Noble Metal Catalysed Reductions and Rearrangements

ALBAN CADU
Abstract

The focus of this thesis has been organometallic catalysis applied to compounds containing heteroatoms which are usually poisonous to metal catalysts, by channelling their innate reactivity advantageously. The studies described in this thesis concentrate, in the first part, on iridium catalysed asymmetric hydrogenation (papers I and II) and in the second part, on gold catalysed internal rearrangements (papers III and IV). In each case, two classes of compounds are studied: pyridinium salts or sulphurous compounds. The asymmetric hydrogenation of pyridinium compounds was performed with 2% loading of N,P-ligated Ir catalyst with I₂ additive (paper I) to achieve moderate to good enantiomeric excess (up to 98%). In paper II, olefinic sulphones were hydrogenated with an efficient 0.5% catalytic loading. In most cases full conversion was obtained and with good to excellent ees (up to 99%). The products of these reductions are chiral compounds, which could constitute further chemical building blocks. Palladium and gold were used sequentially in paper III, in order to perform a “Click” thiol-yne reaction followed by a semi-Pinacol rearrangement, leading to isolated yields of up to 98%. In paper IV The gold catalysed rearrangement of alkyl-pyridinium diynes was conducted, with a number of substrates providing >90% NMR yield. A highly selective hydrogenation was performed with a heterogeneous palladium catalyst to yield single diastereomer products. This methodology consists of up to three steps, with two catalysts in one pot.

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urn:nbn:se:uu:diva-272383 (http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-272383)
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 papers, which are referred to in the text by their Roman numerals.

I  Alban Cadu, Puspesh K. Upadhyay and Pher G. Andersson.  
Iridium catalyzed hydrogenation of substituted pyridines.  

II  Byron K. Peter, Taigang Zhou, Janjira Rujiwanich, Alban Cadu, Wanchuk Rabten, Suttichat Kerdphon and Pher G. Andersson.  
An Enantioselective Approach to the Preparation of Chiral Sulfones by Ir-Catalyzed Asymmetric Hydrogenation.  
*Journal of the American Chemical Society*, 2014, 136, 16557-16562

III  Alban Cadu, Rahul A. Watile, Srijit Biswas, Andreas Orthaber, Per Sjöberg and Joseph S.M. Samec.  
One Pot Synthesis of Keto-Thio-Ethers by Pd/Au Catalyzed Click and Pinacol Reactions.  
*Organic Letters*, 2014, 16, 5556–5559

IV  Svetlana Tšupova,† Alban Cadu,† Fabian Stuck, Frank Rominger, Matthias Rudolph, Joseph S. M. Samec, A. Stephen K. Hashmi.  
Dual Gold (I) Catalysed Cyclisation of Dialkynyl Pyridinium salts, *Manuscript*

Reprints are made with permission from the respective publishers.
The author wishes to clarify his contribution to the papers:

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

II Synthesised and screened part of the substrates, contributed in writing the paper, supporting information and analysing results.

III Synthesised the majority of the substrates, performed most of the optimisation, performed all analysis except X-ray and HRMS, wrote the manuscript and the supporting information.

IV Synthesised some of the substrates, performed part of the catalysis, devised, optimised and performed the hydrogenation steps, wrote the manuscript, contributed to the analysis of the data and writing of the supplementary information. †:authors having contributed evenly.
Publications not included in this thesis

V  **Alban Cadu**; Alexander Paptchikhine and Pher G. Andersson.
Birch Reaction followed by Asymmetric Iridium-Catalysed Hydrogenation.
*Synthesis*, 2011, 3796-3800 (*Practical Synthetic Procedure*)

VI  **Alban Cadu** and Pher G. Andersson.
*Journal of Organometallic Chemistry*, 2012, 714, 3-11 (*Review*)

VII  **Alban Cadu** and Pher G. Andersson.
Iridium Catalysis: Application of Asymmetric Reductive Hydrogenation.
*Dalton Transactions*, 2013, 42, 14345-14356 (*Perspective*)
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<td>*</td>
<td>Centre of chirality</td>
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<td>Ac</td>
<td>Acetyl</td>
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<tr>
<td>Ar</td>
<td>Aryl</td>
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<td>Bn</td>
<td>Benzyl</td>
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<td>Bz</td>
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<td>cat.</td>
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<td>Dichloromethane</td>
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<tr>
<td>DCE</td>
<td>1,2-Dichloroethane</td>
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<tr>
<td>DIBAL-H</td>
<td>Diisobutylaluminium hydride</td>
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<td>ee</td>
<td>Enantiomeric excess</td>
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<td>Ethyl</td>
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<td>Estrogenic Receptor</td>
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<td>HPLC</td>
<td>High performance liquid chromatography</td>
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<tr>
<td>iPr</td>
<td>Isopropyl</td>
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<tr>
<td>mCPBA</td>
<td>meta-Chloroperoxybenzoic acid</td>
</tr>
<tr>
<td>Me</td>
<td>Methyl</td>
</tr>
<tr>
<td>BuLi</td>
<td>n-Butyl lithium</td>
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<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
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<td>O.N.</td>
<td>Overnight</td>
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<tr>
<td>o-tol</td>
<td>Ortho-tolyl</td>
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<tr>
<td>Pd/C</td>
<td>Palladium on charcoal</td>
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<tr>
<td>Ph</td>
<td>Phenyl</td>
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<tr>
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<td>tert-Butyl</td>
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<tr>
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Main Catalysts and Counter-Ions in this Thesis
(catalysts referred to in the text by capital bold letters)
1. Introduction

As the Enlightenment bore fruit, Alchemy evolved into Chemistry and natural philosophers became scientists.\(^1\) This brought about the discovery of the elements, hydrogen (Cavendish, 1766), oxygen (Lavoisier, 1778) and later iridium (Tennant,\(^2\) 1804 and Wollaston,\(^3\) 1805).

For over a century, organometallic chemistry (the science of incorporating metals to erstwhile organic compounds) has been a core field of chemistry. Victor Grignard received the Nobel Prize for his eponymous addition of organomagnesium halides to “aldéhydes” and “cétones”, which to this day remains relevant.\(^4\) Nor would he be the last organometallic chemist to be awarded this Laureate; in the 21\(^{st}\) century, a further ten have been similarly honoured.

1.1. Catalysis

1.1.1. Defining Catalysis

The purpose of the catalyst is to “increase the rate of reaction”. This facilitation occurs because the catalyst alters the reaction pathway, normally with lower energetic barriers through binding to the reagent.

The use of metal containing catalysts constitutes the crux of this research. Scheme 1 illustrates a reaction between two reactants a and o both with and without a catalyst. The catalyst will usually bind reversibly to a reagent to facilitate the chemical reaction. Ideally solely the catalytic cycle depicted would occur, repeating itself immutably until the total consumption of all reactants. In practice, alternate catalyst deactivating pathways occur, such as nitrogen or sulphur containing compounds binding irreversibly to the metal centre, leading to a loss of catalytic activity, or even side product formation; not a snake biting its own tail but a multi-headed hydra.
1.1.2. The Forms of Catalysis

Catalysis can be divided into three main fields: biocatalysis (using naturally occurring molecular systems, such as enzymes), organocatalysis (using small organic molecules) and metal based catalysis.

In metal based catalysis, a metal acts as the catalytic centre. Metals are present as structural features in some organocatalysts, such as Fu’s chiral DMAP, though for the purpose of this discussion, only active metal centres will be considered. Likewise the occurrence of metal in natural bio-inorganic systems, such as iron in haemoglobin, is well known however these tend to be folded in within biocatalysis. This thesis will explore facets of organometallic catalysis.

1.1.2.1. Heterogeneous catalysis

This consists of having the reactant (often referred to as substrate) in a separate phase from the catalyst. Most commonly this means a solid-liquid system or although the solid-gas systems exist (for example cars’ catalytic converter). This allows for an easier separation of the catalyst from the reaction media, upon completion and possibly its re-use. Its drawbacks come from the surface area acting as a limiting factor to the rate of reaction and the greater difficulty in studying the catalyst’s behaviour during the reaction.

1.1.2.2. Homogeneous catalysis

This is the use of a catalyst and the reactant in the same reaction medium, most often in solution. This normally requires the use of ligand(s) to form metal complexes, thus enabling its solvation. Its advantages over homogeneous catalysts are the often higher selectivity and faster reaction rates. The downside is the difficulty in recovery for re-use.
1.1.3. Catalyst Deactivation

Catalysts can be deactivated through physical or chemical means. The former corresponds to the inactivation of a heterogeneous catalyst surface (abrasion, blocked by ashes or residues etc) whereas the latter is the irreversible coordination of atoms to the metal centres preventing further participation in catalytic cycles.

Catalyst poisoning stems from the ratio of bonding energy between the desired reagent and the “poison”. What is a poison in one reaction (thiols in hydrogenation) might not be so in another (thiol-yne reaction, as described in Paper III). Through their ability to bond to metal strongly, nitrogen and sulphur containing compounds are often considered poisons, in particular to platinum group metal catalysis.

1.2. Sustainable, Efficient and Green Chemistry

Sustainable chemistry is a complex issue that can be approached in many ways. The most visible of which are atom economy, atom efficiency and “Click”. Whether from an ecological or economical point of view, waste is undesirable; hence steps should be taken to either prevent or at least minimise its production.

1.2.1. Catalysis

Catalysis offers a wealth of opportunities, to circumvent classical stoichiometric chemistry. By opening new reaction routes to the synthetic chemist, classical methods which had historically generated stoichiometric amounts of waste can be avoided in favour of more atom efficient routes. If there is an energetic mountain, the catalytic reaction uses a tunnel whereas a stoichiometric reaction must climb. Catalytic addition of hydrogen across a double bond is waste-free, in stark contrast to a DIBAL-H reduction (Scheme 2).

\[ \text{Scheme 2. Catalytic and stoichiometric reduction of a double bond} \]
1.2.2. Selectivity

This directly impacts the yield. Whether it is chemo-, regio- or stereo-selectivity, it is important to control which group reacts, where and how. Poor selectivity converts (valuable) starting material to waste, which requires additional purification to remove (Scheme 3).

