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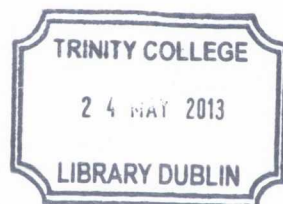
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New Methodologies
for Catalysis
and Combinatorial
Chemistry

Robin Frauenlob

2013



Thesis 9846

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Summary

The enantioselective synthesis of chiral molecules, such as those required by the pharmaceutical industry, is one of the most important tasks in chemistry. Asymmetric catalysis is an attractive way to synthesise enantiopure compounds. Thus, the synthesis of chiral ligands has shown a great interest. Catalytic methods for the generation of enantiomerically pure compounds traditionally can be a difficult and time consuming process. The selectivity of a reaction depends not only on the catalyst but also on the substrate, which makes the quest of finding a catalyst for a specific substrate harder. The existing combinatorial methods to find a specific chiral ligand for a substrate are discussed in chapter 1. In chapter 2 new methodologies to elaborate bidentate ligand libraries are displayed. The ligands were generated *in situ* by assembling two fragments together using high yielding reactions. The fragments were prepared easily from cheap and commercially available starting materials. Many type of ligands were successfully synthesised *in situ* including imines, imidazolidines, oxazolidines, oxazolines and imidazolines. The ligands were tested in two reactions: a transfer hydrogenation of ketones catalysed by rhodium in water and a zinc catalysed hydrosilylation of ketones with PMHS. Enantiomeric excesses and yields of the products were assessed by CSP-HPLC and ^1H NMR. It was proven that ligands synthesised *in situ* gave comparable results to purified ligands with a good reproducibility.

Multicomponent reactions are reactions in which three or more starting materials yield a product retaining the majority of the starting material atoms. MCRs are economically advantageous, environmentally friendly and a good way to produce bioactive compound libraries. Among them the Petasis reaction has generated great interest. The features of the reaction are discussed in chapter 3. Also in chapter 3, a review of boronic acids nucleophiles in copper catalysed reactions is presented to show the potential of this cheap way of carbon-carbon coupling. To broaden the scope of the existing Petasis reaction, a new copper catalysed version is described in chapter 4. The new reaction requires a boronic acid, a secondary amine, an aldehyde with a coordinating group and a catalytic

amount of copper with a bidentate ligand. The scope of the reaction was investigated and a mechanism proposed based on experimental data. Chiral ligands were tested in an attempt to obtain enantio-enriched aminoesters. EEDQ, another substrate, was also used to add boronic acids, a process catalysed by copper again. As for the copper catalysed Petasis reaction chiral ligands were tested and mechanisms proposed.

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Finally, I thank my family for their support, and I have a special thought for my grandfather.

Abbreviations

Acac	Acetylacetone
apt	Apparent
atm	Atmosphere
B.p.	Boiling point
Bipy	2,2'-Bipyridine
Boc	<i>tert</i> -Butyloxycarbonyl
br	Broad
calcd	Calculated
Conv.	Conversion
Cp	Cyclopentadienyl
CSA	L-(-)-Camphor sulfonic acid monohydrate
CSP-HPLC	Chiral stationary phase high performance liquid chromatography
Cy	Cyclohexyl
d	doublet
DCE	1,2-Dichloroethane
DCM	Dichloromethane
<i>de</i>	Diastereomeric excess
DEPC	Diethyl pyrocarbamate
DME	Dimethoxyethane
DMF	Dimethylformamide
dppf	1,1'-Bis(diphenylphosphino)ferrocene
<i>dr</i>	Diastereomeric ratio
<i>ee</i>	Enantiomeric excess
EEDQ	2-Ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline
equiv.	Equivalent
<i>er</i>	Enantiomeric ratio
ESI	Electrospray ionization
GC	Gas chromatography
HFIP	Hexafluoroisopropanol
HRMS	High-resolution mass spectrometry
HTE	High-throughput experimentation

IR	Infra red
m	Multiplet
M.p.	Melting point
MCR	Multicomponent reaction
Mol. sieves	Molecular sieves
MOM	Methoxymethyl ether
Ms	Mesyl
MTBE	Methyl <i>tert</i> -butyl ether
Nbd	Norbornadiene
NHC	<i>N</i> -Heterocyclic Carbene
NMR	Nuclear magnetic resonance
Np	4-Nitrophenyl
Phen	Phenanthroline
PHPB	Pyridinium hydrobromide perbromide
Pip	Piperidine
Piv	Pivalolyl
Py	Pyridine
PMHS	Polymethylhydrosiloxane
PTSA	<i>p</i> -Toluenesulfonic acid
Pybox	Pyridine bis(oxazoline)
q	Quartet
quint	Quintuplet
rt	Room temperature
s	Singlet
t	Triplet
TBAT	Tetrabutylammonium difluorotriphenylsilicate
TEA	Triethylamine
Tf	Triflate
THF	Tetrahydrofuran
TMS	Trimethylsilyl
Ts	Tosyl
TsDEPN	<i>N</i> -Tosyl-1,2-Diphenyl-1,2-ethylenediamine

***Chapter 1: Combinatorial chemistry for finding
new ligands and the Petasis reaction***

1.1 General introduction

“The universe is asymmetric and I am persuaded that life, as it is known to us, is a direct result of the asymmetry of the universe or of its indirect consequences. The universe is asymmetric.”¹

Very early in the history of modern chemistry, Louis Pasteur understood the importance of asymmetry in our world. In 1848, he separated manually two forms of tartrate crystals according to their different crystalline structures and observed that, after passing a plane-polarised light through the two different compounds in solution, the polarised light planes obtained were rotated in opposite directions. He concluded that an asymmetry in a crystal is a result of an asymmetry in the molecule. The notion of chirality was introduced in chemistry.²

The term chiral in general is used to describe an object that is non-superimposable on its mirror image. The word chiral is derived from the Greek, *χειρ*, the "hand", the most universally recognised example of chirality. The two mirror images of a chiral molecule are called enantiomers, term, also derived from the Greek *ένάντιος*, opposite, and *μέρος*, part.

Enantiomers have identical chemical and physical properties in a symmetric environment except for their capacity to rotate plane-polarized light by equal amounts but in opposite directions. A mixture of equal enantiomers is called racemic and does not rotate plane-polarized light. Diastereoisomers are stereoisomers that are not enantiomers. Unlike enantiomers, they possess different physical and chemical properties.

The development of asymmetric synthesis is driven by the importance of stereochemically pure compounds in the field of pharmaceutical industry, agrochemicals and flavours,^{3,4} since most of the biological targets are chiral such as G proteins, enzymes, ion channels, monoclonal antibodies and metabolites. A dramatic example was the commercialization of Thalidomide as a sedative and antiemetic drug in the late 1950s that was often used to cure morning sickness. In 1961, it was withdrawn due to birth defects since this medication was often prescribed to pregnant woman.⁵ It was estimated that the number of victims were between 10,000 to 20,000 worldwide. Only one of the two enantiomers was proven to give the terrible side effects.⁶

The synthesis of molecules containing one or several chiral centres is then, one of the major challenges for chemists for the last few decades.⁷

There are three widespread methods of asymmetric synthesis: chiral pool synthesis, chiral auxiliaries and asymmetric catalysis (single enantiomers can also be isolated from a racemic mixture by classical resolution to obtain enantiopure compounds, however since this is a separation technique it does not fall under the heading of asymmetric synthesis).

A search on SciFinder shows that the number of publications related to asymmetric catalysis has substantially increased from 1990 to achieve a high constant number of publications released annually in 2004 (Figure 1.1).

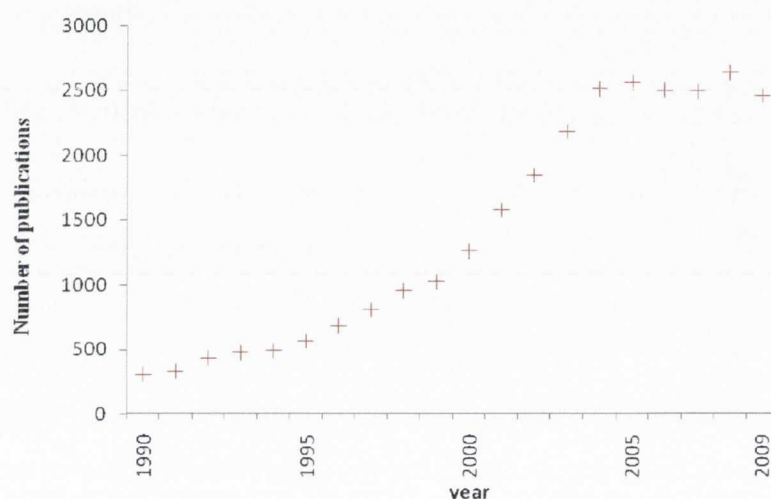


Figure 1.1. Number of asymmetric catalysis related papers released per year.

Of these three methods, asymmetric catalysis is perhaps the most attractive. This is because only small amounts of chiral materials, usually 0.1-10 mol%, need to be used in order to synthesize a large amount of enantiomerically enriched product. In enantioselective catalysis the prochiral substrate can go through two pathways which have at least one different transition state. The majority of the substrate will proceed through the lowest activation energy (E_{a1}) pathway, thus one enantiomer will be formed favorably (Figure 1.2). In asymmetric catalysis, one needs to find the catalyst which will give the greatest energy activation difference, leading to the highest enantiomeric excess, and at the same time, a low energy activation for the desired enantiomer so it will be produced with a high yield.

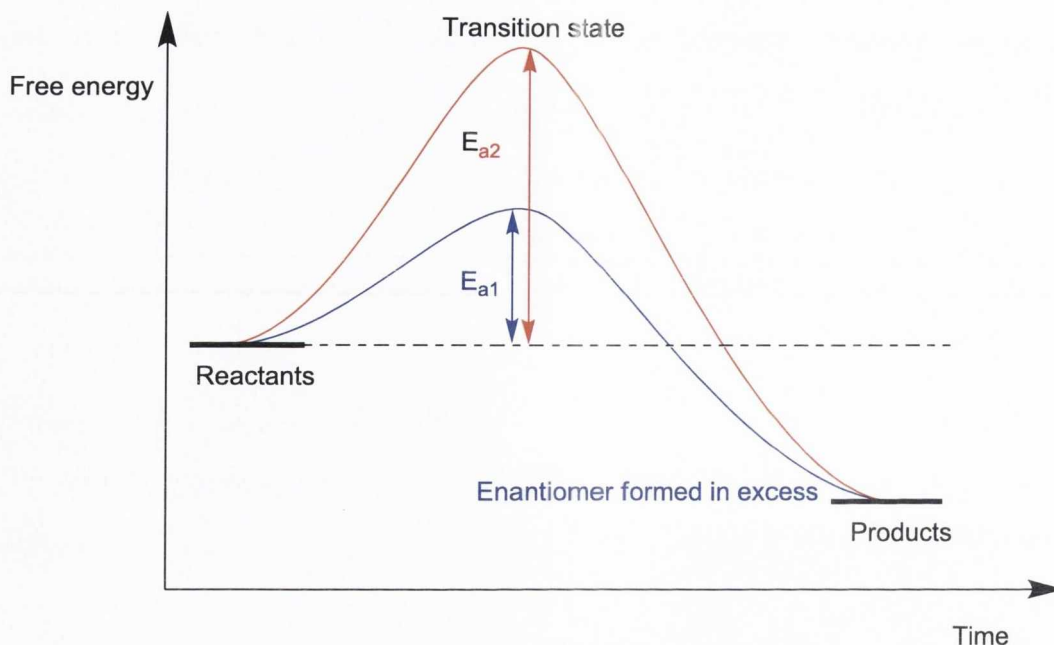


Figure 1.2. Energy difference between two intermediates in an enantioselective catalysis.

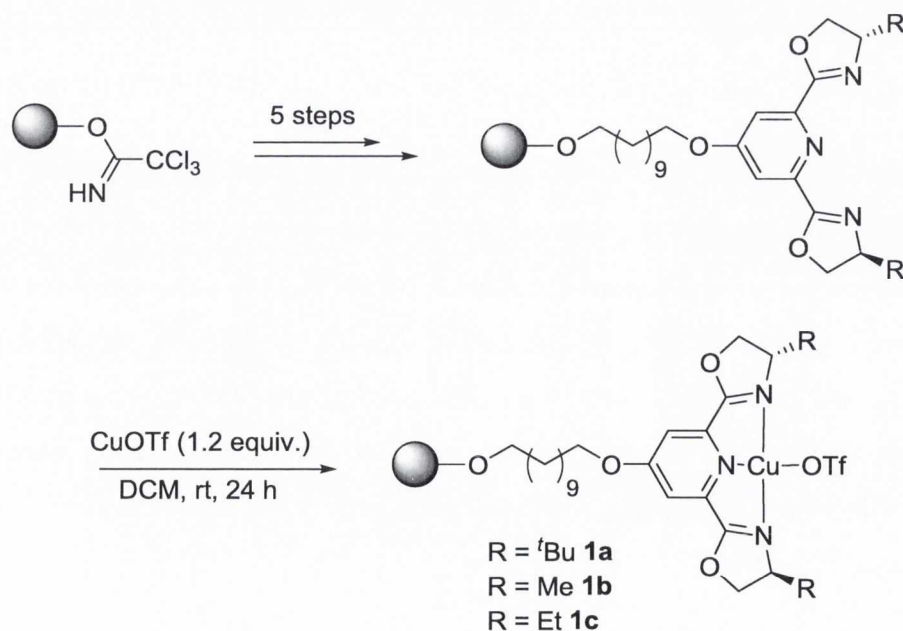
In 1983, William S. Knowles claimed “*Since achieving 95% ee only involves energy differences of about 2 kcal, which is no more than the barrier encountered in a simple rotation of ethane, it is unlikely that before that the fact one can predict what kind of ligand structures will be effective.*”⁸ As a consequence, the unpredictable results given by new catalysts make the design of effective ones a long and costly work. For pharmaceutical companies it is important to launch a new drug immediately upon approval by the regulatory authorities due to the limited time of patent protection. Thus, industry often uses procedures that seem outdated in an academic setting, such as classical resolution.⁹ Nevertheless, asymmetric catalysis is an interesting approach to synthesise enantiopure compounds in an economical and environmentally friendly way, since catalysts are used in a small amount. To answer these problems, combinatorial chemistry is a method of choice, and thus in the 1990s, combinatorial asymmetric catalysis emerged.^{10,}

1.2 Combinatorial chemistry for finding chiral ligands

1.2.1 Solid phase and peptide synthesis

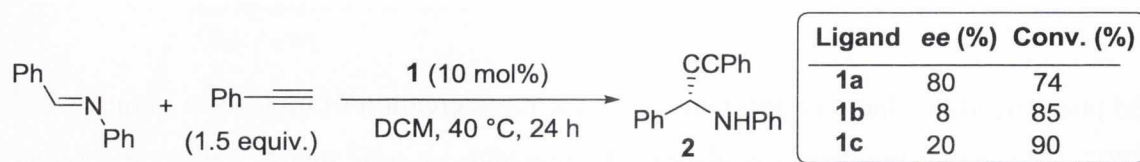
Solid phase synthesis has an important role in the rapid creation of molecules libraries.^{12,13} In 1995, Ellman was the first to synthesize chiral ligands on solid phase. This methodology proved attractive as the ligands are easily isolated by a simple cleavage from the solid support and reactions are driven to completion by the use of excess reagents.¹⁴ He synthesised derivatives of 2-pyrrolidinemethanol, and used them for 1,2-additions of diethylzinc to aldehydes.

Numerous types of ligands have been synthesised on solid-phase ever since, such as amino-alcohols¹⁵, pentamines¹⁶, binols¹⁷, peptides¹⁸, oxazolines¹⁹ and diazaphospholanes.²⁰ Pyridine-2,6-bis(oxazoline) (Pybox) ligands were synthesised in five steps by Weissberg on a polystyrene support (Scheme 1.1).²¹ The oxazoline group comes from a base-induced intracyclization of an amido fluorine moiety.



Scheme 1.1. Chiral Pybox based catalyst synthesised on solid phase.

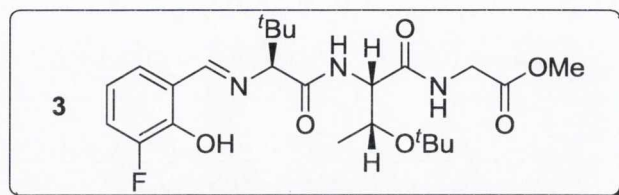
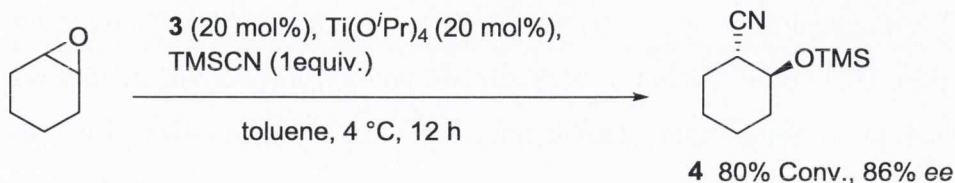
Although the oxazoline functions were hydrolysed during the acidic cleavage, the solid phase bound ligands were used in a heterogeneously catalysed chiral addition of alkynes to imines leading to propargylamines (Scheme 1.2). Bulkier R groups gave **2** with a higher enantioselectivity. When R is *t*Bu the enantiomeric excess achieved was 80% against 8% when R was Me.



Scheme 1.2. Enantioselective addition of phenylacetylene to benzylideneaniline.

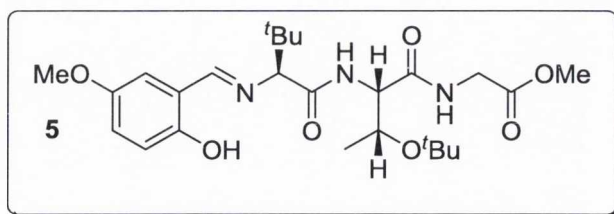
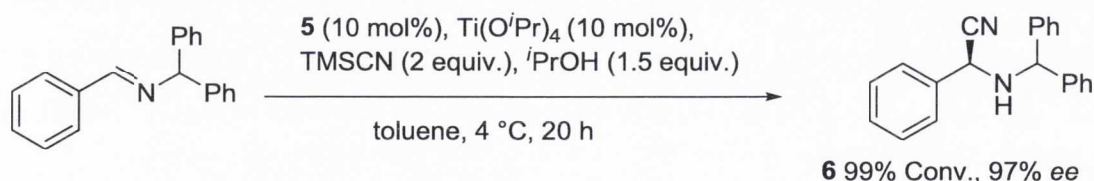
Peptide derived ligands are attractive for finding an optimal catalyst since they have modular chiral structures and the building blocks are readily available and inexpensive. In 1992, Inoue and co-workers elaborated a library of dipeptide-based ligands for an enantioselective addition of hydrogen cyanide to aldehydes catalysed by titanium dipeptide Schiff base complexes producing chiral cyanohydrins.²² The ligands were dipeptide esters whose amino terminals were condensed with salicylaldehyde derivatives to obtain Schiff bases in order to facilitate the complexation with metallic compounds. Classical liquid phase peptide synthesis was used to obtain 14 ligands. The most suitable ligand was obtained by “positional scanning”, each ligand is tested before one module of the molecule is changed at the time. This approach is time effective and may fail finding the best absolute ligand.

In 1996, Hoveyda and co-workers reported the first enantioselective formation of β -cyanohydrins achieved by the asymmetric addition of TMS-CN to *meso* epoxides using a Ti-tripeptide-based catalyst.²³ The ligands were rapidly synthesised on solid phase, cleaved, and screened collectively. After the first screening each moiety was optimised by “scanning position”. In total 39 ligands were synthesised and the best ligand allowed the formation of **4** with a high *ee* and conversion (Scheme 1.3).



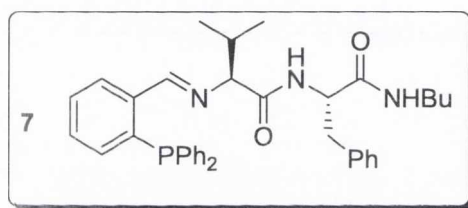
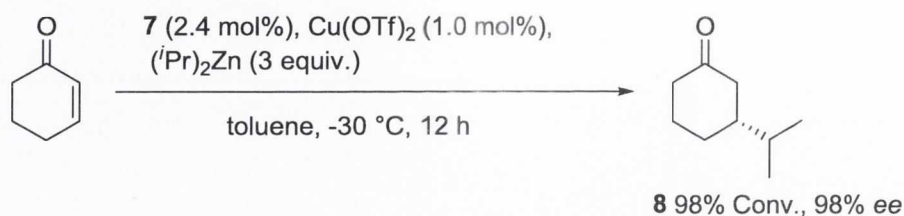
Scheme 1.3. Titanium catalysed enantioselective trimethylsilyl cyanide addition to cyclohexane oxide.

This method was then extended to find complexes which can enantioselectively add hydrogen cyanide to imines forming cyanoamines (the Strecker reaction).¹¹ The resulting product can then be converted to an amino acid after the deprotection of the amino group and hydrolysis of the cyanide in one acidic hydrolysis step. After optimizing the reaction conditions such as solvent, cyanide source and imine type, some outstanding results were achieved including the addition of TMSCN to *N*-benzylidene-1,1-diphenylmethanamine giving **6** (Scheme 1.4).



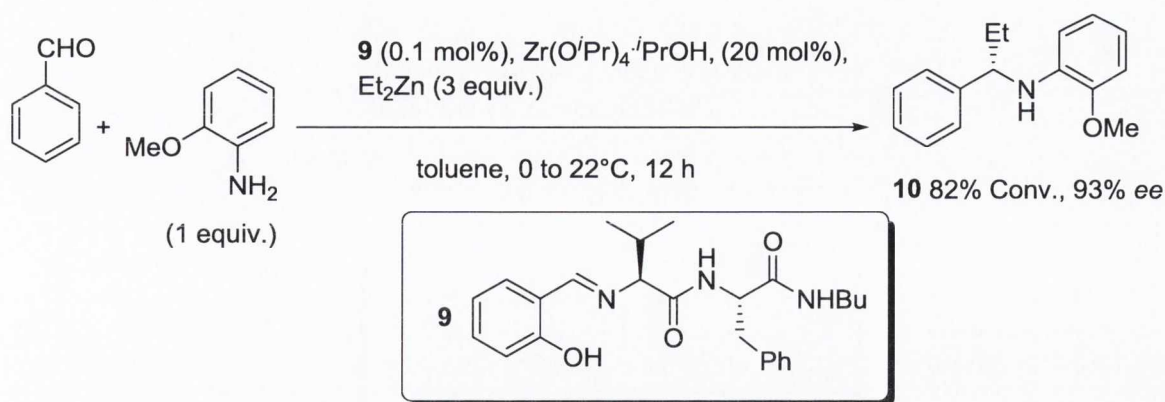
Scheme 1.4. Titanium catalyzed enantioselective cyanide addition to *N*-benzylidene-1,1-diphenylmethanamine.

The same strategy was used to find suitable phosphine ligands for enantioselective copper catalysed conjugated additions of dialkylzinc to cyclic enones.²⁴ P-containing ligands were more appropriate to bind to late transition metals, and so, the phenolic moiety was replaced by a diphenyl phosphine group. The ligands structures were investigated by changing the peptide sequence. Five, six and seven membered ring enones were tested as substrates. A very good result was achieved for the addition of diisopropylzinc to cyclohex-2-enone giving **7** with high conversion and enantioselectivity (Scheme 1.5).



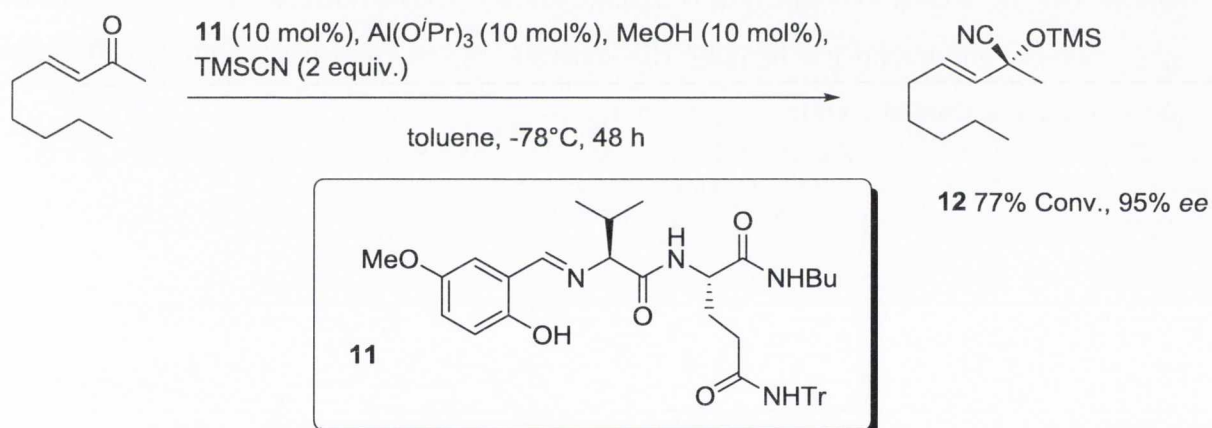
Scheme 1.5. Enantioselective addition of diisopropylzinc to cyclohex-2-enone catalysed by copper.

The authors used this highly modular class of amino acid-based ligands to develop a wide range of important catalytic asymmetric reactions. An efficient zirconium catalyzed enantioselective alkylation of imines was elaborated (Scheme 1.6).^{25,26} The deprotection of the product *o*-anisyl group with silver nitrate yields the derived optically enriched arylamines.



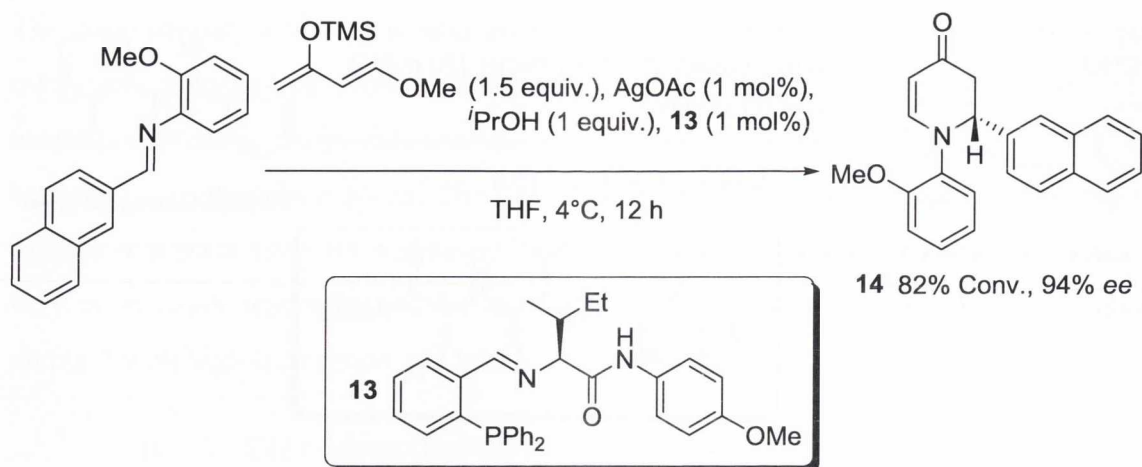
Scheme 1.6. Zirconium catalysed enantioselective alkylation of imines.

The peptidic ligands were also used to promote highly selective additions of cyanide to ketones catalyzed by aluminium isopropoxide (Scheme 1.7).²⁷ Both aliphatic and aromatic ketones are transformed with good enantioselectivities and conversions into their corresponding protected cyanohydrin.



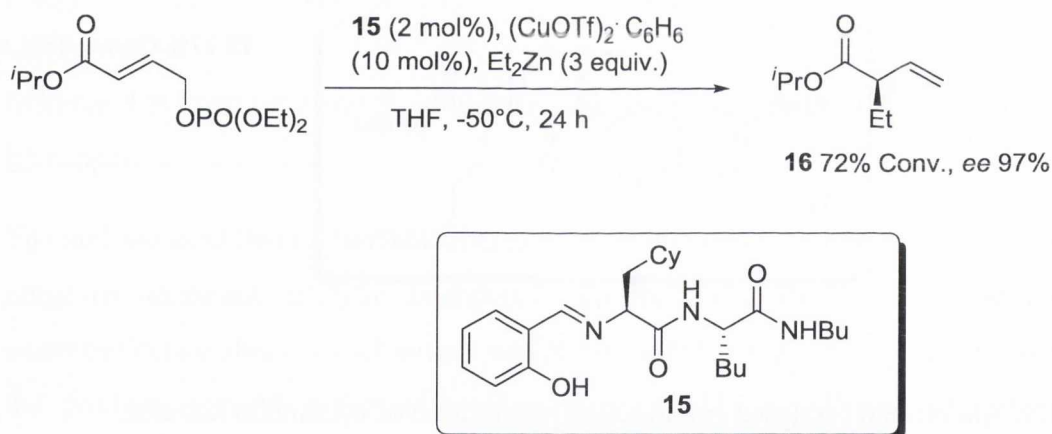
Scheme 1.7. Aluminium catalysed enantioselective addition of cyanide to ketones.

In 2003, the authors reported silver catalyzed cycloadditions between arylamines and the Danishefsky diene (Scheme 1.8).²⁸ P-based ligands were found to be more efficient at catalysing this reaction. The chiral N-containing heterocycle product can be converted to functionalized piperidine.



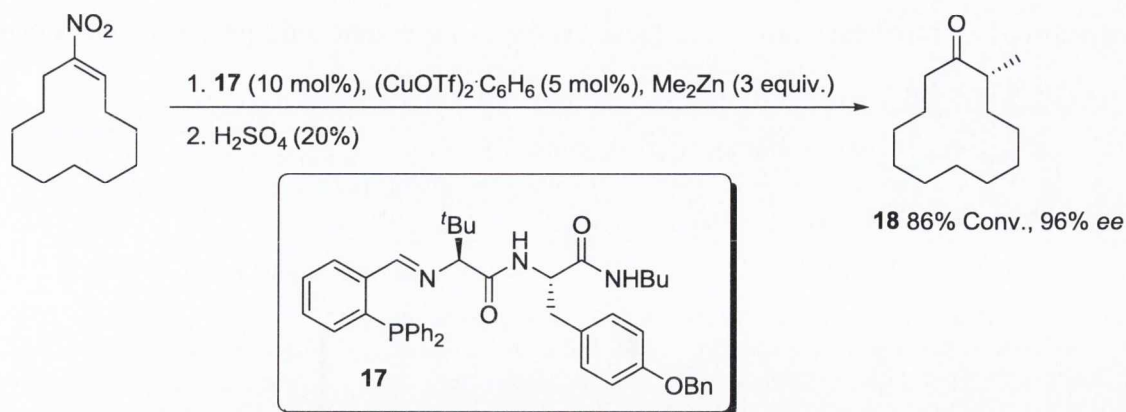
Scheme 1.8. Silver catalyzed cycloadditions between arylamines and the Danishefsky diene.

A copper catalyzed enantioselective allylic substitution between various alkylzincs and various allylic phosphates proved to be surprisingly more efficient when salicyl-based peptide ligands were used instead of P-based ligands.^{29,30} The optimal catalyst was found after screening more than 100 ligands. This example, again, emphasis the utility of highly modular ligands (Scheme 1.9).



Scheme 1.9. Copper catalysed addition of diethylzinc to allylic phosphates.

A copper catalyzed conjugated additions of alkylzinc to nitroalkenes was developed with P-based peptidic ligands (Scheme 1.10).³¹ Depending on the reaction conditions, either the nitro or the corresponding α -substituted ketone product can be obtained after an acidic treatment. All these examples show how suitable catalysts can be found quickly by synthesizing highly modular ligands on solid phase.



Scheme 1.10. Copper catalysed conjugated addition of dimethylzinc to nitroalkenes.

An asymmetric vanadium catalyzed oxidation of phenyl sulfide with hydrogen peroxide was elaborated by Bolm.³² The apparent requirement for the ligand of two hydroxy groups and one imine function to coordinate to vanadium, suggested Jackson and co-workers a possibility of synthesizing a library of ligands on solid phase using standard peptide coupling techniques (Figure 1.3).³³

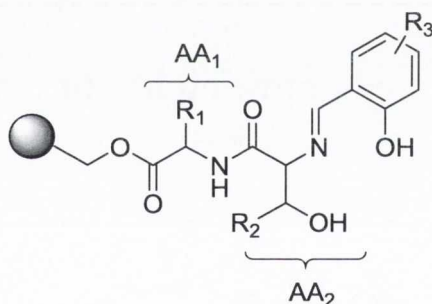
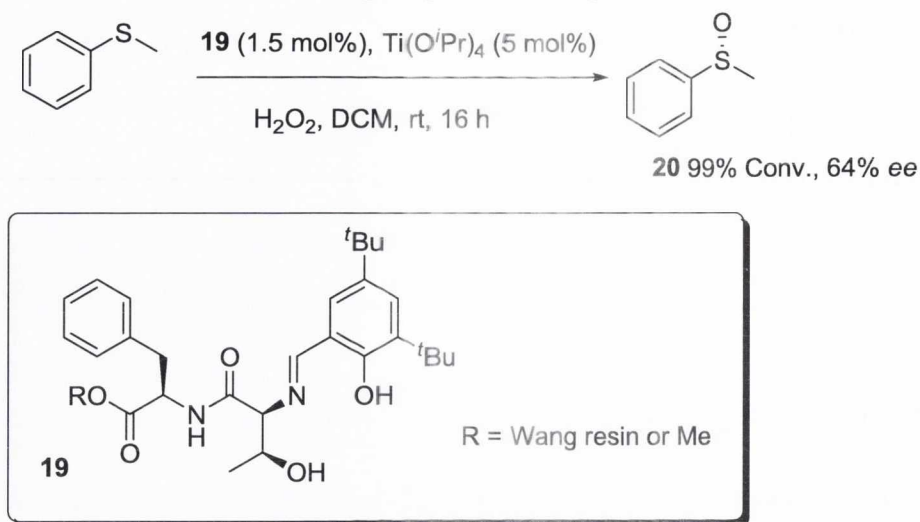


Figure 1.3. Ligands made from two amino acids and a salicylaldehyde derivative on solid phase for the asymmetric metal catalyzed oxidation of phenyl sulfide.

The ligands were prepared on a Wang resin. A first library of 72 ligands was made using six AA₂, two AA₁ and six aldehydes (Figure 1.3). After incubating the resin with VO(acac)₂ and filtering, the resulting the complexes were tested still attached to the solid support. *Allo*-threonine was found to be the best amino acid AA₁. Another library was elaborated by using different salicylaldehyde derivatives and more amino acids AA₁ to find ligand **19** which was tested with different metals. The best result was achieved with titanium isopropoxide (Scheme 1.11). It is worth noting that the same results were achieved whether the ligand was cleaved from the resin or used attached, which shows clearly the advantages of solid phase chemistry over conventional synthesis to find high

functionalized asymmetric ligands. All these examples show that solid phase synthesis can be a valuable tool for the rapid, simple synthesis of ligand libraries.



Scheme 1.11. Enantioselective titanium catalyzed oxidation of phenyl sulfide.

1.2.2 Supramolecular approach to generate ligands libraries

A rapid way to generate bidentate ligands is to mix two monodentate ligands together which subsequently link together *via* non covalent interactions such as π -stacking, cation- π interactions, Van der Waals interactions, electrostatic interactions, or hydrogen bonding.³⁴ In 2003, Reetz and co-workers tried various combinations of two different monodentate ligands in a rhodium catalyzed hydrogenation of acetamidoacrylate.^{35,36} The mixture results in an equilibrium between three different catalysts, two homocombinations and one heterocombination. The enantioselectivities achieved with such catalysts mixtures are then compared with the ones obtained with the two corresponding homocombinations. However, the optimization of the catalyst is not possible if, at least, one of the homodimers is more reactive than the heterodimer. To shift the catalysts equilibrium towards the formation of heterodimers non covalent bonds were used (Figure 1.4).³⁷ This mixture of monodentate ligands can mimic bidentate ligands, allowing the rapid generation of a huge number of ligands.

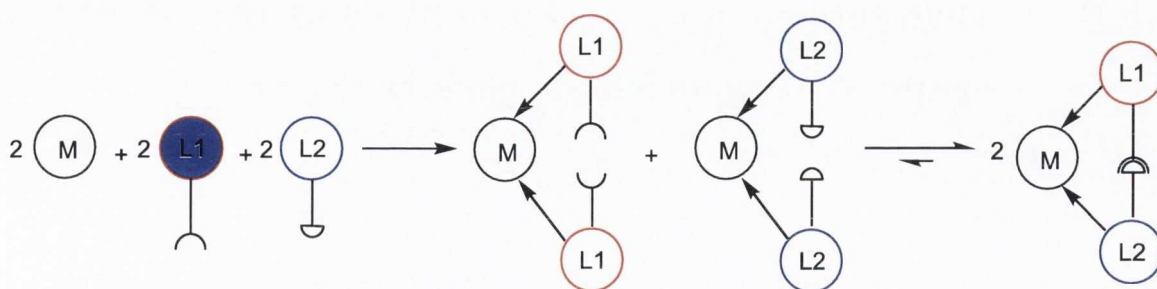
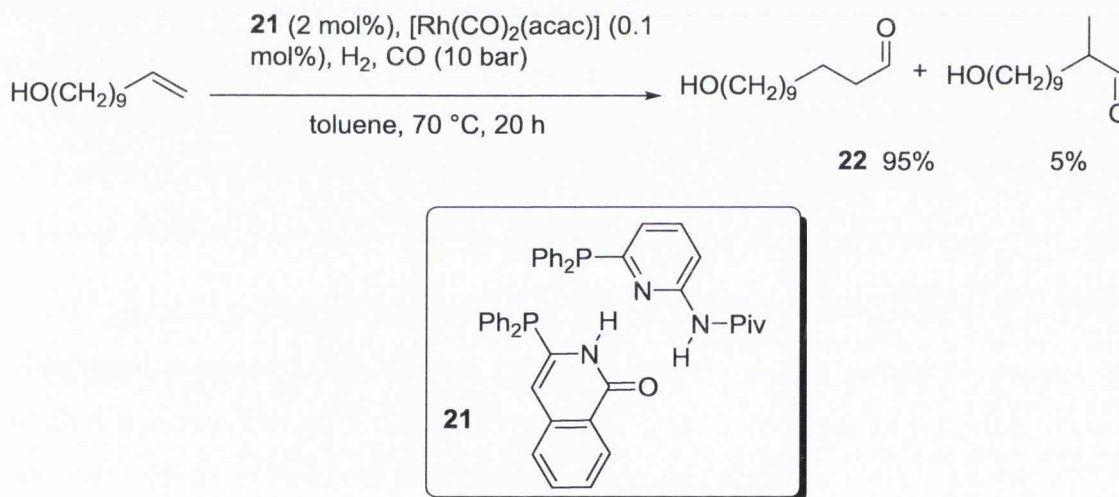


Figure 1.4. Formation of heterodimeric complexes *via* non covalent bonds.

A good application of this method is the formation of P,P ligands used in a regioselective hydroformylation of terminal alkenes (Scheme 1.12).³⁸ To check the structure of the ligands, the authors mixed one equivalent of each monodentate ligand with one equivalent of a Pt^{II} salt and observed by X-ray the expected heterodimeric ligand assembly. Due to weak hydrogen bonding interactions between the two monodentate ligands the method is limited by employing temperatures under 110 °C and by using aprotic solvents.



Scheme 1.12. Regioselective hydroformylations of undec-10-en-1-ol with bidentate ligands.

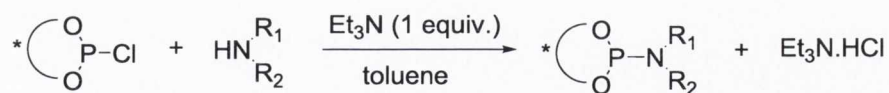
1.2.3 High-throughput experimentations applied to *in situ* synthesis of monodentate ligands

Although the combinatorial methods mentioned previously greatly simplify the search for a suitable ligand, they suffer from important drawbacks. The range of chemical reactions available on solid phase is limited due to different kinetics compared to solution phase and the need to have high yielding steps. Moreover, solid phase chemistry suffers from limited number of analysis methods to monitor a reaction and the polymer cost. The cleavage of the desired product from the solid phase can also be a problem as seen previously.²¹ Peptide synthesis requires purifications and is restricted by the functions provided by amino acids to design ligands. In addition peptide coupling produces stoichiometric amounts of waste, raising environmental and economic concerns. Although ligand synthesis *via* weak interactions is a promising strategy to make bidentate ligands, it relies on heavily functionalised fragments to allow strong, selective binding.

High-throughput screening is a method that allows rapid testing a huge number of compounds in the field of biology, biochemistry and chemistry using robotics, control software, liquid handling devices and sensitive detectors. The chemistry problem is changed in to a chemical engineering problem, due to the requirement to have accurate temperatures and pressures.

In situ organic reactions are an effective method as they can provide a formidable opportunity not only to generate organic molecules that could be unstable and hard to purify by conventional techniques but can save starting material, time and can be environmentally friendly.³⁹

High-throughput screening methods for synthesising chiral ligands *in situ* are at an early stage, yet this approach is already used in industry and is very promising. Monodentate phosphites⁴⁰, phosphonites⁴¹, and phosphoramidites⁴² have been developed as ligands for rhodium catalysed asymmetric hydrogenations. For this reaction monodentate ligands have shown comparable enantioselectivities to bidentate ligands.^{43,44} DSM, in collaboration with the group of De Vries and Feringa^{45,39,46} used high-throughput experimentation to design a library of monodentate phosphoramidites ligands. The ligands were generated *in situ* by reacting a chlorophosphite and an amine together (Scheme 1.13).



Scheme 1.13. Synthesis of phosphoramidite ligands.

The reaction is high yielding and thus, suitable for synthesising the ligands *in situ*. The product only needs a filtration of the triethylammonium chloride to be used, results are then reasonably consistent between purified ligands and *in situ* synthesised ligands (in practice the results for the non-purified ligands are slightly reduced, but it still allows the rapid identification of the most appropriate ligand since the relative results between ligands are consistent). The chlorophosphites made from chiral diols and phosphorus trichloride were reacted with primary or secondary amines which can be either chiral or achiral. It is worth noting that primary amines have not been widely used since they lead to phosphoramidites which decompose during purification as such they can only be employed by using *in situ* methods. These reactions carried out in a 96-well oleophobic filterplate in the presence of 1 equivalent of triethylamine and vortexed using an orbital shaker for 2 h, allowing the synthesis of up to 96 ligands in the same time. After filtration of the triethylammonium chloride under reduced pressure, the 32 phosphoramidite ligands were used without further purification (Figure 1.5).

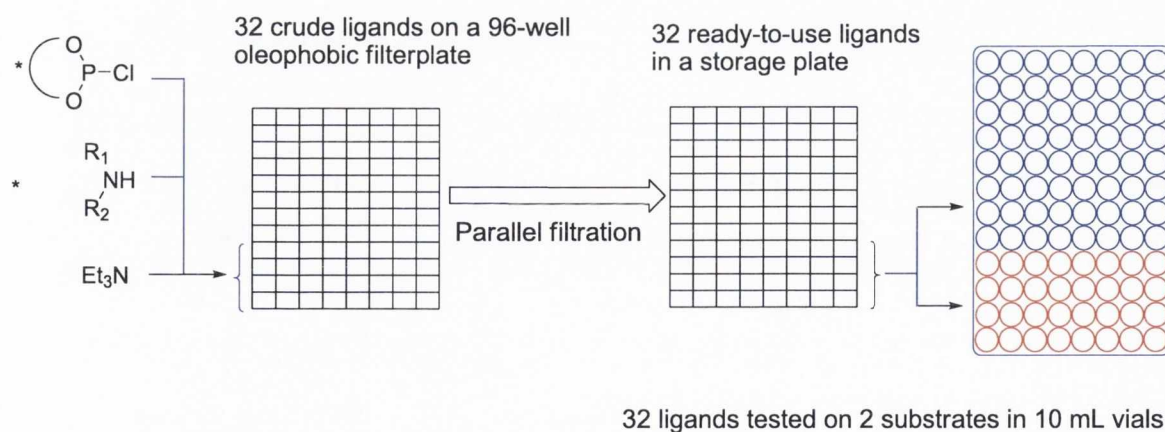
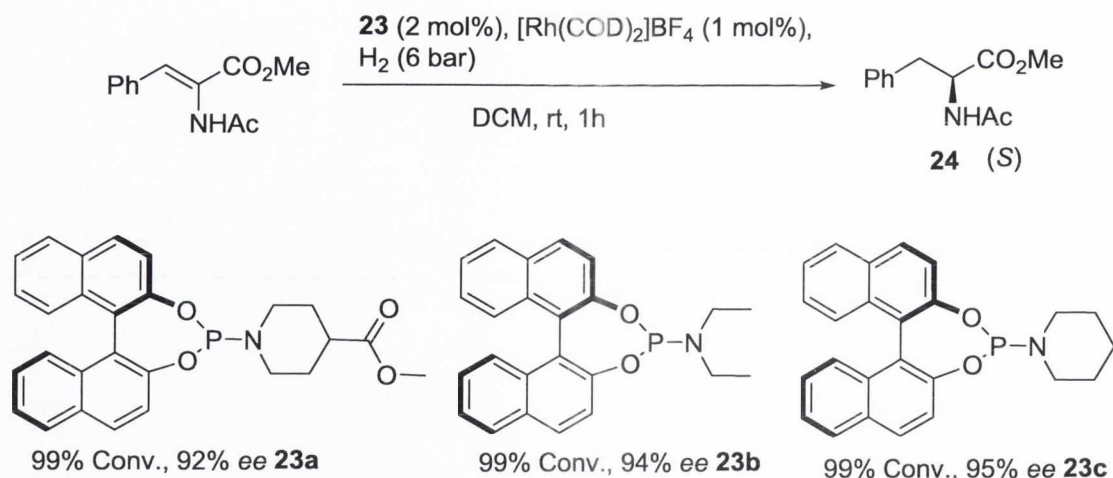


Figure 1.5. Automated synthesis and screen of a ligand library.³⁹

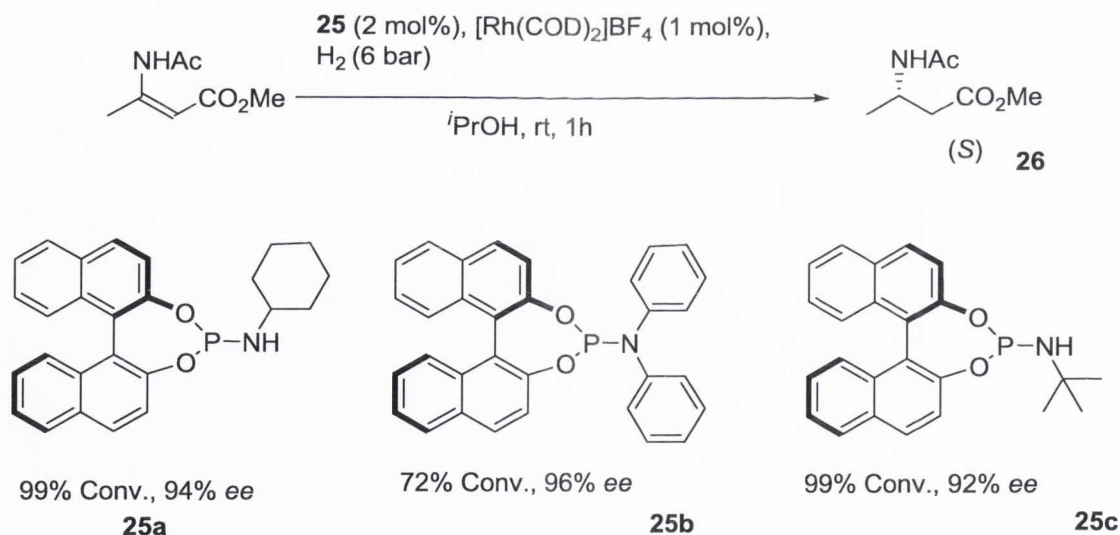
Then, a sample of each ligand was transferred into a Premex[®] 96-Multi Reactor and, they were used crude, for a rhodium catalysed hydrogenation of methyl 2-acetamidocinnamate (Scheme 1.14) and *Z*-methyl 3-acetamido-2-butenate (Scheme 1.15) in the same experiment (Figure 1.5).³⁹



Scheme 1.14. *In situ* prepared phosphoramidite ligands used in rhodium catalysed asymmetric hydrogenation of methyl 2-acetamidocinnamate.

For the methyl 2-acetamidocinnamate substrate ligands **23a**, **23b**, **23c** were found to give **24**, with high enantioselectivities and with complete conversion (Scheme 1.14).

As mentioned previously a fraction of the same 32 ligands were used for the reduction of *Z*-methyl 3-acetamido-2-butenate (Scheme 1.15). **25a**, **25b** and **25c** are the ligands which gave **26** with the best enantiomeric excesses.³⁹

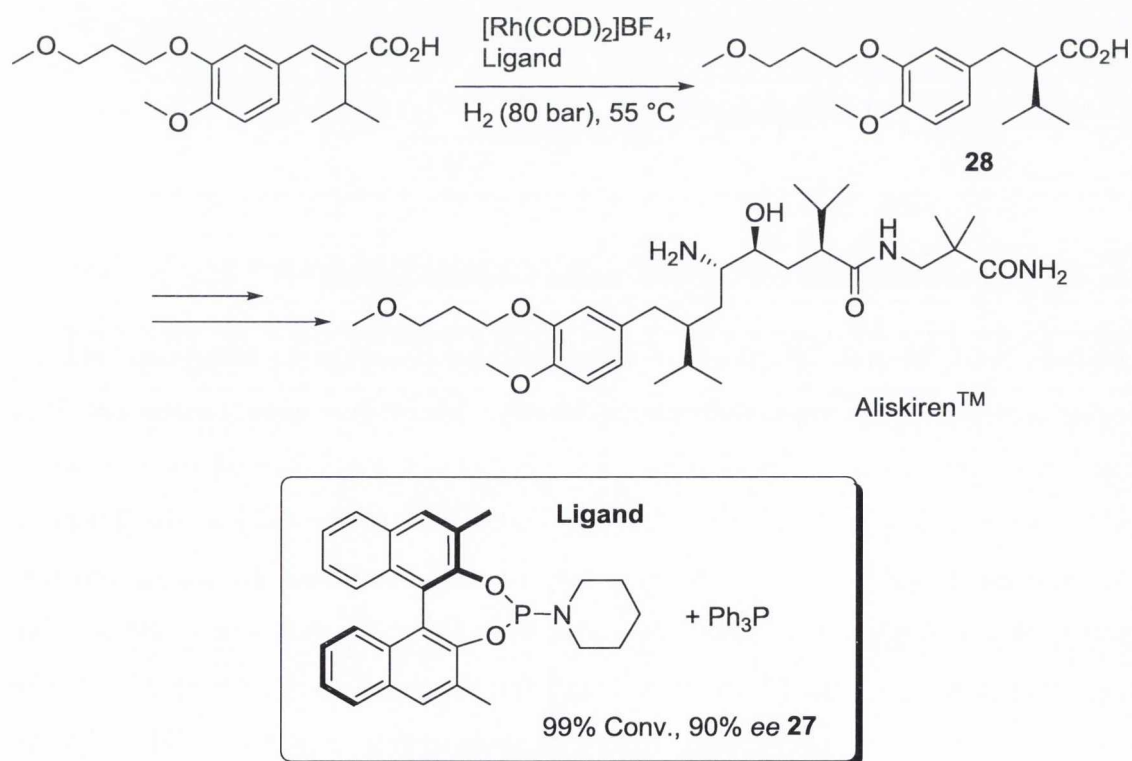


Scheme 1.15. *In situ* prepared phosphoramidites ligands used in rhodium catalysed asymmetric hydrogenation of *Z*-methyl 3-acetamido-2-butenate.

The ligands giving the best results for the formation of **26** are different to the ones giving the best results for the formation of **24**; the conversion and the enantiomeric excess highly depend on the substrate. This example perfectly emphasizes the fact that high-throughput screening can have a dominant place in the quest for finding suitable ligands. **25a** and **25c**

are made from primary amines and, due to their instability, would not have been screened under normal conditions. This method does not only allows one to find a good ligand but also to test additives or combinations of monodentate ligands.⁴⁷

HTE was then used by DSM to find a ligand for the asymmetric hydrogenation of the α -alkylated cinnamic acid derivative, **28** which is an intermediate in the synthesis of AliskirenTM, a blood pressure lowering drug (Scheme 1.16).⁴⁵ HTE was also used to find an additive which enhances the results. Many achiral ligands (phosphines, phosphites, amines and pyridine derivatives) were tested in association with phosphoramidites, and triphenylphosphine (0.5 equiv. to the chiral ligand) showed to boost the conversion and the enantioselectivity. This catalyst is currently used on a ton-scale commercial process.⁴⁸ This example shows the utility of HTE to find an optimal ligand which differs from one substrate to another. Also, besides finding the best catalyst for a substrate, parallel screening can identify a catalyst for a new and unusual substrate thanks to capacity of screening a huge number of ligands in a short period of time.



Scheme 1.16. Asymmetric hydrogenation step in the synthesis of AliskirenTM.

In 2004, Reetz and Feringa developed a facile one-pot multisubstrate procedure to measure the enantioselectivity in a parallel manner.⁴⁹ This method consists in testing a catalyst in a vial containing 8 substrates (enamides) and avoid the need of an expensive high-throughput autoclave. Thus one single chiral GC run of a sample containing the products of the 8 reactions can determine the 8 enantiomeric excesses. This methods considerably speeds up the ligand screening but has the major disadvantage of being long to set because of chiral GC product peaks overlaps.

In 2009, Reek⁵⁰ combined a supramolecular approach with HTE to generate ligands libraries to find convenient ligands for the rhodium catalyzed asymmetric hydrogenation of five challenging substrates relevant to industry. The modular ligand is composed of three parts: a urea binding moiety, a spacer and the ligand backbone which contains the phosphorus atom (Figure 1.6). Twelve new ligands were made with different steric and electronic profiles.

