THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

Synthesis and Applications of P-Chirogenic and Axially Chiral P,N-Phosphines as Ligands and Organocatalysts

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Cover:
Clockwise from the top left: 10 g of starting material for compound **60a** in a round-bottom flask. Catalytic amount (~3 mg) of compound **60a** in the tip of a glass pipette. Purification of an attempted synthesis of a P-chirogenic phosphine. Structure drawing of compound **60a**.

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”If you can dream – and not make dreams your master;

If you can think – and not make thoughts your aim;

If you can meet with Triumph and Disaster

And treat those two impostors just the same;”

Rudyard Kipling – “If-”

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Abstract

This thesis deals with the enantioselective synthesis of chiral mixed phosphorous/nitrogen compounds and some of their applications in asymmetric synthesis. For the most part, the compounds are P-chirogenic, with the chirality centered on the phosphorous atom. The last part of the thesis deals with axially chiral phosphoramidites.

Papers I-III deals with the enantioselective synthesis of P-chirogenic mixed P,N-ligands. The chirality was placed on the phosphorous atom through the use of either asymmetric deprotonation of prochiral phosphine-boranes or through application of (-)-ephedrine as chiral auxiliary. These are well-known methods for preparing optically pure phosphorus and give high to excellent enantiomeric purity. We have used these methods to prepare P,N- P,N,N- and P,N,N,P-compounds with the chirality on phosphorus through α-formyl or α-carboxyphosphine intermediaries. The α-formylphosphines allow a one-step synthesis of β-aminophosphines in high yields. The α-carboxyphosphines meanwhile allow for the production of both amino- and amidophosphines. The described methodology is truly modular in nature, as the steric and electronic properties of both the phosphorous and amine parts can be varied easily. Moreover, we have shown that the use of microwave accelerated synthesis and solid phase purification is an efficient tool in the preparation of some of the final products.

Paper IV presents the first study of exclusively P-chirogenic phosphines as organocatalysts. The asymmetric reaction chosen for this purpose was the [3+2]-cycloaddition of allenic esters to acrylates (the Lu reaction). A variety of phosphines with different steric and electronic properties were screened and shown to induce stereoselectivity, where the results can act as a guide to further development of organocatalysts with optically pure phosphorus.

Paper V considers the use of axially chiral phosphoramidites as ligands in an asymmetric version of the Nicholas reaction. For the first time, a method that does not rely on chiral substrates or nucleophiles or chirality transfer protocols to introduce asymmetry is presented. The ligands were based on a BINOL-framework and were prepared with different aromatic, aliphatic and benzylic amines.

In summary, the work detailed herein has furthered the preparation of P-chirogenic P,N-compounds by facilitating rapid and modular synthesis of such products. Furthermore, chiral P,N-ligands and organocatalysts have shown promise for further investigation.

Keywords: asymmetric synthesis, P-chirogenic, phosphine, aminophosphine, modular synthesis, asymmetric hydrogenation, organocatalysis, Nicholas reaction, phosphoramidite

List of publications

This thesis is based on the following publications, which are referred to in the text by the roman numerals I-V.

I Modular Synthesis of P-Chirogenic β-Aminophosphine Boranes.
Johansson, M. J.; Andersson, K. H. O.; Kann, N.
J. Org. Chem. **2008**, *73*, 4458.

II Exploring the Role of the Phosphorous Substituents on the Enantioselectivity of Ru-Catalyzed Ketone Hydrogenation Using Tridentate Phosphine-Diamine Ligands.
Phillips, S. D.; Andersson, K. H. O.; Kann, N.; Kuntz, M. T.; France M. B.; Wawrzyniak P.; Clarke, M. L.
Catal. Sci. Technol. **2011**, *1*, 1336.

III Modular Synthesis of P-Chiral PNN- and PNNP-Type Ligands and Applications in Asymmetric Hydrogenation.
Andersson, K. H. O.; Lundberg, K.; Philips, S. D.; Clarke, M. L.; Johansson, M. J.; Kann, N.
Manuscript

IV P-Chiral Phosphines as Catalysts in [3+2]-Cycloaddition Reactions – Moving the Chirality Onto the Nucleophilic Atom.
Andersson K. H. O.; Jonsson, F.; King, G. D.; Kelly, B.; Johansson, M. J.; Kann, N.
Manuscript

V The Development of an Asymmetric Nicholas Reaction Using Chiral Phosphoramidite Ligands.
Ljungdahl, N.; Parera-Pera, N.; Andersson, K. H. O.; Kann, N.
Synlett, **2008**, 394.

Contribution Report

Paper I Contributed to the formulation of the research project, performed the major part of the experimental work and characterization, contributed to the writing of the manuscript.

Paper II Contributed to the formulation of the research project, performed the synthesis and characterization of all P-chirogenic ligands, contributed to the writing of the manuscript.

Paper III Contributed to the formulation of the research project, performed the major part of the experimental work and characterization, major contribution to the writing of the manuscript.

Paper IV Contributed to the formulation of the research project, performed the major part of the experimental work and characterization, major contribution to the writing of the manuscript.

Paper V Minor contribution to the formulation of the research project, performed the synthesis of phosphoramidite ligands and assisted in the analysis of the products, minor contribution to the writing of the manuscript.

Abbreviations

Ac	acetyl
AcOH	acetic acid
Ar	aryl
Aq	aqueous
BINAM	1,1'-bi(2-naphthylamine)
BINAP	2,2’-bis(diphenylphosphino)-1,1’-binaphthyl
BINOL	1,1’-bi-2-naphthol
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BSA	*N*,*O*-bis(trimethylsilyl)acetamide
Bu	butyl
Bz	benzoyl
CAMP	(2-methoxyphenyl)-cyclohexylmethylphosphine
COD	1,5-cyclooctadiene
DABCO	1,4-diazabicyclo[2.2.2]octane
DBTA	dibenzoyl-tartaric acid
DCE	1,2-dichloroethane
DCC	*N*,*N*’-dicyclohexylcarbodiimide
DCM	dichloromethane
DiPAMP	bis[(2-methoxyphenyl)phenylphosphine]ethane
DMF	*N*,*N*-dimethylformamide
DMS	dimethyl sulfide
dpen	1,2-diphenylethylenediamine
dtbm	3,5-di-*tert*-butyl-4-methoxyphenyl
EDCI	*N*-(3-dimethylaminopropyl)-*N*’-ethylcarbodiimide
Et	ethyl
Fc	ferrocenyl
HOBt	1-hydroxybenzotriazole
HPLC	high performance liquid chromatography
LDBB	lithium 4,4’-di-*tert*-butylbiphenylide
MBH	Morita-Bayliss-Hillman
Me	methyl
Men	menthyl
MTBE	methyl *tert*-butyl ether
NMR	nuclear magnetic resonance
PAMP	(2-methoxyphenyl)-phenylmethylphosphine
Ph	phenyl
r.t.	room temperature
SCX-2	strong cationic ion-exchanger
TADDOL	1,1,4,4-tetraphenyl-2,3-*O*-isopropylidene-L-threitol
TEA	triethylamine
TfOH	trifluoromethanesulfonic acid
THF	tetrahydrofuran
TMSCl	trimethylsilyl chloride
Tol	tolyl

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1. Introduction

1.1. On Chirality

Sleep thou, and I will wind thee in my arms.
So doth the Woodbine the sweet Honeysuckle
Gently entwist;

--- William Shakespeare, *Midsummer Night's Dream*, Act IV Sc. 1 (47).

Chirality. It is all around us and encompasses our lives to a degree that most are unaware of. We find it in our physical appearance, inside our cells, in the nature that surrounds us. Like the vines in the Shakespeare quote above it wraps itself around us and the world, and also science. The concept of chirality can be found in mathematics, physics, biology and of course chemistry. In the broadest sense, chirality can be defined by something that is not identical to its mirror image. In other words, in cannot be superimposed onto it. Hence, the word chirality derives from the Greek *kheir*, meaning hand, since the human hands are mirror images of each other but are not identical. Other examples from nature include the left and right handed helical structures found in escargot snails, left and right eyed starry flounders and the left and right handed spirals formed by Woodbine and Honeysuckle plants.

The term chirality was first used by Lord Kelvin in one of his Baltimore lectures wherein he stated: "*I call any geometrical figure, or group of points, 'chiral', and say that it has chirality if its mirror image in a plane mirror, ideally realized, cannot be brought to coincide with itself*."[1] Before this, the discovery of chirality in a chemical context was made by Louis Pasteur in 1848.[2] He separated, by hand, different crystal forms of sodium ammonium tartrate obtained from a racemic mixture of tartaric acid. This and other processes which separate enantiomers are called resolutions. Pasteur also performed the first diastereomeric resolution as well as the first bacterial resolution using *Penicillium Glaucum*.[3]

When we talk about chirality within the context of organic chemistry we most often refer to a sp^3-hybridized, tetrahedral carbon atom with four different substituents. Chirality is not limited to carbon, but other tetrahedral atoms can also be asymmetric. Nitrogen comes to mind, but it is most often not used a stereogenic center due to its fairly low barrier of inversion, about 25 kJ per mol. Arsenic is another possibility but is seldom used due to its inherent toxicity. Sulphur on the other hand is often used as a source of chirality in optically pure sulphoxides, which are well known as chiral auxiliaries in asymmetric synthesis.[4] An example from the pharmaceutical industry were a chirogenic sulphur atom features prominently is esomeprazole (Nexium), the (*S*)-enantiomer of omeprazole and one of the world's top-selling drugs.[5] Of course, phosphorus is another element which can carry and impart stereogenic information and will be covered in the rest of this thesis.

It is important to realize that while we most often associate point source stereogenic centers with chirality, other sources of asymmetry are also possible. Figure 1 shows molecules with different forms of chirality. Apart from the typical point source chiral carbon atom (Figure 1a) or the similar P-chirogenic instance (Figure 1b), there is also *axial chirality* (Figure 1c). Here, the substituents of a compound are "locked" in a certain spatial orientation due to limited rotation around a bond because of steric hindrance. If a molecule has two non-coplanar ring systems which are connected through a bond around which rotation is hindered, we instead say that it has *planar chirality* (Figure 1d). A relatively new chiral descriptor is *inherent chirality* which refers to otherwise symmetric systems that are rendered chiral by a curvature in the structure (Figure 1e).[6]

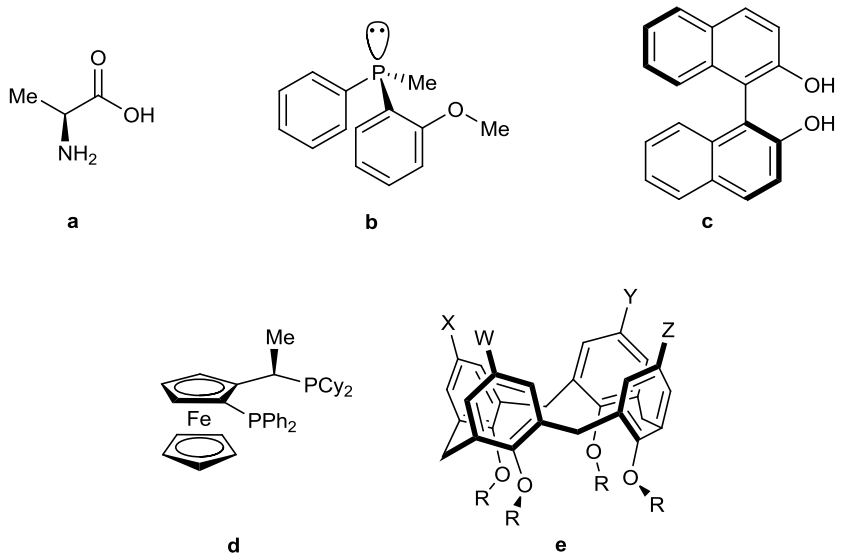


Figure 1. Compounds exhibiting different types of asymmetry: a) C-centered chirality b) P-chirogenic c) axial chirality d) planar chirality e) inherent chirality.

It is well-known that different enantiomers can have different properties; the most obvious manifestation is when two stereoisomers differ in smell. Examples include limonene were the (*R*)-enantiomer smells like citrus and the (*S*)-enantiomer reminds one of turpentine. Since our bodies are made up of the chiral building blocks of L-amino acids and D-carbohydrates it is not surprising that some chiral pharmaceuticals also vary in effect between their optical isomers. For instance, the common analgesic ibuprofen is only active as its (*S*)-enantiomer. In this case however, the substance can be industrially produced as a racemate since the (*R*)-isomer is converted *in vivo* to the (*S*)-form. In fact, by 2006, 80% of the small-molecule drugs approved by the FDA in the US were chiral and 75% were single enantiomers.[7] Considering the different effects that optical isomers can have on biological systems it is very important to ensure efficient asymmetric synthesis, i.e. to prepare an excess of one enantiomer, of these compounds. Although racemates of pharmaceuticals can still be marketed, a thorough study must nowadays be made of the biological effect of each enantiomer.

There are several tools available to chemists who wish to introduce chirality in a molecule.[8] The oldest is to *resolve racemic mixtures* with a suitable resolving agent. If one is disinclined to start from racemates, it is possible to use *the chiral pool*. Nature contains an abundance of stereochemically pure compounds that can be isolated and methods for doing so have been known a long time. The downside is that it limits the structural features available and that it requires isolation of natural products which can be inefficient and tedious. Another option is to use *chiral auxiliaries*, chiral elements which can be incorporated into a reaction sequence to induce a certain stereochemical outcome. They can then either be removed with suitable reagents or kept, this is also sometimes called *asymmetric induction*. A more attractive option is to use *asymmetric catalysis*. Indeed, the application of small amounts of a chiral catalytic reagent is something which is used to a large degree in both laboratory and industrial scale. The most common variant of this is the use of transition metals together with some organic, chiral ligands. Recently, increased attention has been directed towards *organo- or biocatalytic* methods that do not rely on expensive and potentially toxic metals.

However one looks at it, the production of optically pure compounds is an extremely important task, not only to chemists but to society as a whole. Due to its chemical properties, phosphorus is capable of interacting with both transition metals and organic substrates. Consequently, if a phosphorus containing molecule features asymmetry it can then impart chirality to other compounds in chemical reactions. As a part of the "asymmetric toolbox", chiral phosphorus containing compounds are a valuable component and their use and preparation will be further elaborated on in the rest of this thesis.

1.2. Chemistry of Phosphorus

The name phosphorus is derived from Greek and literally means "light-bringer". This comes from the fact that some forms of phosphorus tend to glow in the dark, hence the term phosphorescence. It was first discovered, as far as is known, by the German alchemist Henning Brandt in 1669 by distilling putrefied urine and condensing the vapors to form ammonium sodium hydrogen phosphate, $(NH_4)NaHPO_4$.[9] Phosphorus is the eleventh-most common element in the earth's crust and also features prominently in biological systems, not least as part of the DNA/RNA backbone, and the phosphate cycle.[10] A fully grown human contains about 1 kg of phosphorus, mostly concentrated in the bones and teeth. In pure form, it occurs as white, red, violet or black allotropes.

Phosphorus is situated in group V, row 3 of the periodic table, just below nitrogen. Like nitrogen, it has a free electron pair which is central to much of its chemistry. Unlike N_2 however, it does not form dimeric, gaseous units unless heated to temperatures in excess of 700 °C. This is due to the fact that the triple bond strength for phosphorus is only about 2.5 times that of a single bond, compared to 6 times for nitrogen and so forming three single bonds is advantageous to forming a single triple bond.[10a] Much of this can be rationalized by the greater radius of the phosphorus atom (1 Å vs. 0.65 Å) and the greater spatial distribution of its 3p orbitals.[11] As a consequence P-based nucleophiles tend to be softer than their corresponding nitrogen analogues as their interactions are governed more by orbital orientation than local charge distribution. Furthermore,

phosphorus is capable of hypervalency and can be found in pentavalent (for example phosphine oxides, phosphates, phosphinates, phosphinates and halides) or hexavalent (PF_6^-) states. The P lone electron pair forms a very stable oxygen bond with dissociation energies of around 535-582 kJ/mol and will react promptly with many potential oxidizers, even air.[12] In fact, it is the violent oxidation of white phosphorus with oxygen in the air that probably brought on the "light-bringer" name in the first place, as it spontaneously ignites at >30 °C when exposed to the atmosphere. Only the white allotrope of elemental phosphorus exhibits this trait, but it is more or less common in organophosphorus compounds, with triaryl phosphines generally being air stable, while primary alkyl phosphines oxidize readily.[13] Another benefit of the size and orbital spread of the phosphorus atom is that it remains resistant to pyramidal inversion even at higher temperatures. A tetrahedral phosphine has a barrier of inversion around 125-145 kJ/mol, although this is dependent on the steric and electronic properties of its substituents.[14] For most organic phosphines this means heating to well above 100 °C for racemization to take place.[12] For amines, however, pyramidal inversion occurs rapidly at room temperature.

Phosphorus compounds are Lewis bases and as such, tend to be high-field ligands when coordinating to transition metals.[15] They are also often good π acids and as such can fulfill a σ-donor/π-acceptor role in such complexes (Figure 2). Donation of the phosphorus lone electron pair from its σ-orbital occurs to one of the empty metal d-orbitals. As the electron density around the metal increases, the soft/soft nature of the M-P species facilitates a favorable overlap between a filled metal d_π orbital and an empty phosphorus σ^* orbital. This moves some of the electron density back onto the phosphorus atom and tends to stabilize the M-P bond. It might seem that the donation into the antibonding σ^* orbital would increase the bond distances between phosphorus and its substituents. However, upon complexation the steric strain on the substituents tends to decrease, allowing for more flexibility in the bond angles which in turn shortens the distance between the atoms.

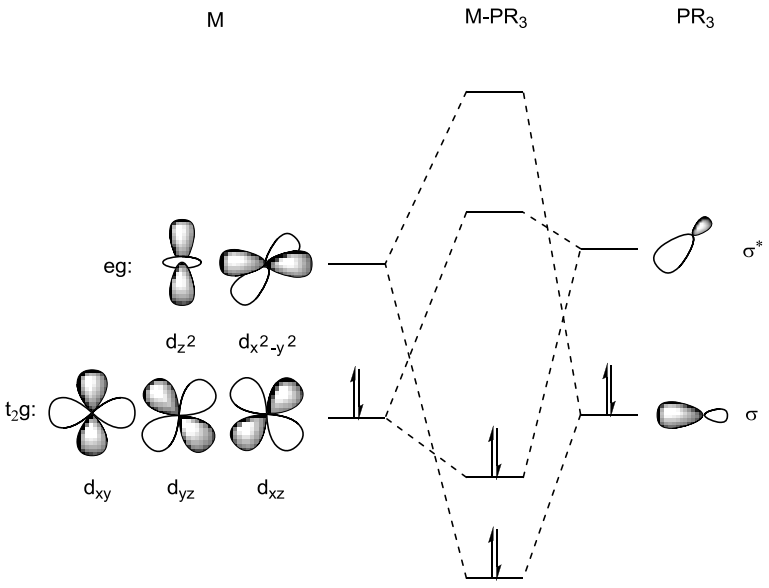


Figure 2. Orbital diagram of an octahedral metal-phosphine complex.[16]

The electronic properties of a phosphorus ligand are greatly affected by its substituents. As the electronegativity of the side chains increases, any σ-donation tendency decreases but the π-acceptor nature increases in its stead. For a phosphorus with three electron-withdrawing substituents like PF_3, the π-accepting capabilities are similar to that of the carbonyl (CO) group.[15] While such a ligand might be a poor free electron pair donor, the stabilization of a formed complex can be greatly increased through back-donation. In no small part due to this, phosphorus compounds are very popular as ligands as one can achieve great variation of their electronic properties by altering their sidechains.

As previously stated, phosphorus reacts readily with a variety of oxidizing agents, and this prevents the free electron pair from partaking in any further chemistry. To circumvent this problem, it has been common practice to prepare P-chirogenic compounds as pentavalent oxides or sulfides and reduce them back to the trivalent state once the stereochemistry is in place.[17] Another advantage of protecting groups is that they tend to stabilize the stereochemical integrity of the phosphorus atom and guard against inversion. The problem with using O or S protecting groups is that they require fairly harsh reduction methods such as $LiAlH_4$[18] or $HSiCl_3$,[19] under which the phosphorus stereocenter can undergo partial racemization. Another problem is the formation of side products which can be difficult to remove. A more easily manageable protecting group was reported in 1980 by Schmidbaur who found that it is possible to effect complex formation between the phosphorus free electron pair and borane.[20] Due to the low polarity and polarisability of the P-B bond the borane group remains remarkably stable, complexation of the free electron pair also activates any α-hydrogens in the same way as the more electronegative oxygen or sulfur groups, something which can be used in the derivatization of phosphine borane compounds. The low polarity of the P-B bond further makes the borane hydrides lose most of their reducing potential when in phosphorus complexes, thus phosphine-boranes are compatible with a wide variety of functional groups.

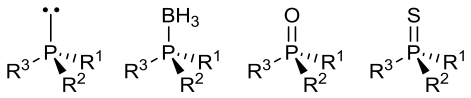
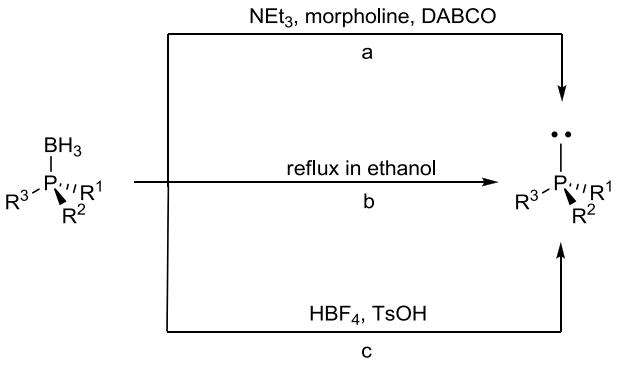


Figure 3. Trivalent free phosphine and phosphine borane as well as pentavalent phosphine oxide and sufide.

The borane is much easier to remove from phosphorus than the analogous oxide or sulphide. As shown in Scheme 1, deprotection of phosphine boranes can be carried out using nucleophilic amines,[21] protic solvents[22] or under acidic conditions.[23] A convenient method for certain metal catalyzed applications is to perform the deprotection *in situ* using a transition metal which is in a higher oxidation state than is required for the catalytic cycle.[24] This simultaneously reduces the metal and removes the borane and has been shown to be effective for Pd(II), Rh(III) and Cu(II) catalysts. The borane-phosphorus bond is quite stable at elevated temperatures for most tertiary phosphines while secondary phosphines tend to form polymers with loss of hydrogen when heated.[25] $PH_3{\cdot}BH_3$ and $PF_3{\cdot}BH_3$ meanwhile, dissociate readily at room temperature.



Scheme 1. Deprotection of a phosphine borane under: a) basic conditions[21] b) neutral conditions[22] c) acidic conditions[23].

1.3. Preparation of P-Chirogenic Compounds

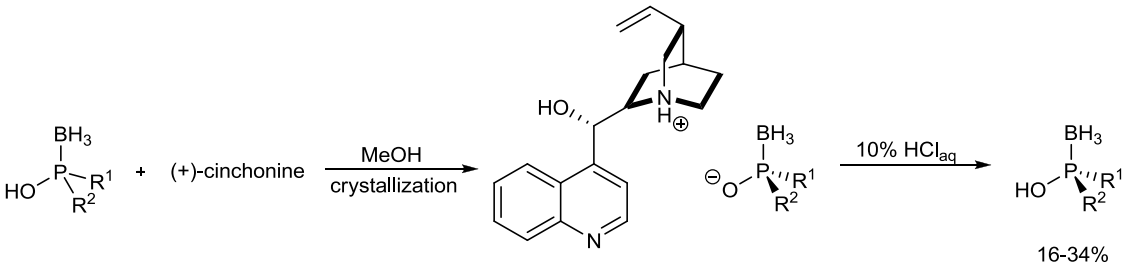
It has been well established that chiral phosphines are efficient in asymmetric catalysis, both on laboratory and industrial scale.[26] However, such compounds are traditionally prepared with the chirality residing on the surrounding carbon skeleton and not the phosphorus atom itself. This is not surprising when one considers the amount of chiral, carbon based building blocks that are available. As such, greater effort has been required to synthesize P-chirogenic phosphines than to simply place the chirality on other atoms. However, with the pioneering work of Horner[27] and Knowles[28] the value of incorporating a chiral phosphorus atom into a catalytic system was firmly established. This was evidenced by the 2001 Nobel Prize in chemistry, awarded to Knowles, Sharpless and Noyori for their work on catalytic, asymmetric reactions. Moving the chirality onto the phosphorus atom means that the stereoinducing center is closer to the reaction site and that the electronic and steric properties can be varied during the synthesis of the ligand. Since then, P-chirogenic compounds have received an increase in attention.[29] Still, one cannot deny that their preparation remains more challenging than the corresponding C-chiral phosphines and over the years, relatively few synthetic protocols for the synthesis of P-chirogenic compounds have emerged.

As this works concentrates on P-chirogenic phosphines, this section aims at providing an overview of the most commonly used methods for preparing optically pure phosphorus sites as well as recent developments in the area. For further studies on the topic, there are excellent reviews available.[17,29-30]

1.3.1. Resolution

Resolution of racemic mixtures is the oldest method of preparing P-chirogenic compounds and dates back to 1911 when Meisenheimer resolved phosphine oxides.[31] The procedure was further

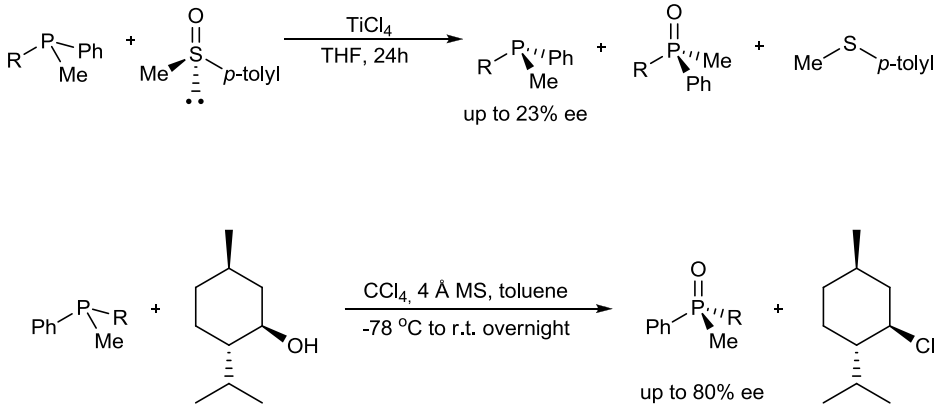
developed by Kumli et al. who employed tartaric acid as a chiral counterion in the formation of quaternary phosphonium salts.[32] After resolution, the tartaric acid was liberated through cathodic reduction with retention of configuration at phosphorus. More recent variations of this technique includes the use of DBTA to resolve C_2-symmetric diphosphines as reported by Shiori[33] and Imamoto,[34] or employing chinchonine for the resolution of phosphinic acid boranes (Scheme 2).[35] Another method developed by Imamoto employs a chiral thioester in the synthesis of both enantiomers of secondary phosphine boranes.[36]



Scheme 2. Use if (-)-chinchonine as a resolving agent.

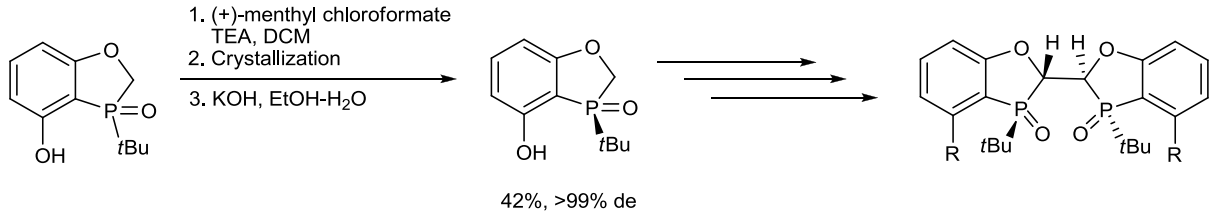
Imamoto and coworkers have also performed resolution through the use of chiral HPLC on a preparative scale. In this case, racemic 1,1'bis[(*tert*-butyl)methylphosphino]ferrocene was resolved using a Daicel Chiralpak AD-column.[37] The advantages of this method are that no chiral resolving agent needs to be introduced, which adds diversity to the types of compounds that can be prepared. Furthermore, the phosphines were handled as the corresponding borane-protected compounds, not the phosphine oxides, this avoids the use of powerful reducing agents. Since it is a HPLC based methodology, both enantiomers can be obtained rapidly without relying on crystallizations which sometimes can be fickle. The drawbacks are that large scale chiral columns are expensive and that UV-absorbing functional groups are required to facilitate detection during the separation, as well as the fact that large amounts of organic solvents are expended.

Another method which bears mentioning is the kinetic oxidation of racemic phosphines as a resolving measure. This can be carried out through use of a mixture of chiral sulfoxide and $TiCl_4$ (Scheme 3, top),[38] or as a dynamic kinetic resolution under Appel conditions with chiral alcohols (Scheme 3, bottom).[39]



Scheme 3. Resolution of P-chirogenic phosphines through selective oxidation.

Although the use of resolution tends to be considered as a somewhat inelegant approach due to the use of resolving agents and the limitations it places on the yield when producing only a single, desired enantiomer, it can be a powerful tool and is still in use. A recent example was published by Tang et al. using (+)-menthyl chloroformate to resolve heterocyclic oxaphospholanes which were then dimerized to diphosphine oxides (Scheme 4).[40] These novel phosphines were in turn shown to be efficient ligands in the rhodium catalyzed hydrogenation of a variety of olefins. Another current instance where resolution has been used is in the chromatographic separation of palladium-phenoxaphosphanol complexes as reported by Doro et al.[41] Overall, the topic of resolution to produce P-chirogenic phosphines has been well-covered in reviews and will not be further elaborated on here.[17,29a,30b,42]



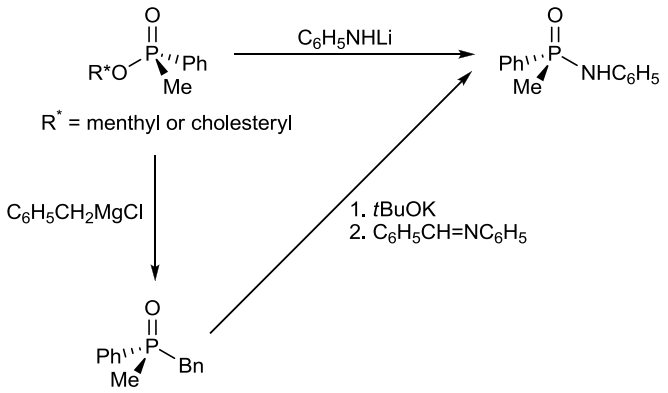
Scheme 4. Resolution of an oxaphospholane towards the preparation of diphosphine oxides.

1.3.2. Chiral Auxiliaries

Similar to resolution, the notion of introducing a chiral handle into a molecule is well-established. The difference is that while resolution relies on employing an additional chiral center at the end of a synthesis to separate a 1:1 diastereomeric mixture, a chiral auxiliary is introduced earlier and thus induces stereoselectivity during the synthesis. This means that the theoretical limit of 50% yield of a single enantiomer which is present during resolution can be

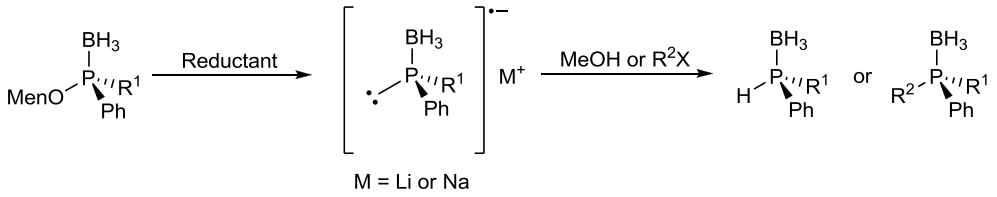
circumvented. As such, the method has been a cornerstone in the preparation of P-chirogenic compounds since its inception.

The first example of a chiral handle used as a means to produce P-chirality was when Mislow and coworkers reacted unsymmetric menthyl phosphinates, derived from phosphinyl chlorides, with a selection of Grignard reagents.[19] The nucleophilic Grignard compounds displaced menthol with inversion of configuration to give optically pure phosphine oxides.
The group further described how this methodology could be used in conjunction with ^{1}H NMR to detect both enantiomers of P-chirogenic compounds.[43] The same approach was used by Nudelman et al. to produce phosphinic amides with either menthol or cholesterol as the auxiliary, and Grignard or lithiated species to displace the chiral handle with inversion of configuration (Scheme 5).[44]



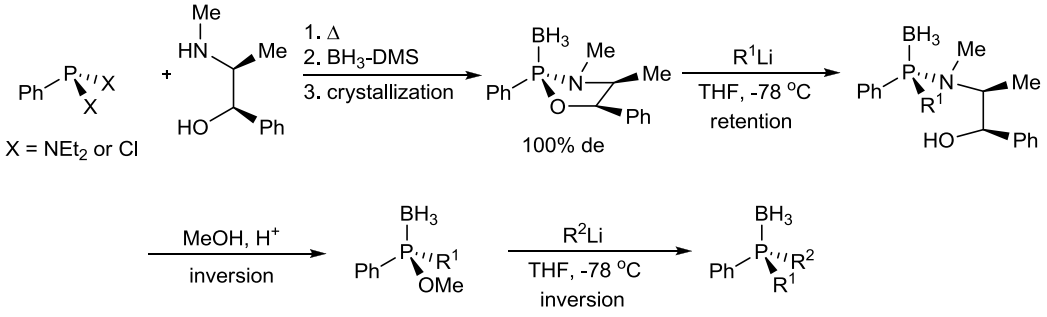
Scheme 5. Use of menthol or cholesterol as chiral auxiliaries in the synthesis of phosphinic amides.

Similarily, Imamoto et al. used menthol and menthyl choloroacetate in the preparation of both mono- and diphosphines with the chirality on phosphorus.[21c,45] The Imamoto group also reported the first stereoselective cleavage of the menthyl group using one-electon reducing agents such as lithium naphthalenide or LDBB.[46] The resultant metallated species can be reacted with methanol or alkyl halides to produce optically pure secondary or tertiary phosphines with retention of configuration as shown in Scheme 6. Recent use of menthol has been reported by the Buono group who employed this chiral handle towards the preparation of bulky phosphines and phosphinous acids.[47]



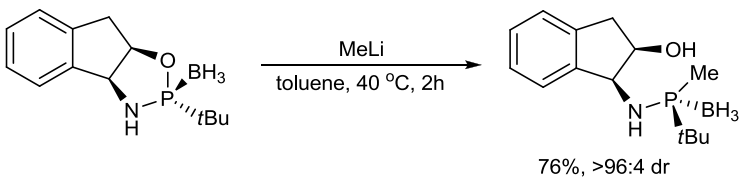
Scheme 6. Reduction of the phosphorus-alkoxy bond by one-electron reducing agents.

Arguably, the most commonly utilized chiral handle for preparing P-chirogenic phosphines is ephedrine. Via a pathway developed by Jugé and Genêt, it is possible to synthesize P-chiral compounds by forming an oxazaphospholidine complex containing two different heteroatoms bonded to phosphorus (Scheme 7). This enables chemo- and stereoselective ring-opening at oxygen by lithium reagents with subsequent removal of ephedrine under acidic conditions in methanol, or as later reported, using hydrochloric acid. The resulting methoxy group can then be substituted from phosphorus using a second alkyl/aryl lithium reagent which gives the optically pure phosphine. Jugé has recently used the method to prepare mixed aminophosphine-phosphinite ligands based on the ephedrine skeleton.[48]



Scheme 7. The Jugé / Genêt methodology of using ephedrine as a chiral auxilliary

The sequence gives retention, inversion and finally inversion again. Thus the original stereochemistry after addition of the first lithium reagent is preserved in the end product. Although tetrahedral phosphorus tends to undergo substitution with inversion of configuration, the retention initially observed here has been rationalized to be due to attack of the lithium reagent on the less hindered side of the P-O bond, i.e. opposite nitrogen. It is proposed that the reaction thus proceeds via a pentavalent complex with coordination of the metal to the oxygen atom before the actual ring opening occurs. Interestingly, in a recent study, León et al. published the use of a similar chiral auxiliary: (1*S*,2*R*)-cis-1-amino-2-indanol.[49] Although it forms similar oxazaphospholidenes, the ring opening proceeds with inversion of configuration in this case (Scheme 8). If the free amino functionality which is present here is methylated, as it is in ephedrine, the reaction no longer takes place. This suggests that the pentacoordinated moiety has the metal reagent coordinated to the nitrogen atom and not the oxygen for this chiral handle.



