

Iridium Catalysed Asymmetric Hydrogenation of Pyridines

Filosofie Licenciat - Uppsala Universitet

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Abstract

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This thesis presents the hydrogenation of substituted pyridines using N,P-ligated iridium catalysts in homogeneous media. These iridium catalysts were developed within this research group in the past decade. This method of hydrogenation is highly stereoselective, and in several cases good to excellent *ees* were obtained.

The hydrogenation of substituted pyridines was studied: by screening for the catalyst giving the highest conversion and *ee*, by optimising the reaction conditions and by attempting to improve existing catalysts. New substrates were synthesised for this process, in particular alkyl substituted *N*-protected pyridines. Their reduction provided chiral piperidines, which could be used as chiral building blocks once deprotected.

Keywords: asymmetric synthesis, iridium, hydrogenation, heterocycle, pyridine.

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*And courage never to submit or yield:
And what is else not to be overcome?*

*John Milton, Paradise Lost
Book I, v. 108-109*

List of Papers

This thesis is based on the following paper, which is referred to in the text as a Roman numeral.

- I **Alban Cadu**; Puspesh K. Upadhyay and Pher G. Andersson.
Iridium catalysed hydrogenation of substituted pyridines.
Manuscript

Contribution Report

The author wishes to clarify his contribution to paper I.

- I Performed the catalyst screening and optimised the reaction conditions. Performed most of the substrate synthesis. Hydrogenated all substrates, interpreted the results and wrote the manuscript.

Publications not included in this thesis

- I **Alban Cadu**; Alexander Paptchikhine and Pher G. Andersson.
Birch Reaction followed by Asymmetric Iridium-Catalysed Hydrogenation.
Synthesis, **2011**, 3796-3800 (*Practical Synthetic Procedure*)
- II **Alban Cadu** and Pher G. Andersson.
Development of Iridium-Catalyzed Asymmetric Hydrogenation: New Catalysts, New Substrate Scope.
Journal of Organometallic Chemistry, **2012**, 714, 3-11 (*Review*)
- III **Alban Cadu** and Pher G. Andersson.
Iridium Catalysis: Application of Asymmetric Reductive Hydrogenation
Dalton Transactions, submitted May **2013** (*Perspective*)

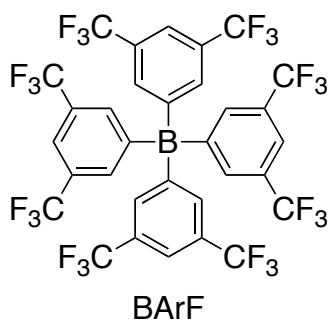
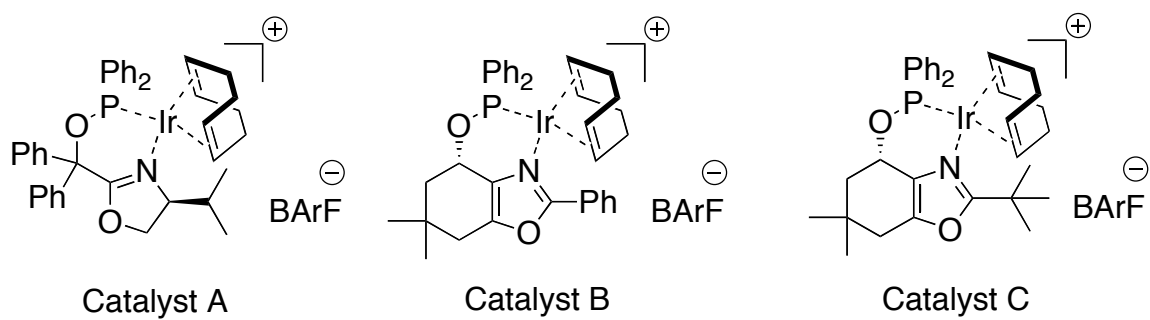
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Abbreviations

*	Stereocentre
Ac	Acetyl
Ar	Aryl
BArF	<i>Tetrakis</i> [3,5 <i>bis</i> (trifluoromethyl)phenyl]borate
Bn	Benzyl
Bz	Benzoyl
cat.	Catalyst
COD	Cyclooctadiene
Conv.	Conversion
Cy	Cyclohexyl
DCM	Dichloromethane
DFT	Density Functional Theory
DIBAL-H	<i>Diisobutylaluminium</i> hydride
<i>ee</i>	Enantiomeric excess
Et	Ethyl
GC	Gas Chromatography
gr	Gram
h	Hour(s)
HPLC	High performance liquid chromatography
<i>iPr</i>	<i>Isopropyl</i>
LAH	Lithium aluminium hydride
mCPBA	<i>meta</i> -Chloroperoxybenzoic acid
Me	Methyl
<i>n</i> -BuLi	<i>n</i> -Butyl lithium
NMR	Nuclear Magnetic Resonance
O.N.	Overnight
Pd/C	Palladium on carbon
Ph	Phenyl
<i>p</i> F-Ph	<i>para</i> -fluorophenyl
rac.	Racemic
R.T.	Room Temperature
<i>t</i> Bu	<i>tert</i> -Butyl
THF	Tetrahydrofuran
Ts	Tosyl

Most Discussed Catalysts in this Thesis



1. Introduction

1.1. Historical Perspective of Organometallic Chemistry

Progress in the use of metals has supported the advancement of civilisation over time: the crafting of bronze, iron and later steel items permitted the hegemony of civilisations over others.¹

Following the movement of Enlightenment in Europe, men of learning turned their gaze to chemistry discovering first the lighter elements (hydrogen by Cavendish in 1766, oxygen by Lavoisier in 1778), and later heavier elements such as iridium in 1804-1805 by Tennant² and Wollaston from platinum ore.³

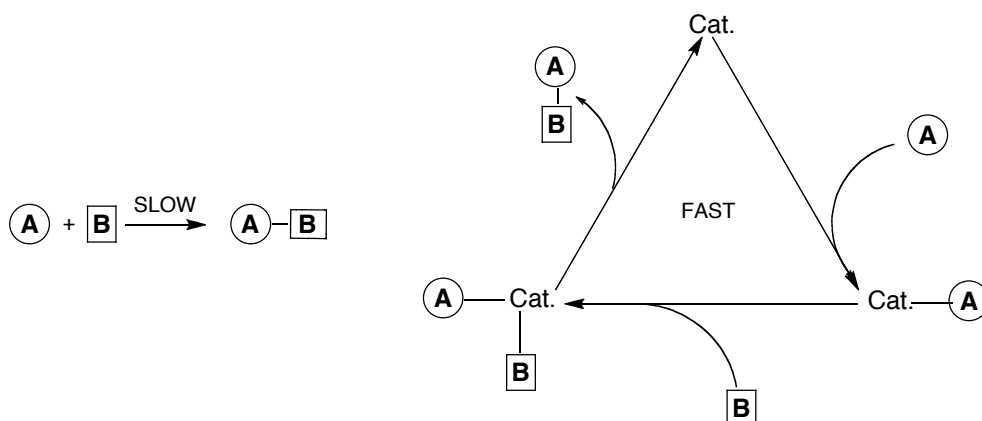
“As it is necessary to give some name to bodies which have not been known before, and most convenient to indicate by it some characteristic property, I should incline to call this metal Iridium, from the striking variety of colours which it gives, while dissolving in marine acid [HCl]”²

The use and mastery of metals has long been at the forefront of chemical research. Possibly the most famous early organometallic reaction, was discovered by Victor Grignard: the addition of organomagnesium halides to “aldéhydes” and “cétones”, thus earning him in 1912 the Nobel Prize.⁴ The field of organometallic chemistry (the combination of carbon based molecules with metals) has become very common, garnering numerous Nobel Prizes in the past century, and especially in the last 12 years: 2001 (Knowles, Noyori, Sharpless), 2005 (Chauvin, Grubbs, Shrock), 2007 (Ertl) 2010 (Heck, Negishi, Suzuki).

1.2. Catalysis

1.2.1. What is Catalysis?

Catalysis consists of the use of a compound (the catalyst) in a sub-stoichiometric amount to facilitate a chemical reaction. To illustrate this, two molecules, **A** and **B** are assumed to react together forming the product **A-B**. Either the molecules **A** and **B** can react directly in a non-catalysed way or they can do so using a catalyst. In the latter case, the starting materials will go through a pathway that in most cases requires both **A** and **B** to bind to the catalyst before finally giving the product **A-B**. After this, the product will be liberated from the catalyst allowing the catalyst to react again with new starting materials (**A** and **B**) and repeating the cycle (Scheme 1.1).



