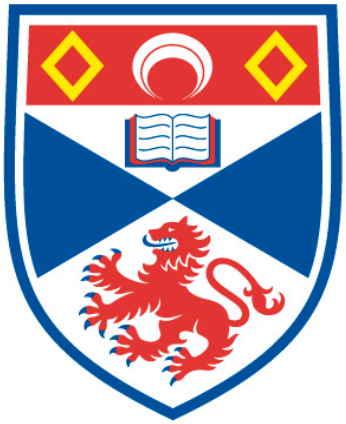
# RH CATALYSED HYDROGENATION OF ENAMINES : FACTORS AFFECTING THE RATE OF ENANTIOSELECTIVITY

Sergey Tin

A Thesis Submitted for the Degree of PhD
at the
University of St Andrews



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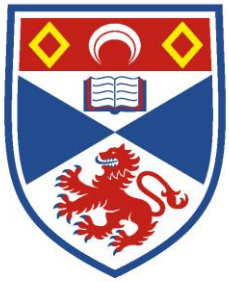
# Rh Catalysed Hydrogenation of Enamines: Factors Affecting the Rate and Enantioselectivity

Sergey Tin




This thesis is submitted in partial fulfilment for the degree of PhD at the University of St Andrews

Supervisor: Dr Matthew L. Clarke

Date of Submission: 6th December 2016

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**Abstract**

The main goal of this work was to understand factors affecting the rate of catalytic enamine hydrogenation, define promising chiral ligand scaffolds to perform the reaction enantioselectively, to prepare new efficient catalysts and to understand the reaction mechanism.

Enamines were prepared by three different routes, one of which is a regio-selective intramolecular hydroaminovinylation of an amine-functionalised alkene. Achiral phosphorous ligands were tested in hydrogenation of these enamines. It was shown that electron-withdrawing ligands are beneficial in the reaction. Steric bulk within the ligands or the substrates also results in higher productivity. Electron-deficient phosphine ligands were able to perform hydrogenation of enamines with tetrasubstituted double bonds, which, to the best of our knowledge, have never been described in the literature. An unprecedented TON of up to 4550 mol mol$^{-1}$ was achieved with one of the substrates.

Hydrogenation of the enamines with chiral PHANEPHOS (in this project, 4,12-bis(di-aryl-phosphino-[2.2]-paracyclophane) ligands revealed that the electronic effect in the rhodium-catalysed hydrogenation of enamines is also of a paramount importance when chiral bis-phosphine ligands are used. The beneficial effect of iodine as co-catalyst is described. Addition of $I_2$ improves both the rate of the reaction, as well as the ee of the product, exerting a dramatic effect in boosting the latter. An electron-deficient PHANEPHOS / Rh catalyst in the presence of $I_2$ is able to hydrogenate even enamines with tetrasubstituted double bond.

Chiral phospholane complexes of rhodium (complexes of chiral BPE (bis-(phospholanyl)ethane) (e.g. (+)-{1,2-Bis[(2*R*,5*R*)-2,5-diethylphospholan-1-yl]ethane}(cycloocta-1,5-diene)rhodium(I) tetrafluoroborate) and DuPhos (bis-(phospholanyl)benzene) (e.g (-)-{1,2-Bis[(2*S*,5*S*)-2,5-diethylphospholan-1-yl]benzene(cycloocta-1,5-diene)rhodium(I) tetra-fluoroborate) were also explored in this study. The use of an iodine co-catalyst proved to be very useful with the Rh / phospholane catalysts as well: addition of it resulted not only in the improvement of the rate of the reaction and increase in the enantioselectivity, but also caused the inversion of the absolute configuration of the product. An especially dramatic enantioselectivity switch was observed when chlorobenzene was used as a solvent. Mechanistic studies revealed that the enamine hydrogenation in the presence of a phospholane / Rh catalyst and iodine proceeds *via* the formation of the iminium ion, followed by the reduction of it with metal hydride. The actual catalyst is proposed to be a fairly acidic $[Rh(ligand^*)I_2(H_2)]^+$ complex.

## Table of contents

**Abbreviations**

| | |
|---|---|
| BArF | tetrakis[3,5-bis(trifluoromethyl)phenyl]borate |
| Bn | benzyl group (-$CH_2C_6H_5$) |
| BPE | bis-(phospholanyl)ethane) |
| br | broad (NMR spectroscopy) |
| Bu | *Neo*butyl group (-$CH_2CH_2$ $CH_2CH_3$) |
| $^t$Bu | tert-butyl group (-$C(CH_3)_3$) |
| $^o$C | degrees celsius |
| COD | 1,5-cyclooctadiene |
| COSY | correlation spectroscopy |
| Cy | cyclohexyl group (-$C_6H_{11}$) |
| δ | checial shift (NMR spectroscopy) |
| d | doublet (NMR spectroscopy) |
| DABCO | 1,4-diazabicyclo[2.2.2]octane |
| DuanPhos | 2,2'-di-tert-butyl-2,2',3,3'-tetrahydro-1*H*,1'*H*-biisophosphinadole |
| DuPhos | bis-(phospholanyl)benzene |
| *E* | corresponds to *trans* isomer |
| ee | enantiomeric excess |
| ES | electron spray (mass spectrometry) |
| Et | ethyl group (-$C_2H_5$) |
| HMBC | heteronuclear multiple-bond correlation |
| HRMS | high resolution mass spectrometry |
| HSQC | heteronuclear single quantum coherence |
| Hz | hertz |
| *J* | coupling constant (NMR spectroscopy) |
| K | kelvin (temperature) |
| L | litres |
| m | multiplet (NMR spectroscopy); milli |
| *m*- | meta |
| M | mega; molecular ion (MS); concentration (moles per litre) |
| Me | methyl group (-$CH_3$) |
| mol | moles |
| MS | mass spectrometry |
| naphth | naphthyl group (-$C_{10}H_7$) |
| NMR | nuclear magnetic resonance |
| *o*- | *ortho* |
| *p*- | *para* |
| Ph | phenyl group (-$C_6H_5$) |
| PHANEPHOS | 4,12-bis(phosphino)-[2.2]-paracyclophane |
| ppm | parts per millon |
| $^i$Pr | *iso*propyl group (-$CH(CH_3)_2$) |
| $^n$Pr | *neo*propyl group (-$CH_2CH_2CH_3$) |
| q | quartet (NMR spectroscopy) |

| | |
|---|---|
| qu | quintet (NMR spectroscopy) |
| RT | room temperature |
| s | singlet (NMR spectroscopy) |
| syngas | synthesis gas (mixture of CO and $H_2$) |
| t | triplet (NMR spectroscopy) |
| TBME | tert-butyl methyl ether |
| tert | tertiary |
| Tf | triflate |
| THF | tetrahydrofuran |
| tol | tolyl |
| *Z* | corresponds to *cis* isomer |

## 1.0 Introduction

## 1.1 Importance of chiral amines

Enantiomerically pure amines are extensively used in the synthesis of agrochemicals and particularly in pharmaceutical industry.[1] They play a huge role being present in a significant proportion of drugs and drug candidates.[2] For example, in the 2012 US Retail sales from top 200 pharmaceutical products many contain chiral amines. Some examples are shown in Figure 1.1.[3] Further examples are shown in Figure 1.2.[4]

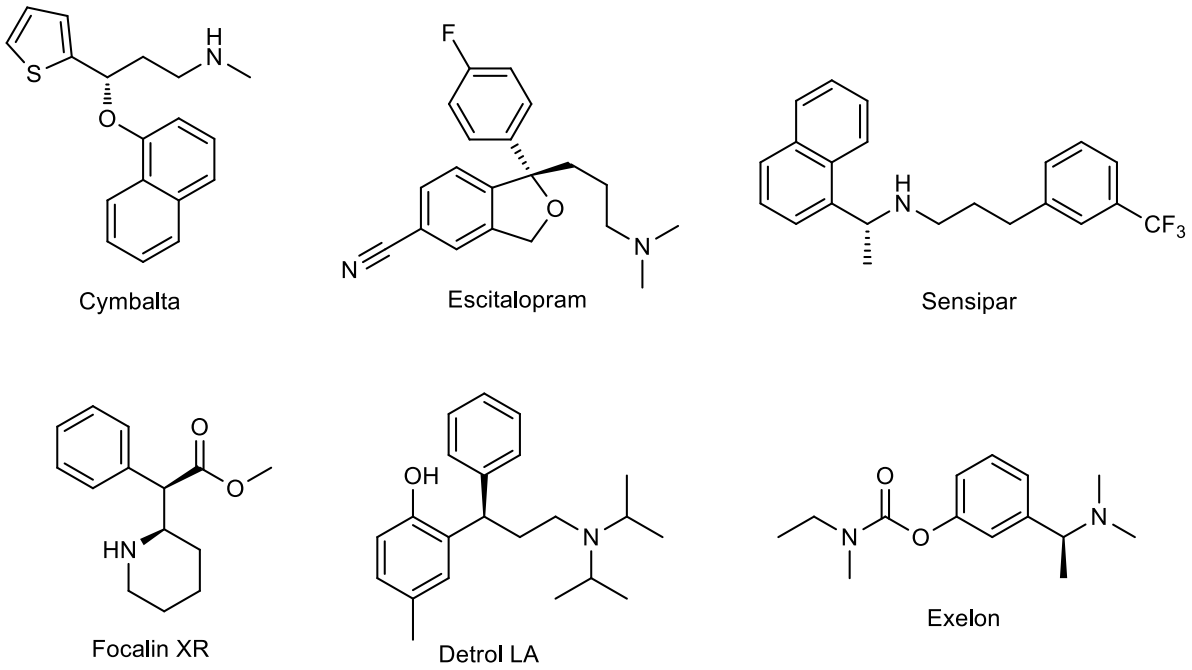



**Figure 1.1**. Selected examples from top 200 pharmaceuticals (by sales) in US in 2012.

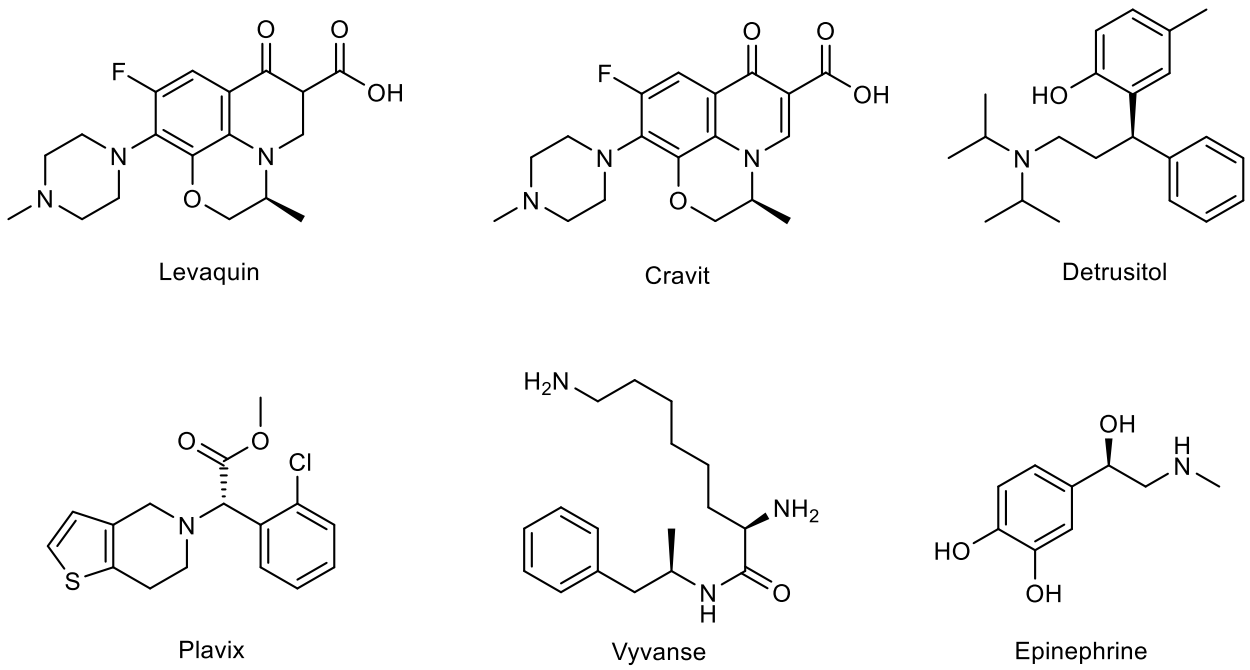
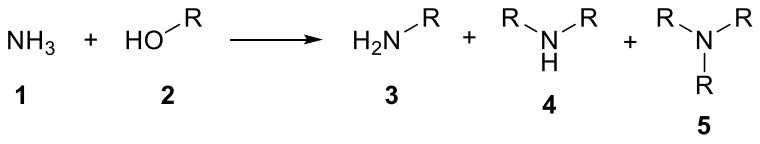



**Figure 1.2**. Several examples of chiral amine pharmaceuticals.

Despite the importance of chiral amines, the industrial enantioselective synthesis of tertiary amines, is sometimes difficult[5] and often relies on racemic synthesis, followed by classical resolution to separate the enantiomers.

## 1.2 Synthetic routes towards amines

In industry, simple alkyl amines are usually produced by a reaction between ammonia and alcohol, which produces a mixture of the primary (**3**), secondary (**4**) and tertiary (**5**) amines (Scheme 1.1). The amines are then separated (usually by distillation).[6,7]

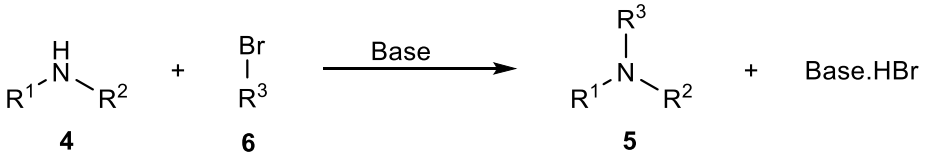



**Scheme 1.1**. Reaction between ammonia and alkyl alcohol.

Depending on the choice of catalyst, selectivities towards each product can be adjusted, the reaction usually requires high temperatures (typically above 300 $^{o}$C for catalysed reactions and around 400 $^{o}$C when no catalyst is used),[7] which makes the process energy intensive. In

addition, this type of reaction is unlikely to be suitable for more functionalised fine chemicals and pharmaceuticals due to the harsh conditions.

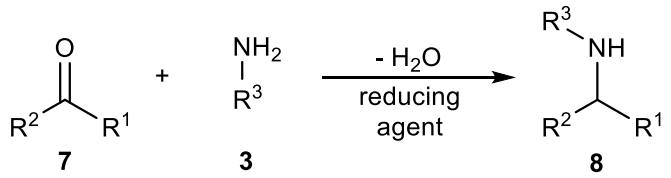
In order to produce amines with different groups attached to the nitrogen atom, alkylation of amines can also be performed (Scheme 1.2).




**Scheme 1.2**. General scheme for an alkylation reaction with alkylbromide.

There are a few issues with this reaction. First of all, it is difficult to control the number of substitutions. For example, if a secondary amine is desired, an excess of primary amine will be required to stop di-substitution (i.e. formation of the tertiary amine). In some cases there are also risks of formation of quaternary ammonium salts. While this kind of reaction can be used to prepare small amounts of the required products, it is highly undesirable in industrial applications since it forms a lot of halogenated salt waste. If arylation of an amine is required, the same reaction can be performed *via* cross-coupling using a transition metal catalyst. While the catalyst required can be very inexpensive (e.g. Ni salt which does not require any ligand),[8] the issue of large waste still makes these reactions unviable for a large scale synthesis.

A significantly improved route towards the production of amines is reductive amination, where the carbonyl group of the molecule is converted to the imine (or enamine) followed by the reduction of the species to the amine (Scheme 1.3). This can be carried out as a tandem reductive amination, or in a two-step process. Either way the methods are free from halogenated salts.




**Scheme 1.3**. Reductive amination of carbonyl compound **7**.

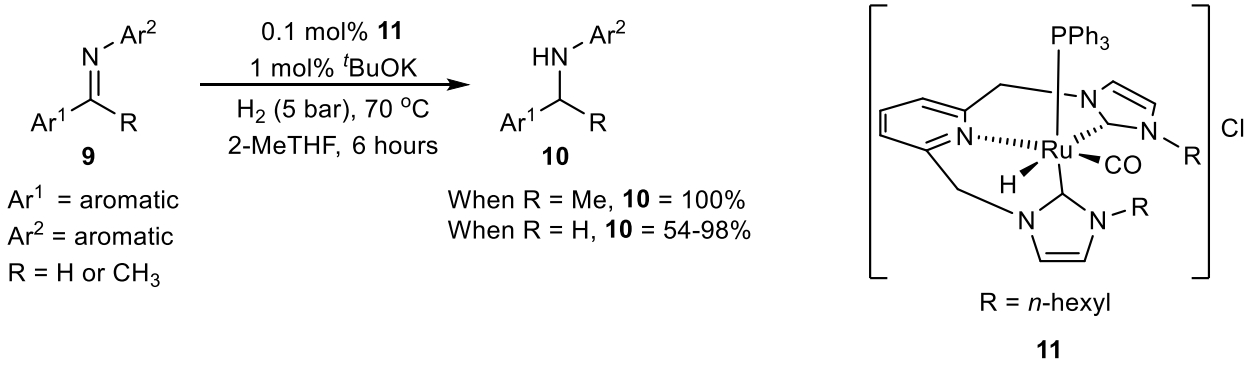
The reduction of the double bond can occur using stoichiometric amounts of some common reducing agents such as sodium cyanoborohydride, sodium triacetoxyborohydride etc., or more recently introduced methods with an excess of $BH_3$·THF.[9-11] Apart from the requirement of the stoichiometric amount of the reductant, typically equimolar amounts of acid will be

required as well, which could bring some limitations if other functional groups are present. In industrial processes it is highly-undesirable to allow the use of such compounds due to generation of waste and the potential hazards associated with some reducing agents. Therefore, a reduction procedure using hydrogen gas and catalyst can be applied. The use of a chiral reducing catalyst does not only avoid the need to use the undesired reducing agents, but also can produce the desired chiral amine straight away.

### 1.3 Catalytic routes towards amines

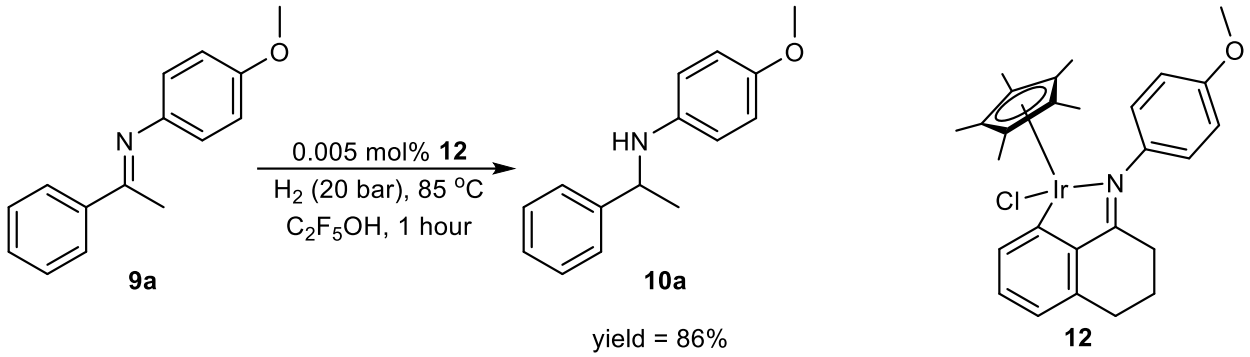
#### 1.3.1 Hydrogenation of imines

Catalytic hydrogenation of imines is a well-explored field, where the most common transition metals used are iridium, rhodium and ruthenium.[12] An example of using Ru metal as a catalyst comes from the work of Suárez and co-workers, where it was shown that the reaction can be performed under low pressure of hydrogen and S/C ratio of 1000 for a good range of substrates (Scheme 1.4).[13]




**Scheme 1.4.** Hydrogenation of imines with iridium catalyst **11.**

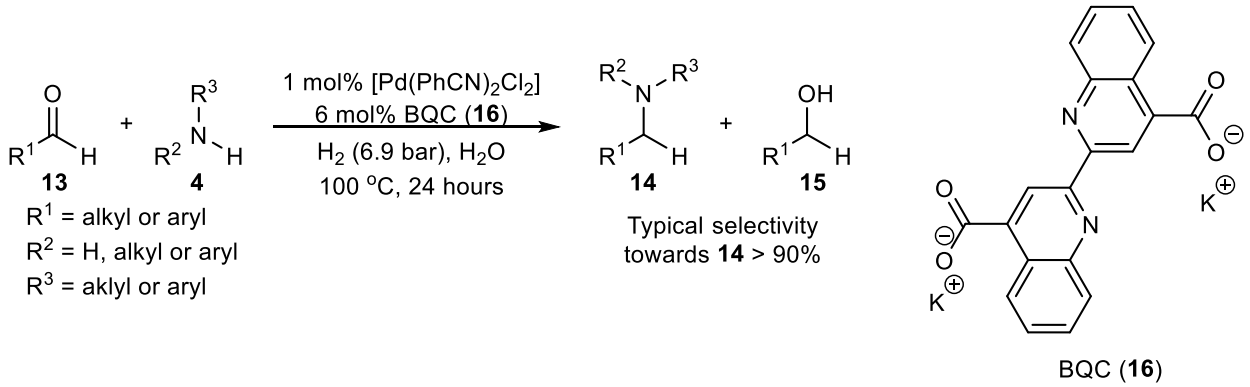
After one year, Xiao and co-workers reported an iridium catalyst which is able to perform the hydrogenation of imines at very low catalyst loadings (typically 0.01 mol%).[14] An example of the catalyst performing the process at 0.005 mol% loading is shown in Scheme 1.5.




**Scheme 1.5.** Hydrogenation of imine **9a** using Xiao and co-workers Ir catalyst **12**.

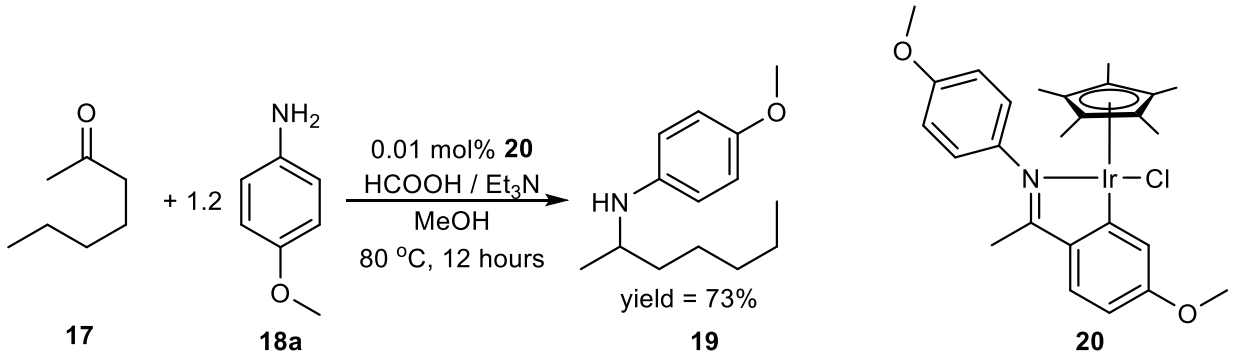
### 1.3.2 Reductive amination of carbonyl compounds by hydrogenation

Catalytic reductive amination is a well explored field.[15] Being known for a long time as a powerful way of preparation of amines,[15,16] it has received a lot of attention over time. In 2006, Ajjou and co-workers reported the first example of this reaction between an aldehyde and a primary or secondary amine performed in water as a solvent, where the reducing agent is hydrogen gas (Scheme 1.6).[17] Since water is the only side product of the reaction, the use of water as a solvent is an ideal scenario.



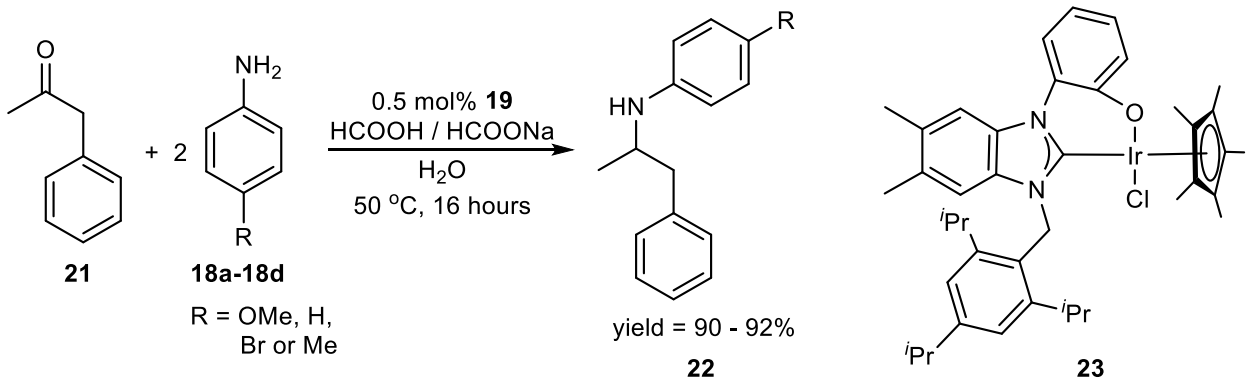

**Scheme 1.6**. Catalytic reductive amination of aldehydes in water.

In 2010, Xiao and co-workers reported iridium catalyst **20**, which was able to perform the reaction by transfer hydrogenation with a wide range of ketones (both aromatic and aliphatic) and mainly primary amines (a few examples with secondary amines where an aliphatic ketone was used) at S/C ratios of 1000.[18] Some reactions were shown to perform at as low as 0.01 mol% of iridium metal (an example is shown in Scheme 1.7).




**Scheme 1.7.** Reductive amination of ketone **17**.

A few years later, the same group reported an Ir catalyst that is able to perform the reaction in water as a solvent.[19] In comparison to the Pd catalyst shown in Scheme 1.6, the catalyst loading is reduced to 0.5 mol% for some substrates, depending on the choice of the substrates. A few examples are shown in Scheme 1.8. In methanol, the catalyst was shown to work efficiently at S/C ratio of 1000.

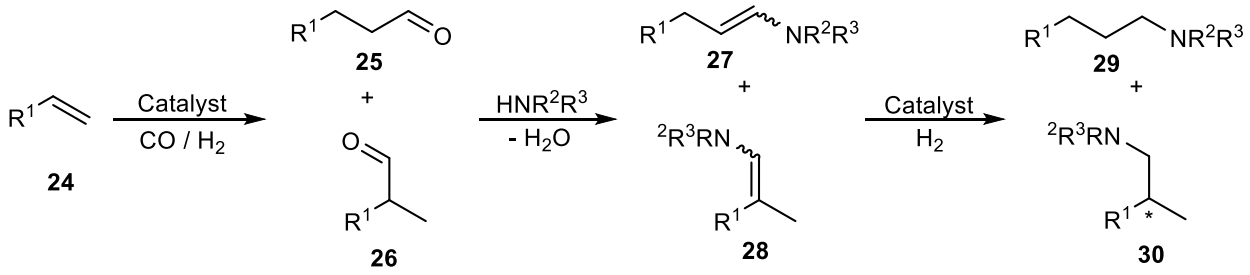



**Scheme 1.8.** Reductive amination of ketone **21**.

Although there are many examples of the catalytic processes of this reaction being performed with a variety of reducing agents and catalysts (including examples of catalyst loadings that are reasonably low (0.1 mol%)),[9-23] some limitations still exist. Further improvements in these reactions, including enantioselective variants are anticipated to improve practically.

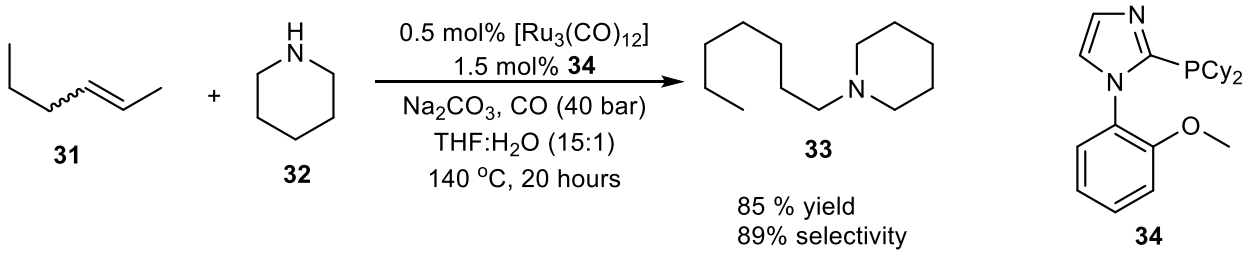
### 1.3.3 Hydroaminomethylation

Hydroaminomethylation was first discovered in 1953 by Reppe *et. al.*[24] and since then a lot of research have been carried out in this area.[25-28] It was described as a "perfect reaction" by Hartwig[29] since it produces a tertiary amine from a terminal alkene in a one pot reaction producing water as the only side product. A general reaction representing hydroaminomethylation is shown in Scheme 1.9.



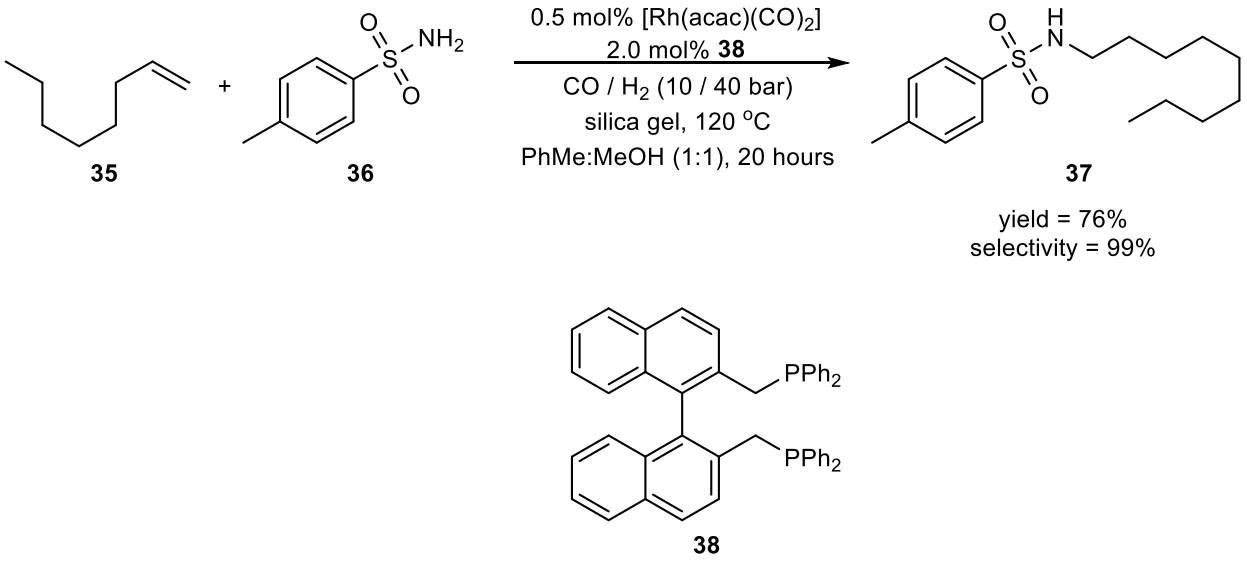

**Scheme 1.9.** General scheme for hydroaminomethylation.

After lots of literature examples of this reaction being performed in a variety of solvents under different conditions,[26] the field was developed a lot further. One of the recent examples in the literature describes a ruthenium catalyst that is able to perform hydroaminomethylation of internal alkenes with high selectivities to the linear amines (an example is shown in Scheme 1.10).[30] It is interesting to note that the source of hydrogen for the reduction of the enamine double bond is water.



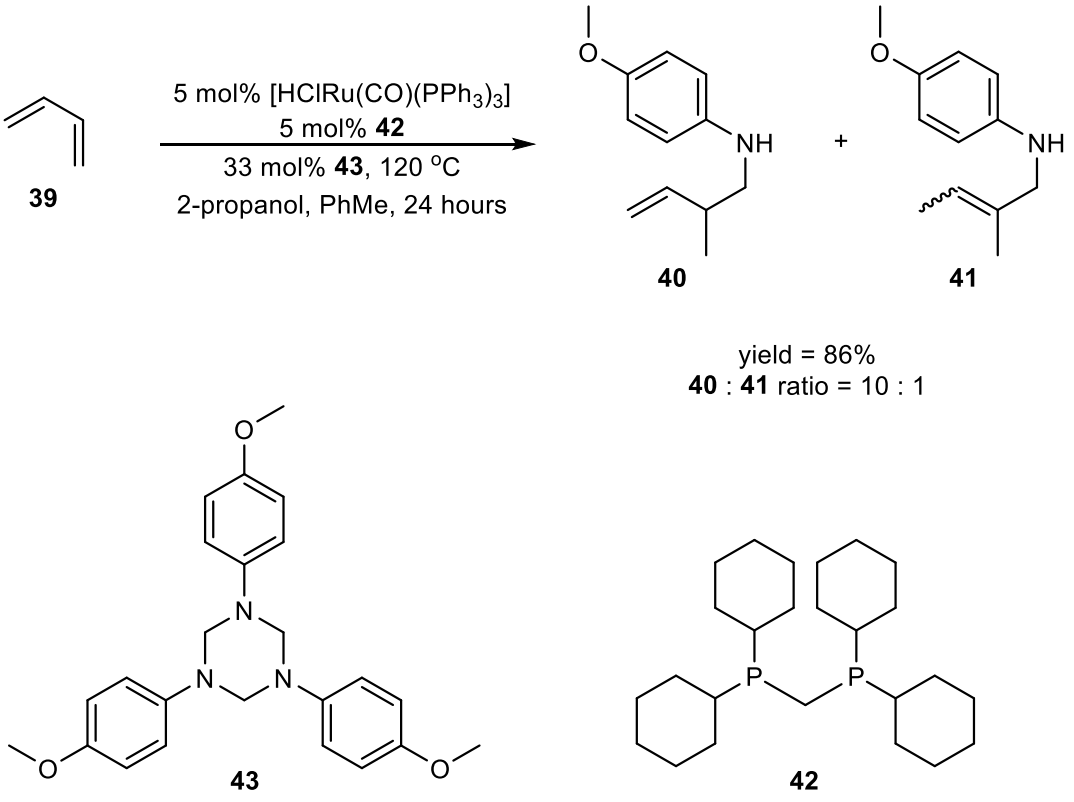

**Scheme 1.10.** Example of selective hydroaminomethylation reaction.

Hydroaminomethylation is not limited to the synthesis of amines. For example, recent work of Beller and co-workers shows that it can be used to produce sulfonamides.[31] It was shown to work best in a mixture of solvents such as toluene and methanol (Scheme 1.11).




**Scheme 1.11.** Synthesis of sulphonamide by hydroaminomethylation.

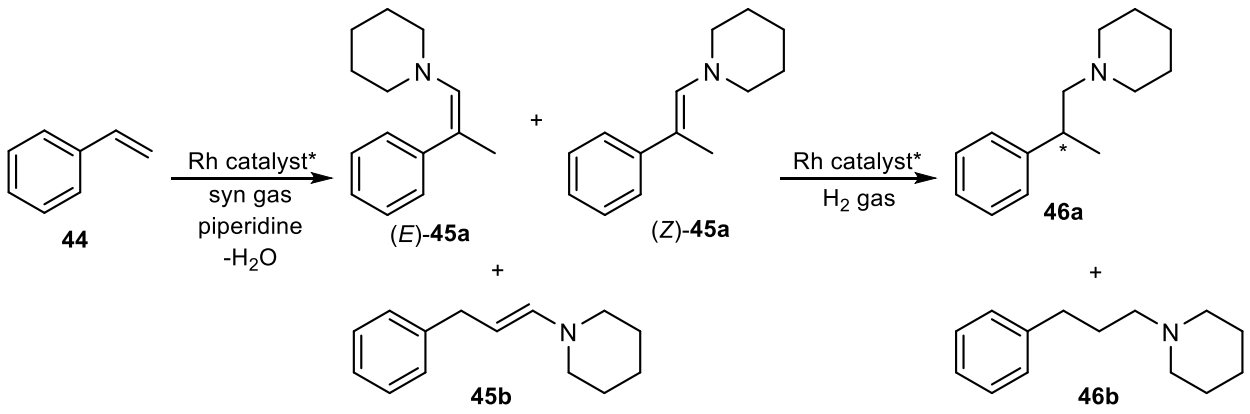
Apart from terminal and internal alkenes, Krische and co-workers achieved hydroaminomethylation of 1,3-dienes (Scheme 1.12).[32] Not only good selectivity towards a potentially useful intermediate was achieved (compound **40**), but also this method is advantageous due to an absence of a requirement of the toxic and flammable syngas. The drawback of the protocol is a very high catalyst loading.




**Scheme 1.12.** Hydroaminomethylation of 1,3-diene.

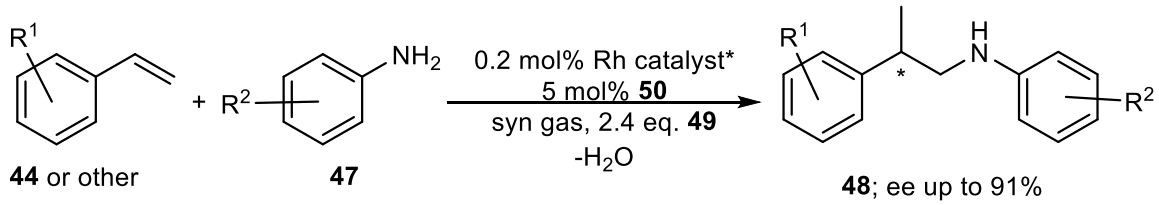
When amines are prepared synthetically or catalytically using achiral catalysts, in order to obtain enantio-pure products, an expensive chiral starting material would be required. Alternatively, a racemic sample could be resolved in several ways, typically by resolution with an enantio-pure carboxylic acid[1,33] (or Dutch resolution, where a mixture of chiral acids of the same family is used)[1,34] or kinetic resolution (typically using enzymes).[1,35] While some of these methods are used nowadays in industry, resolution methods are expensive, and not atom efficient due to the requirement of stoichiometric amounts of chiral carboxylic acids or enzymes. Since an amine produced is racemic initially, the maximum possible yield of the desired enantiomer after resolution can be only 50%. The most desirable method to produce a chiral amine industrially is by enantioselective catalytic reaction, which would be the most economic route towards an enantio-pure product.

Despite many publications in this area, a one-pot enantioselective version of the reaction was unknown for a long time. Part of the reason is that vast majority of the literature examples of this process report linear product (**46b**) as a major one (in some cases the only one).[26] Kalck and co-workers reported an attempt to perform the process enantioselectively with styrene and piperidine (Scheme 1.13).[36] Although some branched amine **46a** was produced, it was always racemic. A good library of various chiral ligands was tested, and after the hydroformylation step, the branched enamine is formed as a mixture of equal ratio of *E*- and *Z*- isomers. DFT calculations suggest that during hydrogenation step, each regio-isomer is hydrogenated to a different enantiomer of the amine, and the pathway energies are almost the same for both. Therefore, regardless of the chiral catalyst used in the study, the desired amine **46a** had an ee of 0%.




**Scheme 1.13.** Hydroaminomethylation of styrene with piperidine.

To the best of our knowledge, the very first, and the only example that might be described as an enantioselective hydroaminomethylation in the literature is the reaction shown in Scheme 1.14.[37] Several derivatives of styrene and amines were used, where an ee of up to 91% was achieved. The major draw-backs of the process are the requirements of high amounts of expensive chiral organocatalyst **50**, as well as excess of the reducing agent Et-HEH (**49**) (Figure 1.3) have to be used in order for the reaction to proceed. The need of the use of excess of the reducing agent Et-HEH rules out one of the positive advantages of the idea of hydroaminomethylation overall, where hydrogen gas from syngas can act as a reducing agent, and therefore, there are no extra requirements for another reducing agent.




**Scheme 1.14.** Enantioselective tandem hydroformylation – reductive amination of styrene.

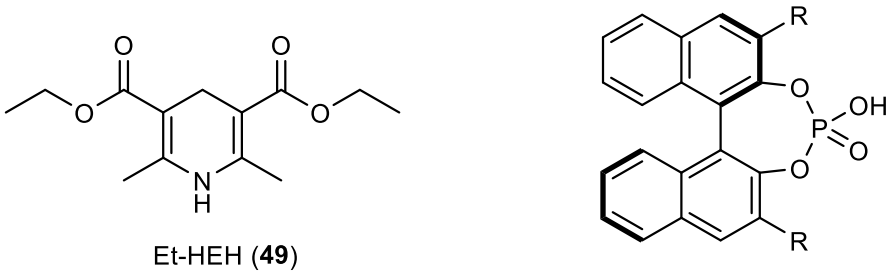



**Figure 1.3.** TRIP (**50**) and Et-HEH (**49**).

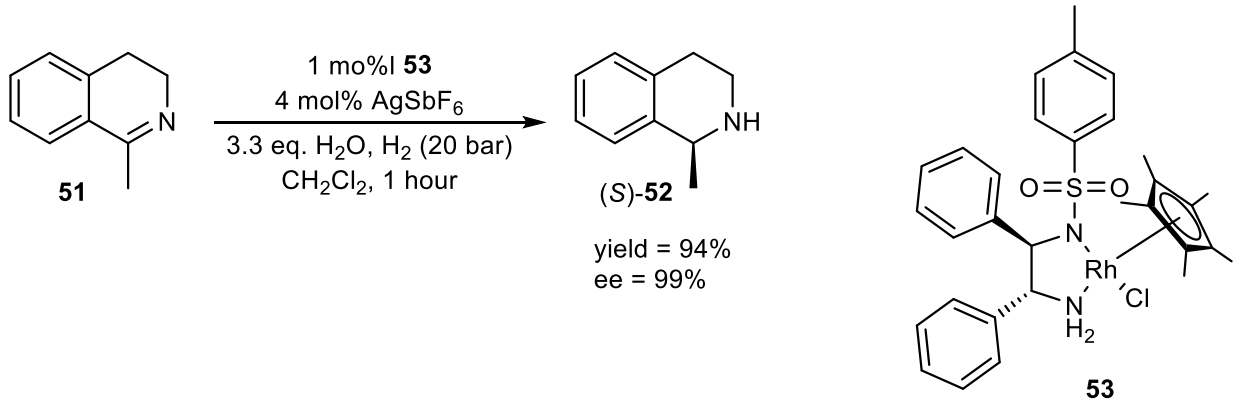
This paper is a big step forward, since it proves that the enantioselective version of the reaction is not impossible. However, there are some limitations in this process. The use of a primary amine to perform the reaction is crucial, since the reaction proceeds *via* formation of an imine intermediate (not enamine!). As only the primary amine can be used here as a starting material, the product of the reaction will always be the secondary amine. Therefore, to date, a one-pot enantioselective hydroaminomethylation where the final product formed is a chiral branched tertiary amine remains unknown. In order for it to proceed, a good branched-selective

hydroformylation catalyst is required, as well as enantioselective enamine hydrogenation catalyst, which are very rare (ideally, the same catalyst for both reactions). The catalyst must be stable in the presence of water as it is produced during formation of an enamine. If the two catalysts are used in one-pot, it is also important that they are not going to be in conflict with each other.

## 1.4 Catalytic routes towards chiral amines

### 1.4.1 Enantioselective imine hydrogenation

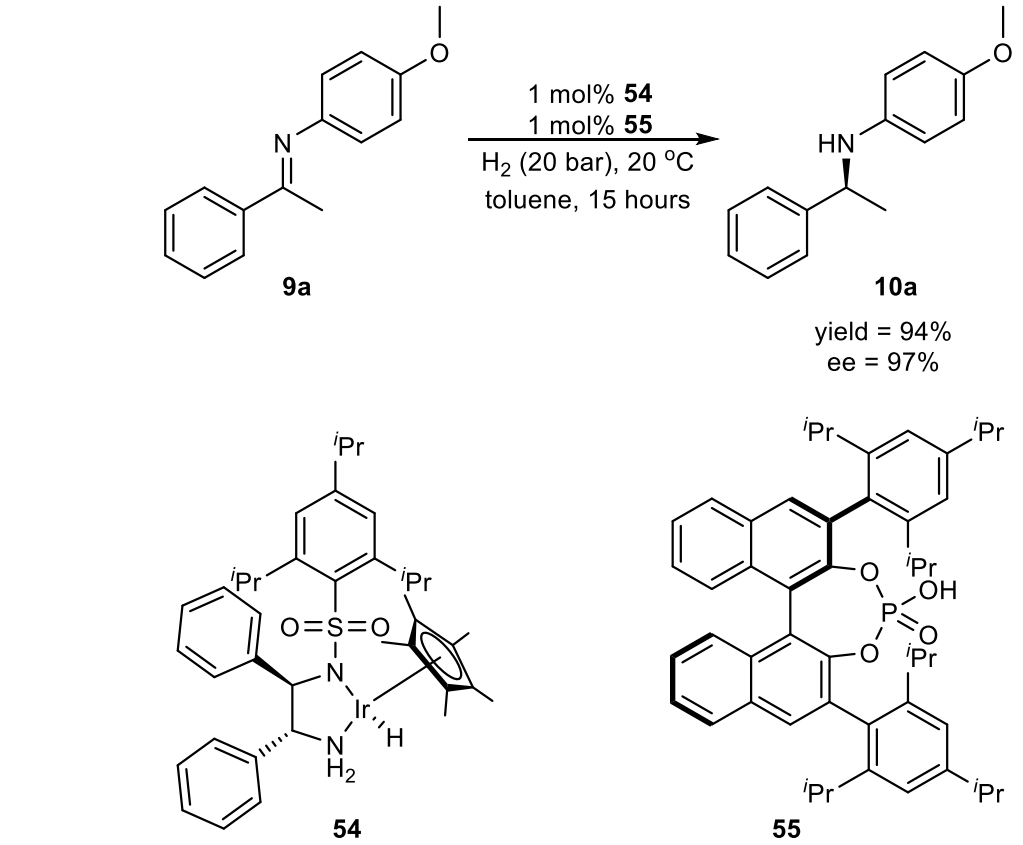
Enantioselective imine hydrogenation is a relatively well-studied field.[12,38] It was first discovered in 1975 by Scorrano and co-workers,[39] where an ee of only 22% was achieved. Since then, this reaction has received an increasing interest where many Rh, Ru and especially Ir complexes were explored.[12,38] An example of a highly-enantioselective process using a Rh catalyst is shown in Scheme 1.15,[40] where complex **53** is a modified version of Ikariya-Noyori catalyst.[41]



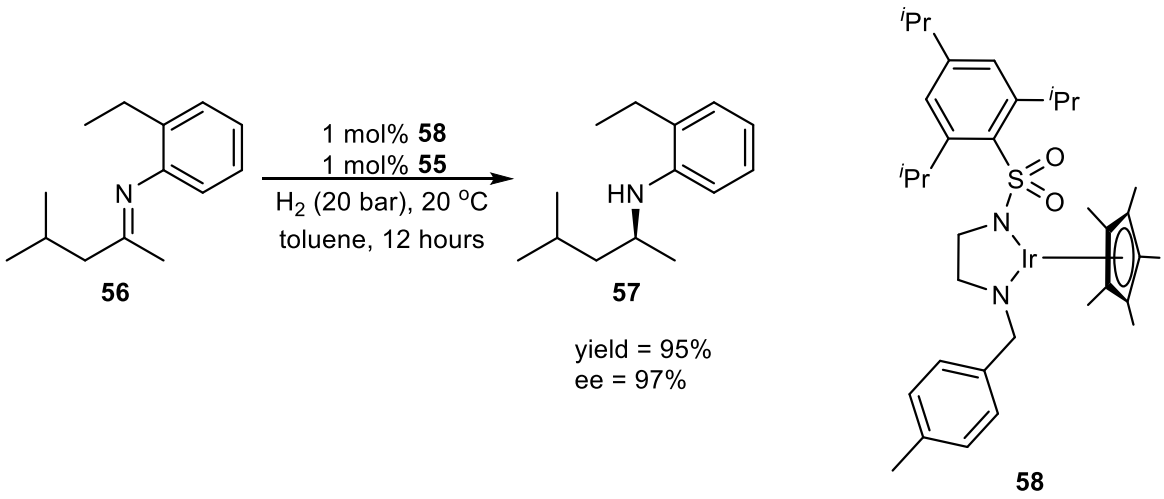

**Scheme 1.15.** Enantioselective hydrogenation of imine with high enantioselectivity.

Apart from cyclic imines, Xiao and co-workers reported highly-enantioselective hydrogenation of acyclic imines derived from both aromatic and non-aromatic ketones (examples are shown in Schemes 1.16 and 1.17).[42-44] The reaction was shown to work even *via* transfer hydrogenation with formic acid as a source of hydrogen, where computational and mechanistic experiments indicate that an iminium ion and Ir hydride are formed, following the reduction of the iminium cation to the secondary imine.[45] Although the same group reported hydrogenation of an imine with an achiral Ir catalyst with very low loadings of the transition

metal (the reaction was shown to work with as low as 0.005 mol% of iridium),[14,46] the chiral catalysts which were able to perform the reaction with high enantioselectivities required high catalyst loadings (too high for an industrial application).

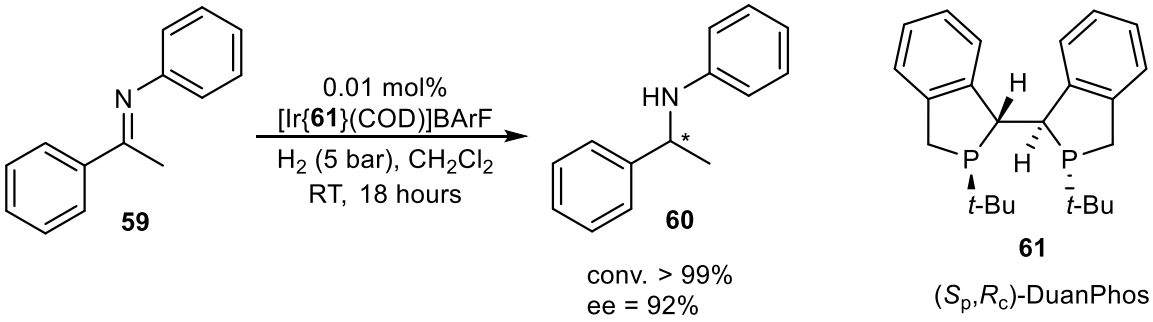



**Scheme 1.16.** An example of enantioselective hydrogenation of acyclic imine derived from aromatic ketone.[42]



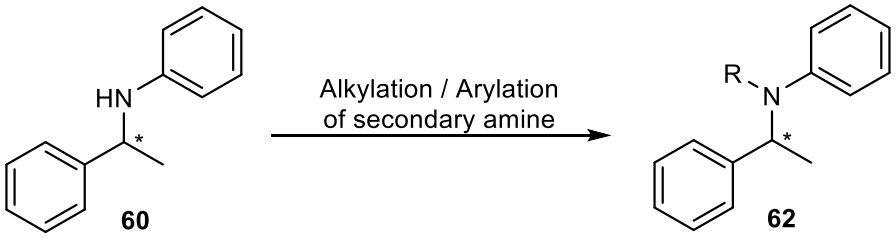

**Scheme 1.17.** An example of enantioselective hydrogenation of acyclic imine derived from aliphatic ketone.[43]

There is a good number of publications in this field, but examples of this reaction that exhibit very low catalyst loadings (0.01 mol% or lower) and high enantioselectivities (above 90%) are rare.[12,38] One such example comes from the work of Zhang and co-workers (Scheme 1.18).[47]




**Scheme 1.18**. Highly–active enantioselective hydrogenation of an imine.

While still being a challenging reaction, it can only produce a secondary amine (or sulfonamide and other protected primary amines). If a tertiary amine is desired, an extra alkylation / arylation step will be required (Scheme 1.19).

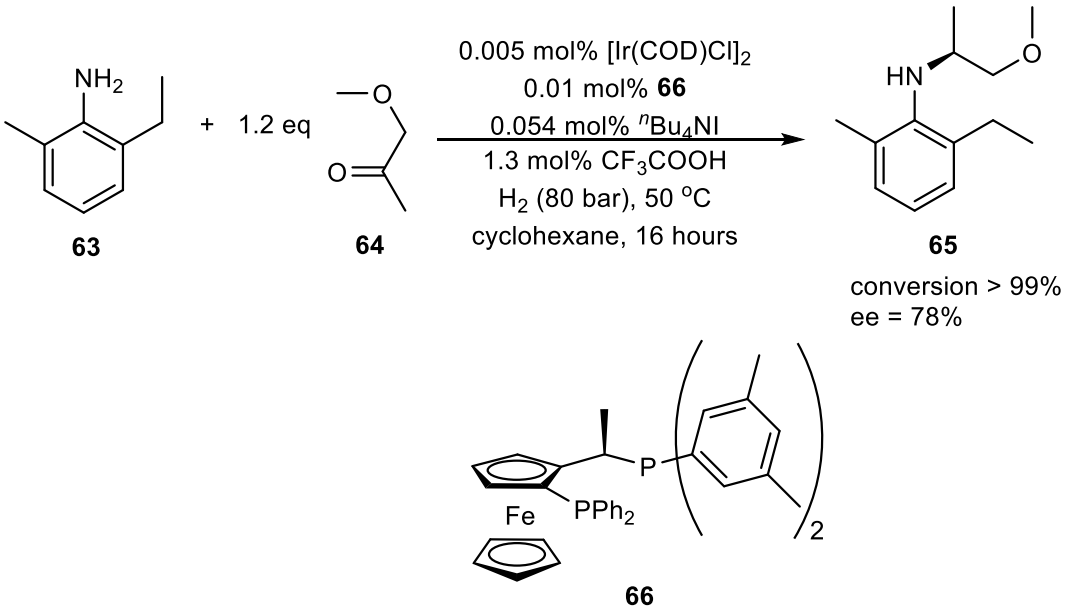



**Scheme 1.19**. Alkylation / arylation of secondary amine **60**.

### 1.4.2 Enantioselective reductive amination of carbonyl compounds by hydrogenation

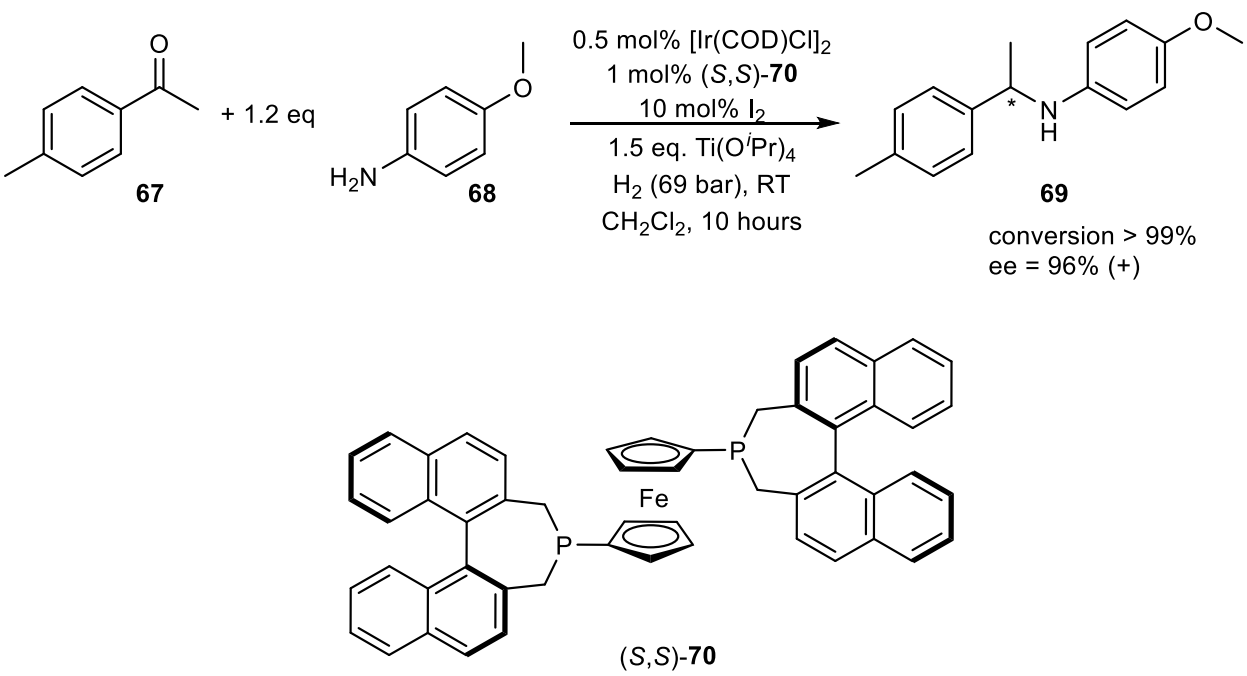
Enantioselective reductive amination is a very effective way of producing chiral amines.[15,48] The first example of enantioselective reductive amination by hydrogenation comes from the work of Blaser *et. al.* (Scheme 1.20).[49] While an excellent S/C ratio of 10000 is achieved, enantioselectivity of only up to 78% ee was achieved. Interesting to note, that the hydrogenation of the corresponding imine works with the same catalyst at S/C ratio of 1000000, affording the same enantioselectivity. It was also noted that wet starting materials slow the rate

of the reaction significantly. Therefore, it was thought that the slowest step in the reaction is the formation of the imine. The two stage procedure is preferred industrially and was the largest scale application of an enantioselective catalytic process.[50]



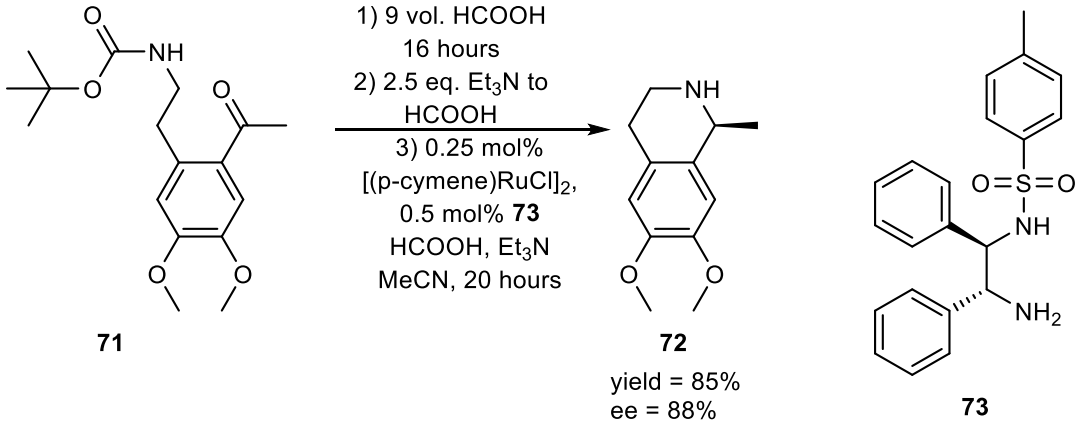

**Scheme 1.20**. The first example of enantioselective reductive amination.

In 2003, Zhang and co-workers reported a highly-enantioselective reductive amination of aromatic ketones.[51] Since aromatic ketones are in general less prone towards the formation of imines or enamines, supporting reagents such as titanium isopropoxide and iodine were required. While high enantioselectivities were achieved (an example is shown in Scheme 1.21), the requirements of high catalyst loading and big amounts of additives are disadvantageous.