Scheme 3. Stereo-selective reduction of a pro-chiral double bond

This has been one of the guiding principles behind the reactions studied in this thesis. A successful asymmetric hydrogenation is clean, yielding a single enantiopure product, the only loss stems from the venting of the reaction vessel. Rearrangements are supremely sustainable reactions since the molecule is reshaped at no atomic loss.

1.3. Asymmetry and Chirality

In 1874, Le Bel defined asymmetry:

“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.”

A tetra substituted carbon (as described above) will adopt a tetrahedral configuration, which in turn leads to the possibility of symmetry. A simpler way to visualise this would be a figure.

Figure 1. Illustration of two mirror image tetra substituted carbons

The two illustrative molecules above (Figure 1) are identical but for the distribution of the four substituents around the centre of chirality. The term chirality derives from the Greek for hand, hands being the most recognisable asymmetric (or chiral) objects.
These two mirror images are called stereomers (enantiomers, if there is a single centre of chirality). Each centre is labelled as \( R \) (rectus) or \( S \) (sinister) according to the Cahn-Ingold-Prelog rules. A judicious choice of catalyst and reactants can selectively convert a pro-chiral molecule into one of the desired stereomer.

![Figure 2. Two stereomers of Naxolone](image)

For example: \(-\) -Naxolone acts as a potent opioid antagonist administered to remedy opiate overdoses whereas \( +\) -Naxolone has no significant binding to opioid receptors (Figure 2).  

The body reacts specifically to different isomers, as receptors are most often designed for a single stereomer; much like a glove is designed for either a left or right hand. This applies to a wide variety of drugs.

The notation of \( +\) and \(-\) for different enantiomers originates from the initial use of polarimeters to characterise compounds, as the reading would indicate either a positive (dextro) or negative value (levo) depending on the observed rotation of polarised light. This led to the use of enantiomeric excess or \( ee \) to measure optically the purity of a sample. The \( ee \) is defined as the ratio of the excess of one enantiomer over the other, divided by the total amount of both enantiomers present. Should there be no such excess (i.e. a 1:1 ratio of \( R \) and \( S \)) then the mixture is said to be racemic, even though the constituting elements are chiral.

There are three main ways of obtaining a chiral molecule: chiral pool, chiral resolution and asymmetric synthesis. Each of the three has its own uses and limitations.

### 1.3.1. The Chiral Pool

This approach consists of using a naturally occurring chiral compound as a starting material for the synthesis. This compound acts only as a source of chirality in the molecule. Amino acids are particularly popular by virtue of their high functionalisation by weight, their wide availability, low price and high enantiopurity. However, the limitation of this method is the availability of the desired enantiomer or diastereomer.
1.3.2. Chiral Resolution

Chiral resolution consists of separating one of the enantiomers from a racemic mixture. There are three principal ways of doing this.

The simplest and most time consuming is chiral chromatography. A racemic mixture is run through an HPLC column which has a chiral solid phase, retaining one enantiomer longer than the other. Through iteration, the whole of the racemic mixture can be separated into two optically pure fractions.

The second method is co-crystallisation with a chiral compound to obtain a diastereomerically pure salt. Much like the above, it aims to separate a racemic mixture into two chirally pure fractions.

Lastly, kinetic resolution consists of exploiting the difference in reaction speeds between two enantiomers to obtain a mixture of enantiomerically pure unreacted starting material and enantiomerically pure product. The most advanced systems will include a racemising agent to convert the undesired enantiomer back to its racemate; this is called dynamic kinetic resolution. Resolution is limited at 50% yield (except in the dynamic kinetic case), and while this leads to a waste of material it is easy and reliable, hence it’s widespread application, especially in industry.

1.3.3. Asymmetric Synthesis

This is the introduction of chirality to a pro-chiral molecule where there was none before, as opposed to starting with chiral compounds (see 1.3.1). This can be done either with the use of chiral auxiliaries added temporarily or by using a chiral catalyst which will transfer its chiral nature to the substrate.

There are many examples of chiral moieties (Oppolzer’s sultam,14 Evan’s moiety…15), which have proved themselves invaluable, especially in Aldol chemistry. However they are needed in stoichiometric amount, require two additional steps (one to attach then one to remove them) and cannot always be recovered for reuse.

Alternatively, a chiral catalyst can be employed. This is one of the foci of the research described here. Asymmetric hydrogenation relies on optically active ligands to generate a sterically controlled chiral environment around the metal reaction centre, which translate into an imposition of chirality onto the pro-chiral substrate as shall be discussed in Chapter 2.

1.4. Aims of this Thesis

The aim of this thesis is to overcome intrinsic problems of using substrates with strongly coordinating heteroatoms in noble metal catalysis. Sulphur and nitrogen containing substrates were chosen for study in different catalytic reactions. These reactions are: iridium catalysed asymmetric hydrogenation
of olefinic bonds and gold catalysed rearrangements. These principal inves-
tigations form the two core chapters of this thesis. Since these coordinating
substrates are very challenging, and known to inhibit catalysis, especially in
noble metal based reactions, the underlying question at the heart of each
project has been:

*How to overcome the heteroatoms’ detrimental effects in order to operate
highly efficient noble metal catalysis?*

Both nitrogen and sulphur are known to poison catalysts through coordi-
nation to the metal centre, in each project this had to be addressed. In all
cases, the presence of a heteroatom (sulphur or nitrogen) had intrinsic limita-
tions, which had to be overcome to achieve the following objectives:

- To improve on current methods of asymmetric hydrogenation of pyri-
dinium compounds, through catalyst and condition optimisation
- To expand the scope of iridium catalysed asymmetric hydrogenation, to
electron-poor olefinic sulphones
- To harness gold catalysed semi-Pinacol rearrangement for C-C bond
formation
- To rearrange dialkyne pyridines, using dual gold catalysis, by overcom-
ing pyridine’s catalyst deactivating properties

As nitrogen and sulphur bind strongly to metals through their free electron
pairs, the hypothesis underpinning this work is that harnessing these electrons
would circumvent their intrinsic limitation.
2. Iridium Catalysed Asymmetric Hydrogenation (Papers I and II)

“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]” Smithson Tennant

2.1. Introduction

In 2001, Noyori and Knowles received jointly the Nobel Prize in chemistry for their work in asymmetric hydrogenation.\cite{Noyori2001} The use of platinum group metal for hydrogenation has become highly popular due to their high reliability and their potential for selectivity when required. In particular, palladium adsorbed on charcoal is a staple of any modern lab.

Scheme 4. Examples of historical platinum group hydrogenation catalysts

Wilkinson’s catalyst (Scheme 4. 1), is one of the most famous examples of platinum group catalysts,\cite{Wilkinson1973} earning him (along with Ferrocene) the Nobel Prize in 1973. A similar catalyst, Vaska’s complex, was synthesised, by the Estonian-born chemist, using an iridium metal centre (Scheme 4. 2).\cite{Vaska1990} Further improvement on these catalysts were made by changing the counter-ions
to less binding ones, the *altebate* counter-ion appears to be the least binding to be employed with iridium to date.\textsuperscript{19}

Additionally, diminishing the ratio of ligand to metal and switching from mono- to poly-dentate ligands improved catalytic performances and stability drastically. The active species are generated *in situ* by the hydrogenation of the COD ligand into a non-binding cyclooctane (freeing previously occupied reaction sites). This discovery was made by Schrock and Osborn, with a rhodium catalyst (*Scheme 4. 3*).\textsuperscript{20} Crabtree discovered his eponymous iridium catalyst, which was able to hydrogenate even non functionalised olefins with unprecedented results (*Scheme 4. 4*).\textsuperscript{21}

Switching from multiple monodentate ligands to a single chiral polydentate ligand (*Scheme 4. 5-6*) enabled the asymmetric hydrogenation of double bonds (olefins, ketones, imines). A famous application of this is the L-DOPA process.\textsuperscript{16a}

### 2.1.1. Asymmetric Hydrogenation

The PHOX-ligand was initially designed for palladium chemistry, in 1993, simultaneously by Pfaltz,\textsuperscript{22} Helmchen\textsuperscript{23} and Williams.\textsuperscript{24} However, its use by Pfaltz in 1998 gave birth to asymmetric hydrogenation of non-functionalised olefins (*Scheme 4. 6*).\textsuperscript{25} Previously this was an arduous task as rhodium and ruthenium catalysts would need a nearby coordinating group (typically ketones, ester or amides) in addition to the targeted double bond to bind the substrate *via* a bidentate mode in order to achieve high *ees*. This was extensively studied, especially by the Halpern group, leading to an elucidation of the mechanism.\textsuperscript{26}

Iridium catalysed asymmetric hydrogenation has been a very active field since its inception in 1998. Many reviews have been written, covering its different aspects.\textsuperscript{27}

Following on an early X-ray and NMR study,\textsuperscript{28} two mechanisms were proposed for iridium catalysed hydrogenation, either Ir (I/III)\textsuperscript{29} or Ir (III/V).\textsuperscript{30} While broadly similar, they differed in the number of hydrides bound to the metal at the key reactive states (*Scheme 5*). Due to the difficulty in isolating intermediates for study, it is only recently that an NMR study by Pfaltz *et al* proved that the Ir (III/V) mechanism is in fact correct.\textsuperscript{31} This was achieved by operating the reaction in comparatively low hydrogen pressure (3 bars) which prevented the reaction from reaching completion, until the pressure was increased. These results show that Ir\textsuperscript{III} does not lead to reaction completion, but instead Ir\textsuperscript{V} is required.