Scheme 1.1. Illustrative chemical reaction and catalytic cycle

1.2.2. The Different Types of Catalysis

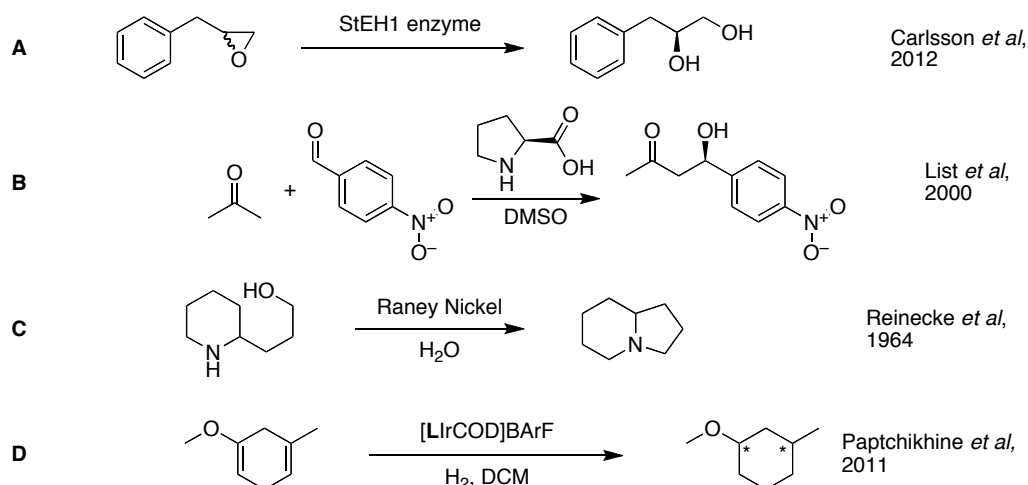


Figure 1.1. Examples of the three types of catalysis

There are different varieties of catalysis:

Biocatalysis:

It consists of the use of naturally occurring catalysts (usually enzymes) for catalysis.⁵ These reactions can be highly enantioselective (Figure 1.1. example **A**). In this example, the asymmetric hydrolysis of an epoxide proceeds with excellent enantioselectivity.⁶ However the enzymes require very specific conditions (temperature, pH, solvent) to survive and function.

Organocatalysis

This is similar to the above method, but this consists of the use of small organic compounds to catalyse a reaction. The use of proline has become extremely common for such a purpose, as it is readily available in an enantiomerically pure form (Figure 1.1. example **B**).⁷ This method often requires high catalyst loading, but the catalysts tend to be cheaper than the transition metal based ones.

Organometallic catalysis, further divided into two main classes:

Heterogeneous catalysis:

In this type of catalysis, the substrates and the catalyst are not in the same phase. Most commonly this would involve a solid catalyst (often an uncomplexed metal) and a substrate in solution (Figure 1.1. example **C**). In day-to-day life, the catalytic pots of modern cars use metal catalysts to reduce the emission of certain side products of petroleum combustion.

Overall this method's advantage is that the catalyst can be easily removed once the reaction is complete, and depending on cases, be reused. However, the catalysts require large surface areas to reach high turnover frequencies.

Homogeneous catalysis:

In this case, the catalyst and the substrate are in the same phase (usually in a liquid solution). The ligand(s) complexed to the metal allow its solubilisation. The asymmetric hydrogenation of olefins, using N,P-ligated iridium catalysts, usually comes under this category (Figure 1.1. example **D**).⁸ This is the field of catalysis explored in this thesis: the ligated iridium catalysts are dissolved in the DCM solution along with the olefins.

This method usually gives high selectivity, but recovering the catalyst requires a more complex work up which may or may not leave it available for re-use.

Industry has grown to rely tremendously on catalysis, as it is in most cases an economically efficient method of conducting a reaction and in the case of hydrogenation, the use of a catalyst is unavoidable. This has led to 70 to 90% of large-scale reaction conducted by industrials to employ catalysis.⁹ One of the most famous examples of this is the L-DOPA synthesis by Knowles (*vide infra*).

1.3 Asymmetry and Chirality

It is now well known that the quaternary substituted carbon atom adopts a tetrahedral configuration. From this, follows the principle of molecular asymmetry, which constitutes the very foundation to the work performed for this thesis.

The term asymmetry was defined by Le Bel in 1874 in the following terms:

The group of substituents R, R', R'' and A, each different from the others, form a structure that is not superimposable over its mirror image.¹⁰

The atom spoken of in the above passage is a tetra-substituted carbon, possessing four different substituents. To aid the visualisation of this the Figure 1.2, below, is provided.

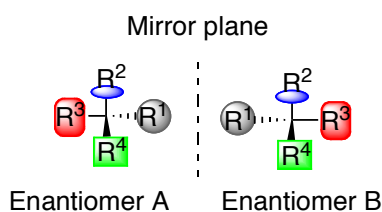


Figure 1.2. Illustration of an asymmetric carbon along with its non superimposable mirror image.

As can be seen, the two schematic model compounds are identical in all respect (a carbon atom bound to four substituents R¹ to R⁴) but one: the three dimensional arrangement of the substituents around the central carbon. This is commonly referred to as chirality, from the Greek word for hand (*kheir-χειρ*) Hands are the simplest and most widely recognised chiral object: they are virtually identical to each other, however they are superimposable only upon themselves but not on their mirror image. Two isomers sharing this property are called enantiomers. This phenomenon is ubiquitous in nature, particularly observed in natural molecules such as proteins and DNA.

The terms *R* (*rectus*) and *S* (*sinister*) are used to differentiate the enantiomers from each other, as *per* the Cahn-Ingold-Prelog (CIP) rules¹¹. A molecule that can be converted into a chiral one is called prochiral and can generate either an *R* or *S* enantiomer depending on the CIP-importance of the incoming group.

A concrete example of the above principle is illustrated by the odorous chemical limonene (Figure 1.3.). The (*R*)-enantiomer is the most commonly found in nature and is the natural fragrance of orange, while the (*S*)-enantiomer has a more bitter citrus-like smell.

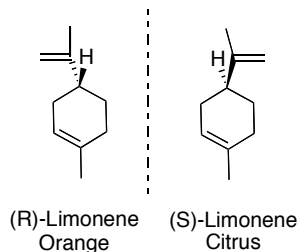


Figure 1.3. Molecules of both limonene enantiomers

The natural receptors in a body interact differently with the two enantiomers. To simplify this, one can imagine their hands as the incoming molecules and the receptors as gloves: a left hand will fit poorly in

the right glove. Such examples as above (Figure 1.3.) illustrate the different biological response to different enantiomers, this also governs the action of drugs, both recreational¹² and medical (such as the tragically infamous drug thalidomide).¹³

Historically, polarimeters were employed to determine the rotation of polarised light of chiral compounds. From this, the enantiomeric excess (*ee*, normally given as a percentile) was determined by the following formula (Equation 1.1.) and it is still taken as a measurement of the enantiomeric purity of a material. It is the ratio of the difference in amounts of the enantiomers over the total amount of both enantiomers. A 1:1 ratio of the (*R*) and (*S*) enantiomers is said to be racemic (*ee* = 0%).

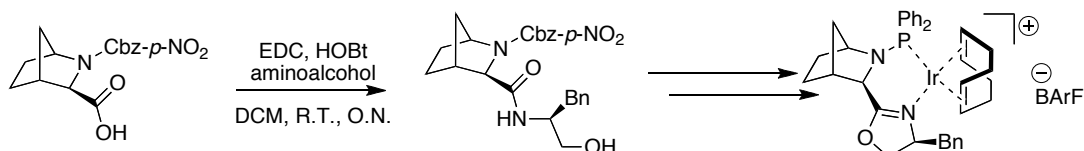
$$ee = \frac{(R) - (S)}{(R) + (S)}$$

Equation 1.1. Equation used to calculate the *ee* of a sample.

Chiral molecules can be obtained through different methods, such as the *chiral pool*, *chiral resolution* and *asymmetric synthesis*. Each method has its own advantages and disadvantages.

1.3.1 The Chiral Pool

The chiral pool consists of naturally occurring chiral compounds found in our environment. By this method, one begins the synthesis with a pre-existing chiral compound, which is built upon to generate a more complex molecule. The chiral pool is commonly employed, in organic synthesis, particularly by using readily available (and cheap) amino acids. For example it can be used in the synthesis of more specialised compounds, such as chiral N,P-ligands employed in iridium catalysis (see Scheme 1.2.).^{14,15} Some remarkably complex compounds can be found in high enantiomeric purity. However, the sources of these chiral molecules are finite and while many simple chiral compounds are abundant, even more are not. The cost of L-tyrosine is 1/30th of that of D-tyrosine. Too often only one enantiomer is naturally occurring and abundant, which limits the synthetic utility of the chiral pool approach.



Scheme 1.2. Use of a natural amino alcohol in the synthesis of an iridium catalyst.¹⁴

These factors contribute to making the chiral pool a limited source of building blocks, and one must turn their eyes further afield for many compounds.

1.3.2. Chiral resolution

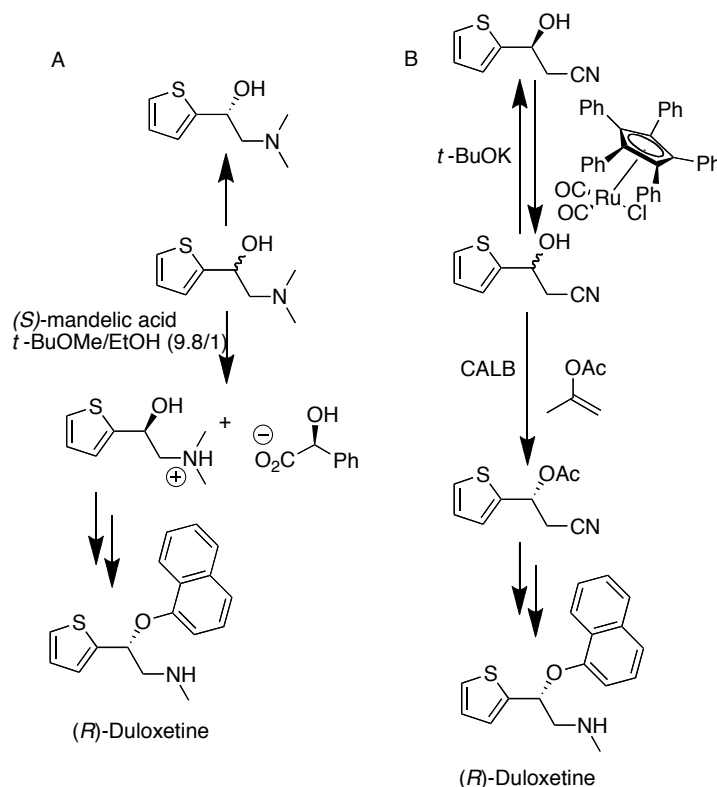
The chiral resolution of racemic mixtures is a very common method of obtaining enantiomerically pure materials. The racemic product is normally much more easily synthesised than its optically pure version. The chiral resolution involves the separation of one enantiomer from a racemic mixture. Chiral resolution can be divided into three categories: *preparative HPLC*, *crystallisation* and *kinetic resolution*.

