Synthesis of New Chiral $N$-Heterocyclic Carbenes and Abnormal Carbenes

A Thesis Submitted by

Jean-Noel Levy

In partial fulfilment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

Department of Chemistry
Imperial College London
South Kensington
London
SW7 2AZ

January 2011
Declaration of Originality

I, Jean-Noel Levy, hereby confirm that I solely produced the presented thesis under the supervision of Doctor Matthew J. Fuchter at the Department of Chemistry, Imperial College London, and that I did not use any other material that cited or known to the public domain.

London, 10\textsuperscript{th} January 2011

Jean-Noel Levy
Abstract

Chapter 1

Carbenes have fascinated organic chemists ever since the first evidence of their existence. The isolation and first crystallographic analysis of a stable NHC by Arduengo, in 1991, has had a major impact on the application of NHCs in chemistry. NHCs are widely used as ligands for transition metals, but also as catalysts in their own right.

The aim of this project is to synthesise novel monodentate chiral NHCs 1 in order to induce a high level of stereocontrol in a selection of asymmetric reactions. The rigid ring structure, $C_2$ symmetry and the presence of bulky groups ($R$) that project directly toward the reactive centre are important concepts in the design of our molecules. During the first part of my thesis, we developed a one-pot synthesis of allylic chlorides from benzaldehyde. A mechanistic study was carried out, as well as studying the scope of the reaction. We then achieved the synthesis of the desired NHCs precursors in 13 or 14 steps and carried out studies of their coordination and application in asymmetric α-arylation and allylic alkylation.

Chapter 2

Recently novel coordination modes have been noted for NHCs. The so-called “abnormal” NHCs, due to their isomeric relationship between $C2$- and $C4$-bound imidazolylidene ligands are one type of relatively unexplored ligand. We have therefore developed a strategy to access chiral abnormal NHCs.

Two different chiral abnormal NHC precursors: 1,2,3-triazolidinenes 2 and isomeric Hartwig’s NHCs 3 were synthesised via a short synthesis (2 or 3 steps) and metallated with a transition metal.
Acknowledgements

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### Abbreviations

<table>
<thead>
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<th>Definition</th>
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<tbody>
<tr>
<td>Δ</td>
<td>Heat</td>
</tr>
<tr>
<td>Ac</td>
<td>Acetyl</td>
</tr>
<tr>
<td>acac</td>
<td>Acetylacetonyl</td>
</tr>
<tr>
<td>Ad</td>
<td>Adamantyl</td>
</tr>
<tr>
<td>aq.</td>
<td>Aqueous</td>
</tr>
<tr>
<td>Ar</td>
<td>Aryl</td>
</tr>
<tr>
<td>ATR</td>
<td>Attenuated total reflectance</td>
</tr>
<tr>
<td>BARF</td>
<td>Tripentafluorophenylborane</td>
</tr>
<tr>
<td>BINAP</td>
<td>2,2’-bis(diphenylphosphino)-1,1’-binaphthyl</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl</td>
</tr>
<tr>
<td>br. s</td>
<td>Broad singlet</td>
</tr>
<tr>
<td>Bu</td>
<td>Butyl</td>
</tr>
<tr>
<td>°C</td>
<td>Degrees Celsius</td>
</tr>
<tr>
<td>cat.</td>
<td>Catalytic</td>
</tr>
<tr>
<td>CDCl$_3$</td>
<td>Deuterated chloroform</td>
</tr>
<tr>
<td>CH$_2$Cl$_2$</td>
<td>Dichloromethane</td>
</tr>
<tr>
<td>Cl</td>
<td>Chemical ionisation</td>
</tr>
<tr>
<td>COD</td>
<td>1,5-cyclooctadiene</td>
</tr>
<tr>
<td>conc.</td>
<td>Concentrated</td>
</tr>
<tr>
<td>conv.</td>
<td>Conversion</td>
</tr>
<tr>
<td>cy</td>
<td>Cyclohexyl</td>
</tr>
<tr>
<td>δ</td>
<td>Chemical shift</td>
</tr>
<tr>
<td>d</td>
<td>Doublet</td>
</tr>
<tr>
<td>dba</td>
<td>Dibenzylideneacetone</td>
</tr>
<tr>
<td>dd</td>
<td>Doublet of doublets</td>
</tr>
<tr>
<td>DIBAL-H</td>
<td>Diisobutyl aluminium hydride</td>
</tr>
<tr>
<td>Dip</td>
<td>2,6-Diisopropylphenyl</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>DMA</td>
<td>N,N'-Dimethylacetamide</td>
</tr>
<tr>
<td>DME</td>
<td>1,2-Dimethoxyethane</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-Dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethylsulfoxide</td>
</tr>
<tr>
<td>dppp</td>
<td>1,3-<em>bis</em>(diphenylphosphino)propane</td>
</tr>
<tr>
<td>dq</td>
<td>Doublet of quartets</td>
</tr>
<tr>
<td>dt</td>
<td>Doublet of triplet</td>
</tr>
<tr>
<td>ee</td>
<td>Enantiomeric excess</td>
</tr>
<tr>
<td>El</td>
<td>Electron ionisation</td>
</tr>
<tr>
<td>equiv</td>
<td>Equivalent</td>
</tr>
<tr>
<td>ESI</td>
<td>Electrospray</td>
</tr>
<tr>
<td>Et</td>
<td>Ethyl</td>
</tr>
<tr>
<td>Et$_3$N</td>
<td>Triethylamine</td>
</tr>
<tr>
<td>Et$_2$O</td>
<td>Diethyl ether</td>
</tr>
<tr>
<td>EtOAc</td>
<td>Ethyl acetate</td>
</tr>
<tr>
<td>EtOH</td>
<td>Ethanol</td>
</tr>
<tr>
<td>GC-MS</td>
<td>Gas chromatography mass spectrometry</td>
</tr>
<tr>
<td>h</td>
<td>Hour</td>
</tr>
<tr>
<td>HCl</td>
<td>Hydrochloric acid</td>
</tr>
<tr>
<td>HMPA</td>
<td>Hexamethylphosphoric acid triamide</td>
</tr>
<tr>
<td>H$_2$O</td>
<td>Water</td>
</tr>
<tr>
<td>HPLC</td>
<td>High-pressure liquid chromatography</td>
</tr>
<tr>
<td>HRMS</td>
<td>High-resolution mass spectrometry</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz</td>
</tr>
<tr>
<td>i</td>
<td>Iso</td>
</tr>
<tr>
<td>IR</td>
<td>Infrared spectroscopy</td>
</tr>
<tr>
<td>J</td>
<td>Coupling constant</td>
</tr>
<tr>
<td>LiHMDS</td>
<td>Lithium hexamethyl disilazide</td>
</tr>
<tr>
<td>Ln</td>
<td>Ligand</td>
</tr>
<tr>
<td>m</td>
<td>Multiplet</td>
</tr>
</tbody>
</table>
μ  Micro \(10^{-6}\)
M  Molar
Me  Methyl
Mes  Mesityl
min  Minute
mol  Mole (s)
m.p.  Melting point
MS  Mass spectrometry
m  Meta
m/z  Mass to charge ratio
n  Normal
Nap  Naphthyl
NHC  N-Heterocyclic Carbene
NMO  N-Methylmorpholine-N-Oxide
NMR  Nuclear magnetic resonance spectroscopy
Np  Naphtyl
o  Ortho
p  Para
Ph  Phenyl
PPh₃  Triphenylphosphine
ppm  Part per million
Pr  Propyl
pyr  Pyridine
q  Quartet
R  General substituent
R*  General chiral substituent
rt  Room temperature
sat.  Saturated
t  Triplet
t  Tertiary
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>Tf</td>
<td>Triflate</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin layer chromatography</td>
</tr>
<tr>
<td>TMS</td>
<td>Trimethylsilyl</td>
</tr>
<tr>
<td>Tol</td>
<td>Toluene</td>
</tr>
<tr>
<td>UV</td>
<td>Ultra-violet</td>
</tr>
</tbody>
</table>
CHAPTER I

Synthesis of new chiral N-Heterocyclic Carbenes
Introduction

1. Overview

1.1. History

Carbenes, which are defined as neutral divalent carbon based compounds where the carbon atom has only six valence electrons (see 1.1.2), have played an important role in organic chemistry ever since the first evidence of their existence. Nef announced that the isolation of methylene would be his next challenge in 1895, but after a variety of attempts failed to isolate such a compound, it was thought to be impossible to isolate carbenes. The first complex with heteroatom-stabilised carbene ligand was however synthesised by Tschugajeff in 1925 as the Tschugajeff “red salt” 4 and “yellow salt” 5 (Scheme 1). Their structures were only determined in 1970 as diaminocarbene complexes with platinum.

![Scheme 1: Tschugajeff “red salt” 4 and “yellow salt” 5]

A few decades later, Fisher and Maasböl first unambiguously isolated carbene bound complexes.² By addition of MeLi to W(CO)₆, they were able to isolate a salt by precipitation from aqueous solution which was then methylated with diazomethane to give a structure that they characterised by IR and proton NMR. They were able to show that the additional methyl group was not attached to the tungsten but to the oxygen and then proposed that the structure was a “methoxymethylcarbene” bound to W(CO)₃ and thus represented the first transition-metal complex of a carbene (Figure 1). In 1968, the first N-heterocyclic carbene - metal complex was reported by Öfele and Wanzlick et al (Figure 1). While these discoveries were the starting point of an increasing interest in NHCs for coordination chemistry, their instability was a major drawback for further isolation and study.
The subsequent remarkable work undertaken by Arduengo and co-workers has had a major impact on the applications of NHCs in chemistry. Arduengo managed to isolate and characterise the first crystalline NHC 10 in 1991, almost 100 years after the work of Nef. It was the first example of a NHC stable against dimerisation. They obtained this free N-Heterocyclic Carbene (NHC) by deprotonation of the corresponding imidazolium salt 9 (Scheme 2). The NHC isolated was particularly stable with a melting point of 240°C with no decomposition observed. NMR and X-ray diffraction analysis showed a decrease in aromaticity in the NHC structure compared to the corresponding imidazolium salt.

Subsequently, the development of free or metal-complexed carbenes has increased exponentially, as shown in Graph 1. They have been extensively used as transition metal ligands for example in palladium catalysed reactions, or as organocatalysts. They have also been used as reacting group for silicon chemistry or hydroboration.
1.2. Electronic properties

Carbenes are defined as neutral divalent carbon based compounds where the carbon atom has only six valence electrons. Two bonding situations are possible (Figure 2).\textsuperscript{11}

- The non-bonding electrons occupy two degenerate p orbitals ($p_x, p_y$): the carbene carbon atom is sp-hybridised and the geometry linear.

- More often, the carbenes contain an sp$^2$-hybridised carbon atom. The energy of one of the p orbitals, called $p_y$, does not change upon transition from sp- to sp$^2$-hybridisation state. The newly formed sp$^2$-hybrid orbital, described as $\sigma$ orbital, exhibits partial s character and is energetically stabilised relative to the original p orbital (Figure 2). The geometry of this carbene carbon atom is trigonal planar. In this case the two non-bonding electrons occupy either the $\sigma$ or $p_y$ orbital:
  
  i. If the electrons occupy the two empty orbitals with a parallel spin orientation, that leads to a \textit{triplet ground state}. This is the case for the simplest carbenes such as methylene.

  ii. Alternatively, the two electrons can occupy the $\sigma$ orbital with an antiparallel spin orientation leading to the \textit{singlet ground state}, which is the case for NHCs.
The multiplicity of the ground state determines the properties of a carbene. Singlet carbenes have a full $\sigma$ orbital and an empty $\pi$ orbital; they have ambiphilic reactivity. Triplet carbenes have a radical-like reactivity because of their two unpaired electrons.

In our study, we were interested in carbenes derived from nitrogen heterocycles, such as imidazole, imidazolidine, triazole or thiazole (Figure 3). Only the NHCs derived from imidazole or imidazolidine will be discussed in this chapter.

Due to the presence of the two $\pi$-donor nitrogen atoms on either side of the carbene carbon atom, the NHCs are in the singlet ground state. In fact, interaction of the $\pi$-electron pairs on the nitrogen with the $\pi$ orbital of the carbene carbon atom results in the increase of the relative energy of the $\pi$ orbital. The relative energy of the $\sigma$-orbital at the carbene carbon is not affected by the $\pi$-interaction, but some stability may be gained from the $\sigma$-electron-withdrawal effects on the carbene...
carbon atom by the more electronegative nitrogens. Therefore, the combination of these $\pi$- and $\sigma$-effects serves to increase the singlet-triplet gap and stabilise the singlet carbene over the more reactive triplet (Figure 4).\(^{12}\)

![Figure 4](image)

**Figure 4.** Electronic configuration of heterocyclic five-membered carbenes.

The NHCs are known to have exceptional stability, which originates from the three following factors; according to theoretical studies:

- **Thermodynamic stabilisation:** Electron donation of the lone pair from both nitrogen atoms to the empty $p_\pi$ orbital of the carbene carbon atom, which is very efficient due to the rigidity of their cyclic structure. An inductive effect, which contributes the decrease of electrondonation on the central carbon. The presence of a $C\equiv C$ double bond in the backbone provides additional thermodynamic stabilisation.

- **Unsaturated NHC** are considered as aromatic and therefore delocalisation of the six $\pi$-electrons for compound 11 add more stabilisation (Scheme 3).

![Scheme 3](image)

**Scheme 3.** Stabilisation effects of the nitrogen atoms and aromaticity on the carbene.
- The presence of sterically demanding groups on the nitrogen atoms sterically shield the carbene carbon atom and prevent dimerisation of the NHCs. In 1962, Wanzlick proposed that there was equilibrium between the dimer 17 and the free NHC 12 (Scheme 4).\(^\text{13}\)

![Scheme 4. Wanzlick's equilibrium.](image)

However, in 1964, Lemal \textit{et al.} showed that the dimer did not dissociate under even more drastic conditions than those used by Wanzlick.\(^\text{14}\) To prove their theory, they carried out a negative crossover experiment (Scheme 5, a). They proposed instead that the dissociation proceeded by electrophilic attack on the dimer (Scheme 5, b) to form one equivalent of imidazolium and a NHC which reacts immediately with the electrophile. However, Denk and co-workers claimed that they found evidence of crossover under similar conditions.\(^\text{15}\) This result was challenged by Lemal and Liu who showed that no crossover occurred and that impurities were responsible for the observed crossover product.\(^\text{16}\)

![Scheme 5. Lemal crossover experiment and proposed mechanism.](image)

However, the mechanism for NHC dimerisation was later proved to be simply the reverse Lemal's mechanism (Scheme 5, b). Alder and co-workers were able to prove this mechanism
by isolating the protonated dimer intermediate 24 in a favourable case and characterise it by $^{13}$C-NMR (Scheme 6).$^{17,18}$

As free NHCs are obtained by deprotonation of the H$_2$-proton with a strong base, it is clear that NHCs are very strong Brønsted bases. This behaviour follows the rule that a weak acid (the imidazolium salt) has a strong conjugate base (NHC). However it was very difficult to determine how strong a base these NHCs and calculate a representative value of this basicity (pKa). Indeed classical Brønsted bases are defined within the medium water to limit the pH value, however, while water will protonate a carbene to azolium salt, the hydroxide ion leads to decomposition reactions under ring opening.$^{19}$ Alder et al. proposed a method to determine the pKa of 1,3-diisopropyl-4,5-dimethylimidazol-2-ylidene. They reacted this imidazolium with several acidic hydrocarbons with known pKa values in deuterated DMSO and followed the reaction by $^1$H-NMR spectroscopy. A value of 24.0 was found for this substrate.$^{20}$ However Denk and Rodezno showed that DMSO was not an inert solvent for NHC as the NHC 1,3-di-tert-butylimidazol-2-ylidene reacted rapidly with $d_6$-DMSO under H/D exchange of the ring protons.$^{19}$ Therefore another method should be investigated to determine the pKa of NHCs with protons in the ring. Kim and Streitwieser have investigated the basicity of NHC in THF using UV-Vis spectroscopy: they found a value of 20.0 in THF for 1,3-di-tert-butylimidazol-2-ylidene.$^{21}$ THF was an inert solvent to generate the free NHC from imidazolium salt compared to DMSO.

The exceptionally strong basicity of the NHC is also reflected in their equally great σ-donicity. Electronic properties were evaluated by the calculation of the carbonyl stretching frequencies of the corresponding transition metal carbonyl complexes. A comparison of σ-donicity between saturated,
unsaturated and acyclic and more basic NHCs was performed by Herrmann and co-workers (Figure 5). These results showed that the unsaturated NHCs are better net donors than the saturated NHCs even if the absolute differences are very small and are unlikely to play a major role in catalyst performance.

![Figure 5. Evaluation of NHC σ-donicity.](image)

1.2.1. Generation of free NHCs

Several methods allow the formation of free NHCs with deprotonation of an imidazolium salt being by far the most common one. The advantage of this method is the availability and stability of the precursor and the mild deprotonation procedure. However, it is difficult to separate the free NHCs from the protonated base and also the strong bases used are often incompatible with many functional groups in the pendant sidechains. Some additional, less commonly applied methods to obtain free NHCs exist and are listed below (Scheme 7):

- Desulphurisation of thioureas with potassium in boiling THF. The advantage of this method is the insolubility of the by-product. However, the reduction of the thione often fails or the C=S group is directly reduced to a methylene carbon rather than carbene.
- Vacuum pyrolysis of NHC-adduct under removal of by-products such as MeOH, CHCl₃, CHF₃ or C₆F₅H. However, thermal decomposition often leads to dimerisation of the NHC.
- The use of NHC-CO₂ or NHC-metal (Snᴵᴵ, Mgᴵᴵ, Znᴵᴵ) for an *in-situ* formation of the free NHC.
- Treatment of chloro amidinium and azolium salts with bis(trimethylsilyl)mercury, providing Hg, TMSCl and the free NHC.
1.2.2. Synthesis of imidazolium salts

As mentioned above, the procedure developed by Arduengo is the most frequently used to prepare NHCs, and consists of the deprotonation of the imidazolium salt. Several different routes to the required imidazolium salts have been reported.

The Herrmann synthesis consists of the multicomponent reaction between two equivalents of a primary amine, glyoxal and formaldehyde in the presence of a Brønsted acid (Scheme 8). This reaction leads to the formation of symmetrically N,N'-substituted imidazolium salts 39 in a one pot reaction, from which the diimine 40 intermediate could also be isolated.31

A related reaction where unsymmetrically N,N’-substituted imidazolium salts 43 were obtained from a multicomponent cyclization followed by N-alkylation, was reported by Gridnev (Scheme 9).32
For certain unsymmetrically $N,N'$-substituted imidazolium salts, alkylation of nitrogen atoms is difficult or even impossible. Recently Fürstner and co-workers reported a new route to these imidazolium salts. A substituted oxazolium salt was synthesised and converted to the corresponding imidazolium salt by reaction with a primary amine. The resulting imidazolium salt eliminates water upon heating under acid-catalysis (Scheme 10).

Glorius described the synthesis of imidazolium salts derived from bisoxazolines from which the general procedure with formaldehyde failed. Their preparation started with the synthesis of the bisoxazoline from condensation of an amino alcohol with diethyl oxalate. The last step consisted of a ring-closing reaction with chloro-methylpivalate and silver triflate to form the imidazolium salt (Scheme 11).
Formation of imidazolinium salts was performed by conversion of vicinal N,N'-disubstituted-1,2-diamines (symmetric or unsymmetric) under acidic conditions. This synthesis was used intensively for the formation of N-aryl substituted imidazolinium salts 54 (Scheme 12).\cite{37-39}

![Scheme 12. Orthoformate synthesis method for formation of imidazolinium salt 54.](image)

Bertrand and co-workers developed a method to synthesise imidazolinium with a different retrosynthetic approach.\cite{40,41} Addition of “dielectrophiles” 56 to lithiated formamidines 55 gave them the desired imidazolinium compounds 57 (Scheme 13).

![Scheme 13. Bertrand synthesis of imidazolinium 57.](image)

Kuhn and Grubbs used this strategy to form unsymmetric imidazolinium salt that involves reaction of a formamidine with dichloroethane and a base (Scheme 14).\cite{42}

![Scheme 14. Kuhn and Grubbs synthesis of unsymmetric imidazolinium 60.](image)
1.2.3. Synthesis of NHC-metal complexes

The formation of NHC-metal complexes is generally based on five different methods: (i) reaction of the NHC-dimer with a transition metal complex; (ii) reaction of a transition metal complex with a free NHC (preformed or generated in situ); (iii) reaction of an imidazolium salt with a transition metal complex possessing a basic anion; (iv) by using a NHC transfer agent; and (v) reaction of an imidazolium salt with a transition metal salt in the presence of a weak base (Scheme 15).

\[
\begin{align*}
2 \begin{array}{c}
\text{N} \\
\text{N} \\
\text{R} \\
\text{R}
\end{array}
\quad & + \quad [\text{Pd(cod)I}_2] \\
\text{11} \\
\text{61}
\end{align*}
\]

\[
\begin{align*}
2 \begin{array}{c}
\text{N} \\
\text{N} \\
\text{R} \\
\text{R}
\end{array}
\quad & + \quad \text{Pd(OAc)}_2 \\
\text{62} \\
\text{63}
\end{align*}
\]

\[
\begin{align*}
\text{IAg} \quad & \quad \text{Ag}_2\text{O} \\
\text{65} \\
\text{61}
\end{align*}
\]

\[
\begin{align*}
\text{PdI}_2 + \text{K}_2\text{CO}_3 + \quad & \quad 2 \begin{array}{c}
\text{N} \\
\text{N} \\
\text{R} \\
\text{R}
\end{array} \\
\text{66} \\
\text{67} \\
\text{62}
\end{align*}
\]

Scheme 15. Major methods leading to NHC-metal complexes.

i. The first method employed was to heat the NHC-dimers which are usually highly electron-rich alkenes, in the presence of a metal complex. This method was used when stable NHCs were not accessible and nowadays is not often used.

ii. The common method is the direct complexation of the stable NHC by a metal. The NHC is obtained by deprotonation of the azolium salt and can then be reacted with a suitable transition metal complex. The NHC is often not isolated but formed in situ prior to addition of the metal complex. This method allows a great variety of choice for transition metal complexes as starting materials; however, as explained above (see 1.2.1), the choice of the NHC is limited by the tolerance of functional groups towards strong bases.

iii. The deprotonation of an azolium to form a NHC requires a base which can be supplied by the anion of a transition metal compound. In that case, the azolium will be deprotonated in situ and the NHC will coordinate immediately to the metal by
oxidative addition. This method proved to be successful with Pd(OAc)$_2$\textsuperscript{44} or Pd$_2$(dba)$_3$\textsuperscript{45} and proved to be a mild method to prepare NHC-metal complexes in high yield.

iv. In 1998, Lin and co-workers developed another method to obtain NHC-metal complexes, \textit{via} a transmetallation reaction.\textsuperscript{46} The first step consisted of the formation of a silver complex containing the NHC 65 (which can be considered as a protected form of the free NHC) followed by metal exchange (Scheme 15). It is therefore known as a NHC transfer agent. The mechanism of the complexation of the azolium with silver oxide to give a silver-NHC complex was studied theoretically by Lledós and co-workers.\textsuperscript{47} They showed that the mechanism was divided into four steps: deprotonation 1, metalation 1 followed by deprotonation 2 and metalation 2. The proposed mechanism is presented in Scheme 16. The formation of the silver complex 65 with Ag$_2$O offers a number of advantages: firstly, the silver NHC complex can be prepared in air and secondly, specially purified solvents or additional bases are not necessary. This method is especially useful if base sensitive groups are present on the nitrogen atom. This method has become a standard procedure and allows access to NHC complexes where alternative methods were low yielding or unsuccessful.

v. The reaction of an imidazolium salt with a weak base and the transition metal complex which generates an equilibrium between the imidazolium salt and its deprotonated form, the NHC. Although the equilibrium is very much towards the imidazolium salt (weaker conjugate acid), the reaction is shifted to the right by strong coordination of the NHC ligand to the transition metal. Several weak bases were used for this process such as Na$_2$CO$_3$,\textsuperscript{48} K$_2$CO$_3$,\textsuperscript{49,50} Cs$_2$CO$_3$,\textsuperscript{51} NEt$_3$,\textsuperscript{52,53} pyridine,\textsuperscript{50} and NaOAc.\textsuperscript{54}
2. The application of NHCs in catalysis

Despite the fact that NHC-metal complexes have been known for 35 years, their successful use in catalysis only began in 1990. A large number of transition metals have been coordinated to NHCs including all elements of the d-block from group 7 to group 11. Only a small number of these however have been shown to be catalytically competent. Pd-NHC complexes have perhaps shown the greatest utility and have found application in C-C coupling reactions (Heck, Stille, Suzuki, Sonogashira reactions) and arylation reactions. Ru-NHC complexes have also shown huge potential as enabling ligands in olefin metathesis and hydrogenation reactions.
2.1. Representative applications of Pd-NHC complexes

Phosphine and phosphite ligands have been used intensively for homogeneous catalysis due to their ability to protect low-valent metal centres from aggregation (stabilisation effect) and create coordination sites to promote the catalytic cycle (activation effect). Unfortunately, an excess of phosphine ligands – compared to the metal - is generally needed to compensate the degradation of these ligands by P-C bond cleavage. Also phosphines and phosphites are often air- and water-sensitive. Due to these drawbacks, Herrmann and co-workers were one of the first groups to investigate Pd-NHC complexes for catalytic purposes. In fact, Pd-NHC complexes could be synthesised easily and were very stable to heat, oxygen and moisture. Bidendate catalyst 78, formed by the reaction between palladium acetate (63) and the corresponding imidazolium salt 77, was developed in 1995 and enabled C-C bond formation between aryl bromides and different vinylic compounds, arylboronic acids or alkynes (Table 1). They demonstrated the versatility of N-heterocyclic imidazol-2-ylidene ligands in homogeneous catalysis. However, a limitation was observed when Sonogashira reactions were performed: only activated bromo arynes reacted with phenylacetylene.

\[
\text{PdI}_2 + \text{Pd(OAc)}_2 \rightarrow \text{PdI}_2
\]

<table>
<thead>
<tr>
<th>Reaction type</th>
<th>Substrates</th>
<th>Base</th>
<th>Conditions (ligand % mol, temp., time)</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heck</td>
<td>(\text{On-Bu})</td>
<td>(\text{Br-} \text{OMe})</td>
<td>n-Bu(_3)N OAc</td>
<td>0.5%, 140 °C, 12 h</td>
</tr>
<tr>
<td>Suzuki</td>
<td>(\text{B(OH)}_2)</td>
<td>(\text{Br-} \text{OMe})</td>
<td>K(_2)CO(_3)</td>
<td>1.0%, 120 °C, 22 h</td>
</tr>
<tr>
<td>Sonogashira</td>
<td>(\text{Et}_3)N</td>
<td></td>
<td></td>
<td>1.0%, 90 °C, 48 h</td>
</tr>
</tbody>
</table>

Table 1. Herrmann’s work on C-C coupling with Pd-NHC complexes.

As a general trend of reactivity, aryl bromides are more reactive than aryl chlorides. Reaction with aryl chlorides is often very challenging and only few phosphine ligands have been used to perform such coupling reactions as described by Beller and co-workers. In 2002, Nolan and co-
workers published a mini-review on catalytic cross-coupling reactions mediated by palladium / nucleophilic NHC systems. In this review they described the difficulty to perform Heck, Sonogashira or α-arylation with aryl chlorides. The same year, they reported a palladium π-allyl complex 86 bearing a single NHC ligand, which was formed via reaction of the corresponding NHC 84 with \([\eta^3\text{-allyl}]\text{Pd(Cl)}\)\(_2\) (85). This complex was successfully used to perform coupling reactions with aryl chlorides (Table 2).\(^{57,58}\) Very good yields were obtained using even lower temperatures than those reported by Herrmann.

![Diagram](image)

<table>
<thead>
<tr>
<th>Reaction type</th>
<th>Substrates</th>
<th>Base</th>
<th>Conditions (ligand % mol, temp., time)</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-arylation of ketones</td>
<td><img src="image" alt="substrate" /> <img src="image" alt="substrate" /></td>
<td>NaO(\text{tBu})</td>
<td>1.0%, 70 °C, 1 h</td>
<td>98%</td>
</tr>
<tr>
<td>Suzuki</td>
<td><img src="image" alt="substrate" /> <img src="image" alt="substrate" /></td>
<td>NaO(\text{tBu})</td>
<td>2.0%, 80 °C, 1.5 h</td>
<td>95%</td>
</tr>
<tr>
<td>Buchwald-Hartwig</td>
<td><img src="image" alt="substrate" /> <img src="image" alt="substrate" /></td>
<td>NaO(\text{tBu})</td>
<td>1.0%, 50 °C, 1 h</td>
<td>95%</td>
</tr>
</tbody>
</table>

Table 2. Nolan’s work on C-C coupling with Pd-NHC complexes.

While Herrmann and Nolan developed very useful Pd-NHC complexes for cross-coupling chemistry, these catalysts required rigorously anhydrous conditions. In 2006, Organ and co-workers introduced the concept of PEPPSI catalyst (PEPPSI = Pyridine Enhanced Precatalysts Preparation, Stabilisation and Initiation) which could be made easily from commercially available starting materials and prepared in air (Figure 6).\(^{59}\)
The mechanism of the activation of the catalytic cycle was studied. A rapid reduction facilitated by the organometallic reagent was found to take place, followed by pyridine dissociation from the generated palladium (0) species (Scheme 17). They showed that bulky NHC ligands lead to fast reductive elimination, which was able to suppress undesired side reactions or catalyst decomposition which occurred with bulky phosphine ligands. It was also observed that the rate of the reaction was considerably higher with this palladium complex as compared with the same NHC ligand with Pd$_2$(dba)$_3$. 

Figure 6. PEPSI ligand.
The catalyst was submitted into a variety of Suzuki-Miyaura reactions under no special anhydrous precautions and gave excellent catalytic activity. *iso*-Propanol or methanol proved to be the best solvents as excellent yield were obtained at ambient temperature (Table 3). These types of PEPPSI-catalysts have proved since to be very useful and therefore widely used for palladium cross-coupling.\(^{62-70}\)

<table>
<thead>
<tr>
<th>Substrates</th>
<th>Solvent</th>
<th>Base</th>
<th>Conditions (ligand % mol, temp., time)</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>81 (\text{B(OH)}_2)</td>
<td>Cl-(\text{B(OH)}_2)_OMe 96</td>
<td>MeOH</td>
<td>MeOH</td>
<td>2.0%, 25 °C, 24 h</td>
</tr>
<tr>
<td>97 (\text{BF}_3)K</td>
<td>Cl-(\text{BF}_3)_OMe 96</td>
<td>(\text{K}_2\text{CO}_3)</td>
<td>(\text{K}_2\text{CO}_3)</td>
<td>2.0%, 25 °C, 24 h</td>
</tr>
</tbody>
</table>

}*Table 3. Suzuki-Miyaura reaction with PEPPSI ligand.*
2.2. Representative applications of Ru-NHC complexes

Since 1990, metal-catalysed olefin metathesis has become a powerful tool for carbon-carbon bond formation in organic chemistry.\(^{71}\) The development of catalysts for this reaction has been remarkable including both the molybdenum catalysts developed by Schrock\(^{72}\) and the ruthenium catalysts developed by Grubbs and Hoveyda (Figure 7).\(^{73-75}\)

Herrmann and co-workers reported the first Ru-NHC complex in 1998 for ring closing metathesis (RCM) and ring-opening metathesis polymerisation (ROMP).\(^{76}\) They developed this catalyst as an analogue of the Grubbs I catalyst (Figure 7). Reaction of 2.2 equivalents of imidazolin-2-ylidene with phosphine complex 99 yielded Ru-complexes 101 and 102 as air-stable solid (Figure 8).

ROPM of cyclooctadiene with these catalysts gave nearly quantitative yields at ambient temperature with complexes 101 and virtually no reaction with 102, which showed the high dependence of the reaction to the nature of the NHC. While preliminary results with these complexes in RCM showed interesting results even if no major improvements over phosphines were
obtained, this work however inspired Grubbs and co-workers who developed their second generation catalyst 103 in 1999.77 By replacing one of his phosphine ligands by an NHC ligand they were able to dramatically increase the substrate scope for the ring closing metathesis. As shown in Table 4, the Grubbs II catalyst was able to increase RCM activity towards more sterically demanding olefins (Table 4, entry 2). Also tetra-substituted olefin could be prepared with this new catalyst (Table 4, entry 3).

![Image of catalyst 103](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Time</th>
<th>Yield Grubbs I</th>
<th>Yield Grubbs II</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>104</td>
<td>105</td>
<td>30 min</td>
<td>82 %</td>
<td>100 %</td>
</tr>
<tr>
<td>2</td>
<td>106</td>
<td>107</td>
<td>1 h</td>
<td>0 %</td>
<td>100 %</td>
</tr>
<tr>
<td>3</td>
<td>108</td>
<td>109</td>
<td>1.5 h</td>
<td>0 %</td>
<td>95 %</td>
</tr>
</tbody>
</table>

Table 4. Metathesis with the catalyst 103 (E = CO2Et).

Following the discovery of catalyst 103, variation on the NHC group was attempted. The influence of the N-substituent has been studied by a number of groups78-81 but only the SiMes analogue bearing two 2,6-diisopropylphenyl groups displayed greater activity than Grubbs II for the metathesis of terminal olefins.79 Other analogues generally displayed lower reactivity. For example, substitution on the backbone of the NHC ligand with two chlorides afforded little change in reactivity.78 NHC complex using the triazol-5-ylidene NH82C showed great catalytic activity but has a limited lifetime in solution, which is a problem for more demanding reactions.78 Addition of an adamantyl substituent resulted in very poor results most likely due to steric reasons.83 Extensive studies were made to obtain phosphine-free NHC-ruthenium complexes that would have good catalytic activities. The Hoveyda84 and Blechert85 groups reported simultaneously a new ligand 110 which is now one of the most widely used ruthenium catalyst for metathesis reactions alongside the
Grubbs I and II catalysts (Figure 9). This complex was also able to perform metathesis reactions involving electron-deficient partners such as acrylonitrile and fluorinated olefins.

![Figure 9. Phosphine-free catalyst 110.](image)

**2.3. Representative applications of Cu-NHC complexes**

Copper-NHC complexes were used efficiently for the hydrosilylation of olefins, alkynes and ketones. At an early stage, Lipshutz and co-workers explored various phosphine-ligated copper hydride systems for the transformation of simple aldehydes and ketones leading to reduced products.\(^{86-90}\) However hydrosilylation of highly sterically demanding substrates was not studied at the time. Consequently Nolan and co-workers were keen to develop efficient and general catalytic methods for the reduction of hindered and functionalised carbonyl compounds. They recently developed copper-NHC complexes that enable hydrosilylation of very bulky carbonyl compounds without a large quantity of reducing agent (Table 5).\(^{91}\) In this paper, a variety of NHC ligands were screened to try to understand the influence of the ligand on the reaction. Very bulky ligands such as adamantyl substituted NHCs yielded the hydrosilylated product in a good reaction time which showed that steric effects were not a major factor on this reaction. Possible electronic effects were difficult to rationalise. A comparative study of Cu-NHC complexes and Cu-phosphine complexes was performed and showed that NHCs were more efficient ligands in the hydrosilylation of ketones than tertiary phosphines which may be due to the specific shape of the ligand which protects and stabilises the metal centre facilitating the coordination of the substrate (Table 5).
Synthesis of new chiral NHCs

Table 5. Nolan’s work on hydrosilylation of ketone with NHCs.

To enlarge the scope of the reaction, functionalised ketones were also subjected to hydrosilylation reactions. Amines and ethers were suitable substrates. The presence of halogen and trifluoromethyl substituents on the aromatic ring was tolerated contrary to electron-donating substituents which led to slower reaction rates. No reaction occurred in the case of an acetylbenzonitrile.

In 2001, Woodward and co-workers reported the use of a copper-NHC complex for 1,4-Michael addition.\(^9\) This work was developed following the report of Alexakis who discovered that phosphine ligands provided a strong acceleration rate of copper-catalysed ZnEt\(_2\) addition to cyclohexenone.\(^9\) Theoretical studies suggested that this acceleration was due to the σ-donor stabilisation of the copper (III) transition state (Scheme 18).\(^9\) Woodward and co-workers reasoned that this effect should be independent of the nature of the σ-donor. Therefore, replacing the phosphine ligand by an Arduengo type NHC would provide the same type of effect.

Scheme 18. Transition state for copper catalysed 1,4-addition.
They showed that NHCs could accelerate the rate of reaction and increase the yield of 1,4-Michael addition reactions using diethyl zinc and a copper complex (Table 6). However this reaction was very sensitive to the steric requirements of the Michael acceptor: reactions with more ketones gave very poor yields or no reaction.

![Reaction scheme](image)

<table>
<thead>
<tr>
<th>Enone</th>
<th>Ligand</th>
<th>Conversion</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Enone 121" /></td>
<td>None</td>
<td>43 %</td>
<td>14 %</td>
</tr>
<tr>
<td><img src="image" alt="Enone 121" /></td>
<td><img src="image" alt="Ligand 122" /></td>
<td>100 %</td>
<td>100 %</td>
</tr>
<tr>
<td><img src="image" alt="Enone 123" /></td>
<td>None</td>
<td>2 %</td>
<td>2 %</td>
</tr>
<tr>
<td><img src="image" alt="Enone 123" /></td>
<td><img src="image" alt="Ligand 122" /></td>
<td>100 %</td>
<td>85 %</td>
</tr>
</tbody>
</table>

*Table 6. Woodward’s study on 1,4-addition with NHC.*

### 3. Chiral NHC-metal complexes: Applications to enantioselective reactions

The successful results obtained with NHCs in catalysis led to the synthesis of chiral NHCs, the use of which should be promising in asymmetric catalysis. The first chiral NHC-metal complexes were synthesised by Lappert in 1983 (Figure 10), before the isolation of the first stable NHC by Arduengo in 1991. However, these complexes were only reported as the first route to access chiral complexes as sources of optically active carbenoids, diastereoisomeric transition metal complexes having a chiral metal centre, and were not used in catalysis.
Synthesis of new chiral NHCs

The application of chiral NHCs to asymmetric catalysis started in 1996 with the work of Herrmann\textsuperscript{96,97} and Enders\textsuperscript{98-100} on the enantioselective hydrosilylation of methyl ketones (Scheme 19).

\begin{figure}  
\centering  
\includegraphics[width=\textwidth]{figure10.png}  
\caption{Lappert’s first chiral NHCs.}  
\end{figure}

\begin{figure}  
\centering  
\includegraphics[width=\textwidth]{scheme19.png}  
\caption{Herrmann and Enders’ works on enantioselective hydrosilylation.}  
\end{figure}

Despite the fact that poor enantioselectivity was obtained (32 % and 42 %), these results showed that it was possible to use chiral NHCs to induce asymmetry within catalytic reactions. Since these initial studies, a great deal of research has been undertaken with variable levels of success. Four different classes of chiral NHC complexes used in asymmetric catalysis can be distinguished: (a) monodentate and bidentate NHCs possessing stereogenic centres on the nitrogen substituents, (b) monodentate and bidentate NHCs possessing stereogenic centres within the N-heterocycle, (c) monodentate and bidentate NHCs containing an element of planar chirality, and (d) bidentate NHCs containing an element of axial chirality. A representative example of each class will be presented and discussed.
3.1. Monodentate and bidentate NHCs possessing stereogenic centres on the nitrogen substituents

In 2001, Hartwig and co-workers reported the first optically active NHC ligand that gave substantial enantioselectivity for the palladium-catalysed intramolecular arylation reaction of enolates and aromatic bromides. During their optimisation, they showed that base, counterion and solvent were important factors for the control of the enantioselectivity contrary to the ligand-to-metal ratio. The best conditions found used sodium tert-butoxide as the base and DME as the solvent. Good enantioselectivity was obtained when the reaction was performed at ambient temperature; even better e.e. was obtained using the imidazolinium salt 135, which contains a (+)-bornyl moiety, because the temperature could be dropped to 10 °C (Table 7). The reaction was less effective when the bromide was replaced by more reactive iodide (no enantioselectivity was observed with ligand 134) or less reactive chloride (very poor yield obtained with ligand 135). Substitution in the aromatic ring of the starting material resulted in lower enantioselectivity. Although many chiral phosphine and NHC ligands were screened in this paper, only moderate enantioselectivities were obtained.

![Chemical structures](image)

Table 7. Hartwig’s work on α-arylation of amide with monodentate NHCs.

<table>
<thead>
<tr>
<th>Substrate (R₁, R₂)</th>
<th>Catalyst (Pd/L)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bn, 1-Np</td>
<td>Pd(dba)₂/134</td>
<td>88</td>
<td>67</td>
</tr>
<tr>
<td>Bn, 1-Np</td>
<td>Pd(dba)₂/135</td>
<td>75</td>
<td>76</td>
</tr>
<tr>
<td>Me, 1-Np</td>
<td>Pd(dba)₂/135</td>
<td>91</td>
<td>69</td>
</tr>
<tr>
<td>Me, Ph</td>
<td>Pd(dba)₂/135</td>
<td>74</td>
<td>57</td>
</tr>
</tbody>
</table>

Recently, Kündig and co-workers reported of several novel bulky chiral imidazolylidene ligands which gave much higher e.e.’s (up to 94%) with aryl bromides as substrates. Glorius and co-workers were interested in improving the results obtain by Hartwig and co-workers. In 2002, Glorius reported a new method to synthesise imidazolium salts derived from bisoxazolines as shown...
His first attempt for intramolecular arylation with bisoxazoline derivatives ligand gave good conversions but poor enantioselectivity. In 2003 and 2004, he reported a series of sterically demanding bioxazoline-derived NHC ligands with restricted flexibility named IBiox which were the base of our design strategy (see 1.4). Remarkably results were obtained with these ligands for the formation of biaryls at ambient temperature with non-activated aryl chloride as substrates. In 2009, Glorius and co-workers reported on the synthesis of a most sterically demanding, monodentate and chiral NHC ligand 138 and its successful application in palladium catalysed asymmetric α-arylation of amides. They quantify the steric demand by calculation of the buried volume - measure of the space occupied by an organometallic ligand in the first coordination sphere of the metals centre (see R&D, 2.) – and found that their ligand was by far the largest buried volume ever reported. For the first time, this extremely bulky ligand allowed the conversion of generally less reactive aryl chloride under mild conditions with high yields and high enantioselectivity (Table 8). Furthermore, very bulky substrates gave even higher enantioselectivity which contrasted with the results obtained previously by Kündig (Entries 5 and 6, Table 8). These remarkable results were encouraging for our developed NHCs as very bulky ligands seemed to lead to very high enantioselectivity.