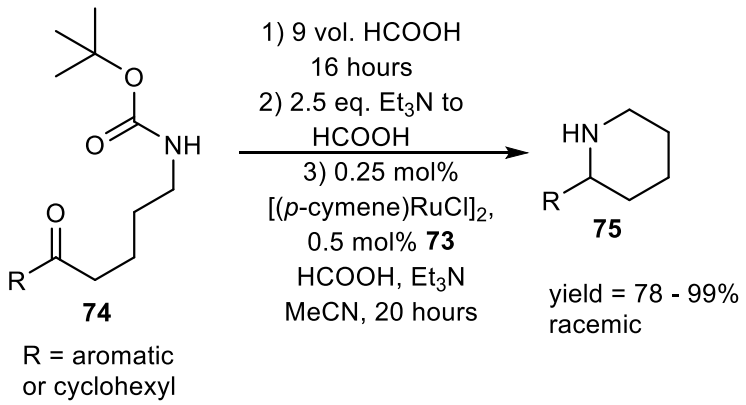



**Scheme 1.21**. Highly enantioselective reductive amination with Ir comples of ligand **70**.

The same year, Wills and co-workers reported an enantioselective intramolecular reductive amination, which consisted of the deprotection of amine **71**, followed by intramolecular imine formation, and its enantioselective reduction under transfer hydrogenation conditions (Scheme 1.22).[52] While good enantioselectivity was obtained with the substrate shown in Scheme 1.22, the process was shown to work for a few other substrates, although with no enantioselectivity (Scheme 1.23).




**Scheme 1.22**. Deprotection / enantioselective reductive amination of amine **71**.




**Scheme 1.23**. Deprotection / reductive amination of amines **74**.

One of the interesting observations is that in the imine intermediates formed, it is important to have the lone pair in the nitrogen atom *trans* to the aromatic ring (i.e. like in imine **76**). Whenever the lone pair is *cis* to the phenyl ring (for example imine **77**), no enantioselectivity was obtained.

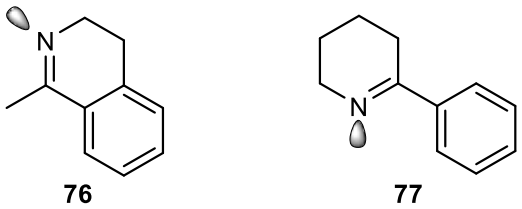


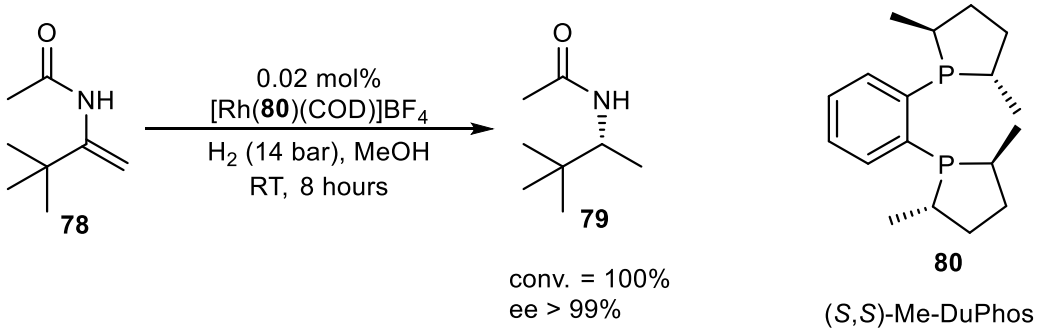

**Figure 1.4**. The lone pairs of the nitrogen atoms in imines **76** and **77**.

There are other papers in the literature for this process. For example, in 2009 Cabrera and co-workers reported a chiral Pd catalyst, which afforded especially good enantioselectivities with aliphatic ketones.[53] While the process did not require any additives (apart from molecular sieves to absorb water which is produced during formation of the imine), very high catalyst loadings were required (2.5 mol%) and a toxic and industrially undesirable solvent, chloroform, was used. Later on, Xiao and co-workers reported that Ir catalyst **54** with chiral phosphoric acid co-catalyst **55** (both shown in the scheme on page 12), is able to perform enantioselective reductive amination of a good library of ketones (both aromatic and aliphatic) with high enantioselectivities.[54,55] The only disadvantage of the protocol is a typical problem of the requirement of high loadings of the expensive chiral catalyst and acid. The limitation of the process is the same as for an achiral catalyst – i.e. more sterically hindered ketones (e.g. aromatic

ketones) have not been reported to react in this manner with secondary amines in order to produce tertiary amine products.

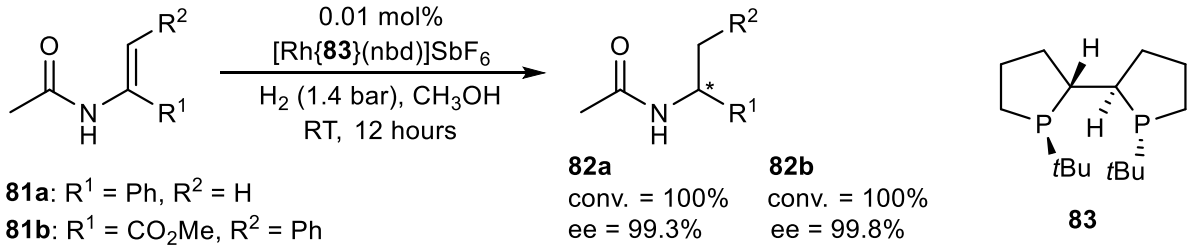
### 1.4.3 Enantioselective hydrogenation of enamides

Enantioselective hydrogenation of enamides is the most explored enantioselective hydrogenation process up-to-date.[12] The best early results were reported by Knowles and co-workers in 1970s,[56] and the field has developed extensively since then with many publications and industrial applications.[12,56,57] This resulted in a Nobel Prize being awarded to Knowles in 2001.[58] Many of the best examples of enamide hydrogenation are of a specific subclass of dehydroaminoacids.[59] However, simple enamides can also be reduced. One such example comes from the work of Johnson and co-workers in 1998, where the Rh complex of ligand **80** was shown to be very efficient for hydrogenation of *N*-(3,3-dimethylbut-1-en-2-yl)acetamide **78** as shown in Scheme 1.24.[60]



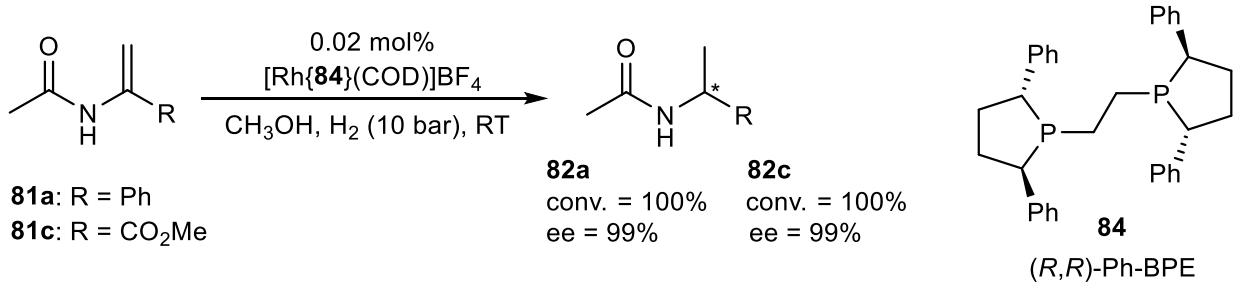

**Scheme 1.24.** Highly-efficient enantioselective enamide hydrogenation.

Another example of this process, carried out with a very low catalyst loading and excellent enantioselectivity comes from the work of Tang and Zhang in 2002 (Scheme 1.25).[61]



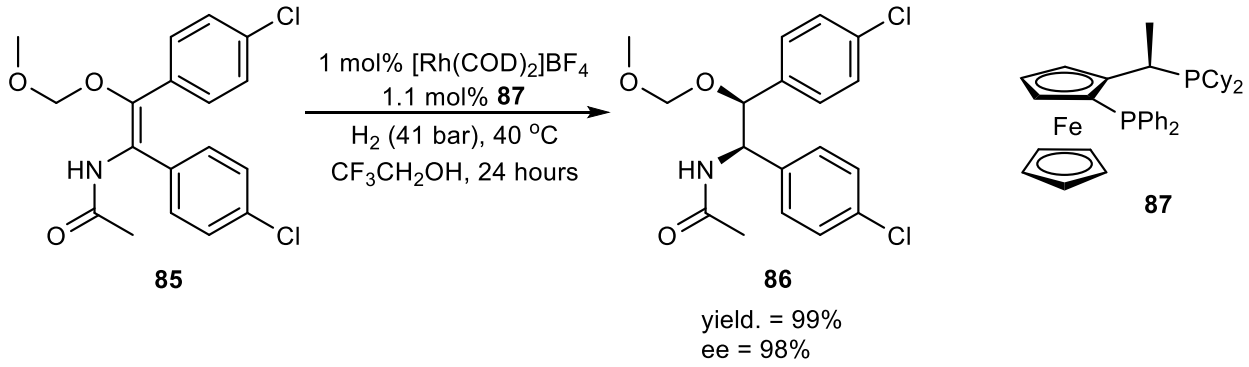

**Scheme 1.25.** Hydrogenation of enamides **81** with low catalyst loadings and excellent ee's.

One year later, another publication appeared in the literature from the work of Pilkington and Zanotti-Gerosa, where excellent activities and enantioselectivities were achieved with the rhodium complex of ligand **84**, as shown in Scheme 1.26.[62]



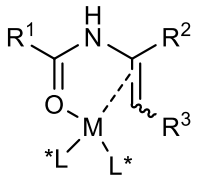

**Scheme 1.26.** Highly-efficient enantioselective enamide hydrogenation with the Rh complex of (*R*,*R*)-Ph-BPE ligand **84**.

Recent work of Zhang and co-workers shows that the reaction can be performed with enamides with tetrasubstituted double bonds with no other activation groups.[63] During the reaction two new chiral centres are formed, both of which are in very high ee (example is shown in Scheme 1.27).




**Scheme 1.27.** Highly selective enamide hydrogenation with the Rh complex of (*R*,*S*)-JosiPhos ligand **87**.

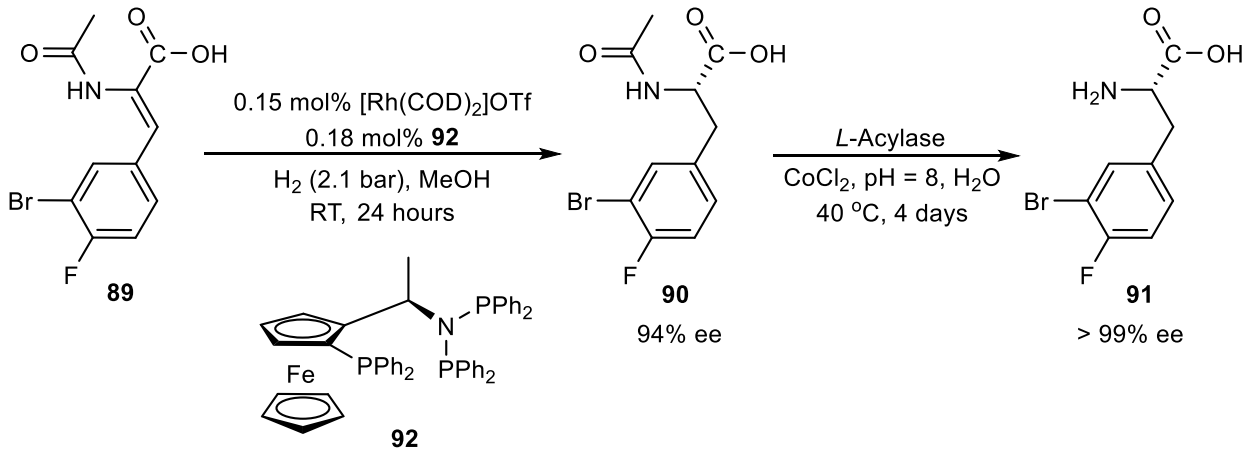
The reason why enamides work so well in the enantioselective hydrogenation is that the oxygen atom stabilises an intermediate of type **88** (Figure 1.5) and the transition state in the catalytic cycle, where the transition metal is in position to perform hydrogenation of the double bond.[12]




**88**

**Figure 1.5.** Stabilised intermediate of enamide (**88**) with a metal complex.

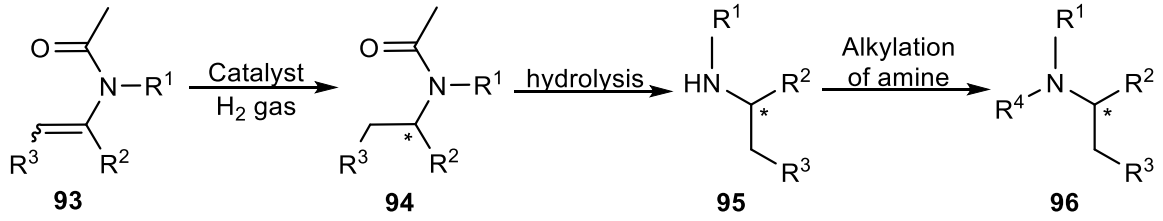
Very few desired pharmaceutical products are *N*-acetyl amides, so the acetyl group needs to be removed. For acylated primary amines, such as **90**, this can be done with acid or enzymatically (an example is shown in Scheme 1.28).[64] The enzymatic 'upgrade' approach is becoming popular in industry, since it can also improve the ee by kinetic resolution.




**Scheme 1.28.** Enamide hydrogenation followed by enzymatic amide hydrolysis with kinetic resolution.

In order to obtain a tertiary amine from **91**, a formation of two new nitrogen-carbon bonds is required which adds extra steps to the whole process.

The enantioselective hydrogenation of an *N*-alkylenamide followed by hydrolysis and alkylation (Scheme 1.29) is already unwieldy, adding extra steps, but has a second disadvantage: the removal of the *N*-acetyl group on acetylated secondary amines is more difficult since they are more stable towards acids and appear to be poor substrates for enzymes.[65] Finally, there are fewer examples of enantioselective hydrogenation of enamides with two alkyl / aryl substituents.[12]

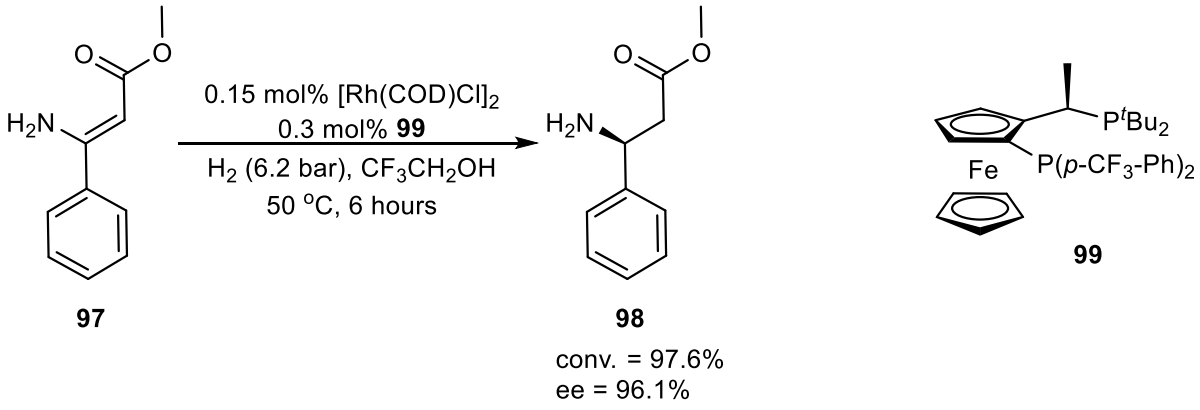



**Scheme 1.29.** Three-step synthesis of tertiary chiral amine from enamide *via* enantioselective hydrogenation of enamide.

### 1.4.4 Enantioselective hydrogenation of enamines

#### 1.4.4.1 Enantioselective hydrogenation of (*Z*)-aminoacrylates

A way to produce a specific type of chiral primary amine is the hydrogenation of (*Z*)-aminoacrylates (for example **97**). Enantioselective hydrogenation of this type of substrates is well explored.[12,57,66-68] An example of this reaction being performed efficiently with high enantioselectivity is shown in Scheme 1.30.[66] In the paper the substrate scope was limited to aromatic groups attached to the pro-chiral carbon atom (i.e. in the chosen example in the scheme the phenyl group).




**Scheme 1.30**. Enantioselective hydrogenation of (*Z*)-aminoacrylate **97**.

The reason for the high activity and enantioselectivity of this reaction is that **97** forms the imine tautomer where the lone pair of oxygen atom coordinates to the transition metal and therefore promotes the formation of intermediate **101**, which is involved in the catalytic cycle (Figure 1.6).[57,66]

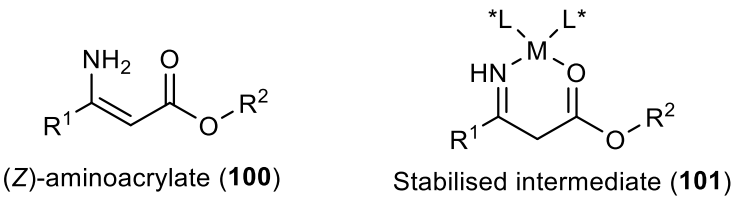
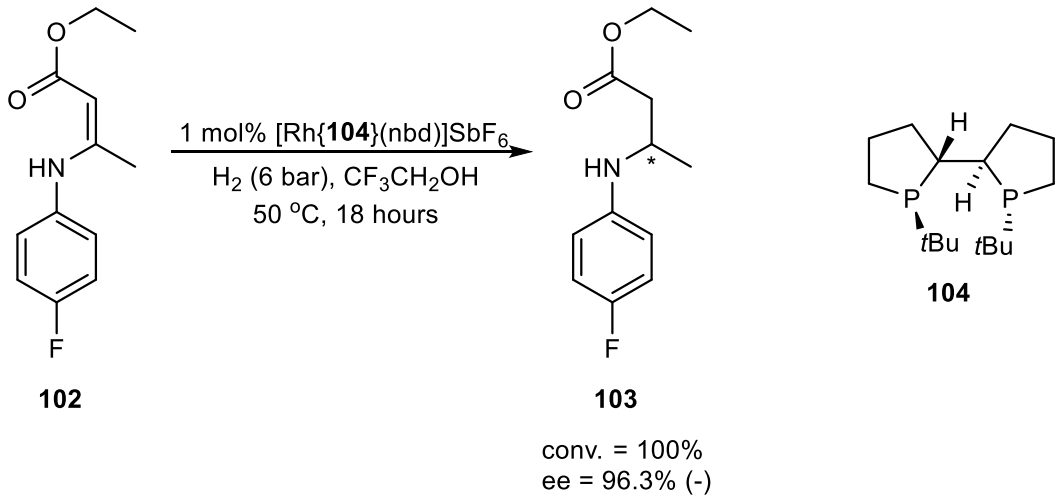



**Figure 1.6.** (*Z*)-aminoacrylate (**100**) and stabilised intermediate with a metal complex (**101**).

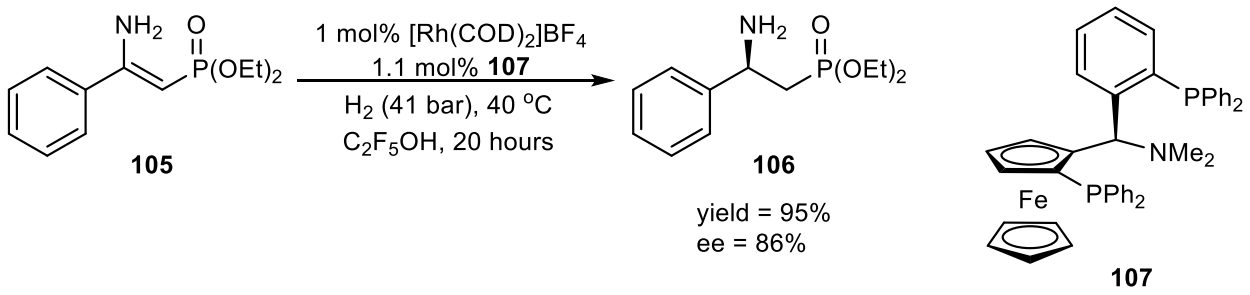
Presence of the intermediate **101** suggests that the reaction is an imine hydrogenation rather than enamine hydrogenation, but in any case the extra functionality present here means these are cultivated substrates rather like enamides.

In 2005, Zhang and co-workers reported highly-enantioselective hydrogenation of a different substrate scope, where the secondary amines were used.[69] Also non-aromatic substituents were present on the carbon 1, where very high enantioselectivities were achieved (Scheme 1.31).




**Scheme 1.31**. Enantioselective hydrogenation of (*Z*)-aminoacrylate **102**.

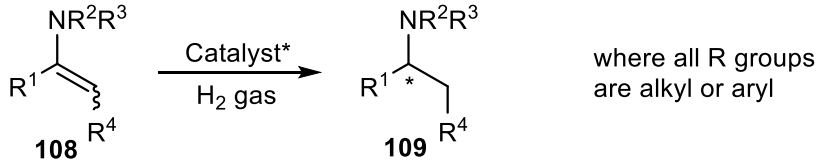
Apart from (*Z*)-aminoacrylates, recently Zhou *et. al.* reported the enantioselective hydrogenation of a more challenging substrate, β–enamine phosphonate (**105**) (Scheme 1.32).[70] Although a high catalyst loading is required, the reaction proceeds well without any protection groups on the amine (typically an acyl group is required).[70,71] In the paper, several examples with very good enantioselectivities are reported.




**Scheme 1.32**. Enantioselective hydrogenation of β–enamine phosphonate **105**.

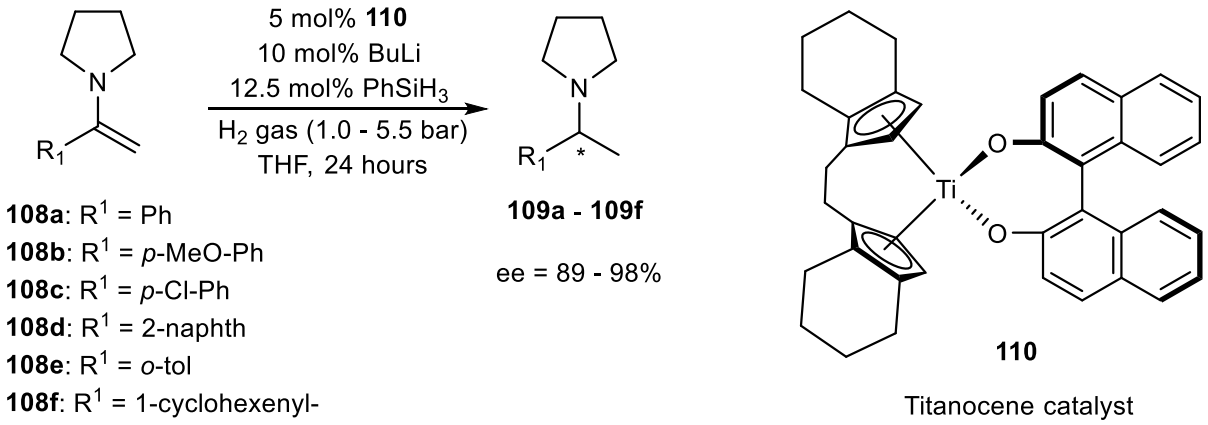
### 1.4.4.2 Enantioselective hydrogenation of unfunctionalised enamines

In 2007, at a meeting of the Green Chemistry Pharmaceutical Roundtable, enantioselective enamine hydrogenation (Scheme 1.33) (as well as enantioselective hydroaminomethylation) was voted to be one of the most desirable but unrealised transformations.[72]



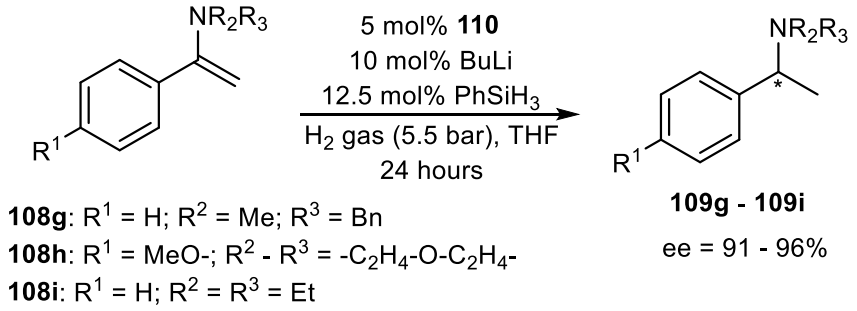

**Scheme 1.33.** General scheme for enantioselective enamine hydrogenation.

Although hydrogenation of enamides or (*Z*)-aminoacrylates are very well explored fields, enantioselective enamine hydrogenation has been barely explored. The first encouraging results in enantioselective hydrogenation of unfunctionalised enamines were achieved only in 1994 by Lee and Buchwald, where titanocene catalyst **110** was applied as shown in the Scheme 1.34.[73] Although an ee of 98% was achieved with enamine **108e**, only a limited number of substrates was explored. Very high catalyst loading (5 mol%) and a requirement for catalyst activation (large amounts of BuLi and $PhSiH_3$) makes it unviable to be applied in industry.



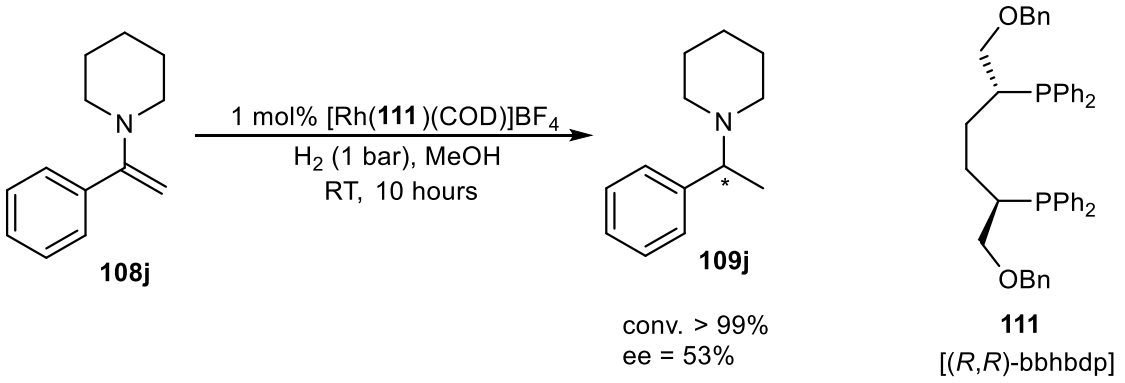

**Scheme 1.34.** Enantioselective hydrogenation of unfunctionalised enamine using titanocene catalyst.

Apart from the pyrrolidine moiety, a few other substituents on the nitrogen atom were explored as well (Scheme 1.35).

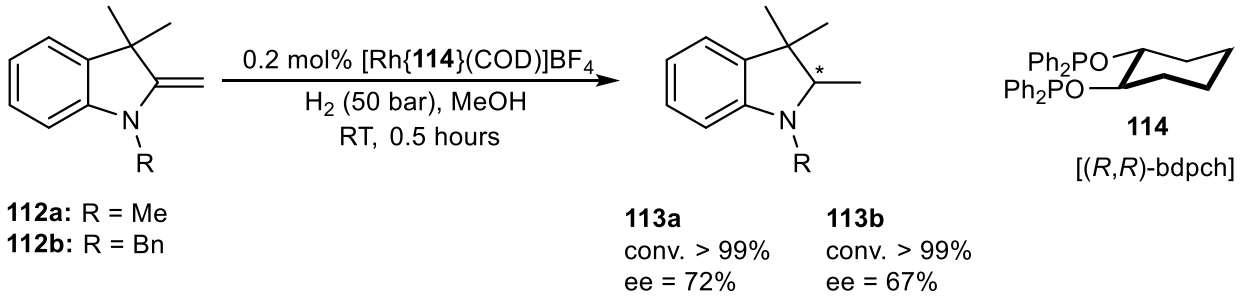



**Scheme 1.35.** Enantioselective hydrogenation of unfunctionalised enamine using titanocene catalyst.

Six years later, the second example of an enantioselective enamine hydrogenation appeared in the literature where Rh complexes of bidentate chiral phosphorous ligands **111** and **114** were used as catalysts for the enantioselective hydrogenation of unfunctionalised enamines (Schemes 1.36 and 1.37).[74] While the catalyst loading was reduced to 0.2 mol% in cases of hydrogenating **112a** and **112b** (which is still very high for an industrial process) (Scheme 1.37), an ee of only up to 72% was achieved.

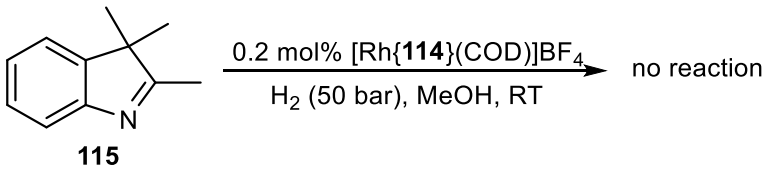



**Scheme 1.36.** Enantioselective hydrogenation of enamine **108j**.




**Scheme 1.37.** Enantioselective hydrogenation of enamines **112a** and **112b**.

Interestingly, [Rh{**114**}(COD)]$BF_4$ hydrogenates the enamine only, while does not do so with imine **115** (Scheme 1.38):

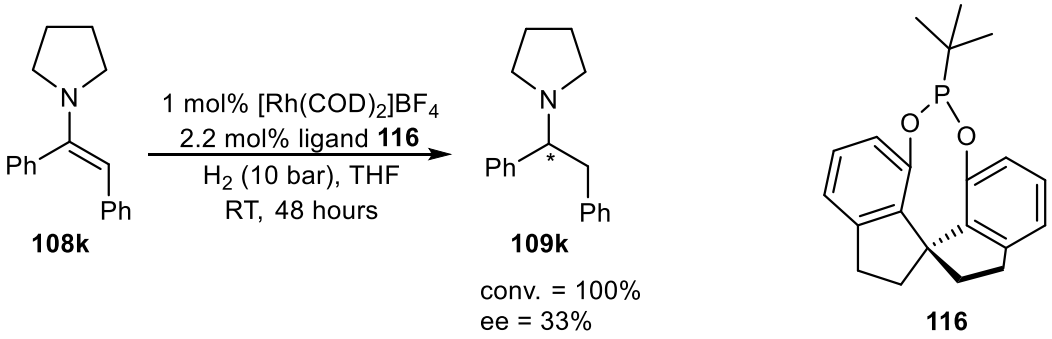



**Scheme 1.38.** Unsuccessful attempt to hydrogenate an imine with [Rh{**114**}(COD)]$BF_4$.

In 2006, Zhou and co-workers reported a rhodium catalyst for the hydrogenation of pyrrolidine-derived enamines (Scheme 1.39).[75] The best ligand identified was the monodentate ligand **116**. It afforded the desired product **109k** with an ee of 33%. When $I_2$ (2 mol%) was used as an additive for the same reaction, the ee of the product went up to 83%. But if 1 mol% or 5 mol% of the iodine relative to the substrate were used, the ee values were 71% and 77% respectively. At this stage, Zhou did not suggest any possible reason for this iodine effect. It was

also discovered that if an additional 20 mol% of acetic acid relative to the substrate were added, the ee increased to 87% and the reaction time was decreased by four times. If acetic acid (or $H_2SO_4$, or *o*-phthalimide) was added without iodine, the catalyst was deactivated.

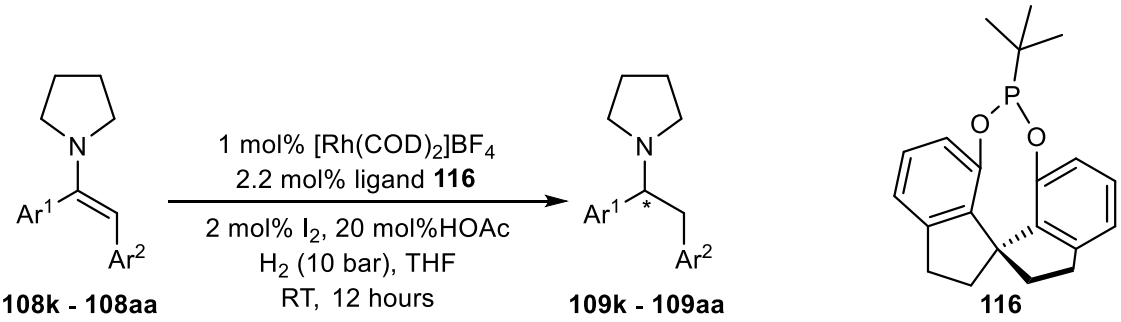
In this reaction different solvents were also screened (diethyl ether, dichloromethane, dioxane, toluene, methanol and THF), where it was shown that the highest ee was obtained when the reaction was performed in THF.




**Scheme 1.39.** Asymmetric hydrogenation of enamine **108k**.

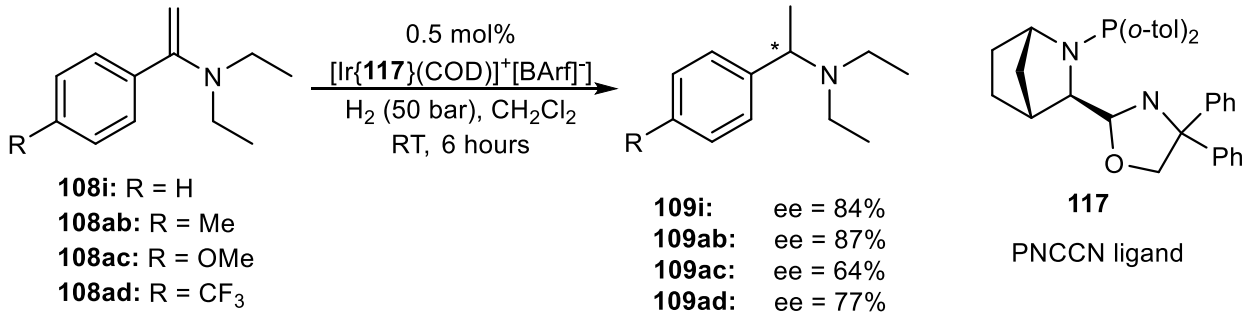
After optimisation of this process was complete, a library of pyrrolidine-derived enamines **108k** – **108aa** was screened for the enantioselective hydrogenation (Table 1.1). The highest ee (99.9%) was achieved when **108x** was hydrogenated. If the pyrrolidine moiety found in substrate **108k** was changed to a morpholine or piperidine, the enantioselectivities were reduced to 77% and 75% respectively.

**Table 1.1.** Asymmetric hydrogenation of substrates **108a - 108q**.



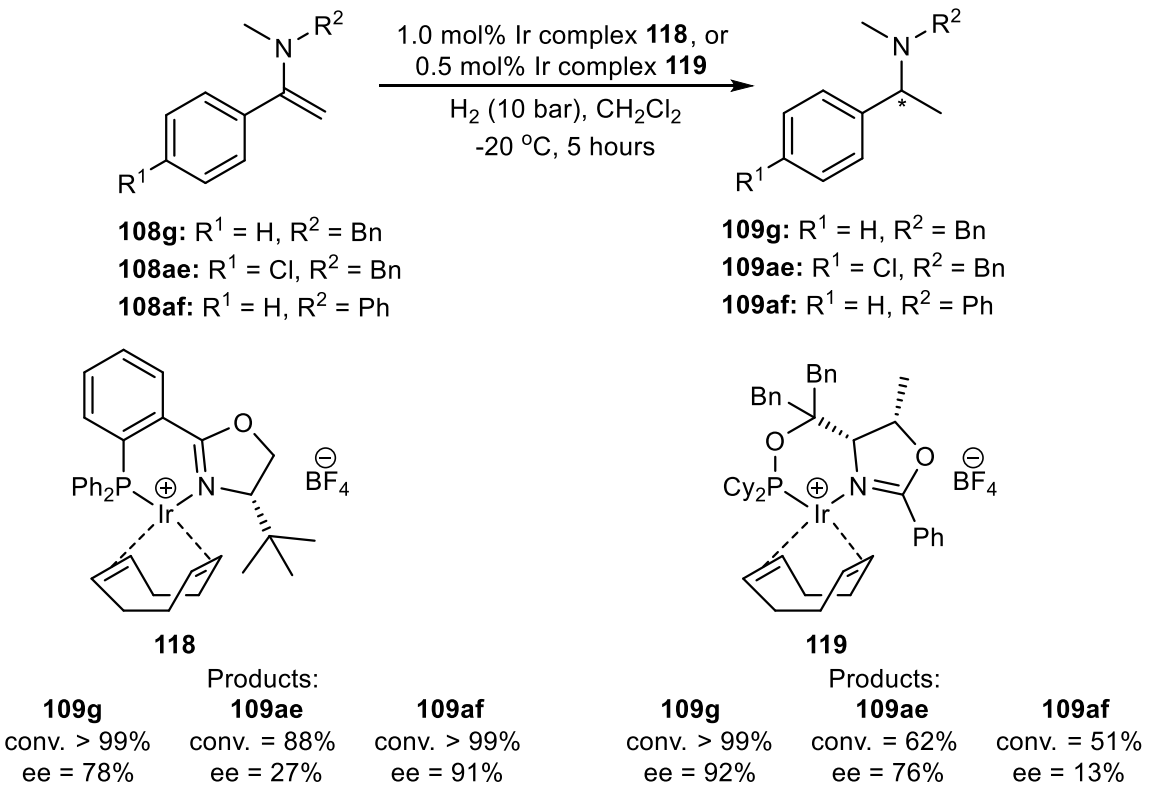

| Entry | Enamine | $Ar^1$ | $Ar^2$ | Product | ee, % |
|---|---|---|---|---|---|
| 1 | **108k** | Ph | Ph | **109k** | 87 |
| 2 | **108l** | *p*-tol | Ph | **109l** | 91 |
| 3 | **108m** | *m*-tol | Ph | **109m** | 90 |
| 4 | **108n** | *o*-tol | Ph | **109n** | 90 |
| 5 | **108o** | 4-$MeOC_6H_4$ | Ph | **109o** | 95 |
| 6 | **108p** | 3,4-$(MeO)_2C_6H_3$ | Ph | **109p** | 99 |
| 7 | **108q** | 4-$ClC_6H_4$ | Ph | **109q** | 73 |
| 8 | **108r** | Ph | *o*-tol | **109r** | 94 |
| 9 | **108s** | Ph | 2-$ClC_6H_4$ | **109s** | 93 |
| 10 | **108t** | Ph | 3-$ClC_6H_4$ | **109t** | 90 |
| 11 | **108u** | Ph | *p*-tol | **109u** | 80 |
| 12 | **108v** | Ph | 4-$ClC_6H_4$ | **109v** | 96 |
| 13 | **108w** | Ph | 4-$BrC_6H_4$ | **109w** | 97 (*R*) |
| 14 | **108x** | Ph | 4-$FC_6H_4$ | **109x** | 99.9 |
| 15 | **108y** | *m*-tol | 4-$FC_6H_4$ | **109y** | 90 |
| 16 | **108z** | 4-$MeOC_6H_4$ | 4-$FC_6H_4$ | **109z** | 95 |
| 17 | **108aa** | 4-$MeOC_6H_4$ | 4-$ClC_6H_4$ | **109aa** | 93 |

Several examples appeared in the field subsequently, where chiral Ir catalysts are explored.[76-78] In 2008, Andersson and co-workers tested a few Ir complexes with the bidentate ligands of PNCCN class.[76] The most enantioselective ligand out of those tested (**100**) is shown in Scheme 1.40. The iridium complex of this ligand shows good activity affording full conversions for the substrates shown in the scheme after 6 hours at room temperature using 0.5 mol% of catalyst. The highest ee achieved was 87% when **91ab** was hydrogenated. When the 4-methyl group on the aromatic ring was changed to H, $CF_3$ or methoxy groups (substrates **91i**, **91ac** and **91ad**), drops in enantioselectivities were observed. Attempts to use substrates, where the ethyl groups on the nitrogen atom in **91ab** were changed to pyrrolidine or morpholine moieties gave lower activities and enantioselectivities in both cases.




**Scheme 1.40.** Enantioselective enamine hydrogenation with an Ir complex of PNCCN ligand **117**.

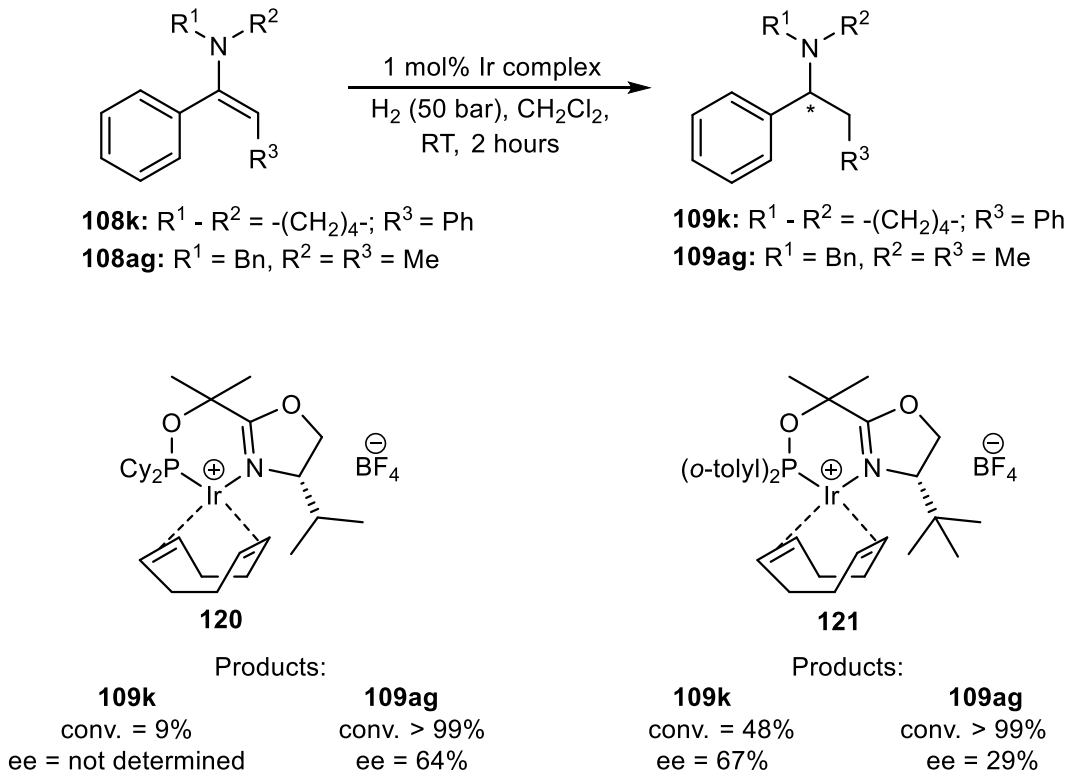
In 2009, Baeza and Pfaltz discovered several Ir complexes capable of performing enantioselective hydrogenation of unfunctionalised enamines.[77] In their work it is clearly shown that the problem of the existing catalysts for this process is that they only give high enantioselectivities for a selected narrow range or specific examples of substrates only. For example, as shown in Scheme 1.41, two of the Ir complexes are compared for hydrogenation of several 1-arylethenamines (**108g**, **108ae**, **108af**).




**Scheme 1.41.** Enantioselective hydrogenation of 1-arylethenamines.

This example shows that a small modification of the enamine can result in a change of the choice of catalyst: for enamines **108g** and **108ae**, iridium complex **119** gives higher enantioselectivities in the hydrogenation reaction, while for the substrate **109af**, the ee of the product is higher when complex **118** is used.

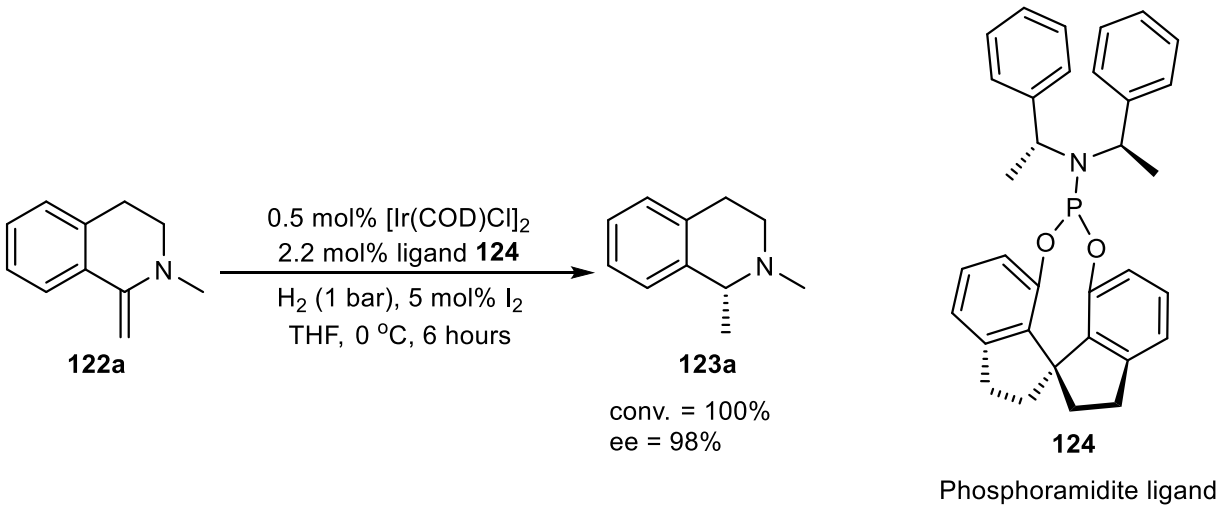
When slightly different enamines are hydrogenated, different catalysts appeared to be more enantioselective (Scheme 1.42). With variations in $R^1$, $R^2$ and $R^3$ groups the enantioselectivities of iridium complexes **120** and **121** vary significantly.




**Scheme 1.42.** Enantioselective hydrogenation of (*Z*)-2-aryl/alkyl-1-phenylenamines.

These results clearly suggest that not only different types of enamines require different catalysts, but also substitution of some groups in enamines can have a massive effect on the enantioselectivities. A couple of extra examples are present in the paper which support the observation that for every enamine the most enantioselective catalyst can be different for no obvious reason. The lowest catalyst loading used in this work was 0.5 mol% – i.e. much too high for application in an industrial process.

An important example of Ir catalysed enantioselective hydrogenation of unfunctionalised enamines comes from 2009 where monodentate phosphoramidite ligand **124** was shown to be efficient for enantioselective enamine hydrogenation (Scheme 1.43).[78]

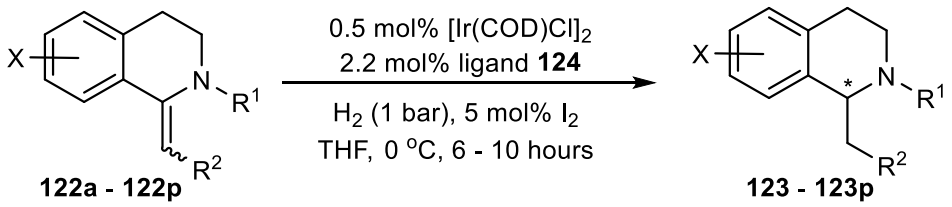



**Scheme 1.43.** Ir catalysed enantioselective hydrogenation of unfunctionalised enamines.

As had been noted previously,[75] the use of $I_2$ as an additive leads to a dramatic increase in enantioselectivity (10% ee without the iodine to 98% ee with iodine co-catalyst). Other iodine-containing additives such as KI (ee of **123a** = 95%) and $Bu_4NI$ (ee of **123a** = 92%) were applied with a similarly clear effect on enantioselectivity. For the additive-free system, the replacement of $[Ir(COD)Cl]_2$ with $[Ir(COD)I]_2$ also leads to the increase of ee of the product from 10% to 90%. This suggests that the role of iodine is a formation of a new catalytic iridium-iodine species which is able to catalyse the reaction enantioselectively, but no further role of iodine on enantioselectivity was commented. The success of $[Ir(COD)I]_2$ suggests that the catalytic cycles of modified and unmodified catalysts go through the same oxidation states.

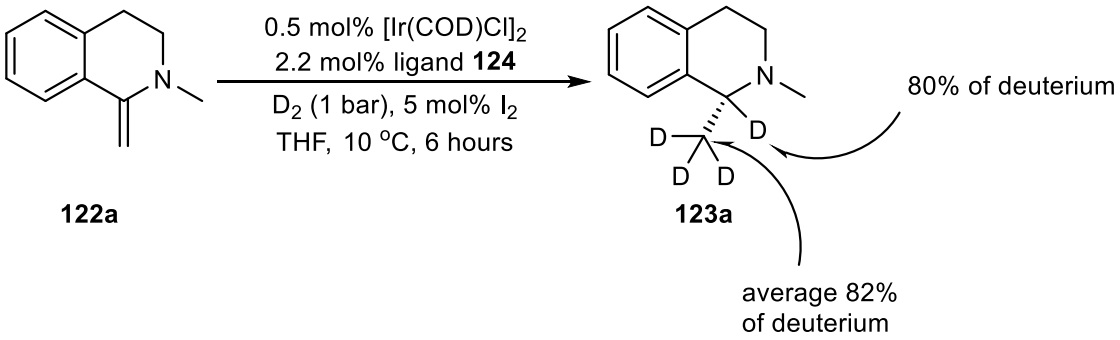
A solvent screen revealed THF to be the best for this process in terms of enantioselectivity of the catalyst. After these optimisations, Zhou and co-workers explored more substrates for this catalytic system (Table 1.2).

**Table 1.2.** Asymmetric hydrogenation of substrates **122a** – **122p**.



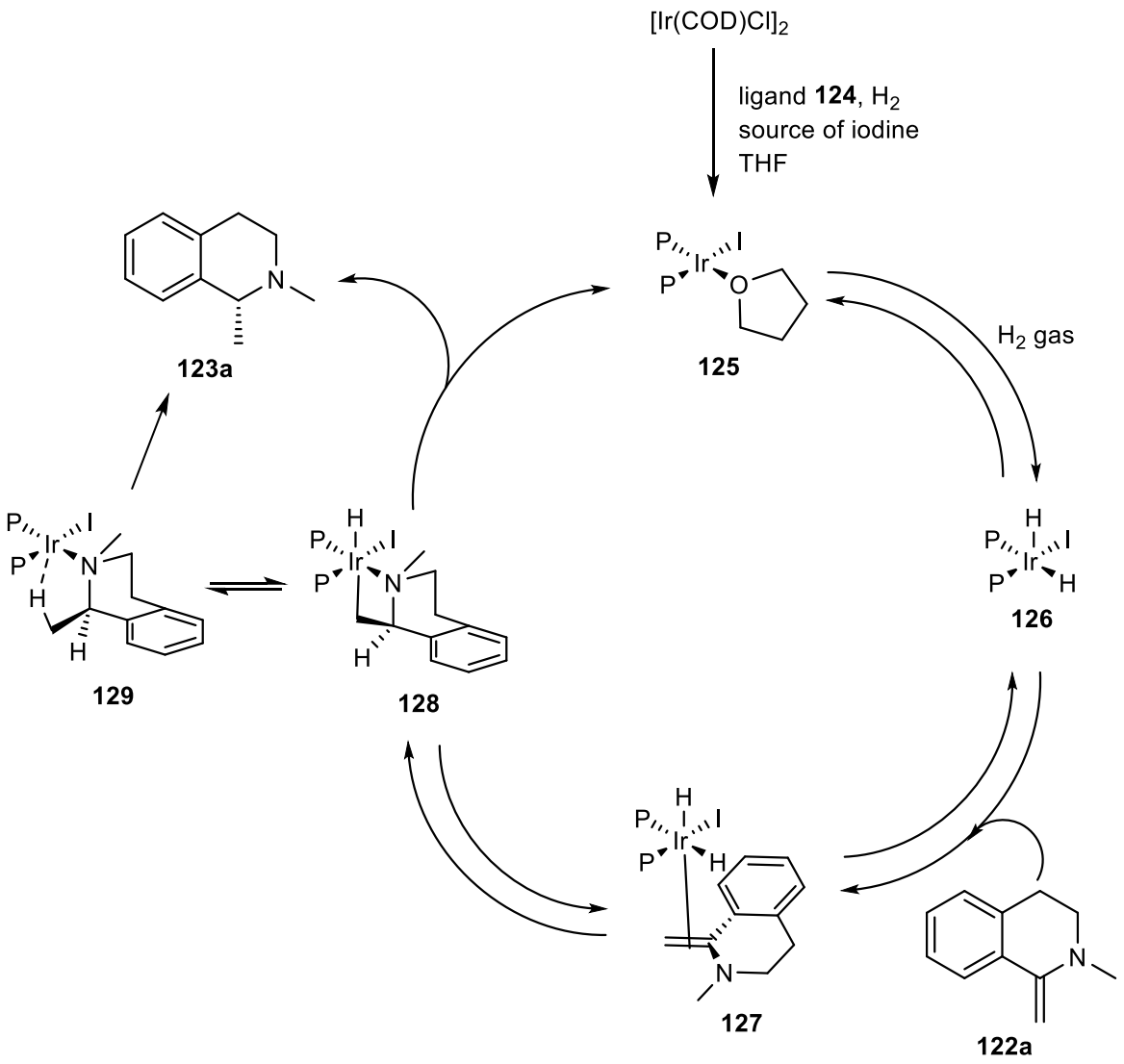

| Enamine | *E* / *Z* | $R^1$ | $R^2$ | X | Time, h | Amine | ee, % |
|---|---|---|---|---|---|---|---|
| **122a** | n.a. | Me | H | H | 6 | **123a** | 98 (*R*) |
| **122b** | n.a. | Me | H | 7-Me | 6 | **123b** | 98 |
| **122c** | n.a. | Me | H | 6-MeO | 6 | **123c** | 96 |
| **122d** | n.a. | Me | H | 7-MeO | 6 | **123d** | 94 |
| **122e** | n.a. | Me | H | 6,7-$(MeO)_2$ | 6 | **123e** | 95 (*R*) |
| **122f** | n.a. | Et | H | H | 6 | **123f** | 98 |
| **122g** | n.a. | Bn | H | H | 10 | **123g** | 90 |
| **122h** | n.a. | $^i$Pr | H | H | 10 | **123h** | 71 |
| **122i** | 3.5 / 1 | Me | Me | H | 7 | **123i** | 95 |
| **122j** | 3.0 / 1 | Me | Me | 6-MeO | 7 | **123j** | 92 |
| **122k** | 3.2 / 1 | Me | Me | 7-MeO | 7 | **123k** | 92 |
| **122l** | 7.3 / 1 | Et | Me | H | 7 | **123l** | 96 |
| **122m** | 3.4 / 1 | Me | $^n$Pr | H | 10 | **123m** | 60 |
| **122n** | 5.7 1 | Et | Et | H | 10 | **123n** | 58 |
| **122o** | 4.3 / 1 | Me | Ph | H | 5 | **123o** | 74 |
| **122p** | 5.2 / 1 | Et | Ph | H | 5 | **123p** | 73 |

An increase in steric bulk of $R^1$ results in a drop of enantiomeric excess of the product (substrates **122g** and **122h** compared to **122a**). In order to define some mechanistic features of this process, **122a** was hydrogenated with $D_2$ gas (Scheme 1.44).



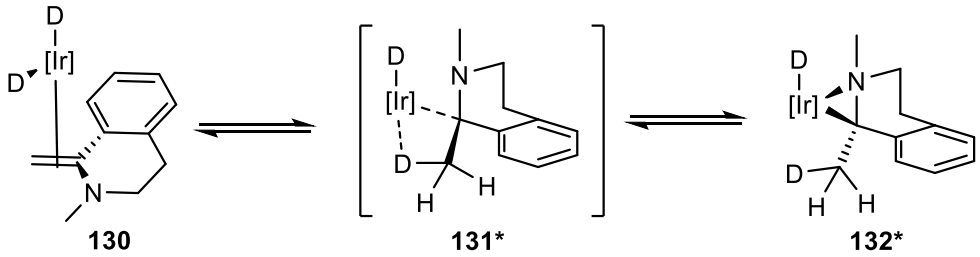

**Scheme 1.44.** Hydrogenation of enamine with $D_2$ gas.

Such an unexpected distribution of deuterium in **123a** suggests that hydrogen-deuterium exchange occurs when intermediate between iridium and enamine is already formed. A catalytic cycle was therefore proposed, which could explain such an observation (Scheme 1.45). Fast interchange between **128** and **129** would result in the deuterium incorporation observed.



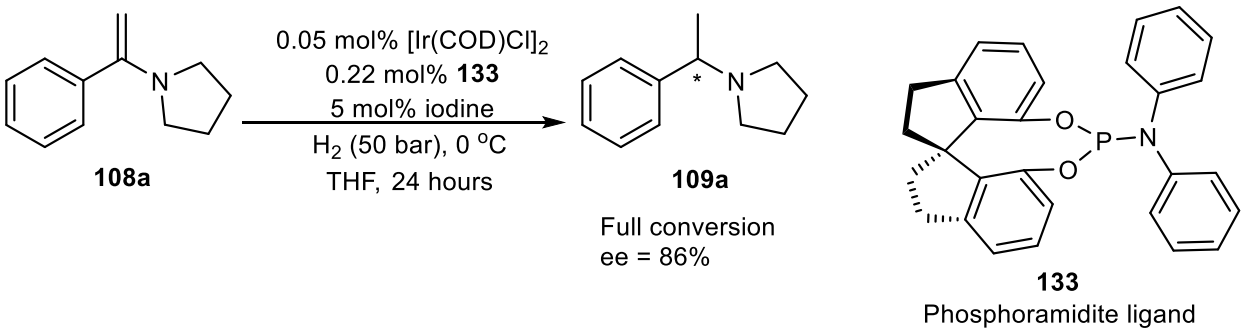

**Scheme 1.45.** Proposed enamine hydrogenation mechanism by Zhou *et. al.*

The reason for an unexpected deuterium distribution could alternatively be due to the formation of intermediate **132*** – i.e. the insertion into the Ir-H bond occurs at the opposite end of the bond resulting in the reversible formation of a 3-membered ring with Ir metal. A 3-membered ring pathway for enamine hydrogenation was calculated to be viable in 2011 by Bühl, Clarke and co-workers (Scheme 1.46).[5]



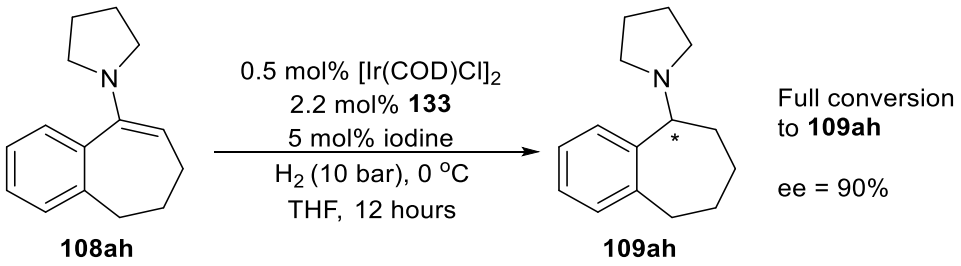

**Scheme 1.46.** Alternative mechanism for the formation of catalytic transition state **131*** and intermediate **132*** before the reductive elimination.

In 2010, Zhou and co-workers reported the same class of ligand (*N*,*N*-diarylphosphoramidite) to be efficient in the hydrogenation of not only cyclic enamines, but also simple di-substituted enamine **108a**.[79] It was shown that the reaction can proceed at Ir / substrate ratio of 1 / 1000 (Scheme 1.47).