1.3.2.1. Preparative HPLC

Chiral compounds can be separated from racemic mixtures using preparative HPLC (which is employed in this work, see section 2.2.2). The racemate is run through a solid supported chiral column that interacts differently with each enantiomer, and will give different retention times for the enantiomers. This method is very time consuming and requires both intensive investment in expensive, fragile and sensitive apparatus and consumes large amounts of solvents. In spite of these drawbacks, this remains the most reliable and general method of separation and is ubiquitously used.

1.3.2.2. Crystallisation

The second method is crystallisation. Either one can precipitate a specific enantiomer out of a racemic solution by seeding with an enantiopure crystal¹⁶ or by co-crystallisation with a chiral salt. One such example of the use of co-crystallisation with a chiral salt is observed during the synthesis of (*R*)-Duloxetine where (*S*)-mandelic acid is employed to separate the two enantiomers by crystallisation (see scheme 1.3).¹⁷ However, this too limits the yield to 50% as the undesired enantiomer goes to waste (unless it can be racemised and re-subjected to co-crystallisation).



Scheme 1.3. A. Resolution by crystallisation with mandelic used towards the synthesis of (*R*)-Duloxetine. B. Dynamic Kinetic Resolution by combining CALB lipase and a ruthenium catalyst towards the synthesis of (*R*)-Duloxetine.

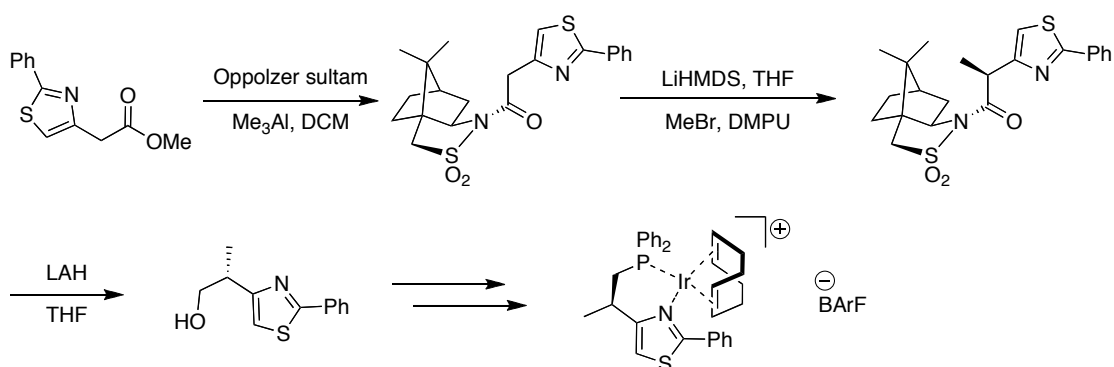
1.3.2.3. Kinetic Resolution

A third method to achieve enantiopure compounds is kinetic resolution.¹⁸ One subjects the racemic mixture to either a chiral reagent or to an achiral reagent and a chiral catalyst. One enantiomer will react faster than the other; therefore one of the enantiomers will be left unreacted. This is conducted with great success, particularly on secondary alcohols.¹⁹ For example, secondary allylic alcohols are reported to be acetylated with excellent selectivity by Fu (99% *ee*).²⁰ Kinetic resolution also suffers from being limited to 50% yield as the unwanted enantiomer is discarded, unless it is racemised and re-subjected to kinetic resolution.

Finally, as an improvement on the above methods, Dynamic Kinetic Resolution (DKR) was developed. This consists of the continuous racemisation of the unreacted starting material, while simultaneously undergoing kinetic resolution.²¹ A significant example of this is the synthesis of enantiomerically pure (*R*)-Duloxetine by Bäckvall and coworkers.²² This method employs both the *Candida Antarctica lipase B* enzyme to conduct kinetic resolution, and a ruthenium catalyst to racemise the non-acetylated secondary alcohol (Scheme 1.3.).

1.3.3. Asymmetric Synthesis

Asymmetric synthesis consists of introducing chirality to a molecule that previously lacked it. A reaction that generates an excess of one enantiomer over the other is said to be enantioselective and will lead to a non-racemic product mixture. A common method is the addition of an easily removed chiral auxiliary to the starting material, to induce a temporary steric bulk and chirality, which will transfer the chirality to further reactions before being removed. A related example of this is the use of Oppolzer's sultam; a steric bulk is added along with a centre of chirality, which will cause a difference in reactivity between the two diastereomers formed (Scheme 1.4). Alternatively, asymmetric catalysis can be employed to impart the chirality from a chiral catalyst to the formed product: this is the focus of this research. This can be performed provided the starting material has a prochiral centre.



Scheme 1.4. Example of Oppolzer's sultam used to generate an optically pure product (d.e. >95%) followed by its removal, to achieve the synthesis of an N,P-ligated iridium catalyst.²³

1.4. Catalytic Asymmetric Hydrogenation

The focus of this thesis is the stereoselective reduction of unsaturated bonds by employing N-P ligated iridium catalysts and hydrogen gas. The field of hydrogenation of double bonds (also called π -bonds) to single bonds (σ -bonds) has been very carefully examined in the past 50 years.²⁴

Iridium's most famous application remained for many years its alloyed use for the "mètre étalon" (the international prototype metre). Overall it knew little early use as a catalyst, as late as 1967, Rylander expressed:

"...its [iridium] lack of use stems partly from neglect and partly from the fact that some platinum metal has usually proved more suitable, whenever a comparison was made."²⁵

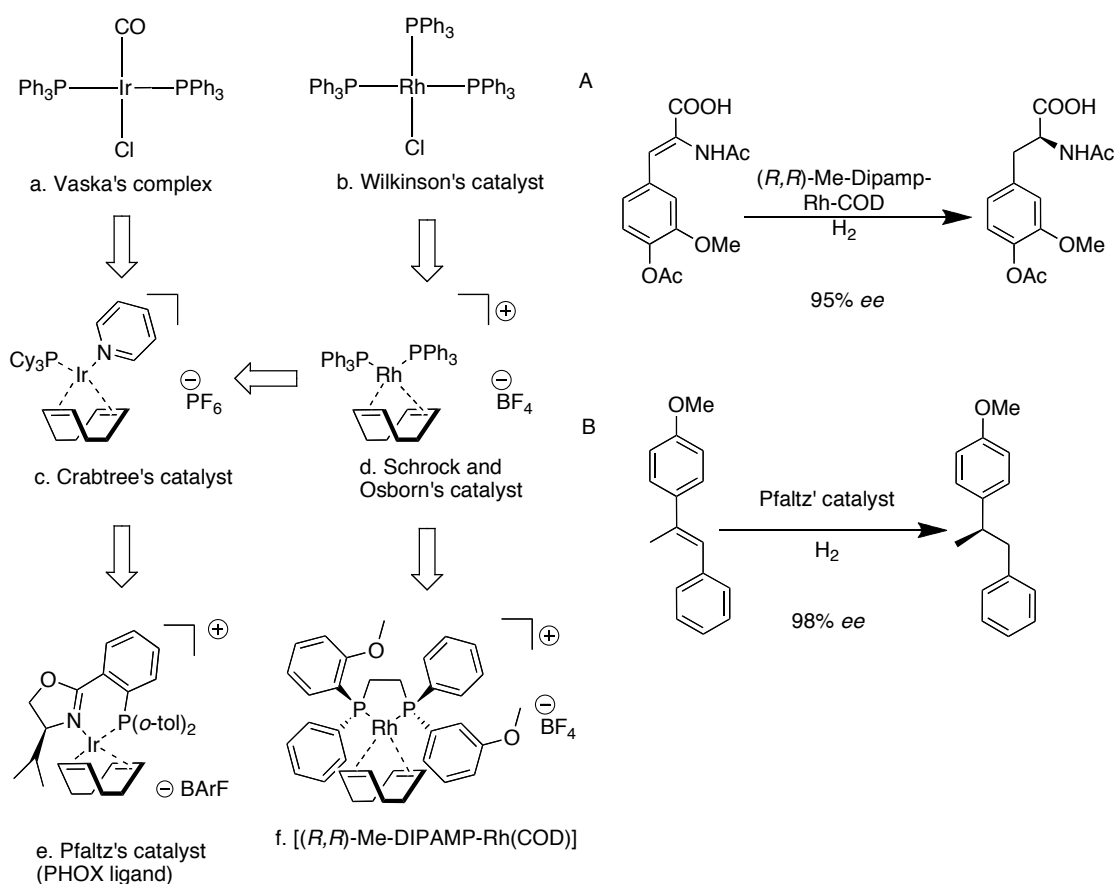
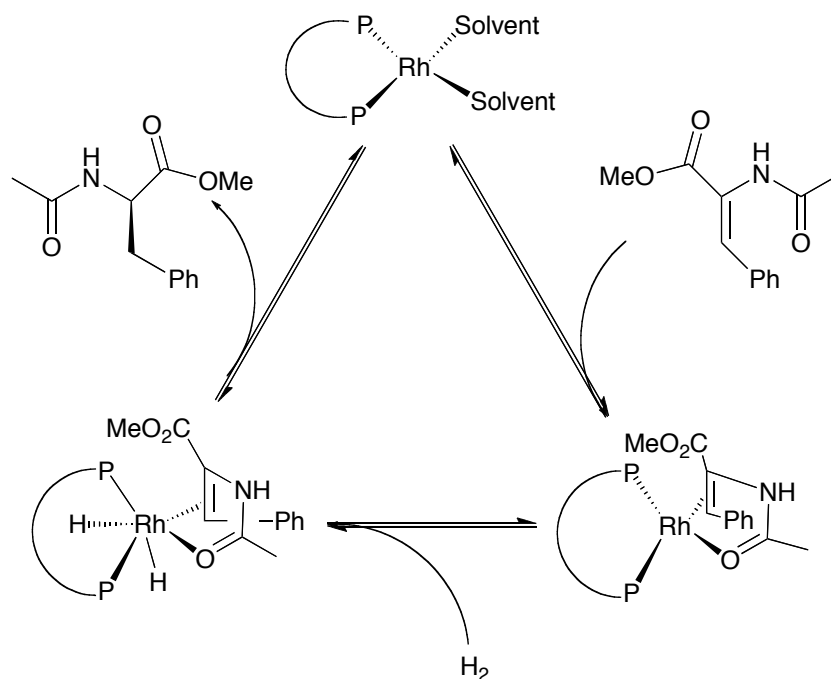