Scheme 8. Use of (1*S*,2*R*)-cis-1-amino-2-indanol as chiral handle and ring opening with inversion of configuration at phosphorus.

Other chiral auxiliaries that have recently been shown to be effective in the synthesis of P-chirogenic compounds include α-diaminonitriles derived from (-)-carvone,[50] Ugi's amine,[51] and chiral triamines.[52]

1.3.3. Enantioselective Deprotonation

Methyl substituted phosphines can be deprotonated by a sufficiently powerful base and then derivatized with a variety of suitable electrophiles. This process is further facilitated by protecting groups on phosphorus as these tend to be electron withdrawing, thus activating any available α–hydrogens.[20] If a chiral inductor is present during the deprotonation, it is possible to differentiate between two equivalent methyl substituents, i.e. a *prochiral* substrate, and perform an enantioselective proton abstraction from only one group. A suitable combination for this purpose consists of buthyllithium as the base and some form of optically pure diamine as the source of chirality. In combination, these form a chiral lithium-amide complex which can perform enantioselective deprotonation of prochiral phosphines.[53]

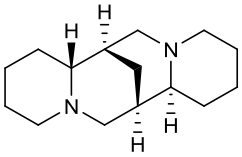
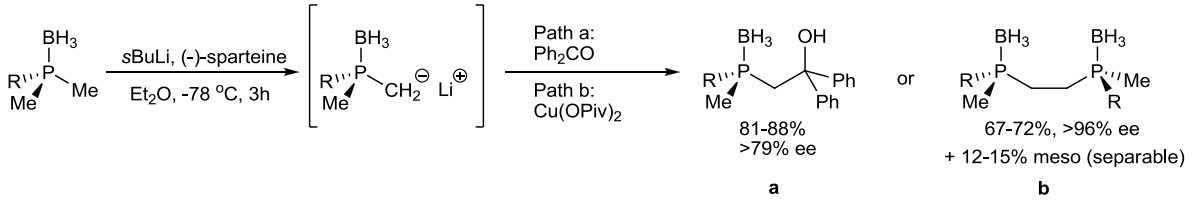


Figure 4. (-)-Sparteine.

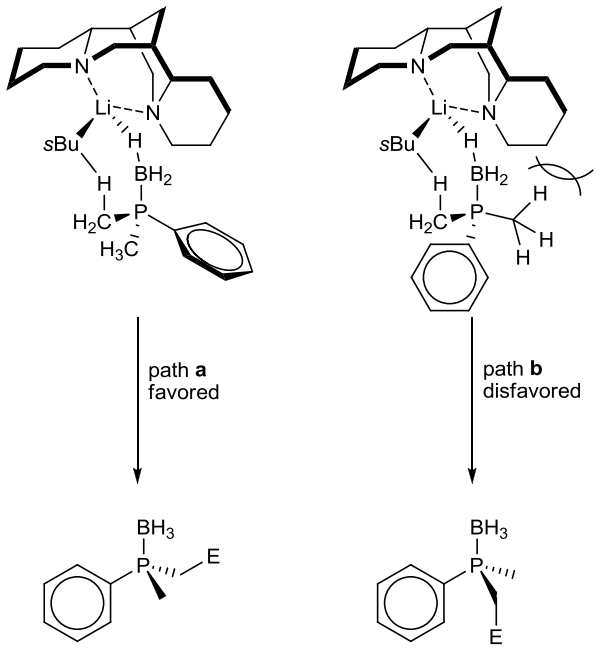
One of the most commonly used diamine for this purpose is (-)-sparteine (Figure 4), a naturally occurring alkaloid found in plants of the Fabaceae family. (-)-Sparteine was first used in a complex with *sec*-buthyllithium by Hoppe et al. to deprotonate *O*-alkylated carbamates in the synthesis of chiral alkanoic acids and secondary alcohols with greater than 95% enantioselectivity.[54] As shown in Scheme 9, the successful application of (-)-sparteine in the preparation of P-chirogenic compounds was pioneered by Muci and Evans in the mid 1990's.[55]

After kinetically controlled deprotonation of dimethyl substituted phosphine boranes at -78 °C the chiral anion was either trapped with benzophenone or oxidatively coupled with copper(II) pivalate to form diphosphines.



Scheme 9. Enantioselective deprotonation of prochiral phosphines with (-)-sparteine. Path a: trapping of the chiral anion by benzophenone. Path b: oxidative coupling using Cu(II).

Muci also later performed calculations on simple phosphine derivatives in order to understand the stereochemical outcome of such enantioselective deprotonations and the binding properties involved between the reactant and the reagent.[56] The suggested model is shown below in Scheme 10. As can be seen, lithium is placed between the two nitrogen atoms of the chiral ligand, and is also coordinating to the electron rich hydride of the borane. This allows the basic butyl chain to abstract a proton from whichever methyl group that is oriented in the same direction. For the favored pathway **a** in Scheme 10, the other methyl is pointing away from the piperidine ring of sparteine whilst the free rotation of the P-aryl bond allows for minimum steric hindrance. In the case of the disfavored pathway **b** however, the hydrogens of the second methyl group are brought into conflict with those of the piperidine ring, effectively blocking this configuration.



Scheme 10. Model that rationalizes the stereochemical outcome from deprotonation of dimethylphosphine boranes with (-)-sparteine / *sec*-buthyllithium.[56]

This model provides a fairly simple means of producing a wide variety of different phosphines with stereogenic phosphorus and different functionalities. Some examples are phosphinic acids, alcohols and secondary phosphines.[57] Phosphine/sulfphide hybrid ligands,[58] diphosphines,[59] phosphine oxazolines[60] and ortho-substituted diaryl phosphines[61] have also been prepared through this methodology.

The major drawback of the methodology is that due to the lack of any readily available (+)-sparteine, the opposite enantiomer could for some time not be produced. However, this has been remedied by the application of surrogate compounds, the most prominent being derivatives of another naturally occurring alkaloid, namely (-)-cytisine (see Figure 5).[62] The natural product can be procured from the flower seeds of the golden rain tree (*Laburnum Anagyroides*) via a protocol published by Lasne and coworkers.[63] A further complication when performing the deprotonation is that some care must be taken when considering the solvent for the reaction. As for other lithium-base complexes, polar and coordinating solvents will affect the aggregation state and reactivity. Hence, asymmetric deprotonations are usually performed in a relatively non-coordinating solvent such as diethyl ether and the enantiomeric purity is relatively high. If for instance THF is used instead, the selectivity tends to suffer as a consequence. This is often thought to true in general, but a recent study by Hilmersson and O'Brien has shown that the degree of loss of stereochemical integrity is dependent on the diamine.[64] Indeed, in some instances the enantioselective deprotonation of prochiral phosphines can be performed almost as well in THF as in diethyl ether.

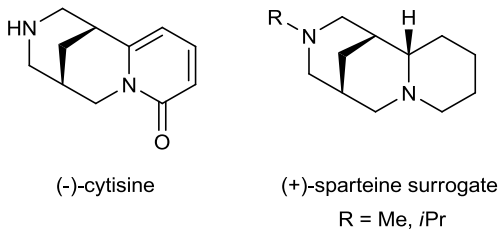
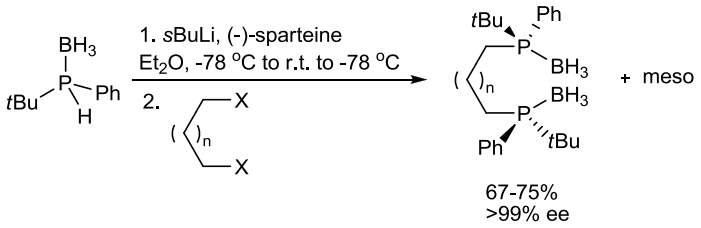


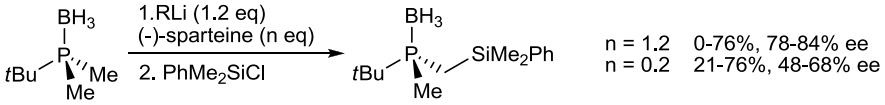
Figure 5. (+)-Sparteine surrogates derived from (-)-cytisine.

As shown in Scheme 11, another possibility is to use the asymmetric deprotonation as a dynamic resolution of racemic, secondary phosphines. This has been carried out by the Livinghouse group with *tert*-butylphenylphosphine. After deprotonation, the anion was allowed to isomerize at room temperature and then quenched with different dihalides, yielding diphosphines in up to >99% enantiomeric excess after recrystallization. This approach has also been used by Marsden who studied the effect of the phosphorus substituents on the stereochemical outcome of the dynamic resolution.[65]



Scheme 11. Dynamic resolution of secondary phosphines.

Providing that the diamine-coordinated lithium complex is more reactive than the corresponding free base, it is possible to use catalytic amounts of (-)-sparteine instead. Early investigations were carried out by the Evans group using 0.7 equivalents of sparteine without any major loss of enantioselectivity.[56] O'Brien has published extensively in this area and the same group has used as little as 0.2 equivalents of (-)-sparteine (Scheme 12), as well as performed resolutions with catalytic amounts.[66]



Scheme 12. Asymmetric deprotonation with stochiometric and catalytic amounts of (-)-sparteine.

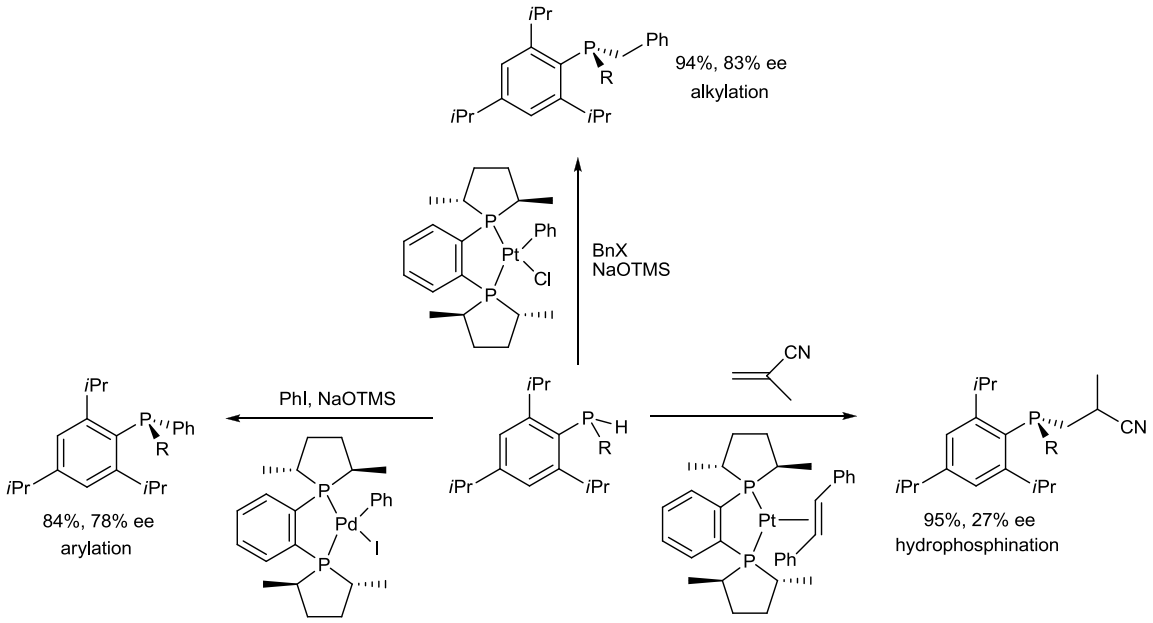
Considering the power and versatility of the Evans methodology, it is not surprising that there have been few optional techniques available. There are two other methods featuring chiral lithium agents, although these have not reached the same acclaim. One approach that was reported by Simkins and coworkers involves using a lithium amide with resident chirality, (+)-bis[(*R*)-1-phenylethyl]lithium amide, thus obviating the need for an extra ligand.[67] Deprotonation of a phospholane oxide proceeded readily and this was subsequently reacted with different electrophiles in 80-92% enantiomeric excess, followed by deprotection of the phosphine oxide. The other pathway performed by Mioskowski and coworkers, features a chiral borane moiety coordinated to phosphorus as the stereoinducing agent. *sec*-Buthyllithium was used as the base, and after reaction with a variety of electrophiles the borane group could be removed without racemization and the products obtained in 49-74% enantiomeric excess.[68]

1.3.4. Asymmetric Catalysis and Metal Promoted Reactions

Most methods used to prepare P-chirogenic compounds involve stoichiometric amounts of reagents. As this is neither cost effective nor environmentally friendly, there has been some interest in devising synthetic protocols that rely on the use of catalytic systems instead.[29c,d,69] Early progress in this area came from the Glueck group with the phosphination of aryl halides or triflates with palladium-DuPhos catalysts.[70] While there were earlier examples on the coupling of

phosphinates with palladium, these processes were not asymmetric.[71] Similarily, Helmchen and coworkers have developed an asymmetric cross-coupling reaction of secondary diaryl phosphines using $Pd_2(dba)_3$ and FerroTANE-type ligands. Treatment with triethylamine and a suitable additive (either LiBr or TBAB) and an aryl iodide produces the desired triaryl phosphines in up to 93% enantiomeric excess.[72] Moreover, Gaumont and coworkers showed that Pd_2dba_3 could be used in a catalytic approach towards the preparation of PAMP-type phosphines without resorting to the Jugé/Genêt methodology. The best results were obtained with a PHOX-class oxazoline ligand, and for secondary alkyl-aryl phsophines the product from coupling with aryl iodides was achieved with up to 48% stereoselectivity. However, aryl-aryl secondary phosphines gave completely racemic product.[73]

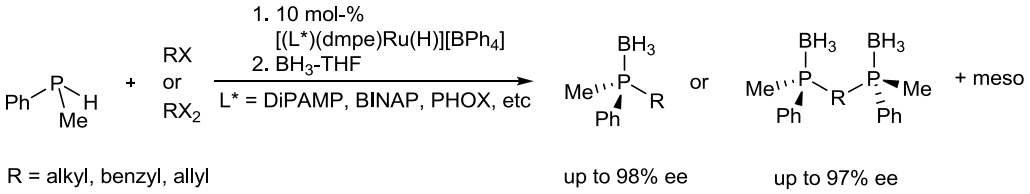
As shown in Scheme 13, Glueck has gone on to describe other applications of DuPhos-based systems with generally good results.[69,74] Note that the use of a platinum catalyst together with a strong base allows for the alkylation of benzylic substrates.[75] Previously, the asymmeric, catalytic preparation of P-chirogenic phosphines mainly featured aryl halides as substrates due to their traditionally high reactivity in cross coupling reactions. However, the mechanism, which involves deprotonation of a secondary phosphine coordinated to an electron rich metal center, tends to enhance nucleophilicity on the phosphorus atom. This also allows for quick interconversion of the phosphorus chirality which enables a dynamic kinetic alkylation to take place.[76]



Scheme 13. Transition metal catalyzed cross couplings of secondary phosphines as reported by Glueck.[69,74-75]

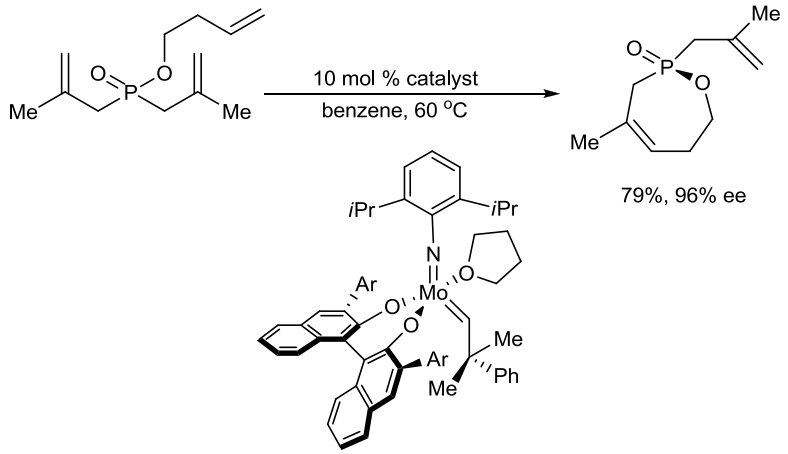
The same idea occurred to the Toste group at Berkley who developed a ruthenium catalyst featuring a mix of dmpe and chiral phosphines such as PHOX, diPAMP or BINAP to couple secondary phosphines and alkyl halides with enantiomeric excesses as high as 97% (Scheme 14).[77] The group has also employed FerroTANE as ligand in the palladium catalyzed,

enantioselective dynamic kinetic arylation of silylphosphines with a variety of functionalized aryl iodides.[78] Other, similar methods for hydrophosphinations have been reported by Gaumont[79] and Marks.[80]



Scheme 14. Ruthenium catalyzed dynamic kinetic alkylation to form P-chirogenic phosphines.

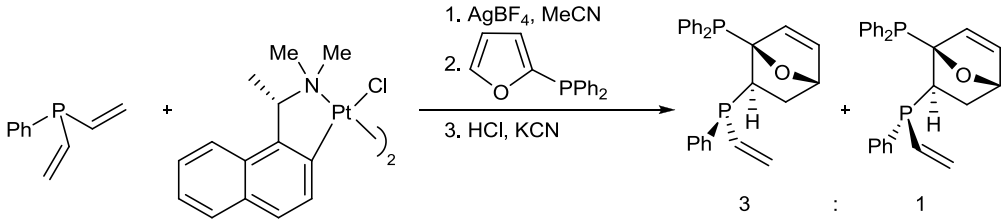
Shown in Scheme 15 is another interesting way to prepare P-chirogenic compounds by transition metal catalysis that was recently published by Hoveyda and Gouverneur.[81] By taking prochiral divinyl phosphine oxides and subjecting them to asymmetric ring closing metathesis (ARCM) with a molybdenum catalyst, five, six or seven membered P-heterocycles can be formed in up to 97% enantiomeric excess. The reaction occurs between one of the enantiotopic vinyl groups and an alkenyl or olefinic ether sidechain which can be varied in length to give the different products. Ogasawara et al. have performed analogous ARCM of C_S-symmetric phosphaferrocenes.[82] Although the resultant planar chiral phosphaferrocenes are completely devoid of chiral centres, the similarity of the method to that of Gouverneur and Hoveyda nonetheless makes it worth mentioning. It was found that by using molybdenum catalysts, the products could be obtained in up to 83% yield and 99% enantiomeric excess.



Scheme 15. An example of the formation of a P-chirogenic phosphinate through intramolecular ARCM.

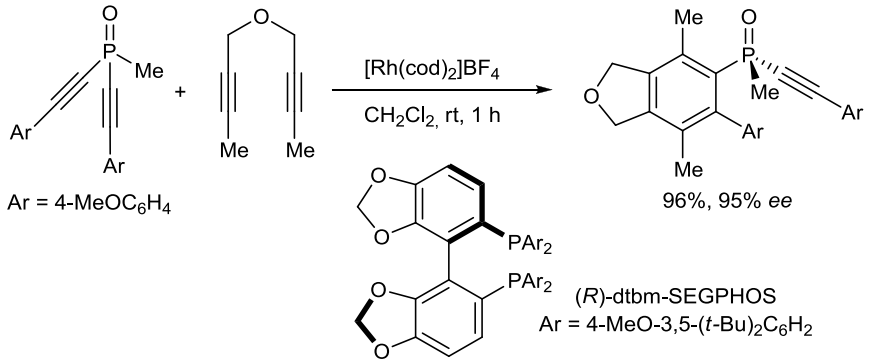
Stereogenic phosphorus centers have also been installed into prochiral phosphines by the use of chiral metal templates. Leung performed a stereoselective Diels-Alder cycloaddition with a phosphine carrying two enantiotopic vinyl groups using platinum and a chiral benzylic amine

(Scheme 16). A phosphinofuran was used as the addition partner and the resultant [4+2]-product was cleaved from platinum using HCl and KCN. The chiral product undergoes slow inversion of the phosphorus stereocenter and equilibrates in a 3:1 ratio of the (-)-stereoisomer, although this could be suppressed if the other vinyl group was hydrogenated while complexed to the metal. Leung has also recently used a similar strategy to prepare bimetallic complexes with stereogenic phosphorus from bisalkyne substituted phosphines.[83]



Scheme 16. Metal template promoted asymmetric Diels-Alder reaction.

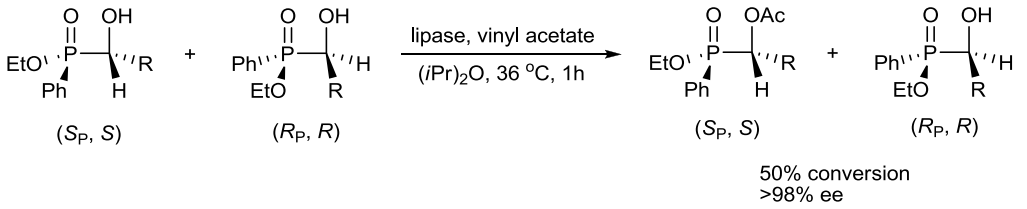
Shown in Scheme 17 is another reaction which differentiates between two alkyne groups, the [2+2+2]-cycloaddition with 1,6-diynes published by Tanaka and coworkers.[84] With a rhodium catalyst and axially chiral (*R*)-dtbm-SEGPHOS as the ligand, up to 95% enantiomeric excess was achieved with aromatic alkyne substituents on phosphorus. The reaction works for alkyl derived alkynes as well but the enantioselectivity is lower.



Scheme 17. Desymmetrization of prochiral bisalkynes through rhodium-catalyzed [2+2+2]-cycloaddition.

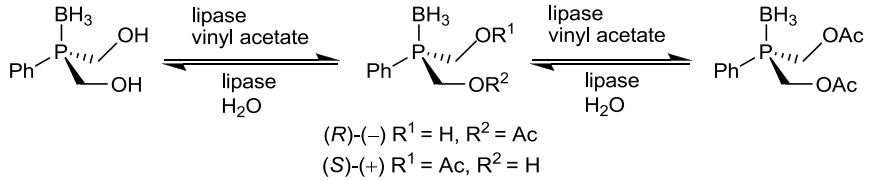
Metal-free catalytic approaches to P-chirogenic compounds, apart from the Evans/O'Brien catalytic deprotonation, exist in the form of stereoselective enzymes. For example, lipase enzymes have been used to kinetically resolve hydroxyphosphine oxides by acylation. This has been carried out by Okuma and gave complete conversion of one phosphorus enantiomer to its corresponding acetate in greater than 98% enantiomeric excess (Scheme 18).[85] The

corresponding acetate hydrolysis was earlier used to the same effect by the Mikolajçzyk group, albeit with lower yields and enantioselectivities.[86]



Scheme 18. Lipase catalyzed enzymatic kinetic resolution

Our group has shown that CALB lipase is capable of enantioselectively acylating prochiral dihydroxyphosphines in a catalytic manner.[87] By starting from either a diacetate or a diol, both enantiomers of the product can be obtained using the same enzyme as its propensity to react at one preferred site is the same, regardless of if it is fulfilling an acylating or hydrolyzing role (Scheme 19). Similar procedures has been reported by Mikolajçzyk and Kiełbasiński.[88] Also, there has been a report of fungal biooxidation of diastereomeric mixtures of α-hydroxy phosphinates by Lejczak and coworkers. After oxidation of the alcohol moiety, the two products which were diastereomers at phosphorus could be isolated in >99% enantiomeric excess.[89]



Scheme 19. Lipase catalyzed desymmetrication

1.4. Aims and Purpose

As has been stated above, P-chirogenic phosphines can be an effective tool in asymmetric synthesis. A subclass of these compounds incorporates one or more nitrogen atoms as well. Although both phosphorus and nitrogen are part of the same period in the periodic table, hence both featuring free electron pairs, their chemistry is different. Having both phosphorus and nitrogen in a ligand makes it possible to take advantage of their varying properties when coordinating to a metal centre. As will be demonstrated in the coming chapters, mixed P,N-ligands have proven to be useful in a variety of chemical transformations. However, P-chirogenic examples of this ligand class is rare and their preparation is at times lengthy and limited in scope.

It was our desire to find a method of synthesizing a variety of P,N-ligands that would allow for variation of both the phosphine and amine properties as well as being robust and rapid. Chapters 2-4 deal with our efforts in this regard.

We also realized that even though phosphines have found increasing value as organocatalysts, i.e. catalyzing chemical reactions by themselves without the need of additional metals, P-chirogenic examples were relatively unexplored. In Chapter 5, we undertake a study of phosphines with asymmetric phosphorus in cycloaddition reactions.

In Chapter 6, an asymmetric version of propargylic substitution of cobalt stabilized cations (the Nicholas reaction) is covered. Earlier examples of enantioselective Nicholas reactions mainly featured the use of chiral substrates, chiral nucleophiles or chirality transfer. We instead present the use of axially chiral phosphoramidite ligands towards the same purpose.

2. Modular Synthesis of P-Chirogenic β-Aminophosphines (Paper I)

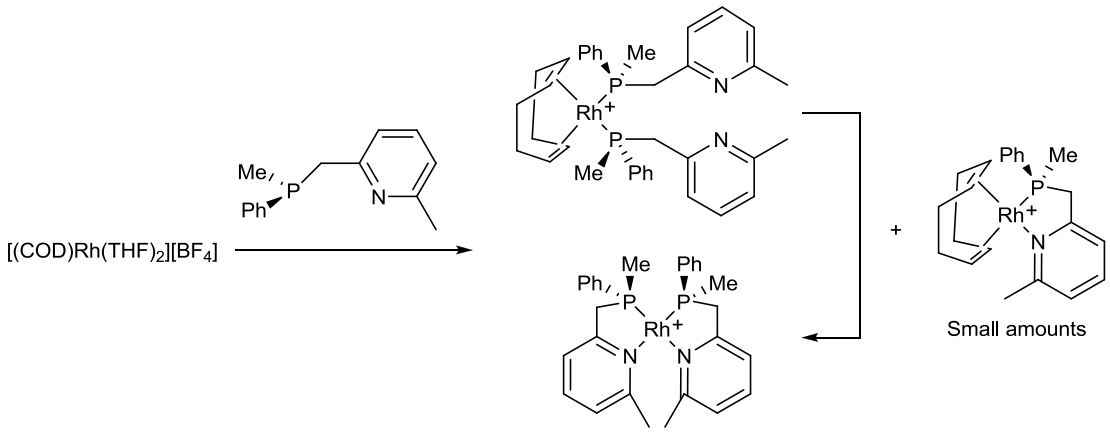
2.1. Introduction

2.1.1. Previously Published P-Chirogenic β-Aminophosphines

The attention that has been garnered by aminophosphines as ligands derives from their incorporation of both a soft nucleophilic phosphorus atom and a hard nucleophilic nitrogen. Indeed, the interesting properties of P,N-compounds have led to them being successfully employed in metal catalyzed reactions such as hydrogenations, conjugate additions and allylic alkylations.[90]

Of special interest is when the two potential donor atoms are separated by a two carbon linker. Such a β-aminophosphines has the possibility to coordinate a metal center in a structurally beneficial five-membered chelate.[15] Due to the inherently different properties of the donor atoms however, the ligand has the capability to act in both a monodentate and bidentate fashion which allows for interesting flexibility in reaction dynamics.[91]

As an example, studies by Mathieu has shown that reaction of an aminophosphine with $[(COD)Rh(THF)_2][BF_4]$ gives rise to three different products with the favored one being a species where two ligands coordinate in a κ^2-manner to rhodium. The corresponding κ^1-moiety is slowly interconverted to the favored form by dissociation of cyclooctadiene (Scheme 20).[92] The manner in which the ligand binds to the metal can be influenced by varying the steric hindrance around the pyridyl nitrogen as removing the methyl group on the pyridine ring leads to only a monoligand κ^1-complex.



Scheme 20. Aminophosphine-rhodium complexes.

In spite of the interest directed towards β–aminophosphines there exists only a handful of examples of P-chirogenic ligands of this class. This is due to the inherent difficulty associated with preparing compounds with an optically pure phosphorus center and despite recent progress in this field, little attention has been diverted to the synthesis of P-chirogenic β–aminophosphines. As such, there exists a clear opportunity for the introduction of new methods towards this purpose.

Early examples of P-chirogenic β-aminophosphines were prepared through resolution of racemates, some of which (**1**-**5**) are shown in Figure 6.[17,93] The drawback of such an approach is that large amounts of chiral resolving agent is used, including in some cases a noble metal such as palladium. Also, only a maximum 50% yield of the desired enantiomer can be obtained.

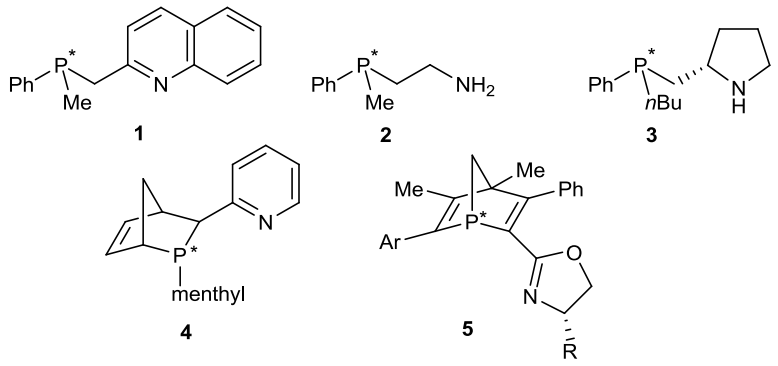


Figure 6. Examples of P-chirogenic β–aminophosphines prepared via resolution.

To counteract such shortcomings, more efficient methods were soon to follow. In 1995, Bianchini et al. reported the stereoselective conjugate addition between a chiral nitrone and a phosphole to yield a tricyclic isooxazolidine which was then converted to phosphine oxide **6** (Figure 7) in three steps. Following deprotection with $HSiCl_3$ / NEt_3 in refluxing benzene for 12 hours, the corresponding free phosphine was obtained in 55 % overall yield.[94]

Another example was performed by the Mathieu group in the previously mentioned coordination study. Here, the Jugé methodology was adapted, and in the final step of the corresponding PAMP-synthesis, lithiation of disubstituted pyridines gave compounds of type **7** (Figure 7).[92] This pathway was also employed by Lam et al. in 2005 when they prepared P,N,P-compounds **8** (Figure 7) by amide coupling of the phosphinic carboxylic acid derived from PAMP with proline derivatives.[95] Subsequent reduction of the amide with borane, and finally borane removal from the phosphorus with triethyl amine gave the free phosphines.

The same year, the Kobayashi group also made use of a P-chirogenic carboxyphosphine in amide couplings with tetrahydroisoquinoline.[96] The stereogenic center was in this instance installed through asymmetric deprotonation of a prochiral substrate.[97] When the amide coupling was carried out at room temperature, a mixture of the *cis*- and *trans*-isomers were obtained. While diastereomeric resolution could be easily effected by column chromatography, running the

coupling at 0 °C gave mainly the *trans*-product. After borane reduction and deprotection, compound **9** (Figure 7), as well as its diastereomer, was obtained in a 58 % overall yield for the *trans*-isomer.

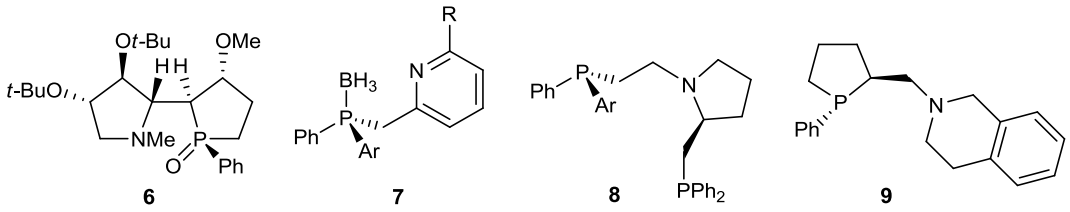
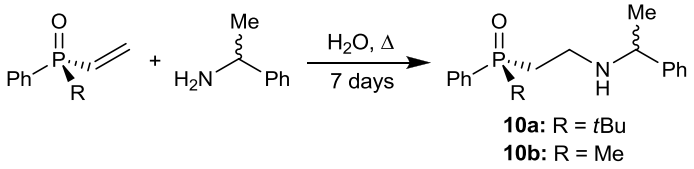


Figure 7. β-Aminophosphines featuring *N*-heterocycles as the amine component.

Some of these P,N-compounds were subsequently used as ligands in Pd-catalyzed allylic substitution reactions. With racemic (*E*)-1,3-diphenylallyl acetate as the substrate and dimethyl malonate as the nucleophile, ligand **5** (Ar = Ph, R = *i*Pr) afforded total conversion and 94% enantiomeric excess of the (*S*)-isomer.[93] Ligand **8** (Ar = *o*An) also gave total conversion, but a mere 37% excess of the (S)-enantiomer.[95] The phosphacycle **9** achieved 99% conversion and 94% enantiomeric excess of the same stereoisomer.[96]

The previously mentioned aminophosphines have mostly featured a nitrogen-containing heterocycle as the amine component. This class of ligands is not however, limited to this functionality. In 1999 Mortreux and coworkers reported the addition of α-methyl benzyl amine to a vinyl phosphine oxide (Scheme 21).[98] The group also compared the aminophosphine oxides against the free aminophosphines in Ru-catalyzed transfer hydrogenation of aryl ketones. It is interesting to note that the P,N,O-ligands do induce catalytic activity, generally higher than the free phosphines. The P,N-compounds on the other hand, gave the higher enantioselectivities, another argument for moving the chirality onto the phosphorus.



Scheme 21. P,N ligands derived from vinyl phosphine oxides.

The Hii group at King's College has also worked extensively with benzylic aliphatic aminophosphines.[99] They modified the vinyl phosphine procedure described earlier, and discovered that by the simple expedient of performing the reaction in the presence of methanol shortened the reaction time from days to hours. Using this protocol, a variety of aminophosphine oxides were produced, some examples of which are shown in Figure 8.

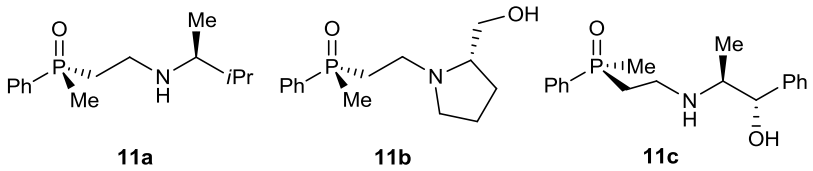
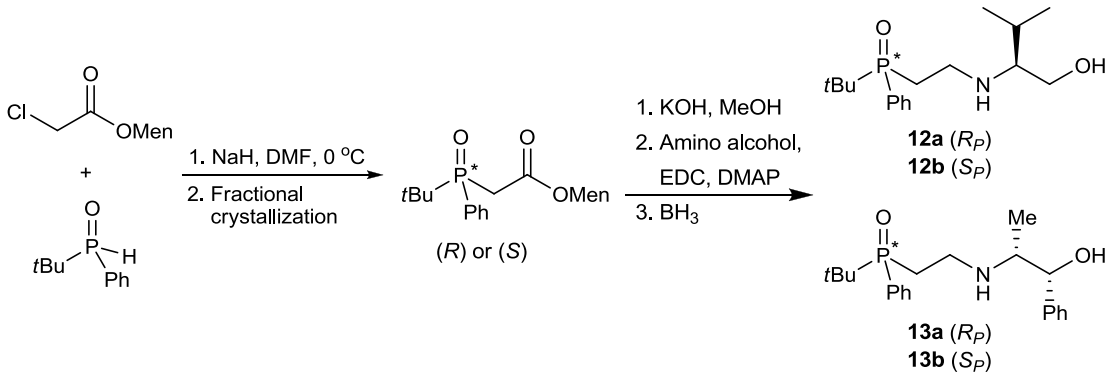


Figure 8. β-Aminophosphines prepared by the Hii group.

