brine (10 cm³) and dried over magnesium sulfate. Removal of the solvent *in vacuo* afforded the title compound as a white solid (184 mg, 72%). m.p. 141 °C (lit.[REF] 140 – 142 °C); δ_H (250 MHz, $CDCl_3$) 2.30 – 2.47 (4H, m, 2 × C*H*$_2$), 4.97 – 5.09 (2H, m, CH=C*H*$_2$), 5.87 (1H, ddt, *J* 16.9 10.3 5.6, CH_2CH=CH_2), 7.43 – 7.59 (6H, m, ArC*H*), 7.70 – 7.84 (4H, m, ArC*H*).

Benzyl 2-methoxyphenyl(phenyl)phosphinate **270**



Benzyl phosphinate **239** (472 mg, 2 mmol) was added to a solution of palladium(II) acetate (44 mg, 0.2 mmol), 1,4-*bis* (diphenylphosphino)butane (84 mg, 0.2 mmol) and 2-iodoanisole (0.1 cm³, 1 mmol) in acetonitrile (5.0 cm³). Triethylamine (0.6 cm³, 4 mmol) was introduced and the resulting mixture heated to 60 °C for 48 hours. Upon cooling to room temperature the volatiles were removed *in vacuo* and the residue purified by flash column chromatography on silica gel using an eluent of 100% ethyl acetate to afford the title compound as an orange oil (220 mg, 71%). υ_{max} / cm^{-1} (ATR) 3058, 3021, 1688, 1438; δ_H (400 MHz, $CDCl_3$) 3.62 (3H, s, OC*H*$_3$), 5.06 (2H, d, *J* 7.0, C*H*$_2$), 6.80 – 6.86 (1H, m, ArC*H*), 7.05 (1H, tdd, *J* 7.5 2.6 0.7, ArC*H*), 7.27 – 7.52 (9H, m, ArC*H*), 7.87 – 7.92 (2H, m, ArC*H*), 8.03 (1H, ddd, *J* 13.3 7.6 1.8, ArC*H*); δ_C (101 MHz, $CDCl_3$) 55.3 (OC*H*$_3$), 66.0 (d, $J_{C\text{-}P}$ 6.0, *C*H$_2$), 111.2 (d, $J_{C\text{-}P}$ 7.0, Ar*C*H), 119.0 (d, $J_{C\text{-}P}$ 134.0, Ar*C*), 120.6 (d, $J_{C\text{-}P}$ 13.0, ArC*H*), 127.7 (2 × Ar*C*H), 128.0 (d, $J_{C\text{-}P}$ 6.0, 2 × Ar*C*H), 128.1 (Ar*C*H), 128.4 (2 × Ar*C*H), 131.7 (d, $J_{C\text{-}P}$ 8.0, 2 × ArC*H*), 131.9 (Ar*C*H), 132.2 (d, $J_{C\text{-}P}$ 141.0, Ar*C*), 134.6 (Ar*C*H), 134.8 (d, $J_{C\text{-}P}$ 7.0, ArC*H*), 136.8 (d, $J_{C\text{-}P}$ 8.0, Ar*C*), 161.0 (d, $J_{C\text{-}P}$ 5.0, Ar*C*OCH$_3$); δ_P (101 MHz, $CDCl_3$) 30.6; *m/z* (TOF ES^+) 339.3345 (MH^+, 100%, $C_{20}H_{20}O_3P$ requires 339.3348).

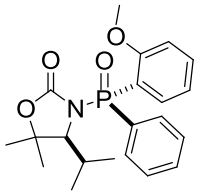
2-Methoxyphenyl(phenyl)phosphoric acid **269**[122]



Prepared according to general procedure **M** using benzyl phosphinate **270** (203 mg, 0.6 mmol). Removal of the solvent *in vacuo* afforded the title compound as a white solid (124 mg, 81%). m.p. 218 – 220 °C (lit.[122] 219 – 220 °C); δ_H (400 MHz, CD_3OH) 3.61 (3H, s, OC*H*$_3$), 6.94 (1H,

dd, *J* 8.0 6.0, ArC*H*), 7.01 – 7.04 (1H, m, ArC*H*), 7.35 – 7.53 (4H, m, ArC*H*), 7.71 (2H, ddd, *J* 13.0 6.0 2.0, 2 × ArC*H*), 7.81 (1H, ddd, *J* 13.0 6.0 2.0, ArC*H*); δ_P (101 MHz, $CDCl_3$) +28.2. All data is in accordance with that of the literature.