From this understanding of the catalytic cycle, a quadrant model (similar to the one used in asymmetric Sharpless dihydroxylation)\textsuperscript{32} was devised in order to understand and predict the chirality of the product, this has guided the design of ligands in the Andersson group.\textsuperscript{33}
Scheme 5 Mechanism of Ir catalysed hydrogenation (charge and counter-ion omitted for clarity)

Figure 3. Quadrant model (top) Schematised 3D view Overlaid onto iridium catalyst B and a simple alkene (bottom)

The chirality is imparted to the substrate in the two marked steps (Scheme 5) and is dictated by the spatial arrangement of the steric bulk of the ligands around the metal centre (Figure 3). A plane exists, which contains all the hydrogen, iridium and nitrogen atoms. The quadrants are considered to be open if there is no bulk coming “forward” from this plane (with the olefin
binding in the front). Reciprocally, the quadrants are considered (semi-) hindered if bulk juts out from this plane. The hydrides will be added stepwise from the “rear” face of the olefin. Figure 3 illustrates this special arrangement for a commonly used N,P ligands. The open quadrants are diagonally opposite to each other, as are the hindered and semi-hindered ones. The greatest steric hindrance is caused by the phenyl ring (in the illustrated case) being orthogonal to the plane and blocking the quadrant for bulkier groups. The phosphorous bound phenyl group has a smaller encroachment into the plane and leads only to partial hindrance. The orientation of the substrate at the binding site will depend on its own spatial arrangement. Supposing a tri-substituted olefin, the bulkiest substituent will place itself into an open quadrant and the H will find itself opposing the most hindered group on the catalyst ligand, so as to minimise the steric clash. This model fits best for trans-like olefins, as will be seen later in this chapter.

By modifying the size of the relevant groups, the relative steric hindrance around the coordination centre can be modulated to fit the desired substrate. Ortho-tolyl is a common replacement for the phenyl groups, as they differ only modestly electronically and increase the bulk marginally, as in the case of catalyst D.34

High ees and yields depend on the ability to tailor the size of the reaction pocket to the substrate: too encumbered and the yield will suffer, too open and the selectivity risks dropping.

2.1.2. Asymmetric Hydrogenation of Pyridines

The asymmetric hydrogenation of nitrogen containing compounds remains difficult. Nitrogen is able to competitively bind to the metal centre, displacing the ligand or irreversibly binding to the reactive site, both of these phenomena lead to catalytic deactivation. Nonetheless, iridium catalysed hydrogenation has been successfully employed to that effect. Most commonly, P,P ligands are employed, along with an additive,35 though N,P ligands have also yielded results.36,37a Pyridines are especially difficult substrates because of the energetically unfavourable loss of aromaticity. N-substitution of the substrate is a convenient way of destabilising the aromaticity prior to the hydrogenation.37 The attached moiety can fulfill additional roles, such as generating bulk or acting as a chromophore. Though simple salt formation has been shown to work for isoquinolines and was recently studied by Mashima et al.38

While the exact mechanism of hydrogenation of pyridines is yet to be elucidated, one can assume similar pathways to those of the hydrogenation of imines.39 The alternative, an outer-sphere and low pressure mechanism, similar to that of the hydrogenation of quinolines,40 seems less likely due to need for high pressure (as was discovered during the reaction optimisation).
2.1.4. Synthesis of Asymmetric Sulphone

A few examples of medical uses of chiral sulphones exist, such as Tazobactam and Remikiren. However their synthesis remains challenging due to the small number of methods available to generate chiral sulphones. Copper catalysts can generate chiral sulphones, as per studies by the Carretero and Charrette groups. Most recently, two publications have sought to offer more accessible routes to their synthesis, one by the Zhang group, via rhodium catalysed asymmetric hydrogenation and the other by the Fu group, via a Negishi cross couplings. One can only hope that these new methodologies will offer more tools to the pharmaceutical industry, to facilitate the discovery and synthesis of novel medication.

2.2. Aims and Objectives

The aim of the work described in this chapter was to expand on the substrate scope of Ir catalysed asymmetric hydrogenation. Since nitrogen and sulphur are catalytic poisons, workarounds must be found to prevent their deactivation of the catalyst. For pyridines, the formation of a pyridinium salt was chosen to harness the nitrogen’s free electron pair, an improvement on pre-existing results was sought by optimisation of the metal ligand and of the reaction conditions. The oxidation of sulphur to a sulphone was presumed to negate its poisonous character as it would leave the sulphur with no free electron pairs with which to bind to the metal. This was probed by synthesising and reacting a broad range of olefinic sulphones, and by varying the distance of the sulphur to the double bond.

The work described in this chapter consisted of the asymmetric hydrogenation of N-substituted pyridines and of olefinic sulphones, as summarised in Scheme 6.

Scheme 6. Work performed for this chapter
2.3. Substrate Synthesis

2.3.1. N-Substituted Pyridines

Scheme 7. Synthesis of N-substituted pyridines

\[ \text{i: } 1. \text{NET}_3, \text{acetone. } 2. \text{2,4-dinitro-chlorobenzene, R.T. 2h. } ii: \text{H}_2\text{N-NH}_2 \text{ in MeOH, DCM, 0°C, O.N., then HCl. } iii: \text{sealed vessel, 40°C, 1:1 H}_2\text{O:THF, O.N. } 2. \text{10% NaOH aq, BzCl, R.T., 4h. } iv: \text{1. BuLi, THF, 2h. 2. MeI, R.T. O.N. } v: \text{1. NaH, THF, 0°C, 10 mins. 2. BnBr, 0°C, 20 mins} \]

The pyridine substrates were synthesised following the established protocol by Charrette as outlined in Scheme 7 (7-11). In some cases, the starting pyridines were not commercially available, those were synthesised as illustrated. The first steps \(i\) and \(ii\) are quantitative, step \(iii\) proceeded with moderate (30-68%) yields, with a drop in yield linked to an increased steric bulk, especially for 2,6-dimethyl pyridine.

2.3.2. Sulphones

The synthesis of the sulphone substrates was operated along three similar pathways depending on the desired product.

Allylic sulphones were generated as per the pathway depicted in Scheme 8. Step \(i\) gave a mixture of the \(E\) and \(Z\) isomers of 16 with ratios varying from 3:1 to 9:1 in the best cases. The separation of the two isomers was performed after the reduction of the ester group to the more polar alcohol 17. The following steps \(ii\) to \(iv\) proceeded easily and in good yields. Since publication, a novel one pot synthesis of allylic sulphones has been reported, which would have enabled a faster generation of the substrates library.
Scheme 8. Synthesis of allylic sulphone substrates

\( i: \text{NaH, THF, R.T., O.N.} \quad ii: \text{DIBAL-H, Et}_2\text{O, R.T., O.N.} \quad iii: \text{PBr}_3, \text{Et}_2\text{O, R.T., O.N.} \quad iv: \text{R'SH, NaOMe, THF, R.T., O.N.} \quad v: \text{mCPBA, 0°C, DCM, 2-4h.} \)

2.4. Catalyst screening

2.4.1. Pyridines

Having synthesised a first substrate (11), a number of catalysts were screened, see Scheme 9 for a few representative examples.

Scheme 9. Catalytic screening for selected catalysts.

The \( ee \) was only measured for the products of the reactions with satisfactory conversion. Initial screening were performed with 2% catalyst loading, 2% \( \text{I}_2 \) additive, 30 bars of \( \text{H}_2 \) gas and at room temperature for six hours, as per the methodology devised by Charette.\(^{37a}\)
In parallel to the above trend, phosphinite containing ligands outperformed the phosphine ligands. The P-O bond involves more orbitals than the P-C one and alters the phosphorous electron donation into the Ir-P bond.

As a result of the screening, the ligands could be subdivided into three main classes. The first group was the bicyclic ligands, which are strongly sterically encumbered, proved a poor match for the substrate (5 to 27% conversion, 22). The conversion was affected negatively by the increase in size of the phosphinic aryls as can be seen from the thiazole containing ligands (45 vs. 50%, 23 and 24). The thiazole ligands did not perform as well as the oxazoline ligands (25-26). A possible explanation could lie in the less basic nature of the oxazoline, which would lead to weaker electron donation to the iridium.

2.4.2. Ligand Design

Out of a desire to increase the ee of the product, an alternate ligand 28 was devised, based on the above screening, as well as Charrette’s (Scheme 10). Two key aspects seemed to differ between the two ligands: the size of the substituent in the “hindered” quadrant (tBu vs Ph) and the presence of a fluorine atom in the para position of the phosphinite aryl. The former would be a steric effect whereas the latter would be mostly electronic. Hence the target ligand was designed.

![Scheme 10. Ligand design](image)

Based on previous protocols a reaction scheme was devised as a test, prior to synthesising the presumed optimised catalyst (Scheme 11). However as catalyst B provided superior results to C, to the para-fluorinated version was not synthesised.
Scheme 11. Synthesis of catalyst C

i. TsN₃, NEt₃, DCM, RT, 3h. ii: tBuCN, Rh₂(OAc)₄, 60°C, 7h. iii: NaBH₄, EtOH, ON, RT. iv: HPLC separation. v: Ph₂PCl, BuLi, THF, -78°C, 1.5h. vi: 1. [COD-IrCl]₂, DCM, 1hr.

2.4.3. Sulphones

The ligand screening, to find the optimal catalysts for the asymmetric hydrogenation of olefinic sulphones, was performed in a previous communication. Due to the similarity between the substrates in the communication and those described in paper II, the same catalyst D, was employed in all but two cases.

2.5. Hydrogenation Results

2.5.1. Pyridines

In order to obtain the best possible results, the conditions for the reaction were optimised, employing compound 11a. This was done by varying the pressure and solvent. As expected an increase in pressure to 50 bars led to full conversion. A screening of solvents showed that DCM led to the best results.

Having determined the optimal solvent and pressure, the effect of the additive was probed. The use of halides as additives is known to have positive effects on the hydrogenation of some pyridine like substrates, such as quinolines, or in the synthesis of the herbicide metolachlor. The use of an additive was found to be essential to the reaction. The optimal ratio of I₂ to catalyst was found to be 1:1 as a drop in ee was observed when this was deviated from. In the review by Vogl et al., the use of halides as additives was touched upon, and inspired the screening of Br₂ and ICl. However neither of these halide compounds proved as effective as iodine (Table 1).
**Table 1. Optimisation of the additive**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive</th>
<th>Conversion (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0% I2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>1% I2</td>
<td>full</td>
<td>64</td>
</tr>
<tr>
<td>3</td>
<td>2% I2</td>
<td>full</td>
<td>86</td>
</tr>
<tr>
<td>4</td>
<td>4% I2</td>
<td>full</td>
<td>35</td>
</tr>
<tr>
<td>5</td>
<td>2% Br2</td>
<td>full</td>
<td>63</td>
</tr>
<tr>
<td>6</td>
<td>2% ICl</td>
<td>full</td>
<td>50</td>
</tr>
</tbody>
</table>

\(a\) as determined by NMR. \(b\) as determined by chiral HPLC

A screening of catalyst C against some of the synthesised substrates was performed (**Table 2**). However the results proved disappointing, with a poor ee observed in every case, whether the substitution pattern on the pyridine was small (entry 1) or large (entry 3). Since the steric bulk of the \(t\)-Bu substituent proved too cumbersome, no attempt was made to synthesise a para-fluorinated version of catalyst C.

