Synthesis of new 
*N-heterocyclic carbene metal complexes*

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Synthesis of new

$N$-Heterocyclic carbene metal complexes

By

Véronique Serre M.Sc.

A Doctoral Thesis

Submitted in partial fulfilment of the requirements
for the award of

Ph.D. of Loughborough University
February 2004

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Abstract

Synthesis of new N-heterocyclic carbene metal complexes

Véronique Serre

This thesis describes the synthesis of new N-heterocyclic carbene complexes through the synthesis of 1,4-bis substituted imidazolium salts or tricyclic saturated imidazolium salts. The introduction highlights some of the most successful methods for preparing N-heterocyclic carbenes and corresponding metal complexes. Examples of the use of these complexes in transition-metal-catalysed processes are provided towards the end of this chapter.

The second chapter is dedicated to our efforts to synthesize 1,4-bis substituted imidazolium salts as precursors for the synthesis of N-heterocyclic carbene complexes. The first part of this chapter describes the synthesis of 1,4-bis substituted imidazolium salts using 1,4-bis substituted diazabutadienes. Following this, attempts to deprotonate imidazolium salts to afford the desired N-heterocyclic carbenes are discussed. On the basis of the results obtained for the synthesis of 1,4-bis substituted imidazol-2-ylidenes, the synthesis of N-heterocyclic carbene complexes, where the carbene is generated in situ are explored at the end of this chapter.

The synthesis of enantiomerically pure tricyclic saturated imidazolium salts via enantiomerically pure diamines is discussed in the third chapter. Firstly, different methods were tested for the preparation of diamines from 6,6'-dimethyl-2,2'-bipyridine, 2,2'-biquinoline and (S,S)-6,6'-bis-(1-methoxy-2,2'-dimethylpropyl)-2,2'-bipyridine. Following this, is reported the synthesis of tricyclic saturated imidazolium salts. Suzuki cross coupling of 4-chlorotoluene with phenylboronic acid was investigated in the presence of different imidazolium salts. This chapter concludes with a few suggestions for the synthesis of enantiomerically pure 2,6-bipiperidines.

The fourth chapter is the experimental section and is dedicated to the methods of synthesis and characterization of the compounds mentioned in the previous chapters.

X-ray reports regarding the crystallographic representation of the structures presented in chapter two and three are provided in chapter five.
« En essayant continuellement on finit par réussir. Donc :
Plus ça rate, plus on a de chances que ça marche. »

« By constantly trying, you finish by succeeding, as :
The more you fail, the more chances you have to succeed. »
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Thanks to Loughborough University, EPSRC and Synetix for the funding and equipment provided for my research.

Finally, all my love and thanks to my family and to Sarah for always being here when I needed it the most.
### Abbreviations

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Å</td>
<td>Ångström</td>
</tr>
<tr>
<td>[α]D</td>
<td>specific optical rotation at the sodium D line</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>aq.</td>
<td>aqueous</td>
</tr>
<tr>
<td>Ar</td>
<td>aromatic</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>b.p.</td>
<td>boiling point</td>
</tr>
<tr>
<td>n-Bu</td>
<td>normal butyl</td>
</tr>
<tr>
<td>t-Bu</td>
<td>tert-butyl</td>
</tr>
<tr>
<td>°C</td>
<td>degrees Celsius</td>
</tr>
<tr>
<td>c</td>
<td>concentration</td>
</tr>
<tr>
<td>cat.</td>
<td>catalyst (catalytic amount)</td>
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<tr>
<td>Cbz</td>
<td>benzylxycarbonyl</td>
</tr>
<tr>
<td>cm⁻¹</td>
<td>wavenumber</td>
</tr>
<tr>
<td>cp</td>
<td>cyclopentadiene</td>
</tr>
<tr>
<td>δ</td>
<td>chemical shift</td>
</tr>
<tr>
<td>d</td>
<td>doublet</td>
</tr>
<tr>
<td>DCE</td>
<td>1,2-dichloroethane</td>
</tr>
<tr>
<td>DCM</td>
<td>dichloromethane</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-(N,N-dimethylamino)pyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethyl sulphoxide</td>
</tr>
<tr>
<td>DMSO-d₆</td>
<td>dimethyl sulphoxide (deuteriated)</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>eq</td>
<td>equivalent</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>EtOH</td>
<td>ethanol</td>
</tr>
<tr>
<td>g</td>
<td>gram(s)</td>
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</table>
GC  gas chromatography
h  hour(s)
Hz  Hertz
Ipc  isopinocamphenylamine
IR  infra red
$J$  coupling constant
LAH  lithium aluminium hydride
Lit.  literature
m  multiplet
M  molar
$m$-CPBA  $m$-chloroperbenzoic acid
Me  methyl
MeOH  methanol
MHz  megahertz
min  minute(s)
mmHg  millimeter of mercury
mmol  millimole(s)
mL  millilitre(s)
m.p.  melting point
nm  nanometer
NMR  nuclear magnetic resonance
Pd/C  palladium on carbon
Ph  phenyl
ppm  parts per million
$i$-Pr  isopropyl
psi  pounds per square inch
quat.  quaternary
R  alkyl
r.t.  room temperature
s  singlet
t  triplet
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBDMS</td>
<td>tert-butyldimethylsilyl</td>
</tr>
<tr>
<td>Tf</td>
<td>trifluoromethanesulfonyl</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>Ts</td>
<td>p-toluene sulfonyl</td>
</tr>
<tr>
<td>UV</td>
<td>ultra violet</td>
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Chapter 1: Introduction

Since the discovery of the stable imidazol-2-ylidene 1, first isolated by Arduengo et al. in 1991 (Figure 1),1 much interest has been generated in the chemistry of both free heteroatom carbenes and metal complexes of these ligands.

![Figure 1: 1,3-bis-(1-adamantyl)imidazol-2-ylidene 1.](image)

This interest has been stimulated by the realisation that this family of carbenes acts as efficient ligands in several transition metal-catalysed processes.

1.1 N-Heterocyclic carbenes in the literature

The typical carbon atom in a carbene has a free pair of electrons and at the same time, an electron deficiency. As a result of the deficit of electrons they have electrophilic character, provided that the two substituents R are not electron donors. If this is not the case as, for example in the system C \leftrightarrow C' (Figure 2), the donor groups enforce nucleophilic character at the carbene centre. The ambiphilic carbenes B having both a donor and an acceptor substituent occupy a position between carbene A and C. Only carbenes of type C can be isolated as stable compounds, and these were discovered just a few years ago.2

![Figure 2: Different types of carbenes.](image)
The beginnings of the chemistry of nucleophilic carbenes C date back to the early 1960s and are associated with H. W. Wanzlick. Wanzlick was the first to recognize that the electron-rich imidazole moiety should be able to stabilize a carbene centre at the 2-position, between the two nitrogens (Figure 3), although much of his work was on the saturated imidazoline ring in which the double bond between carbons 4 and 5 is absent (Compound D, Figure 3). There are, however, reports by Wanzlick of his work involving unsaturated analogues (Compound E, Figure 3). Serious attempts to isolate carbenes of type D and E were not undertaken until 1991.

![Figure 3: Saturated and unsaturated imidazolyl carbenes.](image)

H. W. Wanzlick and co-workers demonstrated in 1970 that imidazolium salts 2a and 2b could be deprotonated by potassium tert-butoxide to afford the corresponding imidazol-2-ylidenes 3a and 3b, which were trapped with phenyl isothiocyanate (S=C=NPh) but not isolated (Scheme 1).

![Scheme 1: Carbenes trapped but not isolated by H. W. Wanzlick.](image)
This principle was used almost two decades later by A. J. Arduengo et al.\textsuperscript{1} to isolate electronically stabilized, nucleophilic carbenes for the first time.

When bis-(1-adamantyl)imidazolium chloride 4 was deprotonated with sodium hydride in tetrahydrofuran in the presence of a catalytic amount of dimethyl sulphoxide anion, the corresponding carbene 1 precipitated as a colourless, crystalline, and thermally stable compound, melting at 240-241 °C without decomposition (Scheme 2).\textsuperscript{1} The crystal structure analysis confirmed this result; in the $^{13}$C NMR spectrum the lowfield position of the signal for the carbene carbon atom ($\delta = 211.4$) is characteristic.

\textit{Reagents and conditions:} (i) t-BuOK, cat. DMSO, THF, 96%.

\textbf{Scheme 2:} First isolated stable imidazol-2-ylidine 1 by A. J. Arduengo et al.