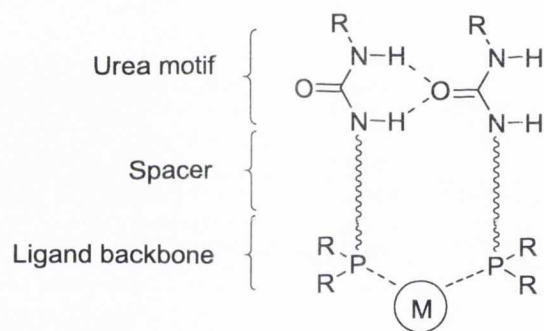
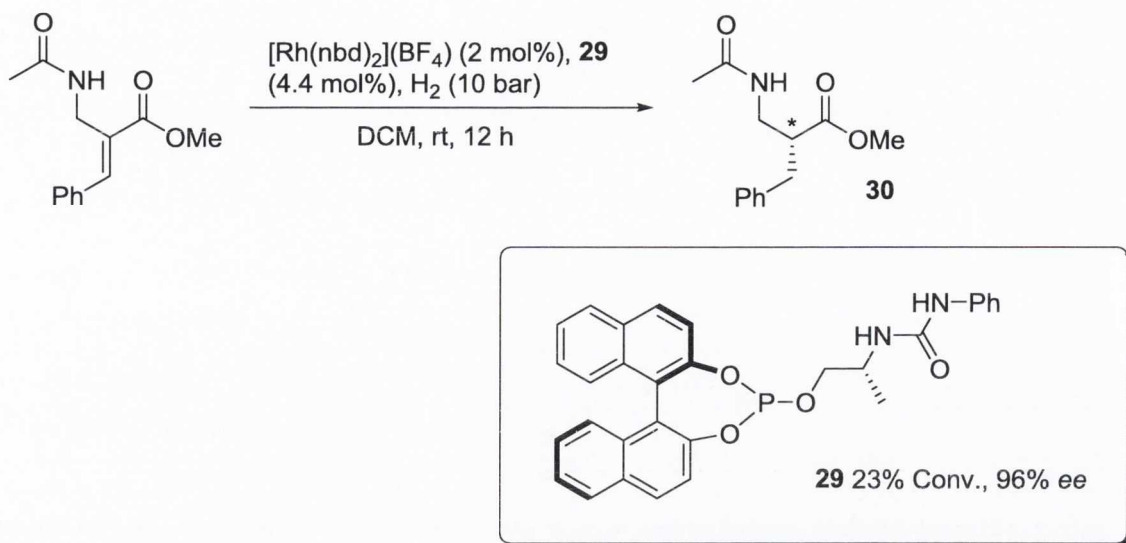


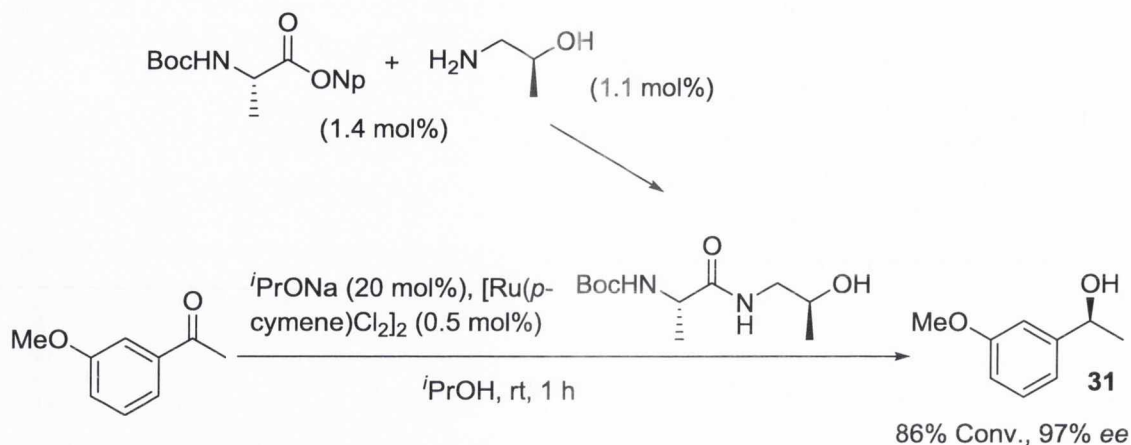
Figure 1.6. Supramolecular interactions to mimic bidentate ligands.

The authors used ^1H and ^{31}P NMR to investigate the coordination behaviour and the hydrogen bonding in the supramolecular assembly. The HTEs were carried out in a Chemspeed accelerator SLT workstation. One good result was obtained on a substrate which is an interesting building block for the synthesis of biologically active β -peptide chains (Scheme 1.17).⁵⁰ After investigating the reaction conditions the conversion was improved; **30** was formed with 84% yield rather than 23% with the same *ee* (96%). The pressure was increased from 10 to 30 bars and the temperature was set at 45 °C. The ligands were synthesized easily from diverse, commercially available building blocks allowing a facile scale-up and a high potential for modularity.



Scheme 1.17. Enantioselective rhodium catalysed hydrogenation of an enone.

There is only one case of polydentate ligands made *in situ*. This was used in a ruthenium catalysed transfer hydrogenation in isopropanol.⁵¹ Tridentate ligands were synthesised from a peptide coupling, rapidly creating a small ligand library without having the opportunity to use HTE. The ligands were made from Boc protected amino esters and amino alcohols. As the methyl ester was shown to be not reactive enough for the coupling, it was replaced by a more reactive 4-nitrophenyl analogue. As a consequence, the side product of the amidation is 4-nitrophenol which affected by its acidity the transfer hydrogenation carried out in the presence of sodium isopropoxide. This example perfectly shows the importance to remove the side products of the *in situ* made ligand as it can influence the catalysis results. The authors solved this problem by increasing the amount of the base. Using a stoichiometric ratio of the two building blocks led to an incomplete formation of the ligand. As the amino alcohol can play the role of ligand, a slight excess of the amino ester was used to ensure the complete conversion of the undesired starting material. 10 ketones were tested on the ruthenium catalysed transfer giving, in general, high *ees* and good conversions. For instance, the reduction of 3-methoxyacetophenone to **31** was carried out with 86% of conversion and 97% of *ee* (Scheme 1.18).



Scheme 1.18. Polydentate ligand made *in situ* and used in an enantioselective ruthenium catalysed transfer hydrogenation.

1.3 Transfer hydrogenation catalyzed by ruthenium, iridium or rhodium

In 2001 the Nobel prize of chemistry was divided, one half was obtained by Noyori and Knowles “for their work on chirally catalyzed hydrogenation reactions”.⁵² Noyori developed an enantioselective hydrogenation of ketones and imines using BINAP-ruthenium catalysts under H₂.⁵³

Catalyzed transfer hydrogenation is a widespread method to hydrogenate compounds without using gaseous hydrogen.⁵⁴ The most common hydrogen donors are formic acid and isopropanol which are converted to carbon dioxide and acetone.^{54,55} Ruthenium, iridium and rhodium are used catalytically to reduce ketones or imines to chiral alcohols or amines.^{56,57} This cheaper and safer method is appreciated in industry where large amount of material need to be reduced.^{58,59}

A mechanism for the transfer hydrogenation of ketones in formic acid catalyzed by ruthenium, iridium or rhodium and TsDPEN was proposed by Noyori and co-workers (Figure 1.7).⁵⁵ The metal complex **32** is formed from the ligand TsDPEN and the initial metal salt. Complex **32** generates the active catalyst by losing HCl. The primary amino

group loses a proton and becomes an anionic ligand. Formic acid reacts with compound **33** giving a hydride ligand to the metal and a proton to the amino group. Complex **34** can then interact with ketone **35** to form intermediate **36**. The hydride and the proton are then transferred to the ketone forming the chiral alcohol **37** and regenerating the catalyst **33**.

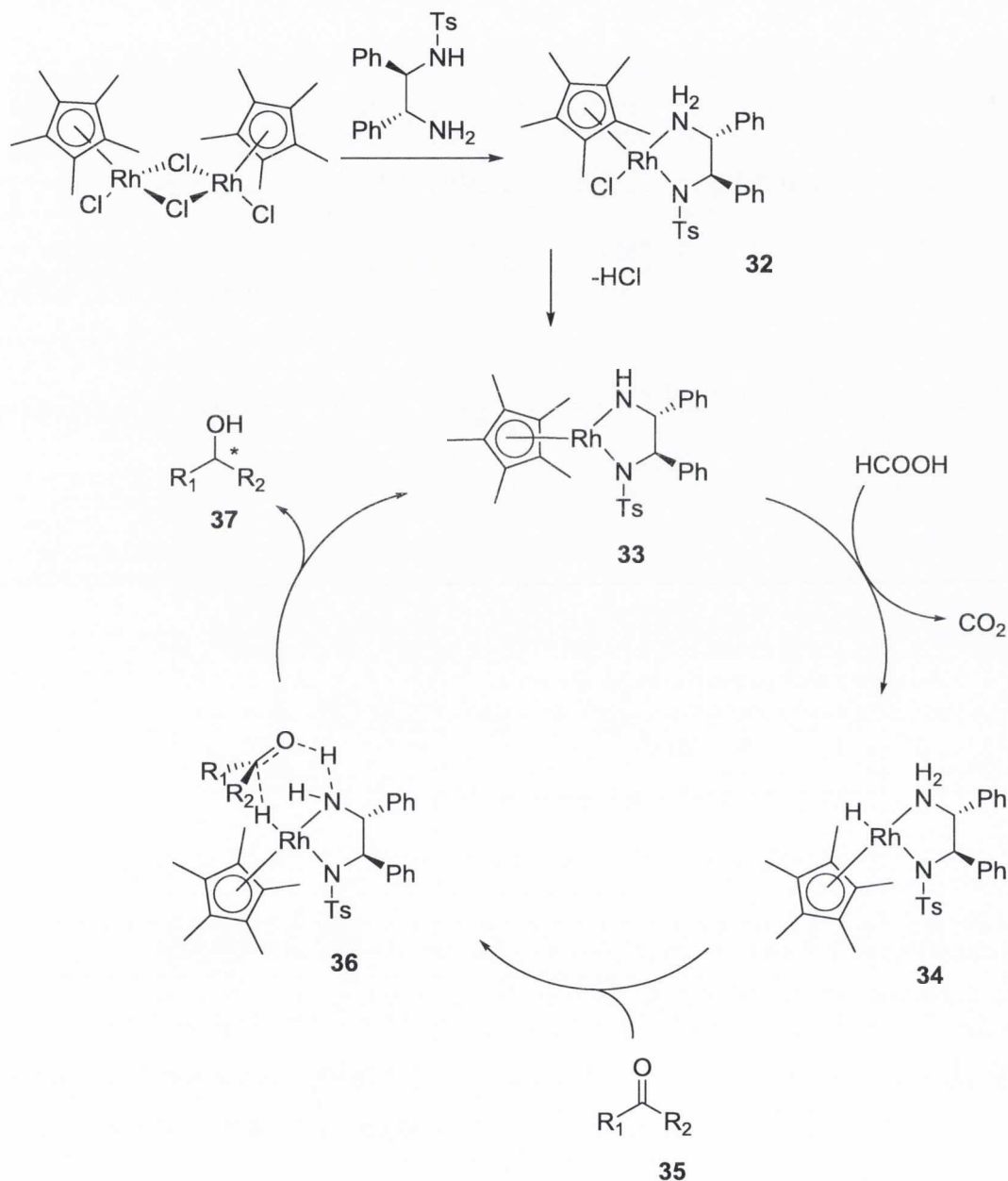
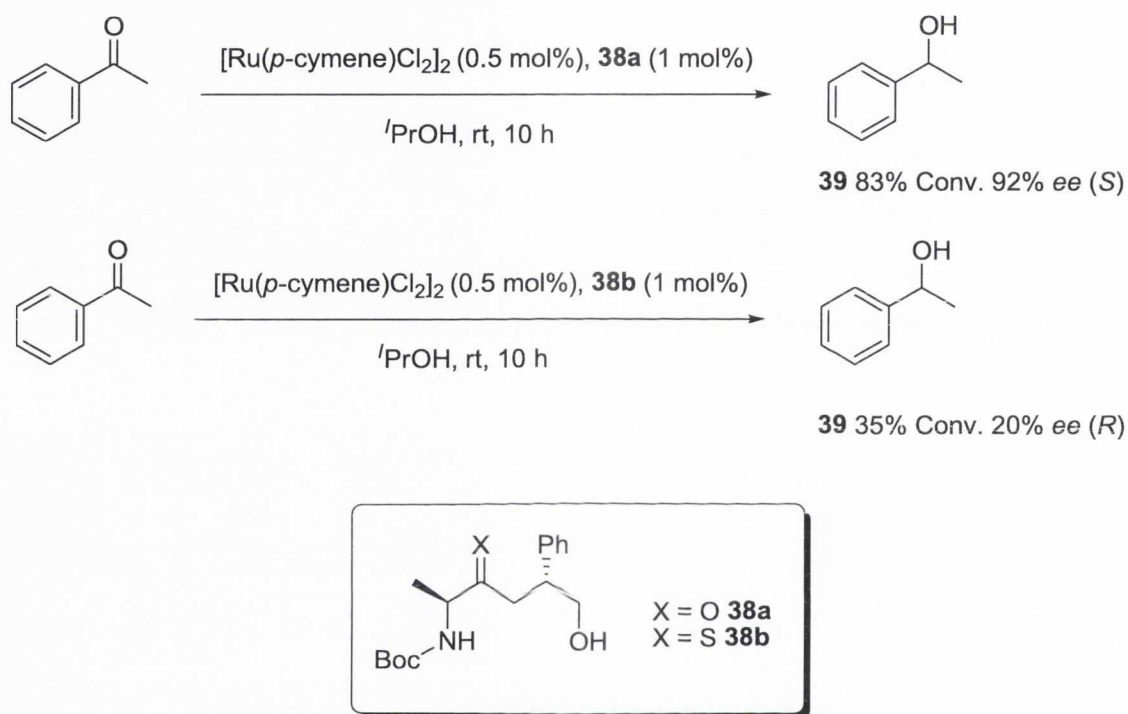


Figure 1.7. Mechanism of transfer hydrogenation catalysed by rhodium and TsDPEN.

Throughout the process the oxidation state of Rh^{III} does not change (Figure 1.7).

A subtle change in the ligand structure has a dramatic influence on the activity and selectivity of the reaction.⁶⁰ Zaitsev et al. developed pseudodipeptides ligands, and noticed that changing the amide function on the thioamide function not only changes the conversion and enantiomeric excess but also the configuration of the product (Scheme 1.19).⁶⁰



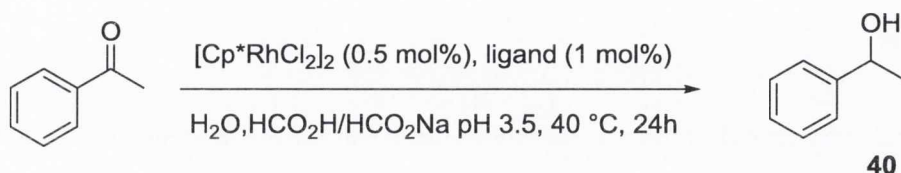
Scheme 1.19. Switch of enantioselectivity in the reduction of acetophenone.

This surprising result is explained by the acidity of the NH functions in the amides, thioamide and carbamate functions. For compound **38b** the thioamide NH bond is the acidic site and the BocNH the basic one. For ligand **38a** the role of the NH is reversed.

N-Heterocyclic carbenes were shown to be efficient ligands for an iridium transfer hydrogenation.⁶¹ They can reduce ketones, aldehydes, alkenes and imines but no enantioselective versions examples are reported.

Imines have also shown to be good ligands for the transfer hydrogenation catalysed by rhodium.^{62,63} Tetradentate Schiff based ligands allowed acetophenone to be reduced with moderate to high yields.⁶² The mechanism is thought to involve a cationic Rh^I complex.

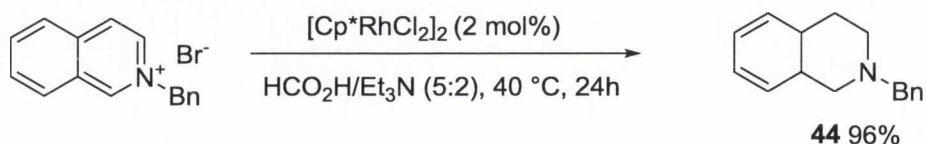
Only one example of chiral imine based ligands has been reported for this reaction (Scheme 1.20).⁵⁶ As bipyridine produced **40** with a high yield a chiral bipyridine based ligand **42** was tried but gave **40** as a racemic mixture. Then chiral imine ligands were tried including **43** giving **40** with an enantiomeric excess.



Ligand	Yield (%)	ee (%)
 41	99	n/a
 42	99	0
 43	60	34 (S)

Scheme 1.20. Different ligands in a rhodium catalysed transfer hydrogenation.

Another transfer hydrogenation was elaborated to reduce successfully isoquinolinium salt catalysed by rhodium without addition of ligands forming **44** (Scheme 1.21).⁶⁴ Substituted isoquinolinium were also reduced with high yields but since no chiral ligands were used, the products were obtained as racemic mixtures.



Scheme 1.21. Cp*Rh catalysed transfer hydrogenation of isoquinolinium salts.

The variety of substrates and ligands make this reaction a good candidate for testing new chiral bidentate ligands.

1.4 Hydrosilylation catalyzed by zinc

Hydrosilylation of unsaturated organic compounds forms organosilicon species which can be easily hydrolysed. This way to reduce simply, safely and efficiently alkenes, alkynes, aldehydes and ketones is an attractive alternative to gaseous hydrogen, sodium borohydride and lithium aluminium hydride.^{65,66}

Transition metals such as platinum,⁶⁷ iron,⁶⁸ palladium,⁶⁹ ruthenium,⁷⁰ titanium,⁷¹ and rhodium⁷² have been reported to catalyse hydrosilylations but using inexpensive zinc instead has shown great interest.^{73,74}

Enthaler reported a one pot synthesis of secondary amines.⁷⁵ The reaction consists of a condensation between an aldehyde and a primary amine, the resulting imine subsequently undergoes hydrosilylation. PMHS, an innocuous, stable and cheap hydride source was used. The author screened many zinc salts and found $\text{Zn}(\text{OTf})_2$ to be the most efficient. A mechanism was proposed (Figure 1.8). It starts with an interaction between the *in situ* formed imine and the Lewis acid $\text{Zn}(\text{OTf})_2$. The silicon from PHMS interacts then with a triflate and the hydride with the imine. After transferring the hydride to the imine the organosilicon compound is formed and hydrolysed *in situ*. The reaction tolerates many functional groups and is carried out under mild conditions.

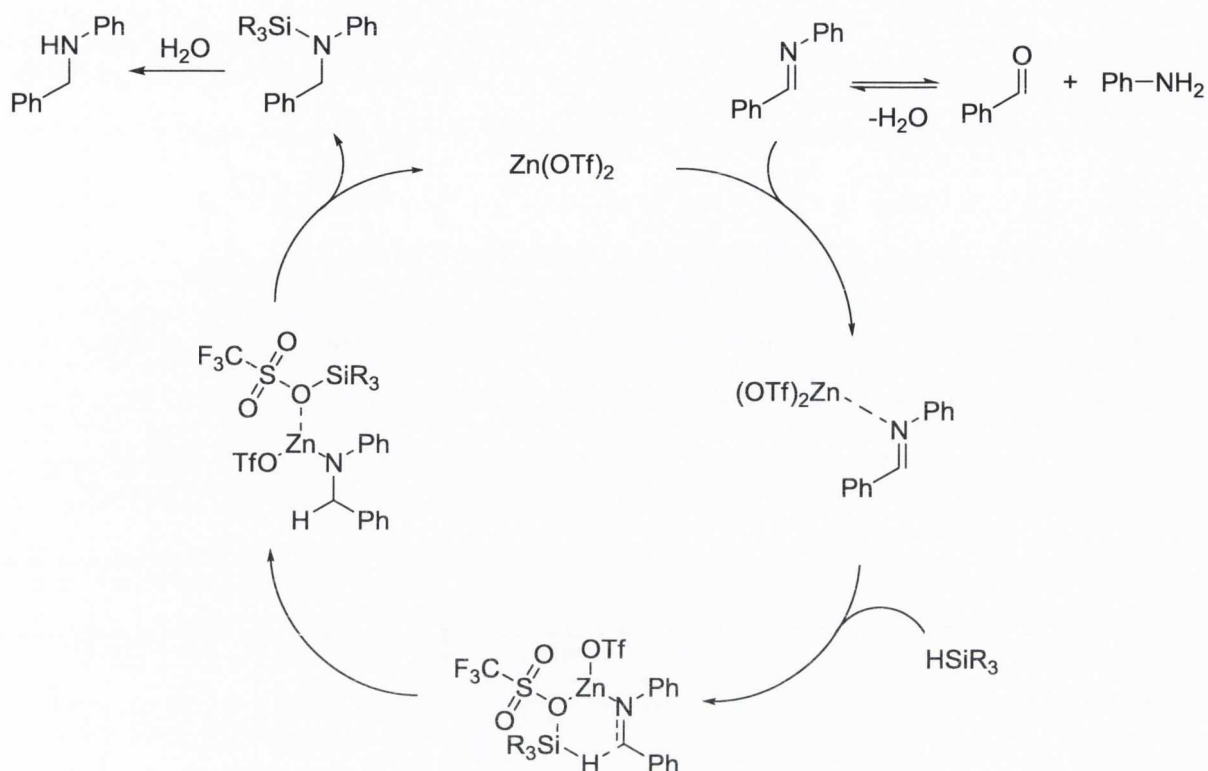
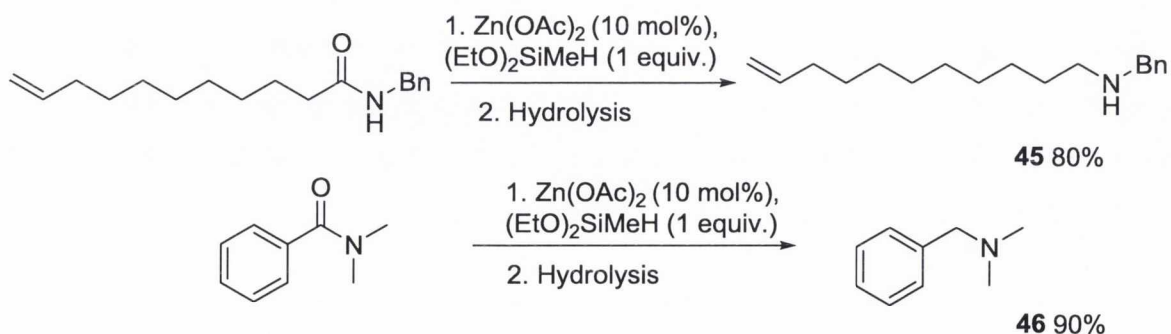


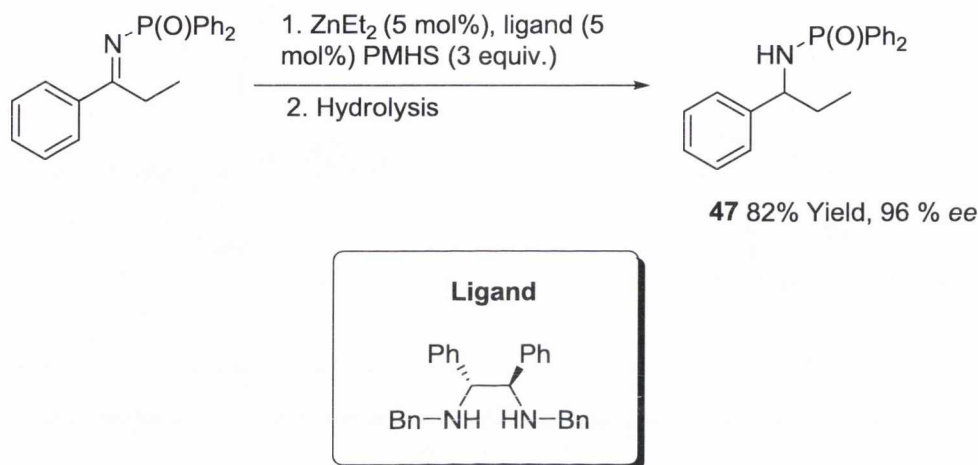
Figure 1.8. Proposed catalytic cycle for the one pot synthesis of secondary amines catalysed by zinc.

Secondary and tertiary amides can also be reduced chemoselectively to amines in the presence of zinc salts and a hydrosilane with good to high yields (Scheme 1.22).⁷⁶ Both amides with aliphatic and aromatic chains can be reduced. For instance, amines **45** and **46** are obtained with high yields under mild conditions (Scheme 1.22). This example shows that hydrosilylation can be a good alternative to reagents such as lithium aluminium hydride⁷⁷ which is a hazardous reagent or gaseous H₂ which requires high temperatures and pressures.⁷⁸



Scheme 1.22. Zinc catalysed hydrosilylation of amides.

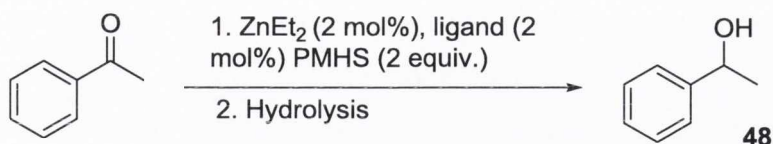
Another hydrosilylation, enantioselective this time, was elaborated by Yun and co-workers.⁷⁹ The authors reduced *N*-diphenylphosphinylimines with PMHS and a catalytic amount of zinc and a chiral bidentate ligand. They found a catalytic system which provides **47** with a high yield and outstanding *ee* (Scheme 1.23).



Scheme 1.23. Enantioselective hydrosilylation of *N*-diphenylphosphinylimines .

Ketones can also be reduced by using a catalytic amount of zinc and a silane compound.⁸⁰ The addition of a catalytic amount of a formamidine ligand was shown to accelerate the reaction. After optimizing the reaction conditions such as the zinc to ligand ratio, the silane type, the solvent and the temperature, many aliphatic and aromatic ketones with different electronic features were reduced with high yields. Yet, the alcohols obtained were racemic.

An enantioselective hydrosilylation of ketones has been reported by using chiral N,N,S,S ligands.⁸¹ Tetradendate ligands were used to reduce a large variety of aromatic ketones. Whereas the yields were high, the enantiomeric excesses remained moderate. Good to high enantiomeric inductions were obtained by Mimoun et al.⁷³ Chiral diamines and bisimines were used in a zinc catalysed hydrosilylation of acetophenone. Later, Carpentier and co-workers investigate more deeply the ligand structures in order to obtain higher enantiomeric excesses with diamines (Scheme 1.24).^{82,83} Diamines produced **48** with high yield. Whereas enantioselectivities are good, they are perfectible.



Ligand	Yield (%)	ee (%)
	99	22 (<i>R</i>)
	99	76 (<i>S</i>)

Scheme 1.24. Hydrosylation of acetophenone catalysed by ZnEt_2 and diamine ligands.

1.5 Petasis reaction and boronic acids as nucleophiles in copper catalysed reactions

1.5.1 Multicomponent reactions

Multicomponent Reactions (MCRs) sometimes referred to as a multi-component assembly processes, are convergent reactions, in which three or more starting materials react in a single reaction vessel to form a product, most of the atoms contributing to the newly formed product. MCR synthesis has many advantages over standard linear synthesis. It is environmentally friendly, economically advantageous and a very fast way to make bioactive compound libraries.⁸⁴

In order to be efficient, MCRs need to have compatible components which do not undergo alternative irreversible side reactions.

In 1850, Strecker reported the first MCR which allows one to synthesize α -aminonitriles in one pot from an aldehyde (or ketone), potassium cyanide and ammonium chloride (Scheme 1.25).⁸⁵ The product can then be hydrolysed to the corresponding racemic amino acid. The reaction has subsequently been rendered asymmetric by using chiral auxiliaries⁸⁶ or asymmetric catalysts.⁸⁷

Over time numerous other MCRs have been developed and become popular in organic and medicinal chemistry. Some selected examples are in Scheme 1.25.

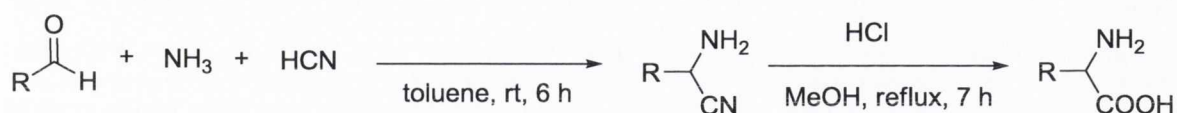
Hantzsch synthesized dihydropyridine derivatives via MCR from an aldehyde, 2 equivalents of β -keto ester and ammonium acetate or ammonia.⁸⁸ The product can then be oxidised easily to the corresponding pyridine derivative by ferric chloride or potassium permanganate (Scheme 1.25).⁸⁹

The Biginelli reaction leads to 3,4-dihydropyrimidin-2(1H)-ones from ethyl acetoacetate, an aryl aldehyde and urea.⁹⁰ These products have found uses as a calcium channel blocker,⁹¹ anti-hypertensive agent,⁹² alpha blocker⁹³ and have shown more recently to have an inhibitory activity against HIV-1 replication.⁹⁴ The reaction can now be carried out enantioselectively by using chiral catalysts.⁹⁵

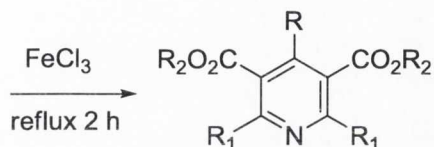
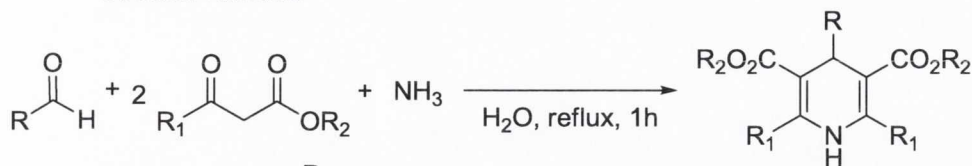
Mannich made β -amino-carbonyls from an aldehyde, a primary or secondary amine and an enolizable carbonyl.⁹⁶ As two chiral centres are created many examples of diastereoselective and enantioselective variants have emerged recently.^{97,98,99,100}

The Passerini reaction allows one to synthesis α -hydroxy carboxamides from a ketone (or aldehyde), an isocyanide and a carboxylic acid.¹⁰¹ It is a very challenging reaction to control stereochemically.^{102,103,104}

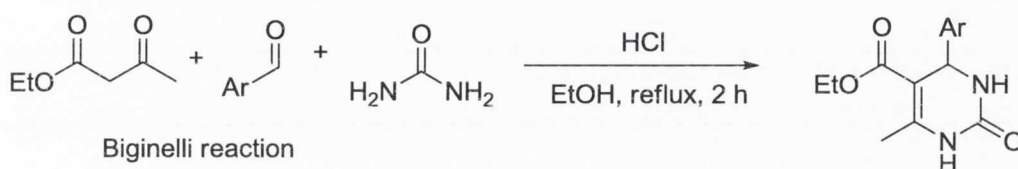
The Ugi reaction is a four component reaction between a ketone, an aldehyde, isocyanide, an amine and a carboxylic acid to form a bis-amide.¹⁰⁵



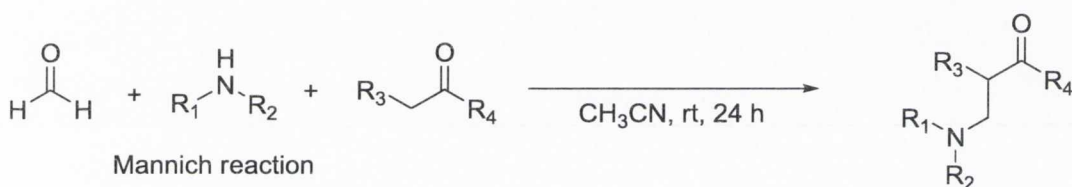
Strecker reaction



Hantzsch reaction



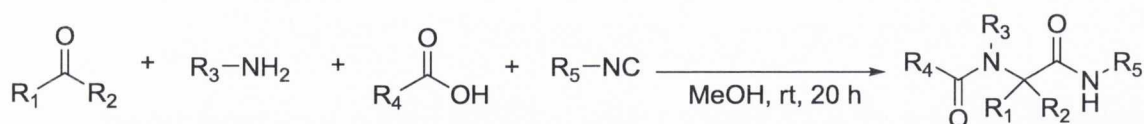
Biginelli reaction



Mannich reaction



Passerini reaction



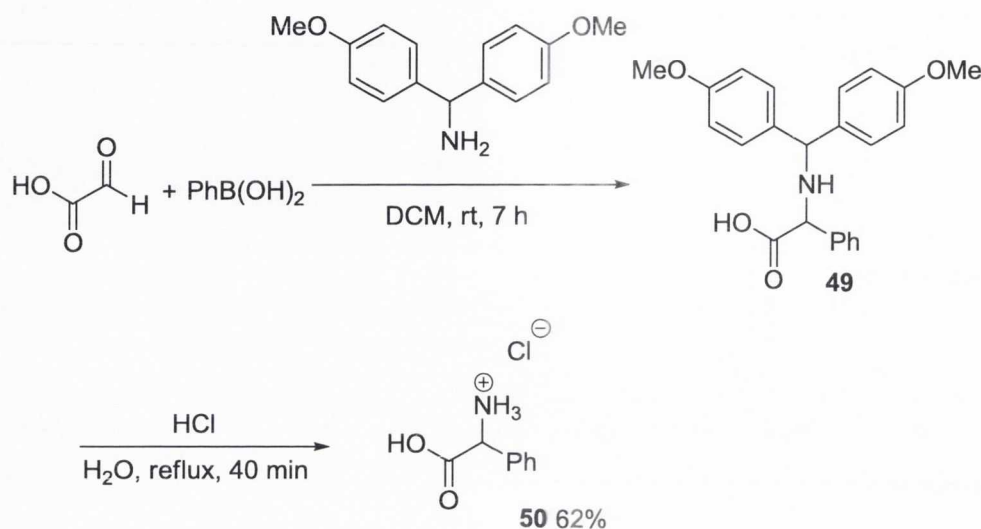
Ugi reaction

Scheme 1.25. Popular multicomponent reactions.

1.5.2 The Petasis reaction

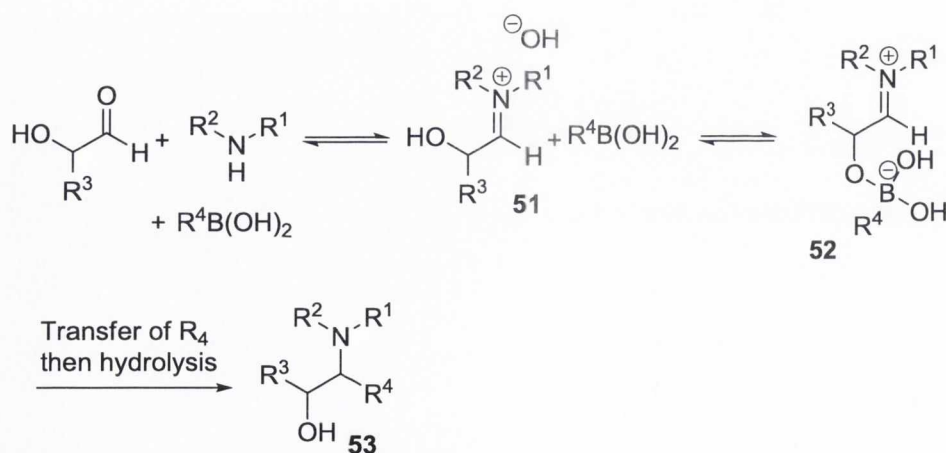
The Petasis reaction is a 3 component reaction that enables the preparation of tertiary amines and their derivatives from, originally, a primary amine, glyoxylic acid and an aryl

or allyl boronic acid (Scheme 1.26).^{106,107} The product **49** can then be converted to α -arylglycines **50** by deprotecting the amine (Scheme 1.26), bearing in mind that α -arylglycines are selective agonists or antagonists of the glutamate receptors of the central nervous system.¹⁰⁸



Scheme 1.26. Synthesis of arylglycine *via* the Petasis reaction.

According to Petasis the reaction involves a condensation between the aldehyde and the amine forming an iminium **51**.¹⁰⁷ The adjacent hydroxyl group activates the boronic acid forming a tetrahedron boronate salt **52**.¹⁰⁹ The quaternary boron salt can then transfer its aryl or allyl group to the iminium giving the product **53** (Scheme 1.27).¹¹⁰

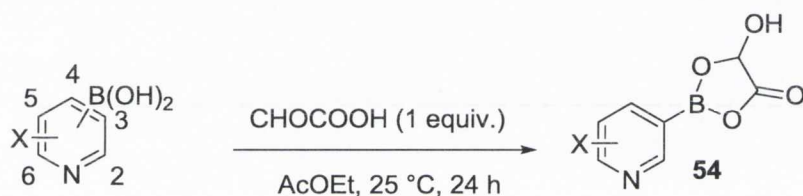


Scheme 1.27. Mechanism of the Petasis reaction

1.5.2.1 Scope of the reaction

1.5.2.1.1 Influence of the different components

Boronic acids with strong electron withdrawing groups have shown poor or no results in the Petasis reaction. The main reasons are a lack of nucleophilicity of the organoboron and a condensation between the boronic acid with the carboxyaldehyde giving a boronate ester **54**. The latter was observed, interestingly, by Rault who mixed one equivalent of glyoxylic acid with one equivalent of an electron withdrawing group bearing boronic acid (Table 1.1).¹¹¹

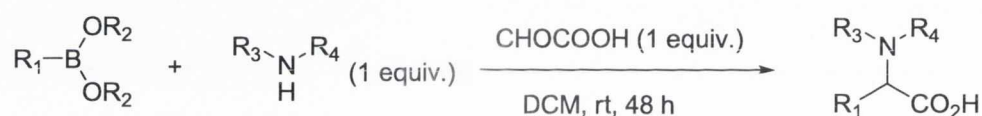


Entry	B(OH)_2 position	X	Yield (%)
1	3	6-Br	80
2	3	6-Cl	74
3	3	6-F	57
4	2	6-Br	75
5	3	5-Br	62
6	3	2-Cl	89
7	3	2-Br	78
8	3	2-F	36

Table 1.1. Effect of different substituted pyridinylboronic acids on a condensation with glyoxylic acid.

The position of the halogen has only a slight effect on the product formation (Table 1.1, entries 1, 5 and 7). No substantial yield difference was observed when the position of the boronic acid was changed (Table 1.1, entries 1 and 4). When fluorine was used, a significant drop of yield was noticed when compared to bromide and chloride (Table 1.1, entries 1, 2, 3 and entries 6, 7, 8).

Southwood et al. investigated many factors influencing the yield of the Petasis reaction including the electronic and steric nature of the boronic acid and the amine.¹¹² They carried out a series of Petasis reactions with glyoxylic acid and various amines and boronic acids or boronate esters (Table 1.2).



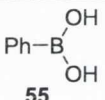
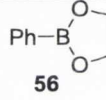
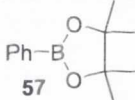
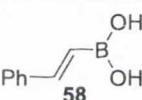
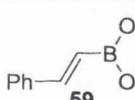
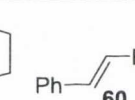
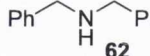
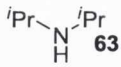
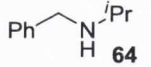
						
	10	0	-	79	20	0
	64	35	35	64	77	90
	84	19	0	84	19	0
	89	43	0	90	39	3

Table 1.2. Yields (%) of the Petasis reaction, using glyoxylic acids DCM, rt, 48 h.

The authors examined the reactivity of the boronate species by comparing phenylboronic acid **55**, phenylboronic acid ethylene glycol ester **56**, phenylboronic acid pinacol ester **57** and their corresponding styrenyl boronic homologues **58**, **59**, **60**. Additionally, steric effects and the degree of the amine substitution were investigated by testing, benzylamine **61**, dibenzylamine **62**, diisopropylamine **63** and *N*-isopropylbenzylamine **64**. Compound **55** gave a very poor yield (10%) with benzylamine **61** under standard conditions. No

product was observed when the corresponding ethylene glycol ester **60** was used instead of **55**. Since **56** gave no products, the authors chose not to try a more sterically hindered boronic ester **57**. Styrenyl boron reagents proved to give much higher yields and again the same trend was observed: **58** gave the highest yield, then **59**, and finally **60** gave no products.

The same reactions were carried out with a secondary amine **62**. Phenylboronic acid **55** and dibenzylamine **62** gave a much higher yield than when primary amine **61** was used. In this case the two boronate esters **56** and **57** gave some products. When the electron rich boronic acid **58** and the boronate esters **59** and **60** were used the products were obtained with higher yields.

The authors then investigated the effect of the amine steric bulk by using diisopropylamine **63**. No reaction was observed with the two boronic acid pinacol esters **57** and **60**. Interestingly, the styrenylboron species **58**, **59**, **60** gave similar results to the phenylboron counterparts **55**, **56**, **57**.

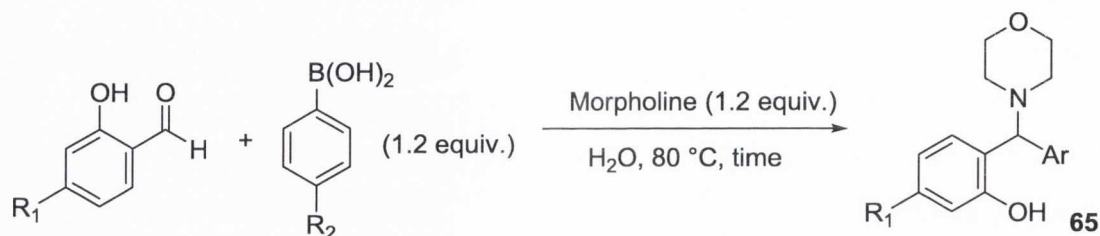
Finally the authors, in order to confirm the effects of branching, performed the reaction with *N*-isopropylbenzylamine **64**. All the yields obtained were between the yields acquired with **62** and **63**.

This study showed that secondary amines give higher yields in the Petasis reaction than primary amines. This can be simply explained by the easier formation of the iminium from a secondary amine and an aldehyde rather than made from a primary amine and an aldehyde. Bulky amines and boronate esters tend to decrease the product yield. Using electron rich boronic acid or boronate ester lead to higher conversions. Boronate esters have shown to be less effective than boronic acids in the Petasis reaction.

1.5.2.1.2 Petasis reaction in water

Water is a highly desirable solvent due to its non-toxicity, non-flammability and low cost. Candeias *et al.* developed the Petasis reaction in water.^{113,114} The iminium formed from the aldehyde and the amine partitions to the aqueous phase which contains the solubilised

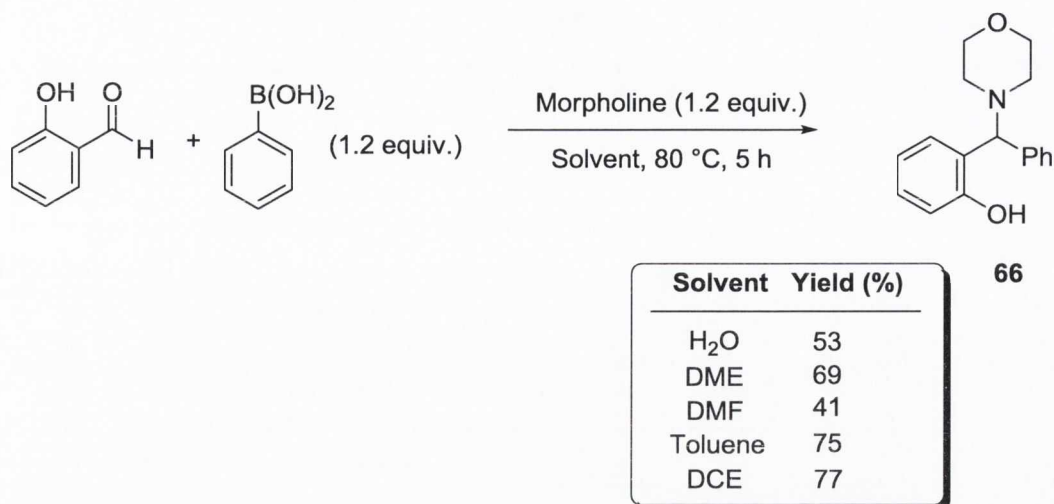
boronic acid. The author started to use salicylaldehyde derivatives, morpholine and some aryl boronic acids to form the corresponding tertiary amine **65** (Table 1.3).¹¹⁴ Surprisingly, substituents on the salicaldehyde derivatives have essentially no effect on the reaction result (Table 1.3, entry 1 against 2 and 3). When the boronic acid bears electron donating groups the yields are increased (Table 1.3, entry 4 against 5 and 6).



Entry	R ₁	R ₂	Time (h)	Yield (%)
1	H	H	24	75
2	Me	H	24	70
3	OMe	H	24	72
4	H	H	4.5	54
5	H	Me	4.5	85
6	H	OMe	4.5	81

Table 1.3. Electronic effect on the reactants in the Petasis reaction in water.

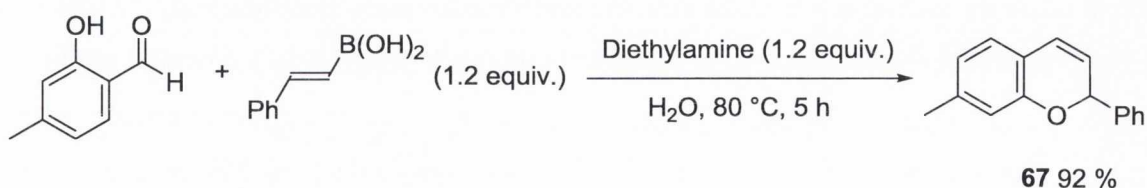
Water was compared to other solvent by performing the Petasis reaction with morpholine, phenylboronic acid and salicylaldehyde giving **66** (Scheme 1.28).



Scheme 1.28. Effect of different solvents on the Petasis reaction involving salicylaldehyde, phenyl boronic acid and morpholine.

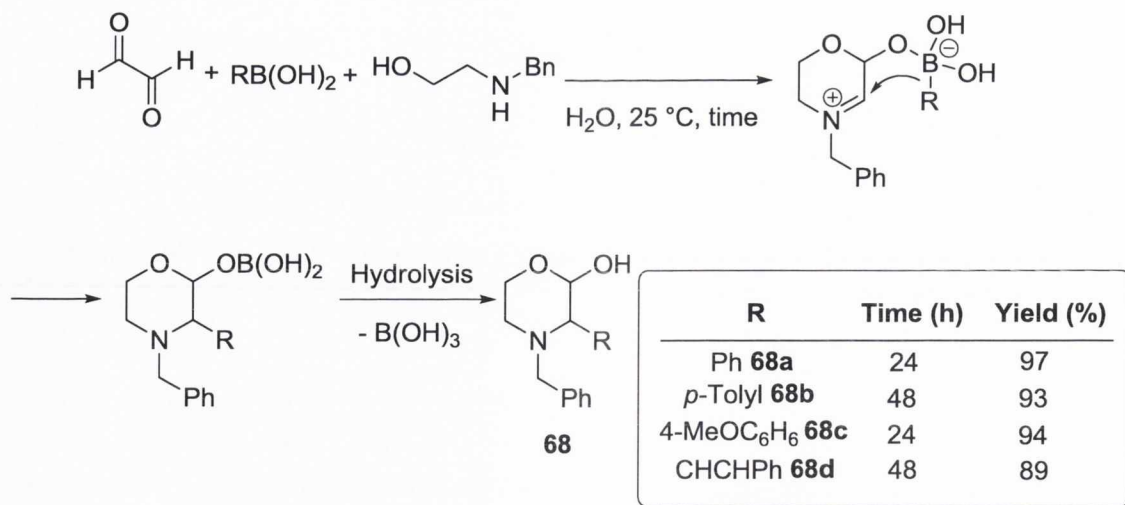
Toluene and DCE proved to be much more efficient than water whereas DMF gave a lower yield.

Subsequently, the authors synthesised *2H*-chromenes in water. The Petasis reaction has already been used to synthesize *2H*-chromenes.¹¹⁵ This reaction consists in a standard Petasis reaction between a secondary amine, a salicaldehyde derivative and a vinylic boronic acid. After the condensation, the free hydroxyl group on the aldehyde attacks the vinyl group and the amine is ejected forming **67**. While the amine can be used in a catalytic amount,¹¹⁵ the reaction in water seems to proceed with a better yield by using a slight excess of amine (Scheme 1.29).¹¹⁴



Scheme 1.29. Synthesis of *2H*-chromenes *via* the Petasis reaction in water.

The authors also synthesized 2-hydroxymorpholines *via* the Petasis reaction from glyoxal, benzyloethanolamine and a boronic acid.¹¹³ The reaction starts with a condensation and cyclisation between the amine and the aldehyde. The free hydroxyl group created can then react with the boronic acid and the aryl or allyl group can be transferred to the iminium producing **68** (Scheme 1.30).



Scheme 1.30. The Petasis reaction used to synthesize 2-hydroxymorpholines.

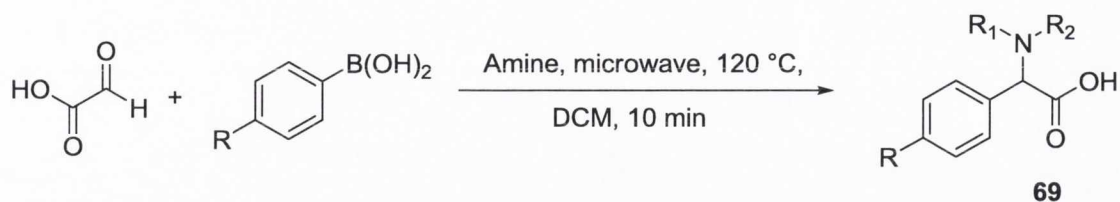
The 2-hydroxymorpholines were synthesized with high yields with different boronic acids, phenyl, *p*-tolyl, 4-methoxyphenyl and styryl (89-97%) (Scheme 1.30). It is worth noting that the product did not need to be purified by a chromatographic step but just extracted.

1.5.2.1.3 Microwave assisted Petasis Reaction

A microwave is composed of a magnetic field and an electric field. The latter interacts with any molecule containing a dipole or which is ionic. The molecule dipole is continuously aligned with the oscillating field causing the molecule to rotate and thus heat.¹¹⁶ Increasing organic chemical reactions rates by using microwaves irradiation is a powerful technique which has emerged in the 80s.¹¹⁷ Microwave energy is accurately controllable, which allows reactions to be scaled-up easily and to be more selective. Microwave assisted reactions are also environmental friendly and economically advantageous as solvent-free procedures can be elaborated. Additionally due to the immediate volumetric heating, this technique is time saving.¹¹⁸

In 2003, McLean et al. developed the first microwave assisted Petasis reaction.¹¹⁹ They performed the reaction using glyoxylic acid or salicylaldehyde, many different boronic acids and secondary or primary amines yielding **69**. The reactions proceeds well with reaction times of only 10 minutes. The same general trends were observed as when no

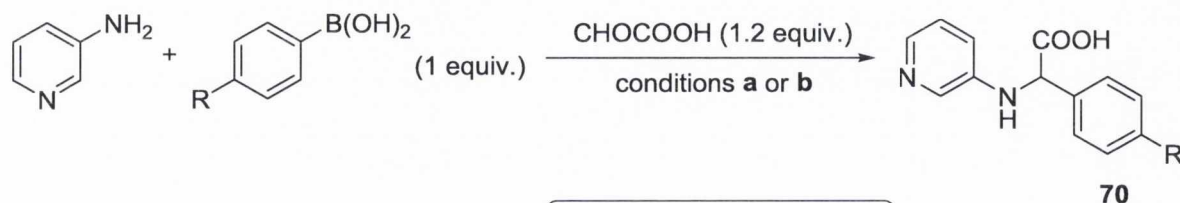
microwave irradiation is used: electron withdrawing groups on the boronic acids decrease the yield and primary amines are less efficient than secondary amines (Scheme 1.31).



R	Amine	Conversion (%)
H 69a	Morpholine	63
F 69b	Morpholine	53
H 69c	<i>p</i> -Anisidine	52

Scheme 1.31. Microwave assisted Petasis reaction using glyoxylic acid arylboronic acids and amines.

Hamley and co-workers used electron-poor aromatic amines in a Petasis reaction under microwave and they compared the results given by the same reactants under standard conditions.¹²⁰ In general the reaction proceeded in the same manner giving **70** with similar yields and thus electron rich boronic acids are, again, more reactive (Scheme 1.32). The main advantage of carrying out the reaction under microwave is time saving.

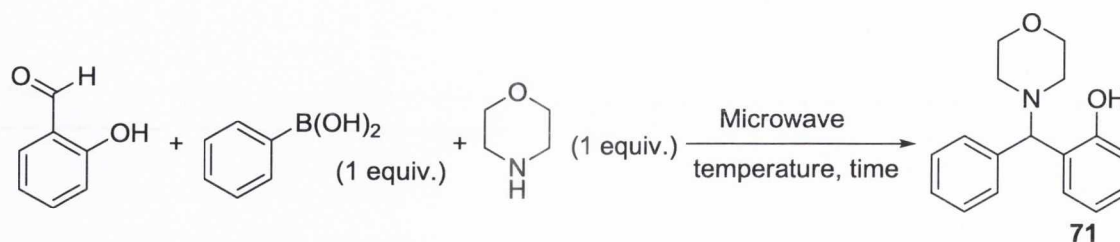


R	Yield (%) ^a
H 70a	25
MeO 70b	87

Scheme 1.32. Comparison of the Petasis reaction carried out under microwave and conventional conditions. Condition **a**: MeCN/DMF (10:1), microwave, 120 °C, 10 min. Condition **b**: MeCN/DMF (10:1), 82 °C, 4h. ^aYields are identical for both conditions.

Nun et al. elaborated a microwave assisted Petasis reaction with neat equimolar amounts of reactants.¹²¹ First, the authors optimized the reaction conditions by forming **71** from

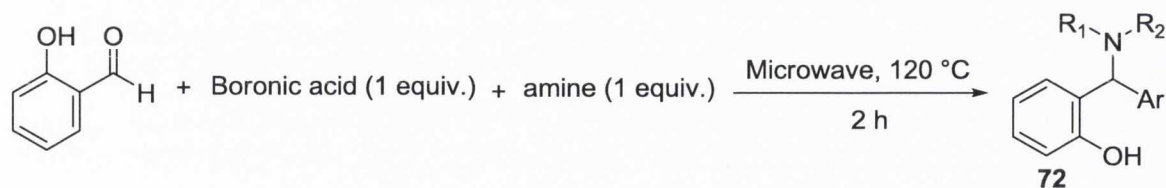
salicylaldehyde, phenyl boronic acid and morpholine by changing the time of reaction and the temperature (Scheme 1.33).



Temp (°C)	Time (h)	Conv. (%)
90	2 h	87
120	2 h	99
150	45 min	99

Scheme 1.33. Effect of different temperatures in the microwave assisted Petasis reaction.

Carrying out the reaction at 90 °C did not lead to full conversion whereas 120 °C, the temperature used in the previous examples, gave 99% of conversion after 2 hours. Accomplishing this Petasis reaction at 150 °C yielded **71** with a conversion of 99% after only 45 min but 120 °C was chosen as this temperature is more appropriate for the stability of the tertiary amines synthesized. Many boronic acids and different amines were tested giving **72** with different yields and illustrated in Table 1.4.