**Scheme 1.47.** Enantioselective hydrogenation of enamine **108a** with an Ir catalyst of chiral ligand **133**.

While this example represents a clear improvement of the TON compared to any previously reported enantioselective enamine hydrogenation literature examples, there was only a single example of metal loading of 0.1 mol% in the paper (which is still too high for an application in industrial process), and a more common loading of iridium was 1 mol%. Another important aspect of the reaction to note is that in order to achieve high enantioselectivity, the reaction was performed at 0 °C, which is undesirable for an industrial process. The catalyst was not active enough for some substrates, and in those cases higher temperature (50 °C) had to be used which resulted in a negative effect on the enantioselectivities. The best ee achieved in this study is 90% (Scheme 1.48).




**Scheme 1.48.** Enantioselective hydrogenation of enamine **108ah**.

A few years later, an attempt was made to use an enantioselective enamine hydrogenation process to prepare a single enantiomer of mequitazine.[80] This compound is an antihistamine drug which is used to treat allergies.[81] While it can be used as a racemic mixture since both enantiomers are non-toxic, it was found that only the (*S*)-enantiomer (Figure 1.7) is actually active in the body.[81]

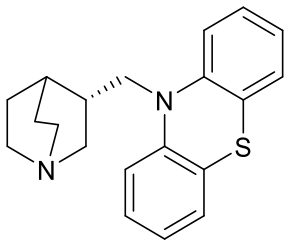
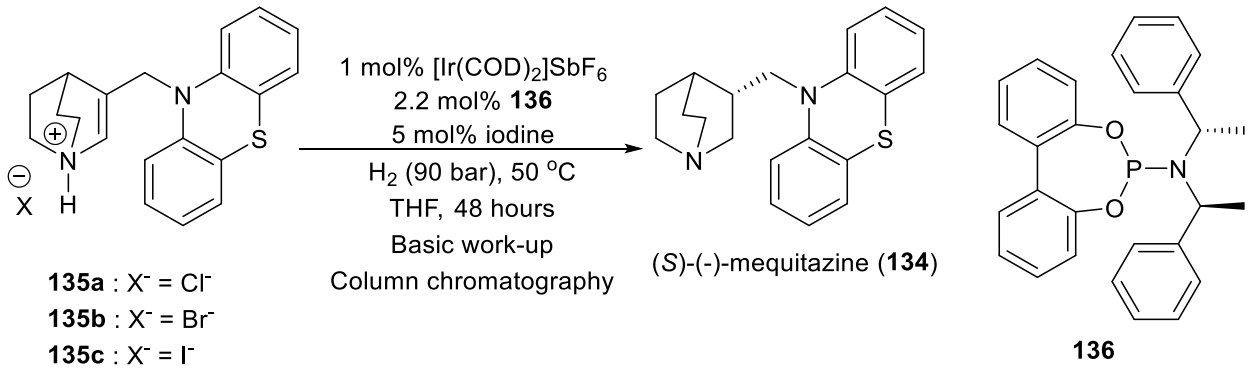



**Figure 1.7.** (–)-(*S*)-mequitazine (**134**).

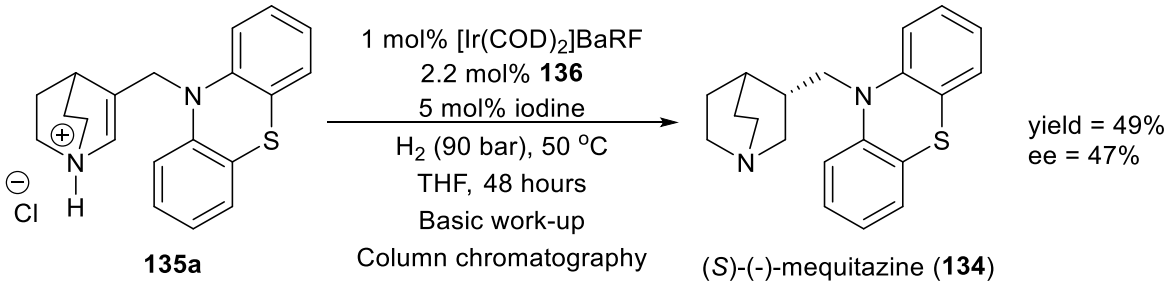
Ratovelomanana-Vidal and co-workers decided to prepare *endo*-dehydromequitazine salts (**135a**-**135c**) and target the enantioselective hydrogenation of the enamine double bonds in those. It was shown that chloride salt **135a** was significantly more active in the process compared to other salts used (Scheme 1.49).




| Salt used | Yield of **134** | ee of **134** |
|---|---|---|
| **135a** | 84 | 46 |
| **135b** | 20 | n.d. |
| **135c** | 15 | n.d. |

**Scheme 1.49.** Hydrogenation of salts **135a-135c** with iridium catalyst of chiral ligand **136**.

A wide range of ligands was tested as well, where ligand **136** was shown to be the most enantioselective one. Overall, the reaction was performed under a big variety of conditions. Different solvents were also tested (toluene, methanol, dichloromethane, ethanol, diethyl ether), but the best results were achieved in tetrahydrofuran. Attempts to use several chiral ruthenium complexes were not successful as no conversion towards the desired product was achieved. The counter-ion of the Ir precursor was shown to have some significance, where the best enantioselectivity of 47% was achieved with $[Ir(COD)_2]BARF$ as a catalyst precursor (although the yield towards the desired product was significantly lower than in the example shown in Scheme 1.49) (Scheme 1.50). Overall, this study is a good representative example of the fact that enantioselective hydrogenation of enamines is still far from being applied on an industrial scale, as the catalyst loading of 1 mol% is required, while only up to 47% ee was achieved.

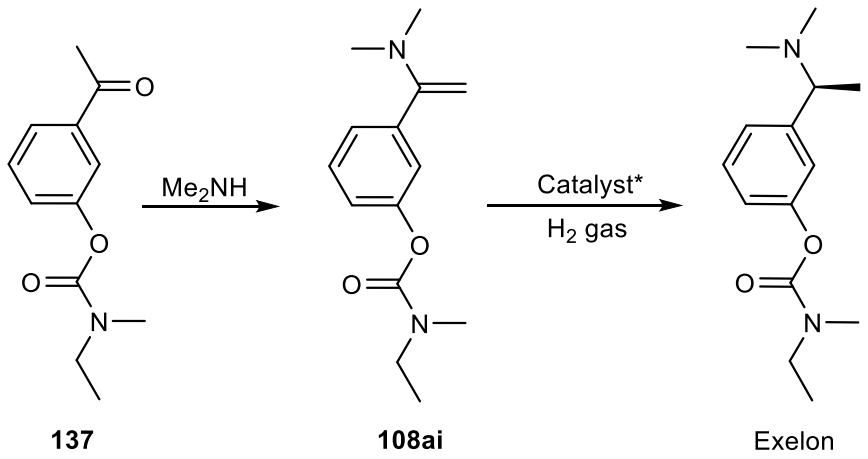



**Scheme 1.50.** Hydrogenation of **135a** with chiral iridium catalyst of ligand **136**.

To the best of our knowledge, all papers from the literature on enantioselective hydrogenation of unfunctionalised enamines are discussed here. From the very rare examples it was shown that there is no good catalyst so far in the literature that can be applied in industry because:

- All catalyst loadings are high to very high (typically 1 mol%)
- Catalysts were tested / proved to be efficient only for selected substrates
- Very few examples of very high enantioselectivities (only 4 papers represent enantioselectivities of over 90%)

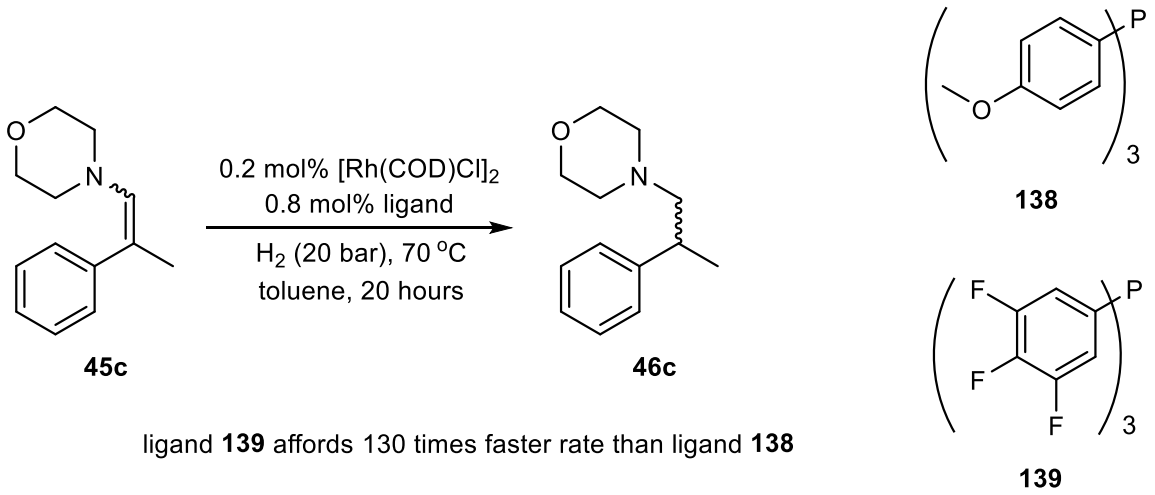
Being such a difficult transformation, it could be an excellent way to produce chiral tertiary amines. For example, synthesis of Exelon requires the formation of a primary amine from ketone **137**, resolution and dimethylation of the primary amine,[82] while a potentially good way towards it, starting from the ketone **137**, could be the formation of enamine **108ai** and its enantioselective hydrogenation (Scheme 1.51).




**Scheme 1.51**. Enantioselective enamine hydrogenation route to Exelon.

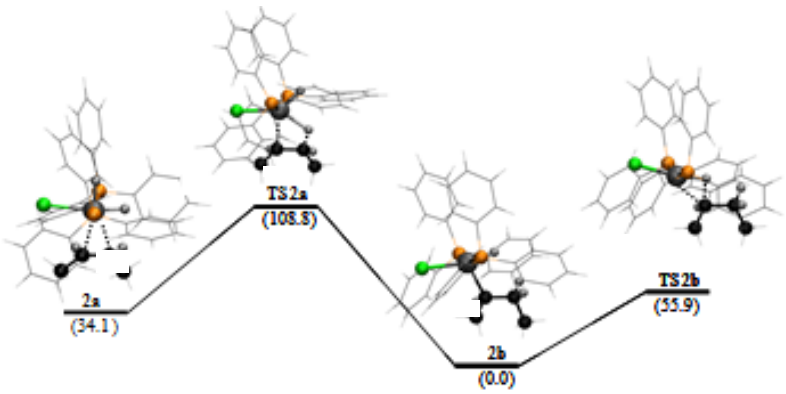
## 1.5 Electronic effect in enamine hydrogenation

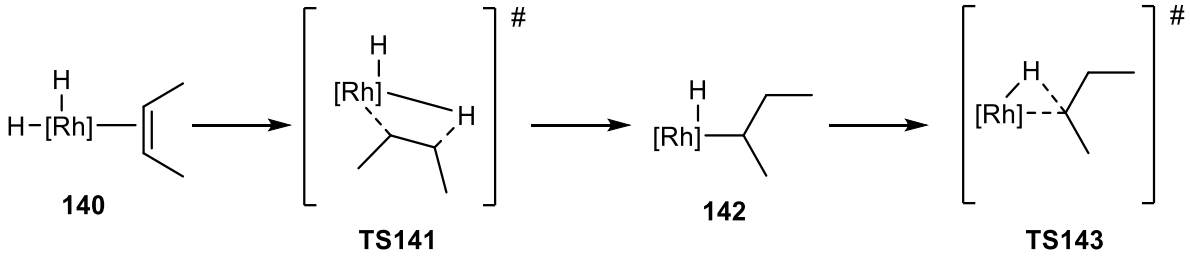
A generally accepted concept is that for an alkene hydrogenation, electron donating ligands accelerate the rate of the reaction.[83] A quite surprising discovery earlier in the group shows that electron-withdrawing ligands accelerate hydrogenation of enamines (Scheme 1.52).[5]

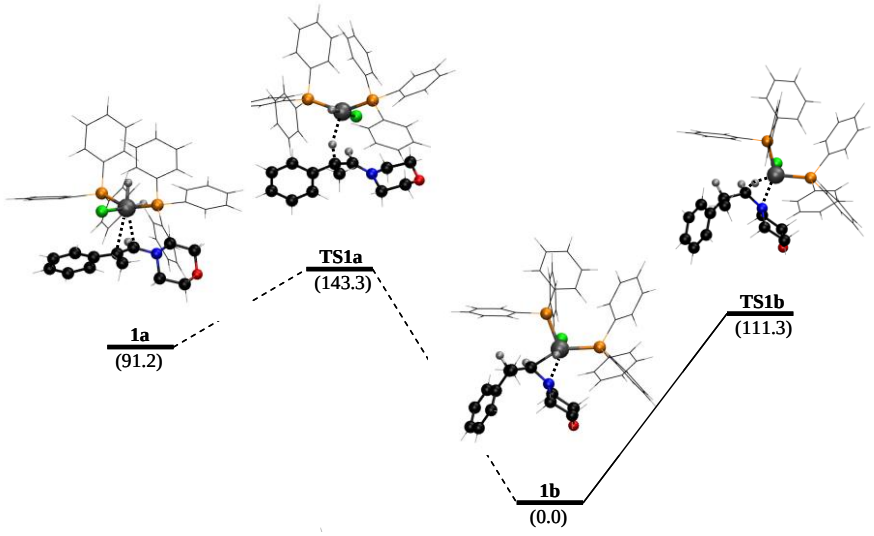


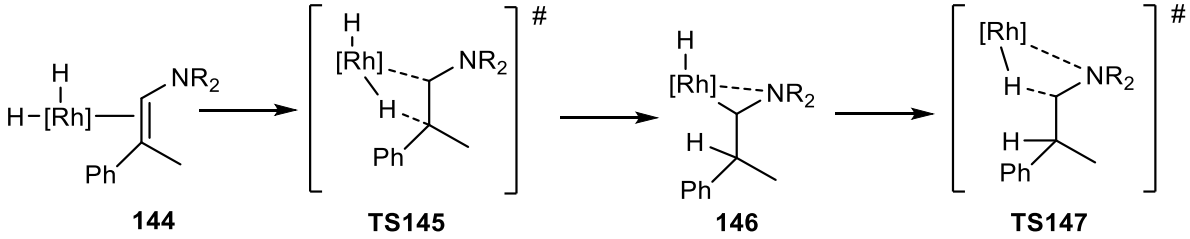

**Scheme 1.52.** Comparison of ligands **138** to **139** in hydrogenation of enamine **45c**.

Kinetic studies showed that the reaction goes 130 times faster with the electron-poor phosphine ligand **139** compared to the electron-rich **138**. Computational studies were run for a model hydrogenation of 2-butene (Figure 1.8a) and 4-(2-phenylprop-1-en-1-yl)morpholine (**45c**) (Figure 1.8b) using a Rh / triphenylphosphine as catalyst.




**Figures 1.8a and 1.8b.** DFT calculations for Rh-catalysed hydrogenation of 2-butene (top – **Figure 1.8a**) and **45c** using (bottom – **Figure 1.8b**) using $PPh_3$ as a ligand. Relative energies are shown in brackets for each intermediate and transition state.

For 2-butene it was shown that the biggest energy gap occurs during hydride insertion – i.e. going from intermediate **140** to the transition state **TS141** (Figure 1.8a) – and this step will be accelerated by an electron donating ligand, while in the enamine hydrogenation the biggest energy gap comes during reductive elimination – i.e. going from **146** to **TS147** (Figure 1.8b). The nitrogen atom stabilises the catalytic intermediate **146** and therefore makes it harder to undergo a reductive elimination. This explains a much faster rate of the reaction with an electron withdrawing ligand since it is a well-established fact that electron-poor ligands accelerate reductive eliminations.[31]

### 1.6 Project aims

When this project commenced in 2012 (and even up to today's date) the literature covering enantioselective hydrogenation of enamines consisted of a very few examples. The existing catalysts always operated at very high catalyst loadings. Despite that, examples of enantioselectivities over 90% were even more rare, while usually a specific choice of catalyst was required for each substrate for no obvious reason in order to achieve high enantioselectivities. The broad aim of this project was to develop catalysts that can reduce unfunctionalised enamines with high enantioselectivities using hydrogen gas at low catalyst loadings (e.g. 0.05 mol% or lower). Since the problem of high catalyst loadings in enamine hydrogenation is one of the unsolved challenges preventing application, the starting point of the project was the exploration of the factors that affect the rate of the reaction for a range of enamines. After establishment of the general trends, selected chiral catalysts would be tested in the process. Once a promising catalyst scaffold was identified, the reaction was to be studied with a variety of conditions, including effects of solvents and additives. Based on the knowledge obtained regarding the rate of the reaction and enantioselectivity, synthesis of new efficient chiral catalysts was also attempted. Finally, kinetic and mechanistic studies were of interest in order to understand the mechanism of the reaction.

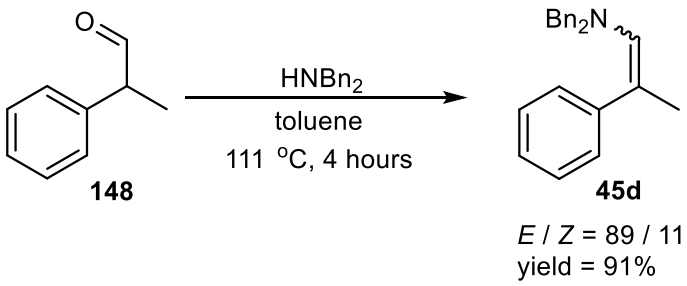
## 2. Synthesis and hydrogenation of enamines with achiral Rh catalysts

The initial aim of the research was to identify factors affecting the rate of enamine hydrogenation. As discussed in the introduction, there are no chiral enamine hydrogenation catalysts that operate at the sort of catalyst loadings that would make them viable for industrial application (0.05 mol% or lower). The discovery of a highly active catalyst is therefore at least as important as getting high enantioselectivities. In order to do so, a range of enamine substrates was prepared. With these in hand, ligands with different electronic \ steric properties were tested for rhodium-catalysed hydrogenation of these enamines.

### 2.1. Synthesis of enamines

#### 2.1.1 From aldehydes

Enamine **45d** was prepared according to Scheme 2.1. It was isolated by distilling off the remaining starting materials, and was a 89:11 *E*:*Z* mixture (> 95% purity by $^{1}$H NMR). Distillation of the enamines themselves is the best and most commonly used technique to purify them, but in the case of **45d** further purification was impossible due to the fact that the enamine is a heavy oil which decomposes before reaching its boiling point even under reduced pressure.

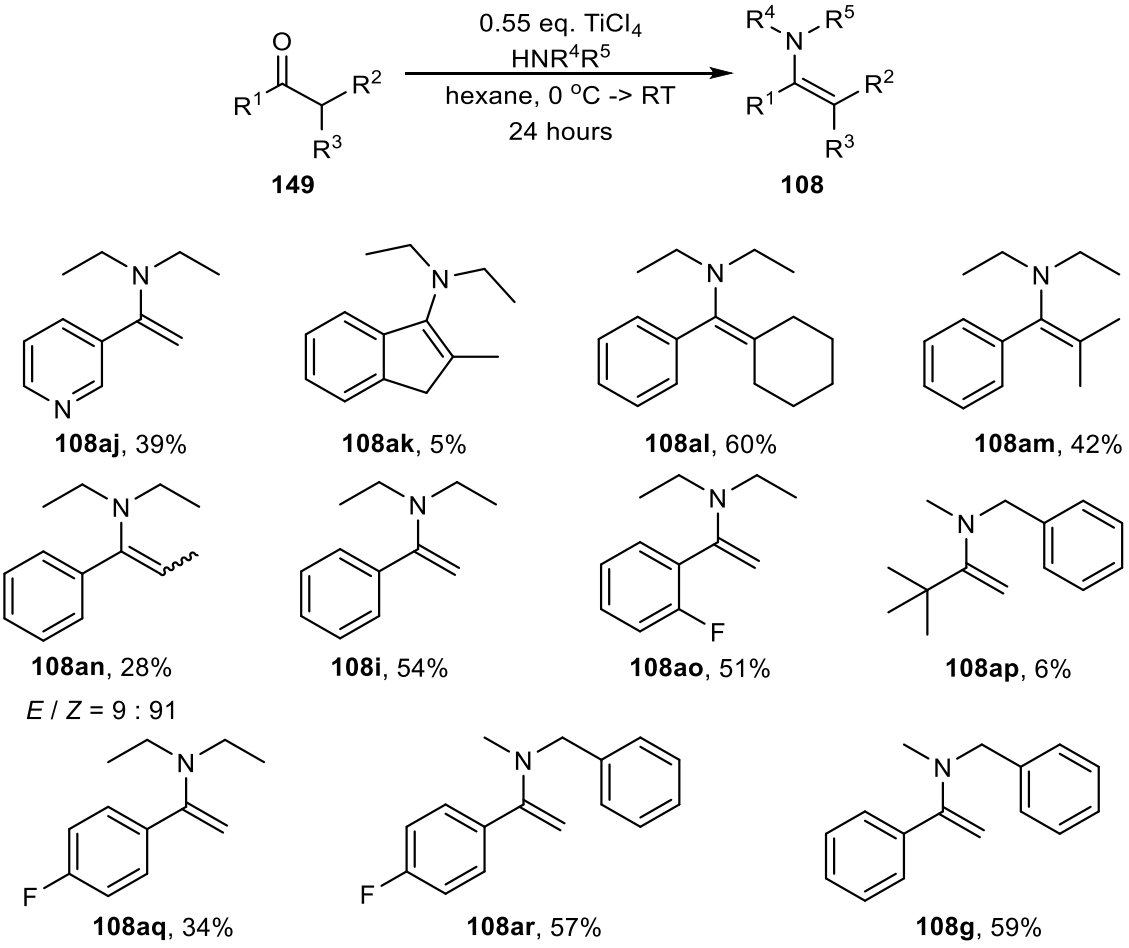



**Scheme 2.1.** Preparation of enamine **45d**.

#### 2.1.2 Lewis-acid catalysed synthesis

Ketones are less reactive substrates for the formation of enamines and therefore often an additional reagent is required. Enamines shown in Scheme 2.2 were prepared according to the literature procedure.[84] The only modification of the procedure was the addition of wet diethyl ether at the end of the reaction in order to precipitate all titanium salts (this methodology was previously reported in imine synthesis using $TiCl_4$).[85]

All enamines shown in the scheme, apart from **108al** and **108am** were purified using distillation techniques under reduced pressure (see Chapter 6 for details). The low yields are compensated by the high purities (98% or higher by $^1$H NMR). Enamines **108al** and **108am** are exceptionally stable due to the tetrasubstituted double bond. They do not undergo hydrolysis readily even under acidic conditions and were isolated by acid-basic work-ups with exceptional purities of >99% by $^1$H NMR. Enamine **108ak** also does not fully decompose on acid-basic work-up, but it could not be isolated by this purification technique due to the presence of some impurities, so distillation was required.




**Scheme 2.2.** Synthesis of enamines **108g**, **108i** and **108aj** – **108ar**.

It is worth mentioning that out of all disubstituted enamines shown in Scheme 2.2, **108ao** is the most stable one towards hydrolysis (typically disubstituted enamines will show 3 – 5% hydrolysis in $CDCl_3$ after 1 hour under aerobic conditions, while no indication of hydrolysis was observed for **108ao** even after 6 hours).

Although the titanium (IV) tetrachloride promoted synthetic route worked well for a selected range of substrates, enamines shown in Figure 2.1 could not be prepared according to this method. Increasing reaction times and temperature, or performing them with addition of extra titanium (IV) tetrachloride did not lead to success.

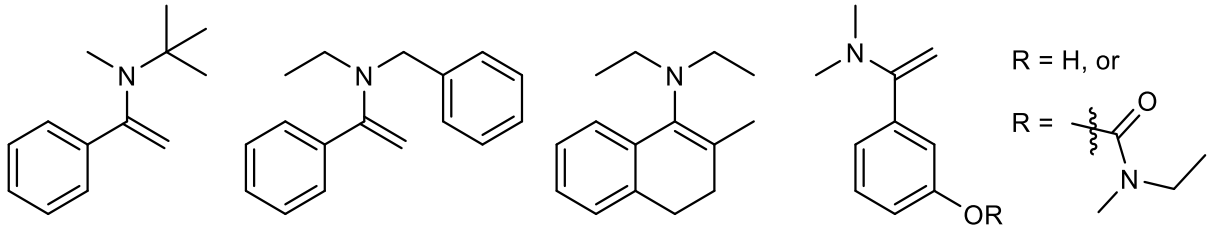
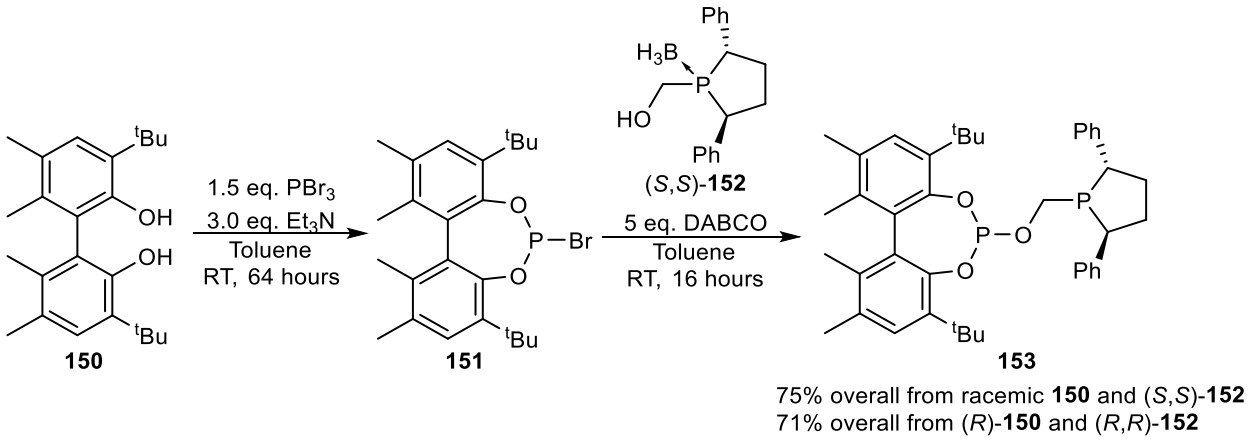



**Figure 2.1.** Enamines which could not be prepared using the titanium (IV) tetrachloride promote method.

### 2.1.3 Hydroaminovinylation

Regio-selective hydroaminovinylation is an alternative way to prepare pro-chiral enamines which are hard or impossible to access by any other synthetic strategy. We felt the best way to prepare cyclic enamine **108as** (see Figure 2.2 on page 45) would be a branched-selective hydroaminovinylation. A branched-selective hydroformylation catalyst would be required. Previously, our group reported BOBPHOS as an excellent ligand for branched- and enantio-selective Rh-catalysed hydroformylation.[86,87] Unfortunately, the existing 3-step synthetic route affords a fairly low yield of the desired ligand. It was decided to develop a slightly modified, higher-yielding synthetic route towards this ligand. The successful attempt involved preparation of the bromo-phosphite **151** and reaction of it with the alcohol **152** (Scheme 2.3). The previously published synthesis of this ligand involved preparation of chloro-phosphite, then a low yielding conversion of it to an iodo-phosphite that is reacted with the alcohol **152** to give BOBPHOS in 35% overall yield. Therefore, the new route is not only higher-yielding, but also one step shorter. Since the ligand was required to perform branched-selective hydroaminovinylation, producing non-chiral enamine, a racemic diol **150** was used as a starting material. A single enantiomer of ($R_{ax}$,*R*,*R*) BOBPHOS was also prepared by the same strategy on a gram scale of the starting diol. After further purification, an overall yield of 71% with >99% purity was achieved.

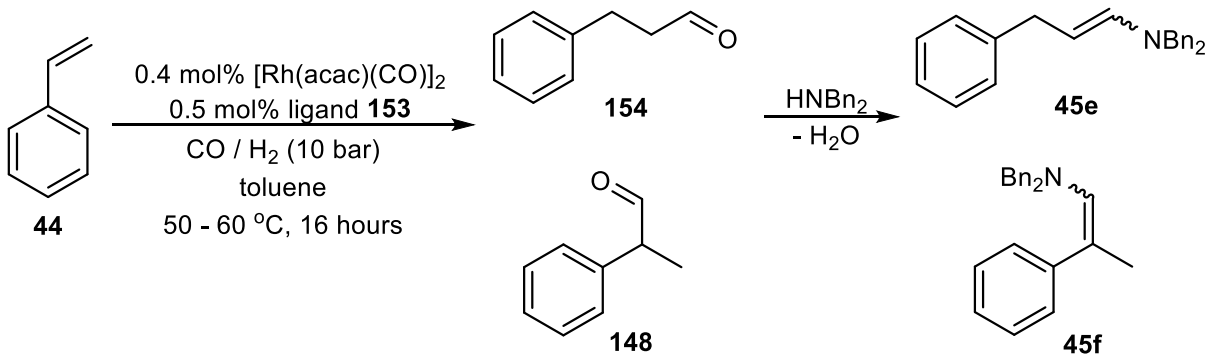



**Scheme 2.3.** Alternative synthetic route towards BOBPHOS **153**.

The starting point of the branched-selective hydroaminovinylation was an attempt to perform it with styrene and dibenzylamine (Table 2.1). Entries 1 and 4 from the table below suggest that an increase in temperature promotes the formation of the enamine. $Bi(OTf)_3$ as an additive deactivates the catalyst significantly (entry 5). Doubling the amount of dibenzyl amine (entry 3 compared to entry 1) does not have any pronounced effect. Addition of a drying agent, such as activated molecular sieves (entry 6) significantly promotes the formation of the enamine from the aldehyde due to the absorption of water and, therefore, preventing the reverse hydrolysis reaction. It is also worth mentioning that *E* \ *Z* ratios of the product **45f** are different when the enamine is made by hydroaminovinylation to those obtained by heating pure aldehyde and dibenzylamine (see section 2.1.1.).

This study revealed that there was no advantage to synthesising compound **45f** using hydroaminovinylation, since the aldehyde is commercially available and the enamine synthesis route is straightforward. However, more complex enamines derived from non-commercial aldehydes may be best prepared using this method after further optimisation. The most problematic aspect was the conversion of the aldehyde to the enamine. It is possible that dibenzylamine is not a very effective amine in this regard. The levels of branched selectivity were good, but were expected to be so based on the very high selectivity observed in styrene hydroformylation using Rh catalyst derived from ($S_{ax}$,*S*,*S*)-BOBPHOS.[86,87] It was also encouraging that the catalysis works in presence of secondary amine and water (which is produced during the enamine formation step).

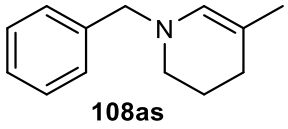
**Table 2.1.** Hydroaminovinylation of styrene.




| Entry[a] | Temperature, °C | Additives, mmol | **44**, %[b] | **154**, %[b] | **148**, %[b] | **45e**, %[b] | **45f**, % (*E* / *Z*)[b] |
|---|---|---|---|---|---|---|---|
| 1 | 50 | - | < 1 | 2 | 77 | < 1 | 21 (1.09 : 1) |
| 2 | 50 | $MgSO_4$, 4.2 | < 1 | 2 | 70 | < 1 | 28 (1.74 : 1) |
| 3 | 50 | $Bn_2NH$, 1.0 | < 1 | 2 | 69 | < 1 | 29 (0.88 : 1) |
| 4 | 60 | - | < 1 | 2 | 51 | < 1 | 47 (1.43 : 1) |
| 5 | 60 | $Bi(OTf)_3$, 0.5 | 79 | < 1 | 21 | < 1 | < 1 (n.d.) |
| 6 | 60 | Mol. sieves[c] | < 1 | 2 | 20 | < 1 | 78 (2.39 : 1) |

[a]Conditions: 0.04 mmol of $[Rh(acac)(CO)]_2$, 0.05 mmol of ligand **153**, 1 mmol of styrene, 1 mmol of dibenzylamine; $Et_4Si$ as an internal standard (0.1 mL), toluene as a solvent, 10 bar of syngas (1:1), 16 hours. [b]Data obtained from $^1H$ NMR spectra of reaction solutions. [c]Mass = 0.5 g.

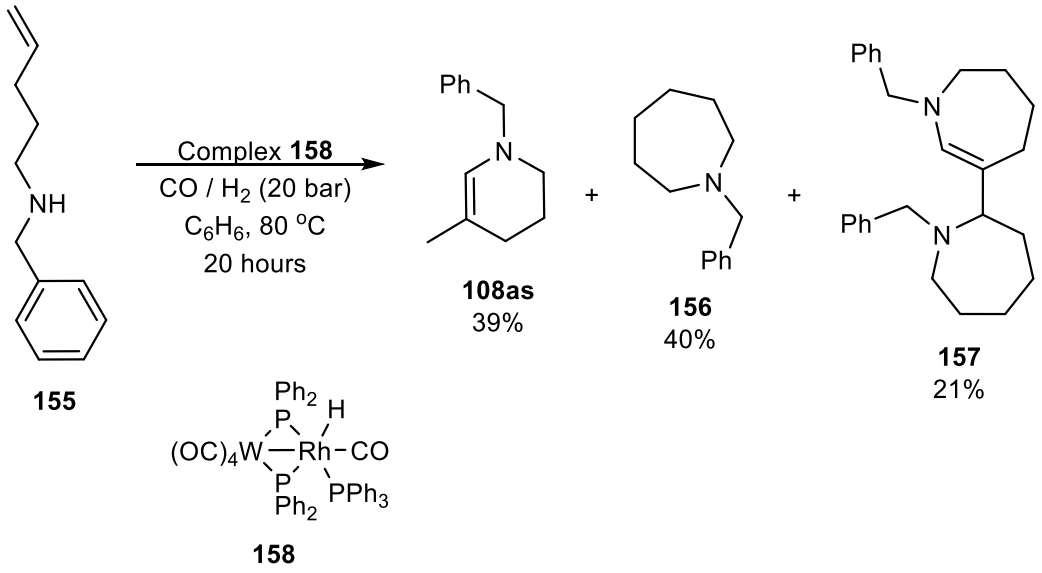
While enamine **45f** can be prepared synthetically in a straightforward manner (as described above), enamine **108as** (Figure 2.2) cannot be made by any simple synthetic route, since the amino aldehyde synthesis would be lengthy.




**108as**

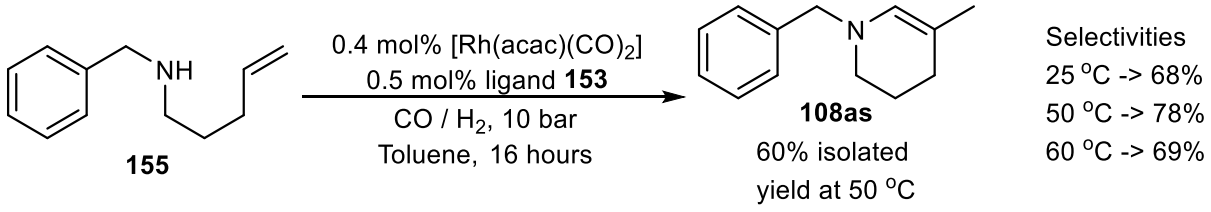
**Figure 2.2.** Targeted enamine **108as**.

An attempt to prepare **108as** by regio-selective hydroaminovinylation of *N*-benzylpent-4-en-1-amine **155** was previously reported by Dickson *et. al.*.[88] A number of catalysts were tested for this reaction, where the most selective one (**158**) afforded only 39% selectivity towards the desired compound (Scheme 2.4).




**Scheme 2.4.** Hydroaminovinylation / hydroaminomethylation of *N*-benzylpent-4-en-1-amine (**155**).

In order to improve selectivity towards the desired enamine **108as**, the same strategy was targeted, but with the Rh / ($R_{ax}$/$S_{ax}$,*S*,*S*)-BOBPHOS (**153**) catalyst. Compound **155** was prepared by a literature method (see Chapter 6 for details).[89] The hydroaminovinylation of **155** with Rh / BOBPHOS catalyst clearly shows a significant improvement from the literature, as the selectivity towards **108as** is doubled (to 78%) at 50 °C (Scheme 2.5). To check that each diastereomer of BOBPHOS gives the same result, the same reaction was performed with the single enantiomer of BOBPHOS ligand ($R_{ax}$,*R*,*R*) at 50 °C, where the same selectivity was observed. The reaction was finally performed on 8 mmol scale, and the target compound **108as** was isolated by distillation under reduced pressure with an overall yield of 60% and excellent purity.

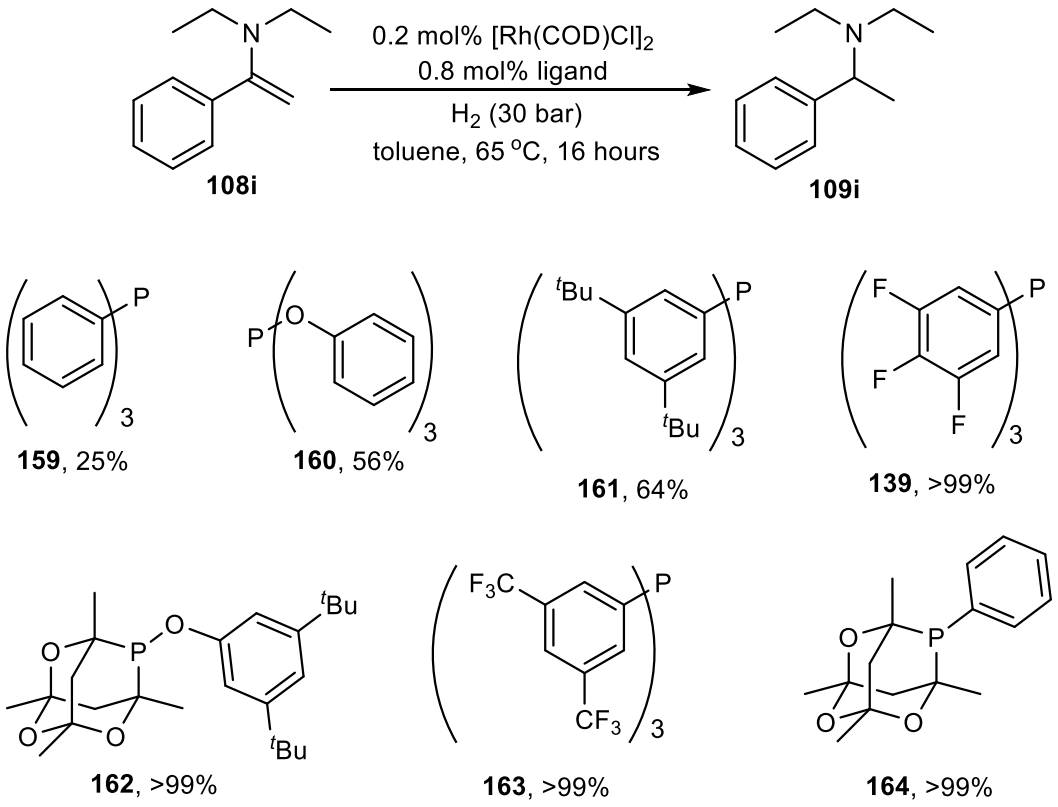



**Scheme 2.5.** Hydroaminovinylation of **155** using ligand **153**.

## 2.2. Hydrogenation of enamines with achiral catalysts

### 2.2.1 Monodentate ligands: influence of electronic and steric effects

Previously in our group, it was found that electron-deficient ligands improve the rate of an enamine hydrogenation (See Chapter 1 for details).[5] The starting point of the research was to test a number of monodentate ligands in hydrogenation of enamine **108i** to establish that these observations were more general. A range of bulky or electron-deficient phosphorous ligands were compared to triphenylphosphine (**159**) in Rh catalysed hydrogenation of enamine **108i** at 65 $^{o}$C, 30 bar of hydrogen gas and S/Rh ratio of 250 (Scheme 2.6). The results show that more electron-deficient \ more bulky ligands improve the rate of the reaction. For example, ligand **164** (phenyl-phosphatrioxa-adamantane) has a cone angle of 202$^{o}$,[90] and affords a much higher conversion than triphenylphosphine (**159**), which has only a cone angle of 145$^{o}$.[91] It is also less electron-donating and a better π–acceptor. Ligand **139** and commercially available ligand **163** were chosen as outstanding ligands.




**Scheme 2.6.** Monodentate achiral ligands for Rh-catalysed hydrogenation of enamine **108i**.

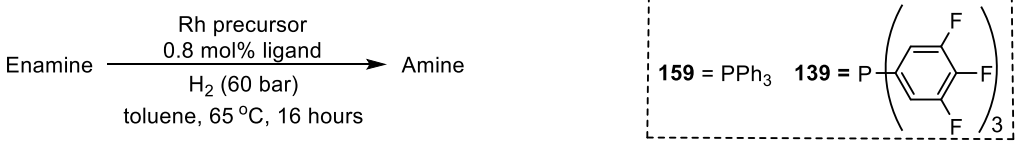
Based on our previous study, the most plausible explanation for this phenomenon is that the reductive elimination, a step promoted by e-deficient or bulky ligands, is rate determining in enamine hydrogenation, in contrast to hydrogenation of other alkenes.[5,83,92,93]

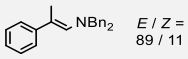
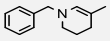
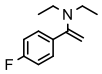
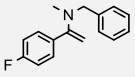
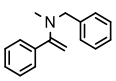
The next aim was to confirm the beneficial effect of the electron withdrawing ligands for a range of enamines. All prepared substrates were tested in hydrogenation using ligands **159** and **139** (Table 2.2). To obtain pure samples of the amines after hydrogenation of enamines, selected entries were chosen (usually cases that went to full conversion) and the products were isolated by acid-basic work-ups (for isolation of amine **109ak**, see Chapter 4). The exception is amine **109al**, which was purified by column chromatography. Due to inability of even electron-withdrawing ligand **139** to hydrogenate **108aj**, a sample of amine **109aj** was not obtained. The likely reason is that the nitrogen atom from the pyridine ring binds to the metal and deactivates the catalyst. This suggestion is supported by the result shown in entry 14 in Table 2.2: where some pyridine is added to the reaction, the conversion goes down significantly.

First of all, the results clearly prove that the beneficial ligand electronic effect on catalyst productivity is a general phenomenon for enamine hydrogenation. This is clearly seen in Table 2.2 for enamines **45d**, **108i**, **108ak** – **108ao**, **108as**. As expected, it is more difficult to hydrogenate tetrasubstituted double bonds. Even in simple alkene hydrogenation, tetrasubstituted double bonds are challenging, often requiring specially designed catalysts (such as Crabtree's catalyst).[94,95] To the best of our knowledge, these are the first examples of tetrasubstituted enamine double bonds to be hydrogenated catalytically. Trisubstituted enamines **45d** and **108am** were also slower than most disubstituted enamines (entries 12 and 15). In contrast to those, **108as** was actually even more active towards the reduction (entry 19) than the disubstituted enamine **108i** (entry 17). The most likely driving force of the reduction of **108as** is that the saturated 6-membered ring is formed, where the ring constraint is lost.

Electron-deficiency of the enamine is also an important factor (comparing entries 17 to 21 and 25), since the presence of the electron-withdrawing group in the substrate still helps to promote reductive elimination. The most likely reason for enamine **108ao** to be slower in this process than enamine **108aq** is the higher stability of it (see enamine synthesis section). In general, it makes this enamine a less reactive substrate.

**Table 2.2.** Hydrogenation of enamines using monodentate ligands.

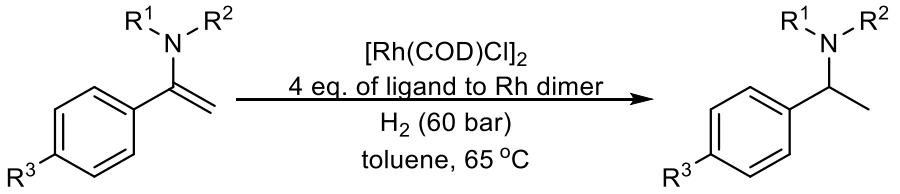



| Entry[a] | Enamine | Ligand | Amine, % (isolated yield, %)[b] |
|---|---|---|---|
| 1 | **108aj**  | **159** | < 1 |
| 2 | | **139** | 1 |
| 3[c] | **108ak**  | **159** | < 1 |
| 4[c] | | **139** | 48[d] |
| 5 | **108al**  | **159** | < 1 |
| 6 | | **139** | 47 |
| 7[e] | | **139** | 67 (32) |
| 8 | **108am**  | **159** | 2 |
| 9 | | **139** | 77 |
| 10[e] | | **139** | 90 |
| 11[e,f] | | **139** | > 99 (74) |
| 12 | **108an**  *E* / *Z* = 9 : 91 | **159** | 6 |
| 13 | | **139** | > 99 (91) |
| 14[g] | | **139** | 10 |
| 15 | **45d**  *E* / *Z* = 89 / 11 | **159** | 16 |
| 16 | | **139** | > 99 (68) |
| 17 | **108i**  | **159** | 35 |
| 18 | | **139** | > 99 (83) |
| 19 | **108as**  | **159** | 54 |
| 20 | | **139** | > 99 (74) |
| 21 | **108ao**  | **159** | 57 |
| 22 | | **139** | > 99 (55) |
| 23 | **108ap**  | **159** | > 99 |
| 24 | | **139** | > 99 (71) |
| 25 | **108aq**  | **159** | > 99 |
| 26 | | **139** | > 99 (57) |
| 27 | **108ar**  | **159** | > 99 |
| 28 | | **139** | > 99 (88) |
| 29 | **108g**  | **159** | > 99 |
| 30 | | **139** | > 99 (91) |
| 31[h] | | **139** | > 99 |

[a]General conditions: 1 mmol of enamine, 0.2 mol % of $[Rh(COD)Cl]_2$, 0.8 mol % ligand, 0.1 mL of 1-methylnaphthalene as an internal standard, 60 bar of $H_2$ gas, toluene as a solvent, 16 hours. [b]Determined by $^1H$ NMR relative to 1-methylnaphthalene. Amines were isolated by acid-base work-up. [c]A pure sample of the amine was isolated in Chapter 5. [d]Reaction scale = 0.25 mmol. [e]Time = 24 h. [f]Catalyst loading doubled. [g]30 equivalents of pyridine relative to Rh were added. [h]Pressure of $H_2$ = 5 bar; scale is 2.0 mmol of enamine.

Despite the clear advantages of electron-deficient ligands, more bulky enamines are clearly the substrates which are more prone towards the hydrogenation. Enamines **108ap**, **108ar** and **108g** are hydrogenated to full conversions under the conditions in Table 2.2 even with triphenylphosphine as a ligand. This is consistent with the reductive elimination being the rate determining step in the enamine hydrogenation (since they are bulky and the reductive elimination occurs more readily). As a simple way to prove the ligand electronic effect for these more reactive enamines, compounds **108aq**, **108ar** and **108g** were hydrogenated at lower catalyst loadings (Table 2.3). Entries 1 – 6 clearly support the concept. As was observed in the results in the previous table, more bulky enamines **108ar** and **108g** are more active than **108aq**. Entries 7 and 8 represent the use of some very low catalyst loadings. The more bulky and electron-deficient ligand **163** was more active than the ligand **139** and afforded TON of 4550 mol $mol^{-1}$. To the best of our knowledge, this is the highest TON ever achieved in catalytic hydrogenation of enamines.

**Table 2.3.** Hydrogenation of enamines **108aq**, **108ar**, **108g** at low catalyst loading.




**108aq**: $R^1 = R^2 = Et$; $R^3 = F$
**108ar**: $R^1 = Me$; $R^2 = Bn$; $R^3 = F$
**108g**: $R^1 = Me$; $R^2 = Bn$; $R^3 = H$

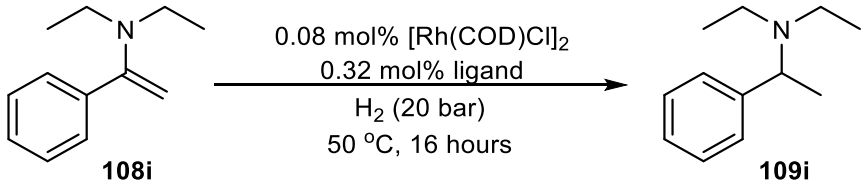
**109aq**: $R^1 = R^2 = Et$; $R^3 = F$
**109ar**: $R^1 = Me$; $R^2 = Bn$; $R^3 = F$
**109g**: $R^1 = Me$; $R^2 = Bn$; $R^3 = H$

| Entry[a] | Enamine | Ligand | Cat. Loading, mol% | Time, h | Conversion, %[b] |
|---|---|---|---|---|---|
| 1 | **108aq** | **159** | 0.025 | 16 | 5 |
| 2 | **108aq** | **139** | 0.025 | 16 | 23 |
| 3 | **108ar** | **159** | 0.025 | 16 | 14 |
| 4 | **108ar** | **139** | 0.025 | 16 | 64 |
| 5 | **108g** | **159** | 0.025 | 16 | 15 |
| 6 | **108g** | **139** | 0.025 | 16 | 70 |
| 7[c] | **108g** | **139** | 0.01 | 90 | 83 |
| 8[c] | **108g** | **163** | 0.01 | 66 | 91[d] |

[a]General conditions: 1 mmol of enamine, $[Rh(COD)Cl]_2$, 4 equivalents of ligand to the Rh dimer, 0.1 mL of 1-methylnaphthalene as an internal standard, 60 bar of $H_2$ gas, toluene as a solvent. [b]Determined by $^1H$ NMR relative to 1-methylnaphthalene. [c]Scale = 10 mmol of enamine. [d]Product isolated by acid-basic work-up as a 9:1 misture of the amine **109g** and *N*-methylbenzylamine.

While the electronic effect clearly holds for a range of substrates in toluene as a solvent, it was important to check if enamines were going to behave in a similar manner in some other different solvent (e.g. protic / polar). Since methanol is green, inexpensive and renewable solvent, it was chosen for the experiment. Hydrogenation of enamine **108i** was performed in an Argonaut system comparing methanol and toluene as solvents for the reaction (Table 2.4). Although the electronic effect is not as dramatic in methanol, it is still clear that electron-deficient ligand **139** affords a faster rate, which could suggest that the rate determining step is the reductive elimination in methanol as well. Moreover, toluene is a better solvent for these reactions giving a higher yield.

**Table 2.4.** Hydrogenation of enamine **108i** using toluene and methanol as solvents.



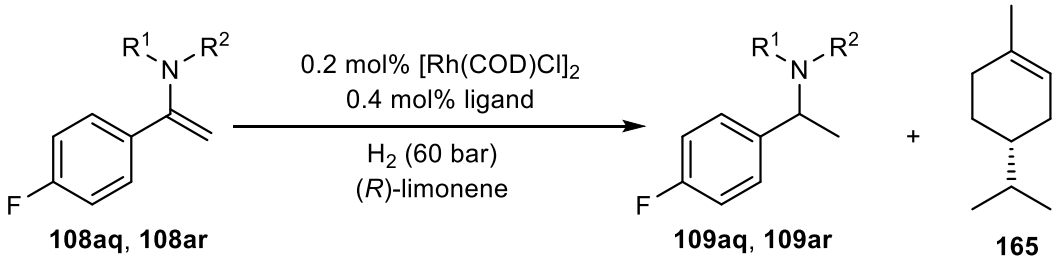

| Entry[a] | Solvent | Ligand | Amine, %[b] |
|---|---|---|---|
| 1 | Toluene | **159** | 4 |
| 2 | Toluene | **139** | 93 |
| 3 | Methanol | **159** | 43 |
| 4 | Methanol | **139** | 57 |

[a]General conditions: Argonaut was used for the catalytic experiments, 5.0 mmol of **108i**, 0.08 mol% of $[Rh(COD)Cl]_2$, 0.32 mol% ligand, 0.5 mL of 1-methylnaphthalene as an internal standard, 20 bar of $H_2$ gas, solvent, 16 hours. [b]Determined by $^1H$ NMR relative to 1-methylnaphthalene.

Since the ligand electronic effect is more striking in non-polar hydrocarbons, the idea of using a renewable solvent was tested. (*R*)-Limonene is obtained from orange peel and currently being used as a replacement for hexane in cleaning applications. It is renewable and fairly cheap organic hydrocarbon and has only just began to attract interest as a reaction solvent.[96] Although it might look very counter-intuitive to use it, since it has 2 alkene double bonds in it, electron-deficient ligands are less active in hydrogenation of alkenes than electron-rich ligands.[83] The hope was that the Rh catalyst derived from ligand **139** will selectively hydrogenate the double bond in the enamine, while avoiding the double bonds in the solvent. In any case, this experiment gave us an opportunity to investigate the relative rates of hydrogenation of enamine, 1,1-alkene and 1,2-alkene. The results summarised in Table 2.5 show that Rh / triphenylphosphine (**159**) is much more selective in hydrogenating the disubstituted double bond of the solvent, while electron-deficient ligand **139** hydrogenates the enamine to a greater extent (given the excess of solvent used, it is not actually selective for the enamine over the solvent). (*R*)-limonene is a high-boiling point solvent, which is difficult to remove by distillation. However, in this case, as examples, amines in entries 2 and 6 were isolated by acid-basic work-ups (**108aq** in >99% purity and **108ar** as a 9:1 mixture of the product and *N*-methyl-4-fluorobenzylamine. Thus, in case of enamine hydrogenation, the high boiling point of this solvent is not a problem. It is also feasible that (*R*)-dihydrolimonene or a mixture of (*R*)-

limonene and (*R*)-dihydrolimonene could be recycled and re-used as solvents, so the tendency of limonene to hydrogenate may not be a major issue.

**Table 2.5.** Hydrogenation of enamines **108aq** and **108ar** using (*R*)-limonene as a solvent.




**108aq**, **108ar** **109aq**, **109ar** **165**

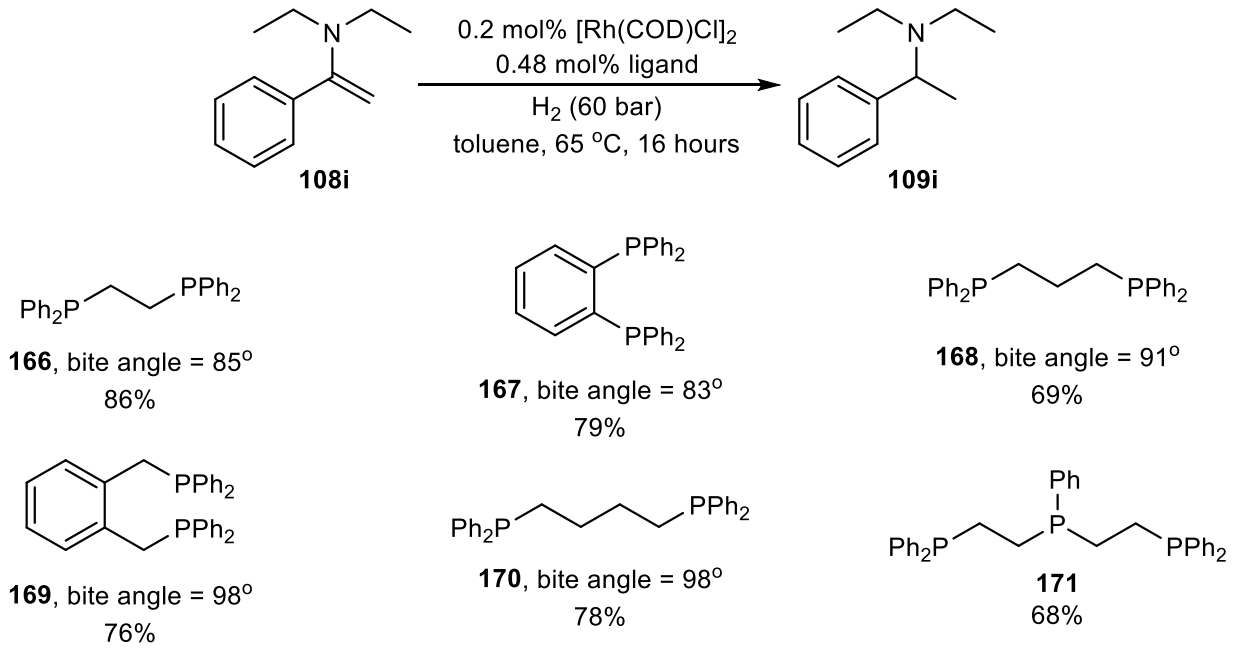
| Entry[a] | Enamine | Ligand | Time, h | T, °C | Amine, %[b] | **165**, %[b,c] |
|---|---|---|---|---|---|---|
| 1[d] | **108aq** | **159** | 16 | 65 | 34 | > 95 |
| 2[d] | **108aq** | **139** | 16 | 65 | > 99 | 91 |
| 3 | **108ar** | **159** | 16 | 40 | 0 | 48 |
| 4 | **108ar** | **139** | 16 | 40 | 74 | 20 |
| 5 | **108ar** | **159** | 20 | 45 | 11 | 65 |
| 6 | **108ar** | **139** | 20 | 45 | 92 | 23 |

[a]General conditions: 1.5 mmol of enamine, 0.2 mol% of $[Rh(COD)Cl]_2$, 0.8 mol% ligand, 0.15 mL of 1-methylnaphthalene as an internal standard, 60 bar of $H_2$ gas, (*R*)-limonene. Ratio of solvent / enamine = 6.68 / 1. [b]Determined by $^1$H NMR relative to 1-methylnaphthalene. [c]In all cases, none or traces of the product with hydrogenated trisubstitited double bond of (*R*)-limonene are present. [d]Ratio of solvent / enamine = 6.74 / 1.

### 2.2.2 Bidentate ligands: comparison of bite angles of ligands on catalyst activities

After introduction of the concept of the cone angle by Tolman,[97] Casey and Whinteker described a concept of the natural bite angle, where this angle is measured for a bidentate phosphines as a P-M-P angle, once the ligand coordinates to the metal centre.[98,99] Bidentate / tridentate ligands **166-171** were also tested in the hydrogenation of enamine **108i** (Scheme 2.7), where the bite angles of bidentate ligands are shown.[100-102] As the results suggest, the bite angles of the ligands do not have a major effect on the activity of the catalyst. For example, difference in the bite angles between ligands **166** and **170** is 13°, while the difference in conversion is not significant. This is not unexpected, since there is no change in metal valence angle (90°) during

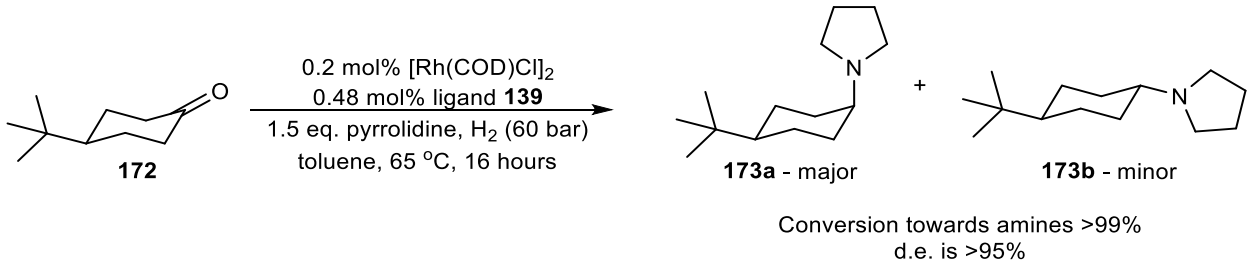
hydrogenations. Overall, these results suggest that when chiral ligands will be examined, a selection of chiral catalysts with a wide range of bite angles can be used.