![NHC ligands](image)

### Table 8. Glorius' α-arylation of amides.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate (R₁, R₂)</th>
<th>X</th>
<th>Aryl</th>
<th>Yield (%)</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me, Me</td>
<td>Br</td>
<td>Ph</td>
<td>91</td>
<td>81</td>
</tr>
<tr>
<td>2</td>
<td>Bn, Et</td>
<td>Cl</td>
<td>Ph</td>
<td>99</td>
<td>85</td>
</tr>
<tr>
<td>3</td>
<td>Bn, Me</td>
<td>Br</td>
<td>1-Np</td>
<td>95</td>
<td>97</td>
</tr>
<tr>
<td>4</td>
<td>Me, Me</td>
<td>Cl</td>
<td>1-Np</td>
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<tr>
<td>5</td>
<td>Me, Me</td>
<td>Cl</td>
<td>o-Tol</td>
<td>89</td>
<td>95</td>
</tr>
<tr>
<td>6</td>
<td>Bn, Bn</td>
<td>Cl</td>
<td>o-anisyl</td>
<td>80</td>
<td>92</td>
</tr>
</tbody>
</table>
In 2001, Burgess and co-workers synthesised a chiral bidentate NHC 141 which was very efficient for asymmetric hydrogenation.\(^{105}\) At that time, several chiral NHC ligands had been used as ligands in catalytic reactions but the best enantioselectivities obtained were less than 76%. In fact, they reported the first application of a chiral NHC which gave good asymmetric induction. For the design of these ligands, they were inspired by the Pfaltz/Hemlchen/Williams asymmetric phosphino-oxazoline (PHOX) ligands 142 which gave very good yields and enantioselectivities for the iridium-catalysed hydrogenation of unfunctionalised alkenes.\(^{106,107}\) A direct comparison of the Burgess’ ligand 141 and Pfaltz’s ligand 142 for the asymmetric hydrogenation of E-aryl alkenes showed that comparable results were obtained (Table 9).

![Chemical structures](https://example.com/structures.png)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkene</th>
<th>Loading (mol %); YIELD (%)</th>
<th>e.e. (%)</th>
<th>Loading (mol %); Yield (%)</th>
<th>e.e. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeO-143</td>
<td>0.6; 99; 91 (S)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>MeO-144</td>
<td>0.6; 99; 97 (S)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>MeO-145</td>
<td>1.0; 95; 78 (R)</td>
<td></td>
<td>1.0; 97; 61 (S)</td>
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</tr>
<tr>
<td>4</td>
<td>MeO-146</td>
<td>0.3; 91; 31 (R)</td>
<td></td>
<td>1.0; &gt;99; 60 (S)(^a)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) performed with H\(_2\) (1 bar)

Table 9. Comparison of Burgess’ and Pfaltz’s ligands for asymmetric hydrogenation.

In 2003, Burgess and co-workers synthesised a new ligand and a direct comparison with Pfaltz and Crabtree ligands was reported.\(^{108}\) Very good yields and high enantioselectivities were obtained with the use of iridium NHC-oxazoline complexes 149 for E- and Z-aryl alkenes (Table 10); but the main benefits were the ambient temperature and only the need for an atmospheric pressure of H\(_2\).
3.2. Monodentate and bidentate NHCs possessing stereogenic centres within the N-heterocycle

Recently Dorta et al. synthesised new monodentate NHC ligands with a chiral N-heterocycle and naphthyl side chains. Three different isomers were observed, separated and used as ligands for asymmetric intramolecular α-arylation of amides: \((R_a, R_a)\)-154, \((R_a, S_a)\)-154, \((S_a, S_a)\)-154 (Figure 11).

![Figure 11. Isomers of Dorta NHC ligands.](image-url)
The asymmetric intramolecular α-arylation of amides was performed with the three different isomers and the results are summarised in Table 11. As shown, the same reactivity occurred for the different catalysts. The same configuration (R-configuration) was always obtained as the major product, which showed that it was the chiral groups on the N-heterocycle that determined the absolute configuration. However, significant differences of stereoselectivity were observed. The isomer \((R_a, R_a)\) proved to be the ligand with the highest stereoselectivity (82-88 %) which was an improvement on the results obtained by Hartwig and Glorius at that time as they failed to have more than 76% e.e. for the same substrates (see 3.1). The isomer \((R_a, S_a)\) led to variable levels of enantiomeric excess (45 to 79 %) and was substrate-dependent, whereas the isomer \((S_a, S_a)\) failed to give products in more than 50 % ee.

![Catalyst diagram](#)

<table>
<thead>
<tr>
<th>R</th>
<th>Ar</th>
<th>(R_a, R_a)</th>
<th>(R_a, S_a)</th>
<th>(S_a, S_a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>Ph</td>
<td>98 (86)</td>
<td>98 (67)</td>
<td>98 (20)</td>
</tr>
<tr>
<td>Bn</td>
<td>Ph</td>
<td>98 (88)</td>
<td>98 (45)</td>
<td>97 (50)</td>
</tr>
<tr>
<td>Me</td>
<td>(\rho)-Tol</td>
<td>99 (87)</td>
<td>98 (79)</td>
<td>97 (44)</td>
</tr>
<tr>
<td>Bn</td>
<td>1-Nap</td>
<td>93 (82)</td>
<td>96 (66)</td>
<td>93 (49)</td>
</tr>
</tbody>
</table>

*Table 11. Dorta’s results for intramolecular α-arylation.*

To explain these different selectivities, a model was proposed in Scheme 22, which showed the different intermediates obtained with the three isomers. The steric pressure exerted by the chiral NHC-phenyl groups onto the naphthyl side chains and subsequently onto the enantiodiscriminating side of the substrate would predominantly give intermediates 157 and, after reductive elimination, products with the observed (R)-configuration. The isomer \((R_a, R_a)\), with the higher steric hindrance, will lead to the \((R_a, R_a)-157(R)\), which is highly favoured over \((R_a, R_a)-157(S)\). Due to the lack of a plane of symmetry in the isomer \((R_a, S_a)\), two different intermediates are possible: the left one with low steric hindrance and the right one with higher steric hindrance, which explained the different enantiomeric excess observed. Finally, a substantial amount of (S)-configuration was obtained with the \((S_a, S_a)\) due to the lower steric hindrance.
Hoveyda and co-workers developed a chiral bidentate silver-NHC based on a chiral N-heterocycle and an achiral biphenol N-substituent. This silver-NHC, in the presence of a copper chloride complex, proved to be a very good catalyst for the allylic substitution of trisubstituted olefins, using sterically hindered dialkylzincs, to generate quaternary stereogenic centres in a good yield and excellent enantiomeric excess (Table 12, entries 1 to 4). They could also isolate the chiral copper-NHC which showed the same activity and selectivity. These chiral alkylation catalysts are remarkable due to the small loading (1%) and the low temperature (-15 °C) needed for the reaction. However, they noticed that when corresponding cis allylic phosphates were used as the substrate, Cu-catalysed allylic alkylation were less effective and proceeded with lower enantioselectivity to afford the opposite product enantiomer as compared with the trans allylic phosphates (Table 12, entry 5).
3.3. NHCs containing an element of planar chirality

In 2003, Andrus and co-workers reported a selection of chiral monodentate NHC ligands which were very effective for asymmetric 1,4-addition.\textsuperscript{111} They contained paracyclophanes as bulky planar chiral N-substituents and were complexed \textit{in situ} to Rh(acac)(C\textsubscript{5}H\textsubscript{4})\textsubscript{2} to be used as catalysts for the reaction of phenyl boronic acid and cyclohex-2-enone to afford good yields and high selectivity (Table 13). The best enantiomeric excess was obtained by the rhodium catalyst derived from ligand 162\textsubscript{d}, bearing anisyl units on the paracyclophane motif.
Synthesis of new chiral NHCs

![Chemical Structure](image)

162a \( R = H \)
162b \( R = \text{Ph} \)
162c \( R = \text{Cy} \)
162d \( R = \alpha\text{-anisyl} \)

\[
\begin{align*}
\text{121} + \text{PhB(OH)}_2 & \rightarrow \text{ligand (3 mol%)} \\
& \quad \text{[Rh(acac)(C_2H_4)_2] (163, 2 mol%)} \\
& \quad \text{(THF/H}_2\text{O (10:1))}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>162a</td>
<td>4</td>
<td>69</td>
<td>61</td>
</tr>
<tr>
<td>162b</td>
<td>8</td>
<td>86</td>
<td>91</td>
</tr>
<tr>
<td>162c</td>
<td>6.5</td>
<td>89</td>
<td>97</td>
</tr>
<tr>
<td>162d</td>
<td>3</td>
<td>96</td>
<td>98</td>
</tr>
</tbody>
</table>

*Table 13.* Andrus’ work on asymmetric 1,4-addition.

The best ligand proved to be the ligand 162d and optimal reaction conditions were surveyed. These conditions were applied to the addition of various aryl boronic acids and potassium trifluoroborates to several cyclic enones (Table 14). Phenylboronic acid reacted with all three enones in high yield and with good selectivity (Table 14, entry 1). Bulkier reagents such as p-methoxyphenyl gave similar results (Table 14, entry 3). The electron-deficient reagents also gave excellent yield and selectivities (Table 14, entry 5). Under these conditions, the potassium trifluoroborate reacted faster but with a lower enantioselectivity (Table 14, entries 2, 4 and 6).
Two years later, Andrus and co-workers reported that these ligands could also be used for asymmetric hydrosilylation of ketones using ruthenium complexes.\textsuperscript{112} The catalyst formed \textit{in situ} from the bis-paracyclophane imidazolium precursor in the presence of [RuCl$_2$(PPh$_3$)$_3$] (174), reacted with acetophenone in the presence of silver triflate to obtain the (S)-phenylethanol in high yield and with excellent selectivity (Table 15). The anisyl units on the paracyclophane motif were not necessary for this reaction however only traces of asymmetric induction were observed if the phenyl
group was removed completely. A large range of aryl ketones were employed in this reaction and moderate to excellent selectivity was obtained (58 to 97%).

\[
\begin{array}{c}
\text{R}^1\text{C}=\text{O} + \text{Ph}_2\text{SiH}_2 \\
\text{2.5 equiv.}
\end{array}
\]

<table>
<thead>
<tr>
<th>Ligand</th>
<th>(R_1)</th>
<th>(R_2)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>162a</td>
<td>Ph</td>
<td>Me</td>
<td>16</td>
<td>98</td>
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<tr>
<td>162b</td>
<td>Ph</td>
<td>Me</td>
<td>16</td>
<td>98</td>
<td>97</td>
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<tr>
<td>162d</td>
<td>Ph</td>
<td>Me</td>
<td>16</td>
<td>98</td>
<td>97</td>
</tr>
<tr>
<td>162d</td>
<td>2-Np</td>
<td>Me</td>
<td>20</td>
<td>98</td>
<td>96</td>
</tr>
<tr>
<td>162d</td>
<td>o-MeOPh</td>
<td>Me</td>
<td>15</td>
<td>92</td>
<td>96</td>
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<tr>
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<td>p-MeOPh</td>
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<td>93</td>
</tr>
<tr>
<td>162d</td>
<td>Ph</td>
<td>'Pr</td>
<td>18</td>
<td>95</td>
<td>93</td>
</tr>
</tbody>
</table>

Table 15. Andrus’ work on asymmetric hydrosilylation.

3.4. NHCs containing an element of axial chirality

In 2003, Shi and co-workers developed a novel axially-chiral biscarbene. This NHC is based on a 1,1'-binaphthalenyl unit and can be considered as an NHC analogue of the BINAP chiral diphosphine ligand. The rhodium-NHC complex 176 was used in the catalytic enantioselective hydrosilylation of various ketones. Very good enantiomeric excesses (> 92%) were obtained for aryl
ketones and bulky alkyl ketones (Table 16). Slightly lower selectivities were obtained with less bulky alkyl ketones.

![Catalyst Structure](image)

**Table 16.** Shi’s work on asymmetric hydrosilylation.

<table>
<thead>
<tr>
<th>Ketone</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>87</td>
<td>98</td>
</tr>
<tr>
<td>2-Np</td>
<td>91</td>
<td>96</td>
</tr>
<tr>
<td>p-Tolyl</td>
<td>93</td>
<td>98</td>
</tr>
<tr>
<td>Ad</td>
<td>96</td>
<td>96</td>
</tr>
<tr>
<td>p-AcPhC_{2}H_{4}</td>
<td>87</td>
<td>71</td>
</tr>
<tr>
<td>C_{8}H_{15}</td>
<td>86</td>
<td>67</td>
</tr>
</tbody>
</table>

**4. Concept and design of novel chiral NHCs**

The aim of our project is to synthesise a range of novel monodentate chiral NHCs 1 ligands, explore their coordination chemistry and test them in an asymmetric transformation.

![Figure 12](image)

*Figure 12. Novel chiral NHCs.*
The concept of our design for these ligands is outlined below.

Chiral bisoxazoline ligands have been known since 1989 and have been used extensively in various catalytic processes. Many impressive results have been reported in enantioselective carbon-carbon bond forming reactions, hydrosilylations, oxidations and reductions. The bisoxazoline ligands are structurally related to the semicorrins pioneered by Pfaltz and co-workers, however, the use of the bisoxazoline structure adds a degree of flexibility in ligand design. For our purposes, the work of Glorius, presented above (see 3.1), inspired us to design novel NHCs as bisoxazoline mimics.\textsuperscript{35,36}

The presence of a C\textsubscript{2}-symmetry axis is widely known to be very useful in asymmetric catalytic reactions. In 1989, Whitesell reported that the presence of a C\textsubscript{2}-symmetry axis in a chiral ligand could dramatically reduce the number of possible competing diastereomeric transition states.\textsuperscript{115} He reported a large number of enantioselective reactions with good results following this principle.

![Figure 13. C\textsubscript{2}-symmetry axis.](image)

In 2007, Herrmann and co-workers published a remarkable study on restricted flexibility in asymmetric NHC catalysis.\textsuperscript{116} In this paper, they synthesised comparable NHCs with different degrees of flexibility and used their corresponding iridium complexes in asymmetric hydrogenation. The results demonstrated that the most restricted NHCs (179 and 181) proved to give higher levels of asymmetric induction than the unrestricted ones (177, 180 and 182). The addition of substituents in C\textsubscript{3}-C\textsubscript{3}' positions also provided better results in terms of asymmetric induction (in comparison with 178 and 179, Figure 14).
In our design, the NHC is structurally rigid and therefore should provide informative results. Additionally, the bulky substituents (R), which project directly into the reactive centre, should further tune the stereocontrol.

5. Retrosynthesis of the corresponding imidazolium salt

Our short retrosynthetic analysis was based on the elegant work of Glorius for the formation of NHCs derived from bisoxazolines (Scheme 21). Thus, the imidazolium salt could be obtained by cyclisation of the corresponding bisoxazoline 184 with chloromethyl pivalate in the presence of silver triflate. Bisoxazoline should be readily available from aminoundanol 185, following the three-step procedure reported by Glorius and co-workers. Aminoundanol 185 should be available in two steps via enantioselective epoxidation of the corresponding indene 186 followed by a Ritter reaction to afford the enantiomeric pure aminoundanol 185.
Scheme 21. Retrosynthesis of the imidazolium salt 183.
Results and Discussion

1. Synthesis of novel chiral NHCs

1.1. Synthesis of indene derivatives

1.1.1. Attempted synthesis via Mg alkoxides

As detailed in the retrosynthesis, the first objective was the formation of suitably substituted indenes 186. Synthesis of unsubstituted indene is generally carried out at high temperatures and tends to be low yielding. In 1983, Wylie reported a synthesis of indene by extrusion of SO₂; the trans-cinnamyl benzyl sulfone was pyrolysed at 640˚C and indene was obtained in 46% yield.109 The same year, Parrick obtained indene by pyrolysis of o-ethyl benzylidene chloride with a yield of 34%.117,118 Whilst numerous, modern methods have become available, many have limitations such as the need for substitution on the alkene.119,120 For our studies, a one pot reaction was planned to afford the desired indene derivatives in good yields at low temperatures via a mechanistically distinct pathway. Our strategy was to form a carbocation 190 which should undergo annulation to form an indene 186 (Scheme 22). Since such a carbocation could be derived from an allylic alcohol, we considered the options for mediating C-O bond cleavage under less-acidic conditions (known to polymerise indene). Addition of vinylic organometallic reagents 188 to commercially available benzaldehyde derivatives 187 would give allylic alkoxide intermediates 189 that, in principle, could form carbocations 190 with formal elimination of a metallic oxide (Scheme 22).

![Scheme 22. Envisaged reaction to form indene.](image)

Within this proposal however, alternative side-reactions could be envisaged: A) Attack of the counter anion (recombination of the ion pair) or, B) addition of an exogenous nucleophile (Scheme 23).
Synthesis of new chiral NHCs

Recent work by Kabalka and co-workers demonstrated the possible cleavage of lithium alkoxides using several Lewis acids such as boron trichloride (BCl₃) and iron trichloride (FeCl₃) followed by cation capture by allyl silanes.¹²¹,¹²² However, for our synthetic route, formation of magnesium alkoxides by addition of vinyl magnesium halides to benzaldehyde derivatives was preferred due to the ready availability of the corresponding Grignard reagents. The cleavage of magnesium alkoxides was largely undocumented except one study by Tolbert in which he showed that indenes could be obtained from isolated, heavily substituted magnesium alkoxides (generated by addition of phenylmagnesium bromide to α,β-unsaturated ketones).¹²³ The cleavage of the C-O bond occurred following pyrolysis at 160°C under vacuum. Not only was a poor yield obtained, but high temperatures were required, along with the need for highly substituted compounds to avoid side reactions such as elimination and hydride abstraction. To focus on milder reaction conditions, we decided to explore the use of titanium tetrachloride as a reaction partner in light of its powerful dehydrating capabilities¹²⁴ and its moderate cost.

The initial studies were performed by addition of vinylmagnesium chloride (194) to benzaldehyde (193) to give magnesium alkoxide 195, followed by addition of half an equivalent of titanium tetrachloride and heating the reaction to reflux. The reaction did not result in the formation of indene, but addition of the chloride counterion to the proposed carbocationic intermediate, giving (E)-allylic chloride 197 (Scheme 24). Alcohol 198 was also recovered.

![Scheme 23. Possible carbocation side reactions.](image)

![Scheme 24. One-Pot formation of (E)-allylic chloride 197.](image)
11.1.1. One-pot synthesis of allylic chlorides

The allylic chloride products are important substrates in a variety of reactions including metal-catalyzed allylation reactions.\textsuperscript{125} For example, they have been recently been reported as substrates in nickel-catalysed Negishi reactions\textsuperscript{126} and in stereospecific zirconium-mediated S\textsubscript{n}2' substitutions.\textsuperscript{127} Although the developed reaction did not yield the desired indene, we therefore decided to examine the scope of this reaction further and, first, decided to further explore the reaction. The results are summarised in Table 17.

![Diagram of reaction]

\[
\begin{align*}
\text{Benzaldehyde (193)} & \xrightarrow{\text{MgCl}} \text{MgCl} \xrightarrow{\text{TiCl}_4} \text{Cl} \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equiv. of Benzaldehyde (193)</th>
<th>Equiv. of vinyl magnesium chloride (194)</th>
<th>Equiv. of TiCl\textsubscript{4}</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Conc. (M)</th>
<th>Ratio of 197:198:193</th>
<th>Isolated yield of 197 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(1) 1</td>
<td>(2) 1</td>
<td>(3) 0.55</td>
<td>Et\textsubscript{2}O</td>
<td>-78 to rt</td>
<td>0.3</td>
<td>1:4:0</td>
<td>n.d.</td>
</tr>
<tr>
<td>2</td>
<td>(1) 1</td>
<td>(2) 1</td>
<td>(3) 1</td>
<td>Et\textsubscript{2}O</td>
<td>-78 to rt</td>
<td>0.3</td>
<td>1:1:0</td>
<td>n.d.</td>
</tr>
<tr>
<td>3</td>
<td>(1) 1</td>
<td>(2) 1</td>
<td>(3) 1</td>
<td>THF</td>
<td>-78 to rt</td>
<td>0.3</td>
<td>1:7:0</td>
<td>n.d.</td>
</tr>
<tr>
<td>4</td>
<td>(1) 1</td>
<td>(2) 1</td>
<td>(3) 1.5</td>
<td>THF</td>
<td>-78 to rt</td>
<td>0.3</td>
<td>1:1.5:0</td>
<td>n.d.</td>
</tr>
<tr>
<td>5</td>
<td>(1) 1</td>
<td>(2) 1</td>
<td>(3) 1</td>
<td>THF / Et\textsubscript{2}N</td>
<td>-78 to rt</td>
<td>0.3</td>
<td>0:1:0</td>
<td>n.d.</td>
</tr>
<tr>
<td>6</td>
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<td>(2) 1</td>
<td>(3) 1</td>
<td>THF</td>
<td>-78 to rt</td>
<td>0.15</td>
<td>1:3:0</td>
<td>n.d.</td>
</tr>
<tr>
<td>7</td>
<td>(1) 1</td>
<td>(3) 1</td>
<td>(2) 1</td>
<td>THF</td>
<td>-78 to rt</td>
<td>0.3</td>
<td>1:0:0.5</td>
<td>n.d.</td>
</tr>
<tr>
<td>8</td>
<td>(1) 1</td>
<td>(3) 1</td>
<td>(2) 1.5</td>
<td>THF</td>
<td>-78 to rt</td>
<td>0.3</td>
<td>1:0:1.2</td>
<td>n.d.</td>
</tr>
<tr>
<td>9</td>
<td>(1) 1</td>
<td>(3) 1</td>
<td>(2) 2</td>
<td>THF</td>
<td>-78 to rt</td>
<td>0.3</td>
<td>1:0:1.2</td>
<td>n.d.</td>
</tr>
<tr>
<td>10</td>
<td>(1) 1</td>
<td>(3) 2</td>
<td>(2) 1</td>
<td>THF</td>
<td>-78 to rt</td>
<td>0.3</td>
<td>0:1:0</td>
<td>n.d.</td>
</tr>
<tr>
<td>11</td>
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<td>(3) 1.5</td>
<td>(2) 1</td>
<td>THF</td>
<td>-78 to rt</td>
<td>0.3</td>
<td>1:0:4:0.1</td>
<td>n.d.</td>
</tr>
<tr>
<td>12</td>
<td>(1) 1</td>
<td>(3) 1.5</td>
<td>(2) 1</td>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>-78 to rt</td>
<td>0.3</td>
<td>1:0:1.5</td>
<td>n.d.</td>
</tr>
<tr>
<td>13</td>
<td>(1) 1</td>
<td>(3) 1.5</td>
<td>(2) 1</td>
<td>Et\textsubscript{2}O</td>
<td>-78 to rt</td>
<td>0.3</td>
<td>1:0:0.5</td>
<td>n.d.</td>
</tr>
<tr>
<td>14</td>
<td>(1) 1</td>
<td>(3) 2</td>
<td>(2) 2</td>
<td>THF</td>
<td>-78 to 80</td>
<td>0.3</td>
<td>1:0:0</td>
<td>32%</td>
</tr>
<tr>
<td>15</td>
<td>(1) 1</td>
<td>(3) 1</td>
<td>(2) 1</td>
<td>THF</td>
<td>-78 to 80</td>
<td>0.3</td>
<td>1:0:0</td>
<td>52%</td>
</tr>
<tr>
<td>16</td>
<td>(1) 1</td>
<td>(3) 1</td>
<td>(2) 1</td>
<td>THF</td>
<td>-78</td>
<td>0.3</td>
<td>1:2.5:0</td>
<td>n.d.</td>
</tr>
<tr>
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<td>(3) 1</td>
<td>(2) 1</td>
<td>THF</td>
<td>0</td>
<td>0.3</td>
<td>1:5:2.5</td>
<td>n.d.</td>
</tr>
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<td>(3) 1</td>
<td>(2) 1</td>
<td>THF</td>
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<td>n.d.</td>
</tr>
<tr>
<td>19</td>
<td>(1) 1</td>
<td>(3) 1</td>
<td>(2) 1</td>
<td>THF</td>
<td>80</td>
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<td>1:0:0.2</td>
<td>52%</td>
</tr>
<tr>
<td>20</td>
<td>(1) 1</td>
<td>(2) 1</td>
<td>(3) 0.5</td>
<td>THF</td>
<td>-78 to 80</td>
<td>0.3</td>
<td>1:0:0</td>
<td>77%</td>
</tr>
</tbody>
</table>

**Legend:** The numbers in red: (1), (2), (3) correspond to order of addition.

*Table 17. Optimisation of formation of (E)-[3-chloroprop-1-enyl]benzene (197).*
When vinylmagnesium chloride (194) was added first, followed by TiCl$_4$ (Table 17, entries 1 to 6) a large amount of alcohol 198 was obtained. By adding more than 0.5eq of TiCl$_4$ or changing the solvent (Table 17, entries 2 to 6), the proportion of alcohol decreased, but was still the major product.

To limit the formation of alcohol 198 and facilitate the low temperature addition of vinylmagnesium chloride, TiCl$_4$ was added to benzaldehyde (193) before the Grignard reagent 194 (Table 17, entries 7 to 15). It was thought this may increase the electrophilicity of the carbonyl carbon following coordination of the Lewis acid. Although improved results were obtained, residual benzaldehyde (193) was observed due to possible attack of the Grignard reagent 194 onto the titanium centre, initiating subsequent side reactions such as homocoupling, and reducing the number of equivalents of active vinyl nucleophile. Different solvents were investigated to try to improve the conversion (Table 17, entries 12, 13) but the best solvent found was THF. When the reaction was performed at a higher temperature (80 °C), only (E)-(3-chloroprop-1-enyl)benzene (197) was obtained (Table 17, entries 14 and 15), however in poor yield. In attempts to optimise this result, the reaction was performed at four different temperatures (Table 17, entries 16 to 19) and the best conditions found involved heating the reaction to 80 °C (Table 17, entry 19).

Finally, to avoid side reactions and using the optimised temperature, the order of reagent addition was switched once again and the reaction was performed with the addition of vinylmagnesium chloride (194) followed by 0.5 equivalents of TiCl$_4$ with careful monitoring of the Grignard addition. After entire consumption of benzaldehyde, the reaction was heated to 80 °C and the yield increased substantially to 77% (Table 17, entry 20).

Employing the developed conditions, several reactions were performed with substituted benzaldehydes (Table 18). Substrates were employed with one or two methyl substituents on the aromatic ring (Table 18, entries 1 and 2), electron-rich aromatics (Table 18, entries 3 and 4), and electron-poor aromatics (Table 18, entries 5 and 6). Aromatic substrates containing nitro groups (Table 18, entry 7) proved problematic most likely due to the reactivity of the nitro group with Grignard reagents, whereas amino substrates (Table 18, entry 8) gave some decomposition possibly due to the known oxidative reactions of aniline derivatives with TiCl$_4$. Two other reactions were carried out, albeit with slight variations: a reaction between acetophenone (87) and vinylmagnesium chloride (Table 18, entry 9) and a reaction between benzaldehyde (193) and 2-methyl-1-propenylmagnesium bromide (Table 18, entry 10). These gave 214 in moderate yield and the diene 215 after elimination respectively.
Table 18. Scope of chlorination reaction with substituted benzaldehydes and acetophenone.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substituted Benzaldehyde</th>
<th>Final product</th>
<th>Yield (%)</th>
<th>Entry</th>
<th>Substituted benzaldehyde</th>
<th>Final product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>198</td>
<td>67</td>
<td>6</td>
<td></td>
<td></td>
<td>76</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>200</td>
<td>73</td>
<td>7</td>
<td></td>
<td></td>
<td>/</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>202</td>
<td>95[a]</td>
<td>8</td>
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<td>/</td>
</tr>
<tr>
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<td>206</td>
<td>47</td>
<td>10</td>
<td></td>
<td></td>
<td>62</td>
</tr>
</tbody>
</table>

[a] Product isolated crude (ca. 95% pure) as unstable to SiO₂ chromatography.

To further extend this methodology, an investigation into the use of more heavily substituted Grignard reagents as nucleophiles, as well as the use of both aromatic aldehydes and ketones, and aliphatic aldehydes was initiated. As seen in Table 18, the reaction between acetophenone (87) and vinylmagnesium chloride (194) gave the product 214 in only a moderate yield due to the lower reactivity of Grignard reagents towards acetophenone. The same low reactivity was observed for the reaction of substituted Grignard reagents with benzaldehyde, and furthermore, competitive reduction was observed. Kharasch and Weinhouse investigated the reduction of ketones by Grignard reagents in 1936.¹³¹ They proposed a radical mechanism for this reduction (Scheme 25) and showed that substituted Grignard reagents, prone to give stable radical species, were highly efficient for the reduction of ketones.

\[
\begin{align*}
R'\text{MgX} & \rightarrow R^\cdot + \cdot\text{MgX} \\
216 & \rightarrow 217, 218 \\
\end{align*}
\]

\[
\begin{align*}
\text{R} = \text{C} = \text{O} + \cdot\text{MgX} & \rightarrow \text{R} = \text{CH} + \cdot\text{MgX} \\
219 & \rightarrow 218, 220, 221 \\
\end{align*}
\]

Scheme 25. Proposed mechanism for the reduction of ketones by Grignard reagents.
To combat these side reactions, additives were investigated such as HMPA and/or dimethoxyethane (DME), but only residual benzaldehyde was obtained. An increase in the number of equivalents of the Grignard reagent resulted in the minimisation of this reduction side-reaction, however this was not compatible with our one-pot system. For this reason, a two-step procedure was developed whereby allylic alcohols were synthesised and then treated with isopropylmagnesium chloride to regenerate the magnesium alkoxide followed by addition of TiCl₄. The results of these reactions are seen in Table 19.

\[
\begin{align*}
\text{Alkoxide} & \quad \text{Final product} & \quad \text{Yield (\%)} \\
1 & \quad \text{NC} & \quad \text{NC} & \quad 78 \\
2 & \quad \text{OMgCl} & \quad \text{226} & \quad 78 \\
3 & \quad \text{OMgCl} & \quad \text{227} & \quad 50 \\
4 & \quad \text{OMgCl} & \quad \text{229} & \quad 95 \\
5 & \quad \text{OMgCl} & \quad \text{231} & \quad 80 \\
6 & \quad \text{OMgCl} & \quad \text{232} & \quad 80 \\
7 & \quad \text{OMgCl} & \quad \text{234} & \quad 60 \\
8 & \quad \text{OMgCl} & \quad \text{236} & \quad 50
\end{align*}
\]

Table 19. Rearrangement reaction with substituted alkoxides

The two-step procedure was well tolerated and the yield greatly improved compared to the one-pot reaction for more hindered substrates (Table 19, entries 1 & 2, cf Table 18, entries 5 & 9). Substrates with a tertiary alkoxide centre (Table 19, entries 2, 3 and 6) gave good conversion including the formation of a tetrasubstituted double bonds 228 (Table 19, entry 3) which are known to be challenging synthetic targets. Monosubstitution of the terminal alkene position posed no problem (Table 19, entry 4), and the product 230 was isolated in excellent yield. In general, for the more heavily substituted products, elimination of HCl to give an olefin was observed. Disubstitution of the terminal alkene also resulted in unavoidable elimination (Table 19, entries 5 and 6), although the corresponding dienes 215 and 233 were isolated in good yield. A mixture of the both regioisomers was obtained for compound 233. Finally, entries 7 and 8 (Table 19) demonstrate the feasibility of aliphatic substrates to participate in the reaction, although longer reaction times were required.
For this novel methodology, two different mechanisms could be envisaged: a cationic pathway with anion capture of the most stable conformer (pathway A, Scheme 26) or by a six-membered transition state (pathway B, Scheme 26) either somewhat concerted or SNi'. In order to investigate these possibilities, several rearrangement reactions were performed with the inclusion of molecular sieves, calcium carbonate or silver carbonate as chloride scavengers but all gave the same \((E)\)-allylic chloride 197. The fact that these were not able to scavenge the free chloride anion suggested that the reaction may not proceed \(via\) a cationic pathway.

![Scheme 26. Potential reaction mechanisms for the formation of \((E)\)-(3-chloroprop-1-enyl)benzene (197).](image)

In order to further investigate the mechanism, follow up studies were performed. Kabalka and co-workers have previously highlighted the ability of allyl trimethylsilane to capture cationic intermediates in a related reaction of titanium alkoxides to give allylated products.\(^{121,122}\) In our reaction, the same allylic chloride was obtained in the presence of allyl trimethylsilane (240) i.e. no capture was observed (Scheme 27). Once again this was in line with the reaction proceeding \(via\) a concerted pathway.

![Scheme 27. Rearrangement in the presence of allyl trimethylsilane (240).](image)

As a potentially more conclusive probe, a chiral alcohol 247 was prepared by a modification of the method of Kenyon, Partridge, and Phillips.\(^{134,135}\) Alcohol 247 was prepared by addition of phenylmagnesium bromide (241) to crotonaldehyde (242). The product was resolved by formation
of a phthalate ester 245, addition of quinidine (246) and separation of both diastereoisomers by crystallisation, followed by treatment with sodium hydroxide to give the chiral alcohol 247 (75% ee, Scheme 28).

\[
\begin{align*}
\text{MgBr} & + \text{alkene} \rightarrow \text{MgCl} \quad \text{THF} \quad 30 \text{ min, rt} \quad 95\%
\end{align*}
\]

**Scheme 28.** Formation of the chiral alcohol 247.

The rearrangement was then performed (Scheme 29). In measuring the degree of chirality transfer upon reaction, it should be possible to provide mechanistic evidence for the two proposed pathways. No transfer of chiral information (75% ee to 0% ee) was observed upon reaction, as judged by chiral HPLC analysis of the product. This suggests that the reaction proceeded via a cationic pathway (pathway A, Scheme 26). It is, however, relevant to note that since the HPLC showed the presence of a side product (i.e., diene) resulting from HCl elimination, we cannot rule out the possibility that product 230 racemised on the HPLC column. Unfortunately, our attempts to analyse this reaction by other methods failed to resolve the enantiomers of 230. Flash chromatography resulted in both elimination and decomposition, and the average crude optical rotation of the product was 4 degrees. It is also possible that the reaction mechanism depends on the substrate: while the reaction with a terminal alkene could proceed via a concerted mechanism, reaction with more substituted alkenes could proceed via a cationic pathway as the cation will be more stabilised. This methodology was published in Organic Letters.136

\[
\begin{align*}
\text{OH} & \quad \text{iPrMgCl} \quad \text{THF} \quad \text{ii) TiCl}_4 \quad (0.5 \text{ eq}) \quad 75\% \text{ e.e.} \\
\text{Cl} & \quad 0\% \text{ e.e.}
\end{align*}
\]

**Scheme 29.** Rearrangement of chiral alcohol 247.
1.1.1.2. Attempted formation of indene

Since the original goal of this work was to prepare indene derivatives, extensive conditions were surveyed to try and enable the synthesis of the desired substituted indene from the isolated allylic chloride. The first attempt was to form indene (248) from the isolated (E)-(3-chloroprop-1-enyl)benzene (197, Scheme 30, Table 20).

![Scheme 30. Attempts at indene formation. Reagents and conditions: see Table 20.](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents</th>
<th>Solvent</th>
<th>Temp. (˚C)</th>
<th>Time (h)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DMF</td>
<td></td>
<td>200[a]</td>
<td>0.5</td>
<td>Decomposition</td>
</tr>
<tr>
<td>2</td>
<td>InCl₃</td>
<td>CH₂Cl₂</td>
<td>25</td>
<td>24</td>
<td>Decomposition</td>
</tr>
<tr>
<td>3</td>
<td>Pd(Ph₃)₄; PPh₃; K₂CO₃</td>
<td>DMA</td>
<td>100</td>
<td>1</td>
<td>Decomposition</td>
</tr>
<tr>
<td>4</td>
<td>Pd(Ph₃)₄; K₂CO₃</td>
<td>DMA</td>
<td>100</td>
<td>24</td>
<td>Decomposition</td>
</tr>
<tr>
<td>5</td>
<td>Pd(OAc)₂; PPh₃; Et₃N</td>
<td>DMA</td>
<td>100</td>
<td>1</td>
<td>Decomposition</td>
</tr>
<tr>
<td>6</td>
<td>Pd(OAc)₂; K₂CO₃</td>
<td>DMA</td>
<td>100</td>
<td>1</td>
<td>Decomposition</td>
</tr>
</tbody>
</table>

[a] microwave reaction

Table 20. Different conditions tested to produce indene (248).

The first attempt (Table 20, entry 1) was to use a high temperature to encourage re-ionisation, bond rotation and ring closure, but unfortunately this resulted in decomposition. Considering the recent work of Cook, Hayashi and co-workers in the field of intramolecular Friedel-Crafts reactions catalysed by InCl₃, the addition of InCl₃ to (E)-(3-chloroprop-1-enyl)benzene (197) was attempted but failed to produce indene (248, Table 20, entry 2). Another idea was the use of palladium to effect the cyclisation via a π-allyl intermediate (Scheme 31). Unfortunately, all attempts failed (Table 20, entries 3 to 6) and only decomposition was observed.
Due to these unsuccessful results, further studies were performed on our one-pot system, rather than using the isolated allylic chloride (Scheme 32, Table 21). By adding a chloride scavenger to the reaction, it was hoped that the addition of the chloride anion could be avoided and the ring should be able to close to form indene (248, Table 21, entries 1 and 2). However, as alluded to above, in both cases, the allylic chloride product 197 was obtained. Alternative Lewis acids (BF₃, FeCl₃ and SnCl₂) were surveyed to replace TiCl₄, but all afforded 197 (Table 21, entries 3 to 7). The use of other titanium species did not result in the formation of indene (248, Table 21, entries 8 to 11).

**Scheme 32.** Attempts to form indene from benzaldehyde (193). See conditions Table 21.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Scavengers</th>
<th>Lewis acid</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CaCO₃, molecular sieves</td>
<td>TiCl₄</td>
<td>THF</td>
<td>80</td>
<td>1</td>
<td>197</td>
</tr>
<tr>
<td>2</td>
<td>Ag₂CO₃</td>
<td>TiCl₄</td>
<td>THF</td>
<td>25</td>
<td>24</td>
<td>197</td>
</tr>
<tr>
<td>3</td>
<td>BCl₃</td>
<td>THF</td>
<td>80</td>
<td>3</td>
<td>197</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>FeCl₃</td>
<td>THF</td>
<td>80</td>
<td>3</td>
<td>197</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>BCl₃</td>
<td>DME</td>
<td>150</td>
<td>2</td>
<td>Decomposition</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>FeCl₃</td>
<td>DME</td>
<td>150</td>
<td>2</td>
<td>Decomposition</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>SnCl₂</td>
<td>THF</td>
<td>80</td>
<td>24</td>
<td>197</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>TiCl₂(OTf)₂</td>
<td>THF</td>
<td>25</td>
<td>24</td>
<td>197</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>TiCl₂(O'Bu)₂</td>
<td>THF</td>
<td>25</td>
<td>24</td>
<td>197</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>TiCl₂(OTf)₂</td>
<td>THF</td>
<td>80</td>
<td>24</td>
<td>197</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Ti(OTf)₄</td>
<td>THF</td>
<td>80</td>
<td>24</td>
<td>Starting material</td>
<td></td>
</tr>
</tbody>
</table>

**Table 21.** Different conditions tested to form indene (248) from benzaldehyde (193).
In light of this survey, the strategy to form indene (248) from benzaldehyde (193) via metallic alkoxides was abandoned.

1.1.2. An alternative approach to indene derivatives

Since our first attempts to produce indenes did not succeed, a new strategy was envisaged. In line with previous reports, the desired indene derivatives 186 could be obtained by elimination of water from 7-hydroxyindan-1-one (253, Scheme 33). We then thought that several functional group interconversions of the phenoxy group could be effected to produce a large range of indenes, substituted in our desired position.

\[
\begin{align*}
\text{R} & \quad \text{R} \\
\text{186} & \quad \text{252} \\
& \quad \text{253}
\end{align*}
\]

*Scheme 33. Proposed retrosynthesis of substituted indene from 7-hydroxyindan-1-one (253).*

Formation of an ester followed by Fries rearrangement and intramolecular Friedel Crafts reaction should afford 7-hydroxyindan-1-one (253, Scheme 34). Indeed, the reaction between phenol (254) and chloropropionic acid chloride (255) at 90 °C over several hours resulted in the formation of ester 256. Then, addition of aluminium trichloride to the crude product, followed by fusion at 200 °C afforded 7-hydroxyindan-1-one (253) in a moderate yield (45%).

\[
\begin{align*}
\text{OH} & \quad \text{Cl} \quad \text{Cl} \\
254 & \quad 255 \\
& \quad 256 \\
& \quad \text{AlCl}_3 \quad 200 \degree C \\
& \quad 45\% \\
\text{OH} & \quad \text{253}
\end{align*}
\]

*Scheme 34. Synthesis of 7-hydroxyindan-1-one (253) by Fries rearrangement.*

In 1954, Loudon and Razdan reported an alternative synthesis of 7-hydroxyindan-1-one (253) from chromanone (258) in the presence of aluminium trichloride. In our hands the rearrangement occurred after heating at high temperature in good yield (75%) after a short reaction time (Scheme 35).
Once 7-hydroxyindan-1-one (253) was produced, diversification of the phenoxy group was planned (Scheme 36). We envisaged that alkylation would lead to simple alkoxy substituents whereas a variety of aryl- and alkyl-substituted derivatives should be obtainable via cross-coupling, following conversion of the phenoxy group to an aryl triflate 261.

The methoxyindanone 259 was obtained by reaction of dimethylsulfate with hydroxyindanone 253 in presence of potassium carbonate (Scheme 37). A good yield (87%) was obtained after destruction of the residual dimethylsulfate by addition of a NaOH solution and flash column chromatography. The iso-propoxyindanone 260 was obtained by reaction of 2-iodopropane with hydroxyindanone 253 in the presence of potassium carbonate to afford the product 260 in good yield (94%, Scheme 37).
Synthesis of new chiral NHCs

Scheme 37. Formation of methoxyindanone 259 and iso-propoxyindanone 260.

Alkyl- or aryl-substitution via cross-coupling required the formation of aryltriflate 261. Exposure of N-phenyltrifluoromethanesulphonimide to hydroxyindanone 253 in the presence of triethylamine afforded the aryltriflate 261 in excellent yield (99%) after 24 hours (Scheme 38).\textsuperscript{147} The methylindanone 262 was obtained by a nickel-mediated cross-coupling (Scheme 38). The reaction of dimethylzinc in the presence of a nickel catalyst 264 with the aryltriflate afforded the methylindanone 262 in excellent yield (96%).\textsuperscript{148} While the same procedure using diphenylzinc should give phenylindanone 263, considering the price of the zinc reagent, another strategy was applied. A palladium-mediated cross-coupling reaction with phenylboronic acid (265) afforded the phenyl indanone 263 in excellent yield (98%, Scheme 38).\textsuperscript{149}

Scheme 38. Formation of the aryltriflate 261 followed by methyl 262 and phenyl 263 derivatives.