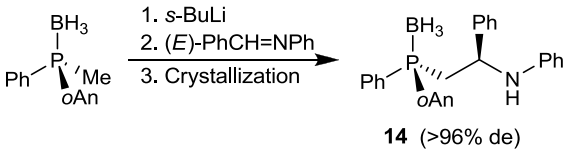
Another one of their methods, shown in Scheme 22, involves the reaction of menthyl chloroacetate and a secondary phosphine oxide. By separation of the diastereomeric menthyl esters and subsequent hydrolysis, an amide coupling could be performed using different amino alcohols.[100] A similar approach was used by Imamoto to synthesize phosphine / oxazoline bidentate ligands. Here, after coupling of the amino alcohol, cyclization was effected using mesityl chloride and triethyl amine, thus forming the oxazoline structure.[60]



Scheme 22. P-chirogenic aminoalcohols through amide coupling.

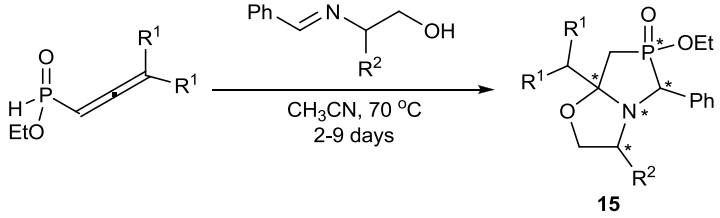
As, previously mentioned, P,N,O-ligands of this type have been put to good use in Ru-catalyzed transfer hydrogenations, once again vindicating the particular chemical structure of this ligand class. Ligand **10a** achieved 85% conversion and 84% enantiomeric excess in the transfer hydrogenation of isobutyrophenone.[98] With aminophosphine oxide **10b** the conversion was 93% and the stereoselectivity 76%.[98] When **11c** was used with acetophenone as the substrate, the product was obtained with 96% conversion and 96% stereoselectivity.[99] Ligand **12a** afforded 98% conversion but only 34% enantiomeric excess.[100] **13a** was employed in the transfer hydrogenation of butyrophenone and gave 99% conversion and 92% enantiomeric excess.[100]

Another procedure of note was reported by Jugé through an extension of the oft used ephedrine method. In this instance, stereochemically pure (*S*)-(+)-*o*-anisylphenylmethylphosphine borane (i.e. (*S*)-PAMP) was lithiated and the amine installed by addition of a prochiral imine. Taking advantage of the chirality at phosphorus, a new stereocenter is formed and the diastereomeric mixture separated by fractional crystallization with greater than 96 % d.e. (Scheme 23).[101]



Scheme 23. A β-aminophosphine derived from (*S*)-PAMP.

Although not strictly aminophosphines, reported syntheses that nonetheless deserve mention here are the recent preparation of bicyclic aminophosphinates by Fourgeaud et al. (Scheme 24). Allenyl *H*-phosphinates can be reacted with iminoalcohols to form bicyclic compounds **15** in 45-80% yield.[102] Currently, the method gives a roughly equal mix of up to 4 diastereomers with the major ones being epimers at phosphorus which can be separated by chromatography. The reaction is proposed to proceed through initial hydrophosphination of the imine and then subsequent Aza-Michael addition to the allene. A similar synthesis of racemic monocyclic aminophosphinates has previously been published by Montchamp.[103]



Scheme 24. Synthesis of P-chiral bicyclic aminophosphinates.

2.2. Results and Discussion

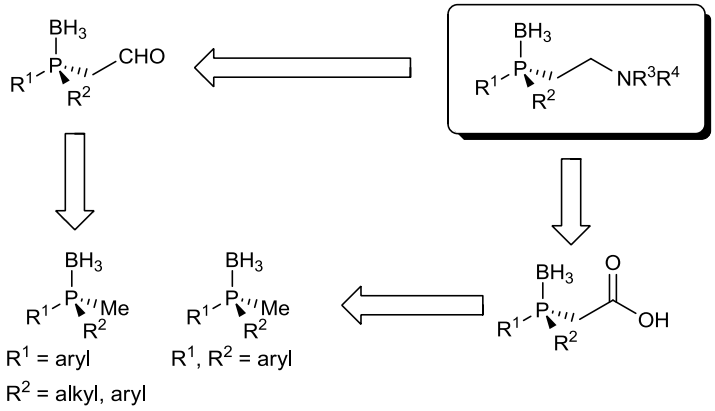
2.2.1. Development of a Modular Protocol for the Synthesis of P-Chirogenic β-Aminophosphines

Considering the promise shown by P-chirogenic β–aminophosphines in catalytic reactions, we wanted to expand on the already known methods, and so, both enable preparation of more diverse compounds and facilitate the synthesis of previous ligands. We aimed at finding a method that would allow for easy variation of both the phosphorus and nitrogen substituents, making it possible to vary the steric as well as the electronic properties of the ligands.

It was realized that the desired amine backbone could originate from the reductive amination of an aldehyde.[i] This would have the added benefit of combining both C-N bond formation and

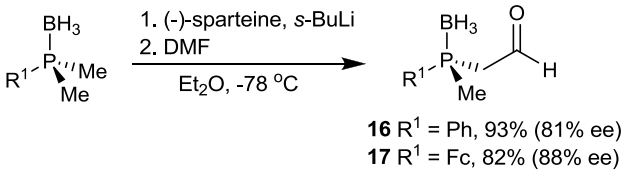
[i] For a recent example of a formylphosphine, see reference 66d.

reduction in a one-pot procedure. In order to access the required α-formyl phosphines, we decided to employ the asymmetric deprotonation pioneered by Evans.[55] Such a pathway would make it possible to prepare both enantiomeric forms of the phosphine since both (-)-sparteine, which is normally used to form the chiral base, and analogues of (+)-sparteine are available.[62-63,104] Moreover, the prerequisite prochiral dimethylphosphines can be prepared with a variety of substituents.[105] In order to consolidate the asymmetric deprotonation with our desired goal we opted to use DMF, a well-known building block for aldehydes, as the electrophile in this reaction.



Scheme 25. Possible routes to P-chirogenic β–aminophosphines.

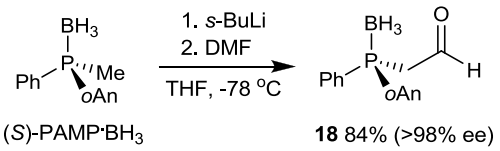
The phosphines we initially selected for this study were phenyldimethylphosphine borane (**16**) and ferrocenyldimethylphosphine borane (**17**). Deprotonation with *sec*-butyl lithium and (-)-sparteine at -78 ºC proceeded readily and after addition of DMF and subsequent quenching and workup, the desired compounds were obtained in good yields and enantioselectivities (Scheme 26).



Scheme 26. Preparation of P-chirogenic phosphine aldehydes.

The next step was to synthesize an aryl/aryl-substituted α-formylphosphine. As this cannot be done via the desymmetrization protocol, it was instead accomplished by lithiation of (*S*)-(+)-*o*-anisylphenylmethylphosphine borane ((*S*)-PAMP). The latter compound was prepared via Jamison's version of the Jugé/Genêt ephedrine-methodology with greater than 98% ee.[106] Subjecting (*S*)-PAMP to deprotonation of its methyl group using *sec*-butyl lithium and treatment

with DMF gave the α-formyl phosphine **18** in 84% yield as shown in Scheme 27. All of the obtained aldehydes were stable to flash chromatography on silica gel and could be stored under argon in the freezer for about three months without detrimental effect.



Scheme 27. Synthesis of (*S*)-PAMP derived aldehyde.

The P-chirogenic phosphine aldehydes were then subjected to microwave-accelerated reductive amination with sodium triacetoxyborohydride as the reducing agent.[107] For this purpose we selected amines with varying steric and electronic properties, **a-d** in Figure 9. After reaction at 120 ºC for 6 minutes in DCE, the crude mixture was purified via elution through a solid cation-exchange resin (SCX-2). After washing with DCM and then methanol, the desired products were liberated from the resin using ammonia in methanol and pure aminophosphines **19**-**21** were obtained. These results are summarized in Table 1.

We were pleased to see that even when using an amine exhibiting fairly poor N-nucleophilicity such as *para*-anisidine, **c**,[108] the observed yields were above 85% (entries 3, 7, 11). Indeed, this amine gave the best yields for products **16** and **18**, probably due to the stabilizing effect of the *para*-methoxy substituted phenyl ring on the intermediate cation. When using the chiral amines, **a** and **b**, no match/mismatch effect could be seen except for the bulky ferrocenylphosphine **18**. In this instance a marked drop in yield was found for product **17b**, entry 6. It is noteworthy to observe that when attempting the synthesis using unpurified aldehydes and at room temperature, as was our initial approach, only small amounts of product were obtained and purification by preparative HPLC was required to obtain pure product.

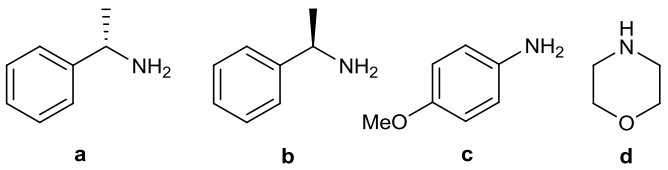
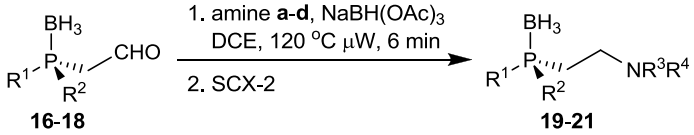


Figure 9. Amines used in the reductive amination.

Table 1. Synthesis of P-chirogenic β-aminophosphines via microwave-accelerated reductive amination and solid phase workup.



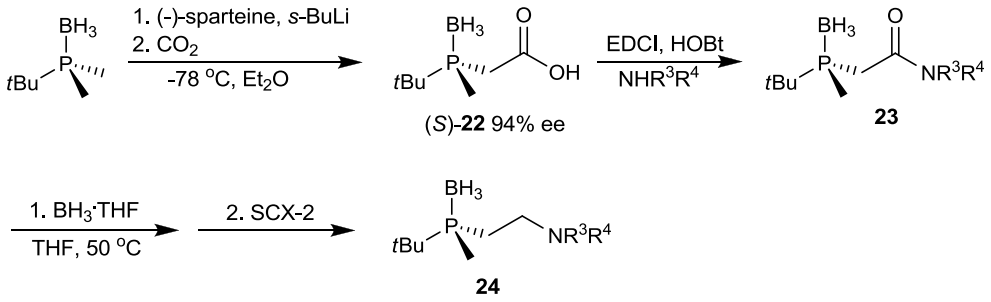
Entry	R^1	R^2	Product	Yield (%)[a]
1	Ph	Me	**19a**	88
2	Ph	Me	**19b**	88
3	Ph	Me	**19c**	98
4	Ph	Me	**19d**	90
5	Fc	Me	**20a**	95
6	Fc	Me	**20b**	71
7	Fc	Me	**20c**	88
8	Fc	Me	**20d**	83
9	Ph	*o*An	**21a**	84
10	Ph	*o*An	**21b**	89
11	Ph	*o*An	**21c**	96
12	Ph	*o*An	**21d**	90

[a] Isolated yields after purification using an SCX-2 ion-exchange resin.

Heartened by these promising results we next set out to prepare a purely alkyl-substituted formylphosphine. Alas, when performing the reaction using *tert*-butyldimethylphosphine borane the resultant aldehyde decomposed upon the acidic workup used to remove sparteine. Performing the workup under neutral conditions led to a rather impure crude product which proved non-amenable to purification even on neutral alumina. It is our belief that the electron-rich nature of the alkyl substituted phosphine facilitates aldol condensations of the aldehyde in this case. Clearly, another approach was required. As such, it was decided to prepare these compounds via amide coupling of the corresponding carboxyphosphine according to the procedure previously reported by Imamoto.[109]

tert-Butyldimethylphosphine borane was treated using the same desymmetrization protocol as previously and the lithiated species was quenched with cabon dioxide. The α–carboxyphosphine **22** was obtained in 94% ee and was subsequently coupled with amines **a**-**d** using EDCI and HOBt. Following this, the resulting amides **23** were reduced using borane. Purification was effected using the same cation-exchange resin as before, this also had the serendipitous benefit of selectively removing any borane that coordinated to the nitrogen during the reduction of the carbonyl group. As is shown in Table 2, the yields for preparation of both the amidophosphine and the reduced amines (**24**) were over 70%.

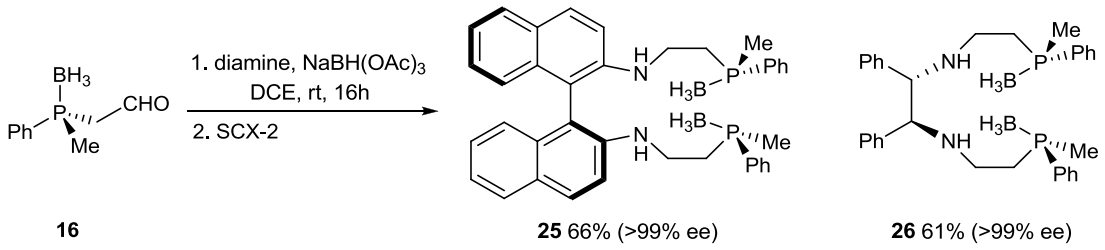
Table 2. Synthesis of purely alkyl substituted P-chirogenic β–aminophosphines through amide coupling.



Entry	Prod.[a]	yield (%)[a]	Entry	Prod.[b]	Yield (%)[c]
1	**23a**	92	5	**24a**	87
2	**23b**	89	6	**24b**	95
3	**23c**	88	7	**24c**	71
4	**23d**	71	8	**24d**	77

[a] Crude yield. [b] See Figure 9 for amine structures. [c] Isolated yields.

Having successfully prepared both alkyl/alkyl, alkyl/aryl and aryl/aryl substituted aminophosphines we next turned out attention to the preparation of tetradentate P,N,N,P-ligands with *C2*-symmetric amine backbones. Towards this end, we used phosphine aldehyde **16** and reacted it with (*R*,*R*)-1,1'-binaphtyl-2,2'-diamine ((*R*)-BINAM) and (*S*,*S*)-1,2-diphenylethane-1,2-diamine ((*S*,*S*)-dpen). Using the reductive amination protocol at room temperature to minimize disubstitution, and purifying the products on preparative HPLC. gave the diphosphines **25** and **26** in moderate yields but excellent optical purity (Scheme 28).



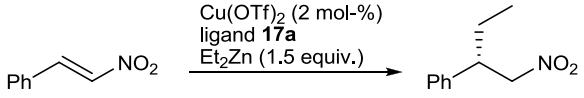
Scheme 28. Preparation of *C2*-symmetric P,N,N,P-ligands.

2.2.2. P-Chirogenic β-Aminophosphines as Ligands in the Cu(I)-Catalyzed Michael Addition of Diethyl Zinc to *trans*-β-Nitrostyrene

With a variety of P-chiral P,N-pre-ligands at hand, we next decided to perform a quick screening of these in a transition-metal catalyzed reaction. Traditional reactions for P,N-compounds, as mentioned before, include hydrogenation, transfer hydrogenation, and palladium-catalyzed allylic substitution or alkylation and high enantiomeric excesses have been achieved in these cases. We instead opted for the slightly less studied copper-catalyzed asymmetric Michael addition of diethyl zinc to *trans*-β-nitrostyrene as reported by Alexakis.[22a,110] In order to avoid having to handle the free phosphines and so expose them to risk of oxidation, we choose to remove the borane in situ according to the Jugé protocol.[24] As such, $Cu(II)(OTf)_2$ was used as the precatalytic species together with the phosphine borane. The deprotection was attempted at both room temperature and at 50 ºC in different solvents (toluene, DCM, THF). No loss of borane could be detected at room temperature while full deprotection occurred at elevated temperature in toluene and DCM.

Screening of the actual reaction conditions using ligand **17a** was then carried out according to Table 3. As the ligand can coordinate in both monodentate, bidentate and bridging manners, a metal-to-ligand ratio of both 1:1 and 1:2 was examined. Performing the reaction in toluene with two equivalents of ligand compared to metal gave slightly better enantioselectivity at room temperature than at –78 ºC. The yield of the product was, however, markedly higher at ambient temperature (entries 1-3). Lowering the ligand ratio to 1:1 gave virtually the same enantioselectivity but a much lower yield (entry 4). As trimethylsilyl halides are known to have a beneficial effect when used as additives in conjugate additions involving lithium cuprates, we also tried adding trimethylsilyl iodide to the reaction.[111] However, this was found to be detrimental to the reaction and no product was detected (entry 5). Changing the solvent to DCM gave roughly the same results as with toluene (entry 6), while performing the reaction in diethyl ether gave inferior results. This is accordance with previous reports that the use of increasingly coordinating solvents slows down the reaction.[112] Using copper(I) triflate and deprotecting the ligand with HBF_4, did not show any benefits, nor did the use of copper(I) acetylacetonate (entries 8 and 9). Seeing as the screened ligand contained two stereogenic centers, we also tried using **17b** which has the opposite stereochemistry on the amine moiety. This gave slightly lower enantioselectivities, but otherwise no great difference could be seen (entries 10 and 11).

Table 3. Optimization of reaction conditions for the asymmetric copper-catalyzed conjugate addition of diethyl zinc to trans-β-nitrostyrene using ligand **17b.**



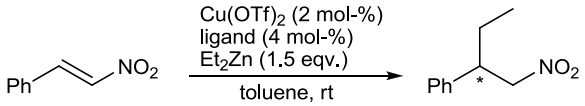
27

Entry	[Cu]:L	Temp. (ºC)	Solvent	Time (h)	Yield (%)	Ee (%)[a]
1	1:2	0	Toluene	12	35	19
2	1:2	-78	Toluene	24	35	14
3	1:2	25	Toluene	12	70	17
4	1:1	25	Toluene	12	45	16
5[b]	1:1	25	Toluene	18	n.r.	n.a.
6	1:2	25	CH_2Cl_2	20	69	16
7[c]	1:2	0	Et_2O	24	15	5
8[d]	1:2	25	CH_2Cl_2	20	30	10
9[e]	1:2	25	CH_2Cl_2	20	10	20
10[f]	1:2	0	Toluene	12	33	14
11[f]	1:2	25	CH_2Cl_2	20	47	13

[a] Determined by chiral HPLC, Daicel Chiracel OD-H column, 5% 2-PrOH in hexane, 0.5 ml/min.
[b] Trimethylsilyl iodide added. [c] Deprotection in toluene. [d] Cu(I)OTf used. [e] Cu(I)(acac) used. [f] **17b** used as ligand.

Having settled on reaction conditions, we next performed a screening of P,N-preligands **19**-**20**, **24**, **25** and **26**. These results are summarized in Table 4. Phosphines bearing a planar phenyl ring and a methyl group, such as in **19**, only induced stereoselectivity if a chiral amine component was present (entries 1 and 2). The best yield of the product was obtained when using ferrocenylphosphine **20a**, entry 10, 70 %. However the enantiomeric excesses remained between 10-17% for these ligands. Among the PAMP-type aminophosphines, **21a** gave the highest yield but racemic product (entry 9) whilst its diastereomer **21b** gave lower yield but the highest enantioselectivity in this study (37%, entry 10), indicating a match/mismatch situation. The bulky *tert*-butylphosphines (entries 13-16) were among the most promising compounds in this instance, producing yields in the range of 50-60% and enantiomeric excesses between 6-28%. Looking at the tetradentate ligands, **25** which is built around a binaphthyl framework gave nearly racemic product (entry 17) while the more flexible **26** gave similar enantiomeric excesses as the other ligands (entry 18).

Table 4. Cu(I)-Catalyzed Michael Addition of Diethyl Zinc to trans-β-Nitrostyrene with P-Chirogenic β-Aminophosphines as Ligands.



a27

Entry	Ligand	Yield (%)	Ee (%)[a]
1	**19a**	39	16 (*S*)
2	**19b**	47	21 (*S*)
3	**19c**	47	0
4	**19d**	22	0
5	**20a**	70	17 (*R*)
6	**20b**	56	10 (*R*)
7	**20c**	22	10 (*R*)
8	**20d**	59	12 (*R*)
9	**21a**	58	0
10	**21b**	18	37 (*S*)
11	**21c**	20	9 (*S*)
12	**21d**	49	14 (*S*)
13	**24a**	57	6 (*S*)
14	**24b**	56	14 (*S*)
15	**24c**	63	5 (*S*)
16	**24d**	53	28 (*S*)
17	**25**	30	2 (*R*)
18	**26**	44	16 (*S*)

[a] Determined by chiral HPLC, Daicel Chiracel OD-H column, 5% 2-PrOH in hexane, 0.5 ml/min.

2.2.3. Conclusion

In conclusion, we have created a highly adaptable modular route to P-chirogenic β–aminophosphine boranes which in turn can be used as chiral ligands in metal catalyzed reactions. The intermediate aldehydes or carboxylic acids can be prepared with a variety of substituents, both alkyl and aryl, on the phosphorus atom. This allows for unparalleled possibility to tune the steric and electronic properties of the ligands. The preparation of the aminophosphines is rapid, mere minutes when starting from the aldehyde and hours from the acid. The use of a solid phase workup of the products eliminates the need for time- and solvent consuming chromatographic methods. Furthermore, the method also enables the synthesis of tetradentate P-chiral P,N,N,P-ligand, a class of compounds that have not been extensively studied so far. Employing the aminophosphines as ligands in the copper(I) catalyzed asymmetric conjugate addition of diethyl zinc to trans-β-nitrostyrene gave moderate yields and low enantioselectivities in most cases. Nonetheless, stereoselectivity was obtained and the varying results among the different ligands shows the versatility of our method in varying the characteristics of this class of compounds. Also, the advantages of using borane as a protecting group are demonstrated by the capability of

deprotecting our ligands *in situ* by using a metal in a higher oxidation state than required for the catalytic cycle. This completely obviates the need to handle the free phosphines.

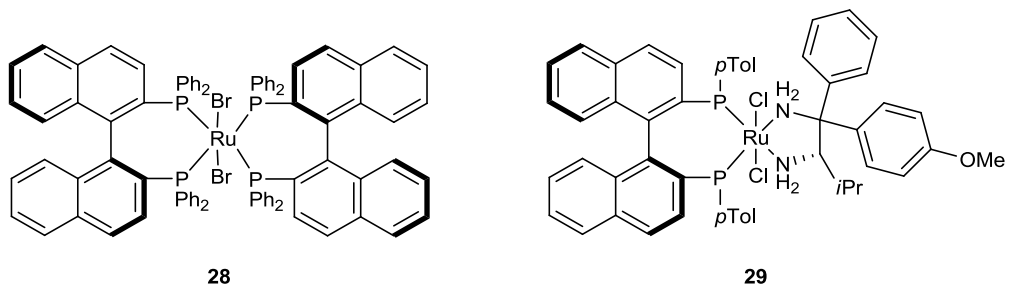
3. P-Chirogenic P,N,N-Tridentate Ligands and Their Application in the Catalyst Design of Ruthenium Complexes for the Hydrogenation of Ketones (Paper II).

3.1. Introduction

3.1.1. P,N,N,P-Ruthenium Complexes as Ketone Hydrogenation Catalysts

The catalytic hydrogenation of ketones to secondary, chiral alcohols is a very important synthetic transformation and used in the production of a variety of pharmaceuticals and fine chemicals.[26b] Indeed, this importance is showcased by the award of the 2001 Nobel Prize to Knowles, Noyori and Sharpless for their work on asymmetric catalysis of which enantioselective hydrogenations were an important part.[113] When dealing with ketones as substrates, initial work by Noyori employing ruthenium-diphosphine catalysts has been greatly expanded on and today there are a number of publications on this area.[114]

The early catalytic systems developed in the 1980's used a combination of BINAP-derivatives and ruthenium halogen complexes (Figure 10). Although these were quite effective, they only were so for functionalized ketones containing a coordinating group such as β-ketoesters.[115] What Noyori found was that when the catalysts also contained a chiral diamine as well as the diphosphines, even non-functionalized substrates could be hydrogenated effectively.[116]



28 **29**

Figure 10. Early hydrogenation catalysts by Noyori. **28:** Ru-BINAP-System for functionalized ketones. **29:** BINAP-DAIPEN-derived system for unfunctionalized ketones.

The rationalization of this increase in reactivity is that the amine hydrogens are activated by the complexation of the sp^3-nitrogen to the metal. At the same time, the increase of electron density at the metal also makes any hydrides more nucleophilic. The ketone substrate is guided into place by hydrogen bonding between the carbonyl oxygen and one of the amine hydrogens. This places the carbonyl carbon in close proximity to the hydride on the metal and allows for facile transfer between these two centers (Figure 11).[117] The oxygen atom is then protonated by the amine hydrogen.

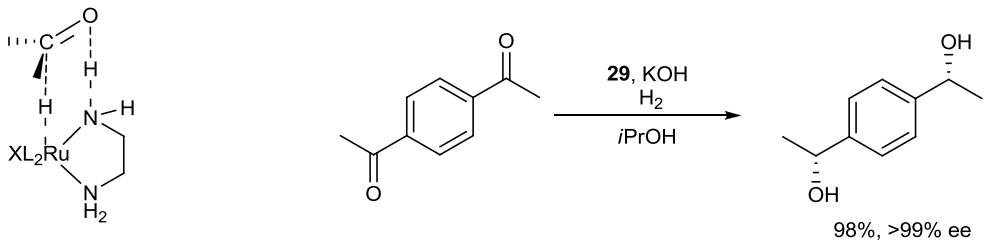
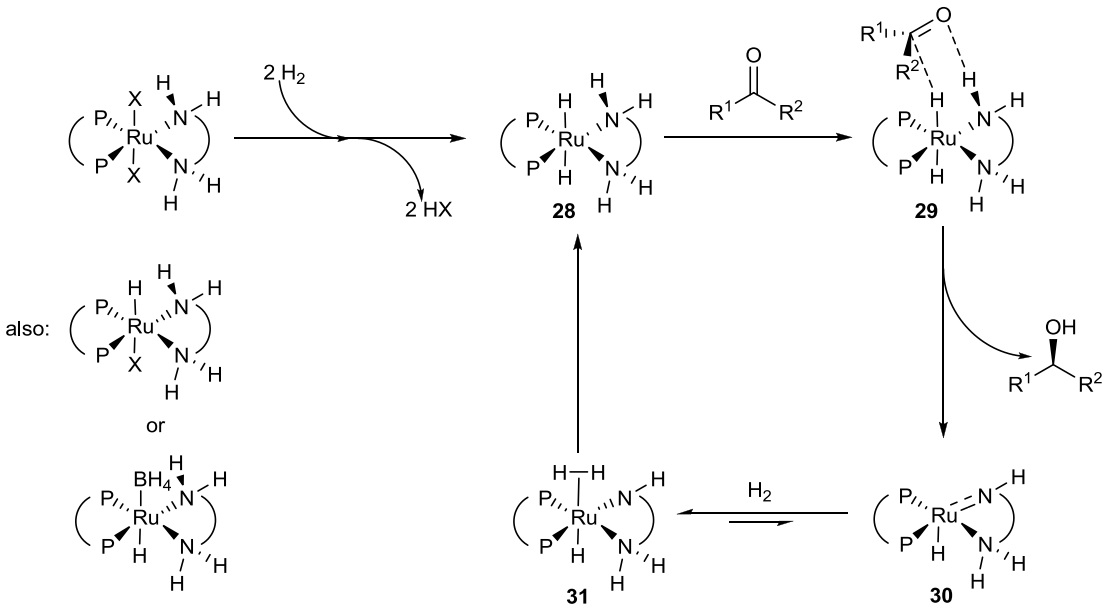


Figure 11. Left: Hydrogen bonding between a non-functionalized ketone and the hydrogen atom of a ruthenium complexed diamine. Right: Example of hydrogenation using complex **29**.

The mechanism for the hydrogenation has been studied by many groups and is summarized in Scheme 29.[117-118] Typically, the precatalyst is a ruthenium dihalogen compound which is activated by addition of H_2 with release of acid to form active *trans*-dihydride species **28**. In order to neutralize the acid, the reaction is carried out with addition of a base such as K_3PO_4. Another common precatalyst is the hydride-halogen analogue or a borate moiety. In this latter case, no addition of base is necessary.[117] Coordination of the ketone as described above yields complex **29** and after formation of the product, ruthenium-amide **30** is obtained. Coordination of another molecule of hydrogen forms cationic species **31**. Finally, heterolytic cleavage of the H-H bond regenerates **28**. Calculations have shown that this cleavage is the rate-determining step.[118b]



Scheme 29. Summary of the catalytic cycle for hydrogenation of ketones by Ru-diphosphine-diamine complexes.

In many instances, modification of both the diphosphine- and the diamine part of the catalyst has been carried out with successful results. Xu et al. have reported the use of monodentate phosphonite ligands instead of bidentate phosphines.[119] Studies showed that this structure was most efficient in hydrogenations of ketones when containing an *orto*-bromophenyl substituent (**32**, Figure 12). Another interesting modification of the phosphorus substituent was carried out by Ding and coworkers who performed the hydrogenation of acetophenone using a ruthenium complex with achiral monophosphines (**33**, Figure 12).[120] With only the chiral amine to induce stereoselectivity, enantiomeric excesses above 90% were still obtained. Similar studies have been carried out using diamines which are not optically active, Ager has published the use of chiral bisphosphanes and non-stereogenic diamines or thioamines (**34**, Figure 12).[121] The work also showcased that the choice of solvent has an impact on the stereochemical outcome, with the lowest optical purities obtained in isopropanol and the highest in *n*-butanol.

Another original catalytic system is the Kitamura hybrid complexes which feature both sp^2-pyridine nitrogens and tetrahedral sp^3-nitrogens.[122] Eschewing the phosphorus component completely, these catalysts employ axially chiral diamines (**35**, Figure 12) and work excellently on a variety of substrates. β-Aminophosphines have also been used for this purpose and the Morris group have reported such systems derived from norephedrine[123] (**36**, Figure 12) and proline (**37**).[118e] A similar ligand incorporating a phosphine / oxazoline framework (**38**, Figure 12) has been showed by Naud et al. to be effective both in hydrogenations and transfer hydrogenations.[124]

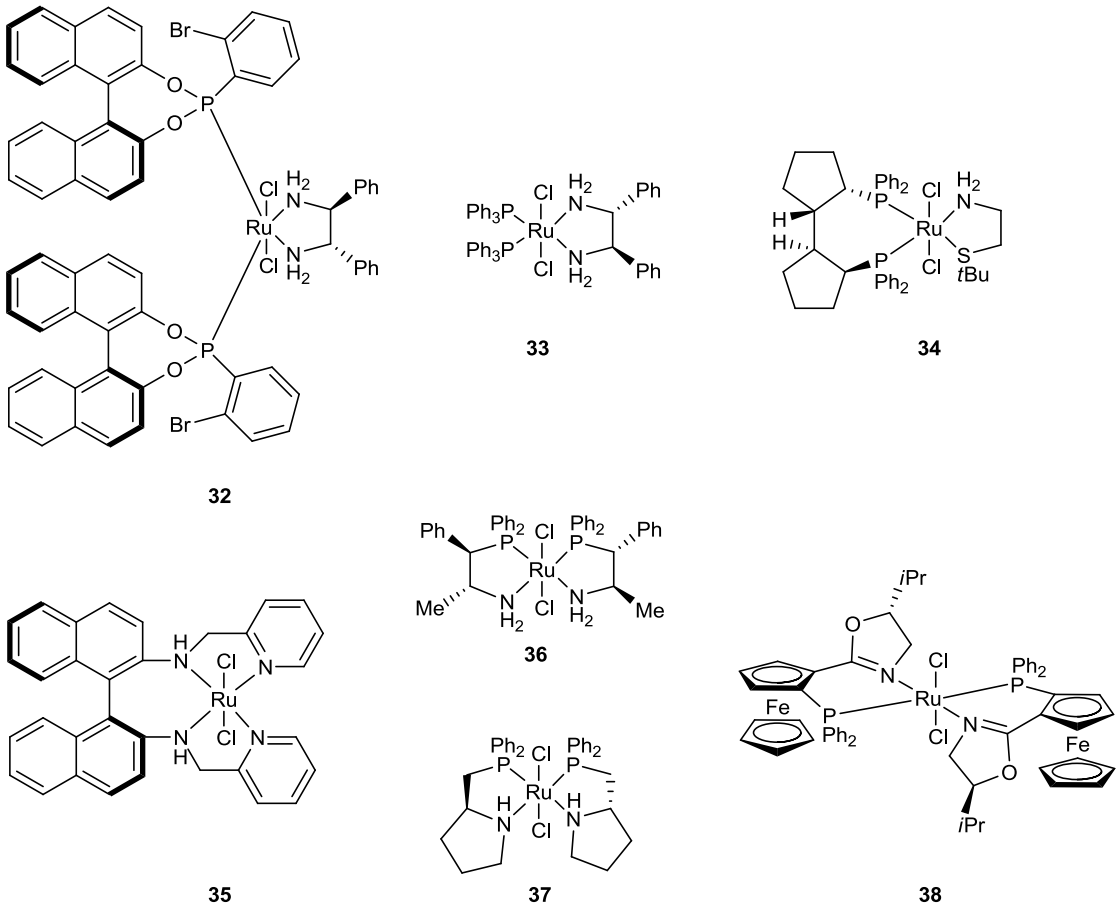
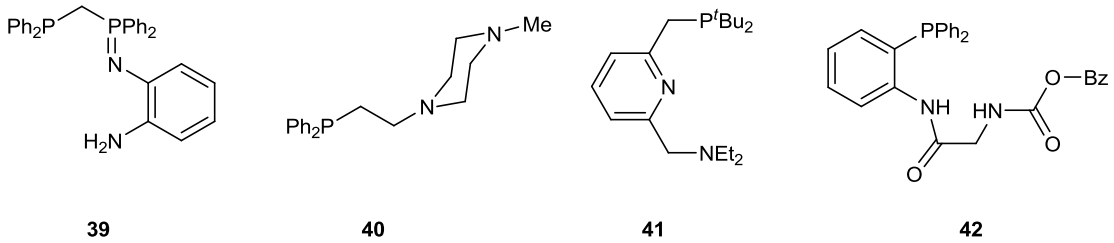


Figure 12. Other systems used for the hydrogenation of ketones.

3.1.2. Tridentate P,N,N-Ligands

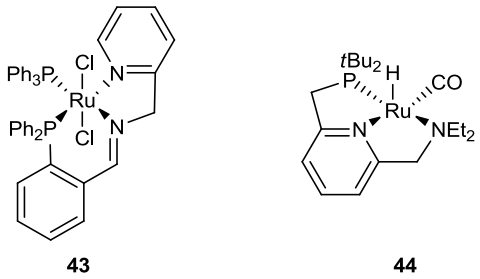
Although there are not many reports on the use of tridentate P,N,N-class ligands in catalytic systems, some late transition-metal complexes have nevertheless been published in the latter half of the past decade. Shown in Figure 13 are some ligands used for this purpose which include iminophosphorane-aminophosphines **39**,[125] phosphine-piperazines **40**,[126] phosphine-aminopyridines **41**[127] and diamidophosphines **42**.[91b]



39 **40** **41** **42**

Figure 13. Examples of P,N,N-Ligands.

Not all studies of this ligand class are focused on determining the structures of their metal chelates however. There are examples where these types of ligands have shown promise in a variety of chemical reactions (Figure 14). For instance, ruthenium complex **43** has been reported by Del Zotto et al. to catalyze the transfer hydrogenation of both aliphatic and aromatic ketones with greater than 95% yield.[128] Another exciting ruthenium complex, **44**, has been found effective in splitting water into hydrogen and oxygen, probably a quite important application for the development of renewable energy sources.[129]



43 **44**

Figure 14. P,N,N-Ruthenium complexes.