**Table 2. Results of hydrogenation employing catalyst C**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>R</th>
<th>Conversion (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11a</td>
<td>Me</td>
<td>full</td>
<td>24</td>
</tr>
<tr>
<td>2</td>
<td>11b</td>
<td>(n)-pentyl</td>
<td>&lt;20</td>
<td>25</td>
</tr>
<tr>
<td>3</td>
<td>11c</td>
<td>Bn</td>
<td>full</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>11d</td>
<td>(CH(_2)_3)OBn</td>
<td>&lt;20</td>
<td>12</td>
</tr>
</tbody>
</table>

\(a\) as determined by NMR. \(b\) as determined by chiral HPLC

Knowing the optimal conditions, catalyst and additive, a series of substrates were hydrogenated. As can be seen from **Table 3**, a satisfactory full conversion was obtained for all but one substrates.

Linear alkyl substitution gave rise to good ee, with a slight increase in ee accompanying a shortening of the chain from pentyl to methyl (77 - 86%, entry 1). The system proved to be highly affected by the steric bulk of the side group. Phenyl- and \(iso\)-propyl- containing substituents gave poor ee, most likely due to a poor steric differentiation engendered by their larger bulk (entries 2 - 3). These substrates have the worst fit according to the quadrant model, which explains the drop in selectivity compared to the other substrates. The benzylic group offers a medium bulk, and unsurprisingly finds itself with selectivity between that of the phenyl and alkyls (entry 4).
Table 3. Asymmetric hydrogenation of substituted pyridines

<table>
<thead>
<tr>
<th>entry</th>
<th>compound</th>
<th>R</th>
<th>R'</th>
<th>conversion (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>21a</td>
<td>Linear alkyl</td>
<td>H</td>
<td>full</td>
<td>77 - 86</td>
</tr>
<tr>
<td>2</td>
<td>21e</td>
<td>iPr</td>
<td>H</td>
<td>full</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>21f</td>
<td>Ph</td>
<td>H</td>
<td>full</td>
<td>40</td>
</tr>
<tr>
<td>4</td>
<td>21c</td>
<td>Bn</td>
<td>H</td>
<td>full</td>
<td>61</td>
</tr>
<tr>
<td>5</td>
<td>21d</td>
<td>(CH₂)₃OBn</td>
<td>H</td>
<td>full</td>
<td>90 (98)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>21g</td>
<td>Me</td>
<td>3-Me</td>
<td>35&lt;sup&gt;e&lt;/sup&gt;</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>21h</td>
<td>Me</td>
<td>5-Me</td>
<td>full</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>21i</td>
<td>Me</td>
<td>6-Me</td>
<td>full</td>
<td>-</td>
</tr>
</tbody>
</table>

<sup>a</sup>: as determined by NMR. <sup>b</sup>: as determined by chiral HPLC. <sup>c</sup>: 6h reaction time. <sup>d</sup>: recrystallised once from boiling EtOAc.

The best result was obtained for the propyloxy-ether (entry 5). This could be attributed to an ancillary binding of the oxygen to the iridium centre, as was observed by Burgess <i>et al</i> in the case of (protected) allylic alcohols.<sup>50</sup> An initial 20 mg scale reaction was conducted, then owing to the good result a larger, 400 mg batch was converted, and then recrystallised with a view towards an application (see section 2.6).

Finally, the di-substituted compounds gave poor results. Tetra-substituted olefins had always been elusive targets for the ligands developed in the Andersson group, and the poor conversion of entry 6 came as little surprise. The two other disubstituted compounds (entries 7 - 8) suffered from partial hydrogenation: while no starting material was observed, a mixture of partly and fully hydrogenated (one, two or three reduced double bonds) as well as a mixture of diastereomers made characterisation of the products unfeasible.

2.5.2. Sulphones

2.5.2.1. Allylic sulphones

An optimal sulphone substituent was sought for allylic substrates 20, to this effect a number of moieties was screened (Table 4). In most cases full conversion and excellent ees were obtained. Two substrates do not follow this trend: pyridine and benzothiazole. These substrates are liable to bind irreversibly to the metal centre or to displace the ligand, as it seems plausible that the heteroaromatic nitrogen would bind strongly to the catalyst through the nitrogen and deactivate it (entry 1). This is regrettable as the products of these hydrogenations would have been prime candidates for the Julia olefination. The reaction was rather tolerant towards the different sulphone
groups, a bulky di-Me substituted phenyl group provided the best results (entry 3).

Table 4. Effect of sulphone substitution on allylic compounds.

<table>
<thead>
<tr>
<th>entry</th>
<th>compound</th>
<th>R</th>
<th>conversion (%)(^a)</th>
<th>ee(%)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>35a</td>
<td>N-Heterocycles</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>35b</td>
<td>Ph</td>
<td>&gt;99</td>
<td>96 (-</td>
</tr>
<tr>
<td>3</td>
<td>35c</td>
<td>2,6-diMe-C(_6)H(_3)</td>
<td>&gt;99</td>
<td>99 (-</td>
</tr>
<tr>
<td>4</td>
<td>35d</td>
<td>Bn</td>
<td>&gt;99</td>
<td>97 (-</td>
</tr>
<tr>
<td>5</td>
<td>35e</td>
<td>alkyls</td>
<td>&gt;99</td>
<td>97-98 (-</td>
</tr>
<tr>
<td>6</td>
<td>35f</td>
<td>MeOOCCH(_2)</td>
<td>&gt;99</td>
<td>97 (-</td>
</tr>
</tbody>
</table>

\(^a\): as determined by NMR. \(^b\): as determined by chiral HPLC or GC.

Having determined the optimal sulphone group to be 2,6-diMe phenyl, a selection of E-\(\gamma,\gamma\)-allylic sulphones \(20'\) were hydrogenated. A summary of these results is contained in Table 5.

Table 5. Asymmetric hydrogenation of allylic sulphones

<table>
<thead>
<tr>
<th>entry</th>
<th>compound</th>
<th>catalyst</th>
<th>R</th>
<th>conversion (%)(^a)</th>
<th>ee(%)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>35g</td>
<td>D</td>
<td>Ph</td>
<td>&gt;99(^c)</td>
<td>99 (-</td>
</tr>
<tr>
<td>2</td>
<td>35h</td>
<td>D</td>
<td>(p)-Cl-C(_6)H(_4)</td>
<td>&gt;99(^d)</td>
<td>96 (-</td>
</tr>
<tr>
<td>3</td>
<td>35i</td>
<td>D</td>
<td>(p)-Me-C(_6)H(_4)</td>
<td>&gt;99(^e)</td>
<td>96 (-</td>
</tr>
<tr>
<td>4</td>
<td>35j</td>
<td>D</td>
<td>(o)-Me-C(_6)H(_4)</td>
<td>14(^d)</td>
<td>84 (-</td>
</tr>
<tr>
<td>5</td>
<td>35k</td>
<td>E</td>
<td>Cy</td>
<td>62(^e)</td>
<td>93 (-</td>
</tr>
<tr>
<td>6</td>
<td>35k</td>
<td>E</td>
<td>Pentyl</td>
<td>72(^e)</td>
<td>94 (+</td>
</tr>
</tbody>
</table>

\(^a\): as determined by NMR. \(^b\): as determined by chiral HPLC or GC. \(^c\): 0.5% catalyst. \(^d\): 2% catalyst. \(^e\): 1% catalyst.

Most aromatic substituents gave excellent results (entries 1-3), with full conversion and excellent \(ee\)s observed. However, the ortho-tolyl containing substrate proved too bulky for the reaction pocket (entry 4), leading to poor conversion, even with an increased catalytic loading. Similarly, an increase in steric hindrance from Ph to Cy also resulted in a lower selectivity and a drop in reaction rate (entry 5). While the selectivity remained comparable to the more successful aromatic substrates, the slow rate of reaction was surprising for the comparatively unhindered pentylic containing substrate (entry
Attempts were made to hydrogenate di-aryl substituted compounds (Ph, naphthyl and Ph, o-Tol) however negligible conversion was observed.

Scheme 12. Asymmetric hydrogenation of a symmetrical diallylic sulphone

To further explore the scope of the reaction di-allylic sulphone 36 (Scheme 12) was synthesised. This reaction worked comparably to the mono-allylic equivalent (Table 5, entry 1), with full conversion to 37 and excellent ee.

The recent report by the Milstein group of an alcohol olefination, which employs symmetrical sulphones as reactant, opens many possibilities for this procedure: as an otherwise difficult chiral centre could be synthesised separately and easily before finally being grafted in an efficient convergent synthesis.

2.5.2.2. Vinylic and homo allylic sulphones

As can be seen in Scheme 13, the enantioselectivity was good to excellent in all cases (88-96% ee), while it remained comparable for both isomers, the conversion was heavily affected by the configuration of the double bond. The Z isomers of 38 have a better fit according to the quadrant model (see section 2.1.1), this translated into a much better match for the catalyst and therefore faster reaction time, hence the difference in conversions. Benzyl was found to be the optimal group in this case.

Scheme 13. Hydrogenation of vinyl sulphones

Having determined the optimal sulphone group, the scope of the reaction was explored by screening a selection of vinylic substrates 38 (Table 6).

A very large disparity in the conversions of the E (entries 1-6) and Z (entries 7-9) isomers was observed. In most cases the substrates in the E pattern offered full conversion (entries 1-4) as their steric bulk was able to fit within the empty quadrants of the catalyst. The two substrates bucking this trend were those bearing coordinating groups: alcohol and ester (entries 5-6).