Figure 1.4. a-f. Evolution of organometallic catalysts used in hydrogenation. A. Asymmetric hydrogenation as key step of the L-DOPA process. B. Model enantioselective hydrogenation, used to demonstrate the scope of N,P-ligated iridium catalyst used with a BARF counter anion.

Vaska's complex ($[\text{IrCl}(\text{CO})(\text{PPh}_3)_2]$) (Figure 1.4.a) was the first iridium catalyst to reach notoriety.²⁶ Schrock and Osborn, through their work with rhodium, determined that a 2:1 mono-dentate ligand to metal ratio was superior to the previously employed 3:1 ratio, since it obviated the need for the PPh_3 extrusion step (Figure 1.4.d).²⁷ This in turn led to the discovery by Crabtree of his now famous catalyst $[(\text{COD})\text{Ir}(\text{PCy}_3)(\text{C}_5\text{H}_5\text{N})]\text{PF}_6$ (Figure 1.4.c).²⁸

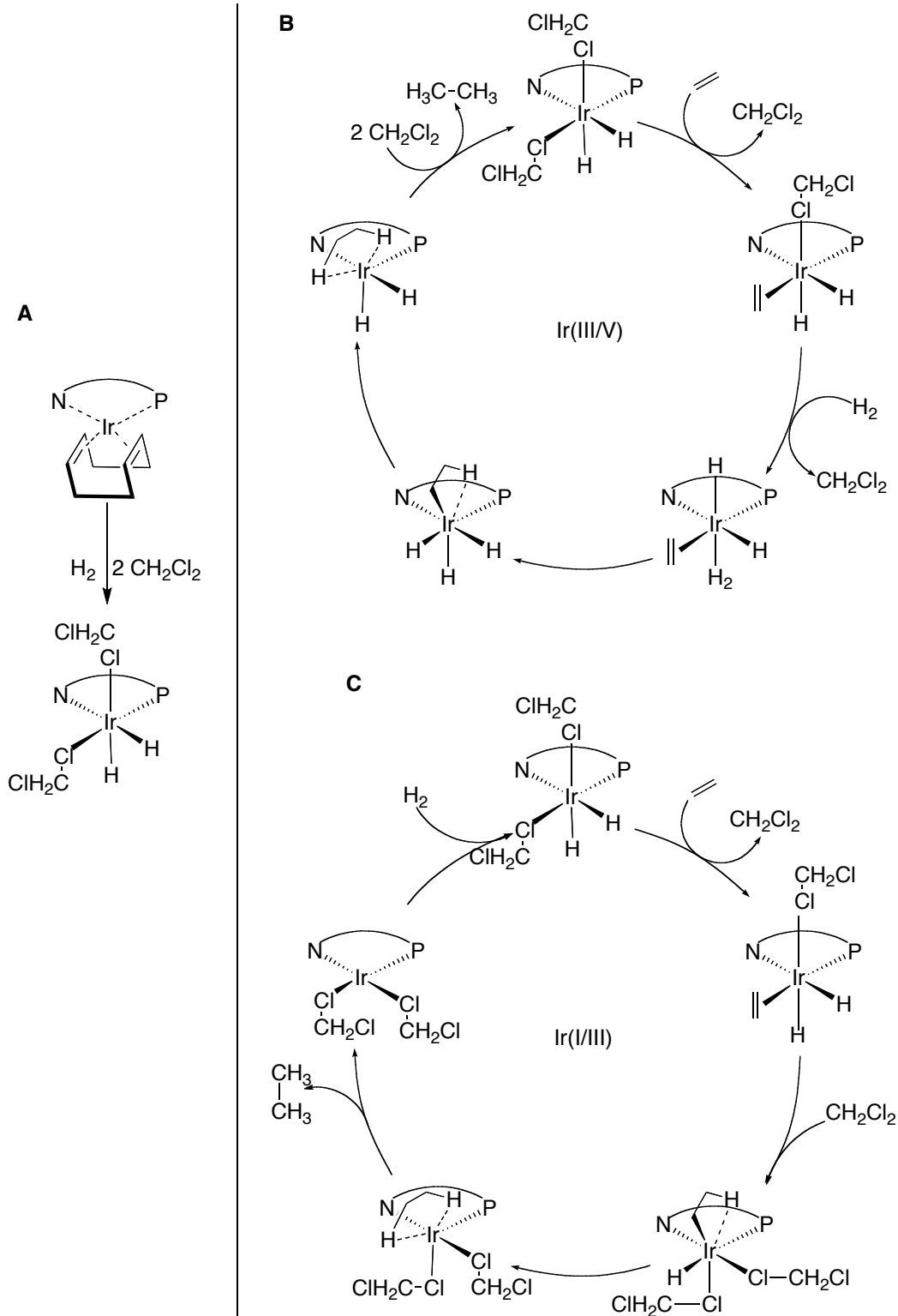
Early catalysts for hydrogenation of alkenes to alkanes relied on transition metal centres with multiple simple mono-dentate ligands. Examples of this include the eponymous organometallic catalyst discovered by Wilkinson (which earned him the Nobel Prize in 1973),²⁹ and Crabtree's catalyst³⁰ (see Figure 1.4). However over time, more complex chiral poly-dentate ligands were synthesised which could transfer their chirality to the product. Amongst the most common examples of these ligated metals is rhodium-(*R,R*)-DIPAMP (Figure 1.4.f and A) famously used by Knowles in the synthesis of L-DOPA process (earning him the Nobel Prize in 2001).³¹ Rhodium and ruthenium catalysts have been used extensively and their mechanisms studied.³² However they suffer from one critical flaw compared to iridium catalysts: they require a coordinating group, typically a carbonyl, vicinal to the olefin (see Scheme 1.5), and thus the chirality of the catalyst is imparted to the product.

In 1998, Pfaltz and coworkers reported the discovery of a new iridium catalyst, which opened the possibility to the field of chemistry explored in this thesis.³³ The use of a PHOX-type ligand (a type previously associated with palladium catalysis, Figure 1.4.e³⁴) in combination with iridium allowed for the asymmetric hydrogenation of a new class of olefins (Figure 1.4. B).



Scheme 1.5. Catalytic cycle of a (*R*)-P,P-ligated Rh catalyst, according to the mechanism determined by Halpern.

Conversely, the iridium catalyst binds in a mono-dentate manner to the substrate and is therefore able to hydrogenate “largely unfunctionalised alkenes”.³⁵ As can be seen in the mechanisms overleaf (Scheme 1.6), the olefinic bond is able to coordinate to the iridium centre without the intervention of an adjoining chelating group. Computational DFT studies have been performed to investigate the mechanism of the hydrogenation, but due to their similarity (the main difference is the oxidation state of the metal, and the binding of H₂ or DCM to the metal centre) and the difficulty in isolating intermediates, neither has been proven correct over the other. A similar study was conducted by Burgess, but using a carbene rather than a phosphine ligand.³⁶ In both cycles, the key steps are the migratory insertions of hydrogen into C-Ir (π then σ) bonds.



Scheme 1.6. A. Hydrogenation and loss of the COD to generate the active catalyst. B. Generalised catalytic cycle as proposed by Andersson.³⁷ C. General catalytic cycle as proposed by Chen³⁸ and Pfaltz.^{24a}
 N.B. in all three cases, the formal charge and counter ion were omitted to reduce visual crowding.