**Scheme 2.7.** Hydrogenation of enamine **108i** with achiral ligands **166** - **171**.

### 2.2.3 Highly-diastereoselective reductive amination

Apart from hydrogenation of already prepared enamines, the catalysts were tested in the reductive amination of 4-*tert*-butyl-cyclohexanone (**172**). This aliphatic ketone was chosen since it is more prone towards the formation of the enamine than aromatic ketones, and, therefore, does not require $TiCl_4$ as a reagent for its preparation. The reductive amination of this substrate with pyrrolidine and stoichiometric amounts of reducing agents was performed in the past, where the best d.r. achieved was about 3:1 with a stoichiometric amount of $NaBH(OAc)_3$.[10] When using Rh precursor with ligand **139** as a catalyst, a full conversion of the starting material towards the desired product was achieved with a diastereomeric excess (d.e.) of over 95% (assigned by $^1H$ NMR) (Scheme 2.8). The likely reason for such a high selectivity is that the $^t$Bu group is a bulky substituent, which makes it problematic for the substrate to approach the metal center on the side where the bulky $^t$Bu group is located.




**Scheme 2.8.** Reductive amination of 4-*tert*-butyl-cyclohexanone (**172**).

After purification of the product by an acid-basic work-up and analysing it by NMR, the major compound was crystalised by slow evaporation of $CDCl_3$. The crystal structure obtained suggests that only diastereomer **173a** is present in the sample (Figure 2.3).

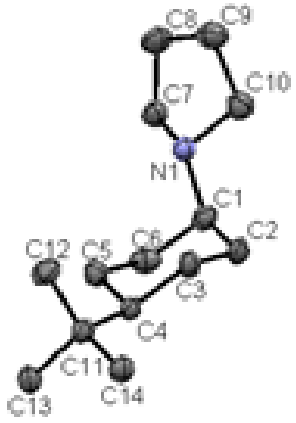



**Figure 2.3.** Crystal structure of compound **173a**.

Overall, this chapter describes the work on preparation of enamines and hydrogenation of those with non-chiral catalysts. While the majority of enamines were prepared by the literature procedure, an improved catalytic hydroaminovinylation process is described as well. The use of Rh \ BOBPHOS catalyst significantly improves the selectivity towards the desired enamine compared to the catalyst previously described in the literature. This technology could be used for preparation of enamines, which are difficult (if at all possible) to prepare by any other synthetic routes.

It is likely that reductive elimination is the rate determining step in enamine hydrogenation. The ligand electronic effect, as well as the effect of the bulk of ligands and substrates on the rate of the reaction are now clearly a general phenomenon. With very electron withdrawing and bulky ligand **163** an unprecedented TON of 4550 mol $mol^{-1}$ was achieved,

which is to the best of our knowledge, by far the best TON in hydrogenation of enamine with a homogeneous catalyst. While the key aim of the project is to develop a highly-active and enantioselective catalyst, no further research was made on the improvement of the rate of the reaction with the achiral ligands. But, using the knowledge described in this chapter, preparation of a lot more active achiral catalyst for hydrogenation of enamines is a decent possibility.

Since enamine and alkene require opposite properties of the catalyst (i.e. steric and electronic properties of the ligand), it was shown that (*R*)-limonene is a possible solvent to use in this process. The product of the reaction is easily separable from the solvent by acid-base work-up, which withdraws the requirement of distillation.

For bidentate ligands, it was shown that the bite angle does not have a major effect on the activity of the catalyst. Therefore, in the future search for chiral catalysts suitable for the process ligands with wide range of bite angles can be tested.

The Rh / electron-deficient ligand catalyst was shown to perform very well in reductive amination. The reaction affords very good TON, as well as excellent diastereoselectivity.

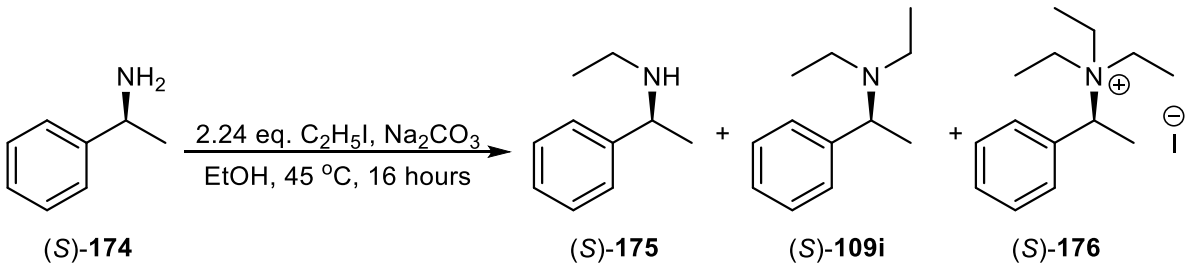
The next aim was to find chiral catalysts that would be able perform enamine hydrogenation enantioselectively. In the case of finding these types of ligands, the discoveries from this chapter could be applied in order to prepare very active catalyst.

## 3. Enantioselective hydrogenation of enamines

In order to study enantioselective hydrogenation of enamines, first of all, it was important to identify ligand scaffolds which are able to form enantioselective enamine hydrogenation catalysts with Rh. This chapter describes initial catalyst testing, and in greater details, the hydrogenation of enamines with Rh / PHANEPHOS catalysts.

### 3.1 Method development for assigning absolute configuration of amine 109i.

The starting point of this project was to test a variety of chiral ligands and complexes in Rh-catalysed hydrogenation of enamine **108i**. In order to determine the enantiomer of the amine formed, an authentic sample of (*S*)-**109i** was prepared (Scheme 3.1). The synthetic strategy was taken from the literature[103] and slightly modified to obtain the mixture of starting primary amine (*S*)-**174**, secondary amine (*S*)-**175**, the desired tertiary amine and chiral ammonium salt (*S*)-**176**. Amine (*S*)-**109i** was isolated by column chromatography in overall yield of 6% (see experimental for details).




**Scheme 3.1.** Synthesis of amine (*S*)-**109i**. In $^{1}$H NMR spectrum in the N-C<u>H</u> region four different environments are observed which correspond to (*S*)-**174**, (*S*)-**175**, (*S*)-**176** and the desired (*S*)-**109i**.

Initially, it was attempted to resolve a racemic sample of amine **109i** (obtained as described in Chapter 2) using HPLC and AD-H, OD-H, AS, AS-H, OJ-H and OJ columns. The OJ column showed some separation of the enantiomers, but full separation was not achieved. In Figure 3.1, it is shown how (*R*)-methoxyphenylacetic acid resolves the two enantiomers of the racemic sample by $^{1}$H NMR. The absolute configurations of the products from the catalytic experiments were determined by assigning the peaks after resolution of the samples with the chiral acid. In the experiments where the amines were isolated, the absolute configurations were additionally approved by the measurements of the optical rotations.

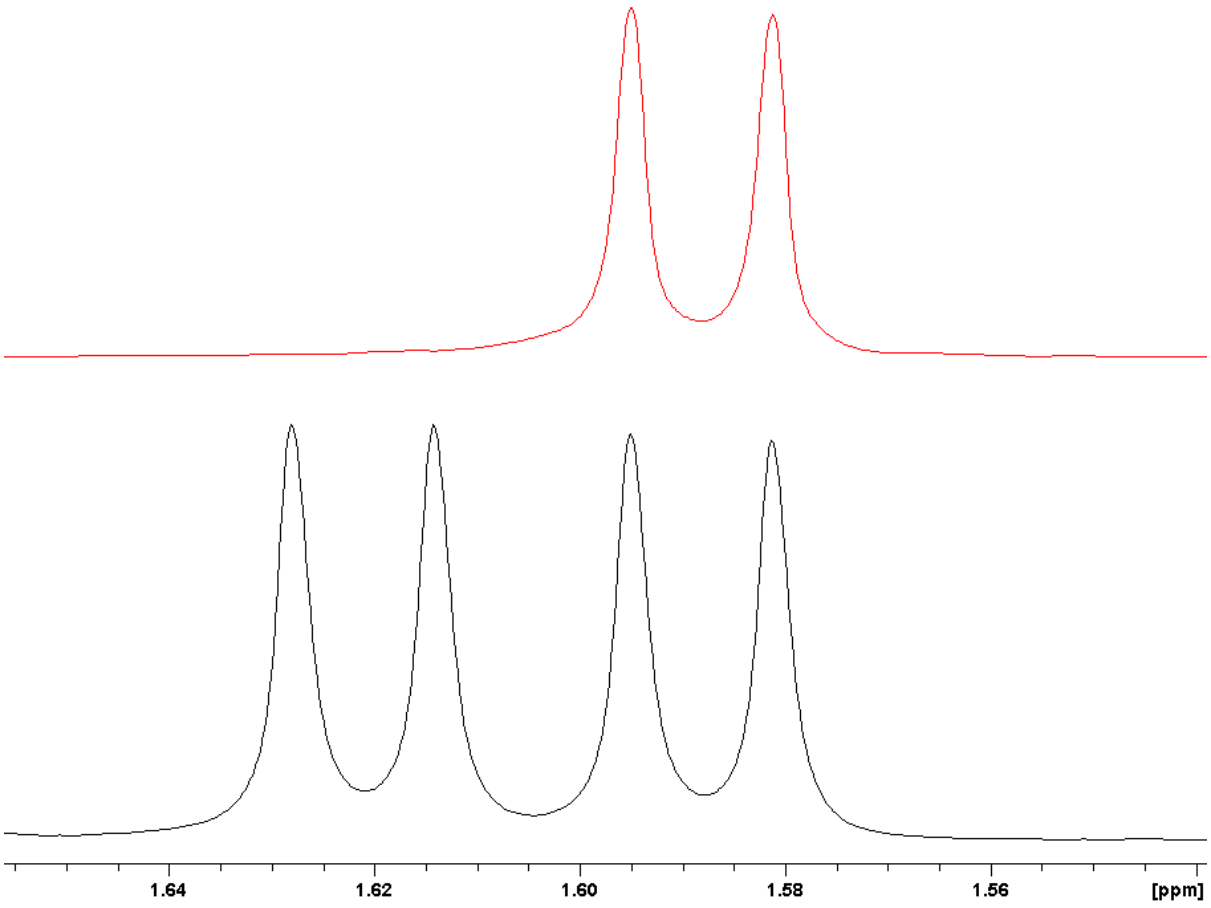
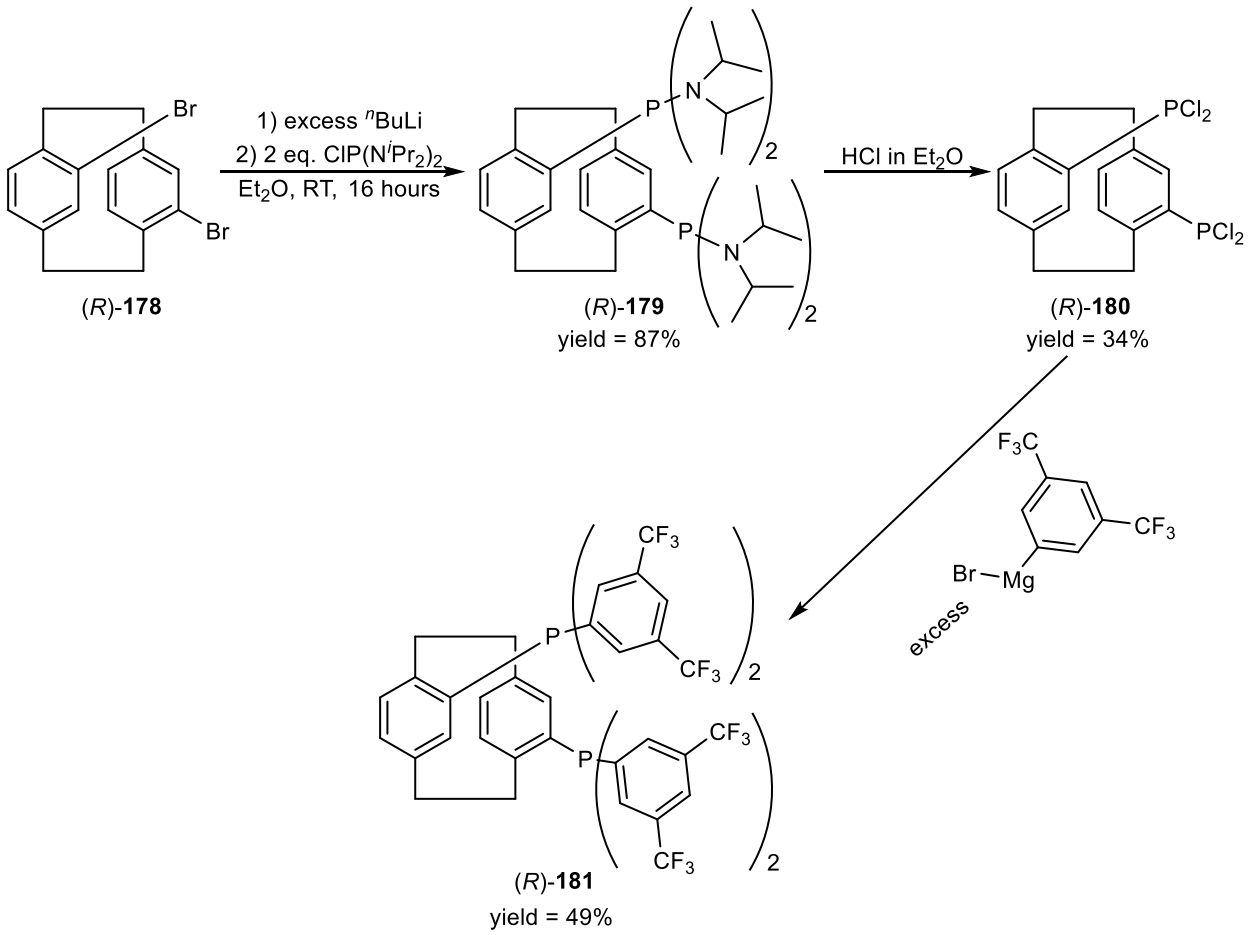



**Figure 3.1.** Selected region in $^{1}$H NMR after resolution of (*S*)-**109i** (top spectrum) and racemic **109i** (bottom spectrum) with (*R*)-methoxyphenylacetic acid (**177**) (represents the N-CH-$\underline{CH_3}$ groups of the salts formed).

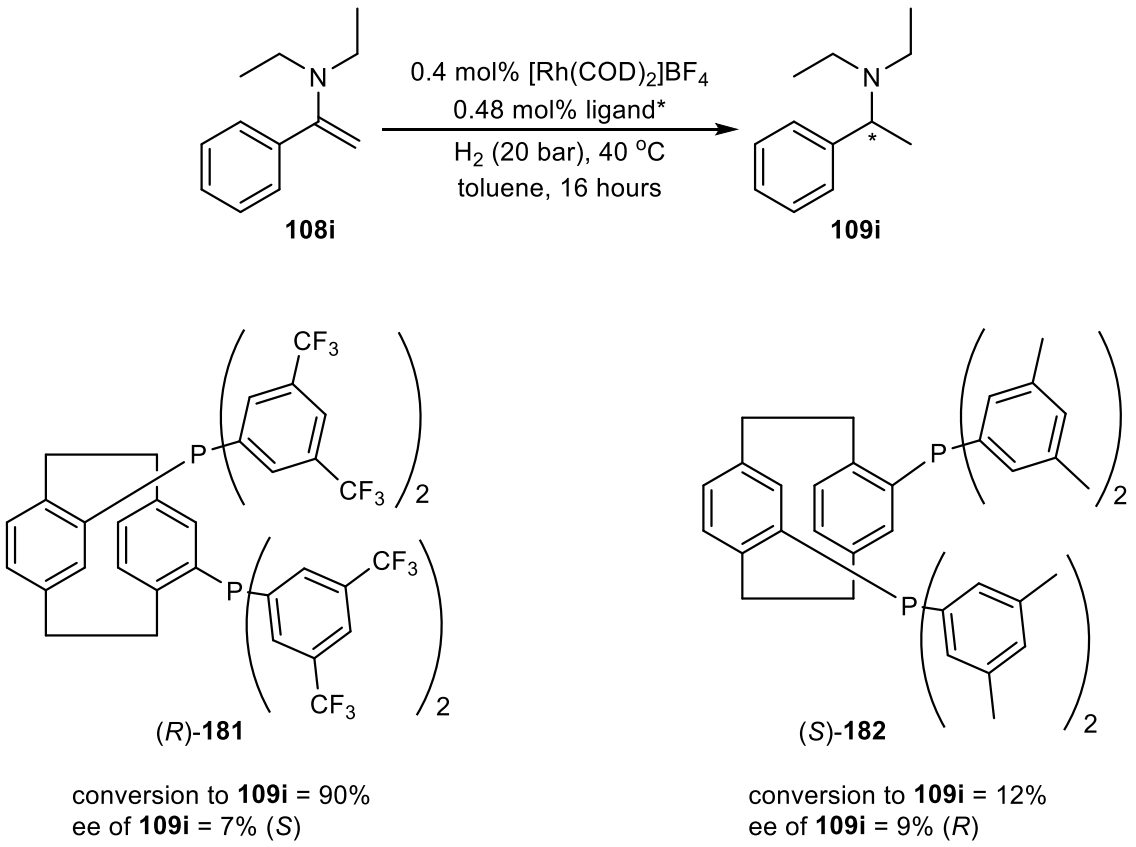
### 3.2 Initial testing of chiral ligands and rhodium complexes

Initially, it was decided to explore PHANEPHOS ligands. Transition metal catalysts of them are known to be highly-active and enantioselective in a number of catalytic processes, including enantioselective hydrogenation.[104-106] While (*S*)-Xylyl-PHANEPHOS ligand (**182** – see Scheme 3.3) is commercially available, the synthesis of the electron-deficient PHANEPHOS ligand **181** was carried out according to the procedure previously described by our group (Scheme 3.2).[106]




**Scheme 3.2.** Synthesis of chiral PHANEPHOS ligand (*R*)-**181**.

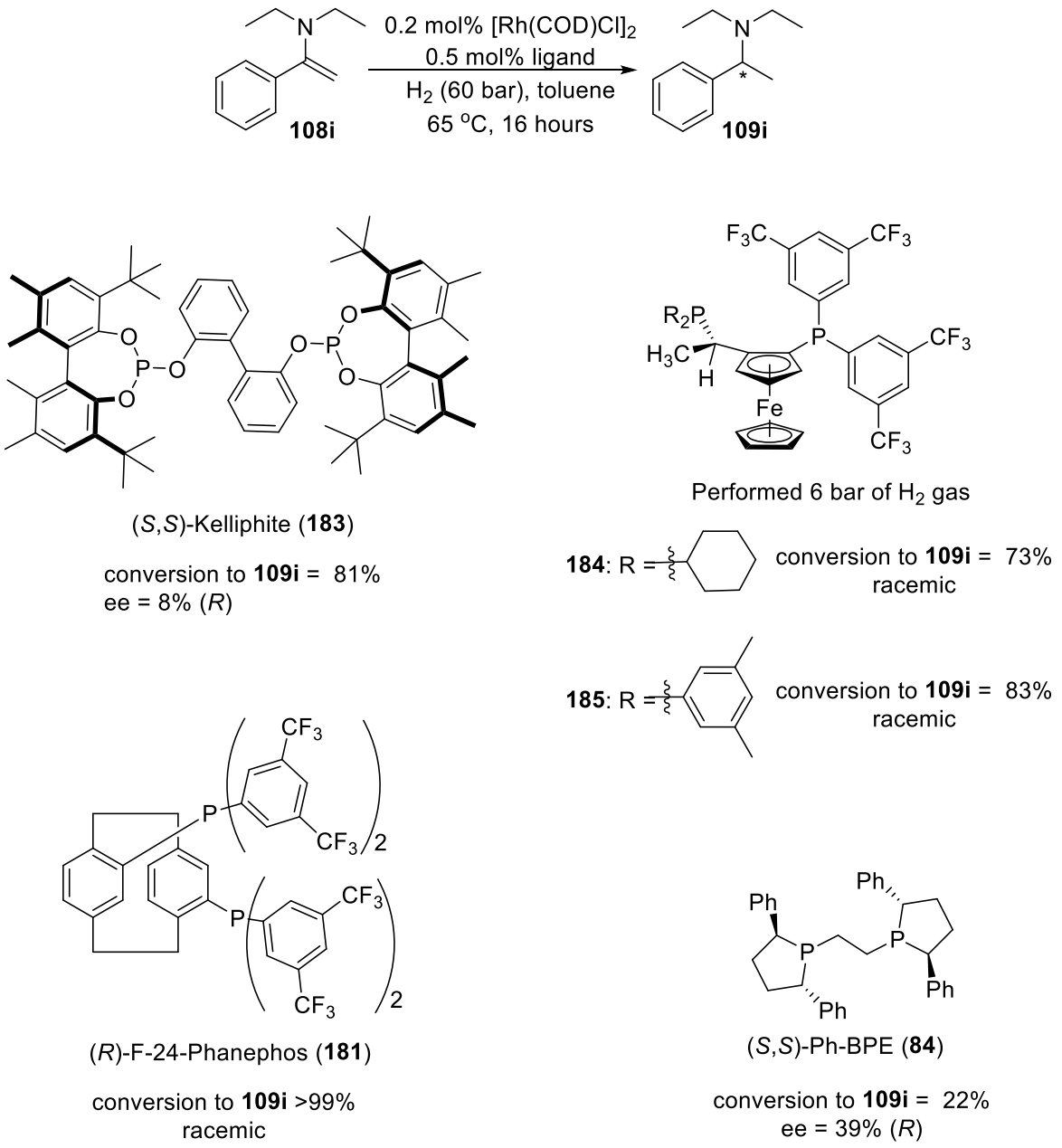
Initially, it was of interest to establish the electronic effect of the bidentate ligands. In order to do so, electron-rich ligand **181** and electron-deficient (and more bulky) ligand **182** were compared in the hydrogenation of enamine **108i** (Scheme 3.3). As expected, the Rh catalyst of electron-deficient ligand (*R*)-**181** afforded a significantly faster rate of reaction in comparison to the Rh catalyst of ligand (*S*)-**182**. At this stage, the enantioselectivities were very poor, as almost racemic samples of the amine were obtained with both catalysts.




**Scheme 3.3.** Enantioselective hydrogenation of **108i** with PHANEPHOS ligands **181** and **182**.

A few other ligands with $[Rh(COD)Cl]_2$ as a metal precursor were examined as catalysts with the results shown in Scheme 3.4. (*S*,*S*)-Kelliphite ligand (**183**) proved itself to be a useful one in rhodium-catalysed enantioselective hydroformylation of allyl cyanide,[107] and is known to be an electron-deficient ligand. Diphosphine ligands which are isostructural to ligands **184** and **185** have proved themselves to be useful in a number of enantioselective catalytic processes, including hydrogenation of amides and (*Z*)-aminoacrylates, as well as enantioselective reductive amination.[50,63,66] Phospholane ligand (*S*,*S*)-**84** was chosen since phospholanes were explored in the past as a very useful type of ligands in a good number of enantioselective processes, including hydrogenation of amides.[60,62,108]

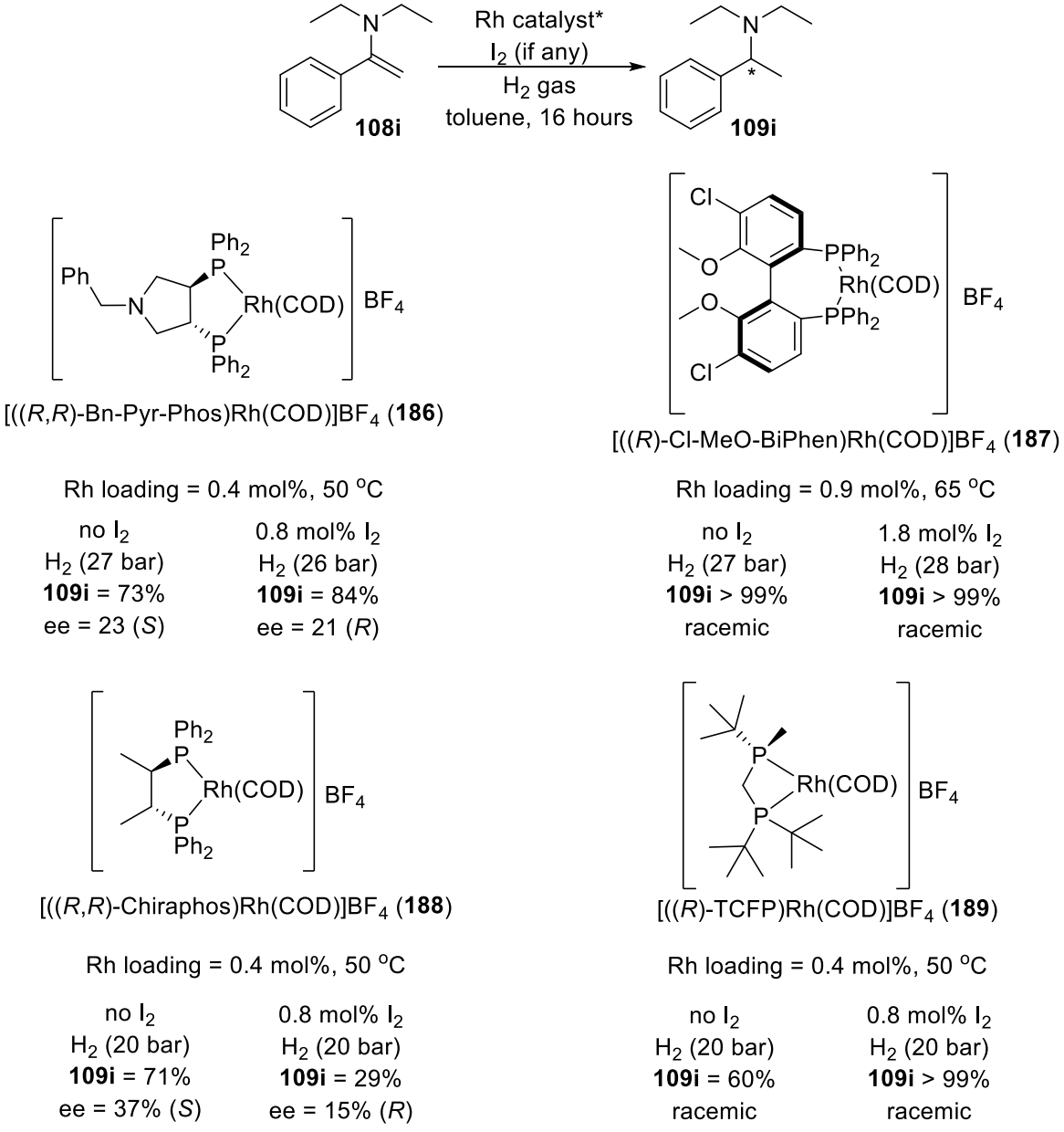
Although most of the chiral catalysts afforded no enantioselectivity, phospholane-type ligands were thought to be potentially promising in terms of enantioselectivity (such as ligand (*S*,*S*)-**84**). The best activity was achieved with the catalyst derived from Rh / chiral PHANEPHOS ligand **181**. This ligand is very active in this process due to having bulky and electron-withdrawing substituents on the phosphorous atoms.




**Scheme 3.4.** Chiral phosphorous ligands **84**, **181**, **183** – **185** used in the Rh-catalysed enantioselective hydrogenation of enamine **108i**.

In addition to some chiral ligands which were available in the lab for testing, some chiral Rh complexes were also available from the industrial sponsor. Rhodium complex **186** was of interest since the dendrimer of this ligand proved itself to be enantioselective in the allylic amination reaction.[109] Chiral Cl-MeO-BiPhen ligand justified itself to be very useful in enantioselective hydrogenation of keto-esters, with examples of ees being >99%.[110] Chiraphos ligand was used in the past in enantioselective hydrogenation of double bonds of 1,1'-disubstituted alkenes.[111,112] The Rh complex of TCFP ligand (**189**) afforded outstanding

enantioselectivities in hydrogenation of enamido-esters and alkenenitriles, the latter being performed with the S/C ratio of as low as 27000.[113] The work of Zhou and co-workers represents the beneficial effect of iodine co-catalyst in the reaction when $[Rh(COD)_2]BF_4$ as a metal precursor is used.[75] It was demonstrated that an addition of it improves the enantioselectivity of the catalyst dramatically. Therefore, the chiral Rh complexes were tested on their own, as well as in the presence of iodine co-catalyst (the results are shown in Scheme 3.5). Interestingly, for complexes **186** and **189** addition of iodine improves the activities of the catalysts. Chiraphos Rh complex **188** was opposite, and addition of iodine caused not only reduction of the rate of the reaction, but also a decrease in enantioselectivity.




**Scheme 3.5.** Enantioselective hydrogenation of enamine **109i** with chiral rhodium complexes **186**-**189**.

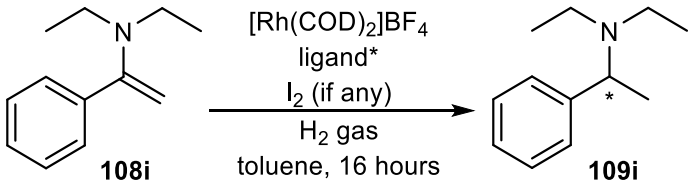
While the enantioselectivities of reductions using complexes **186** and **188** are very poor, surprisingly, the addition of iodine co-catalyst inverted the enantio-preference of the product, affording the opposite enantiomer as the major one in comparison to the reaction where no iodine was used. This effect of iodine will be discussed in detail in Chapter 4.

### 3.3 Enantioselective hydrogenation of enamines with Rh catalysts of PHANEPHOS ligands

Hydrogenation of enamine **108i** was performed using $[Rh(COD)_2]BF_4$ as a metal precursor and ligands (*R*)-**181** and (*S*)-**182** (Table 3.1). Interesting to note, addition of iodine significantly improves the catalyst activities (comparing entries 3 to 4, as well as 5 to 6). Even in the presence of iodine co-catalyst, electron-poor ligand (*R*)-**181** is more active, than (*S*)-**182** (entries 7 and 8). It was also shown that there is no advantage to use a pre-formed catalyst (pre-formed by mixing the ligand and $[Rh(COD)_2]BF_4$, stirring it in dichloromethane and removal of solvent *in vacuo*), and the *in-situ* formation of the complex affords, within the experimental error, the same result (entries 8 and 9). It is worth mentioning, that even at low catalyst loading (0.1 mol%) ligand (*R*)-**181** was able to afford a full conversion at room temperature (entry 12). It is also unusual, that this ligand bears almost the same enantioselectivity at 25 $^{o}$C as it does at 65 $^{o}$C.

While enantioselectivity of only up to 50% was achieved in toluene as a solvent, it was of a huge interest to test these reactions in chlorobenzene (see Chapter 4 – where chlorobenzene appears to be a very interesting solvent for phospholane catalysts). As shown in entries 15 – 18, catalysts afforded good activities. Even electron-rich ligand was able to afford the full conversion to the product at low catalyst loading in the presence of iodine co-catalyst (entry 18). It is also clear that the electron-poor ligand is more active in the process than the electron-rich one in this solvent as well (entries 15 and 17). Although the catalysts displayed very good activities, chlorobenzene does not solve the problem of enantioselectivity for these catalysts, and only an equivalent selectivity was obtained for Rh / ligand (*R*)-**181** as a catalyst (entry 16) in comparison to the same reaction in toluene.

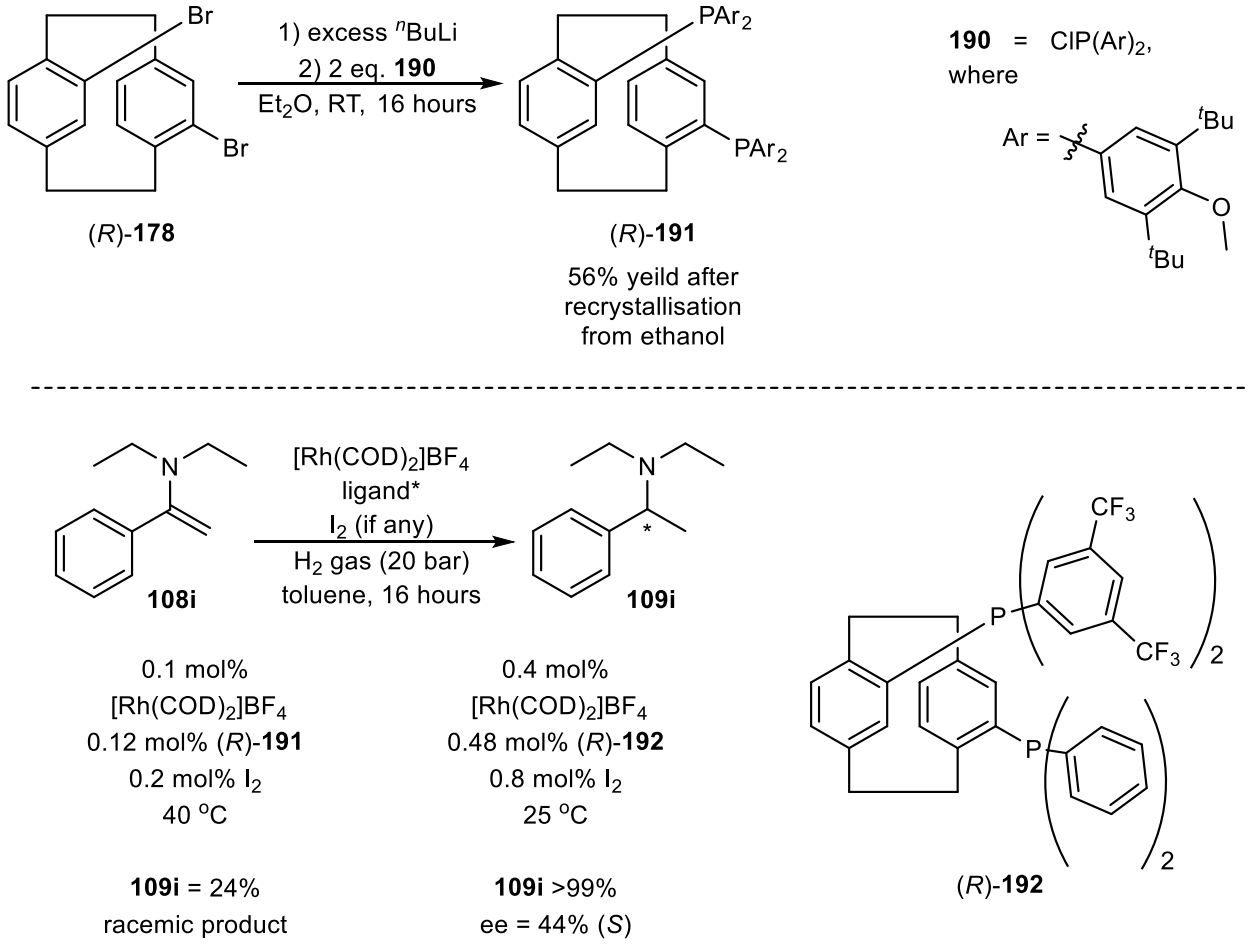
**Table 3.1.** Hydrogenation of **108i** using Rh \ PHANEPHOS catalysts.




| Entry[a] | Ligand | Rh, mol% | $I_2$, mol% | T, °C | P, bar | Remaining **108i**, %[b] | **109i**, %[b] [isolated yield][c] | ee, %[d] |
|---|---|---|---|---|---|---|---|---|
| 1 | (*R*)-**181** | 0.4 | 0.8 | 65 | 60 | <1 | 99 | 45 (*S*) |
| 2 | (*S*)-**182** | 0.4 | 0.8 | 65 | 60 | <1 | 99 | 16 (*R*) |
| 3 | (*R*)-**181** | 0.4 | - | 40 | 20 | 9 | 90 | 7 (*S*) |
| 4 | (*R*)-**181** | 0.4 | 0.8 | 40 | 20 | <1 | 99 | 50 (*S*) |
| 5 | (*S*)-**182** | 0.4 | - | 40 | 20 | 88 | 12 | 9 (*R*) |
| 6 | (*S*)-**182** | 0.4 | 0.8 | 40 | 20 | 1 | 98 | 11 (*R*) |
| 7 | (*R*)-**181** | 0.1 | 0.2 | 40 | 20 | <1 | >99 | 50 (*S*) |
| 8 | (*S*)-**182** | 0.1 | 0.2 | 40 | 20 | 64 | 33 | racemic |
| 9[e] | (*S*)-**182** | 0.1 | 0.2 | 40 | 20 | 73 | 25 | racemic |
| 10 | (*R*)-**181** | 0.4 | 0.8 | 25 | 60 | <1 | >99 [77] | 50 (*S*) |
| 11 | (*S*)-**182** | 0.4 | 0.8 | 25 | 60 | <1 | >99 | 20 (*R*) |
| 12 | (*R*)-**181** | 0.1 | 0.2 | 25 | 60 | <1 | >99 | 50 (*S*) |
| 13 | (*S*)-**182** | 0.1 | 0.2 | 25 | 60 | 47 | 52 | 18 (*R*) |
| 14 | (*R*)-**181** | 0.4 | 0.8 | 25 | 20 | 6 | 93 | 50 (*S*) |
| 15[f] | (*R*)-**181** | 0.1 | - | 40 | 20 | 20 | 79 | racemic |
| 16[f] | (*R*)-**181** | 0.1 | 0.2 | 40 | 20 | <1 | >99 | 46 (*S*) |
| 17[f] | (*S*)-**182** | 0.1 | - | 40 | 20 | 53 | 46 | racemic |
| 18[f] | (*S*)-**182** | 0.1 | 0.2 | 40 | 20 | <1 | >99 | racemic |

[a]General conditions: 1 mmol of enamine **108i** for the reactions with 0.4 mol% catalyst loading, or 1.5 mmol for the reactions with 0.1 mol% catalyst loadings, $[Rh(COD)_2]BF_4$, 1.2 eq. of chiral ligand to Rh, 0.1 mL of 1-methylnaphthalene as an internal standard, $H_2$ gas, toluene as a solvent, 16 hours. [b]Determined by $^1H$ NMR relative to 1-methylnaphthalene. Data for remaining enamine **108i** and amine **109i** formed is present. Ketone (acetophenone) makes up remaining mass balance due to hydrolysis of some starting material. [c]Isolated by acid-base work-up. [d]Enantiomeric excess determined by $^1H$ NMR after addition of excess of (*R*)-(–)-α-methoxyphenylacetic acid. Enantiomer of the product determined after comparison to an authentic sample of (*S*)-**109i** (by $^1H$ NMR shift of the peak of the salt, and, in case of isolated yields, by optical rotation as well). [e][((*S*)-**182**)-Rh(COD)]$BF_4$ was used with no additional equivalents of ligand. [f]Solvent = chlorobenzene.

The known symmetric (*R*)-**191** PHANEPHOS ligand was prepared according to the literature procedure,[106] and non-symmetric chiral PHANEPHOS ligand (*R*)-**192** was borrowed from Jamie Durrani, who studied synthesis and use of PHANEPHOS ligands during his PhD project in the group (Scheme 3.6).[114] An experiment performed with ligand (*R*)-**191** is comparable to entries 7 and 8 from Table 3.1. As expected, the conversion towards the desired amine was low due to electron-donating groups on the aromatic ring in the ligand. Non-symmetric PHANEPHOS ligand (*R*)-**192** was very active in the process, affording similar enantioselectivity as (*R*)-**181** (comparable to entry 14 in Table 3.1).

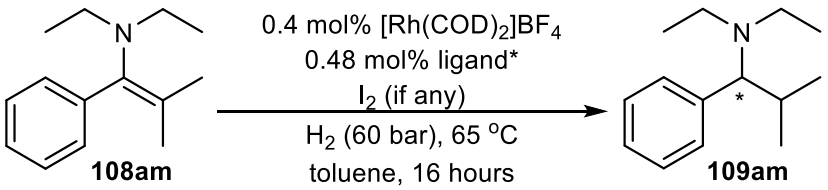



**Scheme 3.6.** Synthesis of ligand (*R*)-**191** and the use of ligands (*R*)-**191** and (*R*)-**192** in hydrogenation of enamine **108i**.

Since Rh \ PHANEPHOS catalysts afforded very good activities, attempts to hydrogenate a tetrasubstituted enamine double bond were performed (Table 3.2). The same trends in catalytic

activity are observed here as for hydrogenation of enamine **108am** (i.e. the electron-deficient ligand is more active, and addition of an iodine co-catalyst improves the rate of the reaction). It is worth mentioning that catalyst derived from ligand (*R*)-**181** is so active, that is able to hydrogenate a tetrasubstituted enamine double bond. To the best of our knowledge, enantioselective hydrogenation of enamines with tetrasubstituted double bonds have never been described in the literature.

**Table 3.2.** Hydrogenation of **108am** using Rh \ PHANEPHOS catalysts.




| Entry[a] | Ligand | $I_2$, mol% | Remaining **108am**, %[b] | **109am**, %[b] (isolated yield)[c] | ee, %[d] |
|---|---|---|---|---|---|
| 1 | (*S*)-**182** | - | 89 | 11 | n.d. |
| 2 | (*S*)-**182** | 0.8 | 80 | 20 | n.d. |
| 3 | (*R*)-**181** | - | 44 | 56 | 30 (+) |
| 4 | (*R*)-**181** | 0.8 | 6 | 94 (51)[c] | 25 (+) |

[a]General conditions: 1 mmol of enamine **108am**, 4 μmol $[Rh(COD)_2]BF_4$, 4.8 μmol of ligand, 0.1 mL of 1-methylnaphthalene as an internal standard, 60 bar of $H_2$, toluene as a solvent, 65 °C, 16 hours. [b]Determined by $^1H$ NMR relative to 1-methylnaphthalene. Data for remaining enamine **108am** and amine **109am** formed is present. [c]Isolated by acid-base work-up, followed by column chromatography. [d]Enantiomeric excess determined by $^1H$ NMR after addition of excess of (*R*)-(–)-α-methoxyphenylacetic acid. For low conversion cases, ee was not determined. Sing was determined by measuring optical rotation of the isolated sample in entry 4.

Overall, this chapter describes the use of PHANEPHOS ligands in Rh-catalysed hydrogenation of enamines. As expected from Chapter 2, benefit of the electron-deficient catalyst is certain. Iodine co-catalyst appears to play a major role in improvement of the activity and enantioselectivity of the catalysts. The electron-poor ligand (*R*)-**181** was able to hydrogenate even a tetrasubstituted enamine's double bond.

Despite the fact that only moderate selectivity was achieved (up to 50% ee), it is worth noting that (*R*)-**181** affords the same selectivity at different temperatures, which is unusual and, potentially, very beneficial. If the activity of the process needs to be improved, it can be achieved by raising the reaction temperature, since it won't affect the enantioselectivity.

Another ligand class that showed some promise in the initial testing were the bis-phospholanes, and the performance of these, especially in the presence of iodine co-catalyst was investigated next (Chapter 4).

# 4. Enantioselective hydrogenation of enamines using phospholanes as ligands

This chapter presents studies of the hydrogenation of enamines with different phospholane Rh complexes under variety of conditions (e.g. different solvents / additives). In addition, the mechanism of the reaction was also studied. The findings suggest that enamines hydrogenate in a quite different way from other alkenes, at least in the presence of iodine additives.

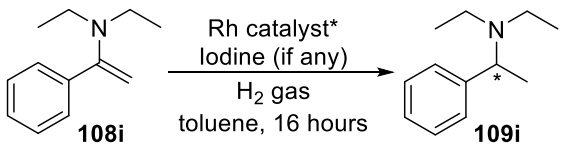
## 4.1 Catalytic enamine hydrogenation using phospholane Rh catalysts: effect of iodine co-catalyst

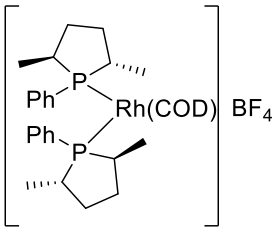
Initially, commercially available phospholane complexes were tested in the hydrogenation of enamine **108i**. Since in the case of PHANEPHOS / Rh catalysts, iodine proved itself to be a very useful co-catalyst, the complexes were tested in the presence of $I_2$ (some examples show the reaction without iodine co-catalyst) (Scheme 4.1).

Although catalyst (*S*,*S*)-**193** afforded no selectivity in the presence and absence of iodine co-catalyst, the rate of the reaction is significantly faster in the presence of it. Under the chosen conditions, it is clear as well that for complexes (*S*,*S*)-**196b** and (*R*,*R*)-**196a** the presence of iodine improves the rates of the reaction as well.

Apart from beneficial effect on the rates of the reactions, $I_2$ improves enantioselectivities significantly for (*R*,*R*)-**196a**, (*S*,*S*)-**196b** and (*R*,*R*)-**198b**. More to that, in the case of catalysts (*S*,*S*)-**196b** and (*R*,*R*)-**198b** (which afforded the best enantioselectivities in these test experiments) the major enantiomer of the product is opposite to the one which is formed in the absence of the co-catalyst.

In order to understand this unusual effect of iodine and to rationalize the findings further, the rhodium complexes of BPE ligand (**196**) and DuPhos (**198**) were selected for further studies. Since the more bulky substituent (-isopropyl group instead of -ethyl group) resulted in a clear drop in enantioselectivity of the catalysts, it was decided to avoid using chiral complexes **196c** and **198c**.



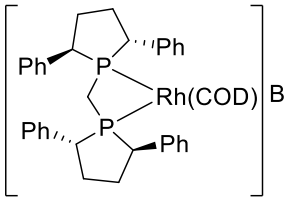



[((*S*,*S*)-Me-Phospholane)Rh(COD)]$BF_4$

(*S*,*S*)-**193**

Rh loading = 0.4 mol%, 50 °C

| no $I_2$ | 0.8 mol% $I_2$ |
|---|---|
| $H_2$ (20 bar) | $H_2$ (20 bar) |
| **109i** = 17% | **109i** > 99% |
| racemic | racemic |

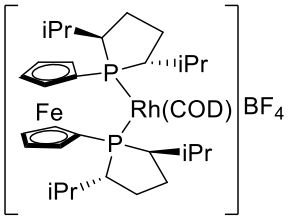


[((*R*,*R*)-Ph-BPM)Rh(COD)]$BF_4$

(*R*,*R*)-**194**

Rh loading = 0.4 mol%, 50 °C

0.8 mol% $I_2$
$H_2$ (20 bar)
**109i** > 99%
racemic

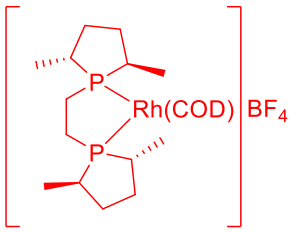


[((*R*,*R*)-*i*Pr-5-Fc)Rh(COD)]$BF_4$

(*R*,*R*)-**195**

Rh loading = 0.4 mol%, 50 °C

0.8 mol% $I_2$
$H_2$ (26 bar)
**109i** = 5%
ee n.d.

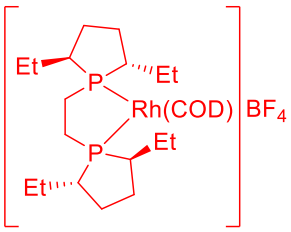


[((*R*,*R*)-Me-BPE)Rh(COD)]$BF_4$

(*R*,*R*)-**196a**

Rh loading = 0.4 mol%, 50 °C

| no $I_2$ | 0.8 mol% $I_2$ |
|---|---|
| $H_2$ (20 bar) | $H_2$ (20 bar) |
| **109i** = 80% | **109i** > 99% |
| racemic | ee = 40% (*S*) |

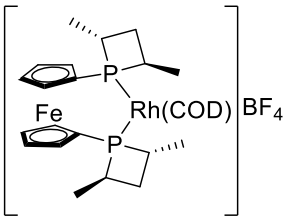


[((*S*,*S*)-Et-BPE)Rh(COD)]$BF_4$

(*S*,*S*)-**196b**

Rh loading = 0.4 mol%, 40 °C

| no $I_2$ | 0.8 mol% $I_2$ |
|---|---|
| $H_2$ (20 bar) | $H_2$ (20 bar) |
| **109i** = 12% | **109i** > 99% |
| ee = 17% (*S*) | ee = 62% (*R*) |

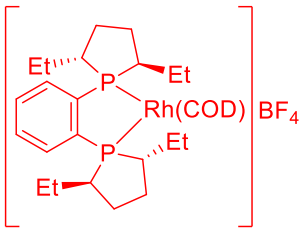


[((*R*,*R*)-Me-Ferrotane)Rh(COD)]$BF_4$

(*R*,*R*)-**197**

Rh loading = 0.4 mol%, 50 °C

0.8 mol% $I_2$
$H_2$ (20 bar)
**109i** > 99%
racemic

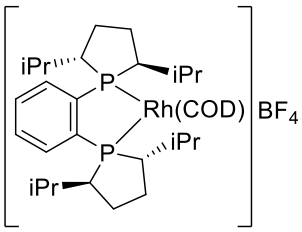


[((*R*,*R*)-Et-DuPhos)Rh(COD)]$BF_4$

(*R*,*R*)-**198b**

Rh loading = 0.4 mol%, 65 °C

| no $I_2$ | 0.8 mol% $I_2$ |
|---|---|
| $H_2$ (60 bar) | $H_2$ (60 bar) |
| **109i** > 99% | **109i** > 99% |
| ee = 28% (*R*) | ee = 58% (*S*) |

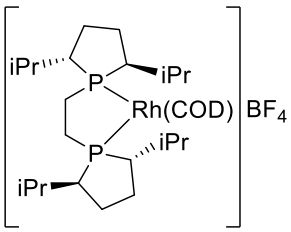


[((*S*,*S*)-*i*Pr-DuPhos)Rh(COD)]$BF_4$

(*S*,*S*)-**198c**

Rh loading = 1.0 mol%, 65 °C

2.0 mol% $I_2$
$H_2$ (29 bar)
**109i** = 40%
racemic



[((*S*,*S*)-*i*Pr-BPE)Rh(COD)]$BF_4$

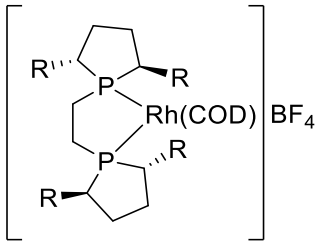
(*S*,*S*)-**196c**

Rh loading = 1.0 mol%, 65 °C

2.0 mol% $I_2$
$H_2$ (29 bar)
**109i** > 99%
racemic

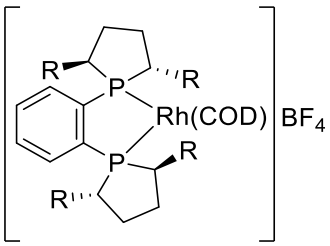
**Scheme 4.1.** Hydrogenation of enamine **108i** in the presence (and absence for several examples) of iodine co-catalyst.

Chiral rhodium complexes **196** and **198** shown in Figure 4.1 were used in the experiments described later on. Attempts to prepare new electron-deficient phospholane ligands were unsuccessful (see Appendix A for details), and therefore all further studies were performed with the available complexes.




[(BPE)*Rh(COD)]$BF_4$

(*R,R*)-**196a** : R = Me
(*R,R*)-**196b** : R = Et
(*S,S*)-**196d** : R = Ph




[((*S,S*)-R-DuPhos)Rh(COD)]$BF_4$

(*S,S*)-**198a** : R = Me
(*S,S*)-**198b** : R = Et

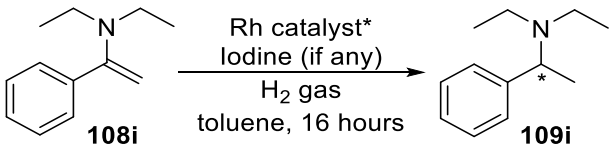
**Figure 4.1.** BPE (**196**) and DuPhos (**198**) catalysts used in further screening.

The results in Table 4.1 show a study of the performance of the catalysts shown in Figure 4.1 in the enantioselective hydrogenation of enamine **108i**. As observed in the previous experiments, the reaction is faster in the presence of iodine co-catalyst (comparing entries 2 and 14 as well as 4 and 15). Activities of BPE complexes (**196**) are higher than those of similarly substituted DuPhos ones (**198**) in the presence and absence of $I_2$ (compare entry 2 to entry 4, and 14 to 15). Despite being the complexes of electron-rich ligands, they are quite active in the presence of iodine co-catalyst. A TON of above 1000 mol $mol^{-1}$ was achieved (entry 16) which proves that these complexes are able to perform an enamine hydrogenation at low catalyst loadings even with electron-donating alkyl substituents on the ligands.

Addition of iodine does not only improve the activities of the phospholane catalysts, but also improves their enantioselectivities. Several experiments were carried out to check that the product does not racemise over time in the presence of the active catalyst (see experimental for details). Entries 6 and 7 also support this statement since in the experiment in entry 6 all the enamine is consumed within 2 hours, and no reduction in enantioselectivity is observed compared to the one performed for 2 hours only. As observed in the initial screening, the enantiopreference of the product changes in the presence of iodine co-catalyst. For example, catalyst (*R,R*)-**198b** in entry 4 affords the amine with the ee of only 27% with the *R* enantiomer of the product being the major one. When the reaction is performed under the same conditions, but in the presence of iodine co-catalyst (entry 15), the ee of the product is 69% where the major

enantiomer of the product has *S* configuration. An even more dramatic change is observed with catalyst **196b** (entries 2 and 14). In entry 2, 74.5% of the amine formed is of *R* configuration. The same reaction with iodine co-catalyst afforded the opposite enantiomer of the product with an ee of 69% (i.e. 84.5% is the *S*-enantiomer). This unusual and dramatic switch in enantiopreference of the product suggests some significant changes in the mechanism of the reaction when iodine is present.

**Table 4.1.** Hydrogenation of enamine **108i** with chiral Rh complexes **196*** and **198***.

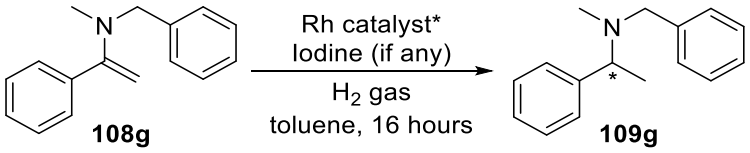



| Entry[a] | Catalyst*, mol% | $I_2$, mol% | Time, hours | T, °C | P, bar | Conversion of **108i**, %[b,c] | **109i**, %[b,c] [yield][d] | ee, %[e,f] |
|---|---|---|---|---|---|---|---|---|
| 1 | (*R*,*R*)-**196b**, 0.4 | - | 16 | 65 | 60 | > 99 | > 99 | 14 (*R*) |
| 2 | (*R*,*R*)-**196b**, 0.4 | - | 16 | 25 | 60 | 38 | 36 | 49 (*R*) |
| 3 | (*R*,*R*)-**198b**, 0.4 | - | 16 | 65 | 60 | > 99 | > 99 | 28 (*R*) |
| 4 | (*R*,*R*)-**198b**, 0.4 | - | 16 | 25 | 60 | 18 | 16 | 27 (*R*) |
| 5[g] | (*R*,*R*)-**196a**, 1.0 | - | 18 | 65 | 20 | > 99 | 93 | racemic |
| 6[g] | (*R*,*R*)-**196a**, 1.0 | 2.0 | 18 | 65 | 20 | > 99 | 97 | 40 (*S*) |
| 7[g] | (*R*,*R*)-**196a**, 1.0 | 2.0 | 2 | 65 | 20 | > 99 | 98 | 36 (*S*) |
| 8[g] | (*R*,*R*)-**198a**, 1.0 | 2.0 | 16 | 65 | 20 | > 99 | 84 | 15 (*S*) |
| 9 | (*R*,*R*)-**196b**, 0.4 | 0.8 | 16 | 65 | 60 | > 99 | > 99 | 48 (*S*) |
| 10 | (*R*,*R*)-**198b**, 0.4 | 0.8 | 16 | 65 | 60 | > 99 | > 99 | 58 (*S*) |
| 11 | (*S*,*S*)-**196d**, 0.4 | 0.8 | 16 | 65 | 60 | 39 | 35 | 24 (*S*) |
| 12 | (*S*,S)-**196b**, 0.4 | 0.8 | 16 | 40 | 60 | > 99 | > 99 [75] | 61 (*R*) |
| 13 | (*R*,*R*)- **198b**, 0.4 | 0.8 | 16 | 40 | 60 | 62 | 60 | 61 (*S*) |
| 14 | (*S*,*S*)-**196b**, 0.4 | 0.8 | 16 | 25 | 60 | > 99 | > 99 [76] | 65 (*R*) |
| 15 | (*R*,*R*)-**198b**, 0.4 | 0.8 | 16 | 25 | 60 | 48 | 44 | 69 (*S*) |
| 16[g,h] | (*R*,*R*)-**196a**, 0.05 | 0.1 | 16 | 50 | 20 | 61 | 56 | 38 (*S*) |
| 17[g,h] | (*R*,*R*)-**196a**, 0.1 | 0.2 | 16 | 25 | 20 | 58 | 56 | 47 (*S*) |

[a]General conditions: 1 mmol of enamine **108i**, 0.4 mol% of Rh catalyst, 0.1 mL of 1-methylnaphthalene as an internal standard, $H_2$ gas, toluene as a solvent, 16 hours.. [b]The only side product observed is a ketone which is formed due to partial hydrolysis of the enamine. [c]Determined by $^1$H NMR relative to 1-methylnaphthalene. [d]Isolated yield (by acid-base work-up). [e]Enantiomeric excess determined by $^1$H NMR after addition an excess of (*R*)-(–)-α-methoxyphenylacetic acid. [f]Stereochemistry of amines was assigned after comparison to authentic samples of chiral amine (*S*)-**109i**. [g]Reaction was performed in Argonaut on 2.0 mmol scale. [h]Reaction scale is 7.8 mmol.

In order to prove that enamine **108i** is not a special case, selected hydrogenation experiments were performed with enamine **108g** (Table 4.2). In order to determine the exact enantiomer of the product, amine (*R*)-**109g** was prepared from an enantiopure precursor (see Experimental for details).

**Table 4.2.** Enantioselective hydrogenation of enamine **108g** with Rh / phospholane catalysts.




| Entry[a] | Catalyst*, mol% | $I_2$, mol% | T, °C | P, bar | Conversion of **108g**, %[b,c] | **109g**, %[b,c] [yield][d] | ee, %[e,f] |
|---|---|---|---|---|---|---|---|
| 1 | (*R*,*R*)-**196b**, 0.4 | - | 65 | 60 | > 99 | > 99 [83] | 8 (*R*) |
| 2 | (*R*,*R*)-**196b**, 0.4 | 0.8 | 65 | 60 | > 99 | > 99 | 46 (*S*) |
| 3[g] | (*R*,*R*)-**196a**, 0.4 | - | 30 | 20 | 44 | 37 | 23 (*R*) |
| 4[g] | (*R*,*R*)-**196a**, 0.4 | 0.8 | 30 | 20 | > 99 | 92 | 40 (*S*) |
| 5[g,h] | (*R*,*R*)-**196a**, 0.05 | 0.1 | 50 | 20 | 91 | 90 | 34 (*S*) |
| 6[g,i] | (*R*,*R*)-**196a**, 0.1 | 0.2 | 25 | 20 | 58 | 58 | 34 (*S*) |
| 7[g,j] | (*R*,*R*)-**196a**, 1.0 | 2.0 | 65 | 20 | > 99 | 98 | 36 (*S*) |
| 8[g] | (*R*,*R*)-**198a**, 1.0 | 2.0 | 65 | 20 | > 99 | 94 | 44 (*S*) |
| 9[g] | (*R*,*R*)-**198a**, 0.4 | 0.8 | 30 | 26 | > 99 | 97 | 67 (*S*) |
| 10 | (*R*,*R*)-**196b**, 0.4 | - | 25 | 60 | 31 | 30 | 29 (*R*) |
| 11 | (*R*,*R*)-**196b**, 0.4 | 0.8 | 25 | 60 | > 99 | > 99 [85] | 60 (*S*) |
| 12 | (*R*,*R*)-**198b**, 0.4 | - | 25 | 60 | 12 | 11 | 21 (*R*) |
| 13 | (*R*,*R*)-**198b**, 0.4 | 0.8 | 25 | 60 | 59 | 56 | 77 (*S*) |
| 14[g,j] | (*R*,*R*)-**196d**, 1.0 | 2.0 | 65 | 20 | 30 | 15 | racemic |

[a]General conditions: 1 mmol of enamine **108g**, Rh catalyst, iodine (if any), 0.1 mL of 1-methylnaphthalene as an internal standard, $H_2$ gas, toluene as a solvent, 16 hours. [b]The only side product observed is a ketone which is formed due to partial hydrolysis of enamine. [c]Determined by $^1$H NMR relative to 1-methylnaphthalene. [d]Isolated yield (by acid-base work-up). [e]Enantiomeric excess determined by $^1$H NMR after addition an excess of (*R*)-(–)-α-methoxyphenylacetic acid. [f]Stereochemistry of amines was assigned after comparison to the authentic samples of chiral amine (*R*)-**109g**. [g]Reaction performed in Argonaut on 2.0 mmol scale unless otherwise stated. [h]Reaction scale is 7.8 mmol. [i]Reaction scale is 6.4 mmol. [j]Reaction time 2 hours.