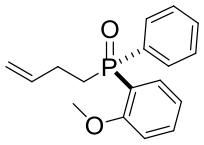
(*S*)-4-*iso*-Propyl-3-[(R_P)-(2-methoxyphenyl)(phenyl)phosphoryl]-5,5-dimethyloxazolidin-2-one **268**



Phosphoric acid **269** (249 mg, 1 mmol) was suspended in dichloromethane (5 cm³) and cooled to 0 °C. Thionyl chloride (10 cm³, 13.7 mmol) was added dropwise over a period of 10 minutes and the solution heated at reflux for 3 hours. The solvent and excess thionyl chloride were removed *in vacuo* to afford the phosphinic chloride as a yellow oil that required no further purification. The phosphinic chloride (260 mg, 1 mmol) was added to a solution of the oxazolidinone **174** (157 mg, 1 mmol) pre-treated with methylmagnesium bromide (1 cm³, 1 mmol, 1M in Et_2O) in THF (5 cm³) for 1 hour at 0 °C. The mixture was warmed to room temperature and stirred for 24 hours. The solution was poured into a saturated aqueous solution of ammonium chloride (10 cm³) and dichloromethane (15 cm³) added. The organic phase was separated and the aqueous layer extracted with dichloromethane (2 × 15 cm³). The organic phases were combined, washed with brine (20 cm³) and dried over magnesium sulfate. Removal of the solvent *in vacuo* yielded the title compound as a 4:1 mixture of diastereoisomers as determined by analysis of the crude ^{1}H NMR spectroscopic data. Purification and isolation of the major isomer by flash column chromatography on silica gel using an eluent of 50% ethyl acetate: petroleum ether 40 – 60 °C afforded the diastereotopically pure compound as a white solid (240 mg, 62%). m.p. 131 - 132 °C; $[\alpha]_D^{25}$ + 24.0 (*c* 0.5 in $CHCl_3$); υ_{max} (ATR) / cm^{-1} 2991, 2928, 1739; δ_H (400 MHz, $CDCl_3$) 1.05 [3H, d, *J* 7.1, 1 × CH(C*H*$_3$)$_2$], 1.13 [3H, d, *J* 7.1, 1 × CH(C*H*$_3$)$_2$], 1.37 (3H, s, C*H*$_3$), 1.50 (3H, s, C*H*$_3$), 2.01 – 2.08 [1H, m, C*H*(CH$_3$)$_2$], 3.74 (3H, s, OC*H3*), 3.94 (1H, dd, *J* 3.5 1.2, C*H*), 6.96 (1H, dd, *J* 8.0 6 .7, ArC*H*), 7.13 (1H, td, *J* 8.0 2.2, ArC*H*), 7.41 – 7.59 (4H, m, ArC*H*), 7.88 – 7.94 (2H, m, ArC*H*), 8.06 (1H, ddd, *J* 15.4 7.7 1.6, ArC*H*); δ_C (101 MHz, $CDCl_3$) 16.9 (*C*H$_3$), 20.4 (*C*H$_3$), 21.6 (*C*H), 28.9 (*C*H$_3$), 30.4 (*C*H$_3$), 55.6 (OCH$_3$), 69.2 (*C*HN), 83.7 [d, $J_{C\text{-}P}$ 5.0 *C*(CH$_3$)$_2$], 111.4 (d, $J_{C\text{-}P}$ 7.9, Ar*C*H), 118.3 (d, $J_{C\text{-}P}$ 131.5, Ar*C*), 120.8 (d, $J_{C\text{-}P}$ 13.7, Ar*C*H), 128.0 (d, $J_{C\text{-}P}$ 13.7, 2 × Ar*C*H), 130.5 (Ar*C*), 131.9 (d, $J_{C\text{-}P}$ 11.1, 2 × Ar*C*H), 132.2 (d, $J_{C\text{-}P}$ 2.6, Ar*C*H), 156.1 (d, $J_{C\text{-}P}$ 6.1, Ar*C*), 161.1 (d, $J_{C\text{-}P}$ 3.8, *C*O); δ_P

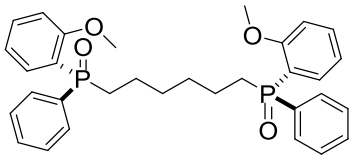
(121 MHz, $CDCl_3$) 34.5; *m/z* (TOF ES^+) 388.1683 (100%, MH^+, $C_{21}H_{27}NO_4P$ requires 388.1678).