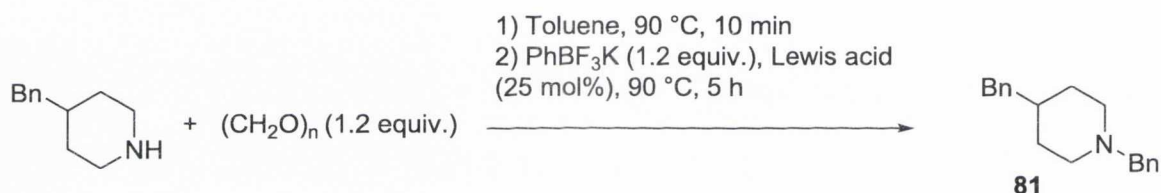
	 73	 74	 75
 76	78%	85%	85%
 77	87%	82%	92%
 78	72%	87%	90%
 79	87%	80%	-
 80	-	80%	-

Table 1.4. Effect of different boronic acids and amines on a microwave assisted Petasis reaction.

Morpholine **73**, piperidine **74** and a non-cyclic secondary amine **75** were tried. All gave high yields (>72%). Many phenyl boronic acids derivatives were used varying the electron density of the aryl groups on boronic acids **76-80**. Electron withdrawing groups (**79**) or electron donating groups (**80**) on aryl boronic acids gave the same yield. Interestingly *p*-tolylboronic acid **77** and *o*-tolylboronic acid **78** afforded the products with very similar yields, indicating that a small group in the ortho position does not affect the reaction.

1.5.2.1.4 Organotrifluoroborates in the Petasis reaction

In 2000, Schlienger et al. reported the first Petasis reaction with trifluoroborate derivatives and catalyzed by trimethylsilyl chloride in order to increase the reaction scope.¹²² This work has been extended later by Tremblay-Morin et al.¹²³ They started to work on a Petasis-like reaction which consists of a condensation between a piperidine derivative and paraformaldehyde, the intermediate bears a hydroxyl group which attack the potassium organotrifluoroborate reagent forming a tetraboronate species. The boronate species transfers then its aryl group to the non piperidine carbon alpha to the nitrogen yielding **81**. The reaction does not give any product in the absence of Lewis acids (Table 1.5, entry 1) implying the formation of an organoboron difluoride species. Using 1 equivalent of BF_3OEt_2 increases the yield whereas 2 equivalents gave no product.

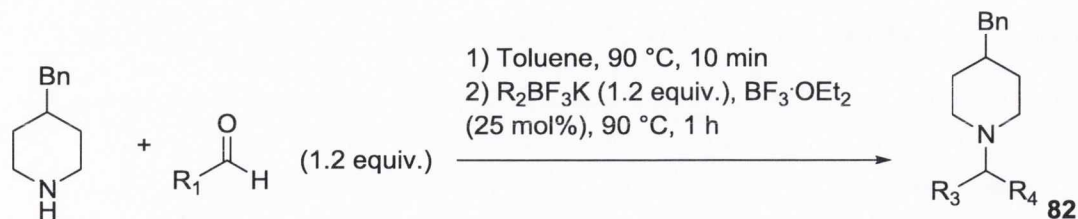


Entry	Lewis acid	Isolated yield (%)
1	No	0
2	BF_3OEt_2 (10 mol%)	59
3	BF_3OEt_2 (1 equiv.)	78
4	BF_3OEt_2 (2 equiv.)	No reaction

Table 1.5. Effect of a Lewis acid Petasis reaction with organotrifluoroborates .

After doing a screen of 12 potassium organotrifluoroborates the authors found that electron poor aryltrifluoroborates lead to low yields.

Then, the scope of the reaction was investigated further by trying different types of aldehydes yielding different *N*-substituted piperidine derivatives **82** (Table 1.6).



Entry	R ₁ CHO	R ₂ BF ₃ K	Yield
1			75
2			0
3			78
4			21
5			58

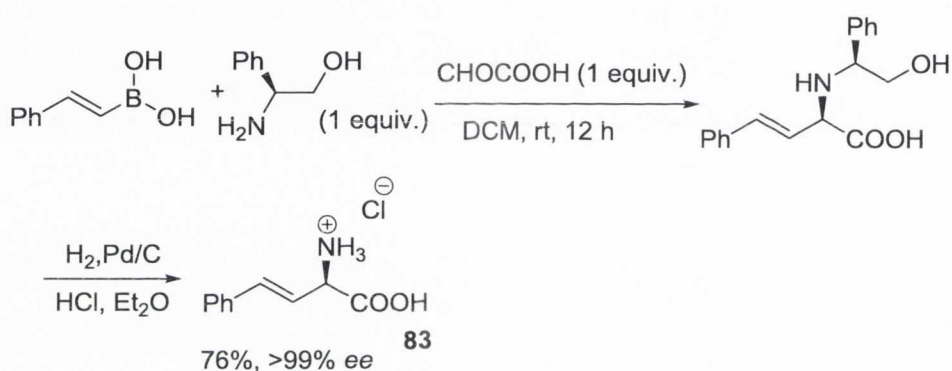
Table 1.6. Different aldehydes and organotrifluoroborates in the Petasis reaction.

It is worth noting that the aldehyde does not necessarily require a hydroxyl group adjacent to the aldehyde, but does require at least a coordinating group in the α or ortho position (Table 1.6, entries 4 and 5) and, hydroxyl group is still very much preferred (Table 1.6, entry 1 against entry 2). The reason for this tolerance appears to be the extremely high reactivity of the trifluoroborates. However, even with electron rich vinyl organotrifluoroborates, the yield is low when ethyl glyoxalate is used (Table 1.6, entry 4).

1.5.2.2 Asymmetric Petasis reaction

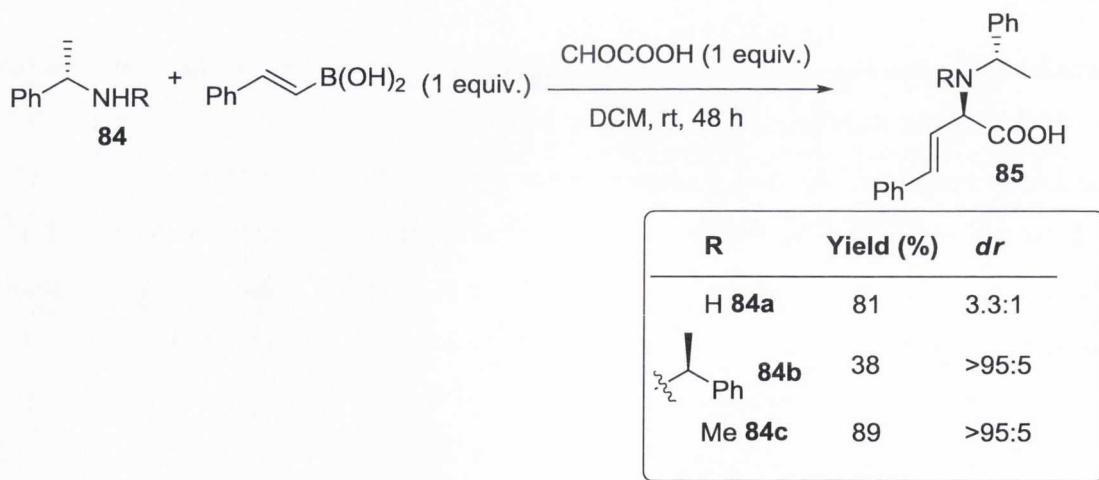
1.5.2.2.1 Petasis reaction using chiral amines or aldehydes

In 1997, Petasis and co-workers obtained good stereoselectivities by using chiral amines in the eponymous reaction in order to obtain enantiopure amino acids **83** after the amine deprotection (Scheme 1.34).¹²⁴



Scheme 1.34. Asymmetric Petasis reaction using a chiral amine.

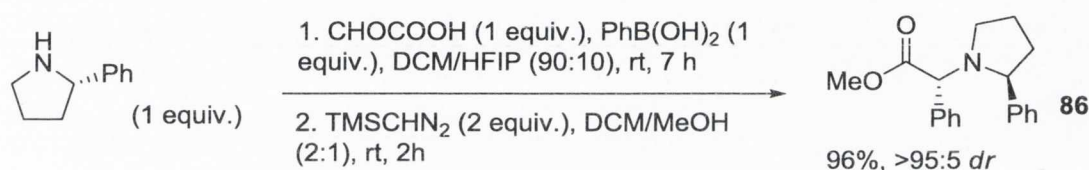
Southwood et al. investigated briefly the effect of the bulk of chiral amines on the stereoselectivity (Scheme 1.35).¹¹²



Scheme 1.35. Comparison of yields and diastereomeric ratios using different chiral amines in the Petasis reaction.

While the primary amine **84a** gave **85** in good yield as expected (81%), the diastereomeric ratio remains low (3.3:1). The bulkiest amine **84b** provided a high asymmetric induction but the lowest yield (38%). **84c**, a less bulky secondary amine seems to give the best results in terms of *dr* and yield.

Hexafluoroisopropanol (HFIP) as a co-solvent has shown to accelerate the process while preserving the diastereoselectivities and yields.¹²⁵ Pyrrolidine derivatives as secondary amines, glyoxylic acid, and aryl boronic acids were used to yield arylglycines which were directly converted to the corresponding methyl ester **86** with high yields and diastereomeric ratios (Scheme 1.36).



Scheme 1.36. Hexafluoroisopropanol as a co-solvent to accelerate the Petasis reaction.

The *anti* configuration of the product is explained by an attack of the aryl group from the face opposite the pyrrolidine substituent (Figure 1.9).¹²⁵

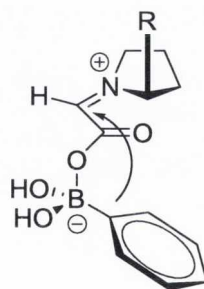
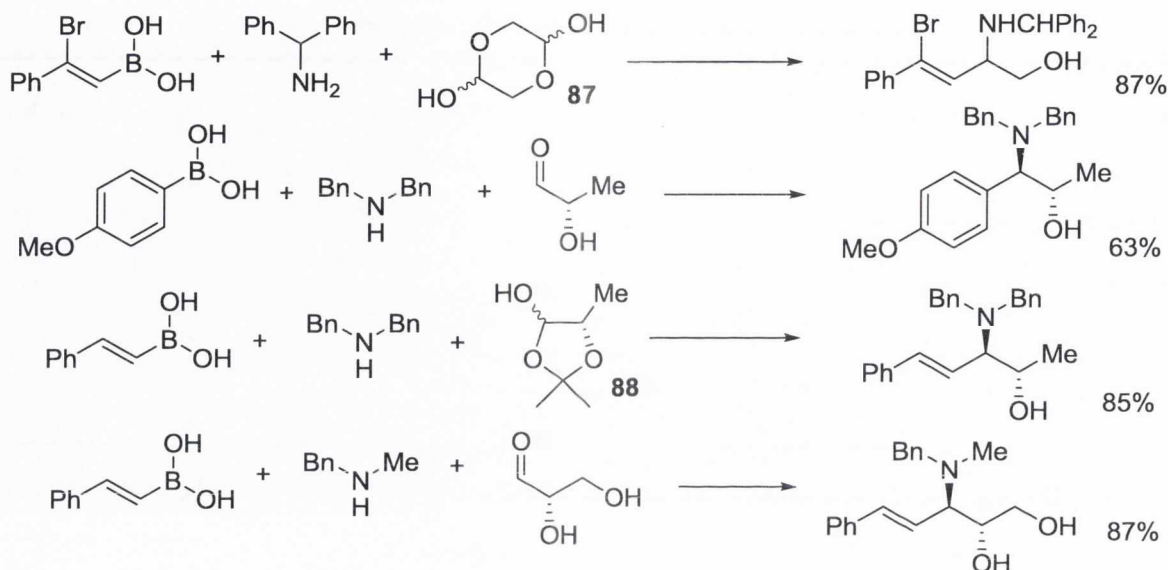


Figure 1.9. *Anti* configuration explained by the aryl group approach from the face opposite the pyrrolidine 2-substituent.

The authors Petasis and co-workers synthesised chiral β -amino alcohols by using optically pure α -hydroxyaldehydes.¹²⁶ Because aldehyde racemization does not occur under the reaction conditions, the product is obtained as a single diastereoisomer (*de* >99%). Many types of aldehydes and acetals **88** were found to be successful, while the boronic acid has

still to be electron rich and the amine contains at least one benzyl group. It is worth noting that glyoxaldehyde dimers **87** can be used in this reaction and give a good yield even if the reaction does not yield enantioenriched products (Scheme 1.37).



Scheme 1.37. Diastereoselective Petasis reactions using chiral aldehydes or acetals. Reaction conditions: 1 equiv. of each reactant in EtOH at rt for 24 h.

The reason for the exclusive *anti* conformation was suggested by Pyne and co-workers.¹²⁷ They speculate that the reaction proceeds via the boronate complex **89**, which adopt a minimisation of 1,3-allylic strain conformation (Figure 1.10).

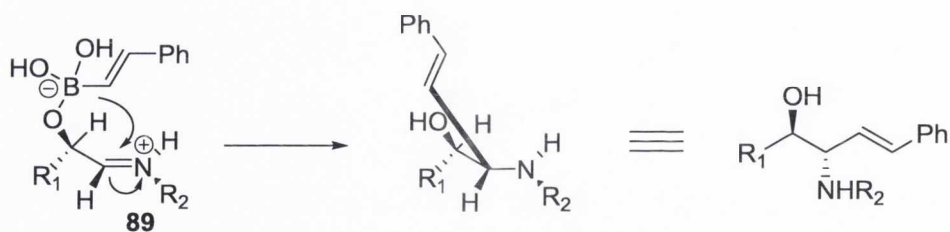
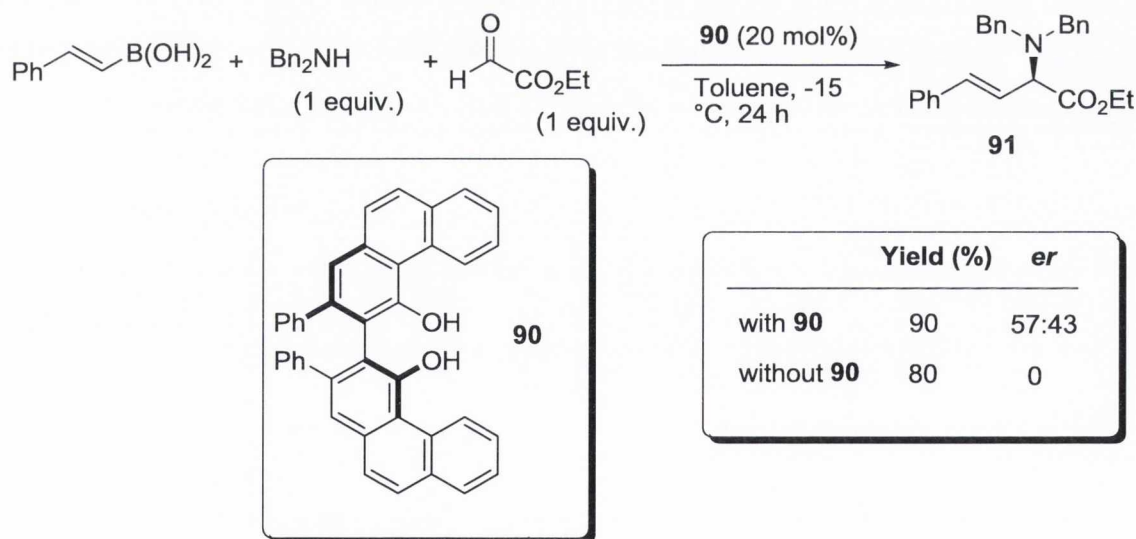


Figure 1.10. Formation of the *anti* α -hydroxy amine.

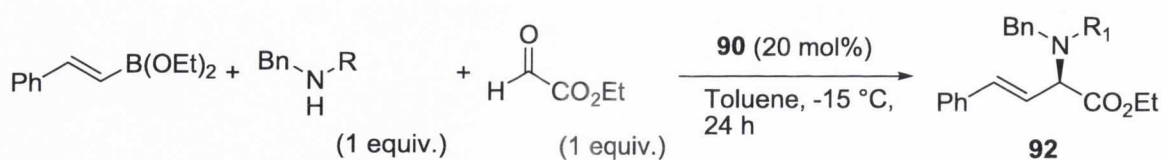
1.5.2.2.2 Asymmetric catalyzed Petasis reaction

Koolmeister et al. elaborated the first enantioselective Petasis reaction by using chiral boronic esters derived from a condensation between chiral diols and vinylboronic acid,¹²⁸ though the *ees* remain very low (15% maximum) and stoichiometric amounts of chiral alcohol are required. Important development in reactions involving additions of boronic acids or esters to diverse substrates catalyzed by chiral biphenols has been made recently.^{129,130,131} This led to another enantioselective Petasis reaction, this time catalyzed by chiral biphenols, developed by Schaus and co-workers.¹³² The authors tried many chiral biphenols in a Petasis reaction, involving ethyl glyoxalate, dibenzylamine, allylic boronic acids and found (*S*)-VAPOL **90** to give the best enantiomeric ratio and yields. When the rate of uncatalyzed reaction is high the enantioselectivities of **91** significantly drop due to the competition between the catalyzed and uncatalysed reactions (Scheme 1.38). It is worth noting that only the reactive vinyl boronic acids worked: no examples with aryl boronic acids were shown.



Scheme 1.38. Enantioselective Petasis reaction catalysed by (*S*)-VAPOL.

Using boronate esters was shown to increase yields and *ers*. The authors chose to investigate the scope of secondary amines by using diethyl boronates (Scheme 1.39). The reaction yielded **92** and shows good functional group tolerance while giving high yields and enantiomeric ratios.

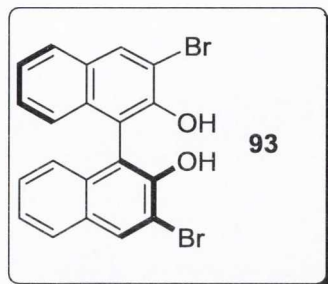
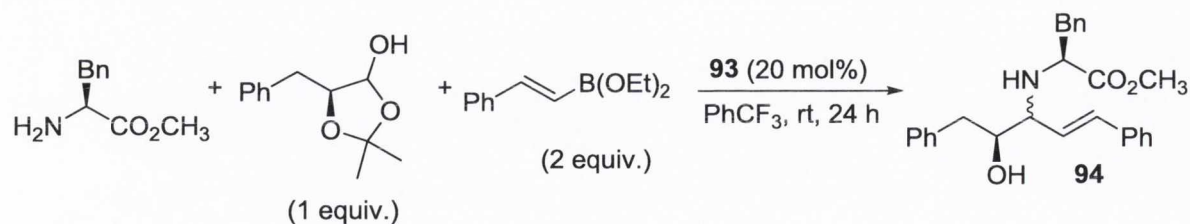


R	Yield (%)	er
CH ₂ CH ₂ CN	80	98.5:1.5
CH ₂ CO ₂ Et	94	95:5
CH ₂ TMS	84	95.5:4.5

Scheme 1.39. Different amines used in a (*S*)-VAPOL catalyzed Petasis reaction.

Interestingly, the conformation of the new stereocentre formed is the same when two enantiomeric chiral amines are used, showing that the catalyst strongly control the stereoselectivity of the reaction.

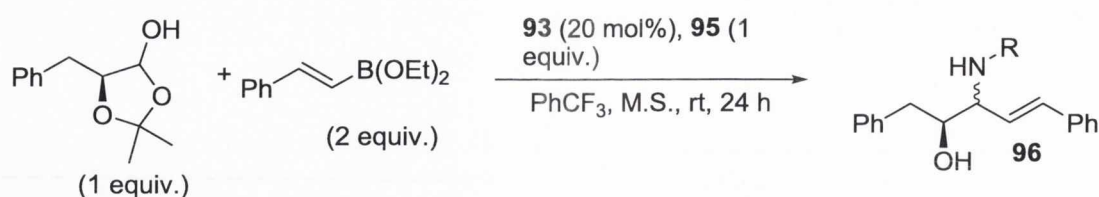
The formation of *syn* β -amino alcohol diastereoisomers has been investigated by carrying out the reaction with chiral amines, chiral acetals, boronate esters and a chiral catalyst giving a product with 3 chiral centers.¹³³ When the reaction is carried out in the absence of catalyst, only the *anti* **94** is formed as seen previously (Figure 1.2)¹²⁷ but when the same reaction is run with a catalytic amount of (*S*)-3,3'-Br₂-BINOL **93**, the configuration of the major diastereoisomer formed is *syn* (Scheme 1.40). As the two diastereoisomers can be separated by normal-phase chromatography, the *syn* β -amino alcohol can be isolated in an optically pure form.



Catalyst	Yield (%)	<i>dr syn/anti</i>
-	24	<i>anti</i>
93	68	5.5:1

Scheme 1.40. *Syn* β-amino alcohol synthesized by a (*S*)-3,3'-Br₂-BINOL catalysed Petasis reaction.

This reaction tolerates many functionalities on the amine moiety such as esters or acetals. Moreover, aryl boronates can be used but do not always lead to high diastereoselectivities. Diastereomeric ratios depend on the chiral amine configuration and bulk. Indeed, amines bearing smaller groups yield **96** with higher quantities of *syn* β-amino alcohol (Table 1.7, entry 1 vs. 3 and entry 2 vs. 4). Despite the catalyst the *anti* **96** is still favoured in some cases depending on the amine configuration (Table 1.7, entry 2 and 4).

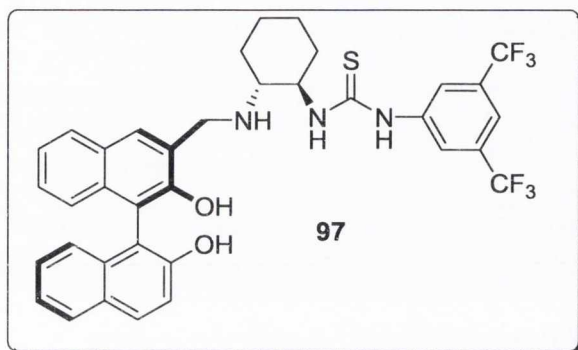
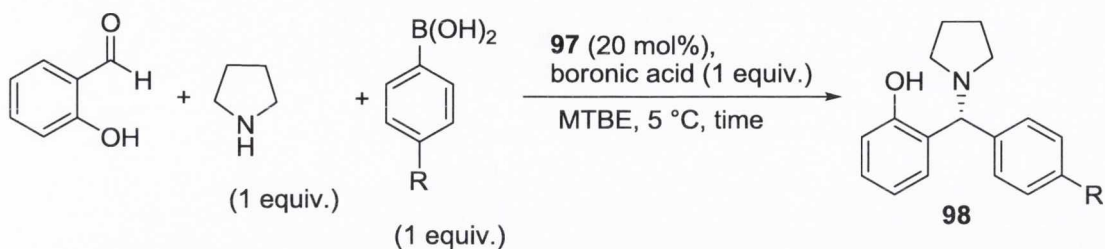


Entry	Amine	Yield (%)	dr syn/anti
1	 95a	55	2:1
2	 95b	57	1:20
3	 95c	80	7.5:1
4	 95d	71	1:2

Table 1.7. Effect of different chiral amines on the selectivity in the (*S*)-3,3'-Br₂-BINOL catalysed Petasis reaction.

Another enantioselective organocatalyzed Petasis reaction was developed by Yuan and co-workers using salicylaldehydes, amines and boronic acids.¹³⁴ The authors screened many catalysts in a reaction involving salicylaldehyde, morpholine, (*E*)-styrylboronic acid and found a thiourea-binol **97** to be very effective. After investigating the reaction conditions MTBE was shown to be the most efficient solvent and carrying out the reaction at a low temperature yielded the product with a high enantiomeric excess and yield. The reaction scope was then examined by testing different aryl boronic acids forming **97**. Electron withdrawing groups on the aryl boronic acid decrease the yield and the *ee* (Scheme 1.41) whereas functional groups on the salicylaldehyde seem to have only a poor effect on the

yield and enantioselectivity. Finally only cyclic amines were used in this reaction but they were all converted with high yields and a good asymmetric induction.



R	Time (h)	Yield (%)	ee (%)
OMe 98a	96	92	90
OMOM 98b	96	74	95
Cl 98c	36	61	74

Scheme 1.41. Thiourea-binol catalyzed enantioselective Petasis reaction.

While a detailed mechanism has not been elucidated yet, the authors propose that the boronic acid reacts with the BINOL catalyst forming a boronate ester (Figure 1.11). The salicylaldehyde reacts with the amine forming an iminium ion. The thiourea moiety is associated to the phenol anion, and then the R group can be transferred to the iminium. The catalyst is regenerated by hydrolysis.

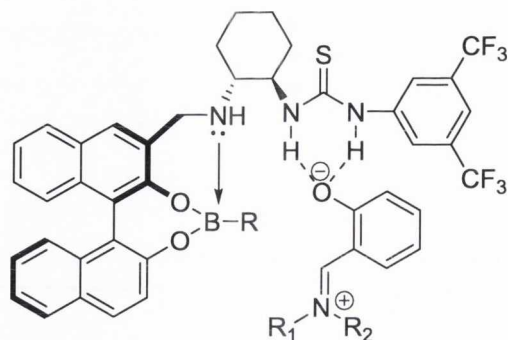
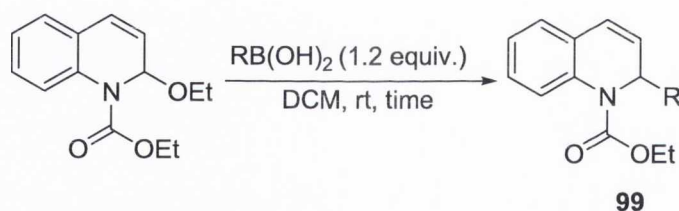
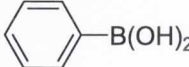
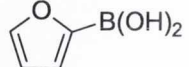
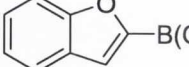


Figure 1.11. Possible intermediate in a thiourea-binol catalyzed enantioselective Petasis reaction.

1.5.2.2.3 Quinolines in an asymmetric Petasis-Type reaction

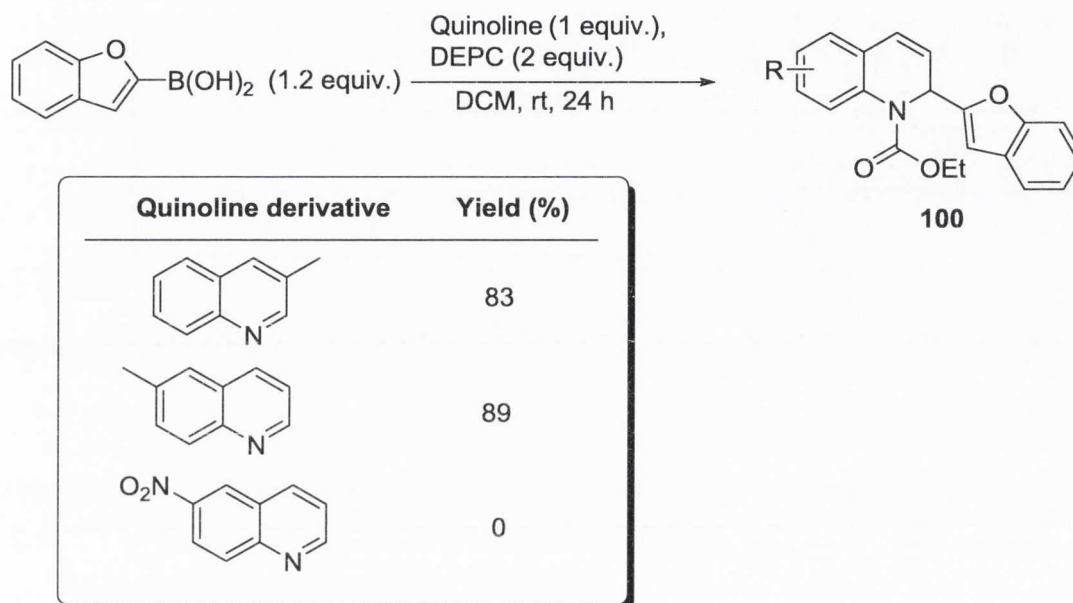
Yoon and co-workers reported a Petasis reaction with boronic acids, quinolines, and chloroformates.¹³⁵ They started to work on the addition of boronic acids to EEDQ and found DCM to be the best solvent. Then, different boronic acids were tested and phenyl boronic acid did not yield **99a** even after 48 h, only electron rich boronic acids gave the products **99b**, **99c** in good yields (Scheme 1.42).



RB(OH) ₂	Time (h)	Yield (%)	Product
	48	0	99a
	1	96	99b
	3	91	99c

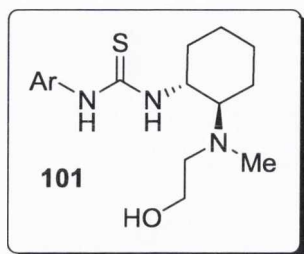
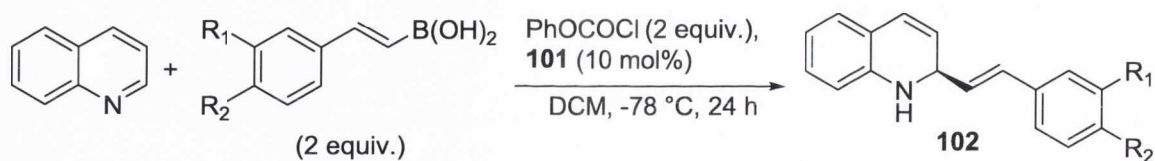
Scheme 1.42. Activated quinolines in a Petasis type reaction.

Several activating agents such as phenyl chloroformate, ethylchloroformate and DEPC were tested in the three components reaction using quinolines and boronic acids. DEPC allowed the reaction to proceed the reaction with the best results. Many quinolines and isoquinolines bearing electron donating and withdrawing groups were converted to the corresponding product **100** with high yields (Scheme 1.43). Only 6-nitroquinoline did not react because the nitrogen was not nucleophilic enough to react with DEPC.



Scheme 1.43. Different quinoline derivatives in Petasis type reaction.

Yamaoka et al. developed the first enantioselective Petasis type transformation of quinolines to **102** by using thiourea based organocatalysts.¹³⁶ After testing many catalysts they found **101** to be the most efficient. To obtain high enantioselectivities a low temperature is necessary and even with the presence of a catalyst electron rich boronic acids are required (Scheme 1.44).



R ₁ , R ₂	Yield (%)	ee (%)
R ₁ = OMe, R ₂ = H 102a	70	97
R ₁ = R ₂ = OCH ₂ O 102b	59	82
R ₁ = R ₂ = OMe 102c	60	89

Scheme 1.44. A thiourea based catalyst in an enantioselective Petasis type transformation of quinolines.

The authors proposed the following intermediate (Figure 1.12) suggesting that the thiourea moiety coordinates the activated quinoline, and the boronic acid is activated by a 1,2 amino alcohol group. The addition of H₂O was shown to increase the enantioselectivity as a proton source is assumed to help the catalyst regeneration.

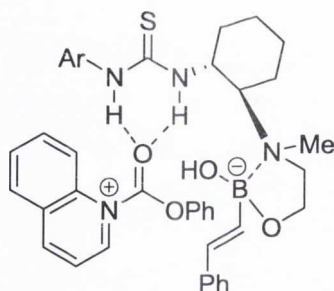
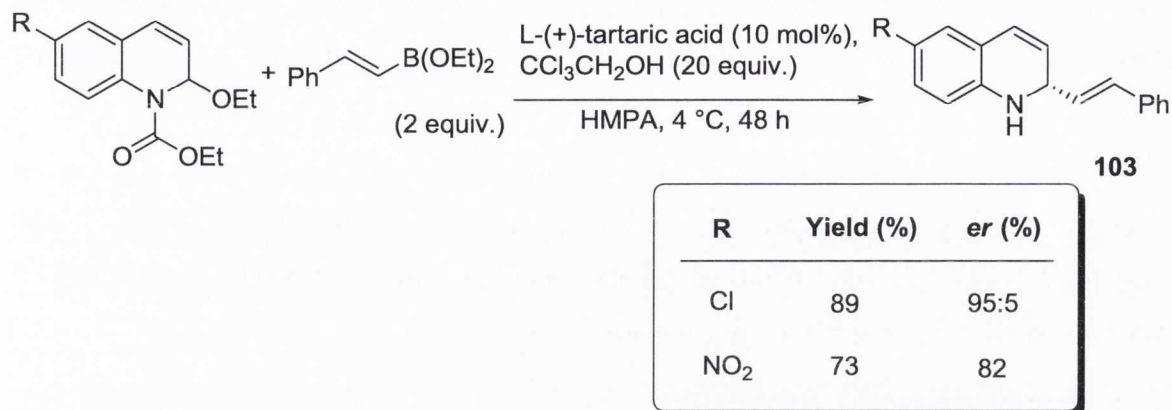


Figure 1.12. Possible intermediate in a thiourea based catalyzed enantioselective Petasis type transformation of quinolines.

Another successful enantioselective addition of boronates to activated quinolines to form dihydroquinolines was reported by Schaus and co-workers.¹³⁷ Tartaric acid was used as an organocatalyst. It reacts with the boronate to form a chiral boronate ester. Again, a protic media improves the results as the catalyst can be regenerated by hydrolysis more easily. Electron rich *N*-acyl quinolinium are more reactive because the positive charged iminium intermediate is stabilised, but electron poor EEDQ derivatives did give **103** with high

yields and *ers* (Scheme 1.45). Again, only the highly reactive and electron rich vinyl boronic acids were used.



Scheme 1.45. Tartaric acid as an organocatalyst in an enantioselective Petasis type transformation of activated quinolines.

In conclusion, while there has been a significant amount of work carried out on the Petasis and related reactions, there are still a number of drawbacks. Firstly electron deficient nucleophiles often give significantly reduced yields or, in some cases, no products. Secondly for the three-component couplings almost invariably a free hydroxyl group is required on the aldehyde starting material (normally glyoxylic acid or salicylaldehyde derivatives). In the isolated cases where weaker coordinating groups, such as esters, are employed, only extremely reactive allyl boronic acids or trifluoroborates yield any products.

1.5.3 Activation of boronic acids and boronate esters catalyzed by copper salts

In 1941, Kharasch et al. discovered the first 1,4 addition of Grignard reagents to α,β -unsaturated ketones in the presence of CuCl by investigating the addition of different metals to a Grignard reagent.¹³⁸ Later, in 1952, Gilman et al. formed lithium diorganocuprate (Me₂CuLi) from two equivalents of MeLi and a Cu^I salt.¹³⁹ These Gilman reagents subsequently found many applications as they can undergo substitutions,^{140,141} conjugate additions¹⁴² and carbocupration reactions.¹⁴³ Copper is now utilized catalytically

in various reaction including the coupling of terminal alkynes (Glaser reaction),¹⁴⁴ aryl halides with various nucleophiles (Ullmann reaction),^{145,146} terminal alkynes with haloalkynes (Cadiot–Chodkiewicz reaction)¹⁴⁷ and terminal alkynes with aryls or vinyl halides using palladium as a co-catalyst (Sonogashira reaction).¹⁴⁸ Boronic acids transmetallate both Cu^I and Cu^{II}.^{149,150} The Chan-Lam coupling is a good example of an aryl boronic acid transmetallating Cu^{II} salts (Figure 1.13).¹⁵¹ After a reductive elimination forming the desired product and Cu⁰, the copper can be reoxidised to Cu^{II} by O₂. Many substrates can play the role of the nucleophile such as amines,¹⁵¹ imides,¹⁵² alcohols,¹⁵³ carboxylic acids,¹⁵⁴ azides,¹⁵⁰ or phosphonates.¹⁵⁵

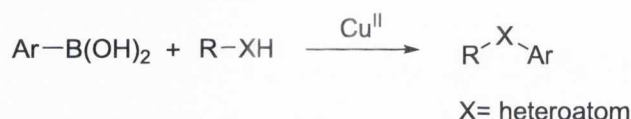
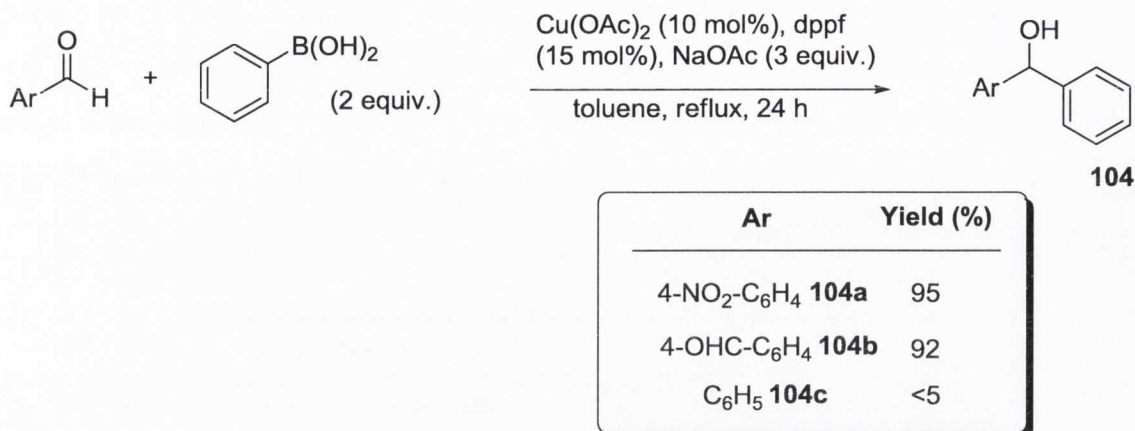


Figure 1.13. Chan-Lam reaction.

1.5.3.1 Addition to carbonyls catalyzed by Cu^{II} salts

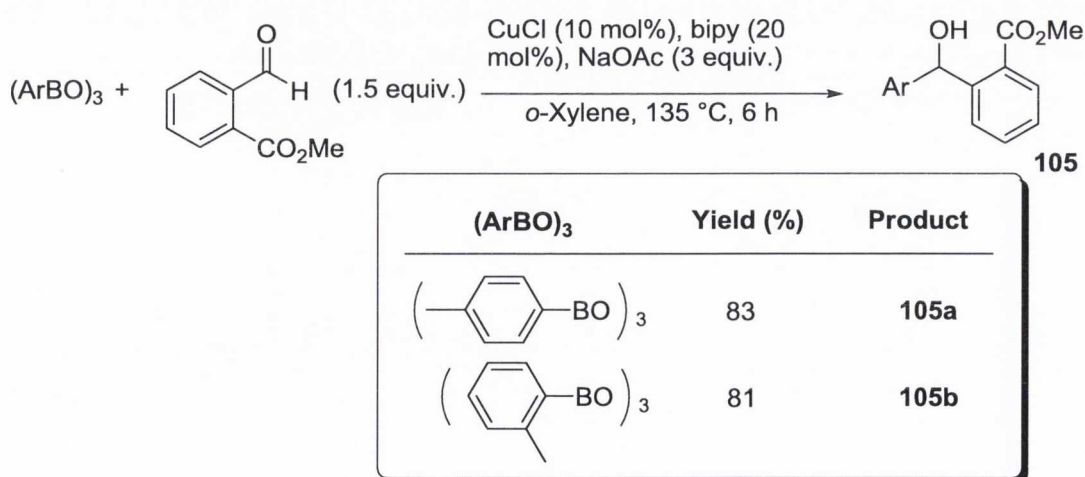
Zheng et al. synthesised carbinol derivatives from an aryl aldehyde and an aryl boronic acid in the presence of a catalytic amount of Cu(OAc)₂ and ligand.¹⁵⁶ This reaction has been reported to be catalyzed by rhodium¹⁵⁷, ruthenium¹⁵⁸ or palladium¹⁵⁹ but using copper instead decreases the cost of the reaction dramatically and the reaction can be carried out under air. After investigating P-based ligand structures, the authors found dppf allowed the reaction to proceed with the best results. After optimizing the reaction conditions, carrying out the reaction in toluene with 3 equivalents of NaOAc gave the product with the highest yield. The reaction scope was then examined. Electronic variation on the arylboronic acids had dramatic effect on the reaction yield. Electron poor aryl aldehydes gave **104** with good yields due to a more electrophilic carbonyl, for instance, 4-nitrobenzaldehyde produced **104a** with 95% yield (Scheme 1.46). Interestingly 4-formylbenzaldehyde was converted to **104b** with 92% yield leaving one formyl group intact, which can be explained by the fact

that the di-formyl starting material is considerably more reactive than the product. The reaction did not proceed well with electron neutral or electron-rich aldehydes.



Scheme 1.46. Cu^{II} and dppf catalysed addition of phenylboronic acids to benzaldehyde derivatives.

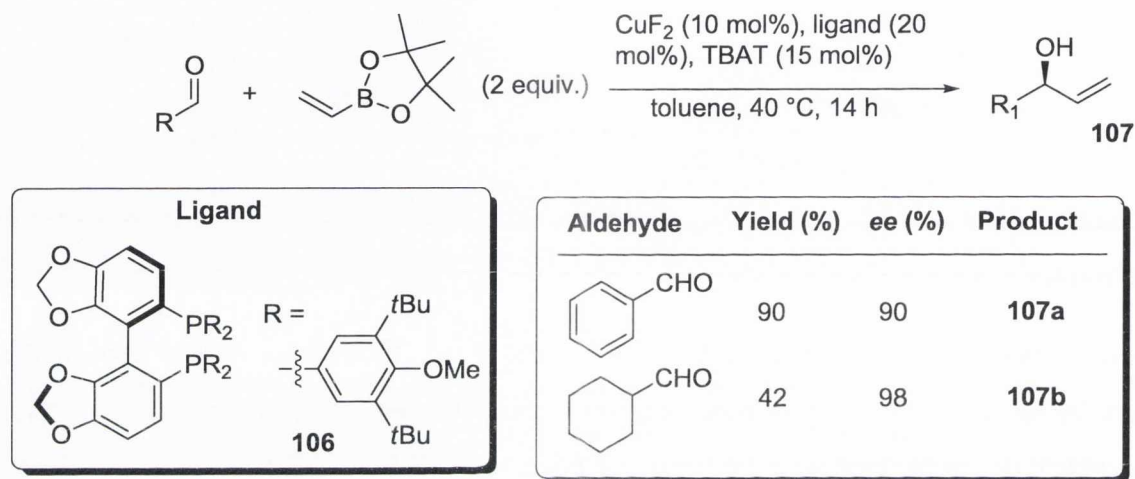
Noticing the poor result given by benzaldehyde Hu and co-workers tried to expand the scope of this reaction by trying many Cu^I and Cu^{II} based catalysts in a reaction involving benzaldehyde, phenylboroxine and NaOAc under anhydrous conditions.¹⁶⁰ They found CuCl and bipy to allow the reaction to proceed with a conversion of 86%. The same tendency was observed as aromatic aldehydes with electron-withdrawing groups were more reactive. Interestingly, the reaction tolerates ester groups on the aldehyde and boroxines bearing small steric groups yield **105a** and **105b** with good yields (Scheme 1.47).



Scheme 1.47. Cu^I and bipy catalysed addition of arylboroxines to methyl 2-formylbenzoate.

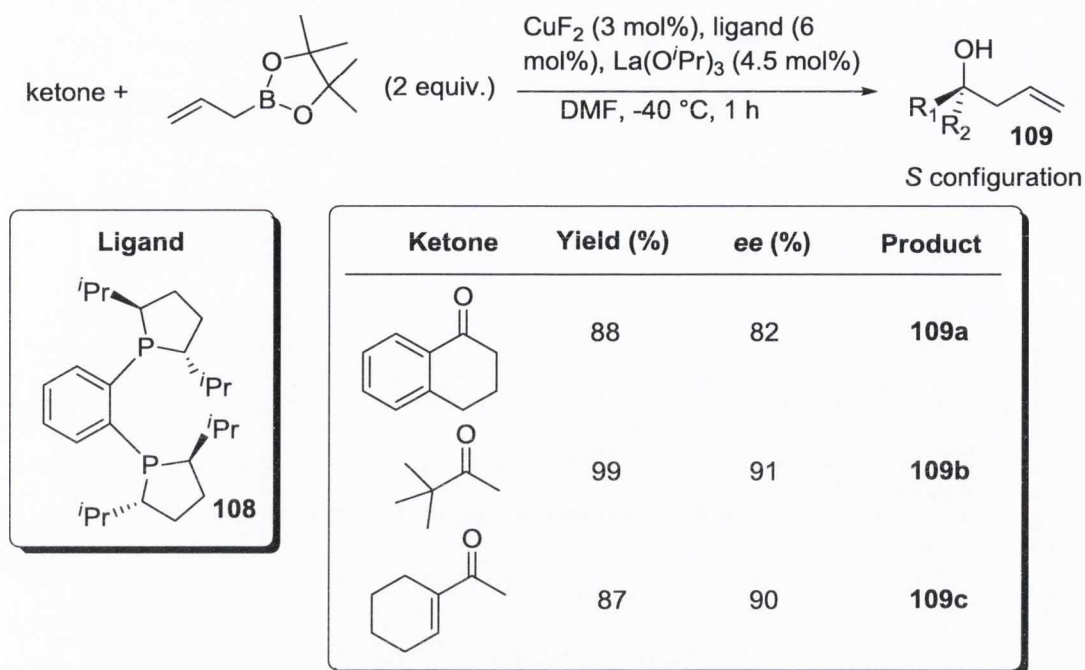
The racemic alcohol obtained can be easily converted to the corresponding diaryl ketone by allowing the reaction mixture to reflux under an oxygen atmosphere.¹⁶¹

A copper catalysed enantioselective addition of boronate ester to aldehydes was reported by Shibasaki and co-workers.¹⁶² The reaction proceeds well in the presence of TBAT, an additive which facilitates the catalyst turnover and a SEGPHOS derivative as a ligand. High yields are obtained for aromatic aldehydes whereas aliphatic aldehydes gave **107** with poor to moderate yields (Scheme 1.48).



Scheme 1.48. Cu^{II} catalysed enantioselective alkenylation of aldehydes

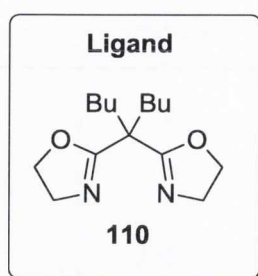
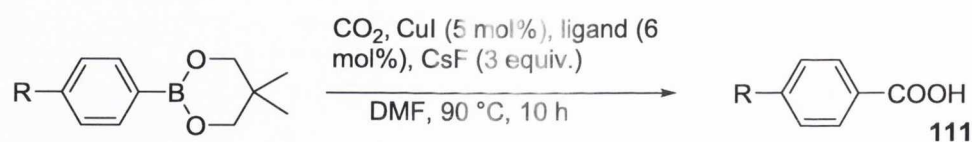
The authors also elaborated an allylboration of ketones catalysed by CuF₂, a ligand and La(O^{*i*}Pr)₃ as an additive.¹⁶³ Compound **109** was obtained with high enantioselectivities from aromatic, heteroaromatic, cyclic and aliphatic ketones using a DuPHOS ligand derivative **108** in a short reaction time at a low temperature (Scheme 1.49).



Scheme 1.49. Copper catalyzed enantioselective alkenylation of ketones.

1.5.3.2 Addition catalyzed by Cu^I salts

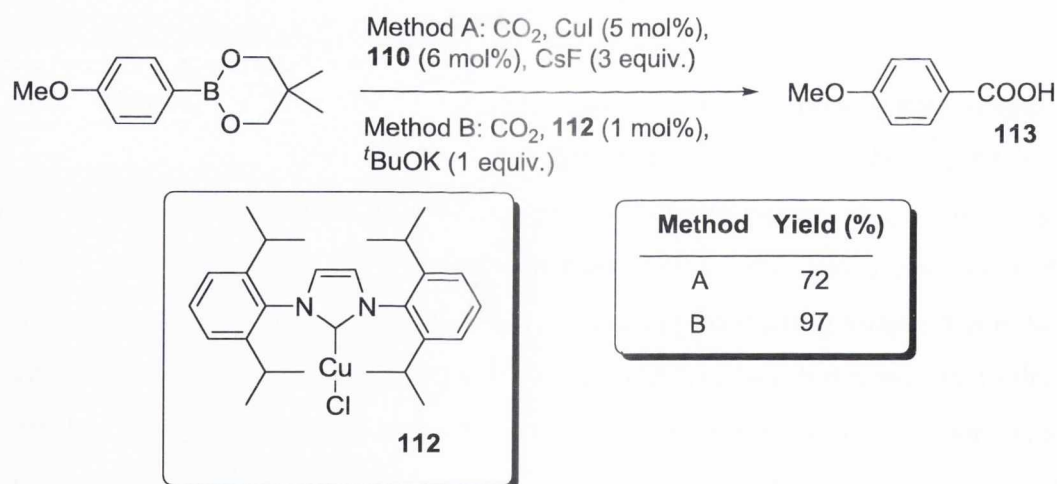
Iwasawa and co-workers reported a Rh^I catalyzed carboxylation of boronate esters in the presence of CO₂.¹⁶⁴ However arylboronate esters bearing functionalities such as vinyl or alkynyl gave little or no product because of side reactions, and additionally rhodium is an extremely expensive metal. The authors then developed a Cu^I catalyzed version of the reaction after investigating many copper salts.¹⁶⁵ Cu^{II} salts gave no products and among all the Cu^I salts CuI converted a phenyl boronate ester with the highest yield. Bisoxazoline ligands were found to be the most effective in this reaction. Arylboronate esters bearing either electron donating or electron withdrawing groups were converted to benzoic acid derivative with high yields. The Cu^I catalysed version tolerates vinyl and alkenyl aryl boronate esters yielding **111** in contrast to the Rh^I version (Scheme 1.50). The reaction also works well with alkenylboronate esters. The reaction can convert well alkenylboronate esters.



R	Yield (%)	Yield using Rh (%)
-Ph 111a	86	0
111b	70	0
-NO ₂ 111c	76	0

Scheme 1.50. Carboxylation of boronate esters catalysed by Cu^I.

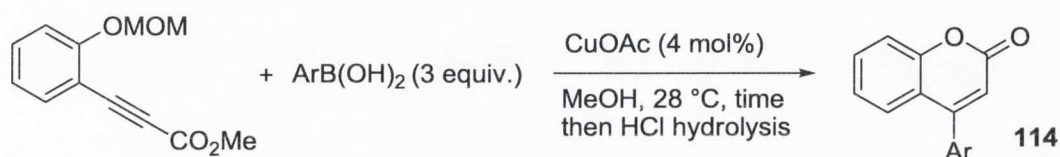
The mechanism involves a transmetallation generating an aryl or alkenylcopper species which undergoes a CO₂ insertion. The catalyst is regenerated with CsF. The mechanism is confirmed by Hou and co-workers who worked on the same carboxylation of boronate esters catalysed by Cu^I but used *N*-heterocyclic carbene as ligands which gave higher yields for the same compounds.¹⁶⁶ For instance the yield of 4-methoxybenzoic **113** acid synthesized with **110** was 72% against 97% with *N*-heterocyclic carbene ligand **112** (IPrHCl) (Scheme 1.51).



Scheme 1.51. Copper catalysed carboxylation of boronate ester using *N*-heterocyclic carbene ligand.

Cu^I has also been used, catalytically, in a 1,4-addition of arylboroxine to α,β -unsaturated ketones.¹⁶⁰ This was used by Kirai and co-workers to synthesise 4-arylcoumarins, a set of

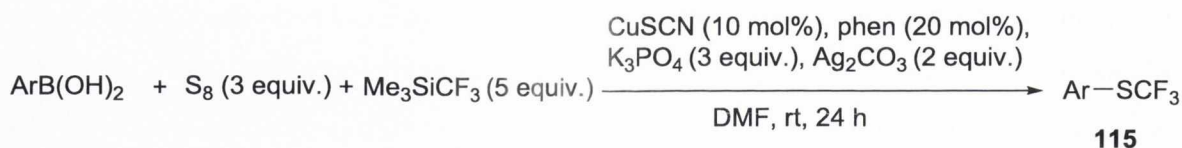
compounds which exhibit important biological activities.¹⁶⁷ The authors used methyl phenylpropiolate with a MOM protected hydroxy group at the ortho position, aryl boronic acid and a catalytic amount of CuOAc (Scheme 1.52). Carrying out the reaction with a free hydroxyl promoted the addition of methanol instead of the desired aryl group, so the catalysis is effected with a MOM protected hydroxyl group. A simple acidic hydrolysis deprotects the hydroxyl group and allows the lactonisation to occur. The reaction tolerates aryl boronic acids bearing electron donating or withdrawing groups. Compound **114** is obtained with high yields without any ligand.



Ar	Time (h)	Yield (%)
<i>p</i> -OHCC ₆ H ₄ 114a	3	89
<i>p</i> -MeOC ₆ H ₄ 114b	2	90
<i>p</i> -IC ₆ H ₄ 114c	6	89

Scheme 1.52. Copper catalysed addition of arylboronic acids to phenylpropiolates to synthesize coumarins.

In 2012, Qing and co-workers used Cu^I salts for the trifluoromethylthiolation of aryl boronic acids forming a C-S bond in mild conditions.¹⁶⁸ The trifluoromethylthio group is important in pharmaceuticals and agrochemicals as it is a strong electron withdrawing group with a high lipophilicity.¹⁶⁹ First, the authors investigated different copper salts, bases and oxidants in order to find the best reaction conditions (Table 1.8). The reaction tolerates many functional groups such as nitrile **115a**, sulfonyl **115b**, vinyl **115c**, ester **115d** and amide **115f**. The products are formed with moderate to high yields. Interestingly, a product with a bromide **115e**, reactive to Pd⁰ can be formed with a high yield (84%). This functional group tolerance allows further transformation of the aryl trifluoromethyl thioethers.