As previously observed for enamine **108i**, addition of iodine improves activities of the catalysts (comparing entries 3 to 4, 10 to 11 and 12 to 13). Partial conversions of enamine are observed in experiments shown in entries 12 and 13, so provide a good estimate of the relative

rates of reaction. These suggest that the rate of the reaction for the catalyst (*R*,*R*)-**198b** increases by about 5 times when iodine co-catalyst is present. Entry 5 represents a low catalyst loading experiment (S/C ratio of 2000). A TON of 1800 mol $mol^{-1}$ is achieved, which is, to the best of our knowledge, higher than anything published in the literature for an enantioselective hydrogenation of an unfunctionalised enamine.

Apart from good activities of the catalysts in hydrogenation of **108g**, the same effects are observed on enantioselectivity as in iodine-promoted hydrogenation of **108i**. Addition of iodine co-catalyst improves the enantioselectivity significantly, as well as inverts the absolute configuration of the product. As in the hydrogenation of enamine **108i**, it is clear that [((*R*,*R*)-Ph-BPE)-Rh(COD)]$BF_4$ complex ((*R*,*R*)-**196d**) is less active and selective compared to other phospholane Rh complexes. While DuPhos complexes (**198**) are less active than comparable BPE complexes (**196**), they are certainly a lot more selective for this substrate. The highest enantioselectivity observed is 77% ee (entry 13).

Having observed unprecedented TONs and quite good ees in the presence of iodine, the next step was to explore the unusual additive effect further, as well as to work on the improvement of the enantioselectivity of the reaction.

### 4.2 Exploration of the effects of additives

Since the presence of iodine co-catalyst appears to play an important role in the hydrogenation of enamines with the chiral Rh-phospholane complexes, some more additives and conditions were tested for the enantioselective hydrogenation of **108i** with (*R*)-**196b** or (*S*)-**196b** as catalyst (Table 4.3). The first seven entries report on the experiments conducted with no additive, or an additive containing 4 equivalents of halogen atoms relative to Rh. Interestingly, addition of sodium iodide (entry 2) had a similar effect on enantioselectivity – i.e. the ee of the product improved and the absolute configuration of the product was inverted. Although the presence of NaI in the reaction is beneficial, presence of iodine co-catalyst afforded a better enantioselectivity. Lithium chloride (entry 3) reduced the activity of the catalyst, but improved enantioselectivity. In the case of using it, no inversion of the enantiopreference was observed.

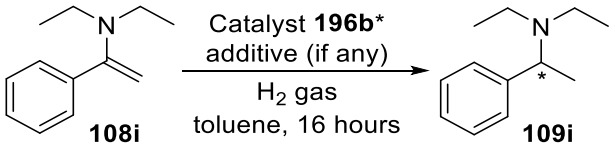
Bromine as an additive clearly reduced the activity of the catalyst (entry 6). The likely cause of that could be that it creates stronger bonds with Rh, and therefore deactivates it. Another reason could be that bromine simply reacted with the enamine (a slow reaction), which could explain the appearance of traces of an unidentified product. The reaction afforded a reasonable enantioselectivity, and as in the case of iodine co-catalyst, inverted the stereochemistry of the major enantiomer of amine **109i**. Iodine co-catalyst (entry 7), compared to

$Br_2$ co-catalyst is a lot more beneficial, since it does not only make the catalyst significantly more reactive, but also more enantioselective.

Addition of pyridine poisons the catalyst (entry 8). As previously described in Chapter 2, presence of a compound with a pyridine moiety in it reduces the activity of the catalyst dramatically. The likely reason for that is because it binds to the metal center through the nitrogen atom on the pyridine ring, and therefore deactivates it.

Since iodine appears to be the best performing co-catalyst out of the ones chosen in this study, it was important to identify the most optimum amount of it in the reaction. Zhou and co-workers reported in their study that two equivalents of $I_2$ relative to a Rh catalyst is the required amount to achieve the best enantioselectivity, and that addition of any extra equivalents of $I_2$ on the top of that reduces both the activity and enantioselectivity of it.[75] Entries 9 – 14 represent the experiments under the same conditions, but with different amounts of the iodine in them. Clearly, when 2 equivalents of iodine to metal is added, an ee of 62% is obtained, as well as the full conversion of the enamine is achieved (entry 12). Further addition of iodine has no effect on the selectivity of the catalyst at all. In order to rationalise the effect on the activity better, several experiments under milder conditions and lower catalyst loadings (shown in entries 15 – 18) were performed. Although, as observed previously, enantioselectivity does not improve on addition of more iodine, it is now clear that the activity of the catalysts improve up to 3 equivalents.

**Table 4.3.** Different additives for hydrogenation of **108i** using **196b*** as a catalyst.




| Entry[a] | Catalyst, mol% | Additive, mol% | T, °C | P, bar | Conversion of **108i**, %[b,c] | **109i**, %[b,c] | ee, %[d,e] |
|---|---|---|---|---|---|---|---|
| 1 | (*R*,*R*)-**196b**, 0.4 | - | 65 | 60 | > 99 | > 99 | 14 (*R*) |
| 2 | (*R*,*R*)-**196b**, 0.4 | NaI, 1.6 | 65 | 60 | > 99 | 93 | 38 (*S*) |
| 3 | (*R*,*R*)-**196b**, 0.4 | LiCl, 1.6 | 65 | 60 | 91 | 87 | 32 (*R*) |
| 4 | (*R*,*R*)-**196b**, 0.4 | $I_2$ | 65 | 60 | > 99 | > 99 | 48 (*S*) |
| 5 | (*R*,*R*)-**196b**, 0.4 | - | 25 | 60 | 38 | 36 | 49 (*R*) |
| 6 | (*R*,*R*)-**196b**, 0.4 | $Br_2$, 0.8 | 25 | 60 | 20[f] | 11[f] | 43 (*S*) |
| 7 | (*S*,*S*)-**196b**, 0.4 | $I_2$, 0.8 | 25 | 60 | > 99 | > 99 | 65 (*R*) |
| 8 | (*S*,*S*)-**196b**, 0.4 | pyridine, 0.45 | 40 | 20 | 7 | 5 | n.d.[g] |
| 9 | (*S*,*S*)-**196b**, 0.4 | - | 40 | 20 | 13 | 12 | 17 (*S*) |
| 10 | (*S*,*S*)-**196b**, 0.4 | $I_2$, 0.2 | 40 | 20 | 19 | 15 | 29 (*R*) |
| 11 | (*S*,*S*)-**196b**, 0.4 | $I_2$, 0.4 | 40 | 20 | 59 | 55 | 56 (*R*) |
| 12 | (*S*,*S*)-**196b**, 0.4 | $I_2$, 0.8 | 40 | 20 | > 99 | > 99 | 62 (*R*) |
| 13 | (*S*,*S*)-**196b**, 0.4 | $I_2$, 1.2 | 40 | 20 | > 99 | > 99 | 62 (*R*) |
| 14 | (*S*,*S*)-**196b**, 0.4 | $I_2$, 2.0 | 40 | 20 | > 99 | > 99 | 62 (*R*) |
| 15 | (*R*,*R*)-**196b**, 0.2 | $I_2$, 0.2 | 25 | 20 | 27 | 25 | 52 (*S*) |
| 16 | (*R*,*R*)-**196b**, 0.2 | $I_2$, 0.32 | 25 | 20 | 48 | 46 | 59 (*S*) |
| 17 | (*R*,*R*)-**196b**, 0.2 | $I_2$, 0.4 | 25 | 20 | 51 | 48 | 59 (*S*) |
| 18 | (*R*,*R*)-**196b**, 0.2 | $I_2$, 0.6 | 25 | 20 | 75 | 73 | 60 (*S*) |

[a]General conditions: 1 mmol of enamine **108i**, chiral Rh complex **196b***, additive, 0.1 mL of 1-methylnaphthalene as an internal standard, $H_2$ gas, toluene as a solvent, 16 hours. [b]The only side product observed is a ketone which is formed due to partial hydrolysis of enamine. [c]Determined by $^1$H NMR relative to 1-methylnaphthalene. [d]Enantiomeric excess determined by $^1$H NMR after addition an excess of (*R*)-(–)-α-methoxyphenylacetic acid. [e]Stereochemistry of amines was assigned after comparison to the authentic samples of chiral amine (*S*)-**109i**. [f]Traces of unidentified product are present as well. [g]Not determined.

Overall, iodine is a particularly important additive in this reaction. Since good TONs were achieved with two equivalents of the co-catalyst relative to Rh, and the key interest was to improve the enantioselectivity of the reaction, further experiments were performed with only two equivalents of iodine relative to the metal. The next step of this study was to explore the effect of the solvent in this reaction.

### 4.3 Solvents – unusual chlorobenzene effect

Zhou and co-workers described THF as the best solvent for this reaction when their chiral Rh catalyst was used.[75] Another solvent of interest was methanol, since it is green and cheap. Chlorobenzene was tested as well. Although it is a halogenated solvent, it appears to be one of the most environmentally friendly of the halogenated solvents, and is described in a number of patents and books as a very important solvent for industrial applications.[115,116] Some dramatic results were obtained in $C_6H_5Cl$ as a solvent (Figure 4.2). As previously observed in toluene as a solvent, addition of iodine caused an improvement in the activity and enantioselectivity of the catalysts, while the absolute configuration of the product switched. In chlorobenzene as a solvent the switch of absolute configuration of the product is very dramatic, and good enantioselectivities were achieved even without iodine co-catalyst. Thus, both enantiomers of the product can be produced from the same enantiomer of the catalyst just by addition of a small amount of iodine to the reaction. Full details of the experiments are shown in Table 4.4.

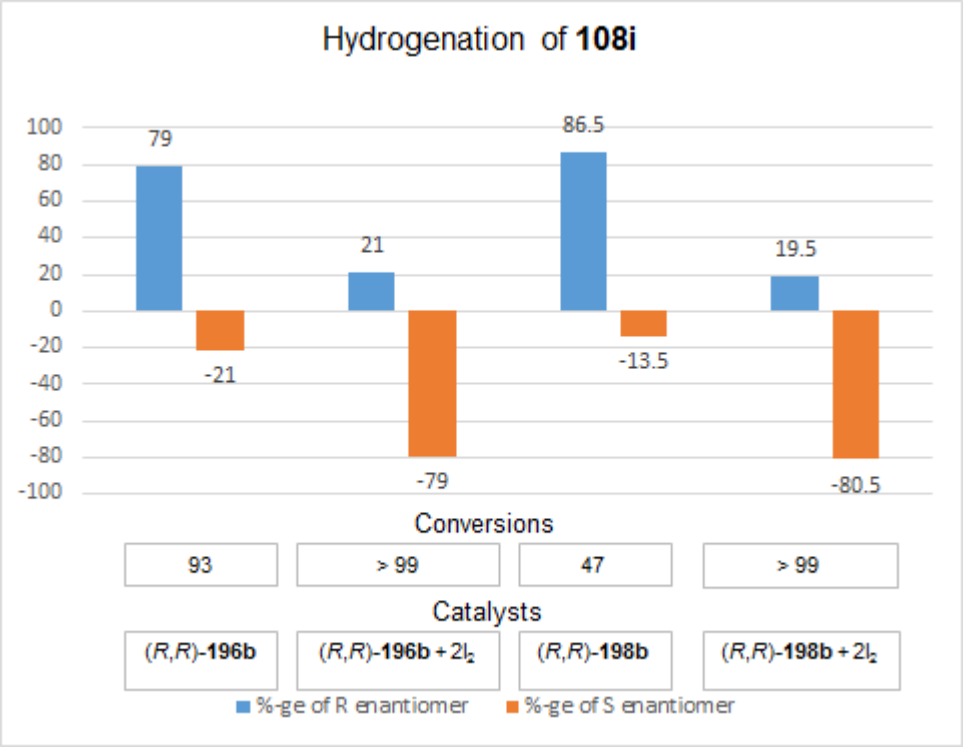
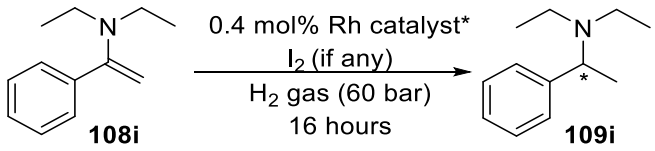



**Figure 4.2.** Remarkable effect of chlorobenzene as a solvent in enantioselective hydrogenation of enamine **108i** using phospholane Rh complexes as the catalysts. The full reaction conditions are present in Table 4.4.

It is an important thing to note that activities of the catalysts are higher than in toluene as a solvent – e.g. the experiment shown in the left hand side of Figure 4.2 (Table 4.4 entry 10)

(93% of the amine formed) was conducted under the same conditions in toluene (Table 4.4 entry 8), but only 36% of the amine was produced. The same behaviour is observed for the catalyst (*R*,*R*)-**198b** (comparable data in toluene as a solvent can be found in Table 4.1). As in the cases when toluene was used as a solvent, iodine co-catalyst improves the rate of the reaction, except for catalyst (*S*,*S*)-**196d**. Chiral Ph-BPE rhodium complex **196d** is not a suitable catalyst for the hydrogenation of the enamine.

**Table 4.4.** Different solvents used in the hydrogenation of **108i** using phospholane Rh complexes.




| Entry[a] | Catalyst* | $I_2$, mol% | Solvent | T, °C | Conversion of **108i**, %[b,c] | **109i**, %[b,c] [yield][d] | ee, %[e,f] |
|---|---|---|---|---|---|---|---|
| 1 | (*S*,*S*)-**196b** | 0.8 | THF | 65 | > 99 | > 99 | 51 (*R*) |
| 2 | (*R*,*R*)-**198b** | 0.8 | THF | 65 | > 99 | 96 | 10 (*S*) |
| 3 | (*S*,*S*)-**196b** | 0.8 | MeOH | 65 | > 99 | 83 | racemic |
| 4 | (*R*,*R*)-**198b** | 0.8 | MeOH | 65 | > 99 | 83 | racemic |
| 5 | (*S*,*S*)-**196d** | 0.8 | THF | 65 | 40 | 38 | 25 (*S*) |
| 6 | (*R*,*R*)-**196d** | 0.8 | MeOH | 65 | > 99 | 82 | racemic |
| 7 | (*R*,*R*)-**196b** | 0.8 | Toluene | 65 | > 99 | > 99 | 48 (*S*) |
| 8 | (*R*,*R*)-**196b** | - | Toluene | 25 | 38 | 36 | 49 (*R*) |
| 9 | (*S*,*S*)-**196b** | 0.8 | Toluene | 25 | > 99 | > 99 [76] | 65 (*R*) |
| 10 | (*R*,*R*)-**196b** | - | Chlorobenzene | 25 | 94 | 93 [60] | 58 (*R*) |
| 11 | (*R*,*R*)-**196b** | 0.8 | Chlorobenzene | 25 | > 99 | > 99 [71] | 58 (*S*) |
| 12 | (*R*,*R*)-**198b** | - | Chlorobenzene | 25 | 48 | 47 | 73 (*R*) |
| 13 | (*R*,*R*)-**198b** | 0.8 | Chlorobenzene | 25 | > 99 | > 99 | 61 (*S*) |
| 14 | (*S*,*S*)-**196d** | - | Chlorobenzene | 25 | 32 | 32 | racemic |
| 15 | (*S*,*S*)-**196d** | 0.8 | Chlorobenzene | 25 | 10 | 10 | n.d.[g] |

[a]General conditions: 1 mmol of enamine **108i**, 0.4 mol% of Rh catalyst, 0.8 mol% of iodine or no iodine, 0.1 mL of 1-methylnaphthalene as an internal standard, $H_2$ gas (60 bar), solvent, 65 °C or 25 °C, 16 hours.. [b]The only side product observed is a ketone which is formed due to partial hydrolysis of the enamine. [c]Determined by $^1$H NMR relative to 1-methylnaphthalene. [d]Overall isolated yield (by acid-base work-up). [e]Enantiomeric excess determined by $^1$H NMR after addition an excess of (*R*)-(–)-α-methoxyphenylacetic acid. [f]Stereochemistry of amines was assigned after comparison to the authentic samples of chiral amine (*S*)-**109i**. [g]Not determined.

Although the reaction afforded reasonable ee with the BPE complex as the catalyst in THF (comparable to the same reaction in toluene) (entries 1 and 7), the selectivity with the DuPhos-Rh complex was very low (Table 4.4 entry 2). The products from the reactions in methanol as a solvent were racemic, so this solvent was not utilised further. As was observed previously in toluene as solvent, (*R*,*R*)-**196d** appears a lot less reactive than all other phospholane complexes, affording fairly low ees of the product.

In order to prove that substrate **108i** is not a particularly special and unusual case, hydrogenation of **108g** was also tested in chlorobenzene as a solvent under the same conditions with several chiral rhodium phospholane complexes. The same dramatic effect was observed (the results shown in Figure 4.3 are from Table 4.5 entries 1, 2, 4 and 5).

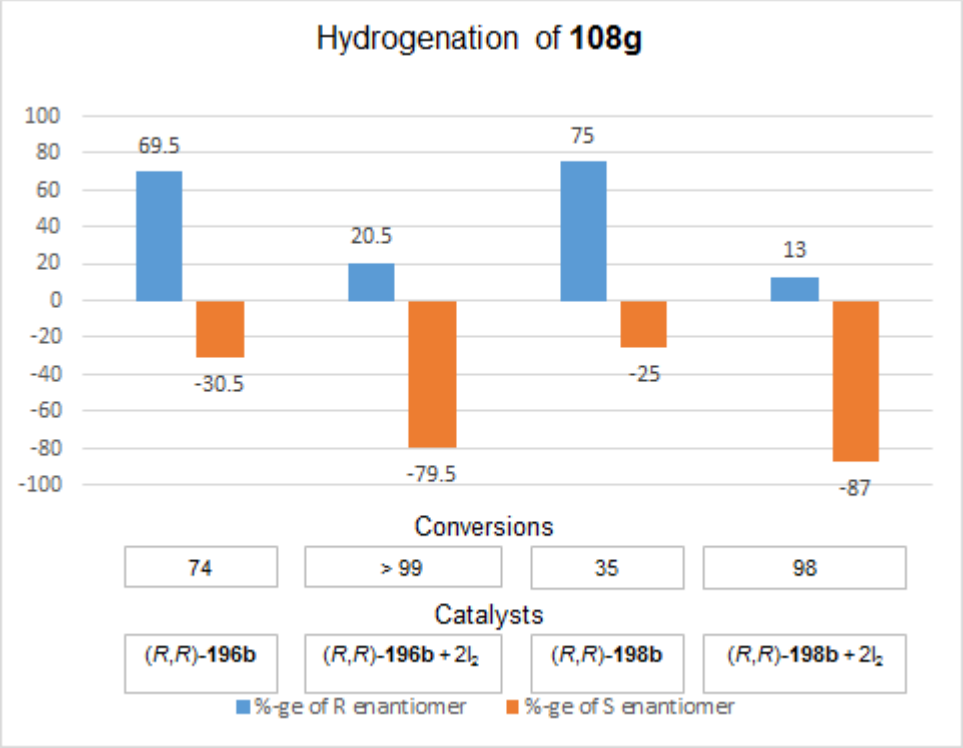
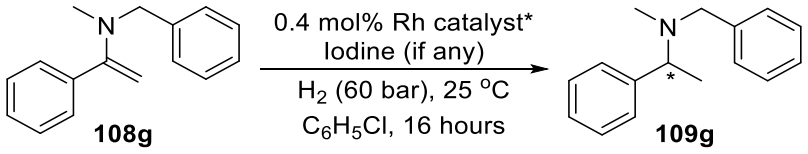



**Figure 4.3.** Remarkable effect of chlorobenzene as a solvent in enantioselective hydrogenation of enamine **108g** using phospholane Rh complexes as the catalysts. The full reaction conditions are present in Table 4.5.

The full details of the experiments with more examples are present in Table 4.5. Clearly, the results do show the same type of behavior of this enamine if compared to enamine **108i**. Some dramatic switches of the absolute configurations of the product upon addition of iodine co-catalyst are observed here as well. The experiment in entry 3 proves that the reaction can proceed at very low catalyst loadings (S/C ratio of 2000) even at 25 $^{o}$C.

**Table 4.5.** Hydrogenation of enamine **108g** with Rh complexes of BPE and DuPhos ligands in chlorobenzene as a solvent.



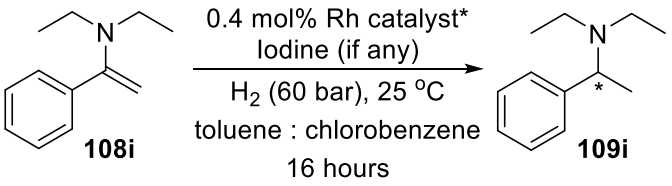

| Entry[a] | Catalyst* | Iodine, mol% | Conversion of **108g**, %[b,c] | **109g**, %[b,c] [yield][d] | ee, %[e,f] |
|---|---|---|---|---|---|
| 1 | (*R*,*R*)-**196b** | - | 77 | 74 | 39 (*R*) |
| 2 | (*R*,*R*)-**196b** | 0.8 | > 99 | > 99 [82] | 59 (*S*) |
| 3[g] | (*R*,*R*)-**196b** | 0.1 | 55 | 54 | 53 (*S*) |
| 4 | (*R*,*R*)-**198b** | - | 38 | 35 | 50 (*R*) |
| 5 | (*R*,*R*)-**198b** | 0.8 | > 99 | 98 | 74 (*S*) |
| 6 | (*S*,*S*)-**198a** | - | 77 | 75 | 44 (*S*) |
| 7 | (*S*,*S*)-**198a** | 0.8 | > 99 | > 99 | 77 (*R*) |

[a]General conditions: 1 mmol of enamine **108g**, 0.4 mol% of Rh, 0.1 mL of 1-methylnaphthalene as an internal standard, $H_2$ gas (60 bar), chlorobenzene as a solvent, 25 °C, 16 hours. [b]The only side product observed is a ketone which is formed due to partial hydrolysis of enamine. [c]Determined by $^1$H NMR relative to 1-methylnaphthalene. [d]Overall isolated yield (by acid-base work-up). [e]Enantiomeric excess determined by $^1$H NMR after addition an excess of (*R*)-(–)-α-methoxyphenylacetic acid. [f]Stereochemistry of amines was assigned after comparison to the authentic samples of chiral amine (*R*)-**109g**. [g]Catalyst loading of 0.05 mol% was used.

Since chlorobenzene appears to play a major role here, it was of interest to test the reaction in a mixture of chlorobenzene and toluene. Table 4.6 describes the experiments performed where toluene / chlorobenzene mixtures of different ratios were used as solvents (entries 1 – 8). For comparison, entries 9 – 16 represent the experiments performed under the same conditions in pure toluene or pure chlorobenzene as a solvent. As the proportion of chlorobenzene is reduced, the activity of the catalyst goes down for both catalysts studied. This is true for the experiments conducted with iodine co-catalyst (for example, comparing entries 4, 8, 12 and 16), as well as for the once without it (for example, comparing entries 3, 7, 11 and 15).

Even a fairly small proportion of chlorobenzene present in the solvent causes the dramatic switches enantio-preferences of the product observed previously. In particular, this is very clear if (*R*,*R*)-**198b** is used as the catalyst for the experiments performed without iodine co-catalyst.

**Table 4.6.** Hydrogenation of enamine **108i** with Rh complexes of BPE and DuPhos ligands in the mixture of toluene and chlorobenzene.




| Entry[a] | $C_6H_5Cl$ : toluene | Catalyst* | Iodine, mol% | Conversion of **108i**, %[b,c] | **109i**, %[b,c] | ee, %[d,e] |
|---|---|---|---|---|---|---|
| 1 | 1 : 4 | (*R*,*R*)-**196b** | - | 45 | 44 | 58 (*R*) |
| 2 | 1 : 4 | (*R*,*R*)-**196b** | 0.8 | > 99 | > 99 | 60 (*S*) |
| 3 | 1 : 4 | (*R*,*R*)-**198b** | - | 41 | 40 | 43 (*R*) |
| 4 | 1 : 4 | (*R*,*R*)-**198b** | 0.8 | 64 | 61 | 51 (*S*) |
| 5 | 1 : 9 | (*R*,*R*)-**196b** | - | 40 | 38 | 53 (*R*) |
| 6 | 1 : 9 | (*R*,*R*)-**196b** | 0.8 | > 99 | > 99 | 63 (*S*) |
| 7 | 1 : 9 | (*R*,*R*)-**198b** | - | 25 | 20 | 41 (*R*) |
| 8 | 1 : 9 | (*R*,*R*)-**198b** | 0.8 | 55 | 53 | 60 (*S*) |
| 9 | toluene | (*R*,*R*)-**196b** | - | 38 | 36 | 49 (*R*) |
| 10 | toluene | (*S*,*S*)-**196b** | 0.8 | > 99 | > 99 | 65 (*R*) |
| 11 | toluene | (*R*,*R*)-**198b** | - | 18 | 16 | 27 (*R*) |
| 12 | toluene | (*R*,*R*)-**198b** | 0.8 | 48 | 44 | 69 (*S*) |
| 13 | $C_6H_5Cl$ | (*R*,*R*)-**196b** | - | 94 | 93 | 58 (*R*) |
| 14 | $C_6H_5Cl$ | (*R*,*R*)-**196b** | 0.8 | > 99 | > 99 | 58 (*S*) |
| 15 | $C_6H_5Cl$ | (*R*,*R*)-**198b** | - | 48 | 47 | 73 (*R*) |
| 16 | $C_6H_5Cl$ | (*R*,*R*)-**198b** | 0.8 | > 99 | > 99 | 61 (*S*) |

[a]General conditions: 1 mmol of enamine **108i**, 0.4 mol% of Rh, 0.1 mL of 1-methylnaphthalene as an internal standard, $H_2$ gas (60 bar), chlorobenzene : toluene mixture as a solvent, 25 °C, 16 hours. [b]The only side product observed is a ketone which is formed due to partial hydrolysis of enamine. [c]Determined by $^1$H NMR relative to 1-methylnaphthalene. [d]Enantiomeric excess determined by $^1$H NMR after addition an excess of (*R*)-(–)-α-methoxyphenylacetic acid. [e]Stereochemistry of amines was assigned after comparison to the authentic samples of chiral amine (*S*)-**109i**.

Overall, it was shown that iodine co-catalyst plays a major role in enantioselective hydrogenation of enamines with the rhodium complexes of phospholane ligands. The presence of it in the reaction improves both activities and enantioselectivities for most of the phospholane-Rh catalyst systems studied here. In addition to that, it also causes the switch of the absolute

configuration of the product. In order to understand that, some further mechanistic studies were performed.

Apart from the huge role of the co-catalyst, the role of solvent was proven to be crucial as well. A surprisingly unusual effect of chlorobenzene in these reactions shows the importance of the presence of this solvent, even in a partial amount, while the hydrogenation is performed.

## 4.4. Mechanistic studies

### 4.4.1 Kinetic data

In order to understand more about the reaction mechanism, some kinetic experiments were performed in an Argonaut (Biotage Endeavor Catalyst Screening System). Enamine **108i** was hydrogenated in the presence of catalyst (*R*,*R*)-**196b**. Figure 4.4 shows a typical example of the product formation over time. Average TOF during the first hour of the reaction shown in the figure is 54 mol $mol^{-1}$ $h^{-1}$. Two mmol of enamine was used in the experiment shown in the figure. Since the procedures in Argonaut were more difficult to set up in a perfectly dry manner, some hydrolysis always occurred. Therefore, the actual amount of the enamine left for the hydrogenation process is always lower. From the graph, it is clear that the reaction was complete in about 5 hours.

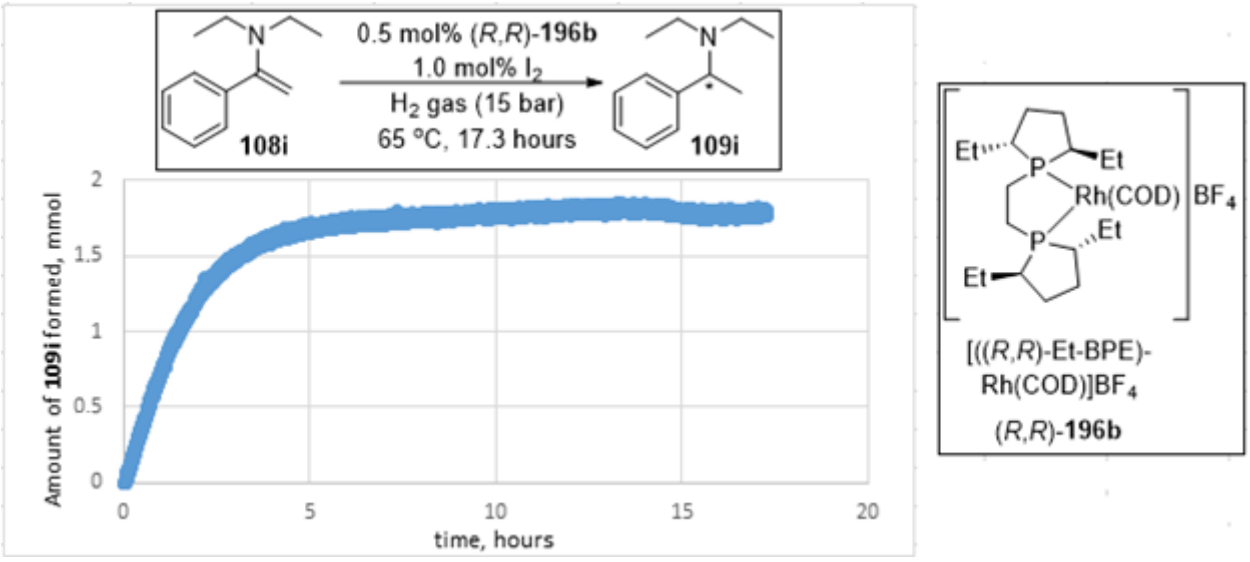



**Figure 4.4.** Formation of amine **109i** over time.

When the order of the reaction with respect to substrate is one, the plot of ln[SM] (SM = starting material) versus time should produce a straight line. The data from the experiment

shown in Figure 4.4 was used to plot the graph. As can be seen from Figure 4.5, the hydrogenation of **108i** is first order with respect to the substrate.

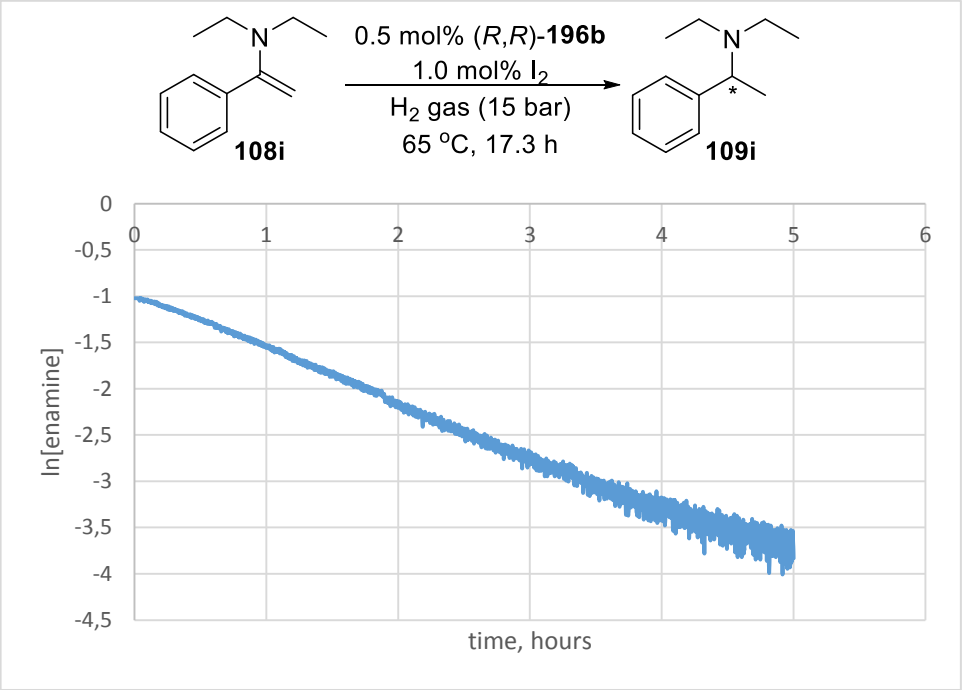



**Figure 4.5.** Plot of ln[SM] versus time.

In order to determine the order of the reaction with respect to catalyst, different catalyst loading experiments were performed under the same reaction conditions. The method described by Burés suggests, that the plots of the concentration of the starting material versus time multiplied by the catalyst concentration to the power of "n" should be plotted on the same graph.[117] Then different values of "n" should be tried. When the "n" coefficient is the same and the graphs overlay, that means that the reaction order with respect to catalyst is "n".[117] In simpler words, the required graphs are the plots of [Product] vs. time*[catalyst]$^n$. Two experiments were conducted with 0.9 mol% of (*R*,*R*)-**196b** (blue plots) and 0.7 mol% of (*R*,*R*)-**196b** (orange plots) (Figure 4.6 – Figure 4.8). For a better accuracy, only initial reaction times were used. Figure 4.6 represents the plots where the order of the value of the power "n" is 0.5, Figure 4.7 represents the value of "n" being 1, and Figure 4.8 shows two plots where the "n" = 2. As can be seen from the graphs, the reaction is 1$^{st}$ order with respect to catalyst, as the graphs overlay when the value of n = 1 (Figure 4.7).

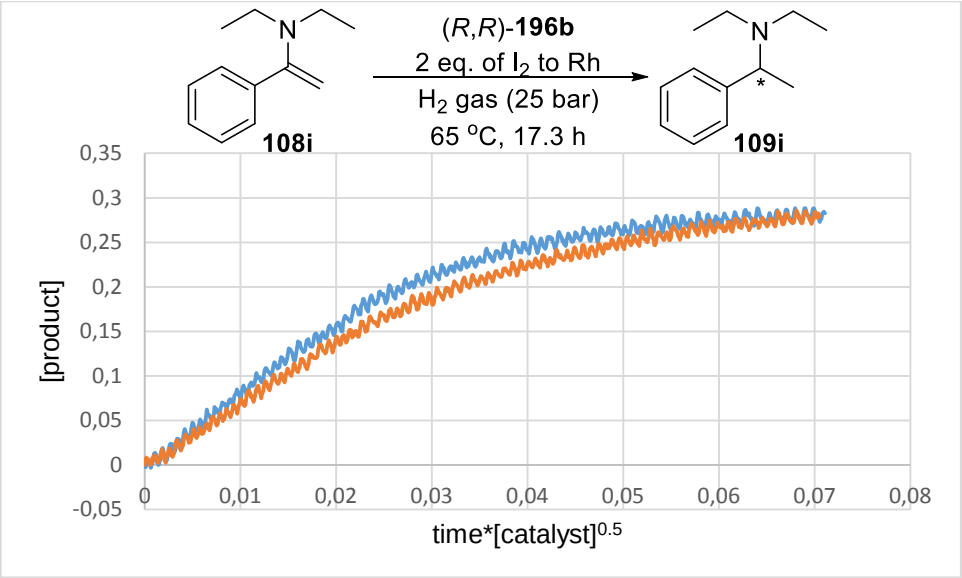



**Figure 4.6.** Plots of concentration of the product versus time multiplied by catalyst concentration to the power of 0.5.

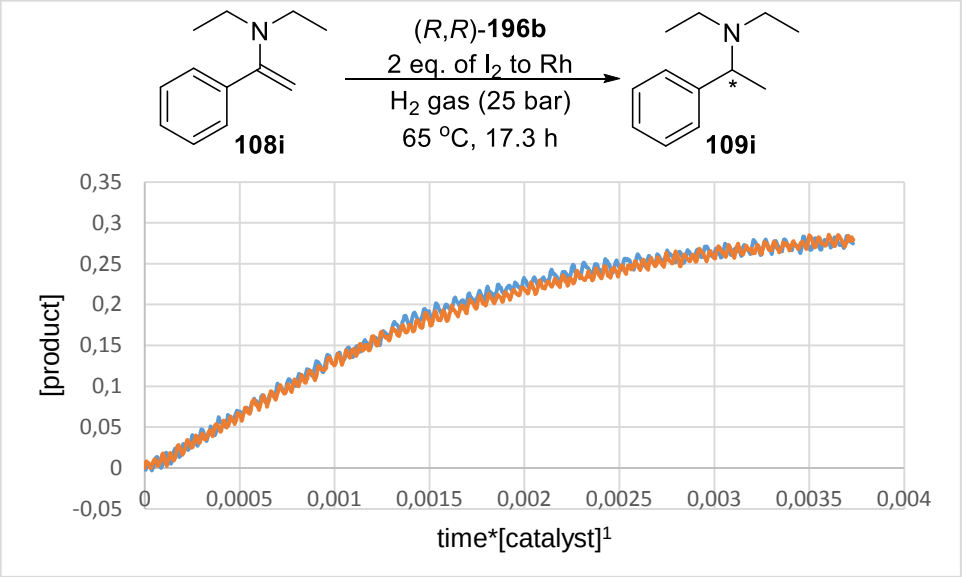



**Figure 4.7.** Plots of concentration of the product versus time multiplied by catalyst concentration to the power of 1.

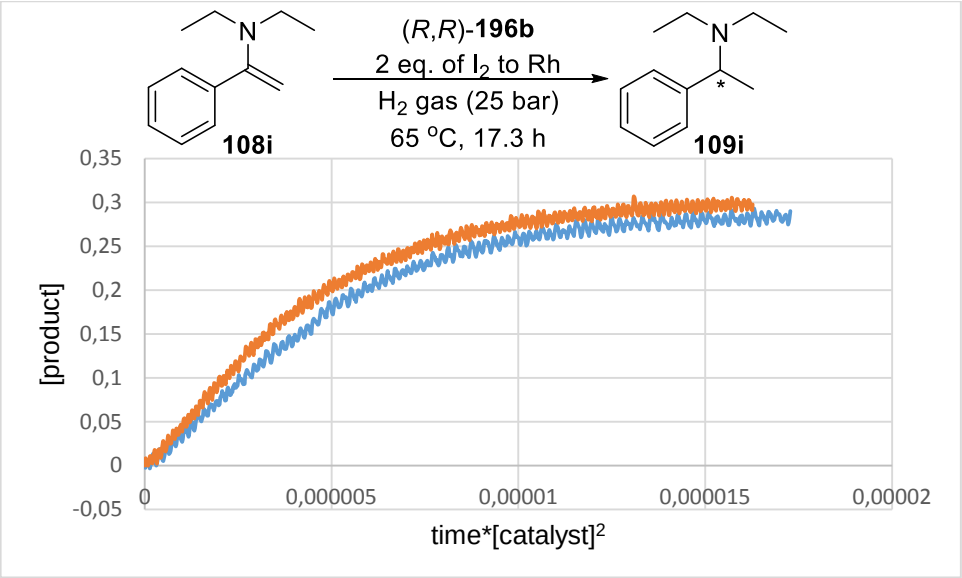



**Figure 4.8.** Plots of concentration of the product versus time multiplied by catalyst concentration to the power of 2.

To determine the reaction order with respect to pressure of hydrogen gas, a graph of initial rate of the reaction versus pressure of hydrogen gas was plotted (Figure 4.9). This suggests that, within the experimental error, the graph is a straight line. Therefore, the reaction is most likely the first order with respect to the hydrogen gas.

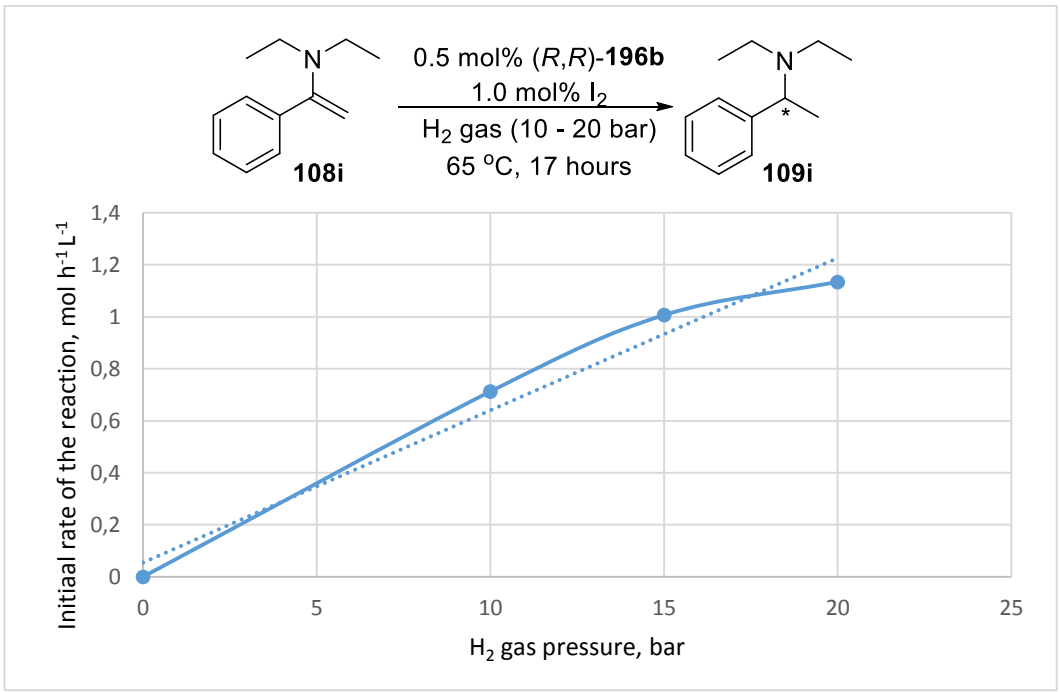



**Figure 4.9.** A plot of the initial rate of the reaction versus hydrogen gas pressure.

Overall, it is clear that the reaction is first order with respect to substrate. The order of the reaction with respect to hydrogen gas is most likely 1 as well (in any case, it is certainly positive). These suggest that the rate determining step occurs once both reactants have interacted with the catalyst. The catalyst order (which is 1) implies that there are not two separate catalysts involved in the rate determining step.

The next step of this project was to understand the mechanism of enamine hydrogenation process when a phospholane based Rh catalyst and iodine co-catalyst are used.

### 4.4.2 Reaction of the phospholane complex with iodine

[((*R*,*R*)-Et-BPE)-Rh(COD)]$BF_4$ ((*R*,*R*)-**196b**) complex was reacted with 1 equivalent, 1.5 equivalents and 2 equivalents of iodine (Figure 4.10). At the top the $^{31}P\{^1H\}$ NMR spectrum of complex (*R*,*R*)-**196b** in deuterated dichloromethane is shown. Only one doublet is observed since the phosphorus environments are equivalent. Once 1 equivalent of iodine is added, two new doublets appeared ($^{31}P\{^1H\}$ NMR: $\delta$ = 114.5, $^1J_{P\text{-}Rh}$ = 113 Hz; $\delta$ = 108.9, $^1J_{P\text{-}Rh}$ = 115 Hz) (2$^{nd}$ spectrum). There are also signals present for the initial complex. It is clear that a new compound is forming, and all of the starting material gets converted to the new species when 3 atoms of iodine are present per each atom of Rh – i.e. 1.5 equivalents of iodine to the rhodium complex (3$^{rd}$ spectrum). There are no intermediate species observed. Addition of 2 equivalents of iodine to the metal does not change anything (the bottom spectrum) – and once a new catalytic species is formed, extra iodine does not affect it at all.

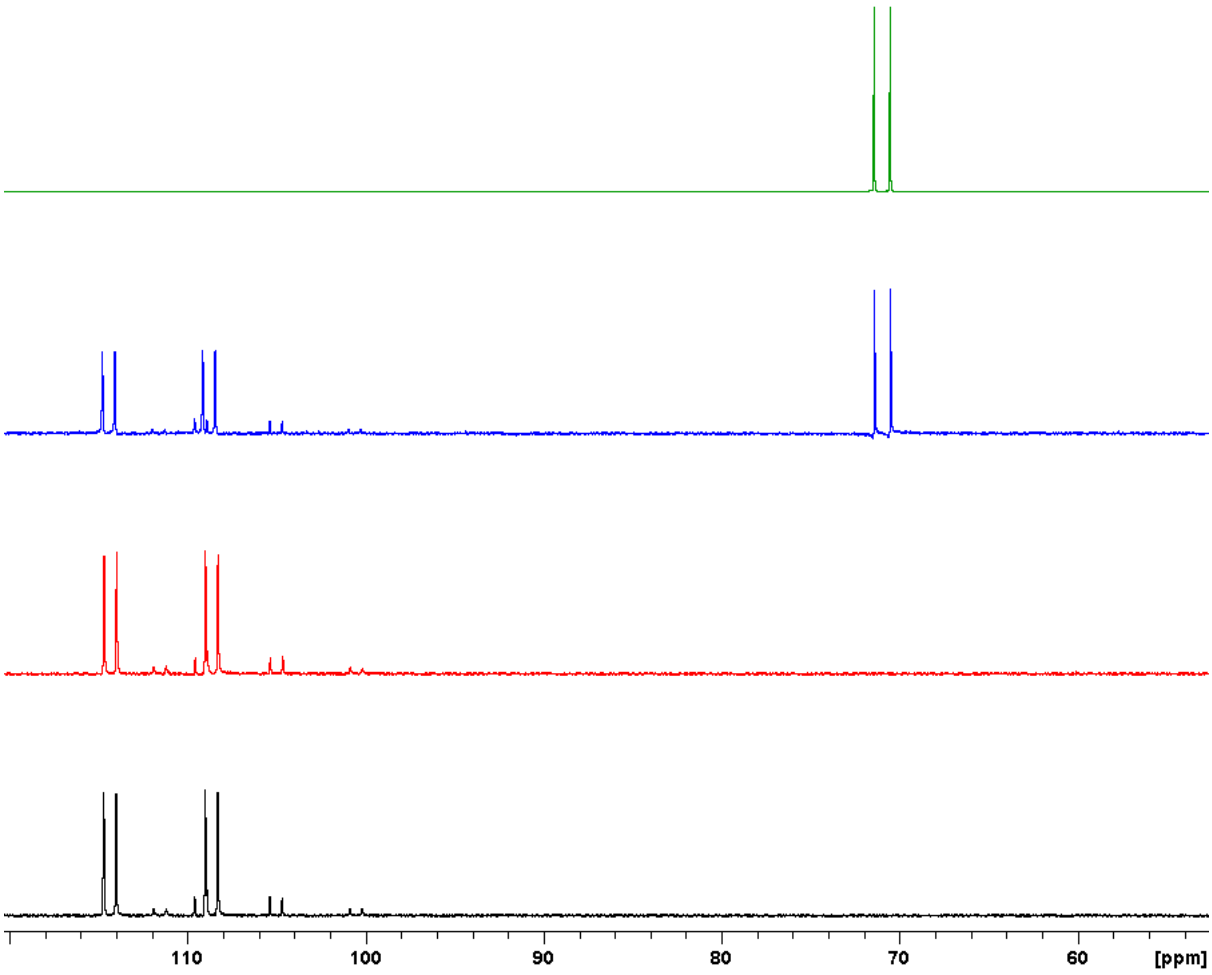


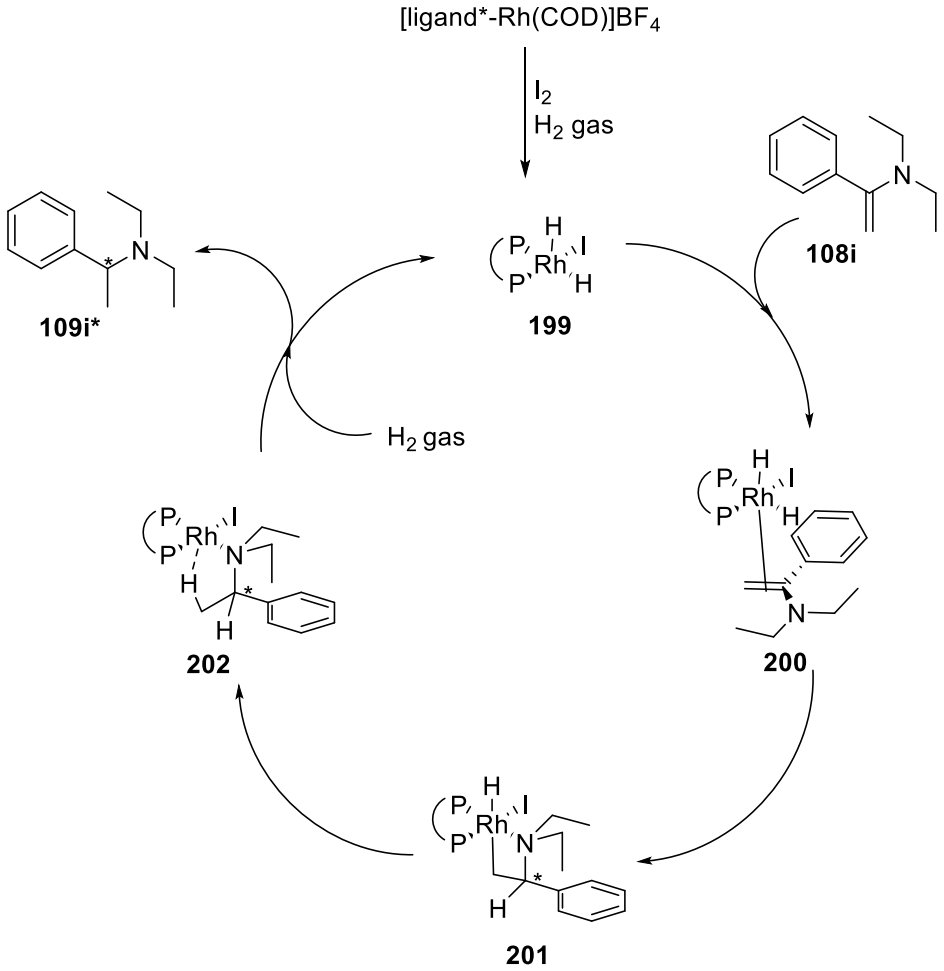

**Figure 4.10.** $^{31}P\{^{1}H\}$ NMR spectra after reaction of [((*R*,*R*)-Et-BPE)-Rh(COD)]$BF_4$ ((*R*,*R*)-**196b**) with iodine. The top spectrum represents the complex in $CD_2Cl_2$, the 2nd one shows a reaction of the complex with 1 equivalent of $I_2$, the 3rd shows the species present after addition of 1.5 equivalents of iodine, and the bottom spectrum represents the outcome after the complex reacted with 2 equivalents of $I_2$.

After the NMR studies, the solvent was removed *in vacuo* and the new complex was analysed my HRMS. A molecular ion $[C_{36}H_{72}I_5P_4Rh_2]^+$ is present. One of the possible structures of the newly formed complex is shown in Figure 4.11. Possible counter-ions are $BF_4^-$ or $I^-$.


**Figure 4.11.** Possible structure of the compound formed after reaction of (*R*,*R*)-**196b** with iodine.

### 4.4.3 Understanding the reaction of the iodinated Rh complex with enamine

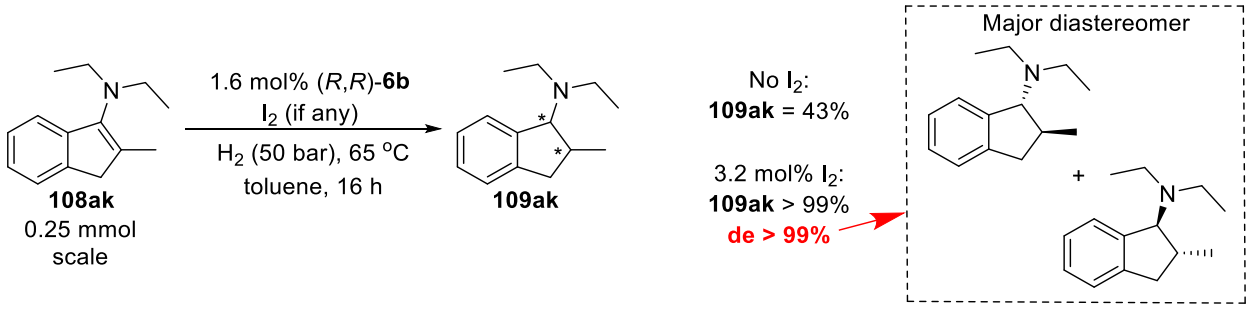
A mechanism describing enamine hydrogenation could be expected to be similar to what was suggested by Zhou and co-workers.[67] A general proposal for such a mechanism is shown in Scheme 4.2. Presumably, after formation of $Rh^{III}$ dimer with iodine, it could react with hydrogen gas to form catalytic $Rh^{III}$-dihydride species **199**. Then **199** would perform the enamine hydrogenation as shown in the scheme, and would be regenerated at the end of the process. While this is a reasonable pathway for an enamine to be hydrogenated, it was decided to explore it further, since catalysis *via* iminium ions is also a possibility.




**Scheme 4.2.** Expected mechanistic pathway for Rh-catalysed hydrogenation of enamine **108i**.

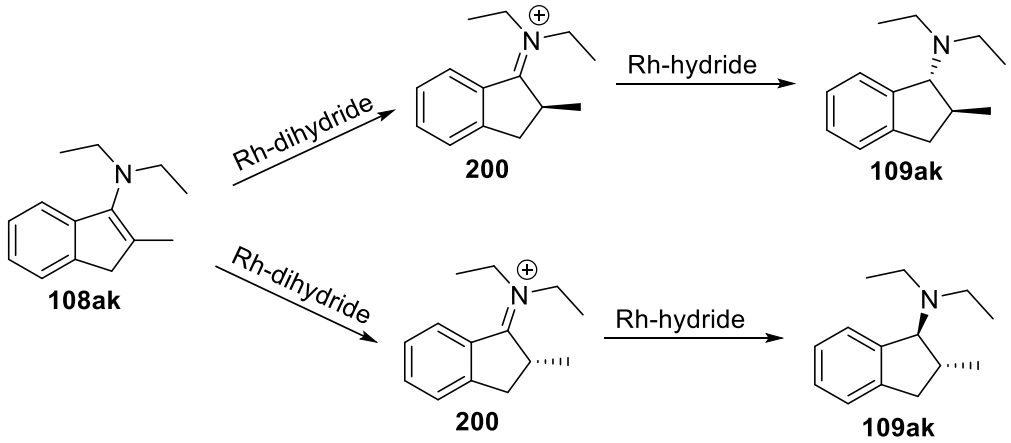
As the first step, hydrogenation of enamine **108ak** was performed with the phospholane complex (*R,R*)-**196b** (Scheme 4.3). Since **108ak** is a tetrasubstituted enamine, the reactions were performed at lower S/C ratios in order to achieve good conversions. In any normal hydrogenation reaction, which undergoes similar mechanism to the one shown in Scheme 4.2, it will always be a *syn*-addition of the hydrogen to the enamine. The reactions were performed on a relatively small scale. Since the reaction does not go to full conversion without iodine co-

catalyst, the amine was not isolated, as the tetrasubstituted enamines (at least described in these studies in Chapter 2, including **108ak**) do not hydrolise even in the presence of hydrochloric acid, and, therefore, isolation of the product could be problematic due to the small scale of the reaction. When iodine co-catalyst is present, the hydrogenation goes to full completion and amine **109ak** was isolated (in 65% yield – fairly low due to the small scale of the reaction) and characterised by NMR. Surprisingly, the detailed NMR studies suggest that the exact opposite is observed to what was expected initially – the hydrogen undergoes *trans*-addition to the double bond.



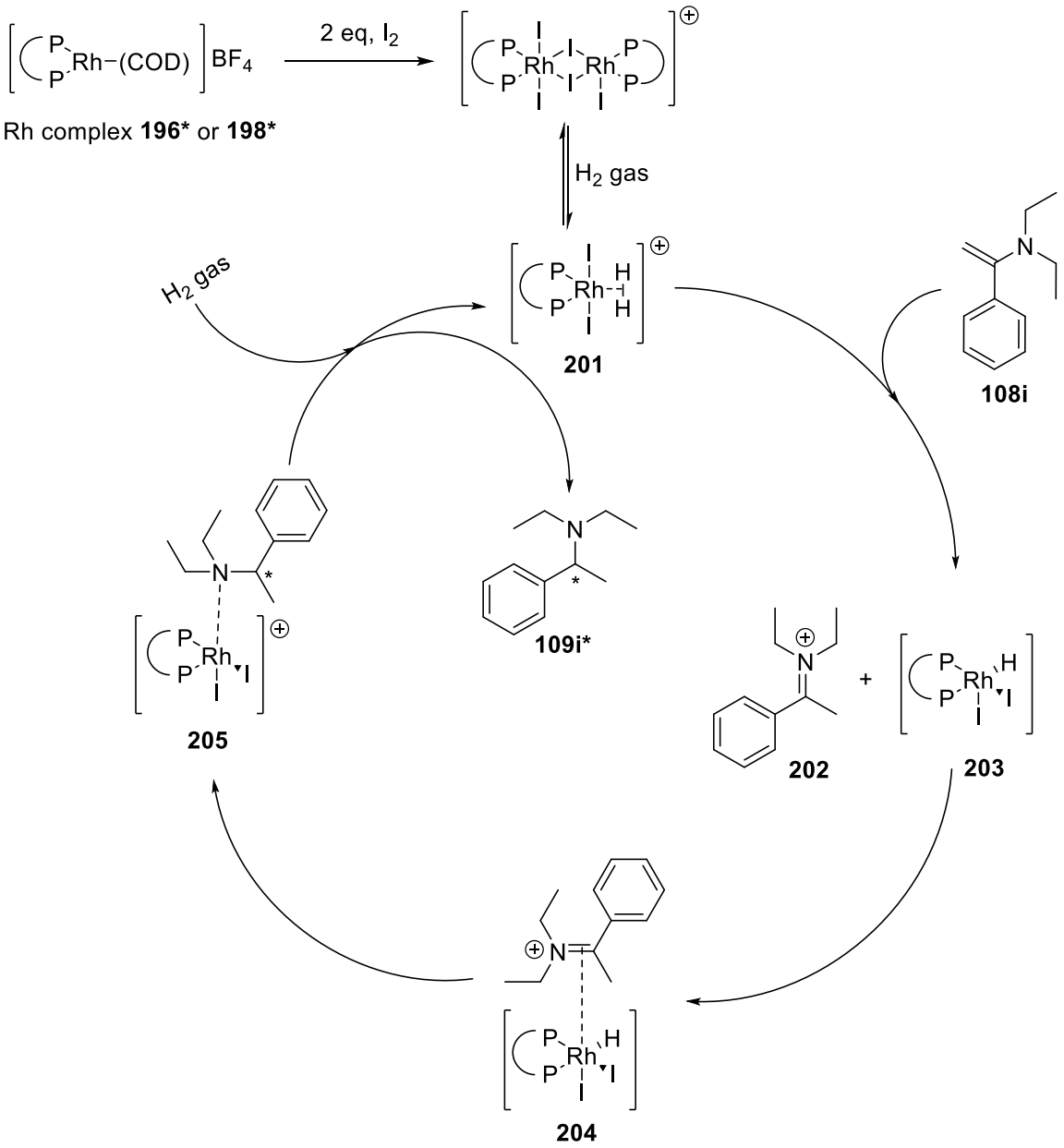

**Scheme 4.3.** Hydrogenation of **108ak** with (*R*,*R*)-**196b** in the presence and absence of iodine co-catalyst.

While we would have preferred this to be backed by X-ray evidence, such an unusual result could not be left unnoticed. This result suggests that the mechanism shown in Scheme 4.2 cannot take place. An idea came across, that in order to form exclusively *trans*-isomer of the product **109ak**, the key steps in the transformation of the enamine **109ak** to amine could be the formation of iminium ion **200** after addition of the first hydrogen atom, which could then undergo the reduction by Rh-hydride species (Scheme 4.4). If the hydride attack itself was not excessively inhibited by steric hindrance, there would be a tendency to form the less crowded *trans* product.