The final step of the indene synthesis was the reduction of the carbonyl group, followed by elimination of the resultant benzylic alcohol. Treatment of the methoxy-, iso-propoxy-, methyl- and
phenyl-indanones (259, 260, 262 and 263) with NaBH₄ afforded the benzylic alcohols (266, 267, 268 and 269) in good yield (Scheme 39).

\[
\begin{align*}
R &= \text{OMe (259)} \\
    &= \text{O}^{i\text{Pr}} (260) \\
    &= \text{Me (262)} \\
    &= \text{Ph (263)} \\
\end{align*}
\]

Scheme 39. Reduction of the carbonyl group.

Elimination of the alcohol was surveyed next. As a model, methoxyindene 270 was chosen as it was the cheapest and simplest compound to synthesise. Diverse reaction conditions were surveyed in an attempt to prepare methoxyindene 270 (Scheme 40, Table 22):

\[
\begin{align*}
\text{OMe} & \rightarrow \text{OMe} (266, 97\%) \\
    & \rightarrow \text{O}^{i\text{Pr}} (267, 85\%) \\
    & \rightarrow \text{Me (268, 91\%)} \\
    & \rightarrow \text{Ph (269, 98\%)} \\
\end{align*}
\]

Scheme 40. Formation of methoxyindene 270. Conditions in Table 22.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Solvent</th>
<th>T (˚C)</th>
<th>Time (h)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PTSA cat.</td>
<td>Toluene</td>
<td>80</td>
<td>2</td>
<td>Decomposition</td>
</tr>
<tr>
<td>2</td>
<td>PTSA cat.</td>
<td>Benzene</td>
<td>60</td>
<td>0.5</td>
<td>Decomposition</td>
</tr>
<tr>
<td>3</td>
<td>PTSA cat.</td>
<td>CHCl₃</td>
<td>25</td>
<td>2.5</td>
<td>Ethanol addition</td>
</tr>
<tr>
<td>4</td>
<td>PTSA cat.</td>
<td>CH₂Cl₂</td>
<td>25</td>
<td>2.5</td>
<td>Starting material</td>
</tr>
<tr>
<td>5</td>
<td>Amberlyst 15</td>
<td>CH₂Cl₂</td>
<td>25</td>
<td>0.5</td>
<td>Oligomers</td>
</tr>
<tr>
<td>6</td>
<td>TsCl, Et₃N</td>
<td>CH₂Cl₂</td>
<td>25</td>
<td>13</td>
<td>Decomposition</td>
</tr>
<tr>
<td>7</td>
<td>MsCl, Et₃N</td>
<td>THF</td>
<td>0 to 25</td>
<td></td>
<td>Decomposition</td>
</tr>
<tr>
<td>8</td>
<td>Ac₂O, Et₃N</td>
<td>CH₂Cl₂</td>
<td>25</td>
<td>10</td>
<td>Starting material + trace of 270\textsuperscript{a}</td>
</tr>
<tr>
<td>9</td>
<td>TFAA, Et₃N</td>
<td>CH₂Cl₂</td>
<td>25</td>
<td>10</td>
<td>270 major product + Oligomers\textsuperscript{a}</td>
</tr>
</tbody>
</table>

\[\text{[a] by } ^1\text{H NMR}\]

Table 22. Attempts to form methoxyindene 270.

Janda and co-workers reported the formation of meta-chloroindene by addition of a catalytic amount of para-toluenesulfonic acid (10%) to a solution of meta-chloroindanol in toluene and refluxing for two hours. In our case, significant decomposition was observed (Table 22, entry 1).\textsuperscript{150} In 1965, Winter and co-workers reported the synthesis of the 6-methoxyindene via the 6-methoxy-1-indanol.\textsuperscript{151} The elimination was carried out with a catalytic amount of para-toluenesulfonic acid and a reaction time of 30 minutes in refluxing benzene but also resulted in
decomposition in our case (Table 22, entry 2). Recently Fang and co-workers published their work on the synthesis of 4,7-dimethoxyindene via a mild dehydration.\textsuperscript{152} A catalytic amount of para-toluenesulfonic acid (10\%) in chloroform with stirring at ambient temperature for 2.5 hours gave the product in 95\% yield. The possible carbocation formed during the reaction was captured by residual ethanol in the chloroform solvent (Table 22, entry 3). The same reaction with distilled dichloromethane resulted in unreacted starting material (Table 22, entry 4). In 1999, Polo reported that polymerisation of indene is rapidly observed following dehydration under acidic conditions.\textsuperscript{153}

To reduce this problem and improve the yield, they used Amberlyst 15, a strongly acidic ion-exchange resin, to reduce the work-up time. Reaction of methoxyindanol 266 with Amberlyst 15 in dichloromethane followed by simple filtration resulted in less decomposition but a variety of oligomers were observed (Table 22, entry 5).

Since acidic conditions were shown to be problematic for this substrate, basic conditions were surveyed. Addition of tosyl chloride in presence of one equivalent of triethylamine did not result in the formation of an indene but gave decomposition (Table 22, entry 6). Likewise addition of methylsulfonylchloride in the presence of triethylamine at 0 ˚C followed by stirring at ambient temperature gave decomposition (Table 22, entry 7). Formation of an ester by addition of acetic anhydride in presence of triethylamine looked promising by TLC analysis, but was very slow (Table 22, entry 8). Alternatively addition of trifluoroacetic anhydride was attempted and gave the indene as the major product as observed in the crude reaction mixture (Table 22, entry 9). However, all attempted purification methods resulted in polymerisation or decomposition.

Another strategy to form methoxyindene 270 directly from the methoxyindanone 266 involved formation of an enol triflate and then addition of palladium in the presence of tributyltin hydride or triethyl silane (Scheme 41).\textsuperscript{154,155} Stille and co-workers reported the palladium-catalysed reaction of vinyl triflates and organostannanes in 1984 and a mechanism for the reaction was proposed in 1986 (Scheme 41). Formation of a complex with lithium chloride and palladium to give chloropalladium(0) anion followed by oxidative addition of the vinyl triflate would yield intermediate 272. Transmetallation of 272 with tributyltin hydride would afford tributyltin chloride and 273, which rapidly would undergo reductive elimination to yield indene 270 and regenerate the palladium(0) catalyst. However, such a strategy formation proved problematic due to the stability of the enol triflate 271.
While none of the methods attempted were totally satisfactory, the best conditions identified for the dehydration (Table 22, entry 9) were then applied to an alternative substrate; the methylindanol 268. Disappointedly, addition of trifluoroacetic anhydride in the presence of triethylamine gave the trifluoroacetic ester in a moderate yield (37%), along with recovered starting material. As this substrate appeared to be less reactive than methoxyindanol 266, the method employing Amberlyst 15 was applied. A single addition of Amberlyst 15 at room temperature resulted in the formation of small amounts of polymers alongside the final product. Modified conditions (reaction at 0°C, successive additions of resin, dilution) were applied to the methyl and phenyl derivatives 268 and 269 and gave the indene products 274 and 275 in 85% and 92% yield respectively (Scheme 42). Purification by column chromatography was not possible as it resulted in polymerisation; however the material was of sufficient purity by NMR analysis.
Unfortunately the optimised method was not reproducible for the more electron rich methoxy 266 or iso-propoxyindanol 267. Non-acidic, mild conditions were needed to obtain the product in good yield. We reasoned that pyridinium p-toluenesulfonate (276, PPTS) was a good candidate for this dehydration, with the pyridium salt acting as a basic buffer. PPTS was added to a solution of methoxy indene 266 in dichloromethane and stirred at ambient temperature; after 30 minutes, a small amount of indene had formed as visualised by TLC. After 2h and the addition of two further equivalents of PPTS, no more starting material was observed. However, the reaction was not clean, and unwanted side-products were present.

The reaction was then attempted with the isopropoxyindanol 267; two equivalents of PPTS were added and the reaction warmed to reflux for 3h. No side products or starting material were observed; just residual pyridine and indene 277 were obtained (Scheme 43). Removal of the pyridine under reduced pressure resulted in the partial evaporation of the desired product. Instead, a modified work-up with a saturated solution of copper sulphate to remove the pyridine gave indene 277 in sufficient purity for the next step.

This method proved to be efficient and reliable and was therefore applied to all four substrates with good to excellent conversions. No purification was attempted on these substrates and the material was pure enough to continue to the next step (Scheme 44).
1.2. Synthesis of cis-1-amino-2-indanol derivatives

The next step in our synthetic plan consisted of the synthesis of cis-1-amino-2-indanol derivatives 185 from the isolated indenes 186. Palucki et al. have developed an anhydrous, low-temperature protocol for the (salen)Mn-catalyzed epoxidation reaction employing the combination of \( m \)-chloroperbenzoic acid (\( m \)-CPBA) and \( N \)-methylmorpholine \( N \)-oxide (NMO) as the terminal oxidant.\(^{156,157} \) A simple mechanism for this reaction is drawn in Scheme 45. The first step is the reaction of alkene 278 with a (salen)-Mn(V) oxo species 279 to form a radical intermediate 280 and the first C-O bond. The second C-O bond formation occurs via a collapse or rotation/collapse process to provide the observed mixture of cis 281 and trans 282 epoxides.

![Scheme 45. Simple mechanism for enantioslective epoxidation.](image)

In 1991, Jacobsen and co-workers reported the dramatic catalyst electronic effect on the enantioselectivity of Mn-catalysed epoxidation.\(^{158} \) They showed that electron-donating substituents on the ligand led to higher enantiomeric excess, while electron-withdrawing substituents led to lower enantioselectivity. They proposed that the ligand substituents had an effect on the reactivity of the (salen)Mn oxo intermediate. Electron-withdrawing substituents made the intermediate more...
reactive and therefore lower enantioselectivity were observed. They also showed that the 5,5’-substituents had a dramatic effect on the enantioselectivity and therefore studied these substituents in more detail. In 1998, Jacobsen and co-workers studied in detail temperature effects in the epoxidation of indenes and showed that the best ligand for this reaction was the (salen)Mn 283 displaying 96% ee for the epoxidation of indene 248 (Scheme 46).156

![Scheme 46. Enantioselective epoxidation of indene 285.](image)

Exposure of the indene compounds 186 (R = H, Ph) to analogous conditions gave high yields and good enantioselectivities of the products (Scheme 47, Table 23). Attempts at a rapid chromatographic purification of the product failed due to conversion of indene oxide 286 to 2-indanone 287 (Scheme 47).

![Scheme 47. Enantioselective epoxidation of indene derivatives. See Table 23.](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Equiv. m-CPBA</th>
<th>Time (h)</th>
<th>Catalyst (mol%)</th>
<th>Product</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>248</td>
<td>2</td>
<td>5</td>
<td>285</td>
<td>96</td>
</tr>
<tr>
<td>3</td>
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<td>274</td>
<td>2.4</td>
<td>2.5</td>
<td>288</td>
<td>88</td>
</tr>
</tbody>
</table>

*Table 23. Conditions and results for the epoxidation of indene derivatives.*
Crude epoxide 286 was then directly subjected to a Ritter reaction followed by hydrolysis of the oxazoline intermediate 292 using a procedure developed by Reider and co-workers.\textsuperscript{159,160} When the reaction was conducted at low temperature in acetonitrile with two equivalents of oleum, sulfur trioxide captures the epoxide 286 to form the novel cyclic sulfate 289 which they observed by low temperature NMR. Following warming to room temperature, the highly reactive carbenium ion 290 was trapped by acetonitrile to provide the nitrilium intermediate 291; conformationally biased \textit{cis}-5,5-ring formation then affords the desired compound 295. Along with the formation of bicyclic compound 292 minor non cyclic products were formed. Upon refluxing in water, the intermediate 293 hydrolysed to yield aminoisindanol 295 (Scheme 48).

\begin{center}
\textbf{Scheme 48.} Mechanism of the modified Ritter reaction developed by Merck.
\end{center}

The phenyl epoxide 288 was also subjected to the Ritter reaction but a low yield (20\%) was obtained for the same conditions used for unsubstituted epoxide 285. The addition of oleum to the epoxide was performed at -40 °C instead of -5° C, and the organic solvents were removed under vacuum following the addition of water. Extended reaction times were also employed. Aminoisindanol 297 was isolated in good yield (72\%) following neutralisation of the corresponding salt (Table 24).
1.3. Synthesis of imidazolium triflate derivatives

In 2002, Glorius and co-workers described the synthesis of imidazolium salts 52 from aminoalcohols 49.\textsuperscript{34,161,162} Their preparation was based on the finding that bisoxazolines 50, obtained from condensation of an amino alcohol 49 with diethyl oxalate 48, can be converted into imidazolium salts with AgOTf and chloromethyl pivalate 52 (Scheme 49).

The desired salt was generally obtained in more than 60% overall yield from diethyl oxalate 48 and aminoalcohol 49. They reported this method to be very reliable for the cyclisation of (bis)oxazolines, imineoxazolines, and (bis)imines. It has the advantage of leading to the formation of triflate salts, which are soluble in dichloromethane and THF, and can be chromatographed in contrast to the much less soluble standard imidazolium chlorides.

The application of this methodology to our aminoidanol derivatives 299 proved problematic. Firstly, the condensation displayed only a modest yield (63%) of 300 (Scheme 50).
In 2008, Struble and Bode described the synthesis of the imidazolium salt \( \text{303} \) derived from \((1R,2S)-1\)-amino-2-indanol \((\text{301})\).\(^{163}\) The first step of their synthesis was the condensation of the aminooindanol \((\text{301})\) with ethyl formate in THF with catalytic glacial acetic acid (Scheme 51).

To our delight, exposure of our compound \( \text{299} \) to the same conditions but with diethyl oxalate \( \text{48} \) instead of ethyl formate gave the desired product \( \text{300} \) quantitatively (Scheme 52). The presence of a catalytic amount of acetic acid was important for the initiation and completion of the reaction.

Unfortunately, the subsequent chlorination step resulted in the degradation of the product at 90 °C using the conditions reported by Glorius and co-workers. No product was observed after six hours at 25 °C (Scheme 53).
Due to these unsuccessful results, a method developed in 2006 by Glorius and Schwekendiek to synthesise 2-oxazolines 311 was considered (Scheme 54).\textsuperscript{164} They showed that the condensation of an aldehyde 305 with an amino alcohol 306 in dichloromethane, in the presence of 4 Å molecular sieves lead to an oxazolidine 308 and that subsequent oxidation with N-bromosuccinide yielded an oxazoline 311. This one-pot synthesis was characterised by mild reaction conditions, broad scope, high yields, and its preparative simplicity.

With the intention of forming the bisoxazoline compound 314, glyoxal 312 was used as the dialdehyde. Glyoxal is commercially available, in monomer form, as a 40% aqueous solution; therefore the first step was carried out under aqueous conditions as described in the literature (Scheme 55).\textsuperscript{165}
After stirring overnight at room temperature, the mixture obtained under these conditions did not contain the desired compound or the intermediate 313. The $^{13}$C NMR spectrum did not display the typical peak around 160 ppm for the $sp^2$ imino carbon. Glyoxal appeared to be too reactive with $\beta$-aminoalcohols as only degradation products were obtained. Thus, it was decided to return to our original idea which was to cyclise the amidoalcohol 300 obtained by condensation between 299 and 48.

As the original Glorius’ cyclisation protocol was unsuccessful (see Scheme 53), a new strategy was required. Either the hydroxyl group or our aminooindanol needed to be converted into a good leaving group$^{166}$ or the electrophilic amide activated.$^{167,168}$ In the reported synthesis, the chlorination step resulted in a retention of configuration (Scheme 53). This would give the chlorine atom on the same face as the attacking amide, and hence backside attack in an $S_N2$ displacement impossible within a 5-membered ring. The first strategy we therefore employed was to use pyridine to promote inversion during the chlorination step (Scheme 57, Table 25, entry 1).$^{169}$ This is a well known process described by Cram in 1953 (Scheme 56). Without pyridine the mechanism of the reaction is an $S_{Ni}$ type mechanism where the loss of sulphur dioxide molecule and its replacement by chloride is concerted leading to a retention configuration. Pyridine reacts with the intermediate sulphite to replace chlorine. The dislodged chloride will react and attack from the rear in a classical $S_n2$ mechanism.

Unfortunately, however this approach resulted in degradation of the product. Alternatively, we attempted to activate the amide with either Brønsted or Lewis acids (Table 25, entries 2 to 5). Ring closure usually requires a high temperature, which may have caused competing decomposition in all instances (Table 25, entries 2, 4 and 5) except for whilst using $Bu_2SnCl_2$ (Table 25, entry 3). In this case a low yield (15%) of the product 314 was isolated.
Synthesis of new chiral NHCs

Scheme 57. Attempted cyclisation of 300. For conditions see Table 25.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>Time (h)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
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<td>SOCl\textsubscript{2} with pyridine</td>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>25</td>
<td>6</td>
<td>Degradation</td>
</tr>
<tr>
<td>2</td>
<td>DAST\textsuperscript{170}</td>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>-78</td>
<td>16</td>
<td>Degradation</td>
</tr>
<tr>
<td>3</td>
<td>Bu\textsubscript{2}SnCl\textsubscript{2} \textsuperscript{171}</td>
<td>Xylene</td>
<td>140</td>
<td>24</td>
<td>15% 314</td>
</tr>
<tr>
<td>4</td>
<td>Zn(OAc)\textsubscript{2} \textsuperscript{172}</td>
<td>tert-butanol</td>
<td>140</td>
<td>24</td>
<td>Degradation</td>
</tr>
<tr>
<td>5</td>
<td>Ti(OiPr)\textsubscript{4} \textsuperscript{173}</td>
<td>/</td>
<td>145</td>
<td>8</td>
<td>Degradation</td>
</tr>
<tr>
<td>6</td>
<td>BF\textsubscript{3} Et\textsubscript{2}O \textsuperscript{168}</td>
<td>/</td>
<td>120</td>
<td>5</td>
<td>Degradation</td>
</tr>
<tr>
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<td>BF\textsubscript{3} Et\textsubscript{2}O (2eq)</td>
<td>THF</td>
<td>25</td>
<td>16</td>
<td>no reaction</td>
</tr>
<tr>
<td>8</td>
<td>BF\textsubscript{3} Et\textsubscript{2}O (8eq)</td>
<td>THF</td>
<td>50</td>
<td>16</td>
<td>no reaction</td>
</tr>
<tr>
<td>9</td>
<td>BF\textsubscript{3} Et\textsubscript{2}O (8eq)</td>
<td>Toluene</td>
<td>60</td>
<td>6</td>
<td>no reaction</td>
</tr>
</tbody>
</table>

Table 25. Attempts for the cyclisation of 300.

Following these unsuccessful attempts, we focused on a method reported by Davies \textit{et al.} for the concise synthesis of conformationally constrained Pybox ligands (e.g. 322). This method comprised of an analogous ring closure \textit{via} heating a 15% w/v solution of (bis)amide 321 in BF\textsubscript{3} Et\textsubscript{2}O at 120°C (Scheme 58).\textsuperscript{168}

Disappointedly, under these conditions, our product decomposed (Table 25, entry 6). We hoped that milder conditions would prevent decomposition, as 300 should be more reactive than 321. Indeed, the pyridine functionality in 321 deactivates the electrophilicity of the two carbonyl groups. Performing the reaction in THF (Table 25, entries 7 and 8) resulted in recovered starting material, possibly due to the polar solvent de-activating the Lewis acid. However, reaction of the bis-
amid 300 with 8 equivalents of BF$_3$Et$_2$O in toluene (Table 25, entry 9) did not result in the formation of the desired compound 314.

Due to the multiple problems encountered with this strategy, another was envisaged, starting instead from the trans isomer of aminoindanol 323, rather than the cis isomer 295 (Scheme 59).

Scheme 59. New strategy for the formation of imidazolium salt 183.


As a model system this strategy was performed initially with the unsubstituted commercial trans-aminoindanol. The condensation of trans-aminoindanol 324 was performed using the same procedure as for the cis-aminoindanol 299. 324 and diethyl oxalate (48) were heated under reflux in the presence of catalytic amounts of acetic acid to afford the condensed product 325 in good yield (88%, Scheme 60). Chlorination of the obtained product 325 was performed as described in the Glorius’ procedure. Reflux of 325 with 5 equivalents of thionyl chloride for 12h followed by evaporation of all the volatile material afforded the desired product 326 in good yield (91%, Scheme 60). In this case, neither elimination nor degradation was observed which confirmed our previous hypothesis that the trans-configuration would promote ring closure. To our delight, heating 326 in the presence of sodium hydroxide for 3h in THF gave the cyclised product 314 in a good yield (80%,
Scheme 60. The reaction sequence was repeated without purification of intermediates in each step and the bisoxazoline 314 was obtained in 85% yield over the three steps.

Since our strategy had proved successful we proceeded to prepare trans-aminindanol derivatives 323. Starting from the epoxide synthesised above (Scheme 47), addition of an azide nucleophile should give the product 327 with the required trans configuration. A simple reduction of azide 327 should afford the desired aminindanol 323 (Scheme 61).

Regioselective opening of the crude epoxide 328, 288, 329 and 330 with sodium azide in the presence of ammonium chloride in refluxing aqueous ethanol afforded the trans-azido alcohols 331 to 334 in a good yield after chromatography (Scheme 62). At the stage the enantiomeric excess was determined by chiral HPLC. Pleasingly the results corresponded to the enantiomeric excesses reported by Jacobsen and co-workers for the epoxidation of indene. Reduction of the azide group via hydrogenation using activated palladium on charcoal was performed and the reaction mixture then filtrated through celite® to give the desired trans-aminindanols 335 to 338. Further purification on
silica gel resulted in some degradation; therefore the crude material was directly used in the next step (Scheme 62).

\[
\begin{align*}
\text{NaN}_{3}, \text{NH}_{4}\text{Cl}, \\
\text{EtOH/H}_2\text{O} \quad &\quad \text{2h, reflux} \\
\end{align*}
\]

88% e.e.

\[
\begin{align*}
R \text{NH}_2 \text{OH} \\
\text{MeOH, 30min} \quad &\quad > 90\% \\
\end{align*}
\]

Scheme 62. Formation of trans-azido alcohols followed by reduction of azide group via hydrogenation.

In an analogous approach to that described earlier, the trans-aminooindanols 323 were then condensed to give amides 339 and the crude material was chlorinated using an excess of thionyl chloride. The chloride 340 was then converted to the bisoxazolines 341 and 342 in the presence of sodium hydroxide. This three step procedure allowed the synthesis of the bisoxazolines 341 and 342 in good yield (Scheme 63).

\[
\begin{align*}
\text{diethyl oxalate} \\
\text{THF, 90°C, 16h} \\
\end{align*}
\]

R = Me, 328
R = Ph, 288
R = ’PrO, 329
R = OMe, 330

over 3 steps

R = Me, 331, 55%, 94% e.e.
R = Ph, 332, 58%
R = ’PrO, 333, 40%, 96% e.e.
R = OMe, 334, 42%, 96% e.e.

Scheme 63. Formation of bisoxazolines 341 and 342.

Condensation of our aminooindanols gave amides 339 enantiopure. We reasoned that, statistically, only one enantiomer was present in the mixture with a small amount of the meso compound 344 that was removed during the purification of the bisoxazoline (Scheme 64). Indeed, as
only 2\% of enantiomer 343 was present, only 0.04\% of the enantiomer 345 should be obtained giving 99.92\% e.e. for our desired product.

![Scheme 64.](image)

Although this route was successful for the alkyl substituted aminoindanols 335 and 336, the final step proved to be problematic for the alkoxy derivatives 337 and 338. The condensation reaction with diethyl oxalate was also unreliable since mono condensation products were often obtained. Therefore a different approach was studied (Scheme 65). Firstly, the condensation was performed in two steps: initial condensation to give monosubstituted products with an excess of diethyl oxalate in good yields to give 346 to 348; subsequent condensation with extended reaction times and higher temperatures. Performing the reaction in the microwave at 150 °C, and addition of catalytic quantities of acetic acid allowed the desired compounds 349 to be obtained in approximately 60\% over the two steps. Secondly, we found the formation of the bisoxazoline 184 was achievable in one step from the alcohol 339 by using deoxofluor (350). This had previously proved successful in work reported by Wipf and co-workers to promote the direct cyclisation of amino alcohols to oxazoline rings.\textsuperscript{170} The O-S intermediate, which is postulated to be formed rapidly, rearranges to give a C-F species that cyclises immediately to the desired oxazoline ring in very good yields. This method allowed the formation of our bisoxazoline derivatives 341 and 351 in one step from compound 339, and in general proved to be a faster and more reliable strategy (Scheme 65).
The final step of our reaction sequence consisted of the formation of the desired imidazolium salt 183. Firstly, the Glorius procedure, using chloromethyl pivalate (51) and silver triflate was attempted. Chloromethyl pivalate (51) was stirred with silver triflate at ambient temperature for one hour in the dark, followed by transfer of the resultant reagent to a solution of the bisoxazoline 314 in dichloromethane. Unfortunately, there was no formation of the imidazolium salt 352. After 70h at 40 °C, starting material was still observed along with some decomposition. After some experimentation, we found that degassing and drying the dichloromethane with molecular sieves and performing the reaction in the microwave at 90 °C gave the imidazolium salt 352 in low yield (22%, Scheme 66).
Synthesis of new chiral NHCs

A crystal structure of 352 was solved from crystals obtained following slow evaporation of a THF (1), toluene (4) and hexane (4) solution which shows its helical structure (Figure 15). The crystal structure shows both the bisoxazoline structure and the C$_2$-symmetry axis, key to our design (see Introduction, 1.4).

In order to improve the yield of the reaction, several alternative conditions were surveyed. Solvents with increased polarity, such as THF, were used but did not improve the yield of the reaction. We hypothesised that the high propensity of the pivalate group to leave gave the subsequent undesired side reactions. In term of alternative reagents, Hong and co-workers have previously synthesised constrained imidazolium salts with chloromethyl ethylether under ambient temperature in THF.$^{175}$ Indeed this was the original reagent used by Arduengo and co-workers to...
form the precursors of NHCs. Unfortunately these conditions did not yield the desired imidazolium salt 352 in our case. A modified version of the Arduengo procedure was therefore attempted. Reaction with one equivalent of chloromethyl ethylether and silver triflate in dichloromethane showed consumption of the starting material after two hours at ambient temperature and the crude NMR showed the desired compound 352 as the main product. Unfortunately, purification by column chromatography resulted in decomposition. To combat this, the triflate anion was immediately converted to iodide 355 with an excess of sodium iodide in acetone which proved to be more stable to chromatography. The yield of the reaction increased dramatically to 61% (Scheme 67).

\[
\text{Scheme 67. Synthesis of the imidazolium salt 355 with chloromethyl ethyl ether.}
\]

Thus the last step was performed with the derivatives 341 and 342 to give the desired imidazolium salts 356 and 357 (Scheme 68). Pleasingly, these modified conditions gave cleaner reactions than for the unsubstituted compound 355.

\[
\text{Scheme 68. Formation of imidazolium salts.}
\]

A crystal structure of methyl derivative 356 was solved from crystals obtained by slow evaporation of a THF (1), toluene (4) and hexane (4) solution (Figure 16). This crystal structure shows perfectly the two methyl groups projecting directly into the reactive centre as described in our design strategy (see Introduction 1.4).
The $^1$H-NMR of the different ligands synthesised gave surprisingly results. Indeed the proton of the imidazolium salt is generally around 9 to 10 ppm. This is the case for the unsubstituted imidazolium salt: 9.51 ppm for 352 and 10.2 ppm for 355 where the shift is apparently dependant on the counterion. However, this value changes for the methyl derivative 356 where the signal appeared at 8.75 ppm. A dramatic change was observed for the phenyl derivative 357: the proton appears at 4.71 ppm. It could be explained by the fact that the proton is strongly shielded by both aromatic rings.

2. Buried volumes

As shown in the crystal structures, our NHC ligands have groups pointing directly into the reactive centre which makes them bulky around the metal centre. It was therefore interesting to quantify and describe the shape and steric demand of our ligands. Such steric interactions are challenging to quantify for NHCs as it depends strongly upon the nitrogen substituents and upon rotation around the metal-NHC bond. The concept of buried volume was therefore introduced by Nolan, Cavallo and co-workers as a measure of the space occupied by an organometallic ligand in the first coordination sphere of a metal. The buried volume ($V_{bur}$) represents the part of the sphere around the metal that is buried by the atoms of the ligand. Therefore the more sterically demanding a ligand, the larger the $V_{bur}$ value. This strategy was then used to calculate and compare the buried volume of NHCs as well as other ligands such as mono- or bidentate ligands, phosphines, or cyclopentadienyl based ligands.

![Figure 16. Crystal structure of methyl derivative 356.](image-url)
Buried volume can be calculated from crystallographic or quantum mechanically calculated data. In addition, it can be calculated from different objects such as free NHCs, imidazolium salts or any metal complex. It is however necessary to be careful when comparing %$V_{\text{bur}}$ data as different metals may change the shape of the ligand. Therefore, in an exhaustive study, Clavier and Nolan examined the buried volume of numerous NHC complexes with a linear geometry which leads to minimisation of the steric influence of additional spectator ligands on the metal centre. As predicted, they showed that the buried volume of the NHCs increases with bulkier nitrogen substituents. The buried volume for the most commonly used NHCs ranges from 35 to 47% (Table 26, entries 1 to 4).

Glorius reported the synthesis and application of a sterically demanding chiral NHC ligand which has shown great applicability to enantioselective $\alpha$-arylation (see Introduction 3.1). He stipulated that his catalysts were by far the largest buried volume ever reported for any monodentate ligand (Table 26, entry 5).

In order to quantify the steric demand of our ligands, the buried volume was calculated using SambVca: a program developed by Cavallo and co-workers. Whereas the buried volume obtained for the unsubstituted imidazolium salt 352 was 36.3 which is comparable to IMes (Table 26, entry 6 and 1), that of methyl substituted imidazolium salt 356 was 50.1 (Table 26, entry 7). It is therefore apparent that the two methyl groups, which project directly into the reactive centre, make the ligand extremely bulky.
### Table 26. \%V\textsubscript{bur} of several carbenes and our ligands.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligands</th>
<th>%V\textsubscript{bur} (Cu)</th>
<th>%V\textsubscript{bur} (Ag)</th>
<th>%V\textsubscript{bur} (Au)</th>
<th>%V\textsubscript{bur} (imidazolium)</th>
</tr>
</thead>
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<td></td>
<td></td>
<td>50.1</td>
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### 3. Coordination of imidazolium salts

With our imidazolium salts in hand, we decided to study the formation of free NHCs upon treatment of the ligand salt with base using NMR. Treatment of 355 with \textsuperscript{1}BuONa indicated partial formation of the NHC whereas treatment with NaH in \textit{d}-THF showed complete conversion to the NHC, which unfortunately proved to be very unstable. The \textsuperscript{1}H-NMR showed the disappearance of the C2-proton but after several minutes the solution became dark and the NMR extremely messy. The formation of the NHC was therefore repeated in a glove box to minimise the risk of atmospheric degradation but the same phenomena occurred.
Whilst the free NHC was unstable, we envisaged coordination to a metal should provide stabilisation. In order to prove that the NHC-palladium complex was being formed in situ, palladium was added to a $d_8$-THF solution followed by salt 355 and finally the base. A clear spectrum was obtained using Pd(OAc)$_2$, salt and sodium tert-butoxide as the base (Figure 18). The two aromatic protons, which project directly into the reactive centre (4 and 4'), shift downfield compared to the imidazolium salt. Interestingly for protons close to the metallic centre (2, 4, 5 and 2', 4', 5') two signals appear on the $^1$H-NMR spectrum whereas for the protons on the “back” of the molecule (6, 7, 9 and 6', 7', 9') the protons are equivalent.

Figure 18. $^1$H NMR spectrum of Pd-NHC complex 362.
Reaction of our methylated imidazolium salt 356 with silver oxide in the presence of molecular sieves gave us the desired NHC-silver complex as shown in the crude NMR spectrum (Figure 19 and 20). The $^1$H-NMR spectrum shows the disappearance of the C2-proton which implies that coordination occurred. Furthermore, the $^{13}$C-NMR spectrum shows the peak at 172 ppm for the carbene carbon – silver bond. In both spectra one can notice the broader or smaller signals of the methyl groups which are pointing into the reactive centre. The split of signals observed with the Pd-NHC complex 362 was not observed in that case.

![Scheme 69. Formation of the silver-NHC complex 363.](image)

![Figure 19. $^1$H NMR spectrum of Ag-NHC complex 363.](image)
Preliminary attempts at transmetallation of this Ag-NHC complex with PdCl₂(MeCN)₂ in toluene at 110 °C returned a complex NMR spectra which showed degradation. The high temperature required for such transmetallation could be an explanation of the degradation observed.

4. Use of the imidazolium salts as NHC ligand precursors

4.1. α-arylation reactions

As shown in the introduction (see Introduction, 1.3.1 and 1.3.2), the asymmetric intramolecular α-arylation reaction was previously used to compare chiral NHC ligands. This reaction was particularly interesting for us as Glorius, Kündig (see Introduction, 1.3.1) and Dorta (see Introduction, 1.3.2) showed that sterically demanding ligands were ideal to obtain high enantioselectivity. Therefore we choose to use our ligands in an asymmetric α-arylation reaction. The conditions developed by Kündig and co-workers were chosen as the test reaction. They reported an asymmetric intramolecular α-arylation of amide 365 to cyclic species 366, under palladium catalysis using NHC 367 as the ligand (Scheme 71).
We attempted to repeat Kündig’s conditions using our ligand (Scheme 72, Table 27). In each instance the palladium-NHC species was pre-formed by adding base to a solution of imidazolium salt 368 or 352 and then the palladium source. The substrate was then added to the solution and the reaction mixture was stirred overnight at different temperatures (Table 27). Using the triflate salt of our ligand in both DME and dioxane (Table 27, entries 1 and 2) with Pd(dba)2 only recovered starting material was observed. Switching to the iodide salt (Table 27, entries 3 to 8), changing the solvent to THF (Table 27, entries 5 and 6), changing the palladium source (Table 27, entries 5 to 6), changing the base (Table 27, entries 4 and 5) or increasing the temperature (Table 27, entries 7 and 8), all gave the same result.

![Scheme 70. Kündig’s α-arylation reaction.](image)

![Scheme 71. Attempted α-arylation using our ligand 368 and 352. See Table 27 for conditions.](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Base</th>
<th>[Pd] Source</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Temp. (˚C)</th>
<th>Product</th>
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</thead>
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<td>Pd(dba)2</td>
<td>DME</td>
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<td>Sm</td>
</tr>
<tr>
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<td>Dioxane</td>
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<td>70</td>
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<tr>
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<tr>
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<td>Sm</td>
</tr>
<tr>
<td>5</td>
<td>352</td>
<td>NaH</td>
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<td>d-THF</td>
<td>17</td>
<td>70</td>
<td>Sm</td>
</tr>
<tr>
<td>6</td>
<td>352</td>
<td>NaO’Bu</td>
<td>Pd(OAc)2</td>
<td>d-THF</td>
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<td>[PdallylCl]</td>
<td>Dioxane</td>
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<td>100</td>
<td>Sm</td>
</tr>
</tbody>
</table>

Table 27. Different conditions for the α-arylation.
Interaction between the palladium and the two protons pointing into the reactive centre at high temperature could be an explanation for the failure of the reaction. In order to avoid this problem, the methyl derivative 356 was used. A series of experiments were performed with the methyl ligand 356 (Scheme 73, Table 28).

![Scheme 72. Attempted α-arylation using our ligand 356. See Table 28 for conditions.](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>[Pd]</th>
<th>Loading</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Ratio 365 : 366 : 369</th>
<th>e.e.</th>
</tr>
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<td>Pd(dba)$_2$</td>
<td>10%</td>
<td>Toluene</td>
<td>μν 110</td>
<td>0.2</td>
<td>100 : 0 : 0</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Pd(dba)$_2$</td>
<td>10%</td>
<td>Toluene</td>
<td>μν 110</td>
<td>0.4</td>
<td>100 : 0 : 0</td>
<td></td>
</tr>
<tr>
<td>3</td>
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<td>10%</td>
<td>Toluene</td>
<td>μν 110</td>
<td>3</td>
<td>99 : 1 : 0</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>[Pd(Allyl)Cl]$_2$</td>
<td>10%</td>
<td>Toluene</td>
<td>μν 110</td>
<td>0.4</td>
<td>100 : 0 : 0</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>[Pd(Allyl)Cl]$_2$</td>
<td>10%</td>
<td>Toluene</td>
<td>μν 110</td>
<td>2</td>
<td>78 : 18 : 4</td>
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<td>[Pd(Allyl)Cl]$_2$</td>
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<td>THF</td>
<td>70</td>
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<td>81 : 14 : 5</td>
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<td>THF</td>
<td>μν 110</td>
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<td>77 : 20 : 3</td>
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<td>THF</td>
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<td>68 : 28 : 4</td>
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</tr>
<tr>
<td>9</td>
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<td>THF</td>
<td>μν 130</td>
<td>2</td>
<td>62 : 38 : 0</td>
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</tr>
<tr>
<td>10</td>
<td>Pd(OAc)$_2$</td>
<td>10%</td>
<td>THF</td>
<td>μν 130</td>
<td>2</td>
<td>43 : 42 : 15</td>
<td>17%</td>
</tr>
<tr>
<td>11</td>
<td>Pd(OAc)$_2$</td>
<td>5%</td>
<td>THF</td>
<td>μν 130</td>
<td>1</td>
<td>89 : 7 : 4</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Pd(OAc)$_2$</td>
<td>20%</td>
<td>THF</td>
<td>μν 130</td>
<td>1</td>
<td>18 : 63 : 19</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Pd(OAc)$_2$</td>
<td>20%</td>
<td>THF</td>
<td>μν 100</td>
<td>2</td>
<td>0 : 89 : 11</td>
<td>28%</td>
</tr>
<tr>
<td>14</td>
<td>Pd(OAc)$_2$</td>
<td>20%</td>
<td>THF</td>
<td>μν 60</td>
<td>3</td>
<td>100 : 0 : 0</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Pd(OAc)$_2$</td>
<td>20%</td>
<td>THF</td>
<td>μν 80</td>
<td>5</td>
<td>100 : 0 : 0</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>PdCl$_3$</td>
<td>20%</td>
<td>THF</td>
<td>μν 100</td>
<td>2</td>
<td>35 : 41 : 24</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Pd(tfa)$_2$</td>
<td>20%</td>
<td>THF</td>
<td>μν 100</td>
<td>2</td>
<td>15 : 65 : 20</td>
<td></td>
</tr>
</tbody>
</table>

*Table 28. Different conditions for the asymmetric α-arylation with imidazolium 356.*
Marsden, Kündig and co-workers reported asymmetric α-arylation using a palladium(0) source and showed that toluene was the best solvent for their system. Therefore, a reaction was attempted with Pd(dba)\(_2\) and carried out in toluene under microwave conditions for short periods of time (Table 28, entries 1 to 3). Unfortunately this still gave no product in our case. Nolan has reported the use of palladium-NHC complexes in α-arylation using palladium allyl chloride as the source of palladium. Changing the palladium source to [Pd(allyl)Cl]\(_3\), and still using microwave irradiation gave no product after 20 minutes (Table 28, entry 4), but after 2 hours (Table 28, entry 5), 18% of product was observed along with trace of a side-product. Interestingly, the reaction became darker as the reaction progressed most likely indicating the presence of palladium black. The solvent was changed to THF (Table 28, entries 6 to 9) and improved conversion was observed when microwave conditions were employed (Table 28, entries 7 and 8). A 38% conversion of product was found when the temperature was increased to 130 °C (Table 28, entry 9). Changing the palladium source to Pd(OAc)\(_2\) gave a higher yield under the same conditions (Table 28, entry 10). Decreasing the catalyst loading (Table 28, entry 11) did not improve conversion, instead increasing the catalyst loading to 20% (Table 28, entries 12 to 15) and lowering the temperature to 100 °C (Table 28, entry 13) gave 89% of product. Importantly, lowering the temperature further (Table 28, entries 14 and 15) resulted in no reaction. Formation of the active palladium(0) from the palladium(II) pre-catalyst seemed to be the problem as the reaction at lower temperatures did not darken as observed when the reaction occurred. Also the fact the NHC is not stabilising the palladium(0) sufficiently from formation of palladium black may indicate it is a poor ligand for palladium(0). Several alternative palladium sources were investigated but neither Pd(Cl)\(_2\) (Table 28, entry 16) nor Pd(tfa)\(_2\) (Table 28, entry 17) resulted in an improved result. The enantiomeric excess was determined by chiral HPLC. After reaction at 130 °C in microwave conditions, a 17% e.e. was measured (Table 28, entry 10). Lowering the temperature had an immediate effect on the enantioselectivity as 28% e.e. was measured for the reaction at 100 °C. Therefore it was essential to lower the temperature further in order to obtain a better enantioselectivity.

Due to the fact that the reaction seemed to be limited by the formation of palladium(0) or the stability of the ligand-Pd(0) complex, other strategies were attempted. The nature of the palladium pre-catalyst is often responsible for the smooth introduction of the active catalyst into the catalytic cycle and therefore to the success of the coupling reaction. In 2003, Nolan and co-workers reported the first NHC-palladacycle complex as a useful pre-catalyst and their use in α-ketone arylation (scheme 74). We were therefore interested by this approach for our ligands.
In addition, Ying and co-workers developed recently a new palladacycle that was easily prepared and used for a cross-coupling reaction (Scheme 75).\textsuperscript{181}

The two palladacycle precursors 370 and 372 were synthesised following literature procedures.\textsuperscript{181,182} Our imidazolium salt was then stirred in the presence of a base followed by addition of these precursors (Scheme 74 and 75). The reaction mixture was then stirred for two hours in THF. The substrate was added to the crude mixture and stirred overnight. Preliminary results did not show any improvement in the reaction as only starting material was recovered when the reaction was conducted at ambient temperature and also at 80 °C (Scheme 76). Further evidence that the NHC-palladacycle complex successfully formed was therefore necessary; however preliminary studies of these complexes gave very complex NMR spectra and often decomposition of the NHC was observed. As stated earlier, the formation of the NHC by addition of a strong base such as sodium hydride or potassium tert-butoxide prior to addition of the palladacycle precursors proved to be complicated as these NHCs were unstable as free NHCs.
4.2. Copper-free asymmetric allylic alkylation with grignard reagents

The copper catalysed allylic alkylation (CAAA) was extensively studied for the last decade, but only recently have NHC ligands been used for this reaction with good success. The groups of Okamoto,\(^{183,184}\) Hong\(^{175,185}\) and Tomioka\(^{186}\) used Grignard reagents as the organometallic reagent, whereas Hoveyda and coworkers\(^{110,187-190}\) reported the use of diorganozinc and triorganoaluminum reagents. C2-symmetric chiral NHCs were used in particular for this reaction. Alternatively, Hoveyda reported a series of bidentate ligands wherein a free hydroxy group forms an intermediate alkoxycopper species.