(S_P)-Phenyl(2-anisyl)but-3-enephosphine oxide **264**



N-phosphinoyl oxazolidinone **268** (120 mg, 0.3 mmol) was dissolved in THF (2.0 cm³) and added by syringe pump (1.0 cm³ / hr) to a solution of but-3-enylmagnesium bromide (4 cm³, 1M in THF, 4 mmol) and THF (4.0 cm³). Once addition was complete the reaction mixture was quenched through addition of an aqueous saturated solution of ammonium chloride (5.0 cm³) and the aqueous phase extracted with dichloromethane (3 × 10 cm³). The organic layers were combined, washed with brine (10 cm³) and dried over magnesium sulfate. Removal of the solvent *in vacuo* yielded a crude yellow oil. Purification of the crude material by flash column chromatography on silica gel using a gradient eluent of 75% ethyl acetate: petroleum ether 40 – 60 °C to 5% methanol: dichloromethane afforded the oxazolidinone **174** (44 mg, 91%) as a white solid and the phosphine oxide as a colourless oil (63 mg, 77%). t_R 10.5 (minor isomer) and 18.8 (major isomer) (Celluose-1, 90: 10 hexane: propan-2-ol, 210 nm); $[\alpha]_D^{25}$ + 23.0 (*c* 1.0 in $CHCl_3$); υ_{max} / cm^{-1} (ATR) 3076, 2976, 1640, 1590; δ_H (400 MHz, $CDCl_3$) 2.22 – 2.60 (4H, m, 2 × C*H*$_2$), 3.76 (3H, s, OC*H*$_3$), 4.93 – 5.04 (2H, m, CH=C*HH*), 5.84 (1H, ddt, *J* 16.8 10.2 6.4, C*H*=CHH), 6.88 (1H, dd, *J* 8.3 5.4, ArC*H*), 7.08 – 7.12 (1H, m, ArC*H*), 7.39 – 7.52 (4H, m, ArC*H*), 7.75 – 7.81 (2H, m, ArC*H*), 7.97 – 8.03 (1H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 25.7 (d, $J_{C\text{-}P}$ 3.0, *C*H$_2$), 28.5 (d, $J_{C\text{-}P}$ 73.0, *C*H$_2$), 55.3 (O*C*H$_3$), 110.8 (d, $J_{C\text{-}P}$ 6.6, Ar*C*H), 114.8 (CH=*C*HH), 119.3 (d, $J_{C\text{-}P}$ 95.7, Ar*C*), 121.2 (d, $J_{C\text{-}P}$ 10.6, Ar*C*H), 128.2 (d, $J_{C\text{-}P}$ 11.8, 2 × Ar*C*H), 130.6 (d, $J_{C\text{-}P}$ 9.7, 2 × Ar*C*H), 131.3 (d, $J_{C\text{-}P}$ 2.4, Ar*C*H), 133.5 (Ar*C*), 133.9 (*C*H=CHH), 134.5 (d, $J_{C\text{-}P}$ 5.2, Ar*C*H), 137.8 (d, $J_{C\text{-}P}$ 16.3, Ar*C*H), 159.7 (d, $J_{C\text{-}P}$ 5.0, Ar*C*); δ_P (101 MHz, $CDCl_3$) 31.4; *m/z* (TOF ES^+) 287.1195 (100%, MH^+, $C_{17}H_{20}O_2P$ requires 287.1201).

1,6-*bis*[(S_P)-(2-Methoxyphenyl)(phenyl)phosphinoyl]hexane **224**



Phosphine oxide **264** (90 mg, 0.3 mmol) was added to a solution of dichloromethane (3 cm³) and Hoveyda-Grubbs II catalyst (18 mg, 0.03 mmol) and the solution heated at reflux for 18 hours.

Upon cooling to room temperature, the volatiles were removed *in vacuo* and the residue purified by flash column chromatography on silica gel using a gradient eluent of 100% ethyl acetate to 5% methanol: dichloromethane to afford a yellow oil. The oil (54 mg, 0.1 mmol) was dissolved in methanol (2 cm^3) and subjected to a single cycle through a Pd/C Thalesnano Catcart H-CubeTM under 1 atmosphere of hydrogen at 30 °C. Removal of the solvent *in vacuo* afforded the title compound as a colourless oil (50 mg, 61% over 2 steps). $[\alpha]_D^{25}$ + 42.0 (*c* 1.0 in $CHCl_3$). All other spectroscopic data is in accordance with the racemic *bis*-phosphine oxide **224** previously prepared on page 184.

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