Stable carbenes of similar structure can also be obtained by deprotonation of imidazolium salts bearing less bulky substituents in the 1 and 3-positions (Table 1).\textsuperscript{2} These species also exhibit characteristic $^{13}$C NMR signals ($\delta = 213.7-219.7$) for the carbene carbon atom.
Entry | R¹ | R² | Reaction conditions | Yield/\%  
--- | --- | --- | --- | ---  
1 | Me | Me | NaH, t-BuOK (cat.), THF, r.t. | 6a 89²a  
2 | Me | H | NaH, t-BuOK (cat.), THF, r.t. | 6b 6a ²a  
3 | Mesityl | H | t-BuOK, THF, r.t. | 6c 84²a  
4 | lPr | H | t-BuOK, THF, r.t. | 6d 80⁶  
5 | p-toluene | H | t-BuOK, THF, r.t. | 6e 45²a  
6 | p-methoxyphenyl | H | t-BuOK, THF, r.t. | 6f 45²a  
7 | p-chlorophenyl | H | t-BuOK, THF, r.t. | 6g 43²a  
8 | (-)ICMe | H | t-BuOK, THF, r.t. | 6h 78²b  
9 | (+)IPCamp | H | t-BuOK, THF, r.t. | 6i 95²b  

*: Unstable oily liquid, which persists in solution for days without decomposition.

Stable triscarbene 7 (Figure 4), in which the imidazolylidene units are attached to a benzene ring, can be prepared by deprotonating the corresponding trisimidazolium salt in tetrahydrofuran with sodium hydride/potassium tert-butoxide in 56% yield.⁷ The biscarbene 8 shown in Figure 4 is stable and accessible in 95% yield by a similar method, except that sodium hydride in liquid ammonia/tetrahydrofuran is used as the deprotonating agent.⁸a
Advantages of this alternative method are low reaction temperatures (−40 °C) and short reaction times (30 minutes); oxygen, nitrogen, and phosphorus N-functionalized as well as chiral imidazol-2-ylidene have been prepared following this procedure (Figure 5).\(^8\)

In 1993, N. Kuhn and co-workers developed a new and versatile approach to alkyl-substituted \(N\)-heterocyclic carbenes 16 (Scheme 3).\(^9\) This original synthetic strategy relied on the reduction of imidazol-2(3H)-thiones 15 with metallic potassium in boiling tetrahydrofuran.
Reagents and conditions: (i) K, THF, 80 °C, 93-96%.

Scheme 3: Synthesis of imidazol-2-ylidene 16 by reduction of imidazole-2(3H)-thiones 15.

A few years later, Hahn and co-workers reported the synthesis of a new stable carbene 18 using the method described by Kuhn et al. This was the first free carbene derived from benzimidazole (Scheme 4).\(^{10}\)

Reagents and conditions: (i) Na/K, toluene, 60%.

Scheme 4: First free carbene 18 derived from benzimidazole.

Faust and Göbelt have shown recently that the deprotonation of a dialkynyl imidazolium salt 19 with \(n\)-butyllithium in tetrahydrofuran at \(-78\) °C affords the corresponding carbene 20 (Scheme 5).\(^{11}\) When potassium tert-butoxide, sodium or potassium hydride in either tetrahydrofuran or dimethyl sulphoxide were used, only decomposition products were observed even at temperatures as low as \(-100\) °C.
Reagents and conditions: (i) n-BuLi, THF, –78 °C.

Scheme 5: Synthesis of 4,5-dialkynyl imidazol-2-ylidene 20 by deprotonation of the corresponding imidazolium salt 19 with n-butyllithium.

In 1995, Arduengo et al. reported the isolation and structural characterization of two stable carbenes 22a and 22b in the saturated imidazol-2-ylidene series. These structures are closely related to two unsaturated imidazol-2-ylidenes 6c and 6d previously reported and differs only in the absence of the C4-C5 double bond on the imidazole ring. This result conclusively demonstrated that unsaturation in the imidazole ring is not required to produce a stable nitrogen-substituted carbene. Deprotonation of 1,3-bis-(2,4,6-trimethylphenyl) imidazolium salt 21a or 1,3-bis-(2,6-diisopropylphenyl) imidazolium salt 21b with potassium hydride in tetrahydrofuran at room temperature led to the corresponding saturated imidazol-2-ylidenes 22a and 22b in 72% and 42% yield respectively (Scheme 6). The two saturated carbenes 22a and 22b are remarkably stable in the absence of oxygen and moisture; they are colourless crystalline solids that melt at 107-109 °C and 167-168 °C respectively, without decomposition.
Scheme 6: Synthesis of the two stable saturated carbenes 22a and 22b.

Arduengo et al. were not the only research group to have identified the diaminocarbenes as likely targets. Alder et al. reported the isolation of an acyclic diaminocarbene (bis(diisopropylamino)carbene 23 (Figure 6) in 1996.13

Figure 6: Saturated carbene 23.

In 1997, Arduengo and co-workers discovered that carbon tetrachloride can chlorinate the 4- and 5-positions of imidazol-2-ylidene (Scheme 7).14 The resulting 4,5-dichloroimidazol-2-ylidene 24 possesses remarkable stability and can even be handled in moist air without decomposition.

Scheme 7: Synthesis of 4,5-dichloroimidazol-2-ylidene 24.
Recently Bolm and co-workers have reported the synthesis of the first planar-chiral free \( N \)-heterocyclic carbene 26 following Arduengo's protocol.\(^{15}\) The deprotonation of \((R)-3\)-methyl-1-[2-(trimethylsilyl)ferrocenylmethyl] imidazolium iodide 25 to give the corresponding \((R)\)-imidazol-2-ylidene 26 was performed in tetrahydrofuran at room temperature with 5 mol\% of potassium \( \text{tert-butoxide} \) and a stoichiometric amount of sodium hydride (Scheme 8). The resulting planar-chiral free carbene 26 is reasonably stable in tetrahydrofuran at room temperature.

\[
\begin{align*}
\text{Reagents and conditions: (i) } t-\text{BuOK (5 mol\%), NaH, THF, r.t., 1 h.}
\end{align*}
\]

**Scheme 8:** Synthesis of the first planar-chiral carbene 26.

Stable pyridine- and phosphine-functionalized \( N \)-heterocyclic carbenes 28 and 30 have been synthesized by deprotonation of the corresponding imidazolium salts 27 and 39 with KHMDS in tetrahydrofuran in good yield (60-80%) (Scheme 9).\(^{16}\)
Reagents and conditions: (i) KHMDS, THF, -10 to 0 °C, 60-80%.

Scheme 9: Synthesis of new stable carbenes 28 and 30 by deprotonation with KHMDS.

The enantiomerically pure imidazolium triflate 31, a derivative of a bisoxazoline, can be deprotonated with 10 mol% potassium tert-butoxide and a stoichiometric amount of potassium hydride to give the corresponding carbene 32, which is reasonably stable in tetrahydrofuran at room temperature (Scheme 10).17

Reagents and conditions: (i) t-BuOK (10 mol%), KH, THF, r.t.

Scheme 10: Synthesis of new stable carbenes 32 derived from a bisoxazoline.
1.2 Synthesis of transition metal N-heterocyclic carbene complexes in the literature

N-Heterocyclic carbene complexes have been shown to have considerable potential as efficient catalysts for several transition metal-catalysed processes, apparently owing to the stability imparted to the active species by the strong donor heterocyclic carbene ligands. Nucleophilic N-heterocyclic carbenes, so-called "phosphine-mimics", have attracted considerable attention as possible alternatives for the widely used phosphine ligands in homogeneous catalysis. The primary advantage of these ligands appears to be that they do not dissociate from the metal centre, and as a result an excess of the ligand is not required to prevent aggregation of the catalyst to yield the bulk metal.

Although N-heterocyclic carbene complexes of almost all transition metals and various others metals of the periodic table are known, access to all these compounds is mainly based on two routes: (i) the in situ deprotonation of ligand precursors and (ii) the complexation of the free, pre-isolated, N-heterocyclic carbene.

1.2.1 In situ deprotonation of ligands precursors

The in situ complexation of the ligand has the advantage of not requiring preparation of the free N-heterocyclic carbene. In cases where the carbene is unstable or difficult to handle, this approach is the only way to prepare the desired complex.

1.2.1.1 Deprotonation by basic anions

The action of basic anions on the metal precursors can provide the desired ligand in situ by deprotonation.

In 1968, Wanzlick introduced the use of acetate salts in his synthesis of a mercury bis-N-heterocyclic carbene complex starting from mercury diacetate (Scheme 11).
Reagents and conditions: (i) Hg(OAc)$_2$, DMSO, 80 °C, 10 min, quantitative yield.

**Scheme 11**: Preparation of transition metal carbene complex 34 by Wanzlick.

More than 25 years later, this method was used for palladium and nickel complexes starting from the corresponding metal diacetates and imidazolium salts.$^{8b,20,21,22}$

For palladium, it is possible to apply the *in situ* deprotonation method even without solvent,$^8b$ but the use of tetrahydrofuran or dimethyl sulphoxide provides higher yields of the complex.$^{21,23}$ Additionally, palladium and nickel methylene bridged N-heterocyclic carbene complexes were only accessible by this route (Scheme 12)$^{21}$ until these bidentate ligands were recently isolated as free carbenes.$^{24}$

Reagents and conditions: (i) Pd(OAc)$_2$, DMSO, 50 °C, 4 h, (ii) DMSO, reflux, 20 min, 92%.