Alexakis, Mauduit and co-workers reported in 2006 on the copper catalysed CAAA using for the first time NHCs as ligands. For this reaction, they found that using Grignard reagents was advantageous as they are easily available and also able to deprotonate imidazolium salts.\(^{191}\) Therefore there was no need for a strong base or pre-formed copper or silver NHC complex. The procedure was also more convenient and more reproducible. Recently Alexakis and co-workers showed that the allylic alkylation could be equally as efficient without copper. Therefore they developed the first copper-free allylic alkylation.\(^{192}\) Several ligands were screened and the results are shown in the Table 29 below.
Synthesis of new chiral NHCs

**Table 29.** Allylic alkylation reaction developed by Alexakis and co-workers.

<table>
<thead>
<tr>
<th>Entry</th>
<th>L</th>
<th>Conversion (%)</th>
<th>385/386</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>374</td>
<td>&gt;99</td>
<td>76:24</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>375</td>
<td>&gt;99</td>
<td>70:30</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>376</td>
<td>70</td>
<td>70:30</td>
<td>57</td>
</tr>
<tr>
<td>4</td>
<td>377</td>
<td>80</td>
<td>75:25</td>
<td>53</td>
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<tr>
<td>5</td>
<td>378</td>
<td>98</td>
<td>70:30</td>
<td>51</td>
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<tr>
<td>6</td>
<td>379</td>
<td>98</td>
<td>72:28</td>
<td>61</td>
</tr>
<tr>
<td>7</td>
<td>380</td>
<td>&gt;99</td>
<td>67:33</td>
<td>63</td>
</tr>
<tr>
<td>8</td>
<td>381</td>
<td>&gt;99</td>
<td>67:33</td>
<td>53</td>
</tr>
<tr>
<td>9</td>
<td>382</td>
<td>99</td>
<td>69:31</td>
<td>36</td>
</tr>
<tr>
<td>10</td>
<td>383</td>
<td>&gt;99</td>
<td>9:91</td>
<td>34</td>
</tr>
</tbody>
</table>

**Figure:** Various new chiral NHCs synthesized by Alexakis and co-workers.
The results showed that the counterion of the imidazolium salt had no significant effect on the reaction (Table 29, entries 1 and 2). However, the regiochemistry seemed to be directed by the nitrogen substituent on the right side of the molecule: a benzyl group instead of a mesityl group shifted the regioselectivity in favour of the S_N2 product (Table 29, entry 10). On the other hand, the enantioselectivity seemed to be dependent of the other nitrogen substituent. The presence of hydroxyl groups on the phenyl substituent improved the enantioselectivity of the reaction (Table 29, entry 1 and 4). They observed that the best result was obtained when three carbon atoms separated the nitrogen to the hydroxyl group. With these results in hand, they proposed a mechanism for the reaction (Scheme 77). The first step was the deprotonation of the imidazolium salt 374 by two molecules of the Grignard reagent. The bromine atom was then exchange by an ethyl group via the reaction of complex 387 with an equivalent of Grignard reagent. Complex 388 was used to explain the observed regio- and enantioselectivities. They proposed that interaction of the substrate with complex 388 lead to complex 389, which adopted a pseudo-chair conformation. The first complex 387 was then regenerated to begin another cycle and product 385 obtained.

Scheme 76. Proposed mechanism for the free-copper allylic alkylation.
A successful collaboration with Woodward and co-workers allowed us to test our NHC ligands in this reaction. The same conditions developed by Alexakis were employed. After slow addition of the Grignard reagent to a solution of cinnamyl bromide and the ligand at -15 °C the reaction was stirred for 19h at -15 °C. The results are shown in Table 30. Unsubstituted 355 and methylated 356 ligands showed full conversion to the products whereas the phenyl derivative 357 showed no reaction. The enantiomeric excess was calculated using a chiral GC.

<table>
<thead>
<tr>
<th>Entry</th>
<th>L</th>
<th>Conversion (%)</th>
<th>385/386</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>355</td>
<td>&gt;99</td>
<td>26:74</td>
<td>87</td>
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<tr>
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<td>&gt;99</td>
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<td>3</td>
<td>357</td>
<td>23</td>
<td>0:100</td>
<td>/</td>
</tr>
</tbody>
</table>

Table 30. Asymmetric allylic alkylation reaction.

Despite the fact the major compound was not the desired S_N2' regioisomer, the e.e. obtained were comparable or even better than those reported by Alexakis (see Table 29). In the case of the phenyl derivative, no effect on the reaction was observed. This is most likely due to the large steric bulk of this ligand. These results were obtained in one attempt and further conditions screening will be investigated in future work to invert the regioselectivity of the reaction without sacrificing the enantiomeric excess. Alternative solvents, reaction temperatures will be surveyed and may show improvements.
Conclusion

As described in the introduction extensive studies are ongoing in the field of $N$-heterocyclic carbene chemistry since the discovery of the first stable NHC by Arduengo in 1991. These NHCs have proved to be useful in many catalytic processes such as palladium-catalysed cross-coupling, ruthenium-catalysed metathesis, copper-catalysed 1,4 addition. Importantly, chiral NHCs have been used successfully in asymmetric catalysis. The aim of our study was to design and develop new chiral NHC ligands, study their coordination and test them in asymmetric catalysis.

During the course of this study, we developed the one-pot synthesis of allylic chloride. The scope of the reaction was studied, as well as the mechanism. We published these results in Organic Letters in 2008.

Then we were able to successfully synthesise our designed ligands. Three different derivatives were synthesised and two (methyl and unsubstituted NHC) were fully characterised by crystallography highlighting the position of the substituent into the reactive centre and the C2 symmetry. The buried volume was calculated for these two ligands and showed that the methyl-NHC 356 was one of the most bulky monodentate NHC ligand reported to date. Coordination of these NHCs was performed and the resulted complexes were characterised by NMR. Two preliminary asymmetric reactions were attempted with the synthesised ligands. While $\alpha$-arylation showed low asymmetry induction possibly due to steric reasons, allylic alkylation using Grignard reagents showed promising results.

Further developments are needed in future studies. Crystallisation of the phenyl derivative and calculation of the buried volume should give us an idea of the steric hindrance of this ligand which should be the highest ever reported for a NHC ligand. Formation and characterisation of a PEPPSI-Pd-NHC complex via the silver-NHC intermediate and its use in asymmetric $\alpha$-arylation should give us more details about the reactivity of our ligands for this reaction. Finally reaction conditions should be surveyed to improve the promising results obtain for the copper-free allylic alkylation.
CHAPTER 2

Synthesis of new chiral abnormal carbenes
Introduction

Generally, metallation of imidazolium ligands results in the coordination of the metal to the C2 carbon to give the NHC ligands described in Chapter I. More recently, a serendipitous discovery of a new coordination mode was discovered by Crabtree, Albrecht and co-workers.\textsuperscript{193,194} They found coordination of iridium to their chelating ligand (see 1.3.1) gave a C4-bound complex, rather than the common C2 binding mode (Scheme 78).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{scheme77.png}
\caption{Different sites of metallation.}
\end{figure}

The name “abnormal” carbene was given to this ligand due to the isomeric relationship with its C2 counterpart. However, the properties of this “abnormal” carbene differ from the C2-bound NHC. For example, no canonical resonance form can be drawn without introducing additional charges (Scheme 79).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{scheme78.png}
\caption{Different resonance forms.}
\end{figure}
1. Abnormal carbenes properties

The principal difference between abnormal and normal N-Heterocyclic carbene ligands is that just one nitrogen atom is bonded to the carbenic atom coordinated to the metal. Thus, the group attached to the nitrogen N3 has a strong effect on the metal coordination sphere, when there is no substitution of the C5-carbon. This fact has an impact on the torsion angle between the heterocyclic carbene ligand and the metal coordination plane (Figure 21). Crystallographic analysis of square-planar dicarbene palladium (II) complexes showed that this angle was 20-30˚ for abnormal NHCs and 35-45˚ for NHCs. The C4-bound NHCs are consequently more appropriately oriented for exploiting ligand-metal π-backbonding interactions and ligand tuning may therefore become more efficient. This configuration may allow a better accessibility to the metal centre, which should increase the sensitivity of the M-C bond and, also, facilitate the bonding of larger substrates for catalytic transformations.  

![Figure 21. Newman-projection of a metal-NHC fragment along the M-C bond in a square-planar complex; a) Reduced repulsion on abnormal NHCs containing a proton on the α-position (C5) as compared to b) NHC with relatively bulky substituents on the α-position nitrogen N1.](image)

The optimised geometries of free abnormal NHCs by DFT calculation showed that they are less stable than their free C2 analogues (average of 16kcal mol⁻¹). This may be due to the presence of just one heteroatom next to the C-M bond. In fact, as stated in Chapter I (see Introduction, 1.2) in the case of C2 NHC, the two nitrogen atoms participate in stabilisation via resonance and inductive carbon-heteroatom interactions.

Several theoretical and experimental studies demonstrate that abnormal NHCs are stronger donors than their C2-bound analogues. Several methods have been developed to assess the electronic property of ligands. The Tolman’s electronic parameter (TEP), which is the measured frequency of A₁ carbonyl mode of (Ni(CO)₃L) complexes, is the most well-known parameter for phosphines and other classical ligands. One experiment tool for the estimation of donation, which is derived from the TEP, is calculation of the carbonyl stretching frequencies (ν_CO) of square-planar
metal carbonyl complexes. Crabtree and co-workers demonstrated a good correlation between the average of both stretching frequencies for trans \([\text{Ir(CO)}_2\text{Cl}(L)]\) and the Tolman electronic parameter.$^{201}$ Other metals could also be used such as nickel and rhodium.$^{203}$ However, Gusev argued that, even if this method was useful for ranking ligands of the same category (phosphines, C2-NHCs, amines...), this method is not suitable for comparing ligands of different classes.$^{204}$ Also the donor properties are often compared by using the trans-CO stretching frequency which is supposed to be less influenced by steric effects.$^{205}$ However, the IR spectrum gives access to two values which are the symmetric and asymmetric stretching vibrations and these values cannot be correlated to the cis- or trans-CO modes. A variety of complexes of the type \([\text{IrCl(CO)}_2(L)]\) have been synthesised and IR data shows that C4-bound NHCs in complexes induce a considerably lower stretch frequency (\(\nu_{av}(\text{CO})\ 1999-2015\text{ cm}^{-1}\)) than sterically similar C2-bound NHCs (\(\nu_{av}(\text{CO})\ 2017-2020\text{ cm}^{-1}\))$^{201}$ which are lower than the most basic alkyl phosphines (\(\nu_{av}(\text{CO})\ 2028\text{ cm}^{-1}\) for \(L = \text{PCy}_3\)). Bertrand and co-workers reported symmetrical, asymmetrical and average CO stretching frequencies of cis-[\(\text{RhCl(CO)}_2(L)\)] complexes of cyclic non-stable carbenes (Figure 22).$^{206}$ Abnormal NHCs appear to be stronger donor than C2 NHCs but not as strong as other more unusual stable carbenes.

\[\text{Ph}_{3}\text{P} \quad 402 \quad \text{Ph}_{3}\text{P} \quad 403 \quad \text{Ph}_{2}\text{S} \quad 404 \quad \text{Ph}_{2}\text{S} \quad 405 \quad \text{N}^\text{Pr}_{2} \quad 406 \quad \text{N}^\text{Pr}_{2} \quad 407 \]

\[\text{Ph} \quad (\text{N}^\text{Pr}_{2})_2 \quad \text{P} \quad 401 \quad \text{Mes}^+ \quad \text{Ph} \quad 408 \quad \text{Mes}^- \quad \text{N}^\text{Pr}_{2} \quad 409 \quad \text{Dipp}^+ \quad \text{Ph} \quad 410 \quad \text{Dipp}^- \quad \text{N}^\text{Pr}_{2} \quad 411 \quad \text{Dipp}^+ \quad \text{N}^\text{Pr}_{2} \quad 412 \quad \text{N}^\text{Mes} \quad \text{Ph} \quad 413 \]

**Figure 22.** Average CO stretching frequencies for cis-RhCl(CO)$_2$L

Theoretically, Phukan and co-workers compared the energies of the \(\sigma\) symmetric orbital of C2-bound and C4-bound NHCs. They showed that the substituent on the heteroatom dramatically
changes the basicity of these molecules. In general, compounds with H, NH₂, CH₃, Ph and 'Bu as substituent on the heteroatoms were found to have higher electron donating ability. The fluoro-substituted derivatives were found to have the lowest electron donating ability. However, irrespectively of the substituents on the heteroatom, the σ symmetric electron donating orbital of abnormal NHCs lies at a higher energy than their normal isomers.²⁰⁶

2. Formation of abnormal NHC complexes

2.1. By C-H bond activation of unsubstituted 2H-imidazolium salt

Crabtree and co-workers were the first to observe abnormal C4 coordination by reaction of pyridine-functionalised imidazolium salt 416 and IrH₅(PPh₃)₂ (415). The structure of this complex was characterised by X-ray crystallographic analysis. The activation of the C4-H bond rather than the C2-H was an interesting result as the C2-proton is more acidic (pKₐ = 24.9)²⁰⁷ than the C4-proton (pKₐ = 33.0)²⁰⁸. The formation of this unusual coordination was therefore studied in detail. Crabtree and co-workers realised, during their studies of the formation of C2- (417) or C4- (418) metalated NHC complexes from N-pyridyl functionalised imidazolium salts, that a modification of the counterion of the imidazolium salt was responsible of the coordination mode obtained (Table 31).²⁰⁴,²⁰⁹ As reviewed by Macchioni, in 2005, the role of ion-pairing is very important in transition metal organometallic chemistry.²¹⁰ It affects many chemical reactions mediated by ionic metal organometallic compounds. Indeed, the ability to control anion-cation interactions is often key to optimising the yield, chemoselectivity, regioselectivity, and stereoselectivity of chemical processes.

![Chemical structure of 415, 416, 417, and 418](image)

<table>
<thead>
<tr>
<th>R</th>
<th>X</th>
<th>Yield of 417 (%)</th>
<th>Yield of 418 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>Br</td>
<td>91</td>
<td>9</td>
</tr>
<tr>
<td>Me</td>
<td>OAc</td>
<td>80</td>
<td>20</td>
</tr>
<tr>
<td>Me</td>
<td>PF₆</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Me</td>
<td>BF₄</td>
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<tr>
<td>Me</td>
<td>SbF₆</td>
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</tr>
<tr>
<td>'Pr</td>
<td>BF₄</td>
<td>0</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 31. Influence of the choice of anion.
The use of BF₄⁻ particularly favoured the formation of the C4-metalated NHC 418, while a Br anion favoured the formation of the C2-NHC 417. The strong capability of bromine to form ion-pair by C-H⁻Br hydrogen bonding at the C2-position facilitated the formation of the C2-NHC 417 obtained, while changing the counterion along the series Br, BF₄⁻, PF₆⁻, SbF₆ progressesively switched the kinetic product to the abnormal C4-NHC 418. Crabtree and co-workers carried out important computational studies of this reaction mechanism (Scheme 80). The abnormal NHC 423 formation, via an oxidative addition, does not show a significant change in its charge distribution which makes the reaction independent of the anion. On the other hand, the C2-NHC 426 is formed via a C-H heterolysis facilitated by the Br⁻ H-bond. The reason for the different mechanism observed was due to the intrinsic properties of the C2- and C4- NHCS: the strong donor character of the abnormal NHC 423 favoured attainment of Ir⁵⁺, while the highly acidic character of the C2-H favoured heterolytic C-H activation.

Scheme 79. Proposed mechanism for the formation of abnormal or normal NHC.
2.2. By C-H activation of a C2-substituted imidazolium salt.

Since the C2-H proton is more acidic than the C4-H proton, selective protection of the more acidic C2 position by an alkyl or aryl group has been developed as a more consistent rational route towards the formation of abnormal NHC complexes. Ooi and co-workers used this method to form a platinum hydride complex 428 with the mixed C2- and C5-bound NHCs both attached to the platinum (Scheme 81).\(^\text{211}\)

![Scheme 80. Ooi’s platinum-abnormal NHC complex.](image)

As in the case of C2 bound NHCs, C4-bound NHC metal complexes can also be formed by transmetallation of an abnormal-silver complex intermediate.\(^\text{212}\) Crabtree and co-workers used this method to form abnormal NHC metal complexes with a variety of metal such as Pd, Au, Rh, Ir, and Cu. During the synthesis of these C4-bound NHCs via transmetallation of silver complexes, they realised that C2-bound NHCs were obtained even when the C2 position was blocked with a methyl or benzyl groups. They demonstrated an important consideration when selecting the blocking group. By using a bulky groups such as \(^{1}\)Pr or Ph, they avoided silver cleavage of the C2-R bond (Scheme 82, Table 32).\(^\text{213}\)

![Scheme 81. Cleavage of the blocking group.](image)

<table>
<thead>
<tr>
<th>R</th>
<th>Yield of 430 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>PhCH(_2)</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>Et</td>
<td>&lt;50%</td>
</tr>
<tr>
<td>(^{1})Pr</td>
<td>No reaction</td>
</tr>
<tr>
<td>Ph</td>
<td>No reaction</td>
</tr>
</tbody>
</table>

*Table 32. Cleavage of the blocking group*
The mechanism of this unusual C-C cleavage was studied by Crabtree and co-workers (Scheme 83). Detailed analysis of the reaction revealed that silver oxide was oxidising the carbon attached to the C2 position (four electron oxidation) to yield an acyl imidazolium salt and metallic silver. In the presence of the water formed during this process, the acyl group is a good leaving group and therefore promotes the metallation at the C2 position. The complete mechanism needs four equivalents of silver for the oxidation step and one equivalent for the complex formation. This was consistent with the measured quantity of silver (0) obtained after the reaction and the need of a large excess of silver oxide for completion of this reaction. A similar mechanism is not possible when a quaternary or tertiary carbon is attached to the C2 position, therefore iso-propyl or phenyl groups are the best candidate to block the C2 position.

\[
\text{N}_\text{N}^+ \text{R} \text{N}_\text{N}^+ \text{N}^+ - 2 \text{Ag}_2\text{O} - 4 \text{Ag} - \text{H}_2\text{O} \rightarrow \text{N}_\text{N}^+ \text{R} \text{N}_\text{N}^+ \text{N}^+ \rightarrow \text{Ag}_2\text{O} \cdot \text{H}_2\text{O} \rightarrow \text{R} \text{COOH}
\]

Scheme 82. C-C cleavage by silver oxide.

Using a similar C-H bond activation, Albrecht and co-workers synthesised a rhodium(III) diNHC 434 (Scheme 84). The reaction was performed using [Rh(cod)Cl]₂ in the presence of air, potassium iodide and acetate. A mechanistic study showed that the acetate did not act as a strong base but as a proton scavenger. Also, after oxidation of iodide by aerobic O₂, rhodium(I) was obtained prior to Rh-C bond formation. It is apparent that a methyl blocking group is sufficient for this reaction.

\[
\text{N}_\text{N}^+ \text{R} \text{N}_\text{N}^+ \text{N}^+ \rightarrow \text{[Rh(cod)Cl]}_2 \text{KI, air, NaOAc} \rightarrow \text{KBf}_4, \text{MeCN} \rightarrow \text{BF}_4
\]

Scheme 83.
Lassaletta and co-workers also synthesised abnormal NHC rhodium(I) complex \(436\) via in situ formation of the base-containing metal precursor obtained by reaction of \([\text{Rh(cod)Cl}]_2\) with \(\text{KN(SiMe}_3\text{)}_2\) (Scheme 84). The C2 position was protected by a phenyl ring.

2.3. By oxidative addition

Abnormal NHC complexes have also been obtained by oxidative addition to palladium(0). This method is particularly attractive as metallation is independent of the ligand CH acidity. Albrecht and co-workers synthesised complexes such as \(438\) using this method (Scheme 85).

![Scheme 84. Albrecht synthesis of C4-bound NHC–palladium complexes.](image)

3. Isolation of free abnormal NHCS

As mentioned in the Introduction of Chapter I, the first isolation of a free NHC by Arduengo in 1991 was the starting point for a huge interest in NHCS for catalysis. It was therefore an interesting challenge to synthesise the first free abnormal NHC knowing that these NHCS as reported by Albrecht in his recent review one “among the most basic neutral donors known thus far”. Until very recently no groups were able to isolate a free abnormal NHCS but by deprotonation in the presence of Rh, Lassaletta and co-workers were able to isolate the abnormal NHC complex which infers the generation of a free abnormal NHC prior to coordination (see Scheme 84). In 2009, Bertrand and co-workers suggested that it was possible to isolate the free abnormal NHC. They protected the C2 position with a phenyl group, introduced bulky substituents on both nitrogen atoms (Dip) and attached a phenyl group to the C4 position to offer kinetic protection to the C5 position. Several imidazolium salts were synthesised with various counterions. All attempted deprotonation of the C5-H position failed with the tetrafluoroborate salt as counterion. However, with a smaller anion such as \(\text{Cl}^-\), deprotonation of the C5-H occurred with two equivalents of butyl lithium to form the Li adduct \(440\) (Scheme 86). Alternatively deprotonation with potassium hexamethyldisilazide (KHMDS) provided the first isolated free abnormal NHC \(409\) that they characterised by NMR spectroscopy and crystallographic analysis (Figure 23).
4. Application of abnormal NHC complexes

Due to the high basicity of the metal centre in a C4-bound NHC, reactions with oxidative addition sequences as key steps will be more likely to benefit from these strongly donating ligands. Therefore hydrogenation and cross-coupling were chosen and a direct comparison of reactivity was studied between C4-bound and C2-bound NHC ligands.

4.1. Transfer hydrogenation reaction

In 2008, Albrecht and co-workers studied the catalytic transfer hydrogenation of ketones using ‘PrOH as a dihydrogen source. A comparative study between structurally similar C2-bound and C4-bound rhodium complexes was performed and demonstrated that the C4-bound complex outperforms the C2-bound analogue in this reaction (Scheme 87, Table 33). Albrecht and co-workers hypothesised that this result was due to the electron density of the metal centre. This was supported by the catalytic activity of the chloro complex: the insertion of a more donating chloride on the rhodium centre doubles the turnover frequency compare to the initial iodide ligand.
A variety of ketones were efficiently hydrogenated with catalyst 446.217 Aromatic methyl or ethyl ketones were very well tolerated (Table 34, entries 2 and 3), whereas a longer reaction time was required for aliphatic methylketones (Table 34, entry 4). Even longer reaction time was required for sterically demanding substrates such as 3-octanone (Table 34, entry 5). Imines appeared to poison the catalytically active species and no amine formation was observed (Table 34, entry 6).

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>R</th>
<th>R₁</th>
<th>Conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>O</td>
<td>Ph</td>
<td>Ph</td>
<td>97</td>
</tr>
<tr>
<td>2</td>
<td>O</td>
<td>Ph</td>
<td>Me</td>
<td>93</td>
</tr>
<tr>
<td>3</td>
<td>O</td>
<td>Ph</td>
<td>Et</td>
<td>74</td>
</tr>
<tr>
<td>4</td>
<td>O</td>
<td>Me</td>
<td>Hex</td>
<td>57</td>
</tr>
<tr>
<td>5</td>
<td>O</td>
<td>Et</td>
<td>Pent</td>
<td>40</td>
</tr>
<tr>
<td>6</td>
<td>NMe</td>
<td>PhCH₂</td>
<td>H</td>
<td>&lt;2</td>
</tr>
</tbody>
</table>

*Table 34. Hydrogenation of ketones using 446 as ligand.*

\[ \text{Conv. After} \ 2 \ h \ (\%) \quad \text{TOF}_{50^\circ C}/\text{h}^1 \]

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>R</th>
<th>X</th>
<th>Conv. After 2 h (%)</th>
<th>TOF_{50^\circ C}/h^1</th>
</tr>
</thead>
<tbody>
<tr>
<td>443</td>
<td>nBu</td>
<td>I</td>
<td>17</td>
<td>n.a.</td>
</tr>
<tr>
<td>434</td>
<td>nBu</td>
<td>I</td>
<td>97</td>
<td>111</td>
</tr>
<tr>
<td>434</td>
<td>iPr</td>
<td>I</td>
<td>87</td>
<td>94</td>
</tr>
<tr>
<td>434</td>
<td>Mes</td>
<td>I</td>
<td>91</td>
<td>121</td>
</tr>
<tr>
<td>434</td>
<td>Mes</td>
<td>Cl</td>
<td>95</td>
<td>300</td>
</tr>
</tbody>
</table>

*Turnover frequency as mol (mol catalyst h)^1 at 50% conversion*
4.2. Suzuki-Miyaura cross-coupling

Recently Hong and co-workers reported a comparative study for the abnormal and normal NHC promoted Suzuki-Miyaura coupling reaction.\textsuperscript{218} They showed that the yield of the reaction was slightly better using an abnormal NHC complex as the catalyst but more interestingly, undesirable homocoupling of aryl boronic acids was not observed with abnormal NHCs, unlike with the correspondent C2-NHC (Scheme 88, Table 35).

![Scheme 87. Suzuki-Miyaura coupling reaction with abnormal NHC.](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R\textsubscript{1}</th>
<th>R\textsubscript{2}</th>
<th>449</th>
<th>450</th>
<th>449</th>
<th>450</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OMe</td>
<td>Me</td>
<td>58</td>
<td>35</td>
<td>67</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>Me</td>
<td>77</td>
<td>15</td>
<td>88</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>OMe</td>
<td>62</td>
<td>11</td>
<td>75</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>F</td>
<td>12</td>
<td>2</td>
<td>44</td>
<td>&lt;0.1</td>
</tr>
</tbody>
</table>

*Table 35. NHC-Promoted Suzuki-Miyaura cross-coupling reactions.*

The scope of the Suzuki-Miyaura coupling reaction was explored by Hong and co-workers with abnormal NHC ligand 452 and it showed excellent activity with electron-deficient aryl bromides and good functional group tolerance (Table 36, entries 1 to 6). However, reduced yields or no activity was observed with unactivated electron-rich aryl bromides (Table 36, entries 7 and 8), sterically bulky substrates (Table 36, entry 9), and aryl chlorides (Table 36, entry 10). They proposed, in accordance with the studies made for phosphine or C2-NHC ligands, more sterically bulky...
abnormal NHC precursors should further improve the use of abnormal NHC in the Pd-catalysed cross-coupling reactions.

\[
\begin{align*}
&\text{Entry} & X & R_1 & R_2 & R_3 & R_4 & R_5 & R_6 & R_7 & R_8 & R_9 & R_{10} & 455 \% \\
&1 & \text{Br} & H & \text{CHO} & H & H & H & H & OMe & H & 84 \\
&2 & \text{Br} & H & H & \text{COCH}_3 & H & H & H & H & OMe & H & 93 \\
&3 & \text{Br} & H & H & \text{COCH}_3 & H & H & OMe & H & H & OMe & 55 \\
&4 & \text{Br} & H & H & \text{NO}_2 & H & H & H & H & Me & H & 87 \\
&5 & \text{Br} & H & \text{NO}_2 & H & H & H & H & H & H & Me & 82 \\
&6 & \text{Br} & H & H & \text{CN} & H & H & H & H & H & H & 92 \\
&7 & \text{Br} & H & \text{Me} & H & H & H & H & H & Me & H & 67 \\
&8 & \text{Br} & H & \text{Me} & H & H & H & H & H & H & H & 9 \\
&9 & \text{Br} & \text{Me} & H & \text{Me} & H & \text{Me} & \text{Me} & H & H & Me & 0 \\
&10 & \text{Cl} & H & H & H & H & H & H & H & H & H & 4
\end{align*}
\]

Table 36. Scope of the Suzuki-Miyaura coupling reaction.

A comparison of the reaction progress by GC showed that the rate of the reaction was faster for abnormal NHCs than their C2 isomers, especially at the initial stage. They proposed that the more electron-donating abnormal NHC promoted oxidative addition faster as claimed by Albrecht (see above) for it is known to be the rate-determining step for some cross-coupling reactions. However it was also thought that the C2-NHC, with a more acidic C2-proton might generate the palladium complex faster and therefore affect the rate of the reaction. They synthesised well-defined PEPPSI-Pd-abnormal 457 and normal 456 NHC complexes (Figure 24): X-ray analysis showed similar Pd-NHC bond for abnormal and normal NHCs. Surprisingly the reaction rate did not change with abnormal NHC 457 as compare with 453 which could reflect the promoted oxidative addition step by abnormal NHCs. A much faster reaction rate was observed with 456 compared to 451.
5. **Concept and design of novel chiral abnormal NHCs**

As reported above, abnormal NHCs are of growing interest for catalysis. However, thus far, no chiral version of these abnormal NHC ligands has been reported. The aim of our project was therefore to synthesise and characterise the first chiral abnormal NHCs and explore their coordination chemistry.

Our design was driven by the need to form these ligands as few synthetic steps as possible. We hypothesised that by installing a chiral N-substituent from the chiral pool in the first reaction we could have access to an abnormal NHC precursor in a limited number of steps. We decided to synthesise two different abnormal NHC complexes: an imidazolium derived compound 2 and a triazolium derived compound 3 as shown in Figure 25.

![Figure 24. PEPSI-Pd-abnormal and normal NHCs.](image)

![Figure 25. Design of our chiral abnormal NHCs.](image)
The imidazolium derived abnormal NHC precursor was designed following precedent from Hartwig and co-workers on NHCs.\textsuperscript{101} They were able to form NHC in three steps starting with a chiral pool-derived amine. Our strategy was to block the C2 position of an unsaturated version of Hartwig’s NHC and coordinate a metal to the C4 position.

The triazolium derived abnormal NHC precursor was designed following a recent report by Albrecht and co-workers on the formation of triazolylidene abnormal NHC. They synthesised their ligand in three steps via the well documented [3 + 2] cycloaddition of an azide and an alkyne. A similar strategy with a chiral azide was proposed to obtain our desired abnormal NHC with the 2 position blocked by a nitrogen atom and the C4 position protected with a phenyl group. The cheap and readily available pinene group was chosen as our chiral pool substituent.
Results and Discussion

1. Synthesis of new chiral imidazolium derived abnormal NHCs

1.1. Synthesis of chiral imidazolium derived abnormal NHCs via diimine 461

As a starting point we used the work reported by Hartwig in 2001, on the synthesis of chiral NHCs in three steps as inspiration for our abnormal NHC design (Scheme 89). In their studies, formation of the intermediary diimine 461, reduction to the diamine 462, and reaction with triethyl orthoformate and sodium tetrafluoroborate gave them the desired NHC precursor 134. The chiral pool was introduced during the first step from a commercially available isopinocampheylamine (460).

![Scheme 88. Hartwig’s formation of NHC precursor 134.](image)

We wished to use a similar approach while introducing a blocking group at the C2 position. Starting from the diimine 461, synthesised by the reaction of chiral amine 460 and glyoxal (36), two different strategies were envisaged. Nolan has reported the formation of imidazolium salts unsubstituted at the C2 position using paraformaldehyde in the presence of an acid. We hypothesised that the desired abnormal NHC precursor 464 could be formed by a similar method using benzaldehyde as an electrophile (Path A, Scheme 90). Alternatively, imidazolium salt 466 could be synthesised from the diimine 461 following the Glorius method using chloromethyl pivalate and...
silver triflate.\textsuperscript{35,36} The desired C2 blocking group could be inserted by reaction of the \textit{in situ} formed NHC 465 with an alkyl iodide (Path B, Scheme 90).

![Scheme 89. Strategies to access imidazolium salts.](image)

Our first goal was to reproduce Hartwig’s work and synthesise the diimine 461 by reaction between (-)-isopinocampheylamine (460) and an aqueous solution of glyoxal (36). After precipitation, the diimine 461 was obtained in a very good yield (94\%, Scheme 91). The same reaction was carried out with (+)-bornylamine (467) and gave diimine 468 also in excellent yield (94\%, Scheme 91).

![Scheme 90. Synthesis of diimines 461 and 468.](image)

Reaction of the isolated diimine 461 in toluene with benzaldehyde and acetic acid (Path A, Scheme 90) at ambient temperature for one hour did not form the desired imidazolium salt 469 (Scheme 92). Longer reaction times, reflux conditions and several solvents (dichlorethane, toluene / ethanol mixture) to improve solubility of the diimine and to increase the temperature were surveyed.
but starting material was always recovered. Benzaldehyde is most likely not reactive enough for this reaction compared to the standard paraformaldehyde electrophile used by Nolan.

The formation of imidazolium salt 470 was attempted using the Arduengo method: reaction with chloromethylethyl ether for 5 days at room temperature, however this did not result in the formation of imidazolium salt 470. As highlighted in the introduction of Chapter I (Scheme 11, Introduction, 1.2.2), Glorius used chloromethyl pivalate (51) and silver triflate to access the imidazolium salts. Reaction of the diimine 461 with chloromethyl pivalate (51) at 40 °C for 24 h afforded imidazolium 470 in a moderate yield (68%, Scheme 93).

Prior to introduction of a blocking group in the C2 position, an anion exchange was carried out to purify the imidazolium salt obtained. Glorius mentioned that the iodide imidazolium salt was easier to purify by column chromatography than the triflate. Therefore treatment of 470 with excess sodium iodide in acetone afforded the expected product 471. However, traces of triflate anion were still observed in the mixture by negative ion mass spectrometry and the purification was difficult as a side product could not be separated from the desired product by column chromatography. To avoid this problem and to increase the yield, no purification was performed following the formation of the imidazolium salt 470, and the anion was immediately exchanged with an excess of sodium iodide in acetone (Scheme 94). Following purification, a white solid was obtained in 77% yield over two steps and with no trace of the triflate anion as visualised by negative ion mass spectrometry. The same conditions were used to synthesise the imidazolium salt 472 in good yield (76%, Scheme 94).
The final step of our strategy was to insert an iso-propyl group at the C2 position of the imidazolium salt 471. As mentioned in the introduction (see 1.3.2), the choice of the blocking group is crucial for the formation of abnormal NHC complexes. Crabtree and co-workers have highlighted that the two best blocking groups are phenyl and iso-propyl. We reasoned that deprotonation at C2 followed by addition of 2-iodopropane should afford the product. In 1975, Begtrup reported the synthesis of a similar compound 474 by deprotonation of the imidazolium salt with NaH and addition of an excess of 2-iodopropane (Scheme 95). In 1988, Zoller showed that deprotonation of an imidazolium salt with butyllithium gave lithium complex 475 which was quenched with methyl bromide to afford abnormal NHC precursor 476 (Scheme 95).
Unfortunately, the use of several bases (n-BuLi, NaH) followed by addition of 1.2 equivalents of 2-iodopropane in several solvents (THF, DMF) did not result in the formation of the desired product 477 (Scheme 96), but in the recovery of the starting material.

![Chemical structure 471](image1)

Scheme 95. Strategy to block the C2 position.

The basicity\(^{20}\) of the NHC 465 formed \textit{in situ} could explain this failure. Indeed NHC 465 induced elimination of HI and would give recovered starting material and propene (478, Scheme 97).

![Chemical structure 465](image2)

Scheme 96. Proposed mechanism of elimination by the NHC 465 formed \textit{in situ}.

To confirm that the deprotonation of the imidazolium salt 471 had occurred, methyl iodide was added following deprotonation with NaH. The expected imidazolium salt 479 was obtained with an excellent yield of 81\% (Scheme 98). This result is in accord with our hypothesis regarding the competing elimination reaction. While this product could in theory be used as an abnormal NHC precursor we were concerned about the low stability of the blocking group (see Introduction, 1.3.2).

![Chemical structure 471](image3)

Scheme 97. Insertion of methyl group in C2 position.
1.2. Other strategies to access new chiral abnormal NHCs

In light of our failure to form the chiral abnormal NHCs 464 and 466, other routes were considered. As shown in Scheme 99, the C2 blocking group (i.e. Ph) could be introduced at the start of the synthesis (Path C). Formation of the amide 483, followed by conversion to the imidoyl chloride and subsequent amine addition should give amidine 482. The last step would consist of a cyclisation with 2-bromo-aryl-ethanone (481) to form the new chiral imidazolium salt 480.

![Scheme 98. Retrosynthetic analysis to form imidazolium salt 480 (Path C).](image)

Another plausible route (Path D) would involve the formation of an aminal 487 which should then cyclise to the abnormal NHC precursor 485 in the presence of glycoxylic compounds 486 (Scheme 100).

![Scheme 99. Strategy to synthesise the abnormal NHC precursor 485 (Path D).](image)
The first step in the synthesis of the imidazolium salt 480 was the formation of amide 483. Reaction of benzoyl chloride (484) with (-)-isopinocampheylamine (460), in the presence of three equivalents of triethylamine gave the amide 483 in a good yield (91%, Scheme 101).²²²

![Scheme 100. Formation of the amide 483.](image)

The formation of amidine 482 was performed by adding three equivalents of phosphoryl trichloride to a solution of amide 483 in dichloromethane. After three hours, one equivalent of amine 460 was added to the solution and it was stirred overnight. Following column chromatography, the amidine 482 was obtained in a poor yield (38%, Scheme 102). The low yield could be attributed to the excess of phosphoryl trichloride, which can react with the amine 460. Another experiment was carried out with just one equivalent of POCl₃ and amide 483 for three hours in refluxing toluene. No more starting material was visualised on TLC. After evaporation of the solvent, one equivalent of the amine 460 in dichloromethane was added to the crude mixture and stirred overnight. None of the expected amidine 482 was obtained as observed in the crude ¹H-NMR spectrum.

![Scheme 101. Synthesis of amidine 482.](image)

To allow reaction optimisation, the expensive chiral amine 460 was replaced by cyclohexylamine (488). The formation of the amide 489 was then performed with analogous conditions to the formation of amide 483 (Scheme 103). Formation of amidine 490 was then attempted (Table 37).
Addition of one equivalent of POCl₃ in dichloromethane and refluxing for four hours followed by addition at ambient temperature of one equivalent of cyclohexylamine (488) resulted in the recovery of the starting material 489 (Table 37, entry 1). By using a higher boiling point solvent such as DCE (Table 37, entries 2 and 3) or toluene (Table 37, entries 4 and 5) either decomposition was observed upon reflux, or starting material after a long reaction time at ambient temperature. The intermediate seemed not stable at high temperature but not reactive enough at ambient temperature. Addition of a base to sequester HCl (Table 37, entry 6) or a polar solvent (Table 37, entry 7) and refluxing in dichloromethane for a long period of time returned only starting material. The use of other chlorinating agents such as phosphorus pentachloride²²³ (Table 37, entry 8) or thionyl chloride²²⁴ (Table 37, entry 9) and an excess of the amine did not afford the desired amidine 490; once again starting material was recovered.

Alternative routes were therefore explored to the desired amidine 490. In 1987, Forsberg et al. reported the formation of an amidine by reaction of benzonitrile with cyclohexylamine at 100 °C in the presence of a lanthanide salt.²²⁵ Our reaction was attempted with three different lanthanide salts but did not give the expected product (Scheme 104). Indeed reaction with the triflate salts 492 of samarium, ytterbium and lanthanum resulted in recovery of starting materials. Longer reaction times resulted in decomposition.
Synthesis of new chiral abnormal carbenes

In 1974, Pornet and Miginiac reported the synthesis of amidines via the reaction of phenyllithium with a carbodiimine.\textsuperscript{226} A yield of 94\% was obtained in the case of cyclohexane. We therefore investigated this approach. The reaction between N-dicyclohexylcarbodiimide (493) and phenyllithium was performed at ambient temperature but did not result to the formation of the expected amidine 490. Indeed, when the phenyllithium was formed \textit{in situ} by reaction of iodobenzene with butyllithium in ether, side products were observed: at ambient temperature, butylbenzene was formed and therefore the reaction did not give the desired amidine 490. Using commercial phenyllithium in dibutylether and performing the reaction in hexane resulted in precipitation of the desired amidine as its lithium salt 495. The desired product 495 was then filtered and isolated pure in a moderate yield (50\%, Scheme 105).

Reaction of the lithium salt 495 with bromoacetophenone (481) resulted in decomposition at -20 °C and no reaction at -78 °C (Scheme 105). This may be due to the lithium salt 495 being too reactive and prone to decomposition. Careful addition of an equivalent of water to obtain the free
amidine 490 and reaction with bromoacetophenone (481) may have provided a solution\textsuperscript{227} however the route was abandoned in light of an alternative, successful strategy.

For the synthetic strategy involving aminal 487, cyclohexylamine 488 was used as a model to develop the best conditions to form the imidazolium salt (Path D). The reaction of cyclohexylamine with benzaldehyde 193 in the presence of hydrochloric acid failed to give the expected aminal 496 (Scheme 106). The route was abandoned in light of an alternative, successful strategy.

\[
\begin{align*}
\text{Cyclic} & \quad \text{HCl (1eq)} \\
\text{Ketone} & \quad \text{CH}_2\text{Cl}_2, \text{rt}
\end{align*}
\]

Scheme 105. First attempt to synthesise aminal 496.

1.3. Synthesis of the imidazolium salt 464 via phenylchlorodiazirine

As none of these initial strategies were successful, a recent paper reported by Bonneau and co-workers drew our attention. They showed that 6-phenyldipyrido[1,2-\text{c}:2',1'e]imidazoliumchloride (501) could be synthesised by reaction of 2,2'-bipyridyl (497) with phenylchlorocarbene (498, PCC, Scheme 107).\textsuperscript{228} PCC is generated by photolysis or thermolysis of phenylchlorodiazirine (503, PCD).

\[
\begin{align*}
\text{2,2'-bipyridyl (497)} & \quad \text{PCC (503, PCD)} \\
\text{497} & \quad \text{498} \\
\text{499} & \quad \text{500} \\
\text{501}
\end{align*}
\]

Scheme 106. Bonneau synthesis of 6-phenyldipyrido[1,2-\text{c}:2',1'e]imidazoliumchloride (501).