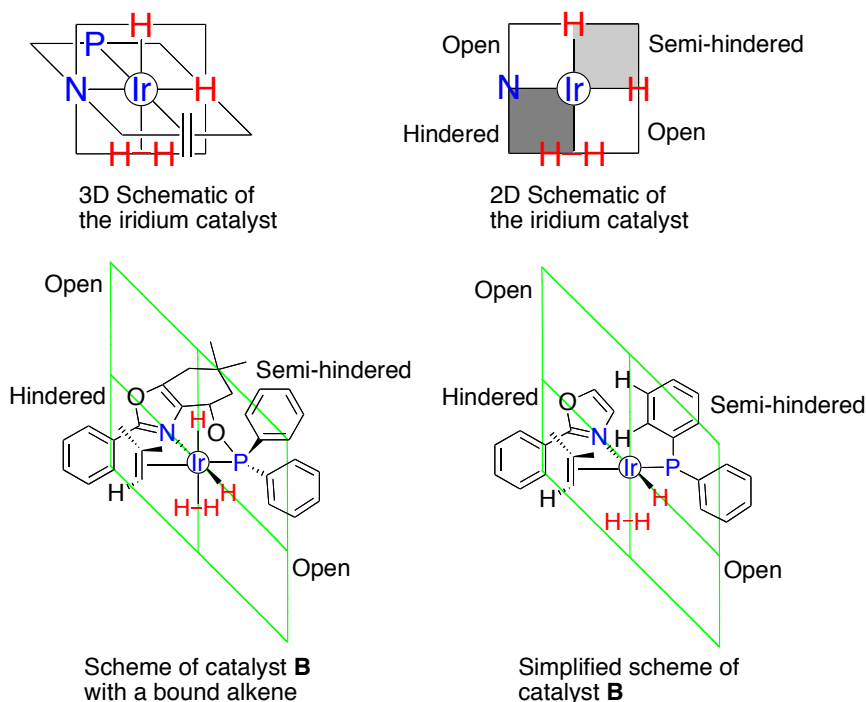


Figure 1.5. (top) Quadrant model schematised in 2D and 3D. (bottom) and superimposed over catalyst B.

Stemming from these two similar catalytic cycles, a quadrant model was determined to both rationalise and predict the configuration of the resulting products. The first N,P-ligand, designed in the Andersson group, was devised with the quadrant model in mind (see Figure 1.5).³⁹

With N,P-ligated iridium catalysts, the enantioselectivity stems from the bulk of the chiral ligand. As shown in Figure 1.5, the iridium centre is surrounded by two bulky groups that generate steric hindrance towards the alkene. The heterocycle bears a group (often phenyl), pointing out of the plane, which generates the main bulk: the hindered quadrant. The diaryl phosphine, has only a small portion of its bulk coming out of the plane thus generating the semi hindered quadrant, as can be seen in the simplified scheme. The other two quadrants are relatively free at the coordination site. An increase in size of the heterocycle's substituent group or of the phosphine aryl can be beneficial: a smaller reaction pocket means a tighter fit. However this runs the risk of generating an overly hindered reaction site in which case the extra steric bulk will cause a drop in both yield and *ee* as the substrate is unable to fit properly.

As can be seen in Figure 1.5, the alkene has limited space to bind to the Ir centre since the reaction pocket is blocked in the hindered quadrant by the phenyl ring on the heterocycle. The phenyl ring can be replaced by another group and thereby tailor the ligand to the substrate. The semi-hindered quadrant stems from a smaller steric bulk, in a *trans*-like position to the hindered quadrant, if viewed from the substrate. Overall, the substrate will attempt to align itself to the catalyst with the hydrogen atom matched to the hindered quadrant, and the smaller of the two groups (of the prochiral carbon) will occupy the semi-hindered quadrant. (Figure 1.6.)

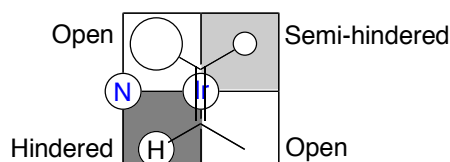


Figure 1.6. Preferred binding of a tri-substituted substrate to an N,P-ligated iridium catalyst, according to the quadrant model.

2. Asymmetric Hydrogenation of Pyridines (Paper I)

2.1. Introduction

2.1.1. Pyridines and Piperidines in Modern Chemistry.

Heterocycles, especially nitrogen containing ones, are abundant in natural,⁴⁰ scented⁴¹ and drug^{12,42} compounds, with chirality as a key element to their biological properties. The piperidine moiety is ubiquitous amongst these heterocycles and correspondingly, efficient methods to synthesise them in high enantioselectivity are desirable. Many opioids, such as morphine, feature a piperidine chiral moiety, which is also found in other drugs, for example in the anti-Alzheimer drug Pergolide (Figure 2.1). Correspondingly, a number of synthetic routes have been developed to synthesise piperidines.⁴³

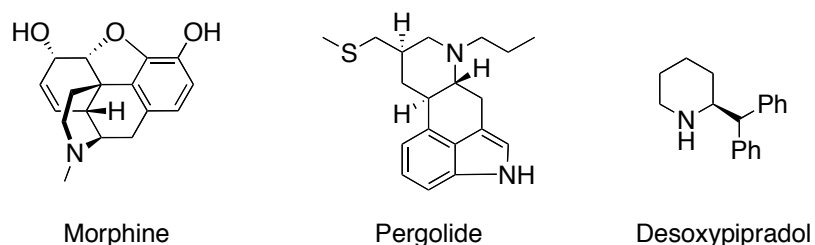


Figure 2.1. Examples of chiral piperidine containing biologically active compounds

2.1.2. Asymmetric Reduction of Imines and Pyridines.

Iridium hydrogenation has been applied to imines to generate chiral amines. In this reaction P,P-ligands are often used and normally require iodine as an additive to enable the reaction.⁴⁴ Some attempts have also been made to employ N,P-ligands to such compounds with varying results.⁴⁵ A famous example of an asymmetric imine hydrogenation through iridium catalysis, is the industrial synthesis of the herbicide (*S*)-Metolachlor.⁴⁶ As seen in Figure 2.2, an application of iridium hydrogenation allowed the synthesis of a key intermediate to the antibiotic (*S*)-levofloxacin and was published by Satoh *et al.*⁴⁷

Pyridines constitute cheap commercially available starting material. However, pyridines represent an additional challenge, as the aromaticity of the ring is broken in the reaction, which is energetically disfavoured.

A number of studies on the asymmetric hydrogenation of pyridines and pyridine-like compounds have been conducted and a few of these results are summarised in Figure 2.2.⁴⁸ Recently, *N*-protected and mono substituted pyridines were hydrogenated in high enantioselectivity by Zhou's research team, using P,P-ligands.⁴⁹

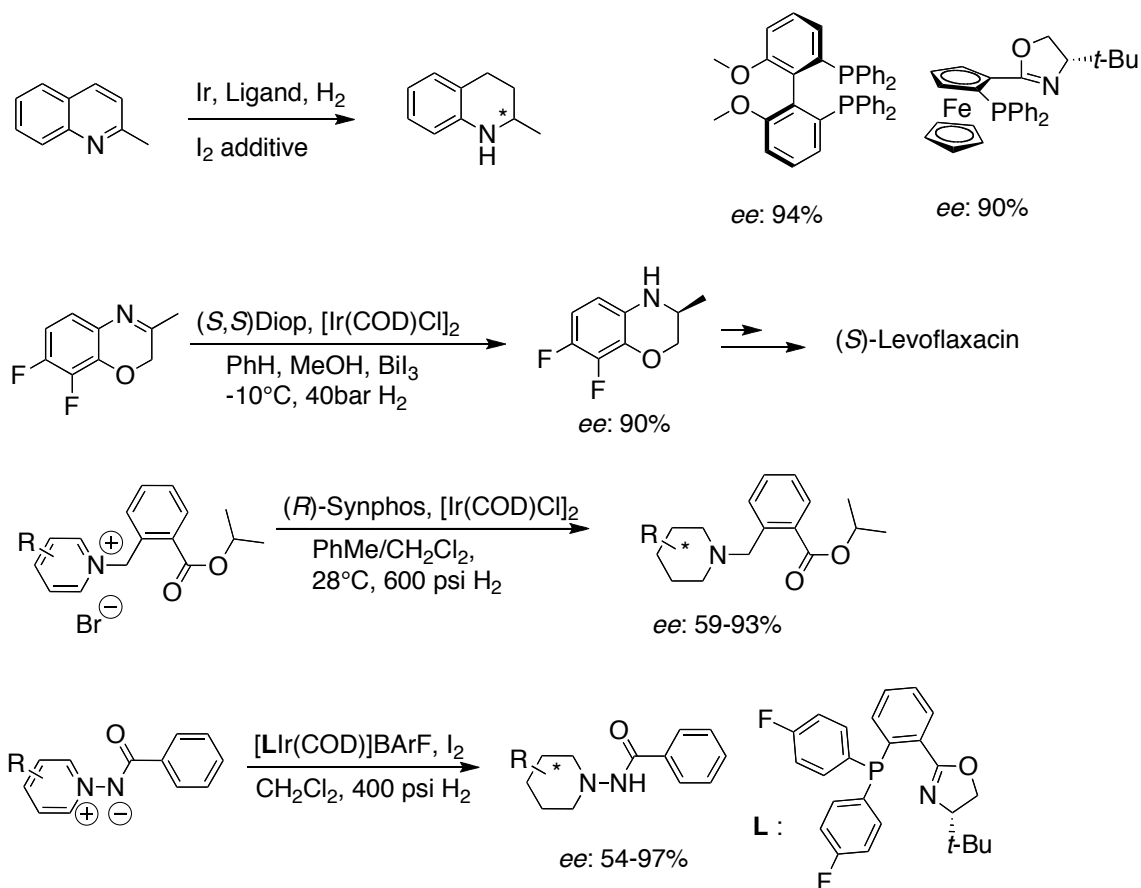


Figure 2.2. Examples of hydrogenation of imine- and pyridine-like compounds.