**Scheme 12**: Preparation of palladium N-heterocyclic complex 37.

Rhodium or iridium alkoxide complex generated *in situ* by addition of the chlororhodium 38 or chloroiridium complex to a solution of sodium ethoxide in
alcohol can act as deprotonating agent. Indeed, using rhodium ethoxide complex 39 with 1,3-bis-(diphenylmethyl) imidazolium bromide 40 leads to the corresponding \( N \)-heterocyclic carbene complex 41 at room temperature (Scheme 13).\(^{25}\)

\[
\begin{align*}
\text{Reagents and conditions:} & \quad \text{(i) NaOEt, EtOH, r.t., 10 min, (ii) 1,3-bis-(diphenylmethyl) imidazolium bromide 40, 60 °C, 2 days, 94%}. \\
\end{align*}
\]

**Scheme 13:** Preparation of carbene complex of rhodium 41 from a metal alkoxide 39.

The ruthenium complex \([\text{CpMe}_5\text{Ru(OCH}_3\text{)}]_2\) 42 undergoes dimer cleavage on reaction with imidazolium salts such as 5c at 45 °C in tetrahydrofuran and allows isolation of the corresponding stable ruthenium \( N \)-heterocyclic carbene complex 43 (Scheme 14).\(^{26}\)

\[
\begin{align*}
\text{Reagents and conditions:} & \quad \text{(i) THF, 45 °C, 1 h, 89%}. \\
\end{align*}
\]

**Scheme 14:** Preparation of carbene complex of ruthenium 43 by dimer cleavage of \([\text{CpMe}_5\text{Ru(OCH}_3\text{)}]_2\) 42.

Basic silver oxide is a convenient precursor to silver bis-\( N \)-heterocyclic complexes 45,\(^{27,28}\) silver \( N \)-heterocyclic carbene linked cyclophane complexes 46,\(^{29}\) and silver alkoxy carbene complex 47 (Figure 7).\(^{30}\) The reaction is performed either
in dichloromethane at room temperature or in dimethyl sulphoxide at 50-75 °C (Scheme 15).

Figure 7: Silver N-heterocyclic carbene linked cyclophane complexes 46 and silver alkoxy carbene complex 47.

Reagents and conditions: (i) Ag₂O, DCM, r.t., 2 h, 89%.

Scheme 15: Preparation of silver carbene complex 45.

Silver N-heterocyclic carbene complexes can be used as carbene transfer agents (Scheme 16). These silver complexes can be pre-isolated or generated in situ.
Reagents and conditions: (i) Ag₂O, DCM, r.t., 2 h, (ii) (CH₃CN)₂PdCl₂, DCM, r.t., 30 min, 87%.

**Scheme 16:** Complex 48 preparation by transfer of imidazol-2-ylidene ligands from silver pre-isolated or generated *in situ.*

Cyclopentadienyl anions can also serve as the base to deprotonate imidazolium salts. When chromocene 49 is reacted with the imidazolium salt 5e in tetrahydrofuran, the metal precursor loses one molecule of cyclopentadiene to form the corresponding chromium *N-*heterocyclic carbene complex 50 (Scheme 17).³¹

Reagents and conditions: (i) THF, 90 min, 67%.

**Scheme 17:** Reaction of chromocene 49 with imidazolium salt 6e.

1.2.1.2 Deprotonation by external base

The addition of external base for the *in situ* deprotonation of the imidazolium salt can give different products as compared with the use of metal salts with basic anions. As an example, the use of potassium tert-butoxide with an imidazolium
perchlorate 51 and one equivalent of palladium diacetate in the presence of sodium iodide forms a dinuclear $N$-heterocyclic carbene complex 52 (Scheme 18).$^{32,33}$

\[
\text{Reagents and conditions: (i) Pd(OAc)$_2$ (1 eq), t-BuOK, NaI, THF, r.t., 94%}.
\]

Scheme 18: Preparation of dinuclear palladium carbene complex 52.

However, the use of 0.5 equivalent of palladium diacetate under the same reaction conditions indicated above forms a mononuclear $N$-heterocyclic carbene complex 53 (Scheme 19).$^{17,33,34}$

\[
\text{Reagents and conditions: (i) Pd(OAc)$_2$ (0.5 eq), t-BuOK, NaI, THF, r.t., 90%}.
\]

Scheme 19: Preparation of mononuclear palladium carbene complex 53.

The dimeric $N$-heterocyclic carbene complex 52 can be used as a precursor for the introduction of other ligands such as phosphine or different $N$-heterocyclic carbenes by dimer cleavage (Scheme 20).$^{35}$
Reagents and conditions: (i) PPh₃, xylene, r.t., 10 min.

Scheme 20: Introduction of phosphine by dimer cleavage.

It is also possible to deprotonate imidazolium salts 55 in the presence of rhodium complex with lithium tert-butoxide in tetrahydrofuran at room temperature (Scheme 21).³⁶

Reagents and conditions: (i) t-BuOLi, [Rh(COD)Cl]₂, THF, r.t.

Scheme 21: Preparation of rhodium N-heterocyclic carbene complex 56.

Using potassium tert-butoxide or sodium hydride in tetrahydrofuran also generates the desired N-heterocyclic carbene from imidazolium salts. The ligands can be coordinated to different metals such as W(CO)₆ in situ.⁸ᵃ

Addition of n-butyllithium to a suspension of palladium diiodide and methylene-bridged bisimidazolium salt 36 leads to the in situ complexation of the N-heterocyclic carbene to form the corresponding complex 57 (Scheme 22).³⁷
Reagents and conditions: (i) PdI₂ (0.5 eq), n-BuLi, THF, r.t., 6 h, 12%.

Scheme 22: Deprotonation with n-butyllithium and reaction with palladium diiodide.

1.2.1.3 Elimination of small molecules from neutral ligand precursors

Imidazolium salts can be transformed into the corresponding 2-methoxy imidazoles, for example, compound 58. The desired imidazol-2-ylidene can then be formed by elimination of methanol and subsequently be trapped by a metal. N-heterocyclic carbene complexes of ruthenium such as compound 59 were prepared in situ at elevated temperature by this method (Scheme 23). 38

Reagents and conditions: (i) CH₃ONa, MeOH, r.t., (ii) [RuCl₂(=CHPh)(PCy₃)$_₂$], benzene, 60-80 °C, .

Scheme 22: Formation of the ruthenium complex 59 starting from 2-methoxy imidazole 58.
1.2.2 Complexation on the pre-formed free N-heterocyclic carbene

The use of isolated N-heterocyclic carbenes has the advantage that a large variety of metal precursors can be used for the preparation of complexes.

Various methods have been developed to prepare N-heterocyclic carbenes from imidazolium salts (See section 1.1).

1.2.2.1 Cleavage of dimeric complexes

Nucleophilic N-heterocyclic carbenes can cleave dimeric complexes with bridging ligands such as halides or carbon monoxide. Examples of this type of complex formation are the reaction of [(COD)RhCl]_2 60 with free N-heterocyclic carbenes such as 6b (Scheme 23).^8

\[
\begin{align*}
\text{Reagents and conditions:} & \quad (i) \text{THF, r.t., 15 min, 91%}. \\
\text{Scheme 23:} & \quad \text{Cleavage of dimeric complex 60 by imidazol-2-ylidene 6b.}
\end{align*}
\]

Cleaving [Rh(CO)_2Cl]_2 with N-heterocyclic carbenes gives the complex (carbene)Rh(CO)_2Cl. ^8b Dimer cleavage and incorporation of one N-heterocyclic carbene occurs also with [(cymene)RuCl]_2 ^8a,b,39 and [Os(CO)_3Cl]_2. ^8b

1.2.2.2 Exchange of ligands

Phosphine and other ligands can also be exchanged for N-heterocyclic carbenes. For example, both phosphines in [RuCl_2(=CHPh)(PCy)_3]_2 62 can be
displaced by $N$-heterocyclic carbenes 9 (Scheme 24).\textsuperscript{40} The use of bulky $N$-heterocyclic carbenes leads to the substitution of only one of the phosphines to yield a mixed phosphine-$N$-heterocyclic carbene complex such as 63.\textsuperscript{41}

\begin{center}
\textbf{Scheme 24:} Phosphine exchange with ruthenium complexes.
\end{center}

The same approach allows the formation of palladium complexes of various $N$-heterocyclic carbenes. Starting from bis(tri-ortho-tolylphosphine)palladium 65, bis-$N$-heterocyclic carbene palladium complex 67 is obtained by the exchange of two ligands (Scheme 25).\textsuperscript{42}

\begin{center}
\textbf{Scheme 25:} Preparation of $N$-heterocyclic carbene palladium complex 67 by phosphine exchange.
\end{center}
Nickel complexes can also be prepared by phosphine exchange; for example, both triphenylphosphines in \([(\text{Ph}_3\text{P})_2\text{NiCl}_2]\) can be displaced by \(N\)-heterocyclic carbene ligands.\(^{22a}\)

In carbonyl complexes such as \(\text{W}(<\text{CO})_6\) or \(\text{Ni}(<\text{CO})_4\), one molecule of carbon monoxide can also be displaced by \(N\)-heterocyclic carbene ligands.\(^{8a,8c}\)

1.3 Transition metal-catalysed processes

1.3.1 Furan synthesis

\(N\)-Heterocyclic complexes of ruthenium have been used as catalysts in the synthesis of the 2,3-dimethylfuran 69 starting from (Z)-3-methylpent-2-en-4-yn-1-ol 68;\(^{43,44}\) yields of around 80\% were reported (Scheme 26).