We decided to apply this reaction to our system. The 3-chloro-3-phenyl-3\textit{H}-diazirine (503) was carefully synthesised from benzamidine (502) in a good yield following the procedure of Rosenberg \textit{et al} (Scheme 108).\textsuperscript{229} It is important that to note that the diazirine 503 formed is reported to be explosive when concentrated and precaution must be taken.\textsuperscript{230}
Synthesis of new chiral abnormal carbenes

Reaction of PCD with diimine 461 was performed in the photochemistry reactor of a level of irradiation wavelength of 350 nm (Scheme 109). Conversion to the expected product 504 was observed by LCMS but purification of the product proved to be difficult using silica chromatography. Furthermore, the reaction was very slow and the estimated yield of the reaction was only around 10-20%. The major components of the reaction mixture observed were the starting materials even after a reaction time of one week. The reaction was also attempted with a broad wavelength UV lamp. The desired product was observed but side products were also formed, along with a large amount of starting material 461.

To our delight, however, refluxing a mixture of the diimine 461 and freshly prepared PCD (503) in hexane for eight hours resulted in the formation of the desired compound 504 in excellent yield (90%). Conversion of the anion to the iodide by addition of sodium iodide in acetone for two hours gave us the iodo-imidazolium salt 464 which proved to be easier to purify by column chromatography on silica gel due to his better solubility in dichloromethane (Scheme 110).
1.4. Coordination of the imidazolium derived abnormal NHC to metals

With the desired imidazolium abnormal NHC precursor 464 in hand, a variety of conditions were surveyed in order to coordinate 464 to a metal. Lassaletta and co-workers previously used the Herrmann procedure to obtain a rhodium complex via deprotonation of an imidazolium salt. They showed that a similar method could be used for the formation of abnormal NHCs: deprotonation with KHMDS in the presence of \([\text{Rh(COD)}\text{Cl}]_2\) to give complex 436 (Scheme 111, (a)). Bertrand and co-workers likewise used KHMDS or n-BuLi to isolate their free abnormal NHC 409 (Scheme 111, (b)).

Unfortunately neither of these conditions resulted in the formation of the abnormal NHC complex as visualised by crude NMR: only starting material was recovered. Addition of the base (KHMDS) to our abnormal NHC precursor in tetrahydrofuran and quenching of the intermediate formed with deuterated methanol or deuterium oxide did not show the disappearance of the C4-proton. Formation of a free abnormal NHC, prior to coordination with the metal therefore seemed to be the problem in our case. Another strategy was applied to avoid formation of the free abnormal NHC which could have stability issues. Complexation of our imidazolium salt with silver oxide should form the intermediary silver complex which would potentially be a more stable precursor to our
desired abnormal NHC-Rh complex. Addition of silver oxide in dichloromethane to imidazolium salt 464 for 12h at ambient temperature or even under reflux only resulted in the recovery of starting material. However, by adding molecular sieves in an effort to sequester water, conversion of the starting material was observed by NMR. While no more starting material was observed, surprisingly, the molecule still had C2 symmetry by 1H-NMR. The mass spectrum gave a molecular ion which corresponds to the starting material and the negative ionisation method showed the presence of AgI2 as an anion. In order to clarify the structure and synthesise a more stable complex, transmetallation of the silver complex at ambient temperature for one hour with [Rh(cod)Cl]2 was attempted which gave a different NMR spectra of a complex that was still C2 symmetric by 1H-NMR and the C4 and C5 protons integrated for 1.7. As shown in Figure 26, the protons C4 and C5 were shifted downfield and the aromatic protons and those next to the nitrogen atoms were shifted upfield. The NMR spectrum also showed COD signals that were unaltered compared to the starting material [Rh(cod)Cl]2. The mass spectrum once again showed the presence of a molecular ion of the starting material and AgI2 as an anion.

![Figure 26](image-url)  
*Figure 26. 1H NMR of the starting material, silver and rhodium complexes.*

With all the data in hand, we tentatively assign the structure of this complex to a π-complex between the starting material and rhodium (Figure 27). It is clear a σ-complex is not obtained as the carbon NMR does not show a doublet signal for C4/5 characteristic of a carbon-rhodium bond. An alternative option may be that the product is simply the starting imidazolium salt with a different counterion.
The COD ligand was replaced by carbon monoxide by bubbling CO gas through a solution of the rhodium complex 505 in THF (Scheme 112). The NMR spectrum showed the disappearance of the COD signals. An IR spectrum was performed and showed two stretches for the CO bond at 2059 and 1981 cm\(^{-1}\) (Figure 28). Surprisingly these values correspond to the value obtained by Crabtree and Albrecht for an abnormal NHC (see Introduction, 1).\textsuperscript{201} Since, Albrecht and co-workers previously wrote that these IR studies “do not clearly allow for dividing bonds into \(\sigma\)- and \(\pi\)-contributions”,\textsuperscript{232} in our case it could be plausibly only showing a \(\pi\)-contribution. A crystal structure of the complex would possibly confirm the structure. Unfortunately all attempts to date to crystallise 505 have been unsuccessful.
During their synthesis of a rhodium abnormal NHC complex, Li and co-workers reported that reaction of silver oxide with an imidazolium salt 507 unsubstituted at the C4 and C5 positions gave decomposition. However, by blocking one of the positions with a methyl group, they obtained a clean reaction with silver oxide to form the corresponding silver complex 509 that was transmetallated immediately without isolation (Scheme 113). Therefore, to avoid potential π-complex formation, we decided to insert a methyl group into the C5 position.

![Scheme 112. Li synthesis of abnormal NHC-Rh complex.](image)

The reaction of the chiral amine with methyl glyoxal solution afforded the desired diimine 512 in a good yield (Scheme 114). However, preliminary attempts to cyclise diimine 512 with PCD afforded the desired compound in a very low yield as shown in the mass spectrum. It may be due to the formation of enamine 513.

![Scheme 113. Formation of the diimine 512 and attempts formation of 504.](image)
2. Synthesis of a new chiral triazolidinene-based abnormal NHC 517

2.1. Formation of triazolidinene 517 from α-pinene (514)

Recently, Albrecht and co-workers reported the use of 1,2,3-triazolidinenes as abnormal NHC precursors.\textsuperscript{234} Substitution of the C2 carbon by a nitrogen atom avoids the formation of a C2-bound NHC. We hypothesised a similar strategy could be applied to form chiral abnormal NHCs. Starting with α-pinene (514), formal addition of hydrazoic acid across the double bond should form compound 515. Due to steric shielding of one face of the prochiral double bond, good diastereoselectivity would be expected. [3 + 2] Cycloaddition of phenyl acetylene (82) with the azide under copper catalysis (“click” chemistry) should provide an easy route to heterocycle 516. Finally, methylation should give the triazolium salt 517 precursor to the desired abnormal NHC (Scheme 115).

![Scheme 114. Proposed synthesis of a 1,2,3-triazolidinene 517 as an abnormal NHC precursor.](image)

We therefore explored the first proposed step which consists of the formal addition of hydrazoic acid across the double bond of α-pinene (514). Addition of azidotrimethylsilane (518) in the presence of silica and trifluoromethanesulfonic acid should result in the addition of the azide to the more substituted position as reported previously.\textsuperscript{235} The reaction was performed and monitored by GC-MS which showed the disappearance of the starting material after 15 minutes at ambient temperature with two new peaks which could correspond to two diastereoisomers (Scheme 116). Attempted purification by column chromatography on silica gel failed to give a pure product. An IR analysis showed the presence of an azide stretch. We assumed that the desired compound was formed and therefore attempted the next reaction on the crude mixture.
Numerous conditions were tested on this substrate in an attempt to engage the azide in a cycloaddition reaction with phenylacetylene (Table 38).²³⁶-²³⁸ Reaction of crude presumed azide 515 with phenylacetylene (82) in the presence of copper in a mixture of water and tert-butanol gave decomposition at high temperature (Table 38, entry 2). At ambient temperature, a mixture of several products was obtained but the desired compound was not identified by NMR spectroscopy or mass spectroscopy (Table 38, entry 3). By changing the copper source (entry 4) or adding a selection of additives (entry 5) did not change the result. We finally reasoned that a clean azide compound should be synthesised to allow full investigation of this cycloaddition reaction.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Copper source</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>Time (h)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>H₂O</td>
<td>80</td>
<td>24</td>
<td>Degradation</td>
</tr>
<tr>
<td>2</td>
<td>Cu / CuSO₄</td>
<td>tBuOH / H₂O (1/1)</td>
<td>150°</td>
<td>10</td>
<td>Degradation</td>
</tr>
<tr>
<td>3</td>
<td>Cu</td>
<td>tBuOH / H₂O (2/1)</td>
<td>25</td>
<td>24</td>
<td>No desired product observed</td>
</tr>
<tr>
<td>4</td>
<td>Cu / Asc (10%)</td>
<td>tBuOH / H₂O (1/1)</td>
<td>25</td>
<td>24</td>
<td>No desired product observed</td>
</tr>
</tbody>
</table>

Table 38. Attempted cycloaddition reactions.
2.2. Formation of the triazolidinene from β-pinene (519) via ozonolysis

Another pathway was then attempted in order to afford a similar compound starting with ozonolysis of the (-)-β-pinene (519) to afford the (+)-nopinone (520) in high yield (88%, Scheme 117). Reduction of the ketone with NaBH₄ afforded the alcohol 521 in good yield (79%) and only one diastereoisomer was observed. This selectivity was due to attack of the hydride to the Re face of the ketone as shown in Scheme 117.

![Chemical structure](image)

Scheme 116. Formation of the alcohol 521.

Conversion of the alcohol to a leaving group (mesyl, tosyl) was then performed using mesylchloride or tosylchloride and a base. Displacement of this azide with retention or inversion of configuration was our next challenge (Scheme 118, Table 39).
Reaction with trimethylsilylazide in DMF did not result in the formation of the desired azide (Table 39, entry 1). Even after refluxing for only 14 hours, starting material was recovered. Reaction with the more reactive sodium azide did not improve the reaction (Table 39, entry 2). As direct addition of an azide to the alcohol did not yield the desired product, we reasoned that addition of Lewis acid could facilitate the reaction. Peterson and co-workers have previously reported the synthesis of an azide from a secondary alcohol by adding a Lewis acid to the reaction of either a mesyl or tosyl substrate and obtained the desired azide with retention of configuration. After screening several Lewis acids, they proved that BF$_3$.Et$_2$O was the most efficient. Reaction in the presence of BF$_3$.Et$_2$O returned starting material in our case (Table 39, entries 3 and 4). Thompson et al. reported a direct conversion of alcohols to azides with retention of configuration using phosphorazidate as an alternative to Mitsunobu conditions. Reaction of our substrate with phosphorazidate in the presence of DBU did not afford the desired azide but formed diphenylphosphate (Table 39, entry 5). Reaction of this intermediate with sodium or trimethylsilyl-azide and a Lewis acid returned phosphate (Table 39, entries 6 and 7).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Azide source</th>
<th>Solvent</th>
<th>Lewis acid</th>
<th>Temp. (˚C)</th>
<th>Time (h)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>521</td>
<td>TMSN$_3$</td>
<td>DMF</td>
<td></td>
<td>70</td>
<td>14</td>
<td>521</td>
</tr>
<tr>
<td>2</td>
<td>521</td>
<td>NaN$_3$</td>
<td>DMF</td>
<td></td>
<td>70</td>
<td>12</td>
<td>521</td>
</tr>
<tr>
<td>3</td>
<td>522</td>
<td>TMSN$_3$</td>
<td>CH$_2$Cl$_2$</td>
<td>BF$_3$.Et$_2$O</td>
<td>40</td>
<td>17</td>
<td>522</td>
</tr>
<tr>
<td>4</td>
<td>523</td>
<td>TMSN$_3$</td>
<td>CH$_2$Cl$_2$</td>
<td>BF$_3$.Et$_2$O</td>
<td>40</td>
<td>14</td>
<td>523</td>
</tr>
<tr>
<td>5</td>
<td>521</td>
<td>(PhO)$_2$P(O)N$_3$</td>
<td>toluene</td>
<td></td>
<td>40</td>
<td>12</td>
<td>526</td>
</tr>
<tr>
<td>6</td>
<td>526</td>
<td>NaN$_3$</td>
<td>DMF</td>
<td></td>
<td>25</td>
<td>14</td>
<td>526</td>
</tr>
<tr>
<td>7</td>
<td>526</td>
<td>TMSN$_3$</td>
<td>CH$_2$Cl$_2$</td>
<td>BF$_3$.Et$_2$O</td>
<td>40</td>
<td>14</td>
<td>526</td>
</tr>
<tr>
<td>8</td>
<td>522</td>
<td>NaN$_3$</td>
<td>DMPU</td>
<td></td>
<td>25</td>
<td>6</td>
<td>522</td>
</tr>
</tbody>
</table>

Table 39. Various attempts to form the desired azide 525.
with retention of configuration seemed to be impossible in our case most likely due to the steric hindrance of our molecule. Therefore we pursued formation of our desired azide by inversion of configuration: attack of the azide would then be from the Re face of the molecule. Rivera and co-workers have previously reported the synthesis of an azide by inversion of configuration via nucleophilic displacement of a mesylate with sodium azide. Reaction of the mesylate 522 with sodium azide and DMPU as a solvent returned the starting material (Table 39, entry 8).

2.3. Formation of triazolidinene 517 from β-pinene (519)

Recently, Carreira and co-workers published a cobalt catalysed synthesis of azides in the presence of tert-butyl hydroperoxide as activating agent and phenylsilane as reductant. Addition of the preformed cobalt complex to the reaction mixture followed by (-)-β-pinene (519), tosyl azide and tert-butyl hydroperoxide and finally slow addition of phenylsilane afforded the desired product 515 in an excellent yield (92%) and good diastereoselectivity (6:1, Scheme 119).

The mechanism of the reaction was proposed by Carreira and co-workers which hypothesises a role of each reagent (Scheme 120). The first step is the initiation of the catalytic cycle via formation of cobalt-hydride complex by reaction of the cobalt ligand with phenylsilane. Hydrocobaltation would then give the cobalt-alkyl complex. Then two mechanisms were envisaged for the formation of the azide: a radical mechanism or a direct reaction of the Co-alkyl complex with TsN₃. Regeneration of the Co-H complex was not fully understood and they therefore supposed that the peroxide was responsible for the acceleration of the last step to allow useful turnover.
With the desired product in hand the next step was the formation of the triazole via cycloaddition with phenyl acetylene under copper catalysis (“click” chemistry). This reaction was first developed by Huisgen in 1967,245-247 but possibly due to the concern about the safety of azide species the reaction had not been fully exploited. In 2001, Sharpless and co-workers reported on the concept of reliable, robust and selective reactions for the rapid synthesis of useful new compounds and combinatorial libraries through highly favourable reactions which they named “click” chemistry.248 In this review they cited the work of Huisgen on the dipolar cycloaddition of azides and alkynes as “the cream of the crop”. Only once Sharpless and others reported the copper catalysis, the cycloaddition was widely used especially in medicinal chemistry and numerous improvements were reported depending on the azide used. Several conditions were attempted to form the desired triazole 516 (Scheme 121, Table 40).
Scheme 120. Synthesis of the triazole 516. See Table 40 for conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents</th>
<th>Solvent</th>
<th>Temp. (˚C)</th>
<th>Time (h)</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuSO₄ (1%) – Asc (10%)</td>
<td>H₂O/tBuOH</td>
<td>25</td>
<td>12</td>
<td>0%</td>
</tr>
<tr>
<td>2</td>
<td>CuSO₄ (1%) – Asc (10%)</td>
<td>H₂O/tBuOH</td>
<td>100</td>
<td>24</td>
<td>Degradation</td>
</tr>
<tr>
<td>3</td>
<td>CuSO₄ (1%) – Asc (10%)</td>
<td>H₂O/tBuOH</td>
<td>80</td>
<td>24</td>
<td>Degradation</td>
</tr>
<tr>
<td>4</td>
<td>CuSO₄ (1%) – Asc (10%)</td>
<td>H₂O/tBuOH</td>
<td>25</td>
<td>48</td>
<td>10%</td>
</tr>
<tr>
<td>5</td>
<td>CuSO₄ (1%) – Asc (10%)</td>
<td>H₂O/tBuOH</td>
<td>25</td>
<td>96</td>
<td>15%</td>
</tr>
<tr>
<td>6</td>
<td>CuSO₄ (1%) – Asc (10%)</td>
<td>H₂O/tBuOH</td>
<td>25</td>
<td>24</td>
<td>0%</td>
</tr>
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<td>24</td>
<td>0%</td>
</tr>
<tr>
<td>8</td>
<td>CuI (1eq.)</td>
<td>H₂O</td>
<td>100 (μν)</td>
<td>1</td>
<td>Degradation</td>
</tr>
<tr>
<td>9</td>
<td>CuI (1eq.)</td>
<td>Toluene</td>
<td>25</td>
<td>24</td>
<td>0%</td>
</tr>
<tr>
<td>10</td>
<td>CuI (1eq.)</td>
<td>Toluene</td>
<td>120</td>
<td>12</td>
<td>Degradation</td>
</tr>
<tr>
<td>11</td>
<td>CuSO₄ (1%) – Asc (10%)</td>
<td>H₂O/CH₂Cl₂</td>
<td>40</td>
<td>48</td>
<td>30%</td>
</tr>
<tr>
<td>12</td>
<td>CuSO₄ (1%) – Asc (10%)</td>
<td>CH₂Cl₂</td>
<td>40</td>
<td>96</td>
<td>10%</td>
</tr>
<tr>
<td>13</td>
<td>CuSO₄ (10%) – Asc (1eq.)</td>
<td>H₂O/MeCN</td>
<td>40</td>
<td>48</td>
<td>30%</td>
</tr>
<tr>
<td>14</td>
<td>CuSO₄ (10%) – Asc (10%) + CuSO₄ (10%) – Asc (10%)</td>
<td>H₂O/tBuOH</td>
<td>50</td>
<td>120</td>
<td>60%</td>
</tr>
</tbody>
</table>

Table 40. Various conditions to obtain the triazole 516.

The standard procedure with sodium ascorbate (10% mol) and copper sulphate (1% mol) in water/tert-butanol at ambient temperature did not afford the desired product after 12h (Table 40, entry 1). By warming the solution to 80 or 100 ˚C, only decomposition was observed (Table 40, entries 2 and 3). A longer reaction time afforded the product in very low yield (Table 40, entries 4 and 5). Solvent free reaction returned only the starting material (Table 40, entry 6). Fokin and co-workers previously reported the synthesis of 1,2,3 triazoles with copper sulphate and copper(0).236 Unfortunately, in our case, only starting material was recovered (Table 40, entry 7). Wang and Qin,
in 2003, showed that the reaction could be performed without copper, using water as a solvent.\textsuperscript{238}

For our substrate, heating the reaction to 100 °C resulted in degradation and indicated our compound was not stable to high temperature possibly due to the tertiary azide which could form a stable carbocation (Table 40, entry 8). Addition of copper iodide and reaction in toluene returned the starting material at ambient temperature or decomposition at higher temperatures (Table 40, entries 9 and 10). Various mixtures of solvents were surveyed in order to improve the yield and water/dichloromethane was found to be the best solvent system, but the yield was still very low (30%, Table 40, entries 11 to 13). Finally using the standard solvent system but ensuring it was degassed for 30 min afforded the desired triazole in a good yield (60% of a single diastereoisomer) after 5 days at 50 °C (Table 40, entry 14). A second dose of copper sulphate and ascorbic acid were added after 24h which gave improved conversion.

Albrecht previously reported the formation of triazolium salts by addition of methyl iodide to the triazole under overnight reflux in acetonitrile.\textsuperscript{234} Unfortunately, possible Hofmann elimination was observed in our case when high temperatures were used (Scheme 122).\textsuperscript{249} Indeed the pinene group was no longer attached to the triazole as shown by the \textsuperscript{1}H-NMR. No desired product was observed at lower temperatures.

Using the more reactive methyl triflate in dichloromethane at ambient temperature gave a mixture of two methylated compounds after exchange of the anion in a moderate yield. Lowering the temperature to -78 °C and allowing it to warm up overnight to ambient temperature gave us only the desired product 528 in 90% yield (Scheme 123).
The regioselectivity of the addition of the methyl group was confirmed by NOE NMR analysis which showed the proximity of the methyl group to the phenyl group. As a more definitive probe a crystal structure was partially solved for the compound 528 (Figure 29). The geometry of the pinene group (R in Figure 29) was highly disordered and could not be solved. However, the pattern of the substitution around the triazolium ring was solved and showed that the desired regioisomer 528 was obtained.

2.4. Coordination of the triazolidinene abnormal NHC with transition metal

The formation of an abnormal NHC complex from our new ligand was performed by formation of the silver complex with silver oxide followed by transmetallation. The silver complex formation was first attempted with the triazolium salt with the triflate anion but this failed to form the desired complex. It was therefore decided to exchange the triflate anion to halogen as formation of a silver-halogen bond would possibly be the driving force for the reaction. Exchange of the triflate to iodine with sodium iodide in acetone was therefore performed, however problems were observed during purification. Traces of molecular iodine were observed and the desired triazolium salt partially decomposed. Instead, exchange to a bromine anion was successful with tetra-butyl...
ammonium bromide in acetone. Attempted complexation of the bromine triazolium salt with silver oxide failed to give the desired complex; only starting material was recovered. The iodine anion therefore seemed to be essential for the formation of the silver complex. Therefore a three-step procedure was performed to form the iodine triazolium salt. Exchange of the triflate anion to bromine followed by a second exchange with sodium iodide provided a stable white solid. However decomposition was observed in solution after several hours. With the triazolium iodide 517 in hand, the silver complex was obtained by reaction of half an equivalent of silver oxide in dichloromethane in the dark (96% yield, Scheme 124). The crude $^1$H-NMR of the silver-NHC complex 517 showed the disappearance of the C4 proton. Further purification resulted in decomposition, therefore transmetallation was performed on the crude mixture.

Transmetallation of the silver complex 529 at ambient temperature for two hours with [Rh(cod)Cl]$_2$ gave us the desired complex 530 as evidenced by mass spectrometry (Scheme 124). $^1$H and $^{13}$C NMR were difficult to analyse as a highly complex NMR was observed possibly due to interconverting species in solution; however the $^{13}$C NMR spectrum showed the characteristic doublet assigned to a carbon-rhodium bond.

The COD ligand was replaced by carbon monoxide by bubbling CO gas through a solution of the rhodium complex in THF (Scheme 126). The NMR spectrum showed the disappearance of the
COD signals. An IR spectrum was performed and showed the two stretches of CO bond at 2061 and 1985 cm\(^{-1}\) (Figure 30). These values match the stretch obtained for previous abnormal NHC complexes (see Introduction, 1.1). \(^{201}\)

![Scheme 125. Formation of CO-Rh-complex 531.](image)

![Figure 30. IR spectrum of Rh-complex 531.](image)
Conclusion

As shown in the introduction, abnormal NHCs are attracting the attention of many research groups due to their interesting properties (strong $\sigma$-donor, “among the most basic neutral donors”). Our aim was to synthesise and study the first chiral abnormal NHC complexes.

We successfully synthesised the imidazolium salt 464 in two steps in high yield and high enantioselectivity starting from a chiral commercial amine. During this synthesis, a novel reaction to form the desired imidazolium salt 464 from diimine 461 was developed using a diazirine. This reaction proved to be very efficient to introduce our desired phenyl C2 blocking group. Coordination of this imidazolium salt to a metal proved to be complicated but an interesting complex was formed that we presumed to be a $\pi$-complex. More definitive proof of the structure of this complex is needed such as a crystal structure. We also initiated the synthesis of a C5 protected imidazolium salt which should be a better precursor for the formation of an abnormal NHC complex.

The synthesis of triazolium salt 517 was achieved successfully in three steps starting from commercially available $\beta$-pinene. Coordination of the triazolium salt 517 with silver oxide and transmetallation with [Rh(cod)Cl]$_2$ gave us our desired complex. Improved purification and characterisation are required prior to in depth study. In future, asymmetric reactions with this chiral ligand will be studied.
Experimental
General Experimental Procedure:

All reagents and solvents were supplied from commercial sources mainly Sigma-Aldrich and Alfa Aesar and used as received unless otherwise indicated. Reactions requiring anhydrous conditions were conducted in flame-dried glassware. All reactions were carried under dry N₂ conditions. All reactions were monitored by analytical thin-layer chromatography (TLC) performed using indicated solvent on E. Merck silica gel 60 F254 plates (0.25 mm). TLC plates were visualized using UV light (254 nm) and/or by staining in basic potassium permanganate KMnO₄ followed by heating. Solvents were removed via rotary evaporation below 50 °C and the compounds further dried using vacuum. Purification of products was achieved by column chromatography using Merck Flash Silica Gel 60 (230 – 400 mesh).

Melting points were obtained on a Reichert-Thermovar melting point apparatus and are uncorrected. Optical rotations were recorded at 25 °C on a Perkin-Elmer 241 polarimeter with a path length of 1 dm, using the 589.3 nm D-line of sodium. Concentrations (c) are quoted in g/100mL. Infrared spectra were recorded on a Unicam FTIR spectrometer with automated background subtraction and on a Perkin Elmer Spectrum BX II FT-IR System with ATR technique. Samples were prepared as thin films on sodium chloride places (Unicam) or coated on the diamond (Perkin Elmer); solid sample were pressed on the diamond (120 Nm). Reported absorptions are strong or medium strength unless stated otherwise and given in wavenumbers (cm⁻¹). ¹H and ¹³C NMR were recorded on a Bruker Advance 400 spectrometer at 400 MHz and 100 MHz respectively. Chemical shifts (δ H) are quoted in ppm (parts per million) and referenced to CDCl₃ residual chloroform signal ¹H δ= 7.26, ¹³C δ= 77.0 or d₆-DMSO residual dimethyl-sulphoxide signal ¹H δ= 2.54, ¹³C δ= 40.45. Low and high resolution mass spectrometry (EI, CI, ESI) were recorded by the Imperial College London Department of Chemistry Mass Spectroscopy Service using a Micromass Platform II and Micromass AutoSpec-Q spectrometer. LCMS samples were run on a C18 Waters column (2.1 mm diameter, 30 mm length, 3 micron particle size) with MeCN : H₂O (0.1 % formic acid) 5 : 95 to 95 : 5 over 10 min, flow rate 0.6 mL/min. Elemental analyses were determined by the University of North London Analytical Service. Chiral HPLC was performed following different methods: Method A: Chiralcel OD-H, eluent: n-hexane : iso-propanol, 95 : 5, flowrate: 1mL/min, 26 °C; Method B: Chiralcel OJ-H, eluent: n-hexane : iso-propanol, 95 : 5, flowrate: 1mL/min, 26 °C; Method C: Chiralpack IC, eluent: n-hexane, flowrate: 1mL/min, 26 °C.; Method D: Chiralpack IC, eluent: n-hexane : iso-propanol, 99 : 1, flowrate: 1mL/min, 26 °C; Method E: Chiralpack IC, eluent: n-hexane : iso-propanol, 95 : 5, flowrate: 1mL/min, 26 °C; Method F: Chiralpack IC, eluent: n-hexane : iso-propanol, 98 : 2, flowrate: 0.7mL/min, 26 °C.
Chapter I

One-Pot Formation of Allylic Chlorides

General Procedure A for the synthesis of (3-chloroprop-1-enyl) substituted aromatic derivatives:

Benzaldehyde derivatives were diluted in dry tetrahydrofuran (5 mL). Vinylmagnesium chloride (1 equiv.) was then added slowly at ambient temperature. The mixture was stirred and monitored by TLC. Following full consumption of the benzaldehyde derivative, the mixture was cooled to -78 ºC. \( \text{TiCl}_4 \) (0.5 equiv.) was added and the reaction allowed to rise to ambient temperature, before warming to 80 ºC. The reaction was stirred for several minutes at 80 ºC, and then quenched with water (10 mL). Ethyl acetate (10 mL) was added and the resulting phases separated. The organic layer was washed with water and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic phase was dried over anhydrous \( \text{MgSO}_4 \). Removal of the solvent under reduced pressure followed by flash column chromatography (Silica, Eluent: Petroleum ether/EtOAc 6/1) afforded (3-chloroprop-1-enyl) substituted aromatic derivatives.

\( \text{(E)-(3-Chloroprop-1-enyl)benzene (197)} \)\(^{136,250} \)

\[
\begin{align*}
\text{Cl} & \quad \text{CH-CH}_2
\end{align*}
\]

Following the procedure A with benzaldehyde (193, 0.2 mL, 1.88 mmol), vinylmagnesium chloride 1.6 M (1.2 mL, 1.90 mmol) and \( \text{TiCl}_4 \) (0.1 mL, 0.95 mmol) gave the compound 197 (218 mg, 1.43 mmol, 77%) as a pale yellow liquid: IR (ATR) 3083, 3027, 1644, 1579, 1488, 775 cm\(^{-1}\); \( ^1\text{H} \) NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.38-7.41 (m, 2H, Ar-\( \text{H} \)), 7.31-7.35 (m, 2H, Ar-\( \text{H} \)), 7.26-7.29 (m, 1H, Ar-\( \text{H} \)), 6.66 (d, \( J = 15.6 \text{ Hz}, 1\text{H}, \text{Ar-CH} \)), 6.32 (dt, \( J = 15.6, 7.2 \text{ Hz}, 1\text{H}, \text{CH-CH}_2\text{Cl} \)), 4.25 (dd, \( J = 7.2, 1.2 \text{ Hz}, 2\text{H}, \text{CH}_2\text{-Cl} \)); \( ^{13}\text{C} \) NMR (100 MHz, CDCl\(_3\)) \( \delta \) 135.5, 134.2, 128.6 (2C), 128.3, 126.7 (2C), 124.9, 45.4; MS (EI) \( m/z \) 152 / 154 (M); HRMS (EI) \( m/z \) calc for C\(_9\)H\(_9\)\(^{35}\text{Cl} \) 152.0393, found: 152.0393.
(E)-1-(3-Chloroprop-1-enyl)-2-methylbenzene (199):

Following the procedure A with tolualdehyde 198 (0.2 mL, 1.66 mmol), vinlylmagnesium chloride 1.6 M (1.06 mL, 1.70 mmol) and TiCl₄ (0.09 mL, 0.85 mmol) gave the compound 199 (184 mg, 1.11 mmol, 67%) as a pale yellow liquid: IR (ATR) 2945, 1600, 1484, 749 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.43-7.46 (m, 1H, Ar-H), 7.14-7.20 (m, 3H, Ar-H), 6.88 (d, J = 15.6 Hz, 1H, Ar-CH), 6.21 (dt, J = 15.6, 7.3 Hz, 1H, CH₂Cl), 4.27 (d, J = 7.3 Hz, 2H, CH₂-Cl), 2.36 (s, 3H, Ar-CH₃); ¹³C NMR (100 MHz, DMSO) δ 135.4, 134.5, 131.3, 130.3, 128.0, 126.5, 126.1, 125.5, 45.9, 19.2; MS (EI) m/z 166 / 168 (M); HRMS (EI) m/z calc for C₁₀H₁₁Cl 166.0549, found: 166.0551.

(E)-1-(3-Chloroprop-1-enyl)-2,4-dimethylbenzene (201):

Following the procedure A with 2,4-dimethylbenzaldehyde 200 (0.2 mL, 1.49 mmol), vinlylmagnesium chloride 1.6 M (0.94 mL, 1.50 mmol) and TiCl₄ (0.08 mL, 0.75 mmol) gave the compound 201 (195 mg, 1.08 mmol, 73%) as a pale yellow liquid: IR (ATR) 3012, 2919, 1610, 1497, 630 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.35 (d, J =7.7 Hz, 1H, Ar-H), 6.98-7.00 (m, 2H, Ar-H), 6.85 (d, J = 15.3 Hz, 1H, Ar-CH), 6.18 (dt, J = 15.6, 7.0 Hz, 1H, CH₂Cl), 4.26 (dd, J = 7.3, 1.0 Hz, 2H, CH₂-Cl), 2.32 (s, 3H, Ar-CH₃), 2.31 (s, 3H, Ar-CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 138.1, 135.7, 132.2, 132.0, 131.3, 127.0, 126.0, 125.4, 46.0, 21.2, 19.8; MS (EI) m/z 180 / 182 (M); HRMS (EI) m/z calc for C₁₁H₁₃Cl 180.0706, found: 180.0709.

(E)-1-(3-Chloroprop-1-enyl)-2-methoxybenzene (203)

(251)
Following the procedure A with 2-methoxybenzaldehyde 202 (0.2 mL, 1.47 mmol), vinylmagnesium chloride 1.6 M (0.94 mL, 1.50 mmol) and TiCl₄ (0.08 mL, 0.75 mmol) gave the compound 203 (255 mg, 1.40 mmol, 95% without purification) as a pale yellow liquid: IR (ATR) 2940, 1598, 1488, 1242, 748 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.43 (d, J = 7.7 Hz, 1H, Ar-H), 7.23-7.27 (m, 1H, Ar-H), 6.97 (d, J = 15.8 Hz, 1H, Ar-C), 6.93 (t, J = 7.7 Hz, 1H, Ar-H), 6.87 (d, J = 7.7 Hz, 1H, Ar-H), 6.35 (dt, J = 15.8, 7.3 Hz, 1H, CH-CH₂Cl), 4.26 (d, J = 7.3 Hz, 2H, CH₂-Cl), 3.83 (s, 3H, O-CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 157.1, 129.5, 129.3, 127.4, 125.7, 125.0, 120.8, 111.0, 55.6, 46.3; MS (EI) m/z 182 / 184 (M); HRMS (EI) m/z calc for C₁₀H₁₁ClO 182.0498, found: 182.0497. Further purification (SiO₂) resulted in decomposition.

(E)-1-(3-Chloroprop-1-enyl)-3-methoxybenzene (205):

Following the procedure A with 3-methoxybenzaldehyde 204 (0.2 mL, 1.47 mmol), vinylmagnesium chloride 1.6 M (0.94 mL, 1.50 mmol) and TiCl₄ (0.08 mL, 0.75 mmol) gave the compound 205 (157 mg, 0.87 mmol, 59%) as a pale yellow liquid: IR (ATR) 1579, 1488, 776 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.25 (t, J = 8.0 Hz, 1H, Ar-H), 6.99 (d, J = 7.7 Hz, 1H, Ar-H), 6.93 (t, J = 1.8 Hz, 1H, Ar-H), 6.83 (dd, J = 7.9, 2.4 Hz, 1H, Ar-H), 6.63 (d, J = 15.6 Hz, 1H, Ar-CH), 6.31 (dt, J = 15.6, 7.2 Hz, 1H, CH-CH₂Cl), 4.24 (dd, J = 7.2, 1.0 Hz, 2H, CH₂-Cl), 3.82 (s, 3H, O-CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 160.0, 137.5, 134.2, 129.8, 125.4, 119.5, 114.1, 112.1, 55.4, 45.5; MS (EI) m/z 182 / 184 (M); HRMS (EI) m/z calc for C₁₀H₁₁ClO 182.0498, found: 182.0497.

(E)-Methyl 4-(3-chloroprop-1-enyl)benzoate (209):

Following the procedure A with methyl 4-formylbenzoate 208 (200 mg, 1.22 mmol), vinylmagnesium chloride 1.6 M (0.77 mL, 1.23 mmol) and TiCl₄ (0.065 mL, 0.62 mmol) gave the compound 209 (194 mg, 0.92 mmol, 76%) as a pale yellow solid: IR (ATR) 3043, 2956, 1716, 1431, 1104, 761 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.00 (d, J = 8.3 Hz, 2H, Ar-H), 7.44 (d, J = 8.3 Hz, 2H, Ar-H), 6.69 (d, J = 15.7
Hz, 1H, Ar-CH₃), 6.43 (dt, J = 15.7, 7.0 Hz, 1H, CH₂-Cl), 4.25 (dd, J = 7.0, 1.2 Hz, 2H, CH₂Cl), 3.91 (s, 3H, O-CH₃); ¹³C NMR (100 MHz, CDCl₃, δ ppm) 166.8, 140.5, 133.1, 130.1 (2C), 129.8, 127.6, 126.7 (2C), 52.2, 45.0; MS (Cl) m/z 228 / 230 (M⁺NH₄⁺); HRMS (Cl) m/z calc for C₁₁H₁₅NO₂Cl 228.0791, found: 228.0799.

**General Procedure B for the formation of allylic alcohols:**

Benzaldehyde or ketone derivatives were diluted in dry tetrahydrofuran (6 mL). The grignard reagent was added slowly at 0 °C. The mixture was stirred 30 min and allowed to warm to ambient temperature. The reaction was monitored by TLC. Following full consumption of the substrate, the mixture was quenched with a saturated solution of NH₄Cl (10 mL) and extracted with ether (3 x 10 mL). The combined organic phase was dried over anhydrous MgSO₄. Removal of the solvent under reduced pressure followed by flash column chromatography (Silica, Eluent: Petroleum ether/EtOAc 4/1) afforded the alcohol derivatives.

**4-(1-Hydroxyallyl)benzonitrile**

Following the procedure B with 4-formylbenzonitrile (200 mg, 1.53 mmol), vinylmagnesium chloride 1.6 M (1.15 mL, 1.83 mmol) gave the compound (197 mg, 81%) as a pale yellow liquid: ¹H NMR (400 MHz, CDCl₃) δ 7.64 (dt, J = 8.4, 1.7 Hz, 2H, Ar-H), 7.49 (d, J = 8.3 Hz, 2H, Ar-H), 5.97 (ddd, J = 16.2, 12.4, 3.8 Hz, 1H, CH-CH₂), 5.37 (dt, J = 17.1; 1.0 Hz, 1H, CH₂), 5.23-5.26 (m, 2H, CH₂ and CH-OH); ¹³C NMR (100 MHz, CDCl₃) δ 147.8, 139.4, 132.4 (2C), 127.0 (2C), 118.9, 116.7, 111.4, 74.8.
**2-Phenylbut-3-en-2-ol**

Following the procedure B with acetophenone (0.4 mL, 3.34 mmol), vinyl magnesium chloride 1.6 M (5 mL, 8.0 mmol) gave the compound (530 mg, 84%) as a pale yellow liquid: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.48 (d, $J$ = 8.0 Hz, 2H, Ar-$H$), 7.37 (t, $J$ = 8.0 Hz, 2H, Ar-$H$), 7.37 (t, $J$ = 7.6 Hz, 1H, Ar-$H$), 6.20 (dd, $J$ = 17.2, 10.4 Hz, 1H, CH-CH$_2$), 5.32 (d, $J$ = 17.2 Hz, 1H, CH$_3$), 5.17 (d, $J$ = 10.8 Hz, 1H, CH$_2$), 1.08 (s, 3H, CH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 146.4, 144.9, 128.3 (2C), 127.0, 125.2 (2C), 112.4, 74.8, 29.4.

**3-Methyl-2-phenylbut-3-en-2-ol**

Following the procedure B with acetophenone (1 mL, 8.35 mmol), isopropenylmagnesium bromide 0.5 M (30 mL, 15 mmol) gave the compound (1.2 g, 89%) as a pale yellow liquid: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.44-7.47 (m, 2H, Ar-$H$), 7.31-7.35 (m, 2H, Ar-$H$), 7.23-7.27 (m, 1H, Ar-$H$), 5.20-5.21 (m, 1H, CH$_2$), 4.96-4.98 (m, 1H, CH$_3$), 1.70 (s, 3H, CH$_3$-COH), 1.62-1.63 (m, 3H, CH$_3$-CCH$_2$); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 150.3, 146.1, 128.3 (2C), 127.0, 125.4 (2C), 110.8, 77.1, 28.8, 19.2.

(E)-**1-Phenylbut-2-en-1-ol**

Following the procedure B with crotonaldehyde (0.9 mL, 11 mmol), phenylmagnesium bromide 1 M (15 mL, 15 mmol) gave the compound (1.47 g, 90%) as a pale yellow liquid: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.32-7.38 (m, 4H, Ar-$H$), 7.24-7.29 (m, 1H, Ar-$H$), 5.66-5.80 (m, 2H, CH-CH$_2$ and CH-CH$_3$), 5.15 (dd, $J$ = 6.3; 3.4 Hz, 1H, CH-OH), 1.93 (d, $J$ = 3.6 Hz, 1H, OH), 1.72 (d, $J$ = 5.9 Hz, 1H, CH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 143.5, 133.8, 129.7 (2C), 128.6, 127.6, 126.2 (2C), 75.3, 17.8.
**3-Methyl-1-phenylbut-2-en-1-ol**\(^{256}\)

![Structure of 3-Methyl-1-phenylbut-2-en-1-ol]

Following the procedure B with benzaldehyde (0.6 mL, 5.64 mmol), 2-methyl-1-propenylmagnesium bromide 0.5 M (15 mL, 7.5 mmol) gave the compound (782 mg, 86%) as a pale yellow liquid: \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.33-7.40 (m, 4H, Ar-H), 7.24-7.28 (m, 1H, Ar-H), 5.40 – 5.49 (m, 2H, CH-OH, CH-COH), 1.81 (s, 3H, CH\(_3\)), 1.76 (s, 3H, CH\(_3\)); \(^1\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 144.2, 135.4, 128.5 (2C), 127.7, 127.3, 125.8 (2C), 70.8, 25.9, 18.3.

**4-Methyl-2-phenylpent-3-en-2-ol**\(^{257}\)

![Structure of 4-Methyl-2-phenylpent-3-en-2-ol]

Following the procedure B with acetophenone (1 mL, 8.35 mmol), 2-methyl-1-propenylmagnesium bromide 0.5 M (30 mL, 15 mmol) gave the compound (1.37 g, 94%) as a pale yellow liquid: \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.46-7.49 (m, 2H, Ar-H), 7.29-7.33 (m, 2H, Ar-H), 7.19-7.23 (m, 1H, Ar-H), 5.73 (s, 1H, CH), 1.74 (s, 3H, CH\(_3\)-COH), 1.60 (s, 3H, CH\(_3\)), 1.48 (s, 3H, CH\(_3\)); \(^1\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 149.0, 136.7, 132.4, 128.0 (2C), 126.3, 125.1 (2C), 74.0, 33.8, 26.8, 19.1.