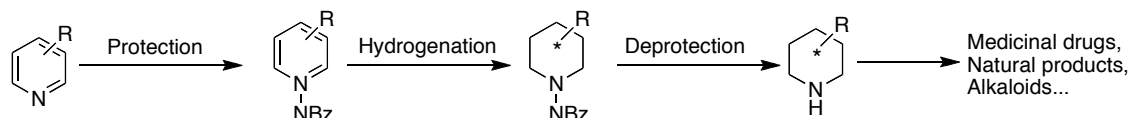
In this case the aromatic character of the molecule can be diminished by adding a substitution group to the nitrogen atom. In the study the formation of an *N*-ylidinium zwitterion was conducted as it offered several advantages:

- The group is a strong chromophore, enabling easy monitoring by chromatographic methods.
- The synthesis has been reported, but with room for improvement.⁵⁰

The work by Legault and Charette provided a straightforward (if toxic) route to the pyridine substrates.

2.1.3. Aim of this Project

The aim of the research constituting this chapter was to synthesise a small library of *N*-iminopyridinium ylides from substituted pyridines, which would be screened against pre-existing catalysts to hydrogenate the substrates in high stereoselectivities and to finally to conduct a deprotection. These obtained chiral piperidines could then be used as chiral building block in further organic synthesis.

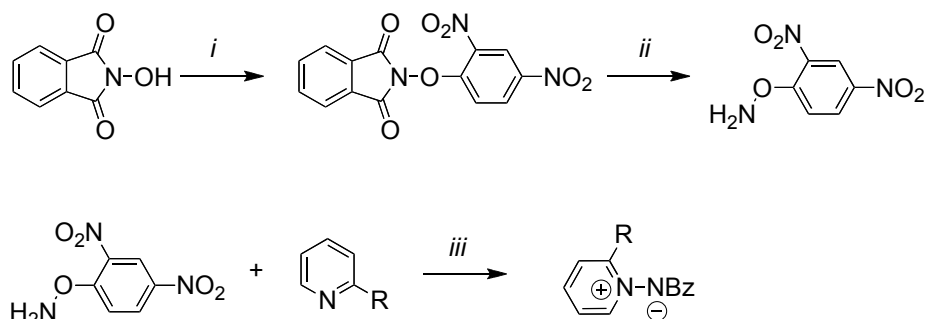


Scheme 2.1. Outline of the work performed in this chapter.

2.2. Substrate Synthesis and Asymmetric Hydrogenation

2.2.1. Substrate Synthesis

Charette's method of synthesis of the *N*-protected substituted pyridines was followed both for the previously reported substrates and the novel ones. The synthesis is straightforward, however great care must be taken regarding several aspects (Scheme 2.2. below).

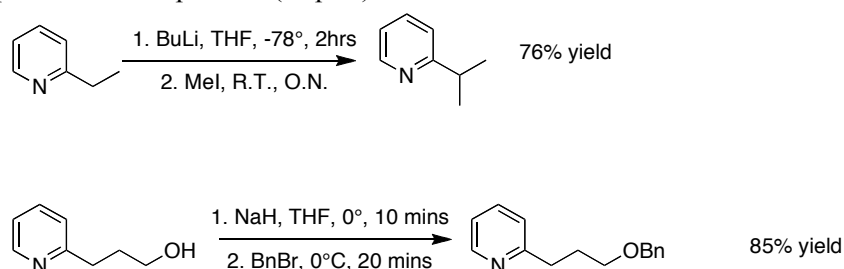


i: 1. NEt_3 , acetone. 2. 2,4-dinitro-chlorobenzene, R.T. 2h. *ii*: $\text{H}_2\text{N-NH}_2$ in MeOH, DCM, 0°C , O.N., then HCl. *iii*: 1. sealed vessel, 40°C , 1:1 $\text{H}_2\text{O}:\text{THF}$, O.N. 2. 10% NaOH aq, BzCl, R.T., 4h.

Scheme 2.2. Synthesis of the protected pyridines.

Firstly, the phthalimide N-oxide was deprotonated in order to perform a $\text{S}_{\text{E}}\text{Ar}$ addition to the 2,4-dinitrochloro-benzene (step *i*). This reaction was performed quantitatively, repeatedly and on large scale (up to 20g). Secondly, the obtained compound was deprotected using hydrazine in a DCM/MeOH solution, by resting overnight without stirring at 0°C (step *ii*). This reaction was also quantitative in yield.

Finally, the obtained aminating agent was employed to convert the pyridine to an ylide under basic conditions in a sealed microwave vial overnight. Benzoylation was performed at room temperature in a one-pot manner from the previous crude product (step *iii*).



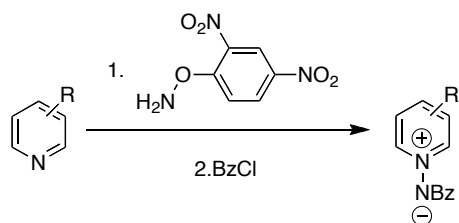
Scheme 2.3. Synthetic schemes to non-commercially-available pyridines.

Non-commercial 2-alkylpyridines were prepared. (Scheme 2.3.) This was done following the methods shown above. The 2-*iso*-propylpyridine was synthesised by methylation of 2-ethylpyridine. The 2-propanolpyridine was protected using benzyl bromide in high yield.

As can be seen in Table 2.1, the pyridines were protected with average yields, in most cases. The notable exception is entry 10, the nitrogen atom was the most sterically hindered and so the ylide synthesis proceeded in poorer yield.

For all the compounds, the highest loss of product occurred during the purification by flash chromatography. The storage of the compounds was problematic as they degraded overtime to brown oils even when kept under argon in a freezer.

Table 2.1. Yields of protection of substituted pyridines.



Entry	R	yield (%)
1	2-Me	67
2	2-Et	55
3	2- <i>i</i> Pr	43
4	2-pentyl	54
5	2-Ph	63
6	2-Bn	68
7	2-(CH ₂) ₃ OBn	66
8	2,3- <i>di</i> Me	64
9	2,5- <i>di</i> Me	61
10	2,6- <i>di</i> Me	30

2.2.2. Catalyst Screening

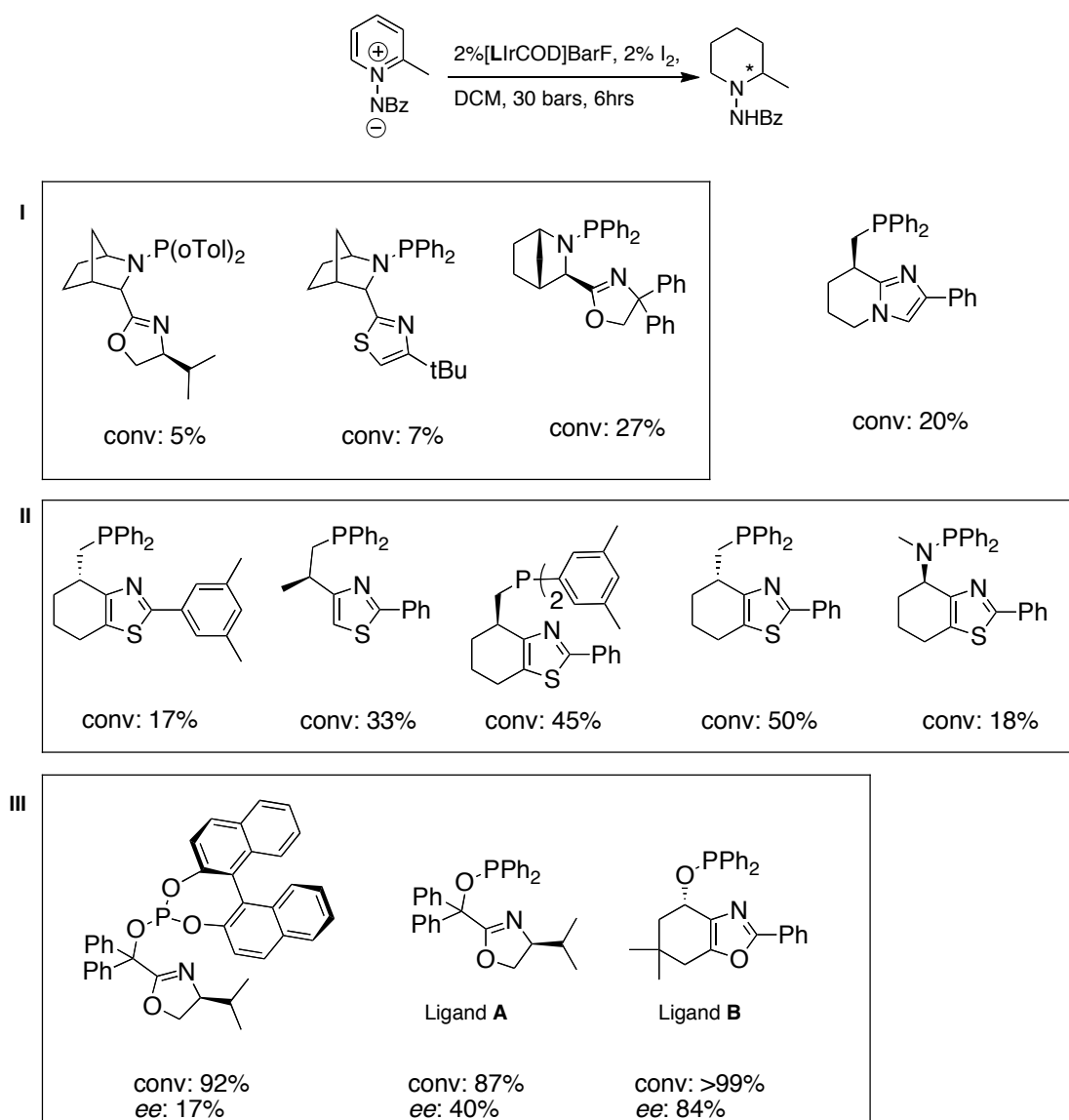
The protected 2-Me-pyridine, was screened against the group's catalyst library. Initially the catalysts were screened for conversion, and the *ee* was measured in good to full conversion (Scheme 2.4. below). The preliminary screening was conducted using 2% catalyst loading, 2% I₂ additive, 30 bars of H₂ gas and at room temperature for six hours.