Also, tridentate P,N,N-ligands have been successfully employed in traditional carbon-carbon bond forming reactions (Figure 15). Wang has reported the use of nickel complex **45** in Kumada cross-couplings of aryl Grignard reagents and aryl chlorides.[130] Although the study also featured P,N,P- and N,N,N-ligands, the best results were obtained with mixed iminophosphorane-aminophosphines. Dixon and coworkers published the use of cinchona-derived amido-aminophosphines, **46**, in silver catalyzed isocyanoacetate aldol reactions and found that the catalyst gave high yields and enantiomeric excesses even at loadings down to 0.5 mol%.[131] It is not known how coordination to silver occurs; the authors have postulated that the sp^3 nitrogen of the cinchona backbone acts as a Brønstedt base and not as a coordinating center. Whether the ligand is tridentate or not remains to be seen. There have also been reports of P,N,N-compounds used in the oligomerization of ethylene,[110,132] as well as the polymerization of norborene.[133]

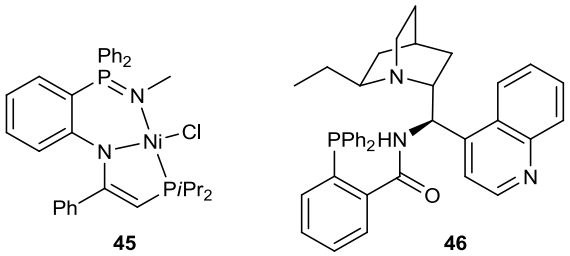
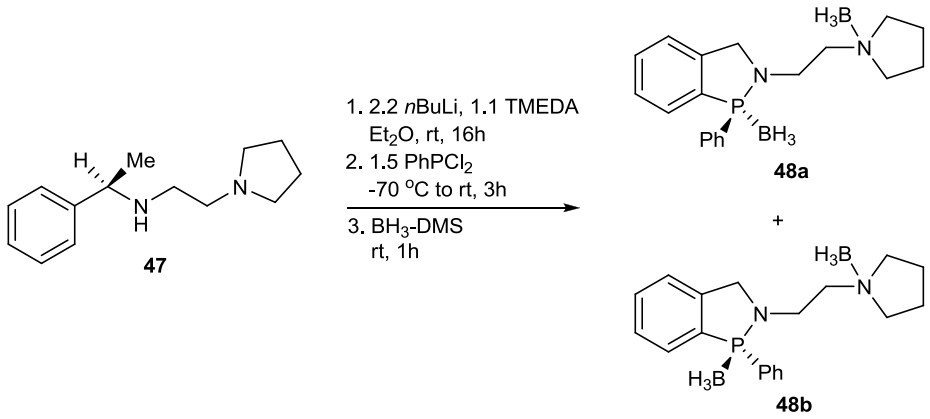


Figure 15. P,N,N-Phosphines used in carbon-carbon bond forming reactions.

Even though a variety of chemical transformations have been effected using P,N,N-ligands, P-chirogenic compounds of this type are almost unknown. One example reported in 1994 by Wills featured such a ligand in palladium catalyzed allylic substitution where it showed some promise.[134] The synthesis of the stereogenic phosphine is shown in Scheme 30 and was carried out by *ortho*-lithiation of optically pure diamine **47** and addition of dichlorophenylphosphine to yield five membered P,N-heterocyclic compound **48** in 74% yield. The 1:1 diastereomeric mixture was resolved by flash chromatography and the structure validated by X-ray analysis.



Scheme 30. Synthesis of optically pure P-chirogenic P,N,N-ligand.

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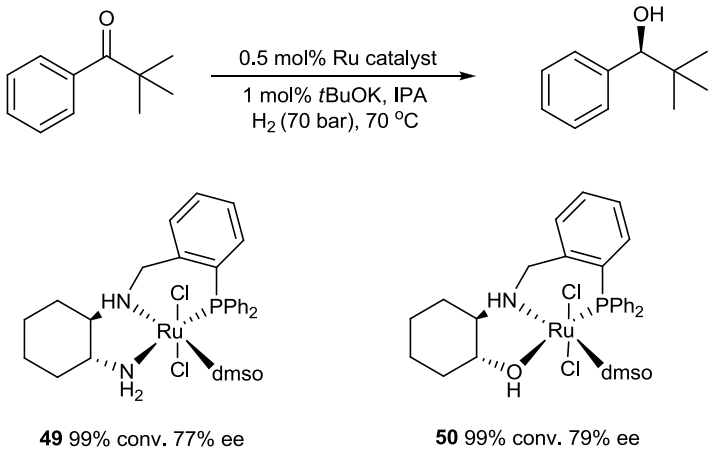
3.2. Results and Discussion

3.2.1. Synthesis of New P-Chirogenic P,N,N-Ligands

For all the work that has been carried out on improving the Noyori diphosphine-diamine hydrogenation systems there are still some substrates that remain troublesome, such as tetralones, dialkyl ketones and other, bulky ketones. The Clarke group at St Andrews have previously reported the use of P,N,N-complexes built around a diaminocyclohexane framework (Scheme 31) in the hydrogenation of bulky ketones.[135] The group has also developed analogous P,N,O-ligands and found that these are more effective for certain substrates.[136]



49 99% conv. 77% ee

50 99% conv. 79% ee

Scheme 31. Examples of the St Andrews catalytic systems.

Seeing as we had previously reported an efficient synthesis of P-chirogenic P,N-ligands,[137] we decided to initiate a collaboration with the Clarke group and pool our resources towards the design of more effective hydrogenation catalysts. We decided not to employ a "trial and error" strategy by screening ligands at random, instead we opted to design the ligands around what is currently known about the mechanism of ketone hydrogenation. As mentioned previously, an important step in the catalytic cycle is the interaction of the ketone with the protons of the diamine scaffold and the metal hydride. A kinetic study by the St Andrews group has indicated that the NH-group of the diamine seems to play a more important part than the NH_2-moiety.[136] If the substrate coordinates to the amine closest to the phosphorus, this would mean that the substituents on the ketone and the phosphine substituents would be in close proximity. Thus, if the schematic transition state in Figure 16 is accurate, the steric hindrance between spatially adjacent groups would make the production of the resultant (*R*)-enantiomer of phenethyl alcohol disfavored and thus lead to an excess of the (*S*)-enantiomer instead.

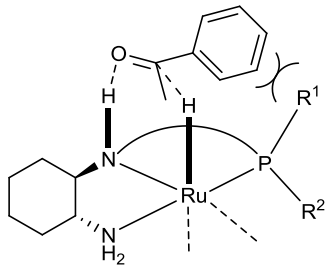
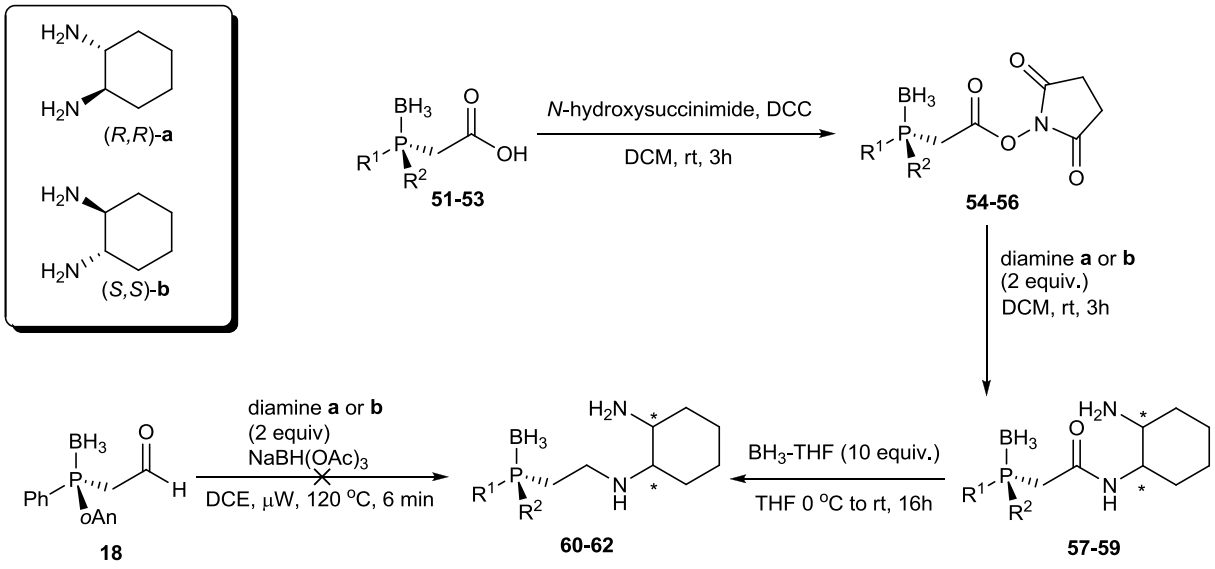


Figure 16. Possible transition state in the hydrogenation of acetophenone yielding (*R*)-1-phenylethanol. Note the disfavored steric hindrance between the ketone phenyl ring and R^1.

We thus decided to prepare a variety of P-chirogenic P,N,N-ligands based on the cyclohexyldiamine backbone with varying sterically hindered groups on the phosphorus atom. The St Andrews group would meanwhile modify their previous ligands and add bulkier substituents on phosphorus.



Scheme 32. Synthesis of P-chirogenic P,N,N-ligands.

Scheme 32 shows our efforts in this regard. We initially attempted to form the desired ligands through the microwave accelerated reductive amination of aldehyde **18**, derived from (*S*)-(+)-*o*-anisylphenylmethylphosphine borane ((*S*)-PAMP) as previously reported.[137] Disappointingly, this proved non-efficient as we only obtained a small amount of product and the result could not be reproduced. Instead, we aimed at proceeding via carboxyphosphines **51-53**. These can be produced readily in high enantiomeric excesses according to known procedures.[109,138] It was found that preparation of active esters **54-56** using *N*-hydroxysuccinimide and DCC proceeded readily at room temperature and produced the desired compounds in moderate to good yields (Table 5).

Table 5. Synthesis of P-chirogenic activated esters suitable for amide coupling.

Entry	Product	R^1	R^2	Yield (%)[a]	Ee (%)[b]
1	**54**	Ph	*o*An	84	>98
2	**55**	Ph	Me	92	90
3	**56**	Cy	Me	84	90

[a] Isolated yield. [b] Enantiomeric excess of the carboxyphosphine starting material.[109,138]

The activated esters were subsequently reacted with both enantiomers of *trans*-1,2-cyclohexyldiamine, **a** and **b**, with near quantitative yields. The final step was effected by reduction of the carbonyl group using borane. These results are summarized in Table 6. We found that the desired diaminophosphines **60-62** were difficult to purify, most likely owing to the instability of the diamine. Also, LCMS-analysis following flash chromatography showed that a mixture of adducts was present, with excess borane coordinating to both nitrogens to a varying degree. Attemps to perform the amide reduction with less than 10 equivalents of borane gave a decrease in yield of the desired products, however. As the compounds needed to be deprotected of borane prior to use as ligands, this did not present any concern vis-à-vis the actual hydrogenation. It did however complicate the NMR and elemental analysis or high resolution mass spectroscopy required for full characterization. We eventually managed to resolve this by deprotecting diarylphosphines **60a** and **60b** by gentle heating in neat diethyl amine, 3 hours at 50 °C, with subsequent chromatography of the free phosphines on neutral alumina. While this operation is feasible for electron-poor and thus, oxidation stable phosphines it is not suitable for the more electron rich compounds **61** and **62**. Therefore, only compounds **60** were included in the published paper. The results from the complete set of P-chirogenic ligands in the hydrogenation of ketones is presented here.

Table 6. Preparation of tridentate P,N,N-amides and amines with the chirality residing on phosphorus.

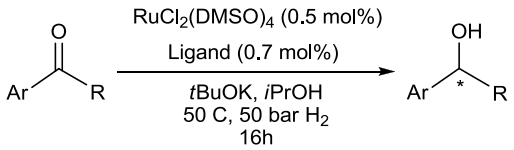
Entry	Product	R^1	R^2	Yield (%)[a]
1	**57a**	Ph	*o*An	64
2	**57b**	Ph	*o*An	68
3	**58**	Ph	Me	71
4	**58b**	Ph	Me	99
5	**59a**	Cy	Me	97
6	**59b**	Cy	Me	98
7	**60a**	Ph	*o*An	12
8	**60b**	Ph	*o*An	26
9	**61a**	Ph	Me	95[b]
10	**61b**	Ph	Me	97[b]
11	**62a**	Cy	Me	58[b]
12	**62b**	Cy	Me	63[b]

[a] Isolated yield unless otherwise indicated. [b] Crude yield.

3.2.2. Hydrogenation of Ketones Employing Ru-Catalysts and P,N,N-Ligands

The P-chirogenic P,N,N-ligands were screened by the Clarke group at St Andrews and these findings are summarized in Table 7. As stated earlier, the borane protecting group needed to be removed prior to reaction. This can be accomplished by a variety of methods,[21b,c,22-23] and the free phosphine then reacted with a suitable ruthenium precursor and isolated as the active complex. A more convenient method is to perform the deprotection *in situ* to avoid handling the free phosphine and to speed up screening.[24] It was found that by mixing the borane-preligand with $[RuCl_2(DMSO)_4]$ and an increase of base gives the same yield and enantioselectivity in the hydrogenation as when using the pre-isolated complex.

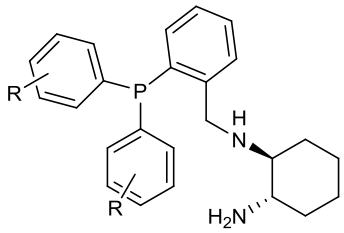
Table 7. Hydrogenation of aromatic ketones bearing various substituents employing a P-chirogenic aminophosphine-ruthenium complex.



Entry[a]	Ligand	Ar	R	Conversion (Yield) (%)[b]	Ee (%)[c]
1	**60a**	Ph	CH_3	>99 (95)	29 (*S*)
2	**60a**	Ph	$CH(CH_3)_2$	>99 (91)	2 (*S*)
3	**60a**	Ph	$C(CH_3)_3$	>99 (89)	74 (*S*)
4	**60a**	2-naphthyl	CH_3	>99	20 (+)
5	**60a**	9-anthracene	CH_3	>99	17 (-)
6	**60b**	Ph	CH_3	>99	13 (*R*)
7	**60b**	Ph	$CH(CH_3)_2$	>99	9 (*S*)
8	**60b**	Ph	$C(CH_3)_3$	>99	67 (*R*)
9	**60b**	2-naphthyl	CH_3	>99	33 (-)
10	**60b**	9-anthracene	CH_3	>99	36 (-)
11[d]	**61a**	Ph	CH_3	>99	17 (*S*)
12[d]	**61a**	Ph	$C(CH_3)_3$	>99	11 (*R*)
13[d]	**61a**	2-napththyl	CH_3	12	0
14[d]	**61b**	Ph	CH_3	>99	16 (*R*)
15[d]	**61b**	Ph	$C(CH_3)_3$	35	11 (*R*)
16[d]	**62a**	Ph	CH_3	>99	5 (*S*)
17[d]	**62a**	Ph	$C(CH_3)_3$	>99	64 (*S*)
18[d]	**62a**	2-napththyl	CH_3	2	0
19[d]	**62b**	Ph	CH_3	73	33 (*R*)
20[d]	**62b**	Ph	$C(CH_3)_3$	11	42 (*S*)
21[d]	**62b**	2-napththyl	CH_3	6	0

[a] Unless otherwise indicated, reactions were carried out using 0.33 mmol mL^{-1} of ketone, 0.5 mol% $RuCl_2(DMSO)_4$, 0.7 mol% ligand at 50 °C and 50 bar of hydrogen pressure with a 16 h reaction time using *t*BuOK as base. Ligand and $RuCl_2(DMSO)_4$ were stirred together in solution for 1 h before addition of base and ketone. [b] Conversions were determined by ^1H NMR analysis of the crude reaction mixtures (all peaks assigned). [c] The ee value was determined by chiral HPLC. The absolute configuration was determined by comparison of optical rotation values with literature values where available. [d] 70 °C.

Generally, the ligands gave quite high conversions, the main exception occurring for 2-naphthyl substituted ketones with phenyl/methyl or cyclohexyl/methyl substituted phosphines (entries 13, 18 and 21) and for catalyst **62b** (entries 19-21). The highest stereoselectivity was obtained when using **60** (entries 3 and 8) together with a bulky *tert*-butyl ketone. Interestingly, changing the chirality of the diamine gave the opposite configuration of the product here. However, this trend could not be seen for the more sterically demanding cyclohexylphosphine **62** (entries 17 and 20). This seems to indicate that the chirality of the amine backbone is more important to the stereochemical outcome of the hydrogenation when the substituents on phosphorus are two relatively flat, aromatic moieties as compared to the larger cyclohexyl group.



(*R*,*R*)-**63** R = H
(*R*,*R*)-**64** R = 4-Cl
(*R*,*R*)-**65** R = 4-OMe
(*R*,*R*)-**66** R = 3,5-di-Me
(*R*,*R*)-**67** R = 3,5-di-*t*Bu

Figure 17. Non-P-chiral tridentate ligands prepared by the Clarke group at St Andrews. See Paper II for details on the preparation of these compounds.

Presented in Table 8 is the performance of **60** and the new, bulkier St Andrews P,N,N-ligands (**64-67**, Figure 17) in the hydrogenation of acetophenone and 1,1'-dimethyl propiophenone. As can be seen, the highest enantiomeric excesses came from the use of the quite bulky ligand **67** (entries 14 and 11) although the conversions were lower in this case. We were pleased to find that all of these new ligands gave selectivity in the hydrogenation of acetophenone, in contrast to the previous St Andrews catalyst (entry 5). Also, in all cases save for those mentioned previously regarding **60b** (entries 3 and 4), the expected (*S*)-selectivity as predicted in Figure 16 was produced. This gives further credence to this hypothesis regarding the mechanism of hydride transfer to the substrate. It also showcases how rational catalyst design has significantly improved a completely unselective system. The use of more sterically demanding substituents on the coordinating phosphorus atom leads to an increase in enantiomeric excess from 0% to 85% as the substrate strives to minimize spatial conflict with the P-aryl groups. It should be mentioned that simultaneously with the completion of our study, Zhou also reported highly efficient P,N,N-ligands for the hydrogenation of ketones.[139]

Table 8. Hydrogenation of acetophenone (R = CH_3) and 1,1'-dimethyl propiophenone (R = $C(CH_3)_3$) with new ruthenium complexes employing chiral tridentate P,N,N-ligands.

Entry[a]	Ligand	Ketone R =	Conversion (%)[b]	Ee (%)[c]
1	(*R*,*R*)(*S*$_P$)-**60a**	CH_3	>99	29 (*S*)
2	(*R*,*R*)(*S*$_P$)-**60a**	$C(CH_3)_3$	>99	74 (*S*)
3	(*S*,*S*)(*S*$_P$)-**60b**	CH_3	>99	13 (*R*)
4	(*S*,*S*)(*S*$_P$)-**60b**	$C(CH_3)_3$	>99	67 (*R*)
5[d]	(*R*,*R*)-**63**	CH_3	>99	0
6[d]	(*R*,*R*)-**63**	$C(CH_3)_3$	>99	74 (*S*)
7[e]	(*R*,*R*)-**63**	$C(CH_3)_3$	>99	74 (*S*)
8	(*R*,*R*)-**66**	CH_3	>99	35 (*S*)
9	(*R*,*R*)-**66**	$C(CH_3)_3$	>99	77 (*S*)
10	(*R*,*R*)-**67**	CH_3	24	56 (*S*)
11[f]	(*R*,*R*)-**67**	CH_3	84	60 (*S*)
12[g]	(*R*,*R*)-**67**	CH_3	>99	58 (*S*)
13	(*R*,*R*)-**67**	$C(CH_3)_3$	5	83 (*S*)
14[h]	(*R*,*R*)-**67**	$C(CH_3)_3$	21	85 (*S*)

[a] Unless otherwise indicated, reactions were carried out using 0.33 mmol mL^{-1} of ketone, 0.5 mol% $[RuCl_2(DMSO)_4]$, 0.7 mol% protected ligand and 1 mol% *t*BuOK, at 50°C and 50 bar of hydrogen pressure with a 16 h reaction time. [b] Conversions were determined by ^1H NMR analysis of the crude reaction mixtures (all peaks could be assigned). [c] see experimental for ee determinations and configurations. [d] Using preformed catalyst Conditions: 0.33 mmol mL^{-1} ketone, 0.5 mol% catalyst, 1 mol% KO*t*Bu, *i*PrOH, H_2 (50 bar), 50°C, 16 h. [e] 0.5 mol% $[RuCl_2(DMSO)_4]$, 0.7 mol% original PPh_2 ligand converted to BH_3 adduct and 1 mol% *t*BuOK. [f] 70 °C. [g] 70 °C, 24h. [h] 90°C

3.2.3. Conclusion

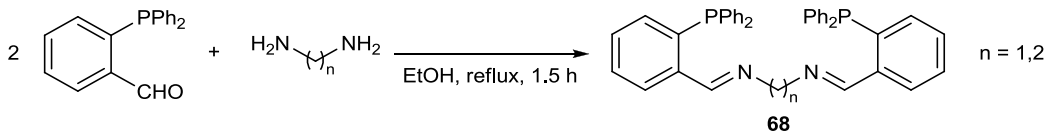
In summary, we have reported the synthesis of new chiral P,N,N-tridentate ligands with both stereogenic and non-stereogenic phosphorus and shown that they are viable for ruthenium-catalyzed hydrogenation of ketones. Through consideration of the structure of the diaminophosphines we have managed to tune a previous, completely unselective catalyst to show a high degree of stereoselectivity in the hydrogenation of acetophenone. Although new catalysts for the production of phenylethyl alcohol may appear as somewhat superfluous, we are confident that this ligand class and the approach employed in their design make them a highly interesting target for further study.

4. Modular Synthesis of P-chirogenic Multidentate Mixed P,N-Ligands (Paper III).

4.1. Introduction

4.1.1. Examples of Already Known P,N,N,P-Ligands and Complexes.

Tetradentate chiral P,N,N,P-ligands are interesting in transition metal catalysis because their rigidity and steric bulk creates a chiral pocket around the metal center and therefore limits the possible orientation of an incoming substrate.[140] This would transfer into a high degree of both regio- and stereoselective control. One of the first P,N,N,P-compounds and their corresponding copper complexes were reported by Rauchfuss in 1980.[141] Prepared by condensation of the precursor phosphine aldehyde with aliphatic diamines (Scheme 33), this initial publication heralded what is one of the most widely studied class of P_2N_2-ligands, namely those featuring a diimino functionality.



Scheme 33. The first reported synthesis of a P,N,N,P-ligand,

The usefulness of tetradentate P,N,N,P-ligands (Figure 18) was demonstrated by Noyori in 1998 with the publication of an efficient ruthenium catalyst for the transfer hydrogenation of ketones, **69**.[142] It was found that the diamine complex was much more efficient in this regard than its diimino counterpart **70**. As has been discussed previously in this thesis, the capability of the protons on transition metal coordinated amines to "direct" approaching carbonyl groups is very important for reactivity.[ii] Nevertheless, ligands incorporating a diimino moiety have found a firm foundation in a variety of catalytic transformations, including asymmetric epoxidation (**70**, **71**), asymmetric cyclopropanation (**70**, **72**), fluorination (**70**) and heteroatom transfer reactions (**70**).[143] More recent applications where complex **70** was employed are Michael additions,[144] imine aziridination,[145] Diels-Alder reactions,[146] and [2+2]-cycloadditions.[147] An interesting effect of the chain length between the chelating atoms was shown by Feringa in the synthesis of similar ligands **73** and **74**.[148] It was found that for **73**, where the imine-phosphine linker consists of three carbon atoms, mononuclear complexes were formed with palladium. For **74** however, the two carbon bridge rather induced binuclear palladium systems.

[ii] See Paper II for details.

It should be mentioned that reduced, diamine analogues of **69** have been synthesized and studied extensively by Gao et al.[149] These sp^3-nitrogen containing ligands are efficient transfer hydrogenation catalysts, and are also known for rhodium and iridium transition metal complexes.[150] Aminophosphine analogues are also known for type **74**, two carbon linker ligands. Examples here include early cobalt complexes such as those by Fujita[151] and Andersen.[152] Also, Willis has reported binuclear P,N,N,P-palladium complexes of this type exhibiting cytotoxic activity towards leukemia.[153]

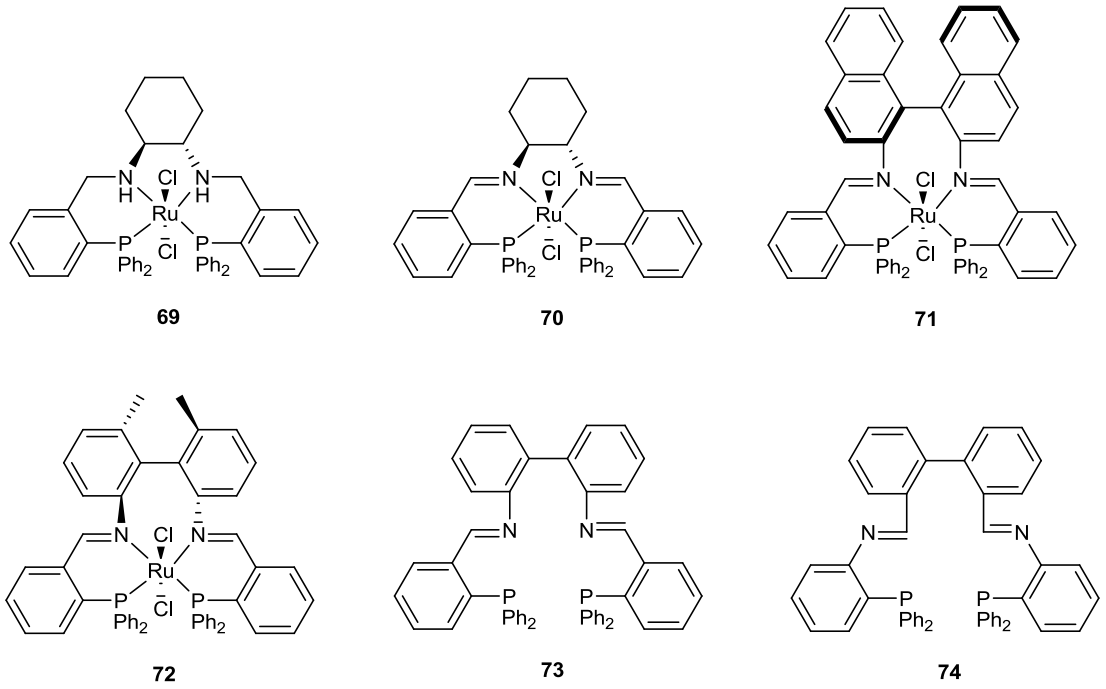


Figure 18. P,N,N,P-Ruthenium complexes and free ligands.

Similar ligands have also found their way into the expanding field of iron catalysis (Figure 19). Seeing as iron is much cheaper than ruthenium and many other transition metals, successful application of tetradentate P,N,N,P-compounds in this area makes them even more interesting for future study. The Morris group reported a template synthesis of a variety of iron complexes utilizing different diamines and phosphonium salts as starting materials.[154] In a later study it was found that these catalysts worked in transfer hydrogenations of ketones, despite not having the amine protons which appears to be more critical to ruthenium based systems.[142,155] Catalyst **75** gave 72% conversion and 35% enantiomeric excess in the transfer hydrogenation of acetophenone, while **76** managed 99% conversion and 60% stereoselectivity. Further studies have managed to improve the enantiomeric purity to 84% for acetophenone with **76** and up to 99% on other substrates.[156] The use of P,N,N,P-iron complexes in carbon dioxide reduction has also been examined by Chen et al.[157]

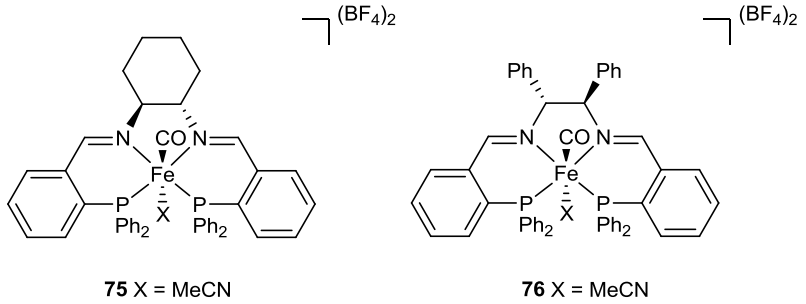
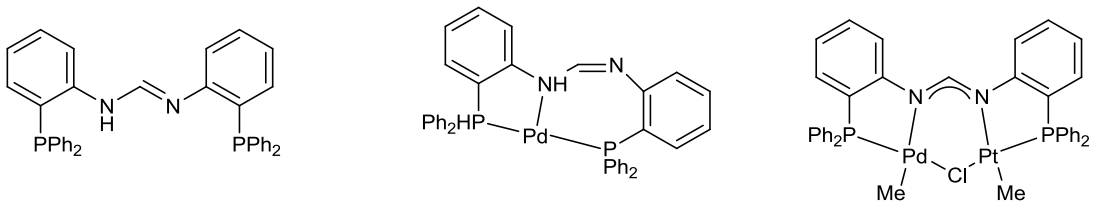


Figure 19. Iron complexes featuring P,N,N,P-ligands.

Another noteworthy P,N,N,P-compound was prepared by Inoue in 2003. Here, **77** also called Hdpfam, features both imine and amine functionalities in close proximity.[158] This fact makes it possible for the ligand to form bimetallic complexes, but it can do so in a sequential manner. It is therefore possible to introduce first one transition metal and then a different one, forming heterobimetallic systems (Figure 20). Both homo- and heterobimetallic catalysts were successfully applied in the double carbonylation of iodobenzene with triethylamine and have been examined in other organic transformations since.[159] Son et al. have recently expanded the study to other transition metals and to trinuclear complexes.[160]



Hdpfam **77** **78** **79**

Figure 20. Hdpfam and examples of its mono- and dinuclear complexes.

Ligands that are structurally similar to those mentioned previously but foregoing the imine or amine functionality in place of amide groups were prepared by Trost in 1992 (Figure 21).[161] This was done by performing amide couplings of 2-(diphenylphosphino)benzoic acid with a variety of diamines. This new ligand class was then shown to be efficient in palladium catalyzed alkylations. Today, this ligand family is popularly called "Trost Modular Ligands" of which the most well-known is arguably the "DACH-Phenyl Trost Ligand", **80**.

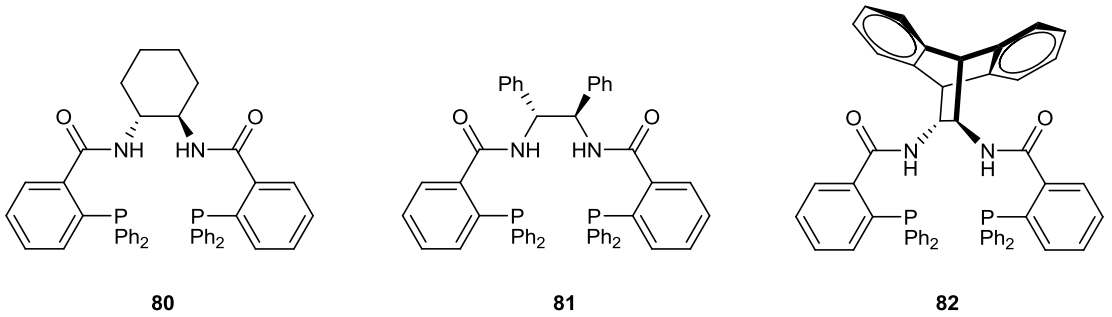


Figure 21. Examples of early Trost Ligands.

In fact, compound **80** has shown to be a remarkably general ligand for various stereoselective allylation reactions (Figure 22), even on substrates that are troublesome with other systems, and also, with a variety of nucleophiles.[162] As such, it comes as no surprise that **80** has been the focus of many studies aiming at providing a rationale for its high reactivity and selectivity. It is generally thought that the four phosphorus phenyl rings aid with the stereochemical induction, with two of the rings acting as "walls" and blocking one face of the substrate from the nucleophile. The other two phenyl groups are "flaps" and oriented at a wider angle out from the metal which facilitates attack from this face.[163] The ligand tends to coordinate to palladium as P,P-monomeric or oligomeric complexes.[164] Under typical reaction conditions the amide group is not involved in coordination, however, recent structural and computational studies have shown that hydrogen bonding between an amide proton and the nucleophile have an accelerating effect.[165]

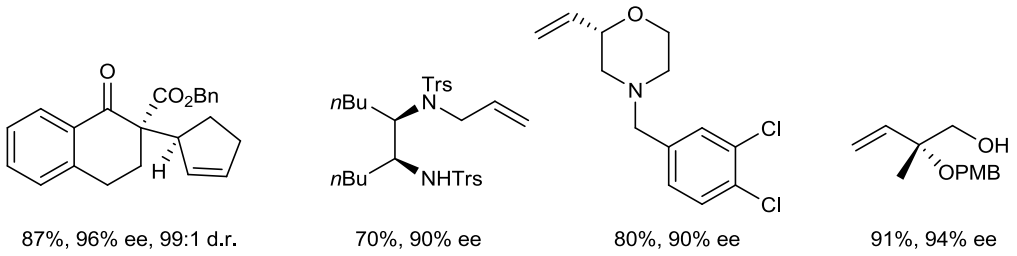
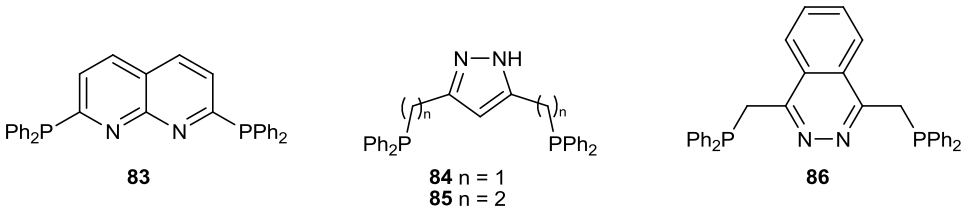


Figure 22. Examples of products obtained through palladium catalyzed asymmetric allylic alkylations using the"Standard Trost Ligand", **80** (see reference 162 for details).

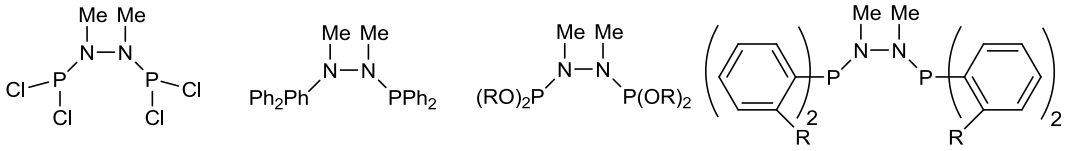
P,N,N,P-compounds can also be built around a framework where the two nitrogen atoms are part of the same aromatic system (Figure 23). Such an instance was reported by Ziessel, were a naphthyridine backbone was used and ligand **83** formed P,P-coordinated bimetallic complexes with rhodium.[166] Other metals that have been employed together with **83** include molybdenum,[167] silver and gold.[168] Utilization of a pyrazole aromatic moiety in a similar compound (**84**) has been published by Bosnich.[169] The Akita group have subsequently further examined **84** and its derivatives **85** and **86** in chelation to rhodium carbonyl complexes.[170]



83 **84** n = 1 **85** n = 2 **86**

Figure 23. P,N,N,P-ligands incorporating two nitrogen donors in the same aromatic system.

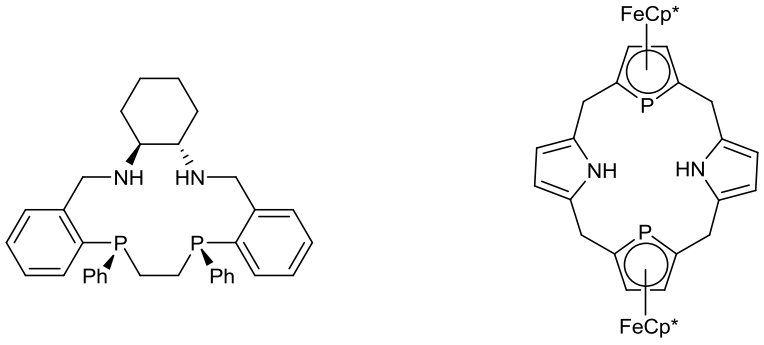
Also of interest are ligands which share the N-N bond of the above ligands, but without the heterocyclic aromatic system (Figure 24). Compounds of such structure has been known since the early 1970's,[171] but relatively little work was done in the area until the 1990's. At that time, Reddy et al. reported an easily applicable preparation of tetrachlorodiphosphines **87** and their associated palladium and platinum complexes.[172] In later work, the halides were displaced to give **88** and similar phosphonites, **89**.[173] A more recent synthesis of this ligand type is the preparation of **90,** which has been applied in the oligomerization of olefins and dienes.[174]



87 **88** **89** **90**

Figure 24. Hydrazine derived diphosphines.