**1-Cyclohexylprop-2-en-1-ol**\(^{258}\)

![Structure of 1-Cyclohexylprop-2-en-1-ol]

Following the procedure B with cyclohexanecarbaldehyde (0.54 mL, 4.5 mmol), vinylmagnesium chloride 1.6 M (3.4 mL, 5.4 mmol) gave the compound (530 mg, 84%) as a pale yellow liquid: \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 5.86 (ddd, \(J =\) 17.3, 13.4, 3.9 Hz, 1H, CH-CH\(_2\)), 5.20 (dt, \(J =\) 17.3, 1.4 Hz, 1H, CH\(_2\)), 5.14 (dt, \(J =\) 10.4, 1.4 Hz, 1H, CH\(_2\)), 3.85 (m, CH-OH), 1.81-1.88 (m, 1H, CH-COH), 1.63-1.78 (m, 4H), 0.94-1.44 (m, 6H); \(^1\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 140.0, 115.6, 77.9, 43.7, 28.9, 28.5, 26.7, 26.3, 26.2.
5-Phenylpent-1-en-3-ol:\(^{259}\)

\[
\begin{array}{c}
\text{phenyl} \\
\text{pent-1-en-3-ol}
\end{array}
\]

Following the procedure B with 3-phenylpropanal (0.5 mL, 3.7 mmol), vinylmagnesium chloride 1.6 M (2.7 mL, 4.3 mmol) gave the compound (538 mg, 90%) as a pale yellow liquid: \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.28-7.33 (m, 2H, Ar-H), 7.21-7.24 (m, 3H, Ar-H), 5.94 (ddd, \(J = 16.8, 12.4, 4.2\) Hz, 1H, CH-CH\(_3\)), 5.28 (dt, \(J = 17.2, 1.4\) Hz, 1H, CH\(_2\)), 5.17 (dt, \(J = 10.5, 1.2\) Hz, 1H, CH\(_2\)), 4.16 (m, 1H, CH-OH), 2.68-2.82 (m, 2H, CH\(_2\)-Ar), 1.86-1.92 (m, 2H, CH\(_2\)-CH-OH); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 142.0, 141.2, 128.6 (2C), 128.5 (2C), 126.0, 115.0, 72.6, 38.7, 31.8.

General Procedure C for the rearrangement of allylic alcohols to allylic chlorides:

Alcohol derivatives were diluted in dry tetrahydrofuran (5 mL). iso-Propyl magnesium chloride (1 equiv.) was added slowly at ambient temperature. The mixture was stirred for 10 min and then cooled to -78 °C. TiCl\(_4\) (0.5 equiv.) was added and the reaction was allowed to rise to ambient temperature before warming to 80 °C. The reaction was stirred for several hours at 80 °C, then quenched with water (10 mL) and cooled to ambient temperature. Ethyl acetate (10 mL) was added. The organic layer was washed with water and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic phase was dried over anhydrous MgSO\(_4\). Removal of the solvent under reduced pressure followed by flash column chromatography (Silica, Eluent: Petroleum ether/EtOAc 6/1) afforded (3-chloroprop-1-ethyl) substituted aromatic derivatives.
(E)-4-(3-Chloroprop-1-enyl)benzonitrile (207):

Following the procedure C with 4-(1-hydroxyallyl)benzonitrile (180 mg, 1.13 mmol), iso-propyl magnesium chloride 2 M (0.6mL, 1.2mmol) and TiCl₄ (0.06 mL, 0.57 mmol) gave the compound 207 (155 mg, 0.88 mmol, 78%) as a pale yellow solid: IR (ATR) 2966, 2223, 1702, 836 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.62 (dt, J = 8.3, 1.7 Hz, 2H, Ar-H), 7.47 (dt, J = 8.3, 1.7 Hz, 2H, Ar-H), 6.67 (d, J = 15.7 Hz, 1H, Ar-CH), 6.43 (dt, J = 15.7, 6.9 Hz, 1H, CH-CH₂Cl), 4.25 (dd, J = 6.9, 1.1 Hz, 2H, CH₂Cl); ¹³C NMR (100 MHz, CDCl₃, δ ppm) 140.4, 132.6, 132.2, 128.9, 127.3, 118.8, 111.7, 44.6; MS (CI) m/z 195 / 197 (M+NH₄); HRMS (CI) m/z calc for C₁₀H₁₀N₂Cl 195.0689, found: 195.0689.

(E)-4-Chlorobut-2-en-2-yl)benzene (214):

Following the procedure C with 2-phenylbut-3-en-2-ol (200 mg, 1.35 mmol), iso-propyl magnesium chloride 2 M (0.7 mL, 1.40 mmol) and TiCl₄ (0.07 mL, 0.67 mmol) gave the compound 214 (174 mg, 1.05 mmol, 78%) as a pale yellow liquid: IR (ATR) 3038, 2960, 1492, 758, 695 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.33 (m, 5H, Ar-H), 5.91 (tq, J = 7.8, 1.5 Hz, 1H, CH-CH₂Cl), 4.19 (d, J = 8.0 Hz, 2H, CH₂-Cl), 2.06 (d, J = 1.4 Hz, 3H, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 142.4, 141.0, 128.9, 127.8, 126.0 (2C), 122.9, 41.2, 15.9; MS (EI) m/z 166 / 168 (M); HRMS ( EI) m/z calc for C₁₀H₁₁Cl 166.0549, found: 166.0550.

(E)-(4-Chloro-3-methylbut-2-en-2-yl)benzene (228):

Following the procedure C with 3-methyl-2-phenylbut-3-en-2-ol (1 g, 6.17 mmol), iso-propyl magnesium chloride 2 M (3.1 mL, 6.2 mmol) and TiCl₄ (0.33 mL, 3.13 mmol) gave the compound 228 (900 mg, 5mmol, 81% without purification) as a yellow liquid: IR (thin film) 2953, 2924, 2855, 2357,
1H NMR (400 MHz, CDCl$_3$) δ 7.32-7.36 (m, 2H, CH-Ar), 7.19-7.28 (m, 2H, CH-Ar), 3.96 (s, 2H, CH$_2$-Cl), 2.02 (s, 3H, CH$_3$-Ar), 1.93 (s, 3H, CH$_3$-CH$_2$Cl); 13C NMR (100 MHz, CDCl$_3$) δ 143.1, 137.5, 128.3 (2C), 127.7 (2C), 127.4, 126.8, 48.8, 21.4, 16.7; MS (EI) m/z 180 / 182 (M); HRMS (EI) m/z calc for C$_{11}$H$_{13}$Cl 180.0706, found: 180.0703.

(3-Methylbuta-1,3-dien-2-yl)benzene:

Obtained after purification of 228 on flash chromatography: colourless liquid diene (480 mg, 3.33 mmol, 54%): IR (thin film) 3093, 3027, 2929, 2857, 897, 701 cm$^{-1}$; 1H NMR (400 MHz, CDCl$_3$) δ 7.26-7.33 (m, 5H, CH-Ar), 5.32 (s, 1H, CH$_2$-CAr), 5.14 (s, 1H, CH$_2$-CAr), 5.11 (s, 1H, CH$_2$-CCH$_3$), 4.87 (s, 1H, CH$_2$-CCH$_3$), 2.00 (s, 3H, CH$_3$); 13C NMR (100 MHz, CDCl$_3$) δ 151.0, 143.6, 141.5, 128.6 (2C), 127.9 (2C), 127.1, 116.9, 113.9, 21.2; MS (EI) m/z 144 (M); HRMS (EI) m/z calc for C$_{10}$H$_{12}$Cl 144.0939, found: 144.0935.

(E)-(3-Chlorobut-1-enyl)benzene (230):

Following the procedure C with (E)-1-phenylbut-2-en-1-ol (200 mg, 1.34 mmol), iso-propyl magnesium chloride 2 M (0.7 mL, 1.40 mmol) and TiCl$_4$ (0.08 mL, 0.75 mmol) gave the compound 230 (210 mg, 1.26 mmol, 95% without purification) as a pale yellow liquid: IR (thin film) 3026, 2970, 2926, 1448, 693 cm$^{-1}$; 1H NMR (400 MHz, CDCl$_3$) δ 7.26-7.40 (m, 5H, CH-Ar), 6.59 (d, J = 16 Hz, 1H, CH-Ar), 6.30 (dd, J = 16, 8.4 Hz, 1H, CH-CHCl), 4.70-4.78 (m, 1H, CH-Cl), 1.71 (d, J = 6.8 Hz, 3H, CH$_3$); 13C NMR (100 MHz, CDCl$_3$) δ 135.9, 131.0, 130.9, 128.6 (2C), 128.1, 126.7 (2C), 58.3, 25.3; MS (EI) m/z 166 / 168 (M); HRMS (EI) m/z calc for C$_{10}$H$_{12}$Cl 166.0549, found: 166.0546.
(E)-(3-Methylbuta-1,3-dienyl)benzene (215):\(^{261}\)

Following the procedure C with 3-methyl-1-phenylbut-2-en-1-ol (500 mg, 3.08 mmol), iso-propyl magnesium chloride 2 M (1.6 mL, 3.20 mmol) and TiCl\(_4\) (0.17 mL, 1.61 mmol) gave the compound \(\text{215}\) (357 mg, 2.48 mmol, 80\%) as a colourless solid: IR (ATR) 2909, 1605, 1375, 1239, 753 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.46 (d, \(J = 7.4\) Hz, 2H, Ar-\(H\)), 7.33-7.37 (m, 2H, Ar-\(H\)), 7.23-7.27 (m, 1H, Ar-\(H\)), 6.91 (d, \(J = 16.2\) Hz, 1H, Ar-\(C\H\)), 6.57 (d, \(J = 16.2\) Hz, 1H, Ar-CH-CH\(_2\)), 5.15 (s, 1H, C-CH\(_3\)), 5.12 (s, 1H, C-CH\(_2\)), 2.01 (s, 3H, C\(\H_3\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 142.2, 137.6, 131.8, 128.8, 128.7 (2C), 127.5, 126.6 (2C), 117.4, 18.7.

(E)-(4-Methylpenta-2,4-dien-2-yl)benzene (233a):\(^{262}\)

Following the procedure C with 4-methyl-2-phenylpent-3-en-2-ol (1 g, 5.58 mmol), iso-propyl magnesium chloride 2 M (2.8 mL, 5.60 mmol) and TiCl\(_4\) (0.29 mL, 2.74 mmol) gave the compound \(\text{233a}\) (400 mg, 2.53 mmol, 45\%) as a colourless liquid: IR (thin film) 3080, 3021, 2967, 2919, 893, 756, 696 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.45-7.47 (m, 2H, Ar-\(H\)), 7.33-7.38 (m, 2H, Ar-\(H\)), 7.28-7.30 (m, 1H, Ar-\(H\)), 6.24 (s, 1H, CH-CH\(_2\CH_3\)), 5.13 (s, 1H, CH\(_3\)), 4.97 (s, 1H, CH\(_2\)), 2.26 (s, 3H, CH\(_3\)), 1.98 (s, 3H, CH\(_3\))); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 144.2, 142.2, 136.2, 129.7, 128.2 (2C), 126.9, 125.9 (2C), 115.3, 23.8, 17.5; MS (El) \(m/z\) 158 (M); HRMS (El) \(m/z\) calc for C\(_{12}\)H\(_{14}\) 158.1096, found: 158.1092.

(4-Methylpenta-1,3-dien-2-yl)benzene (233b):\(^{263}\)

Following the procedure C with 4-methyl-2-phenylpent-3-en-2-ol (1 g, 5.58 mmol), iso-propyl magnesium chloride 2 M (2.8 mL, 5.60 mmol) and TiCl\(_4\) (0.29 mL, 2.74 mmol) gave the compound \(\text{233b}\) (300 mg, 1.90 mmol, 35\%) as a colourless liquid: IR (thin film) 3080, 3025, 2969, 2929, 2911,
895, 773, 703 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 7.40-7.42\) (m, 2H, Ar-H), 7.26-7.33 (m, 3H, Ar-H), 5.95 (s, 1H, CH-CH\(_3\)), 5.52 (s, 1H, CH\(_2\)), 5.07 (s, 1H, CH\(_2\)), 1.88 (s, 3H, CH\(_3\)), 1.72 (s, 3H, CH\(_3\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta 145.3, 141.3, 137.0, 128.1\) (2C), 127.3, 126.5 (2C), 124.9, 114.3, 26.3, 19.6; MS (EI) \(m/z\) 158 (M); HRMS (EI) \(m/z\) calc for C\(_{12}\)H\(_{14}\)Cl 158.1096, found: 158.1092.

**(E)-(3-Chloroprop-1-enyl)cyclohexane (235):**

![Chemical structure](image)

Following the procedure C with 1-cyclohexylprop-2-en-1-ol (150 mg, 1.07 mmol), iso-propyl magnesium chloride 2 M (0.7 mL, 1.40 mmol) and TiCl\(_4\) (0.07 mL, 0.66 mmol) gave the compound 235 (101 mg, 0.64 mmol, 60%) as a colourless liquid: IR (ATR) 2923, 1448, 683 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 7.71\) (dd, \(J = 15.6, 6.8\) Hz, 1H, CH-CH), 5.52-5.59 (m, 1H, CH-CH\(_2\)-Cl), 4.03 (d, \(J = 7.2\) Hz, 2H, CH\(_2\)-Cl), 1.94-2.02 (m, 1H, CH), 1.70-1.74 (m, 4H, CH\(_2\)), 1.02-1.32 (m, 6H, CH\(_2\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta 141.9, 123.7, 46.0, 40.3, 32.7\) (2C), 26.2, 26.1 (2C); MS (EI) \(m/z\) 158 / 160 (M); HRMS (EI) \(m/z\) calc for C\(_9\)H\(_{15}\)Cl 158.0862, found: 158.0859.

**(E)-(5-Chloropent-3-enyl)benzene (237):**

![Chemical structure](image)

Following the procedure C with 5-phenylpent-1-en-3-ol (160 mg, 0.99 mmol), iso-propyl magnesium chloride 2 M (0.5 mL, 1.00 mmol) and TiCl\(_4\) (0.06 mL, 0.57 mmol) gave the compound 237 (98 mg, 0.54 mmol, 55%) as a colourless liquid: IR (thin film) 3027, 2929, 2856, 1453, 966, 698 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 7.27-7.31\) (m, 2H, Ar-H), 7.17-7.22 (m, 3H, Ar-H), 5.78-5.85 (m, 1H, CH-CH\(_2\)-Cl), 5.61-5.70 (m, 1H, CH-CH\(_2\)-CH\(_2\)-Cl), 4.03 (d, \(J = 7.2\) Hz, 2H, CH\(_2\)-Cl), 2.72 (t, \(J = 7.2\) Hz, 2H, CH\(_2\)-Ar), 2.36-2.42 (m, 2H, CH\(_2\)-CH\(_2\)-Ar); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta 141.4, 135.0, 128.4\) (2C), 128.3 (2C), 126.5, 125.9, 45.3, 35.2, 33.8; MS (EI) \(m/z\) 180 / 182 (M); HRMS (EI) \(m/z\) calc for C\(_{11}\)H\(_{13}\)Cl 180.0706, found: 180.0701.
Chiral studies:

\( \text{(E)-1-Phenylbut-2-en-1-ol (247)}: \)

\[
\begin{align*}
\text{OH} \\
\text{H}
\end{align*}
\]

Chiral alcohol 247 was prepared as previously reported.\textsuperscript{134,135}

Characterisation as previously reported.

Chiral HPLC (Method A): major (Rt = 9.57 min) : minor (Rt = 11.56 min) 87.5 : 12.5

\( \text{(E)-(3-Chlorobut-1-enyl)benzene (230)}: \)

\[
\begin{align*}
\text{Cl} \\
\text{H}
\end{align*}
\]

Characterisation as previously reported.

Chiral HPLC (Method B): major (Rt = 17.36 min) : minor (Rt = 20.49 min) 50 : 50
Synthesis of imidazolium salts

7-Hydroxyindan-1-one (233)

A mixture of 4-chromanone 258 (10.00 g, 67.50 mmol) and anhydrous, powdered AlCl₃ (26.00 g, 195.00 mmol) was fused at 250 °C for 10 min. After allowing the reaction mixture to cool to ambient temperature, dichloromethane (50 mL) and cold hydrochloric acid (50 mL) were added to the mixture. The resulting black slurry was extracted with dichloromethane (2 L). Removal of the solvent under reduced pressure followed by flash column chromatography (eluent: EtOAc : Petroleum ether 1 : 4) afforded 7-hydroxyindan-1-one (233, 7.1 g, 48.00 mmol, 72 %) as yellow solid: m.p. (Petroleum ether / EtOAc) = 48 – 50 °C; IR (thin film) 3360, 1678, 1176 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 9.07 (s, 1H, O-H), 7.47 (t, J = 8.0 Hz, 1H, Ar-H), 6.94 (d, J = 7.2 Hz, 1H, Ar-H), 6.75 (d, J = 8.0 Hz, 1H, Ar-H), 3.11 (t, J = 5.6 Hz, 2H, CH₂-CH₂CO), 2.72 (t, J = 6.0 Hz, 2H, CH₂CO); ¹³C NMR (100 MHz, CDCl₃) δ 210.1, 157.5, 155.3, 137.6, 117.4, 113.5 (2C), 36.0, 25.9; MS (EI) m/z 148 (M); HRMS (EI) m/z calc for C₉H₈O₂ 148.0524, found: 148.0524.

7-Methoxyindan-1-one (259)

Anhydrous K₂CO₃ (4.85 g, 35.10 mmol) was added to a solution of 7-hydroxyindan-1-one (5.00 g, 33.80 mmol) and dimethylsulfate (3.33 ml, 35.11 mmol) in acetone (130 ml). The reaction mixture was stirred under reflux for 18 h and was allowed to cool to ambient temperature. Water was added and the organic phase was extracted with ethyl acetate. After the addition of sodium hydroxide (80 ml, solution 1M) the mixture was stirred 1 h at ambient temperature. The phases were separated and the organic phase was dried over anhydrous MgSO₄. Removal of the solvent under reduced pressure followed by flash column chromatography (eluent: EtOAc : Petroleum ether 1 : 4) afforded the 7-methoxyindan-1-one (259, 4.90 g, 30.25 mmol, 89 %) as yellow oil: IR (neat) 1692, 1589, 1482, 1277, 1062 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.51 (t, J = 7.6 Hz, 1H, Ar-H), 7.01 (d, J = 7.6 Hz, 1H, Ar-
H), 6.78 (d, J = 8.0 Hz, 1H, Ar-H), 3.95 (s, 3H, O-CH₃), 3.08 (t, J = 6.4 Hz, 2H, CH₂-CH₂CO), 2.67 (t, J = 6.4 Hz, 2H, CH₂CO);¹³C NMR (100 MHz, CDCl₃) δ 204.9, 158.2, 158.0, 136.4, 118.5, 108.8 (2C), 55.8, 36.8, 25.6, MS (EI) m/z 162 (M); HRMS (EI) m/z calc for C₁₀H₁₀O₂ 162.0681, found: 162.0678.

7-isoPropoxyindan-1-one (260)

Anhydrous K₂CO₃ (965 mg, 7.00 mmol) was added to a solution of 7-hydroxyindan-1-one (1.00 g, 6.75 mmol) in DMF (20 mL). Then 2-iodopropane (1.35 mL, 13.50 mmol) was added and the mixture was stirred for 2h at reflux. The reaction was quenched with water (10 mL) and extracted with ethyl acetate (2 x 40 mL). The organic phase was dried over anhydrous MgSO₄. Removal of the solvent under reduced pressure followed by flash column chromatography (eluent: EtOAc : Petroleum ether 1 : 4) afforded the 7-isopropoxyindan-1-one (260, 1.21 g, 6.37 mmol, 94 %) as colourless oil: IR (thin film) 1704, 1594, 1475, 772 cm⁻¹;¹H NMR (400 MHz, CDCl₃) δ 7.45 (t, J = 7.3 Hz, 1H, Ar-H), 6.96 (d, J = 6.8 Hz, 1H, Ar-H), 6.77 (d, J = 7.8 Hz, 1H, Ar-H), 4.66 (sep., J = 5.8 Hz, 1H, O-CH-(CH₃)₂), 3.06-3.03 (m, 2H, CH₂-CH₂OH), 2.64-2.61 (m, 2H, CH₂-CHOH), 1.42 (d, J = 5.8 Hz, 6H, CH₃);¹³C NMR (100 MHz, CDCl₃) δ 204.3, 157.9, 156.8, 135.9, 126.1, 118.1, 111.7, 71.2, 36.8, 25.4, 21.9 (2C), MS (EI) m/z 190 (M); HRMS (EI) m/z calc for C₁₂H₁₄O₂ 190.0994, found: 190.0995.

3-Oxoinden-4-yltrifluoromethanesulfonate (261)

N-phenyltrifluoromethanesulphonimide (2.50 g, 7.00 mmol) was added to a solution of 7-hydroxyindan-1-one 253 (1.00 g, 6.75 mmol) and triethylamine (1.05 mL, 7.50 mmol) in dichloromethane (30 mL). The resulting mixture was stirred 24 h at ambient temperature. The reaction was washed with water (30 mL) and brine (30 mL) and extracted with dichloromethane (2 x 50 mL). The organic phase was dried over anhydrous MgSO₄. Removal of the solvent under reduced pressure followed by flash column chromatography (eluent: EtOAc : Petroleum ether 1 : 4) afforded
the 3-oxoinden-4-yltrifluoromethanesulfonate (261, 1.85 g, 6.61 mmol, 99 %) as colourless solid: m.p. 42-44 °C; IR (thin film) 1727, 1210, 1139, 959 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.65 (t, J = 8.0 Hz, 1H, Ar-), 7.51 (d, J = 8.0 Hz, 1H, Ar-), 7.17 (d, J = 8.0 Hz, 1H, Ar-), 3.20 (t, J = 6.0 Hz, 2H, CH₂-CH₂CO), 2.77 (t, J = 6.0 Hz, 2H, CH₂CO); ¹³C NMR (100 MHz, CDCl₃) δ 202.2, 157.6, 136.0, 127.0, 120.2, 36.6, 25.7; MS (Cl) m/z 298 (M+NH₄⁺); HRMS (Cl) m/z calc for C₁₀H₁₁NO₄F₃S 298.0361, found: 298.0359.

7-Methylindan-1-one (262)²⁶⁵

![7-Methylindan-1-one](image)

To a solution of 3-oxoinden-4-yltrifluoromethanesulfonate 261 (600 mg, 2.14 mmol) in tetrahydrofuran (200 mL) were added sequentially (dpdp)NiCl₂ (114 mg, 0.21 mmol), dimethylzinc (1.2M solution in toluene, 6.70 mL, 8.00 mmol) at ambient temperature. The mixture was stirred 12 h at ambient temperature. The reaction was quenched with sat. aq. NaH₂PO₄ (50 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic phase was washed with water (30 mL), brine (30 mL) and dried over anhydrous MgSO₄. Removal of the solvent under reduced pressure followed by flash column chromatography (eluent: EtOAc : Petroleum ether 1 : 6) afforded the 7-methylindan-1-one (262, 300 mg, 2.05 mmol, 96 %) as colourless oil: IR (neat)2924, 1703, 1596, 1191, 711, 674 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.43 (t, J = 7.6 Hz, 1H, Ar-), 7.28 (d, J = 7.6 Hz, 1H, Ar-), 7.09 (d, J = 7.2 Hz, 1H, Ar-), 3.08 (t, J = 6.0 Hz, 2H, CH₂-CH₂CO), 2.66 (t, J = 6.0 Hz, 2H, CH₂CO), 2.64 (s, 3H, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 144.0, 142.9, 135.2, 128.9, 128.0, 122.4, 75.5, 35.1, 30.1, 18.3; MS (EI) m/z 146 (M); HRMS (EI) m/z calc for C₁⁰H₁₀O 146.0732, found: 146.0725.

7-Phenylindan-1-one (263)²⁶⁶

![7-Phenylindan-1-one](image)

To 3-oxoinden-4-yltrifluoromethanesulfonate 261 (1.00 g, 3.14 mmol), phenylboronic acid (488 mg, 4.00 mmol) and Pd(PPh₃)₄ (410 mg, 0.31 mmol) were placed in a round-bottom flask, fitted with a
condenser, under nitrogen. Tetrahydrofuran (100 mL, degassed with argon) and aqueous sodium carbonate (1.0 M, 30 mL) were added via a septum. The mixture was heated under reflux overnight then poured onto aqueous hydrochloric acid (1 M, 50 mL). The aqueous phase was extracted with dichloromethane (2 x 100 mL), the extracts washed with water (3 x 100 mL), dried over anhydrous MgSO₄. Removal of the solvent under reduced pressure followed by flash column chromatography (eluent: EtOAc : Petroleum ether 1 : 6) afforded the 7-phenylindan-1-one (263, 640 mg, 3.08 mmol, 98 %) as white powder: m.p. (EtOAc / Petroleum ether) = 78 – 79 °C; IR (neat) 1701, 1587, 1466, 1231, 759, 699 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.59 (t, J = 8.0 Hz, 1H, Ar-H), 7.38-7.46 (m, 6H, Ar-H), 7.25-7.27 (m, 1H, Ar-H), 3.16 (t, J = 5.6 Hz, 2H, CH₂-CH₂CO), 2.69 (t, J = 6.0 Hz, 2H, CH₂CO); ¹³C NMR (100 MHz, CDCl₃) δ 205.6, 156.4, 141.5, 138.0, 133.9, 133.1, 129.5, 129.3 (2C), 127.8 (2C), 125.7, 36.9, 25.4, MS (EI) m/z 208 (M); HRMS (EI) m/z calc for C₁₅H₁₂O 208.0888, found: 208.0877.

**General procedure D for the formation of indanol:**

![Indanol structure](R)

Sodium borohydride (3 equiv.) was added to a solution of indane (1 equiv.) in methanol at 0 °C. The mixture was then allowed to warm to ambient temperature and was stirred 1 h. The mixture was washed with water, extracted with dichloromethane and dried over anhydrous MgSO₄.

**7-Methoxyindan-1-ol (266)**

![Methoxyindan structure](OMe)

Following general procedure D with sodium borohydride (3.43 g, 90.70 mmol) and 7-methoxyindan-1-one (259, 4.90 g, 30.20 mmol) afforded the 7-methoxyindan-1-ol (266, 4.40 g, 26.83 mmol, 89 %) as yellow oil: IR (neat) 3417, 1591, 1479, 1262, 1073 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.23 (t, J = 7.6 Hz, 1H, Ar-H), 6.86 (d, J = 7.6 Hz, 1H, Ar-H), 6.71 (d, J = 8 Hz, 1H, Ar-H), 5.48 (t, J = 5.6 Hz, 1H, CH-OH), 3.87 (s, 3H, CH₃), 3.12-3.05 (m, 1H, CH₂-CH₂CHOH), 2.85-2.78 (m, 1H, CH₂-CH₂CHOH), 2.49-2.41 (m,
1H, CH₂-CHOH), 2.07-2.00 (m, 1H, CH₂-CHOH); ¹³C NMR (100 MHz, CDCl₃) δ 156.4, 145.6, 132.2, 130.0, 117.5, 108.0, 74.5, 55.2, 33.9, 30.4; MS (EI) m/z 164 (M); HRMS (EI) m/z calc for C₁₀H₁₂O₂ 164.0837, found: 164.0830.

7-isoPropoxyindan-1-ol (267)

Following general procedure D with sodium borohydride (715 mg, 18.90 mmol) and 7-isopropoxyindan-1-one (260, 1.20 g, 6.31 mmol) afforded the 7-isopropoxyindan-1-ol (267, 1.02 g, 5.31 mmol, 85 %) as yellow oil: IR (thin film) 2976, 1591, 1475, 1262, 1116, 752 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.19 (t, J = 7.8 Hz, 1H, Ar-H), 6.82 (d, J = 7.8 Hz, 1H, Ar-H), 6.70 (d, J = 7.8 Hz, 1H, Ar-H), 5.47 (dd, J = 7.3, 5.4 Hz, 1H, CH-OH), 4.64 (sep., J = 5.8 Hz, 1H, O-CH-(CH₃)₂), 3.05 (dddd, J = 16.1, 13.7, 9.3, 4.9 Hz, 1H, CH₂-CHOH), 2.84-2.76 (m, 1H, CH₂-CHOH), 2.50-2.41 (m, 1H, CH₂-CHOH), 2.05-1.97 (m, 1H, CH₂-CHOH); ¹³C NMR (100 MHz, CDCl₃) δ 154.6, 145.5, 133.1, 129.6, 117.1, 109.9, 74.7, 69.8, 33.6, 30.3, 22.2, 22.1, MS (EI) m/z 192 (M); HRMS (EI) m/z calc for C₁₂H₁₆O₂ 192.1150, found: 192.1146.

7-Methylindan-1-ol (268)

Following general procedure D with sodium borohydride (227 mg, 6.00 mmol) and 7-methylindan-1-one (262, 300 mg, 2.00 mmol) afforded the 7-methylindan-1-ol (268, 270 mg, 1.82 mmol, 91 %) as pale yellow solid: IR (neat) 3268, 2924, 1599, 1464, 1181, 1045, 960, 764 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.18 (t, J = 7.2 Hz, 1H, Ar-H), 7.09 (d, J = 7.2 Hz, 1H, Ar-H), 7.02 (d, J = 7.2 Hz, 1H, Ar-H), 5.32-5.31 (m, 1H, CH-OH), 3.19-3.11 (m, 1H, CH₂-CHOH), 2.86-2.79 (m, 1H, CH₂-CHOH), 2.43 (s, 3H, CH₃), 2.43-2.33 (m, 1H, CH₂-CHOH), 2.08-2.03 (m, 1H, CH₂-CHOH), 1.60 (s, 1H, OH); ¹³C NMR (100 MHz, CDCl₃) δ 144.0, 142.9, 135.2, 128.9, 128.0, 122.4, 75.5, 35.1, 30.1, 18.3; MS (EI) m/z 148 (M); HRMS (EI) m/z calc for C₁₀H₁₂O 148.0888, found: 148.0883.
7-Phenylindan-1-ol (269)

Following general procedure D with sodium borohydride (160 mg, 4.30 mmol) and 7-phenylindan-1-one (263, 300 mg, 1.44 mmol) afforded the 7-phenylindan-1-ol (269, 300 mg, 1.43 mmol, 98%) as white solid: m.p. \((\text{CHCl}_3) = 60 \text{ – } 61 \, ^\circ\text{C}\); IR (neat) 3236, 1592, 1468, 955, 755, 699 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 7.60-7.57 (m, 2H, Ar-H), 7.47-7.43 (m, 2H, Ar-H), 7.39-7.32 (m, 2H, Ar-H), 7.29-7.21 (m, 2H, Ar-H), 5.41 (dd, \(J = 6.4, 3.2 \text{ Hz}\), 1H, CH-OH), 3.25-3.17 (m, 1H, CH\(_2\)-CH\(_3\)CHOH), 2.93-2.85 (m, 1H, CH\(_2\)-CH\(_3\)CHOH), 2.41-2.32 (m, 1H, CH\(_2\)-CHOH), 2.11-2.03 (m, 1H, CH\(_2\)-CHOH), 1.65 (s, 1H, OH); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) δ 144.6, 142.3, 140.4, 139.1, 128.9, 128.6 (2C), 127.6, 127.4, 124.1, 75.1, 35.0, 30.0; MS (El) \(m/z\) 210 (M); HRMS (El) \(m/z\) calc for C\(_{15}\)H\(_{14}\)O 210.1045, found: 210.1035.

General procedure E for the formation of indene:

PPTS (2 equiv.) was added to a solution of indan-1-ol (1 equiv.) in dichloromethane. The reaction was refluxed. After consumption of the starting material, the reaction was cooled to ambient temperature and a concentrated solution of CuSO\(_4\) was added. Extraction with dichloromethane and evaporation of the solvent afforded the corresponding indene.

4-Methyl-1H-indene (274)

Following general procedure E with 4-methylindan-1-ol (268, 1.00 g, 6.76 mmol) and PPTS (3.40 g, 13.46 mmol) afforded indene 274 as pale yellow oil. The crude product was used in the next step without further purification: IR (thin film) 2924, 1599, 1476, 1047, 768 cm\(^{-1}\); \(^1\)H NMR (400 MHz,
CDCl₃ δ 7.33 (d, J = 6.8 Hz, 1H, Ar-H), 7.15-7.09 (m, 2H, Ar-H), 7.03-7.00 (m, 1H, CH-Ar), 6.57-6.55 (m, 1H, CH-CH-Ar), 3.43-3.41 (m, 2H, CH₂-CH), 2.47 (s, 3H, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 143.7, 143.5, 133.5, 130.2, 127.2, 124.6, 121.1, 39.3, 18.6; MS (EI) m/z 130 (M); HRMS (EI) m/z calc for C₁₀H₁₀ 130.0783, found: 130.0779.

4-Phenyl-1H-indene (275)

![4-Phenyl-1H-indene](image)

Amberlyst 15 was gradually added to 4-phenylindan-1-ol (269, 500 mg, 2.38 mmol) in hexane (10 mL). The solution was stirred for 1 h at 0 °C and 2 h at ambient temperature and then filtrated. The solvent was evaporated and indene 275 was obtained as pale yellow solid. The crude product was used in the next step without further purification: IR (thin film) 3059, 1594, 1464, 763, 699 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.33 (d, J = 6.8 Hz, 1H, Ar-H), 7.15-7.09 (m, 2H, Ar-H), 7.03-7.00 (m, 1H, CH-Ar), 6.60-6.59 (m, 1H, CH-CH-Ar), 3.50-3.49 (m, 2H, CH₂-CH); MS (EI) m/z 192 (M); HRMS (EI) m/z calc for C₁₅H₁₂ 192.0939, found: 192.0932.

4-isopropoxy-1H-indene (277)

![4-isopropoxy-1H-indene](image)

Following general procedure E with isopropoxyindan-1-ol (267, 640 mg, 3.33 mmol) and PPTS (1.70 g, 6.66 mmol) afforded indene 277 as yellow oil. The crude product was used in the next step without further purification: IR (thin film) 2977, 1589, 1476, 1264, 1116, 752 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.15-7.19 (m, 2H, Ar-H), 7.05-7.03 (m, 1H, Ar-H), 6.81 (d, J = 7.3 Hz, 1H, CH-Ar), 6.46-6.43 (m, 1H, CH-CH-Ar), 4.58 (sep., J = 5.8 Hz, 1H, O-CH-[CH₃]₂), 3.41 (br, 2H, CH₂-CH), 1.37 (d, J = 5.9 Hz, 6H, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 151.4, 145.9, 135.0, 132.0, 128.6, 125.6, 116.7, 111.8, 70.8, 39.5, 22.3 (2C); MS (EI) m/z 174 (M); HRMS (EI) m/z calc for C₁₆H₁₄O 174.1045, found: 174.1045.
4-Methoxy-1H-indene (270)

Following general procedure E with methoxyindan-1-ol (266, 1.07 g, 6.52 mmol) and PPTS (3.27 g, 13.04 mmol) afforded indene 270 as off white oil. The crude product was used in the next step without further purification: IR (thin film) 1473, 1260, 1057, 747 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.20-7.14 (m, 2H, Ar-H), 7.07-7.05 (m, 1H, Ar-H), 6.81 (d, J = 7.8 Hz, 1H, CH-Ar), 6.48 (d, J = 6.4 Hz, 1H, CH-CH-Ar), 3.91 (s, 3H, O-CH₃), 3.43 (br, 2H, CH₂-CH); ¹³C NMR (100 MHz, CDCl₃) δ 153.1, 145.8, 133.4, 132.3, 128.2, 125.8, 116.7, 108.2, 55.4, 39.5; MS (EI) m/z 147 (M+H).

Catalyst 283

Following literature procedure. NMR of the precursor: ¹H NMR (400 MHz, CDCl₃) δ 13.52 (s, 2H), 8.29 (s, 2H), 7.12-7.21 (m, 10H), 7.04 (d, J = 7.6 Hz, 2H), 6.76 (d, J = 1.5 Hz, 2H), 4.67 (s, 2H), 2.17 (s, 6H), 1.42 (s, 18H).

General procedure F for the conversion of indene to epoxide:

A solution of indene (1 equiv.), NMO (5 equiv.), and catalyst (0.07 eq.) in dry dichloromethane was cooled to -78 °C for 15 min before the addition of solid m-CPBA (2 to 2.5 equiv.). After stirring for 2 to 3 h at -78 °C, 3N NaOH and water were added to the solution followed by celite. After filtration, the organic phase was separated, washed with brine, and dried over anhydrous MgSO₄. The solvent
was evaporated to provide the epoxide.

(1S,2R)-Indene oxide (285)

Following general procedure F with indene (400 mg, 3.40 mmol), NMO (2.02 g, 17.20 mmol), catalyst (117 mg, 0.17 mmol) and solid m-CPBA (1.17 g, 6.80 mmol) gave indene oxide (430 mg, 95%, 96% e.e.): Chiral HPLC (Method C): major (Rt = 22.65 min) : minor (Rt = 23.57 min) 98 : 2; 1H NMR (400 MHz, CDCl3) δ 7.51 (d, J = 7.3 Hz, 1H, Ar-H), 7.30-7.18 (m, 3H, Ar-H), 4.29 (dd, J = 2.8, 0.9 Hz, 1H, CH-CH-CH2), 4.15 (t, J = 2.9 Hz, 1H, CH-CH-CH2), 3.24 (d, J = 18.1 Hz, 1H, CHtransHcis), 3.05 (dd, J = 18.1, 2.9 Hz, 1H, CHtransHcis).

(1S,2R)-Epoxy-7′-methylindane (328)

Following general procedure F with 4-methylindene (274, 6.76 mmol), NMO (4.30 g, 36.40 mmol), catalyst (310 mg, 0.44 mmol) and solid m-CPBA (2.32 g, 13.42 mmol) gave epoxide 328 as brown oil. The crude product was used in the next step without further purification: IR (thin film) 2917, 1721, 1598, 1477, 831, 768 cm−1; 1H NMR (400 MHz, CDCl3) δ 7.16-6.94 (m, 3H, Ar-H), 4.35 (m, 1H, CH-CH-CH2), 4.10 (t, J = 2.9 Hz, 1H, CH-CH-CH2), 3.21 (d, J = 18.1 Hz, 1H, CHtransHcis), 2.98 (dd, J = 18.1, 2.9 Hz, 1H, CHtransHcis), 2.48 (s, 3H, Ar-CH3); 13C NMR (100 MHz, CDCl3) δ 143.4, 139.6, 135.1, 128.5, 127.5, 123.4, 57.6, 57.3, 34.7, 18.3; MS (El) m/z 146 (M); HRMS (El) m/z calc for C10H10O 146.0732, found: 146.0729.

(1S,2R)-Epoxy-7′-phenylindane (288)
Following general procedure F with 4-phenylindene (275, 2.38 mmol), NMO (1.51 g, 12.80 mmol), catalyst (109.4 mg, 0.16 mmol) and solid m-CPBA (821 mg, 4.75 mmol) gave epoxide 288 as brown oil. The crude product was used in the next step without further purification: Chiral HPLC (Method D): major (Rt = 7.37 min) : minor (Rt = 10.56 min) 94 : 6; IR (thin film) 2917, 1714, 1469, 761 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.58 (d, \(J = 7.2\), 2H, Ar-H), 7.48 (t, \(J = 7.3\), 2H, Ar-H), 4.41-4.21 (m, 4H, Ar-H), 4.31 (dd, \(J = 2.8\), 1Hz, 1H, CH-CH-CH\(_3\)), 4.13 (t, \(J = 3\) Hz, 1H, CH-CH-CH\(_3\)), 3.31 (d, \(J = 18\) Hz, 1H, CH\(_{trans}\)H\(_{cis}\)), 3.06 (dd, \(J = 18\) Hz, 3.1 Hz, 1H, CH\(_{trans}\)H\(_{cis}\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 144.4, 142.3, 140.0, 139.5, 128.8 (2C), 128.6 (2C), 127.3, 126.6, 124.9, 124.1, 59.0, 58.3, 34.8; MS (EI) m/z 208 (M); HRMS (EI) m/z calc for C\(_{15}\)H\(_{12}\)O\(_2\) 208.0888, found: 208.0884.

(1S,2R)-Epoxy-7'-isopropoxyindane (329)

Following general procedure F with 4-isopropoxyindene (277, 560 mg, 3.22 mmol), NMO (2.15 g, 18.20 mmol), catalyst (155 mg, 0.22 mmol) and solid m-CPBA (1.16 g, 6.71 mmol) gave epoxide 329 as brown oil. The crude product was used in the next step without further purification: IR (neat) 2977, 2926, 1720, 1591, 1478, 1265, 1112, 735 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.16 (t, \(J = 7.8\) Hz, 1H, Ar-H), 6.80 (d, \(J = 7.3\) Hz, 1H, Ar-H), 6.71 (d, \(J = 8.3\) Hz, 1H, Ar-H), 4.57 (sep, \(J = 5.9\) Hz 1H, CH-CH\(_3\)), 4.48-4.46 (m, 1H, CH-CH-CH\(_3\)), 4.08 (t, \(J = 3.9\) Hz, 1H, CH-CH-CH\(_3\)), 3.19 (d, \(J = 18.1\) Hz, 1H, CH\(_{trans}\)H\(_{cis}\)), 2.95 (dd, \(J = 17.6\), 3.9 Hz, 1H, CH\(_{trans}\)H\(_{cis}\)), 1.37 (d, \(J = 5.9\) Hz, 3H, CH\(_3\)), 1.36 (d, \(J = 5.9\) Hz, 3H, CH\(_3\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 145.8, 130.2, 129.8, 118.2, 111.8, 70.8, 57.4, 56.7, 34.9, 22.2 (2C); MS (Cl) m/z 191 (M+H); HRMS (Cl) m/z calc for C\(_{15}\)H\(_{12}\)O 191.1072, found: 191.1070.

(1S,2R)-Epoxy-7'-methoxyindane (330)

Following general procedure F with 4-methoxyindene (270, 6.52 mmol), NMO (4.01 g, 34.23 mmol), catalyst (0.34 g, 0.48 mmol) and solid m-CPBA (2.38 g, 13.79 mmol) gave epoxide 330 as brown oil.
The crude product was used in the next step without further purification: IR (neat) 1589, 1483, 1264, 1076 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.20 (t, \(J = 7.8\) Hz, 1H, Ar-H), 6.82 (d, \(J = 5.9\) Hz, 1H, Ar-H), 6.71 (d, \(J = 6.8\) Hz, 1H, Ar-H), 4.48-4.47 (m, 1H, CH-CH\(_2\)-CH\(_3\)), 4.10-4.08 (m, 1H, CH-CH\(_2\)-CH\(_3\)), 3.87 (s, 3H, O-C\(_3\)); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 154.5, 145.8, 130.0, 128.8, 118.3, 108.7, 57.4, 56.4, 55.4, 34.9; MS (EI) \(m/z\) 162 (M); HRMS (EI) \(m/z\) calc for C\(_{10}\)H\(_{10}\)O\(_2\) 162.0681, found: 162.0681.