![Scheme 26: Furan synthesis.](image)

Reagents and conditions: (i) 70 (1 mol\%), 60 °C, 25 h, 79\%\(^{43}\) or 80 °C, 2 h, 82\%\(^{44}\).

1.3.2 Olefin metathesis

Ruthenium carbene complexes have been successfully employed as catalysts in olefin metathesis. Typical catalysts with \(N\)-heterocyclic ligands for olefin metathesis such as 71-73 are shown in Figure 8.\(^{6a,40b,38,41,45}\)
Figure 8: Typical catalysts with N-heterocyclic ligands for olefin metathesis.

Ring-opening and ring-closing metathesis are the most well-understood metathesis reactions. There is reports, written by both Grubbs\textsuperscript{41} and Fürstner\textsuperscript{46} on the rapid development in this area. N-heterocyclic carbenes have made ruthenium the most useful olefin metathesis metal, predominantly because of the high tolerance to functional groups and the mild reaction conditions required (normally room temperature).

The C-C saturated derivatives 73a and 73b shown in Figure 8 show good activities in ring-opening metathesis polymerization. For example, ruthenium complex 73a was found to promote the ring-opening metathesis polymerization of norbornene to afford polynorbornene under mild conditions in good yield (Scheme 27).\textsuperscript{47}

\textit{Reagents and conditions:} (i) 73a, ClCH\textsubscript{2}CH\textsubscript{2}Cl, 55 °C, 12 h, 95%.

\textbf{Scheme 27:} Ring-opening metathesis polymerization of norbornene 74.
Various applications in the ring-closing metathesis of olefins have been reported recently.\textsuperscript{6a,38,39,40b,41,45,48} Scheme 28 shows the ring closure of 2-methyl diethyl diallyl malonate ester 76 using 4–7 mol\% of the catalyst 78 in toluene at 80 °C. Under those reaction conditions the corresponding trisubstituted cycloolefin 77 was obtained in good yield.\textsuperscript{45a}

\[
\begin{array}{c}
\text{EtO}_2\text{C} \quad \text{CO}_2\text{Et} \\
\text{EtOOC} \quad \text{N} \quad \text{Mes} \\
\text{Cl} \quad \text{Ru} \quad = \quad \text{Ph} \\
\text{Cl} \quad \text{PCy}_3
\end{array}
\]

\[
\begin{array}{c}
\text{EtO}_2\text{C} \quad \text{CO}_2\text{Et} \\
\text{Cl} \quad \text{PCy}_3 \quad \text{Ph}
\end{array}
\]

Reagents and conditions: (i) 78, toluene, 80 °C, 91%.

Scheme 28: Ring-closing metathesis.

Enantioselective ring-closing metathesis (Scheme 29) can give up to 90% enantiomeric excess depending on the ruthenium catalyst used.\textsuperscript{49}

\[
\begin{array}{c}
\text{Ph} \quad \text{Ph} \\
\text{Ph} \quad \text{N} \quad \text{N} \\
\text{Cl} \quad \text{PCy}_3 \quad \text{Ph}
\end{array}
\]

\[
\begin{array}{c}
\text{Ph} \quad \text{Ph}
\end{array}
\]

\[
\begin{array}{c}
\text{Ph} \\
\text{Ph}
\end{array}
\]

\[
\begin{array}{c}
\text{Ph} \\
\text{N} \quad \text{N} \\
\text{Cl} \quad \text{PCy}_3 \quad \text{Ph}
\end{array}
\]

Reagents and conditions: (i) 81 (5 mol\%), THF, 38 °C, 85% ee.

Scheme 29: Enantioselective ring-closing metathesis
Recently, Hoveyda and co-workers reported the synthesis, structure and reactivity of a new chiral ruthenium catalyst 85. Ru-catalysed ring-opening metathesis of tricyclic norbornenes 82 (Scheme 30) gave 80-98% ee. Interestingly, no by-products were observed during the reaction, and the chiral catalyst 85 could be recovered after chromatography (88-96% yield) and reused without significant loss of enantioselectivity and with similar reactivity.

\[
\begin{align*}
&\text{82} + \text{83} \\
&\overset{(i)}{\longrightarrow} \text{84}
\end{align*}
\]

\[
\text{Me} \quad \text{Me}
\]
\[
\text{Me} \quad \text{N} \quad \text{N}
\]
\[
\text{RuCl} \quad \text{O}
\]
\[
\text{N} \quad \text{N}
\]
\[
\text{Me} \quad \text{Me}
\]
\[
\text{85}
\]

\textit{Reagents and conditions}: (i) 85 (10 mol%), THF, 50 °C, 60 min, > 98% ee, 60% yield.

\textbf{Scheme 30}: Ru-catalysed ring-opening metathesis of tricyclic norbornene 82.

\textbf{1.3.3 Olefin cross-metathesis}

\(\alpha,\beta\)-Unsaturated amides\(^1\), trisubstituted\(^2\) and functionalized olefins\(^3\) can be synthesized by olefin cross-metathesis. \textbf{Scheme 31} shows the synthesis of a trisubstituted alkene 88 using olefin cross-metathesis.\(^2\)
Scheme 31: Synthesis of trisubstituted alkene 88 using olefin cross-metathesis.

1.3.4 Olefin cyclopropanation

Rhodium and ruthenium complexes 92 and 93 were successfully used as catalysts for the cyclopropanation of styrene 89 with ethyldiazoacetate 90 (Scheme 32). This reaction is of industrial use in the synthesis of insecticides.
1.3.5 Hydrosilylation of ketones

Various rhodium carbene complexes have been tested in the hydrosilylation of terminal alkenes and alkynes, as well as ketones. Hydrosilylation is a mild way to reduce ketones to the corresponding secondary alcohols. Rhodium carbene complexes and mixed phosphine-carbene systems such as [RhCl(PPh$_3$)$_2$(carbene)] have been proved to be efficient catalysts for the reaction of triethylsilane with acetophenone. All these catalysts have remarkably long lifetimes, no signs of decomposition being observed after reaction times in excess of two weeks.

With chiral complex 98, optical induction of higher than 30% was achieved for the reaction of acetophenone 94 with diphenylsilane 95 (Scheme 33).$^{85,34}$ This was the first reported example of asymmetric catalysis using chiral carbene complexes. The enantiomeric excesses reported at that time (>30%) were subsequently improved to >70%.

Reagents and conditions: (i) 98 (1 mol%), THF, –20 °C, (ii) p-toluene sulfonic acid, MeOH, 90%.

Scheme 33: Hydrosilylation of acetophenone 94.
1.3.6 Copolymerization

Herrmann et al. recently reported that the copolymerization of ethylene 99 and carbon monoxide 100 catalyzed by palladium N-heterocyclic carbene complex 102 gave high molecular weight and strictly alternating poly-(C<sub>2</sub>H<sub>4</sub>CO) under mild conditions and low pressures (Scheme 34).<sup>55</sup>

![Scheme 34: Copolymerization.]

1.3.7 Aryl amination

Palladium or nickel-mediated coupling of aryl halides with amines has attracted much interest due to the use of this methodology in organic synthesis. Aryl chlorides are the most desired starting materials simply because of their low cost. Nolan et al. have demonstrated that sterically hindered imidazolium salts in the presence of Pd<sub>2</sub>(dba)<sub>3</sub>.CHCl<sub>3</sub> are efficient in the amination of aryl chlorides (Scheme 35, conditions (i)) even when the use of elevated temperature was required.<sup>56</sup>

![Scheme 35: Aryl amination.]

Instead, Hartwig's group has used the dihydroimidazolium salt with Pd(dba)<sub>2</sub> (Scheme 35, conditions (ii)) and obtained near quantitative yields at room temperature when strong bases such as sodium tert-butoxide were used to deprotonate the ligand precursor.<sup>57</sup>
Recently, Fort et al. reported the first example of carbon-nitrogen couplings mediated by a nickel-N-heterocyclic carbene catalyst (Scheme 35, conditions (iii)).

Reagents and conditions: (i) t-BuOK, Pd$_2$(dba)$_3$.CHCl$_3$/5d. (1 mol%), dioxane, 100 °C, 82% or (ii) t-BuONa, Pd(dba)$_2$/106 (1 mol%), ethylene glycol dimethyl ether, r.t. quantitative yield or (iii) t-BuONa, Ni(acac)$_2$/22a (5 mol%), THF, 65 °C, 87%.

Scheme 35: Amination of aryl chloride using palladium or nickel $N$-heterocyclic carbene complexes.

Readily available heteroaryl halide 107 can also be used in a cross-coupling amination which employs $N$-heterocyclic carbene-based catalysts (Scheme 36).

Reagents and conditions: (i) t-BuONa, Pd$_2$(dba)$_3$.CHCl$_3$/110 (4 mol%), dioxane, 100-110 °C, 67%.