The final class of ligands that should be mentioned is the P_2N_2-macrocycles. A variety of such compounds have been prepared by means of template synthesis[175] and lithiation.[176] These ligands have the possibility to be stereogenic at phosphorus, in those examples mentioned however, the desired products were all isolated in their *meso*-forms. Mezzetti has attempted to rectify this by taking a *meso*-diformylphosphine and combining it with optically pure diaminocyclohexane.[177] By the virtue of the carbon-centered chirality of the diamine the resulting ligand **91**, is enantiomerically pure and the first example of such a compound. Another, recent example of a P,N-macrocycle is the calixpyrrole analogue prepared by the Mathey group (**92**).[178]



91 **92**

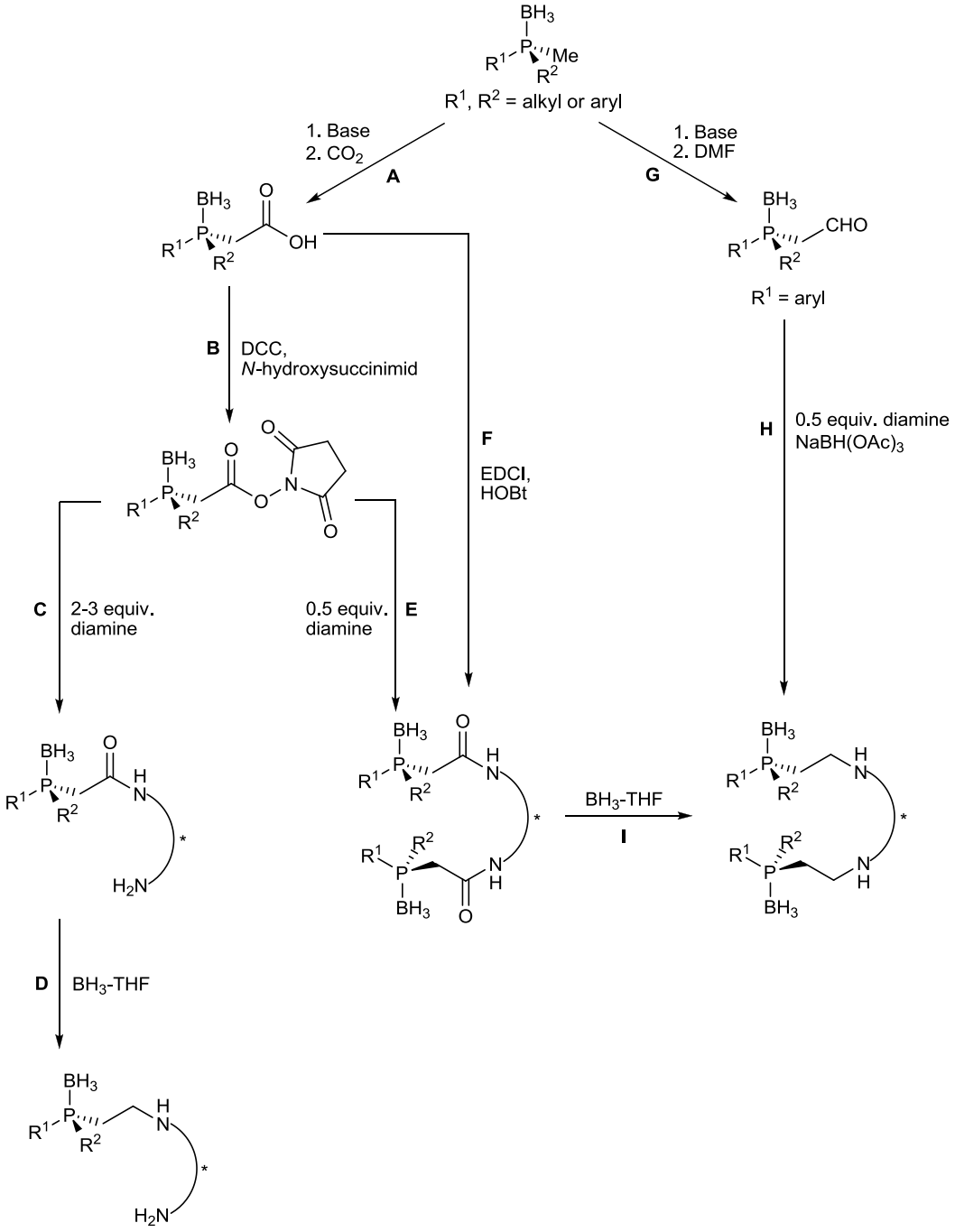
Figure 25. Two examples of P,N,N,P-macrocyclic compounds.

4.2. Results and Discussion

4.2.1. Synthesis of P-chirogenic P,N,N-Ligands

There is a definitive scarcity of P,N,N,P-compounds with optically pure phosphorus. The Mezzetti group's macrocyclic ligand is one,[177] and there has been a synthesis of a N,P,P,N-aminophosphine with P-chirality published by Willis.[153] In this instance though, the ligand was separated from its *meso*-isomer and isolated as a racemate. Seeing as we recently have published a protocol for the preparation of P-chirogenic β-aminophosphines[137] and also for tridentate P,N,N-ligands,[179] it occurred to us that we had the tools necessary for the preparation of P,N,N,P-species with the chirality residing on phosphorus.[iii] By extending our methodology to this kind of multidentate systems we could produce ethyl-bridged phosphorus-nitrogen frameworks featuring either amide or amine functionalities. We envisioned that such ligands would be interesting to study not only as components in transition metal catalyzed reactions, but also as metal complexes since they may have the ability to coordinate in a multitude of ways.

[iii] See Paper I and Paper II for details.



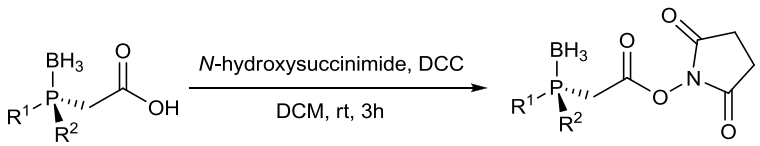
Scheme 34. The modular synthetic routes to P-chirogenic P,N,N- and P,N,N,P-ligands.

Scheme 34 shows an overview of our planned approach to this sort of novel ligands. The starting point is either a prochiral or chiral phosphine borane with at least one methyl substituent. By deprotonation with a chiral,[55] or non-chiral, base and quenching of the lithiated species with either carbon dioxide (route **A**),[109,138] or *N*,*N*-dimethylformamide[137] (route **G**), carboxy- or formylphosphine intermediates can be produced in a stereoselective manner. Through amide

coupling (path **B**-**F**) or reductive amination (step **H**) the desired P,N,N / P,N,N,P-compounds can be produced as either amido- or aminophosphines with a variety of different amines.

As such, we prepared the activated esters of a variety of carboxyphosphines, shown in Table 9. Reaction of the acid with DCC and N-hydroxysuccinimide in DCM for three hours gave good yields in most cases, except for when a naphthyl substituent was present (entry 4). The enantiomeric purity was consistently high. For **54**, **96** and **98** the chirality of the starting material was introduced through the Jugé / Genêt ephedrine methodology which is well known for the high degree of optical purity it induces.[106b,180] For **55**, **56** and **97** this was instead accomplished via the Evans asymmetric deprotonation of prochiral dimethylphosphine boranes.[55]

Table 9. Preparation of active esters suitable for amide couplings (Step **B**).



51-53, 93-95 **54-56, 96-98**

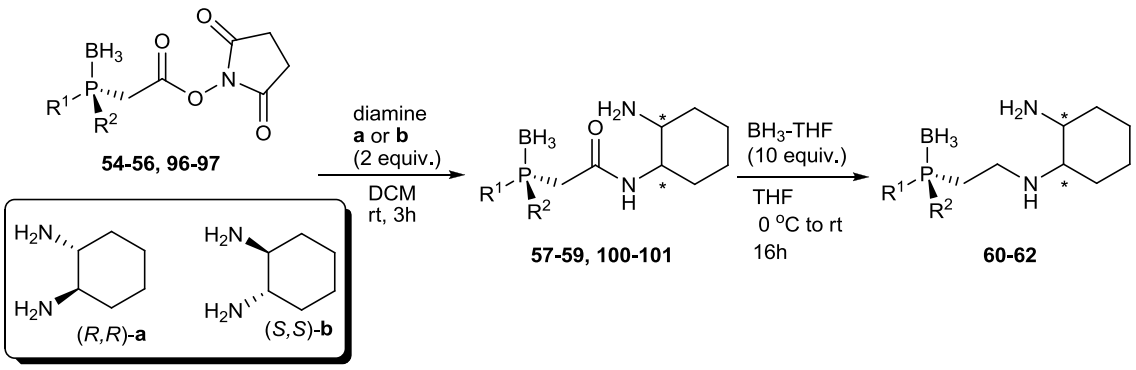
Entry	Substrate	Product	R^1	R^2	Yield (%)[a]	Ee (%)[b]
1	**51**	**54**	Ph	*o*An	84	>98
2	**52**	**55**	Ph	Me	92	90
3	**53**	**56**	Cy	Me	84	90
4	**93**	**96**	Ph	2-naphtyl	66	>98
5	**94**	**97**	*t*Bu	Me	85	94
6	**95**	**98**	4-biphenyl	Me	99	>98

[a] Isolated yield. [b] Enantiomeric excess of the carboxyphosphine starting material.[109,138]

With the activated substrates on hand we next set out to perform the synthesis of P,N,N-compounds with cyclohexyldiamine backbones. The desired functionality here was the pure P,N,N-diamine as these ligands would be used in collaboration with the Clarke group at St Andrews to study the hydrogenation of ketones with ruthenium systems.[iv] Nonetheless, it occurred to us that the corresponding mixed amide-amine phosphines could also be used as ligands in the future.

[iv] See Paper II for details.

Table 10. Coupling of activated phosphine esters to yield P-chirogenic P,N,N-amido and amino ligands (Steps **C**-**D**).



Entry	Product	Diamine	R^1	R^2	Yield (%)[a]
1	**57a**	(*R*,*R*)-**a**	Ph	*o*An	84
2	**57b**	(*S*,*S*)-**b**	Ph	*o*An	78
3	**58a**	(*R*,*R*)-**a**	Ph	Me	71
4	**58b**	(*S*,*S*)-**b**	Ph	Me	99
5	**59a**	(*R*,*R*)-**a**	Cy	Me	97
6	**59b**	(*S*,*S*)-**b**	Cy	Me	98
7	**99a**	(*R*,*R*)-**a**	Ph	2-naphthyl	39
8	**99b**	(*S*,*S*)-**b**	Ph	2-naphthyl	31
9	**100a**	(*R*,*R*)-**a**	*t*Bu	Me	55
10	**100b**	(*S*,*S*)-**b**	*t*Bu	Me	30
11	**60a**	(*R*,*R*)-**a**	Ph	*o*An	12
12	**60b**	(*S*,*S*)-**b**	Ph	*o*An	26
13	**61a**	(*R*,*R*)-**a**	Ph	Me	95[b]
14	**61b**	(*S*,*S*)-**b**	Ph	Me	97[b]
15	**62a**	(*R*,*R*)-**a**	Cy	Me	58[b]
16	**62b**	(*S*,*S*)-**b**	Cy	Me	63[b]

[a] Isolated yield unless otherwise indicated. [b] Crude yield.

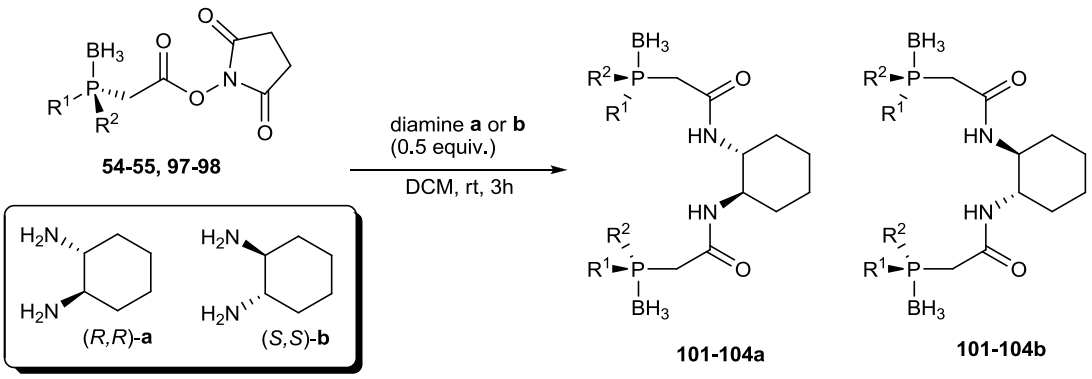
The amide coupling of the activated esters and the subsequent reduction of the amides using borane is shown in Table 10. To avoid disubstitution, 2 equivalents of either enantiomer of *trans*-1,2-diaminocyclohexyl was used and after three hours in DCM the desired amides **57-59** and **99-100** were obtained. The yields were generally high (entries 1-6) except for the naphthyl substituted derivatives (entries 7-10). It is worth mentioning that these substrates were consistently cantankerous, from the preparation of the precursor methylphosphine borane and the carboxylation thereof, to the amide coupling. As an implication of this, these amides were not reduced to their amine form due to the small amount of substrate available. However, **57-59** were reduced using borane-THF for sixteen hours and yielded the desired products. We did find that the P,N,N-amines are difficult to purify, most likely due to instability of the diamine. Furthermore, a mixture of products that have borane coordinated in varying degrees to the

nitrogen atoms is obtained due to the large excess of borane required to fully perform the reduction of the carbonyl functionality. Therefore only diaryl substituted phosphines **60** were isolated (entries 11-12). This was accomplished by removing all borane groups completely using diethylamine and then purifying the free phosphines on neutral alumina using flash chromatography. Of course, this opens up the phosphorus site for oxidation by molecular oxygen. While we found that the relatively electron poor ligands **60** are fairly stable towards air, we did not attempt this on the more electron rich compounds **61-62**.

It should also be mentioned that we originally attempted the synthesis of P-chirogenic P,N,N-amines using the conditions of step **H**, that is to say, by direct reductive amination of a phosphine aldehyde using *trans*-1,2-diaminocyclohexane and sodium triacetoxyborohydride as the reducing agent. Seeing that this pathway would be shorter, it was considered as the ideal option. Unfortunately, we only obtained a small amount of product and we did not manage to reproduce the results. Hence, the route via the amidophosphine was elected instead.

4.2.2. Preparation of P-chirogenic P,N,N,P-Ligands

Table 11. Synthesis of P-chirogenic P,N,N,P-ligands with a cyclohexyldiamine backbone (Step **E**).

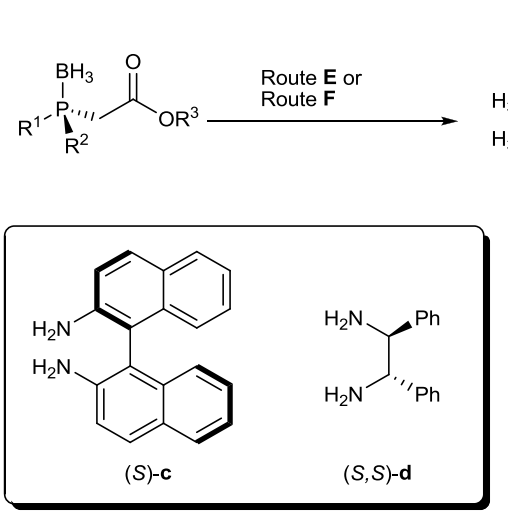


Entry	Product	Diamine	R^1	R^2	Yield (%)[a]
1	**101a**	(*R*,*R*)-**a**	Ph	*o*An	84
2	**101b**	(*S*,*S*)-**b**	Ph	*o*An	78
3	**102a**	(*R*,*R*)-**a**	Ph	Me	59
4	**102b**	(*S*,*S*)-**b**	Ph	Me	56
5	**103a**	(*R*,*R*)-**a**	*t*Bu	Me	99
6	**103b**	(*S*,*S*)-**b**	*t*Bu	Me	53
7	**104**	(*R*,*R*)-**a**	4-biphenyl	Me	82

[a] Isolated yield.

We next moved on to the synthesis of analogous P,N,N,P-ligands with a diaminocyclohexyl backbone (Table 11). The procedure is identical to that discussed in Table 10 with the exception that the amount of diamine was lowered to 0.5 equivalents. The desired products were obtained with a favorable result and proved amenable to isolation using standard chromatographic techniques. The yields were generally good although the phenyl-methyl substituted activated ester **55** gave a somewhat more modest outcome (entries 3-4). We also found that the yield was markedly lower for one of the diastereomers of *tert*-butyl substituted phosphine **103** (entries 5-6), indicating a match / mismatch relationship for this bulkier group.

Table 12. Preparation of P-chirogenic P,N,N,P-ligands incorporating C_2-symmetric diamines.

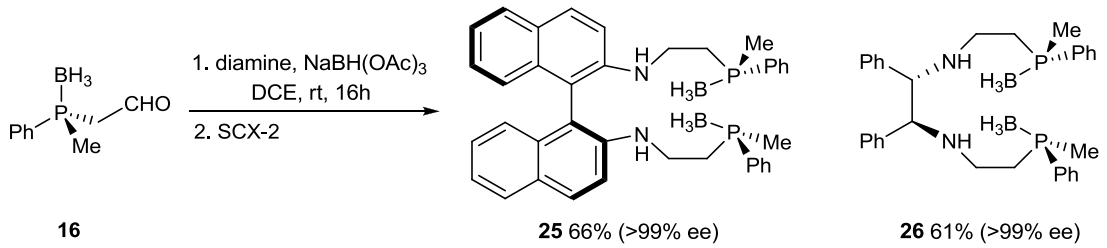


Entry	Product	Diamine	R^1	R^2	R^3	Route[a]	Yield (%)[b]
1	**105**	(*S*)-**c**	*t*Bu	Me	*N*-succinimide	**E**	51
2	**106**	(*S*)-**c**	Cy	Me	*N*-succinimide	**E**	92
3	**107**	(*S,S*)-**d**	*t*Bu	Me	H	**F**	47
4	**108**	(*S,S*)-**d**	Cy	Me	H	**F**	63

[a] Route **E**: 0.5 equiv. diamine **c** or **d**, DCM r.t. 16h. Route **F**: 0.5 equiv. diamine **c** or **d**, EDCI, HOBt, DCM r.t. 16h.
[b] Isolated yield.

We also prepared P,N,N,P-compounds of this type with other C_2-symmetric amine backbones. As shown in Table 12 the use of (*R*)-1,1'-binaphtyl-2,2'-diamine, (*R*)-**c**, and (*S,S*)-1,2-diphenylethane-1,2-diamine, (*S,S*)-**d**, was also successful. Chronologically, the syntheses of some of these amidophosphines were carried out prior to that of the cyclohexyldiamine compounds (entries 3-4). In these instances, the reaction was performed using the method we used in our publication of P-chirogenic β-aminophosphines, i.e. with coupling of the carboxylic acid and the amines together with EDCI and HOBt (step **F**).[137] As can be seen from Table 12 this clearly works, although the yields were rather modest. When starting from the activated ester however (step **E**), the yields were much higher. Even though an extra step is required to

introduce the *N*-hydroxysuccinimide leaving group with subsequent purification and isolation, the overall yield is still higher.



16 **25** 66% (>99% ee) **26** 61% (>99% ee)

Scheme 35. Direct preparation of P-chirogenic P,N,N,P-aminophosphines through reductive amination (Step **H**, See Paper I for further details).

As has been discussed in Paper I, we have prepared P,N,N,P-aminophosphines **25** and **26** by reductive amination of phosphine aldehyde **25**. This protocol is reproduced in Scheme 35 as it is clearly relevant to the results mentioned in this section. By using sodium triacetoxyborohydride with the aldehyde and diamine and stirring for sixteen hours in DCM at room temperature (step **H**) the target products were achieved in respectable yields and excellent enantiomeric purity. However as has been previously stated, the production of phosphine-aldehydes has some inherent limitations, namely, that when using an electron-rich phosphine the product is not stable. We envision that this can be overcome through the use of pathway **I**. By preparing the corresponding amidophosphines and then reducing them using borane, ligands like **25** and **26** are likely to be obtainable for a great many different phosphorus substituents.

4.2.3. Conclusion

In summary, we have developed a robust methodology which is modular in nature and allows for the synthesis of a large variety of P-chirogenic P,N,N- and P,N,N,P-ligands. We have showed that the protocol is valid for different C_2-symmetric diamines and that the products can incorporate both amide and amine functionalities. The different pathways tend to give respectable yields and high to very high enantiomeric purity of the phosphorus center. What is more, the use of well-established chemical transformations such as amide couplings and reductive amination, of which there are many variations available, make it possible to accommodate even difficult substrates. Also, the starting materials can be prepared with a variety of substituents on the phosphorus atom through well-known methods, which allows for variation of steric and electronic properties, making this a truly modular synthesis.
These types of P-chirogenic, ethyl bridged, mixed P,N-ligands are not well known. It is our hope that our efforts will provide the first steps into the area and further investigation into these compounds is underway in our laboratory.

5. P-chirogenic Phosphines as Organocatalysts in [3+2]-Cycloadditions (Paper IV)

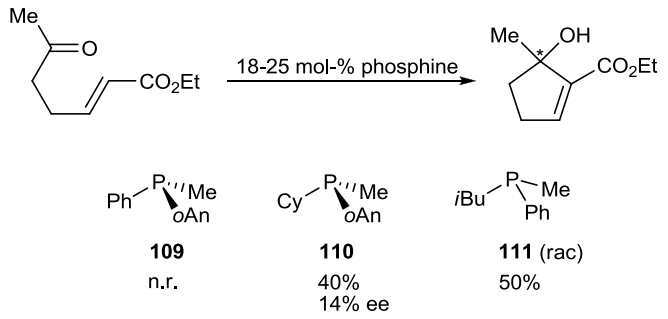
5.1. Introduction

5.1.1. Examples of P-chirogenic and Axially Chiral Organocatalysts

The term ”organocatalysis” was coined by McMillan in 2000 although the actual process is much older. The first reported instance of an organocatalytic reaction was in 1860 when von Liebig oxidized cyanogens with water using acetaldehyde as the catalyst.[181] Today, the prospect of using small amounts of organic molecules to effect a transformation instead of relying on expensive and toxic transition-metal based catalysts is an appealing one. Arguably, the most interesting application within the field of organocatalysis is the possibility of performing stereoselective reactions. As such, there has been a steadily increasing amount of attention directed into this area and there is now a variety of such protocols available.[182] The earliest known example of an asymmetric organocatalytic reaction was the kinetic resolution of ammonium tartrate by *Penicillum glauca*, reported by Pasteur in the early 20th century.[183]

The most commonly used organocatalysts are nitrogen containing compounds, but there is also a range of P, S and O systems available.[184] For phosphorus based catalysts, phosphines and phosphites have lately found widespread use in several asymmetric reactions. However, similar to regular transition-metal based applications the use of P-chirogenic phosphines in this instance is very limited. Seeing as such species would have the chirality residing on the nucleophilic atom, which means that the source of optical purity would likely be very close to the reaction centre, such limitations are likely due to the inherently more difficult preparation of P-chirogenic compounds.

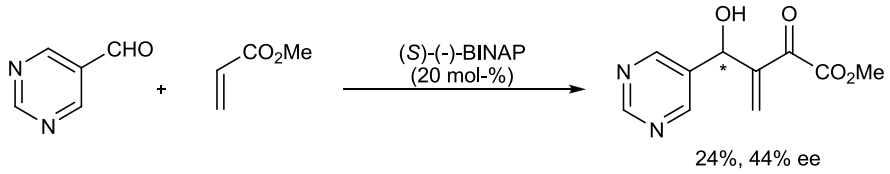
Nonetheless, there are some examples of P-chirogenic organocatalysts. In 1992, Roth et al. employed PAMP-derived phosphines in the asymmetric Morita-Bayliss-Hillman (MBH) reaction. The MBH-reaction involves the addition of a carbonyl compound to a α,β-unsaturated electron withdrawing group. In the Roth example, the addition was performed in an intramolecular fashion to form cyclopentene derivatives (Scheme 36). While (*S*)-(-)-PAMP, **109**, did not catalyze the reaction, (*S*)-(-)-CAMP, **110** gave 14% enantiomeric excess. Using the racemic phosphine **111** meanwhile afforded 50% of the product.



Scheme 36. Early asymmetric, intramolecular Morita-Bayliss-Hillman reaction catalyzed by P-chirogenic phosphines.

Further work on the MBH-reaction was done by the Soai group.[185] The group managed to achieve 24% yield and 44% enantioselectivity through the use of axially chiral (*S*)-(-)-BINAP in the intermolecular addition of pyrimidine-5-carbaldehyde to methacrylate, as shown in Scheme 37. It is worth noting that in these early examples, the catalyst loading was relatively high (20 mol%) for fairly modest yields.

Structurally similar, but non P-chirogenic, axially chiral phosphoramidites have been used as organocatalysts in the stereoselective reduction of carbonyl compounds with borane.[186] Further, this is a rare example of a reaction where increased temperature benefits the stereoselectivity (80% at room temperature vs. 96% at 50 °C). Examples of other similar catalytic scaffolds include BINOL derived phosphoric acids for Pictet-Spengler reactions,[187] 1,3-dipolar cycloadditions,[188] and Aza-Darzens reactions.[189]

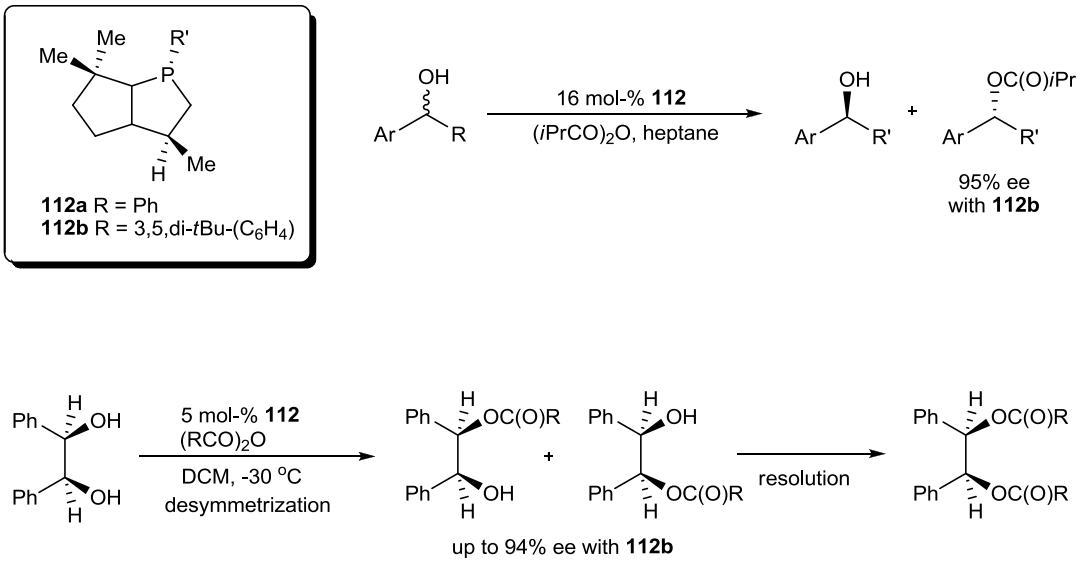


Scheme 37. BINAP-catalyzed MBH-reaction as reported by Soai.

Vedejs et al. prepared phosphacycle **112** with an optically pure phosphorus and showed that it can be an effective organocatalysts (Scheme 38). In acyl transfer from isobutyric andhydride to benzylic or allylic alcohols, both the resolved enantiomer and the acetate are obtained in 95% enantiomeric excess with 50% conversion at -40 °C.[190] It was found that bicyclic catalysts were more efficient than monocyclic ones. The group theorized that this was likely due to a more favorable conformation in the transition state were the P-phenyl group is oriented to minimize eclipsing interactions with the carbonyl of the anhydride.

The same catalyst also effects the desymmetrization of *meso*-diols reaching up to 97% conversion and 94% enantioselectivity.[191] As the reaction is allowed to run past 50% conversion the selectivity between mono- and diacylated product suffers. However, the enantiomeric excess

improves as the second acylation acts as a kinetic resolution. One of the monoacylated diastereomers reacts preferentially before the other, hence the entire process consists of two steps: desymmetrization and resolution.

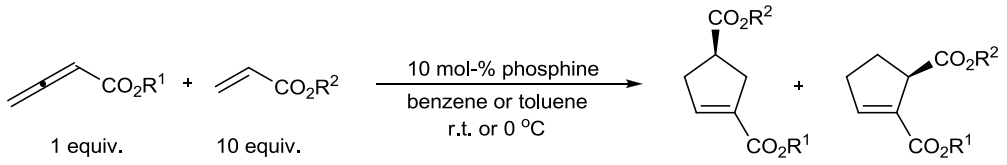


Scheme 38. P-chirogenic phosphacyclic organocatalyst reported by Vedejs et al. and some applications. Top: Kinetic resolution of benzylic or allylic alcohols.[190] Bottom: Desymmetization of *meso*-diols.[191]

There are also examples of phosphine oxides with a stereogenic phosphorus or axial chirality being employed as organocatalysts but in these cases it is the oxygen or another heteroatom that acts as the nucleophile.[52,192] These compounds will not be discussed here.

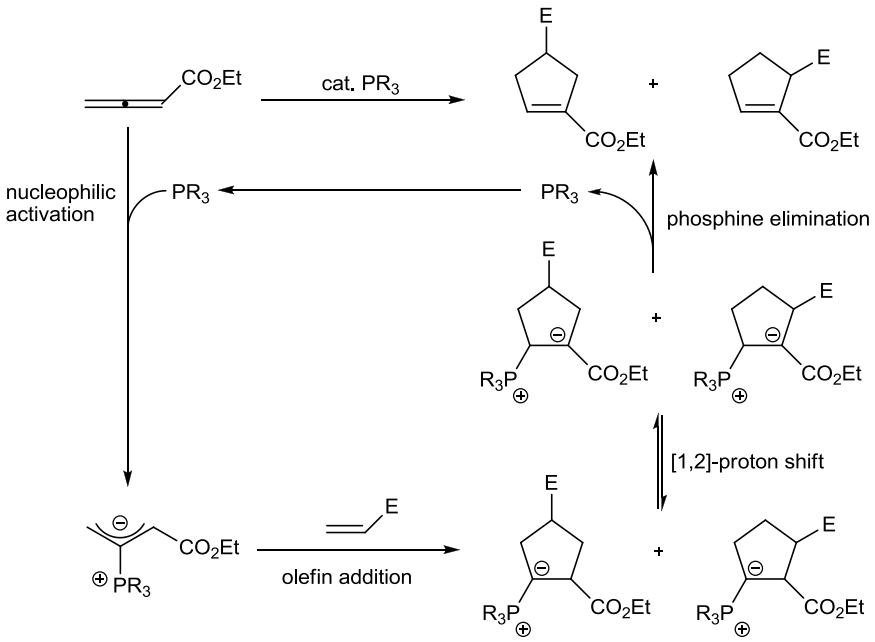
5.1.2. The Lu Reaction

The phosphine catalyzed [3+2]-cycloaddition between allenic esters and electron deficient olefins (also called the Lu reaction) was reported by Zhang et al. in 1995.[193] The group later studied the asymmetric version of this transformation with both PAMP and BINAP.[194] Both of these phosphines catalyze the addition of different acrylates to either ethyl- or tert-butyl-2,3-butadienoate. The desired products were obtained in 80% yield and 56% enantiomeric excess with (*R*)-(+)-PAMP and 33% yield and 12% enantiomeric excess using (*R*)-(+)-BINAP. In both cases the regioselectivity between the two different products was in excess of 70:30. Generally, larger substituents on the allenoate gave higher stereoselectivity while the results of changing the size of the acrylate ester varied with different catalysts.



Scheme 39. The Lu reaction: [3+2]-cycloaddition between electron deficient olefins and allenoates.

Since its inception, there has been a great deal of speculation on the mechanism of the Lu cycloaddition. Only recently has in-depth work been carried out to elucidate the specific workings of this reaction.[195] The generally accepted proposed mechanism is shown in Scheme 40 and involves four key steps which are: 1) formation of a resonance stabilized 1,3-dipole by the phosphine nucleophile (accounting for the regioselectivity); 2) addition of the olefin from one of two possible faces (explaining the stereoselectivity); 3) a [1,2]-proton shift moving the anion into conjugation with the ester group; 4) elimination of the phosphine.



Scheme 40. Suggested mechanism for the [3+2]-cycloaddition of allenoates and electron-deficient olefins.

Studies have suggested that the presence of electron-withdrawing groups on the allene performs a stabilizing role in the formation of the 1,3-dipole.[195b] More specifically, the interaction of the carbonyl oxygen and the phosphorus cation appears to be important. The addition of the olefin to form the cyclopentyl moiety is the rate determining step with an energy barrier of approximately 84 kJ/mol in benzene. Furthermore, Yu and coworkers have shown that the [1,2]-proton shift is catalyzed by trace amounts of water or another protic species. It was long thought that this was a purely intramolecular process, but DFT-calculations and isotope-labeling experiments have demonstrated that the energy barrier for such a transfer is quite high.[195] The stereochemical outcome of the reaction has been rationalized by Zhang based on a bicyclic phosphine and is shown in Figure 26. Basically, one of the substituents on the catalyst blocks the "bottom" side of the dipole and forces the olefin to approach from the "top" instead.

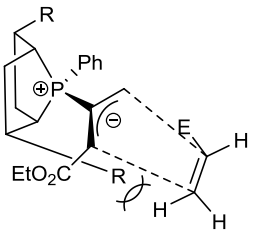


Figure 26. Model for the stereochemical outcome of the Lu [3+2]-cycloaddition with a bicyclic catalyst.

As more investigations into the Lu reaction has been performed, a variety of chiral phosphorus catalysts have proven to be effective for the addition of allenes to both electron deficient olefins as well as other compounds. Some examples of organocatalysts and substrates include (see Figure 27): **113** with enones,[196] **114** with fumarates,[197] **115**–**117** with imines,[198] **118** with a diversity of olefins and **119** with azomethine imines and in the preparation of oxygen heterocycles.[199]

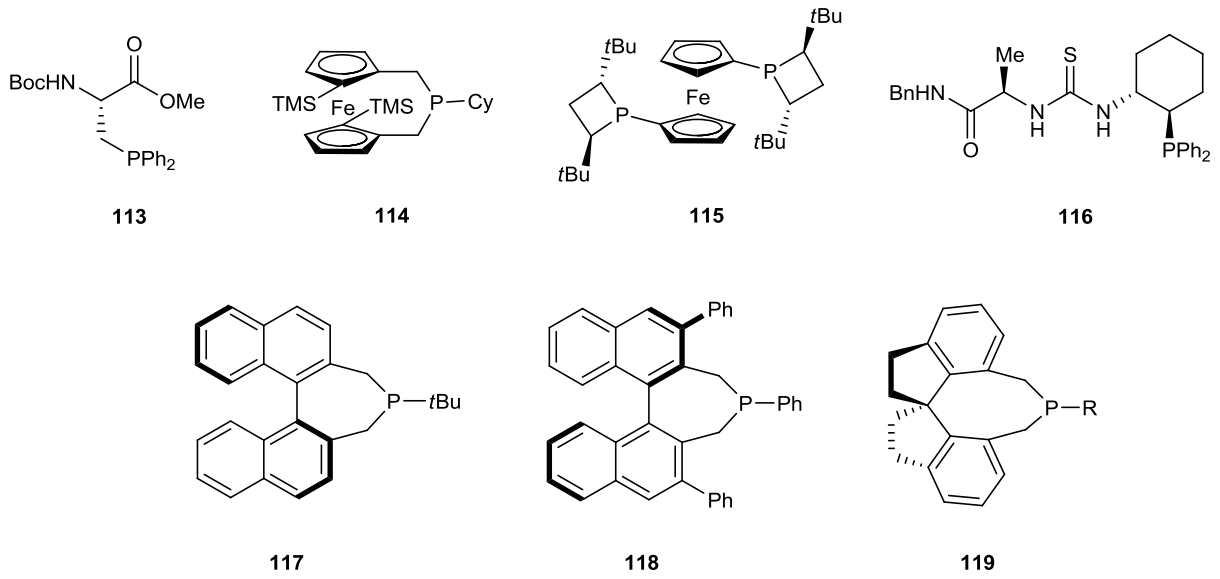


Figure 27. Chiral phosphine organocatalysts that have been used in cycloadditions involving allenic substrates.