* Reactions described in this sub-section were performed solely by co-workers, their inclusion is for comparison, therefore only briefly summarised (see Paper II).
While the oxygen coordination seemed to have a beneficial effect for the pyridine substrate (Table 3, entry 5) in this case it had a negative effect on the conversion of the reactions. The presence of the strongly binding groups proved as deleterious to the ee as it was to the conversion.

Table 6. Hydrogenation of vinylic sulphone, based on the olefinic substitution

<table>
<thead>
<tr>
<th>entry</th>
<th>compound</th>
<th>R</th>
<th>R’</th>
<th>conversion (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ee(%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>39a</td>
<td>n-Bu</td>
<td>Me</td>
<td>&gt;99</td>
<td>93 (+) (R)</td>
</tr>
<tr>
<td>2</td>
<td>39b</td>
<td>Cy</td>
<td>Me</td>
<td>&gt;99</td>
<td>86 (+)</td>
</tr>
<tr>
<td>3</td>
<td>39c</td>
<td>Ph</td>
<td>Me</td>
<td>&gt;99</td>
<td>96 (+) (S)</td>
</tr>
<tr>
<td>4</td>
<td>39d</td>
<td>p-R-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>Me</td>
<td>&gt;99</td>
<td>92-95 (+)</td>
</tr>
<tr>
<td>5</td>
<td>39e</td>
<td>COOMe</td>
<td>Me</td>
<td>23</td>
<td>89 (+)</td>
</tr>
<tr>
<td>6</td>
<td>39f</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;OH</td>
<td>Me</td>
<td>27</td>
<td>30 (-)</td>
</tr>
<tr>
<td>7</td>
<td>39g</td>
<td>Me</td>
<td>n-Bu</td>
<td>&gt;99</td>
<td>93 (-) (S)</td>
</tr>
<tr>
<td>8</td>
<td>39h</td>
<td>Me</td>
<td>Cy</td>
<td>15</td>
<td>82 (-)</td>
</tr>
<tr>
<td>9</td>
<td>39i</td>
<td>Me</td>
<td>Ph</td>
<td>61</td>
<td>96 (-) (R)</td>
</tr>
</tbody>
</table>

<sup>a</sup>: as determined by NMR. <sup>b</sup>: as determined by chiral HPLC or GC

The Z isomers showed more variation in their results: while one yielded excellent results, identically to its E isomers (entries 1 and 7), the conversions were negatively affected as bulkier groups led to a poor fit in the iridium’s reactive pocket. The ees remained broadly unaffected.

In addition to the substrates above, a further vinylic sulphone 40 was generated but with an α,β –substitution (Scheme 14). The conversion to 41 and the ee were comparable to the best entries in Table 6, this indicates that the reaction is most likely sufficiently versatile to tolerate of both α,β and β,β substitution patterns on the substrate.

Scheme 14. Asymmetric hydrogenation of an α,β –substituted vinylic sulphone.

Finally, a pair of E-homo-allylic substrates 42 were synthesised to probe the effect of an increase in chain length on the selectivity and conversion of the reaction. As can be seen in Scheme 15, full conversion to 43 was observed in both cases along with excellent ees. A preference for the benzylic substitution pattern over the bulkier dimethyl-phenyl was observed.
Overall, the results were consistent for allylic, vinylic and homo-allylic substrate with E isomers giving ground in most cases to full conversion and excellent ee's.

2.6. Applications

2.6.1. Pyridines

In order to convert the hydrogenation products into useable synthetic building blocks, a deprotection of the nitrogen atom would be necessary. This would lead, in the case of compound 21d, to compound 44, a precursor to the alkaloid 45: Coniceine. While hydrogenation methods exist to cleave a hydrazine,52 the compound remained unreacted when exposed to Rainey-nickel (excess, 5 bars H₂, overnight) and only experienced deprotection of the alcohol from the more strenuous conditions (Pd/C, 50 bars, 24 hours, 70°C). A double deprotection could have conceivably led to a one pot cyclisation to form the desired alkaloid (Scheme 16), or to at least permit the cyclisation according to reported methods.53 Since the completion of the work, an oxidative iron catalysed hydrazine cleavage has been reported.54

Scheme 16. Planned synthesis of Coniceine.

2.6.2. Sulphones

The sulphone group can undergo further transformations, such as by the Ramberg-Bäcklund reaction (discovered in 1940, in Uppsala University)55 or the Julia olefination. In order to demonstrate the synthetic possibilities opened by our new methodology, three substrates were subjected to the Chan variant of the Ramberg-Bäcklund reaction (see Table 7).56 This method was chosen in preference over others, as it could be conducted in “one pot”.

Scheme 15. Hydrogenation of homo-allylic sulphones
As expected, the $E$ isomer was obtained almost exclusively for both vinylic and allylic substrates (compounds 46-47). No such preference was observed for homo-allylic substrate 48. Much to our satisfaction the $ee$s remained unchanged.

### 2.7. Conclusion

In conclusion, two very different families of substrates were asymmetrically hydrogenated using N,P-ligated iridium catalysts. The electron poor sulphones gave excellent results, especially for the $E$-isomers whose shape espoused best the reactive pocket of the catalyst (often with full conversion and $>95\%$ $ee$). The best results were obtained for allylic substrates by using 2,6 dimethyl phenyl as sulphone group, following a screening. Benzylic sulphones were further subjected to the Ramberg-Bäcklund reaction at no loss of $ee$, and gave excellent selectivity for vinylic and allylic substrates. These results confirm the starting hypothesis that a wide range of olefinic sulphones could undergo hydrogenation.

The pyridine hydrogenation gave more varied results (10 to 98\% $ee$) as they are effectively locked in the $Z$-conformation which is less favourable, as per the quadrant model. Good results were obtained in particular for the benzylic ether, though the novel ligand did not surpass its predecessor.
3. Gold catalysed rearrangements (Papers III and IV)

“There is thy gold, worse poison to men's souls,
Doing more murder in this loathsome world,
Than these poor compounds that thou mayst not sell.”
William Shakespeare, Romeo and Juliet, Act 5, scene 1

3.1. Introduction

Long believed to be unreactive, gold catalysis has known a veritable explosion in the past two decades. A 1998 publication by Teles et al had a thunderous impact and gave rise to the field of homogeneous gold catalysis. As AuI is isoelectronic with HgII, it provides an alternative without its toxicity. The Hashmi phenol synthesis is an example of reaction which can be performed alternatively with PtII or AuIII. Gold catalysis, particularly homogeneous, was comprehensively covered in over 20 reviews and a recent book.

3.1.1. Palladium Catalysed C-S bond formation

Sulphur is known as a poison for many catalysts especially those relying on platinum group metals. However, this is not always the case. The Sonogada group reported that Pd(OAc)2 could selectively catalyse the hydrothiolation of alkynes and propargylic alcohols. Radical initiated (such as by AIBN, light or even O2) thiol-yne “Click” couplings would lead to an anti-Markovnikov addition, whereas the Pd catalyst leads to a Markovnikov adduct (Scheme 17). With its high selectivity and atom efficiency, this reaction was highly desirable.

Scheme 17. Hydrothiolation selectivity (based on scheme by Kuniyasu et al)

A detailed investigation supported by a computational study of this system was reported by Annanikov et al. The thio-palladate is heterogeneous
and the alkyne will $\pi$-bond to an edge Pd before inserting into the Pd-S bond. Finally, protonolysis of the alkene and re-thiolation of the metal centre regenerate the active catalyst.

The high atom efficiency and the absence of side product made the reaction an attractive candidate for its inclusion into a two reactions/one-pot methodology. This is far more desirable than the classical S_N2 methods, such as the one used in Paper II, and plays an important role in Paper III.

3.1.2. Semi-Pinacol Rearrangement

The semi-Pinacol rearrangement is an umbrella term for the variants of the Pinacol reaction. There are two main paths: the elimination of a leaving group or the reduction of a double bond (Scheme 18). The elimination of the hydroxylic group corresponds to the typical Pinacol rearrangement.

In the first case, a leaving group is extruded leading to the same intermediate as the normal Pinacol rearrangement. The leaving group can also be internal to the molecule, such as the ring opening of an epoxide. The Tiffeneau-Demjanov reaction is the combination of the conversion of an amine to a diazo compound followed by its elimination.

Scheme 18. Typical semi-Pinacol rearrangements

In the second case under the influence of a Lewis acid (such as AuCl), the alkene/imine/ketone bond is weakened leading to the formation of an alkane/amine/alcohol. This enables the following work.

3.1.3. Gold Catalysed 1,2-shift

A few relevant examples of the gold catalysed 1,2-shifts are presented in Scheme 19. The Toste group provided an early example of gold catalysed ring expansion of allenylcyclopropanols.\textsuperscript{64} This was followed by a dual photoredox/gold catalysed ring expansion of allylcyclobutanol.\textsuperscript{65} In both cases, it was put forward that the gold catalyst forms a $\pi$-complex with the allyl/allene, weakening the bond and promoting the C-C 1,2-shifts.
While gold often promotes Meyer-Schuster like rearrangement of propargylic esters (a 1,3-shift),\(^{66}\) in some cases a 1,2-shift is observed, as was the case in the studies by the Fiksdahl group.\(^{67}\)

Notably, a di-ketone synthesis was reported by Hashmi et al, by oxidising and rearranging a propargylic alcohol.\(^{68}\) Where appropriate this led to ring expansion. Following on the above work, alkynyl groups were 1,2-shifted as part of the cascade synthesis of 3-formylfurans.\(^{69}\)

### 3.1.4. Previous Work

Previous works in our research group had led the foundations for the work performed in this chapter (Scheme 20). First, the use of AuCl was sufficient to catalyse the selective hydrothiolation and the 1,2 hydride shift.\(^{70}\) This was expanded upon with a computational study.\(^{71}\) A green alternative to the AuCl/DCE system was discovered in the form of a CuI/H\(_2\)O method, in a strictly oxygen free environment.\(^{72}\) However, these were limited to hydride shifts on internal alkynes.
Scheme 20. Previous work performed in the group

The palladium catalysed C-S bond formation outlined in section 3.1.1. was chosen over other methods due to its low toxicity compared to older methods of thio-ether formation.\textsuperscript{73} This was previously employed in tandem with gold catalysis, but limited to the 1,2-hydride shift.\textsuperscript{74}

3.1.5. Dual Activation Catalysis: Previous Work

A great number of gold catalysed cycloisomerisations have been reported and reviewed,\textsuperscript{75} a few examples are presented in Scheme 21.