Scheme 36: Cross-coupling amination of heteroaryl halide 107.
1.3.8 Amide α-arylation

Sterically hindered \(N\)-heterocyclic carbenes have become the ligands of choice for the palladium-catalysed α-arylation of amides. The Hartwig group showed recently that cyclization reactions give excellent yields when bulky ligand precursors such as \(N\)-heterocyclic imidazolium salts are employed in the presence of palladium acetate. An enantiomeric excess up to 67% was obtained when chiral imidazolium salt 113 or 114 was used as a ligand precursor in the cyclization of amides (Scheme 37).

![Scheme 37: Amide α-arylation](image)

_Reagents and conditions: (i) \(t\)-BuONa, Pd(dba)_2/113 (5 mol%), 1,4-dioxane, 25 °C, 24 h, 57\% ee, 74\% or \(t\)-BuONa, Pd(dba)_2.CHCl/114 (10 mol%), ethylene glycol dimethyl ether, 20 °C, 14 h, 43\% ee, 95\%._

1.3.9 Heck coupling and Suzuki coupling

The Heck coupling of aryl bromides and aryl chlorides was first reported in 1995, using the complexes 118 and 119 (Scheme 38). Unexpected were the very low catalyst loadings (0.0004-0.5 mol%) necessary to obtain yields in excess of 99\% in the case of bromides. Aryl chlorides required catalyst loadings of 0.1-1 mol%.
**Reagents and conditions:** (i) 118 or 119 (0.5 mol%), N,N-dimethylacetamide, 125 °C, 10 h, > 99%.

**Scheme 38: Heck coupling**

Following the first reports of Suzuki cross-coupling using carbene ancillary ligands, involved aryl bromides and activated aryl chlorides, non-activated, aryl chlorides were coupled successfully. A typical example is shown in **Scheme 39**. The sterically demanding 1,3-bis(mesityl)imidazol-2-ylidene 6c (generated *in situ* from the imidazolium chloride 5c) proved to be the best choice of ligand.

**Reagents and conditions:** (i) Pd$_2$(dba)$_3$, CHCl$_3$ (1.5 mol%), 5c (3.0 mol%), Cs$_2$CO$_3$ (2 eq), dioxane, 80 °C, 90 min, 99%.

**Scheme 39: Suzuki cross-coupling**
The phosphine-free N-heterocyclic carbene catalyst 123 (Figure 9), both as the isolated complex or generated in situ, is an active catalyst for Suzuki coupling of aryl chlorides to form substituted biphenyls. Reaction times between 2 and 24 hours are sufficient at room temperature, while at 80 °C the reaction is approximately six times faster.$^{62}$

Figure 9: N-heterocyclic carbene complex 123 used in Suzuki cross-coupling

Highly active and very stable catalysts for Heck and Suzuki coupling reactions were discovered in certain palladium complexes of N-heterocyclic carbones with "dangling" $N$-substituents.$^{63}$ Catalyst 124 (Figure 10) performed particularly well, giving for the Suzuki coupling greater than 85% conversion for the coupling of 4-bromoacetophenone with both butyl acrylate and phenylboronic acid.$^{64}$

Figure 10: Palladium N-heterocyclic carbene complex with "dangling" $N$-substituents
High efficiencies in Heck reactions of aryl bromides were reported by the Nolan group, which used palladium in the presence of C,P-chelating N-heterocyclic carbene ligands derived from the sterically demanding imidazolium salt 128 (Scheme 40). A catalyst loading of 0.5 mol% based on palladium was sufficient to obtain good yields. Caesium carbonate turned out to be the most efficient base, much better than potassium tert-butoxide, sodium acetate, and potassium carbonate.

Reagents and conditions: (i) Pd(dba)$_2$/128 (0.5 mol%), Cs$_2$CO$_3$ (1.4 eq), N,N-dimethylacetamide, 120 °C, 4 h, 96%.

Scheme 40: Heck coupling mediated by a palladium/phosphine-imidazolium salt system.

Exceptionally stable nickel and palladium complexes 129 and 130 derived from imidazolium-linked ortho-cyclophanes (Figure 11),$^{22d}$ catalyse both Heck and Suzuki coupling reactions of aryl bromides and iodides with remarkable activities.

Figure 11: Stable nickel and palladium complexes 129 and 130.
Numerous papers confirm the extraordinarily high thermal robustness of $N$-heterocyclic carbene catalysts in Heck and Suzuki coupling reactions.\textsuperscript{22b,66} For example, the bis-(carbene)-palladium catalyst 131 (Figure 12) maintains activity in Heck coupling of aryl bromides even at 184 °C in air.\textsuperscript{22c}

\begin{center}
\includegraphics[width=0.5\textwidth]{131.png}
\end{center}

**Figure 12**: Bis-(carbene) palladium catalyst 131.

### 1.3.10 Sonogashira coupling

The palladium $N$-heterocyclic carbene complex 135, which is active in the Heck and Suzuki C-C coupling, can also be employed in Sonogashira cross-coupling (Scheme 41).\textsuperscript{67}

\begin{center}
\begin{align*}
132 + HC≡CSi & \rightarrow (i) \rightarrow 134 \\
\text{Reagents and conditions: (i) 135 (1 mol%), Cul, Pr}_3\text{NEt, DMF, 85%}. \\
\end{align*}
\end{center}

**Scheme 41**: Sonogashira coupling
Copper-free conditions were reported for the Sonogashira coupling of aryl bromides such as 136 with alkynylsilanes such as 137 (Scheme 42).\textsuperscript{68}

\[
\begin{align*}
\text{H}_2\text{C}-\text{Br} & + \text{TMS-} & \begin{array}{c}
\text{H} \\
\text{H}
\end{array} & \begin{array}{c}
\text{H} \\
\text{H}
\end{array} & \begin{array}{c}
\text{H} \\
\text{H}
\end{array}
\begin{array}{c}
\text{Cl} \\
\text{Cl}
\end{array} \\
\begin{array}{c}
\text{Cl} \\
\text{Cl}
\end{array} \\
\begin{array}{c}
\text{Cl} \\
\text{Cl}
\end{array} \\
\begin{array}{c}
\text{Cl} \\
\text{Cl}
\end{array}
\end{align*}
\]

\begin{align*}
\text{Reagents and conditions:} & \text{ (i) } \text{Pd(OAc)}_2/5c, \text{Cs}_2\text{CO}_3, \text{N,N-dimethylacetamide}, 80 \text{ °C}, 15 \text{ min}, 92%.
\end{align*}

\textbf{Scheme 42: Copper-free Sonogashira coupling}

\begin{center}
\begin{tikzpicture}
\end{tikzpicture}
\end{center}

\textbf{1.3.11 Kumada coupling (Grignard cross-coupling)}

In 1999, Nolan et al. reported a methodology for the Kumada reaction. This methodology proved to be efficient for unactivated aryl chlorides, aryl bromides, and aryl iodides by simply employing a palladium source and an imidazolium salt as the catalytic precursor.\textsuperscript{69} When chlorotoluene 139 was reacted with phenylmagnesium bromide 140 using Pd\(_2\)(dba)\(_3\)/IPrHCl 5d as the catalyst precursor, the desired 4-phenyltoluene 141 was isolated in 99% yield (Scheme 43).

\[
\begin{align*}
\text{H}_3\text{C}-\text{Cl} & + \text{BrMg} & \begin{array}{c}
\text{H} \\
\text{H}
\end{array} & \begin{array}{c}
\text{H} \\
\text{H}
\end{array} & \begin{array}{c}
\text{H} \\
\text{H}
\end{array}
\begin{array}{c}
\text{Cl} \\
\text{Cl}
\end{array} \\
\begin{array}{c}
\text{Cl} \\
\text{Cl}
\end{array} \\
\begin{array}{c}
\text{Cl} \\
\text{Cl}
\end{array} \\
\begin{array}{c}
\text{Cl} \\
\text{Cl}
\end{array} \\
\begin{array}{c}
\text{Cl} \\
\text{Cl}
\end{array}
\end{align*}
\]

\begin{align*}
\text{Reagents and conditions:} & \text{ (i) } \text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3/5d, \text{dioxane/THF}, 80 \text{ °C}, 3 \text{ h}, 99%.
\end{align*}

\textbf{Scheme 43: Kumada coupling}
1.3.12 Stille coupling

Another common type of C-C coupling, named after John Stille, works with catalysts generated from Pd(OAc)$_2$ and imidazolium salts. Scheme 44 shows the cross-coupling of 4-bromoanisole 142 with phenyltrimethyltin 143 catalysed by the Pd(OAc)$_2$/IPrHCl 5d system.

Scheme 44: Stille coupling.

Reagents and conditions: (i) Pd(OAc)$_2$/5d (3 mol%), TBAF (2 equivalents), dioxane/THF, 80 °C, 30 min, 92%.
References for Chapter 1


36


Chapter 2: Synthesis of 1,4-bis substituted imidazolium salts and their corresponding carbene-complexes

2.1 Introduction

![Diagram]

**Figure 1**: New N-heterocyclic carbene complexes.

The aim of this project is to synthesize new N-heterocyclic carbene complexes (Figure 1) where L could be oxygen, nitrogen, sulphur or phosphorus.