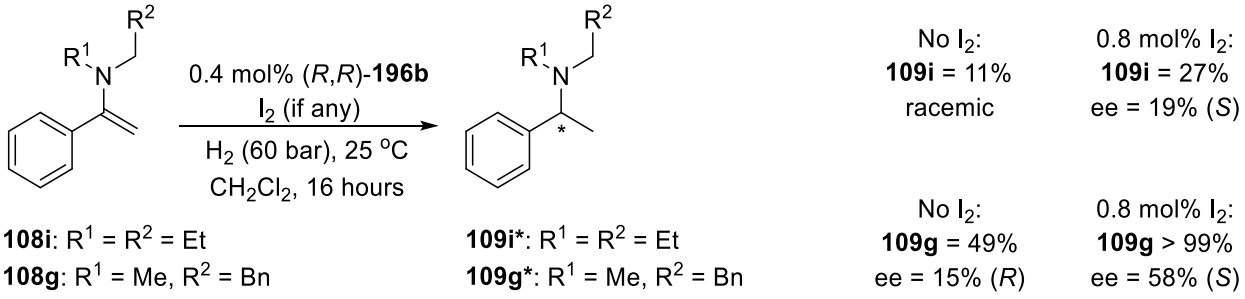

**Scheme 4.4.** Possible hydrogenation pathway for enamine **108ak** with iodine-modified Rh complex.

If the formation of an iminium ion and the reduction of it to the desired amine is the actual catalytic pathway, the mechanism of the hydrogenation of enamine **108i** with Rh catalyst and iodine co-catalyst could be described as shown in Scheme 4.5. After formation of the active pre-catalyst from Rh complex and iodine co-catalyst, the catalytic species **201** could be produced once hydrogen gas is added. Since this is a dihydrogen complex of a Rh cation in +3 oxidation state, it will be acidic.[118-120] The enamine gets converted to the iminium ion **202** with this very acidic Rh species. The counter-ion of the iminium cation could be the $BF_4^-$ or $I^-$ anion. Reduction of the iminium ion with the resulting Rh-hydride **203** leads to the formation of product **109i** and regeneration of active catalyst **201**.




**Scheme 4.5.** Mechanism for hydrogenation of enamine **108i** through the formation of iminium ion **202**.

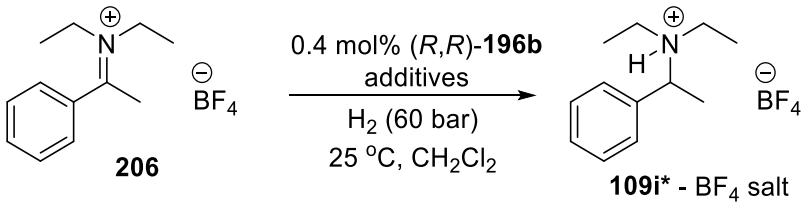
To investigate this idea further, the iminium salt **202**-$BF_4$ (further called **206**) was prepared according to the literature procedure (see Chapter 6).[121] Since the compound is not soluble in any of the potentially interesting solvents tested previously in these studies (i.e. toluene, THF or chlorobenzene), the reactions had to be performed in dichloromethane. Before commencing further study, the viability of the hydrogenation had to be checked in $CH_2Cl_2$. Enamines **108i** and **108g** were hydrogenated in dichloromethane as a solvent with (*R*,*R*)-**196b** catalyst (Scheme 4.6). The key observations are that the reaction can proceed in this solvent and that general trends stay the same in $CH_2Cl_2$ (i.e. the reaction goes faster and more selective in the presence of iodine co-catalyst), even if dichloromethane is a far worse solvent for these processes.




**Scheme 4.6.** Hydrogenation of enamines **108i** and **108g** in $CH_2Cl_2$ as a solvent.

The results for hydrogenation of iminium ion salt **206** are shown in Table 4.7. Entries 1 and 2 clearly show that the reaction does not proceed without any additional additives. The reason is that the active catalyst, Rh-dihydride, cannot react with the iminium ion. According to the proposed mechanism in Scheme 4.5, when the enamine is hydrogenated, it deprotonates the Rh-dihydride, and, therefore, makes Rh-hydride which can reduce the formed iminium ion. Once some base is added to the reaction, the hydrogenation of the iminium ion occurs. In entries 3 and 4, clearly the reaction proceeds, and this time it is faster when no iodine co-catalyst is used. It is worth mentioning that the enamine **108g**, which is used as an additive, undergoes full conversion to the amine in both cases. Presumably, enamine **108g** (or freshly formed amine **109g**) acts as a base here which deprotonated the Rh-dihydride, and the deprotonation is crucially important. Entries 5 – 10 represent the same reaction with trimethylamine as an additive. When the amount of the base is very low, the reaction does not proceed (entries 9 and 10). Entries 7 and 8 again show that the hydrogenation of the iminium ion in the presence of base proceeds faster without iodine co-catalyst. The result in entry 11 proves that the phospholane complex is very active in hydrogenation of **206**. The reaction goes to completion in only 3 hours at S/C ratio of 333.

**Table 4.7**. Hydrogenation of iminium salt **206** with (*R*,*R*)-**196b**.




**206** **109i*** - $BF_4$ salt

| Entry[a] | $I_2$, mol% | Additive, mol% | Time, hours | Conversion of **206**, %[b,c] | **109i***-$BF_4$ salt, %[b,c] [yield of **109i***][d] | ee, %[e,f] |
|---|---|---|---|---|---|---|
| 1 | - | - | 16 | < 1 | < 1 | n.a. |
| 2 | 0.8 | - | 16 | < 1 | < 1 | n.a. |
| 3[g] | - | **108g**, 20 | 16 | 61 | 55 | n.d. |
| 4[g] | 0.8 | **108g**, 20 | 16 | 11 | 8 | n.d. |
| 5 | - | $Et_3N$, 80 | 16 | > 99 | 94 [68] | 51 (*R*) |
| 6 | 0.8 | $Et_3N$, 80 | 16 | > 99 | 94 [67] | racemic |
| 7 | - | $Et_3N$, 22 | 16 | > 99 | 92 [76] | 27 (*R*) |
| 8 | 0.8 | $Et_3N$, 22 | 16 | 14 | 4 | n.d. |
| 9 | - | $Et_3N$, 2.2 | 16 | < 1 | < 1 | n.a. |
| 10 | 0.8 | $Et_3N$, 2.2 | 16 | < 1 | < 1 | n.a. |
| 11[h] | - | $Et_3N$, 100 | 3 | > 99 | 96 | n.d. |

[a]General conditions: 1 mmol of iminium salt **206**, 0.4 mol% (*R*,*R*)-**196b**, iodine (if any), another additive (if any), 0.1 mL of 1-methylnaphthalene as an internal standard, $H_2$ gas (60 bar), 25 °C, dichloromethane as a solvent. [b]The only side product observed is a ketone which is formed due to partial hydrolysis of enamine. [c]Determined by $^1$H NMR relative to 1-methylnaphthalene. [d]Overall isolated yield (by acid-base work-up). [e]Enantiomeric excess determined by $^1$H NMR after addition an excess of (*R*)-(–)-α-methoxyphenylacetic acid to the isolated sample of amine **109i***. Where the amine sample was not isolated, the ee could not be measured. [f]Stereochemistry of the isolated samples of the amines was assigned after comparison to the authentic samples of chiral amine (*S*)-**109i**. [g]Enamine **108g** which is used as an additive undergoes full conversion to the amine, and the reaction was performed on 0.8 mmol scale of the substrate. [h]Catalyst loading of 0.3 mol% used.

It was shown that the iminium ion undergoes the hydrogenation in the presence of a base. In case if, in general, an enamine hydrogenation proceeds *via* the formation of an iminium ion, an enamine (or a freshly formed amine) could act as a base. In order to find some clear proof of the reaction proceeding by the mechanism suggested in Scheme 4.5, the following experiment was performed: phospholane complex (*R*,*R*)-**198b** was reacted with two equivalents of iodine in $CD_2Cl_2$, the reaction vial was transferred to an autoclave and pressurised with 60 bar of hydrogen gas. After being stirred for 3 hours at 25 °C under these conditions, the pressure of the gas was released and a stoichiometric amount of enamine **108i** to Rh metal was added to the vial as a solution in $CD_2Cl_2$. $^1$H NMR spectrum was acquired immediately after that. In Figure 4.12, the top spectrum represents the selected region of the iminium ion salt in the proton NMR. The

signals observed are the two -$CH_2$- groups. In the middle, the same region represents characteristic signals for the enamine. The bottom spectrum represents the NMR of this region observed after the reaction described. Clearly, the iminium ion is formed immediately under the reaction conditions described. Although the signals are in a slightly different place, it is still pretty clear that all enamine is consumed, and that the two quartets represent the iminium ion signals. The slight difference in shifts could come from the fact that iodine might play the role of a counter-ion of the salt formed in the experiment. Another possibility could be an effect of the concentration.

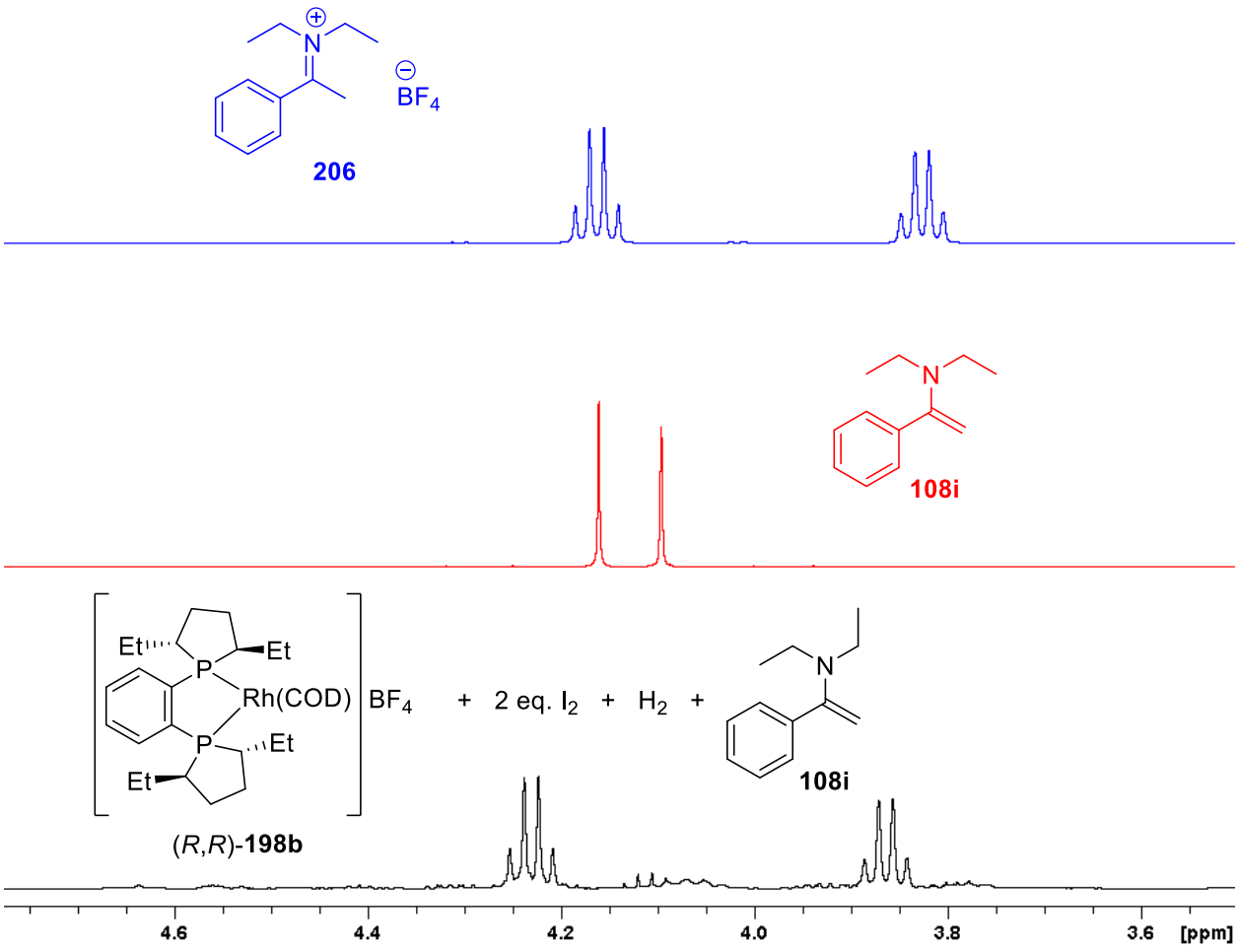
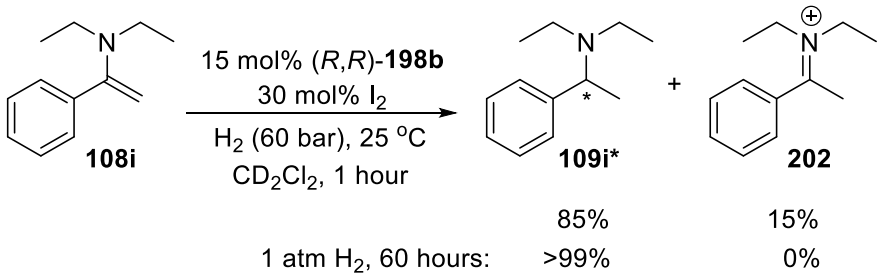



**Figure 4.12.** Selected regions in the $^1$H NMR spectra. All solutions are in $CD_2Cl_2$. The top spectrum is of pure iminium salt **206**. The red one in the middle is of enamine **108i**. The bottom spectrum represents the outcome of the experiment described – the complex formed after the reaction between (*R*,*R*)-**198b** / $I_2$ catalyst with hydrogen gas, followed by the addition of enamine **108i**.

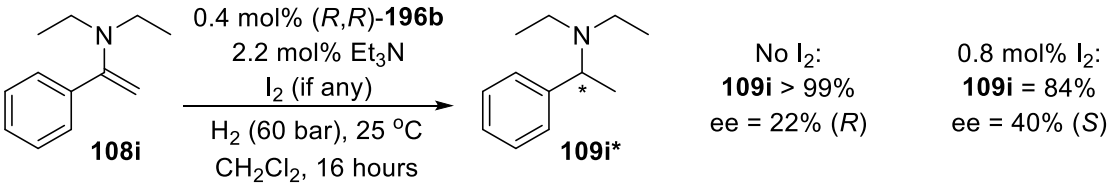
Exactly the same reaction was performed, where no iodine co-catalyst was used. In that case, no signals of the iminium ion were present, while enamine characteristic $^1$H NMR signals were in place.

In order to prove that the iminium ion formed in the previous experiment is hydrogenated by the catalyst, the experiment shown in Scheme 4.7 was performed. After 1 hour at 60 bar of hydrogen gas, the reaction solution was transferred into a medium pressure NMR tube under an atmosphere of hydrogen gas: no starting material was observed. Most of the enamine has got converted into the amine, while some still exists in the form of iminium ion **202**. The NMR tube was allowed to stand over the weekend. After this time, the spectrum was acquired again which suggested that all the iminium ion **202** got converted into the amine. This clearly proves that the key intermediate in this process is the iminium ion, which forms very quickly and then gets hydrogenated into the amine.




**Scheme 4.7.** Hydrogenation of **108i** over short time with high catalyst loading.

Overall, these results suggest a few things. One is that when iodine co-catalyst is added, the reaction goes *via* the formation of the iminium ion (very fast step) and then the reduction of it to the amine occurs. Another observation suggests that either the phospholane complexes on their own without co-catalyst hydrogenate the enamines by the same mechanism, where the formation of iminium ion is more problematic, or that the mechanism there is different. The reaction in Scheme 4.8 shows that the catalyst is more active without iodine when the base is added in the enamine hydrogenation experiment.




**Scheme 4.8.** Hydrogenation of **108i** in the presence of triethylamine as an additive.

Such a significant improvement of the rate of the reaction in the presence of $Et_3N$ without iodine co-catalyst is difficult to confidently rationalise at this stage, and further studies are required to understand it better.

Overall, these studies describe an examination of co-catalysts and solvents for the enantioselective hydrogenation of enamines with Rh-phospholane complexes. Iodine was found to be an important co-catalyst which improves the rate of the reactions, as well as the enantioselectivities while causing the switch of the absolute configurations of the products. A particularly beneficial solvent, chlorobenzene was shown to afford the same catalysts a much improved rate of the reaction, as well as delivering good enantioselectivities. The dramatic switches in the absolute configurations of the products with and without iodine co-catalyst were even more extreme in $C_6H_5Cl$, allowing good enantioselectivities with the same enantiomer of the catalyst towards both enantiomers of the product.

Kinetic studies suggested that in the presence of iodine co-catalyst the reaction is 1$^{st}$ order with respect to catalyst, which indicates a single Rh species involved in catalysis. The reaction is first order in substrate, which along with the observation of very rapid iminium ion formation is in agreement with the iminium ion reduction being a rate determining step. The reaction is of a positive order in hydrogen gas, and the $[H_2]$ could affect the amount of pre-catalyst that can enter the catalytic cycle. Mechanistic studies discovered the fact that the reaction proceeds *via* a different mechanism from what was suggested in the literature in the past by Zhou and co-workers.[78]

The key steps in the mechanism are the formation of the iminium ion, and then the reduction of it to the desired amine. A few groups observed hydrogenation of imines to proceed *via* the iminium ion.[121-123] It is possible, that the iminium ion pathway is a more general mechanism. For example, Wang and co-workers proved that the hydrogenation of indole occurs *via* a protonation of nitrogen atom to form an iminium ion which is then reduced.[123] Norton and co-workers presented a single example of an achiral catalytic hydrogenation of enamine with 2 mol% of Ru catalyst, and suggested that the hydrogenation of enamines could proceed *via* the formation of the iminium ion.[121] It was proven that an enamine stays in equilibrium with an iminium ion in the presence of the Ru-dihydrogen species (and iminium ions can be converted to enamines in the presence of Ru hydride to product Ru dihydride).[120,121] The Ru dihydride complexes are expected to be less acidic relative to the Rh catalysts explored here.

The results from this work clearly prove that Rh / phospholane complexes in the presence of iodine co-catalyst hydrogenate the enamines *via* the mechanism which involves the formation of an iminium ion.

## 5. Conclusions and future work

In this study, factors effecting the rate and enantioselectivity of enamine hydrogenation were studied. At the end, some experiments were performed in order to understand the reaction mechanism.

While most of the enamines were prepared by known literature procedures, a new way of preparation and isolation of a cyclic pro-chiral enamine through branched-selective hydroaminovinylation is described. Although the reaction is known and was described in the past,[88] only low selectivities towards the desired enamine were achieved. This would prevent a pure sample of enamine being obtained. The use of the Rh / BOBPHOS catalyst was shown to be able to do this transformation with a good selectivity towards the desired product. This new way of using BOBPHOS ligand opens a potential to prepare cyclic enamines which are difficult (or impossible) to prepare by any other know synthetic route. One aim for possible future investigation is to test this reaction for a wider range of substrates.

Also during enamine synthesis, some properties were discovered of enamines with tetrasubstituted double bonds which, to the best of our knowledge, were never described previously. They show very high stability, and, unlike other enamines, are not moisture sensitive. They do not undergo hydrolysis even upon treatment with 1M hydrochloric acid. Knowledge of these properties could be useful in synthesis and purification of the enamines with tetrasubstituted double bonds.

Initially, non-chiral Rh catalysts were tested in the hydrogenation of enamines. Based on the previous findings in our group,[5] electron-deficient ligands were of interest. These ligands proved themselves to be very active in the hydrogenation of a range of enamines. It was found that more bulky enamines are more active in the reaction as well. This is proposed to be due to more sterically hindered transition state and, therefore, faster reductive elimination. The rhodium catalyst derived from tris(3,4,5-trifluorophenyl)phosphine proved itself to be an outstanding catalyst by hydrogenating enamines with tetrasubstituted double bonds. To the best of our knowledge, the hydrogenation of tetrasubstituted enamines (not enamides) has never been published before. On the top of that, bulky and electron-poor ligands were able to perform catalysis with S/C ratio of 5000, affording unprecedented TON of up to 4550 mol $mol^{-1}$ using Rh catalyst derived from $[Rh(COD)Cl]_2$ as a metal precursor and tris(3,5-bis(trifluoromethyl)phenyl)phosphine. This method of reducing enamines is much more desired compared to the known reduction processes, where stoichiometric amounts of reducing agents are required.[9-11] Some future work from these results is the synthesis of other bulky and electron-poor monodentate ligands, as the TON of 4550 mol $mol^{-1}$ can be improved. Since cage-

phosphine ligands explored in this study afforded good results, electron-deficient variants of those could be of a particular interest. Since they have very large cone angles,[90] the reductive elimination step (the rate determining step) in the catalytic cycle would benefit from those significantly. Other ligands could be of an interest as well. For examples, very electron-deficient $P(NR)_3$ ligands could be of a huge potential to perform the reaction efficiently.[124]

Using Rh catalysts derived from chiral ligands, it was shown that electron-deficient PHANEPHOS ligands afford much better rates of the reaction in comparison to the electron-rich versions (as expected). Iodine was found to be a very useful and important co-catalyst, improving activities and enantioselectivities of the catalysts. While Rh / PHANEPHOS / iodine catalytic system proved itself to be a very active system, being able to hydrogenate even tetrasubstituted enamines when electron-deficient variant of the ligand was used, the enantioselectivity of only up to 50% was achieved for the explored substrates. Nonetheless, PHANEPHOS ligands cannot be ruled out based on the mediocre enantioselectivities achieved in this project, and other variations of these ligands can be explored. In addition, it is possible that structurally different enamines might be reduced more selectively with the same catalysts.

Particularly interesting catalysts were found to be chiral Rh-phospholane complexes. While these were sluggish under standard conditions, iodine improved both the rate and enantioselectivity of the catalysts, while inverting the configuration of the products. Especially dramatic switches were observed when chlorobenzene was used as a solvent. While improving the rate of the reaction for alkyl-phospholane complexes, some very dramatic switches in selectivity were observed upon addition of iodine co-catalyst. TONs over 1000 mol $mol^{-1}$ were achieved even with electron-rich phospholanes. Although good enantioselectivities of up to 77% were achieved, clearly a better selectivity is desired. Electron-deficient versions of these ligands are highly desired. The approach of cleaving Et-DuPhos ligand to obtain a chiral secondary ethyl-phospholane unit was achievable (Appendix A), but difficult and we could not use it to prepare novel ligands. In the appendix some other speculative attempts to prepare electron withdrawing phospholanes are also described but were unsuccessful. The more obvious approach of making phosphanes with perfluorinated alkyl substituents on the ring has been tried by others and failed due to synthetic problems and configurational instability.[108] Clearly, a new approach is desired in the synthesis of the electron-deficient alkyl-phospholane ligands. One of the potential ideas could be the synthesis of some new phospholano-PHANEPHOS ligands (symmetric and non-symmetric ones). Rhodium complexes of this type of ligands would have the potential to be highly-enantioselective catalysts. In case of the success of preparation of those, bigger substrate scope could be tested. In particular, some precursors to pharmaceuticals can be of a huge interest.

The final part of the studies was about the mechanism of the enamine hydrogenation. For the iodine-modified catalyst, different mechanistic pathway was proven to take place. Instead of the reaction to undergo an expected "usual" hydrogenation mechanism, it was shown that it forms an iminium cation from an enamine first, which is then reduced to the desired amine product. The key steps of the mechanism are the formation of Rh-dihydride, the reaction of that with an enamine to form an iminium ion and Rh-hydride, reduction of the iminium ion to the amine and regeneration of an unusually acidic Rh-diiodo-dihydrogen catalytic species. It is not clear if this mechanism competes with a more traditional mechanism when iodine is absent. It is possible that both pathways are in operation but the combination of an electron-rich ligand makes a very poor catalyst for a traditional mechanism but reacts readily with $I_2$ to make a rather active catalyst for the iminium ion pathway.

There is clearly significant work to be done on developing truly effective catalytic hydrogenation of enamines using Rh catalysts. It may be of a value to other types of co-catalysts. Indeed, it was found that good activity is achievable when Rh / phospholanes are used in the presence of triethylamine. However, the finding that quite good activity can be realised by effectively having a catalyst that contains a proton and a hydride should lead perhaps to considering other metals and types of catalyst that can operate in this way. This concept is starting to be studied by a new researcher in the group. Overall, this thesis in addition to contributing quite useful catalysts, has signposted some new directions to tackle this challenge.

## 6. Experimental

### 6.1 General experimental techniques

Commercially available starting materials were purchased from Sigma Aldrich, Alfa Aesar or Acros and were used as received with the following exceptions: $PBr_3$ was distilled under inert atmosphere, triethylamine was heated with $P_2O_5$ under reflux for 2 hours, and then was distilled under inert atmosphere, *N*-methylbenzylamine was purified by distillation. Chiral Rh-phospholane complexes were supplied by Dr Reddy's. Chiral PHANEPHOS ligands **181** and **191** were prepared according to the literature procedure.[106] $BH_3$-protected (2*R*,5*R*)-diphenylphospholane (**219**) and $BH_3$-protected ((2*R*,5*R*)-diphenylphospholan-1-yl)methanol (**152**) were prepared according to the literature procedures.[125]

All catalytic procedures were carried out under inert conditions using standard schlenk techniques, and all solvents used were dried and degassed. The reactor for hydrogenation processes was a high pressure autoclave or Argonaut (Biotage Endeavor Catalyst Screening System). Work-ups of these reactions (i.e. isolation of amines), were carried out under aerobic conditions. Hydroaminovinylation reactions were carried out in a high pressure autoclave under inert conditions.

Synthetic procedures to prepare enamines using $TiCl_4$ were carried out in dry solvents under a nitrogen atmosphere. Distillations of enamines (except very stable tetrasubstituted ones), including the one prepared by hydroaminovinylation, were carried out using a Kugelrohr approach and high-vacuum pump. Enamines with tetrasubstituted double bonds were isolated by acid-base work-up. All other air-sensitive procedures were carried out using standard schlenk techniques.

All NMR spectra ($^1H$, $^{13}C\{^1H\}$, $^{31}P$, $^{31}P\{^1H\}$, $^{19}F\{^1H\}$) were acquired on Bruker Avance 500, Bruker Avance 400 or Bruker Avance 300. $^1H$,$^1H$ COSY, $^1H$,$^{13}C$ HSQC and $^1H$,$^{13}C$ HMBC spectra were acquired on Bruker 300.

Mass spectroscopy and high-resolution mass spectroscopy were carried out by Mrs Caroline Horsburgh at the University of St Andrews.

Optical rotations were recorded on a Perkin elmer 341 polarimeter using a 1 mL cell with 1 dm path length and Na D-line at 20 $^oC$.

Infrared spectra ($\nu_{max}$) were recorded on Shimadzu IRAffinity-1 using a Pike attenuated total reflectance (ATR) accessory. Only characteristic absorbances were assigned.

Elemental analyses were acquired by Mr. Stephen Boyer from London Metropolitan University.

Melting points were measured on Gallenkamp melting point apparatus (model number 889339).

## 6.2 General catalytic procedures

General experimental for hydroaminovinylation of styrene (**44**)

A high pressure autoclave with 4 internal 10 mL vials was used. Each vial was sealed with a crimped cap, purged with argon *via* a needle for 10 minutes and charged with a toluene solution of [Rh(acac)$(CO)_2$] (0.5 mL, 8 mM, containing 4.0 μmol of [Rh(acac)$(CO)_2$]) and a toluene solution of ligand ($R_{ax}$/$S_{ax}$,*S*,*S*)-**153** (0.5 mL, contains 5.0 μmol of the ligand). This was left to stir for 10 minutes and a toluene solution of styrene (1.0 mL, 1 M, contains 1.0 mmol of styrene and 0.1 mL of 1-methylnaphthalene) was added, followed by the addition of dibenzyl amine (0.2 mL, 1.0 mmol). The vials were sealed in a high-pressure autoclave. The autoclave was purged with syngas (1:1 mixture) 3 times, pressurised with syngas (10 bar), heated to the desired temperature and left to stir for 16 hours. After this time, cooled to room temperature, the pressure of the gas was released and $^1$H NMR spectrum of the crude solution was acquired in order to calculate the conversion.

General experimental for hydroaminovinylation of *N*-benzylpent-4-en-1-amine (**155**)

A high pressure autoclave with 4 internal 10 mL vials was used. Each vial was sealed with a crimped cap, purged with argon *via* a needle for 10 minutes and charged with a toluene solution of [Rh(acac)$(CO)_2$] (0.5 mL, 8 mM, containing 4.0 μmol of [Rh(acac)$(CO)_2$]) and a toluene solution of ligand ($R_{ax}$/$S_{ax}$,*S*,*S*)-**153** (0.5 mL, contains 5.0 μmol of the ligand). This was left to stir for 10 minutes and a toluene solution of **155** (1.0 mL, 1 M, contains 1.0 mmol of **155** and 0.1 mL of 1-methylnaphthalene) was added. The vials were sealed in a high-pressure autoclave. The autoclave was purged with syngas (1:1 mixture) 3 times, pressurised with syngas (10 bar), heated to the desired temperature and left to stir for 16 hours. After this time, cooled to room temperature, the pressure of the gas was released and $^1$H NMR spectrum of the crude solution was acquired in order to calculate the conversion and selectivity towards the desired enamine **108as**.

General experimental for *in-situ* high pressure hydrogenation

This examples describes a general procedure performed with 0.4 mol% Rh and 1 mmol of enamine. A high pressure autoclave with 4 internal 10 mL vials was used. Each pre-dried vial was charged with a monodentate ligand (8.0 μmol) or a bidentate ligand (4.8 μmol). The vials

were sealed with crimped caps and purged with Ar for 10 minutes. A toluene solution of $[Rh(COD)Cl]_2$ (0.5 mL, 4 mM, containing 2.0 μmol of $[Rh(COD)Cl]_2$) was added. For the experiments where iodine co-catalyst was used, a toluene solution of iodine (0.5 mL, 16 mM, 8 μmol) was added. If no iodine was introduced to the reaction, just toluene (0.5 mL) was added. The resulting solution was stirred for 10 minutes before a toluene solution of an enamine (1.0 mL, 1M, contains 1.0 mmol of enamine and 0.1 mL of 1-methylnaphthalene) was added. The vials were sealed in a high-pressure autoclave. The autoclave was purged with hydrogen 3 times, pressurised with $H_2$ gas to the desired pressure, heated to the desired temperature and left to stir for the desired period of time. After this time, the autoclave was cooled to room temperature, pressure of the gas was released and $^1$H NMR of the crude reaction solution was acquired in order to calculate the conversion.

In cases where chiral ligands were used, 0.15 mL of the crude reaction solution was taken, toluene was removed under reduced pressure, the resulting contents were dried *in vacuo* for 10 minutes and (*R*)-(–)-α-methoxyphenylacetic acid (0.020 g, 0.12 mmol) was added. The mixture was dissolved in dichloromethane and the solution was charged into an NMR tube with a $C_6D_6$ capillary. $^1$H NMR on Bruker Avance 500 was acquired to measure the enantiomeric excess.

When amine **109i** is produced, the two characteristic doubles are present at 1.62 ppm (for the *R*-enantiomer) and 1.59 ppm (for the *S*-enantiomer – this was confirmed by the NMR of a mixture of enantio-pure (*S*)-**109i** and (*R*)-methoxyphenylacetic acid). Synthesis of the enantio-pure amine (*S*)-**109i** is shown on page 123. When amine **109g** is produced, the same shifts are observed – i.e. a doublet at 1.59 ppm for the *S*-enantiomer, and a doublet at 1.62 ppm for the *R*-enantiomer of the product (this was confirmed by the NMR of a mixture of enantio-pure (*R*)-**109g** and (*R*)-methoxyphenylacetic acid). Synthesis of the enantio-pure amine (*R*)-**109g** is shown on page 123.

General experimental for high pressure hydrogenation with pre-formed complex

This example describes a general procedure performed with 0.4 mol% Rh and 1 mmol of enamine. A high pressure autoclave with 4 internal 10 mL vials was used. Each pre-dried vial was charged with a metal complex (4.0 μmol). The vials were sealed with crimped caps and purged with Ar for 10 minutes, and toluene (1.0 mL) was added. If iodine as an additive was used in the reaction, instead of toluene, a toluene solution of iodine (1.0 mL, 8 mM, 8.0 μmol) was added. The contents were stirred for 10 minutes and a toluene solution of an enamine (1.0 mL, 1 M, contains 1.0 mmol of enamine and 0.1 mL of 1-methylnaphthalene) was added. The vials were sealed in a high-pressure autoclave. The autoclave was purged with hydrogen 3 times,

pressurised with $H_2$ gas to the desired pressure, heated to the desired temperature and left to stir for the desired period of time. After this time, the autoclave was cooled to room temperature, pressure was released and $^1$H NMR of the crude reaction solution was acquired in order to calculate the conversion. A 0.15 mL of the crude solution was taken, toluene was removed under reduced pressure, dried for 10 minutes and (*R*)-(–)-α-methoxyphenylacetic acid was added (0.020 g, 0.12 mmol). The mixture was dissolved in dichloromethane and the solution was charged into an NMR tube with a $C_6D_6$ capillary. $^1$H NMR on Bruker Avance 500 was acquired to measure the enantiomeric excess of the amine.

The same procedure is followed for the hydrogenation of iminium salt **206**. The only difference is that for the measurement of the ee, the sample was always isolated by acid-base work-up (the same procedure as for isolation of amines after hydrogenation of enamines) before the addition of the chiral acid.

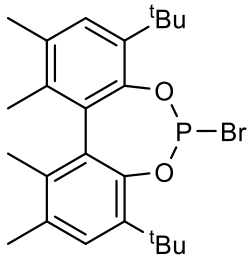
General experimental procedure for catalytic hydrogenation performed in Argonaut

Each Argonaut vial was charged with the desired catalyst and placed into the system. All the set up was sealed and purged with 3 nitrogen cycles (12 bar to atmospheric pressure). Then a toluene / stock solution of iodine in toluene was added followed by the addition of an enamine stock solution (which contained 1-methylnaphthalene as an internal standard). Each vial was charged with further toluene (0.5 mL) in order to wash any remaining materials down to the vial, purged with 3 nitrogen cycles and the machine was programmed to run at the desired pressure for the desired time at the desired temperature. After the catalytic experiment was complete, the system was cooled to RT, hydrogen pressure was released, the solutions were purged with a nitrogen cycle, and the vials were opened to air. The resulting solutions analysed by $^1$H NMR in order to measure the conversions. Small sample (typically containing 0.08 mmol of the mixture of enamine / amine / ketone) was taken from each vial, toluene was removed *in vacuo*, (*R*)-(–)-α-methoxyphenylacetic acid (0.020 g, 0.12 mmol) was added and the resulting mixture was dissolved in dichloromethane. The solution was charged into an NMR tube with a $C_6D_6$ capillary and $^1$H NMR on Bruker Avance 500 was acquired to measure the enantiomeric excess of the amine. For the experiments, where kinetics of the reaction was studies, the gas uptake over time data was analysed and presented in Chapter 4.

### 6.3 Synthesis, purification and characterisation

BOBPHOS-related synthesis

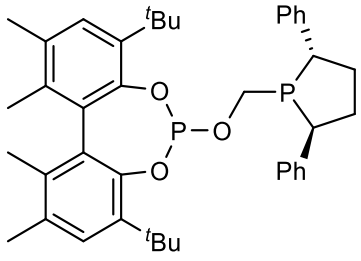
Bromophosphite precursor **151** for ligand **153** (strategy from literature procedure applied)[86]



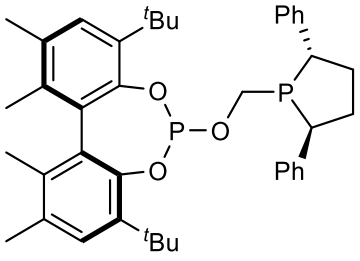

**151**

The same approach was used for the preparation of (*R*)-**151** as for the racemic sample of it.
A toluene solution (4.5 mL) of 3,3'-di-tert-butyl-5,5',6,6'-tetramethyl-[1,1'-biphenyl]-2,2'-diol (**150**) (0.590 g, 1.66 mmol) was cooled to 0 °C. Triethylamine (0.70 mL, 5.02 mmol) was added followed by a dropwise addition of a toluene solution (2.5 mL) of phosphorous tribromide (0.24 mL, 2.55 mmol). The resulting solution was left to stir for 64 hours at room temperature. After this time, the solution was filtered and the volatiles were removed *in vacuo* to afford the desired product (0.755 g, 1.63 mmol, 98%) as a pale yellow solid that is highly air and moisture sensitive. Due to the sensitivity of this intermediate, its purity with respect to phosphorus species was checked with the literature, and then used directly in the next step.
$^{31}P\{^{1}H\}$ NMR (121.5 MHz, $C_6D_6$, 298 K): $\delta_P$ = 181.1 (s).

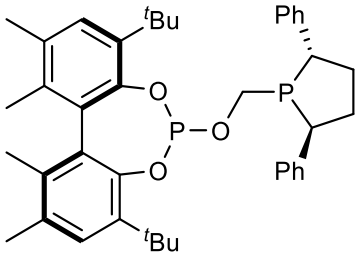
Ligand **153** (1:1 mixture of $S_{ax}$,*S*,*S*-BOBPHOS and $R_{ax}$,*S*,*S*-BOBPHOS).[86]




**153**
diastereomeric mixture




$S_{ax}$/*S*,*S* - **153**




$R_{ax}$/*S*,*S* - **153**

To a borane-protected ((2*S*,5*S*)-2,5-diphenylphospholan-1-yl)methanol (0.465 g, 1.64 mmol) a toluene solution (6 mL) of bromophosphite precursor **151** (0.753 g, 1.62 mmol) was added. Then a toluene solution (15 mL) of DABCO (0.910 g, 8.11 mmol) was added dropwise and the resulting solution was left to stir for 16 hours. After this time, the solution was filtered through neutralised silica and the column was washed with toluene (40 mL). The collected fractions were

combined and the solvent was removed *in vacuo* to afford the desired product (0.816 g, 77%) as a white solid.

$[\alpha]_{D_{20}}$ = +120 (*c* 1.0, $CHCl_3$).

m.p. = 111 – 140 °C.

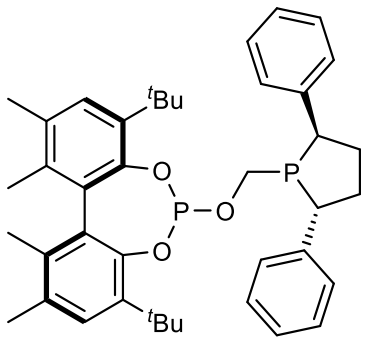
$^1H$ NMR (300 MHz, $C_6D_6$, 298 K): $\delta_H$ = 7.43 – 6.98 (24H, m, Ar-H from both diastereomers), 4.27 – 4.09 (2H, m, 1H from each diastereomer from P-C$H_2$-O), 3.76 – 3.61 (2H, m, 1H from each diastereomer from P-C$H_2$-O), 3.52 – 3.21 (4H, m, 2 x P-CH- from both diastereomers), 2.40 – 1.38 (8H, m, -C$H_2$-C$H_2$- from both diastereomers), 2.13 (3H, s, C$H_3$), 2.12 (3H, s, C$H_3$), 2.03 (6H, s, 2 x C$H_3$), 1.81 (3H, s, C$H_3$), 1.79 (3H, s, C$H_3$), 1.65 (3H, s, C$H_3$), 1.64 (3H, s, C$H_3$), 1.53 (9H, s, *t*Bu), 1.52 (9H, s, *t*Bu), 1.41 (9H, s, *t*Bu), 1.40 (9H, s, *t*Bu).

$^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$, 298 K): $\delta_C$ = 145.3 (s), 144.7 (s), 143.5 (s), 143.2 (s), 143.0 (s), 137.4 (s), 137.0 (s), 135.9 (s), 133.9 (s), 133.2 (s), 131.2 (s), 131.0 (s), 130.2 (s), 129.8 (s), 128.1-126.1 (m), 124.7 (s), 124.6 (s), 45.2-44.6 (m), 44.1 (s), 43.9 (s), 35.2 (s), 35.1 (s), 33.6 (s), 31.8-28.4 (m), 19.1 (s), 15.5 (s), 15.1 (s).

$^{31}P\{^1H\}$ NMR (121.5 MHz, $C_6D_6$, 298 K): $\delta_P$ = 132.7 (s, phosphite), 125.7 (s, phosphite), 9.7 (s, phosphine), 8.7 (s, phosphine)

MS ($ES^+$) *m/z*: 675.15 ($[MNa]^+$, 100%), 455.15 (50), 293.06 ($[C_{17}H_{19}ONaP]^+$, 46); Found($ES^+$) 675.3135 ($[MNa]^+$), $C_{41}H_{50}O_3NaP_2^+$ requires 675.3133.

($R_{ax}$,*R*,*R*)-BOBPHOS (($R_{ax}$,*R*,*R*)-**153**)




($R_{ax}$,*R*,*R*)-**153**

To a borane-protected ((2*R*,5*R*)-2,5-diphenylphospholan-1-yl)methanol (0.750 g, 2.64 mmol) a toluene solution (10 mL) of (*R*)-bromophosphite precursor (*R*)-**151** (1.211 g, 2.61 mmol) was added. Then a toluene solution (25 mL) of DABCO (1.460 g, 13.0 mmol) was added dropwise and the resulting solution was left to stir for 16 hours. After this time, the solution was filtered through silica and the column washed toluene (2 x 30 mL). The collected fractions were combined and the solvent was removed *in vacuo* to afford the desired product with 96% purity.

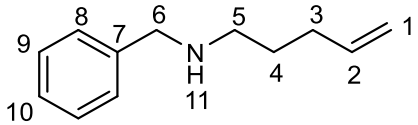
Purity of >99% was achieved by washing the resulting solids with ice-cold hexane (2 x 10 mL) (1.208 g, 1.85 mmol, 71%).

$[\alpha]^{D}_{20}$ = -401 (*c* 1.0, $CHCl_3$).

$^{31}P\{^{1}H\}$ NMR (202.5 MHz, $C_6D_6$, 298 K): $\delta_P$ = 125.8 (s, phosphite), 8.9 (s, phosphine).

The rest of the data is consistent with previously reported one for the ligand.[86]

Synthesis of *N*-benzylpent-4-en-1-amine (**155**) (prepared according to the literature procedure).[89]




**155**

To an ethanol solution (50 mL) of benzylamine (10.9 mL, 100 mmol) bromopentane (2.4 mL, 20.3 mmol) and sodium iodide (0.151 g, 1.01 mmol) were added. The resulting solution was heated under reflux for 16 hours. After this time, the solvent was removed under reduced pressure and dissolved in $CH_2Cl_2$ (100 mL). The solution was washed with aqueous KOH (1M, 50 mL), dried over KOH, filtered and the solvent was removed under reduced pressure. The product was purified by distillation under reduced pressure (90 $^{o}$C, 1.5 mbar) to afford the desired product (2.036 g, 57%) as a colourless liquid.

$^{1}H$ NMR (300 MHz, $CDCl_3$, 298 K): $\delta_H$ = 7.27 – 7.09 (5H, m, 8-H, 9-H and 10-H), 5.72 (1H, ddt, $^{3}J_{HH}$ = 17.0 Hz, $^{3}J_{HH}$ = 10.3 Hz, $^{3}J_{HH}$ = 6.7 Hz, 2-H), 4.98 – 4.62 (2H, m, 1-H), 3.68 (2H, s, 6-H), 2.55 (2H, t, $^{3}J_{HH}$ = 7.3 Hz, 5-H), 2.06 – 1.95 (2H, m, 3-H), 1.51 (2H, qu, $^{3}J_{HH}$ = 7.5 Hz, 4-H), 1.16 (1H, br s, 11-H).

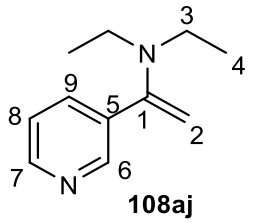
$^{13}C\{^{1}H\}$ NMR (75.5 MHz, $CDCl_3$, 298 K): $\delta_C$ = 141.1 (s, 7-C), 139.0 (s, 2-C), 128.8 (s, Ar-C), 128.5 (s, Ar-C), 127.3 (s, 10-C), 115.1 (s, 1-C), 54.5 (s, 6-C), 49.4 (s, 5-C), 32.0 (s, 3-C), 29.8 (s, 4-C).

MS ($ES^+$) *m/z*: 176.12 ($[MH]^+$, 100%).

Enamines

Majority of enamines prepared in this study are made by the known literature route using $TiCl_4$ as a reagent.[84]

*N*,*N*-diethyl-1-(pyridin-3-yl)ethenamine (**108aj**)[126]



**108aj**

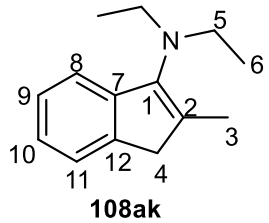
A toluene solution (100 mL) of 3-acetylpyridine (4.0 mL, 36.4 mmol) and diethylamine (22.7 mL, 218 mmol) was cooled to 0 °C and $TiCl_4$ (2.2 mL, 20.1 mmol) was added dropwise. This was warmed to room temperature and left to stir for 24 hours. After this time, the flask was opened to air, the solution filtered, solvent and any remaining diethylamine were removed *in vacuo*, and the product was purified by distillation under reduced pressure (95 °C, 1.5 mbar) to afford a pale yellow oil (2.508 g, 39%).

$^1$H NMR (300 MHz, $C_6D_6$, 298 K): $\delta_H$ = 8.58 (1H, d, $^4J_{HH}$ = 2.2 Hz, 6-H), 8.43 (1H, dd, $^3J_{HH}$ = 4.9 Hz, $^4J_{HH}$ = 1.7 Hz, 7-H), 7.62 (1H, dt, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 2.1 Hz, 9-H), 7.14 (1H, dd, $^3J_{HH}$ = 8.0 Hz, $^4J_{HH}$ = 4.8 Hz, 8-H), 4.10 (1H, s, 2-H), 4.06 (1H, s, 2-H), 2.88 (4H, q, $^3J_{HH}$ = 7.1 Hz, 3-H), 0.93 (6H, t, $^3J_{HH}$ = 7.1 Hz, 4-H).

$^{13}$C NMR (75 MHz, $CDCl_3$, 298 K): $\delta_C$ = 152.0 (s, 1-C), 149.5 (s, 6-C), 149.2 (s, 7-C), 136.8 (s, 5-C), 135.2 (s, 9-C), 123.2 (s, 8-C), 92.5 (s, 2-C), 45.4 (s, 3-C), 11.9 (s, 4-C).

MS ($ES^+$) *m/z*: 177.11 ($[MH]^+$, 100%), 149.12 ($[M - C_2H_5]^+$, 15).

*N*,*N*-diethyl-2-methyl-1*H*-inden-3-amine (**108ak**)



**108ak**

A hexane solution (100 mL) of 2-methyl-1-indanone (5.0 mL, 36.4 mmol) and diethylamine (22.7 mL, 218 mmol) was cooled to 0 °C and $TiCl_4$ (2.2 mL, 20.1 mmol) was added dropwise. This was warmed to room temperature and left to stir for 24 hours. After this time, the flask was opened to air and wet diethyl ether (25 mL) was added. The solution was filtered and the solvents and any remaining diethylamine were removed *in vacuo*. Attempts to purify the product by standard acid-base work-up were not successful (see how enamines 108am and 108al were isolated by acid-base work-up). T product was purified by distillation under reduced pressure (100 °C, 1.5 mbar) to afford a pale yellow oil (380 mg, 1.89 mmol, 5%).

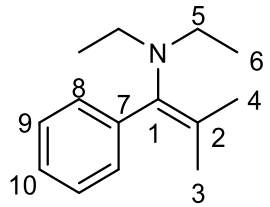
$^{1}$H NMR (400 MHz, $CDCl_3$, 298 K): $\delta_H$ = 7.41 – 7.35 (2H, m, Ar-H), 7.26 – 7.21 (1H, m, Ar-H), 7.15 – 7.10 (1H, m, Ar-H), 3.29 (2H, s, 4-H), 3.20 (4H, q, $^{3}J_{HH}$ = 7.1 Hz, 5-H), 2.10 (3H, s, 3-H), 1.04 (6H, t, $^{3}J_{HH}$ = 7.2 Hz, 6-H).

$^{13}$C{$^{1}$H} NMR (101 MHz, $CDCl_3$, 298 K): $\delta_C$ = 144.8 (s, 7-C), 143.2 (s, 1-C), 141.9 (s, 12-C), 135.5 (s, 2-C), 125.6 (s, Ar-CH), 123.5 (s, Ar-CH), 123.4 (s, Ar-CH), 119.3 (s, Ar-CH), 47.0 (s, 5-C), 40.7 (s, 4-C), 14.2 (s, 3-C), 13.9 (s, 6-C).

MS ($ES^+$) *m/z*: 202.16 ($[MH]^+$, 65%); Found($ES^+$) 202.1588 ($[MH]^+$), $C_{14}H_{20}N^+$ requires 202.1590.

IR (neat) *v*, $cm^{-1}$: 2961, 2820, 1490, 1439, 1350, 1219, 1110, 1062.

*N*,*N*-diethyl-2-methyl-1-phenylprop-1-en-1-amine (**108am**)[127]



**108am**

A hexane solution (100 mL) of 2-methyl-1-phenylpropan-1-one (5.0 mL, 33.3 mmol) and diethyl amine (21.0 mL, 202 mmol) was cooled to 0 $^{o}$C and $TiCl_4$ (2.0 mL, 18.2 mmol) was added dropwise and the resulting suspension was left to stir for further 30 minutes followed by stirring the reaction mixture at room temperature for further 24 hours. After this time, the flask was opened to air and water-saturated diethyl ether (20 mL) was added. The solution was filtered and volatiles were removed *in vacuo*. Crude enamine was dissolved in toluene (150 mL), exctacted into aqueous HCl (1M, 3 x 100 mL) and the combined acidic fractions were basified with aqueous NaOH (1M) until pH = 10 – 12. The enamine was then extracted into ethyl acetate (3 x 70 mL), the combined organic fractions were washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$ and solvent was removed under reduced pressure. The enamine was dried *in vacuo* for 2 hours to afford the desired product (2.848 g, 14.0 mmol, 42%) as a pale yellow liquid.

Due to the high stability of this enamine, it was found that acid-base work-up is a suitable method of purifying enamines with tetrasubstituted double bond studied in this paper (another example is enamine **108al**).

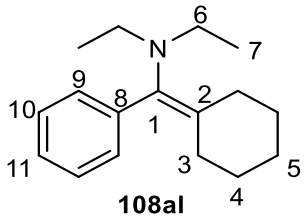
$^{1}$H NMR (400 MHz, $C_6D_6$, 298 K): $\delta_H$ = 7.23 – 7.17 (2H, m, 9-H), 7.16 – 7.07 (3H, m, 8-H and 10-H), 2.61 (4H, q, $^{3}J_{HH}$ = 7.1 Hz, 5-H), 1.96 (3H, s, 3-H or 4-H), 1.58 (3H, s, 3-H or 4-H), 1.03 (6H, t, $^{3}J_{HH}$ = 7.1 Hz, 6-H).

$^{13}$C{$^{1}$H} NMR (101 MHz, $CDCl_3$, 298 K): $\delta_C$ = 140.9 (s, 1-C), 138.1 (s, 7-C), 130.1 (s, 8-C), 127.5 (s, 7-C), 126.7 (s, 2-C), 126.3 (s, 10-C), 47.1 (s, 5-C), 21.0 (s, 3-C or 4-C), 20.0 (s, 3-C or 4-C), 14.2 (s, 6-C).

MS ($ES^+$) *m/z*: 204.17 ($[MH]^+$, 100%); Found($ES^+$) 204.1742 ($[MH]^+$), $C_{14}H_{22}N^+$ requires 204.1747.

IR (neat) *v*, $cm^{-1}$: 2968, 2820, 1489, 1441, 1375, 1219, 1109, 1072.

*N*-(cyclohexylidene(phenyl)methyl)-*N*-ethylethanamine (**108al**)



**108al**

A hexane solution (90 mL) of cyclohexyl(phenyl)methanone (4.911 g, 26.1 mmol) and diethyl amine (16.5 mL, 159 mmol) was cooled to 0 $^{o}$C and $TiCl_4$ (1.6 mL, 14.6 mmol) was added dropwise and the resulting suspension was left to stir for further 30 minutes followed by stirring the reaction mixture at room temperature for further 24 hours. After this time, the flask was opened to air and water-saturated diethyl ether (16 mL) was added. The solution was filtered and volatiles were removed *in vacuo*. Crude enamine was dissolved in toluene (120 mL), exctacted into aqueous HCl (1M, 3 x 80 mL) and the combined acidic fractions were basified with aqueous NaOH (1M) until pH = 10 – 12. The enamine was then extracted into ethyl acetate (3 x 50 mL), the combined organic fractions were washed with water (40 mL) and brine (40 mL), dried over $MgSO_4$ and solvent was removed under reduced pressure. The enamine was dried *in vacuo* for 2 hours to afford the desired product (3.811 g, 15.7 mmol, 60%) as viscous pale yellow oil.
Anal. Calcd. for $C_{17}H_{25}N$ (found): C, 83.89 (83.74); H, 10.35 (10.28); N, 5.75 (5.96).

$^{1}$H NMR (400 MHz, $C_6D_6$, 298 K): $\delta_H$ = 7.24 – 7.08 (5H, m, 9-H, 10-H and 11-H), 2.64 – 2.57 (6H, m, 6-H and one of 3-H), 2.07 – 2.02 (2H, m, 3-H), 1.65 – 1.57 (2H, m, 4-H or 5-H), 1.53 – 1.46 (2H, m, 4-H or 5-H), 1.45 – 1.38 (2H, m, 4-H or 5-H), 1.05 (6H, t, $^{3}J_{HH}$ = 7.1 Hz, 7-H).

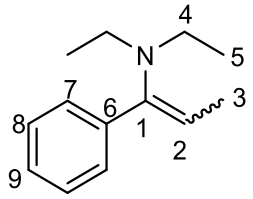
$^{13}$C NMR (101 MHz, $CDCl_3$, 298 K): $\delta_C$ = 137.8 (s, 1-C, 2-C or 8-C), 137.6 (s, 1-C, 2-C or 8-C), 135.5 (s, 1-C, 2-C or 8-C), 129.9 (s, 9-C, 10-C or 11-C), 127.5 (s, 9-C, 10-C or 11-C), 126.3 (s,

9-C, 10-C or 11-C), 47.1 (s, 6-C), 31.5 (s, 3-C, 4-C or 5-C), 29.7 (s, 3-C, 4-C or 5-C), 28.6 (s, 3-C, 4-C or 5-C), 27.9 (s, 3-C, 4-C or 5-C), 27.1 (s, 3-C, 4-C or 5-C), 14.1 (s, 7-C).

MS ($ES^+$) *m/z*: 244.21 ($[MH]^+$, 100%), 214.16 ($[M - C_2H5]^+$, 28), 171.12 ($[M - NEt_2]^+$, 28); Found($ES^+$) 244.2054 ($[MH]^+$), $C_{17}H_{26}N^+$ requires 244.2060.

IR (neat) *v*, $cm^{-1}$: 2920, 2850, 1681, 1447, 1252, 1205, 1072.

*N*,*N*-diethyl-1-phenylprop-1-en-1-amine (**108an**)[128]




**108an**

*E* / *Z* = 91 / 9

A hexane solution (120 mL) of propiophenone (5.0 mL, 37.6 mmol) and diethyl amine (24.0 mL, 231 mmol) was cooled to 0 °C and $TiCl_4$ (2.3 mL, 21.0 mmol) was added dropwise and the resulting suspension was left to stir for further 30 minutes followed by stirring the reaction mixture at room temperature for further 24 hours. After this time, the flask was opened to air and water-saturated diethyl ether (23 mL) was added. The solution was filtered and volatiles were removed *in vacuo*. The product was purified by Kugelrohr distillation (oven T = 85 °C, 1.2 mbar) to afford the desired enamine (2.014 g, 10.6 mmol, 28%) as a pale yellow liquid.

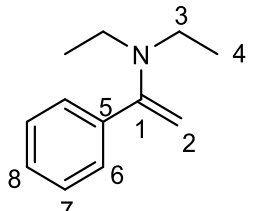
Since the compounds are present as a mixture (*E* / *Z* = 91 / 9), signals are given to them separately where possible.

$^1H$ NMR (400 MHz, $C_6D_6$, 298 K): $\delta_H$ (*E* isomer) = 7.37 – 7.19 (5H, m, 7-H, 8-H and 9-H), 4.53 (1H, q, $^3J_{HH}$ = 7.0 Hz, 2-H), 2.81 (4H, q, $^3J_{HH}$ = 7.0 Hz, 4-H), 1.50 (3H, d, $^3J_{HH}$ = 6.9 Hz, 3-H), 0.94 (6H, t, $^3J_{HH}$ = 7.0 Hz, 5-H); $\delta_H$ (*Z* isomer) = 7.37 – 7.19 (5H, m, 7-H, 8-H and 9-H), 5.08 (1H, q, $^3J_{HH}$ = 7.1 Hz, 2-H), 3.00–2.93 (4H, m, 4-H), 1.73 (3H, d, $^3J_{HH}$ = 7.0 Hz, 3-H), 0.99 (6H, t, $^3J_{HH}$ = 7.1 Hz, 5-H).

$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, 298 K): $\delta_C$ (*E* isomer) = 147.4 (s, 1-C), 139.0 (s, 6-C), 129.8 (s, 7-C, 8-C or 9-C), 127.8 (s, 7-C, 8-C or 9-C), 126.9 (s, 7-C, 8-C or 9-C), 99.8 (s, 2-C), 43.0 (s, 4-C), 14.0 (s, 3-C), 11.5 (s, 5-C). $^{13}C$ NMR signals for *Z*-isomer are not assigned.

MS ($ES^+$) *m/z*: 190.16 ($[MH]^+$, 100%); Found($ES^+$) 190.1588 ($[MH]^+$), $C_{13}H_{20}N^+$ requires 190.1590.