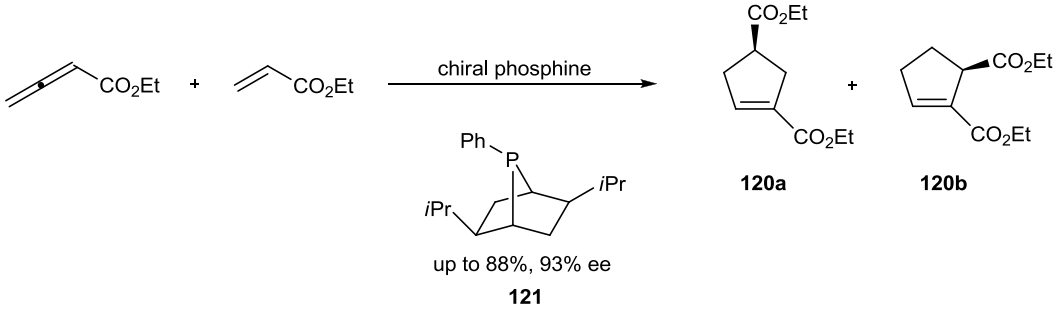
The possibility of creating cyclic compounds through organocatalytic means is an important synthetic tool.[200] As such, recent developments of the Lu reaction has significantly broadened the scope of the available substrates in this and related cycloadditions.[201] Moreover, this synthetic protocol has been put to use towards the preparation of natural products, clearly demonstrating its applicability.[202]

5.2. Results and Discussion

5.2.1. P-chirogenic Phosphines as Organocatalysts in the [3+2]-Cycloaddition of Ethyl-2,3-Butadienoate and *tert*-Butylacrylate

As the field of organocatalysis has received increased attention, there have been several instances of the use of chiral phosphines. [203] As have been previously stated, there is however a marked lack of P-chirogenic compounds reported in a catalytic role and those examples that exists deal with the sporadic use of such nucleophiles. As there recently has been quite some progress in the preparation of stereogenic phosphorus compounds, we foresee an increase of their use in several fields, including organocatalysis. As such, we decided to undertake a study concerning exclusively P-chirogenic phosphines as organocatalysts to provide guidance in the future design of more efficient catalysts. For this purpose we decided to focus on the Lu [3+2] cycloaddition of allenoates to acrylates (Scheme 41), as the reaction is not only stereoselective but also gives rise to two possible regioisomers which would also allow us to study the regioselectivity between **120a** and **120b**.[204] Possibly this would provide further insight into the importance of the catalyst structure. Zhang has reported an 88% yield and 93% enantiomeric excess for this reaction using

a chiral bicyclic phosphine, **121**.[194] There are also some examples of P-chirogenic phosphines employed in cycloadditions involving allenic esters, but with different substrates.[198a,199a,205]



Scheme 41. [3+2]-cycloaddition of ethyl-2,3-butadienoate to ethyl acrylate.

We first selected a range of monophosphines with an optically pure phosphorus for study in this context, these are shown in Figure 28. We have recently published a procedure for the synthesis of P-chirogenic β-aminophosphines (see Chapter 2),[137] and so it was elected to examine some of the phosphines prepared in this study. We selected aminophosphines with an anisidine backbone (**19c**, **20c**, **21c**, and **24c**) as well as one example of a chiral amine (**20a**) to see if an extra stereocenter would benefit the reaction. We also decided to study (*S*)-(-)-PAMP as well as some of its functionalized derivatives, **122a-c**. Another alkoxy substrate of (*R*)-(+)-PAMP was also prepared, **123**. Finally, a bulky adamantly substituted phosphine bearing a carboxyl group, **124**, was also incorporated into the study.[138]

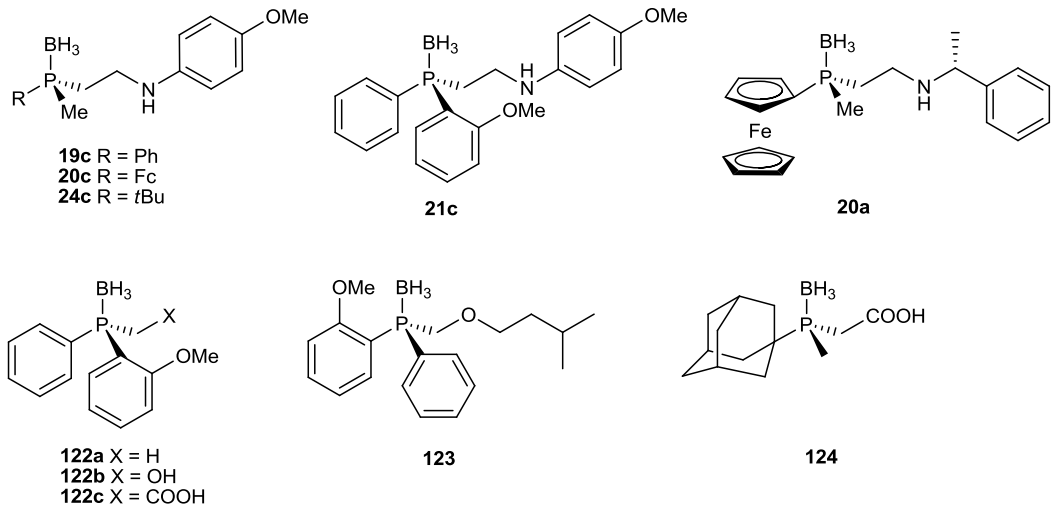
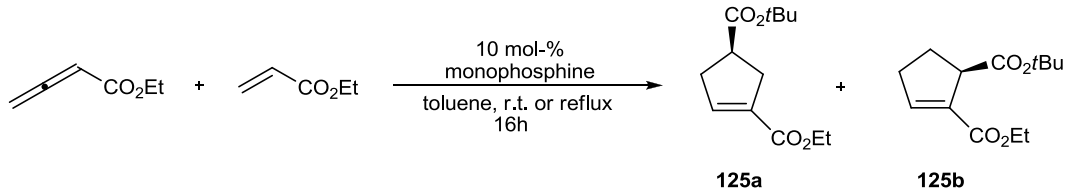


Figure 28. P-chirogenic monophosphines selected as organocatalysts.

The phosphine-boranes were deprotected either by gentle heating in neat diethyl amine or by reflux in ethanol and then screened in the cycloaddition of ethyl-2,3-butadienoate and *tert*-butyl acrylate. The reaction was performed at both room temperature and at 110 °C in toluene using 10 mol% if the phosphine. After 16 hours the desired products **d17a** and **d17b** were isolated by chromatography and the regioselectivity measured by ^{1}H NMR integration of the olefinic proton signals. The enantiomeric excess was determined by chiral HPLC. These results are shown in Table 13.

Table 13. [3+2]-Cycloaddition of ethyl 2,3-butadienoate with *tert*-butyl acrylate using chiral monophosphines as organocatalysts.



125a **125b**

Entry	Catalyst	Temperature	**125a**:**125b** (%)[a]	Yield (%)	Ee (%)[b]
1	**19c**	r.t.	100:0	5	0
2		110 °C	68:32	42	0
3	**20c**	r.t.	100:0	5	65 (*S*)
4		110 °C	61:39	87	26 (*S*)
5	**21c**	r.t.	100:0	23	29 (*R*)
6		110 °C	70:30	45	6 (*R*)
7	**24c**	r.t.	n.a.	n.r.	n.a.
8		110 °C	50:50	18	1 (*S*)
9	**20a**	r.t.	100:0	8	65 (*S*)
10		110 °C	73:27	48	18 (*S*)
11	**122a**	r.t.	76:24	68	37 (*R*)
12		110 °C	67:33	90	52 (*R*)
13	**122b**	r.t.	n.a.	n.r.	n.a.
14		110 °C	63:37	39	4 (*R*)
15	**122c**	r.t.	81:19	25	30 (*R*)
16		110 °C	73:27	65	40 (*R*)
17	**123**	r.t.	66:34	15	6 (*R*)
18		110 °C	80:20	77	4 (*R*)
19	**124**	r.t.	n.a.	n.r.	n.a.
20		110 °C	44:56	17	12

[a] Determined by ^{1}H NMR integration. [b] Determined by chiral HPLC, Daicel Chiracel AD-H column, 3% 2-PrOH in hexane, 0.5 ml/min. Ee value for major isomer **125a**.

For the anisidine substituted aminophosphines, the phenylmethylphosphine **9c** gave racemic product regardless of reaction temperature (entries 1 and 2). Having a larger ferrocenyl substituent improved the enantiomeric excess at room temperature but gave a low yield of product (entry 3). Increasing the temperature, predictably, gave better yield but as expected lowered the stereoselectivity (entry 4) which also held true for the PAMP-derived catalysts. The tert-butyl phosphine **24c** was similar to **19c** in that it gave low yields and nearly racemic product (entries 7 and 8). Also, the chiral amine containing catalyst **20a** did not give any improvement

over the similar **20c** (entries 9 and 10). The PAMP-derived compounds gave the best results with regular (*S*)-(-)-PAMP, **122a**, affording 90% yield and 52% enantiomeric excess. Interestingly, the better result was in this case observed at an elevated temperature (entries 11 and 12). Having a hydroxy group present completely inhibited the reaction at room temperature (entry 13) while a carboxy functionality is tolerated reasonably well giving up to 40% enantiomeric excess and 65% yield (entry 16). In all these cases, the same trend of higher stereoselectivity at elevated temperature was seen. For the isopentyl derived (*R*)-(+)-PAMP ether **123** this was not true, although the difference in optical purity in this case was slight between the different reaction temperatures (entries 17 and 18). The bulky carboxylic acid **124** gave no reaction at ambient temperature and only low yield and selectivities at reflux (entries 19 and 20). Considering that the carboxyl group in **122c** did not seem to negatively influence the outcome, it appears that too much steric bulk on the phosphine is the reason for this outcome.

Considering the fact that amines can act as nucleophilic organocatalysts in their own right, we also performed the reaction without removal of the borane from **19c** as well as with free anisidine. We did not see any reaction when emplying the stand-alone amine nor at room temperature with **19c**. At reflux however, some product did form. We attribute this to partial, thermal decomposition of the phosphorus-borane bond, affording some phosphine in the deprotected form.

We also opted to examine a selection of diPAMP-based diphosphines bearing a variety of substituents (Figure 29).[v] Apart from the change in catalysts, the reaction conditions were the same and the results are summarized in Table 14.

[v] DiPAMP catalysts were provided courtesy of Celtic Catalysts, Dublin.

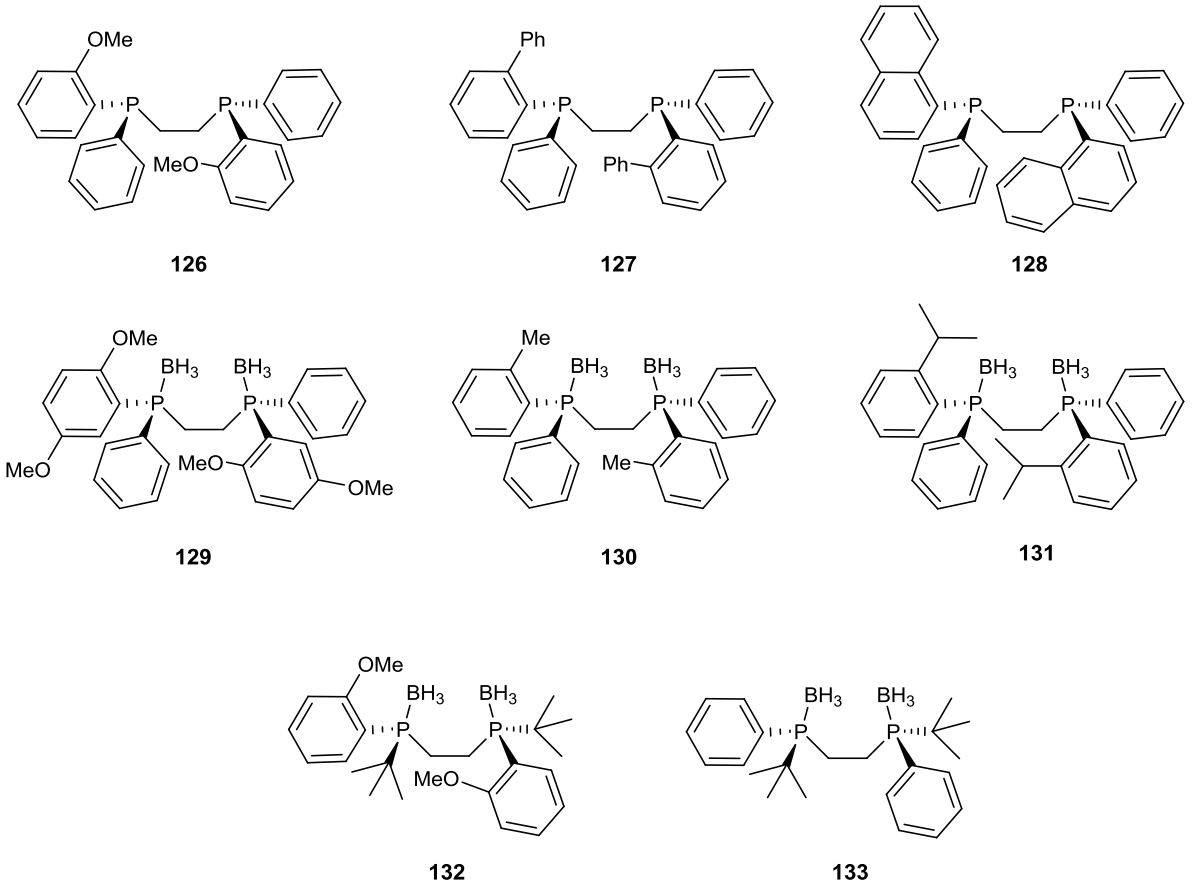
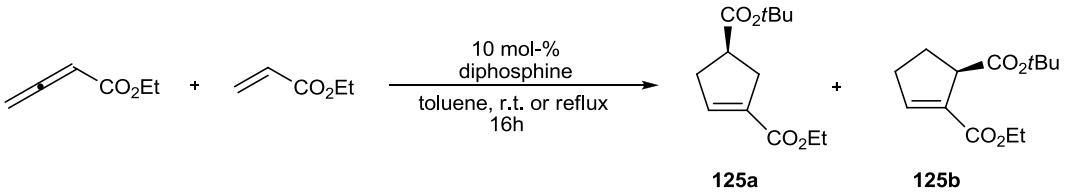


Figure 29. DiPAMP-derived diphosphines chosen for organocatalytic study.

Table 14. [3+2]-cycloaddition of ethyl-2,3-butadienoate with *tert*-butyl acrylate catalyzed by chiral biphosphines.



125a **125b**

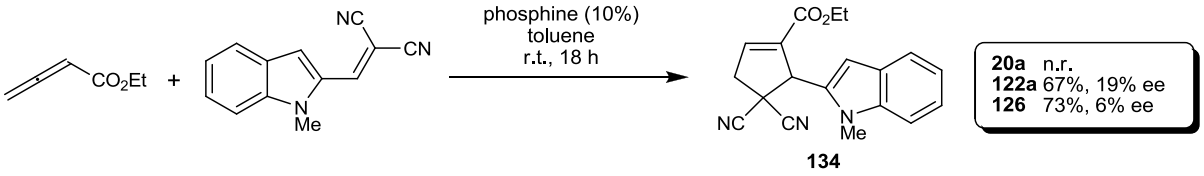
Entry	Catalyst	Temperature	**125a**:**125b** (%)[a]	Yield (%)	Ee (%)[b]
1	**126**	r.t.	89:11	23	19 (*S*)
2		110 °C	78:22	47	28 (*S*)
3	**127**	r.t.	80:20	24	21 (*R*)
4		110 °C	77:23	44	6 (*R*)
5	**128**	r.t.	70:30	34	21 (*S*)
6		110 °C	66:34	78	20 (*S*)
7	**129**	r.t.	86:24	40	22 (*S*)
8		110 °C	88:12	79	14 (*S*)
9	**130**	r.t.	68:32	35	8 (*S*)
10		110 °C	59:41	74	20 (*S*)
11	**131**	r.t.	63:37	48	25 (*S*)
12		110 °C	50:50	72	18 (*S*)
13	**132**	r.t.	99:1	25	48 (*R*)
14		110 °C	67:33	54	10 (*S*)
15	**133**	r.t.	87:13	28	25 (*R*)
16		110 °C	68:32	42	8 (*R*)

[a] Determined by ^{1}H NMR integration. [b] Determined by chiral HPLC, Daicel Chiracel AD-H column, 3% 2-PrOH in hexane, 0.5 ml/min. Ee value for major isomer **125a**.

In most instances the yields were fairly modest, the exeptions being when catalysts **128**-**131** were used at a higher temperature, this produced the desired products in excess of 70% (entries 6, 8, 10 and 12). The downside to this was that the regioselectivity suffered and for catalyst **131** the ratio of **125a**:**125b** became 1:1. Generally, the diphosphines gave somewhat lower selectivity between the 1,3- and 1,2-products. Also, with the exception of ordinary diPAMP **126** (entries 1 and 2), and its similar *ortho*-methyl derivative **130** (entries 9 and 10), no marked increase could be seen in stereoselectivity when heating. Rather most of the diphosphines followed the expected behavior of having a lower optical purity of the product if the reaction temperature was raised. The highest optical purity was afforded by a diphosphine bearing both *orhto*-anisyl and *tert*-butyl substituents (**132**, entries 13 and 14). Here, the enantiomeric excess was 40% and the regioselectivity was excellent although the yield was only 25%. As was previously stated, this catalyst did not improve the stereoselectivity at reflux. However, we did see the only instance of a reversal of selectivity for compound **132**, a small excess of the opposite enantiomer was produced when the temperature was high. It was interesting to notice that **133**, which differs from **132** only in the omission of the *ortho*-methoxy group gave much more modest results (entries 15 and 16). As such, the incorporation of this functionality may be a starting point for future catalyst design. Conversely, if a *meta*-methoxy group is also added, as in **129**, the stereoselectivity again suffers (entries 7 and 8).

To ascertain if the elevated reaction temperatures had any adverse effect on the phosphorus stereocenter, we repeated the reaction using **20a** and reisolated the catalyst afterwards. Analysis by chiral HPLC showed no apparent loss of stereochemical integrity in this case. However, when refluxing **126** and **127** for sixteen hours in toluene, it was found by ^{31}P NMR and optical rotational analysis that near complete epimerization had taken place. As some of the phosphines gave better enantiomeric purity of the products at the higher temperature, we can likely conclude that the stability of the P-stereocenter towards racemization is of key importance here. The major consideration is the ratio of formation of the preferred enantiomer as opposed to the rate of catalyst racemization. Hence, even though the conversion tends to be better, raising the temperature as high as 110 °C is not a suitable recommendation for all P-stereogenic phosphines.

5.2.2. Selected P-Chirogenic Phosphines as Organocatalysts in the [3+2]-Cycloaddition of Ethyl-2,3-Butadienoate and a Maleonitrile



Scheme 42. [3+2]-Cycloaddition of ethyl-2,3-butadienoate and 1,1-dicyano-2(2-*N*-methyl-indolyl)-ethene.

To widen the scope of this study, we also decided to select a few of the phosphines and subject them to further investigation involving another substrate. To this purpose, we exchanged the acrylate for 1,1-dicyano-2(2-*N*-methyl-indolyl)-ethene (Scheme 42, **134**). Lu has previously shown that 1,1-dicyano compounds can be valid substrates in the [3+2] cycloaddition of allenic esters.[206] Furthermore, Marinetti and coworkers have performed asymmetric variants of the same reaction, including with the substrate we selected,[201a] and shown that the cycloaddition product could be obtained with up to 90% enantiomeric excess and 77% yield using catalyst **117**. The phosphines we selected were the P,N-compound **20a**, (*S*)-(-)-PAMP **122a** and (*R*,*R*)-(-)-diPAMP **126**. While the aminophosphine gave no reaction at all after eighteen hours at room temperature, the PAMP-based phosphines gave 67% and 73% yield respectively. Unfortunately the enantiomeric excess was low with the monophosphine faring better than the diphosphine, as seen earlier with the acrylic substrate. Further studies with a larger range of phosphines were thus not pursued.

5.2.3. Conclusion

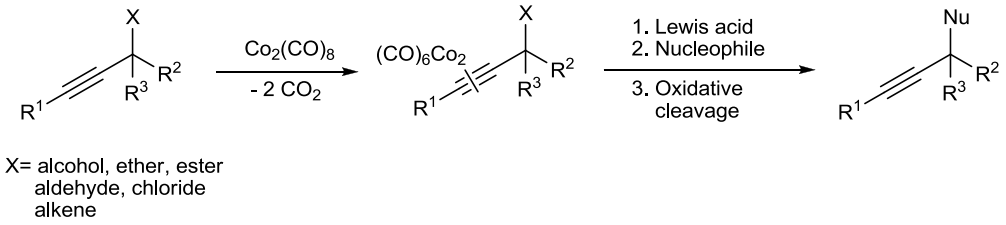
In summary, we have completed the first study of exclusively P-chirogenic phosphines as organocatalysts. A selection of mono- and diphosphines were screened, primarily in the [3+2]-cycloaddition of ethyl-2,3-butadienoate and tert-butyl acrylate. The reactions were performed both at room temperature and at 110 °C. Some selected catalysts were also examined with maleonitrile as the olefinic substrate. It was found that the capability of the phosphorus stereocenter to withstand racemization is of key importance when performing the reactions at higher temperature. In some cases, both the yield and the stereoselectivity can be improved in this manner. While there are undoubtedly more efficient catalysts available for the reactions we have used here, P-chirogenic phosphines clearly work as a metal-free alternative in these transformations. Furthemore, the capability of moving the stereocenter onto the nucleophilic atom and being able to modify its substituents warrants further evaluation in an organocatalytic context in our opinion. As such, this study should be able to give some insight into more efficient catalyst design.

6. Chiral Phosphoramidites in the Development of an Asymmetric Nicholas Reaction (Paper V)

6.1. Introduction

6.1.1. The Nicholas Reaction

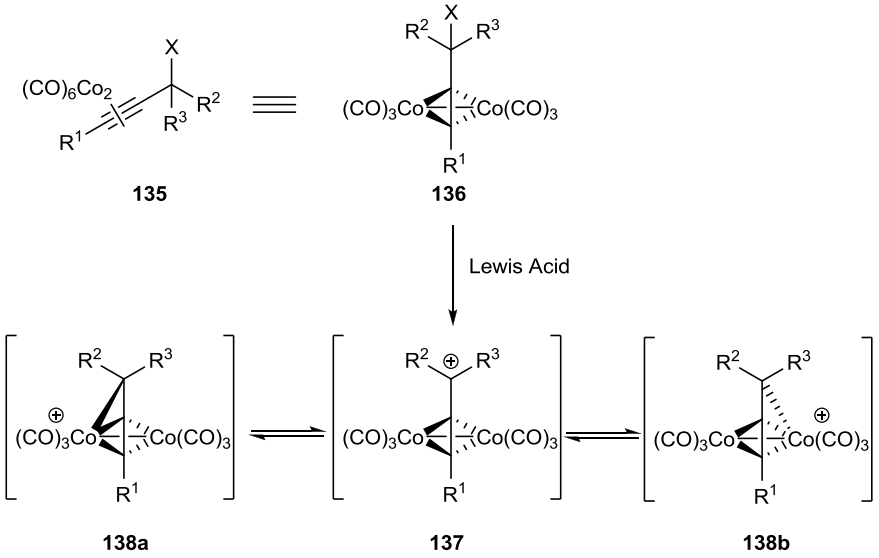
The Nicholas reaction (Scheme 43) involves the nucleophilic attack on a propargylic cation stabilized by a cobalt carbonyl complex. The reaction was discovered by Nicholas and Pettit in 1971 as a continuation of their work with dicobalt hexacarbonyl as a protecting group for alkynes.[207] It was found that the resultant propargylic alcohol complex could undergo acid-catalyzed dehydration and form corresponding 1,3-enynes via a cationic intermediate. However, if the same was attempted with non-complexed alkynes, no reaction occurred. This and the fact that the 1,3-enyne product could also be hydrolyzed under mildly acidic conditions suggested that the chemistry of the cationic cobalt complex featured unique stability.



Scheme 43. The Nicholas reaction.

Dicobalt carbonyl complexes react readily with carbon-carbon triple bonds to form bridging complexes between the two π bonds and the metal-metal bond (Scheme 44).[208] This means that although **135** is how these species are typically represented, a more accurate rendition would be **136**. If a suitable functionality is present in the position α to the alkyne, the addition of a Lewis acid will form a cationic species **137** which is then stabilized by the cobalt atoms. Indeed, the remarkable stability of such complexes allowed Connor and Nicholas to isolate them as their analogous SbF_6 or BF_4 salts.[209] Crystallographic studies have shown that the Co-Co bond is more or less perpendicular to the C≡C bond with a near perfect trigonal arrangement around the central cationic carbon.[210] The cations can be observed by NMR and studies show that alkyl groups positioned α to the propargylic carbon exhibit a smaller deshielding effect than would be expected for **137**.[207a] At the same time, ^{13}C NMR puts the carbonyl carbon atoms somewhat upfield and shielded while the alkyne is more downfield and deshielded than predicted.[211] Furthermore, CO stretching frequencies show a lengthening of the cobalt-carbonyl bond consistent with decreased *d*(Co) to π^*(CO) back-bonding.[209] All this is suggestive of significant

charge delocalization onto the cobalt atoms as shown by **138a** and **138b** which accounts for the stability of the cationic cobalt complexes.



Scheme 44. Charge delocalization and cationic stabilization in cobalt-alkyne cationic complexes.

The cationic intermediate is compatible with a wide variety of nucleophiles and since the reaction was first discovered considerable effort has gone into expanding its scope. Over the years, a number of reviews have been published which deal with this.[212] Among the possible compounds that can be used to substitute propargylic substrates through the Nicholas reaction are for instance hydrides, as well as carbon-based nucleophiles such as alkenes, silyl enol ethers, electron rich aromatics, allyl derivatives or trialkyl aluminum reagents. Heteroatom nucleophiles based on oxygen, nitrogen, sulphur or fluoride are also known. The versatility of the Nicholas reaction in enabling synthetic derivatizations of alkyne substrates that would not otherwise be possible has been put to use in the preparation of natural products such as (+)-bengamide E,[213] anticancer agents[214] and ciguatoxin 1B.[215]

Even after nucleophilic attack on the cation, the complexes are still stable and do not spontaneously decompose back to their parent alkyne form. Therefore, in order to liberate the triple bond, an external oxidizing agent must be employed. This can be done in a number of ways of which the most common is probably ceric ammonium nitrate[216] (CAN) although other methods are available.[212c] Another possibility is to perform the cleavage reductively to obtain the corresponding alkene instead.[212c]

6.1.2. Chiral Monophosphoramidites

The use of phosphoramidites as ligands in asymmetric catalytic chemical transformations is fairly new. Before this they were often used as reagents in the synthesis of oligonucleotides.[217] The change came in 1994 when Feringa published a protocol for the determination of enantiomeric excess among chiral alcohols through the employment of optically active phospholidines.[218] In addition they also prepared chiral phosphoramidites but found them to be less reactive towards nucleophilic substitution by oxygen nucleophiles. After further work, the value of phosphoramidites as ligands in metal catalysis was shown in 1996 when the Feringa group reported copper catalyzed conjugate additions with BINOL-based phosphoramidites.[219]

After that, the race was well and truly on. The turn of the century heralded the use of monodentate phosphoramidite-rhodium(I) complexes for the stereoselective hydrogenation of double bonds. Earlier work by Reetz and Pringle showed that monodentate phosphonites and phosphites together with cationic rhodium complexes could be efficient hydrogenation catalysts.[220] Feringa and coworkers took this strategy and employed it with phosphoramidites as ligands.[221] With (*S*)-MonoPhos (Figure 30, **139**) the hydrogenation of various dehydroamino-acids and itaconic acid achieved complete conversion in 20 hours at both room temperature and at 0 °C. The enantiomeric excess was as high as 99.8% and moreover, the monodentate ligand was more efficient than the corresponding bidentate ethylene bridged bisphosphoramidite.

The field of phosphoramidite based catalysis practically exploded after the year 2000. The scope of possible transformations was expanded and soon included enantioselective allylic substitution reactions, hydroborations, hydrovinylations, hydrosilylations, cycloadditons, alkylation reactions and more.[222] A full overview of all the chemical reactions employing phosphoramidites will not be given here, but Feringa recently published an excellent review covering the field.[223] Of course, there has also been a considerable amount of attention directed towards modifying the structure of the ligands themselves. The most common scaffolds are probably BINOL- and TADDOL-derivatives (Figure 30, **140**)[224] with varying amine components but that is by no means the full range of variations. Some other examples include partially hydrogenated systems ((*R*)-H_8-MonoPhos, Figure 30, **141**), spiro diols with chiral amines (Figure 30, **142**) and catechol variants (Figure 30, **143**).

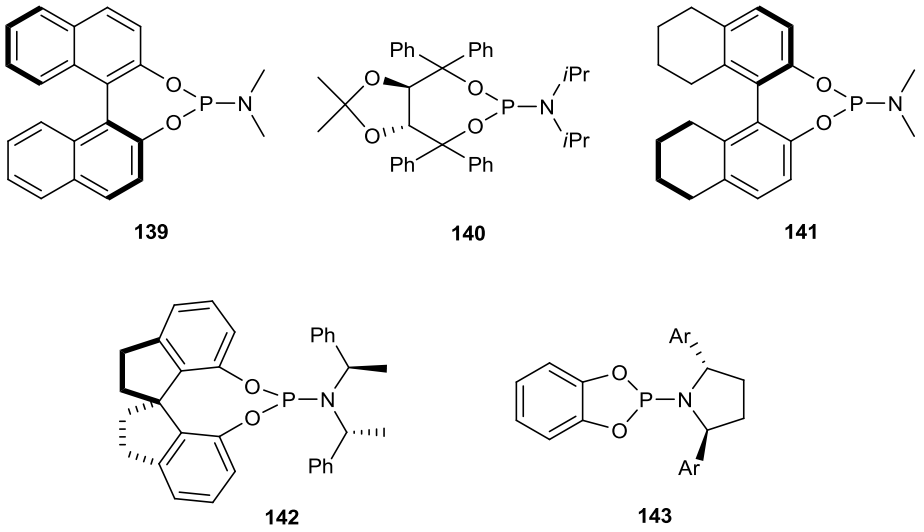
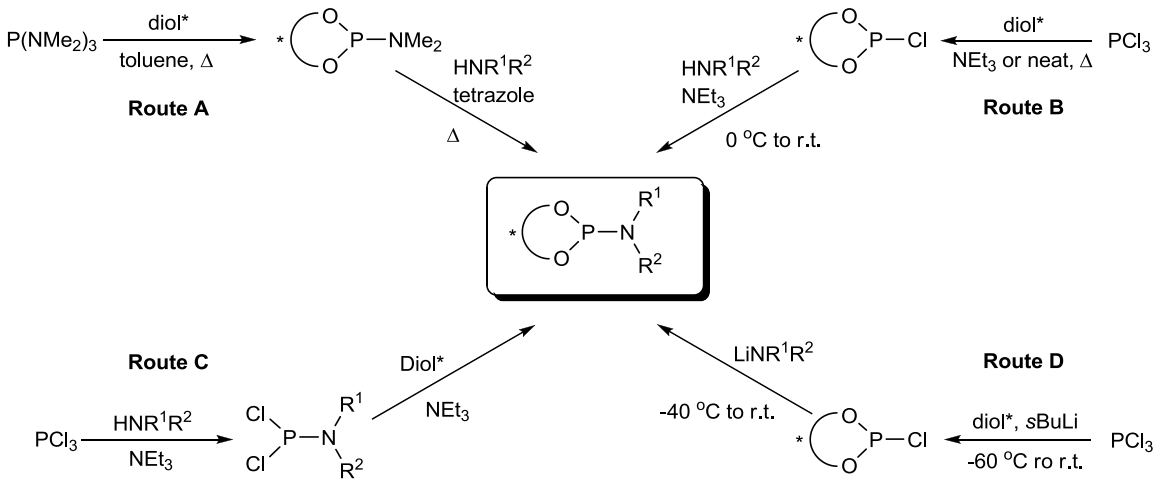


Figure 30. Examples of chiral monodentate phosphoramidite ligands.

One of the advantages of phosphoramidites as ligands is their relative ease of preparation (Scheme 45). They can be synthesized in a modular fashion with a wide variety of commercially available chiral diols and amines in only two steps. Usually, this is performed in one of four ways. If a dimethylamine functionality is desired, one can start from hexamethylphosphoric triamide (HMPA) and heat it together with a suitable diol (Route A).[218] It is possible to derivatize the resultant MonoPhos-type compounds further by amine exchange using a catalytic amount of tetrazole. Another approach which avoids the use of HMPA starts from phosphorus trichloride wich reacts with the diol under reflux (Route B).[225] The intermediate chlorophosphite is quite stable and can then be subjected to nucleophilic substitution with other amines. It is also possible to perform the synthesis with the sequence reversed, adding the amine first and the diol second (Route C).[226] In some instances where the amine is bulky, this approach can be favorable. If however the diol or amine is unreactive they can be converted to the corresponding lithium alkoxide or amide and then added to the phosphorus reagent (Route D).[219,227]

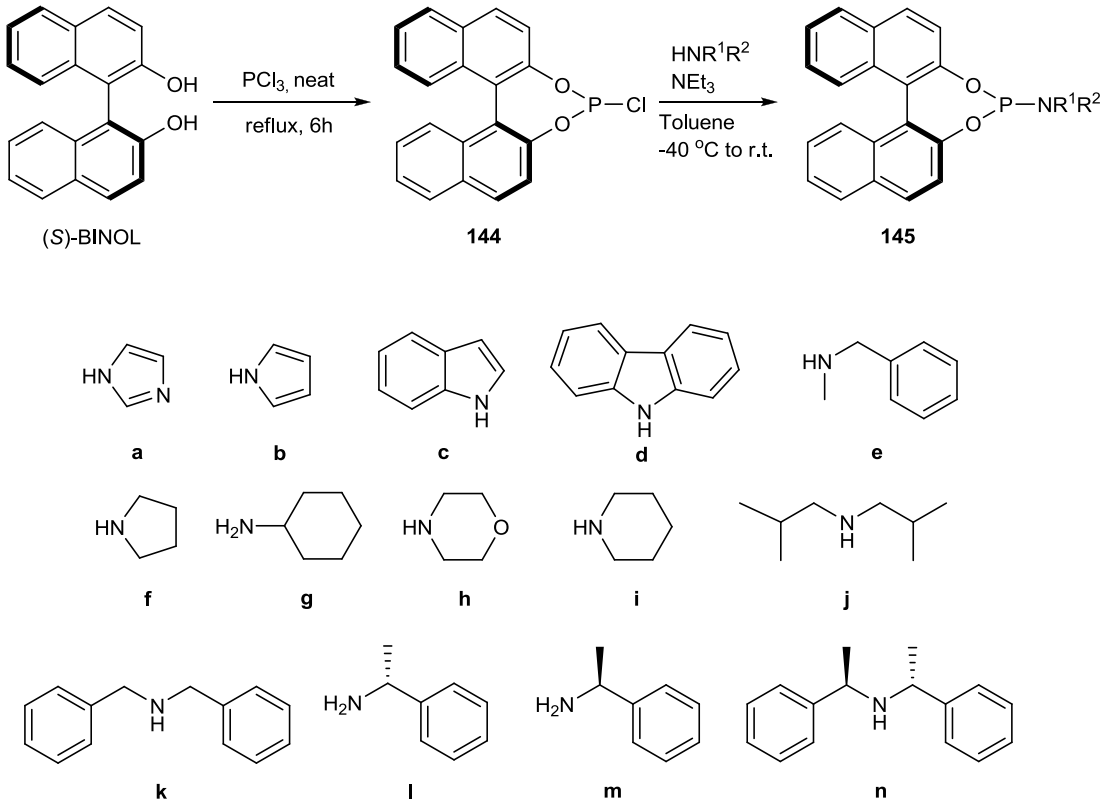


Scheme 45. Synthesis of chiral phosphoramidites.