Scheme 21. Previous examples of dual gold catalysed cycloisomerisation of diynes

The term of dual activation catalysis was coined as a result from the observation that two gold complexes were required to convert the substrates: one to $\sigma$-bond to the terminal alkyne and a second to $\pi$-bond the alkyne. The
gold acts as a π-acid to generate an electrophilic π-bond. Simultaneously, the second gold atom forms a gold acetylide, generating a nucleophilic carbon.

The Gagosz group were the first to suggest that the gold catalyst could both σ- and π-bind two alkyne within the same molecule.\textsuperscript{76} The cyclisation of aromatic diynes using dual gold catalysis was reported initially by the Hashmi and Zhang groups.\textsuperscript{77} Subsequent reports by the Hashmi group showed that the formation of 5- or 6-membered rings was dictated by the substitution pattern of the aromatic core.\textsuperscript{78} The latest report shows the possibilities for further modifications through isomerisation.\textsuperscript{79}

### 3.2. Aims and Objectives

The aim of the work performed in this chapter has been to expand known gold catalysed rearrangements to new substrate classes.

One goal was the expansion of the scope of the gold catalysed semi-Pinacol rearrangement, beyond the hydride shift, in particular for C-C bond formation. The other goal was to expand the scope of gold catalysed cyclisation of diynes from benzenes and thiophenes to the more challenging pyridines. To this effect the pyridinium protecting group, the counter-ion as well as the metal catalysts would have to be screened to offer the best yields and scope for the reaction.

In the first case, the sulphur’s reactivity must be harnessed through the use of a catalyst to prevent an unselective addition, while in the second the poisonous coordination of the pyridine to the metal centre would have to be prevented (Scheme 22).

**Scheme 22. Work performed in this chapter**
3.3. Substrate Synthesis

3.3.1. Propargylic Alcohols

While the symmetrical ketones were commercially available, others had to be synthesised from acyl chlorides protected as Weinreb amides (Scheme 23, 50). The synthesis of the substrates was performed by the nucleophilic attack of Grignard-reagents upon ketones. The two homo-propargylic compounds 55 required an alternate method of preparation, due to the unusual reactivity of propargyl bromide, ZnBr₂ was chosen as a catalyst over mercury, due to safety and environmental concerns.

3.3.2. Pyridinium Substrates

The substrates were synthesised by selective, sequential Sonogashira cross-couplings of alkynes to di-bromo pyridines 56 (see Scheme 24). It should be noted that regioselectivity was obtained through a judicious choice.
of ligands. While the first Sonogashira cross-couplings occurred in near quantitative yields for most substrates (step i), the second showed more varied results (step ii), most likely due to steric effects. The deprotection of TMS occurred in good yields (typically 70–80%). Three different alkyls, from alkyl halides (MeI, BnBr, AllylBr), were employed as protecting groups. As halides are too coordinating to allow for the desired gold catalysis, an aqueous ion exchange was conducted on compounds 60 to generate the substrates 61 for catalysis.

3.4 Semi-Pinacol Rearrangement.

3.4.1. Optimisation

In order to maximise the yields, the reaction conditions were optimised by varying two parameters: the temperature and the solvent employed. As can be seen in Table 8 in the conversion of 53a to 63a, while higher temperatures were necessary for the palladium catalysed “Click” hydrothiolation reaction (entries 1,6-7), room temperature was sufficient for the Pinacol rearrangement (entries1-2).

Table 8. Optimisation of the conditions for the Click and Pinacol reaction

<table>
<thead>
<tr>
<th></th>
<th>t1 (ºC)</th>
<th>t2 (ºC)</th>
<th>solvent</th>
<th>conversion (%)*a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>80</td>
<td>80</td>
<td>MeNO2</td>
<td>&gt;95</td>
</tr>
<tr>
<td>2</td>
<td>80</td>
<td>23</td>
<td>MeNO2</td>
<td>&gt;95</td>
</tr>
<tr>
<td>3</td>
<td>80</td>
<td>-</td>
<td>MeNO2</td>
<td>&lt;5</td>
</tr>
<tr>
<td>4</td>
<td>80</td>
<td>23</td>
<td>1,2-DCE</td>
<td>74</td>
</tr>
<tr>
<td>5</td>
<td>80</td>
<td>23</td>
<td>PhMe</td>
<td>22</td>
</tr>
<tr>
<td>6</td>
<td>60</td>
<td>23</td>
<td>MeNO2</td>
<td>92</td>
</tr>
<tr>
<td>7</td>
<td>40</td>
<td>23</td>
<td>MeNO2</td>
<td>57</td>
</tr>
</tbody>
</table>

*a determined by NMR spectroscopy. b AuCl and Pd(OAc)2 added simultaneously.

An attempt to perform the reaction simultaneously rather than in tandem, by adding both catalysts initially led to the undesired addition of the thiol to the terminal end of the alkyne. This unwanted compound did not undergo further rearrangement. Further investigation (blank reaction, decreased Pd loading) revealed that this unwanted product resulted from a competing reaction which was favoured by the presence of oxygen in the reaction vessel. Freshly distilled thiophenol led to better selectivity.
3.4.2 Results
The scope of the 1,2-shift was probed using AuCl (*Table 9*).

*Table 9. Selected results for acyclic substrates*

<table>
<thead>
<tr>
<th>compound</th>
<th>R&quot;</th>
<th>Product&lt;sup&gt;a&lt;/sup&gt;</th>
<th>yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>53b</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>H, F, iPr</td>
<td>53a</td>
<td>90-94</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>53c</td>
<td>88</td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>53d</td>
<td>79</td>
</tr>
<tr>
<td>5</td>
<td>H</td>
<td>53e</td>
<td>64-82&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>H</td>
<td>53f</td>
<td>73</td>
</tr>
<tr>
<td>7</td>
<td>H</td>
<td>53g</td>
<td>79</td>
</tr>
<tr>
<td>8</td>
<td>H</td>
<td>53h</td>
<td>84</td>
</tr>
<tr>
<td>9</td>
<td>H</td>
<td>55</td>
<td>84</td>
</tr>
</tbody>
</table>

<sup>a</sup> isolated yields. <sup>b</sup> conversion. <sup>c</sup> compound not isolated.

Symmetrical starting materials provided good to excellent yields in most cases (entries 1-4). Other linear alkyls gave good results, especially with an
increase in chain length (entry 5). The starting material was fully consumed in all three cases, with the lower yields for the shorter chains stemming from a lower selectivity between the linear and branched alkyl migration. Conversions were reported as only small amounts of the main isomer could be separated from the isomeric mixture, by preparative TLC. The Ph group displayed a higher migrational aptitude than the (cyclo) alkyl groups (entries 7-8), and provided the products in appreciable yields.

The homo-propargylic compound 55 was prepared, however a terminal addition of the thiol was preferred, leading to an inactive product 63 rather than the desired intermediate. From this, it appears that the location of the oxygen is crucial for the palladium to coordinate and operate a selective addition (entry 9). Finally, different thiophenols were screened (entry 2, see Paper III), and provided the product in excellent yield, much as thiophenol. It would seem that electronics had only a small role in the thiophenol’s reactivity.

However the methyl and phenyl groups showed themselves to be problematic. For both di-Me and di-Ph, the Pinacol rearrangement did not occur. Considering that Ph and Me have both different steric and electronic properties, a trend is hard to predict. The combination of Ph and Me groups gave rise to a complex mixture, composed partly of the undesired terminal addition.

Overall, the migrational ability of the different groups for this rearrangement could be defined as such: H > aromatic > 2° alkyl > 1° alkyl.

Having explored the possibilities of the alkyl shift, the next logical step was to attempt ring expansion, as can be seen in Table 10. In all cases the hydrothiolation occurred in near quantitative yield. The yield of the ring expansion was heavily dependent on the size of the ring. Alleviating the ring strain by expanding from 4 to 5 was favourable, leading to a high yield (entry 1, 65a). Expanding from 5- to 6-membered ring was less advantageous, leading to an average yield (entry 2, 65b). The formation of the seven membered ring did not occur under the conditions, due to the high stability cyclohexyl ring (entry 3).

However, a more strained system, still featuring a 6-membered ring was reacted in excellent yield though with poor selectivity (65ca and 65cb). This was most likely aided by the release of strain of the bridging carbons (entry 4). It should be noted that decreasing the temperature from 80 °C to 20 °C had no measurable effect on the selectivity of the reaction. Finally, an attempt was made to expand the ring by not just 1 but 2 carbons, by operating a less common 1,3-shift (entry 5). This did not occur, but instead a terminal addition followed by an alternate ring expansion pathway (possibly akin to the double bond isomerisation observed by Kuniyasu et al).61
Table 10. Ring expansion of cyclic substrates

\[
\begin{array}{ccc}
\text{compound} & \text{Products} & \text{yield (\%)}^a \\
1 & \begin{array}{c} \text{64a} \\
\text{64b} \\
\text{64c} \\
\text{64d} \\
\text{64e}
\end{array} & \begin{array}{c} \text{65a} \\
\text{65b} \\
\text{66} \\
\text{65ca} \\
\text{65d}
\end{array} & 93 \\
2 & & 58 \\
3 & & \text{d} \\
4 & & 98 \\
5 & & 75 \\
\end{array}
\]

\( ^a \) isolated yields. \(^b \) compound not isolated. \(^c \) ratio determined by NMR spectroscopy. \(^d \) compound not isolated.