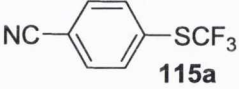
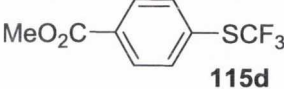
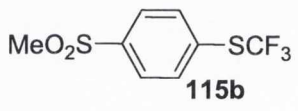
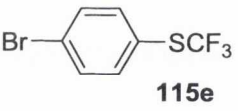
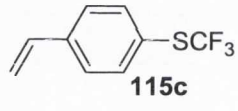
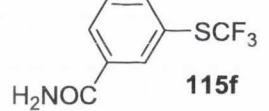
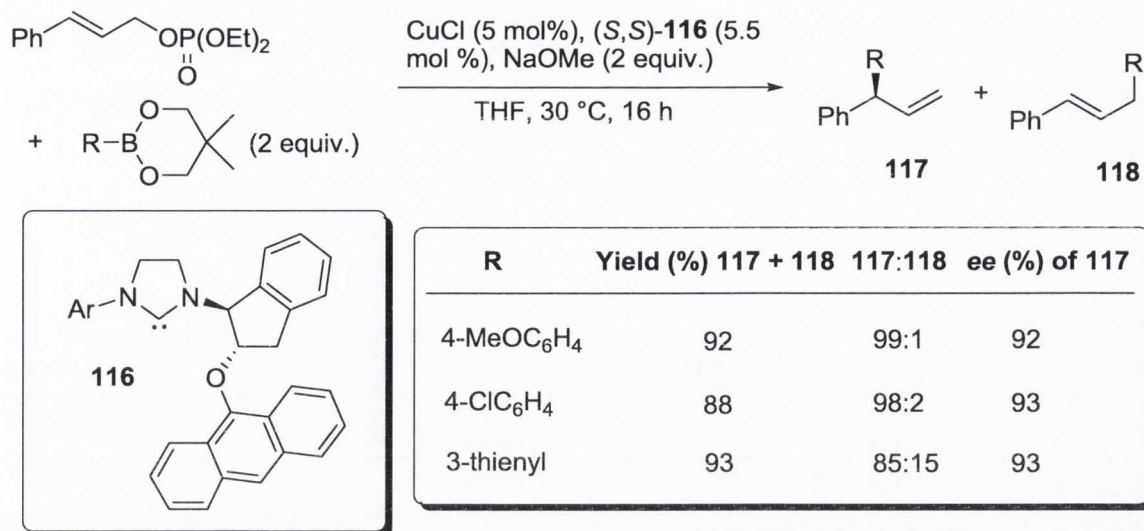
Product	Yield (%)	Product	Yield (%)
 115a	70	 115d	67
 115b	61	 115e	84
 115c	78	 115f	66

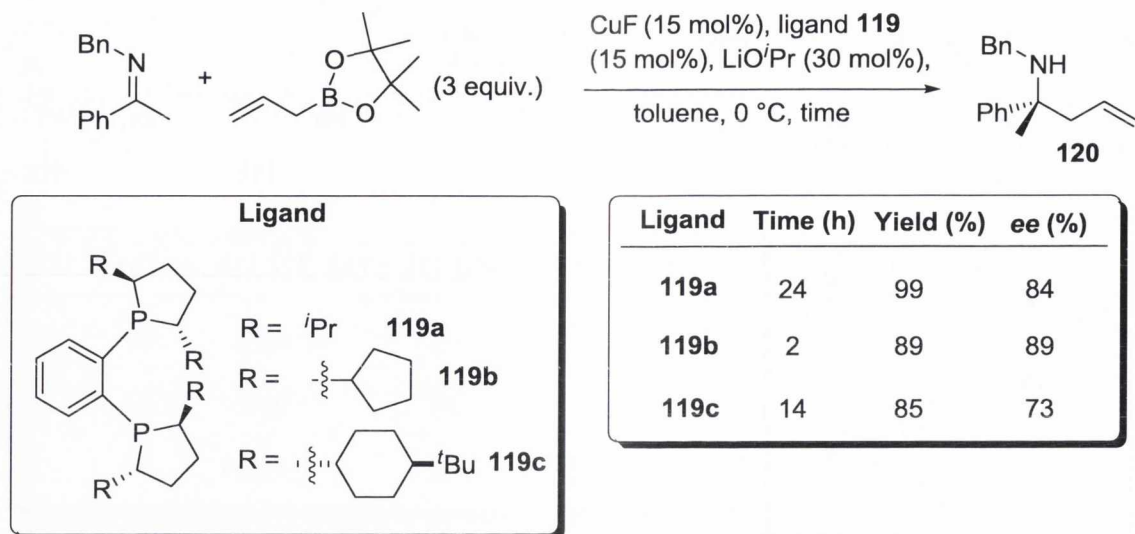
Table 1.8. Scope of the copper catalyzed oxidative trifluoromethylthiolation of aryl boronic acids.

In 2010, a copper catalyzed addition of boronate esters to allylic chlorides yielding a racemic product was reported.¹⁷⁰ Subsequently an enantioselective version was elaborated using chiral allyl phosphates as substrates.¹⁷¹ Based on this work, Hayashi and co-workers used chiral catalysts to add boronate esters to allyl phosphate in 2012.¹⁷² After screening many NHC ligands, **116** showed the best regioselectivity and enantioselectivity. The scope of the reaction was investigated by testing many aryl boronate esters. Boronate esters having either electron donating or withdrawing groups formed **117** with a high *ee*, whereas 3-thienyl boronate ester was shown to give **117** with a high *ee* but with more **118** produced (Scheme 1.53). All the other allyl phosphates with a modified γ group screened by the authors were converted to the corresponding products with high regioselectivities and high enantioselectivities but not always with high yields when the γ group is bulky.



Scheme 1.53. Copper catalysed enantioselective allylic substitution of cinnamyl diethyl phosphate.

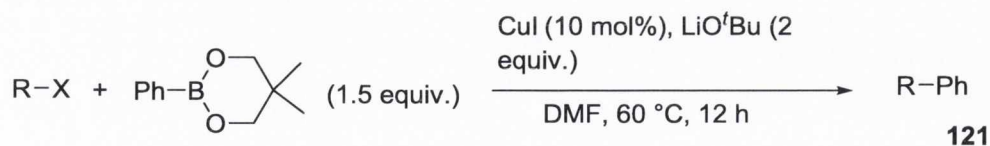
The asymmetric allylation of imines to yield α -trisubstituted homoallylamines has generated great interest.¹⁷³ Shibasaki and co-workers reported the first catalytic enantioselective allylation of imines in 2006.¹⁷⁴ They started to work with the conditions used for the allylboration of ketones.¹⁶³ After optimizing the temperature, catalyst loading, base and solvent in a racemic version of the reaction using triphenylphosphine as ligands, many imines substrates were tested. All the yields obtained were superior to 85%, among the substrates α -aryl groups with electron withdrawing or donating groups as well as aliphatic groups were successfully used. The enantioselective version of the catalysis was studied by using DuPhos ligands **119a**, **119b**, and **119c** (Scheme 1.54). Using cyclopentyl groups **119b** instead of isopropyl **119a** improves the *ee*. Ligand **119c** produced **120** with a lower yield and enantioselectivity.



Scheme 1.54. Copper catalyzed asymmetric allylation of imines.

Ligand **119b** was then used to convert many imines. All the yields were high but a benzyl on the α position was shown to decrease the enantiomeric excess (23%).

Using a lithium base with a Cu^I salt as a catalyst has also been investigated by Liu and co-workers.¹⁷⁵ The lithium cation is believed to stabilize the organocopper species by forming a cuprate-like complex and the ^{*t*}BuO⁻ anion facilitates the transmetalation by forming a tetraboronate species. The authors utilized aryl boronate esters for an alkylation involving primary halides or pseudohalides R-X (X = I, Br, Cl, OTs, OMs). After studying the reaction conditions, water was found to lower the reaction yield and DMF has shown to be the best solvent. The reaction tolerates many functional groups such as ether, **121a**, unsaturated C=C bond **121b**, aryl **121c**, ester **121d**, nitrile **121e** or amide **121f** (Table 1.9).



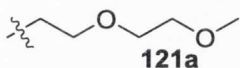
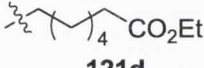
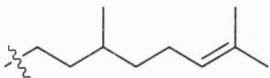
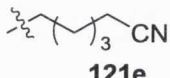
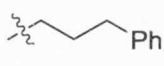
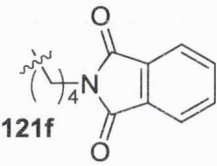
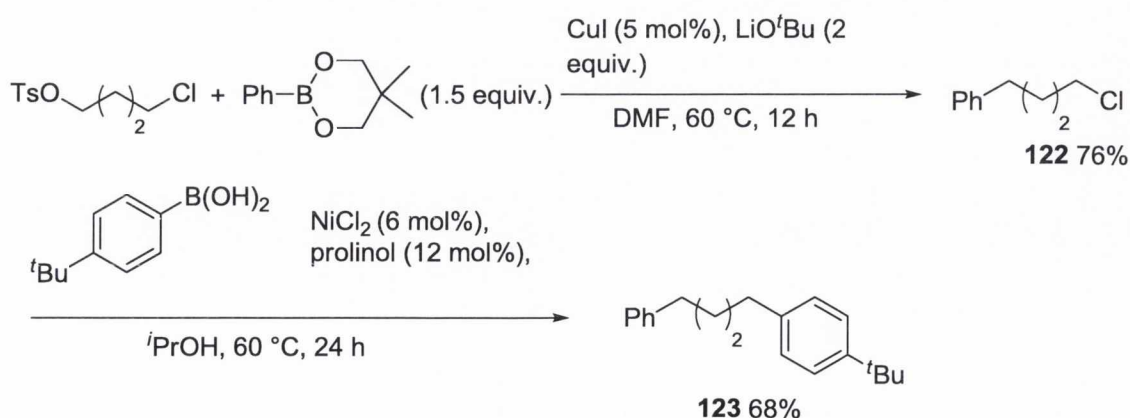
R	Yield (%)	R	Yield (%)
 121a	81	 121d	65
 121b	77	 121e	49
 121c	86	 121f	53

Table 1.9. Scope of the copper catalyzed aryl alkylation.

Different alkyl halides and pseudo halides were investigated and the following order of reactivity was discovered: chloride < MsO < TsO < bromide < iodide. The difference of reactivity allows a selective substitution on a compound possessing a TsO group and a chloride (Scheme 1.55). After a first coupling, the C-Cl site on **122** is available for another coupling reaction giving **123**.



Scheme 1.55. Site selective copper catalyzed alkylation.

This example shows the advantages of copper in cross-coupling. Copper is not only a cheap metal but it is selective in cross-coupling reactions and can be complimentary to more traditional palladium or nickel catalysed reactions.

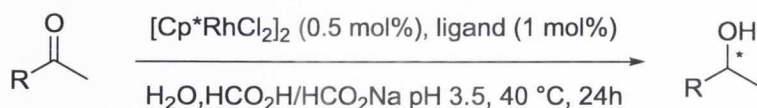
***Chapter 2: Rapid, in situ synthesis of
polydentate ligands***

2.1 Introduction

There has been a great deal of work and huge successes have been achieved for the *in situ* synthesis of monodentate ligands. In spite of this, it is still generally true that many homogeneous catalysed enantioselective reactions still require bidentate ligands for optimal selectivities.^{176,177,178} Unfortunately the development of *in situ* methods for bidentate ligands has proven to be elusive to date due to the increased complexity relative to monodentate synthesis.⁴⁵ This project outlines the first method which allows one to design libraries of chiral bidentate ligands, synthesised *in situ*, which were subsequently screened in homogeneous catalysed reductions and hydrosilylations of ketones.

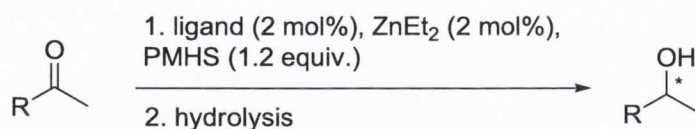
The ligands are generated by assembling two fragments together using high yielding reactions to avoid any purification steps. Many functionalities were tried in order to increase the ligand library diversity. At least one of the two fragments is chiral in order to yield chiral ligands. Moreover the two fragments must be prepared easily from inexpensive starting materials, either commercially available or easily synthesisable, to maximise the abundance of ligands.

The ligands prepared *in situ* were tested on two reactions and some were compared to their counterparts purified by conventional means. The first reaction examined, is a transfer hydrogenation using Rh^{III} in an aqueous media (Scheme 2.1). This reaction is a good alternative to reduction utilizing gaseous hydrogen as it is cheaper and more convenient.⁵⁶ In addition, it is a highly challenging reaction, with a few successful ligand types developed,⁵⁶ and as such is a good test for the methodology.



Scheme 2.1. A rhodium catalysed transfer hydrogenation to test *in situ* formed ligand.

The second reaction examined is a hydrosilylation of ketones using diethylzinc and PMHS (Scheme 2.2).⁷³ This is attractive due to the low cost involved, all reagents are inexpensive, and diethyl zinc is only used in catalytic amounts. Again it is a difficult reaction, with only a few, isolated cases giving reasonable results.⁸²



Scheme 2.2. A zinc catalysed hydrosilylation used to test *in situ* formed ligand.

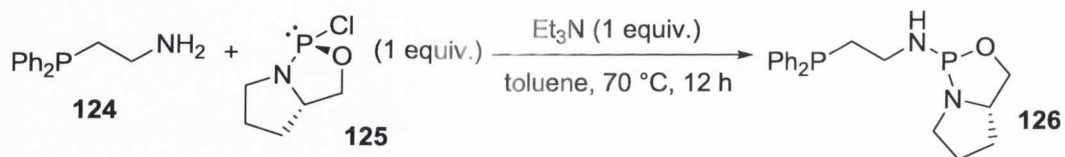
The goal of these libraries is to find a “hit”. Ligands are made in small quantities, and not isolated but screened directly in the process. Once a ligand is found for a given substrate/reaction it can be scaled up and purified by conventional means, meaning that only successful ligands need to be synthesised.

2.2 Synthesis of ligands

The initial attempts focused on simple methods to generate bidentate P,P ligands *in situ*. In order to be suitable candidates for *in situ* library generation the linking reaction should fit three criteria. Firstly the reaction should be high yielding in order to avoid any starting material left in the reaction mixture. Secondly, there should be no side-products, or the side-products should be innocuous and easily removable. Finally the product should be stable under the reaction conditions of the relevant reaction to be screened.

The addition of amino phosphines to chlorophosphoramidites seemed to be a reaction of choice which fulfils the above requirements. Additions to chlorophosphorus compounds tend to be rapid, high yielding and produce a side-product (HCl) which can be trapped by triethylamine and subsequently removed by simple filtration.

Compounds **124** and **125** were synthesized successfully according to the procedure of Honaker¹⁷⁹ and Tsarev¹⁸⁰. Compound **125** could be formed as a single diastereomer, opening up the possibility of producing ligands with phosphorus and carbon based chirality in one step. Equimolar amounts of **124** and **125** were reacted together with one equivalent of triethylamine in anhydrous toluene (Scheme 2.3). Unfortunately, after a cannula filtration **126** was impure by crude ³¹P NMR. Partly this was due to some epimerization at the chiral phosphorus center during the addition on the amino group.



Scheme 2.3. Synthesis of bisphosphine.

Due to the fact that **34** would need to be purified in order to be used, the reaction does not follow the criterias to synthesize ligands *in situ*. The reaction was abandoned for the time being in favour of compounds with no diastereoselective issues. Additionally it was decided to examine compounds that would be less water and air sensitive and thus, more suitable for combinatorial chemistry with standard laboratory equipment.

2.2.1 Imine ligands

The formation of imines by condensing a primary amine with an aldehyde is a simple and high yielding reaction which does not require harsh conditions. Moreover, the only side product, water, can be easily removed by molecular sieves. Aldehydes and chiral primary amines are readily available, so the synthesis of imines is a good candidate reaction to start a bidentate ligand library quickly (Figure 2.1).

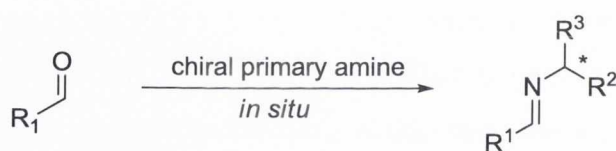
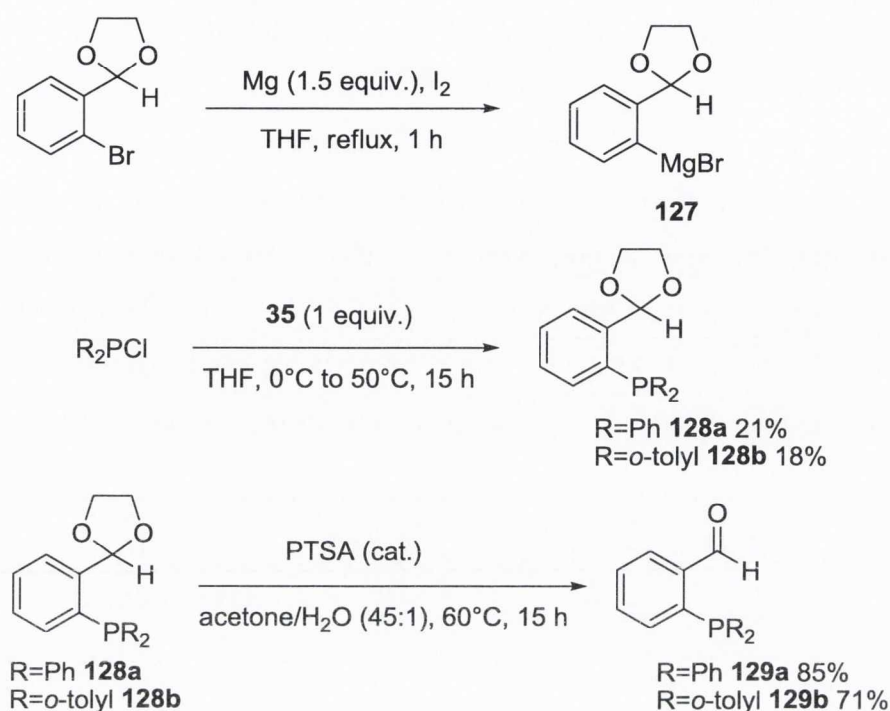


Figure 2.1. Bidentate ligand formation from a condensation reaction (where R^1 contains a coordinating group).

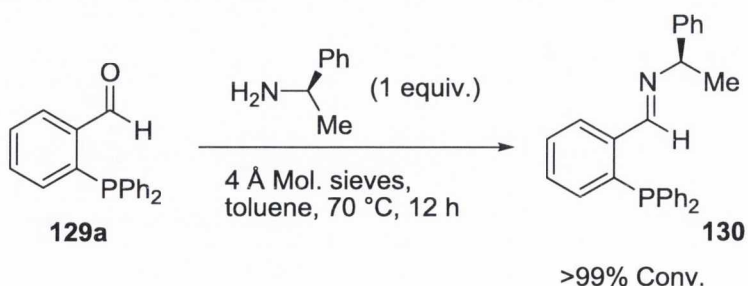
Two phosphine aldehydes were synthesised in order to produce chiral imino phosphine ligands (Scheme 2.4). First tertiary phosphines **128a** and **128b** bearing an acetal group were synthesised from a Grignard reagent **127** with moderate yields. These yields are unoptimised, and it is not clear if the yields are due to the formation of the Grignard reagent or the addition to the chlorophosphine. However, since enough material for library

formation was obtained the synthesis was not re-examined. The aldehydes were then deprotected in an acidic media to yield **129a** and **129b**.



Scheme 2.4. Synthesis of phosphine aldehydes.

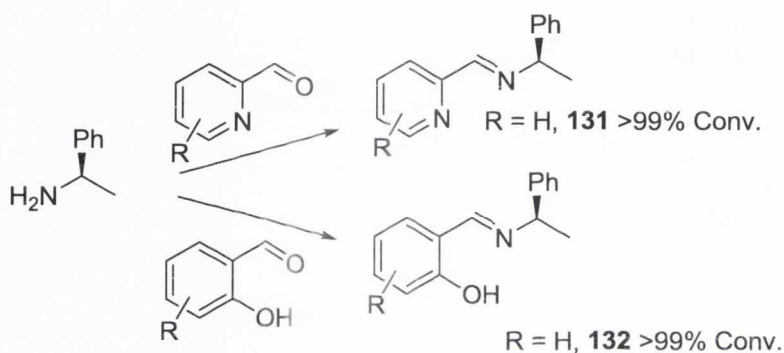
The ligands formations were simply performed at 70 °C in toluene with molecular sieves overnight (Scheme 2.5). After filtering the molecular sieves and evaporating the solvent, **130** was observed with high purity and conversion by NMR (^1H , ^{13}C and ^{31}P). The fact that no other side-products (or starting materials) were observed in the crude mixture was a promising sign, indicating that this chemistry could be a suitable for library formation, without the need for any isolation or purification.



Scheme 2.5. Synthesis of imino phosphine ligands *in situ*.

This synthesis is highly modular, and the introduction of the phosphorus group allows great variability in the products.

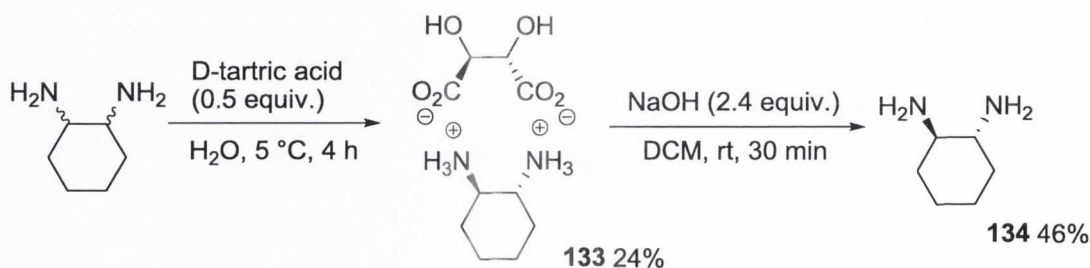
Also, the synthesis is not limited to phosphorus ligands, any aldehyde with a coordinating group is a potential candidate for an *in situ* bidentate ligand synthesis. For instance, important *N,N*- ligands can be prepared from a commercially available chiral primary amine and a 2-pyridinecarboxaldehyde derivative. Salicylaldehyde derivatives can also be used to form iminoalcohols. A huge variety of substituted pyridine carboxaldehydes and salicylaldehydes are commercially available, meaning that molecular diversity can easily be incorporated into these libraries. Those ligands are produced by using the same conditions as the iminophosphine with complete conversions (Scheme 2.6).



Scheme 2.6. Bidentate bisimine and iminoalcohol prepared *in situ*.

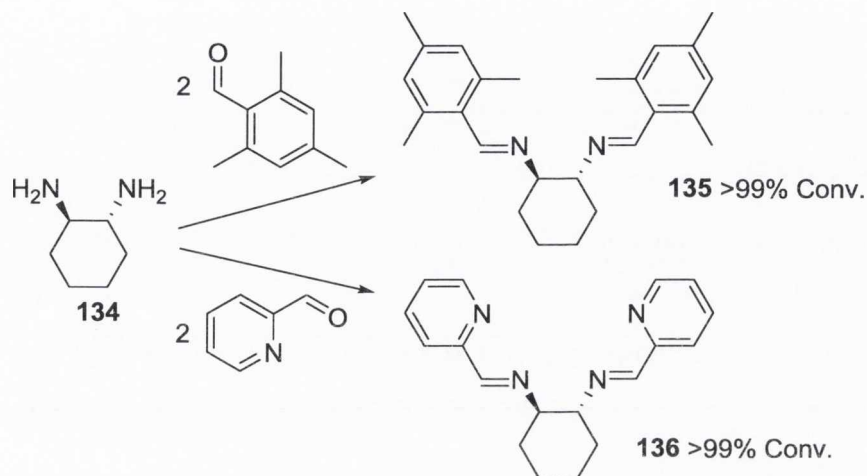
Another way to produce easy tunable polydentate ligands *via* imine linkage is to couple a chiral primary diamine with two equivalent of an aldehyde.

(1*R*,2*R*)-cyclohexane-1,2-diamine was obtained from the resolution of a *trans* and *cis* 1,2-cyclohexane diamine mixture with D-tartaric acid, followed by a sodium hydroxide treatment to liberate the free amine (Scheme 2.7). Compound **134** was obtained from **133** with a moderate yield due to the extraction step.



Scheme 2.7. Resolution of (1*R*,2*R*)-cyclohexane-1,2-diamine.

Condensing diamine **134** with commercially available aldehydes with no coordinating group allowed us to increase considerably the library variety. Also, reacting **134** with 2 equivalents of an aldehyde with a coordinating group led to polydentate ligands (Scheme 2.8). Again, the desired products were observed pure by ^1H NMR and ^{13}C NMR after filtering the molecular sieves and evaporating the solvent.



Scheme 2.8. (1R,2R)-cyclohexane-1,2-diamine based polydentate ligands prepared *in situ*.

2.2.2 Imidazolidines and oxazolidines ligands

While chiral imine ligands have been successful in numerous reactions, it would be desirable to increase the generality of the library using, if possible, the same simple and reliable linking chemistry. As such, the methodology was expanded to the *in situ* synthesis of imidazolidines and oxazolidines which are ligands used in numerous metal catalysed reactions (Figure 2.2).^{181,182} Imidazolidines were synthesized from a condensation between an aldehyde and a secondary diamines while oxazolidine were also produced from a condensation but between an aldehyde and an amino alcohol.

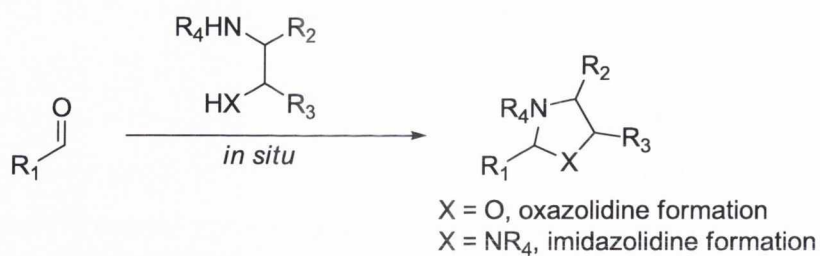
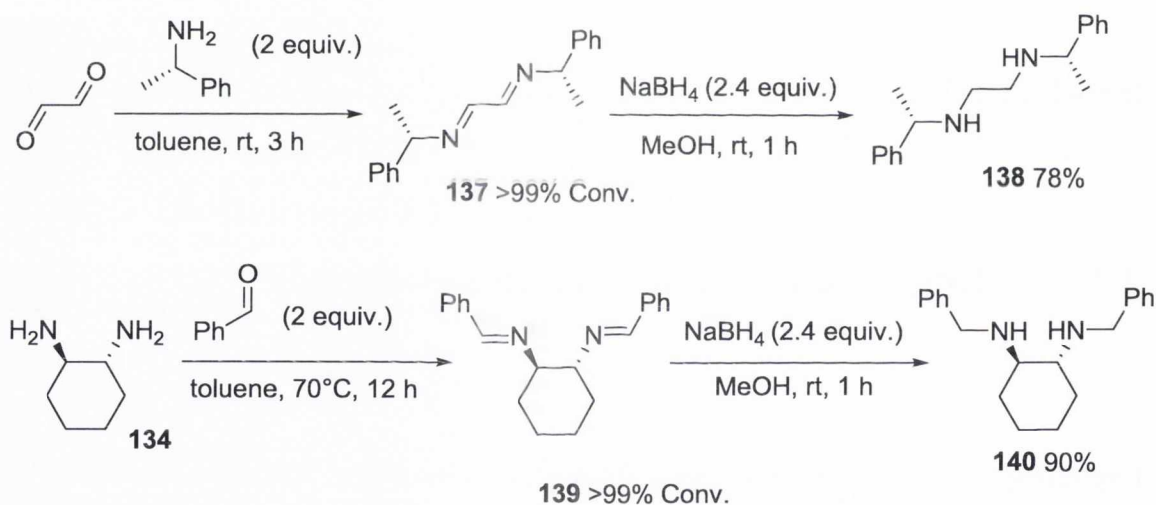


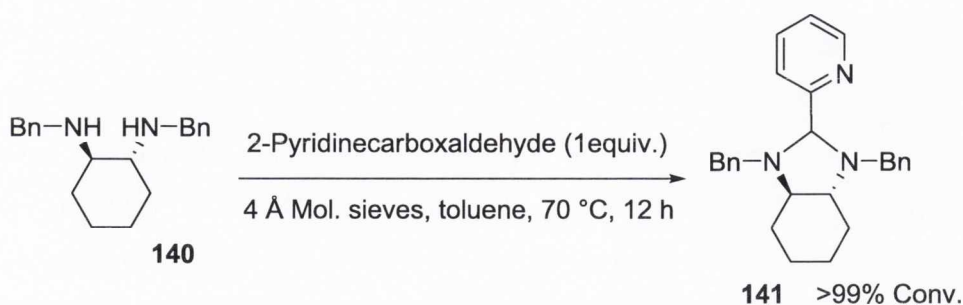
Figure 2.2. Oxazolidine and imidazolidine formations from an aldehyde where R^1 contains a coordinating functionality.

Secondary diamines were obtained easily from the reduction of diimines by sodium borohydride. Chiral diimines were synthesised by two different methods: the first one consisted of condensing 2 equivalents of α -methylbenzylamine with 1 equivalent of glyoxal. The second way was to react **134** with two equivalents of an aldehyde giving the bisimine with high yields (Scheme 2.9).



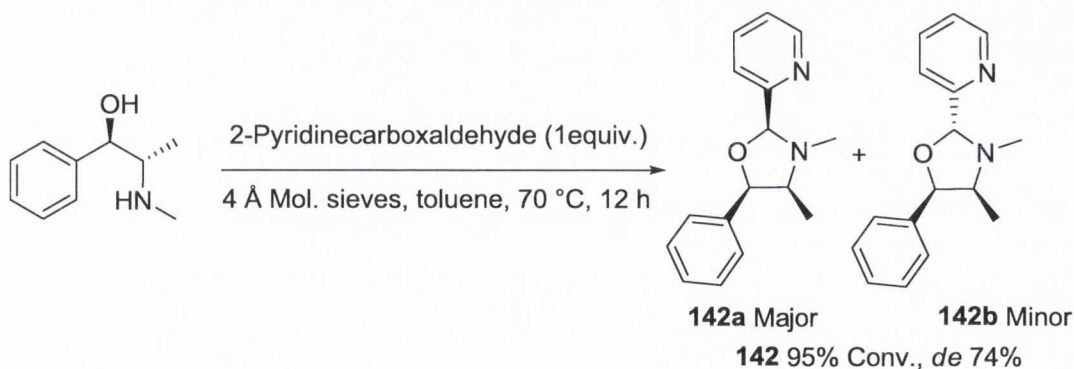
Scheme 2.9. Synthesis of chiral diamines.

The same conditions as the imine ligand formation were used for the formation of oxazolidines and imidazolidines. A clean and complete conversion of **140** to **141** was observed by NMR (^1H and ^{13}C) (Scheme 2.10).



Scheme 2.10. Synthesis of an imidazolidine *in situ*.

The amino alcohols used for the oxazolidine synthesis can come from the reduction of amino acids. Oxazolidines are more problematic than imidazolidines since a new chiral centre is created. For instance, **142a** is the major diastereoisomer synthesised from ephedrine and 2-pyridinecarboxaldehyde (Scheme 2.11). The mixture of diastereoisomers was formed in a 5.6:1 ratio. The idea of synthesising oxazolidines ligand *in situ* was thus abandoned even though the ligand mixture was tested in two metal catalysed reactions. Yet, the oxazolidines were formed with a high yield and no traces of side products or starting materials were observed by NMR (^1H and ^{13}C).



Scheme 2.11. Synthesis of oxazolidine *in situ*.

2.2.3 Oxazolines, imidazoline and thiazoline ligands

While methods were developed to rapidly and cleanly synthesise imines, imidazolines and oxazolidines, it was considered important to also find methods to increase the molecular

diversity of the potential libraries further, and, if possible, allow easy access to some highly successful, privileged ligand structures.

Oxazolines are an important class of ligands. Bisoxazoline, phosphinooxazoline and mono(oxazoline) ligands are widely used in asymmetric catalysis^{183,184} and being classed as “privileged chiral catalysts”¹⁸⁵ are among the most successful ligand structures available. As such bringing these compounds into the range of combinatorial catalysis would be a big step forward for the field, and greatly increase the utility and diversity of potential libraries.

However these more elaborate structures represent a challenge to synthesise *in situ*, due to the fact that more complex chemistry is required. There are many ways to synthesise oxazolines but most of them require an additive or produce undesirable side products (Figure 2.3, **A**¹⁸⁶, **B**¹⁸⁷, **C**¹⁸⁸, **D**¹⁸⁷, **E**¹⁸⁹). There is one way to produce oxazolines which would fulfil our requirements to be used to synthesise ligands *in situ* (i.e. a high yielding reaction with easily removable undesired side products). It consists of reacting an imidate with an amino alcohol producing the oxazoline with methanol and ammonia which can be absorbed by molecular sieves or lost through evaporation (Figure 2.3, **F**).¹⁹⁰

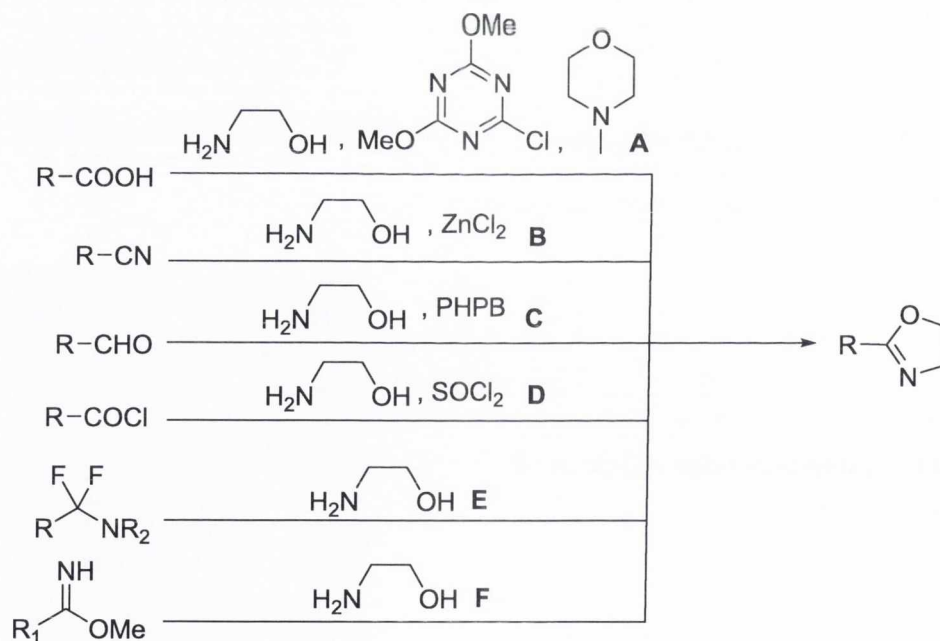


Figure 2.3. Non-exhaustive methods ways to synthesise oxazolines.

The aim is then to synthesise *in situ* oxazolines, imidazolines and thiazolines from an imidate (Figure 2.4).

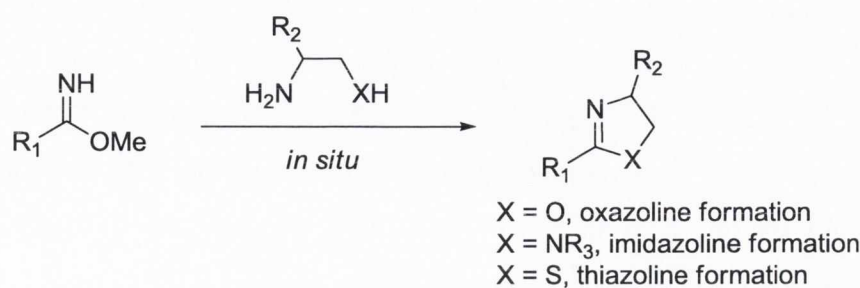
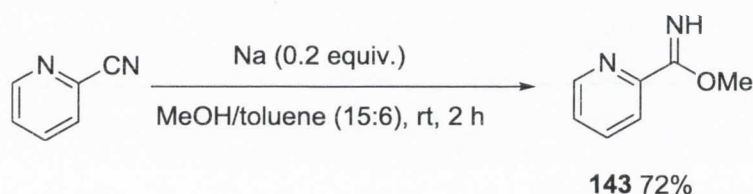


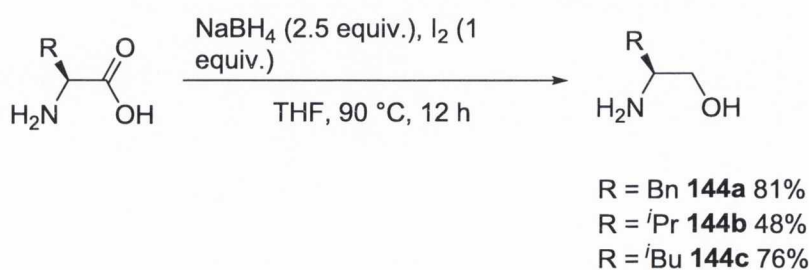
Figure 2.4. Synthesis of oxazolines, imidazolines and thiazolines from an imidate.

The imidate was produced by a methanolysis of 2-cyanopyridine (Scheme 2.12). Compound **143** is obtained with a relatively good yield after distillation under reduced pressure.



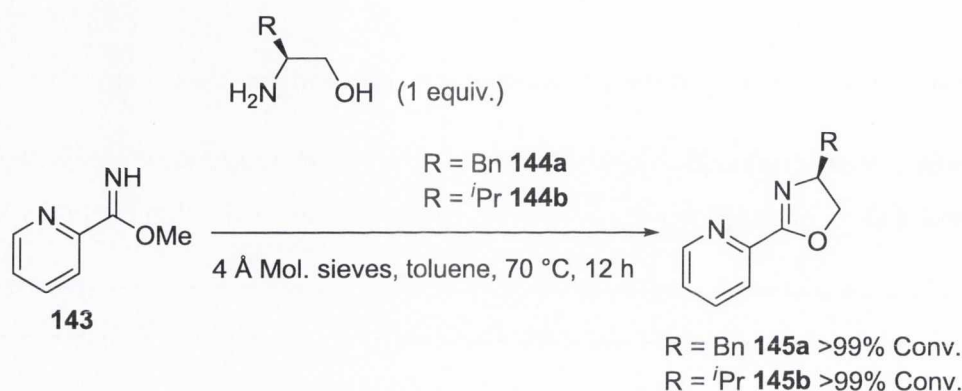
Scheme 2.12. Synthesis of methyl picolinimidate: a precursor of 2-oxazolines.

Oxazolines are then synthesised from **143** and chiral amino alcohols which come from the reductions of amino acids such as L-phenylalanine, L-valine or L-leucine (Scheme 2.13). The reduction of amino acids by a mixture of sodium borohydride and iodine is an easy and inexpensive way to obtain chiral amino alcohols which can be suitable starting materials for oxazoline ligand libraries.¹⁹¹



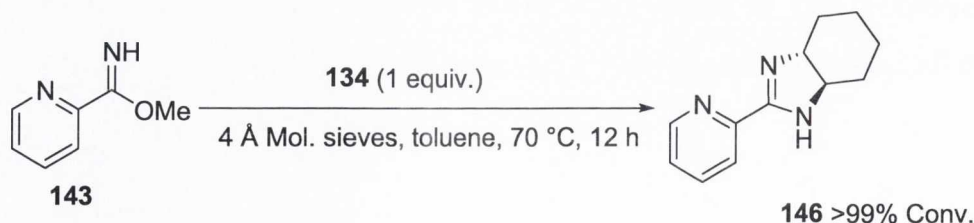
Scheme 2.13. Reduction of amino acids to amino alcohols.

The oxazoline was then synthesised by reacting **143** with 1 equivalent of amino alcohol in toluene at 70 °C for 12 h with molecular sieves (Scheme 2.14). After a simple filtration and evaporation of the solvent, the ligands **145a** and **145b** were pure by NMR (^1H , ^{13}C). Compound **53a** and **53b** were synthesised with high conversion with no side products observed. As such this opens up the possibility of using these ligands in catalysis without any purification step.



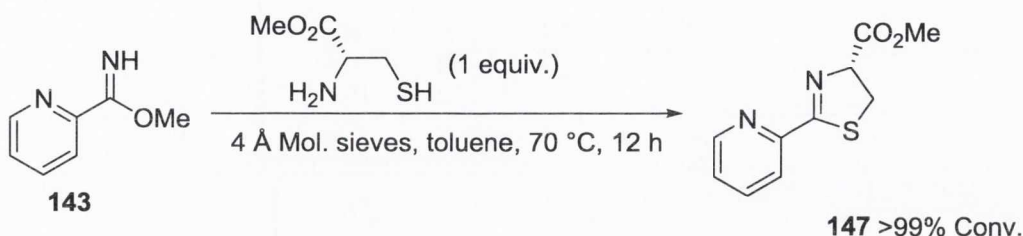
Scheme 2.14. Oxazoline formation from an imidate and amino alcohol.

Imidazolines based ligands are known in transition metal catalysis.^{192,193,194} They have also been synthesised from imidates and diamines.¹⁹⁵ Again, the same conditions were suitable to convert **51** to the imidazoline **54** with one equivalent of the chiral primary amine **42** (Scheme 2.15). The product was obtained with a high conversion (>99%) in a pure form as measured by ^1H and ^{13}C NMR spectroscopy, and so it was decided that these would also be viable candidates for combinatorial screening.



Scheme 2.15. Imidazoline formation from an imidate and diamine.

In the same manner thiazolines were reported to be synthesised from imidates.¹⁹⁵ Thiazoline **147** was synthesised successfully with high conversion from **143** in our research group by Carolyn Walsh (Scheme 2.16), and again was spectroscopically pure.¹⁹⁶ The fact that all three of these ligand types (oxazolines, imidazolines and thiazolines) could be synthesised with complete conversions using exactly the same procedure would be very useful once library synthesis and screening began.



Scheme 2.16. Thiazoline formation from an imide and aminothiol.¹⁹⁶

With these results in hand we now had easy, purification-free access to a large range of chiral bidentate ligands (Figure 2.5). In order to utilize the libraries, we decided to screen them against two test reactions: transfer hydrogenation and hydrosilylation. These were chosen due to the fact that imine-type ligands had given some enantiomeric excesses in these processes, but generally at a low level.

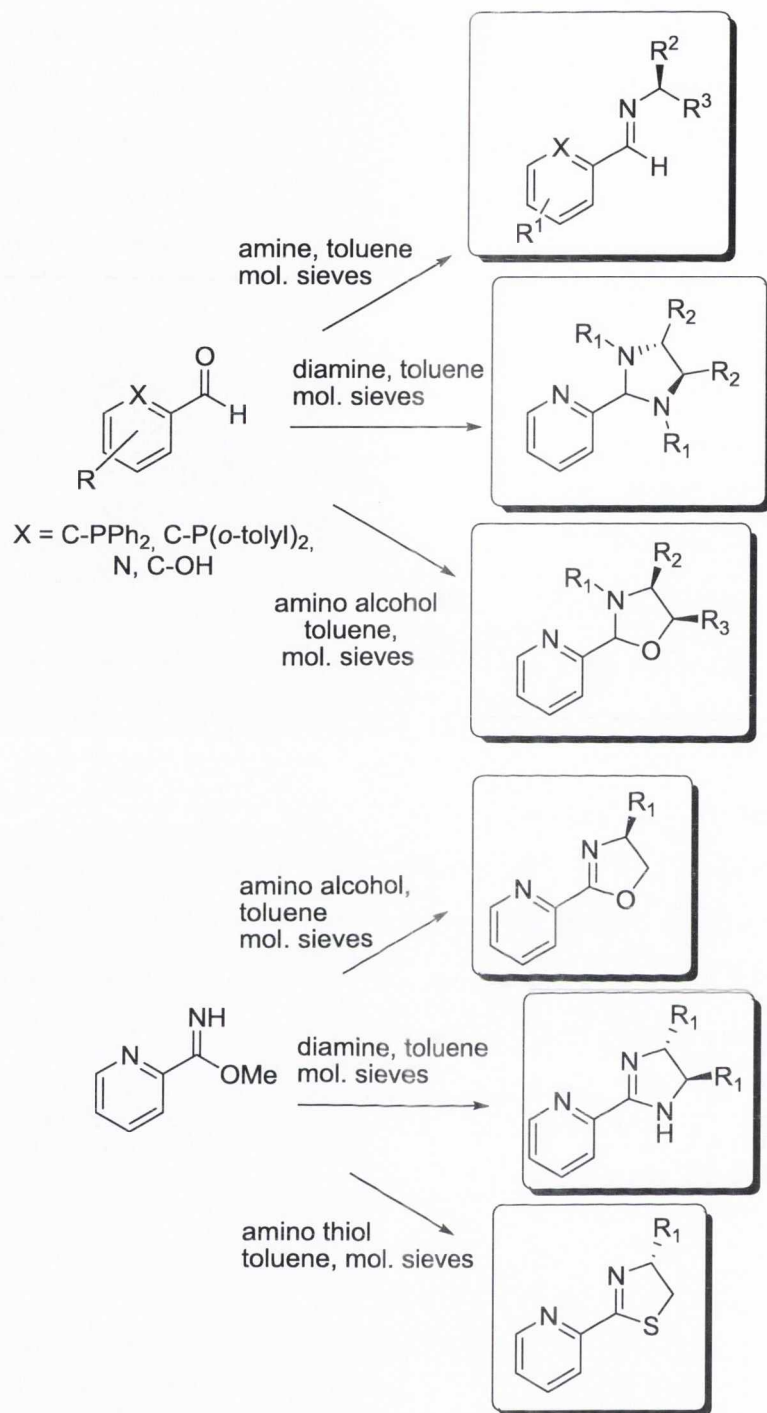


Figure 2.5. Summary of all the ligands structures available *in situ*.

2.3 Transfer hydrogenation of ketones with Rh^{III} in water

Transfer hydrogenation of ketones with Rh^{III} in water is an economical way to enantioselectively reduce ketones to chiral alcohols.⁵⁶ Water is also a non-toxic, non-carcinogenic and non-flammable solvent which is important for operator's safety.¹⁹⁷ Formic acid is used as a hydrogen donor, thereby avoiding the need for high-pressure equipment, or the transport and storage of hydrogen gas. The reaction involves the formation of a water-soluble hydride complex. The mechanism is not fully determined, but the following catalytic cycle is proposed (Figure 2.6).^{55,198} First, the bidentate ligand reacts with the rhodium dimer to form **148**, which loses chloride to generate the catalyst **149**. The hydride species **150** is then formed from **149** and formic acid. Complex **150** can then reduce the ketone and regenerate the catalyst **149**.

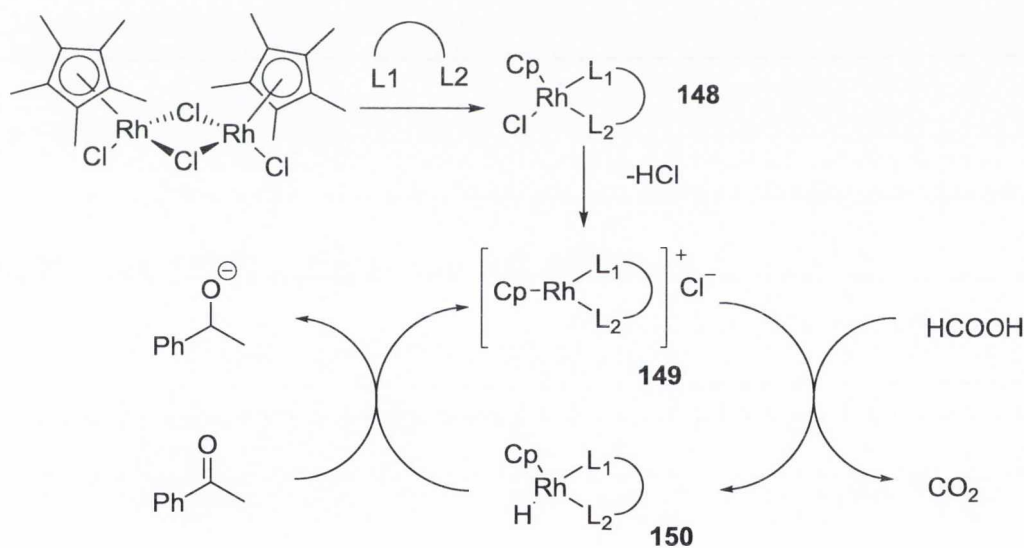
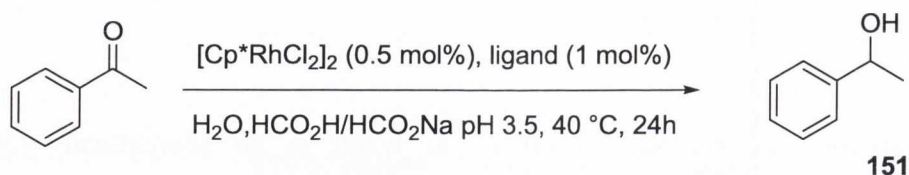


Figure 2.6. Transfer hydrogenation with rhodium salts in water.

Himeda et al. used this reaction to reduce acetophenone with imines ligands, obtaining 1-phenylethanol.⁵⁶ Rhodium was shown to be more reactive than iridium or ruthenium. The reaction proceeds with better yield at a low pH (3.5). Oxazoline ligands were shown to yield **59** with a lower yield and *ee* than imines (Scheme 2.17).



Ligand	Yield (%)	ee (%)
131	99	51 (S)
145b	28	12 (S)

Scheme 2.17. Ligands in transfer hydrogenation of ketones with Rh^{III} in water.⁵⁶

Moderate results given by the imine **131** and oxazoline **145b** makes this reaction a good candidate to test the ligands made *in situ*.

Before starting the chiral ligands screen, a racemic mixture of **151** was successfully separated by CSP-HPLC (Figure 2.7).

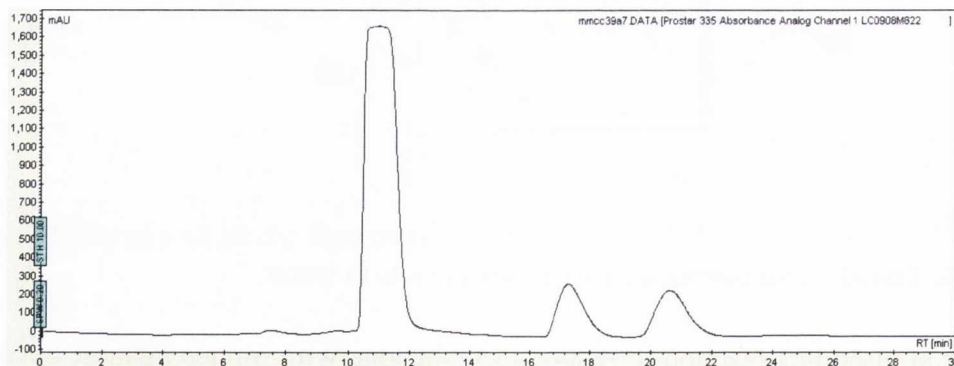
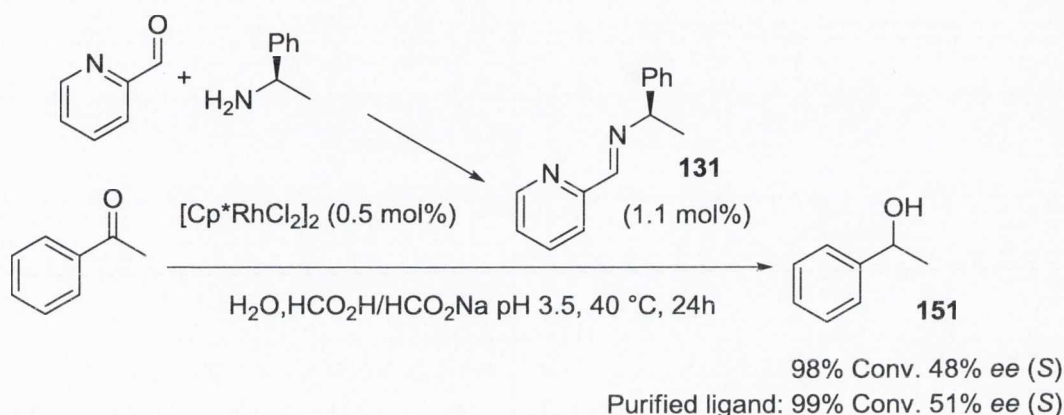


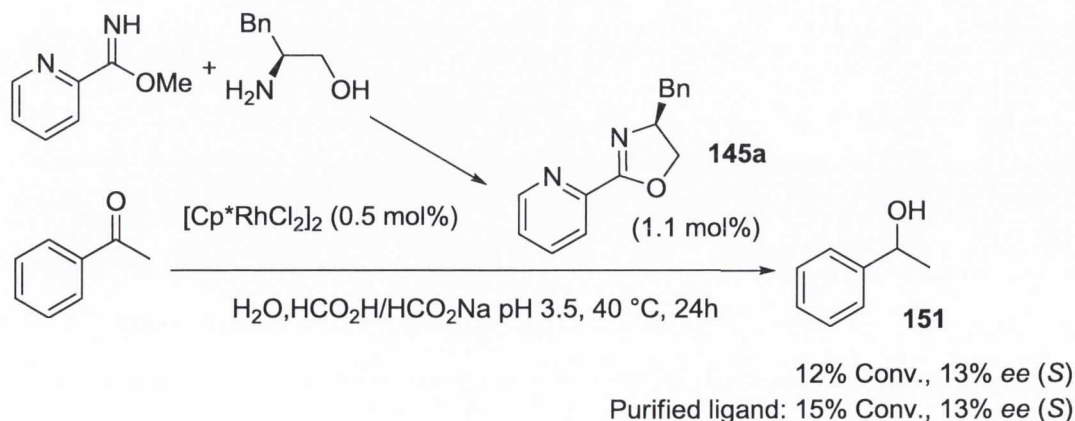
Figure 2.7. HPLC chromatogram of a racemic mixture of **151** with acetophenone. Chiralpak IB, hexane/IPA (97:3), 1.5 mL min^{-1} , UV detection at 254 nm, retention times: 17.5 min (S) and 20.5 min (R).

First, the reaction was carried out with ligand **131** made *in situ* (Scheme 2.18). The results were very similar to those found in the literature (98% Conv., 48% *ee*, vs. 99% Conv., 51% *ee* (Scheme 2.17 and 2.18)). Ligand **131** was also purified by column chromatography and tested in the same reaction. Compound **151** was obtained with the same *ee* and conversion as in the literature (Scheme 2.17 and 2.18).⁵⁶ Thus *in situ* generated imine ligands appeared to be suitable for applications in combinatorial chemistry, giving the same results with only a fraction of the time and resources required.



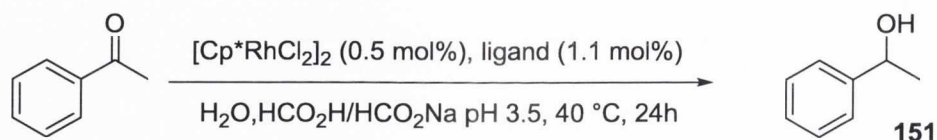
Scheme 2.18. Comparison of an imine ligand purified vs. *in situ*.

In the same manner the behaviour of ligands made from imidate **143** was investigated. When compound **145a** was made *in situ* **151** was obtained with a conversion of 12% and an *ee* of 13%, whereas the purified version of **145a** yielded **151** with a conversion of 15% and an *ee* of 13% (Scheme 2.19). Again, the results given by the *in situ* made ligand closely matched to the purified version. This result is important as it brings the more complex oxazoline ligands into the field of combinatorial chemistry for the first time.



Scheme 2.19. Comparison of an oxazoline ligand purified vs. *in situ*.

With those methods in hands a ligand library was synthesised and used (Table 2.1).



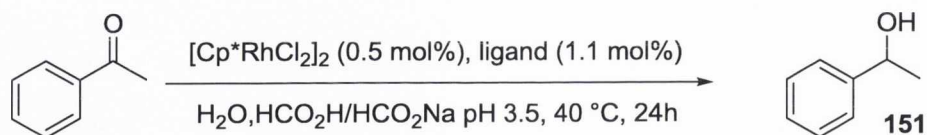
Entry	Ligand	Conv. (%) ^a	ee (%) ^b	Entry	Ligand	Conv. (%) ^a	ee (%) ^b
1		98	48 (S)	7		15	0
2		7	47 (S)	8		6	0
3		25	5 (S)	9		25	43 (S)
4		94	31 (R)	10		48	37 (S)
5		34	12 (S)	11		77	49 (S)
6		58	49 (S)	12		8	26 (R)

Table 2.1. Library of pyridine-based imine ligands made *in situ* tested in a transfer hydrogenation of acetophenone catalysed Rh^{III} in water. ^aDetermined using ¹H NMR spectroscopy. ^bDetermined by CSP-HPLC.