The choice of this type of imidazolium salt (Figure 1) can be justified by the fact that it is believed that the heteroatom L could coordinate the metal M. This would increase the stability of the metal complex. It is also believed, that during a reaction, where the metal complex will be used as catalyst, the coordination between heteroatom L and metal M will be removed, leaving the metal free to react. Then, at the end of the reaction, the heteroatom L will again coordinate the metal M. Schematically, it is believed that the two groups on the imidazole moiety will act as two arms; moving up at the beginning of the reaction and moving down when the reaction is finished and leading to re-coordination of the metal (Scheme 1).
According to the literature, imidazolium salts can be prepared by four different methods as shown in **Scheme 2**. 

**Scheme 1**: Mechanism of a Heck coupling using a carbene complex as catalyst
Method A

\[ 2 \text{R-NH}_2 \rightarrow (i) \rightarrow \text{imidazolium salt} \]

Method B

\[ \text{R}^1-\text{NH}_2 \rightarrow (ii) \rightarrow \text{imidazolium salt} \]

Method C

\[ \text{imidazolium salt} \rightarrow (v) \rightarrow \text{imidazolium salt} \]

Method D

\[ \text{imidazolium salt} \rightarrow (vii) \rightarrow \text{imidazolium salt} \]

Reagents and conditions: (i) glyoxal, (ii) paraformaldehyde, acid, (iii) glyoxal, NH₄Cl, paraformaldehyde, H₃PO₄, (iv) R²-X, (v) K, (vi) R¹-X, (vii) HC(OEt)₃, NH₄BF₄.

Scheme 2: Convenient synthetic routes to imidazolium salts.

In the case of method A, symmetric imidazolium salts can be obtained. The first step is a simple condensation between two equivalents of an amine with glyoxal to afford a diazabutadiene, which can then cyclize with paraformaldehyde in presence of acid to give the corresponding imidazolium salt.

The same method has been used for the synthesis of the ruthenium complex depicted in Figure 2, which has been used as catalyst in ring closing metathesis.¹
Unsymmetrical imidazolium salts can be prepared by method B (Scheme 2), which is a variation of method A. The first step consists in the formation of a mono alkyl imidazole species and the second step is an alkylation of this imidazole species with an alkyl halide, bearing a different group than the one on the amine in the first step, to give the corresponding unsymmetrical imidazolium salt.

Concerning method C, the first step is a simple alkylation between an imidazole anion and alkyl halide to give a mono alkyl imidazole species which is then alkylated with a different alkyl halide to give the corresponding imidazolium salt (Method C, Scheme 2). Unfortunately, this method only works well for primary alkyl halides. For secondary or tertiary alkyl halides, elimination was found to be a major side reaction.²

The advantage of this process is that there is the possibility of obtaining an imidazolium salt having either a chiral residue on one side, or two different chiral residues. This methodology has been applied for the synthesis of a palladium complex which has been used as catalyst in Heck reaction (Figure 3).³

Figure 2: Ruthenium complex synthesized using method A.

Figure 3: Palladium complex synthesised using the method C.
Finally, the orthoformate route (method D, Scheme 2) converts easily accessible 1,2-diamines into the corresponding imidazolium salts using ammonium tetrafluoroborate and triethyl orthoformate.\(^4\)

Imidazolium salts are electron-rich heteroaromatic compounds. Hence, the \(^{13}C\) NMR shift of the N-C-N \(sp^2\) carbon (which later becomes the carbene centre) appears at \(\delta \approx 135-145\) ppm. The C-H ring protons and the C-H acidic proton resonate at \(\delta = 7-9\) and 8-10 ppm, respectively.

In this section, functionalised 1,4-bis-imidazolium salts were synthesised in two steps according to the method described by Huang and Nolan (method A, Scheme 2).\(^5\)

### 2.2 Synthesis of different 1,4-bis substituted diazabutadiene

#### 2.2.1 Synthesis of 1,4-bis-(2,6-diisopropylphenyl) diazabutadiene 1

![Diagram of diazabutadiene 1]

**Reagents and conditions:** (i) glyoxal, formic acid, ethanol, r.t., 2 days, 80%.

**Scheme 3:** Synthesis of the diazabutadiene 1.

Following the procedure of Huang and Nolan,\(^5,6,7\) the diazabutadiene 1 was obtained in 80% yield. The reaction mixture of 2 equivalents of 2,6-diisopropylaniline with 1 equivalent of glyoxal in absolute ethanol in the presence of formic acid as catalyst (Scheme 3) was reacted for 2 days at room temperature. The diazabutadiene 1 was sufficiently pure for the subsequent cyclization reaction.

45
2.2.2 Synthesis of 1,4-bis-(2-methylthiophenyl) diazabutadiene 2

\[
\text{Reagents and conditions: (i) glyoxal, formic acid, ethanol, r.t., 2 days, 74%.
}
\]

Scheme 4: Synthesis of the diazabutadiene 2.

The diazabutadiene 2 was synthesized under the same reaction conditions as those used in the synthesis of 1 (Scheme 4). In this case the 1,4-bis-(2-methylthiophenyl) diazabutadiene 2 was obtained after recrystallization from hot toluene in 74% yield.

2.2.3 Synthesis of 1,4-bis-(2-pyridine) diazabutadiene 3

Table 1: Synthesis of the diazabutadiene 3.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Acid</th>
<th>Reaction conditions</th>
<th>Diazabutadiene 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EtOH</td>
<td>HCOOH</td>
<td>r.t., 3 days, then reflux, overnight</td>
<td>Present</td>
</tr>
<tr>
<td>2</td>
<td>EtOH</td>
<td>HCOOH</td>
<td>r.t., 6 days</td>
<td>Present</td>
</tr>
<tr>
<td>3</td>
<td>-/DCM\textsuperscript{a}</td>
<td>-</td>
<td>0 °C, 30 min, then r.t., 11 days</td>
<td>No trace</td>
</tr>
</tbody>
</table>

\textsuperscript{2}: Solvent added after the addition of all the reagents to keep the reaction mixture to be stirred.

Still following the procedure described by Huang and Nolan, 2 equivalents of 2-aminopyridine was treated with glyoxal in absolute ethanol in the presence of a few drops of formic acid (Entry 1 and 2, Table 1). In both cases no precipitate appeared.
The solvent was evaporated and a black solid was obtained; this was identified by $^1$H NMR spectroscopy as a mixture containing a small amount of the diazabutadiene 3 (signal at 8.44 ppm corresponding to the azomethine proton) along with other unidentified products. The small amount of the diazabutadiene 3 was not isolated due to the instability of this compound on silica or alumina.

A final attempt (Entry 3, Table 1) was made without solvent and without formic acid, but after 11 days, the $^1$H NMR spectrum of the crude reaction mixture showed signals of starting material along with some unidentified compounds. No trace of the desired diazabutadiene 3 was observed. On the basis of these results we decided to abandon the synthesis of this particular diazabutadiene.

### 2.2.4 Synthesis of 1,4-bis-(2-methoxyethyl) diazabutadiene 4

![Chemical structure of 1,4-bis-(2-methoxyethyl) diazabutadiene 4]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Acid</th>
<th>Reaction conditions</th>
<th>Diazabutadiene 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EtOH</td>
<td>HCOOH</td>
<td>r.t., 5 days</td>
<td>Present</td>
</tr>
<tr>
<td>2</td>
<td>EtOH</td>
<td>HCl</td>
<td>r.t., 20 h</td>
<td>No trace</td>
</tr>
<tr>
<td>3</td>
<td>EtOH</td>
<td>HCl</td>
<td>0°C then r.t., 20 h</td>
<td>No trace</td>
</tr>
<tr>
<td>4</td>
<td>EtOH</td>
<td></td>
<td>r.t., 20 h</td>
<td>No trace</td>
</tr>
<tr>
<td>5</td>
<td>EtOH</td>
<td>HCOOH</td>
<td>0°C then r.t., 2 days</td>
<td>Present</td>
</tr>
<tr>
<td>6</td>
<td>-/DCM$^a$</td>
<td>HCOOH</td>
<td>r.t., 2 days</td>
<td>Present</td>
</tr>
</tbody>
</table>

$^a$: Solvent added after the addition of all the reagents to keep the reaction mixture to be stirred.

Table 2: Attempts to synthesise the diazabutadiene 4.

The procedure was then applied to the 2-methoxyethylamine. After 5 days (Entry 1, Table 2), TLC showed complete consumption of starting material. The solvent was evaporated and an orange oil was obtained. The $^1$H NMR spectrum of the crude reaction mixture showed the presence of a mixture containing the desired
product 4 (signal at 8.6 ppm corresponding to the azomethine proton). However, the diazabutadiene 4 could not be isolated by column chromatography due to its instability on silica or alumina.

Further attempts were performed using hydrochloric acid instead of formic acid (Entry 2 and 3, Table 2), but in this case no trace of the desired diazabutadiene 4 was observed even when the addition was carried out at room temperature or at 0 °C.