From the screening, a series of trends were observed. Firstly this group's trademark bicyclic systems proved too sterically encumbered and gave extremely poor conversions (5 to 27%, Scheme 2.4, **I**).

Secondly, thiazoles (conversions of 50% and below Scheme 2.4, **II**) were inferior to oxazoline (up to full conversion and 84% *ee*, Scheme 2.4, **III**) as heterocyclic group on the ligand. This could be due to the lower basicity of the oxazoline, leading to a poorer electron donation to the iridium centre. The weaker base donates less electron density to the metal than the stronger base. From this, an overall more electron accepting iridium centre is obtained through oxazoline ligation than for thiazole ligation.

Thirdly, the ligands bearing an oxygen linker atom to phosphorous were superior to those with a carbon linker to the phosphorus. The oxygen is able to bind more tightly with the phosphorus than the carbon, leading to a stronger Ir-P bond thanks to increased back-donation from the iridium, and a more electron accepting iridium. The oxazoline is more basic than the oxazole or the thiazole (as determined by the pK_a of the corresponding acids), but the effect of the oxygen linker seemed strong enough to override this property to a certain degree (comparing ligands within grouping **III**). The iridium reaction centre benefited from the presence a ligand with a lesser electron-donating characteristic. The pyridine ring is electron rich compared to a more classic olefin bond, and the ylide protection disrupted the aromaticity.

Another key aspect, easily overlooked, is the size difference of the oxygen and the sulphur atoms. From its larger size, the sulphur in a thiazole ring would cause the attached phenyl group to point further inwards towards the iridium centre, altering the direction of bulky group on the ligand and thus sterically crowding the reaction centre further, compared to an oxazole group. Considering the bulk of the substituted pyridine substrate, this could be a potential cause for the poorer conversions observed by thiazole ligated catalysts.



Scheme 2.4. Result of catalyst library screening

2.2.3. Catalyst development

The screening of the catalyst library resulted in catalyst **B** as the best in the library. However an attempt was made to improve the ligand to obtain even higher *ee*.

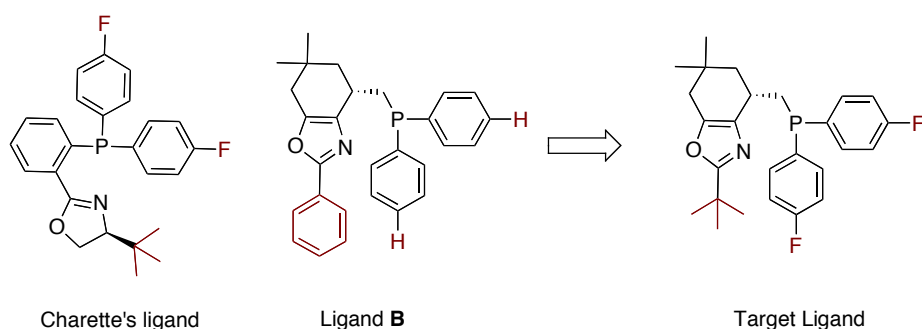
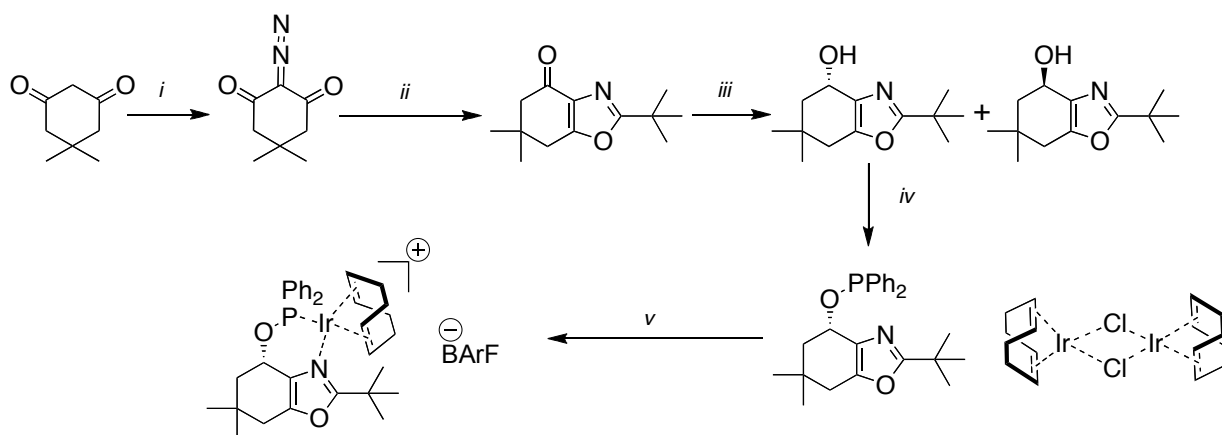


Figure 2.3. Design of the target ligand based on key features of existing ligands

With the structure of Charette's optimal catalyst, it appeared that the pre-existing oxazoline ligand **B** could be further improved by porting over two key features. The first is the replacement of the phenyl

group on the oxazoline ring by a bulkier *tert*-butyl group, which should generate a more crowded reaction pocket on the catalyst. The second feature is the presence of a *para*-fluoro-phenyl as aromatic phosphine group. This was determined to be optimal by a screening process conducted for the PHOX based ligand. The fluorine atom has both an electron donating and withdrawing effect, for a net weakly electron donating result.

Catalyst **C** was synthesised following the methods to obtain similar ligands (Scheme 2.4).^{40,51} Tosyl azide was added drop wise to dimedone, supplying fine yellow crystals in 70% yield (step *i*). The obtained diazodimedone dissolved in neat *tert*-butyl cyanide along with the rhodium acetate and allowed to decompose to the desired oxazole in 14% yield (step *ii*). Sodium borohydride was employed to reduce the ketone to a racemic mixture of secondary alcohols in quantitative yield, after an overnight reflux in ethanol (step *iii*). The enantiomers were separated using preparative HPLC and the (+) fraction was further reacted. It was deprotonated with *n*-BuLi, and Ph₂PCL was added to the mixture drop wise at 0 °C, and allowed to return to room temperature and stir for 90 minutes (step *iv*). The free ligand was complexed to the [Ir(COD)Cl]₂ immediately afterwards and then the anion was exchanged in a DCM:H₂O system with sodium BARf to supply catalyst **C** in 63% yield over two steps.



i: TsN₃, NEt₃, DCM, RT, 3h. *ii*: tBuCN, Rh₂(OAc)₄, 60°C, 7h. *iii*: NaBH₄, EtOH, ON, RT. *iv*: Ph₂PCL, BuLi, THF, -78°C, 1.5h. *v*: 1. [CODIrCl]₂, DCM, 1hr. 2. NaBARf, H₂O, DCM.

Scheme 2.4. Synthesis of Catalyst **C**

The catalyst obtained was then screened against the library of pyridines (Table 2.2). As can be seen from the results, the supposedly optimised catalyst thoroughly underperformed. As mentioned above, the catalyst employed by Charette featured a *tert*-butyl group, however in our catalyst the increased steric bulk did not result in an improvement of the *ee*. On the contrary, the reactive pocket being too crowded for the substrate to find a good fit (as *per* the selectivity model, see Figure 1.5.), which most likely caused the dramatic drop in the *ee*. Given the results obtained with a di-phenyl phosphine group, no attempt was made to synthesise the *para*-fluorophenyl version.

Table 2.2. Results of hydrogenation using the designed ligand

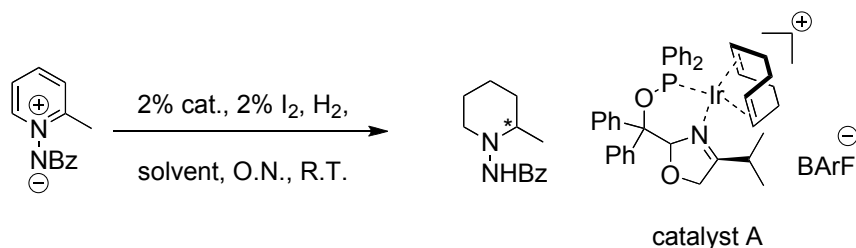
entry	R	conversion (%) ^a	ee (%) ^b
1	2-Me	full	24
2	2-pentyl	<20	25
3	2-Bn	full	10
4	2-(CH ₂) ₃ OBn	<20	12

2.2.4. Optimisation of the Hydrogenation Conditions

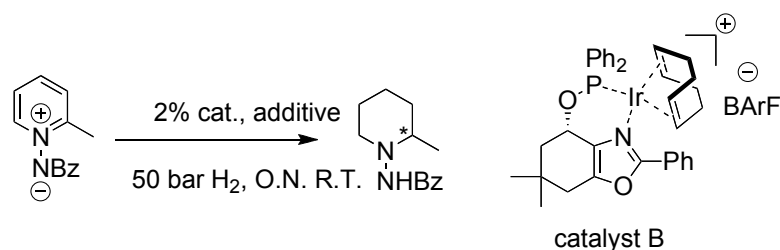
The optimisation of the reaction condition was conducted using catalyst **A** and the simplest substrate, 2-methyl-pyridine, in different solvents and at different hydrogen pressures.