First the library focused on **131** derivatives which consisted of a pyridine ring with an imine functional group at the 2-position. Increasing the bulk of the aldehyde had a

detrimental effect on both the conversion and selectivity, perhaps by inhibiting binding at the metal centre or preventing the substrate approach. For instance a simple methyl group on the aldehyde fragment led to no asymmetric induction and a reduction of the conversion (Table 2.1, entries 1 vs. 7, and 2 vs. 8). This tendency was also observed by using 2-quinolinecarboxaldehyde as an aldehyde instead of 2-pyridinecarboxaldehyde (Table 2.1, entries 9 vs. 1). Interestingly, an electron donating methoxy group instead of a methyl group on the pyridine ring increases the conversion and *ee*, but did not improve the initial results given by **131** (Table 2.1, entries 7 vs. 4 vs. 1). The amine moiety was also investigated. Increasing the steric bulk of the amine seems to reduce the conversion but not the stereoselectivity (Table 2.1, entries 1 vs. 2, 6 and 10). An electron donating group on the amine phenyl group kept the enantioselectivity but a lower conversion was observed (Table 2.1, entries 1 vs. 11). Some other chiral amines were tested but no improvement of the stereoselectivity was observed (Table 2.1, entries 3, 7 and 12). The quick library of pyridine-based imine ligands did not allow us to find a ligand which produces **151** with a higher enantiomeric excess than when ligand **131** was used, but thanks to a rapid ligand screening factors influencing enantiomeric excess and conversions could be probed.

Subsequently a family of ligands derived from chiral cyclohexyldiamine **134** was synthesised (Table 2.2). Both bisimines (1 equivalent of **134** with 2 equivalents of aldehyde) and monoimines (1 equivalent of **134** with 1 equivalent of aldehyde) were screened.



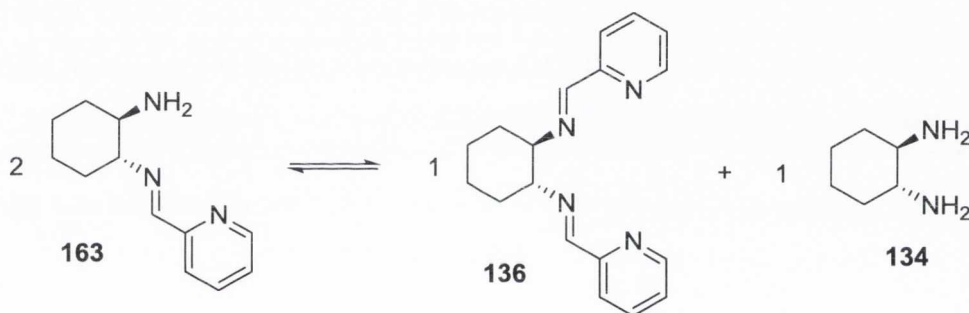
Entry	Ligand	Conv. (%) ^a	ee (%) ^b	Entry	Ligand	Conv. (%) ^a	ee (%) ^b
1		18	68 (R)	5		7	0
2		11	51 (R)	6		6	13 (R)
3		53	43 (R)	7		11	48 (R)
4		2	0				

Table 2.2. Library of (1*R*,2*R*)-(1,2)-cyclohexanediamine-based ligands tested in a transfer hydrogenation of acetophenone catalysed Rh^{III} in water. ^aDetermined using ¹H NMR spectroscopy. ^bDetermined by CSP-HPLC. ^cConsisted of an equilibrium mixture of monoamine (75%) with bis-imine + unreacted cyclohexane diamine (25%).

Reacting one equivalent of 2-pyridinecarboxaldehyde with one equivalent **134** led to a mixture of monoimine **163**, bisimine **136** and **134** (Table 2.2, entry 1). After an attempt to isolate **163**, the product equilibrated back to the initial mixture (Scheme 2.20: note this equilibrium is only possible for ligands made by the condensation of some primary diamines with 1 equivalent of aldehyde, all other combinations tested gave pure

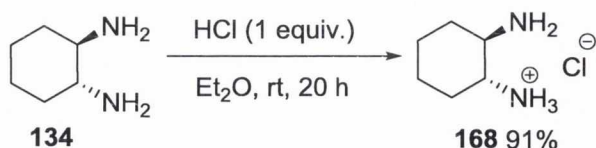
compounds). This proved not to be a major stumbling block, however, as even the mixture of compounds provided the product with the highest *ee* reported to date for an imine based ligand (68%).

Since the mixture converted acetophenone to **151** with the highest enantiomeric excess 68%, the bisimine **136** and **134** were tested in order to find which of the three ligands causes this high asymmetric induction. Unfortunately **136** and **134** yielded **151** with 51% and 43% *ee* respectively (Table 2.2, entries 2 and 3). Those *ees* were disappointing as it appeared that the unstable ligand **163** is then the most selective. It does, however, highlight the utility of combinatorial catalysis: ordinarily structures such as **163** would never have been screened, but the simplicity of this system encourages the use of compounds that otherwise would be rejected as viable candidates. The fact that the best imine ligand used to date in this system was such a candidate is certainly worth noting.



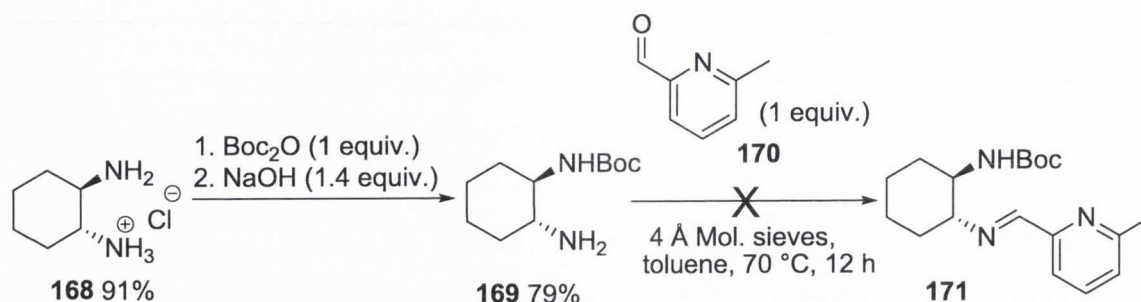
Scheme 2.20. Equilibrium of mono and bisimines.

Yet, a derivative **166** was successfully synthesised and found to be stable. First, one amino group on **134** was protected by a simple protonation giving **168** with a high yield (Scheme 2.21).



Scheme 2.21. Protonation of **134**.

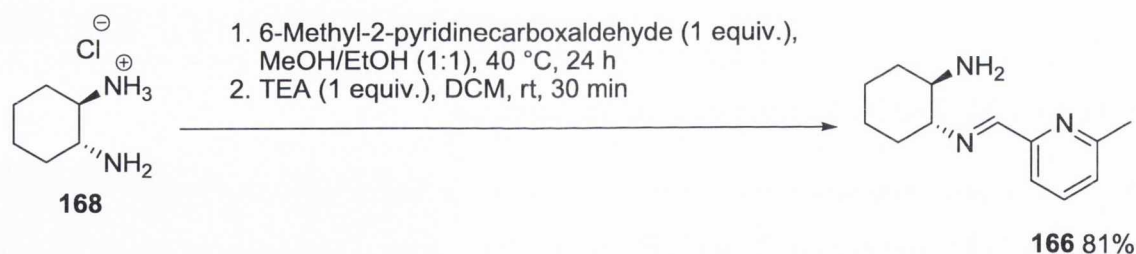
Salt **168** was reacted with Boc_2O and treated with NaOH to yield **169** with a good yield. The condensation between **169** and 6-methyl-2-pyridinecarboxaldehyde using the same conditions as the ligand formation (see Scheme 2.5) did not proceed, probably due to steric hindrance of the protecting group (Scheme 2.22).



Scheme 2.22. Boc strategy to produce **171**.

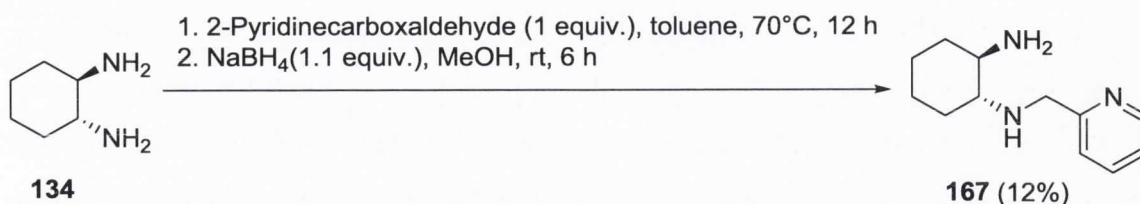
Fortunately, a simple condensation of aldehyde **170** with **168** in a mixture of methanol and ethanol followed by an addition of TEA and filtration of the triethylammonium chloride produced **166** with a high yield 81% (Scheme 2.23).

Ligand **166** was shown to be stable and was tested but the conversion and enantiomeric excess were disappointing (Table 2.2, entry 6).



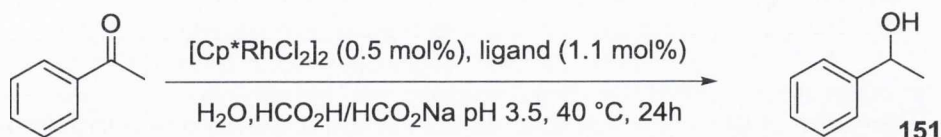
Scheme 2.23. Synthesis of ligand **166**.

The mixture of **163**, **136** and **134** was reduced by NaBH_4 in order to obtain the amine **167** after column chromatography (Himedia showed that similar results for the transfer hydrogenation are achieved in certain cases whether the ligand is an imine or amine) (Scheme 2.24).⁵⁶ Ligand **167** converted acetophenone to **151** with a conversion of 11% and a *ee* of 48% (Table 2.2, entry 7).



Scheme 2.24. Synthesis of ligand **167**.

Thanks to the new combinatorial methods developed structurally diverse ligands were also screened in the reaction (Table 2.3).



Entry	Ligand	Conv. (%) ^a	ee (%) ^b	Entry	Ligand	Conv. (%) ^a	ee (%) ^b
1		6	15 (<i>R</i>)	6		2	0
2		9	3 (<i>R</i>)	7		5	0
3		29	40 (<i>R</i>)	8		79	8 (<i>S</i>)
4		4	2 (<i>R</i>)	9		7	0
5		5	41 (<i>S</i>)	10		4	0

Table 2.3. Library of miscellaneous ligands tested in a transfer hydrogenation of acetophenone catalysed Rh^{III} in water. ^aDetermined using ¹H NMR spectroscopy. ^bDetermined by CSP-HPLC.

P,N-ligands **175**, **176** and **177** uniformly provided the product with low conversions, although **130** gave a fair stereoselectivity (Table 2.3, entries 5, 6, 7 and 10). Imino alcohols **172**, **173**, **132** and **174** were also easily synthesised and tested. Compound **132** gave **151** with a conversion of 29% and an *ee* of 40% (Table 2.3, entry 3). Electronic effects were difficult to probe since both electron donating and withdrawing group gave lower conversions and enantiomeric excesses (Table 2.3, entries 1, 2 and 4). Imidazoline **146** gave a good conversion (79%) but a low stereocontrol with an *ee* of 8% (Table 2.3, entry 8). Finally, oxazolidine **142** proved to be a poor ligand for this reaction (Table 2.3, entry 9).

Overall, a large number of ligands were made directly without the need of purification, and only using very small amounts of materials (in a typical screen, microliter quantities of amine and aldehyde are mixed together). In this particular case the procedure required the isolation of the metal complex prior to catalysis in an aqueous media. Moreover the catalyst formation is done overnight which slows down the screening process. To demonstrate the full capacity of this methodology another reaction was chosen, a hydrosilylation of acetophenone with PMHS catalysed by diethylzinc.

2.4 Hydrosilylation of ketones with diethylzinc and polymethylhydrosiloxane

The hydrosilylation of ketones with diethylzinc and PMHS following by a hydrolysis is a cheap, simple, and mild way to reduce ketones to secondary alcohols.¹⁹⁹ PMHS is a safe and inexpensive polymer coproduct of the silicone industry.⁸³ Moreover the reaction is carried out in toluene, the same solvent as the ligand formation, and no manipulation of intermediates is required. A mechanism was proposed by Mimoun (Figure 2.8).⁷³ Diethylzinc is first chelated by the ligand to form a tetrahedral zinc complex **178**. The activated complex reacts then with PMHS which is the hydride source to form **179**. It is proposed that the zinc hydride reacts then with another equivalent of the silane derivative to form a pentavalent zinc complex **180**. The ketone chelates the zinc center and a hydride is transferred to the carboxyl group giving **182**. Finally, the product **183** is eliminated and the zinc **179** complex is regenerated.

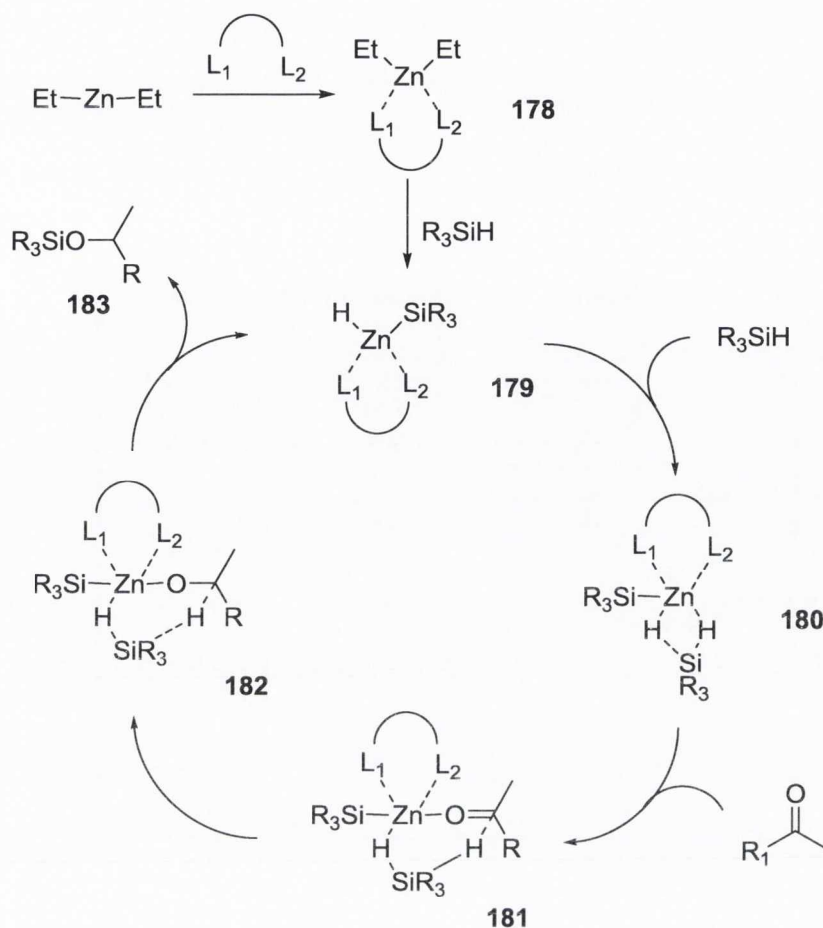
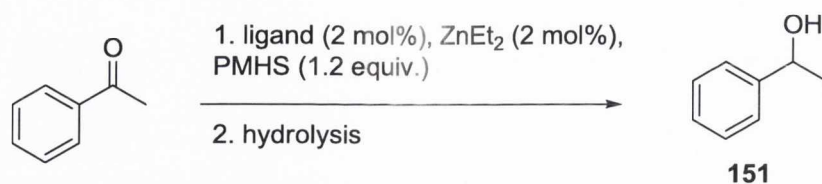
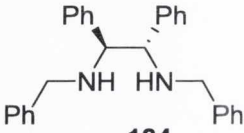
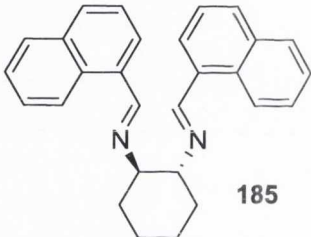


Figure 2.8. Hydrosilylation of ketones with diethylzinc and polymethylhydrosiloxane.

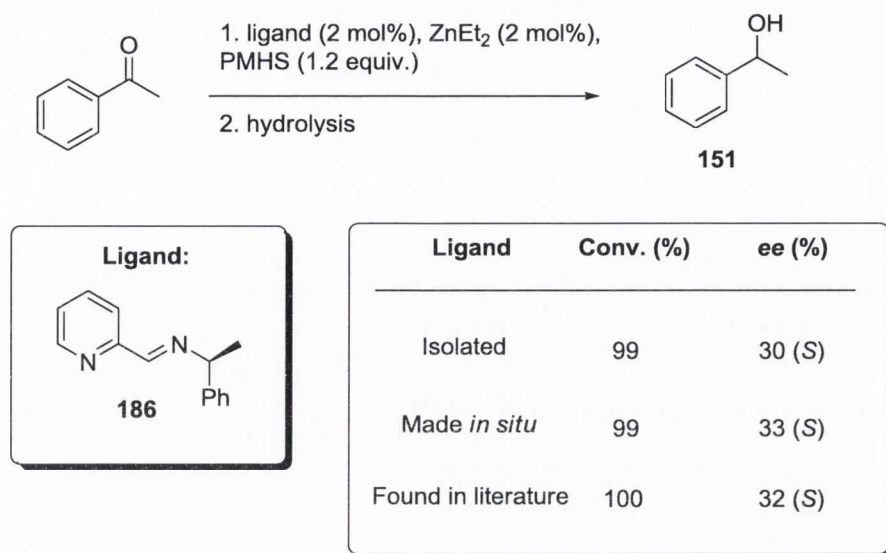
This reaction is highly challenging and very few ligands are capable of delivering high enantioselectivities. To date diamines **184** and diimines **185** ligands were shown to be the most effective (Scheme 2.25).^{73, 82, 83}



Ligand	Conversion (%)	ee (%)
 184	98	88 (S)
 185	95	70 (S)

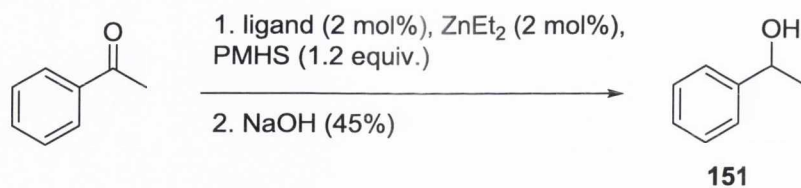
Scheme 2.25. Hydrosilylation of prochiral ketones with Zn^{II} and PMHS.⁷³

As for the rhodium catalysed reaction the results obtained from ligands made *in situ* were compared to the purified ligand version. The results were once again conclusive as both enantioselectivities and conversions were similar (Scheme 2.26). Those results were also consistent with the literature values (Scheme 2.26).⁷³ Since the ligands are directly used in the catalysis just after the molecular sieves filtration, the screening of ligands is then more direct, simpler and thus faster than for the transfer hydrogenation catalysed by rhodium.



Scheme 2.26. Comparison of the efficiency of a ligand synthesised *in situ*, pre-prepared and reported in the literature.⁷³

Since ligand **186** is in our methodology scope many derivatives were synthesised and tested (Table 2.4).



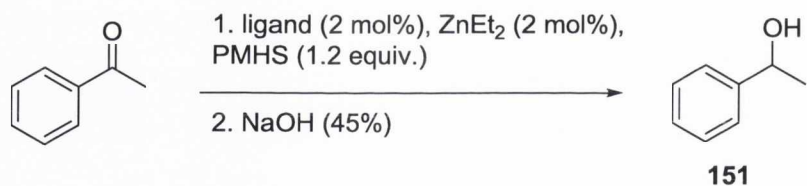
Entry	Ligand	Conv. (%) ^a	ee (%) ^b	Entry	Ligand	Conv. (%) ^a	ee (%) ^b
1		99	19 (<i>R</i>)	7		99	17 (<i>R</i>)
2		99	17 (<i>R</i>)	8		86	20 (<i>R</i>)
3		67	13 (<i>S</i>)	9		74	6 (<i>S</i>)
4		76	14 (<i>R</i>)	10		48	49 (<i>R</i>)
5		88	26 (<i>S</i>)	11		51	50 (<i>R</i>)
6		80	11 (<i>R</i>)				

Table 2.4. Library of pyridine-based imine ligands made *in situ* tested in hydrosilylation of ketones with diethylzinc and PMHS. ^a Determined using ¹H NMR spectroscopy.

^bDetermined by CSP-HPLC.

From a small screen we found 2 ligands which gave higher enantiomeric excess. Ligands **190** and **191** induced a higher asymmetry but to the detriment of a lower conversion (Table 2.4, entries 10 and 11). No trends were established, for instance a substituent at the 6 position of **186** pyridine ring led to a lower selectivity (Table 2.4, entries 3 and 5 vs. Scheme 2.25), whereas a methyl group at the same position on **156** pyridine ring gave a higher selectivity (Table 2.4, entry 8 vs. 10). This unpredictable result shows the utility of combinatorial chemistry to find new ligands for asymmetric catalysis.

As bisimines are known ligands for this reaction (Scheme 2.24), a small library was elaborated (Table 2.5).



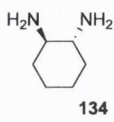
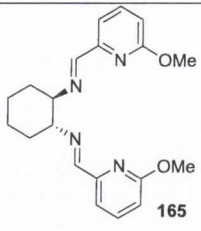
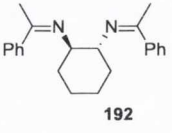
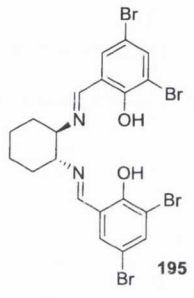
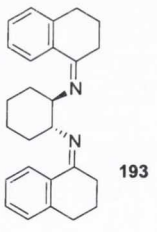
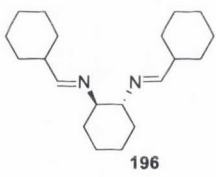
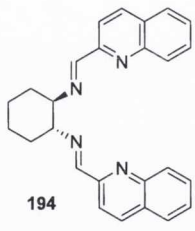
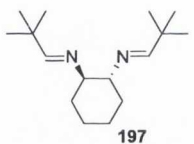
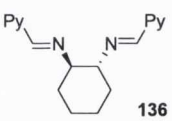
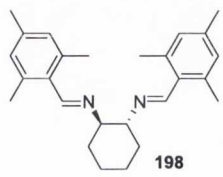
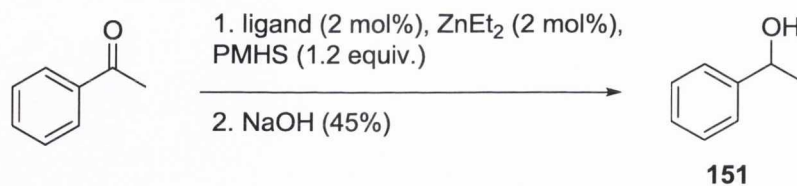
Entry	Ligand	Conv. (%) ^a	ee (%) ^b	Entry	Ligand	Conv. (%) ^a	ee (%) ^b
1	 134	99	24 (<i>S</i>)	6	 165	33	45 (<i>S</i>)
2	 192	7	5 (<i>S</i>)	7	 195	4	0
3	 193	13	0	8	 196	80	51 (<i>S</i>)
4	 194	88	0	9	 197	67	39 (<i>S</i>)
5	 136	99	0	10	 198	31	40 (<i>S</i>)

Table 2.5. Library of (1*R*,2*R*)-(1,2)-cyclohexanediamine-based ligands tested in hydrosilylation of ketones with diethylzinc and PMHS. ^aDetermined using ¹H NMR spectroscopy. ^bDetermined by CSP-HPLC.

As a background test ligand **134** was used in the reaction giving **151** with quite similar asymmetric induction and conversion as previously reported (99% conv., 24% *ee* vs. 98% conv., 18% *ee*) (Table 2.5, entry 1).⁷³ Bisimines synthesised from **134** and ketones were screened but gave very poor results (Table 2.5, entries 2 and 3). This can be partly explained by the fact that it was observed that the formation of ketimines did not always go to completion, unlike the aldimines we had been using previously. Ligands **194** and **136** made from respectively from 2-quinolinecarboxaldehyde and 2-pyridinecarboxaldehyde yielded **151** as a racemic mixture (Table 2.5, entries 4 and 5). Surprisingly, methoxy groups on the 6 pyridine position resulted in a drop of the conversion but also in an *ee* of 45% (Table 2.5, entry 6). Dicyclohexyl bisimine **196** led to a conversion of 80% and enantioselectivity of 51% (Table 2.5, entry 8). When the alkyl group steric bulk was increased, the product was provided with a slight lower *ee* but with a lower conversion (Table 2.5, entry 9). The same observation was made with ligand **198** which has 2,4,6-trimethylphenyl bearing imines (Table 2.5, entry 10). Ligand **195** gave **151** with an extremely low conversion and no *ee* (Table 2.5, entry 7).

Several classes of ligands were also investigated in order to increase the library diversity (Table 2.6).



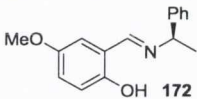
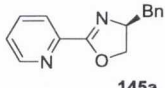
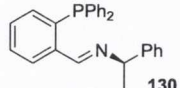
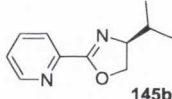
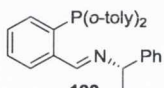
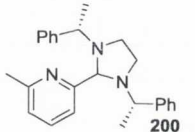
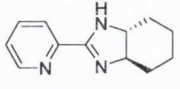
Entry	Ligand	Conv. (%) ^a	ee (%) ^b	Entry	Ligand	Conv. (%) ^a	ee (%) ^b
1	 172	19	0	5	 145a	88	0
2	 130	67	17 (<i>R</i>)	6	 145b	82	7 (<i>R</i>)
3	 199	19	5 (<i>S</i>)	7	 200	47	35 (<i>S</i>)
4	 146	98	15 (<i>R</i>)				

Table 2.6. Library of miscellaneous ligands tested in hydrosilylation of ketones with diethylzinc and PMHS. ^aDetermined using ¹H NMR spectroscopy. ^bDetermined by CSP-HPLC.

Imino alcohol ligand **172** yielded the product as a racemic mixture with a low conversion (Table 2.6, entry 1). Two iminophosphine ligands, **130** and **199** were also screened. The conversions and selectivities were disappointing. Using phosphine bearing tolyl groups instead of phenyl groups led to a decrease in conversion and *ee* (Table 2.6, entry 3 vs. 2). Imidazoline **146** and oxazolines **145a** and **145b** were also screened. Unfortunately those ligands were inferior to the imine based ligands. The best result was given by **146** with a high conversion and a modest selectivity (Table 2.6, entry 4). Ligands **145a** and **145b** also produced **151** with good conversion but with little or no asymmetric induction (Table 2.6, entries 5 and 6). Interestingly amina **200** gave **151** with a *ee* of 50% and conversion of 42%. More amina ligands were investigated by our group.²⁰⁰ In total, 6 other amina ligands were

tested and conversions were quite low compared to imines (47% maximum), and enantiomeric excesses under 41%.

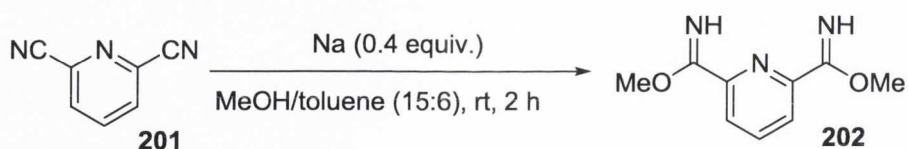
2.5 Conclusions and future work

A method to make quickly and simply bidentate chiral ligands was developed. It consists of reacting an electrophile with one equivalent of nucleophile in toluene at 70°C overnight in the presence of molecular sieves. After a simple filtration of the molecular sieves, the ligands were used crude, avoiding any purification steps.

This not only saves time, it also greatly reduces use of chemicals. Microlitre quantities of the two fragments are sufficient for screening (especially important when dealing with reasonably expensive chiral compounds), and the use of large amounts of solvents and silica gel is also avoided by removing the need for chromatography.

Not only P,N-, N,N- and N,O-imine-based ligands were successfully synthesised but also more complex imidazolidines, oxazolidines, oxazolines and imidazolines which were previously out of the scope of combinatorial chemistry. The robustness of the method was proved by comparing the results given by purified ligands to the same one made *in situ* in two separate catalytic asymmetric reactions. The results found were concordant. Many ligands were then synthesised according to this new method and tested in a short amount of time. This combinatorial methodology allows one to find some unexpected ligands which, probably, would not have been discovered by using traditional methodologies. Once a ligand has shown satisfactory result it can be synthesised on a larger scale in order to be isolated and tested.

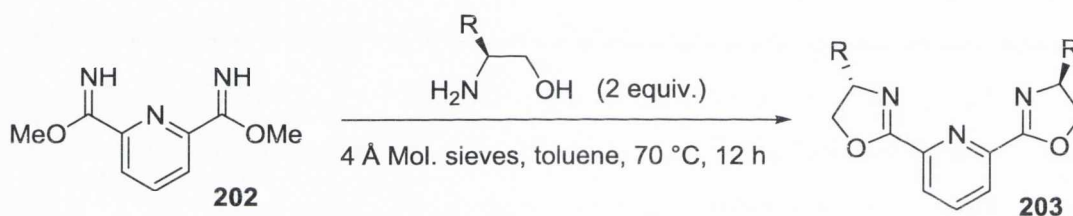
The future work consists in increasing the ligand diversity by synthesising, *in situ*, pybox ligands which are a very important class of ligands in asymmetric catalysis.¹⁸⁴ First a bis-imidate a precursor or pybox ligands is synthesised (Scheme 2.27).



Scheme 2.27. Synthesis of **202** a precursor of pybox ligands.

Bis-imidate **202** can be synthesised from **201** and sodium as described in the literature²⁰¹ or previously (see Scheme 2.12).

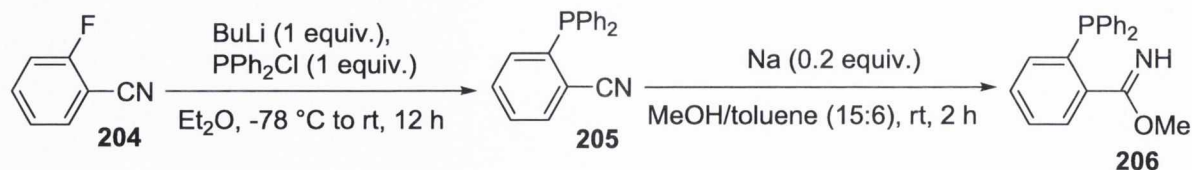
The pybox ligands **203** could then be synthesised *in situ* from **202** and amino alcohol using the same condition as previously (see Scheme 2.12) in toluene at 70 °C in the presence of molecular sieves (Scheme 2.28).



Scheme 2.28. Synthesis of pybox ligands *in situ* from **202** and an amino alcohol.

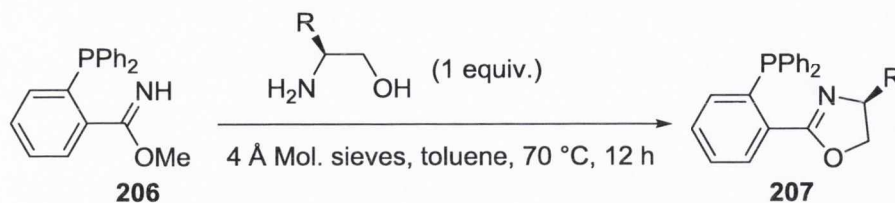
Pybox ligands can be used in a huge number of asymmetric processes, such as asymmetric epoxidation of different olefins catalysed by ruthenium or enantioselective addition of terminal alkynes to imines catalysed by copper.^{202,203}

In the same manner important phosphine oxazoline ligands²⁰⁴ could be synthesised *in situ*. The phosphine-nitrile can be synthesised from **204** and PPh₂Cl in the presence of BuLi.²⁰⁵ Imidate **206** could be obtained by a methanolysis of **205** with sodium (Scheme 2.29) or hydrochloric acid.²⁰⁶



Scheme 2.29. Synthesis of a phosphine oxazoline precursor.

The phosphinooxazoline could then be prepared *in situ* with molecular sieves in toluene at 70 °C for 12 h from imidate **206** and an aminoalcohol (Scheme 2.30).



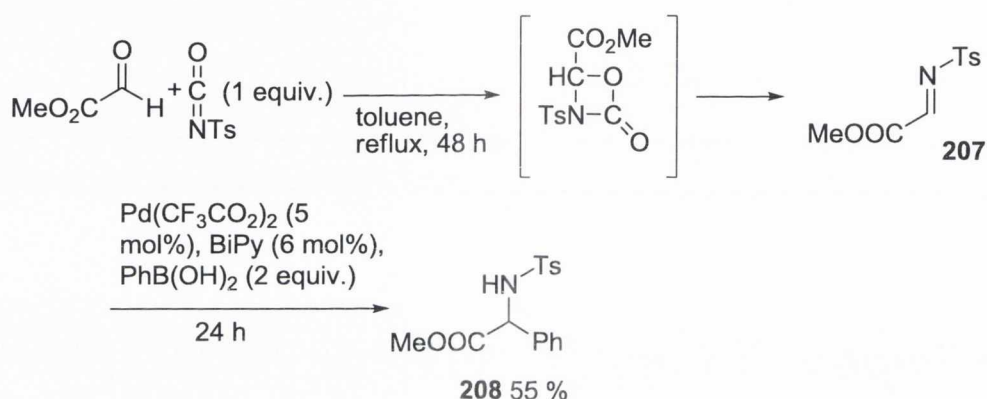
Scheme 2.30. Synthesis of phosphine oxazoline ligands *in situ* from **206** and an amino alcohol.

Those ligands could then be used in the two reactions outlined above (Section 2.3 and 2.4) or in other reactions. Asymmetric hydrogenation of different unfunctionalised olefins catalysed by iridium is carried out by using iminophosphine and phosphinooxazoline ligands.^{7,207,208} The enantioselectivities strongly vary from one substrate to another which makes it an ideal reaction for the use of combinatorial chemistry, and so the synthesis *in situ* of phosphinooxazolines and related compounds.

***Chapter 3: Copper catalyzed Petasis and
Petasis-Type reactions***

3.1 Introduction

Lu and co-workers reported a one pot reaction involving a [2+2] cycloaddition of *p*-toluenesulfonyl isocyanate with methyl glyoxylate forming an *N*-tosylimine which undergoes a Pd^{II} catalyzed addition of boronic acids.^{209,210} The authors synthesised the *N*-tosylimine **207** and then added the catalyst and boronic acid into the mixture to yield **208** with a yield of 55% (Scheme 3.1). Oxazoline chiral ligands gave up to 80% *ee*.



Scheme 3.1. *N*-Tosylimine formed *in situ* for a palladium catalyzed addition of phenylboronic acid.

This reaction is driven by the high electrophilicity of the imine group, meaning that the nucleophilic Pd aryl species can react to form a carbon-carbon bond. The proposed intermediate in the Petasis reaction, an iminium ion would be expected to be similarly electrophilic (Figure 3.1). As such it was hoped that a similar type of procedure could catalyse the Petasis reaction.

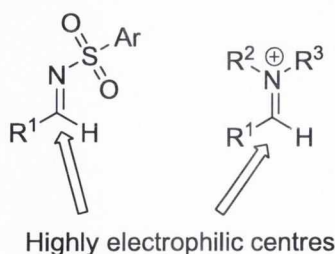


Figure 3.1. Predicted similar reactivity between *N*-tosylimines and iminium ions.

Such a procedure could have a number of advantages. Firstly it could increase reactivity (in general a major drawback of the current Petasis reaction is substrate scope, the aldehyde normally requires pendant hydroxyl or carboxylate groups to generate the boronate intermediate).^{107,124} Secondly it could allow access to an enantioselective Petasis reaction, generating enantioenriched amines by using chiral ligands. Clopidogrel and Prasugrel are two platelet inhibitor which are potential target for an addition of an aryl boronic acid to an iminium (Figure 3.2). The metabolites of those prodrugs bind irreversibly P2Y₁₂, an adenosine diphosphate receptor located on platelet cell membranes.^{211,212}

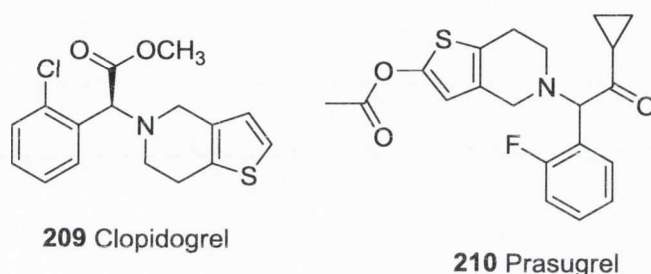
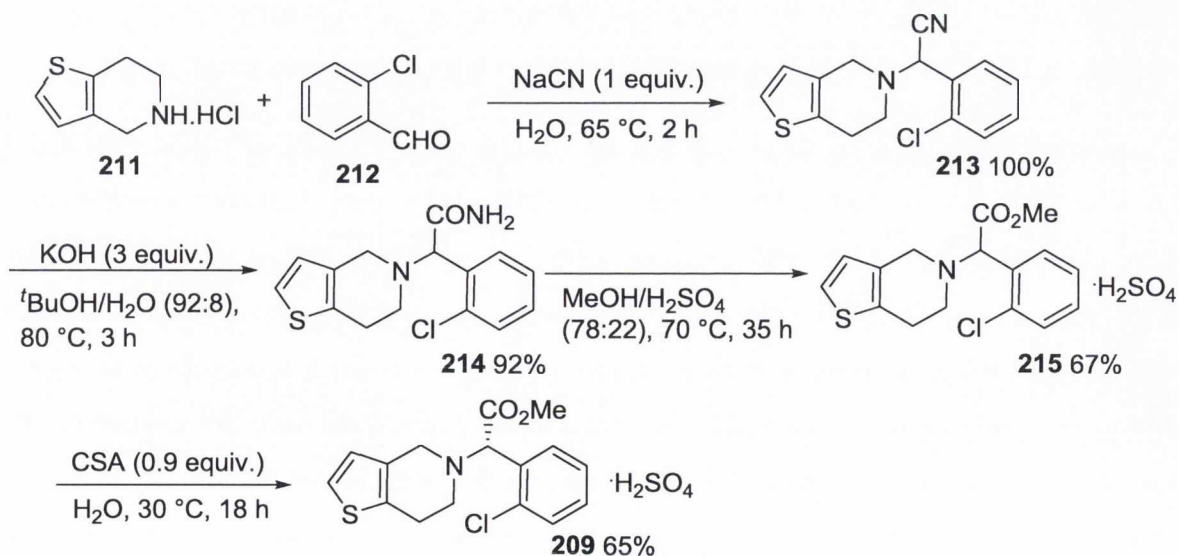


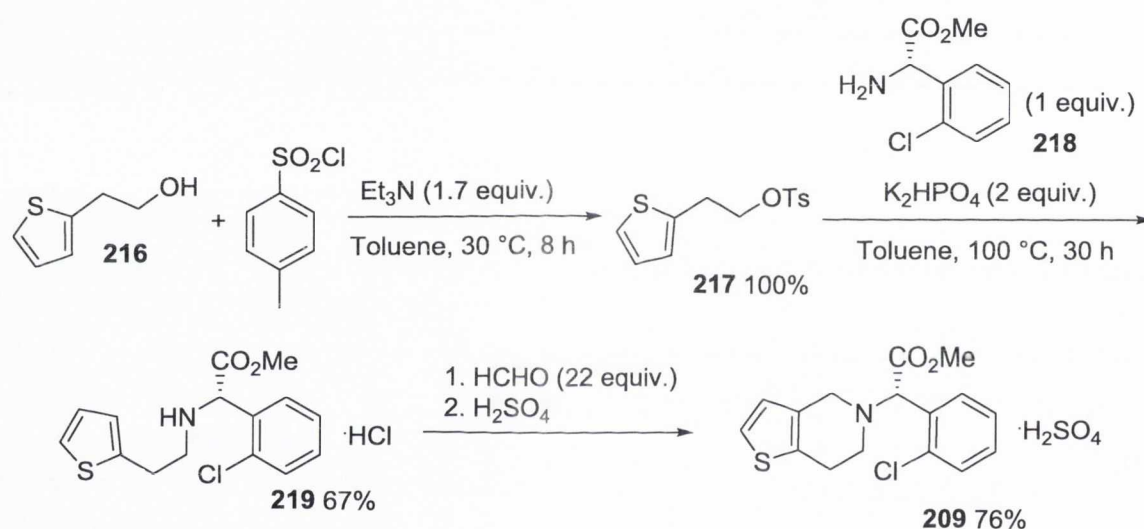
Figure 3.2. Platelet inhibitor: potential targets for an aryl boronic addition to an iminium.

Many ways of synthesizing Clopidogrel are known.²¹³⁻²¹⁷ Bandichhor and co-workers reported the two most recent synthesis at a an industrial scale (Scheme 3.2 and Scheme 3.3).²¹⁸



Scheme 3.2. Industrial scale synthesis of racemic Clopidogrel followed by a resolution.

The first step consists of forming intermediate **213** from **211**, **212** and sodium cyanide in a Strecker reaction. The synthesis was made from 20 kg of **212** and 25 kg of **211**. Compound **213** was hydrolysed to the corresponding amide **214** with a high yield (92%). Racemic Clopidogrel **215** was produced by a methanolysis with a moderate yield 67%. Finally, **209** was obtained by resolution using CSA. Only 65% of the desired enantiomer was obtained. When 350 kg of racemic Clopidogrel was used, only 150 kg of **209** was recovered. This enormous loss in the last step is the main disadvantage of this route and was partially overcome by regenerating racemic Clopidogrel from the mother liquor after filtrating (+)-Clopidogrel camphor sulfonate, adding an additional step to the total synthesis. Additionally, an extremely hazardous cyanide reagent, especially at this scale, was used to perform the first step.



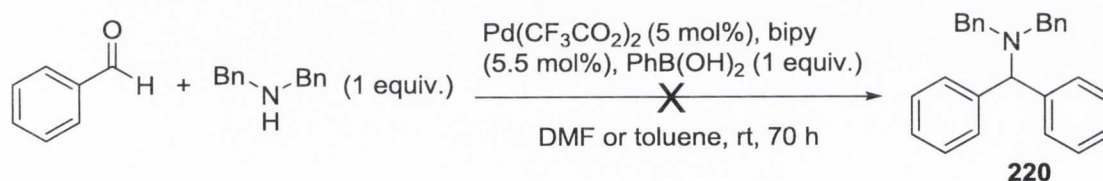
Scheme 3.3. Industrial scale synthesis of clopidogrel with a preformed chiral centre.

The second route starts by tosylating 100 kg of **216** with 163.2 kg of *p*-toluenesulfonyl chloride in the presence of triethylamine giving **217** with a complete conversion (Scheme 3.3). Compound **217** reacts with optically pure **218**, to obtain **219** as the HCl salt after acidic treatment with a 67% yield. In this way no resolution step is needed. Compound **219** was then condensed with formaldehyde, the resulting imine undergoes a cyclisation to give **209** with a yield of 76%. The authors reported many byproducts with **219** explaining the low yield for this step. Moreover the yield of the final step is not particularly high and enantiopure **218** had to be employed and taken through two moderately yielding reaction steps. Those two examples show the need of finding an enantioselective metal catalyzed Petasis reaction to produce antiplatelet drugs and, in general, to have an extra tool to synthesize these structures.

3.2 Development and investigation of a metal catalysed Petasis reaction

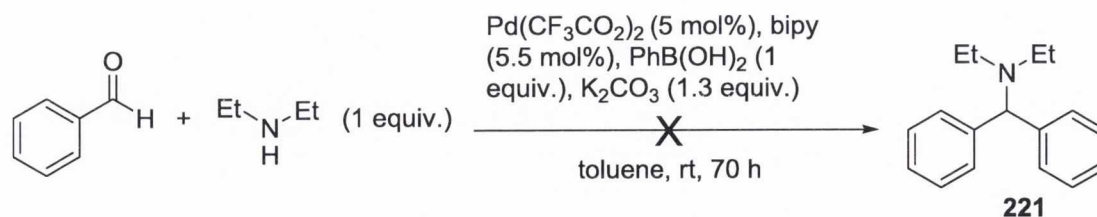
3.2.1 First attempts

The first attempt consisted in reacting benzaldehyde with dibenzylamine catalyzed by Pd^{II} trifluoroacetate and bipyridine in toluene for 70 h, hoping to form an aryl palladium species capable of arylating the iminium (Scheme 3.4). Unfortunately compound **220** was not observed by mass spectrometry or NMR spectroscopy. A polar solvent DMF which might be more suitable for a reaction which involves an iminium formation was also tried giving no positive result (Scheme 3.4).



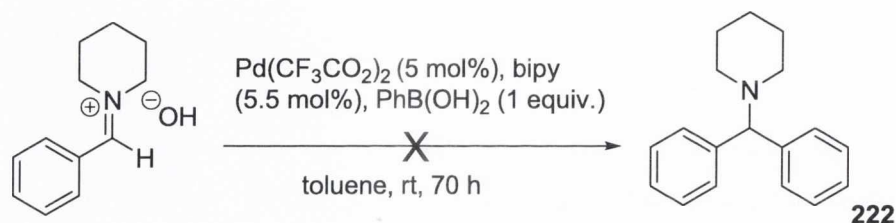
Scheme 3.4. Palladium catalysed Petasis reaction attempt.

Diethyl amine, a less bulky secondary amine with smaller groups was then tried and, in the same time, potassium carbonate was added as it can activate boronic acids for the transmetallation (Scheme 3.5).²¹⁹



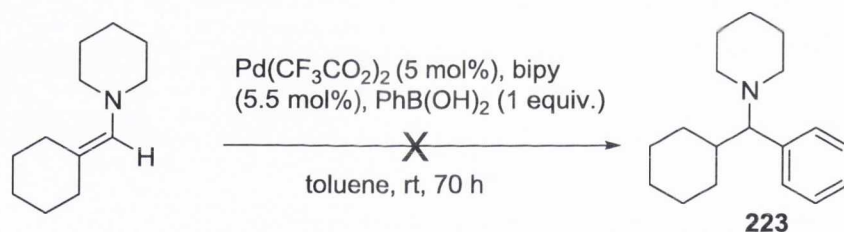
Scheme 3.5. Palladium catalysed Petasis reaction attempt with potassium carbonate.

Unfortunately tertiary amine **221** was not found by mass spectroscopy. To be sure that the iminium formation is not the problem, the iminium was preformed neat from benzaldehyde and piperidine according to Correa procedure (Scheme 3.6).²²⁰ In parallel, the same reaction without pre-forming the iminium was carried out. The two reactions were carried out at room temperature, in toluene with Pd^{II} trifluoroacetate and bipy. Again, compound **222** was not produced in either experiment.



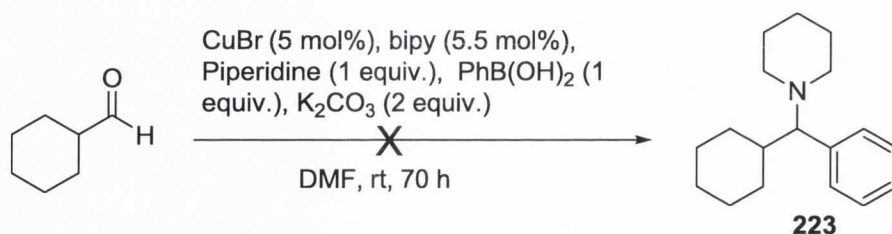
Scheme 3.6. Attempt of phenylboronic acid addition to an iminium catalysed by palladium and bipyridine.

The addition of phenylboronic acid to an enamine which can be on equilibrium with the iminium, catalysed by palladium was also tried but was also unsuccessful (Scheme 3.7). The enamine was made following Bélanger procedure.²²¹



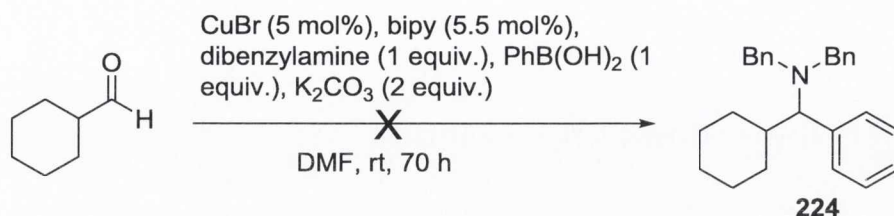
Scheme 3.7. Attempt to add phenylboronic acid on an enamine.

As arylboronic acids can be transmetalated CuBr¹⁶⁷, the latter was used in order to form a reactive organocopper species which can act as a nucleophile and attack the iminium (Scheme 3.8).



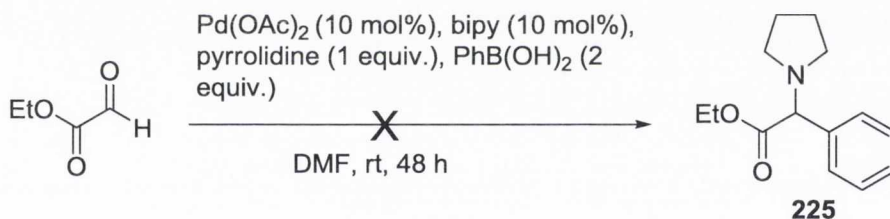
Scheme 3.8. Copper catalysed Petasis reaction attempt with piperidine.

The reaction was carried out in DMF with 2 equivalent of potassium carbonate. Compound **223** was not observed by mass spectrometry. This result was confirmed when dibenzylamine was used instead of piperidine (Scheme 3.9). Again, the product, here **224**, was not found in the reaction mixture.



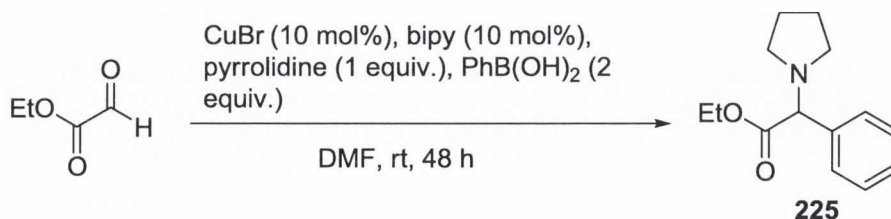
Scheme 3.9. Copper catalysed Petasis reaction attempt with dibenzylamine.

A coordinating group on the aldehyde was tried in a palladium catalysed Petasis reaction. (Scheme 3.10). The metal salt loading was increased from 5 mol% to 10 mol% and the amount of phenyl boronic acid was increased to two equivalents. A less hindered and more nucleophilic amine, pyrrolidine was also tried but again compound **225** was not produced.



Scheme 3.10. Palladium catalysed Petasis reaction attempt with pyrrolidine and ethylglyoxalate.

The same reaction was carried out by using copper instead of palladium (Scheme 3.11).

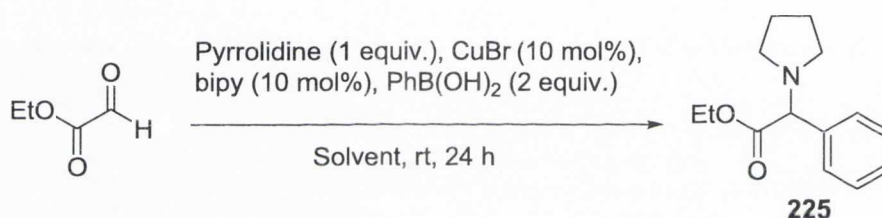


Scheme 3.11. Copper catalysed petasis reaction with ethyl glyoxalate, pyrrolidine and phenylboronic acid.

This time, we were delighted to observe amino ester **225** by mass spectrometry and after column chromatography by NMR spectroscopy. The same experiment was carried out without catalyst to ensure that the reaction is catalysed by copper, and no product was formed confirming the requirement of the copper salt and ligand.

3.2.2 Optimisation of the reaction

The next step consists in optimising the reaction conditions in order to obtain **225** with the best yield. To start, a solvent screen under nitrogen was carried out in order to find out the optimal solvent for this new reaction (Table 3.1).

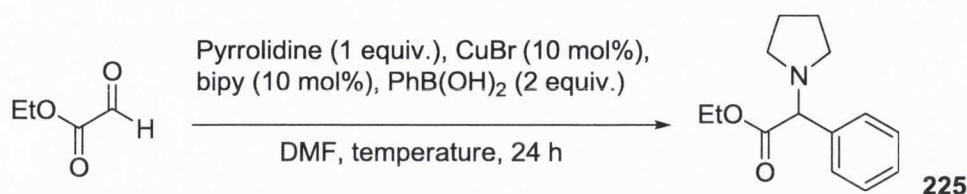


Entry	Solvent	Yield (%) ^a
1	THF	10
2	DCM	25
3	Toluene	<5
4	DMF	48
5	MeCN	17

Table 3.1. Solvent screen for the copper catalysed Petasis reaction. ^aDetermined using ¹H NMR with 4-nitrobenzaldehyde as an internal standard.

From all the solvents tried DMF produced **225** with the highest yield (48%) and thus was chosen for the next reactions (Table 3.1, entry 4). Toluene gave the product with a low yield, possibly due to the poor solubility of the catalyst (Table 3.1, entry 3). Acetonitrile, THF and DCM showed disappointing results (Table 3.1, entries 1, 2 and 5).

With a suitable solvent identified, we next examined other parameters. Firstly a short temperature investigation was undertaken (Table 3.2).



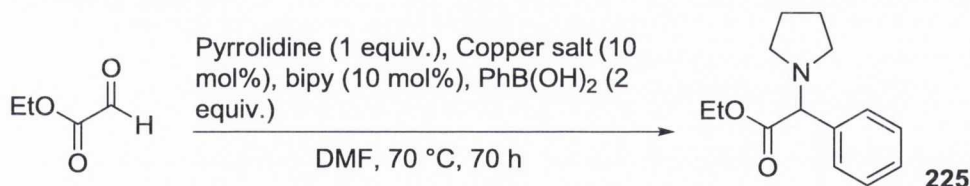
Entry	Temp.	Yield (%) ^a
1	rt	48
2	70 °C	63
3	100 °C	0

Table 3.2. Temperature investigation for the copper catalysed Petasis reaction.

^aDetermined using ¹H NMR with 4-nitrobenzaldehyde as an internal standard.

Carrying the reaction at 70 °C instead of rt improved the yield (Table 3.2, entry 1 vs. 2). Nevertheless, the reaction does not proceed when the temperature is too high, possibly due to the amine volatility (Table 3.2, entry 3).

Next, a screen of copper salts was carried out (Table 3.3).