In order to determine if the use of an acid is required for the formation of the diazabutadiene 4, an attempt was made without adding acid (Entry 4, Table 2). Molecular sieves were used, which were expected to remove the water generated during the condensation reaction and move the equilibrium in the direction of the formation of the desired product. Unfortunately, in this case no trace of the diazabutadiene 4 was observed.

In conclusion, evidence for the formation of 4 was only obtained with the use of a weak acid. As a small amount of the diazabutadiene 4 was obtained at room temperature, the effect of lower reaction temperature was investigated.

A new attempt was performed adding glyoxal and formic acid at 0 °C (Entry 5, Table 2). After 2 days reaction time, a mixture was obtained containing traces of the desired product 4.

Unfortunately, none of the different conditions tested afforded a clean reaction. In order to understand how solvent affects the reaction, an attempt was made without solvent (Entry 6, Table 2), and after 2 days, a mixture containing traces of the diazabutadiene 4 was obtained. This last attempt shows that a solvent-free reaction can produce the desired product, although not cleanly.

Of all the attempted synthesis, only traces of the diazabutadiene 4 were obtained and, due to its apparent instability on silica and alumina, isolation of the desired diazabutadiene was unsuccessful. We believed that protecting the alcohol functionality with a large protecting group might make the diazabutadiene crystalline and therefore easier to isolate in the case of instability on silica or alumina. Synthesis of the diazabutadiene protected by tert-butyldimethylsilyl was thus next investigated.
2.2.5 Attempted synthesis of 1,4-bis-[2-(tert-butyldimethylsilyloxy)ethyl] diazabutadiene 6

Reagents and conditions: (i) Et₃N, TBDMSCI, DMAP, DCM, r.t., overnight, 89%.

Scheme 5: Preparation of 2-(tert-butyldimethylsilyloxy) ethyl amine 5.

A common method used to protect alcohols with tert-butyldimethylsilyl chloride is to use triethylamine as a base in dichloromethane in presence of tert-butyldimethylsilyl chloride and 4-dimethylaminopyridine. This procedure was applied to ethanolamine (Scheme 5) and the desired product 5 was obtained in 89% yield.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Reaction conditions</th>
<th>Diazabutadiene 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EtOH</td>
<td>r.t., 2 days</td>
<td>No trace</td>
</tr>
<tr>
<td>2</td>
<td>—</td>
<td>r.t., 2 days</td>
<td>No trace</td>
</tr>
</tbody>
</table>

Table 3: Synthesis of the diazabutadiene 6.

Following the procedure of Huang and Nolan, 2 equivalents of 2-(tert-butyldimethylsilyloxy) ethyl amine 5 was treated with glyoxal in absolute ethanol (Entry 1, Table 3). Formic acid was not used in order to avoid the cleavage of the protecting group. After 2 days, the solvent was removed under reduced pressure and an orange oil was obtained; this was identified by ¹H NMR spectroscopy as a complex.
mixture containing no traces of the diazabutadiene 6. Another attempt was performed without solvent (Entry 2, Table 3) but the same complex mixture was obtained.

On the basis of these results we decided to abandon the synthesis of this diazabutadiene and instead try to synthesize the phenoxy derivative 7.

2.2.6 Attempted synthesis of 1,4-bis-(2-phenyloxyethyl) diazabutadiene 7

Reagents and conditions: (i) glyoxal, formic acid, ethanol, r.t., 2 days, 35%.

Scheme 6: Synthesis of the diazabutadiene 7.

Condensation of glyoxal with 2-phenyloxyethylamine in absolute ethanol gave, after 2 days, an orange oil which was crystallized in hot toluene to afford light yellow crystals. The $^1$H NMR spectrum showed a signal at 8.20 ppm, which could correspond to the azomethine proton, and a broad signal at 6.25 ppm, which cannot be attributed as a proton from the diazabutadiene 7. The integration of the different signals also confirmed that the product obtained could not be the diazabutadiene 7. X-ray (Appendix 1) of the light yellow crystals show that the product obtained is the formamide 8 (Figure 4).

A possible mechanism proposed to explain the formation of the formamide 8 is shown in Scheme 7.
In order to confirm the proposed mechanism, the reaction was repeated at room temperature without using formic acid. In this case, however, the main product was still the formamide 8, which shows that this mechanism is perhaps unsuitable.

A last attempt was performed at 0 °C using formic acid and in this case the condensation gave the formamide 8 along with an unidentified product.

In conclusion, condensation of 2-phenyloxyethylamine with glyoxal with or without formic acid, at room temperature and at 0 °C, gave the \( N\)-[2-(phenyloxy)ethyl]formamide 8 and not the expected diazabutadiene 7.

**Figure 4:** \( N\)-[2-(phenyloxy)ethyl]formamide 8 suggested by X-Ray analysis.
2.2.7 Synthesis of 1,4-bis-(2-hydroxyphenyl) diazabutadiene 9

Reagents and conditions: (i) glyoxal, formic acid, ethanol, r.t., 3 days, 73%.

Scheme 8: Synthesis of the diazabutadiene 9.

The procedure was then applied to the 2-aminophenol (Scheme 8). In this case the corresponding diazabutadiene 9 was obtained in 73% yield. Interestingly, we observe that the $^1$H NMR spectrum of compound 9 in CDCl$_3$ shows signals at 4.88 ppm and 5.32 ppm. But the $^1$H NMR spectrum in DMSO-d$_6$ shows signals at 5.25 ppm and 7.32 ppm. The very large difference in chemical shift between these two spectra suggests that the compound 9 in CDCl$_3$ and DMSO-d$_6$ does not adopt the same structure. Compound 10 has previously been reported in the literature$^{10}$ and comparison with the $^1$H NMR spectra obtained with the known compound show that the structure adopted by the diazabutadiene in DMSO-d$_6$ is 10. The stereochemistry of the compound 10 is suggested as cis.

The presence of a free hydroxy group might not be favourable during the subsequent cyclization, so the synthesis of the corresponding ditosylated diazabutadiene was then attempted.
2.2.8 Attempted synthesis of 1,4-bis-(2-p-toluene sulfonyl acid phenyl ester) diazabutadiene 12

\[
\begin{align*}
\text{Reagents and conditions: } & (i) \text{ Et}_3\text{N, TsCl, DCM, r.t., overnight, 93%}. \\
\text{Scheme 9: Synthesis of 2-aminophenyl-4-toluene sulfonate 11.}
\end{align*}
\]
Tosylation of the 2-aminophenol was performed using 1.1 equivalents of triethylamine, and 1.1 equivalents of p-toluene sulfonyl chloride in dichloromethane to produce the desired product 11 in 93% yield (Scheme 9).

\[
\begin{array}{c}
\text{H} \\
\text{O}
\end{array}
\text{NH}_2
\begin{array}{c}
\text{O}
\end{array}
\text{Ts} + \begin{array}{c}
\text{O}
\end{array}
\text{CO} \rightarrow \begin{array}{c}
\text{N}
\end{array}
\begin{array}{c}
\text{N}
\end{array}
\text{O}
\begin{array}{c}
\text{O}
\end{array}
\text{Ts} \text{Ts}
\end{array}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Acid</th>
<th>Reaction conditions</th>
<th>Diazabutadiene 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EtOH</td>
<td>HCOOH</td>
<td>r.t., 2 days</td>
<td>No trace</td>
</tr>
<tr>
<td>2</td>
<td>-/DCM(^a)</td>
<td>—</td>
<td>0 °C then r.t., 11 days</td>
<td>No trace</td>
</tr>
</tbody>
</table>

\(^a\): Solvent added after the addition of all the reagents to keep the reaction mixture to be stirred.

**Table 5: Attempts to synthesize the diazabutadiene 12.**

The same condensation method was applied to 2-aminophenyl-4-toluene sulfonate 11 in absolute ethanol (Entry 1, Table 5). After 2 days, a small amount of a white precipitate was collected by filtration and identified by \(^1\)H NMR spectroscopy as a mixture containing traces of starting material and some unidentified compounds. Evaporation of the filtrate gave an orange oil containing no trace of the desired diazabutadiene 12.

Condensation of 2-aminophenyl-4-toluene sulfonate 11 with glyoxal, without solvent and in the absence of formic acid was also carried out (Entry 2, Table 5). The evolution of the reaction was monitored by \(^1\)H NMR spectroscopy and after 11 days the spectrum showed not only that some starting material remained, but also that signals corresponding to the desired diazabutadiene 12 were not evident.

One reason for our inability to form the diazabutadiene could be the bulkiness of the tosyl group. Therefore, the protection of the alcohol function on the 1,4-bis-(2-hydroxyphenyl) diazabutadiene 9 with a less bulky group such as methyl was then attempted.
2.2.9 Synthesis of 1,4-bis-(2-methoxyphenyl) diazabutadiene 13

![Chemical structure of 9 and 13](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction conditions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et$_3$N, DCM, MeI, r.t., 1 day</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>t-BuOK, DCM, MeI, r.t., overnight</td>
<td>9</td>
</tr>
<tr>
<td>3</td>
<td>K$_2$CO$_3$, acetone, MeI, reflux, 6 h$^{12}$</td>
<td>9</td>
</tr>
<tr>
<td>4</td>
<td>NaH, THF, MeI, 0 °C, 24 h</td>
<td>Decomposition</td>
</tr>
<tr>
<td>5</td>
<td>Cs$_2$CO$_3$, DCM, (MeO)$_2$SO$_2$, r.t., 48 h</td>
<td>9</td>
</tr>
<tr>
<td>6</td>
<td>n-BuLi, THF, MeOTf, - 78 °C, 5 h$^{13}$</td>
<td>No trace</td>
</tr>
</tbody>
</table>

Table 6: Attempts to synthesize the diazabutadiene 13.