**General procedure G for the conversion of epoxide to azide:**

![Epoxide and Azide Reaction](image)

Epoxide (1 equiv.), NH\(_4\)Cl (2 equiv.), and NaN\(_3\) (2 equiv.) were dissolved in 80% v/v aqueous ethanol. After stirring for 2 h at reflux, the mixture was cooled to ambient temperature and water was added. The aqueous phase was extracted with ethyl acetate and the organic phase was washed with brine and dried over anhydrous MgSO\(_4\). The solvent was evaporated followed by flash chromatography to give the corresponding azide.

**(1R,2R)-1-Azido-7-methyl-2,3-dihydro-1H-inden-2-ol (331)**

![Azido Indene Structure](image)

Following general procedure G with methylindane 328 (6.76 mmol), NH\(_4\)Cl (680 mg, 12.40 mmol), NaN\(_3\) (812 mg, 12.40 mmol). Flash column chromatography on silica gel (eluent: EtOAc : Petroleum ether 1 : 6) afforded azide 331 (702 mg, 3.71 mmol, 55% over 3 steps, 94% e.e.) as yellow oil: \([\alpha]_D = +16^\circ\) (c 0.1, DCM); Chiral HPLC (Method E): major (Rt = 3.81 min) : minor (Rt = 5.69 min) 97 : 3; IR (thin film) 3378, 2920, 2096, 1600, 770 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.23 (t, \(J = 7.8\) Hz, 1H, Ar-H), 7.12-7.07 (m, 2H, Ar-H), 4.67 (br, 1H, CH-N\(_3\)), 4.56-4.54 (m, 1H, CH-OH), 3.37 (dd, \(J = 16.6, 5.9\) Hz, 1H, CH\(_{\text{trans}}\)-H\(_{\text{cis}}\)), 2.84 (dd, \(J = 16.6, 2.4\) Hz, 1H, CH\(_{\text{trans}}\)-H\(_{\text{cis}}\)), 2.41 (s, 3H, CH\(_3\)); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 141.3, 136.1, 129.7, 128.8, 122.9, 77.8, 71.5, 60.4, 40.1, 21.0, 18.7, 14.2; MS (EI) \(m/z\) 189 (M); HRMS (EI) \(m/z\) calc for C\(_{10}\)H\(_{11}\)N\(_3\)O 189.0902, found: 189.0902.
(1R,2R)-1-Azido-7-phenyl-2,3-dihydro-1H-inden-2-ol (332)

Following general procedure G with phenylindane 288 (2.38 mmol), NH₄Cl (213 mg, 3.92 mmol), NaN₃ (255 mg, 3.92 mmol). Flash column chromatography on silica gel (eluent: EtOAc : Petroleum ether 1 : 6) afforded azide 332 (350mg, 1.39 mmol, 58% over 3 steps) as yellow oil: [α]D = +32.7 ° (c 1.15, DCM); IR (thin film) 3351, 2920, 2097, 1592, 1468, 759 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.47-7.38 (m, 6H, Ar-H), 7.31-7.27 (m, 2H, Ar-H), 4.79 (br, 1H, CH-N₃), 4.52-4.53 (m, 1H, CH-OH), 3.43 (dd, J = 16.6, 4.9 Hz, 1H, C₆H₃trans-Hcis), 2.93 (dd, J = 16.6, 2.4 Hz, 1H, C₆H₃trans-Hcis); ¹³C NMR (100 MHz, CDCl₃) δ 141.8, 140.9, 139.8, 135.5, 129.8, 128.6 (2C), 128.5 (3C), 127.5, 124.6, 77.9, 71.2, 39.9; MS (EI) m/z 251 (M); HRMS (EI) m/z calc for C₁₅H₁₄N₃O₂ 251.1059, found: 251.1059.

(1R,2R)-1-Azido-7-isopropoxy-2,3-dihydro-1H-inden-2-ol (333)

Following general procedure G with isopropoxyindane 329 (3.22 mmol), NH₄Cl (325 mg, 6.00 mmol), NaN₃ (390 mg, 6.00 mmol). Flash column chromatography on silica gel (eluent: EtOAc : Petroleum ether 1 : 6) azide 333 (280 mg, 1.20 mmol, 40% over 3 steps, 96 % e.e.) as yellow oil: [α]D = -22.6 ° (c 0.23, DCM); Chiral HPLC (Method E): major (Rt = 4.56 min) : minor (Rt = 6.81 min) 98 : 2; IR (neat) 3342, 2977, 2101, 1477, 1267, 1115, 770 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.25 (t, J = 7.3 Hz, 1H, Ar-H), 6.82 (d, J = 7.3 Hz, 1H, Ar-H), 6.76 (d, J = 8.3 Hz, 1H, Ar-H), 4.90 (d, J = 2.4 Hz, 1H, CH-N₃), 4.64 (sep, J = 5.8 Hz, 1H, CH-CH₃), 4.40-4.37 (m, 1H, CH-OH), 3.32 (dd, J = 16.6, 4.9 Hz, 1H, C₆H₃trans-Hcis), 2.79 (dd, J = 15.6, 3.4 Hz, 1H, C₆H₃trans-Hcis), 1.39 (d, J = 5.8 Hz, 1H, CH₃), 1.38 (d, J = 5.8 Hz, 1H, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 155.8, 143.3, 131.0, 126.6, 117.1, 110.5, 78.0, 70.7, 69.8, 39.9, 22.2, 21.7; MS (Cl) m/z 251 (M+NH₄⁺); HRMS (Cl) m/z calc for C₁₂H₁₈N₂O₂ 251.1508, found: 251.1513.
Following general procedure G with methoxylindane 330 (6.52 mmol), NH₄Cl (0.69 g, 13.00 mmol), NaN₃ (0.84 g, 13.00 mmol). Flash column chromatography on silica gel (eluent: EtOAc : Petroleum ether 1 : 6) afforded azide 334 (0.55 g, 2.68 mmol, 42 % over 3 steps, 96 % e.e.) as yellow oil: [α]D = - 9.8 ° (c 0.68, DCM); Chiral HPLC (Method E): major (Rt = 7.03 min) : minor (Rt = 8.89 min) 98 : 2; IR (neat) 3347, 2929, 2099, 1592, 1483, 1267, 770 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.30 (t, J = 8.3, 1H, Ar-H), 6.88 (d, J = 7.8 Hz, 1H, Ar-H), 6.79 (d, J = 8.3 Hz, 1H, Ar-H), 4.89 (d, J = 2.4 Hz, 1H, CH-N₃), 4.44-4.41 (m, 1H, CH-OH), 3.87 (s, 3H, O-CH₃), 3.34 (dd, J = 16.6, 6.3 Hz, 1H, CHtrans-Hcis), 2.82 (dd, J = 17.1, 2.9 Hz, 1H, CHtrans-Hcis); ¹³C NMR (100 MHz, CDCl₃) δ 157.4, 143.3, 131.2, 125.5, 117.6, 109.0, 78.0, 70.5, 55.3, 40.0; MS (EI) m/z calc for C₁₀H₁¹N₃O₂ 205.0851, found: 205.0851.

General procedure H for the reduction of the azide:

Azide derivatives were dissolved in methanol and Pd/C added (10% w). The mixture was stirred 20 min under hydrogen atmosphere. Then the mixture was filtrated through celite® and solvent evaporated to give the corresponding amino-indanol.

Following general procedure H with azide 331 (670 mg, 3.54 mmol), Pd/C (67 mg) afforded amino-indanol 335 as pale yellow oil. The crude product was used in the next step without further purification: IR (thin film) 3351, 2916, 1597, 1465, 1042, 768 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.15 (t, J = 7.3 Hz, 1H, Ar-H), 7.08-7.07 (m, 1H, Ar-H), 7.01 (d, J = 7.3 Hz, 1H, Ar-H), 4.24-4.22 (m, 2H, CH-
OH, CH-NH$_2$), 3.38 (dd, $J = 16.6, 5.8$ Hz, 1H, CH$_{trans}$H$_{cis}$), 2.77 (dd, $J = 16.6, 2.4$ Hz, 1H, CH$_{trans}$H$_{cis}$), 2.40 (s, 3H, CH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 141.9, 140.4, 134.9, 128.6, 128.4, 122.9, 80.6, 64.1, 39.3, 18.5; MS (ESI) m/z 147 (M-NH$_2$); HRMS (ESI) m/z calc for C$_{10}$H$_{11}$O 147.0810, found: 147.0813.

(1R,2R)-1-Amino-7-phenyl-2,3-dihydro-1H-inden-2-ol (336)

Following general procedure H with azide 332 (340 mg, 1.35 mmol), Pd/C (34 mg) afforded amino- indanol 336 as dark oil (96 % e.e.). The crude product was used in the next step without further purification: Chiral HPLC (Method E): major (Rt = 31.11 min) : minor (Rt = 36.46 min) 98 : 2; IR (thin film) 2259, 1590, 1467, 1074, 760 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.44-7.43 (m, 4H, Ar-H), 7.39-7.35 (m, 1H, Ar-H), 7.32-7.29 (m, 1H, Ar-H), 7.18 (dd, $J = 15.1, 7.3$ Hz, 2H, Ar-H), 4.43 (d, $J = 4.4$ Hz, 1H, CH$_{trans}$H$_{cis}$), 4.20-4.15 (m, 1H, CH$_{trans}$H$_{cis}$), 3.29-3.23 (m, 1H, CH$_{trans}$H$_{cis}$), 2.82-2.78 (m, 2H, CH$_3$), 1.35 (d, $J = 5.8$ Hz, 3H, CH$_3$), 1.34 (d, $J = 5.8$ Hz, 3H, CH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 141.9, 140.5, 140.2, 139.0, 128.8 (2C), 128.6, 128.5 (2C), 128.2, 127.5, 124.3, 80.7, 63.9, 38.3; MS (ESI) m/z 250 (M+H$_2$+Na); HRMS (ESI) m/z calc for C$_{15}$H$_{17}$NONa 250.1208, found: 250.1213.

(1R,2R)-1-Amino-7-isopropoxy-2,3-dihydro-1H-inden-2-ol (337)

Following general procedure H with azide 333 (270 mg, 1.16 mmol), Pd/C (27 mg) afforded amino- indanol 337 as dark oil. The crude product was used in the next step without further purification: IR (neat) 2937, 2838, 1714, 1591, 1482, 1265, 1068, 713 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.16 (t, $J = 8.3$ Hz, 1H, Ar-H), 6.77 (d, $J = 7.3$ Hz, 1H, Ar-H), 6.70 (d, $J = 7.3$ Hz, 1H, Ar-H), 4.59 (sep., $J = 5.8$ Hz, 1H, CH$_{trans}$H$_{cis}$), 4.34-4.33 (m, 1H, CH$_{trans}$H$_{cis}$), 3.29-3.23 (m, 1H, CH$_{trans}$H$_{cis}$), 2.82-2.78 (m, 2H, CH$_3$), 1.35 (d, $J = 5.8$ Hz, 3H, CH$_3$), 1.34 (d, $J = 5.8$ Hz, 3H, CH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 155.0, 141.7, 129.4, 117.2, 110.7, 80.4, 77.7, 69.8, 65.3, 38.9, 22.2 (2C); MS (Cl) m/z 208 (M+H); HRMS (Cl) m/z calc for C$_{15}$H$_{18}$NO, 208.1338, found: 208.1338.
(1R,2R)-1-Amino-7-methoxy-2,3-dihydro-1H-inden-2-ol (338)

Following general procedure H with azide 334 (1.45 g, 7.00 mmol), Pd/C (145 mg) afforded amino- indanol 338 as pale brown oil. The crude product was used in the next step without further purification: IR (neat) 3343, 2924, 1588, 1480, 1262, 1071, 766 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.20 (t, J = 7.3 Hz, 1H, Ar-H), 6.81 (d, J = 7.8 Hz, 1H, Ar-H), 6.71 (d, J = 8.3 Hz, 1H, Ar-H), 4.34-4.31 (m, 1H, CH-NH₂), 3.83 (s, 3H, O-CH₃), 3.28 (dd, J = 16.1, 5.9 Hz, 1H, CH-OH), 2.84-2.78 (m, 3H, CH₂+OH); ¹³C NMR (100 MHz, CDCl₃) δ 156.8, 141.6, 129.5, 117.5, 108.7, 80.6, 70.0, 63.4, 55.0, 39.0; MS (ESI) m/z 163 (M-NH₂); HRMS (ESI) m/z calc for C₁₀H₁₁O₂ 163.0759, found: 163.0756.

General procedure I for the formation of oxoacetate:

Ethyl 2-((1R,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-ylamino)-2-oxoacetate

Following general procedure I with commercial trans-amino-indanol (100 mg, 0.67 mmol), diethyl oxalate (0.09 mL, 0.70 mmol) and acetic acid (0.004 mL, 0.007 mmol) afforded the desired product as white solid (160 mg, 0.64 mmol, 96 %): m.p. (CH₂Cl₂) = 84 – 86 °C; IR (neat) 3464, 3296, 1756, 1683, 1201, 1074, 743 cm⁻¹; ¹H NMR (400 MHz, d-DMSO) δ 9.22 (d, J = 8.3 Hz, 1H, Ar-H), 7.22-7.16
Experimental

(m, 3H, Ar-H), 7.08-7.05 (m, 1H, Ar-H), 5.37-5.35 (m, 1H, OH), 5.09-5.05 (m, 1H, CH-NH), 4.45-4.38 (m, 1H, CH-OH), 4.26 (q, J = 6.8 Hz, 2H CH₂-CH₃), 3.14 (dd, J = 15.1, 7.3 Hz, 1H, CH₉⁻transH₁₁), 2.71 (dd, J = 15.6, 7.3 Hz, 1H, CH₉⁻transH₁₁), 1.29 (t, J = 6.8 Hz, 3H, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 160.8, 157.6, 140.7, 139.7, 127.7, 126.6 124.6, 123.5, 76.8, 61.9, 61.3, 38.6, 13.7.

**Ethyl 2-((1R,2R)-2-hydroxy-7-methyl-2,3-dihydro-1H-inden-1-ylamino)-2-oxoacetate (346)**

Following general procedure I with trans-amino-indanol 335 (9.80 mmol), diethyl oxalate (2.00 mL, 15.00 mmol) and acetic acid (0.05 mL, 0.90 mmol) afforded the desired product 346 as brown oil (2.00 g, 7.60 mmol, 77 % over 2 steps): IR (neat) 3262, 1653, 1512, 1209, 1065, 765 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.24 (t, J = 7.3 Hz, 1H, Ar-H), 7.12 (d, J = 7.3 Hz, 1H, Ar-H), 7.07 (d, J = 7.3 Hz, 1H, Ar-H), 5.22 (dd, J = 7.3, 2.9 Hz, 1H, CH-NH), 4.53-4.48 (m, 1H, CH-OH), 4.37 (q, J = 6.3 Hz, 2H CH₂-CH₃), 3.38 (dd, J = 17.1, 6.3 Hz, 1H, CH₉⁻transH₁₁), 2.98 (d, J = 2.9 Hz, 1H, OH); 2.91 (dd, J = 17.1, 3.4 Hz, 1H, CH₉⁻transH₁₁), 2.30 (s, 3H, CH₃), 1.40 (t, J = 7.3 Hz, 3H, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 160.2, 157.1, 142.1, 136.4, 135.4, 129.6, 128.9, 123.0, 78.9, 63.8, 63.5, 39.4, 18.5, 13.9; MS (ESI) m/z 264 (M+H); HRMS (ESI) m/z calc for C₁₄H₁₈NO₄ 264.1236, found: 264.1231.

**Ethyl 2-((1R,2R)-2-hydroxy-7-phenyl-2,3-dihydro-1H-inden-1-ylamino)-2-oxoacetate (347)**

Following general procedure I with trans-amino-indanol 336 (1.50 mmol), diethyl oxalate (0.20 mL, 1.50 mmol) and acetic acid (0.02 mL, 0.35 mmol) afforded the desired product 347 as white solid (340 mg, 1.04 mmol, 70% over 2 steps): m.p. (CH₂Cl₂) = 70 – 72 °C; IR (neat) 3279, 1663, 1509, 1025, 758, 700 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.45-7.32 (m, 6H, Ar-H), 7.27-7.23 (m, 2H, Ar-H), 5.42 (t, J = 5.9 Hz, 1H, CH-NH), 4.53-4.48 (m, 1H, CH-OH), 4.16 (q, J = 7.3 Hz, 2H, CH₂-CH₃), 3.40 (dd, J = 15.6, 7.8 Hz, 1H, CH₉⁻transH₁₁), 3.07 (dd, J = 16.6, 7.8 Hz, 1H, CH₉⁻transH₁₁), 1.26 (t, J = 7.3 Hz, 3H, CH₃); ¹³C NMR
(100 MHz, CDCl$_3$) $\delta$ 159.3, 157.6, 151.7, 141.7, 138.8, 138.6, 134.7, 129.5, 128.8, 128.7, 128.3 (2C), 127.9, 124.5, 80.7, 64.7, 63.2, 38.6, 13.9.

**Ethyl 2-((1R,2R)-2-hydroxy-7-methoxy-2,3-dihydro-1H-inden-1-ylamino)-2-oxoacetate (348)**

Following general procedure I with *trans*-amino-indanol 338 (3.50 mmol), diethyl oxalate (0.32 mL, 3.50 mmol) and acetic acid (0.016 mL, 0.30 mmol) afforded the desired product as white solid (950 mg, 3.40 mmol, 95 % over 2 steps): m.p. (CH$_2$Cl$_2$) = 56 – 58 °C; IR (neat) 3347, 1678, 1263, 1232, 1077 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.30 (t, $J$ = 7.8 Hz, 2 H, Ar-$H$), 6.89 (d, $J$ = 7.8 Hz, 1 H, Ar-$H$), 6.79 (d, $J$ = 8.3 Hz, 1 H, Ar-$H$), 5.05 (dd, $J$ = 3.4, 2.4 Hz, 1 H, CH-NH), 4.59-4.64 (m, 1 H, CH-OH), 4.41 (q, $J$ = 6.8 Hz, 2 H, O-CH$_2$-CH$_3$), 3.93 (s, 3 H, O-CH$_3$), 3.35 (dd, $J$ = 8.3, 7.8 Hz, 1 H, CH$_2$-CH-OH), 3.01 (dd, $J$ = 8.8, 8.3 Hz, 1 H, CH$_3$-CH-OH), 1.45 (t, $J$ = 6.8 Hz, 3 H, O-CH$_3$-CH$_2$); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 160.3, 158.2, 156.0, 142.4, 130.6, 117.9, 108.9, 80.0, 65.0, 63.4, 55.3, 38.4, 14.0; MS (ESI) $m/z$ 280 (M+H); HRMS (ESI) $m/z$ calc for C$_{14}$H$_{18}$NO$_5$ 280.1185, found: 280.1188

**General procedure J for the formation of oxalamide:**

Oxoacetate (1 equiv.) was dissolved in tetrahydrofuran. Amino-indanol (1 equiv.) and acetic acid (0.1 equiv.) were added and the reaction was refluxed for 16 h. The solvent was evaporated to afford the corresponding product.
General procedure K for the formation of oxalamide:

Amino-indanol (2 equiv.) was dissolved in tetrahydrofuran. Diethyl oxalate (1 equiv.) and acetic acid (0.1 equiv.) were added and the reaction was refluxed for 16 h. The solvent was evaporated to afford the corresponding product.

\[ \text{N1,N2-bis((1R,2R)-2-Hydroxy-2,3-dihydro-1H-inden-1-yl)oxalamide} \]

Following general procedure K with (1R, 2R)-(-)-trans-1-amino-2-indanol (1.00 g, 6.70 mmol), tetrahydrofuran (20 mL), diethyl oxalate (0.44 mL, 3.35 mmol) and acetic acid (0.040 mL, 0.70 mmol) afforded the desired product as white solid: \(^1\text{H NMR (400 MHz, d-DMSO)} \delta 9.10 (d, J = 8.8 Hz, 2H), 7.21-7.16 (m, 6H, Ar-H), 7.10-7.05 (m, 2H, Ar-H), 5.09 (t, J = 7.8 Hz, 2H, CH-NH), 4.53-4.48 (m, 2H, CH-OH), 3.16 (dd, J = 15.1, 7.3 Hz, 2H, CH\(_2\)), 2.72 (dd, J = 15.1, 7.8 Hz, 2H, CH\(_2\)); \(^13\text{C NMR (100 MHz, d-DMSO)} \delta 160.5, 141.1, 139.7, 127.6, 126.5, 124.6, 123.5, 76.8, 61.3, 25.0; MS (ESI) m/z 353 (M+H); HRMS (ESI) m/z calc for C\(_{20}\)H\(_{21}\)N\(_2\)O\(_4\) 353.1501, found: 353.1497.

\[ \text{N1,N2-bis((1R,2R)-2-Hydroxy-7-methyl-2,3-dihydro-1H-inden-1-yl)oxalamide} \]

Following general procedure K with trans-amino-indanol 335 (2.50 mmol), diethyl oxalate (0.16 mL, 1.75 mmol) and acetic acid (0.016 mL, 0.30 mmol) afforded the desired product as white solid: m.p. (CH\(_2\)Cl\(_2\)) = 276 – 278 °C; IR (neat) = 3262, 1653, 1505, 1070, 765 cm\(^{-1}\); \(^1\text{H NMR (400 MHz, d-DMSO)} \delta \]
Experimental

9.93 (d, $J = 9.8$ Hz, 2H), 7.13 (t, $J = 7.3$ Hz, 2H, Ar-H), 7.03 (d, $J = 7.3$ Hz, 2H, Ar-H), 6.96 (d, $J = 7.8$ Hz, 2H, Ar-H), 5.24 (br, 2H, OH), 5.15 (dd, $J = 9.3$, 3.9 Hz, 2H, CH-NH), 4.34-4.30 (m, 2H, CH-OH), 3.30 (dd, $J = 16.1$, 6.8 Hz, 2H, CH$_{\text{trans}}$H$_{\text{cis}}$), 2.64 (dd, $J = 16.1$, 4.9 Hz, 2H, CH$_{\text{trans}}$H$_{\text{cis}}$), 2.10 (s, 6H, CH$_3$); $^{13}$C NMR (100 MHz, d$_2$-DMSO) $\delta$ 159.5, 141.8, 139.0, 134.3, 127.9, 122.2, 76.8, 61.1, 25.0, 17.7; Anal. Calc for C$_{22}$H$_{24}$N$_2$O$_4$: C, 69.46; H, 6.36; N, 7.36; Found: C, 69.50; H, 6.43; N, 7.37.

**N1,N2-bis((1R,2R)-2-Hydroxy-7-phenyl-2,3-dihydro-1H-inden-1-yl)oxalamide**

Following general procedure K with trans-amino-indanol 336 (3.00 mmol), diethyl oxalate (0.20 mL, 1.50 mmol) and acetic acid (0.020 mL, 0.35 mmol) afforded the desired product as white solid: $^1$H NMR (400 MHz, d$_2$-DMSO) $\delta$ 7.42-7.32 (m, 12H, Ar-H), 7.22 (t, $J = 6.8$ Hz, 4H, Ar-H), 7.10 (d, $J = 5.8$ Hz, 2H, Ar-H), 5.20 (t, $J = 5.4$ Hz, 2H, CH-NH), 4.38-4.33 (m, 2H, CH-OH), 3.32 (dd, $J = 15.6$, 7.3 Hz, 2H, CH$_{\text{trans}}$H$_{\text{cis}}$), 2.97 (dd, $J = 16.1$, 6.4 Hz, 2H, CH$_{\text{trans}}$H$_{\text{cis}}$), $^{13}$C NMR (100 MHz, d$_2$-DMSO) $\delta$ 159.4, 141.7, 139.2, 138.8, 135.0, 129.4, 128.7 (4C), 128.3 (4C), 127.8, 124.4, 80.0, 63.8, 38.6.

**N1,N2-bis((1R,2R)-2-Hydroxy-7-methoxy-2,3-dihydro-1H-inden-1-yl)oxalamide (349)**

Following general procedure J with trans-amino-indanol 338 (2.94 mmol), oxoacetate 348 (645 mg, 2.45 mmol) and acetic acid (25µl, 0.44 mmol) afforded the desired product 349 as white solid (826 mg, 2.00 mmol, 82%): m.p. (CH$_2$Cl$_2$) = 210 – 214 °C; IR (neat) = 3447, 3278, 1666, 1522, 1264, 1072, 764 cm$^{-1}$; $^1$H NMR (400 MHz, d$_2$-DMSO) $\delta$ 8.49 (d, $J = 9.3$ Hz, 2H), 7.23 (t, $J = 7.8$ Hz, 2H, Ar-H), 6.82 (d, $J = 8.3$ Hz, 2H, Ar-H), 6.81 (d, $J = 8.3$ Hz, 2H, Ar-H), 5.21 (d, $J = 4.9$ Hz, 2H, OH), 5.09 (dd, $J = 8.8$, 3.4 Hz, 2H, CH-NH), 4.28-4.24 (m, 2H, CH-OH), 3.71 (s, 6H, O-CH$_3$), 3.28 (dd, $J = 16.1$, 5.9 Hz, 2H, CH$_{\text{trans}}$H$_{\text{cis}}$), 2.63 (dd, $J = 15.6$, 4.4 Hz, 2H, CH$_{\text{trans}}$H$_{\text{cis}}$), $^{13}$C NMR (100 MHz, d$_2$-DMSO) $\delta$ 159.4, 156.5,
144.0, 129.6, 127.2, 117.0, 108.9, 76.9, 59.9, 55.1, 39.8; MS (ESI) m/z 413 (M+H); HRMS (ESI) m/z calc for C$_{22}$H$_{25}$N$_{2}$O$_{6}$ 413.1713, found: 413.1699

**General procedure L for the chlorination of the oxalamide:**

The alcohol (1 equiv.) was partially dissolved in toluene. Thionyl chloride (5 equiv.) was added and the reaction was refluxed for 16 h. All the volatile were removed under reduce pressure to afford the corresponding product.

**N1,N2-bis((1R,2R)-2-Chloro-2,3-dihydro-1H-inden-1-yl)oxalamide**

Following general procedure L with alcohol (3.35 mmol) and thionyl chloride (1.24 mL, 17.0 mmol) afforded the desired product as white solid: $^1$H NMR (400 MHz, d-DMSO) δ 9.47 (d, $J = 9.3$ Hz, 2H), 7.29-7.28 (m, 6H, Ar-H), 7.19-7.16 (m, 2H, Ar-H), 5.44 (t, $J = 8.8$ Hz, 2H, CH-NH), 4.77 (q, $J = 7.8$ Hz, 2H, CH-Cl), 3.55 (dd, $J = 15.1$, 7.3 Hz, 2H, CH$_{trans}$-H$_{cis}$), 3.12 (dd, $J = 15.1$, 7.8 Hz, 2H, CH$_{trans}$-H$_{cis}$); $^{13}$C NMR (100 MHz, d-DMSO) δ 160.2, 157.3, 140.0, 139.1, 128.2, 127.2, 124.4, 123.3, 62.1, 61.1.

**N1,N2-bis((1R,2R)-2-Chloro-7-methyl-2,3-dihydro-1H-inden-1-yl)oxalamide**

Following general procedure L with alcohol (1.70 mmol) and thionyl chloride (0.62 mL, 8.50 mmol) afforded the desired product as white solid: $^1$H NMR (400 MHz, d-DMSO) δ 9.36-9.30 (m, 2H), 7.22-
7.19 (m, 2H, Ar-H), 7.12-7.10 (m, 2H, Ar-H), 7.06-7.04 (m, 2H, Ar-H), 5.48-5.42 (m, 2H, CH-NH), 4.65 (br, 2H, CH-Cl), 3.75-3.69 (m, 2H, CH\textsubscript{trans}H\textsubscript{cis}), 3.05-3.00 (m, 2H, CH\textsubscript{trans}H\textsubscript{cis}), 2.12 (s, 6H, CH\textsubscript{3}).

\textit{N1,N2-bis((1R,2R)-2-Chloro-7-phenyl-2,3-dihydro-1H-inden-1-yl)oxalamide}

Following general procedure L with alcohol (0.47 mmol) and thionyl chloride (0.17 mL, 2.35 mmol) afforded the desired product as white solid: \textsuperscript{1}H NMR (400 MHz, d\textsubscript{-}DMSO) \delta 7.40 (t, J = 7.8 Hz, 2H, Ar-H), 7.32-7.15 (m, 16H, Ar-H), 7.03 (d, J = 7.8 Hz, 2H, Ar-H), 5.42 (dd, J = 7.8, 3.9 Hz, 2H, CH-NH), 4.41-4.38 (m, 2H, CH-Cl), 3.59 (dd, J = 16.6, 6.3 Hz, 2H, CH\textsubscript{trans}H\textsubscript{cis}), 3.21 (dd, J = 16.6, 4.4 Hz, 2H, CH\textsubscript{trans}H\textsubscript{cis}).

\textit{General procedure M for the formation of the oxazole:}

The chloride (1 equiv.) was dissolved in tetrahydrofuran and a solution of NaOH (3.75 equiv.) in ethanol was added. The mixture was refluxed for 3 h and the solvent was evaporated under reduce pressure. Flash chromatography afforded the corresponding oxazole compound.

\textit{General procedure N for the formation of the oxazole:}

The alcohol (1 equiv.) was partially dissolved in dichloromethane and cooled to 0 °C. Then a solution of deoxofluor (50 % in tetrahydrofuran, 1.2 equiv.) was added. The mixture was warmed to ambient
temperature for 1 h and the solvent was evaporated under reduce pressure. Flash chromatography afforded the corresponding oxazole compound.

(3aR,3′aS,8aS,8′aS)-8,8a,8′,8′a-Tetrahydro-3aH,3′aH-2,2′-biinden[1,2-d]oxazole (353)

Following general procedure M with chloride (3.35 mmol) and NaOH (500 mg, 12.5 mmol) afforded oxazole 353 (900 mg, 2.85 mmol, 85 % over 3 steps) as light brown solid: m.p. \((\text{CH}_2\text{Cl}_2) = 178 - 182 ^\circ\text{C}\); \([\alpha]_D = +254.8^\circ\) (c 0.39, DCM); IR (neat) = 2923, 1612, 1121, 981, 747 cm\(^{-1}\); \(^1\)H NMR (400 MHz, \text{d-DMSO}) \(\delta 7.50 - 7.48\) (m, 2H, Ar-\(H\)), \(7.24 - 7.21\) (m, 6H, Ar-\(H\)), \(5.72\) (d, \(J = 8.0\) Hz, 2H, CH-\(N\)), \(5.49 - 5.45\) (m, 2H, CH-\(O\)), \(3.43\) (dd, \(J = 18.0, 6.4\) Hz, 2H, \(\text{CH}_{\text{trans}}\text{H}_{\text{cis}}\)), \(3.35\) (dd, \(J = 17.6, 1.9\) Hz, 2H, \(\text{CH}_{\text{trans}}\text{H}_{\text{cis}}\)); \(^{13}\)C NMR (100 MHz, \text{d-DMSO}) \(\delta 155.1, 140.4, 139.5, 128.8, 127.5, 125.7, 125.3, 84.5, 77.2, 77.1, 39.4\); MS (ESI) \(m/z 317\) (M+H); HRMS (ESI) \(m/z\) calc for C\(_{20}\)H\(_{17}\)N\(_2\)O\(_2\) 317.1290, found: 317.1292.

(3aR,3′aR,8aS,8′aS)-4,4′-Dimethyl-8,8a,8′,8′a-tetrahydro-3aH,3′aH-2,2′-biinden[1,2-d]oxazole (341)

Following general procedure M with chloride (1.75 mmol) and NaOH (256 mg, 6.40 mmol) afforded oxazole 341 (350 mg, 1.02 mmol, 58 % over 4 steps).

Following general procedure N with alcohol (280 mg, 0.73 mmol) and deoxofluor (0.39 mL, 0.87 mmol) afforded oxazole 341 (235 mg, 0.68 mmol, 94%) as light brown solid: m.p. \((\text{CH}_2\text{Cl}_2) = 179 - 181 ^\circ\text{C}\); \([\alpha]_D = +291.0^\circ\) (c 0.10, MeOH); IR (neat) = 3258, 1652, 1511, 1110, 764 cm\(^{-1}\); \(^1\)H NMR (400 MHz, \text{d-DMSO}) \(\delta 7.15\) (t, \(J = 7.8\) Hz, 2H, Ar-\(H\)), \(7.04 - 7.01\) (m, 4H, Ar-\(H\)), \(5.75\) (d, \(J = 8.3\) Hz, 2H, CH-\(N\)), \(5.48 - 5.44\) (m, 2H, CH-\(O\)), \(3.44 - 3.32\) (m, 4H, CH\(_2\)), \(2.38\) (s, 6H, CH\(_3\)); \(^{13}\)C NMR (100 MHz, \text{d-DMSO}) \(\delta 155.0, 139.6, 139.1, 136.0, 129.0, 128.4, 122.4, 83.9, 76.8, 39.6, 19.0\); MS (ESI) \(m/z 345\) (M+H); HRMS (ESI) \(m/z\) calc for C\(_{22}\)H\(_{21}\)N\(_2\)O\(_2\) 345.1603, found: 345.1601.
(3aR,3'aR,8aS,8'aS)-4,4'-Diphenyl-8,8a,8',8'a-tetrahydro-3aH,3'aH-2,2'-biindeno[1,2-d]oxazole (342)

Following general procedure M with chloride (0.40 mmol) and NaOH (60 mg, 1.50 mmol) afforded oxazole 342 as light brown solid (80 mg, 0.17 mmol, 42% over 4 steps): m.p. (CH₂Cl₂) = 182 – 184 °C; [α]₀ = +680.0 º (c 1.02, DCM); IR (neat) = 3055, 1641, 1108, 757, 700 cm⁻¹; ¹H NMR (400 MHz, d-DMSO) δ 7.78 (d, J = 6.8 Hz, 2H, Ar-H), 7.46 (t, J = 6.8 Hz, 4H, Ar-H), 7.38-7.32 (m, 4H, Ar-H), 7.27 (d, J = 6.8 Hz, 2H, Ar-H), 7.20 (d, J = 6.8 Hz, 2H, Ar-H), 5.68 (d, J = 8.3 Hz, 2H, CH-N), 5.47 (dt, J = 7.8, 2.9 Hz, 2H, CH-O), 3.48 (dd, J = 17.1, 7.3 Hz, 2H, CHtrans(CHαα)), 3.36 (dd, J = 18.1, 2.9 Hz, 2H, CHtrans(CHαα)); ¹³C NMR (100 MHz, d-DMSO) δ 154.2, 140.8, 140.5, 140.2, 137.8, 129.3 (6C), 128.5, 128.3 (4C), 127.3, 124.0, 83.2, 76.8 40.3; MS (ESI) m/z 469 (M+H); HRMS (ESI) m/z calc for C₃₂H₂₅N₂O₂ 469.1916, found: 469.1906.

(3aR,3'aR,8aS,8'aS)-4,4'-Dimethoxy-8,8a,8',8'a-tetrahydro-3aH,3'aH-2,2'-biindeno[1,2-d]oxazole (351)

Following general procedure N with alcohol (826 mg, 2.00 mmol) and deoxofluor (0.51 mL, 2.40 mmol) afforded oxazole 351 (360 mg, 0.96 mmol, 48%) as light brown solid: m.p. (CH₂Cl₂) = 195 – 200 °C; IR (neat) = 2924, 1483, 1269, 1121 cm⁻¹, ¹H NMR (400 MHz, CDCl₃) δ 7.19-7.24 (m, 2 H, Ar-H), 6.79 (dd, J = 7.8, 7.3 Hz, 2 H, Ar-H), 6.70 (t, J = 8.3 Hz, 2 H, Ar-H), 5.79 (t, J = 7.8 Hz, CH-N), 5.39-5.45 (m, 2 H, CH-O), 3.87 (s, 3 H, O-CH₃), 3.85 (s, 3 H, O-CH₃), 3.34-3.39 (m, 4 H, CH₂); ¹³C NMR (100 MHz, CDCl₃) δ 156.81, 154.99, 141.76, 130.49, 128.18, 128.11, 116.95, 108.74, 83.64, 75.41, 55.29, 40.13, 40.02; MS (ESI) m/z 377 (M+H); HRMS (ESI) m/z calc for C₂₁H₁₅N₂O₄ 377.1501, found: 377.1492.
General procedure O for the formation of the imidazolium salt:

Chloromethyl ethylether (1.1 equiv.) and silver triflate (1.1 equiv.) were added to a solution of oxazole (1 equiv.) in dichloromethane. The mixture was stirred 2 h at ambient temperature in the dark. The supernatant was collected and the solvent evaporated. The crude was dissolved in acetone and NaI (10 equiv.) was added. After 2 h at ambient temperature, the solvent was evaporated and a column chromatography afforded the desired imidazolium salt.

Imidazolium salt (352)

Chloromethyl pivalate (0.13 mL, 0.96 mmol) was added to a mixture of silver triflate (246 mg, 0.84 mmol) in degassed and dry over molecular sieves CH₂Cl₂ (3 mL). The mixture was stirred 1h at ambient temperature in the dark. Then 2 mL of the mixture was transferred to a solution of diimine (60 mg, 0.19 mmol) in degassed and dry CH₂Cl₂ (1 mL). The mixture reacted in microwave at 90 °C for 30 min. Another 1 mL of the solution was transferred to the solution and the mixture reacted 30 more minutes at 90 °C. Removal of the solvent under reduced pressure followed by flash column chromatography on silica gel afforded the imidazolium salt 15 (20 mg, 22%) as a pale yellow oil: ¹H NMR (400 MHz, CDCl₃) δ 9.51 (s, 1H, N-C₂H-N), 7.84 (d, J = 7.8 Hz, 2H, Ar-H), 7.40-7.28 (m, 6H, Ar-H), 6.32 (d, J = 6.3 Hz, 2H, CH-N), 6.10-6.07 (m, 2H, CH-O), 3.56-3.45 (m, 4H, CH₂); ¹³C NMR (400 MHz, d-DMSO) δ 139.6, 134.8, 130.8, 129.0, 126.1, 125.2, 124.8, 114.4, 95.1, 66.9, 38.3; MS (ESI+) m/z 329 (M+); HRMS (ESI+) m/z calc for C₂₁H₁₇N₂O₃ 329.1290, found: 329.1280; MS (ESI-) m/z 149 (M-); HRMS (ESI-) m/z calc for CF₃O₂S 148.9520, found: 148.9527.
**Imidazolium salt (355)**

![Imidazolium salt structure](image)

Following general procedure H with oxazole 353 (220 mg, 0.69 mmol), chloromethyl ethylether (0.076 mL, 0.70 mmol), silver triflate (245 mg, 0.70 mmol) and NaI (1 g, 7.00 mmol) afforded imidazolium salt 355 (190 mg, 0.42 mmol, 61%) as pale yellow oil: m.p. (CH₂Cl₂) = 112 – 114 °C; [α]₀ = -76.4 ° (c 0.67, DCM); IR (neat) = 2924, 2854, 1707, 1519, 1170, 739, 755 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 10.20 (s, 1H, N-C-H-N), 8.07–8.04 (m, 2H, Ar-H), 7.44–7.41 (m, 4H, Ar-H), 7.32–7.30 (m, 2H, Ar-H), 6.45 (d, J = 6.3 Hz, 2H, C-H-N), 6.13–6.09 (m, 2H, C-H-O), 3.54–3.52 (m, 4H, CH₂₂); ¹³C NMR (100 MHz, d-DMSO) δ 139.6, 134.6, 130.8, 129.1, 126.8, 125.2, 124.8, 115.6, 95.2, 66.8, 38.3; MS (ESI⁺) m/z 329 (M⁺); HRMS (ESI⁺) m/z calc for C₂₁H₁₇N₂O₂ 329.1290, found: 329.1280.

**Methyl Imidazolium salt (356)**

![Methyl imidazolium structure](image)

Following general procedure H with oxazole 341 (20 mg, 0.06 mmol), chloromethyl ethylether (0.007 mL, 0.06 mmol), silver triflate (22 mg, 0.06 mmol) and NaI (100 mg, 0.70 mmol) afforded imidazolium salt 356 as a white solid (16 mg, 0.03 mmol, 55 %): m.p. (CH₂Cl₂/Et₂O) = 146 – 148 °C; [α]₀ = -105.0 ° (c 0.20, DCM); IR (neat) = 2926, 1730, 1514, 1164, 772 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.75 (s, 1H, N-C-H-N), 7.33 (d, J = 7.8 Hz, 2H, Ar-H), 7.15 (d, J = 7.3 Hz, 4H, Ar-H), 6.46 (d, J = 6.8 Hz, 2H, C-H-N), 6.09 (dt, J = 5.4, 2.4 Hz, 2H, C-H-O), 3.52–3.42 (m, 4H, CH₂₂), 2.62 (s, 6H, CH₃); ¹³C NMR (100 MHz, d-DMSO) δ 140.4, 136.7, 132.7, 131.3, 130.1, 125.6 (1C), 123.0, 115.4, 95.2, 67.3, 37.8, 19.6; MS (ESI⁺) m/z 357 (M⁺); HRMS (ESI⁺) m/z calc for C₂₃H₂₁N₂O₂ 357.1603, found: 357.1602; Anal. Calc for C₂₃H₂₁N₂O₂: C, 57.04; H, 4.37; N, 5.78; Found: C, 57.08; H, 4.47; N, 5.69.
**Phenyl Imidazolium salt (357)**

Following general procedure H with oxazole 342 (76 mg, 0.16 mmol), chloromethyl ethylether (0.015 mL, 0.16 mmol), silver triflate (52 mg, 0.16 mmol) and NaI (200 mg, 1.40 mmol) afforded imidazolium salt 357 as pale yellow solid (43 mg, 0.07 mmol, 41 %): m.p. (CH$_2$Cl$_2$/Et$_2$O) = 130 – 134 °C; [α]$_D$ = -17.8 ° (c 0.32, DCM); IR (neat) = 2970, 1507, 1160, 761 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.55-7.52 (m, 8H, Ar-H), 7.45-7.39 (m, 6H, Ar-H), 7.30 (d, J = 7.8 Hz, 2H), 7.16 (d, J = 7.8 Hz, 2H, CH-N), 6.84 (d, J = 5.9 Hz, 2H, CH-O), 6.21-6.18 (m, 2H), 4.71 (s, 1H, N-CH-N), 3.58-3.46 (m, 4H, CH$_2$); $^{13}$C NMR (100 MHz, d$_2$-DMSO) δ 141.6, 140.1, 138.2, 131.4, 131.2, 129.9 (4C), 129.8, 129.1, 128.3 (4C), 125.6 (1C), 124.9, 112.1, 95.9, 68.1, 37.4.

**Palladium complex 362:**

Imidazolium salt 355 (7.60 mg, 0.016 mmol) and palladium acetate (4.00 mg, 0.019 mmol) were dissolved in d$_8$-THF (1 mL) and sodium tert-butoxide (1.4 mg, 0.016 mmol) was added. The solution was stirred for 1h. Flash chromatography with neutral alumina afforded the desired complex 362.