6.2. Results and Discussion

6.2.1. Synthesis of Chiral Monophosphoramidite Ligands

Previous asymmetric versions of the Nicholas reaction have relied on the use of chiral substrates,[212b,228] chiral nucleophiles[229] or chirality transfer protocols.[230] During earlier work in our group to develop a solid-phase Nicholas reaction, it occurred to us that the ability of using racemic alkynols together with chiral ligands would be worth investigating. To our best knowledge, no previous record existed of such an approach. As we have experience of working with chiral phosphorus compounds we decided to focus on the P-building block. Earlier reports by Nicholas and Mayr have shown that standard phosphines exhibit sluggish reactivity when used together with carbon nucleophiles in the nucleophilic substitution of cobalt-stabilized propargylic cations.[231] We could confirm this through some initial studies involving chiral phosphines. However, in another paper, Nicholas and Caffyn had more success with electron-poor phopshites. Inspired by this, we turned instead to the electronically similar phosphoramidite ligands pioneered by Feringa.[223] Not only did we envision that they could perform in a similar manner as phosphites but they could also be prepared readily in a combinatorial fashion. Furthermore, Konya et al. have shown that enantioselective Pauson-Khand reactions can be effected with respectable enantioselectivity using this ligand class.[232] Buono and colleagues have also published a cobalt(I) catalyzed [6+2]-cycloaddition with phosphoramidite ligands.[233]



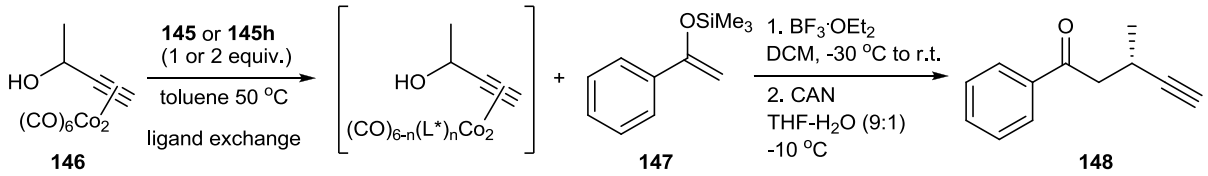
Scheme 46. Preparation of Phosphoramidites derived from (S)-BINOL as reported by Bernsmann et al.[225]

Scheme 46 shows the preparation of axially chiral mono-phosphoramidite ligands which was carried out as earlier reported by Bernsmann et al.[225] We decided to focus on the use of (*S*)-BINOL as the chiral diol framework and then react this with neat phosphorus tricloride under reflux for six hours. The resultant chlorophosphine **144** is stable and can be stored as a 1M stock solution in toluene in the refrigerator for months. We could thus easily prepare compounds **145** with a variety of amine components (Scheme 46, **a**-**n**) in a parallel fashion. We selected both aromatic and aliphatic amines as well as benzylic ones in order to be able to investigate a wide scope of varying structural and electronic properties in the desired ligands. Of the fourteen phosphoramidites that we synthesized in this manner, twelve are known since earlier.[234] Compounds **145b** and **145c** are new however, and incorporate pyrrole and indole moieties respectively. Staring from the chlorophosphite, **145b** was obtained in 72% yield and **145c** in 79%.

6.2.2. The Asymmetric Nicholas Reactions with Chiral Phosphoramidite Ligands.

With a diverse library of chiral phosphoramidites at hand, we next set out to investigate their performance in an asymmetric Nicholas reaction. Since the alkyne-dicobalt carbonyl complex features six CO-ligands which can be displaced by a phosphorus ligand, the first priority was to investigate the ligand to substrate ratio. As shown in Table 15, we decided to attempt this with one and two equivalents of phosphoramidite relative to the metal-alkyne complex and with two different ligands, pyrrolidine substituted phosphoramidite **145f** and MorfPhos (**145h**). For this particular study the relevant ligands were not prepared from (*S*)-BINOL, but from (*R*)-BINOL instead. A commercially available alkynol, racemic 3-butyn-2-ol, was converted to its parent cobalt carbonyl complex **146** as previously reported.[207a] After addition of either one or two equivalents of ligand, the mixture was heated at 50 °C under an argon atmosphere for three hours in order to carry out the ligand exchange. The intermediate complex was not isolated but instead reacted directly with two equivalents of silyl enol ether **147** in the presence of 1.5 equivalents boron trifluoride etherate at -30 °C. After allowing the reaction to reach ambient temperature overnight, it was concentrated and treated with ceric ammonium nitrate (CAN) to liberate product **148**.

Table 15. Optimization of ligand:substrate ratio. In this instance, ligands **145f** and **145h** were prepared from (*S*)-BINOL.



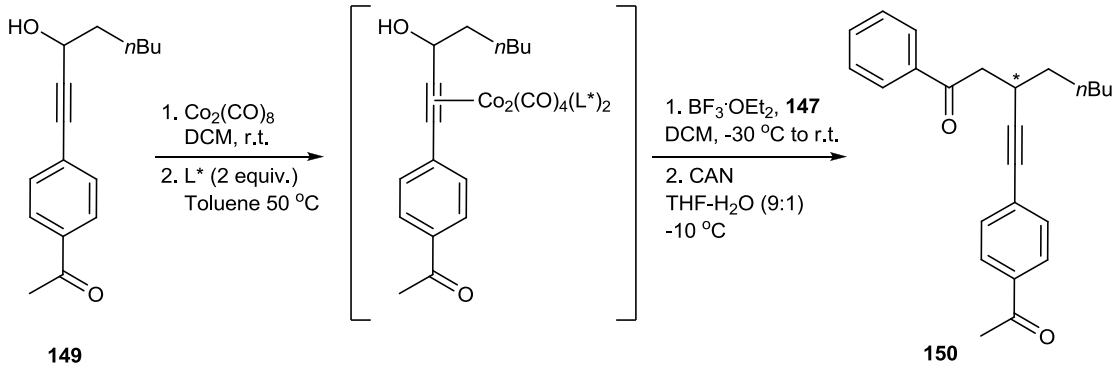
Entry	Ligand[a]	[Ligand:Substrate **146**]	Yield (%)[b]	Ee (%)[c,d]
1	**145f**	1:1	26	16 (*S*)
2	**145f**	2:1	33	24 (*S*)
3	**145h**	1:1	12	20 (*S*)
4	**145h**	2:1	10	26 (*S*)

[a] Prepared from (*R*)-BINOL. [b] Isolated yield calculated from **146**. [c] Determined by chiral HPLC. Daicel Chiralpak AD-H column (hexane *i*-PrOH 9:1). [d] Absolute configuration determined by optical rotation[235] after reduction with RuO_2-oxone to the corresponding carboxylic acid.[236]

As can be seen from Table 15, yields were in the range of 10-33% and the enantiomeric excess varied between 16-26% of the (*S*)-isomer. For both ligands **145f** and **145h**, the stereoselectivity was better when employing two equivalents relative to the substrate **146**. The yields were also better in this case for ligand **145f** while for **145h** it was about the same. Hence, it was decided to perform further investigations with two equivalents of phosphoramidite. It was also found that the enantiomers of ketone **148** were difficult to separate to a satisfactory degree through chiral HPLC. In order to remedy this, we decided to derivatize commercially available alkynols to provide structures which might achieve better separation on the HPLC columns we had available to us. Also, we reasoned that one possible cause of the low yields could be polymerization of the

terminal alkyne.[237] A change of substrate to an internal alkyne might thus provide a more favorable outcome.

Table 16. Asymmetric Nicholas reaction of racemic propargyl alcohol **149** with chiral phosphoramidites as ligands.



149 **150**

Entry	Ligand[a]	Ee (%)[b] of crude product	Yield (%)[b]	Ee (%)[c]
1	**145a**	0	30	0
2	**145b**	n.d.[c]	9	-6
3	**145c**	n.d.[c]	6	16
4	**145d**	8	11	-6
5	**145e**	38	33	40
6	**145f**	74	35	70
7	**145g**	18	35	16
8	**145h**	62	44	60
9	**145i**	68	47	64
10	**145j**	36	47	32
11	**145k**	52	14	54
12	**145l**	n.d.[d]	35	30
13	**145m**	10	8	8
14	**145n**	n.d.[d]	7	0

[a] Prepared from (S)-BINOL. [b] Isolated yield calculated over four steps from **149**. [c] Determined by chiral HPLC. Daicel Chiralpak AD-H column (hexane *i*-PrOH 9:1). [d] Ee of the crude product could not be determined due to overlapping impurities.

The propargylic alcohol **149** shown in Table 16 was prepared through standard Sonogashira cross-coupling of 1-octyn-3-ol and 4-iodoacetophenone.[238] This alkynol was then used as substrate in the asymmetric Nicholas reaction with two equivalents of phosphoramidite ligands **145a-n** according to the procedure described above and depicted in Table 16. After decomplexation of the alkyne diketone **150**, the enantiomeric excess was determined both on the crude product and after subsequent flash chromatography.

In general, the phosphoramidites containing aromatic amine moieties gave low stereoselectivities as shown by entries 1-4 in Table 16. The yields were also among the lowest obtained with the exception of pyrrol-based ligand **145a**. One possible explanation for this is that the aromatic groups on the phosphoramidite ligands can function as internal nucleophiles in cationic cobalt-

alkyne complexes, as previously reported by Castro et al. for tris(pyrrolyl)phosphines.[239] However, the aliphatic amine based phosphoramidites **145f**-**j** gave more promising results. While cyclohexyl amine derived ligand **145g** and diisobutylamine based **145j** gave 16% and 32% enantiomeric excess respectively (entries 7 and 10), the cyclic amines had stereoselectivities equal to or greater than 60%. A ligand incorporating pyrrolidine as the amine component gave the highest optical purity in the product, 70% (**145f**, entry 6). The yields that were achieved with the aliphatic amine ligands were between 35-47%. The benzylic amines meanwhile gave respectable stereoselectivity for ligands **145e** and **145k** although the yields were somewhat lower (entries 5 and 11). Two amines that featured a second stereogenic center and were opposite enantiomers achieved enantiomeric excesses of 30% versus 8% for ligands **145l** and **145m** and 35% against 8% yield of the product (entries 12 and 13) which seems to indicate a match/mismatch relationship in this case. The chiral, C_2-symmetric amine **145n** afforded racemic product in low yield (entry 14) probably due to steric limitations of the formed complex. It is worth noting that while the obtained yields may seem low at first glance, they in fact reflect four distinct steps. For the highest yield of 47%, each step averaged 83%.

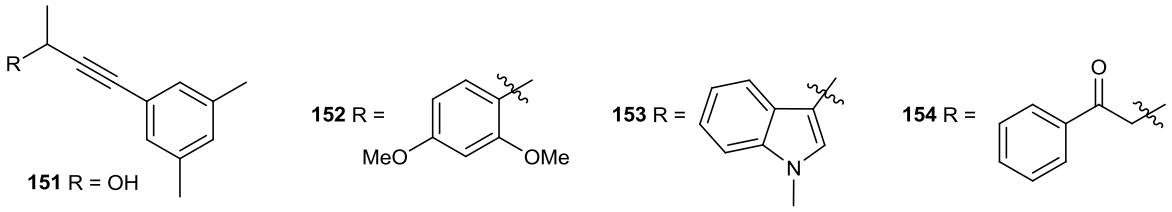


Figure 31. Products obtained from propargylic substitution of alkynol **151** with different nucleophiles.

In order to expand the scope of the reaction, ligands **145f** and **145h** were selected for further screening with another substrate, **151** shown in Figure 31. The alkynol **151** was in turn prepared through Sonogashira coupling of 3-butyn-2-ol and 1-iodo-3,5-dimethylbenzene.[vi] Two other carbon based nucleophiles, 3-methoxyanisole and *N*-methylindole, were also chosen for this purpose and the reaction was performed as earlier. The results of this investigation are presented in Table 17.

Table 17. Reaction of Phosphoramidite ligands **145f** and **145h** with various nucleophiles.

Entry	Ligand[a]	Nucleophile	Product	Yield (%)	Ee (%)[b]
1	**145f**	3-methoxyanisole	**152**	74	12
2	**145f**	*N*-methylindole	**153**	90	22
3	**145f**	**147**	**154**	30	66
4	**145h**	**147**	**154**	17	74

[a] Prepared from (*S*)-BINOL. [b] Determined by chiral HPLC. Daicel Chiralpak AD-H column (hexane *i*-PrOH 9:1).

[vi] See Paper V for details.

It was found that pyrrolidine based phosphoramidite **145** gave high yields, in excess of 70% (entries 1 and 2) with the two new nucleophiles to give products **152** and **156** but the enantioselectivity was fairly low. When using the same silyl enol ether (**147**) as earlier the enantiomeric excess climbed to 66% but the yield dropped to 30% (entry 3). Emplying MorfPhos (**145h**) as the ligand with substrate **151** and nucleophile **147** gave a good enantiomeric excess of 74% but the yield was a modest 17% (entry 4). Nonetheless, these results show that the use of chiral phosphoramidite ligands is valid for different substrates and nucleophiles in the asymmetric Nicholas reaction. With further tuning of the ligands, it is likely that even more promising outcomes can be achieved. It should be mentioned that since we performed this study, there has been substantial progress in developing catalytic protocols for propargylic substitutions using ruthenium, copper and other metals.[240]

6.2.3. Conclusion

To summarize, we report successfully for the first time, an asymmetric version of the Nicholas reaction which employs chiral ligands and does not require the use of chiral substrates, chiral nucleophiles or chirality transfer. We have shown that the use of chiral monophosphoramidites is compatible with dicobalt-hexacarbonyl complexes of propargylic alcohols. Ligand exchange can be carried out easily through gentle heating of the complexes with the phosphoramidite and is complete in a few hours. By using two equivalents of chiral ligand built around a (*S*)-BINOL framework, racemic alkynols have been converted to their substituted alkyne products using different carbon based nucleophiles. In general, it was found that phosphoramidites featuring cyclic aliphatic amines fared best and gave enantiomeric excesses as high as 74% in moderate to good yields. This initial study opens up new possible applications for use of the Nicholas reaction and further work is underway in our laboratory to examine more substrates and different nucleophiles.

7. Conclusions and Outlook

In summary, this thesis presents methods to prepare P-chirogenic multidentate amino- and amidophosphines. Compounds that feature P,N- P,N,N- and P,N,N,P-functionalities have been prepared in a manner that allows for facile variation of the steric and electronic properties of both the phosphorus and amine components. Thus, the synthesis is truly modular in nature. The chirality is emplaced on the phosphorus atom by the well-established methods of asymmetric deprotonation or ephedrine-complex formation giving the desired products in high optical purity. We have also found that the preparation of α-formylphosphine intermediaries is a valuable step on the path to P,N-ligands, this can be complemented with the use of carboxyphosphines for those substrates that are not stable as aldehydes. Furthermore, it has been shown that employment of microwave accelerated synthesis and solid-phase purification are efficient methods for the preparation of some of our compounds. We have, in short, presented the efficient preparation of P-chirogenic substances which have previously only been limitedly examined, or not been known at all. We are currently investigating possible applications for the prepared ligands.

Also, we have investigated different organocatalysts with asymmetry on the phosphorus atom. It was found that the studied phosphines can be used to catalyze the [3+2]-cycloaddition of an allenic ester and *tert*-butyl acrylate in a stereoselective manner. While examples of P-chirogenic organocatalysts are known since earlier, this is the first study featuring exclusively this catalyst class. Even though the results were moderate, we hope that this can provide guidance for future design of organocatalysts with stereogenic phosphorus and further catalyst study is underway in our laboratory.

Finally, we have demonstrated the first example of an asymmetric Nicholas reaction using chiral phosphoramidites as ligands. The stereoselective substitution of three different alkynols has been effected with a silyl enol ether and other carbon based nucleophiles. The ligands are easily and rapidly prepared from commercially available starting materials and can be varied in structure and electronic properties quite readily. Currently, we are engaged in broadening the scope of the reaction through examination of more substrates and different nucleophiles.

We believe that P,N-compounds will continue to find use in the field of asymmetric synthesis and that more attention will be given to P-chirogenic species as new and efficient methods for their preparation are discovered. It is our humble hope that what has been presented herein will assist in leading to further progress in the field.

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9. References

1. Kelvin, W. T., *Baltimore Lectures on Molecular Dynamics and the Wave Theory of Light*. C. J. Clay and sons: London, 1904.
2. Pasteur, L. *Compt. Rend. Acad. Sci.* **1848**, *16*, 53.
3. (a) Pasteur, L., In *Oeuvres de Pasteur*, Vallery-Radot, P., Ed. Masson: Paris, 1922; Vol. 2, pp 129-130; (b) Pasteur, L., In *Oeuvres de Pasteur*, Vallery-Radot, P., Ed. Masson: Paris, 1922; Vol. 1, pp 258-262.
4. Kagan, H. B., In *Catalytic Asymmetric Synthesis*, 2 ed.; Ojima, I., Ed. Wiley-VCH: New York, 2000; pp 327-356.
5. Cotton, H.; Elebring, T.; Larsson, M.; Li, L.; Sorensen, H.; von Unge, S. *Tetrahedron: Asymmetry* **2000**, *11*, 3819.
6. Dalla Cort, A.; Mandolini, L.; Pasquini, C.; Schiaffino, L. *New J. Chem.* **2004**, *28*, 1198.
7. Thayer, A. M. *C&EN* **2007**, *85*, 11.
8. (a) Christmann, M.; Bräse, S., *Asymmetric Synthesis - The Essentials*. Wiley-VCH: Weinheim, 2007; (b) Eliel, E. L.; Wilen, S. H.; Doyle, M. P., *Basic Organic Stereochemistry*. John Wiley & Sons: New York, 2001; (c) Seyden-Penne, J., *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*. John Wiley & Sons: New York, 1995; (d) Eliel, E. L.; Wilen, S. H.; Mander, L. N., *Stereochemistry of Organic Compounds*. John Wiley & Sons: New York, 1994; (e) Aitken, R. A.; Kilényi, S. N., *Asymmetric Syntheis*. Chapman & Hall: Glasgow, 1992; (f) Bassindale, A., *The Third Dimension in Organic Chemistry*. John Wiley & Sons: Chichester, 1984.
9. Weeks, M. E., In *Discovery of the Elements*, Journal of Chemical Education Publ.: Easton, 1956; pp 101-139.
10. (a) Greenwood, N. N.; Earnshaw, A., *Chemistry of the Elements*. 2nd ed.; Elsevier Science Ltd.: Oxford, 1997; (b) Shriver, D. F.; Atkins, P. W., *Inorganic Chemistry*. Oxford University Press: Oxford, 1999.
11. Kutzelnigg, W. *Angew. Chem. Int. Ed.* **1984**, *23*, 272.
12. Quin, L. D., *A Guide To Organophosphorus Chemistry*. 1 ed.; John Wiley & Sons: New York, 2000.
13. Shi, J.; Zhao, Y.-L.; Wang, H.-J.; Rui, L.; Guo, Q.-X. *J. Mol. Struct.: THEOCHEM* **2009**, *902*, 66.
14. Grabulosa, A., In *P-Stereogenic Ligands in Enantioselective Catalysis*, Spivey, J. J., Ed. The Royal Society of Chemistry: Cambridge, 2011; p 14.
15. Crabtree, R. H., *The Organometallic Chemistry of the Transition Metals*. 4th ed.; Wiley: Hoboken, 2005.
16. Crabtree, R. H., In *Organometallic Chemistry of the Transition Metals*, 4 ed.; Wiley: Hoboken, 2005; pp 1-27.
17. Pietrusiewicz, K. M.; Zablocka, M. *Chem. Rev.* **1994**, *94*, 1375.
18. Imamoto, T.; Kikuchi, S.-i.; Miura, T.; Wada, Y. *Org. Lett.* **2001**, *3*, 87.
19. Korpiun, O.; Lewis, R. A.; Chickos, J.; Mislow, K. *J. Am. Chem. Soc.* **1968**, *90*, 4842.
20. Schmidbaur, H. *J. Organomet. Chem.* **1980**, *200*, 287.
21. (a) Sayalero, S.; Pericas, M. A. *Synlett* **2006**, *2006*, 2585; (b) Brisset, H.; Gourdel, Y.; Pellon, P.; Lecorre, M. *Tetrahedron Lett.* **1993**, *34*, 4523; (c) Imamoto, T.; Oshiki, T.; Onozawa, T.; Kusumoto, T.; Sato, K. *J. Am. Chem. Soc.* **1990**, *112*, 5244.

22. (a) Schroder, M.; Nozaki, K.; Hiyama, T. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 1931; (b) Van Overschelde, M.; Vervecken, E.; Modha, S. G.; Cogen, S.; Van der Eycken, E.; Van der Eycken, J. *Tetrahedron* **2009**, *65*, 6410.
23. Gridnev, I. D.; Yamanoi, Y.; Higashi, N.; Tsuruta, H.; Yasutake, M.; Imamoto, T. *Adv. Synth. Catal.* **2001**, *343*, 118.
24. Darcel, C.; Kaloun, E. B.; Merdes, R.; Moulin, D.; Riegel, N.; Thorimbert, S.; Genet, J. P.; Juge, S. *J. Organomet. Chem.* **2001**, *624*, 333.
25. Brunel, J. M.; Faure, B.; Maffei, M. *Coord. Chem. Rev.* **1998**, *180*, 665.
26. (a) Noyori, R., *Asymmetric Catalysis in Organic Synthesis*. Wiley-Interscience: New York, 1994; (b) Ojima, I.; Ed., *Catalytic Asymmetric Synthesis, Second Edition*. Wiley-VCH: Weinheim, 2000; (c) Blaser, H.-U.; Schmidt, E.; Eds., *Asymmetric Catalysis on Industrial Scale. Challenges, Approaches and Solutions*. Wiley-VCH: Weinheim, 2004.
27. Horner, L.; Siegel, H.; Buthe, H. *Angew. Chem. Int. Ed.* **1968**, *7*, 942.
28. (a) Knowles, W. S. *Adv. Synth. Catal.* **2003**, *345*, 3; (b) Knowles, W. S. *Angew. Chem. Int. Ed.* **2002**, *41*, 1999; (c) Knowles, W. S.; Sabacky, M. J. *Chem. Commun.* **1968**, 1445.
29. For recent examples of the preparation of P-chirogenic ligands and their applications, see: (a) Grabulosa, A.; Granell, J.; Muller, G. *Coord. Chem. Rev.* **2007**, *251*, 25; (b) *Phosphorous Ligands in Asymmetric Catalysis*. Wiley-VCH: Weinheim, 2008; (c) Glueck, D. S. *Chem. Eur. J.* **2008**, *14*, 7108; (d) Harvey, J. S.; Gouverneur, V. *Chem. Commun.* **2010**, *46*, 7477; (e) Grabulosa, A., *P-Stereogenic Ligands in Enantioselective Catalysis* The Royal Society of Chemistry: Cambridge, 2011; Vol. 7.
30. (a) Ohff, M.; Holz, J.; Quirmbach, M.; Börner, A. *Synthesis* **1998**, 1391; (b) Johansson, M. J.; Kann, N. C. *Mini Rev. Org. Chem.* **2004**, *1*, 233; (c) Crépy, K. V. L.; Imamoto, T. *Adv. Synth. Catal.* **2003**, *345*, 79; (d) Crépy, K. V. L.; Imamoto, T. *Top. Curr. Chem.* **2003**, *229*, 1.
31. Meisenheimer, J.; Lichtenstadt, L. *Berichte* **1911**, *44*, 356.
32. Kumli, K. F.; McEwen, W. E.; Vanderwerf, C. A. *J. Am. Chem. Soc.* **1959**, *81*, 248.
33. Hamada, Y.; Matsuura, F.; Oku, M.; Hatano, K.; Shioiri, T. *Tetrahedron Lett.* **1997**, *38*, 8961.
34. Miura, T.; Imamoto, T. *Tetrahedron Lett.* **1999**, *40*, 4833.
35. Stankeviç, M.; Pietrusiewiçz, K. M. *Tetrahedron: Asymmetry* **2007**, *18*, 552.
36. Miura, T.; Yamada, H.; Kikuchi, S.; Imamoto, T. *J. Org. Chem.* **2000**, *65*, 1877.
37. Tsuruta, H.; Imamoto, T. *Tetrahedron: Asymmetry* **1999**, *10*, 877.
38. Kikuchi, S.; Konishi, H.; Hashimoto, Y. *Tetrahedron* **2005**, *61*, 3587.
39. Bergin, E.; O'Connor, C. T.; Robinson, S. B.; McGarrigle, E. M.; O'Mahony, C. P.; Gilheany, D. G. *J. Am. Chem. Soc.* **2007**, *129*, 9566.
40. Tang, W.; Qu, B.; Capacci, A. G.; Rodriguez, S.; Wei, X.; Haddad, N.; Narayanan, B.; Ma, S.; Grinberg, N.; Yee, N. K.; Krishnamurthy, D.; Senanayake, C. H. *Org. Lett.* **2009**, *12*, 176.
41. Doro, F.; Lutz, M.; Reek, J. N. H.; Spek, A. L.; van Leeuwen, P. W. N. M. *Eur. J. Inorg. Chem.* **2008**, *2008*, 1309.
42. Valentine, D., Jr. *Asymmetric Synthesis*; Academic Press, Inc.: New York, 1984; pp 263-312.
43. Lewis, R. A.; Korpium, O.; Mislow, K. *J. Am. Chem. Soc.* **1967**, *89*, 4786.
44. Nudelman, A.; Cram, D. J. *J. Org. Chem.* **1971**, *36*, 335.

45. Tsuruta, H.; Imamoto, T. *Synlett* **2001**, 999.
46. Oshiki, T.; Hikosaka, T.; Imamoto, T. *Tetrahedron Lett.* **1991**, *32*, 3371.
47. (a) Moraleda, D.; Gatineau, D.; Martin, D.; Giordano, L.; Buono, G. *Chem. Commun.* **2008**, 3031; (b) Gatineau, D.; Giordano, L.; Buono, G. *J. Am. Chem. Soc.* **2011**, *133*, 10728.
48. Khiri, N.; Bertrand, E.; Ondel-Eymin, M.-J.; Rousselin, Y.; Bayardon, J.; Harvey, P. D.; Jugé, S. *Organometallics* **2010**, *29*, 3622.
49. Léon, T.; Riera, A.; Verdaguer, X. *J. Am. Chem. Soc.* **2011**, *133*, 5740.
50. Rossi, J.-C.; Marull, M.; Larcher, N.; Taillades, J.; Pascal, R.; van der Lee, A.; Gerbier, P. **2008**, *19*, 876.
51. Buergler, J. F.; Togni, A. *Organometallics* **2011**, *30*, 4742.
52. Nemoto, T.; Hitomi, T.; Nakamura, H.; Jin, L.; Hatano, K.; Hamada, Y. *Tetrahedron: Asymmetry* **2007**, *18*, 1844.
53. (a) Clayden, J., *Organolithiums: Selectivity for Synthesis.* 1st ed.; Elsevier Science Ltd.: Oxford, 2002; (b) Hodgson, D. M.; Maxwell, C. R.; Miles, T. J.; Paruch, E.; Stent, M. A. H.; Matthews, I. R.; Wilson, F. X.; Witherington, J. *Angew. Chem. Int. Ed.* **2002**, *41*, 4313.
54. Hoppe, D.; Hintze, F.; Tebben, P. *Angew. Chem. Int. Ed.* **1990**, *29*, 1422.
55. Muci, A. R.; Campos, K. R.; Evans, D. A. *J. Am. Chem. Soc.* **1995**, *117*, 9075.
56. Muci, A. R. Studies on the Enantioselective Deprotonation of Phosphine Derivatives with Alkyllithium-(-)-Sparteine Complexes. PhD Thesis, Harvard University, Cambridge, MA, 1997.
57. Nagata, K.; Matsukawa, S.; Imamoto, T. *J. Org. Chem* **2000**, *65*, 4185.
58. Sugama, H.; Saito, H.; Danjo, H.; Imamoto, T. *Synthesis* **2001**, 2348.
59. Yamanoi, Y.; Imamoto, T. *J. Org. Chem.* **1999**, *64*, 2988.
60. Danjo, H.; Higuchi, M.; Yada, M.; Imamoto, T. *Tetrahedron Lett.* **2004**, *45*, 603.
61. Popovici, C.; Oña-Burgos, P.; Fernández, I.; Roces, L.; García-Granda, S.; Iglesias, M. a. J.; Ortiz, F. L. p. *Org. Lett.* **2010**, *12*, 428.
62. (a) Johansson, M. J.; Schwartz, L.; Amedjkouh, M.; Kann, N. *Tetrahedron: Asymmetry* **2004**, *15*, 3531; (b) Johansson, M. J.; Kann, N. C. *Eur. J. Org. Chem.* **2004**, 1894; (c) Dearden, M. J.; McGrath, M. J.; O'Brien, P. *J. Org. Chem.* **2004**, *69*, 5789; (d) Dearden, M. J.; Firkin, C. R.; Hermet, J.-P. R.; O'Brien, P. *J. Am. Chem. Soc.* **2002**, *124*, 11870.
63. Marriere, E.; Rouden, J.; Tadino, V.; Lasne, M.-C. *Org. Lett.* **2000**, *2*, 1121.
64. Carbone, G.; O'Brien, P.; Hilmersson, G. *J. Am. Chem. Soc.* **2010**, *132*, 15445.
65. Headley, C. E.; Marsden, S. P. *J. Org. Chem.* **2007**, *72*, 7185.
66. (a) Gammon, J. J.; Canipa, S. J.; O'Brien, P.; Kelly, B.; Taylor, S. *Chem. Commun.* **2008**, 3750; (b) Gammon, J. J.; Gessner, V. H.; Barker, G. R.; Granander, J.; Whitwood, A. C.; Strohmann, C.; O'Brien, P.; Kelly, B. *J. Am. Chem. Soc.* **2010**, *132*, 13922; (c) Gammon, J. J.; O'Brien, P.; Kelly, B. *Org. Lett.* **2009**; (d) Granander, J.; Secci, F.; O'Brien, P.; Kelly, B. *Tetrahedron: Asymmetry* **2009**, *20*, 2432; (e) Granander, J.; Secci, F.; Canipa, S. J.; O'Brien, P.; Kelly, B. *J. Org. Chem.* **2011**, *76*, 4794.
67. (a) Adams, D. J.; Simpkins, N. S.; Smith, T. J. N. *Chem. Commun.* **1998**, 1605; (b) Blake, A. J.; Hume, S. C.; Li, W. S.; Simpkins, N. S. *Tetrahedron* **2002**, *58*, 4589.
68. Vedrenne, P.; Le Guen, V.; Toupet, L.; Le Gall, T.; Mioskowski, C. *J. Am. Chem. Soc.* **1999**, *121*, 1090.
69. Glueck, D. *Synlett* **2007**, 2627.

70. Kovaçik, I.; Wicht, D. K.; Grewal, N. S.; Glueck, D. S.; Incarvito, C. D.; Guzei, I. A.; Rheingold, A. L. *Organometallics* **2000**, *19*, 950.
71. (a) Xu, Y. Y.; Zhang, J. *J. Chem. Soc., Chem. Commun.* **1986**, 1606; (b) Oshiki, T.; Imamoto, T. *J. Am. Chem. Soc.* **1992**, *114*, 3975; (c) Al-Masum, M.; Kumaraswamy, G.; Livinghouse, T. *J. Org. Chem.* **2000**, *65*, 4776.
72. (a) Peer, M.; deJong, J. C.; Kiefer, M.; Langer, T.; Rieck, H.; Schell, H.; Sennhenn, P.; Sprinz, J.; Steinhagen, H.; Wiese, B.; Helmchen, G. *Tetrahedron* **1996**, *52*, 7547; (b) Korff, C.; Helmchen, G. *Chem. Commun.* **2004**, 530.
73. Pican, S.; Gaumont, A.-C. *Chem. Commun.* **2005**, 2393.
74. Glueck, D. S. *Coord. Chem. Rev.* **2008**, *252*, 2171.
75. (a) Anderson, B. J.; Guino-o, M. A.; Glueck, D. S.; Golen, J. A.; DiPasquale, A. G.; Liable-Sands, L. M.; Rheingold, A. L. *Org. Lett.* **2008**, *10*, 4425; (b) Anderson, B. J.; Glueck, D. S.; DiPasquale, A. G.; Rheingold, A. L. *Organometallics* **2008**, *27*, 4992; (c) Scriban, C.; Glueck, D. S. *J. Am. Chem. Soc.* **2006**, *128*, 2788.
76. Scriban, C.; Glueck, D. S.; Golen, J. A.; Rheingold, A. L. *Organometallics* **2007**, *26*, 1788.
77. (a) Chan, V. S.; Chiu, M.; Bergman, R. G.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, *131*, 6021; (b) Chan, V. S.; Stewart, I. C.; Bergman, R. G.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 2786.
78. Chan, V. S.; Bergman, R. G.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 15122.
79. Join, B.; Mimeau, D.; Delacroix, O.; Gaumont, A.-C. *Chem. Commun.* **2006**, 3249.
80. Douglass, M. R.; Ogasawara, M.; Hong, S.; Metz, M. V.; Marks, T. J. *Organometallics* **2002**, *21*, 283.
81. Harvey, J. S.; Malcolmson, S. J.; Dunne, K. S.; Meek, S. J.; Thompson, A. L.; Schrock, R. R.; Hoveyda, A. H.; Gouverneur, V. *Angew. Chem. Int. Ed.* **2009**, *48*, 762.
82. Ogasawara, M.; Watanabe, S.; Nakajima, K.; Takahashi, T. *J. Am. Chem. Soc.* **2010**, *132*, 2136.
83. (a) Chen, S.; Ng, J. K.-P.; Pullarkat, S. A.; Liu, F.; Li, Y.; Leung, P.-H. *Organometallics* **2010**, *29*, 3374; (b) Luo, D.; Li, Y.; Tan, K.-W.; Leung, P.-H. *Organometallics* **2009**, *28*, 6266.
84. Nishida, G.; Noguchi, K.; Hirano, M.; Tanaka, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 3410.
85. (a) Shioji, K.; Kurauchi, Y.; Okuma, K. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 833; (b) Shioji, K.; Tashiro, A.; Shibata, S.; Okuma, K. *Tetrahedron Lett.* **2003**, *44*, 1103.
86. Kielbasinski, P.; Zurawinski, R.; Pietrusiewiçz, K. M.; Zablocka, M.; Mikolajçzyk, M. *Tetrahedron Lett.* **1994**, *35*, 7081.
87. Wiktelius, D.; Johansson, M. J.; Luthman, K.; Kann, N. *Org. Lett.* **2005**, *7*, 4991.
88. (a) Kaczmarczyk, S.; Kwiatkowska, M.; Madalińska, L.; Barbachowska, A.; Rachwalski, M.; Błaszczyk, J.; Sieroń, L.; Kiełbasiński, P. *Adv. Synth. Cat.* **2011**, *353*, 2446; (b) Kielbasinski, P.; Zurawinski, R.; Albrycht, M.; Mikolajçzyk, M. *Tetrahedron: Asymmetry* **2003**, *14*, 3379.
89. Klimek-Ochab, M.; Zymanczyk-Duda, E.; Brzezinska-Rodak, M.; Majewska, P.; Lejczak, B. *Tetrahedron: Asymmetry* **2008**, *19*, 450.
90. (a) Guiry, P. J.; Saunders, C. P. *Adv. Synth. Catal.* **2004**, *346*, 497; (b) Kostas, I. D. *Curr. Org. Synth.* **2008**, *5*, 227; (c) Amoroso, D.; Graham, T. W.; Guo, R.; Tsang, C.-W.; Abdur-Rashid, K. *Aldrichimica Acta* **2008**, *41*, 15; (d) Börner, A., *Phosphorous Ligands in Asymmetric Catalysis*. Wiley-VCH: Weinheim, 2008.