*N*,*N*-diethyl-1-phenylethenamine (**108i**)[73]




**108i**

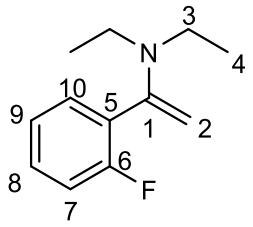
A hexane solution (100 mL) of acetophenone (5.0 mL, 42.8 mmol) and diethylamine (27.0 mL, 261 mmol) was cooled to 0 $^{o}$C and $TiCl_4$ (2.6 mL, 23.7 mmol) was added dropwise. The resulting mixture was warmed to room temperature and left to stir for 24 hours. After this time, the solution filtered, solvent and any remaining diethylamine were removed *in vacuo*, and the product was purified by distillation under reduced pressure (90 $^{o}$C, 1.5 mbar) to afford a pale yellow oil (4.043 g, 54%).

$^{1}$H NMR (300 MHz, $C_6D_6$, 298 K): $\delta_H$ = 7.28 – 7.20 (2H, m, 6-H), 6.92 – 6.78 (3H, m, 7-H and 8-H), 4.13 (1H, s, 2-H), 3.91 (1H, s, 2-H), 2.58 (4H, q, $^{3}J_{HH}$ = 7.0 Hz, 3-H), 0.61 (6H, t, $^{3}J_{HH}$ = 7.0 Hz, 4-H) .

$^{13}$C{$^{1}$H} NMR (75.5 MHz, $CDCl_3$, 298 K): $\delta_C$ = 154.4 (s, 1-C), 141.6 (s, 5-C), 128.5 (s, 6-C or 7-C), 128.4 (s, 6-C or 7-C), 128.1 (s, 8-C), 90.9 (s, 2-C), 43.7 (s, 3-C), 12.1 (s, 4-C).

MS (ES$^{+}$) *m/z*: 176.14 ([MH]$^{+}$, 100%); Found(ES$^{+}$) 176.1430 ([MH]$^{+}$), $C_{12}H_{18}N^{+}$ requires 176.1434.

*N*,*N*-diethyl-1-(2-fluorophenyl)ethen-1-amine (**108ao**)




**108ao**

A hexane solution (120 mL) of 1-(2-fluorophenyl)ethan-1-one (5.1 mL, 42.0 mmol) and diethyl amine (26.0 mL, 250 mmol) was cooled to 0 $^{o}$C and $TiCl_4$ (2.53 mL, 23.1 mmol) was added dropwise and the resulting suspension was left to stir for further 30 minutes followed by stirring the reaction mixture at room temperature for further 24 hours. After this time, the flask was opened to air and water-saturated diethyl ether (26 mL) was added. The solution was filtered and volatiles were removed *in vacuo*. The product was purified by Kugelrohr distillation (oven T =

88 ºC, 1.4 mbar) to afford the desired enamine (4.105 g, 21.2 mmol, 51%) as a pale yellow-green liquid.

Surprisingly – this particular enamine is more stable than other enamines with disubstituted double bonds studied here (no hydrolysis detected in wet chloroform after hours).

Anal. Calcd. for $C_{12}H_{16}FN$ (found): C, 74.58 (74.52); H, 8.34 (8.26); N, 7.25 (7.36).

$^{1}$H NMR (400 MHz, $CDCl_3$, 298 K): $\delta_H$ = 7.40 – 7.33 (1H, m, 10-H), 7.32 – 7.25 (1H, m, 8-H), 7.15 – 7.02 (2H, m, 7-H and 9-H), 4.10 (1H, s, one of 2-H), 3.93 (1H, s, one of 2-H), 3.04 (4H, q, $^{3}J_{HH}$ = 7.0 Hz, 3-H), 1.07 (6H, t, $^{3}J_{HH}$ = 7.0 Hz, 4-H) .

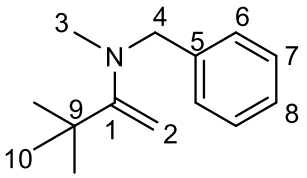
$^{13}$C{$^{1}$H} NMR (126 MHz, $CDCl_3$, 298 K): $\delta_C$ = 160.0 (d, $^{1}J_{CF}$ = 248 Hz, 6-C), 147.9 (s, 1-C), 131.2 (d, $^{3}J_{CF}$ = 3.7 Hz, 10-C), 129.1 (d, $^{3}J_{CF}$ = 8.1 Hz, 8-C), 128.4 (d, $^{2}J_{CF}$ = 14.7 Hz, 5-C), 123.7 (d, $^{4}J_{CF}$ = 3.7 Hz, 9-C), 115.5 (d, $^{2}J_{CF}$ = 22.7 Hz, 7-C), 87.9 (s, 2-C), 43.1 (s, 3-C), 12.0 (s, 4-C).

$^{19}$F{$^{1}$H} NMR (377 MHz, $CDCl_3$, 298 K): $\delta_F$ = -116.0 (s).

MS ($ES^+$) *m/z*: 194.13 ($[MH]^+$, 100%); Found($ES^+$) 194.1334 ($[MH]^+$), $C_{12}H_{17}FN^+$ requires 194.1340.

IR (neat) *v*, $cm^{-1}$: 2971, 2864, 1602, 1493, 1440, 1371, 1220.

*N*-benzyl-*N*,3,3-trimethylbut-1-en-2-amine (**108ap**)[77]




**108ap**

A hexane solution (500 mL) of 3,3-dimethyl-butan-2-one (16.0 mL, 128 mmol) and *N*-methylbenzylamine (99 mL, 767 mmol) was cooled to 0 ºC and $TiCl_4$ (7.7 mL, 70.2 mmol) was added dropwise and the resulting suspension was left to stir for further 30 minutes followed by stirring the reaction mixture at room temperature for further 24 hours. After this time, the flask was opened to air and water-saturated diethyl ether (80 mL) was added. The solution was filtered and volatiles were removed *in vacuo*. The product was purified by Kugelrohr distillation (oven T = 95 ºC, 1.5 mbar) to afford the desired enamine (1.691 g, 8.32 mmol, 6%) as a pale yellow-yellow liquid.

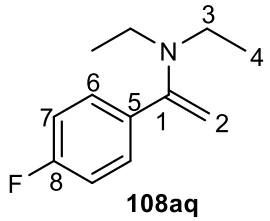
$^{1}$H NMR (500 MHz, $CDCl_3$, 298 K): $\delta_H$ = 7.44 – 7.40 (2H, m, 6-H), 7.38 – 7.33 (2H, m, 7-H), 7.30 – 7.25 (1H, m, 8-H), 4.84 (1H, s, one of 2-H), 4.63 (1H, s, one of 2-H), 3.88 (2H, s, 4-H), 2.40 (3H, s, 3-H), 1.23 (9H, s, 10-H).

$^{13}$C{$^{1}$H} NMR (126 MHz, $CDCl_3$, 298 K): $\delta_C$ = 169.2 (s, 1-C), 140.1 (s, 5-C), 128.2 (s, 6-C or 7-C), 128.1 (s, 6-C or 7-C), 126.7 (s, 8-C), 98.3 (s, 2-C), 61.8 (s, 4-C), 42.7 (s, 3-C), 37.8 (s, 9-C), 29.8 (s, 10-C).

MS ($ES^+$) *m/z*: 204.17 ($[MH]^+$, 100%); Found($ES^+$) 194.1741 ($[MH]^+$), $C_{14}H_{22}N^+$ requires 204.1747.

IR (neat) *v*, $cm^{-1}$: 2982, 2844, 1612, 1483, 1458, 1372, 1212.

*N*,*N*-diethyl-1-(4-fluorophenyl)ethen-1-amine (**108aq**)[129]



**108aq**

A hexane solution (120 mL) of 1-(4-fluorophenyl)ethan-1-one (5.4 mL, 44.5 mmol) and diethyl amine (28.0 mL, 270 mmol) was cooled to 0 °C and $TiCl_4$ (2.7 mL, 24.6 mmol) was added dropwise and the resulting suspension was left to stir for further 30 minutes followed by stirring the reaction mixture at room temperature for further 24 hours. After this time, the flask was opened to air and water-saturated diethyl ether (27 mL) was added. The solution was filtered and volatiles were removed *in vacuo*. The product was purified by Kugelrohr distillation (oven T = 58 °C, 0.9 mbar) to afford the desired enamine (2.913 g, 15.1 mmol, 34%) as a pale yellow liquid.

$^{1}$H NMR (300 MHz, $C_6D_6$, 298 K): $\delta_H$ = 7.35 – 7.25 (2H, m, 6-H), 6.85 – 6.73 (2H, m, 7-H), 4.31 (1H, s, one of 2-H), 4.14 (1H, s, one of 2-H), 2.79 (4H, q, $^{3}J_{HH}$ = 7.0 Hz, 3-H), 0.87 (6H, t, $^{3}J_{HH}$ = 7.0 Hz, 4-H).

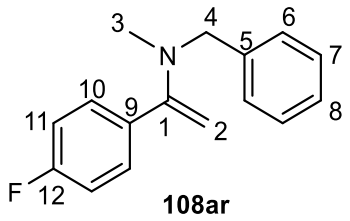
$^{13}$C NMR (125.7 MHz, $C_6D_6$, 298 K): $\delta_C$ = 162.6 (d, $^{1}J_{CF}$ = 246.0 Hz, 8-C), 153.6 (s, 1-C), 137.1 (d, $^{4}J_{CF}$ = 3.0 Hz, 5-C), 129.5 (d, $^{3}J_{CF}$ = 8.0 Hz, 6-C), 114.8 (d, $^{2}J_{CF}$ = 21.5 Hz, 7-C), 91.3 (s, 2-C), 43.0 (s, 3-C), 11.2 (s, 4-C).

$^{19}$F{$^{1}$H} NMR (125.0 MHz, $CDCl_3$, 298 K): $\delta_F$ = – 115.0 (s).

MS ($ES^+$) *m/z*: 194.13 ($[MH]^+$, 100%); Found($ES^+$) 194.1333 ($[MH]^+$), $C_{12}H_{17}FN^+$ requires 194.1340.

IR (neat) *v*, $cm^{-1}$: 2973, 1610, 1519, 1384, 1222, 1093.

*N*-benzyl-1-(4-fluorophenyl)-*N*-methylethen-1-amine (**108ar**)



**108ar**

A hexane solution (120 mL) of 1-(4-fluorophenyl)ethan-1-one (5.2 mL, 42.8 mmol) and *N*-methylbenzylamine (33.1 mL, 256 mmol) was cooled to 0 °C and $TiCl_4$ (2.6 mL, 23.7 mmol) was added dropwise and the resulting suspension was left to stir for further 30 minutes followed by stirring the reaction mixture at room temperature for further 24 hours. After this time, the flask was opened to air and water-saturated diethyl ether (26 mL) was added. The solution was filtered and volatiles were removed *in vacuo*. The product was purified by distilling impurities of using Kugelrohr (oven T = 95 °C, 1.4 mbar) to afford the desired enamine (5.928 g, 24.3 mmol, 57%) as very viscous brown oil.

$^1$H NMR (300 MHz, $C_6D_6$, 298 K): $\delta_H$ = 7.44 – 7.36 (2H, m, 10-H), 7.23 – 7.08 (5H, m, 6-H, 7-H and 8-H), 6.84 – 6.74 (2H, m, 11-H), 4.32 (1H, s, one of 2-H), 4.16 (1H, s, one of 2-H), 3.81 (2H, s, 4-H), 2.41 (3H, s, 3-H).

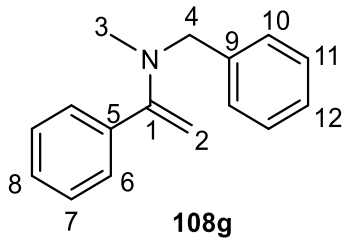
$^{13}$C{$^1$H} NMR (126 MHz, $CDCl_3$, 298 K): $\delta_C$ = 162.5 (d, $^1J_{CF}$ = 246 Hz, 12-C), 155.6 (s, 1-C), 138.5 (s, 5-C), 136.0 (d, $^4J_{CF}$ = 3.0 Hz, 9-C), 129.5 (d, $^3J_{CF}$ = 8.2 Hz, 10-C), 128.2 (s, one of 6-C, 7-C or 8-C), 127.8 (s, one of 6-C, 7-C or 8-C), 126.9 (s, one of 6-C, 7-C or 8-C), 115.0 (d, $^2J_{CF}$ = 20.9 Hz, 11-C), 90.4 (s, 2-C), 56.7 (s, 4-C), 37.9 (s, 3-C).

$^{19}$F{$^1$H} NMR (282 MHz, $C_6D_6$, 298 K): $\delta_F$ = -114.4 (s).

MS ($ES^+$) *m/z*: 242.13 ($[MH]^+$, 100%); Found($ES^+$) 242.1336 ($[MH]^+$), $C_{16}H_{17}FN^+$ requires 242.1340.

IR (neat) *v*, $cm^{-1}$: 3028, 2799, 1601, 1506, 1366, 1219, 1153.

*N*-benzyl-*N*-methyl-1-phenylethenamine (**108g**)[73]



**108g**

A toluene solution (120 mL) of freshly distilled acetophenone (7.5 mL, 64.3 mmol) and freshly distilled *N*-benzyl-*N*-methylamine (50.0 mL, 387 mmol) was cooled to 0 °C and $TiCl_4$ (3.9 mL,

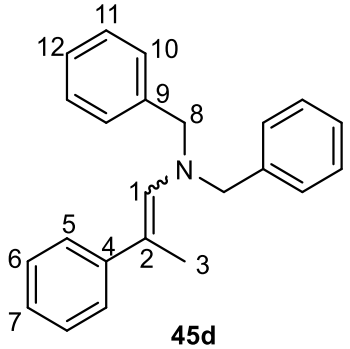
35.6 mmol) was added dropwise. The resulting mixture was warmed to room temperature and left to stir for 24 hours. After this time, the solution filtered, solvent was removed *in vacuo*, and the product was purified by removing any remaining starting materials by distillation under the reduced pressure (90 °C, 1.4 mbar) to afford a pale orange-yellow oil (8.473 g, 59%).

$^{1}$H NMR (300 MHz, $C_6D_6$, 298 K): $\delta_H$ = 7.35 – 7.29 (2H, m, 6-H), 6.92 – 6.74 (8H, m, 7-H, 8-H, 10-H, 11-H and 12-H), 4.12 (1H, s, 2-H), 3.89 (1H, s, 2-H), 3.56 (2H, s, 4-H), 2.13 (3H, s, 3-H).

$^{13}$C NMR (75 MHz, $CDCl_3$, 298 K): $\delta_C$ = 156.9 (s, 1-C), 140.3 (s, 5-C), 138.9 (s, 9-C), 128.5 – 128.0 (m, 6-C, 7-C, 8-C, 10-C, 11-C and 12-C), 90.4 (s, 2-C), 57.0 (s, 4-C), 38.1 (s, 3-C).

MS (ES$^+$) *m/z*: 224.14 ([MH]$^+$, 100%), 122.10 ([$MH_2 - C_8H_7$]$^+$, 70), 91.05 ([$C_7H_7$]$^+$, 41).

*N*,*N*-dibenzyl-2-phenylprop-1-en-1-amine – *E*:*Z* mixture of 89:11 (**45d**)[130]



**45d**

A toluene solution (100 mL) of dibenzyl amine (13.0 mL, 67.6 mmol) and 2-phenylpropionaldehyde (9.5 mL, 70.9 mmol) was heated under reflux while water was constantly removed by Dean-Stark apparatus. After 4 hours, the solution was cooled to room temperature and the product was purified by removing any remaining starting materials by distillation under reduced pressure (115 °C, 1.4 mbar) to afford a yellow viscous oil (19.291 g, 91%) as a 89/11 *E*/*Z* mixture.

*E*-isomer (major)

$^{1}$H NMR (300 MHz, $C_6D_6$, 298 K): $\delta_H$ = 7.31-7.23 (H, m, Ar-H)*, 7.21 – 7.02 (H, m, Ar-H)*, 6.26-6.23 (1H, m, 1-H), 3.87 (4H, s, 8-H), 2.08 (3H, d, $^{4}J_{HH}$ = 1.2 Hz, 3-H).

* - The two multiplets integrate to 15H together. It is impossible to make certain assignments due to overlapping signals from the both geometric isomers.

$^{13}$C NMR (75 MHz, $C_6D_6$, 298 K): $\delta_C$ = 143.4 (s, 4-C or 9-C), 139.6 (s, 4-C or 9-C), 138.9 (s, Ar-C), 128.8 (s, Ar-C), 129.1-127.1 (m, Ar-C), 125.8 (s, Ar-C), 121.0 (s, 2-C), 58.2 (s, 8-C), 15.9 (s, 3-C).

*Z*-isomer (minor)

$^{1}$H NMR (300 MHz, $C_6D_6$, 298 K): $\delta_H$ = 7.47-7.43 (2H, m, Ar-H), 7.31-7.23 (m, Ar-H)**, 7.21 – 7.02 (m, Ar-H)**, 5.95-5.93 (1H, m, 1-H), 3.78 (4H, s, 8-H), 1.93 (3H, d, $^{4}J_{HH}$ = 1.2 Hz, 3-H).

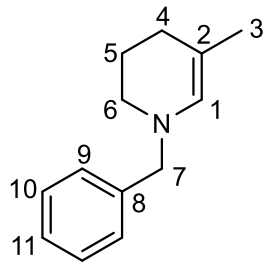
** - together integrate to 13H.

$^{13}$C NMR (75 MHz, $C_6D_6$, 298 K): $\delta_C$ = 129.1-127.1 (m, 1-C and Ar-C), 57.1 (s, 8-C), 23.2 (s, 3-C).***

*** - no quarternary carbons observed (most likely due to low concentration of minor isomer)

MS ($ES^+$) *m/z* (of the mixture): 314.19 ($[MH]^+$, 100%), 198.13 ($[(C_7H_7)_2NH_2]^+$, 86); Found($ES^+$) 314.1895 ($[MH]^+$), $C_{23}H_{24}N^+$ requires 314.1903.

Synthesis of 1-benzyl-5-methyl-1,2,3,4-tetrahydropyridine (**108as**).[88]




**108as**

A flask was purged 3 times with vacuum / argon cycles and charged with a toluene solution of [Rh(acac)$(CO)_2$] (4.0 mL, 8 mM, containing 32.0 μmol of [Rh(acac)$(CO)_2$]) followed by toluene solution of BOBPHOS ligand (4.0 mL, 10 mM, containing 40.0 μmol of the ligand). This was left to stir for 10 minutes and toluene solution of *N*-benzylpent-4-en-1-amine (8.0 mL, 1 M, contains 8.0 mmol of *N*-benzylpent-4-en-1-amine) was added. The flask was charged to the high pressure autoclave, the autoclave was purged with syngas (1:1 mixture) 3 times, pressurised with syngas (10 bar), heated to 50 $^{o}$C and left to stir for 16 hours. After this time, the vessel was cooled to room temperature, the pressure was released and a $^{1}$H NMR of the crude solution was acquired in order to calculate the conversion. The product was isolated by Kugelrohr distillation (oven T = 110 $^{o}$C, 1.5 mbar) as a pale yellow liquid (0.900 g, 4.81 mmol, 60%).

$^{1}$H NMR (300 MHz, $CDCl_3$, 298 K): $\delta_H$ = 7.32-7.10 (5H, m, 9-H, 10-H and 11-H), 5.67 (1H, br s, 1-H), 3.77 (2H, s, 7-H), 2.70-2.62 (2H, m, 6-H), 1.91-1.71 (4H, m, 4-H and 5-H), 1.52 (3H, s, 3-H).

$^{13}$C NMR (75 MHz, $CDCl_3$, 298 K): $\delta_C$ = 139.2 (s, 8-C), 131.8 (s, 1-C), 128.8 (s, Ar-C), 128.7 (s, Ar-C), 127.4 (s, Ar-C), 107.4 (s, 2-C), 60.4 (s, 7-C), 47.8 (s, 6-C), 27.1 (s, Alk-C), 23.1 (s, Alk-C), 21.4 (s, 3-C).

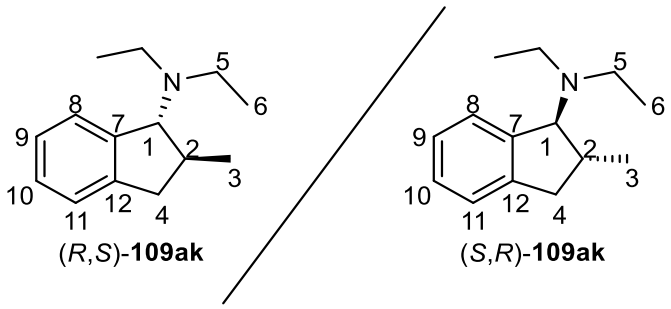
MS ($ES^+$) *m/z*: 188.14 ($[MH]^+$, 100%), 176.14 ($[M – CH]^+$, 26), 91.05 ($[C_7H_7]^+$, 23).

General experimental for isolation of amines after catalytic hydrogenation.

After completion of catalytic run, sample was diluted with toluene (8 mL) and the amine extracted with an aqueous HCl (1M, 3 x 10 mL). The resulting acidic solution was basified with an aqueous NaOH solution (1M) to the pH = 12, extracted with ethyl acetate (2 x 25 mL) and the organic layer dried over $MgSO_4$. The solution was filtered and the solvent removed *in vacuo* to afford the desired product.

In case when chiral catalyst was used, optical rotation was measured after isolation of the amine. In all cases, the values measured were consistent with the assignment of the enantiomer by NMR.

*N*,*N*-diethyl-2-methyl-2,3-dihydro-1*H*-inden-1-amine (**109ak**) – only single diastereomer is observed – determined by NMR




(*R*,*S*)-**109ak** (*S*,*R*)-**109ak**

The product is a pale-yellow oil (33 mg, 0.162 mol, 65%) – (experiment shown on page 89, Scheme 4.3.).

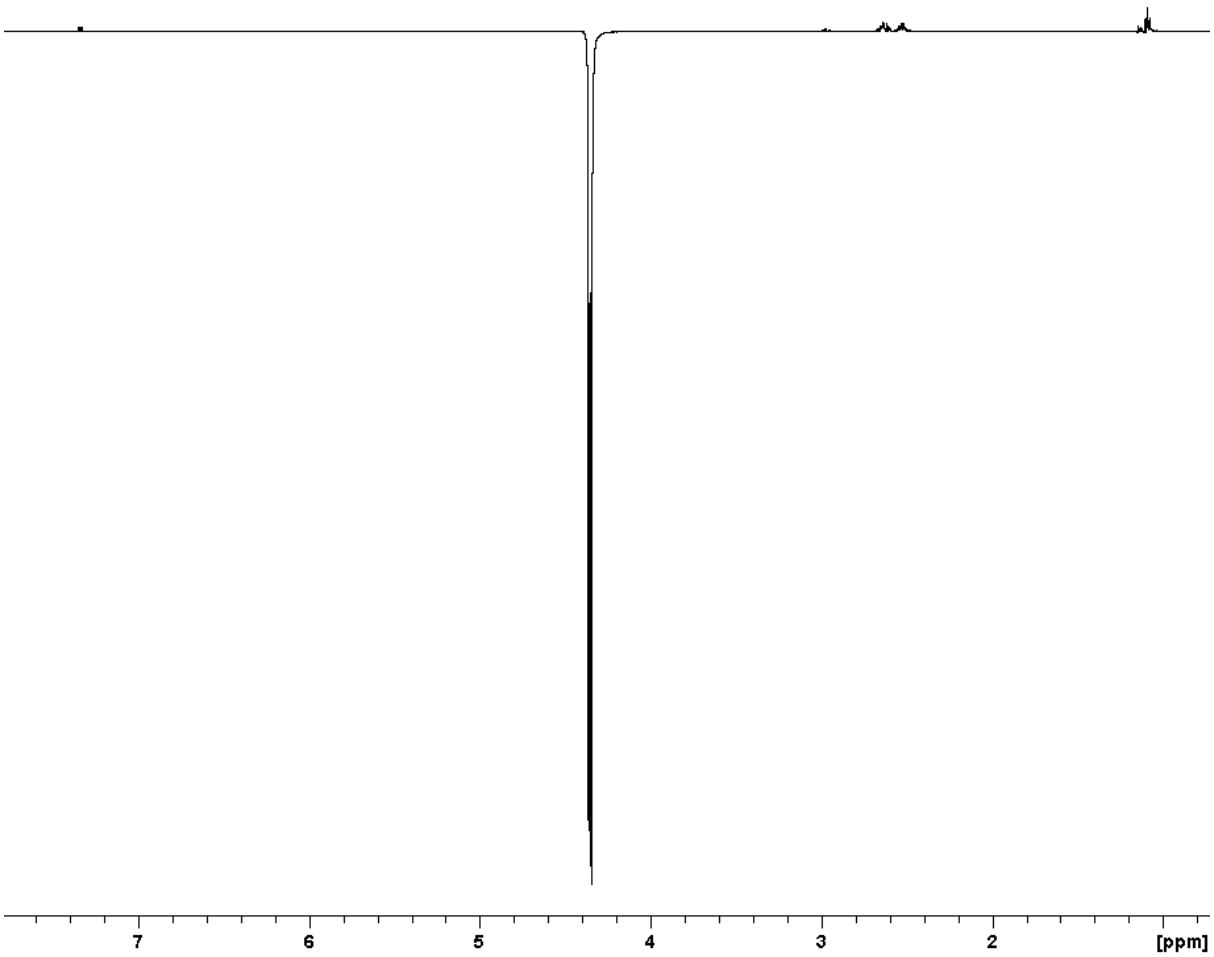
$^1$H NMR (500 MHz, $CDCl_3$, 298 K): $\delta_H$ = 7.35 – 7.31 (1H, m, 8-H or 11-H), 7.24 – 7.17 (3H, m, Ar-H), 4.35 (1H, d, $^3J_{HH}$ = 7.8 Hz, 1-H), 3.02 – 2.94 (1H, m, one of 4-H), 2.70 – 2.58 (2H, m, 2-H and one of 4-H), 2.58 – 2.47 (4H, m, 5-H), 1.13 (3H, d, $^3J_{HH}$ = 6.9 Hz, 3-H), 1.09 (6H, t, $^3J_{HH}$ = 7.1 Hz, 6-H).

$^{13}$C NMR (126 MHz, $CDCl_3$, 298 K): $\delta_C$ = 143.8 (s, 7-C or 12-C), 143.5 (s, 7-C or 12-C), 126.9 (s, Ar-CH), 125.8 (s, Ar-CH), 125.5 (s, Ar-CH), 124.8 (s, Ar-CH), 67.1 (s, 1-C), 45.5 (s, 5-C), 40.1 (s, 4-C), 38.1 (s, 2-C), 15.9 (s, 3-C), 14.8 (s, 6-C).

MS ($ES^+$) *m/z*: 204.17 ($[MH]^+$, 73%), 131.09 ($[M - NEt_2]^+$, 100); Found($ES^+$) 204.1747 ($[MH]^+$), $C_{14}H_{22}N^+$ requires 204.1747.

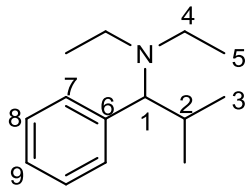
IR (neat) *v*, $cm^{-1}$: 2986, 2843, 1452, 1391, 1073.

1D gs-NOESY spectrum of the molecule where the environment at 4.35 ppm was irradiated is shown on the next page.




As expected, the irradiated environment has a much stronger correlation to one of the protons from environment 4-H than to another one. Although environments 1-H and 2-H are close to each other, the correlation is fairly weak. It is also clear that it has a strong correlation with the methyl group (environment 3-H), which could only happen if proton 1-H and the methyl group (3-H) are pointing in the same direction.

*N*,*N*-diethyl-2-methyl-1-phenylpropan-1-amine (**109am**)




**109am**

The product is a pale-yellow oil (152 mg, 0.740 mmol, 74%).

$^{1}$H NMR (300 MHz, $CDCl_3$, 298 K): $\delta_H$ = 7.34 – 7.19 (3H, m, 8-H and 9-H), 7.17 – 7.11 (2H, m, 7-H), 3.22 (1H, d, $^{3}J_{HH}$ = 9.5 Hz, 1-H), 2.70 – 2.55 (2H, m, 4-H), 2.30 – 2.16 (1H, m, 2-H), 2.15

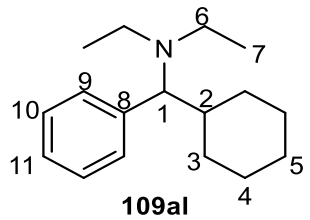
– 2.01 (2H, m, 4-H), 1.06 – 0.98 (9H, m, 5-H and one of the 3-H), 0.70 (3H, d, $^{3}J_{HH}$ = 6.5 Hz, one of the 3-H).

$^{13}$C NMR (75 MHz, $CDCl_3$, 298 K): $\delta_C$ = 138.9 (6-C), 129.2 (s, 7-C), 127.5 (s, 8-C), 126.4 (s, 9-C), 70.6 (s, 1-C), 42.7 (s, 4-C), 28.6 (s, 2-C), 20.9 (s, one of 3-C), 20.1 (s, one of 3-C), 13.3 (s, 5-C).

MS ($ES^+$) *m/z*: 206.19 ($[MH]^+$, 100%), 133.10 ($[M – NEt_2]^+$, 21); Found($ES^+$) 206.1901 ($[MH]^+$), $C_{14}H_{24}N^+$ requires 206.1903.

IR (neat) *v*, $cm^{-1}$: 2966, 2812, 1450, 1381, 1051.

*N*-(cyclohexyl(phenyl)methyl)-*N*-ethylethanamine (**109al**)



**109al**

Since conversion was only 67%, after an acid-base work-up the amine was obtained as a 2:1 mixture with enamine (due to high stability of enamine, it was not hydrolysed). The mixture was dissolved in ethyl acetate and passed through a short column of silica (eluting solvent is EtOAc : Petroleum ether (40-60) : $Et_3N$ as 1 : 3 : 0.08 mixture). This allowed all of the remaining enamine to form some new unidentified compounds. The solvents were removed under reduced pressure and the mixture was purified by a silica column (eluting solvent is EtOAc : Petroleum ether (40-60) : $Et_3N$ as 1 : 14 : 0.08 mixture; $R_f$ = 0.13) to afford the desired amine (77 mg, 0.315 mmol, 32% overall yield) as a colourless viscous oil.

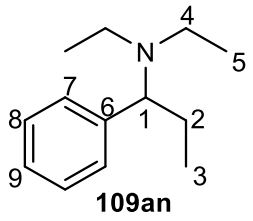
$^{1}$H NMR (400 MHz, $CDCl_3$, 298 K): $\delta_H$ = 7.36 – 7.22 (3H, m, Ar-H), 7.19 – 7.13 (2H, m, Ar-H), 3.37 (1H, d, $^{3}J_{HH}$ = 9.7 Hz, N-CH), 2.71 – 2.60 (2H, m, N-$CH_2$), 2.20 – 2.05 (3H, m,CH and N-$CH_2$), 1.98 – 1.87 (1H, m, one of $CH_2$), 1.85 – 1.76 (1H, m, one of $CH_2$), 1.72 – 1.60 (2H, m, $CH_2$), 1.47 – 1.12 (4H, m, 2 x $CH_2$), 1.05 (6H, t, $^{3}J_{HH}$ = 7.1 Hz, 2 x $CH_3$), 1.00 – 0.87 (1H, m, one of $CH_2$), 0.82 – 0.70 (1H, m, one of $CH_2$).

$^{13}$C NMR (101 MHz, $CDCl_3$, 298 K): $\delta_C$ = 138.7 ($^{Ar}$C), 129.2 (s, $^{Ar}$CH), 127.5 (s, $^{Ar}$CH), 126.4 (s, $^{Ar}$CH), 69.3 (s, N-CH), 42.8 (s, N-$CH_2$), 38.3 (s, CH), 31.2 (s, $CH_2$), 30.8 (s, $CH_2$), 26.9 (s, $CH_2$), 26.4 (s, $CH_2$), 26.3 (s, $CH_2$), 13.4 (s, $CH_2$-$CH_3$).

MS ($ES^+$) *m/z*: 246.22 ($[MH]^+$, 100%), 173.13 ($[M - NEt_2]^+$, 84); Found($ES^+$) 246.2207 ($[MH]^+$), $C_{17}H_{28}N^+$ requires 246.2216.

IR (neat) *v*, $cm^{-1}$: 2972, 2783, 1492, 1448, 1159.

*N*,*N*-diethyl-1-phenylpropan-1-amine (**109an**)[131]



**109an**

The product is a pale-yellow oil (174 mg, 0.909 mmol, 91%).

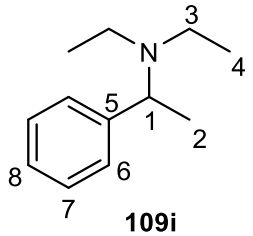
$^1$H NMR (300 MHz, $CDCl_3$, 298 K): $\delta_H$ = 7.34 – 7.19 (5H, m, Ar-H), 3.51 (1H, dd, $^3J_{HH}$ = 9.5 Hz, $^3J_{HH}$ = 5.1 Hz, N-CH), 2.72 – 2.58 (2H, m, N-$CH_2$), 2.44 – 2.29 (2H, m, N-$CH_2$), 2.00 – 1.84 (1H, m, one from $CH_2$), 1.80 – 1.63 (1H, m, one from $CH_2$), 1.00 (6H, t, $^3J_{HH}$ = 7.1 Hz, 2 x N-$CH_2$-$CH_3$), 0.76 (3H, t, $^3J_{HH}$ = 7.3 Hz, $CH_3$).

$^{13}$C NMR (101 MHz, $CDCl_3$, 298 K): $\delta_C$ = 141.8 ($^{Ar}$C), 128.7 (s, $^{Ar}$CH), 127.9 (s, $^{Ar}$CH), 126.6 (s, $^{Ar}$CH), 66.5 (s, N-CH), 43.1 (s, N-$CH_2$), 25.8 (s, CH), 12.5 (s, N-$CH_2$-$CH_3$), 11.4 (s, $CH_3$).

MS ($ES^+$) *m/z*: 192.17 ($[MH]^+$, 100%); Found($ES^+$) 192.1747 ($[MH]^+$), $C_{13}H_{22}N^+$ requires 192.1747.

IR (neat) *v*, $cm^{-1}$: 2966, 2810, 1450, 1379, 1196, 1051.

*N*,*N*-diethyl-1-phenylethanamine (**109i**)[73]



**109i**

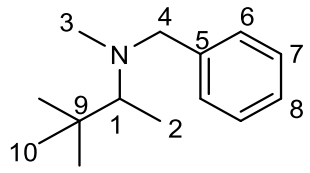
Isolated by the procedure described above as a yellow oil (148 mg, 0.835 mmol, 83% yield).

$^1$H NMR (300 MHz, $CDCl_3$, 298 K): $\delta_H$ = 7.31 – 7.07 (5H, m, 6-H, 7-H and 8-H), 3.70 (1H, q, $^3J_{HH}$ = 6.7 Hz, 1-H), 2.57 – 2.33 (4H, m, 3-H), 1.25 (3H, d, $^3J_{HH}$ = 6.7 Hz, 2-H), 0.90 (6H, t, $^3J_{HH}$ = 7.1 Hz, 4-H).

$^{13}$C NMR (75 MHz, $CDCl_3$, 298 K): $\delta_C$ = 145.3 (s, 5-C), 128.1 (s, Ar-CH), 127.6 (s, Ar-CH), 126.5 (s, 8-C), 59.2 (s, 1-C), 42.9 (s, 3-C), 18.5 (s, 2-C), 12.2 (s, 4-C).

MS ($ES^+$) *m/z*: 178.16 ($[MH]^+$, 86%), 105.07 ($[M - NEt_2]^+$, 100); Found($ES^+$) 178.1586 ($[MH]^+$), $C_{12}H_{20}N^+$ requires 178.1590.

*N*-benzyl-*N*,3,3-trimethylbut-1-en-2-amine (**109ap**)[77]




**109ap**

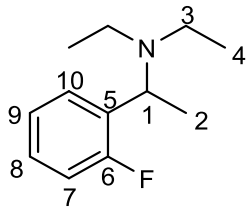
Isolated by the procedure described above as a pale-yellow oil (146 mg, 0.711 mmol, 71%)

$^1$H NMR (300 MHz, $CDCl_3$, 298 K): $\delta_H$ = 7.34 – 7.10 (5H, m, 6-H, 7-H and 8-H), 3.65 (1H, q, $^2J_{HH}$ = 13.8 Hz, one of 4-H), 3.33 (1H, q, $^2J_{HH}$ = 13.8 Hz, one of 4-H), 2.33 (1H, q, $^3J_{HH}$ = 7.0 Hz, 1-H), 2.07 (3H, s, 3-H), 0.92 (3H, d, $^3J_{HH}$ = 7.0 Hz, 2-H), 0.86 (9H, s, 10-H).

$^{13}$C NMR (75 MHz, $CDCl_3$, 298 K): $\delta_C$ = 141.1 (s, 5-C), 128.4 (s, 6-C or 7-C), 128.0 (s, 6-C or 7-C), 126.5 (s, 8-C), 66.9 (s, 1-C), 60.2 (s, 4-C), 40.0 (s, 3-C), 36.3 (s, 9-C), 27.5 (s, 10-C), 7.3 (s, 2-C).

MS ($ES^+$) *m/z*: 206.19 ($[MH]^+$, 100%); Found($ES^+$) 206.1898 ($[MH]^+$), $C_{14}H_{24}N^+$ requires 206.1903.

*N*,*N*-diethyl-1-(2-fluorophenyl)ethan-1-amine (**108ao**)




**108ao**

The product is a pale-yellow oil (107 mg, 0.548 mmol, 55%).

$^1$H NMR (300 MHz, $CDCl_3$, 298 K): $\delta_H$ = 7.48 – 7.40 (1H, m, 10-H), 7.23 – 7.14 (1H, m, 8-H), 7.13 – 7.06 (1H, m, 9-H), 7.04 – 6.95 (1H, m, 7-H), 4.19 (1H, q, $^3J_{HH}$ = 6.8 Hz, 1-H), 2.70 – 2.43 (4H, m, 3-H), 1.35 (3H, d, $^3J_{HH}$ = 6.8 Hz, 2-H), 1.00 (6H, t, $^3J_{HH}$ = 7.1 Hz, 4-H).

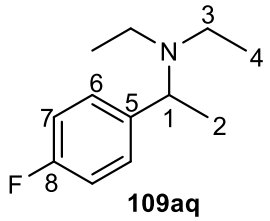
$^{19}$F{$^1$H} NMR (282 MHz, $CDCl_3$, 298 K): $\delta_F$ = -119.1 (s).

$^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$, 298 K): $\delta_C$ = 160.8 (d, $^{1}J_{CF}$ = 245 Hz, 6-C), 131.6 (d, $^{2}J_{CF}$ = 13.6 Hz, 5-C), 128.7 (d, $^{3}J_{CF}$ = 4.9 Hz, 10-C), 127.8 (d, $^{3}J_{CF}$ = 8.4 Hz, 8-C), 123.8 (d, $^{4}J_{CF}$ = 3.5 Hz, 9-C), 115.1 (d, $^{2}J_{CF}$ = 23.3 Hz, 7-C), 51.8 (s, 1-C), 42.8 (s, 3-C), 19.2 (s, 2-C), 11.8 (s, 4-C).

MS ($ES^+$) *m/z*: 196.15 ($[MH]^+$, 100%), 123.06 ($[M - NEt_2]^+$, 40); Found($ES^+$) 196.1492 ($[MH]^+$), $C_{12}H_{20}N^+$ requires 196.1496.

IR (neat) *v*, $cm^{-1}$: 2951, 2789, 1452, 1360, 1094, 1011.

*N*,*N*-diethyl-1-(4-fluorophenyl)ethan-1-amine (**109aq**)




**109aq**

The product is a pale-yellow oil (111 mg, 0.568 mmol, 57%).

$^{1}H$ NMR (300 MHz, $CDCl_3$, 298 K): $\delta_H$ = 7.36 – 7.27 (2H, m, 6-H), 7.03 – 6.92 (2H, m, 7-H), 3.77 (1H, q, $^{3}J_{HH}$ = 6.8 Hz, 1-H), 2.62 – 2.40 (4H, m, 3-H), 1.30 (3H, d, $^{3}J_{HH}$ = 6.7 Hz, 2-H), 0.98 (6H, t, $^{3}J_{HH}$ = 7.1 Hz, 4-H).

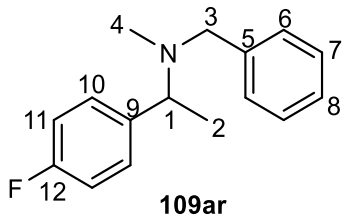
$^{19}F\{^{1}H\}$ NMR (282 MHz, $CDCl_3$, 298 K): $\delta_F$ = - 117.4.

$^{13}C\{^{1}H\}$ NMR (75.5 MHz, $CDCl_3$, 298 K): $\delta_C$ = 161.6 (d, $^{1}J_{CF}$ = 243.8 Hz, 8-C), 141.0 (d, $^{4}J_{CF}$ = 3.1 Hz, 5-C), 128.9 (d, $^{3}J_{CF}$ = 7.7 Hz, 6-C), 114.7 (d, $^{2}J_{CF}$ = 21.0 Hz, 7-C), 58.4 (s, 1-C), 42.7 (s, 3-C), 18.2 (s, 2-C), 12.1 (s, 4-C).

MS ($ES^+$) *m/z*: 196.15 ($[MH]^+$, 100%), 123.06 ($[M - NEt_2]^+$, 16); Found($ES^+$) 196.1492 ($[MH]^+$), $C_{12}H_{20}N^+$ requires 196.1496.

IR (neat) *v*, $cm^{-1}$: 2968, 2810, 1602, 1506, 1221, 1074.

*N*-benzyl-1-(4-fluorophenyl)-*N*-methylethan-1-amine (**109ar**)[132]



**109ar**

The product is a very viscous yellow oil (214 mg, 0.879 mmol, 88%).

$^{1}$H NMR (300 MHz, $CDCl_3$, 298 K): $\delta_H$ = 7.34 – 7.10 (7H, m, 6-H, 7-H, 8-H and 10-H), 7.00 – 6.89 (2H, m, 11-H), 3.55 (1H, q, $^{3}J_{HH}$ = 6.7 Hz, 1-H), 3.47 (1H, d, $^{2}J_{HH}$ = 13.3 Hz, one of 3-H), 3.23 (1H, d, $^{2}J_{HH}$ = 13.3 Hz, one of 3-H), 2.04 (3H, s, 4-H), 1.32 (3H, d, $^{3}J_{HH}$ = 6.7 Hz, 2-H).

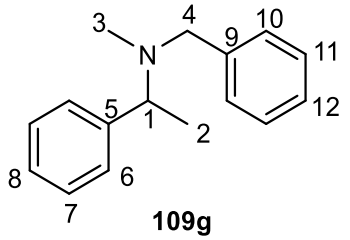
$^{13}$C NMR (75 MHz, $CDCl_3$, 298 K): $\delta_C$ = 161.7 (d, $^{1}J_{CF}$ = 244 Hz, 12-C), 140.0-139.8 (m, 5-C and 9-C), 129.0 (d, $^{3}J_{CF}$ = 7.8 Hz, 10-C), 128.7 (s, 6-C or 7-C), 128.2 (s, 6-C or 7-C), 126.8 (s, 8-C), 114.9 (d, $^{2}J_{CF}$ = 21.0 Hz, 11-C), 62.3 (s, 1-C), 58.7 (s, 3-C), 38.2 (s, 4-C), 18.1 (s, 2-C).

$^{19}$F{$^{1}$H} NMR (282 MHz, $CDCl_3$, 298 K): $\delta_F$ = -116.9 (s).

MS ($ES^+$) *m/z*: 244.15 ($[MH]^+$, 100%); Found($ES^+$) 244.1488 ($[MH]^+$), $C_{16}H_{19}FN^+$ requires 244.1496.

IR (neat) *ν*, $cm^{-1}$: 2972, 2785, 1601, 1506, 1494, 1452, 1219, 1153.

*N*-benzyl-*N*-methyl-1-phenylethanamine (**109g**)[73]



**109g**

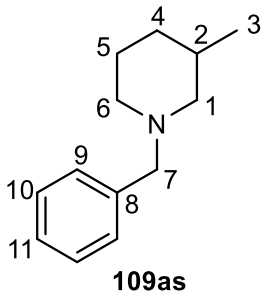
Isolated by the procedure described above as a yellow oil (206 mg, 0.914 mmol, 91% yield).

$^{1}$H NMR (300 MHz, $CDCl_3$, 298 K): $\delta_H$ = 7.36 – 7.09 (10H, m, 6-H, 7-H, 8-H, 10-H,11-H and 12-H), 3.55 (1H, q, $^{3}J_{HH}$ = 6.7 Hz, 1-H), 3.49 (1H, d, $^{2}J_{HH}$ = 13.2 Hz, 4-H), 3.21 (1H, d, $^{2}J_{HH}$ = 13.2 Hz, 4-H), 2.05 (3H, s, 3-H), 1.33 (3H, d, $^{3}J_{HH}$ = 6.7 Hz, 2-H).

$^{13}$C NMR (75 MHz, $CDCl_3$, 298 K): $\delta_C$ = 144.6 (s, 5-C), 140.5 (s, 9-C), 129.2 (s, Ar-C), 128.7 (2 x C, s, Ar-C), 128.2 (s, Ar-C), 127.3 (s, Ar-C), 127.2 (s, Ar-C), 63.7 (s, 1-C) , 59.3 (s, 4-C) , 38.8 (s, 3-C) , 18.9 (s, 2-C).

MS ($ES^+$) *m/z*: 226.16 ($[MH]^+$, 100%).

1-benzyl-3-methylpiperidine (**109as**)[88]




**109as**

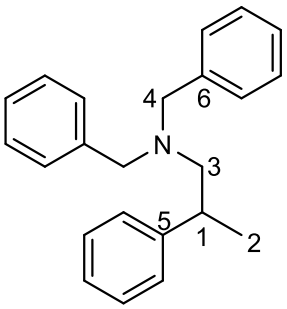
The product is a yellow oil (140 mg, 0.740 mmol, 74% yield).

$^{1}$H NMR (300 MHz, $CDCl_3$, 298 K): $\delta_H$ = 7.27 – 7.02 (5H, m, 9-H, 10-H and 11-H), 3.38 (2H, s, 7-H), 2.76 – 2.64 (2H, m, one from 1-H, and one from 6-H), 1.82 – 1.70 (1H, m, Alk-H), 1.65 – 1.41 (5H, m, Alk-H), 0.84 – 0.67 (1H, m, one from 4-H), 0.74 (3H, d, $^{3}J_{HH}$ = 6.2 Hz, 3-H).

$^{13}$C{$^{1}$H} NMR (75.5 MHz, $CDCl_3$, 298 K): $\delta_C$ = 138.8 (s, 8-C), 129.7 (s, Ar-C), 128.6 (s, Ar-C), 127.4 (s, Ar-C), 64.0 (s, 7-C), 62.3 (s, 1-C or 6-C), 54.4 (s, 1-C or 6-C), 33.4 (s, 4-C), 31.5 (s, 2-C), 25.9 (s, 5-C), 20.2 (s, 3-C).

MS ($ES^+$) *m/z*: 190.16 ($[MH]^+$, 100%); Found($ES^+$) 190.1587 ($[MH]^+$), $C_{13}H_{20}N^+$ requires 190.1590.

*N*,*N*-dibenzyl-2-phenylpropan-1-amine (**45g**)[133]




**45g**

The product is a very viscous yellow oil (215 mg, 0.682 mmol, 68% yield). (Note – contains traces of dibenzylamine).

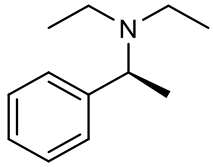
$^{1}$H NMR (500 MHz, $CDCl_3$, 298 K): $\delta_H$ = 7.32 – 7.20 (13H, m, Ar-H), 7.12 – 7.08 (2H, m, Ar-H), 3.62 – 3.53 (4H, m, 4-H), 3.08 – 3.00 (1H, m, 1-H), 2.63 – 2.49 (2H, m, 3-H), 1.25 (3H, d, $^{3}J_{HH}$ = 6.9 Hz, 2-H).

$^{13}$C{$^{1}$H} NMR (126 MHz, $CDCl_3$, 298 K): $\delta_C$ = 146.0 (s, 5-C), 139.7 (s, 6-C), 128.8 (s, Ar-CH), 128.2 (s, Ar-CH), 128.1 (s, Ar-CH), 128.0 (s, Ar-CH), 127.4 (s, Ar-CH), 126.7 (s, Ar-CH), 126.0 (s, Ar-CH), 61.5 (s, 3-C), 58.7 (s, 4-C), 38.0 (s, 1-C), 19.8 (s, 2-C).

GC-MS ($ES^+$) *m/z*: 210.09 ([MH – $C_8H_9$]+, 100%), 91.01 ([$C_7H_7$]+, 95).

Synthesis of enantiopure amines

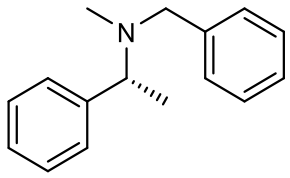
Synthesis of (*S*)-*N*,*N*-diethyl-1-phenylethanamine ((*S*)-**109i**) (prepared according to modified literature procedure)[103]



(*S*)-**109i**

To a suspension of sodium carbonate (1.00 g) in ethanol (24 mL) (*S*)-1-phenylehtanamine (1.0 mL, 7.76 mmol) was added followed by dropwise addition of ethyl iodide (1.4 mL, 17.4 mmol) over 10 minutes. The resulting mixture heated to 45 $^{o}$C and left to stir overnight. After this time, ethanol was removed under reduced pressure, water (25 mL) and diethyl ether (30 mL) were added, the biphasic mixture stirred for 10 minutes, organic layer separated, dried over $MgSO_4$, solvent was removed under reduced pressure to afford a mixture of products (major product is (*S*)-*N*-ethyl-1-phenylethanamine). The desired product was isolated by silica column (EtOAc : Pet. Ether : $Et_3N$ – 1 : 1 : 0.05 as an eluting solvent, $R_f$ = 0.67) as a colourless oil (0.081 g, 6%).
$[\alpha]^{D}_{20}$ = -16.9 (*c* 1.0, $CHCl_3$).
The rest of the characterisation data ($^1$H NMR, $^{13}$C NMR and MS) matches exactly the racemic sample of the amine isolated after catalysis.

Synthesis of (*R*)-*N*-benzyl-*N*-methyl-1-phenylethanamine ((*R*)-**109g**) (prepared according to modified literature procedure)[134]



(*R*)-**109g**

To a solution of (*R*)-*N*-methyl-1-phenylethanamine (1.0 mL, 6.83 mmol) in ethanol (15 mL) benzaldehyde (0.8 mL, 7.88 mmol) was added. The resulting solution was stirred for 5 minutes and sodium acetoxyborohydride (1.732 g, 8.17 mmol) was added and the mixture was left to stir overnight. After this time, ethanol was removed under reduced pressure, the crude mixture was suspended in toluene and extracted with hydrochloric acid (1M, 3 x 25 mL). Combined acid layers were basified with aqueous NaOH (1M) to pH = 12, extracted with ethyl acetate (3 x 25 mL), the organic layers were combined and dried over $MgSO_4$. The solvent was removed under reduced pressure to afford a mixture of the desired product and *N*-methylbenzyl amine. The

desired product was isolated by silica column (EtOAc : Pet. Ether : $Et_3N$ – 1 : 3 : 0.05 as an eluting solvent) as a pale-yellow viscous oil (0.616 g, 40%).

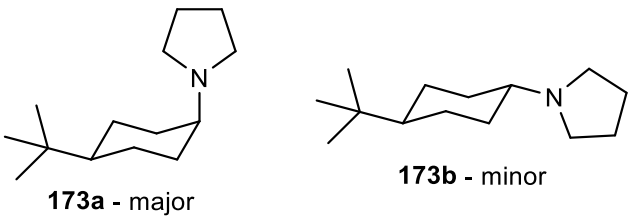
$[\alpha]_{D_{20}}$ = +25.3 (*c* 1.0, $CHCl_3$).

The rest of the characterisation data ($^1H$ NMR, $^{13}C$ NMR and MS) matches exactly the racemic sample of the amine isolated after catalysis.

Reductive amination.

A high pressure autoclave with 4 vials was used. A vial was charged with ligand **8** (3.4 mg, 8.0 μmol), sealed and purged with Ar for 10 minutes. A toluene solution of $[Rh(COD)Cl]_2$ (0.5 mL, 4 mM, containing 2.0 μmol of $[Rh(COD)Cl]_2$) was added. This was left to stir for 10 minutes before a toluene solution of 4-$^t$butyl-cyclohexanone (1.5 mL, 0.67M, contains 1.0 mmol of the ketone and 0.1 mL of 1-methylnaphthalene) followed by addition of pyrrolidine (125 μL, 1.5 mmol). After this time, the vial placed into the pre-purged autoclave, the autoclave was sealed, purged with hydrogen 3 times, pressurised with $H_2$ gas to the desired pressure, heated to 65 $^o$C and left to stir for 16 hours. After this time, the autoclave was cooled to room temperature, the gas pressure was released and $^1H$ NMR of the crude reaction solution was acquired in order to calculate the conversion (full conversion).

The solution was diluted with toluene (8 mL) and the amine was extracted with hydrochloric acid (1M, 3 x 20 mL). Combined acid fractions were basified with aq. NaOH (1M) until pH = 12, and the amine was extracted with ethyl acetate (3 x 25 mL). Combined organic fractions were washed with brine (30 mL), dried over $MgSO_4$ and solvent was removed under reduced pressure. The desired product was dried *in vacuo* for 50 minutes to afford the desired amine (148 mg, 70.7 mmol, 71%) as a pale-yellow crystalline material (this product was reported in the past, but the diastereomer was not assigned).[135]




**173a** - major **173b** - minor

d.e. > 95%

Since no signals are observed for the minor diastereoisomer in the proton NMR, only the signals for the major one are given.

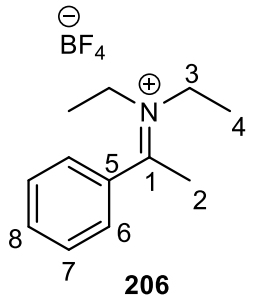
m.p. = 48 – 50 $^o$C.

$^{1}$H NMR (500 MHz, $CDCl_3$, 298 K): $\delta_H$ = 2.50 – 2.41 (4H, m, 2 x N-C$\underline{H}_2$), 1.93 – 1.87 (2H, m, N-CH-C$\underline{H}_2$), 1.74 – 1.70 (4H, m, 2 x N-CH$_2$-C$\underline{H}_2$), 1.46 – 1.27 (6H, m, 3 x C$\underline{H}_2$), 1.03 – 0.94 (1H, m, C-C$\underline{H}$), 0.82 (9H, s, 3 x C$\underline{H}_3$).

$^{13}$C{$^{1}$H} NMR (126 MHz, $CDCl_3$, 298 K): $\delta_C$ (major) = 60.1 (s, N-$\underline{C}$H), 52.0 (s, N-$\underline{C}H_2$), 48.5 (s, $\underline{C}$H), 32.6 (s, $\underline{C}$), 31.1 (s, $\underline{C}H_2$), 27.6 (s, $\underline{C}H_3$), 23.7 (s, $\underline{C}H_2$), 21.5 (s, $\underline{C}H_2$).

MS (ES$^+$) *m/z*: 210.22 ([MH]$^+$, 100%); Found(ES$^+$) 210.2207 ([MH]$^+$), $C_{14}H_{28}N^+$ requires 210.2216.

Synthesis of *N*-(1-phenylethylidene)diethylammonium tetrafluoroborate (prepared according to the literature procedure)[121]




**206**

A solution of *N*,*N*-diethyl-1-phenylethenamine (3.85 g, 22.0 mmol) in diethyl ether (40 mL) was cooled to -10 $^{o}$C and $HBF_4{\cdot}Me_2O$ (2.7 mL, 22.2 mmol) was added dropwise. The solution was left to warm to RT and left to stir overnight. After this time, the oily product settled on the bottom. The diethyl ether was removed by cannula, the oil was washed with diethyl ether (3 x 15 mL) and left to dry *in vacuo* for 4 hours to afford very viscous oily material (4.69 g, 17.8 mmol, 81%) as the desired product.

$^{1}$H NMR (400 MHz, $CDCl_3$, 298 K): $\delta_H$ = 7.54 – 7.46 (5H, m, 6-$\underline{H}$, 7-$\underline{H}$ and 8-$\underline{H}$), 4.12 (2H, q, $^{3}J_{HH}$ = 7.4 Hz, one of 3-$\underline{H}$), 3.77 (2H, q, $^{3}J_{HH}$ = 7.4 Hz, one of 3-$\underline{H}$), 2.81 (3H, s, 2-$\underline{H}$), 1.54 (3H, t, $^{3}J_{HH}$ = 7.4 Hz, one of 4-$\underline{H}$), 1.33 (3H, t, $^{3}J_{HH}$ = 7.3 Hz, one of 4-$\underline{H}$).

$^{19}$F{$^{1}$H} NMR (377 MHz, $CDCl_3$, 298 K): $\delta_F$ = -151.6 (1F, s). -151.5 (3F, s).

$^{13}$C{$^{1}$H} NMR (126 MHz, $CDCl_3$, 298 K): $\delta_C$ = 187.7 (s, 1-$\underline{C}$), 134.2 (s, 5-$\underline{C}$), 131.6 (Ar-$\underline{C}$H), 129.4 (Ar-$\underline{C}$H), 125.2 (Ar-$\underline{C}$H), 52.0 (s, one of 3-$\underline{C}$), 49.8 (s, one of 3-$\underline{C}$), 26.0 (s, 2-$\underline{C}$), 12.8 (s, one of 4-$\underline{C}$), 12.2 (s, one of 4-$\underline{C}$).

MS (ES+) *m/z*: 176.14 ([$C_{12}H_{18}N$]$^+$, 86%); Found(ES$^+$) 176.1432 ([$C_{12}H_{18}N$]$^+$), $C_{12}H_{18}N^+$ requires 176.1434.

**6.4 Other experiments.**

Experiments to rule out racemization.

In order to rule out the possibility of the racemisation of the amine during the reaction, an isolated sample of amine **108i** (61% ee of the *R*-enantiomer) was used (after the reaction shown in Table 4.1 entry 12 (page 71)). The sample of the amine was split into 4 equal portions, and subjected to the general reaction conditions of hydrogenation with catalyst (*S*,*S*)-**196b** at 65 $^{o}$C and 60 bar of hydrogen gas in toluene (in the presence and absence of iodine co-catalyst), as well as in methanol as a solvent (in the presence and absence of iodine co-catalyst). In both cases, no racemisation of the sample occurred (ees were measured of the amines directly from the solutions as was described previously in the general catalytic hydrogenation procedure). The amines were isolated in all cases by acid-base work-up and ees were measured as again. The ee values between 59% and 62% were obtained, where the *R*-enantiomer was always the major one.

Reaction of Rh-iodine dihydrogen complex with enamine **108i**

[((*R*,*R*)-Et-DuPhos)-Rh(COD)]$BF_4$ ((*R*,*R*)-**198b**) (20 mg, 30.3 μmol) and iodine (15.4 mg, 60.7 μmol) were charged into a microwave vial and the vial was flushed with argon for 10 minutes. The complex and iodine were dissolved in $CD_2Cl_2$ (0.6 mL), the vial was charged into a high pressure autoclave, the autoclave was pressurised with hydrogen gas (60 bar) and the content was left to stir for 3 hours. After this time, hydrogen pressure was released and a solution of *N*,*N*-diethyl-1-phenylethenamine (**108i**) (5.3 mg, 30.3 μmol) in $CD_2Cl_2$ (0.2 mL) was added. The resulting solution was immediately transferred to an NMR tube under argon, and $^{1}$H NMR was acquired (Chapter 4, Figure 4.12 – the bottom spectrum (on page 93)).