3.4.1.1. Chiral Transfer

Following on the above work, attempts were made to transfer chirality in the semi-Pinacol step. Though racemisation occurred at room temperature, the concept of memory of chirality offers an opportunity.\(^80 \) As such, after performing the hydrothiolation on optically pure propargylic alcohol 67, the reaction mixture was cooled to the specified temperature and then the AuCl was added (see Table 11). While some chiral transfer was observed, regrettably the final \( ee \) of 68 was too small to be of further interest.
Table 11. Temperature effect on chiral transfer $^a$

<table>
<thead>
<tr>
<th>solvent</th>
<th>$t \ ^\circ\mathrm{C}$</th>
<th>chiral transfer (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 MeNO$_2$</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>2 MeNO$_2$</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>3 MeNO$_2$</td>
<td>-25</td>
<td>23</td>
</tr>
<tr>
<td>4 Et$_2$O</td>
<td>-80</td>
<td>2</td>
</tr>
</tbody>
</table>

$^a$ conditions: alcohol (50 mg, 1equiv), PhSH (1.2 equiv), Pd(OAc)$_2$ (5 mol%), solvent (1 mL) at 80°C, overnight, then AuCl (1 mol%), at $t \ ^\circ\mathrm{C}$. $^b$ determined by chiral HPLC.

3.4.1.2. Internal C-S Bond Formation

In addition to the substrates described in section 3.3.1., compound 69 containing both thiol and propargylic alcohol groups was synthesised, according to a published procedure.$^8$ However, no reaction was observed under any of the attempted conditions (Scheme 25).

Scheme 25. Attempted cyclisation of an internal propargylic alcohol-thiol

3.5. Dual Activation Catalysis

3.5.1. The Influence of the Counter-Ion on the Pyridinium Salt

Early tests showed that free pyridines were not converted by IPr or PPh$_3$ ligated gold catalysts, most likely as they bind irreversibly and poison the catalyst. Following the same logic as in Paper I, the pyridines were converted to pyridinium salts in order to occupy its free electron pair.

Halide counter-ions deactivated the catalyst due to their strong binding, therefore a less coordinating anion had to be selected. Several counter-ions were screened, the most interesting of which were PF$_6^-$, NTf$_2^-$ and BArF$^-$. In Figure 4, the NMR spectra of four methyl pyridinium salts of 61a are shown. As can be seen, the counter-ion exerted a very strong effect on the ortho-proton of the pyridinium depending on the strength of its binding, with differences of 2.5 ppm in the extreme cases.
While PF$_6^-$ and NTf$_2^-$ offered comparable conversions on the test substrate, BArF$^-$ did not lead to any conversion. The stability of the PF$_6^-$ salts was negatively affected by the presence of silica and water in the reaction media as under the conditions the formation of HF as well as F$_2$PO$_2$H were observed. These observations were confirmed by experiments employing a water saturated solvent, deliberate addition of silica gel or both. This was palliated by drying the substrates over molecular sieve and conducting the reactions in the glovebox.

Should this methodology be employed for total synthesis, screening of both PF$_6^-$ and NTf$_2^-$ counter-ions would be recommended.

3.5.2 Gold Catalysis

3.5.2.1. Optimisation

A series of gold catalysts were screened for the cyclo-isomerisation of pyridiniums (see supporting Information of Paper IV for full screening). Overall, F in DCM yielded the best results (entry 1). The lack of activity on the part of the dual activation catalyst (entry 2) could be linked to a greater susceptibility to catalyst poisoning. Other carbene ligands gave very poor results (IMes, IPr*, entry 3) and P-ligated gold catalysts (MorDalPhos, PPh$_3$) did not offer any (Table 12). Several solvents were screened, only CH$_2$Cl$_2$ and CHCl$_3$ offering the desired conversion. Due to the acid-instability of the product, CH$_2$Cl$_2$ was preferred to CHCl$_3$ and shorter reaction times were vital to avoiding degradation.
In an attempt to isolate the gem-di-aurated intermediate of the cyclisation, a stoichiometric reaction was run and crystallised for X-ray analysis. Crystallisation led to the formation of a single large crystal of the proto-deaurated compound, the unit cell of which contained both the (R) and (S) enantiomers, with one NTf₂ ion encased between them and one further out (see Paper IV’s Supporting Information).

**Table 12. Gold catalyst screening**

<table>
<thead>
<tr>
<th>catalyst</th>
<th>Solvent</th>
<th>NMR yield(%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F: IPrAuNTf₂</td>
<td>DCM 53</td>
</tr>
<tr>
<td>2</td>
<td>MeNO₂</td>
<td>&lt;5</td>
</tr>
<tr>
<td>3</td>
<td>Other carbene ligated AuNTf₂</td>
<td>DCM 0 to 9</td>
</tr>
</tbody>
</table>

<sup>a</sup> determined using hexamethylbenzene as internal standard

### 3.5.2.2. Results

In Table 13, selected results from Paper IV are presented for comparison of the main trends. Firstly, linear alkyl chains led to the formation of 70ba-be with excellent results (entries 1-5) whereas starting materials featuring iPr, tBu and iBu did not offer any conversion, even with additional heating and longer reaction times. This most likely stems from a difficulty of the catalyst to bind the sterically encumbered substrates. While cyclo-pentyl and -hexyl are similar to iPr, their bulk is more contained enabling the reaction to occur thus forming products 70bh-bk (entries 8-11).

As discussed in Section 3.5.1, the counter-ion plays a strong role both in the reactivity of the substrate and the stability of the product. The comparison between the two counter-ions shows that PF₆⁻ salts react faster (shorter reaction times) but also degrade faster than those of NTf₂⁻ (able to withstand prolonged heating). Additionally, NTf₂⁻ salts required twice as high a catalytic loading to obtain comparable results. Nonetheless, higher NMR yields were obtained for the NTf₂⁻ salts in one cases, most likely due to hydrolysis of the pivaloyl salt (entries 6-7).

Finally, the backbone methyl improved noticeably the yields of the reaction (entries 2 vs 4 and 8 vs 9). Whereas a fluorine atom in the same position lowered the stability greatly, with decomposition of the substrate precursors observed at every stage.
Table 13. Selected results of gold catalysed cyclo-isomerisation

<table>
<thead>
<tr>
<th>Compound entry</th>
<th>compound</th>
<th>R</th>
<th>R'</th>
<th>A</th>
<th>NMR yield(%) (^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>70ba</td>
<td>Me</td>
<td>H</td>
<td>PF(_6)</td>
<td>&gt;95(^b)</td>
</tr>
<tr>
<td>2</td>
<td>70bb</td>
<td>Et</td>
<td>H</td>
<td>PF(_6)</td>
<td>93(^b)</td>
</tr>
<tr>
<td>3</td>
<td>70bc</td>
<td>Et</td>
<td>H</td>
<td>NTf(_2)</td>
<td>90(^c)</td>
</tr>
<tr>
<td>4</td>
<td>70db</td>
<td>Et</td>
<td>Me</td>
<td>PF(_6)</td>
<td>&gt;95(^b)</td>
</tr>
<tr>
<td>5</td>
<td>70be</td>
<td>nBu</td>
<td>H</td>
<td>PF(_6)</td>
<td>95(^b)</td>
</tr>
<tr>
<td>6</td>
<td>70bf</td>
<td>CH(_2)CH(_2)OPiv</td>
<td>H</td>
<td>PF(_6)</td>
<td>n.r. (^b)</td>
</tr>
<tr>
<td>7</td>
<td>70bg</td>
<td>CH(_2)CH(_2)OPiv</td>
<td>H</td>
<td>NTf(_2)</td>
<td>45(^c)</td>
</tr>
<tr>
<td>8</td>
<td>70bh</td>
<td>n=1,</td>
<td>H</td>
<td>H</td>
<td>PF(_6)</td>
</tr>
<tr>
<td>9</td>
<td>70bi</td>
<td>n=1,</td>
<td>Me</td>
<td>H</td>
<td>PF(_6)</td>
</tr>
<tr>
<td>10</td>
<td>70bj</td>
<td>n=2,</td>
<td>H</td>
<td>H</td>
<td>PF(_6)</td>
</tr>
<tr>
<td>11</td>
<td>70bk</td>
<td>n=1,</td>
<td>OMe</td>
<td>H</td>
<td>PF(_6)</td>
</tr>
</tbody>
</table>

\(^a\) determined from hexamethylbenzene as internal standard; \(^b\) 5 mol% cat, 3h \(^c\) 10 mol% cat, 36h \(^d\) 5 mol% cat, ON

The methoxide containing substrate (entry 11) was used as a test substrate, both to probe the tolerance of proximal ethers, but also for a methoxide protected estrogen-pyridinium compound (see section 3.6. for another example of Mestranol modification). However, while the test substrate worked, the pyridinium-mestanol ether proved unreactive, most likely due to bulk.

3.5.3. Hydrogenation

The products of the cyclisation were highly unstable, especially to acidic conditions (such as that of silica gel column chromatography). In response, the two olefinic bonds were hydrogenated in order to facilitate product isolation. As seen in Table 14 (see Paper IV, Supporting Information for full screening), homogeneous and heterogeneous catalysts were screened for the reduction of 70a into 71a. With paper I’s additive screening in mind Crabtree’s catalyst was screened both with and without iodine (entries 1-2). Heterogeneous catalysts resulted in higher selectivity of 71a formation than the homogeneous one (entries 3-4). This is probably due to a dissociation of the substrate from the Ir centre between catalytic cycles. The partly reduced olefin is likely to remain bound to the heterogeneous metal surface therefore undergoing both hydrogenations from the same face. This finding is in agreement with the work performed by the Glorius group. \(^82\) In the case of benzyl-pyridinium salts, the hydrogenation was highly selective, with only
the olefin bonds reduced under the initial hydrogenation conditions. Acidic conditions are required to deprotect benzyl-pyridinium salts by hydrogenation. As such the crude solution was simply diluted with MeOH and AcOH. Attempts to acidify earlier led to the expected decomposition of the unreduced compound. The same pressure and temperature were employed for this step, to optimise the usage of the autoclave, allowing several reactions in both steps to be conducted simultaneously.