As seen in the Table 2.3, the effect of pressure was studied first. At pressures below 30 bars poor conversion was observed while increasing the pressure to 50 bars not only increased the conversion but also increased the *ee* slightly.

Table 2.3. Result of the optimisation of the hydrogenation.



entry	solvent	pressure	conversion ^a (%)	<i>ee</i> ^b (%)
1	DCM	30	92	40
2	DCM	10	20	-
3	DCM	50	full	42
4	Toluene	50	full	25
5	THF	50	full	30
6	2,2,3 trimethyl pentane	50	-	-



entry	solvent	Additive	conversion ^a (%)	<i>ee</i> ^b (%)
7	DCM	0% I ₂	-	-
8	DCM	1% I ₂	full	64
9	DCM	2% I ₂	full	86
10	DCM	4% I ₂	full	35
11	DCM	2% Br ₂	full	63
12	DCM	2% ICl	full	50

^a: as determined by NMR. ^b: as determined by chiral HPLC.

Different solvents commonly used in conjunction with the N,P-ligated iridium catalysts were screened. Dichloromethane, gave the highest conversion and *ee* of the screened solvents. Toluene and THF provided lower *ees*, with the exception of 2,2,3 *tri*-methyl pentane which failed to dissolve the substrate and therefore gave no conversion.

Finally, the amount of halogens used as additive in the reaction was varied. In its absence the reaction failed to occur, implying that it plays a critical role in the catalytic reaction, as it does in the synthesis of *metolachlor*⁵². An increase in the iodine loading to 4%, twice that of the catalyst caused a slight decrease in *ee*. From this, it is inferable that the ideal amount of I₂ to employ is one that is stoichiometric with regard to the catalyst.

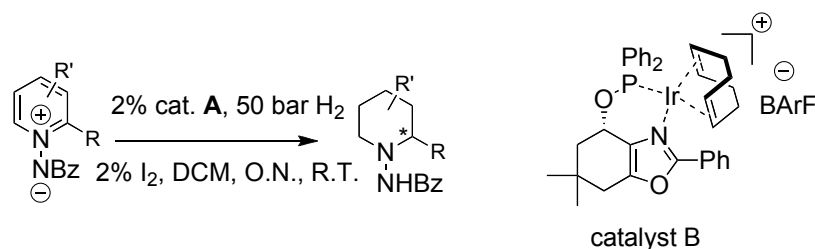
Inspired by the review of Vogl *et al.*,⁵³ different halogens (such as Br₂ and ICl) were screened in an attempt to improve the selectivity and rate of the reaction. However neither provided *ee* as high as the iodine.

2.3. Evaluation of Substrates

2.3.1 Hydrogenation

With the optimised conditions in hand, and the substrate library synthesised, the hydrogenations were performed.

Table 2.4. Result of the hydrogenation employing catalyst **B**.



entry	R,R'	conversion (%) ^a	<i>ee</i> (%) ^b
1	2-Me	full	86
2	2-Et	full	83
3	2- <i>i</i> Pr	full	10
4	2-pentyl	full	77
5	2-Ph ^c	full	40
6	2-Bn	full	61
7	2-(CH ₂) ₃ OBn	full	90 (98) ^d
8	2,3- <i>di</i> Me	35 ^c	-
9	2,5- <i>di</i> Me	full ^c	-
10	2,6- <i>di</i> Me	full	-

^a: as determined by NMR. ^b: as determined by chiral HPLC. ^c: after 6h reaction. ^d: after recrystallisation from boiling EtOAc

As can be seen from Table 2.4. catalyst **B** was able to reduce all the synthesised substrates in full conversion in all cases, except for the tetra-substituted substrate (entry 8). The linear alkyl substrates gave good conversions, with a small decrease in *ee* observed as the chain length increased (84-77% *ee*). The best enantioselectivity was observed for entry 7, which was performed on a significantly larger scale (400mg as opposed to the usual 20mg used in the screening) and after a single recrystallisation from boiling ethyl acetate gave 98% *ee*.

Secondly, the more sterically hindered substituents, entries 3 and 5, gave the lower *ee*. This drop in *ee* is likely caused by their poor fit within the reaction centre and their similarity in steric size with the adjacent nitrogen connected group. Surprisingly, even with a shorter reaction time (6 hours rather than overnight) the phenyl bearing substrate gave full conversion, whereas the other substrates required a longer reaction time (such as the 2-ethyl obtaining only 94% conversion in 6 h). The benzyl containing substrate (entry 6) gave a lower *ee* than alkyls, which would imply that the bulk of the α -substituent is the source of the selectivity.

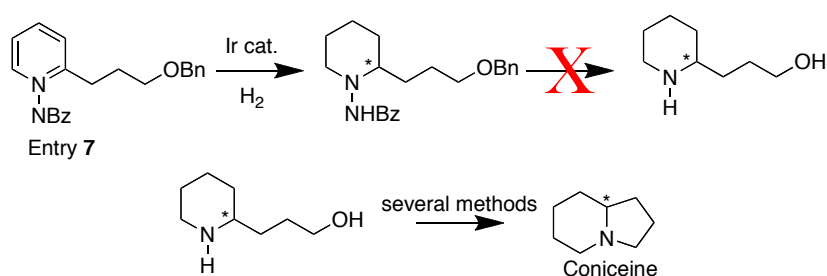
Thirdly, the di-substituted substrates (entries 8-10) gave poor results, but for different reasons. For entries 9 and 10, no starting material was observed after hydrogenation. Due to a poor ratio between fully hydrogenated and partly hydrogenated products, and diastereomers, the spectra recorded for the hydrogenation product proved impossible to interpret. Finally, the tetrasubstituted double bond encountered the expected problem in its hydrogenation, since catalyst **B** has not been reported to be able to successfully hydrogenate tetrasubstituted olefins in the past.

2.3.2. Selectivity

The absolute configurations of the products are not known, however a trend has been observed. The major product eluted first by chiral HPLC, in all cases but two. This inversion of elution order (which could be interpreted as an inversion of chirality) was observed for the substrates giving the lowest *ee* (Table 2.4, entries **3**, **5**). While the mechanisms of the hydrogenation of these pyridines remain to be determined, one can assume that the selectivity of the hydrogenation is tied to the bulk of the substrate's substituent, but not necessarily according to the usual quadrant model.

2.4. Application

The deprotection of the hydrogenated products would yield asymmetric pyridines, which constitute valuable building blocks in organic chemistry. The structures of the deprotected substrates lend themselves well to the synthesis of alkaloids or might even directly constitute biologically active molecules such as 2-benzyl-piperidine.



Scheme.2.5. Supposed synthetic pathway to coniine and coniceine

Another elegant application of this developed methodology would be the short synthesis of indolizidine, commonly referred to as coniceine. Even though it is not an alkaloid in the strictest sense (it is not found in nature), it does constitute the core of several natural products of great interest, such as swainsonine (an anti tumour and cancer drug).⁵⁴

It was intended during the substrate design phase that coniceine would be synthesised *in one pot* from the double deprotection followed by the cyclisation of entry **7** (from table 2.2). The substrate itself had been previously synthesised by Legault *et al.*^{50b} However no further transformation had been conducted, instead two methods were suggested that would simultaneously cleave both protecting groups: employing Birch conditions,⁵⁵ or Raney nickel.⁵⁶ Both methods are reported to work in good yields in literature, but were not reported as attempted by Legault *et al.*

A variety of reaction conditions were tried to deprotect the compound: the mildest was hydrogenation with an excess of Raney nickel under 5 bars H₂ overnight and the most strenuous was Pd/C (activated by heating under vacuum of 3 hours), 50 bars H₂ for 24 hours.

Research into the cyclisation of the deprotected amino alcohol showed that the principal methods employed to convert it (or analogous compounds) to coniceine are the aza-prins reaction⁵⁷ and the use of triphenylphosphine in a tetrahalogenated carbon solvent (CCl₄ or CBr₄).⁵⁸ Iridium could also be used to perform the *N*-alkylation.⁵⁹ The use of Raney nickel to conduct the cyclisation had been reported, and would have constituted an ideal complement to the envisioned deprotection.⁶⁰

4. Conclusion and outlook

Methodology development should not exist in isolation: its very aim is to provide other chemists with the tools to conduct their own research, just as this research was conducted by “*standing on the shoulders of giants*”. By employing the catalysts developed in this group in the past decade the project was brought to fruition.

This project expanded on the previously developed methods both by increasing the number of substituted pyridines to undergo hydrogenation, and by exploring the possible methods of improving on the current reaction conditions. A selection of mono- and disubstituted *N*-Iminopyridinium ylides were synthesised and hydrogenated to yield chiral piperidine building blocks precursors. Full conversion was obtained in most cases, and consistent *ee* (77-88%) were obtained for a selection of alkyl substituents. After a single recrystallisation from boiling ethyl acetate the *ee* was increased to 98% for a synthetically interesting substrate. Further research into the cleavage of hydrazine bond could provide a simple pathway to alkaloids and chiral building blocks from this method.

Though the chemistry of piperidines is as varied, as it is well known, the role and effects of the additive remain uncertain, as does the mechanism of this reaction. Answering these questions would yield valuable insights into how to optimise this reaction further.

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