91. (a) Ménard, G.; Jong, H.; Fryzuk, M. D. *Organometallics* **2009**, *28*, 5253; (b) Elsegood, M. R. J.; Lake, A. J.; Smith, M. B. *Eur. J. Inorg. Chem.* **2009**, *2009*, 1068; (c) Fey, N.; Harvey, J. N.; Lloyd-Jones, G. C.; Murray, P.; Orpen, A. G.; Osborne, R.; Purdie, M. *Organometallics* **2008**; (d) Dugal-Tessier, J.; Dake, G. R.; Gates, D. P. *Organometallics* **2007**.
92. Yang, H.; Lugan, N.; Mathieu, R. *Organometallics* **1997**, *16*, 2089.
93. Gilbertson, S. R.; Genov, D. G.; Rheingold, A. L. *Org. Lett.* **2000**, *2*, 2885.
94. Bianchini, C.; Cicchi, S.; Peruzzini, M.; Pietrusiewiçz, K. M.; Brandi, A. *J. Chem. Soc. Chem. Commun.* **1995**, 833.
95. Lam, H.; Horton, P. N.; Hursthouse, M. B.; Aldous, D. J.; Hii, K. K. *Tetrahedron Lett.* **2005**, *46*, 8145.
96. Sun, X.-M.; Koizumi, M.; Manabe, K.; Kobayashi, S. *Adv. Synth. Cat.* **2005**, *347*, 1893.
97. Kobayashi, S.; Shiraishi, N.; Lam, W. W. L.; Manabe, K. *Tetrahedron Lett.* **2001**, *42*, 7303.
98. (a) Maj, A. M.; Pietrusiewiçz, K. M.; Suisse, I.; Agbossou, F.; Mortreux, A. *J. Organomet. Chem.* **2001**, *626*, 157; (b) Maj, A. M.; Pietrusiewicz, K. M.; Suisse, I.; Agbossou, F.; Mortreux, A. *Tetrahedron: Asymmetry* **1999**, *10*, 831.
99. Oliana, M.; King, F.; Horton, P. N.; Hursthouse, M. B.; Hii, K. K. *J. Org. Chem.* **2006**, *71*, 2472.
100. Cheng, X.; Horton, P. N.; Hursthouse, M. B.; Hii, K. K. M. *Tetrahedron: Asymmetry* **2004**, *15*, 2241.
101. Camus, J. M.; Andrieu, J.; Richard, P.; Poli, R.; Darcel, C.; Jugé, S. *Tetrahedron: Asymmetry* **2004**, *15*, 2061.
102. Fourgeaud, P.; Daydé, B.; Volle, J.-N.; Vors, J.-P.; Van der Lee, A.; Pirat, J.-L.; Virieux, D. *Org. Lett.* **2011**, *13*, 2940.
103. Queffelec, C.; Ribière, P.; Montchamp, J.-L. *J. Org. Chem.* **2008**, *73*, 8987.
104. Dearden, M. J.; Firkin, C. R.; Hermet, J. P. R.; O'Brien, P. *J. Am. Chem. Soc.* **2002**, *124*, 11870.
105. (a) Imamoto, T.; Watanabe, J.; Wada, Y.; Masuda, H.; Yamada, H.; Tsuruta, H.; Matsukawa, S.; Yamaguchi, K. *J. Am. Chem. Soc.* **1998**, *120*, 1635; (b) Oohara, N.; Katagiri, K.; Imamoto, T. *Tetrahedron: Asymmetry* **2003**, *14*, 2171.
106. (a) Jugé, S.; Stephan, M.; Laffitte, J. A.; Genêt, J. P. *Tetrahedron Lett.* **1990**, *31*, 6357; (b) Colby, E. A.; Jamison, T. F. *J. Org. Chem.* **2003**, *68*, 156.
107. Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849.
108. (a) Kanzian, T.; Nigst, T. A.; Maier, A.; Pichl, S.; Mayr, H. *Eur. J. Org. Chem.* **2009**, *2009*, 6379; (b) Brotzel, F.; Chu, Y. C.; Mayr, H. *J. Org. Chem.* **2007**, *72*, 3679.
109. Ohashi, A.; Kikuchi, S.; Yasutake, M.; Imamoto, T. *Eur. J. Org. Chem.* **2002**, 2535.
110. Small, B. L.; Rios, R.; Fernandez, E. R.; Gerlach, D. L.; Halfen, J. A.; Carney, M. J. *Organometallics* **2010**, *29*, 6723.
111. (a) For a study of TMSCl as an additive in lithiumcuprate chemistry see: Bertz, S. H.; Chopra, A.; Eriksson, M.; Ogle, C. A.; Seagle, P. *Chem. Eur. J.* **1999**, *5*, 2680; (b) For an eleboration on conjugate additions, see: Perlmutter, P., *Conjugate Addition Reactions in Organic Synthesis*. Pergamon: Oxford, 1992.
112. (a) Alexakis, A.; Benhaim, C.; Rosse, S.; Humam, M. *J. Am. Chem. Soc.* **2002**, *124*, 5262; (b) Alexakis, A.; Vastra, J.; Mangeney, P. *Tetrahedron Lett.* **1997**, *38*, 7745.

113. (a) Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2024; (b) Noyori, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 2008; (c) Knowles, W. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 1998.
114. Sandoval, C. A.; Li, Y.; Ding, K.; Noyori, R. *Chem. Asian J.* **2008**, *3*, 1801.
115. Kitamura, M.; Ohkuma, T.; Inoue, S.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Ohta, T.; Takaya, H.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 629.
116. Ohkuma, T.; Ooka, H.; Hashiguchi, S.; Ikariya, T.; Noyori, R. **1995**, *117*, 2675.
117. Noyori, R.; Ohkuma, T. *Angew. Chem. Int. Ed.* **2001**, *40*, 40.
118. (a) Abdur-Rashid, K.; Faatz, M.; Lough, A. J.; Morris, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 7473; (b) Abdur-Rashid, K.; Clapham, S. E.; Hadzovic, A.; Harvey, J. N.; Lough, A. J.; Morris, R. H. *J. Am. Chem. Soc.* **2002**, *124*, 15104; (c) Sandoval, C. A.; Ohkuma, T.; Muñiz, K.; Noyori, R. *J. Am. Chem. Soc.* **2003**, *125*, 13490; (d) Hamilton, R. J.; Leong, C. G.; Bigam, G.; Miskolzie, M.; Bergens, S. H. *J. Am. Chem Soc.* **2005**, *127*, 4152; (e) Abdur-Rashid, K.; Guo, R.; Lough, A. J.; Morris, R. H.; Song, D. *Adv. Synth. Cat.* **2005**, *347*, 571.
119. (a) Xu, Y.; Alcock, N. W.; Clarkson, G. J.; Docherty, G.; Woodward, G.; Wills, M. *Org. Lett.* **2004**, *6*, 4105; (b) Xu, Y.; Clarkson, G. C.; Docherty, G.; North, C. L.; Woodward, G.; Wills, M. *J. Org. Chem.* **2005**, *70*, 8079.
120. Jing, Q.; Zhang, X.; Sun, J.; Ding, K. *Adv. Synth. Cat.* **2005**, *347*, 1193.
121. Genov, D. G.; Ager, D. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 2816.
122. Huang, H.; Okuno, T.; Tsuda, K.; Yoshimura, M.; Kitamura, M. *J. Am. Chem. Soc.* **2006**, *128*, 8716.
123. Guo, R.; Lough, A. J.; Morris, R. H.; Song, D. *Organometallics* **2004**, *23*, 5524.
124. Naud, F.; Malan, C.; Spindler, F.; Rüggeberg, C.; Schmidt, A. T.; Blaser, H.-U. *Adv. Synth. Cat.* **2006**, *348*, 47.
125. Boubekeur, L.; Ulmer, S.; Ricard, L.; Mézailles, N.; Le Floch, P. *Organometallics* **2005**, *25*, 315.
126. Anderson, C. E.; Apperley, D. C.; Batsanov, A. S.; Dyer, P. W.; Howard, J. A. K. *Dalton Trans.* **2006**, 4134.
127. Zhang, J.; Gandelman, M.; Shimon, L. J. W.; Milstein, D. *Dalton Trans.* **2007**, 107.
128. Del Zotto, A.; Baratta, W.; Ballico, M.; Herdtweck, E.; Rigo, P. *Organometallics* **2007**, *26*, 5636.
129. (a) Kohl, S. W.; Winer, L.; Schwartzburd, L.; Konstantinovski, L.; Shimon, L. J. W.; Ben-David, Y.; Iron, M. A.; Milstein, D. *Nature* **2009**, *324*, 74; (b) Sandhya, K. S.; Suresh, C. H. *Organometallics* **2011**, *30*, 3888.
130. Wang, Z.-X.; Wang, L. *Chem. Commun.* **2007**, 2423.
131. Sladojevich, F.; Trabocchi, A.; Guarna, A.; Dixon, D. J. *J. Am. Chem. Soc.* **2011**, *133*, 1710.
132. Hou, J.; Sun, W.-H.; Zhang, S.; Ma, H.; Deng, Y.; Lu, X. *Organometallics* **2005**, *25*, 236.
133. Han, F.-B.; Zhang, Y.-L.; Sun, X.-L.; Li, B.-G.; Guo, Y.-H.; Tang, Y. *Organometallics* **2008**, *27*, 1924.
134. Brenchley, G.; Merifield, E.; Wills, M.; Fedouloff, M. *Tetrahedron Lett.* **1994**, *35*, 2791.
135. (a) Díaz-Valenzuela, M. B.; Phillips, S. D.; France, M. B.; Gunn, M. E.; Clarke, M. L. *Chem. Eur. J.* **2009**, *15*, 1227; (b) Clarke, M. L.; Díaz-Valenzuela, M. B.; Slawin, A. M. Z. *Organometallics* **2006**, *26*, 16.
136. Phillips, S. D.; Fuentes, J. A.; Clarke, M. L. *Chem. Eur. J.* **2010**, *16*, 8002.

137. Johansson, M. J.; Andersson, K. H. O.; Kann, N. *J. Org. Chem.* **2008**, *73*, 4458.
138. Dolhem, F.; Johansson, M. J.; Antonsson, T.; Kann, N. *Synlett* **2006**, *20*, 3389.
139. Xie, J.-H.; Liu, X.-Y.; Xie, J.-B.; Wang, L.-X.; Zhou, Q.-L. *Angew. Chem., Int. Ed.* **2011**, *50*, 7329.
140. Marxen, T. L.; Johnson, B. J.; Nilsson, P. V.; Pignolet, L. H. *Inorg. Chem.* **1984**, *23*, 4663.
141. Jeffery, J. C.; Rauchfuss, T. B.; Tucker, P. A. *Inorg. Chem.* **1980**, *19*, 3306.
142. Gao, J.-X.; Ikariya, T.; Noyori, R. *Organometallics* **1996**, *15*, 1087.
143. Mezzetti, A. *Dalton Trans.* **2011**, *39*, 7851.
144. Santoro, F.; Althaus, M.; Bonaccorsi, C.; Gischig, S.; Mezzetti, A. *Organometallics* **2008**, *27*, 3866.
145. Ranocchiari, M.; Mezzetti, A. *Organometallics* **2009**, *28*, 3611.
146. (a) Schotes, C.; Mezzetti, A. *Chimia* **2011**, *65*, 231; (b) Schotes, C.; Mezzetti, A. *J. Am. Chem. Soc* **2011**, *132*, 3652.
147. Schotes, C.; Mezzetti, A. *Angew. Chem. Int. Ed.* **2011**, *50*, 3072.
148. G. J. Ligtenbarg, A.; K. van den Beuken, E.; Meetsma, A.; Veldman, N.; J. J. Smeets, W.; L. Spek, A.; L. Feringa, B. *J. Chem. Soc., Dalton Trans.* **1998**, 263.
149. (a) Zhang, H.; Yang, C.-B.; Li, Y.-Y.; Donga, Z.-R.; Gao, J.-X.; Nakamura, H.; Murata, K.; Ikariya, T. *Chem. Commun.* **2003**, 142; (b) Jing-Xing, G.; Hui-Lin, W.; Wai-Kwok, W.; Man-Chung, T.; Wing-Tak, W. *Polyhedron* **1996**, *15*, 1241; (c) Gao, J.-X.; Zhang, H.; Yi, X.-D.; Xu, P.-P.; Tang, C.-L.; Wan, H.-L.; Tsai, K.-R.; Ikariya, T. *Chirality* **2000**, *12*, 383; (d) Gao, J.-X.; Yi, X.-D.; Xu, P.-P.; Tang, C.-L.; Wan, H.-L.; Ikariya, T. *J. Organomet. Chem.* **1999**, *592*, 290.
150. Dong, Z.-R.; Li, Y.-Y.; Chen, J.-S.; Li, B.-Z.; Xing, Y.; Gao, J.-X. *Org. Lett.* **2005**, *7*, 1043.
151. (a) Atoh, M.; Kashiwabara, K.; Fujita, J. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2793; (b) Atoh, M.; Kashiwabara, K.; Fujita, J. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 3492.
152. Atoh, M.; Osholm Sorensen, H.; Andersen, P. *Acta Chim. Scand.* **1997**, *51*, 1169.
153. Bennett, J.; David Rae, A.; Salem, G.; Ward, N. C.; Waring, P.; Wells, K.; Willis, A. C. *J. Chem. Soc., Dalton Trans.* **2002**, 234.
154. Mikhailine, A. A.; Kim, E.; Dingels, C.; Lough, A. J.; Morris, R. H. *Inorg. Chem.* **2008**, *47*, 6587.
155. Meyer, N.; Lough, A. J.; Morris, R. H. *Chem. Eur. J.* **2009**, *15*, 5605.
156. (a) Mikhailine, A.; Lough, A. J.; Morris, R. H. *J. Am. Chem. Soc.* **2009**, *131*, 1394; (b) Lagaditis, P. O.; Lough, A. J.; Morris, R. H. *J. Am. Chem. Soc.* **2011**, *133*, 9662; (c) Sues, P. E.; Lough, A. J.; Morris, R. H. *Organometallics* **2011**, *30*, 4418.
157. Chen, J.; Szalda, D. J.; Fujita, E.; Creutz, C. *Inorg. Chem.* **2010**, *49*, 9380.
158. Tsukada, N.; Ohba, Y.; Inoue, Y. *J. Organomet. Chem.* **2003**, *687*, 436.
159. (a) Tsukada, N.; Mitsuboshi, T.; Setoguchi, H.; Inoue, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12102; (b) Tsukada, N.; Murata, K.; Inoue, Y. *Tetrahedron Lett.* **2005**, *46*, 7515; (c) Tsukada, N.; Setoguchi, H.; Mitsuboshi, T.; Inoue, Y. *Chem. Lett.* **2006**, *35*, 1164; (d) Tsukada, N.; Ninomiya, S.; Aoyama, Y.; Inoue, Y. *Org. Lett.* **2007**, *9*, 2919; (e) Tsukada, N.; Wada, M.; Takahashi, N.; Inoue, Y. *J. Organomet. Chem.* **2009**, *694*, 1333.
160. Son, K.-S.; Pearson, D. M.; Jeon, S.-J.; Waymouth, R. M. *Eur. J. Inorg. Chem.* **2011**, *2011*, 4256.
161. Trost, B. M.; Van Vranken, D. L. *Angew. Chem. Int. Ed.* **1992**, *31*, 228.

162. (a) Lu, Z.; Ma, S. *Angew. Chem. Int. Ed.* **2008**, *47*, 258; (b) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921.
163. Trost, B. M.; Machacek, M. R.; Aponick, A. *Acc. Chem. Res.* **2006**, *39*, 747.
164. (a) Fairlamb, I. J. S.; Lloyd-Jones, G. C. *Chem. Commun.* **2000**, 2447; (b) Lloyd-Jones, G. C.; Stephen, S. C. *Chem.--Eur. J.* **1998**, *4*, 2539; (c) Trost, B. M.; Breit, B.; Organ, M. G. *Tetrahedron Lett.* **1994**, *35*, 5817; (d) Butts, C. P.; Crosby, J.; Lloyd-Jones, G. C.; Stephen, S. C. *Chem. Commun.* **1999**, 1707.
165. Butts, C. P.; Filali, E.; Lloyd-Jones, G. C.; Norrby, P.-O.; Sale, D. A.; Schramm, Y. *J. Am. Chem. Soc.* **2009**, *131*, 9945.
166. Raymond, Z. *Tetrahedron Lett.* **1989**, *30*, 463.
167. Tanase, T.; Igoshi, T.; Kobayashi, K.; Yamamoto, Y. *J. Chem. Research* **1998**, 538.
168. Uang, R.-H.; Chan, C.-K.; Peng, S.-M.; Che, C.-M. *J. Chem. Soc. Chem. Commun.* **1994**, 2561.
169. (a) Schenck, T. G.; Downes, J. M.; Milne, C. R. C.; Mackenzie, P. B.; Boucher, T. G.; Whelan, J.; Bosnich, B. *Inorg. Chem.* **1985**, *24*, 2334; (b) Schenck, T. G.; Milne, C. R. C.; Sawyer, J. F.; Bosnich, B. *Inorg. Chem.* **1985**, *24*, 2338.
170. (a) Tanaka, S.; Akita, M. *Angew. Chem. Int. Ed.* **2001**, *40*, 2865; (b) Tanaka, S.; Dubs, C.; Inagaki, A.; Akita, M. *Organometallics* **2004**, *24*, 163; (c) Gondoh, A.; Koike, T.; Akita, M. *Inorg. Chim. Acta* **2011**, *374*, 489.
171. Havlicek, M. D.; Gilje, J. W. *Inorg. Chem.* **1972**, *11*, 1624.
172. Sreenivasa Reddy, V.; Katti, K. V. *Inorg. Chem.* **1994**, *33*, 2695.
173. Reddy, V. S.; Katti, K. V.; Barnes, C. L. *Inorg. Chem.* **1995**, *34*, 5483.
174. (a) Slawin, A. M. Z.; Wainwright, M.; Woollins, J. D. *J. Chem. Soc. Dalton Trans.* **2002**, 513; (b) Bowen, L. E.; Charernsuk, M.; Hey, T. W.; McMullin, C. L.; Orpen, A. G.; Wass, D. F. *Dalton. Trans.* **2011**, *39*, 560.
175. (a) Scanlon, L. G.; Tsao, Y. Y.; Cummings, S. C.; Toman, K.; Meek, D. W. *J. Am. Chem. Soc.* **1980**, *102*, 6849; (b) Scanlon, L. G.; Tsao, Y. Y.; Toman, K.; Cummings, S. C.; Meek, D. W. *Inorg. Chem.* **1982**, *21*, 1215; (c) Ansell, C. W. G.; Cooper, M. K.; Dancey, K. P.; Duckworth, P. A.; Henrick, K.; McPartlin, M.; Tasker, P. A. *J. Chem. Soc., Chem. Commun.* **1985**, 439.
176. (a) Kyba, E. P.; John, A. M.; Brown, S. B.; Hudson, C. W.; McPhaul, M. J.; Harding, A.; Larsen, K.; Niedzwiecki, S.; Davis, R. E. *J. Am. Chem. Soc.* **1980**, *102*, 139; (b) Kyba, E. P.; Davis, R. E.; Hudson, C. W.; John, A. M.; Brown, S. B.; McPhaul, M. J.; Liu, L.-K.; Glover, A. C. *J. Am. Chem. Soc.* **1981**, *103*, 3868; (c) Fryzuk, M. D.; Love, J. B.; Rettig, S. J. *Chem. Commun.* **1996**, 2783.
177. Ranocchiari, M.; Mezzetti, A. *Organometallics* **2009**, *28*, 1286.
178. Tian, R.; Mathey, F. *Organometallics* **2011**, *30*, 3472.
179. Phillips, S. D.; Andersson, K. H. O.; Kann, N.; Kuntz, M. T.; France, M. B.; Wawrzyniak, P.; Clarke, M. L. *Catal. Sci. Technol.* **2011**, *1*, 1336.
180. Juge, S.; Stephan, M.; Laffitte, J. A.; Genet, J. P. *Tetrahedron Lett.* **1990**, *31*, 6357.
181. von Liebig, J. *Ann. d. Pharm.* **1860**, *113*, 246.
182. (a) Dalko, P. I., *Enantioselective Organocatalysis*. Wiley-VCH: Weinheim, 2007; (b) Berkessel, A.; Gröger, H., *Asymmetric Organocatalysis*. Wiley-VCH: Weinheim, 2005.
183. Kagan, H. B., In *Comprehensive Asymmetric Catalysis*, Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds. Springer-Verlag: Berlin, 1999; Vol. 1, pp 101-118.

184. (a) Toma, S.; Meciarová, M.; Sebesta, R. *Eur. J. Org. Chem.* **2009**, *2009*, 321; (b) Barbas, C. F. *Angew. Chem. Int. Ed.* **2008**, *47*, 42; (c) Alonso, D. A.; Kitagaki, S.; Utsumi, N.; Barbas, C. F. *Angew. Chem. Int. Ed.* **2008**, *47*, 4588; (d) Dondoni, A.; Massi, A. *Angew. Chem. Int. Ed.* **2008**, *47*, 4638; (e) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem. Int. Ed.* **2008**, *47*, 6138.
185. Hayase, T.; Shibata, T.; Soai, K.; Wakatsuki, Y. *Chem. Commun.* **1998**, 1271.
186. (a) Ma, M. F. P.; Li, K.; Zhou, Z.; Tang, C.; Chan, A. S. C. *Tetrahedron: Asymmetry* **1999**, *10*, 3259; (b) Muller, P.; Nury, P.; Bernardinelli, G. *Helv. Chim. Acta* **2000**, *83*, 843.
187. Sewgobind, N. V.; Wanner, M. J.; Ingemann, S.; de Gelder, R.; van Maarseveen, J. H.; Hiemstra, H. *J. Org. Chem.* **2008**, *73*, 6405.
188. Chen, X.-H.; Zhang, W.-Q.; Gong, L.-Z. *J. Am. Chem. Soc.* **2008**, *130*, 5652.
189. Akiyama, T.; Suzuki, T.; Mori, K. *Org. Lett.* **2009**, *11*, 2445.
190. (a) Vedejs, E.; Daugulis, O.; MacKay, J. A.; Rozners, E. *Synlett* **2001**, 1499; (b) Vedejs, E.; MacKay, J. A. *Org. Lett.* **2001**, *3*, 535.
191. Vedejs, E.; Daugulis, O.; Tuttle, N. *J. Org. Chem.* **2004**, *69*, 1389.
192. (a) Nakajima, M.; Kotani, S.; Ishizuka, T.; Hashimoto, S. *Tetrahedron Lett.* **2005**, *46*, 157; (b) Denmark, S. E.; Barsanti, P. A.; Wong, K.-T.; Stavenger, R. A. *J. Org. Chem.* **1998**, *63*, 2428; (c) Denmark, S. E.; Stavenger, R. A.; Wong, K. T.; Su, X. P. *J. Am. Chem. Soc.* **1999**, *121*, 4982; (d) Denmark, S. E.; Stavenger, R. A. *J. Am. Chem. Soc.* **2000**, *122*, 8837; (e) Denmark, S. E.; Fu, J. P. *J. Am. Chem. Soc.* **2003**, *125*, 2208; (f) Hellwig, J.; Belser, T.; Muller, J. F. K. *Tetrahedron Lett.* **2001**, *42*, 5417; (g) Simonini, V.; Benaglia, M.; Pignataro, L.; Guizzetti, S.; Celentano, G. *Synlett* **2008**, 1061.
193. Zhang, C. M.; Lu, X. Y. *J. Org. Chem.* **1995**, *60*, 2906.
194. Zhu, G. X.; Chen, Z. G.; Jiang, Q. Z.; Xiao, D. M.; Cao, P.; Zhang, X. M. *J. Am. Chem. Soc.* **1997**, *119*, 3836.
195. (a) Liang, Y.; Liu, S.; Yu, Z.-X. *Synlett* **2009**, 905; (b) Liang, Y.; Liu, S.; Xia, Y. Z.; Li, Y. H.; Yu, Z. X. *Chem. Eur. J.* **2008**, *14*, 4361.
196. Cowen, B. J.; Miller, S. J. *J. Am. Chem. Soc.* **2007**, *129*, 10988.
197. Voituriez, A.; Panossian, A. F.-B., N.; Retailleau, P.; Marinetti, A. *Adv. Synth. Cat.* **2009**, *351*, 1968.
198. (a) Wurz, R. P.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 12234; (b) Fang, Y. Q.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 5660; (c) Jean, L.; Marinetti, A. *Tetrahedron Lett.* **2006**, *47*, 2141.
199. (a) Na, R.; Jing, C.; Xu, Q.; Jiang, H.; Wu, X.; Shi, J.; Zhong, J.; Wang, M.; Benitez, D.; Tkatchouk, E.; Goddard, W. A.; Guo, H.; Kwon, O. *J. Am. Chem. Soc.* **2011**, *133*, 13337; (b) Chung, Y. K.; Fu, G. C. *Angew. Chem. Int. Ed.* **2009**, *48*, 2225.
200. Ye, L. W.; Zhou, J.; Tang, Y. *Chem. Soc. Rev.* **2008**, *37*, 1140.
201. (a) Schuler, M.; Voituriez, A.; Marinetti, A. *Tetrahedron Asymmetry* **2010**, *21*, 1569; (b) Xiao, H.; Chai, Z.; Zheng, C. W.; Yang, Y. Q.; Liu, W.; Zhang, J. K.; Zhao, G. *Angew. Chem. Int. Ed.* **2010**, *49*, 4467; (c) Sun, Y.-W.; Guan, X.-Y.; Shi, M. *Org. Lett.* **2010**, *12*, 5664; (d) Pinto, N.; Neel, M.; Panossian, A.; Retailleau, P.; Frison, G.; Voituriez, A.; Marinetti, A. *Chem. Eur. J.* **2010**, *16*, 1033; (e) Guan, X.-Y.; Wei, Y.; Shi, M. *Org. Lett.* **2010**, *12*, 5024; (f) Creech, G. S.; Kwon, O. *Org. Lett.* **2008**, *10*, 429; (g) Kinderman, S. S.; van Maarseveen, J. H.; Hiemstra, H. *Synlett* **2011**, 1693; (h) Pinto, N.; Fleury-Bregeot, N.; Marinetti, A. *Eur. J. Org. Chem.* **2009**, 146; (i) Panossian, A.; Fleury-

Bregeot, N.; Marinetti, A. *Eur. J. Org. Chem.* **2008**, 3826; (j) Fleury-Bregeot, N.; Jean, L.; Retailleau, P.; Marinetti, A. *Tetrahedron* **2007**, *63*, 11920; (k) Sampath, M.; Loh, T. P. *Chem. Commun.* **2009**, 1568.

202. (a) Voituriez, A.; Pinto, N.; Neel, M.; Retailleau, P.; Marinetti, A. *Chem. Eur. J.* **2010**, *16*, 12541; (b) Zhang, X. C.; Cao, S. H.; Wei, Y.; Shi, M. *Org. Lett.* **2011**, *13*, 1142; (c) Deng, H. P.; Wei, Y.; Shi, M. *Org. Lett.* **2011**, *13*, 3348; (d) Zhang, X. C.; Cao, S. H.; Wei, Y.; Shi, M. *Chem. Commun.* **2011**, *47*, 1548; (e) Tan, B.; Candeias, N. R.; Barbas, C. F. *J. Am. Chem. Soc.* **2011**, *133*, 4672.
203. Methot, J. L.; Roush, W. R. *Adv. Synth. Catal.* **2004**, *346*, 1035.
204. For examples of asymmetric organocatalytic cycloaddition reactions, see: Moyano, A.; Rios, R. *Chem. Rev.* **2011**, *111*, 4703.
205. Fujiwara, Y.; Fu, G. C. *J. Am. Chem. Soc.* **2011**, *133*, 12293.
206. Lu, X. Y.; Lu, Z.; Zhang, X. M. *Tetrahedron* **2006**, *62*, 457.
207. (a) Nicholas, K. M.; Pettit, R. *J. Organomet. Chem.* **1972**, *44*, C21; (b) Nicholas, K. M.; Pettit, R. *Tetrahedron Lett.* **1971**, *12*, 3475.
208. Omae, I. *Appl. Organomet. Chem.* **2007**, *21*, 318.
209. Connor, R. E.; Nicholas, K. M. *J. Organomet. Chem.* **1977**, *125*, C45.
210. Melikyan, G. G.; Bright, S.; Monroe, T.; Hardcastle, K. I.; Ciurash, J. *Angew. Chem. Int. Ed.* **1998**, *37*, 161.
211. Padmanabhan, S.; Nicholas, K. M. *J. Organomet. Chem.* **1984**, *268*, C23.
212. (a) Bromfield, K. M.; Graden, H.; Ljungdahl, N.; Kann, N. *Dalton. Trans.* **2009**, 5051; (b) Díaz, D. D.; Betancort, J. M.; Martín, V. S. *Synlett* **2007**, *2007*, 0343; (c) Barry J, T. *Tetrahedron* **2002**, *58*, 4133; (d) Green, J. R. *Curr. Org. Chem.* **2001**, *5*, 809; (e) Muller, T. J. J. *Eur. J. Org. Chem.* **2001**, 2021; (f) Nicholas, K. M. *Acc. Chem. Res.* **1987**, *20*, 207.
213. Mukai, C.; Moharram, S. M.; Kataoka, O.; Hanaoka, M. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2849.
214. Magnus, P.; Carter, P.; Elliott, J.; Lewis, R.; Harling, J.; Pitterna, T.; Bauta, W. E.; Fortt, S. *J. Am. Chem. Soc.* **1992**, *114*, 2544.
215. Kira, K.; Isobe, M. *Tetrahedron Lett.* **2001**, *42*, 2821.
216. Seyferth, D.; Wehman, A. T. *J. Am. Chem. Soc.* **1970**, *92*, 5520.
217. (a) Eritja, R. *Int. J. Pept. Res. Ther.* **2007**, *13*, 53; (b) Müller, S.; Wolf, J.; Ivanov, S. A. *Curr. Org. Synth.* **2004**, *1*, 293; (c) Beaucage, S. L.; Caruthers, M. H. *Tetrahedron: Lett.* **1981**, *22*, 1859.
218. Hulst, R.; de Vries, N. K.; Feringa, B. L. *Tetrahedron: Asymmetry* **1994**, *5*, 699.
219. (a) Feringa, B. L.; Pineschi, M.; Arnold, L. A.; Imbos, R.; de Vries, A. H. M. *Angew. Chem. Int. Ed.* **1997**, *36*, 2620; (b) de Vries, A. H. M.; Meetsma, A.; Feringa, B. L. *Angew. Chem. Int. Ed.* **1996**, *35*, 2374.
220. (a) Reetz, M. T.; Mehler, G. *Angew. Chem. Int. Ed.* **2000**, *39*, 3889; (b) Claver, C.; Fernandez, E.; Gillon, A.; Heslop, K.; Hyett, D. J.; Martorell, A.; Orpen, A. G.; Pringle, P. G. *Chem. Commun.* **2000**, 961.
221. van den Berg, M.; Minnaard, A. J.; Schudde, E. P.; van Esch, J.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L. *J. Am. Chem. Soc.* **2000**, *122*, 11539.
222. Bruneau, C.; Renaud, J.-L., In *Phosphorous Ligands in Asymmetric Catalysis*, Börner, A., Ed. Wiley-VCH: Weinheim, 2008; pp 36-70.
223. Teichert, J. F.; Feringa, B. L. *Angew. Chem. Int. Ed.* **2010**, *49*, 2486.

224. Lam, H. W. *Synthesis* **2011**, 2011.
225. Bernsmann, H.; van den Berg, M.; Hoen, R.; Minnaard, A. J.; Mehler, G.; Reetz, M. T.; De Vries, J. G.; Feringa, B. L. *J. Org. Chem.* **2005**, *70*, 943.
226. Alexakis, A.; Polet, D.; Rosset, S.; March, S. *J. Org. Chem.* **2004**, *69*, 5660.
227. Zhang, F.-Y.; Chan, A. S. C. *Tetrahedron: Asymmetry* **1998**, *9*, 1179.
228. (a) Tyrrell, E.; Millet, J.; Tesfa, K. H.; Williams, N.; Mann, A.; Tillett, C.; Muller, C. *Tetrahedron* **2007**, *63*, 12769; (b) Jacobi, P. A.; Herradura, P. *Tetrahedron Lett.* **1996**, *37*, 8297; (c) Jacobi, P. A.; Murphree, S.; Rupprecht, F.; Zheng, W. J. *J. Org. Chem.* **1996**, *61*, 2413; (d) Jacobi, P. A.; Herradura, P. *Can. J. Chem.* **2001**, *79*, 1727.
229. (a) Montana, A. M.; Cano, M. *Tetrahedron Lett.* **2001**, *42*, 7961; (b) Muehldorf, A. V.; Guzmanperez, A.; Kluge, A. F. *Tetrahedron Lett.* **1994**, *35*, 8755; (c) Montana, A. M.; Cano, M. *Tetrahedron* **2002**, *58*, 933; (d) Diaz, D. D.; Betancort, J. M.; Crisostomo, F. R. P.; Martin, T.; Martin, V. S. *Tetrahedron* **2002**, *58*, 1913.
230. (a) Diaz, D. D.; Ramirez, M. A.; Martin, V. S. *Chem. Eur. J.* **2006**, *12*, 2593; (b) Caffyn, A. J. M.; Nicholas, K. M. *J. Am. Chem. Soc.* **1993**, *115*, 6438.
231. (a) Kuhn, O.; Rau, D.; Mayr, H. *J. Am. Chem. Soc.* **1998**, *120*, 900; (b) Bradley, D. H.; Khan, M. A.; Nicholas, K. M. *Organometallics* **1992**, *11*, 2598.
232. Konya, D.; Robert, F.; Gimbert, Y.; Greene, A. E. *Tetrahedron Lett.* **2004**, *45*, 6975.
233. Achard, M.; Tenaglia, A.; Buono, G. *Org. Lett.* **2005**, *7*, 2353.
234. (a) For ligand **145a**, see: Duursma, A.; Lefort, L.; Boogers, J. A. F.; de Vries, A. H. M.; de Vries, J. G.; Minnaard, A. J.; Feringa, B. L. *Org. Biomol. Chem.* **2004**, *2*, 1682; (b) For ligand **145d**, see: Lefort, L.; Boogers, J. A. F.; de Vries, A. H. M.; de Vries, J. G. *Org. Lett.* **2004**, *6*, 1733; (c) For ligand **145e**, see: Panella, L.; Aleixandre, A. M.; Kruidhof, G. J.; Robertus, J.; Feringa, B. L.; de Vries, J. G.; Minnaard, A. J. *J. Org. Chem.* **2006**, *71*, 2026; (d) For ligand **145f**, see: Boiteau, J. G.; Imbos, R.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2003**, *5*, 1385; (e) For ligand **145g**, see: de Vries, J. G.; Lefort, L. *Chem. Eur. J.* **2006**, *12*, 4722; (f) For ligands **145h** and **145i**, see ref. 231; (g) For ligands **145j** and **145k**, see ref. 217b; (h) For ligands **145l** and **145m**, see: Peña, D.; Minnaard, A. J.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L. *Org. Lett.* **2003**, *5*, 475; (i) For ligand **145n**, see: Imbos, R.; Brilman, M. H. G.; Pineschi, M.; Feringa, B. L. *Org. Lett.* **1999**, *1*, 623.
235. Hoffman, R. V.; Kim, H. O. *J. Org. Chem.* **1995**, *60*, 5107.
236. Yang, D.; Chen, F.; Dong, Z. M.; Zhang, D. W. *J. Org. Chem.* **2004**, *69*, 2221.
237. For an example of Co-catalyzed homocoupling of terminal alkynes, see: Krafft, M. E.; Hirosawa, C.; Dalal, N.; Ramsey, C.; Stiegman, A. *Tetrahedron Lett.* **2001**, *42*, 7733.
238. Gachkova, N.; Cassel, J.; Leue, S.; Kann, N. *J. Comb. Chem.* **2005**, *7*, 449.
239. Castro, J.; Moyano, A.; Pericas, M. A.; Riera, A.; Maestro, M. A.; Mahia, J. *Organometallics* **2000**, *19*, 1704.
240. (a) Ljungdahl, N.; Kann, N. *Angew. Chem. Int. Ed.* **2009**, *48*, 642; (b) Miyake, Y.; Uemura, S.; Nishibayashi, Y. *ChemCatChem* **2009**, *1*, 342; (c) For a review on catalytic propargylic substitution, see: Detz, R. J.; Hiemstra, H.; van Maarseveen, J. H. *Eur. J. Org. Chem.* **2009**, 6263.