Exactly the same reaction was performed where no iodine was used. No iminium ion peaks are observed at all in the spectrum.

Conversion of the enamine to the iminium cation followed by conversion to the amine (Scheme 4.7 on page 94)

[((*R*,*R*)-Et-DuPhos)-Rh(COD)]$BF_4$ ((*R*,*R*)-**198b**) (10 mg, 15.1 μmol) and iodine (7.7 mg, 30.3 μmol) were charged into a microwave vial and the vial was flushed with argon for 10 minutes. The complex and iodine were dissolved in $CD_2Cl_2$ (0.6 mL). A solution of enamine **108i** (18.1 mg, 102 μmol) in $CD_2Cl_2$ (0.7 mL) was added and the vial was charged into a high pressure autoclave. The autoclave was pressurised with hydrogen gas (60 bar) and the content was left to stir for 1 hour at 25 $^{o}$C. After this time, hydrogen pressure was released and the resulting solution was transferred to a Young-tap NMR tube under hydrogen gas, and $^{1}$H NMR spectrum was

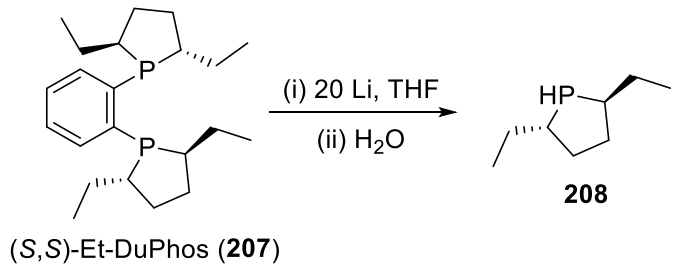
acquired. No sing of enamine was detected. The signals for the iminium ion and of amine **109i** were observed (in the ratio of 15 : 85, where the amine is the major product). The resulting solution was left to stand in the dark under atmospheric pressure of hydrogen gas over the weekend. After this time, the spectrum was acquired again, which showed that the signals for the iminium ion vanished – i.e. all the iminium ion got converted to the amine.

# 7. Appendixes.

## 7.1 Appendix A. Synthetic attempts of new phospholane ligands

### 7.1.1 Cleavage of the DuPhos ligand

Cleavage of triphenylphosphine with lithium metal is a known reaction, where the product obtained, $LiPPh_2$, can be used directly in the synthesis.[136,137] Overall, cleavage of aromatic tertiary phosphines has been shown to work well in the literature, where the resulting P-Li bond can be hydrolysed by water in order to obtain the desired secondary phosphine.[138,139] It was decided to attempt the same strategy for the cleavage of DuPhos ligand **207** in order to obtain a chiral secondary phospholane building block to be used in the synthesis of new chiral ligands. The reaction is shown in Scheme 7.1.




**Scheme 7.1.** Cleavage of ligand **207** in order to get an access to the secondary chiral phospholane unit **208**.

The reaction was performed under different conditions as described below (i.e. under different temperatures).

Attempt 1. Procedure: Small pieces of freshly-cut Li wire (109 mg, 15.7 mmol) were suspended in THF (12 mL) and the suspension was cooled to 0 $^oC$. While vigorously being stirred, a THF solution (10 mL) of ligand **207** (251 mg, 0.692 mmol) was added in portions of 1 mL every 90 seconds. The colourless solution turned to a bright yellow colour after 5 minutes. After the addition of the ligand was complete, the suspension was left to stir at 0 $^oC$ for 1 hour. After this time, the resulting red solution was heated to 55 $^oC$ and left to stir at this temperature for 1 hour. The solution was filtered, and degassed water (0.4 mL) was added. $^{31}P\{^1H\}$ NMR spectrum was acquired (Figure 7.1a – the spectrum is shown in green colour). The solution was dried over $MgSO_4$, filtered and the desired product was distilled under static vacuum. Solvent was removed under reduced pressure at -20 $^oC$ to afford the desired product (8 mg, 55.5 μmol, 8%) as a colourless liquid with a chemical shift of -41.6 ppm in $^{31}P\{^1H\}$ NMR.

Attempt 2. Procedure: Small pieces of freshly-cut Li wire (215 mg, 31.0 mmol) were suspended in THF (25 mL) and the suspension was cooled to 0 $^{o}$C. While vigorously being stirred, a THF solution (8 mL) of ligand **207** (583 mg, 1.61 mmol) was added dropwise using syringe pump over 2 hours. At the end of addition, the solution was of a red colour. After the addition of the ligand was complete, the suspension was left to stir at 0 $^{o}$C for 2 hour. After this time, the resulting red solution was warmed to RT and left to stir overnight. The solution was filtered, and degassed water (0.3 mL) was added. $^{31}P\{^{1}H\}$ NMR spectrum was acquired (Figure 7.1b – the spectrum is shown in blue colour). The solution was dried over $MgSO_4$, filtered and split into 2 equal fractions. Fraction 1 attempted to distill under dynamic vacuum into the flask at -25 $^{o}$C. Although this method is quicker and significantly reduces the chances of oxidation, the yield is very poor (9 mg, 62.4 μmol, 8%). The likely reason is that the product still travels all the way to the cold trap, and majority of it seems to skip the desired reservoir intended for its collection. Fraction 2 was distilled under static vacuum. Solvent was removed under reduced pressure at -18 $^{o}$C to afford the desired product (25 mg, 173 μmol, 22%) as a colourless liquid.

Attempt 3. Procedure: Small pieces of freshly-cut Li wire (207 mg, 29.8 mmol) were suspended in THF (25 mL) and the suspension was cooled to 0 $^{o}$C. While vigorously being stirred, a THF solution (8 mL) of ligand **207** (512 mg, 1.41 mmol) was added dropwise using syringe pump over 2 hours. The colourless solution turned to a bright yellow colour after 5 minutes. After the addition of the ligand was complete, the suspension was left to stir at 0 $^{o}$C for 5 hour. After this time, the resulting red solution was left to stir overnight, very gradually and slowly warming it from 0 $^{o}$C to RT. In the morning, the solution was filtered, and degassed water (0.5 mL) was added. $^{31}P\{^{1}H\}$ NMR spectrum was acquired (Figure 7.1c – the spectrum is shown in red colour). The solution was dried over $MgSO_4$, filtered and the desired product was distilled under static vacuum. Solvent was removed under reduced pressure at -16 $^{o}$C to afford the desired product (77 mg, 0.534 mmol, 38%) as a colourless liquid.

An example of the spectrum of the isolated product is shown in Figure 7.1 – the bottom spectrum (in black colour): $^{31}P\{^{1}H\}$ NMR (121.5 MHz, $C_6D_6$, 298 K): $\delta_P$ = -41.6 (s). In the proton-coupled $^{31}P$ NMR, a 1JPH is clearly observed. Due to 2JPH and 3JPH couplings, the peaks are multiplets, so interpreted as a doublet of multiplets: $^{31}P$ NMR (121.5 MHz, $C_6D_6$, 298 K): $\delta_P$ = -41.6 (dm, $^{1}J_{PH}$ = 188 Hz).

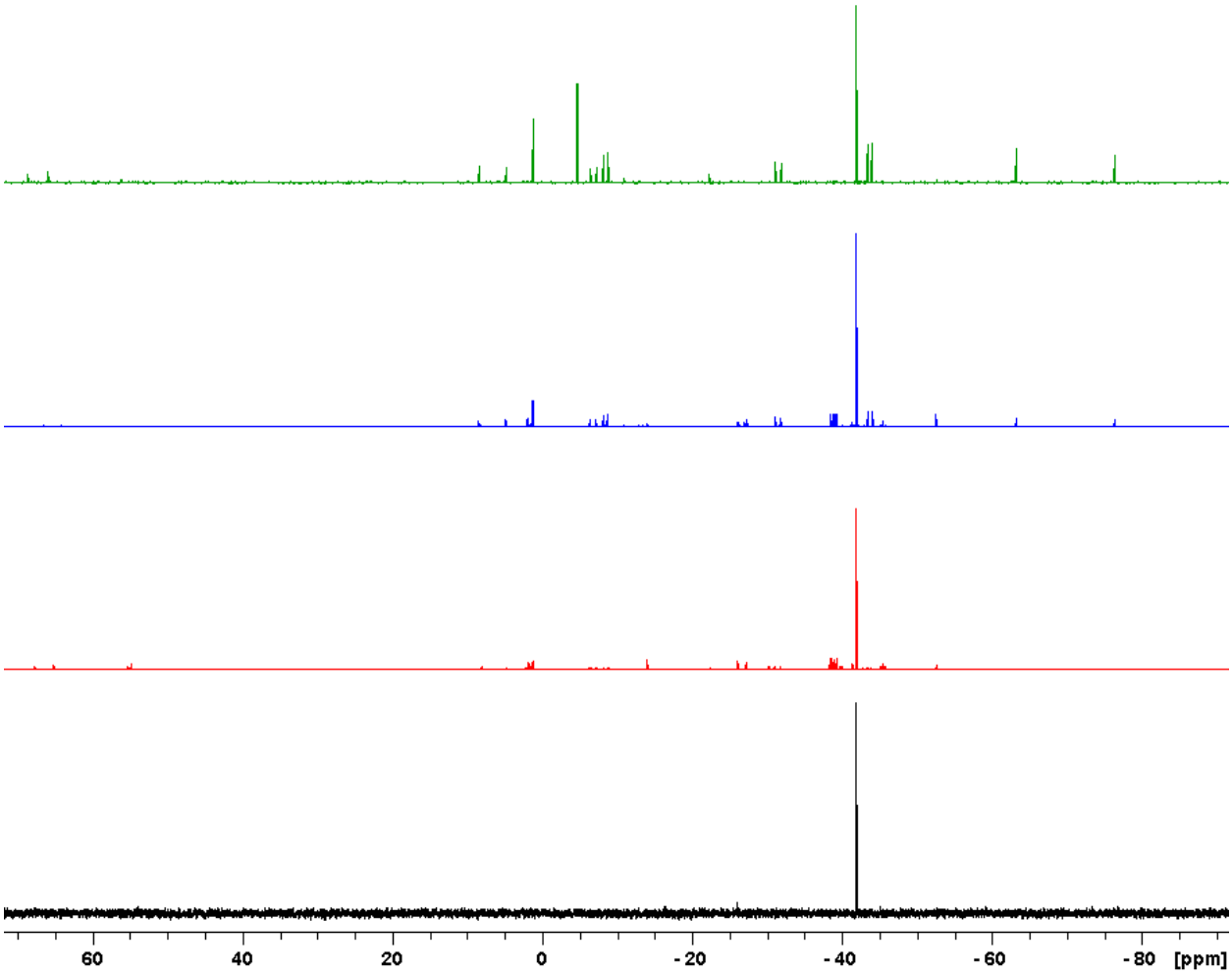


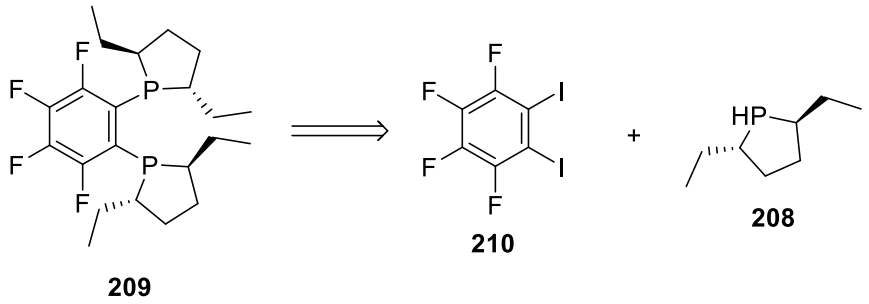

**Figure 7.1.** Selected region in $^{31}P\{^{1}H\}$ NMR spectra of the solutions. The top spectrum is 7.1a, the middle spectrum is 7.1b and the bottom spectrum is 7.1c.

Although a yield of up to 38% was achieved for this reaction with a certain way of the temperature control (attempt 3), the chiral secondary phospholane obtained is very oxygen-sensitive. In some occasions the desired product goes off during the distillation process. Isolation of those secondary phospholanes with alkyl groups was described to be challenging (and basically impossible) in the past in the literature, and it is advised to use them only as intermediates.[140] A potential way to deal with the problem is to protect the phosphorous (for example, with $BH_3$ group) before conducting further synthesis, or to find another synthetic route to obtain an alternative of the desired building block for the new phospholane ligands.

### 7.1.2 Attempts to prepare ligands through bis-coupling of secondary phosphine to 1,2-diiodo-tetrafluorobenzene

Cross-coupling reactions are very well known and explored in the literature, and some published known synthetic strategies were used in this project.[141-144] The initial idea of the

DuPhos cleavage was a preparation of ligand **209** from compounds **210** and **208** (Scheme 7.2) by application of some known literature cross-coupling routes.



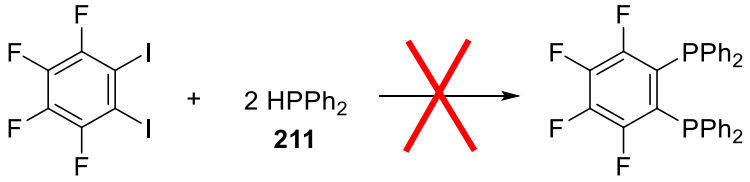

**Scheme 7.2.** Retrosynthetic plan for preparation of ligand **209**.

Since it was found that the secondary chiral phospholane unit **208** is very sensitive (and expensive due to high price of DuPhos ligand **207** and the low yields of the desired secondary phospholane **208**), and also *bis*-coupling is in general considered to be a challenging reaction,[142] it was decided to use diphenyl phosphine as a substitute for **208** for initial attempts of *bis*-coupling of the secondary phosphine to the di-iodo compound **210**. As shown in Table 7.1, a good number of attempts failed to produce any of the ligand **212**.

Example of the procedure – Entry 3 Table 7.1: A microwave vial was charged with 1,2-diiodo-tetrafluorobenzene (200 mg, 498 μmol), $Pd(OAc)_2$ (1.1 mg, 4.90 μmol) and triphenylphosphine (13 mg, 49.6 μmol). The vial was sealed and purged with argon for 10 minutes. After this time, it was wrapped into an alumina foil, and toluene (2 mL) was added. A toluene solution of diphenylphosphine (1M, 1 mL, 1.0 mmol) was added followed by addition of triethyl amine (0.21 mL, 1.51 mmol). The resulting solution was heated to 85 $^{o}$C in an oil bath and left to stir for 18 hours at this temperature. After this time, the solution was cooled to RT, and $^{31}P\{^{1}H\}$ NMR, $^{19}F$ NMR and $^{19}F\{^{1}H\}$ NMR spectra were acquired.

As can be seen from Table 7.1, a good number of attempts and a variety of conditions were tried in this process. In most cases, the diphenylphosphine remains there, or gets converted to the side products (typically, *bis*-diphenylphosphine or iodo(diphenyl)phosphine). In all cases, substrate **210** is not present at the end of the reaction. For some experiments the samples were worked-up by filtration and removal of solvent, but after the removal of the solvent and drying of the contents *in vacuo* all fluorinated species disappear. $^{19}F$ NMR spectra of the crudes showed characteristic signals for 1,2,3,4-tetrafluorobenzene, which is removed with other volatiles when the residues are dried under reduced pressure. Since the initial aim was to attempt to prepare the desired ligand **212**, no further attempts to analyse the outcomes of the reaction were made.

**Table 7.1.** Unsuccessful attempts to perform bis-coupling of the diphenylphosphine (**211**) to the compound **210**.




**210** **212**

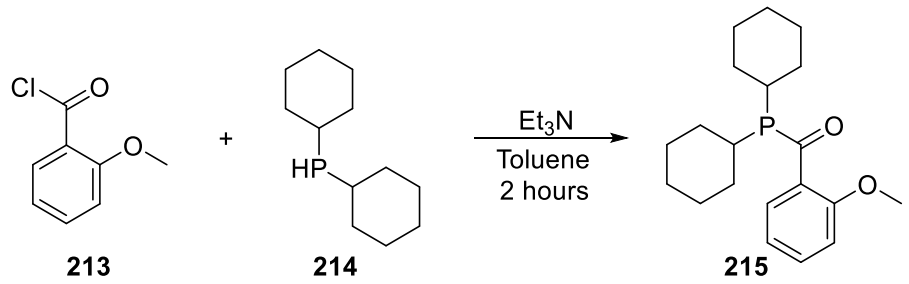
| Entry[a] | Amount of **210**, µmol | Metal reagent / catalyst, mol% | Ligand, mol% | Base, equiv. rel. to **210** | Solvent, mL | Type of heating, °C | Time, hours |
|---|---|---|---|---|---|---|---|
| 1 | 498 | $Pd(PPh_3)_4$, 1.0 | - | $Et_3N$, 3.0 | Toluene, 3.0 | Oil bath, 85 °C | 18 |
| 2 | 498 | $Pd(OAc)_2$, 1.0 | - | $Et_3N$, 3.0 | Toluene, 3.0 | Oil bath, 85 °C | 18 |
| 3 | 498 | $Pd(OAc)_2$, 1.0 | $PPh_3$, 10 | $Et_3N$, 3.0 | Toluene, 3.0 | Oil bath, 85 °C | 18 |
| 4 | 498 | $Pd(OAc)_2$, 1.0 | - | $Et_3N$, 3.0 | $CH_3CN$, 3.0 | Oil bath, 85 °C | 18 |
| 5[b] | 720 | $Pd(OAc)_2$, 1.0 | $PPh_3$, 10 | $Et_3N$, 4.0 | DMF, 4.5 | Oil bath, 65 °C | 18 |
| 6[c] | 249 | $Pd(OAc)_2$, 2.0 | dippf,[d] 3.0 | DABCO, 4.0 | DMF:THF (1:1), 3.0 | microwave, 140 °C | 0.33 |
| 7[c] | 249 | $Pd(OAc)_2$, 2.0 | $PPh_3$, 10 | DABCO, 4.0 | DMF:THF (1:1), 3.0 | microwave, 140 °C | 0.33 |
| 8[e] | 200 | $Pd(PPh_3)_4$, 1.0 | - | $Et_3N$, 4.0 | Toluene, 2.0 | Oil bath, 85 °C | 18 |
| 9[e] | 200 | $Pd(PPh_3)_4$, 1.0 | - | $Et_3N$, 4.0 | $CH_3CN$, 2.0 | Oil bath, 85 °C | 18 |
| 10[e] | 200 | $Pd(PPh_3)_4$, 1.0 | - | $Et_3N$, 4.0 | DMF, 2.0 | Oil bath, 85 °C | 18 |
| 11[e] | 200 | $ZnCl_2$, 10 | - | $Et_3N$, 4.0 | DMF, 2.0 | Oil bath, 85 °C | 18 |

[a]General conditions: Substrate **210**, 2 equivalents of **211** relative to **210**, catalyst / reagent. Vigorous stirring was used, and the vials were wrapped into alumina foil to ensure that the reactions are carried out in the dark. The resulting solutions at the end of the reaction were analysed by $^{31}P\{^1H\}$ NMR. [b]Extra 1 equivanelt of diphenylphosphine was used. [c]Extra 0.4 equivalents of diphenylphosphine was used. [d]dippf = 1,1'-bis(di-iso-propylphosphino)ferrocene. [e]Extra 0.9 equivalents of diphenylphosphine was used.

Due to lack of any success in the preparation of ligand **212** it was decided to stop the plans of preparation of ligand **209** and to continue the project with other chiral electron-deficient phopspholane ligand targets.

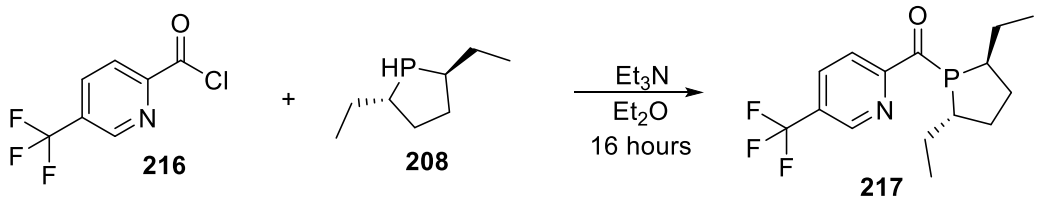
### 7.1.3 Phosphomide ligands

As described by Clarke and co-workers, phosphomide ligands are electron-deficient ligands which can be synthesised by a straightforward one-step synthesis from acyl halide and secondary phosphine.[145] An example of the synthesis of the ligand is shown in Scheme 7.3. This simple synthetic strategy affords the desired ligands in high (usually quantitative) yields and exceptional purities.




**Scheme 7.3.** Synthesis of phosphomide ligand **215** reported by Clarke and co-workers.

Since synthesis of **208** was already optimized and a yield of 38% was achieved, chiral phosphomide ligand **217** based on this secondary chiral phospholane unit was targeted (Scheme 7.4). This ligand can potentially act as a bidentate PN ligand, being an electron-deficient one with the desired chiral phospholane unit in the molecule.




**Scheme 7.4.** Attempt to prepare phosphomide ligand **217**.

Procedure: 5-(trifluoromethyl)picolinoyl chloride (112 mg, 0.534 mmol) was dissolved in $Et_2O$ (9 mL) and triethylamine (0.1 mL, 0.717 mmol) was added. To the resulting solution a diethyl ether solution (6 mL) of the (2*S*,5*S*)-2,5-diethylphospholane **208** (77 mg, 0.534 mmol) was added dropwise and the mixture was left to stir overnight. After this time, $^{31}P\{^{1}H\}$ NMR

spectrum of the solution was acquired (Figure 7.2) which suggested a multiple number of species present, where a good chance of the desired product being a peak at 28.1 ppm.

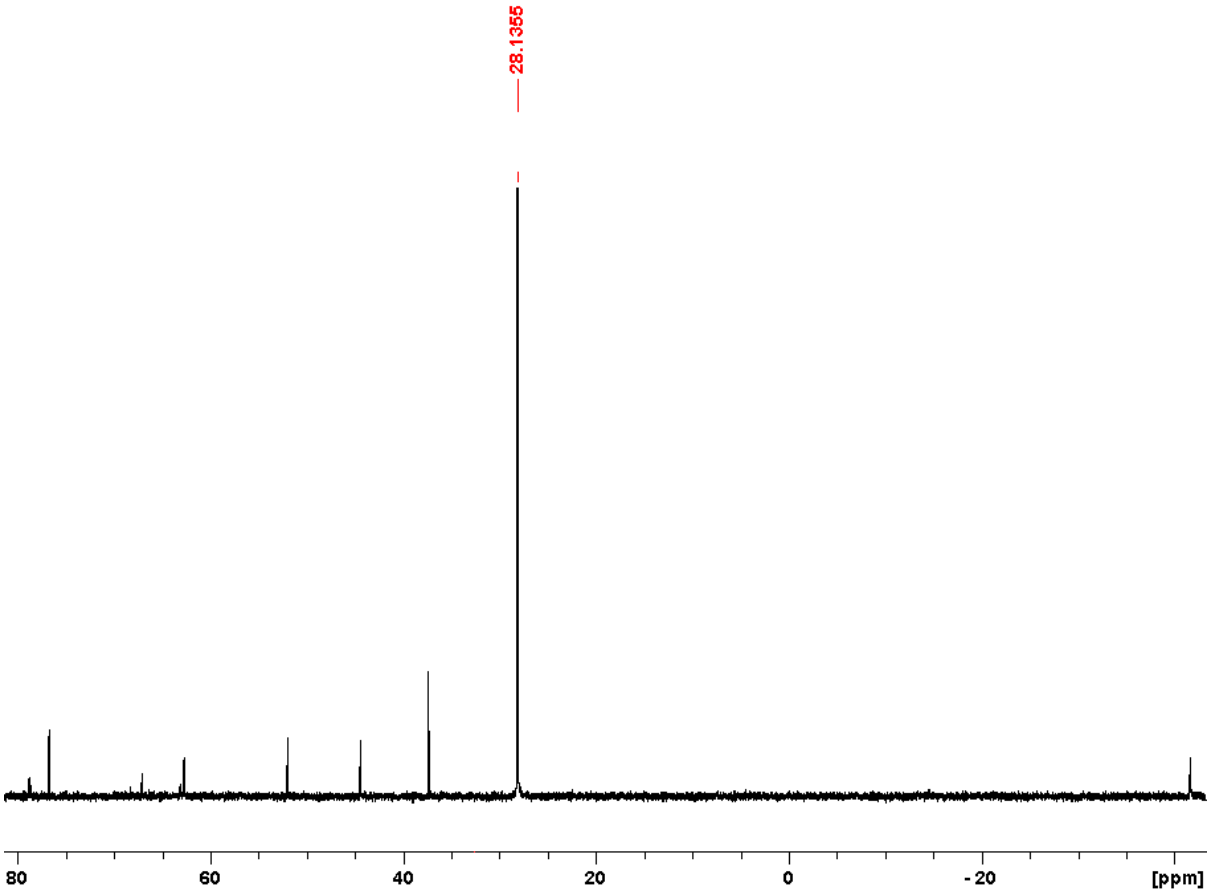
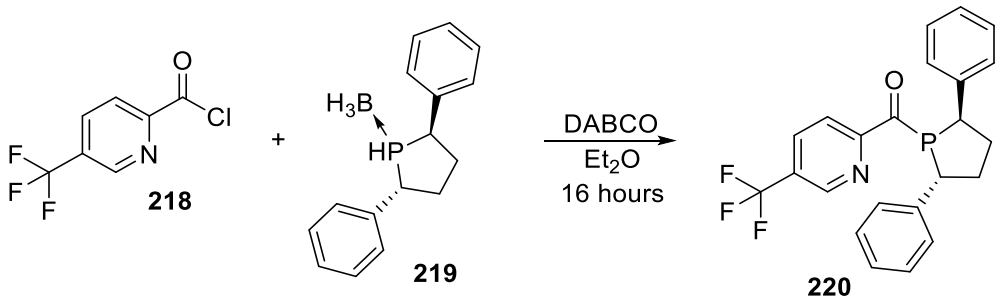



**Figure 7.2.** $^{31}P\{^{1}H\}$ NMR spectrum of the solution.

The solvent was removed *in vacuo* and the solids were suspended in hexane (4 mL). The hexane solution was filtered, and the remaining solids were suspended in toluene (3 mL) and the phosphorous NMR of the toluene solution was acquired, which suggested that no product was present in the solution. The hexane solution was left to stand at -20 $^{o}$C for 2 days. After this time, white solid precipitated from the solution. The hexane solution was filtered, and both, the solution and the solid were analysed by phosphorous NMR. The desired peak at 28.1 ppm was not observed in any of the fraction, which suggested that the product was hydrolysed (or oxidised). The most likely reason could be a very high sensitivity of the ligand towards moisture. Another possibility of the lack of success in purification of the desired ligand **221** could be very high sensitivity of the secondary chiral phospholane unit **208** to oxygen, and therefore, the ligand itself.

Although Ph-BPE ligand was shown to be of a significantly lower interest in enamine hydrogenation, it was still decided to attempt to prepare ligand **220** as shown in Scheme 7.5, since it is expected to be a lot more stable.




**Scheme 7.5.** Preparation of chiral phosphomide ligand **220**.

Procedure: To a solution of DABCO (583 mg, 5.20 mmol) and **219** (264 mg, 1.04 mmol) in toluene a solution of 5-(trifluoromethyl)picolinoyl chloride **218** (217 mg, 1.04 mmol) was slowly added. The resulting yellow solution was left to stir for 2 hours. After this time, a $^{31}P\{^{1}H\}$ NMR spectrum of the solution was acquired, where 2 phosphorous peaks were present ($\delta_P$ = 45.4 ppm and $\delta_P$ = 51.8 ppm). The solution was filtered through neutralised silica (with triethylamine), the short silica column was washed with toluene (2 x 5 mL), all solution fractions were combined and solvent was removed *in vacuo* to afford a bright-yellow solid. $^{1}H$ NMR and $^{31}P\{^{1}H\}$ NMR analysis suggested that still impurities were present in the mixture. The solid was recrystallised from hexane (11 mL) to afford a bright-yellow solid with only one peak in $^{31}P\{^{1}H\}$ NMR ($\delta_P$ = 45.6 ppm) (Figure 7.3) and $^{19}F\{^{1}H\}$ NMR ($\delta_F$ = -62.8 ppm) (Figure 7.4).

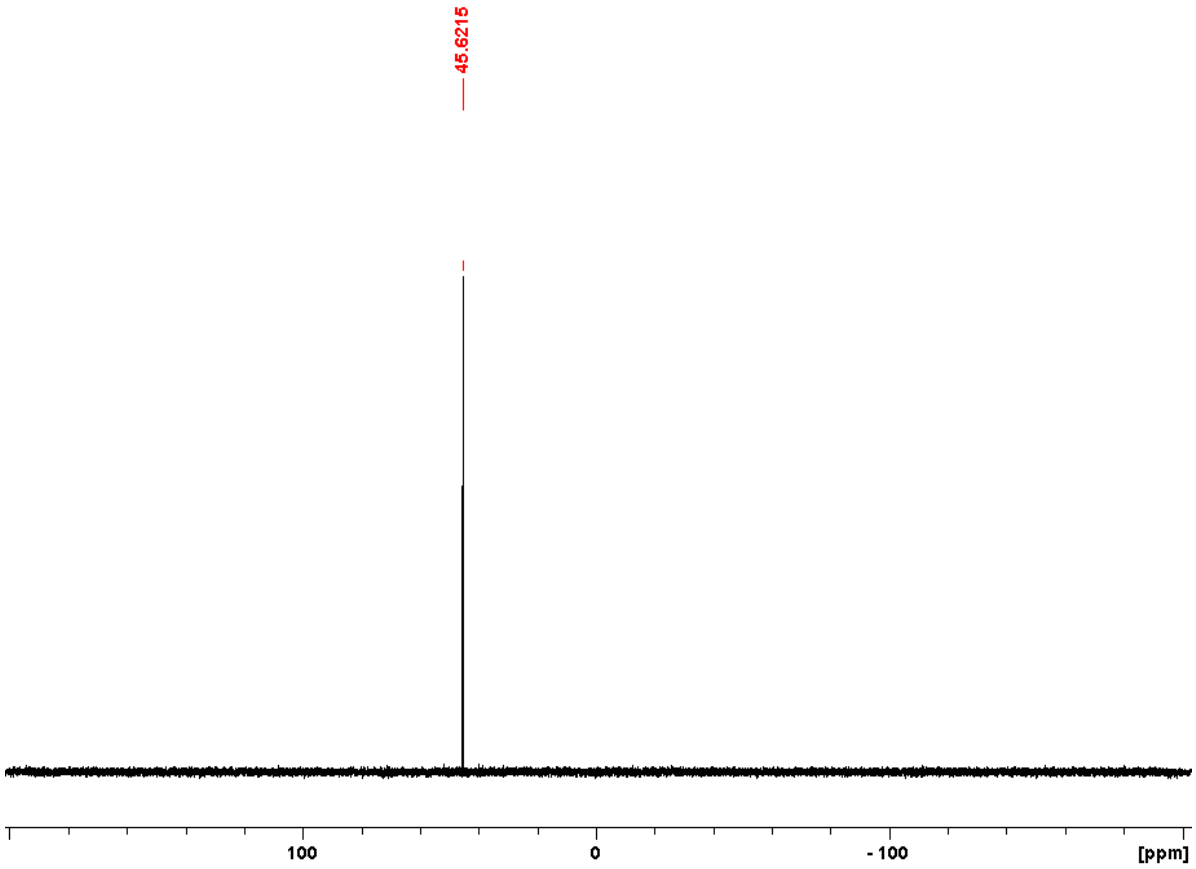



**Figure 7.3.** $^{31}P\{^{1}H\}$ NMR spectrum of the compound.

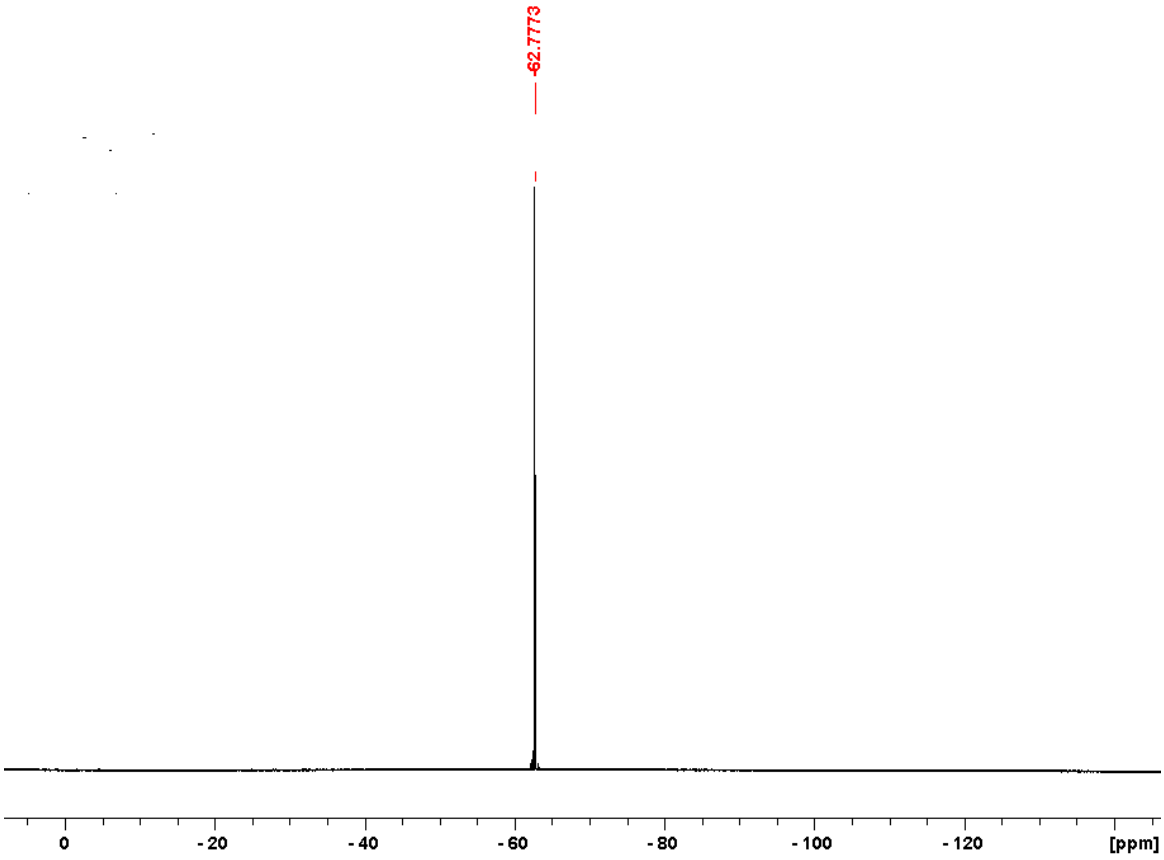
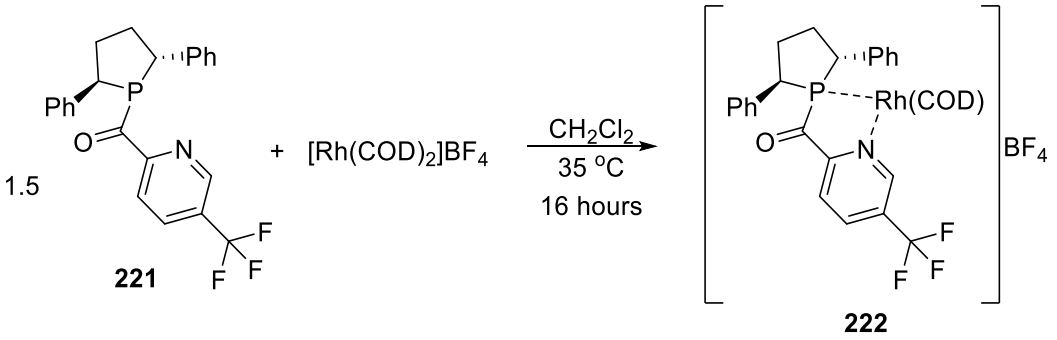



**Figure 7.4.** $^{19}F\{^{1}H\}$ NMR spectrum of the compound.

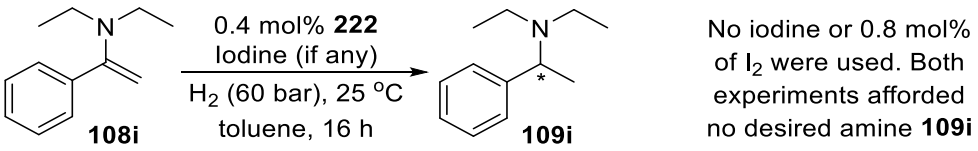
While the compound is clean by phosphorous and fluorine NMR spectra, $^{1}$H NMR still shows some impurities. Since attempts to purify the ligand did not afford a clean product, it was decided to attempt to prepare the Rh complex of it, and then to purify it. Scheme 7.6 represents the synthetic procedure for the complex **222** preparation.




**Scheme 7.6.** Preparation of Rh complex **222**.

Procedure: To a dichloromethane solution (7 mL) of $[Rh(COD)_2]BF_4$ (38 mg, 0.094 mmol) a solution of impure ligand **221** (58 mg, 0.140 mmol in case of 100% purity) in $CH_2Cl_2$ (4 mL) was added and the contents were heated to 35 °C and left to stir overnight. After this time, dark-red solid was present in the mixture.

While some product have precipitated out of the solution and was isolated, it was found to be completely insoluble even in the solvents like chlorobenzene, dichloromethane and acetonitrile. Therefore, characterization was problematic. The hope was that it might dissolve in the presence of hydrogen gas and additives. Unfortunately, as shown in Scheme 7.7, it was totally inactive in the hydrogenation of enamine **108i**, and, as discovered after the reaction, still did not go to the solution.

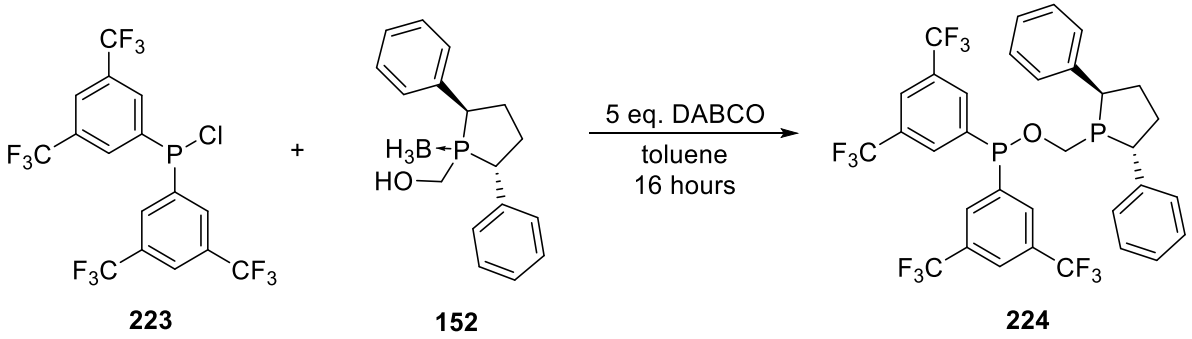



**Scheme 7.7.** Attempt to hydrogenate enamine **108i** with Rh complex **222**.

For the experimental procedure of hydrogenation, see the Chapter 6 – general hydrogenation of enamines with pre-formed Rh complex.

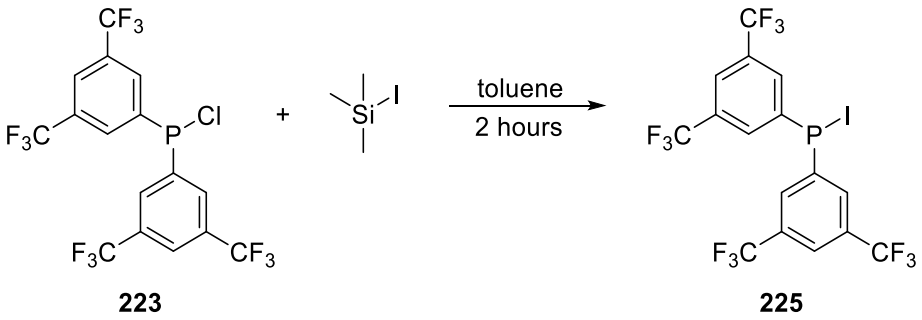
### 7.1.4 Attempts to prepare (2*R*,5*R*)-1-(((bis(3,5-bis(trifluoromethyl)phenyl)phosphanyl)oxy)methyl)-2,5-diphenylphospholane (224)

Synthetic attempt of another potentially interesting bidentate ligand **224** is shown in Scheme 7.8.




**Scheme 7.8.** Attempt to prepare chiral phospholane ligand **224**.

Procedure: To a solution of DABCO (446 mg, 3.98 mmol) in toluene (16 mL) a toluene solution (7 mL) of **152** (226 mg, 0.795 mmol) was added following an addition of a toluene solution (2 mL) of **223** (392 mg, 0.796 mmol) and the resulting mixture was left to stir overnight. After this time, the solution was filtered through neutralised silica (with triethylamine) and the silica was washed with toluene (2 x 12 mL). All toluene fractions were combined and solvent was removed *in vacuo*. The resulting mixture was analysed by $^{31}P\{^{1}H\}$ NMR, which contained a multiple number of species. When proton-coupled spectrum was acquired, it was clear that the secondary phosphine $((CF_3)_2C_6H_3)PH$ was present. No hint of the desired product was observed. It was thought that the phosphine chloride **223** was not reactive enough to perform the desired reaction, and that instead it was involved in the formation of the P-H, where it was possible that the hydrogen atom are transferred from the de-protected $BH_3$ groups. Attempts to de-protect compound **152** prior to the reaction was not successful, as this type of compound is not particularly stable. The last attempt was to use iodo-phosphine with the hope that it would be reactive enough to perform the desired reaction instead of formation of the secondary phosphine. The reaction shown in Scheme 7.9 was performed in order to get an access to the compound **225**.




**Scheme 7.9.** Preparation of iodophosphine **225**.

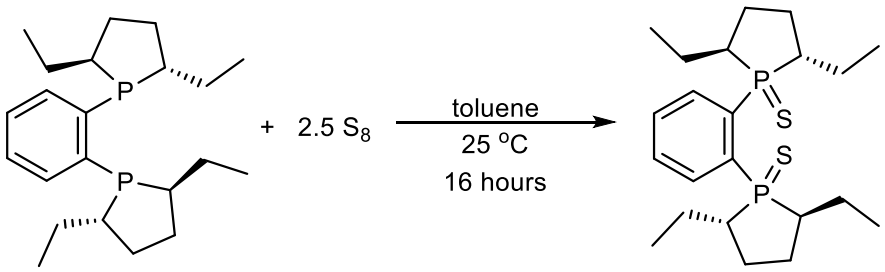
Procedure: chlorophosphine **223** ($\delta_P$ = 71.1 ppm)[146] (1.02 g, 2.07 mmol) was dissolved in toluene (8 mL) and TMS-I (1.2 mL, 8.60 mmol) was added. The resulting solution was left to stir for 2 hours. After this time, the volatiles were slowly removed under reduced pressure to afford the desired product, which was clean by $^{31}P\{^{1}H\}$ NMR ($\delta_P$ = 20.4 ppm).

The compound **225** was used in the attempts to form the desired ligand **224** under the exact same conditions as **223** was, but the synthesis was unsuccessful. The same problem appeared as in the case of the use of the chloride – i.e. the iodophosphine formed the secondary phosphine. Some other impurities were present in the spectrum as well.

At this stage, it was decided to abort further attempts to prepare chiral electron-deficient phospholane ligand from any chiral secondary phospholane. While it is desired to prepare the new ligand with alkyl chains on the secondary phospholane part of the molecule, the building block (for example compound **208**) will always be very sensitive. The cleavage of a very expensive chiral DUPHOS ligand is low-yielding process, producing a low molecular weight product, and is extremely sensitive procedure overall, which failed on several occasions despite all the precautions were taken.

### 7.1.5 Attempts to directly install fluorine atoms on the phospholane ligands

In order to try to install fluorine atoms directly on the DUPHOS molecule, it was first decided to protect phosphorous atoms on the ligand with sulfur. Scheme 7.10 represents successful protection of the ligand with sulfur (this type of reaction is very well known in the literature).[147,148]




**Scheme 7.10.** Protection of ligand **207** with sulfur.

Procedure: Ligand **207** (470 mg, 1.30 mmol) was dissolved in toluene (6.0 mL) and sulfur (850 mg, 26.5 mmol) was added. The resulting mixture was left to stir overnight. After this time, the solution was filtered and the solvent was removed under reduced pressure. The resulting solid was purified by column chromatography (initially hexane is used to remove sulfur, and then hexane : EtOAc (9 : 1) was used) to afford compound **226** (378 mg, 0.886 mmol, 72%) as a white crystalline solid.

Anal. Calcd. for $C_{12}H_{16}FN$ (found): C, 61.94 (62.06); H, 8.51 (8.64); N, < 0.1% (< 0.1%).

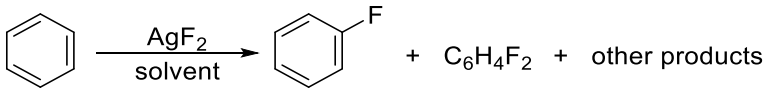
$^{1}$H NMR (400 MHz, $CDCl_3$, 298 K): $\delta_H$ = 7.68 – 7.58 (2H, m, Ar-H next to quarternary Ar-C), 7.55 – 7.46 (2H, m, Ar-H), 3.22 – 3.05 (2H, m, P-CH), 2.63 – 2.50 (2H, m, P-CH), 2.49 – 2.34 (2H, m), 2.27 – 1.96 (4H, m), 1.89 – 1.67 (6H, m), 1.55 – 1.40 (2H, m), 0.99 (6H, t, $^{3}J_{HH}$ = 7.5 Hz, 2 x $CH_3$), 0.83 (6H, t, $^{3}J_{HH}$ = 7.1 Hz, 2 x $CH_3$), 0.78 – 0.64 (2H, m).

$^{13}$C{$^{1}$H} NMR (101 MHz, $CDCl_3$, 298 K): $\delta_C$ = 135.7 (dd, $^{1}J_{PC}$ = 63 Hz, $^{2}J_{PC}$ = 6.0 Hz, Ar-C), 132.8 (apparent t, $^{2}J_{PC}$ = 9.5 Hz, Ar-CH next to Ar-C), 130.2 – 129.9 (m, Ar-CH), 48.7 (d, $^{1}J_{PC}$ = 54 Hz, P-CH), 41.2 (d, $^{1}J_{PC}$ = 54 Hz, P-CH), 28.0 – 27.7 (m), 27.5 (s), 27.4 – 27.1 (m), 21.0 (s), 13.2 – 12.8 (m, -$CH_3$), 12.7 – 12.3 (m, -$CH_3$).

$^{31}$P{$^{1}$H} NMR (162 MHz, $CDCl_3$, 298 K): $\delta_P$ = 72.3 (s).

MS ($ES^+$) *m/z*: 427.18 ($[MH]^+$, 100%); Found($ES^+$) 427.1798 ($[MH]^+$), $C_{22}H_{37}P_2S_2^+$ requires 427.1806.

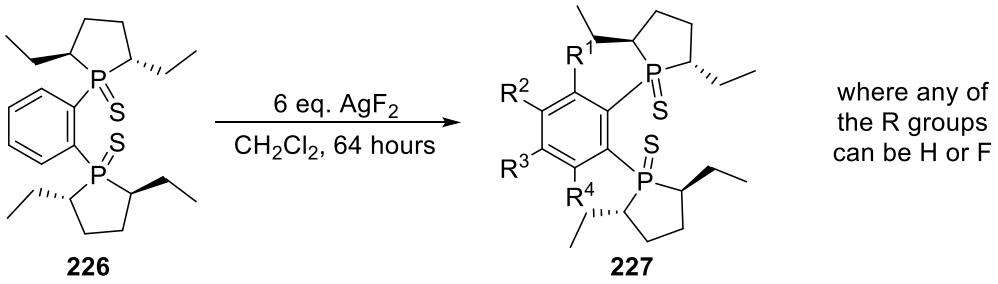
From the work of Zweig *et. al.* it was shown, that it is possible to substitute hydrogen atoms in benzene ring for fluorine atoms using $AgF_2$ (Scheme 7.11).[149] Monitoring the reactions with fluorine NMR, it was found that the major products formed are fluorobenzene and a mix of di-fluorobenzenes (ratios vary depending on the reaction conditions). Apart from benzene, it was shown that substituted benzenes can also react with silver difluoride, where a mixture of products is obtained due to exchange of aromatic hydrogen atoms to fluorine atoms.




**Scheme 7.11.** Direct fluorination of benzene with $AgF_2$.

In 2012, O'Hagan and co-workers described that it is possible to directly multi-fluorinate benzene with $AgF_2$, and use the resulting product in a multi-step synthesis.[150]

The same synthetic strategy was applied to attempt a direct fluorination of **226** (Scheme 7.12).




**Scheme 7.12.** Direct fluorination of sulfur-protected DUPHOS ligand **226**.

Procedure: To silver difluoride (330 mg, 2.26 mmol) a dichloromethane solution (20 mL) of compound **226** (161 mg, 0.377 mmol) was added, and the resulting mixture was left to stir over the weekend. After this time, the solution was filtered and the solids were washed with ethyl acetate (2 x 20 mL). The combined organic layers were washed with water (2 x 20 mL), brine (2 x 15 mL), dried over $MgSO_4$ and solvents were removed under reduced pressure. The resulting solid was dried *in vacuo* for 5 hours to afford a white solid (315 mg).

According to the analysis data, it is not absolutely clear what was formed during the reaction. The new compound is clean (by $^{31}P$ NMR and elemental analysis), and one of the possibilities, according to the analytical data, that two aliphatic protons were substituted in the molecule to fluorine atoms, deprotection of sulfur occurred, as well as an extra fluorine atom is present, which could form bonds with the phosphorous atoms as shown in Figure 7.5.

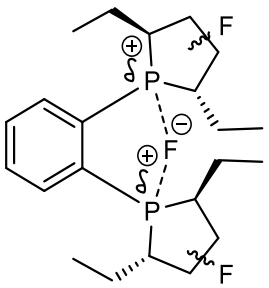


**Figure 7.5.** Possible structure of the compound formed.

Anal. Calcd. for $C_{22}H_{34}F_3P_2$ (found): C, 63.30 (63.59); H, 8.21 (8.18); N, < 0.1% (< 0.1%).

$^1$H NMR (400 MHz, $CDCl_3$, 298 K): $\delta_H$ = 7.85 (2H, br. s, Ar-H), 7.66 – 7.57 (2H, m, Ar-H), 2.50 – 2.18 (8H, m), 1.89 – 1.45 (10H, m), 1.14 – 0.97 (2H, m), 0.91 (6H, t, $^3J_{HH}$ = 7.5 Hz, 2 x $CH_3$), 0.85 (6H, t, $^3J_{HH}$ = 7.4 Hz, 2 x $CH_3$).

$^{13}$C{$^1$H} NMR (125.7 MHz, $CDCl_3$, 298 K): $\delta_C$ = 136.6 (dd, $^1J_{PC}$ = 77 Hz, $^2J_{PC}$ = 6.9 Hz, Ar-C), 133.4 (br. s, Ar-CH), 130.4 (d, $J_{PC}$ = 77 Hz, Ar-CH), 46.9 – 44.5 (m), 42.4 – 40.6 (m), 30.0 – 29.0 (m), 24.3 (br. s), 20.9 (br. s), 13.6 – 13.4 (m, $CH_3$), 13.4 – 13.1 (m, $CH_3$).

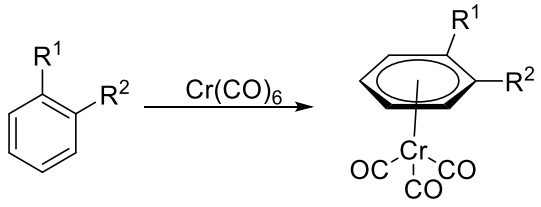
$^{31}$P{$^1$H} NMR (162 MHz, $CDCl_3$, 298 K): $\delta_P$ = 64.5 (br. s).

$^{19}$F{$^1$H} NMR (162 MHz, $CDCl_3$, 298 K): $\delta_P$ = -73.1 (d, $^1J_{PF}$ = 713 Hz), -152.9 (s), -173.5 (s).

MS ($ES^+$) *m/z*: 417.21 ($[M]^+$, 100%); Found($ES^+$) 417.2070 ($[M]^+$), $C_{22}H_{34}F_3P_2^+$ requires 417.2082.

### 7.1.6 Attempts to attach chromium-tricarbonyl groups on the aromatic rings of phospholane ligands

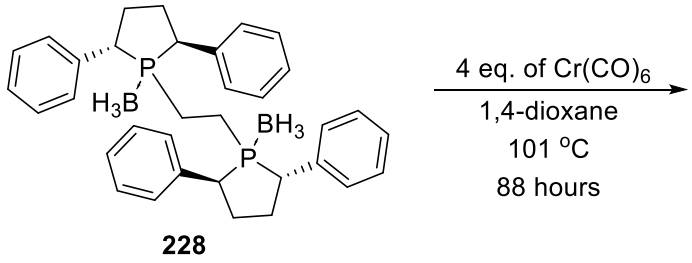
Another strategy was to make the electron-deficient versions of the ligands by installing chromium tricarbonyl groups on the aromatic rings. It is well-known that chromium hexacarbonyl can react with aromatic compounds and, after losing 3 CO groups, is able to bond firmly to the aromatic ring.[151-153]



**Scheme 7.13.** Reaction of addition of $Cr(CO)_3$ to the aromatic ring.

Addition of chromium tricarbonyl to the aromatic ring in this manner in the phospholane ligand would not only make the ring more electron-deficient, but also increases the steric bulk.

Since phosphorous atoms can potentially coordinate to chromium, the ligand has to be protected. Initially, it was decided to test the reaction using $BH_3$-protected (*S*,*S*)-Ph-BPE ligand **228** (Scheme 7.14). Apart from $BH_3$ groups are probably more reliable protection groups than sulfur (since Cr could potentially react with sulfur and deprotect P atoms), the chosen phospholane compound has several aromatic rings, where the chromium tricarbonyl can potentially be attached.




**228**

**Scheme 7.14.** Attempt to coordinate $Cr(CO)_3$ groups to aromatic rings.

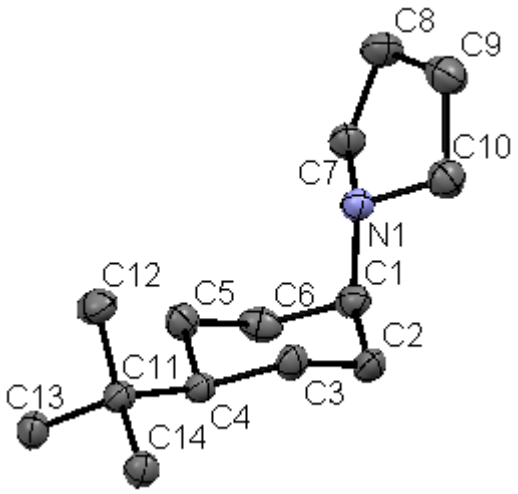
Procedure: chromium hexacarbonyl (140 mg, 0.636 mmol) and compound **228** (85 mg, 0.159 mmol) were dissolved in dioxane (11 mL), and the resulting solution was left to stir at 101 $^oC$ for 88 hours under inert atmosphere. After this time, the solution was cooled to room temperature and $^{31}P\{^1H\}$ NMR was acquired.

The reaction formed a multiple number of products. The first warning was that all the peaks are expected to be broad (since borane group is protecting P environments), but in the spectrum they appear to be fairly sharp. An attempt was made to separate species by column chromatography, where a species with a singlet at 106.1 ppm in phosphorous NMR was isolated. Although it looks clean by phosphorous NMR, the species was absolutely inactive in enamine hydrogenation. In $^1H$ NMR, no sign of $BH_3$ groups was detected. When the compound is dissolved in dichloromethane, and air was bubbled through the solution, no oxidation of the phosphorous atoms occurred. The most likely reason for these observations is that the ligand got de-protected and formed chromium tetracarbonyl complex, where both phosphorous coordinate to the metal displacing 2 CO ligands. MS was acquired, which suggest the presence of [(*S*,*S*)-Ph-BPE(Cr)$(CO)_4$] complex. MS ($ES^+$) *m/z*: 670.15 ($[M]^+$, 100%), 586.16 ($[M - 3\ CO]^+$, 70); Found($ES^+$) 670.1471 ($[M]^+$), $C_{22}H_{34}F_3P_2^+$ requires 670.1488.

Since the protection was thought to be not efficient, another idea was to prepare the desired species by direct addition of chromium tricarbonyl to the Rh-phospholane complex (*S*,*S*)-**198a**. This attempt was also unsuccessful, as the phosphorous NMR spectrum consisted of a single peak, which was a singlet (97.8 ppm). Since no coupling to Rh is observed anymore, it is clear that the complex decomposed. No further attempts were made to repeat the reaction.

Attempts to prepare new electron-deficient phospholanes are described here. Overall, it is a difficult task, and so far, our strategies failed. There is a need for new retrosynthetic plans towards this class of ligands.

## 7.2 Appendix B. Crystal structure of 1-(4-(*tert*-butyl)cyclohexyl)pyrrolidine




Bond lengths:

| Atom 1 | Atom 2 | Bond length, Å |
|---|---|---|
| N1 | C1 | 1.466(2) |
| N1 | C7 | 1.467(3) |
| N1 | C10 | 1.462(3) |
| C1 | C2 | 1.528(3) |
| C1 | C6 | 1.523(3) |
| C2 | C3 | 1.525(2) |
| C3 | C4 | 1.534(3) |
| C4 | C5 | 1.533(3) |
| C4 | C11 | 1.550(2) |
| C5 | C6 | 1.527(2) |
| C7 | C8 | 1.524(3) |
| C8 | C9 | 1.529(3) |
| C9 | C10 | 1.515(3) |
| C11 | C12 | 1.528(2) |
| C11 | C13 | 1.538(3) |
| C11 | C14 | 1.536(3) |

Angles:

| Atom 1 | Atom 2 | Atom 3 | Angle, ° |
|---|---|---|---|
| C1 | N1 | C7 | 113.0(1) |
| C1 | N1 | C10 | 113.5(1) |
| C7 | N1 | C10 | 103.0(1) |
| N1 | C1 | C2 | 111.4(1) |
| N1 | C1 | C6 | 111.5(1) |
| C2 | C1 | C6 | 108.2(1) |
| C1 | C2 | C3 | 112.8(1) |
| C2 | C3 | C4 | 111.2(1) |
| C3 | C4 | C5 | 108.1(1) |
| C3 | C4 | C11 | 115.0(1) |
| C5 | C4 | C11 | 114.4(1) |
| C4 | C5 | C6 | 111.1(1) |
| C1 | C6 | C5 | 112.9(1) |
| N1 | C7 | C8 | 104.8(1) |
| C7 | C8 | C9 | 104.6(2) |
| C8 | C9 | C10 | 104.5(2) |
| N1 | C10 | C9 | 104.8(1) |
| C4 | C11 | C12 | 112.5(1) |
| C4 | C11 | C13 | 109.6(1) |
| C4 | C11 | C14 | 109.6(1) |
| C12 | C11 | C13 | 109.1(1) |
| C12 | C11 | C14 | 108.7(1) |
| C13 | C11 | C14 | 107.2(1) |

## 7.3 Appendix C. Publications from the project.

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3. S. Tin, M. L. Clarke, T. Fanjul, “Remarkable co-catalyst effects on the enantioselective hydrogenation of unfunctionalised enamines: both enantiomers of product from the same enantiomer of catalyst”, *Catal. Sci. Technol.*, **2016**, *6*, 677

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