![Chemical Structure](image)

**Table 14. Hydrogenation catalyst screening**

<table>
<thead>
<tr>
<th>catalyst</th>
<th>Diasteromeric ratio&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 5% Crabtree’s catalyst</td>
<td>1.5:1</td>
</tr>
<tr>
<td>2 5% Crabtree’s catalyst + 5% I&lt;sub&gt;2&lt;/sub&gt;</td>
<td>3:1</td>
</tr>
<tr>
<td>3 10% Rh(COD)&lt;sub&gt;2&lt;/sub&gt;BARF&lt;sup&gt;cis&lt;/sup&gt;</td>
<td>cis only</td>
</tr>
<tr>
<td>4 10% Pd/C&lt;sup&gt;cis&lt;/sup&gt;</td>
<td>cis only</td>
</tr>
</tbody>
</table>

<sup>a</sup>determined by NMR. Full conversion observed in all cases.

**Table 15. Isolated yields of selected pyridinium salts and free pyridines**

<table>
<thead>
<tr>
<th>yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>65</td>
<td>34&lt;sup&gt;c&lt;/sup&gt;</td>
<td>33&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>21</td>
<td>39&lt;sup&gt;d&lt;/sup&gt;</td>
<td>52&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>isolated yield, over 2 steps; <sup>b</sup>isolated yield, over 3 steps; <sup>c</sup>from PF<sub>6</sub>–; <sup>d</sup>from NTf<sub>2</sub>–.

i: 5 or 10 mol% F, 3 or 36 h, 55°C, inert atmosphere; ii: Pd/C (10mol%), 50 bar H<sub>2</sub>, O.N., R.T. iii: MeOH, AcOH (5eq), O.N., R.T.

Some substrates were fully reduced using the optimised conditions, a selection of which is presented in Table 15 (see Paper IV for full results). The
isolated yields in the table above are over two steps (71a and 71b) or three steps (72a-d). One element which showed a positive effect on the isolated yield was the pyridine backbone methyl (71c-d). It is likely that these isolated yields were affected negatively by several factors. The PF$_6^-$ ion was not stable to silica column chromatography, leading to partial decomposition of the salt into HF during the purification process. The decomposition of dienes in the presence of acids during the first hydrogenation and the volatility of the pyridines are other possible sources for loss of yield.

The isolated yield of 71a corresponds to 80% per step over two steps, and similarly the isolated yield of 72d was 52%, which also corresponds to just over 80% yield per step.

3. 6. Application and Evaluation

3.6.1. Steroid Modification: from Mestranol to Uppsalones

Mestranol (53i) was chosen for experimenting owing to its propargylic moiety, its well-studied biological effects and its availability. Due to the poor solubility of Mestranol, the solvent was changed from the usual nitromethane to 1,2-dichloroethane, which had been determined as the second best solvent during the reaction’s optimisation (Table 8). In order to palliate for the slower reaction time a higher palladium loading was chosen.

![Scheme 26](image)

Scheme 26. D-ring expansion of Mestranol (53i) into Uppsalones (63ia-b)

$i$: 8% PdOAc$_2$, ClCH$_2$-CH$_2$Cl, 80 °C, 24 h. $ii$: 5% AuCl, R.T., 24 h

As can be seen in Scheme 26, full conversion was obtained of an equimolar mixture of the two diastereomers 63ia and 63ib (1:1 ratio from NMR analysis), which could be separated by column chromatography in the indicated isolated yields. Each compound was crystallised independently for characterisation and to confirm the chirality at each centre. Pleasingly, the chirality of C13 was maintained during the reaction, though the methyl group C20 did not offer enough steric hindrance to engender any selectivity at C18 (Figure 5).
3.6.2. Evaluation Against Estrogen Receptors

The evaluation of the two Uppsalones (63ia-b) was conducted by Dr. Maria Norlin (department of pharmaceutical biosciences, Uppsala University), according to methodologies developed in her group (see Appendix 5). Luciferase gene expression coupled to estrogen receptor (ER)-mediated response provided a light emitting response based on the interaction of the ER, which are reported in relative light units.

As can be seen in the graphs in the Appendix 5 (bars 3 and 4) neither of the two Uppsalones gave rise to a strong response. In both cases, the ethanol solutions of steroids showed similar agonist activity to the ethanol blank, and a significantly lower response to their precursor, Mestranol or to 17-β estradiol (E2), at the same loading (100 nM).

To probe a possible inhibitory effect, 17-β estradiol (100 nM) and 1μM of either Uppsalone were screened together against the two ER (bars 6-7). ER-α showed a slightly higher response whereas ER-β showed a slight inhibition.

Overall neither showed strong inhibition or induction of the estrogen receptor-mediated response, indicating that the Uppsalones probably cannot bind to estrogen receptors ER-α or ER-β. This is most likely due to the distortion of the D ring and the increased steric bulk from the ancillary aromatic ring, which made docking to the active site difficult.
3.7. Conclusion

In conclusion, Au catalysts were successfully employed for two different types of internal rearrangements.

In one project, a Pd catalyst was employed to selectively operate a thiol-yne coupling, overcoming the usually deleterious behaviour of sulphur. The compounds obtained were able to undergo migration for a variety of groups, by the semi-Pinacol rearrangement. Both acyclic and cyclic compounds were tolerated, and in the latter case ring expansion was observed. Initial difficulties with the expansion of the six-membered ring were overcome through strain release of the bridged substrate. This methodology was applied to the synthesis of a pair of homo-steroids, which were evaluated for activity.

Similarly, gold catalysed rearrangements were operated successfully by overcoming pyridine’s ability to poison gold catalysts via alkylation of the substrates’ nitrogen. Following a counter-ion screening, PF$_6^-$ and NTf$_2^-$ were found to be viable choices, while the first was less stable, the second proved slower to react and required twice the catalytic loading. Overall, unsubstituted alkyl chains provided high yields (>90%), as steric affected negatively the yield. An electron donating pyridine backbone stabilised the product, leading to the highest yields (> 95%). As the diene product was unstable, hydrogenation was chosen to facilitate isolation. A selection of homo- and heterogeneous catalysts were screened and Pd/C was found to provide a single diastereomer. Furthermore, Bn protected compounds could be further deprotected with no additional catalyst, to furnish free pyridines. This methodology consists of three steps performed by two catalysts in one-pot.
This thesis has explored noble metal catalysed reductions and rearrangements of nitrogen and sulphur containing molecules. The papers found herein had two axis: reduction/rearrangement and nitrogen/sulphur. Three metals were used chiefly: iridium, palladium and gold.

In the first two papers (I and II), the aim was to asymmetrically hydrogenate pyridinium salts and olefinic sulphones. N,P-ligated iridium catalysts provided the desired results. The sulphones provided better results than the pyridines, largely owing to their geometry.

In the later papers (III and IV), Au¹ catalysts were employed to rearrange molecules containing double or triple bonds. In the case of pyridines this led to double ring formation whereas for the thio ether, this led to ring expansion, when possible.

Pyridines are poisonous to the catalyst due to their ability to bind the metal centre and therefore deactivate it. However in papers I and IV this was circumvented by the formation of pyridinium salts.

Similarly, in paper II, the oxidation of thio-ethers to sulphones removed the threat of sulphur-metal bonding. Contrastingly, in paper III the formation of Pd-sulphur bonds was necessary for the selective thiol-yne reaction.

In most cases, an attempt was made to find an application for the new methodologies, this was successful in paper II, as the Ramberg-Bäcklund olefination of the sulphones maintained the chirality. While in paper III, the homo-steroids were synthesised cleanly, neither of them showed any strong biological activity.

With future discoveries, this chiral methodology could lead to concrete applications. Sulphone chemistry in particular, is seeing a renewed interest, with recent developments in the field prefiguring an auspicious future.

While present in many target systems, heteroatoms remain often challenging for catalysis; it is my hope that the approaches employed here, to circumvent their limitations, might serve as inspiration to other chemists seeking to react troublesome compounds.
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Figur 1: exempel på den katalytiska cykeln

En av de mest allmänt kända tillämpningarna av kemisk katalys är bilens katalysator som omvandlar avgaser till mindre giftiga produkter. För detta ändamål får gasen (som innehåller bl.a. kolmonoxid och kväveoxider) passera över ädelmetaller (platina, palladium, rodium och osmium) och omvandlas till mindre giftiga produkter (kväve, vatten, koldioxid).

Syftet med denna avhandling är att studera omvandlingen av kemiska molekyler med hjälp av ädelmetaller (iridium, guld). Metallerna fungerar som katalysatorer för att möjliggöra reduktion av dubbelbindningar inom en molekyl, för att binda två molekyler till varandra eller för att ändra molekylers struktur.

Kemin som beskrivs i denna avhandling ska ses ur perspektivet miljövänlig kemi. Hydrering av iridium har ingen biprodukt, de molekylära omflytt-
ningarna sker internt och producerar således inga oönskade produkter. Dessa reaktioner är därmed praktiskt taget avfallsfria.

Figur 2. Symmetrisk molekul.

Inom kemin är principen för assymetri viktig. Till exempel alkohol (se figur 2) är en symmetrisk molekyl, eftersom den kan överlagras över dess spegelbild. Denna princip kommer från observationen att två molekyler kan vara praktiskt taget identiska, men spegelbilder av varandra (så kallade enantiomerer) och då ha radikalt olika egenskaper. Ett vanligt exempel är karvon (se figur 3), som ger en smak av pepparmynta eller kummin beroende på vilken enantiomer som används.

Figur 3. Två enantiomerer av karvon.

Förmågan att kunna styra bildandet av endast en enantiomer är därmed mycket viktig och användningen av asymmetrisk katalys är därför önskvärt för framtagandet av enantiomeriskt rena produkter (innehåller bara en enantiomer). Alternativet är att framställa båda enantiomererna i samma reaktionsblandning och sedan separera dem, vilket leder till ett slöseri av kemikalier.

Denna avhandling består av två delar: asymmetrisk hydrering av dubbelbindningar med hjälp av katalysatorer baserade på iridium (omvandling av dubbelbindningar till enkelbindningar med hjälp av väteatomer) och ändring av molekylers struktur med hjälp av guldkatalysatorer. I båda fallen studeras två typer av system: kvävehaltiga molekyler (pyridiner) och svavelhaltiga molekyler (tioeter, sulfon). Dessa två typer av molekyler används sällan på grund av svårigheten att använda dem (giftighet, lukt) och deras förmåga att förorena katalysatorer.
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