**Silver complex 363:**
Imidazolium salt 356 (10 mg, 0.02 mmol) was dissolved in dichloromethane (2 mL) and molecular sieves and silver oxide (2.3 mg, 0.01 mmol) were added. The solution was stirred for 16h in the dark. Filtration through cotton and evaporation of the solvent afforded the desired complex 363.

**General procedure for the α-arylation:**

![Chemical Structure](image)

Imidazolium salt (10%) was dissolved in THF and palladium acetate (10%) was added to the solution followed by sodium tert-butoxide (10%). The dark orange mixture was stirred 10 min at ambient temperature. Then the substrate 365 (20mg, 0.06 mmol) was dissolved in THF and sodium tert-butoxide (1.5 eq, 0.10 mmol) was added. This violet / pink solution was transferred to the dark orange mixture and heated in the microwave at the desired temperature. The reaction was then followed by GC-MS and the e.e. determined by chiral HPLC: Chiral HPLC (Method F): major (Rt = 20.09 min) : minor (Rt = 25.29 min).

**General procedure for the allylic alkylation:**

![Chemical Structure](image)

Imidazolium salt (1%) and cinnamyl bromide (0.5 mmol) were dissolved in Et₂O. The solution was cooled to -15°C and ethyl magnesium bromide (1.8 eq) was added slowly over four minutes. The mixture was stirred 19h at -15°C and quenched at -15°C with acidified ammonium chloride saturated solution (NH₄Cl Dissolved in ~0.5 M HCl) and the product extracted with ether, dried with MgSO₄. Removal of solvent under vacuum gives the crude product. The reaction was followed by GC-MS and the e.e. was determined by chiral GC in the Woodward’s laboratory.
Chapter II

Synthesis of abnormal NHCs

Synthesis of imidazolium abnormal NHC derivative

\[(1R,1'R,2R,2'R,3R,3'R,5S,5'S,N,N'E,N,N'E)-N,N'-(Ethane-1,2-diylidene)bis(2,6,6-trimethylbicyclo[3.1.1] heptan-3-amine) (461)\]101

\[
\begin{align*}
\text{Glyoxal solution (36, ~40 % in water, 378 mg, 2,60 mmol) was added to a solution of (1R,2R,3R,5S)-} \\
\text{2,6,6-trimethylbicyclo[3.1.1]heptan-3-amine (460, 0.88 mL, 5.20 mmol) in n-propanol (10 mL). To the} \\
\text{mixture were added n-propanol (5 mL) and water (2.5 mL) and the reaction was stirred at ambient} \\
\text{temperature for 12h. Upon addition of water (10 mL), a pale yellow solid precipitated which was} \\
\text{collected by filtration and dried in vacuo. The diimine 461 (780 mg, 2.38 mmol, 91%) was obtained} \\
\text{pure as a pale yellow solid: m.p. (1-propanol / H}_2\text{O) = 68 – 70 °C; lit. ; [\alpha]_D = -17.5 ° (c 1.00, DCM); IR} \\
\text{(neat) = 2968, 2911, 2868, 1371, 1217, 921 cm}^{-1}; \text{^1H NMR (400 MHz, CDCl}_3\text{) δ 7.86 (s, 2H, CH-N), 3.48-} \\
\text{3.43 (m, 2H, CH-CHCH}_3\text{), 2.41-2.39 (m, 2H, CH), 2.28-2.25 (m, 2H, CH), 2.10-2.05 (m, 2H, CH), 1.99-} \\
\text{1.97 (m, 2H, CH), 1.90-1.84 (m, 4H, CH}_2\text{), 1.25 (s, 6H, CH}_3\text{), 1.04 (s, 6H, CH}_3\text{), 1.00 (d, J = 7.6 Hz, 6H,} \\
\text{CH}_3\text{), }\text{^13C NMR (100 MHz, CDCl}_3\text{) δ 159.5, 70.0, 47.4, 43.3, 41.5, 38.8, 35.7, 33.9, 27.9, 23.5, 19.8.}
\end{align*}
\]

\[1,3-bis((1R,2R,3R,5S)-2,6,6-Trimethylbicyclo[3.1.1]heptan-3-yl)-1H-imidazol-3-ium iodide (471)\]

\[
\begin{align*}
\text{Chloromethyl pivalate (0.21 mL, 1.50 mmol) was added to a mixture of diimine 461 (380 mg, 1.16} \\
\text{mmol) and silver triflate (359 mg, 1.40 mmol) in dichloromethane (4 mL). The round bottom flask} \\
\text{was sealed and stirred in the dark at 40 °C for 24h. The solvent was evaporated in vacuo and a dark} \\
\text{oil was obtain (800 mg). Dry acetone (5 mL) and sodium iodide (1.4 g, 9.30 mmol) were added to the} \\
\text{crude product and the mixture was stirred at ambient temperature for 12h. Removal of the solvent}
\end{align*}
\]
under reduced pressure followed by flash column chromatography on silica gel afforded the imidazolium iodide 471 (420 mg, 0.90 mmol, 77%) as a pale yellow powder: m.p. (CH₂Cl₂/Et₂O) = 182 – 184 °C; [α]₀ = -15.7 ° (c 0.47, DCM); IR (neat) = 2910, 1738, 1159, 637 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 10.80 (s, 1H, N-C₃H₇-N), 7.42 (s, 2H, CH-N), 5.30-5.16 (m, 2H, CH-CHCH₃), 2.91-2.89 (m, 2H, CH), 2.62-2.60 (m, 2H, CH), 2.26-2.23 (m, 2H, CH), 2.14-2.12 (m, 2H, CH), 2.03-1.96 (m, 4H, CH₂), 1.29 (s, 6H, CH₃), 1.21 (d, J = 7.2 Hz, 6H, CH₃), 1.14 (s, 6H, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 137.3 (1C), 120.3, 60.1, 45.3, 41.3, 40.0, 36.6, 35.3, 27.9, 23.7, 20.4.

(1R,2S,4R,E)-1,7,7-Trimethyl-N-{(E)-2-((1R,2R,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylimino)ethyldiene)bicyclo[2.2.1]heptan-2-amine (468)

Same procedure than the formation of 461 with (+)-Bornylamine (467, 500 mg, 3.26 mmol), glyoxal (36, 240 mg, 1.65 mmol) afforded, the diimine 468 (500 mg, 1.52 mmol, 94%) as a colourless solid: m.p. (CH₂Cl₂/Et₂O) = 102 – 104 °C; [α]₀ = -16.7 ° (c 0.18, DCM); IR (neat) = 2949, 2870, 1739, 1623, 1454, 1364, 1217, 916 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.94 (s, 2H, C₃H₇-N), 3.42-3.40 (m, 2H, CH-CHCH₃), 2.19-2.13 (m, 2H), 2.05-1.98 (m, 2H), 1.79-1.71 (m, 4H), 1.39-1.23 (m, 6H), 0.93 (s, 6H, CH₃), 0.91 (s, 6H, CH₃), 0.71 (s, 6H, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 161.2, 75.4, 50.7, 48.5, 45.4, 37.3, 28.5, 28.1, 19.7, 18.8, 13.5.

1,3-bis((1R,2S,4R)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yl)-1H-imidazol-3-ium iodide (472)

Same procedure than the formation of 471 with diimine 468 (500 mg, 1.52 mmol), chloromethyl pivalate (0.29 mL, 2.00 mmol), silver triflate (488 mg, 1.90 mmol) afforded, after chromatography, the imidazolium salt 472 (540 mg, 1.15 mmol, 76%) as brown foam: [α]₀ = -3.0 ° (c 0.40, DCM); IR (neat) = 2951, 1738, 1448, 1370, 1217 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 10.32 (s, 1H, N-C₃H₇-N), 7.29 (s, 2H, CH-N), 5.10 (ddd, J = 11.6, 4.8, 2.0 Hz, 2H, CH-CHCH₃), 2.63-2.55 (m, 2H, CH), 1.94-1.88 (m, 4H, CH), 1.80 (dd, J = 14.4, 4.8 Hz, 2H, CH), 1.61-1.41 (m, 6H, CH), 1.08 (s, 6H, CH₃), 0.98 (s, 6H, CH₃), 0.96
(s, 6H, CH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 137.5 (1C), 121.0, 66.9, 51.1, 49.8, 44.6, 34.2, 28.2, 27.6, 19.9, 18.7, 13.7.

2-Methyl-1,3-bis((1R,2R,3R,5S)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)-1H-imidazol-3-ium iodide (479)

Sodium hydride (25 mg, 0.60 mmol) was added to a solution of imidazolium 471 (45 mg, 0.10 mmol) in tetrahydrofuran (1 mL) at 0 °C and stirred for 15 min at ambient temperature. Methyl iodide (0.15 mL, 1.00 mmol) was added and the mixture was stirred at ambient temperature for 1 h. Removal of the solvent under reduced pressure followed by flash column chromatography on silica gel afforded the imidazolium salt 479 (39 mg, 0.08 mmol, 81%) as a pale yellow powder: m.p. (CH$_2$Cl$_2$) = 225 – 230 °C; [α]$_D$ = -16.3 ° (c 0.30, DCM); IR (neat) = 2905, 1573, 1453, 1197, 729 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.68 (s, 2H, CH-N), 4.80-4.74 (m, 2H, CH-CHCH$_3$), 2.94-2.87 (m, 2H, CH), 2.36-2.32 (m, 2H, CH), 2.16-2.13 (m, 2H, CH), 2.06-1.97 (m, 6H, CH), 1.31 (s, 6H, CH$_3$), 1.19 (d, J = 3.6 Hz, 6H, CH$_3$), 1.15 (s, 6H, CH$_3$), 1.15-1.13 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 120.2, 77.2 (1C), 58.6, 47.5, 41.2, 39.0, 36.7, 34.9, 27.8, 23.9, 20.9, 12.7 (1C); Elem. Anal. Calc for C$_{24}$H$_{39}$IN$_2$: C, 59.74; H, 8.15; N, 5.81; Found: C, 59.81; H, 8.23; N, 5.77.

N-((1R,2R,3R,5S)-2,6,6-Trimethylbicyclo[3.1.1]heptan-3-yl)benzamide (483)

Benzoyl chloride (58 μL, 0.60 mmol) and triethylamine (0.27 mL, 1.95 mmol) were added to a solution of (1R,2R,3R,5S)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-amine (460, 100 mg, 0.65 mmol) in dichloromethane (5 mL). The mixture was stirred at ambient temperature for 1 h and quenched with water (10 mL). The organic layer was washed with water and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried over anhydrous MgSO$_4$. Removal of the solvent under reduced pressure followed by flash column chromatography (Silica,
Eluent: Petroleum ether/EtOAc 6/1) afforded amide 483 (140 mg, 0.55 mmol, 91%) as a white solid: 

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.78-7.76 (m, 2H, Ar-H), 7.51-7.41 (m, 3H, Ar-H), 5.99 (br s, 1H, NH), 4.53-4.45 (m, 1H, C$_2$H-NH), 2.76-2.68 (m, 1H, CH), 2.48-2.42 (m, 1H, CH), 2.08-1.97 (m, 1H, CH), 1.90-1.86 (m, 2H, CH$_2$), 1.62 (dd, $J = 14.0$, 6.0, 2.4 Hz, 1H, CH), 1.25 (s, 3H, CH$_3$), 1.18 (d, $J = 6.8$ Hz, 3H, CH$_3$), 0.91 (d, $J = 9.6$ Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 166.9, 135.0, 131.2, 128.5 (2C), 126.8 (2C), 48.4, 47.8, 46.6, 41.6, 38.4, 37.4, 35.4, 28.0, 23.4, 20.8; MS (EI) m/z 257 (M); HRMS (EI) m/z calc for C$_{17}$H$_{23}$NO$_2$ 257.1780, found: 257.1776.

$N,N'$-bis((1R,2R,3R,5S)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)benzimidamide (482)

\[ \text{The amide 483 (70 mg, 0.27 mmol) was diluted in dichloromethane (5 mL), POCl}_3 (0.1 mL, 1.00 mmol) was added and the mixture was stirred for 2h at ambient temperature. Then, (1R,2R,3R,5S)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-amine (460, 50 mg, 0.32 mmol) was added and the mixture was stirred overnight. Removal of the solvent under reduced pressure followed by flash column chromatography afforded the product 482 (40 mg, 0.10 mmol, 38%): $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 10.0-9.97 (m, 1H, NH), 7.67-7.60 (m, 3H, Ar-H), 7.34-7.31 (m, 2H, Ar-H), 3.25-3.19 (m, 2H, CH), 2.40-2.34 (m, 2H, CH), 2.23-2.13 (m, 4H, CH), 2.01-1.95 (m, 2H, CH), 1.90-1.88 (m, 2H, CH), 1.76-1.74 (m, 2H, CH), 1.13 (s, 6H, CH$_3$), 0.84 (d, $J = 7.2$ Hz, 6H, CH$_3$), 0.57 (s, 6H, CH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 165.0 (1C), 132.1, 129.6, 127.1, 126.7 (1C), 54.8, 47.2, 44.0, 41.1, 38.2, 36.7, 34.7, 27.8, 23.1, 20.0.} 

$N$-Cyclohexylbenzamide (489) 

\[ \text{Same procedure than formation of 483 with cyclohexanamine (1 mL, 8.50 mmol), benzoylchloride (0.77 mL, 8.00 mmol), triethylamine (3.5 mL, 25.00 mmol) afforded, after chromatography, the} \]
amide **489** (1.2 g, 5.91 mmol, 70%) as a pale brown solid: \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.73-7.75 (m, 2H, Ar-\(H\)), 7.48-7.46 (m, 1H, Ar-\(H\)), 7.43-7.41 (m, 2H, Ar-\(H\)), 5.99 (br s, 1H, N\(H\)), 4.02-3.93 (m, 1H, C\(H\)-NH), 2.05-2.01 (m, 2H, CH), 1.78-1.62 (m, 4H, CH), 1.47-1.37 (m, 2H, CH), 1.26-1.18 (m, 2H, CH); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 166.6, 135.1, 131.2, 128.5 (2C), 126.8 (2C), 48.7, 33.2 (2C), 25.6, 24.9 (2C); MS (ESI) m/z 204 (M+H); HRMS (ESI) m/z calc for C\(_{13}\)H\(_{18}\)NO 204.1388, found: 204.1390.

**Lithium (E)-cyclohexyl[(cyclohexylimino)(phenyl)methyl]amide (495)**

![Image of compound](image_url)

Dicyclohexyl carbodiimide (**493**, 1 g, 5.00 mmol) was diluted in hexane (4 mL) and a solution of phenyllithium (**494**, 1.8 M in dibutylether, 3 mL, 5.00 mmol) was added. After 3h a precipitate appeared and the mixture was stirred for additional 2h. The precipitate was filtrated and dried to afford the lithium salt **495** (780 mg, 2.69 mmol, 54%) as a pale yellow solid: \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.43-7.35 (m, 3H, Ar-\(H\)), 7.18-7.15 (m, 2H, Ar-\(H\)), 3.64 (m, 1H, C\(H\)), 2.78-2.71 (m, 1H, C-H), 1.97-1.93 (m, 2H), 1.69-1.54 (m, 5H), 1.46-1.42 (m, 3H), 1.30-1.19 (m, 4H), 1.19-1.06 (m, 4H), 1.02-0.94 (m, 2H); MS (EI) m/z 283 (M-Li); HRMS (EI) m/z calc for C\(_{19}\)H\(_{27}\)N\(_2\) 283.2174, found: 283.2176.

**3-Chloro-3-phenyl-3H-diazirine (503)**

![Image of compound](image_url)

CAUTION! (performed behind a safety shield under dim lighting) A solution of LiCl (1.76 g, 41.60 mmol) in DMSO (20 mL) was rapidly stirred. Meanwhile, NaCl (10.6 g, 180.40 mmol) was dissolved in cold NaOCl (10-15%, 98 mL) and stirred. The salty chlorinated bleach solution was transferred in a dropping funnel. Benzamidine (1 g, 8.32 mmol) and pentane (20 mL) were added to the LiCl solution and the reaction was submerged into an ice-salt bath. The NaOCl/NaCl solution was slowly added to the mixture which was then stirred for 30 min. The solution was then extracted with ether (4 x 25 mL). The combined organic phases were collected and washed with water (3 x 20 mL). After drying with MgSO\(_4\), most of the solvent was carefully evaporated and a column chromatography (pure
Experimental

pentane) was done to afford the desired product (1.02 g, 6.71 mmol, 80%) in solution in pentane: \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.42-7.39 (m, 3H, Ar-\(H\)), 7.14-7.11 (m, 2H, Ar-\(H\)); \(^{13}\)C NMR (100 MHz, d-DMSO) \(\delta\) 135.7, 129.3, 128.5 (2C), 126.0 (2C), 47.1.

**2-Phenyl-1,3-bis((1R,2R,3R,5S)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)-1H-imidazol-3-ium iodide (464)**

To a solution of the diimine 461 (50 mg, 0.15 mmol) in hexane (1 mL) was added the solution of diazirine 503 (0.20 mmol) in pentane. The resultant solution stirred at reflux temperature for 8h. Hexane was removed by filtration and the residue diluted in acetone (1 mL). NaI (225 mg, 1.50 mmol) was added and the resultant mixture stirred at ambient temperature for 3h. Acetone was evaporated and the residue dissolved in dichloromethane. The suspension was filtered and the solvent evaporated. The crude product was purified by flash chromatography (eluent: DCM/MeOH 95/5) to afford the desired product 464 (69 mg, 0.13 mmol, 84%) as a brown foam: \([\alpha]_D = -37.1^\circ\) (c 0.70, DCM); IR (neat) = 2920, 2186, 1475, 1193, 917, 724 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.15 (s, 2H, C\(H\)-N), 7.82-7.77 (m, 1H, Ar-H), 7.75-7.70 (m, 2H, Ar-H), 7.61-7.58 (m, 2H, Ar-H), 4.38-4.32 (m, 2H, CH-CH\(_3\)), 2.64-2.56 (m, 4H, CH\(_2\)), 2.46-2.39 (m, 2H, CH), 2.33-2.27 (m, 2H, CH), 2.12-2.11 (m, 2H, CH), 1.91-1.88 (m, 2H, CH\(_2\)), 1.62-1.61 (m, 2H, CH\(_2\)), 1.23 (s, 6H, CH\(_3\)), 0.83 (d, J = 6.8 Hz, 6H, CH\(_3\)), 0.74 (s, 6H, CH\(_3\)); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 144.8, 133.2, 130.3, 130.2, 122.0, 121.8, 59.1, 47.3, 44.6, 41.1, 38.8, 37.2, 34.9, 27.7, 23.2, 20.3; MS (ESI) \(m/z\) 417 (M-I)\(^+\); HRMS (ESI) \(m/z\) calc for C\(_{29}\)H\(_{41}\)N\(_2\) 417.3270, found: 417.3269; Anal. Calc for C\(_{29}\)H\(_{41}\)N\(_2\): C, 63.96; H, 7.59; N, 5.14; Found: C, 63.93; H, 7.52; N, 5.22.

**Synthesis of Ag-complex**

To a solution of imidazolium salt 464 (50 mg, 0.092 mmol) in dichloromethane (4 mL) was added 4Å molecular sieves and Ag\(_2\)O (13 mg, 0.055 mmol). The resultant mixture was stirred for 16 h at ambient temperature and the solvent was evaporated. The residue was dissolved in chloroform and filtered through cotton-wool. The solvent was then evaporated under a steam of nitrogen and a
brown solid was obtained: ¹H NMR (400 MHz, CDCl₃) δ 8.30 (s, 1H, CH-N), 7.77-7.75 (m, 1H, Ar-H), 7.73-7.69 (m, 2H, Ar-H), 7.58-7.56 (m, 2H, Ar-H), 4.36-4.30 (m, 2H, CH-CH₂CH₃), 2.58-2.55 (m, 4H, CH₂), 2.48-2.44 (m, 2H, CH), 2.36-2.30 (m, 2H, CH), 2.12-2.11 (m, 2H, CH), 1.88-1.86 (m, 2H, CH₂), 1.39-1.36 (m, 2H, CH₂), 1.21 (s, 6H, CH₃), 0.81 (d, J = 6.8 Hz, 6H, CH₃), 0.72 (s, 6H, CH₃); ¹³C NMR (125 MHz, CDCl₃) δ 153.7, 144.4, 133.1, 130.2, 130.1, 122.3, 121.9, 59.0, 47.3, 44.4, 41.1, 38.8, 37.2, 34.9, 27.8, 23.3, 20.3.

**Synthesis of Rh-complex 505**

To a solution of crude silver complex (0.038 mmol) in dichloromethane (3 mL) was added [Rh(cod)Cl]₂ (19 mg, 0.038 mmol). The resultant mixture was stirred for 2 h at ambient temperature. The residue was filtered through celite and the solvent was then evaporated and a brown solid was obtained (21 mg, 82%): ¹H NMR (400 MHz, CDCl₃) δ 8.31 (s, 1H, CH-N), 7.79-7.67 (m, 3H, Ar-H), 7.56-7.51 (m, 2H, Ar-H), 4.36-4.20 (m, 6H, CH-CH₂CH₃ + cod), 2.62-2.29 (m, 12H, CH₂ + CH + cod), 2.12-2.07 (m, 2H, CH), 1.89-1.83 (m, 2H, CH₂), 1.75-1.61 (m, 4H, cod), 1.40 (d, J = 10.7 Hz, 2H, CH₂), 1.20 (s, 6H, CH₃), 0.79 (d, J = 6.8 Hz, 6H, CH₃), 0.71 (s, 6H, CH₃); ¹³C NMR (125 MHz, CDCl₃) δ 144.3 (1C), 133.1 (1C), 130.1 (4C), 122.6 (2C), 121.9 (1C), 78.1 (br, cod), 59.0 (2C), 47.2 (2C), 44.3 (2C), 41.1 (2C), 38.7 (2C), 37.1 (2C), 34.9 (2C), 30.9 (cod), 27.8 (2C), 23.2 (2C), 20.3 (2C).
Experimental

Synthesis of triazolium abnormal NHC derivative

\((1R,5S)-6,6\text{-Dimethylbicyclo[3.1.1]heptan-2-one (520)}\)^29

\(-\alpha\)-\(\alpha\)-Pinene (519, 3.13 mL, 20.00 mmol) was dissolved in methanol (10 mL) and dichloromethane (10 mL). The mixture was then cooled to -78 °C and \(O_3\) was bubbled into the solution until a blue colour appeared (3h). Then the reaction was warmed to ambient temperature, quenched with dimethylsulfur (10 equiv.) and stirred at ambient temperature for 12h. Removal of the solvent under reduced pressure followed by flash column chromatography on silica gel afforded the ketone 520 (2.25 g, 16.30 mmol, 82%) as a colourless liquid: \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 2.56-2.48 (m, 3H), 2.31 (ddd, \(J = 18.8, 8.8, 2.0\) Hz, 1H), 2.23-2.19 (m, 1H), 2.06-1.99 (m, 1H), 1.96-1.88 (m, 1H), 1.56 (d, \(J = 10.4\) Hz, 1H), 1.30 (s, 3H, CH\(_3\)), 0.83 (s, 3H, CH\(_3\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 215.0, 57.9, 41.2, 40.3, 32.7, 25.8, 25.2, 22.1, 21.3; MS (EI) \(m/z\) calc for C\(_9\)H\(_{14}\)O 138.1045, found: 138.1048.

\((1R,2R,5S)-6,6\text{-Dimethylbicyclo[3.1.1]heptan-2-ol (521)}\)

Ketone 520 (500 mg, 3.62 mmol) was diluted in methanol (10 mL). Then NaBH\(_4\) (380 mg, 10.00 mmol) was added at 0 °C. The mixture was then stirred at ambient temperature for 2h. Removal of the solvent under reduced pressure afforded the alcohol 521 (400 mg, 2.86 mmol, 79%) as white solid: \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 4.26 (dt, \(J = 9.6, 3.6\) Hz, 1H, CH-OH), 2.34-2.20 (m, 2H), 2.08-1.91 (m, 3H), 1.80-1.72 (m, 1H), 1.70-1.61 (m, 1H), 1.21 (s, 3H, CH\(_3\)), 1.10 (s, 3H, CH\(_3\)), 0.87 (d, \(J = 10.0\) Hz, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 73.6, 48.3, 41.0, 37.6, 28.3, 27.4, 26.0, 24.8, 22.7; MS (Cl) \(m/z\) 140 (M).
(1R,5S)-6,6-Dimethylbicyclo[3.1.1]heptan-2-yl methanesulfonate (522)

![OMs](image)

Alcohol 521 (100 mg, 0.71 mmol) was dissolved in dichloromethane (5 mL). Then triethylamine (0.1 mL, 0.75 mmol) and mesyl chloride (0.06 mL, 0.75 mmol) were added. The mixture was stirred 30 min at ambient temperature. The crude was used in the next reaction: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.46 (d, $J = 4.8$ Hz, 1H, CH-OMs), 2.99 (s, 3H, S-C$_3$H$_3$), 1.85-1.84 (m, 1H), 1.71-1.65 (m, 3H), 1.29-1.25 (m, 1H), 1.07 (s, 3H, CH$_3$), 0.94 (s, 3H, CH$_3$).

(1R,5S)-6,6-Dimethylbicyclo[3.1.1]heptan-2-yl 4-methylbenzenesulfonate (523)

![OTs](image)

Alcohol 521 (100 mg, 0.71 mmol) was dissolved in pyridine (5 mL). Then tosyl chloride (286 mg, 1.50 mmol) was added. The mixture was stirred for 24h at ambient temperature. Removal of the solvent under reduced pressure followed by flash column chromatography on silica gel afforded the tosyl derivative (80 mg, 0.27 mmol, 19%) as a white solid: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.78 (d, $J = 8.4$ Hz, 2H, Ar-H), 7.32 (d, $J = 8.4$ Hz, 2H, Ar-H), 4.24-4.22 (m, 1H, CH-OTs), 2.44 (s, 3H, Ar-CH$_3$), 2.25-2.24 (m, 1H), 1.77-1.76 (m, 1H), 1.68-1.64 (m, 2H), 1.54-1.53 (m, 1H), 1.32-1.24 (m, 2H), 1.19-1.15 (m, 1H), 0.87 (s, 3H, CH$_3$), 0.86 (s, 3H, CH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 144.3, 134.2, 129.6 (2C), 127.8 (2C), 89.6, 47.6, 42.5, 38.3, 33.9, 29.5, 24.1, 21.6, 20.8, 18.9.

4-Methylbenzenesulfonyl azide

![N3SO](image)

A solution of sodium azide (2.91 g, 45.00 mmol) in water (18 mL) was added dropwise to a solution of tosyl chloride (5.73 g, 30.00 mmol) in acetone (60 mL) at 0 °C. The reaction was allowed to warm up to ambient temperature and stirred for 12h. Acetone was removed under reduced pressure and
the reaction mixture extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with water (2 x 50 mL), saturated aq. NaHCO$_3$ (50 mL) and water (50 mL), dried over MgSO$_4$ and the solvent was removed under reduced pressure to afford tosyl azide (5.9 g, 29.95 mmol, 99%) as a pale yellow liquid: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.84 (d, $J = 8.4$ Hz, 2H, Ar-$H$), 7.40 (d, $J = 8.4$ Hz, 2H, Ar-$H$), 2.48 (s, 3H, Ar-CH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 146.2, 135.5, 130.2 (2C), 127.5 (2C), 21.7.

Potassium (E)-3-(3,5-di-tert-butyl-2-hydroxybenzylideneamino)-2-oxo-3,3-diphenylpropanoate (L)$_{244}$

Following the literature procedure: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 15.32 (d, $J = 7.8$ Hz, 1H), 7.49 (d, $J = 6.8$, 1H, N=C-$H$), 7.36-7.35 (m, 1H, Ar-$H$), 7.21-7.18 (m, 4H, Ar-$H$), 7.07-7.03 (m, 5H, Ar-$H$), 6.95-6.94 (m, 1H, Ar-$H$), 6.70 (d, $J = 2.4$ Hz, 1H, Ar-$H$), 1.27 (s, 9H, CH$_3$), 1.23 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 174.4, 163.6, 142.6 (2C), 140.0, 136.1, 129.7, 128.9 (4C), 128.1 (4C), 127.8, 127.6, 127.2, 126.4, 115.8, 34.9, 33.9, 31.3, 31.2 (3C), 29.5 (3C), 29.2.

(1R,2S,5S)-2-Azido-2,6,6-trimethylbicyclo[3.1.1]heptanes (515)$_{244}$

Co(BF$_4$)$_2$$\cdot$H$_2$O (100 mg, 0.30 mmol) and ligand L (140 mg, 0.30 mmol) were dissolved in ethanol (25 mL) at ambient temperature. After 10 min, (-)-β-pinene (0.75 mL, 5.00 mmol) was added to the homogenous orange solution, followed by tosyl azide (2.95 g, 15.00 mmol) and tert-butyl hydroperoxide (5.5 M in decane, 0.25 mL, 1.40 mmol). After 5 min, phenylsilane (1 mL, 8.00 mmol) was added dropwise. The resulting brown solution was stirred at ambient temperature for 16h and quenched with water (20 mL). Then saturated aq. NaHCO$_3$ (20 mL) and brine (50 mL) were added and the reaction mixture was extracted with diethylether. Removal of the solvent under reduced
Experimental

pressure followed by flash column chromatography on silica gel afforded the azide 515 (820 mg, 4.58 mmol, 92%) as an oil: \( ^1 \text{H NMR} (400 \text{ MHz}, \text{CDCl}_3) \delta 2.26-2.22 \text{ (m, 1H)}, 1.98-1.78 \text{ (m, 7H)}, 1.68-1.64 \text{ (m, 2H)}, 1.42 \text{ (s, 3H (84%), CH}_3), 1.41 \text{ (s, 3H (16%), CH}_3), 1.26 \text{ (s, 3H (84%), CH}_3), 1.23 \text{ (s, 3H (16%), CH}_3), 0.99 \text{ (s, 3H, CH}_3), 0.86 \text{ (s, 3H, CH}_3); ^{13} \text{C NMR} (100 \text{ MHz}, \text{CDCl}_3) \delta 67.6, 51.5, 40.2, 38.4, 28.9, 28.7, 27.8, 27.3, 25.1, 24.1, 23.4, 23.2; \text{MS (Cl)} m/z 137 (M-N}_3). 

\[
\begin{align*}
4-\text{Phenyl-1-[(1R,2S,5S)-2,6,6-trimethylbicyclo[3.1.1]heptan-2-yl]-1H-1,2,3-triazole (516)}
\end{align*}
\]

A mixture of diastereoisomers of azide 515 (1 g, 5.58 mmol, 1/6 dr) was dissolved in tert-butanol (30 mL) and water (30 mL). Phenyl acetylene (82, 0.62 mL, 5.60 mmol), CuSO\(_4\) (1 M in water, 0.56 mL, 0.56 mmol) and (+)-sodium L-ascorbate (1 M in water, 0.56 mL, 0.56 mmol) were successively added. The reaction became brown and was warmed to 60 °C for 24h to become orange. CuSO\(_4\) (0.56 mL) and (+)-sodium L-ascorbate (0.56 mL) were added to the mixture and the reaction was stirred at 60 °C for 5 days. The mixture became green and then finally blue. Removal of the solvent under reduced pressure followed by flash column chromatography on silica gel afforded the triazole 516 as a single diastereoisomer (950 mg, 3.36 mmol, 60%) as an oil: [\(\alpha\)]\(\text{D}\) = -28.9 ° (c 0.36, DCM); IR (neat) = 2920, 1451, 1225, 763, 694 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 7.84 \text{ (d, } J = 7.2 \text{ Hz, 2H, Ar-H}), 7.72 \text{ (s, 1H, N-CH}), 7.40 \text{ (d, } J = 7.2 \text{ Hz, 2H, Ar-H}), 7.32-7.30 \text{ (m, 1H, Ar-H)}, 3.31-3.23 \text{ (m, 1H), 2.49-2.47 \text{ (m, 1H), 2.22-2.18 \text{ (m, 2H), 2.03-2.00 \text{ (m, 3H), 1.66 \text{ (s, 3H, CH}_3), 1.35 \text{ (s, 3H, CH}_3), 1.18 \text{ (s, 3H, CH}_3), 0.81 \text{ (d, } J = 8.0 \text{ Hz, 1H); ^{13}C NMR (100 MHz, CDCl}_3 \delta 147.6, 131.3, 130.0 (2C), 128.1, 125.9 (2C), 117.5, 82.1961.} \]
3-Methyl-4-phenyl-1-((1R,2S,5S)-2,6,6-trimethylbicyclo[3.1.1]heptan-2-yl)-1H-1,2,3-triazol-3-ium iodide (517)

Triazole 516 (500 mg, 1.79 mmol) was dissolved in dichloromethane (10 mL) and methyltriflate (0.20 mL, 1.80 mmol) was added to the mixture. The reaction was stirred at ambient temperature for 3h. The solvent was evaporated and acetone (10 mL) was added followed by tetrabutyl ammonium bromide (6.00 mmol). The mixture was stirred for 1h and the solvent evaporated under reduced pressure. Dichloromethane (20 mL) was added and the solution filtrated. The solvent was evaporated and acetone (10 mL) was added followed by sodium iodide (900 mg, 6.00 mmol). The mixture was stirred for 2h and the solvent evaporated under reduced pressure. The residual solid was dissolved in a minimum of dichloromethane and diethyl ether was added. The desired salt 517 (510 mg, 1.20 mmol, 67 %) precipitated as white solid: m.p. (CH$_2$Cl$_2$/Et$_2$O) = 105 – 106 °C; [$\alpha$]$_D$ = +3.5° (c 1.00, DCM); IR (neat) = 2923, 1738, 1449, 1166, 768, 699 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.96 (s, 1H), 7.89-7.87 (m, 2H, Ar-H), 7.59-7.55 (m, 3H, Ar-H), 4.35 (s, 3H,CH$_3$), 2.75 (t, J = 5.0 Hz, 1H), 2.39-2.29 (m, 2H), 2.16-1.97 (m, 4H), 1.88 (s, 3H, CH$_3$), 1.37 (s, 3H, CH$_3$), 1.15 (s, 3H, CH$_3$), 0.94 (d, J = 8.0 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 143.4, 131.8, 130.0 (2C), 129.6 (2C), 127.1, 121.9, 51.5, 44.5, 39.6, 38.7, 33.7, 31.9, 29.2, 28.1, 27.8, 24.9, 23.3; MS (ES$^+$) m/z 296 (M$^+$); MS (ES$^-$) m/z 127 (I$^-$); Elem. Anal. Calc for C$_{19}$H$_{26}$IN$_3$: C, 53.91; H, 6.19; N, 9.93; Found: C, 53.87; H, 6.12; N, 9.84.

Synthesis of Rh-complex 530

To a solution of triazolium salt 517 (20 mg, 0.048 mmol) in dichloromethane (1 mL) was added 4Å molecular sieves and Ag$_2$O (7 mg, 0.03 mmol). The resultant mixture was stirred for 16 h at ambient temperature. To the solution of crude silver complex in dichloromethane (3 mL) was added
[Rh(cod)Cl]₂ (15 mg, 0.03 mmol). The resultant mixture was stirred for 2 h at ambient temperature. The residue was filtered through cotton and the solvent was then evaporated and a yellow solid was obtained: NMR analysis proved to be difficult to interpret. MS (ES+) m/z 533 (M-Cl), HRMS (ES+) m/z calc for C₂₇H₃₇N₃Rh 506.2043, found: 506.2037.
# X-ray data

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Table 1. Crystal data and structure refinement for MF0905.
Crystal colour / morphology  
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θ range for data collection  
4.37 to 72.49°

Index ranges  
-9<=h<=12, -12<=k<=12, -24<=l<=24

Reflns collected / unique  
22029 / 4146 [R(int) = 0.0230]

Reflns observed [F>4σ(F)]  
4004

Absorption correction  
Analytical

Max. and min. transmission  
0.843 and 0.659

Refinement method  
Full-matrix least-squares on F²

Data / restraints / parameters  
4146 / 0 / 298

Goodness-of-fit on F²  
1.049

Final R indices [F>4σ(F)]  
R1 = 0.0270, wR2 = 0.0700

R1+ = 0.0270, wR2+ = 0.0700

R1- = 0.0428, wR2- = 0.1145

R indices (all data)  
R1 = 0.0283, wR2 = 0.0709

Absolute structure parameter  
x⁻ = 0.000(12), x⁺ = 1.003(12)

Largest diff. peak, hole  
0.150, -0.227 eÅ⁻³

Mean and maximum shift/error  
0.000 and 0.001

Table 2. Bond lengths [Å] and angles [°] for MF0905.

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F(000) 1916
Crystal colour / morphology Colourless needles
Crystal size 0.25 x 0.04 x 0.03 mm³
θ range for data collection 2.39 to 73.15°
Index ranges -25<=h<=24, -25<=k<=25, -12<=l<=8
Reflns collected / unique 10176 / 3982 [R(int) = 0.0675]
Reflns observed [F>4σ(F)] 1503
Absorption correction Analytical
Max. and min. transmission 0.792 and 0.375
Refinement method Full-matrix least-squares on F²
Data / restraints / parameters 3982 / 19 / 243
Goodness-of-fit on F² 1.065
Final R indices [F>4σ(F)] R1 = 0.0916, wR2 = 0.2924
R1⁺ = 0.0916, wR2⁺ = 0.2924
R1⁻ = 0.1144, wR2⁻ = 0.3388
R indices (all data) R1 = 0.1600, wR2 = 0.3676
Absolute structure parameter x⁺ = 0.08(3), x⁻ = 0.92(3)
Largest diff. peak, hole 0.258, -0.602 eÅ⁻³
Mean and maximum shift/error 0.000 and 0.001

Table 2. Bond lengths [Å] and angles [°] for MF1008c.
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C(1)–N(2)–C(3) 141.5(16)
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C(4)–C(3)–C(11) 105.3(14)
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N(25)–C(24)–C(16) 104.2(15)
N(25)–C(24)–C(23) 109.7(15)
C(16)–C(24)–C(23) 104.2
C(1)–N(25)–C(14) 110.6(15)
C(1)–N(25)–C(24) 140.8(16)
C(14)–N(25)–C(24) 108.6(15)
Calculation of the Buried Volume of the imidazolium salts

The buried volume ($V_{bur}$; the fraction of the space buried by the NHC ligand of a sphere around the metal) of the IBiox-ligands was calculated by using the web application SambVca developed by Cavallo et al. for the calculation of the buried volume of any type of ligands. As an input file for this computer program, only the coordinates of the ligand must be supplied. This program positions the putative metal atom at 2.10 Å from the coordinating atom of the ligand; a value of 3.5 Å is taken for the radius of the sphere around this metal atom. For our calculations of the buried volumes, we took the coordinates from the crystal structure analyses of the imidazolium salts from which the proton at C2 and the anion were deleted.
Imidazolium salt 352

---

S A M B V C A
Buried Volume in Salerno
http://www.molnac.unisa.it/OM-tools/SambVca
L. Cavallo et al. email: lcavallo@unisa.it
---

Molecule from input:

Imidazolium salt

Number of atoms: 41
Atom that is coordinated: 1
Atoms that define the axis: 2
ID of these atoms: 2 25

Radius of sphere (Angs): 3.500
Distance from sphere (Angs): 2.100
Mesh step (Angs): 0.050
H atoms omitted in the V_bur calculation

Cartesian coordinates from input:

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Atoms and radius in the parameter file

H   1.29
C2  1.99
C3  1.99
C   1.99
N2  1.81
N3  1.81
N   1.81
O   1.78
F   1.72
Si  2.45
P   2.11
S   2.10
Cl  2.05
Br  2.16

Coordinates scaled to put the metal at the origin

C  -1.07833  1.30327  1.24447
N  -0.17285  1.19000  2.21992
C  0.94073  0.30399  2.56254
H  1.62157  0.26540  1.83055
C  0.54979 -1.06646  3.02801
C  -0.06369 -2.06760  2.29338
H  -0.34516 -1.90695  1.39949
C  -0.25976 -3.30449  2.88088
H  -0.66794 -4.00482  2.38506
C  0.13770 -3.52732  4.19370
H  -0.00334 -4.37929  4.58894
C  0.73674 -2.52059  4.93095
H  1.00909 -2.67658  5.82748
C  0.93542 -1.27459  4.33981
C  1.57646 -0.04286  4.93318
H  1.08428  0.25506  5.73844
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C  1.50208  1.01135  3.83590
H  2.40646  1.39813  3.65598
O  0.53957  2.07456  4.18277
C  -0.32602  2.18007  3.16401
C  -1.35088  2.95291  2.73133
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### Results: Volumes in Ångströms³

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The %V_Bur of your molecule is: **36.3**
Imidazolium salt 356:

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<td>L. Cavallo et al. email: <a href="mailto:lcavallo@unisa.it">lcavallo@unisa.it</a></td>
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Molecule from input:

Imidazolium salt

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H atoms omitted in the V_bur calculation

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**Atoms and radius in the parameter file**

- **H**: 1.29
- **C2**: 1.99
- **C3**: 1.99
- **C**: 1.99
- **N2**: 1.81
- **N3**: 1.81
- **N**: 1.81
- **O**: 1.78
- **F**: 1.72
- **Si**: 2.45
- **P**: 2.11
- **S**: 2.10
- **Cl**: 2.05
- **Br**: 2.16

**Coordinates scaled to put the metal at the origin**

- **C**: 0.49430 -1.18281 -1.66332
- **N**: -0.38878 -2.05683 -1.18801
- **C**: -1.3928 -2.25497 -0.08577
- **H**: -0.85598 -2.15868 0.79925
- **C**: -2.58150 -1.51427 -0.12878
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- **C**: -4.10925 0.33191 -0.07609
- **H**: -4.24930 1.26333 0.04757
- **C**: -5.22111 -0.44582 -0.24600
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- **C**: -5.06609 -1.77352 -0.31482
- **H**: -5.82622 -2.33830 -0.39978
- **C**: -3.73934 -2.34941 -0.25890
- **C**: -3.22938 -3.78080 -0.16105
- **H**: -3.43678 -4.15485 0.73258
- **H**: -3.66878 -4.34558 -0.84497
Results: Volumes in Angs^3

N of voxels examined: 1436277
Volume of voxel: 0.125E-03

V Free    V Buried    V Total    V Exact
89.578    89.957    179.535    179.594

%V_Free    %V_Bur    %Tot/Ex
49.895    50.105    99.967

The %V_Bur of your molecule is: 50.1
References

(4) Öfele, K. J. Organomet. Chem. 1968, 12, P42-P43.