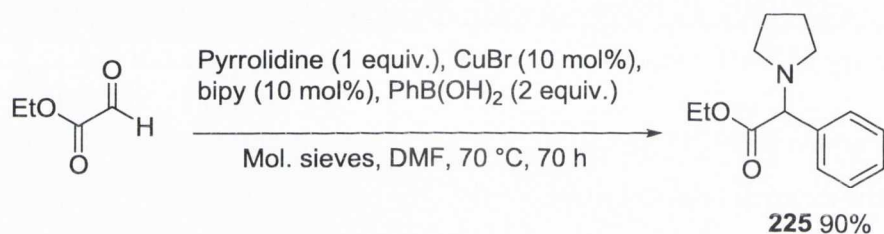


Entry	Copper salt	Yield (%) ^a	Entry	Copper salt	Yield (%) ^a
1	CuBr	63	6	CuCl ₂	0
2	CuCl	54	7	Cu(OTf) ₂	0
3	CuI	64	8	CuBr ₂	0
4	CuBr ^b	42	9	Cu(OAc) ₂	50
5	CuOAc	4			

Table 3.3. Copper salts screening for the copper catalysed Petasis reaction. ^aDetermined using ¹H NMR with 4-nitrobenzaldehyde as an internal standard. ^bReaction run under a noninert atmosphere.

All the Cu^I halides tested, gave **225** with good and comparable yields, 63% for CuBr, 64% for CuI whereas CuCl produced the aminoester with a conversion of only 54% (Table 3.3, entries 1, 2 and 3). Surprisingly, using CuOAc gave a poor result (4%, Table 3.3, entry 5). Cu^{II} salts were also tested since there have also been some reports of them transmetalating phenylboronic acid.¹⁵⁶ Unfortunately most of the Cu^{II} salts tested gave no products. (Table 3.3, entries 6, 7 and 8), indeed only Cu(OAc)₂ yielded **225** (Table 3.3, entry 9). Also, a reaction with CuBr was run under a noninert atmosphere leading to a drop of yield (Table 3.3, entries 1 vs. 4).

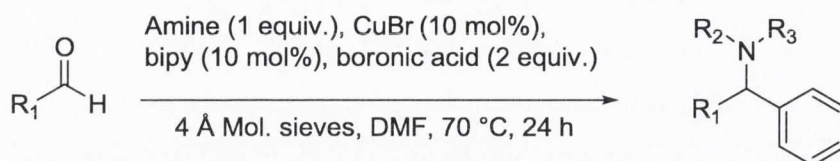
After observing the sensitivity of Cu^I toward oxygen and moisture, the reaction was carried out in degassed DMF with CuBr and 4 Å molecular sieves yielding **225** with a high yield of 90% (Scheme 3.12), making this reaction really synthetically useful.



Scheme 3.12. Optimised conditions for the copper catalysed reactions.

After finding the optimal conditions for this new reaction the scope was investigated by changing the boronic acid, secondary amine and aldehyde.

3.2.3 Investigation of the reaction scope



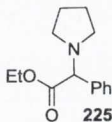
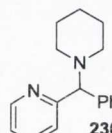
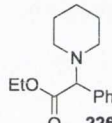
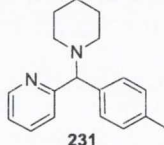
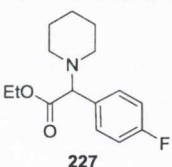
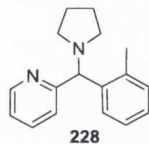
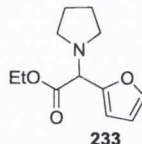
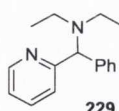
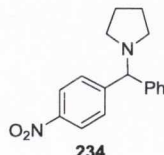
Entry	Product	Yield (%) ^a	Entry	Product	Yield (%) ^a
1	 225	90	6	 230	76
2	 226	51	7	 231	74
3	 227	57	8	 232	<5
4	 228	<5	9	 233	79
5	 229	43	10	 234	0

Table 3.4. Tertiary amines synthesised *via* the copper catalysed Petasis reaction.

^aDetermined using ¹H NMR with 4-nitrobenzaldehyde as an internal standard.

Both electron rich and electron poor arylboronic acids yielded the product with fair yields but boronic acids with a lower electron density gave a better yield. Using 4-fluorophenylboronic instead of phenylboronic acid gave the product with a slightly higher yield (Table 3.4, entry 2 *vs.* 3), and a methyl group on the 4 position of the boronic acid decreased the yield to some extent (Table 3.4, entry 6 *vs.* 7). 2-Furanboronic acid, a more

electron rich boronic acid than phenylboronic acid, produced aminoester **233** with a lower conversion than **226** (Table 3.4, entry 1 vs. 9). With respect to the aldehyde component, pyridine-2-carboxaldehyde gave a higher yield than ethylglyoxalate (Table 3.4, entry 2 vs. 6). To test if a coordinating group was truly required, or if it was simply that the aldehydes were highly electrophilic, we repeated the reaction using 4-nitrobenzaldehyde (Table 3.4, entry 10). No product was observed, indicating that an appropriately placed coordinating atom was required. However the coordinating groups (an ester and pyridine) are much weaker than those required for similar reactions without copper (essentially limited to substrates containing free hydroxyl groups, such as salicylaldehyde and related compounds).

With regard to sterics, bulkier amines produced the amino ester with lower conversions (Table 3.4, entry 1 vs. 2). A non-cyclic secondary amine, diethylamine was tested but the moderate conversion cannot be attributed totally to the steric effect since the low boiling point of diethylamine can affect the yield (Table 3.4, entry 5). Ortho-substituents on the aryl boronic acid decrease dramatically the yield (Table 3.4, entries 4 and 8). Some unsuccessful attempts outline the limits of the reaction (Table 3.5).

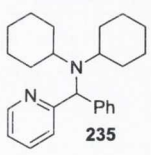
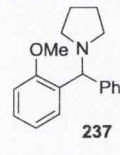
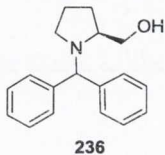
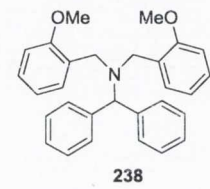
$ \begin{array}{c} \text{R}_1-\text{CHO} \xrightarrow[\text{4 \AA Mol. sieves, DMF, 70 }^\circ\text{C, 24 h}]{\text{Amine (1 equiv.), CuBr (10 mol\%), bipy (10 mol\%), boronic acid (2 equiv.)}} \text{R}_1-\text{CH}(\text{Ph})-\text{N}(\text{R}_2)(\text{R}_3) \end{array} $					
Entry	Product	Yield (%) ^a	Entry	Product	Yield (%) ^a
1	 235	0	3	 237	0
2	 236	0	4	 238	0

Table 3.5. Tertiary amines synthesis attempts *via* the copper catalysed Petasis reaction showing the scope limits. ^aDetermined using ¹H NMR with 4-nitrobenzaldehyde as an internal standard.

When dicyclohexylamine was used, product **235** was not found presumably due to steric effects confirming the trends observed before (Table 3.5, entry 1). The reaction was also tried by using coordinating groups on the amine rather than on the aldehyde but led to no **236** and **238** (Table 3.5, entries 2 and 4). The amines were obtained from co-workers within our research group. A methoxy group was tried as coordinating groups on the aldehyde and the amine fragments but compounds **237** and **238** were not produced (Table 3.5, entries 3 and 4).

3.2.4 Study of the reaction mechanism

After showing the capacity and the limits of this new copper catalysed Petasis, we proposed a mechanism (Figure 3.3).

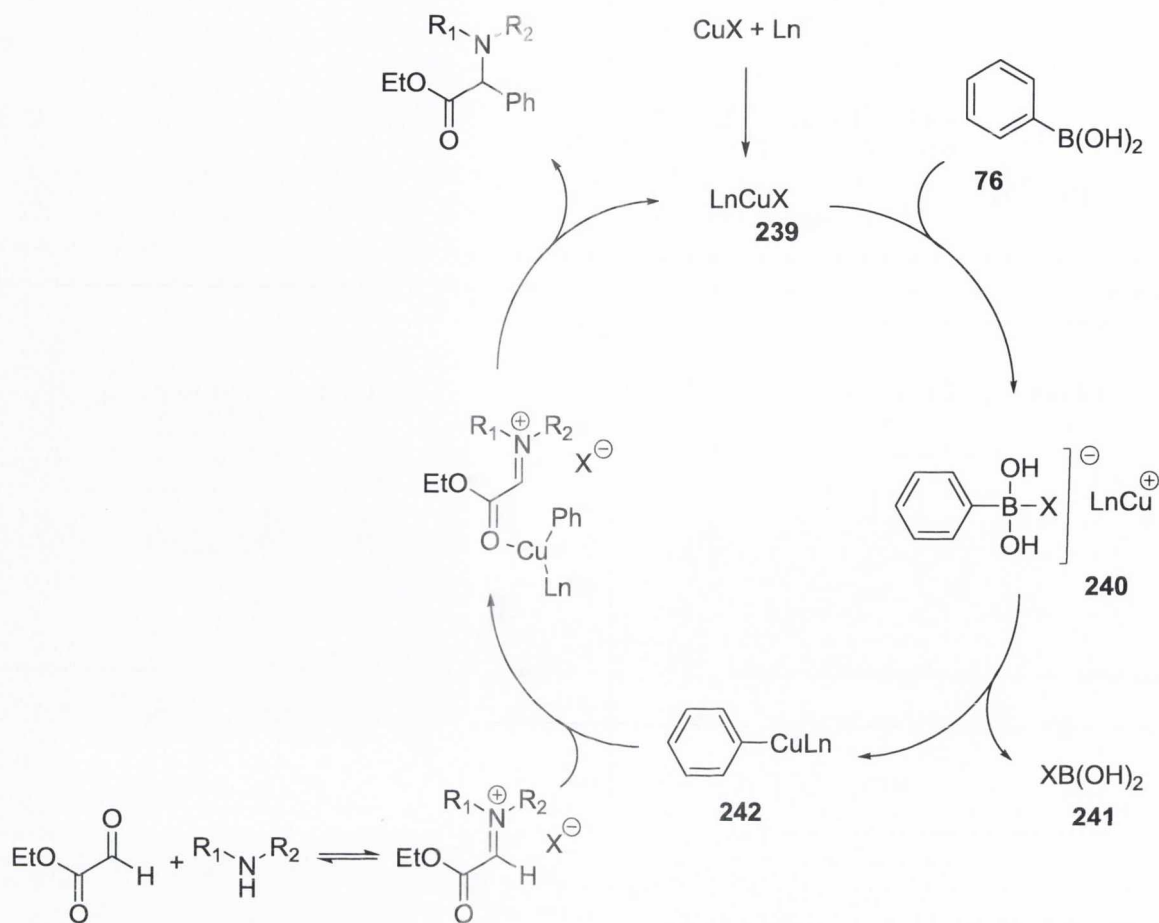


Figure 3.3. Proposed mechanism for the copper catalysed Petasis reaction.

First, complex **239** is formed from a copper salt and a bidentate ligand. The counterion of complex **239** reacts with the boronic acid **76** to produce the tetracoordinated boronate salt **240**. The activated species **240** can then transmetalate copper to produce the organocopper compound **242** and the byproduct **241**. The iminium, formed *in situ* from ethylglyoxylate and a secondary amine, can then undergo a nucleophilic attack. The requirement of a coordinating group on the aldehyde fragment would imply that copper coordinates the iminium to activate the organocopper species and bring the aryl group close to the electrophilic centre. If the mechanism is broadly correct a mixture of boronic acid, ligand and copper salt should lead to 3 major peaks by ^{11}B NMR, the three boron containing compound, the boronic acid **76**, boronate salts **240** and by-product **241**. To investigate the organocopper species a mixture of 4-methoxyphenylboronic acid with one equivalent of CuBr and bipy was monitored by ^{11}B NMR (Figure 3.4). Indeed, we were happy to observe three peaks which correspond to **243**, **244** and **241** according to the values of a similar reaction using alkenyl boronate esters found in the literature.⁸³ The starting material boron is seen at 29.5 ppm. After the addition of the copper salt and ligand a peak at 2.2 ppm

which corresponds to the **244** shielded tetracoordinated boron was observed. From this experiment X cannot be identified, but we assumed that X is a bromide or hydroxide. As the reaction proceeds a third boron containing product is formed which we postulated to be **241** according to the chemical shift. The production of **241** implies the formation of the aryl copper compound.

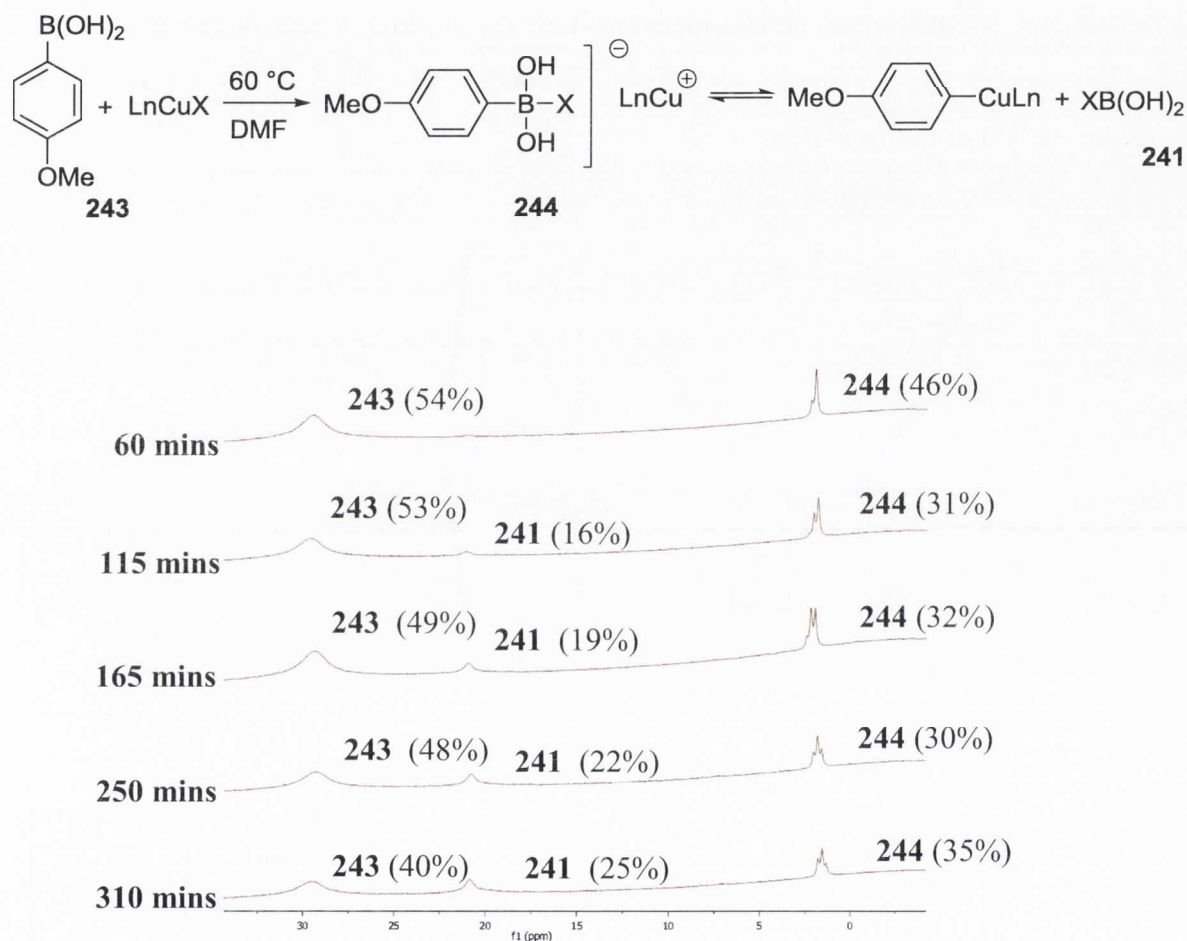


Figure 3.4. ^{11}B NMR analysis of a mixture of 4-methoxyphenylboronic acid with one equivalent of CuBr and bipy.

The tendency observed before which shows that the electron density of the aryl boronic acid influences the reaction yield (Table 3.4) could be explained by a difference of transmetallation efficiency according to the electron nature of the boronic acid. In parallel, a similar experiment was then carried out by using phenylboronic acid instead of 4-methoxyphenylboronic acid by Carlos García (Figure 3.5).²²² Since the boron quantity in the reaction mixture is constant and the volume of the reaction does not change the percentages shown in Figure 23 and 25 are directly related to the concentration of each species.

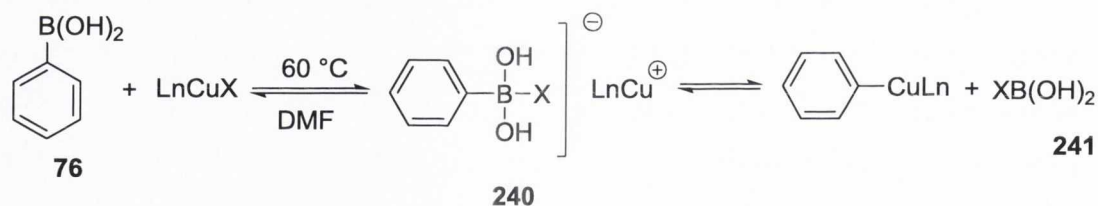


Figure 3.5. Conversion of phenylboronic acid to an arylcopper nucleophile.

To compare the conversion of **76** and **243** to their corresponding arylcopper species, a plot was drawn with the percentage of each boron containing species in the reaction mixture against the reaction time (Figure 3.6).

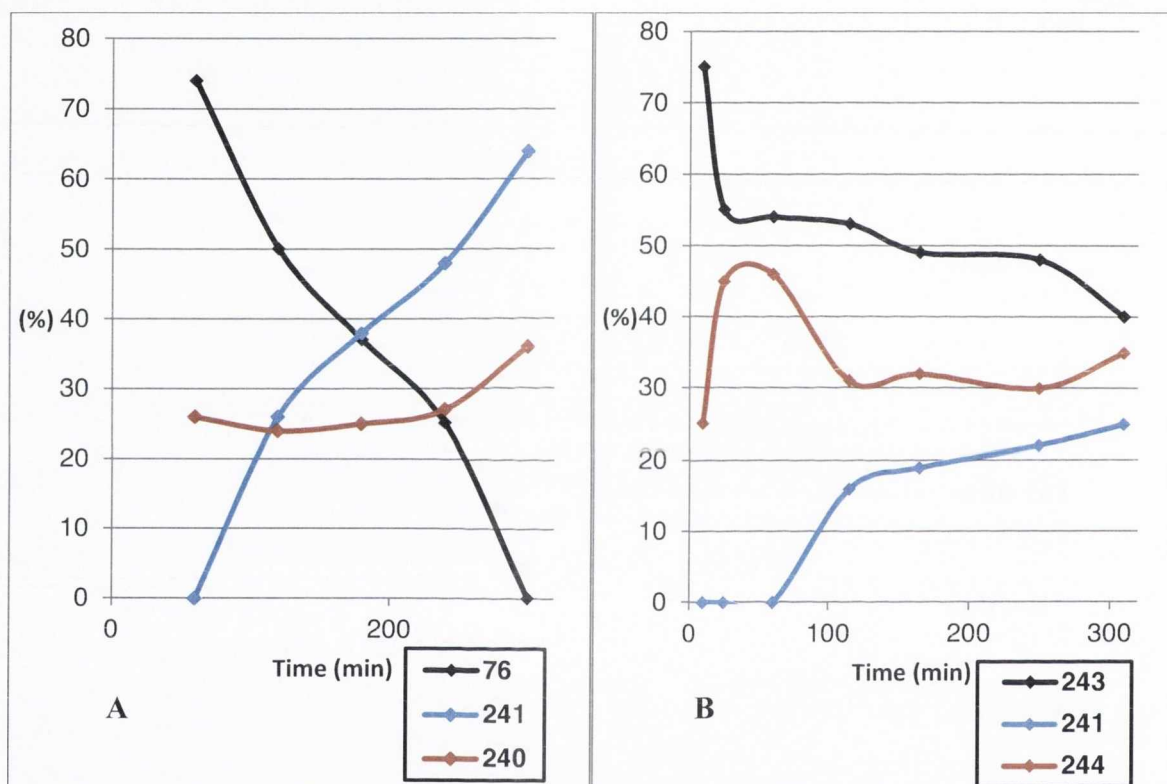


Figure 3.6. Comparison of the organocopper reagents formation from phenylboronic acid (Plot A), and 4-methoxyphenylboronic acid (Plot B).

Boronic acid **76** is fully consumed after 300 minutes in an almost linear manner (Figure 3.6, Plot A) whereas 40% of starting material **243** was still present after 310 minutes (Figure 3.6, Plot B). The concentration of intermediate **240** increases during one hour to achieve 26% of the boron-containing species in the reaction and then remains relatively constant. Since the concentration of **240** is constant and **76** decrease, the percentage of **241** (which corresponds to the amount of active nucleophile) among the other boron containing products increases. When 4-methoxyphenylboronic acid was used the formation of the

tetracoordinated boron species **244** was faster but this had no positive impact on the formation of **241**. Interestingly intermediates **244** and **243** were observed with roughly the same concentration throughout the reaction and yet, more **241** is produced when phenyl boronic acid is used, indicating that the limiting step is the transmetallation as expected. The fact that the transmetallation step is less efficient when electron rich arylboronic acids are used could explain the results observed in Table 3.4. This was further confirmed by experiments that showed electron poor boronic acids 4-fluorophenylboronic acid and 2-chlorophenylboronic acid were converted into the active nucleophiles at a rate faster than either **76** or **243**.

3.2.5 Chiral ligands for the copper catalysed Petasis reaction

Some platelet inhibitors such as clopidogrel are a single enantiomer (Figure 4.2) which is obtained by resolution.^{139,140} Obtaining an enantioenriched iminoester *via* the copper catalysed reaction would be extremely useful way to synthesise drugs such as Clopidogrel in one step.

In our goal at inducing asymmetry firstly, attempts were made to achieve separation on CSP-HPLC of the enantiomers of all the racemic mixtures of tertiary amines shown in Table 3.4 (except **228** and **232**) using two columns (Chiralpak IA and IB). The two enantiomers of **233** were successfully separated (Figure 3.7).

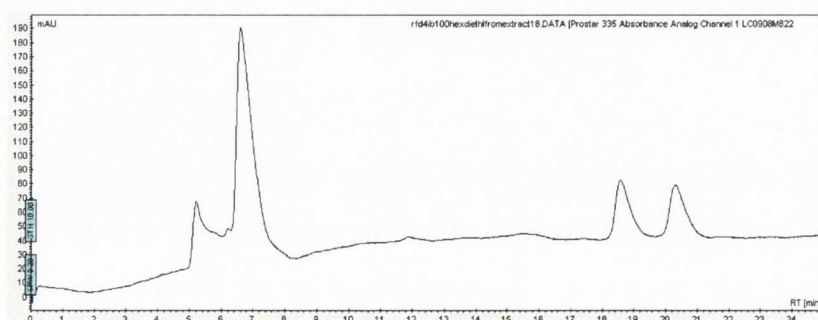
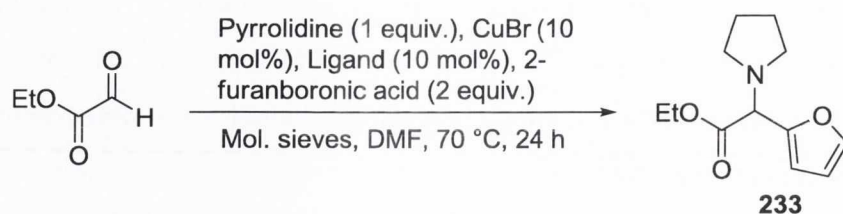


Figure 3.7. Separation of two enantiomers from a racemic mixture of **233**. Chiralpak IA, hexane/Et₂NH (99:1), 1.3 mL min⁻¹, UV detection at 254 nm, retention times: 18.5 min and 20.5 min

2-Furanboronic acid, pyrrolidine and ethylglyoxalate were then chosen as substrates to screen chiral ligands in the hope of obtaining enantioenriched **233** (see Table 3.6).



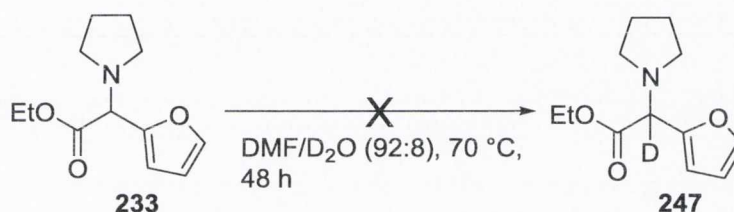
Entry	Ligand	Yield (%) ^a	ee (%) ^b	Entry	Ligand	Yield (%) ^a	ee (%) ^b
1		23	0	4		16	0
2		0	n/a	5		40	0
3		0	n/a	6		16	0

Table 3.6. Screen of chiral ligands for the copper catalysed Petasis reaction. ^aDetermined using ¹H NMR with 4-nitrobenzaldehyde as an internal standard. ^bDetermined by CSP-HPLC.

(*R*)-Binap, which had proven to induce asymmetry in some copper catalysed reactions^{142,143,144} was tried and generated **233** as a racemic mixture with a conversion of 23% (Table 3.6, entry 1). Subsequently, chiral bidentate ligands which were produced in bulk and characterized for the *in situ* synthesised ligand project (see chapter 2) were screened. Unfortunately, none of these ligands yielded **233** with an enantiomeric excess. Surprisingly ligands **156** and **189** did not yield any product (Table 3.6, entries 2 and 3). Oxazoline **246** and imidazolidine **200** gave **233** with a low yield 16% (Table 3.6, entries 4

and 6). From all the ligands screened iminophosphine **177** produced **233** with the highest yield (Table 3.6, entry 5).

Since no enantiomeric excess was observed for **233** despite using various bidentate chiral ligands (Table 3.6), an investigation of the tendency of **233** to racemize was carried out (Scheme 3.13). The chiral centre created bears a proton which could be subject to racemisation due to the adjacent ester and aryl groups. Aminoester **233** was stirred for 48 h in a mixture of DMF and D₂O at 70 °C to produce possibly **247**. After simple evaporation of the solvent, no proton-deuterium exchange was observed by ¹H NMR, meaning that it appears that racemization is not responsible of the racemic mixtures obtained when the reaction was carried out with chiral ligands. As such attempts at developing an asymmetric version of our copper catalysed reaction have been put on hold.



Scheme 3.13. Investigation of possible racemization of **233**.

3.3 *N*-acyliminiums: new substrates for copper nucleophiles

3.3.1 Development of the reaction

The electrophilic reactivity of iminium ions is enhanced with a carbonyl adjacent to the nitrogen, giving an *N*-acyliminium, a more reactive species than its iminium counterpart. Additions of aryl and alkenyl boronic acids to *N*-acyliminium *via* a Petasis reaction have been reported.²²³ The substrate normally needs a hydroxyl group α to the electrophilic site or a vinylboronic acid or ester like for the standard Petasis reaction. Interestingly, a nickel

catalysed addition of boronate esters to EEDQ (without the need for pendant hydroxyl groups) was reported by Graham et al. with a proposed mechanism (shown in Figure 3.8).²²⁴ The authors postulate that Ni^0 adds to EEDQ **248** to afford a Ni^{II} complex **249** which transmetallate the tetracoordinated organoboron species **250**. After a reductive elimination the Ni^0 complex **253** is regenerated and product **252** is formed. In this case, to form an *N*-acyliminium ion *in situ*, the carbon in the α position of the nitrogen needs to bear a leaving group and a Lewis base is required, here boronate species play this role.

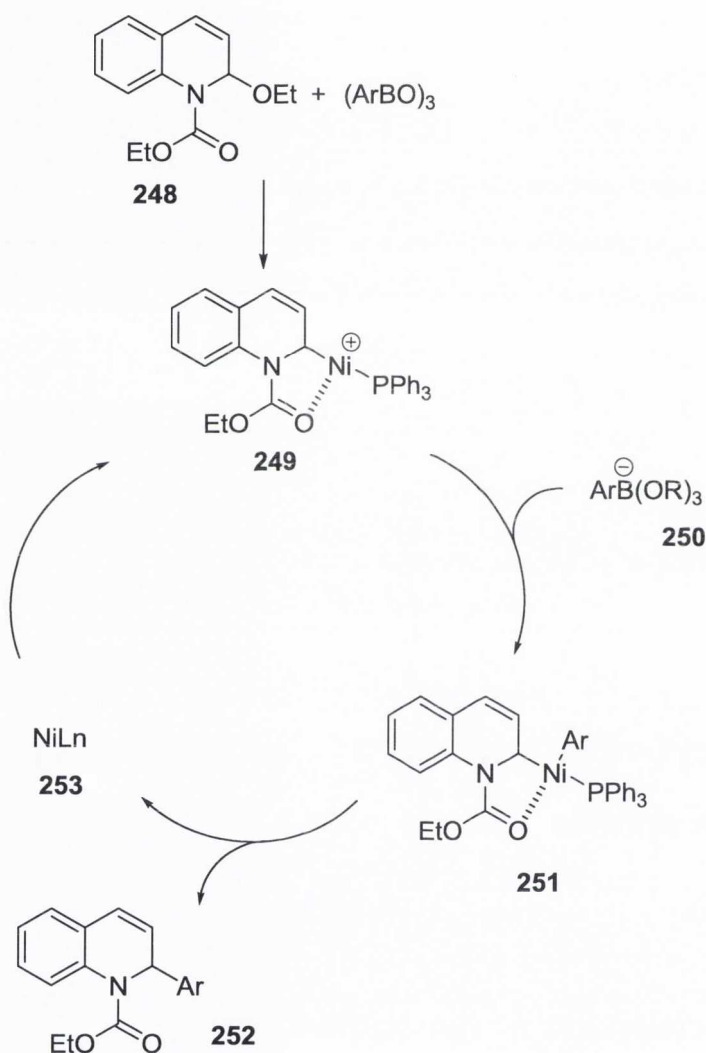
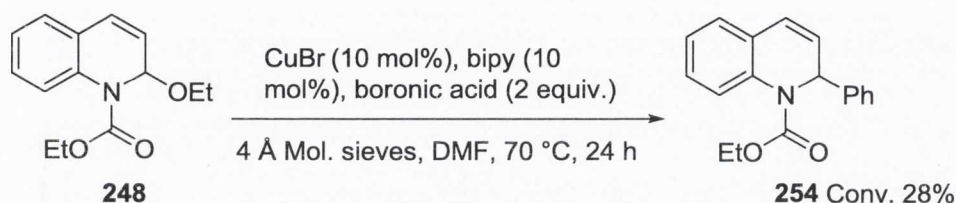


Figure 3.8. Proposed mechanism for a nickel catalysed cross-coupling on EEDQ.²²⁴

The authors report that the metal might coordinate EEDQ carbonyl, which makes it a good potential substrate for a Cu^{I} catalysed Petasis-type addition of boronic acid. By using a MonoPhos ligand with Ni^0 the authors achieved an *ee* of 52% (this is the single example of a chiral ligand giving enantioselectivity in this process). Also, Takemoto and co-workers

elaborated an enantioselective addition of vinylboronic acid to EEDQ using a thiourea organocatalyst.¹³⁶

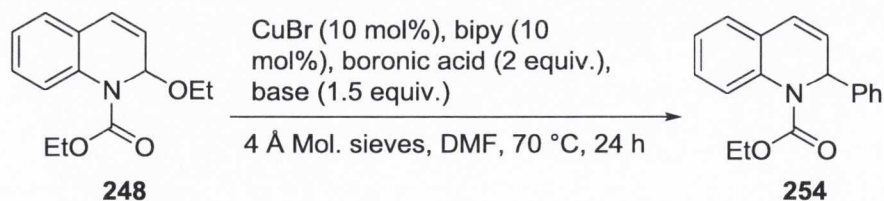
We examined this procedure in order to determine if copper catalysts would be suitable. To start, the same conditions were employed as for the copper catalysed Petasis reaction (Scheme 3.14).



Scheme 3.14. Copper catalysed arylation of EEDQ.

We were delighted to observe **254** by mass spectrometry with conversion of 28% by ¹H NMR spectroscopy, especially considering there had only been one metal catalysed report in the literature to date.

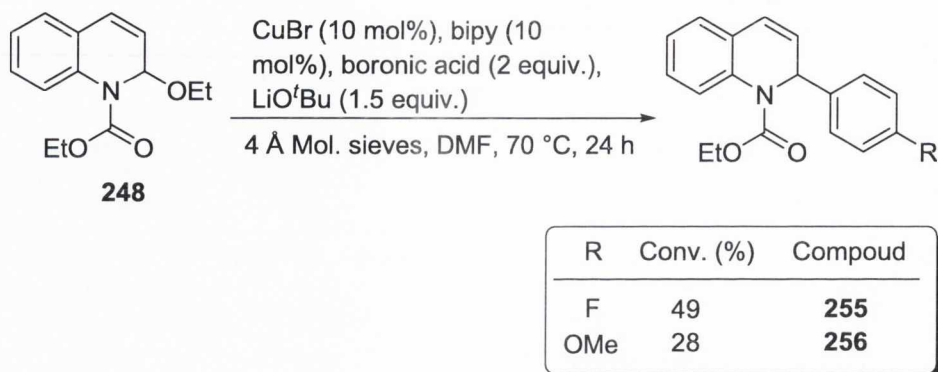
To try to improve yields we examined other factors affecting the reaction. Yang et al. had carried out cross-couplings with an organoboron compound and primary alkyl halides catalysed by CuI. To enhance the yield the authors screened 8 bases and found LiO^tBu to be the most efficient.¹⁷⁵ In the same manner Hou and co-workers used KO^tBu to enhance a carboxylation of boronic acid catalysed by CuCl.¹⁶⁶ KO^tBu and LiO^tBu were then tested and both showed to increase slightly the conversion (Scheme 3.15). LiO^tBu improved the conversion of **248** from 28% to 34% in a small, but reproducible, advance.



Base	Conv. (%)
KO ^t Bu	30
LiO ^t Bu	34
-	28

Scheme 3.15. Effect of tert-butoxide bases on copper catalysed arylation of EEDQ.

To probe the sensitivity of the reaction to electronic factors, the electronic nature of the arylboronic acid was altered by using 4-fluorophenylboronic acid and 4-methoxyphenylboronic acid (Scheme 3.16).



Scheme 3.16. Effect of electron withdrawing and donating groups on aryl boronic acid in copper catalysed arylation of EEDQ.

The same tendency as for the copper-catalysed Petasis reaction was observed. Electron poor aryl boronic acids tended to give better yields than electron rich, with unsubstituted phenyl boronic acid falling in the middle. Compound **255** was observed with a conversion of 49% versus 34% for **254** (Schemes 3.15 and 3.16) and 28% for **256**.

We then proposed then two mechanisms. The first only involves a Cu^I complex (Figure 3.9) whereas the second mechanism implies a Cu^{III} intermediate (Figure 3.10).

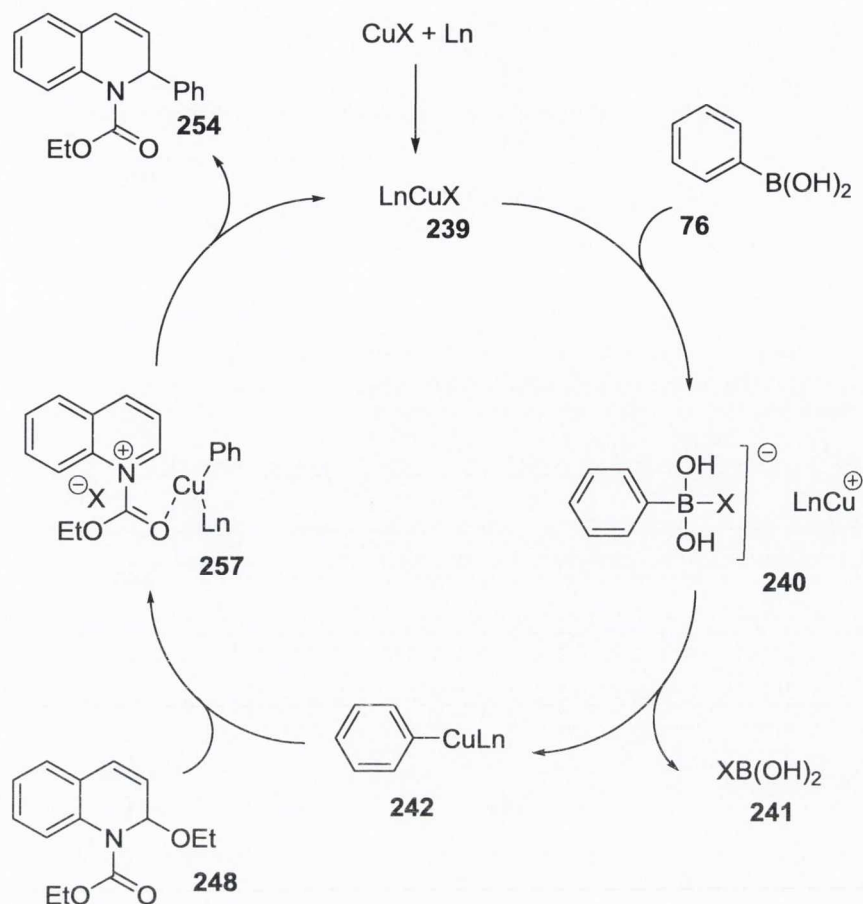


Figure 3.9. Proposed mechanism for a copper catalysed Petasis type addition EEDQ, involving a Cu^{I} complex intermediate.

First, like for the copper catalysed Petasis reaction, a copper complex **239** is made from bipy and CuBr . The arylboronic acid **76** reacts with **239** to form a tetracoordinate boron species **240**. This activated species can then transmetalate to form **242**. N -acyliminiums are easily formed in a presence of a mild Lewis acid.²²⁵ So we propose that compound **248** forms an N -acyliminium from a boron containing species (probably **76** or **241**). It is thought that the copper complex **242** coordinates to the carboxyl group from the N -acyliminium, as per to the work of Graham et al. on nickel catalysed cross-coupling on EEDQ²²⁴ (Figure 3.8). Then **242** attacks the N -acyliminium to form **254** via **257**, and regenerate **239**.

We also proposed another mechanism involving a Cu^{III} intermediate (Figure 3.10)

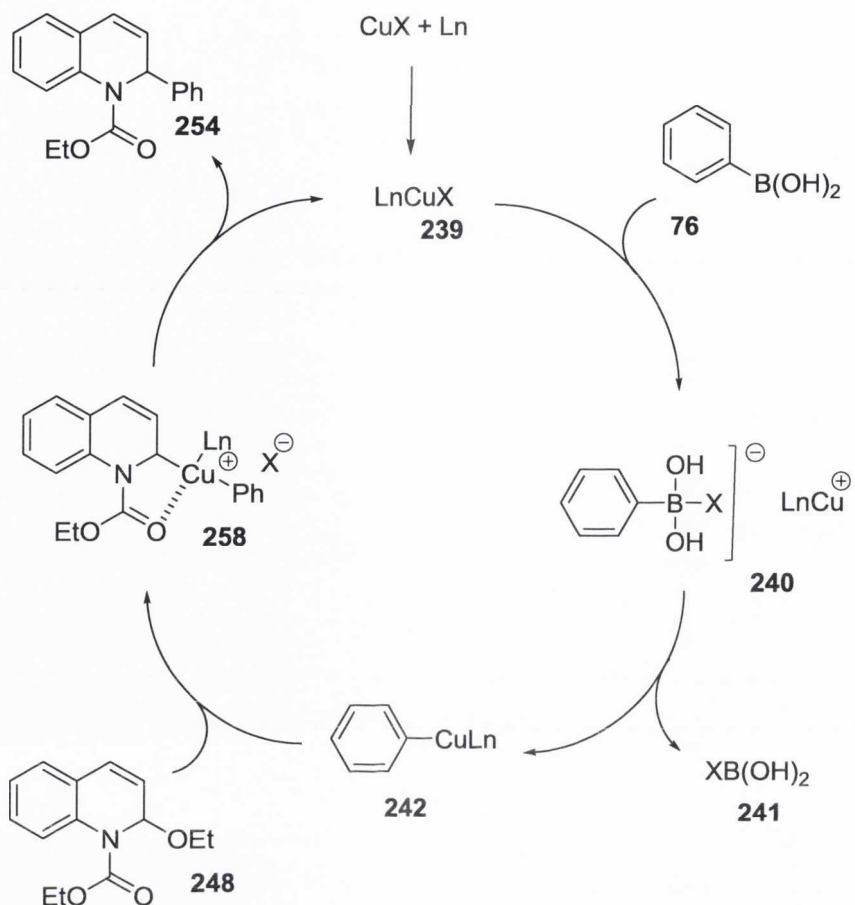


Figure 3.10. Proposed mechanism for a copper catalysed Petasis type addition EEDQ, involving a Cu^{III} complex intermediate.

Like for the previous mechanism we proposed (Figure 3.10), phenylboronic acid **76** transmetalates the Cu^{I} complex **239** giving the reactive organocopper species **242** which inserts **248** to form a Cu^{III} complex **258**. Species **258** undergoes a reductive elimination to yield **254** and regenerate **239**. This mechanism is conceivable because Cu^{I} catalysed reaction involving a Cu^{III} intermediate have been reported.²²⁶ For instance, the Ullman coupling is believed to imply a Cu^{I} organocopper which undergoes a oxidative addition and then a reductive elimination giving the product.²²⁷

Due to similarities of these mechanisms it is difficult to judge between them, though the fact that Cu^{III} intermediates are invoked for most Cu^{I} catalysed processes.²²⁶

3.3.2 Chiral ligands for coupling between EEDQ and phenylboronic acid

Before starting the chiral ligands screen, a racemic mixture of **254** was successfully separated by CSP-HPLC (Figure 3.11).

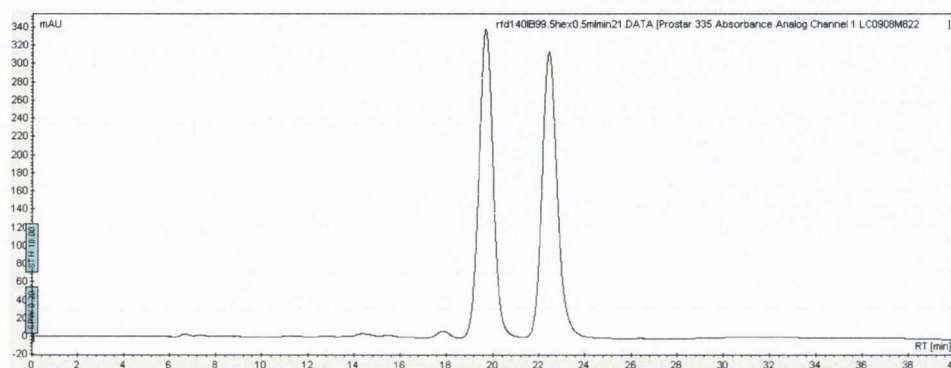
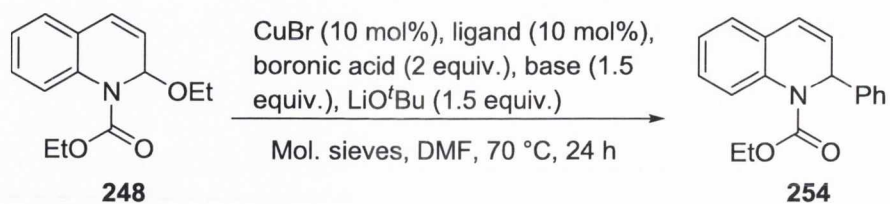


Figure 3.11. Separation of 2 enantiomers from a racemic mixture of **254**. Chiralpak IB, hexane/*i*PrOH (99.5:0.5), 0.5 mL min⁻¹, UV detection at 254 nm, retention times: 19.5 min and 22.5 min.

Again, a ligand screen was carried out by simply replacing bipy with a chiral bidendate ligand synthesized or commercially available (Table 3.7).



Entry	Ligand	Yield (%) ^a	ee (%) ^b	Entry	Ligand	Yield (%) ^a	ee (%) ^b
1		16	0	5		11	0
2		29	0	6		11	0
3		28	0	7 ^c		24	0
4		24	0				

Table 3.7. Screen of chiral ligands for coupling between EEDQ and phenylboronic acid.

^aDetermined using ¹H NMR with 4-nitrobenzaldehyde as an internal standard. ^bDetermined by CSP-HPLC. ^cCarried out at rt.

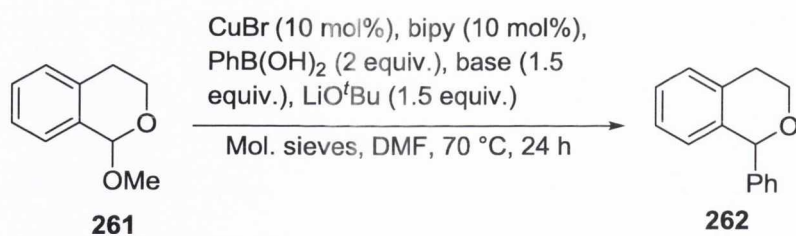
Again, some chiral bidentate ligands made for the combinatorial library synthesis (see section 2.2), were used (Table 3.7, entries 2, 4 and 5). The hope was that if an enantiomeric excess was obtained, it could rapidly be optimised using our high-throughput screening.

From all the chiral ligands screened, **156** produced **254** with the highest yield but did not induce any enantiomeric excess (Table 3.7, entry 2). Imino alcohol **132** also gave **258** as a racemic mixture. Oxazoline **246** and bisoxazoline **260** produced **254** with the same low yield: 11% (Table 3.7, entries 5 and 6). (*R*)-Binap gave disappointing results in term of both yield and *ee* (Table 3.7, entry 1). Pybox **259** allowed the copper catalysed coupling to proceed with a yield of 28% but with no enantiomeric excess. The same ligand was used in a reaction carried out at room temperature to see if the relative harsh conditions were responsible for the racemic mixture obtained but no *ee* was observed (Table 3.7, entry 7). Interestingly if the second mechanism proposed is right (Figure 3.10), the reaction would need chiral monodentate ligands to obtain some *ees*.

3.4 Conclusions and future work

A new copper catalysed Petasis reaction has been elaborated and optimized, allowing a larger reaction scope. Secondary amines, aryl boronic acids and aldehydes bearing even a weakly coordinating heteroatom can then be converted into tertiary amines in a presence of a catalytic amount of a copper salt.

The addition of aryl boronic acids was also developed for a different substrate (*N*-acyliminiums), giving another method of carbon-carbon bond formation using copper salts. For those new reactions mechanisms based on experiments and literature were proposed. Attempts to obtain the products with enantioselectivities by using chiral bidentate ligands were unsuccessful. Nevertheless, trying chiral monodentate ligands such as phosphoramidite or monophosphine could be an important next step to carry out in order to obtain enantioselectivities. Importantly, new substrates could be tested (Scheme 3.17). Acetal **261** was reported to undergo an alkynylation in the presence of a Cu^I salt and a ligand.²²⁸



Scheme 3.17. Proposed addition of phenylboronic acid to acetal **261** catalysed by Cu^{I} .

If the compound **262** is obtained, the reaction could be expanded to carbohydrate derivatives.

Chapter 4: Experimental section

4.1 General

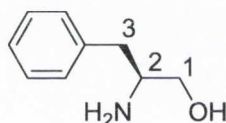
All chemicals were obtained from commercial sources and used as received. NMR spectra were recorded in a Bruker Avance 400 or Agilent 400 spectrometer, operating at 400.13 MHz for ^1H NMR, 100.61 MHz for ^{13}C NMR, 128.41 MHz for ^{11}B NMR and 162.12 MHz for ^{31}P NMR. Shifts are referenced to the internal solvent signals (^1H : δ 7.26 ppm and ^{13}C : δ 77.0 ppm for CDCl_3). Analytical CSP-HPLC was performed using Chiralpak IB (4.6 mm x 25 cm) or Chiralpak IA (4.6 mm x 25 cm) columns. Electrospray mass spectra were recorded on a Mass Lynx NT V 3.4 on a Waters 600 controller connected to a 996 photodiode array detector with methanol, water or ethanol as carrier solvents. Infrared spectra were recorded on a Mattson Genesis II FTIR spectrometer equipped with a Gateway 2000 4DX2-66 workstation and on a Perkin Elmer Spectrum One FT-IR Spectrometer equipped with Universal ATR sampling accessory. Specific rotation measurements were carried out on a Rudolph research analytical Autopol IV instrument. Toluene was distilled from calcium hydride and THF from sodium/benzophenone. TLC analysis was performed using silica 60F₂₅₄ TLC plates and visualized under UV light (254 nm) or I_2 staining. Flash chromatography was carried out using silica gel, particle size 0.063-0.2 mm from Fluka.

4.2 Rapid, *in situ* synthesis of polydentate ligands

4.2.1 Reduction of amino acids

Synthesised according to a literature procedure.¹⁹¹

An L-amino acid (9.0 mmol) was added to a stirred suspension of NaBH₄ (2.5 equiv., 851 mg) in (30 mL) of THF at 0 °C. I₂ (1 equiv., 1.14g) in THF (5 mL) was added dropwise to the reaction mixture. The reaction was then refluxed overnight at 90 °C. MeOH (30 mL) was added slowly to the reaction mixture. After 1 h of stirring the solvent was evaporated under reduced pressure and a white solid was collected. A solution of KOH (17 mL, 20%) was added to the solid and the mixture was stirred for 4 h. The product was then extracted with DCM (3 × 20 mL), dried over MgSO₄ and the solvent was evaporated to yield the L-amino alcohol.



(*S*)-2-Amino-3-phenylpropan-1-ol 144a

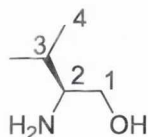
White solid (1.112 g, 81%)

¹H NMR (400 MHz, CDCl₃): δ 2.56 (dd, *J* = 8.6 Hz, *J* = 13.4 Hz, 1H, H-3), 2.82 (dd, *J* = 5.2 Hz, *J* = 13.4 Hz, 1H, H-3), 3.12-3.17 (m, 1H, H-2), 3.42 (dd, *J* = 7.2 Hz, *J* = 10.5 Hz, 1H, H-1), 3.67 (dd, *J* = 3.8 Hz, *J* = 10.6 Hz, 1H, H-1), 7.21-7.32 (m, 5H, Ph).

¹³C NMR (100.62 MHz, CDCl₃): δ 40.8 (C-3), 54.2 (C-2), 66.2 (C-1), 126.5, 128.6, 129.2, 138.6.

ν_{max} (film)/cm⁻¹: 3350, 3291, 3079, 3015, 2942, 2922, 1602, 1523, 982.

Consistent with literature values.²²⁹



(S)-2-Amino-3-methylbutan-1-ol 144b

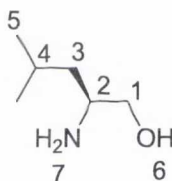
Colorless oil (446 mg, 48%)

^1H NMR (400 MHz, CDCl_3): δ 0.93-0.96 (m, 6H, H-4), 1.54-1.63 (m, 1H, H-3), 2.54-2.59 (m, 1H, H-2), 3.30 (dd, $J = 8.0$ Hz, $J = 10.3$ Hz, 1H, H-1), 3.67 (dd, $J = 4.2$ Hz, $J = 10.4$ Hz, 1H, H-1).

^{13}C NMR (100.62 MHz, CDCl_3): δ 17.3, 18.0, 31.0, 58.0 (C-2), 64.2 (C-1).

ν_{max} (film)/ cm^{-1} : 3290, 2958, 1593, 1467, 1387, 1264, 1052.

Consistent with literature values.²³⁰



(S)-2-Amino-4-methylpentan-1-ol 144c

Colorless oil (802 mg, 76%)

^1H NMR (400 MHz, CDCl_3): δ 0.88-0.92 (m, 6H, H-5), 1.14-1.21 (m, 1H, H-3), 1.64-1.73 (m, 1H, H-4), 2.34 (b, 3H, H-6 and H-7), 2.87-2.93 (m, 1H, H-2), 3.23 (dd, $J = 7.9$ Hz, $J = 10.6$ Hz, 1H, H-1), 3.54 (dd, $J = 3.7$ Hz, $J = 10.4$ Hz, 1H, H-1).

^{13}C NMR (100.62 MHz, CDCl_3): δ 21.7, 22.8, 24.2, 42.7, 50.2 (C-2), 66.1 (C-1).

ν_{max} (film)/ cm^{-1} : 3313, 2955, 2902, 1467, 1375, 1114, 852.

Consistent with literature values.²³¹

4.2.2 Synthesis of ligands *in situ*

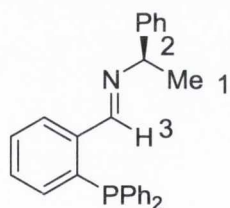
For characterisation, the ligands were synthesised according to the following procedure if not otherwise specified.

General Procedure A: Synthesis of imines, amins and oxazolidines.

To the aldehyde (5.0 mmol or 10.0 mmol for bisimines) in anhydrous toluene (20 mL), was added the amine, amino alcohol or diamine (5.0 mmol). 4 Å molecular sieves were added to the mixture. The reaction was then stirred at 70 °C overnight under N₂. The solvent was evaporated under reduced pressure to yield the ligand.

General Procedure B: Synthesis of oxazolines, imidazolines and thiazolines.

To the imidate (5.0 mmol) in anhydrous toluene (20 mL), was added the amino alcohol, diamine or aminothiols (5.0 mmol). 4 Å molecular sieves were added to the mixture. The reaction was then stirred at 70 °C overnight under N₂. The solvent was evaporated under reduced pressure to yield the ligand.



(*S*)-*N*-(2-(Diphenylphosphino)benzylidene)-1-phenylethanamine 130

Yellow oil.

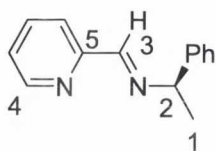
¹H NMR (400 MHz, CDCl₃): δ 1.40 (d, *J* = 6.6 Hz, 3H, H-1), 4.44 (q, *J* = 6.6 Hz, 1H, H-2), 6.89 (m, 1H), 7.16-7.45 (m, 17H, Ar), 8.05 (m, 1H, Ar), 8.97 (d, *J*_{HP} = 4.8 Hz, 1H, H-3).

¹³C NMR (100.62 MHz, CDCl₃): δ 24.5 (C-1), 69.7 (C-2), 126.2, 128.0, 128.1, 128.3, 128.5, 128.6, 128.7, 130.3, 132.7, 133.5, 133.6, 133.7, 133.8, 144.3, 157.6, 157.9.

³¹P NMR (162 MHz, CDCl₃): δ -13.9.

HRMS (ESI) calcd for C₂₇H₂₄NP [M + H]⁺ 394.1725, found 394.1718.

Consistent with literature values.²³²



(*R*)-1-Phenyl-*N*-(pyridin-2-ylmethylene)ethanamine 131

Yellow oil.

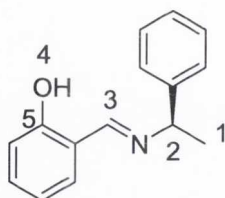
^1H NMR (400 MHz, CDCl_3): δ 1.49 (d, $J = 6.6$ Hz, 3H, H-1), 4.51 (q, $J = 6.6$ Hz, 1H, H-2), 6.98-7.17 (m, 2H), 7.17-7.27 (m, 2H), 7.29-7.39 (m, 2H), 7.49 (dd, $J = 7.6$ Hz, $J = 7.6$ Hz, 1H), 7.95 (d, $J = 7.2$ Hz, 1H, Py), 8.37 (s, 1H, H-3), 8.48 (d, 1H, $J = 4.5$ Hz, H-4).

^{13}C NMR (100MHz, CDCl_3): δ 24.2 (C-1), 69.2 (C-2), 121.0, 124.3, 126.3, 126.6, 128.1, 136.1, 144.1, 148.9 (C-4), 154.3 (C-5), 160.0 (C-3).

ν_{max} (film)/ cm^{-1} : 3059, 2971, 2926, 2860, 1645, 1586, 1467, 1436, 1370, 761.

HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{14}\text{N}_2$ $[\text{M} + \text{H}]^+$ 211.1235, found 211.1239.

Consistent with literature values.²³³



2-(((1-Phenylethyl)imino)methyl)phenol 132

Yellow oil.

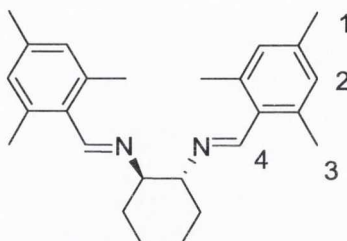
^1H NMR (400 MHz, CDCl_3): δ 1.63 (d, $J = 6.7$ Hz, 3H, H-3), 4.54 (q, $J = 6.7$ Hz, 1H, H-2), 6.87 (dd, $J = 8.0$ Hz, $J = 8.0$ Hz, 1H, Ar), 6.98 (d, $J = 8.3$ Hz, 1H, Ar), 7.17-7.24 (m, 1H, Ar), 7.25-7.41 (m, 6H, Ar), 8.40 (s, 1H, H-3), 13.58 (s, 1H, H-4).

^{13}C NMR (100.62 MHz, CDCl_3): δ 25.0 (C-1), 68.6 (C-2), 117.0, 118.7, 118.9, 126.5, 127.3, 128.7, 131.5, 132.4, 143.9, 161.1 (C-5), 163.5 (C-3).

ν_{max} (film)/ cm^{-1} : 3062, 3032, 2980, 2880, 1664, 1622, 1578, 1454.

HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{15}\text{NO}$ $[\text{M} + \text{H}]^+$ 226.1232, found 226.1234.

Consistent with literature values.²³⁴



(1*R*,2*R*)-*N,N'*-Bis(2,4,6-trimethylbenzylidene)cyclohexane-1,2-diamine 135

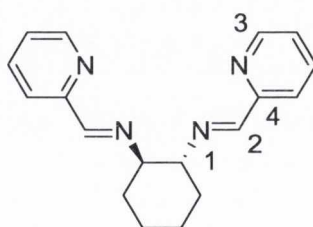
Yellow oil.

^1H NMR (400 MHz, CDCl_3): δ 1.51-1.62 (m, 2H), 1.81-1.94 (m, 6H), 2.28 (s, 6H), 2.31 (s, 12H, H-3), 3.45-3.49 (m, 2H), 6.82 (s, 4H, H-2), 8.60 (s, 2H, H-4).

^{13}C NMR (100.62 MHz, CDCl_3): δ 20.6, 21.2, 24.1, 33.1, 75.2, 128.7, 130.8, 137.4, 137.8, 159.8 (C-4).

HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{34}\text{N}_2$ $[\text{M} + \text{H}]^+$ 375.2800 found 375.2785.

Consistent with literature values.²³⁵



(1*R*,2*R*)-Bis(pyridin-2-ylmethylene)cyclohexane-1,2-diamine 136

Yellow oil.

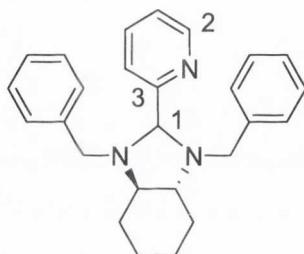
^1H NMR (400 MHz, CDCl_3): δ 1.45-1.53 (m, 2H, Cy), 1.78-1.89 (m, 6H, Cy), 3.42-3.59 (m, 2H, H-1), 7.16-7.23 (m, 2H, Py), 7.61 (dd, $J = 8.8$ Hz, $J = 8.8$ Hz, 2H, Py), 7.86 (d, $J = 7.9$ Hz, 2H, Py), 8.29 (s, 2H, H-2), 8.52 (d, $J = 4.8$ Hz, 2H, H-3).

^{13}C NMR (100.62 MHz, CDCl_3): δ 24.3, 32.7, 73.6 (C-1), 121.3, 124.5, 136.4, 149.2, 154.6 (C-4), 161.4 (C-2).

ν_{max} (film)/ cm^{-1} : 2928, 2842, 1714, 1644, 1587, 1467, 992.

HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{20}\text{N}_4$ $[\text{M} + \text{H}]^+$ 293.1766, found 293.1759.

Consistent with literature values.²³⁶



1,3-Dibenzyl-2-(pyridin-2-yl)octahydro-1H-benzoimidazole **141**

140 (246 mg, 0.84 mmol) was added to 2-pyridinecarboxaldehyde (79.5 μL , 0.84 mmol) in toluene (10 mL). The reaction mixture was stirred for 12 h at 60 $^{\circ}\text{C}$. After filtration, the solvent was evaporated under reduced pressure giving **141** as yellow oil (290 mg, 95%).

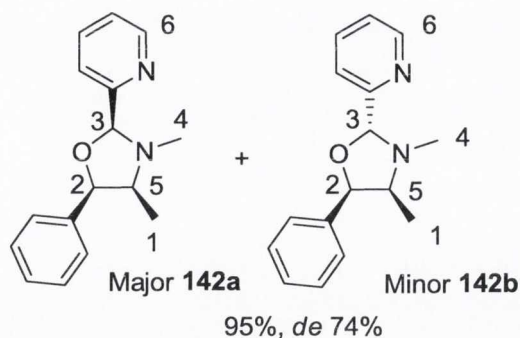
^1H NMR (400 MHz, CDCl_3): δ 1.06-1.40 (m, 4H, Cy), 1.61-1.90 (m, 4H, Cy), 2.59-2.45 (m, 1H, CHN), 3.05-2.91 (m, 1H, CHN), 3.47 (d, J = 14.5 Hz, 1H, Ph-CHH), 3.53 (d, J = 14.5 Hz, 1H, Ph-CHH), 3.80 (d, J = 13.8 Hz, 2H, Ph-CHH), 3.85 (d, J = 13.8 Hz, 2H, Ph-CHH), 4.74 (s, 1H, H-1), 7.23-7.02 (m, 11H, Ar), 7.37 (d, J = 7.8 Hz, 1H, Ar), 7.53 (td, J = 1.6, J = 7.6 Hz, 1H, Ar), 8.40 (d, J = 4.5 Hz, 1H, H-2).

^{13}C NMR (100.62 MHz, CDCl_3): δ 24.08, 24.09, 29.5, 29.8, 52.0, 56.1, 67.0, 68.4, 87.0 (C-1), 121.6, 123.6, 125.8, 126.0, 127.2, 127.3, 127.6, 128.5, 134.9, 138.8, 140.5, 147.7, 161.2 (C-3).

ν_{max} (film)/ cm^{-1} : 3027, 2929, 2857, 1637, 1588, 1452, 1434, 736.

HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{29}\text{N}_3$ $[\text{M} + \text{H}]^+$ 384.2440 found 384.2450.

Consistent with literature values.²³⁷



(2*S*,4*S*,5*R*)-3,5-Dimethyl-4-phenyl-2-(pyridin-2-yl)oxazolidine 142

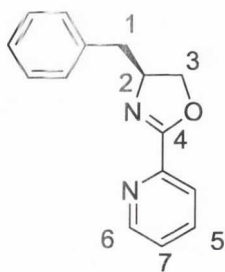
^1H NMR (400 MHz, CDCl_3): δ 0.76 (d, $J = 6.6$ Hz, 3H, H-1, Minor), 0.81 (d, $J = 6.3$ Hz, 3H, H-1, Major), 2.34 (s, 3H, H-4, Major), 2.37 (s, 3H, H-4, Minor), 3.01-3.10 (m, 1H, H-5, Major), 3.71-3.79 (m, 1H, H-5, Minor), 4.87 (s, 1H, H-3, Major), 5.23 (d, $J = 8.1$ Hz, 1H, H-2, Major), 5.44 (s, 1H, H-3, Minor), 5.65 (d, $J = 5.1$ Hz, 1H, H-2, Minor), 7.24-7.34 (m, Ar), 7.38 (dd, $J = 7.0$ Hz, $J = 15.3$ Hz), 7.50 (d, $J = 7.8$ Hz, Ar), 7.63-7.72 (m, Ar), 7.75-7.85 (m, Ar), 8.64 (d, $J = 4.8$ Hz, 1H, H-6, Minor), 8.67 (d, $J = 4.7$ Hz, 1H, H-6, Major).

^{13}C (100.62 MHz, CDCl_3): δ 8.6 (C-1, Minor), 14.4 (C-1, Major), 31.1 (C-4, Minor), 35.6 (C-4, Major), 61.1 (C-2, Minor), 63.8 (C-2, Major), 82.3 (C-5, Minor), 82.4 (C-5, Major), 95.1 (C-3, Minor), 98.4 (C-3, Major), 121.7 (Minor), 123.0 (Major), 123.4 (Minor), 125.4 (Major), 125.9 (Major), 126.9 (Major), 127.3 (Minor), 127.5 (Minor), 127.6 (Minor), 127.7 (Major), 136.4 (Minor), 136.6 (Major), 139.3 (Major), 148.5 (Minor), 148.7 (Major), 157.7 (Minor).

ν_{max} (film)/ cm^{-1} (mixture): 2969, 2846, 2795, 1713, 1591, 1502, 1456, 1437, 1059, 1038, 701.

HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}$ (mixture) $[\text{M} + \text{H}]^+$ 255.1502, found 255.1497.

Consistent with literature values.²³⁸



(S)-4-Benzyl-2-(pyridin-2-yl)-4,5-dihydrooxazole 145a

Colorless oil.

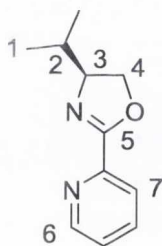
^1H NMR (400 MHz, CDCl_3): δ 2.76 (dd, $J = 9.1$ Hz, $J = 13.8$ Hz, 1H, H-1), 3.30 (dd, $J = 5.0$ Hz, $J = 13.8$ Hz, 1H, H-1), 4.23 (dd, $J = 5.4$ Hz, $J = 5.4$ Hz, 1H, H-3), 4.45 (dd, 1H, $J = 9.6$ Hz, $J = 9.6$ Hz, H-3), 4.61-4.71 (m, 1H, H-2), 7.20-7.28 (m, 3H, Ph), 7.28-7.35 (m, 2H, Ph), 7.40 (dd, $J = 4.7$ Hz, $J = 7.5$ Hz, 1H, H-7), 7.72-7.82 (m, 1H, Py), 8.06 (d, $J = 7.9$ Hz, 1H, H-5), 8.71 (d, $J = 4.7$ Hz, 1H, H-6).

^{13}C NMR (100.62 MHz, CDCl_3): δ 41.2 (C-1), 67.7 (C-2), 72.1 (C-3), 123.5, 125.2, 126.1, 128.2, 128.8, 136.21, 137.3, 146.3, 149.3, 162.7 (C-4).

ν_{max} (film)/ cm^{-1} : 3084, 2980, 2860, 1641, 1469, 1440, 1363, 1099.

HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}$ [$\text{M} + \text{H}$] $^+$ 239.1184, found 239.1189.

Consistent with literature values.²³⁹



(S)-4-Isopropyl-2-(pyridin-2-yl)-4,5-dihydrooxazole 145b

Colorless oil.

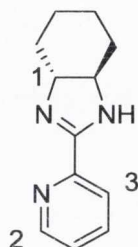
^1H NMR (400 MHz, CDCl_3): δ 0.95 (d, $J = 6.8$ Hz, 3H, H-1), 1.06 (d, $J = 6.8$ Hz, 3H, H-1), 1.89-1.95 (m, 1H, H-2), 4.13-4.25 (m, 2H, H-4), 4.48-4.52 (m, 1H, H-3), 7.37-7.42 (m, 1H, Py), 7.74-7.81 (m, 1H, Py), 8.06 (d, $J = 7.8$ Hz, 1H, H-7), 8.71 (d, $J = 4.7$ Hz, 1H, H-6).

^{13}C NMR (100.62 MHz, CDCl_3): δ 17.7 (C-1), 18.6 (C-1), 32.3 (C-2), 70.3 (C-3), 72.5 (C-4), 123.5, 125.0, 136.2, 146.4, 149.3, 162.1 (C-5).

ν_{max} (film)/ cm^{-1} : 3059, 2960, 2873, 1650, 1583, 1468, 1440, 1363, 1291, 1256, 746.

HRMS (ESI) calcd for $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}$ $[\text{M} + \text{H}]^+$ 119.1179 found, 119.1183.

Consistent with literature values.¹⁹⁰



(3*R*,7*R*)-2-(Pyridin-2-yl)- hexahydro-1*H*-benzoimidazole 146

Colorless oil.

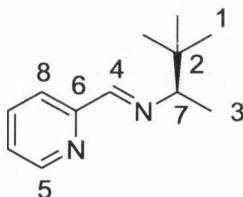
^1H NMR (400 MHz, CDCl_3): δ 1.24-1.36 (m, 2H, Cy), 1.45-1.58 (m, 2H, Cy), 1.72-1.82 (m, 2H, Cy), 2.19-2.31 (m, 2H, Cy), 3.09-3.20 (m, 2H, H-1), 7.29-7.33 (m, 1H, Py), 7.75-7.83 (m, 1H, Py), 8.13 (d, $J = 7.8$ Hz, 1H, H-3), 8.51 (d, $J = 4.6$ Hz, 1H, H-2).

^{13}C NMR (100.62 MHz, CDCl_3): δ 25.0, 30.8, 122.2, 125.3, 136.7, 148.5, 148.8, 165.3. Peak reported at 71.1 as broad not observed.²⁴⁰

ν_{max} (film)/ cm^{-1} : 3644, 3690, 3054, 2987, 1594, 1265, 896.

HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{16}\text{N}_3$ $[\text{M} + \text{H}]^+$ 202.1339, found 202.1344.

Consistent with literature values.²⁴⁰



(*S*)-3,3-Dimethyl-*N*-(pyridin-2-ylmethylene)butan-2-amine 152

Colorless oil.

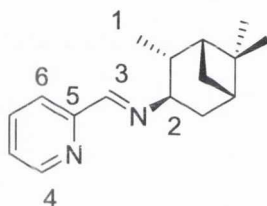
^1H NMR (400 MHz, CDCl_3): δ 0.94 (s, 9H, H-1), 1.18 (d, $J = 6.5$ Hz, 3H, H-3), 3.08 (q, $J = 6.5$ Hz, 1H, H-7), 7.30 (dd, $J = 4.8$ Hz, $J = 7.4$ Hz, 1H, Py), 7.73 (dd, $J = 7.6$ Hz, $J = 7.6$ Hz, 1H, Py), 8.06 (d, 1H, $J = 7.9$ Hz, H-8), 8.34 (s, 1H, H-4), 8.63 (d, $J = 4.8$ Hz, 1H, H-5).

^{13}C NMR (100.62 MHz, CDCl_3): δ 16.8 (C-3), 26.1 (C-1), 33.8 (C-2), 74.8 (C-7), 120.7, 124.0, 136.0, 148.8, 154.6 (C-6), 159.1 (C-4).

ν_{max} (film)/ cm^{-1} : 2964, 2905, 2869, 1648, 1588, 1568, 1436, 1364.

HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{18}\text{N}_2$ $[\text{M} + \text{H}]^+$ 191.1548, found 191.1550.

Consistent with literature values.⁶⁸



(1*R*,2*R*,3*R*,5*S*)-2,6,6-Trimethyl-*N*-(pyridin-2-ylmethylene)bicycloheptan-3-amine 153

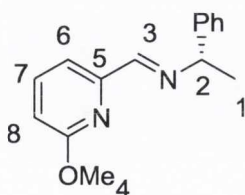
Colorless oil.

^1H NMR (400 MHz, CDCl_3): δ 1.04 (d, $J = 7.6$ Hz, 3H, H-1), 1.09 (s, 3H, CH_3), 1.27 (s, 3H, CH_3), 1.30 (s, 1H), 1.91-1.96 (m, 1H), 1.97-2.01 (m, 2H), 2.11-2.19 (m, 1H), 2.31-2.36 (m, 1H), 2.38-2.46 (m, 1H), 3.56-3.63 (m, 1H, H-2), 7.29-7.34 (m, 1H, Py), 7.34 (t, $J = 8.0$ Hz, 1H, Py), 8.06 (d, $J = 8.0$ Hz, 1H, H-6), 8.28 (s, 1H, H-3), 8.65 (d, $J = 7.8$ Hz, 1H, H-4).

^{13}C NMR (100.62 MHz, CDCl_3): δ 19.8, 23.6, 28.0, 33.8, 35.7, 38.9, 41.7, 43.3, 47.5, 70.1 (C-2), 121.6, 124.4, 136.5, 149.3, 154.9 (C-5), 158.7.

ν_{max} (film)/ cm^{-1} : 2972, 2913, 2873, 2883, 1653, 1592, 1462, 1312.

HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{22}\text{N}_2$ $[\text{M} + \text{H}]^+$ 243.1861, found 243.1850.



(*S*)-*N*-((6-Methoxypyridin-2-yl)methylene)-1-phenylethanamine 154

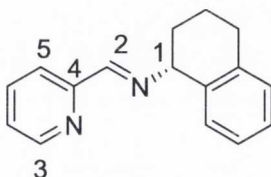
Yellow oil.

^1H NMR (400 MHz, CDCl_3): δ 1.64 (d, $J = 6.8$ Hz, 3H, H-1), 3.99 (s, 3H, H-4), 4.64 (q, $J = 6.8$ Hz, 1H, H-2), 6.79 (d, $J = 9.2$ Hz, 1H, H-8), 7.22-7.42 (m, 3H, Ar), 7.47 (d, $J = 9.2$ Hz, 2H, Ar), 7.64 (dd, $J = 8.0$ Hz, $J = 8.0$ Hz, 1H, H-7), 7.74 (d, $J = 8.0$ Hz, 1H, H-6), 8.40 (s, 1H, H-3).

^{13}C NMR (100.62 MHz, CDCl_3): δ 24.2, 29.4, 69.4, 111.5, 113.7, 126.2, 126.5, 128.0, 138.4, 144.5, 152.1 (C-5), 160.3, 163.6.

ν_{max} (film)/ cm^{-1} : 3162, 2982, 2933, 2872, 1652 1645, 1532.

HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}$ $[\text{M} + \text{H}]^+$ 241.1341, found 241.1344.



(*R*)-*N*-(Pyridin-2-ylmethylene)-1,2,3,4-tetrahydronaphthalen-1-amine 155

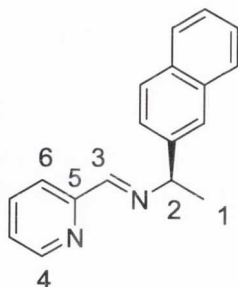
Yellow oil.

^1H NMR (400 MHz, CDCl_3): δ 1.85-1.95 (m, 1H), 2.05-2.20 (m, 3H), 2.82-3.02 (m, 2H), 4.66 (t, $J = 5.7$ Hz, 1H, H-1), 7.06 (d, $J = 6.4$ Hz, 1H), 7.12-7.22 (m, 3H), 7.3-7.37 (m, 1H), 7.76 (t, $J = 7.8$ Hz, 1H), 8.11 (d, $J = 7.6$ Hz, 1H, H-5), 8.53 (s, 1H, H-2), 8.69 (d, $J = 7.8$ Hz, 1H, H-3).

^{13}C NMR (100.62 MHz, CDCl_3): δ 19.5, 29.8, 30.9, 67.7, 121.5, 124.7, 125.5, 126.6, 128.4, 128.9, 136.1, 136.5, 149.0, 154.4 (C-4), 161.1.

ν_{max} (film)/ cm^{-1} : 3072, 2983, 2860, 1682, 1588, 1563, 1438, 1382, 1234.

HRMS (ESI) calcd for $C_{16}H_{16}N_2$ $[M + H]^+$ 237.1392, found 237.1402.



(S)-1-(Naphthalen-2-yl)-N-(pyridin-2-ylmethylene)ethanamine 156

Yellow oil.

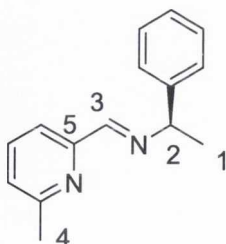
1H NMR (400 MHz, $CDCl_3$): δ 1.74 (d, J = 6.5 Hz, 3H, H-1), 4.85 (q, J = 6.5 Hz, 1H, H-2), 7.31-7.40 (m, 1H, Ar), 7.41-7.55 (m, 2H, Ar), 7.63 (d, 1H, J = 8.4 Hz, Ar), 7.78 (dd, J = 7.6 Hz, J = 7.6 Hz, 1H, Ar), 7.81-7.95 (m, 4H, Ar), 8.16 (d, 1H, J = 7.8 Hz, H-6), 8.56 (s, 1H, H-3), 8.68 (d, 1H J = 3.6 Hz, H-4).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 24.1 (C-1), 69.2 (C-2), 121.1, 124.3, 124.6, 124.8, 126.1, 127.2, 127.5, 127.7, 132.2, 133.0, 136.1, 141.5, 149.0, 154.3 (C-5), 160.2.

ν_{max} (film)/ cm^{-1} : 3048, 3009, 2979, 2966, 2924, 2858, 1648, 1599, 1567, 1436.

$[\alpha]_D^{20}$ = +68.9 (c 1.6, $CHCl_3$).

HRMS (ESI) calcd for $C_{18}H_{16}N_2$ $[M + H]^+$ 261.1392, found 261.1397.



(R)-N-((6-Methylpyridin-2-yl)methylene)-1-phenylethanamine 157

Yellow oil.

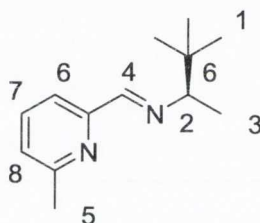
^1H NMR (400 MHz, CDCl_3): δ 1.63 (d, $J = 6.7$ Hz, 3H, H-1), 2.61 (s, 3H, H-4), 4.65 (q, $J = 6.7$ Hz, 1H, H-2), 7.20 (d, $J = 7.7$ Hz, 1H, Ar), 7.33-7.40 (m, 2H, Ar), 7.42-7.51 (m, 2H, Ar), 7.62-7.68 (m, 1H, Ar), 7.95 (d, 1H, $J = 7.7$ Hz, Ar), 8.48 (s, 1H, H-3).

^{13}C NMR (100.62 MHz, CDCl_3): δ 23.9 (C-4), 24.1 (C-1), 69.1 (CH), 117.9, 123.9, 125.4, 126.3, 126.5, 128.0, 136.3, 144.1, 153.8 (C-5), 157.5, 160.4 (C-3).

ν_{max} (film)/ cm^{-1} : 3061, 2971, 2926, 2861, 1711, 1645, 1591, 1453.

HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{16}\text{N}_2$ $[\text{M} + \text{H}]^+$ 225.1392, found 225.1395.

Consistent with literature values.⁶⁸



(*S*)-3,3-Dimethyl-*N*-((6-methylpyridin-2-yl)methylene)butan-2-amine 158

Colorless oil.

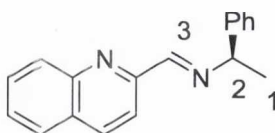
^1H NMR (400 MHz, CDCl_3): δ 0.91 (s, 9H, H-1), 1.15 (d, $J = 6.5$ Hz, 3H, H-3), 2.58 (s, 3H, H-5), 3.04 (q, $J = 6.5$ Hz, H-2), 7.14 (d, 1H, $J = 7.6$ Hz, H-6), 7.60 (dd, $J = 7.4$ Hz, $J = 7.4$ Hz, 1H, H-7), 7.87 (d, 1H, $J = 7.8$ Hz, H-6), 8.30 (s, 1H, H-4).

^{13}C NMR (100.62 MHz, CDCl_3): δ 16.8 (C-3), 23.9 (C-5), 26.2 (C-1), 33.8 (C-6), 74.8 (C-2), 117.6, 123.6, 136.3, 154.1, 157.4, 159.5.

ν_{max} (film)/ cm^{-1} : 2964, 2868, 1653, 1647, 1591, 1575, 1457, 1363, 1120, 783.

$[\alpha]_{\text{D}}^{20} = +51.1$ (c 0.6, CHCl_3).

HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{20}\text{N}_2$ $[\text{M} + \text{H}]^+$ 205.1705, found 205.1710.



(*R*)-1-Phenyl-*N*-(quinolin-2-ylmethylene)ethanamine 159

Yellow oil.

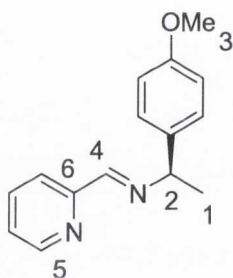
^1H NMR (400 MHz, CDCl_3): δ 1.66 (d, $J = 6.6$ Hz, 3H, H-1), 4.73 (q, $J = 6.6$ Hz, 1H, H-2), 7.25-7.30 (m, 1H, Ar), 7.38 (dd, $J = 7.0$, $J = 8.1$ Hz, 2H, Ar), 7.49 (d, $J = 7.9$ Hz, 1H, Ar), 7.57 (dd, $J = 7.1$ Hz, $J = 8.0$ Hz, 1H, Ar), 7.74 (dd, $J = 7.1$ Hz, $J = 8.3$ Hz, 1H, Ar), 7.83 (d, $J = 8.1$ Hz, 1H, Ar), 8.14 (d, $J = 8.5$ Hz, 1H, Ar), 8.21 (d, $J = 8.6$ Hz, 1H, Ar), 8.27 (d, $J = 8.6$ Hz, 1H, Ar), 8.66 (s, 1H, H-3).

^{13}C NMR (100.62 MHz, CDCl_3): δ 24.2 (C-1), 69.2 (C-2), 118.2, 126.3, 126.6, 127.0, 127.3, 128.1, 128.3, 129.1, 129.3, 136.0, 144.1, 147.3, 154.6, 160.5.

ν_{max} (film)/ cm^{-1} : 3053, 2967, 2861, 1633, 1595, 1560, 1505, 1364.

HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{16}\text{N}_2$ $[\text{M} + \text{H}]^+$ 261.1392, found 261.1388.

Consistent with literature values.²⁴¹



(*R*)-1-(4-Methoxyphenyl)-*N*-(pyridin-2-ylmethylene)ethanamine 161

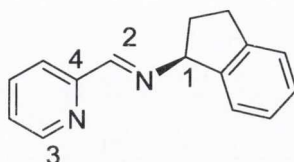
Yellow oil.

^1H NMR (400 MHz, CDCl_3): δ 1.59 (d, $J = 5.5$ Hz, 3H, H-1), 3.74 (s, 3H, H-3), 4.59 (q, $J = 5.5$ Hz, H-2), 6.87 (d, $J = 9.0$ Hz, 2H, Ar), 7.20-7.25 (m, 1H, Ar), 7.35 (d, $J = 9.0$ Hz, 2H, Ar), 7.65 (t, $J = 7.5$ Hz, 1H, Ar), 8.06 (d, $J = 7.7$ Hz, 1H, Ar), 8.45 (s, 1H, H-4), 8.60 (d, $J = 7.2$ Hz, 1H, H-5).

^{13}C NMR (100.62 MHz, CDCl_3): δ 24.1, 54.8, 68.6, 113.5, 120.9, 124.3, 126.4, 127.4, 136.1, 148.9, 154.3 (C-6), 158.2, 159.8.

ν_{max} (film)/ cm^{-1} : 3061, 2970, 2925, 2862, 1639, 1596, 1561, 1503, 1231.

HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}$ $[\text{M} + \text{H}]^+$ 241.1342, found 241.1351.



(*R*)-*N*-(Pyridin-2-ylmethylene)-2,3-dihydro-1H-inden-1-amine 162

Yellow oil.

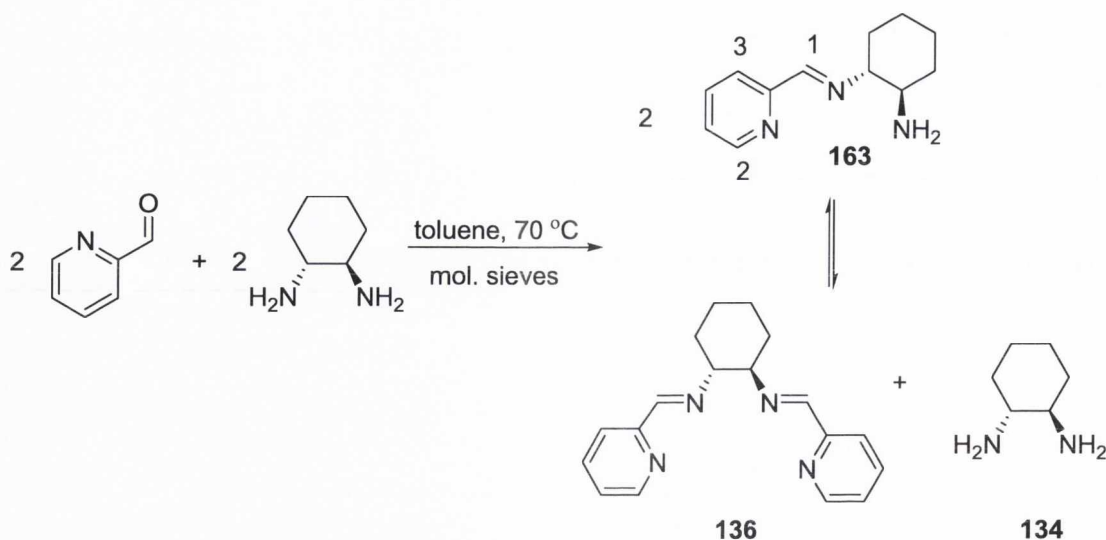
^1H NMR (400 MHz, CDCl_3): δ 2.29 (dddd, $J = 6.6$ Hz, $J = 8.0$ Hz, $J = 8.7$ Hz, $J = 12.8$ Hz, 1H, *CHH*), 2.43-2.60 (m, 1H, CH_2), 2.91-3.05 (m, 1H, CH_2), 3.16 (ddd, $J = 4.2$ Hz, $J = 8.7$ Hz, $J = 15.8$ Hz, 1H, CH_2), 5.03 (dd, $J = 7.2$ Hz, $J = 7.2$ Hz, 1H, H-1), 7.10-7.26 (m, 3H, Ar), 7.26-7.36 (m, 2H, Ar), 7.68-7.77 (m, 1H, Ar), 8.07 (dt, $J = 1.0$ Hz, $J = 8.0$, 1H, Ar), 8.55 (s, 1H, H-2), 8.66 (m, 1H, H-3).

^{13}C NMR (100.62 MHz, CDCl_3): δ 31.1, 34.1, 74.7 (C-1), 121.5, 124.4, 124.8, 124.9, 126.5, 127.8, 136.6, 143.8, 144.0, 149.4, 154.7 (C-4), 161.4.

ν_{max} (film)/ cm^{-1} : 2934, 2851, 1641, 1587, 1567, 1467, 1436.

$[\alpha]_{\text{D}}^{20} = +64.4$ (*c* 1.6, CHCl_3).

HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{14}\text{N}_2$ $[\text{M} + \text{H}]^+$ 223.1236, found 223.1242.

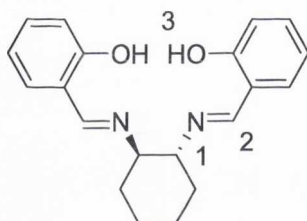


The equilibrium mixture contained monoimine **163** and bisimine **136** (with unreacted diamine **134**) in a 3:1 ratio as measured by ^1H NMR.

N-(Pyridin-2-ylmethylene)cyclohexane-1,2-diamine **163**

^1H NMR (400 MHz, CDCl_3): δ 1.11-2.01 (m, overlapping with compounds **136** and **134**, 8H, 4 x CH_2), 2.85-3.00 (m, 2H, 2 x CHN), 7.30-7.36 (m, 1H, Py), 7.75 (dd, $J = 7.6$ Hz, $J = 7.6$ Hz, 1H, Py), 7.99 (d, $J = 7.9$ Hz, 1H, H-3), 8.46 (s, 1H, H-1), 8.67 (d, 1H, $J = 4.8$ Hz, H-2). The presence of compounds **163**, **136** and **134** was confirmed by mass spectroscopy.

HRMS calcd for $\text{C}_{12}\text{H}_{17}\text{N}_3$ $[\text{M} + \text{H}]^+$ 204.1501, found 204.1512.



(1*R*,2*R*)-Cyclohexane-1,2-diylbis(azanylylidene))bis(methanylylidene)diphenol **164**

Yellow oil.

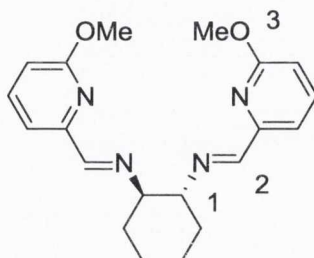
^1H NMR (400 MHz, CDCl_3): δ 1.45-2.02 (m, 8H, H-1, Cy), 3.32-3.36 (m, 2H, H-1), 6.82 (td, $J = 1.0$ Hz, $J = 7.5$ Hz, 2H, Ar), 6.92 (d, $J = 8.1$ Hz, 2H, Ar), 7.18 (dd, $J = 1.5$ Hz, $J = 7.5$ Hz, 2H, Ar), 7.27 (m, 2H, Ar), 8.29 (s, 2H, H-2), 13.37 (s, 2H, H-3).

^{13}C NMR (100.62 MHz, CDCl_3): δ 24.3, 33.0, 72.6 (C-1), 116.8, 118.6, 131.5, 132.2, 160.9, 164.8.

ν_{max} (film)/ cm^{-1} : 3052, 2930, 2858, 1735, 1627, 1579.

HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_2$ $[\text{M} + \text{H}]^+$ 323.1760, found 323.1759.

Consistent with literature values.²⁴²



(1*R*,2*R*)-*N,N'*-Bis((6-methoxypyridin-2-yl)methylene)cyclohexane-1,2-diamine 165

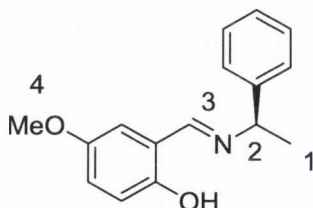
Yellow oil.

^1H NMR (400 MHz, CDCl_3): δ 1.48-1.56 (m, 2H, Cy), 1.81-1.95 (m, 6H, Cy), 3.47-3.55 (m, 2H, H-1), 3.90 (s, 6H, H-3), 6.66-6.72 (m, 2H, Py), 7.50-7.54 (m, 4H, Py), 8.26 (s, 2H, H-2).

^{13}C NMR (100.62 MHz, CDCl_3): δ 24.6, 32.8, 53.5 (C-3), 73.6 (C-1), 111.7, 113.7, 138.8, 152.4, 161.8, 163.6.

ν_{max} (film)/ cm^{-1} : 2924, 2936, 2856, 1645, 1589, 1574.

HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{24}\text{N}_4\text{O}_2$ $[\text{M} + \text{H}]^+$ 353.1978, found 353.1976.



4-Methoxy-2-(((1-phenylethyl)imino)methyl)phenol 172

Yellow oil.

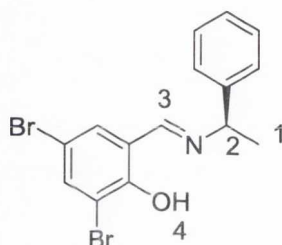
^1H NMR (400 MHz, CDCl_3): δ 1.66 (d, 3H, $J = 6.7$ Hz, H-1), 3.80 (s, 3H, H-4), 4.58 (q, 1H, $J = 6.7$ Hz, H-2), 6.80 (d, 1H, $J = 2.6$ Hz, Ar), 6.92-6.99 (m, 2H, Ar), 7.26-7.34 (m, 1H, Ph), 7.35-7.43 (m, 4H, Ph), 8.40 (s, 1H, H-3).

^{13}C NMR (100.62 MHz, CDCl_3): δ 24.6 (C-1), 55.5 (C-4), 68.2 (C-2), 114.5, 117.2, 118.0, 118.8, 126.0, 126.8, 128.2, 143.3, 151.5, 154.7, 162.7.

ν_{max} (film)/ cm^{-1} : 3032, 2973, 2930, 2899, 1630, 1584, 1490.

HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{17}\text{O}_2\text{N}$ $[\text{M} + \text{H}]^+$ 256.1338, found 256.1346.

Consistent with literature values.²⁴³



2,4-Dibromo-6-(((1-phenylethyl)imino)methyl)phenol 173

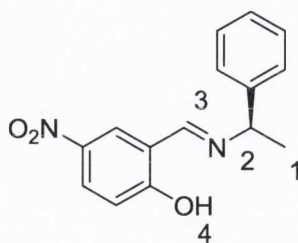
Yellow oil.

^1H NMR (400 MHz, CDCl_3): δ 1.68 (d, $J = 6.5$ Hz, 3H, H-1), 4.66 (q, $J = 6.5$ Hz, 1H, H-2), 7.29-7.42 (m, 6H, Ar), 7.71 (d, $J = 2.2$ Hz, 1H, Ar), 8.27 (s, 1H, H-3), 14.9 (s, 1H, H-4).

^{13}C NMR (100.62 MHz, CDCl_3): δ 24.5 (C-1), 67.5 (C-2), 109.1, 112.7, 119.9, 126.5, 127.8, 129.0, 132.9, 137.7, 142.4, 158.7, 161.7 (C-3).

ν_{max} (film)/ cm^{-1} : 3052, 3028, 2972, 2868, 1628, 1492.

HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{13}\text{Br}_2\text{NO}$ $[\text{M} + \text{H}]^+$ 381.9442, found 381.9446.



4-Nitro-2-(((1-phenylethyl)imino)methyl)phenol 174

Yellow oil.

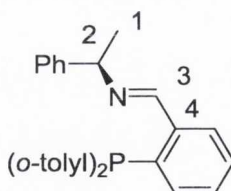
^1H NMR (400 MHz, CDCl_3): δ 1.73 (d, $J = 6.6$ Hz, 3H, H-1), 4.72 (q, $J = 6.6$ Hz, 1H, H-2), 7.01 (d, $J = 9.1$ Hz, 1H, Ar), 7.31-7.51 (m, 5H, Ar), 8.18-8.30 (m, 2H, Ar), 8.43 (s, 1H, H-3), 14.93 (s, 1H, H-4).

^{13}C NMR (100.62 MHz, CDCl_3): δ 23.7 (C-1), 66.7 (C-2), 116.5, 118.4, 126.0, 127.5, 127.75, 127.80, 128.6, 138.5, 141.5, 161.9, 168.4.

ν_{max} (film)/ cm^{-1} : 2971, 1739, 1633, 1481, 1353.

HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}_3$ $[\text{M} + \text{H}]^+$ 255.1134, found 255.1143.

Consistent with literature values.²³⁴



N-(2-(Di-*o*-tolylphosphino)benzylidene)-1-phenylethanamine 175

Yellow oil.

^1H NMR (400 MHz, CDCl_3): δ 1.42 (d, $J = 6.6$ Hz, 3H, H-1), 2.44 (d, $J = 13.8$ Hz, 6H, tolyl), 4.46 (q, $J = 6.6$ Hz, 1H, H-2), 6.81 (dd, $J = 6.6$ Hz, $J = 11.1$ Hz, 2H, Ar), 6.87 (dd, $J = 4.6$ Hz, $J = 6.8$ Hz, 1H, Ar), 7.16-7.05 (m, 3H, Ar), 7.34-7.17 (m, 9H, Ar), 7.43 (dd, $J = 7.5$ Hz, $J = 7.5$ Hz, 1H, Ar), 8.15-8.07 (m, 1H, Ar), 8.98 (d, $J_{\text{HP}} = 5.1$ Hz, 1H, H-3).

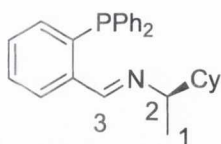
^{13}C NMR (100.62 MHz, CDCl_3): δ 21.3 (d, $J_{\text{CP}} = 21.7$ Hz, tolyl CH_3), 24.4 (C-1), 69.5 (C-2), 126.3, 126.6, 127.8 (d, $J_{\text{CP}} = 4.2$ Hz), 128.3, 128.82, 128.86, 128.9, 130.07 (d, $J_{\text{CP}} = 1.7$

Hz), 130.1 (d, $J = 1.9$ Hz), 130.3, 133.3, 133.5, 133.7, 134.3 (d, $J_{\text{CP}} = 10.3$ Hz), 134.5 (d, $J_{\text{CP}} = 9.9$ Hz), 136.0 (d, $J_{\text{CP}} = 17.5$ Hz), 140.0 (d, $J_{\text{CP}} = 17.6$ Hz), 142.3 (d, $J_{\text{CP}} = 7.5$ Hz, tolyl C-CH₃), 142.6 (d, $J_{\text{CP}} = 7.2$ Hz, tolyl C-CH₃), 144.7, 158.3 (d, $J_{\text{CP}} = 22.8$ Hz, C-3).

^{31}P NMR (162 MHz, CDCl₃): δ -28.5.

ν_{max} (film)/cm⁻¹: 2967, 2923, 1634, 1451, 1376, 908.

HRMS calcd for C₂₉H₂₈NP [M + H]⁺ 422.2038, found 422.2031.



Yellow oil.

(*R*)-1-Cyclohexyl-*N*-(2-(diphenylphosphino)benzylidene)ethanamine 176

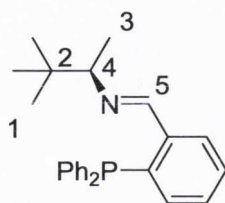
^1H NMR (400 MHz, CDCl₃): δ 0.53-0.70 (m, 1H, Cy), 0.73-0.90 (m, 1H, Cy), 1.03 (d, $J = 6.0$ Hz, 3H, H-1), 1.06-1.49 (m, 5H, Cy), 1.51-1.64 (m, 2H, Cy), 1.64-1.79 (m, 2H, Cy), 2.89 (dq, $J = 4.2$ Hz, $J = 6.0$ Hz, 1H, H-2), 6.86 (dd, $J = 6.2$ Hz, $J = 6.2$ Hz, 2H, Ar), 7.21-7.47 (m, 12H, Ar), 7.99 (dd, $J = 3.9$ Hz, $J = 7.5$ Hz, 1H, Ar), 8.82 (d, $J_{\text{HP}} = 4.6$ Hz, 1H, H-3).

^{13}C NMR (100.62 MHz, CDCl₃): δ 19.3 (C-1), 25.7 (Cy), 25.9 (Cy), 26.1 (Cy), 29.2 (Cy), 43.0 (Cy), 71.5 (C-2), 127.2 (d, $J_{\text{CP}} = 4.1$ Hz), 128.1 (d, $J_{\text{CP}} = 7.3$ Hz), 128.35, 128.38, 129.4, 132.4, 133.6 (d, $J_{\text{CP}} = 3.8$ Hz), 133.6 (d, $J_{\text{CP}} = 3.8$ Hz), 135.9 (d, $J_{\text{CP}} = 9.6$ Hz), 136.6 (d, $J_{\text{CP}} = 18.3$ Hz), 139.3 (d, $J_{\text{CP}} = 16.7$ Hz), 156.9 (d, $J_{\text{CP}} = 21.6$ Hz, C-3).

^{31}P NMR (162 MHz, CDCl₃): δ -12.4.

ν_{max} (film)/cm⁻¹: 3052, 2921, 2849, 1635, 1448, 1434.

HRMS (ESI) calcd for C₂₇H₃₀NP [M + H]⁺ 400.2194, found 400.2183.



***N*-(2-(Diphenylphosphino)benzylidene)-3,3-dimethylbutan-2-amine 177**

Yellow oil.

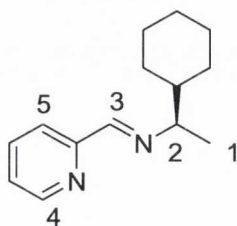
^1H NMR (400 MHz, CDCl_3): δ 0.85 (s, 9H, H-1), 0.91 (d, $J = 6.5$ Hz, 3H, H-3), 2.87 (q, $J = 6.5$ Hz, 1H, H-4), 6.88 (ddd, $J = 1.4$ Hz, $J = 4.8$ Hz, $J = 7.6$ Hz, 1H, Ar), 7.24-7.39 (m, 10H, Ar), 7.42 (dd, $J = 7.5$ Hz, 1H, Ar), 8.03 (ddd, 1H, $J = 1.4$ Hz, $J = 4.0$ Hz, $J = 7.6$ Hz, 1H, Ar), 8.83 (d, $J = 4.8$ Hz, 1H, H-5).

^{13}C NMR (100.62 MHz, CDCl_3): δ 17.1 (C-3), 26.6 (C-1), 34.2 (C-2), 75.7 (C-4), 127.8 (d, $J_{\text{CP}} = 4.2$ Hz, Ar), 128.5, 128.6, 128.9, 129.8, 133.0, 134.0, 134.1, 134.2, 134.3, 136.5 (d, $J_{\text{CP}} = 9.5$ Hz, Ar), 136.7 (d, $J_{\text{CP}} = 9.8$ Hz, Ar), 137.1 (d, $J_{\text{CP}} = 19.3$ Hz, Ar), 139.8 (d, $J_{\text{CP}} = 16.9$ Hz, Ar), 157.3 (d, $J_{\text{CP}} = 20.5$ Hz, H-5).

^{31}P NMR (162 MHz, CDCl_3): δ -12.9.

ν_{max} (film)/ cm^{-1} : 3053, 2968, 2864, 1739, 1637, 1433, 1368.

HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{28}\text{NP}$ $[\text{M} + \text{H}]^+$ 374.2038, found 374.2033.



***(R)*-1-Cyclohexyl-*N*-(pyridin-2-ylmethylene)ethanamine 188**

Colorless oil.

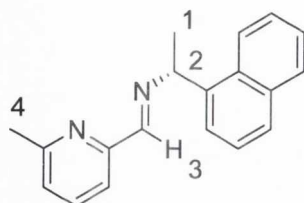
^1H NMR (400 MHz, CDCl_3): δ 0.82-1.92 (m, 14H, Cy and H-1), 3.13 (dq, $J = 3.1$ Hz, $J = 6.0$ Hz, 1H, H-2), 7.31 (m, 1H, Py), 7.74 (d, $J = 8.0$ Hz, 1H, H-5), 8.03 (dd, $J = 8.0$ Hz, $J = 8.0$ Hz, 1H, Py), 8.33 (s, 1H, H-3), 8.65 (d, $J = 7.9$ Hz, 1H, H-4).

^{13}C NMR (100.62 MHz, CDCl_3): δ 19.4 (C-1), 25.8, 25.9, 26.1, 29.3, 29.5, 43.2, 71.3 (C-2), 121.0, 124.7, 136.2, 148.9, 154.3 (C-4), 159.5 (C-3).

ν_{max} (film)/ cm^{-1} : 3023, 2922, 2851, 1646, 1587, 1567.

HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{20}\text{N}_2$ $[\text{M} + \text{H}]^+$ 217.1705, found 217.1708.

Consistent with literature values.²³³



(*R*)-*N*-((6-Methylpyridin-2-yl)methylene)-1-(naphthalen-1-yl)ethanamine 191

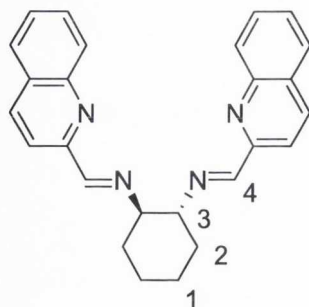
Yellow oil.

^1H NMR (400 MHz, CDCl_3): δ 1.78 (d, $J = 8.0$ Hz, 3H, H-1), 2.60 (s, 3H, H-4), 5.48 (q, $J = 8.1$ Hz, 1H, H-2), 7.19 (d, $J = 5.0$ Hz, 1H, Ar), 7.52-7.58 (m, 2H, Ar), 7.66 (t, $J = 7.8$ Hz, 1H, Ar), 7.82 (t, $J = 7.9$ Hz, 3H, Ar), 7.89 (d, $J = 7.9$ Hz, 1H, Ar), 7.99 (d, $J = 8$ Hz, 1H, Ar), 8.27 (d, $J = 8$ Hz, 1H, Ar), 8.53 (s, 1H, H-3).

^{13}C NMR (100.62 MHz, CDCl_3): 23.4 (CH_3), 23.7 (CH_3), 65 (C-2), 119.4, 123, 123.8, 124, 125.5, 125.7, 126, 128.6, 128.7, 128.2, 129.2, 136.8, 137, 134, 140, 161 (C-3).

ν_{max} (film)/ cm^{-1} : 3052, 3012, 2983, 2961, 2932, 2858, 1648, 1591, 1568.

HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{18}\text{N}_2$ $[\text{M} + \text{H}]^+$ 275.1548, found 275.1552.



(1*R*,2*R*)-*N,N*-Bis(quinolin-2-ylmethylene)cyclohexane-1,2-diamine 194

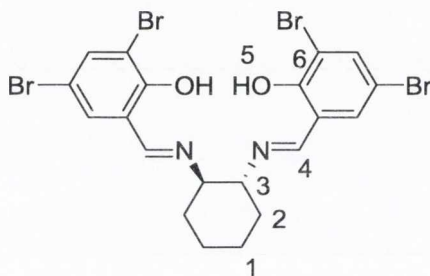
Yellow oil.

^1H NMR (400 MHz, CDCl_3): δ 1.54-1.62 (m, 2H, H-1), 1.85-1.98 (m, 6H, H-1, H-2), 3.66-3.71 (m, 2H, H-3), 7.47 (t, $J = 7.9$ Hz, 2H, Ar), 7.65 (t, $J = 7.8$ Hz, 2H, Ar), 7.72 (d, $J = 7.9$ Hz, 2H, Ar), 8.04 (d, $J = 7.8$ Hz, 2H, Ar), 8.06 (d, $J = 8.5$ Hz, 2H, Ar), 8.10 (d, $J = 8.5$ Hz, 2H, Ar), 8.55 (s, 2H, H-4).

^{13}C NMR (100.62 MHz, CDCl_3): δ 24.3 (C-1), 32.8 (C-2), 73.9 (C-3), 118.6, 127.2, 127.6, 128.4, 129.4, 129.6, 136.4, 147.7, 154.9, 162.0.

HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{24}\text{N}_2$ $[\text{M} + \text{H}]^+$ 393.2079, found 393.2086.

Consistent with literature values.²⁴⁴



(1*R*,2*R*)-Cyclohexane-1,2-diylbis(azanylylidene)bis(methanylylidene)bis(2,4-dibromophenol) 195

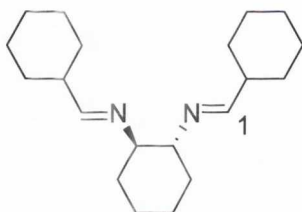
Yellow oil.

^1H NMR (400 MHz, CDCl_3): δ 1.46-1.53 (m, 2H, H-1), 1.61-1.67 (m, 2H, Cy), 1.92-2.00 (m, 4H, Cy), 3.34-3.39 (m, 2H, H-3), 7.25 (d, $J = 2.3$ Hz, 2H, Ar), 7.64 (d, $J = 2.3$ Hz, 2H, Ar), 8.16 (s, 1H, H-4), 14.36 (s, 2H, H-5).

^{13}C NMR (100.62 MHz, CDCl_3): δ 23.9 (C-1), 32.9 (C-2), 72.0 (C-3), 109.8, 112.1, 119.7, 132.9, 137.7, 157.8, 163.3 (C-4).

HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{18}\text{Br}_4\text{N}_2\text{O}_2$ $[\text{M} + \text{H}]^+$ 634.8180, found 634.8193.

Consistent with literature values.²⁴⁵



(1*R*,2*R*)-*N,N'*-Bis(cyclohexylmethylene)cyclohexane-1,2-diamine 196

Colorless oil.

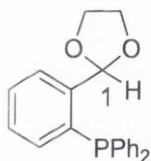
^1H NMR (400 MHz, CDCl_3): δ 1.16-1.52 (m, 14H, Cy), 1.60-1.88 (m, 16H, Cy), 2.14-2.17 (m, 2H, Cy), 3.04-3.13 (m, 2H, Cy), 7.50 (d, $J = 5.6$ Hz, 2H, H-1).

^{13}C NMR (100.62 MHz, CDCl_3): δ 24.9, 25.0, 25.5, 29.7, 32.7, 42.9, 73.1 (C-1), 168.3 (C-2).

HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{34}\text{N}_2$ $[\text{M} + \text{H}]^+$ 303.2800 found 303.2805.

Consistent with literature values.²⁴⁶

4.2.3 Synthesis of building blocks and ligands



(2-(1,3-Dioxolan-2-yl)phenyl)diphenylphosphine 128a

Synthesised according to a literature procedure.²⁴⁷

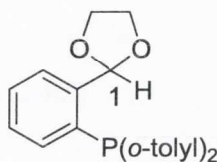
Dry THF (10 mL) was added to magnesium (795 mg, 32.8 mmol), and heated to reflux under N_2 . One chip of iodine was added, followed by a dropwise addition of 2-(2-bromophenyl)-1,3-dioxolane (3.25 mL, 21.9 mmol) in dry THF (32 mL). The reaction mixture was then stirred at reflux for 1 h under N_2 . The mixture was allowed to cool to rt, and added via syringe to a solution of chlorodiphenylphosphine (4.00 mL, 21.9 mmol) in

dry THF (20 mL) at 0 °C under N₂. The reaction mixture was heated to 50 °C for 15 h. After cooling to rt a few drops of 1M H₂SO₄ was added, and the reaction mixture was diluted with diethyl ether (50 mL). The organic layer was washed with an equal volume of H₂O, followed by an equal volume of brine, dried over H₂SO₄ and the solvents were evaporated under reduced pressure. The resulting residue was purified by flash chromatography using hexane/EtOAc (95:5), giving **128a** as a white solid (1.32 g, 21%).

¹H NMR (400 MHz, CDCl₃): δ 4.01 (t, *J* = 6.8 Hz, 2H, OCH₂), 4.12 (t, *J* = 6.8 Hz, 2H, OCH₂), 6.53 (d, *J*_{HP} = 5.0 Hz, 1H, H-1), 7.03 (m, 1H, Ar), 7.23 (m, 1H, Ar), 7.34 (m, 1H, Ar), 7.72 (m, 1H, Ar).

³¹P NMR (162 MHz, CDCl₃): δ -15.2.

Consistent with literature values.²⁴⁸



(2-(1,3-Dioxolan-2-yl)phenyl)di-*o*-tolylphosphine **128b**

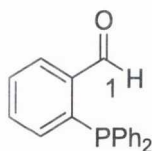
Synthesised according to a literature procedure.²⁴⁷

Dry THF (4.5 mL) was added to magnesium (291 mg, 12.0 mmol), and heated to reflux under N₂. One chip of iodine was added, followed by a dropwise addition of a solution of 2-(2-bromophenyl)-1,3-dioxolane (1.19 mL, 7.99 mmol) in dry THF (8 mL). The reaction mixture was then stirred at reflux for 1 h. The mixture was allowed to cool to rt, and added *via* syringe to a solution of chlorodi(*o*-tolyl)phosphine (1.77 g, 8.04 mmol) in dry THF (8 mL) at 0 °C under N₂. The reaction mixture was heated to 50 °C for 15 h. After cooling to room a few drops of 1M H₂SO₄ was added, and the reaction mixture was diluted with diethyl ether (30 mL). The organic layer was washed with an equal volume of H₂O, followed by an equal volume of brine, dried over Na₂SO₄ and the solvents were evaporated under reduced pressure. The resulting residue was purified by flash chromatography using hexane/EtOAc (95:5), giving **128b** as a white solid (0.55 g, 18%).

^1H NMR (400 MHz, CDCl_3): δ 2.39 (s, 6H, Me), 3.98 (t, $J = 7.2$ Hz, 2H, OCH_2), 4.11 (t, $J = 7.2$ Hz, 2H, OCH_2), 6.45 (d, $J_{\text{HP}} = 3$ Hz, 1H, H-1), 6.72 (m, 2H, Ar), 6.88 (m, 1H, Ar), 7.09 (m, 2H, Ar), 7.22-7.31 (m, 5H, Ar), 7.40-7.49 (m, 1H, Ar), 7.7 (m, 1H, Ar).

^{31}P NMR (162 MHz, CDCl_3): δ -31.81.

Consistent with literature values.²⁴⁷



2-(Diphenylphosphino)benzaldehyde **129a**

Synthesised according to a literature procedure.²⁴⁹

(2-(1,3-dioxolan-2-yl)phenyl)diphenylphosphino **128a** (1.88 g, 5.60 mmol) was dissolved in acetone (90 mL). H_2O (2 mL) and a catalytic amount of *p*-toluenesulfonic acid (48.2 mg, 5 mol%) were added and the reaction mixture was heated to 60 °C for 15 h under N_2 . H_2O (30 mL) and Et_2O (30 mL) were added and the layers were separated. The organic layer was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The resulting residue was purified by flash chromatography using hexane/ EtOAc (95:5) giving **129a** as a yellow solid (1.38 g, 85%). M.p. 115-116 °C.

^1H NMR (400 MHz, CDCl_3): δ 6.97 (m, 1H, Ar), 7.27 (m, 5H, Ar), 7.34 (m, 5H, Ar), 7.45 (m, 2H, Ar), 7.97 (m, 1H, Ar), 10.51 (d, $J_{\text{HP}} = 4.2$ Hz, 1H, H-1).

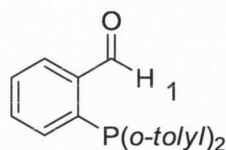
^{13}C NMR (100.61 MHz, CDCl_3): δ 128.7, 128.8, 130.6, 130.7, 132.4, 133.7, 134.2, 136.1, 136.2, 138.4, 138.5, 139.1, 141.1, 141.3, 191.8 (C-1).

^{31}P NMR (162 MHz, CDCl_3): δ -11.6.

ν_{max} (film)/ cm^{-1} : 3008, 2952, 1745, 1429, 1356.

HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{15}\text{OP}$ $[\text{M} + \text{H}]^+$ 291.0939, found 291.0936.

Consistent with literature values.²⁵⁰



2-(Di-*o*-tolylphosphino)benzaldehyde **129b**

Synthesised according to a literature procedure.²⁴⁹

(2-(1,3-dioxolan-2-yl)phenyl)di-*o*-tolylphosphine **128b** (1.33 g, 4.57 mmol) was dissolved in acetone (65 mL). H₂O (1.5 mL) and a catalytic amount of *p*-toluenesulfonic acid (39.3 mg, 5 mol%) were added and the reaction mixture was heated to 60 °C for 15 h under N₂. H₂O (50 mL) and Et₂O (50 mL) were added and the layers were separated. The organic layer was dried over Na₂SO₄ and the solvent was evaporated under reduced pressure. The resulting residue was purified by flash chromatography using hexane/EtOAc (95:5), giving **129b** as a yellow solid (1.03 g, 71%). M.p. 116-117°C.

¹H NMR (400 MHz, CDCl₃): δ 2.43 (s, 6H, Me), 6.69-6.76 (m, 2H, Ar), 6.92-6.99 (m, 1H, Ar), 7.06-7.15 (m, 2H, Ar), 7.23-7.33 (m, 4H, Ar), 7.45-7.55 (m, 2H, Ar), 7.99-8.06 (m, 1H, Ar), 10.59 (d, *J*_{HP} = 5.1 Hz, 1H, H-1).

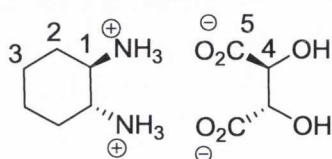
¹³C NMR (100.61 MHz, CDCl₃): δ 21.2, 21.4, 126.3, 128.9, 129.2, 129.8, 129.9, 130.2, 130.3, 133.5, 133.9, 134.1, 134.2, 138.8, 138.9, 140.0, 140.2, 142.5, 142.8, 191.9, 196.6.

³¹P NMR (162 MHz, CDCl₃): δ -28.2.

ν_{max} (film)/cm⁻¹: 3016, 2946, 1755, 1435, 1366.

HRMS (ESI) calcd for C₂₂H₁₉OP [M + H]⁺ 319.1252, found 319.1257.

Consistent with literature values.²⁴⁷



(1*R*,2*R*)-Cyclohexane-1,2-diamine 2,3-dihydroxysuccinate salt **133**

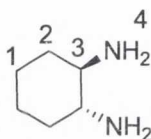
Synthesised according to a literature procedure.²⁵¹

A mixture of *trans* and *cis* 1,2 cyclohexane diamine (24.4 mL, 203 mmol) was added dropwise to a stirred solution of D-tartaric acid (15.01 g, 100 mmol) in water (25 mL). Then, AcOH (3 mL) was added dropwise. The solution was allowed to cool to 5 °C over 4 h. The solid was filtered and washed with cold water (≤ 5 °C, 10 mL) and MeOH (3 x 10 mL). The resulting white solid was dried under reduced pressure to give **133** as a white crystalline solid (12.7 g, 24 %).

¹H NMR (400 MHz, D₂O): δ 1.23-1.32 (m, 2H, H-3), 1.41-4.46 (m, 2H, H-3), 1.71-1.78 (m, 2H, H-2), 1.96-2.09 (m, 2H, H-2), 3.24-3.28 (m, 2H, H-1), 4.23 (s, 2H, H-4).

¹³C NMR (100.61 MHz, D₂O): δ 22.9, 29.5, 52.4, 73.8 (C-4), 178.5 (C-5).

Consistent with literature values.²⁵¹



(1*R*,2*R*)-*N,N*-Dimethylcyclohexane-1,2-diamine **134**

Synthesised according to a literature procedure.²⁵²

NaOH (2.18 g, 54.6 mmol) in a mixture of H₂O (15 mL) and brine (15 mL) was added dropwise to a suspension of **133** (6.01 g, 22.7 mmol) in DCM (60 mL) at rt. The mixture was stirred for 30 min. The organic layer was separated and the aqueous layer extracted with DCM (4 x 45 mL). The combined organic layers were dried over Na₂SO₄, and the solvent was evaporated under reduced pressure to give **134** as a white solid (1.20 g, 46 %).

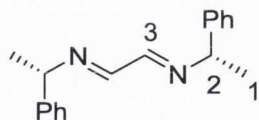
¹H NMR (400 MHz, CDCl₃): δ 1.02-1.17 (m, 2H, H-1), 1.23-1.32 (m, 2H, H-1), 1.37-1.53 (s, 4H, H-4), 1.62-1.76 (m, 2H, H-2), 1.79-1.89 (m, 2H, H-2), 2.20-2.30 (m, 2H, H-3).

¹³C NMR (100.61 MHz, CDCl₃): δ 24.98 (C-1), 35.00 (C-2), 57.17 (C-3).

ν_{max} (film)/cm⁻¹: 2928, 2858, 1579, 1265, 1083.

$[\alpha]_{\text{D}}^{20} = -29.1$ (*c* 8, HCl 2 M); lit.²⁵³ $[\alpha]_{\text{D}}^{20} = -29.7$ (*c* 5, HCl)

Consistent with literature values.²⁵⁴



(1*S*,1'*S*)-*N,N*-(Ethane-1,2-diylidene)bis(1-phenylethanamine) 137

Synthesised according to a literature procedure.²⁵⁵

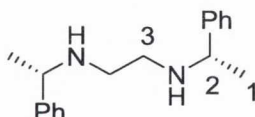
Glyoxal solution (40 wt% in water, 3.40 mL, 30 mmol) was added dropwise over 15 minutes to a solution of (*S*)-(-)-methylbenzylamine (7.72 mL, 60 mmol) in toluene (6 mL) at 0 °C. The resulting suspension was then stirred for 3 h at rt. Water (5 mL) and diethyl ether (15 mL) were then added and the layers were separated. The aqueous layer was washed with a further 100 mL of ether. The organic layers were dried over MgSO₄ and the solvents were removed under reduced pressure giving the **137** as a yellow oil (7.45 g, 94%).

¹H NMR (400 MHz, CDCl₃): δ 1.62 (d, 6H, *J* = 6.8 Hz, H-1), 4.52 (q, 2H, *J* = 6.9 Hz, H-2), 7.23-7.52 (m, 10H, Ph), 8.05 (s, 2H, H-3).

¹³C NMR (100.61 MHz, CDCl₃): δ 25.2 (C-1), 69.9 (C-2), 127.8, 128.2, 129.4, 161.2 (C-3).

ν_{max} (film)/cm⁻¹: 2978, 2953, 1643, 1585, 1556.

Consistent with literature values.²⁵⁵



***N,N*-Bis((*S*)-1-phenylethyl)ethane-1,2-diamine 138**

Bisimine **137** (6.86 g, 26 mmol) was then dissolved in 9 mL of MeOH. NaBH₄ (2.32 g, 66 mmol) was then added slowly to the reaction. The reaction was then stirred for 60 h at rt. The solvent was then removed under reduced pressure. Water (15 mL x 2) and DCM (30 mL x 2) were then added and the layers were separated. The organic layer was then dried

over MgSO_4 and the solvent removed under reduced pressure. The product was distilled under reduced pressure giving **138** as a colorless oil (5.44 g, 78%). B.p. = 70 °C, 0.1 mbar.

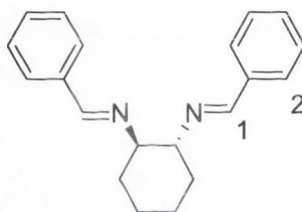
^1H NMR (400 MHz, CDCl_3): δ 1.35 (d, 6H, J = 6.8 Hz, CH_3), 2.55 (q, 4H, J = 7 Hz, CH_2), 3.72 (q, 2H, J = 6.8 Hz, CH), 7.25-7.45 (m, 10H, Ph).

^{13}C NMR (100.62 MHz, CDCl_3): δ 145.7, 128.7, 127, 126.5 (Ph), 58 (CH), 47.5 (CH_2), 24.9 (CH_3).

ν_{max} (film)/ cm^{-1} : 3309, 3032, 2924, 1618, 1402.

HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{24}\text{N}_2$ $[\text{M} + \text{H}]^+$ 269.2009, found 269.2018.

Consistent with literature values.²⁵⁶



(1*R*,2*R*)-*N,N'*-Dibenzylidenecyclohexane-1,2-diamine **139**

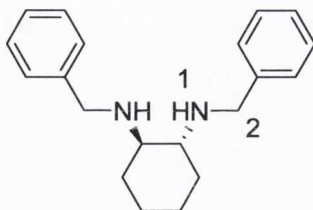
134 (758 mg, 6.64 mmol) was added to benzaldehyde (1.34 mL, 13.3 mmol) in toluene (15 mL). The reaction mixture was stirred 12 h at 60 °C. After filtration, the solvent was evaporated under reduced pressure giving **139** as yellow oil (1.83 g, 95%).

^1H NMR (400 MHz, CDCl_3): δ 1.48-1.51 (m, 4H, Cy), 1.86-1.91 (m, 6H, Cy), 7.32-7.36 (m, 6H, Ar), 7.58-7.64 (m, 4H, H-2), 8.24 (s, 2H, H-1).

^{13}C NMR (100.62 MHz, CDCl_3): δ 24.1, 32.5, 73.4, 127.4, 127.9, 129.7, 135.9, 160.6.

ν_{max} (film)/ cm^{-1} : 2932, 2853, 1711, 1622, 1503.

Consistent with literature values.²⁵⁷



(1*R*,2*R*)-*N,N'*-Dibenzylcyclohexane-1,2-diamine **140**

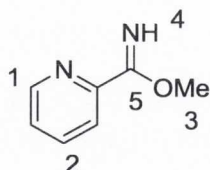
NaBH₄ (370 mg, 9.67 mmol) was added to a stirred solution of **139** (1.08 g, 3.72 mmol) in MeOH (25 mL). The mixture was stirred rt for 1h. The solvent was evaporated under reduced pressure. The residue was dissolved in EtOAc (20 mL) and the solution was washed with H₂O (3 x 50 mL). The organic layer was dried over MgSO₄ and the solvent was evaporated under reduce pressure giving **140** as an orange solid (985 mg, 90%).

¹H NMR (400 MHz, CDCl₃): δ 1.14-1.17 (m, 2H, Cy), 1.23-1.27 (m, 2H, Cy), 1.70-1.74 (m, 2H, Cy), 2.01 (s, 2H, H-1), 2.16-2.19 (m, 2H, Cy), 2.25-2.29 (m, 2H, Cy), 3.65 (d, *J* = 12.9 Hz, 2H, H-2), 3.89 (d, *J* = 12.9, 2H, H-2), 7.31-7.35 (m, 10 H, Ar).

¹³C NMR (100.62 MHz, CDCl₃): δ 24.7, 31.5, 50.6, 60.8, 126.3, 127.9, 128.0, 141.3.

ν_{max} (film)/cm⁻¹: 3314, 3045, 2912, 1622, 1495.

Consistent with literature values.¹⁸¹



Methyl picolinimidate **143**

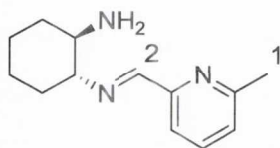
Synthesised according to a literature procedure.²⁵⁸

Sodium (86 mg, 3.74 mmol) was carefully dissolved in 15 mL of MeOH. 2-Cyanopyridine (2.00 g, 19.22 mmol) in 6 mL of toluene was added dropwise to the methoxide solution. After stirring the solution for 2 h at rt, glacial AcOH (0.25 mL, 4.30 mmol) was added to the reaction. The solvent was then evaporated under reduced pressure to give an orange liquid. The product was then distilled under reduced pressure to give **143** (1.88 g, 72%) as a colourless liquid. B.p. = 58 °C, 0.05 mbar.

^1H NMR (400 MHz, CDCl_3): δ 3.69 (s, 3H, H-5), 7.01-7.08 (m, 1H, Ar), 7.42-7.48 (m, 1H, Ar), 7.48-7.53 (m, 1H, H-2), 8.31 (dd, $J = 0.8$ Hz, $J = 5.3$ Hz, 1H, H-1), 9.10 (s, 1H, H-4).

^{13}C NMR (100.61 MHz, CDCl_3): δ 53.4 (C-3), 120.6, 124.9, 136.8 (C-2), 146.9, 148.7, 166.3 (C-5).

Consistent with literature values.²⁵⁸



(1R,2R)-N-((6-Methylpyridin-2-yl)methylene)cyclohexane-1,2-diamine **166**

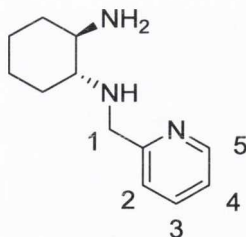
Synthesised according to a literature procedure.²⁵⁹

168 (0.15 g, 1.05 mmol) was dissolved in a mixture of MeOH/EtOH (1:1) (15 mL). Under stirring, 6-methyl-2-pyridine carboxaldehyde (227 mg, 1.05 mmol) and 3 Å molecular sieves were added. The mixture was stirred for 24 h at 40 °C. After filtration and evaporation of the solvents under vacuum, the resulting oil was dissolved in DCM (15 mL). TEA was added (0.15 mL, 1.05 mmol) and the solution was stirred for 30 min at rt. After filtration, the solvent was evaporated under reduced pressure giving **166** as an orange oil (360 mg, 81 %).

^1H NMR (400 MHz, CDCl_3): δ 1.04-1.15 (m, 1H, Cy), 1.44-1.60 (m, 1H, Cy), 1.72-1.95 (m, 3H, Cy), 1.96 (s, 1H), 2.51 (s, 3H, H-1), 3.44-3.60 (m, 1H, Cy), 7.07 (d, $J = 8.0$ Hz, 1H, Py), 7.50 (dd, $J = 8.0$ Hz, $J = 8.0$ Hz, 1H, Py), 7.70 (d, $J = 8.0$ Hz, 1H, Py), 8.29 (s, 1H, H-2).

^{13}C NMR (100.61 MHz, CDCl_3): δ 24.2, 24.4, 32.7, 50.5, 53.5, 60.5 (CN), 73.7 (CN), 118.4 (Py), 124.3 (Py), 136.8 (Py), 155.0 (Py), 158.2 (Py), 162.4 5 (C-2).

HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{19}\text{N}_3$ $[\text{M} + \text{H}]^+$ 218.1657, found 218.1661.



(1*R*,2*R*)-*N*-(Pyridin-2-ylmethyl)cyclohexane-1,2-diamine 167

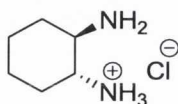
2-Pyridinecarboxaldehyde (0.64 mL, 6.69 mmol) was added to a solution of **134** (1.00 g, 8.70 mmol) in toluene (15 mL) in the presence of molecular sieves. The mixture was stirred overnight at 70 °C. After filtering the solution, the solvent was evaporated under reduced pressure. The resulting mixture was dissolved in MeOH (10 mL) and NaBH₄ (277 mg, 7.34 mmol) was added. The reaction was stirred under nitrogen for 5 h. After evaporating the solvent under reduced pressure, the residue was taken up in Et₂O (20 mL) and saturated NaHCO₃ (20 mL). The two phases were separated, and the aqueous phase was extracted with Et₂O (3 x 15 mL). The combined organic layers were dried over Na₂SO₄ and the solvent evaporated under reduced pressure. The resulting residue was purified by flash chromatography using EtOAc/MeOH (90:10), giving **167** as an orange oil (0.213 g, 16%).

¹H NMR (400 MHz, CDCl₃): δ 0.94-1.34 (m, 4H, Cy), 1.56-2.12 (m, 4H, Cy), 2.25-2.29 (m, 1H, CHN), 2.32-2.37 (m, 1H, CHN), 3.76 (d, *J* = 12.0 Hz, 1H, H-1), 3.96 (d, *J* = 12.0 Hz, 1H, H-1), 7.04-7.08 (m, 1H, H-4), 7.32 (d, *J* = 8.1 Hz, 1H, H-2), 7.55 (dd, *J* = 2.0 Hz, *J* = 8.1 Hz, H-3), 8.43 (d, *J* = 3.0 Hz, H-5).

¹³C NMR (100.62 MHz, CDCl₃): 24.4 (CH₂), 30.9 (CH₂), 32.3 (CH₂), 34.0 (CH₂), 52.1 (NHCH₂), 121.8 (Py), 122.3 (Py), 136.6 (Py), 148.9 (Py).

ν_{max} (film)/cm⁻¹: 3367, 2936, 2858, 1645, 1595, 1571, 1126, 762.

HRMS (ESI) calcd for C₁₂H₁₉N₃ [M + H]⁺ 206.1657, found 206.1659.



(1*R*,2*R*)-1,2-Diaminocyclohexane monohydrochloride 168

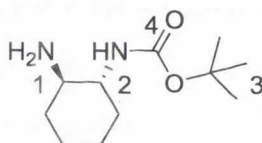
Synthesised according to a literature procedure.²⁶⁰

134 (0.78 g, 6.85 mmol) was dissolved in dry Et₂O under N₂. Under intensive stirring 2 N HCl in Et₂O (3.4 mL, 6.9 mmol) was added at 0 °C, upon which a white solid precipitated. After stirring 20 h at rt, the mixture was filtered and the solid was washed with Et₂O (10 mL) and dried under reduced pressure giving **168** as a white crystalline solid (0.76 g, 97 %). M.p. 140-141 °C .

¹H NMR (400 MHz, D₂O): δ 1.10-1.37 (4H, m, NCHCH₂CH₂), 1.58 (2H, m, NCHCH₂), 1.87 (2H, m, (NCHCH₂), 2.87 (2H, m, NCH).

¹³C NMR (100.62 MHz, D₂O): δ 23.6 (NCHCH₂CH₂), 31.1 (NCHCH₂), 53.8 (NCH).

Consistent with literature values.²⁶¹



tert*-Butyl (1*R*,2*R*)-2-aminocyclohexylcarbamate **169*

Synthesised according to a literature procedure.²⁶²

Compound **168** (241 mg, 2.11 mmol) was dissolved in MeOH (15 mL). To the solution, H₂O (5 mL) and Boc₂O (460 mg, 2.11 mmol) in MeOH (3 mL) were added. The resultant solution was stirred for 1 h at rt and the solvents were evaporated. After titrating the residue with Et₂O (3 mL) an aqueous solution NaOH (2 M, 15 mL) was added. The product was extracted with DCM (3 x 15 mL). The organic layers were dried over MgSO₄ and the solvents were removed under reduced pressure giving **169** as a white solid. (357 mg, 79%).

¹H NMR (400 MHz, CDCl₃): δ 1.02-1.33 (m, 4H), 1.48 (s, 9H, H-3), 1.66-1.75 (m, 2H), 1.80-2.05 (m, 2H), 2.42-2.48 (m, 1H, H-1), 3.10-3.20 (m, 1H, H-2), 4.48 (br s, 1H).

¹³C NMR (100.61 MHz, CDCl₃): δ 24.7, 24.8, 28.0, 32.5, 34.8, 55.3, 57.3, 78.9, 154.3 (C-4).

HRMS (ESI) calcd for C₁₁H₂₂N₂O₂ [M + H]⁺ 215.1754, found 215.1756.

Consistent with literature values.²⁶²

4.2.4 Screen of *in situ* synthesised ligands

Transfer hydrogenation

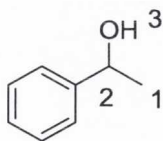
Synthesis of ligands *in situ*

General Procedure A: Synthesis of imines, amins and oxazolidines

To the aldehyde (21 μmol or 42 μmol for bisimines made from **134**) in anhydrous toluene (0.4 mL), was added the amine, amino alcohol or diamine (21 μmol) in a vial. 4 Å molecular sieves were added to the mixture. The reaction was then stirred at 70 °C overnight under N_2 . The solvent was evaporated under reduced pressure to yield the ligand which was then added directly to the catalytic reaction.

General Procedure B: Synthesis of oxazolines, thiazolines and imidazolines

To the imide (21 μmol) in anhydrous toluene (0.4 mL), was added the amino alcohol, amino thiol or diamine (21 μmol) in a vial. 4 Å molecular sieves were added to the mixture. The reaction was then stirred at 70 °C overnight under N_2 . The solvent was evaporated under reduced pressure to yield the ligand which was then added directly to the catalytic reaction.



1-Phenylethanol **151**

Synthesised according to a literature procedure.⁵⁶

A mixture of chiral ligand (21 μmol) and $[\text{Cp}^*\text{RhCl}_2]_2$ (2.6 mg, 10 μmol) in methanol (10 mL) was stirred at 40 °C for 12 h. At this time the solvent was removed under vacuum and sodium formate/formic acid buffer (20 mL, 1.0 M, pH 3.5) was added along with acetophenone (2.0 mmol). This was stirred at 40 °C for 24 h, at which point the reaction was extracted with EtOAc (2 x 15 mL). The organic layers were combined, dried over

MgSO₄ and the solvent was evaporated under reduced pressure. The product was isolated by vacuum distillation as a colorless liquid and analysed by chiral HPLC. Chiralpak IB (4.6 mm x 25 cm), hexane/IPA (97:3), 1.5 mL min⁻¹, rt, UV detection at 254 nm, retention times: 17.0 min (*S*) and 20.0 min (*R*).

¹H NMR (400 MHz, CDCl₃): δ 1.49 (d, *J* = 6.1 Hz, 3H, H-1), 2.38 (br s, 1H, H-3), 4.87 (q, *J* = 6.5 Hz, 1H, H-2), 7.31-7.43 (1H, m, Ph), 7.45-7.56 (m, 4H, Ph).

¹³C NMR (100.61 MHz, CDCl₃): δ 21.0 (C-1), 71.3 (C-2), 126.2, 128.2, 129.2, 144.4.

Consistent with literature values.²⁶³

Hydrosilylation of acetophenone with diethylzinc and PMHS

Synthesis of ligands *in situ*

General Procedure A: Synthesis of imines, amins and oxazolidines:

To the aldehyde (0.085 mmol or 0.170 mmol for bisimines made from **134**) in anhydrous toluene (0.4 mL), was added the amine, amino alcohol or diamine (0.085 mmol) in a vial. 4 Å molecular sieves were added to the mixture. The reaction was then stirred at 70 °C overnight under N₂.

General Procedure B: Synthesis of oxazolines and imidazolines:

To the imidate (0.085 mmol) in anhydrous toluene (0.4 mL), was added the amino alcohol or diamine (0.085 mmol) in a vial. 4 Å molecular sieves were added to the mixture. The reaction was then stirred at 70 °C overnight under N₂.

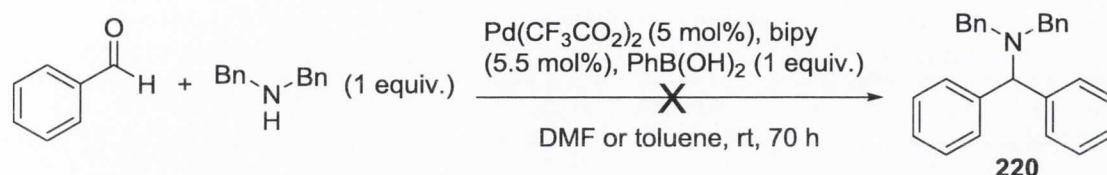
1-Phenylethanol **151**

Synthesised according to a literature procedure.⁷³

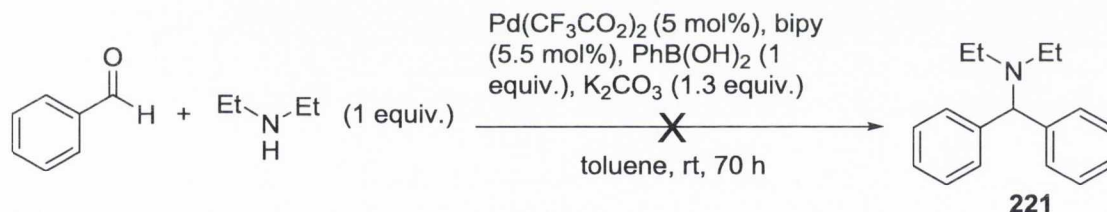
After transferring the ligand solution into a round bottom flask *via* syringe, ZnEt₂ (0.085 mL, 1 M in toluene, 0.085 mmol) was added *via* syringe under N₂. Acetophenone (0.5 mL, 4.3 mmol) and PMHS (0.33 mL, 5.2 mmol) were added to the mixture at 0 °C, and the reaction was allowed to warm to rt. After stirring the solution at rt for 24 h, NaOH (0.9 mL, 45%) was added carefully. After 15 min, 10 mL of water was added to the mixture. The product was extracted with diethyl ether (2 x 10 mL). After evaporating the solvents the product was distilled under reduced pressure.

4.3 Copper catalyzed Petasis reaction and derivatives

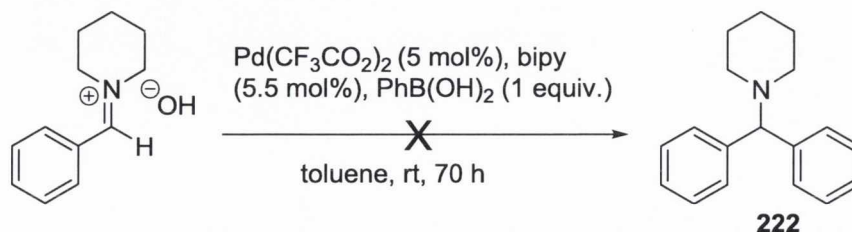
Transition metal catalysed Petasis initial attempts



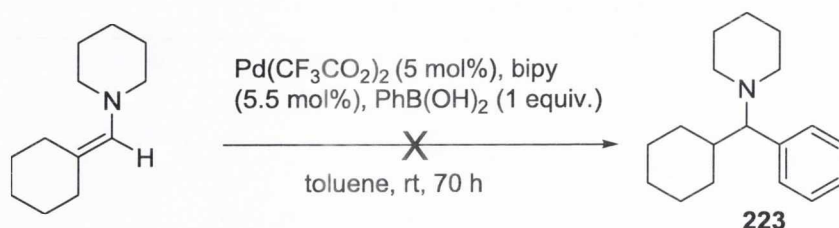
Palladium trifluoroacetate (12.0 mg, 0.036 mmol) and bipyridine (6.4 mg, 0.038 mmol) were stirred in 5 mL of DMF or toluene for 1 h at rt under N₂. To the mixture, benzaldehyde (72.4 μ L, 0.71 mmol) and dibenzylamine (136.6 μ L, 0.71 mmol) were added along with phenylboronic acid (92.6 mg, 0.71 mmol). The reaction was stirred at rt for 70 h. No product was observed.



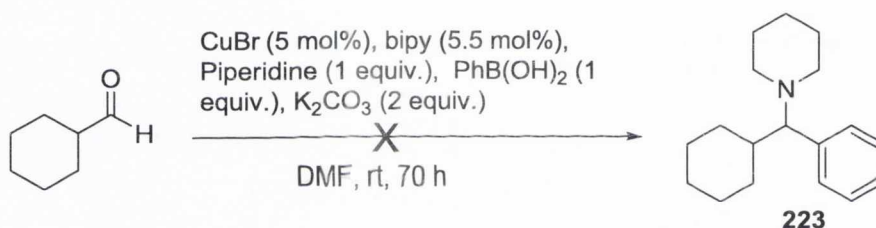
Palladium trifluoroacetate (12.0 mg, 0.036 mmol) and bipyridine (6.4 mg, 0.038 mmol) were stirred in 5 mL of toluene for 1 h at rt under N₂. To the mixture, benzaldehyde (72.4 μ L, 0.71 mmol), diethylamine (74 μ L, 0.71 mmol), phenylboronic acid (86.6 mg, 0.71 mmol) were added along with K₂CO₃ (127.56 mg, 0.92 mmol). The reaction was stirred at rt for 70 h. No product was observed.



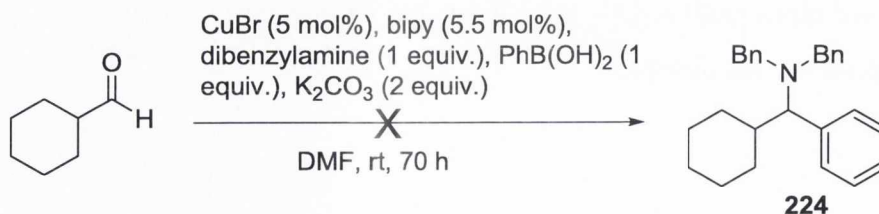
Palladium trifluoroacetate (12.0 mg, 0.036 mmol) and bipyridine (6.4 mg, 0.038 mmol) were stirred in 5 mL of toluene for 1 h at rt under N₂. To the mixture, the iminium (136 mg, 0.71 mmol) was added along with phenylboronic acid (86.6 mg, 0.71 mmol). The reaction was stirred at rt for 70 h under N₂. No product was observed.



Palladium trifluoroacetate (12.0 mg, 0.036 mmol) and bipyridine (6.4 mg, 0.038 mmol) were stirred in 5 mL of toluene for 1 h at rt under N₂. To the mixture, the enamine (127.2 mg, 0.71 mmol) was added along with phenylboronic acid (86.6 mg, 0.71 mmol). The reaction was stirred at rt for 70 h under N₂. No product was observed.

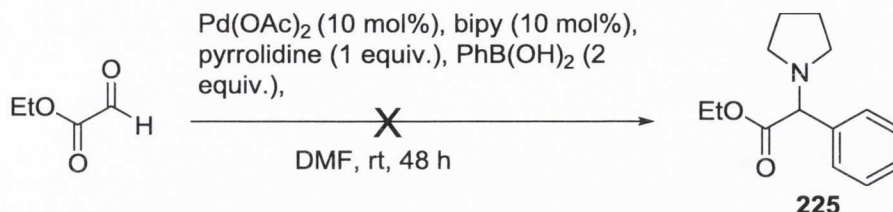


Copper bromide (5.2 mg, 0.036 mmol) and bipyridine (6.4 mg, 0.038 mmol) were stirred in 5 mL of DMF for 1 h at rt under N₂. To the mixture, the aldehyde (86.0 μL , 0.71 mmol), piperidine (70.2 μL , 0.71 mmol) were added along with phenylboronic acid (86.6 mg, 0.71 mmol) and K₂CO₃ (196.2 mg, 1.42 mmol). The reaction was stirred at rt for 70 h under N₂. No product was observed.

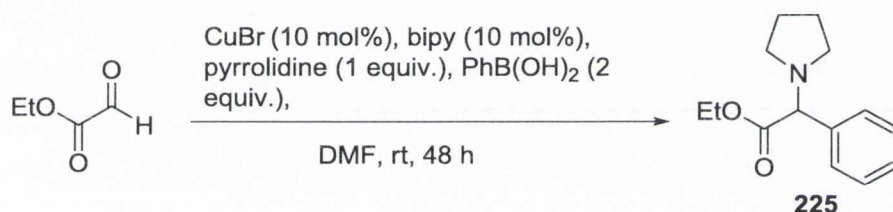


Copper bromide (5.2 mg, 0.036 mmol) and bipyridine (6.4 mg, 0.038 mmol) were stirred in 5 mL of DMF for 1 h at rt under N₂. To the mixture, the aldehyde (86.0 μL , 0.71 mmol), dibenzylamine (136.6 μL , 0.71 mmol) were added along with phenylboronic acid (86.6

mg, 0.71 mmol) and K_2CO_3 (196.2 mg, 1.42 mmol). The reaction was stirred at rt for 70 h under N_2 . No product was observed.



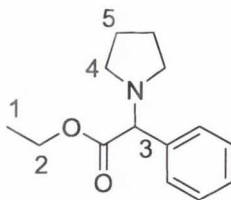
Palladium acetate (16.2 mg, 0.036 mmol) and bipyridine (6.4 mg, 0.038 mmol) were stirred in 5 mL of DMF for 1 h at rt under N_2 . To the mixture, the aldehyde (70.0 μ L, 0.36 mmol) and pyrrolidine (29.2 μ L, 0.36 mmol) were added along with phenylboronic acid (86.6 mg, 0.71 mmol). The reaction was stirred at rt for 70 h under N_2 . No product was observed.



$CuBr$ (5.2 mg, 0.036 mmol) and bipyridine (6.4 mg, 0.038 mmol) were stirred in 5 mL of DMF for 1 h at rt under N_2 . To the mixture, the aldehyde (70.0 μ L, 0.36 mmol) and pyrrolidine (29.2 μ L, 0.36 mmol) were added along with phenylboronic acid (86.6 mg, 0.71 mmol). The reaction was stirred at rt for 70 h under N_2 . The product was observed by mass spectrometry and 1H NMR.

General procedure for the copper catalyzed Petasis reaction

Dry, degassed DMF (12 mL) was added to a mixture of copper bromide (0.142 mmol) and 2,2'-bipyridine (26.4 mg, 0.17 mmol) under N_2 . The solution was stirred at 60 $^{\circ}C$ for 1 h. After this time, aldehyde (1.42 mmol), amine (1.42 mmol), and boronic acid (2.84 mmol) were charged to the flask along with 4 $\text{\AA}$ molecular sieves. The solution was stirred at 70 $^{\circ}C$ for 24 h and subsequently filtered on a short silica pad. (Where internal standards were required 4-nitrobenzaldehyde (15 mg, 0.10 mmol) was added to the reaction mixture at this point). The residue was then purified by column chromatography on silica gel.



Ethyl 2-phenyl-2-(pyrrolidin-1-yl)acetate 225

Isolated as a yellow oil after column chromatography DCM/EtOAc/MeOH (90:9:1), 90 %.

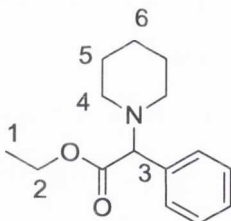
^1H NMR (400 Hz, CDCl_3): δ 1.22 (t, $J = 7.1$ Hz, 3H, H-1), 1.72-1.91 (m, 4H, H-5), 2.40-2.52 (m, 2H, H-4), 2.54-2.68 (m, 2H, H-4), 3.93 (s, 1H, H-3), 4.08-4.27 (m, 2H, H-2), 7.30-7.40 (m, 3H, Ph), 7.50 (d, 2H, $J = 7.6$ Hz, Ph).

^{13}C NMR (100.61 Hz, CDCl_3): δ 14.1 (C-1), 23.3, 52.5, 60.9, 74.1, 128.2, 128.4, 128.5, 137.5.

ν_{max} (film)/ cm^{-1} : 2968, 2791, 1743, 1153, 1024.

HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{20}\text{NO}_2$ $[\text{M} + \text{H}]^+$ 234.1494, found 234.1496.

Consistent with literature values.²⁶⁴



Ethyl 2-phenyl-2-(piperidin-1-yl)acetate 226

Isolated as an orange oil after column chromatography DCM/EtOAc (92:8), 51 %.

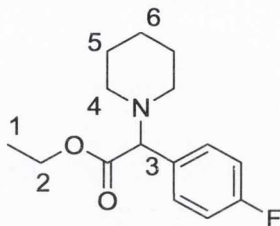
^1H NMR (400 Hz, CDCl_3): δ 1.23 (t, $J = 7.1$ Hz, 3H, H-1), 1.41-1.52 (m, 2H, H-6), 1.56-1.67 (m, 4H, H-5), 2.37-2.47 (m, 4H, H-4), 3.98 (s, 1H, H-3), 4.09-4.28 (m, 2H, H-2), 7.31-7.40 (m, 3H, Ph), 7.43-7.50 (m, 2H, Ph).

^{13}C NMR (100.61 Hz, CDCl_3): δ 14.2 (C-1), 24.4, 25.8, 52.4, 60.7, 75.0, 128.1, 128.4, 128.8, 136.4, 171.9.

ν_{max} (film)/ cm^{-1} : 2933, 2853, 2300, 1741, 1261, 1155, 1122, 801, 696.

HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{22}\text{NO}_2$ $[\text{M} + \text{H}]^+$ 248.1651, found 248.1660.

Consistent with literature values.²⁶⁴



Ethyl 2-(4-fluorophenyl)-2-(piperidin-1-yl)acetate 227

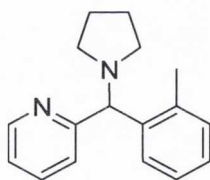
Isolated as a yellow oil after column chromatography DCM/EtOAc (90:10), 57%.

^1H NMR (400 Hz, CDCl_3): δ 1.23 (t, $J = 7.1$ Hz, 3H, H-1), 1.41-1.52 (m, 2H, H-6), 1.53-1.69 (m, 4H, H-5), 2.30-2.46 (m, 4H, H-4), 3.94 (s, 1H, H-3), 4.06-4.30 (m, 2H, H-2), 6.96-7.12 (m, 2H, Ar), 7.37-7.51 (m, 2H, Ar).

^{13}C NMR (100.61 Hz, CDCl_3): 14.2 (C-1), 24.3, 25.8, 52.3, 60.8, 74.2, 115.3 (d, $J_{\text{CF}} = 21.5$ Hz), 130.4 (d, $J_{\text{CF}} = 8.0$ Hz), 132.2, 162.6 (d, $J_{\text{CF}} = 246.4$ Hz), 171.7.

ν_{max} (film)/ cm^{-1} : 2934, 1733, 1604, 1507, 1223, 1150, 805.

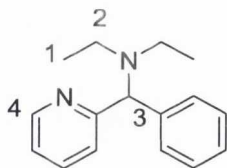
HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{21}\text{FNO}_2$ $[\text{M} + \text{H}]^+$ 266.1556, found 266.1566.



2-(Pyrrolidin-1-yl(*o*-tolyl)methyl)pyridine 228

Yield too low for isolation (<5%).

HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{20}\text{N}_2$ $[\text{M} + \text{H}]^+$ 253.1705, found 253.1715



***N*-Ethyl-*N*-(phenyl(pyridin-2-yl)methyl)ethanamine 229**

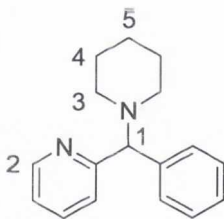
Isolated as a green solid after column chromatography hexane/EtOAc/Et₃N (94:1:5), 43%.

¹H NMR (400 Hz, CDCl₃): δ 1.01 (t, *J* = 7.0 Hz, 6H, H-1), 2.63 (q, *J* = 7.0 Hz, 4H, H-2), 4.90 (s, 1H, H-3), 7.05-7.15 (m, 1H, Ar), 7.21 (dd, *J* = 8.2 Hz, *J* = 8.2 Hz, 1H, Ar), 7.27-7.34 (m, 2H, Ar), 7.53 (d, *J* = 7.5 Hz, 2H, Ar), 7.58-7.68 (m, 2H, Ar), 8.52 (d, *J* = 4.8 Hz, 1H, H-4).

¹³C NMR (100.61 Hz, CDCl₃): δ 10.6 (C-1), 42.8 (C-2), 73.6 (C-3), 121.8, 127.0, 128.3, 128.4, 136.4, 142.1, 149.0, 163.2.

ν_{max} (film)/cm⁻¹: 2969, 2933, 1588, 1432, 746, 730, 699.

HRMS (ESI) calcd for C₁₆H₂₁N₂ [M + H]⁺ 241.1705, found 241.1712.



2-(Phenyl(piperidin-1-yl)methyl)pyridine 230

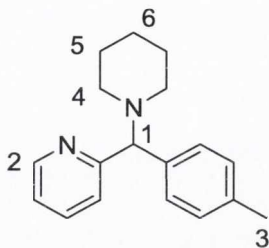
Isolated as an amorphous green solid after column chromatography hexane/EtOAc/Et₃N (80:15:5), 76%.

¹H NMR (400 Hz, CDCl₃): δ 1.40-1.53 (m, 2H, H-5), 1.55-1.70 (m, 4H, H-4), 2.26-2.61 (m, 4H, H-3), 4.42 (s, 1H, H-1), 7.05-7.15 (m, 1H, Ar), 7.17-7.25 (m, 1H, Ar), 7.26-7.36 (m, 2H, Ar), 7.50 (d, *J* = 7.3 Hz, 2H, Ar), 7.58-7.70 (m, 2H, Ar), 8.51 (d, *J* = 5.1 Hz, 1H, H-2).

¹³C NMR (100.61 Hz, CDCl₃): δ 24.6 (C-5), 26.1 (C-4), 53.3 (C-3), 78.7, 121.8, 122.1, 127.0, 128.3, 128.4, 136.5, 141.8, 149.0, 162.9.

ν_{max} (film)/ cm^{-1} : 2931, 2753, 1587, 1431, 746, 699.

HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{21}\text{N}_2$ $[\text{M} + \text{H}]^+$ 253.1705, found 253.1713.



2-((Piperidin-1-yl)(*p*-tolyl)methyl)pyridine 231

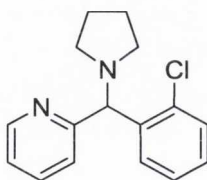
Isolated as an amorphous green solid after column chromatography hexane/EtOAc/Et₃N (80:15:5), 74%.

^1H NMR (400 Hz, CDCl_3): δ 1.40-1.48 (m, 2H, H-6), 1.53-1.63 (m, 4H, H-5), 2.10-2.56 (m, 7H, H-4 with H-3), 4.34 (s, 1H, H-1), 7.00-7.15 (m, 3H, Ar), 7.35 (d, $J = 7.7$ Hz, 2H, Ar), 7.52-7.65 (m, 2H, Ar), 8.48 (d, 1H, $J = 4.6$ Hz, H-2).

^{13}C NMR (100.61 Hz, CDCl_3): δ 21.1 (C-3), 24.6 (C-6), 26.1 (C-5), 53.3 (C-4), 78.4, 121.7, 122.0, 128.2, 129.1, 136.5, 136.6, 138.8, 149.0, 163.1.

ν_{max} (film)/ cm^{-1} : 2930, 2855, 1587, 1432, 797, 753.

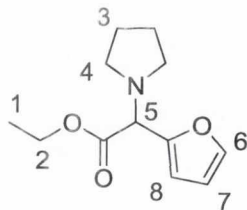
HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{23}\text{N}_2$ $[\text{M} + \text{H}]^+$ 267.1861, found 267.1871.



2-((2-Chlorophenyl)(pyrrolidin-1-yl)methyl)pyridine 232

Yield too low for isolation (<5%).

HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{17}\text{ClN}_2$ $[\text{M} + \text{H}]^+$ 273.1158, found 273.1167.



Ethyl 2-(furan-2-yl)-2-(pyrrolidin-1-yl)acetate 233

Isolated as a yellow oil after column chromatography DCM/EtOAc (98:2), 79%.

^1H NMR (400 Hz, CDCl_3): δ 1.27 (t, $J = 7.1$ Hz, 3H, H-1), 1.74-1.89 (m, 4H, H-3), 2.47-2.74 (m, 4H, H-4), 4.17-4.31 (m, 3H, H-2 and H-5), 6.33-6.41 (m, 2H, H-7 and H-8), 7.40 (dd, 1H, $J = 0.9$, $J = 1.9$ Hz, 1H, H-6).

^{13}C NMR (100.61 Hz, CDCl_3): δ 14.2 (C-1), 23.4, 51.6, 61.3, 65.4 (C-5), 109.0, 110.3, 142.6, 150.0, 169.6.

ν_{max} (film)/ cm^{-1} : 2966, 2809, 1736, 1150, 1012.

HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{18}\text{NO}_3$ $[\text{M} + \text{H}]^+$ 224.1287, found 224.1285.

Study of the reaction mechanism

Dry and degassed DMF (0.7 mL) was added to CuBr (10.9 mg, 0.076 mmol) and bipy (11.9 mg, 0.076 mmol). The solution was stirred for 1 h under N_2 . 4-Phenylboronic acid (11.5 mg, 0.076 mmol) was added to the reaction mixture and then transferred into a sealed NMR tube.

Screen of chiral ligands for the copper catalyzed Petasis reaction

Dry, degassed DMF (12 mL) was added to a mixture of copper bromide (20.4 mg, 0.142 mmol) and the ligand (0.17 mmol) under N_2 . The solution was stirred at 60 $^\circ\text{C}$ for 1 h. After this time, ethyl glyoxalate (280 μL , 1.42 mmol), pyrrolidine (45 μL , 1.42 mmol), and 2-furanboronic acid (317.8 mg, 2.84 mmol) were charged to the flask along with 4Å molecular sieves. The solution was stirred at 70 $^\circ\text{C}$ under N_2 for 24 h and subsequently filtered on a short silica pad. 4-Nitrobenzaldehyde (15.0 mg, 0.10 mmol) was added to the reaction mixture and the yield determined by ^1H NMR. After evaporation of the solvent, the residue was then purified by column chromatography on silica gel and isolated as a yellowish oil. DCM/EtOAc (98:2). The product was analysed by CSP-HPLC. Chiralpak IA

(4.6 mm x 25 cm), hexane/Et₂NH (99:1), 1.3 mL min⁻¹, rt, UV detection at 254 nm, retention times: 18.5 min and 20.5 min.

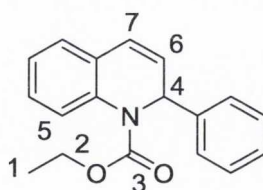
Ligand: **245**, 23%, 0% *ee*. **156**, 0%, n/a *ee*. **189**, 0%, n/a *ee*. **246**, 16%, 0% *ee*. **177**, 40%, 0% *ee*. **200**, 16%, 0% *ee*.

Study of possible racemization of **217**:

Compound (70 mg, 0.314 mmol) was stirred in a mixture of DMF (1.15 mL) and D₂O (0.1 mL) at 70 °C under N₂ for 48 h. The solvents were evaporated under reduced pressure. No proton exchange was observed by NMR.

Copper catalyzed arylation of EEDQ:

Dry, degassed DMF (12 mL) was added to a mixture of copper salt (0.142 mmol) and 2,2'-bipyridine (26.4 mg, 0.17 mmol) under N₂. The solution was stirred at 60 °C for 1 h. After this time, EEDQ (351.2 mg, 1.42 mmol), and aryl boronic acid (2.84 mmol) were charged to the flask along with powdered 3 Å molecular sieves. The solution was stirred at 70 °C under N₂ for 24 h and subsequently filtered on a short silica pad. 4-Nitrobenzaldehyde (15 mg, 0.10 mmol) was added to the reaction mixture and the yield determined by ¹H NMR. After evaporation of the solvent, the yield was determined by ¹H NMR spectroscopy. The residue was then purified by column chromatography on silica gel.



Ethyl 2-phenylquinoline-1(2H)-carboxylate **254**

Yellow oil (34%).

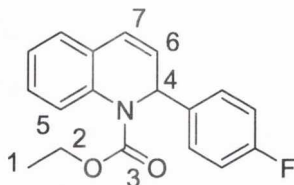
¹H NMR (400 MHz, CDCl₃): δ 1.33 (t, *J* = 7.3 Hz, 3H, H-1), 4.22-4.38 (m, 2H, H-2), 6.17-6.22 (m, 2H, H-4, H-7), 6.62-6.70 (dd, *J* = 6.0 Hz, *J* = 14.1 Hz, 1H, H-6), 7.05 (dt, *J* = 1.2 Hz, *J* = 7.4 Hz, 1H, Ar), 7.12 (dd, *J* = 1.3, *J* = 7.5 Hz, 1H, Ar), 7.17-7.32 (m, 5H, Ar), 7.55 (br s, 1H, H-5).

^{13}C NMR (100.62 MHz, CDCl_3): δ 14.06 (C-1), 55.07 (C-4), 61.89 (C-2), 124.1, 124.5, 125.3, 126.3, 127.0, 127.6, 127.7, 128.2, 128.5, 134.8, 139.7, 154.5 (C-3).

ν_{max} (film)/ cm^{-1} : 3030, 1693, 1395, 1261, 1180, 695.

HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{17}\text{NO}_2$ $[\text{M} + \text{H}]^+$ 280.1338, found 280.1333.

Consistent with literature values.²²⁴



Ethyl 2-(4-fluorophenyl)quinoline-1(2H)-carboxylate 255

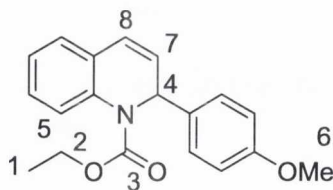
Yellow oil (49%).

^1H NMR (400 MHz, CDCl_3): δ 1.37 (t, $J = 7.6$ Hz, 3H, H-1), 4.25-4.40 (m, 2H, H-2), 6.15-6.21 (m, 2H, H-4, H-7), 6.66-6.72 (dd, $J = 6.3$ Hz, $J = 14.2$ Hz, 1H, H-6), 6.90 (m, 2H, Ar), 7.05-7.11 (m, 1H, Ar), 7.12-7.17 (m, 1H, Ar), 7.17-7.22 (m, 1H, Ar), 7.23-7.30 (m, 2H), 7.51 (s, 1H, H-5).

^{13}C NMR (100.62 MHz, CDCl_3): δ 14.5, 54.8, 62.4, 115.1, 124.2, 124.4, 125.5, 126.3, 127.1, 128.0, 128.1, 129.1, 135.1, 154.8, 161.6, 161.8.

HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{16}\text{FNO}_2$ $[\text{M} + \text{H}]^+$ 298.1243, found 298.1250.

Consistent with literature values.²²⁴



Ethyl 2-(4-methoxyphenyl)quinoline-1(2H)-carboxylate 256

Yellow oil (28%).

^1H NMR (400 MHz, CDCl_3): δ 1.37 (t, $J = 7.1$ Hz, 3H, H-1), 3.75 (s, 3H, H-6), 4.25-4.35 (m, 2H, H-2), 6.11-6.22 (m, 2H, H-4, H-8), 6.71 (d, $J = 8.8$ Hz, 1H, H-7), 6.74-6.80 (m,

2H), 7.04-7.11 (m, 1H), 7.13 (d, $J = 7.5$ Hz, 1H), 7.16-7.20 (m, 3H, H-6), 7.52 (s, 1H, H-5).

^{13}C NMR (100.62 MHz, CDCl_3): δ 14.7, 55.2, 55.4, 62.5, 114.0, 124.3, 124.8, 125.3, 126.5, 127.4, 127.8, 128.7, 128.8, 131.9, 134.8, 154.9, 159.4.

HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{19}\text{NO}_3$ $[\text{M} + \text{H}]^+$ 310.1443, found 310.1451.

Consistent with literature values.²²⁴

Screen of chiral ligands for the copper catalyzed arylation of EEDQ:

Dry, degassed DMF (12 mL) was added to a mixture of copper bromide (20.4 mg, 0.142 mmol) and the ligand (0.17 mmol) under N_2 . The solution was stirred at 60 °C for 1 h. After this time, EEDQ (351 mg, 1.42 mmol), and phenylboronic acid (346 mg, 2.84 mmol) were charged to the flask along with powdered 3 Å molecular sieves. The solution was stirred at 70 °C under N_2 for 24 h and subsequently filtered on a short silica pad. 4-Nitrobenzaldehyde (15 mg, 0.10 mmol) was added to the reaction mixture and the yield determined by ^1H NMR. After evaporation of the solvent, the yield was determined by ^1H NMR spectroscopy. The residue was then purified by column chromatography on silica gel. The product was analysed by CSP-HPLC. Chiralpak IB (4.6 mm x 25 cm), hexane/*i*PrOH (99.5:0.5), 0.5 mL min⁻¹, rt, UV detection at 254 nm, retention times: 19.5 min and 22.5 min.

Ligand: **245**, 16%, 0% *ee*. **456**, 29%, 0% *ee*. **259**, 28%, 0% *ee*. **132**, 24%, 0% *ee*. **246**, 11%, 0% *ee*. **260**, 11%, 0% *ee*. **259**, 24%, 0% *ee*.

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