The methylation of the diazabutadiene 9 was attempted using different bases and different solvents (Table 6), but unfortunately in nearly all of the cases only starting material was recovered (Entry 1, 2, 3 and 5, Table 6). Decomposition of 9 was observed when sodium hydride in tetrahydrofuran with iodomethane was employed (Entry 4, Table 6).
Recently, the Page and Heaney group reported a method to protect a phenolic hydroxy group using n-butyllithium and methyltriflate at \(-78\, ^\circ C\) (Scheme 10).\(^{13}\)

\[
\text{Ph} \quad \text{Me} \\
\text{N} \\
\text{O} \\
\text{OH} \\
\text{C}_{11}\text{H}_{23} \\
\text{(i)} \rightarrow \\
\text{Ph} \quad \text{Me} \\
\text{N} \\
\text{O} \\
\text{OMe} \\
\text{C}_{11}\text{H}_{23}
\]

*Reagents and conditions*: (i) \(n\)-BuLi, MeOTf, THF, \(-78\, ^\circ C\), 84%.

**Scheme 10**: Methylation of a phenolic hydroxy group.

This method was then applied to the diazabutadiene 9, and after 5 hours at \(-78\, ^\circ C\) (Entry 6, Table 6), the TLC showed that the reaction was still not complete and no progression could be observed. The \(^1\text{H}\) NMR spectrum of the brown residue showed no signal around 7-9 ppm, which indicates the absence of the desired diazabutadiene 13.

An alternative to this could be to condense glyoxal with 2-methoxyaniline, which is commercially available.
Entry | Solvent | Acid | Reaction conditions | Diazabutadiene 13
--- | --- | --- | --- | ---
1 | EtOH | HCOOH | r.t., 14 days | Starting material + Unidentified products
2 | -/DCM* | - | 0 °C then r.t., 11 days | Starting material + Unidentified products
3 | -/H₂O* | - | 0 °C then r.t., 14 days | Starting material + 13

*: Solvent added after the addition of all the reagents to keep the reaction mixture to be stirred.

Table 7: Attempts to synthesize the diazabutadiene 13.

Following the same method as employed previously, 2-methoxyaniline was treated with glyoxal in either ethanol in the presence of formic acid (Entry 1, Table 7) or without solvent and without acid (Entry 2, Table 7). The progress of the reaction was followed by TLC (dichloromethane), after 14 and 11 days respectively in both cases the TLC showed that some starting material remained. Further, ¹H NMR spectroscopy of the crude mixture, no matter which reaction conditions had been used, showed some broad signals and several peaks in the area of 8-9 ppm, which make it difficult to identify the presence of the desired diazabutadiene 13.

However, adding pure water after addition of all the reagents (Entry 3, Table 7) gave a brown solid identified by ¹H NMR spectroscopy as a mixture containing traces of the desired diazabutadiene 13 (signal at 8.54 ppm which corresponds to the azomethine protons) along with some starting material. Unfortunately, we were unable to bring the reaction to completion even by addition of more glyoxal. Again, purification of the diazabutadiene 13 by column chromatography was to be avoided due to the instability of this compound 13 on silica or alumina. Attempts to isolate 13 by crystallization were carried out but none of them have been successful.
2.2.10 Synthesis of 1,4-bis-[2-(tert-butyldimethylsilyloxy)phenyl]diazabutadiene 15

Reagents and conditions: (i) Et₃N, TBDMSCl, DMAP, DCM, r.t., overnight, 93%.

Scheme 11: Preparation of 2-(tert-butyldimethylsilyloxy)aniline 14.

Following the same procedure (Scheme 11) used for the preparation of the protected amino alcohol 5, the protected aminophenol 14 was obtained in 93% yield.¹⁴

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Reaction conditions</th>
<th>Diazabutadiene 15</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EtOH</td>
<td>r.t., 2 days</td>
<td>No trace</td>
</tr>
<tr>
<td>2</td>
<td>EtOH</td>
<td>Molecular sieves, r.t., 5 days</td>
<td>Present</td>
</tr>
<tr>
<td>3</td>
<td>–/DCMᵃ</td>
<td>0 °C then r.t., 13 days</td>
<td>Present</td>
</tr>
<tr>
<td>4</td>
<td>–/H₂Oᵃ</td>
<td>0 °C then r.t., 6 days</td>
<td>Present</td>
</tr>
</tbody>
</table>

ᵃ: Solvent added after the addition of all the reagents to keep the reaction mixture to be stirred.

Table 8: Synthesis of the diazabutadiene 15.

Still following the same procedure, the protected aminophenol 14 was treated with glyoxal under different conditions. Formic acid was not used in order to avoid cleavage of the tert-butyldimethylsilyl protecting group. The results of these attempts are summarized in Table 8.
When the reaction was performed in ethanol (Entry 1, Table 8) no trace of the desired diazabutadiene 15 was observed, but a complex mixture was obtained. It was only when the reaction was performed in ethanol using molecular sieves or when the addition of all the reagents was made without solvent (Entry 2, 3 and 4, Table 8) that the $^1$H NMR spectrum of the crude residue obtained showed a signal at 8.36 ppm which could correspond to the proton on the diazabutadiene moiety. Due to the instability of the compound on silica or alumina, isolation by chromatography was not attempted. Attempts to isolate the desired diazabutadiene 15 by crystallization were instead investigated but unfortunately were unsuccessful.

**Conclusion of section 2.2**

In conclusion, several different amines were condensed with glyoxal in a attempt to obtain the corresponding diazabutadienes. Only two of these were successful. The major difficulty, which has been found during the synthesis of such diazabutadienes, is their instability on silica and alumina, which made the isolation of the desired product more difficult if not impossible in those cases where the final product is not crystalline.

**2.3 Synthesis of 1,3-bis substituted imidazolium salts**

**2.3.1 Synthesis of 1,3-bis-(2,6-diisopropylphenyl) imidazolium salts 16 and 17**

![Diagram of imidazolium salts 16 and 17]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction conditions</th>
<th>Imidazolium salt</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(HCOH)$_n$ toluene, 36 h, HCl</td>
<td>16 47%</td>
</tr>
<tr>
<td>2</td>
<td>(HCOH)$_n$ toluene, 90 h, HBF$_4$</td>
<td>17 88%</td>
</tr>
</tbody>
</table>

**Table 9: Synthesis of the imidazolium salts 16 and 17.**
When the diazabutadiene 1 was treated with paraformaldehyde and hydrochloric acid for 36 hours at room temperature (Entry 1, Table 9) the corresponding imidazolium salt 16 was obtained as a colourless solid in 43% yield. The reaction of 1 using tetrafluoroboric acid (Entry 2, Table 9) instead of hydrochloric acid under the same conditions with a reaction time of 90 hours instead of 36 hours gave the corresponding imidazolium salt 17 in 88% yield.

2.3.2 Synthesis of 1,3-bis-(2-methylthiophenyl) imidazolium chloride 18, tetrafluoroborate 19, triflate 20 and tetraphenylborate 21

![Synthesis diagram]

Reagents and conditions: (i) (HCOH)_n, HCl, toluene.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction conditions</th>
<th>Imidazolium salt</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100 °C then addition of HCl at 40 °C then r.t. for 36 h</td>
<td>Traces</td>
</tr>
<tr>
<td>2</td>
<td>50 °C then addition of HCl at r.t. then r.t. for 48 h</td>
<td>55% impure</td>
</tr>
<tr>
<td>3</td>
<td>120 °C Dean-Stark then addition HCl at r.t. then 70 °C overnight then r.t. for 36 h</td>
<td>71% impure</td>
</tr>
</tbody>
</table>

Table 10: Attempts to synthesise the imidazolium salt 18.

When the diazabutadiene 2 was treated with paraformaldehyde under the conditions described by Huang and Nolan (Entry 1, Table 10), the reaction was not clean and a complex mixture containing traces of the required product 18 was obtained.

A further attempt was made using modified reaction conditions (Entry 2, Table 10). Instead of heating at 100 °C in order to dissolve most of the paraformaldehyde, the reaction was heated to 50 °C and the addition of hydrochloric
acid was made at room temperature instead of 40 °C. In this case the reaction was cleaner and a black solid was obtained and identified by $^1$H NMR spectroscopy (DMSO-$d_6$) as containing the desired product 18, recognized by signals at 10.02 ppm and 8.33 ppm, corresponding at the protons on the imidazolium moiety.

A last attempt was performed under Dean-Stark conditions (Entry 3, Table 10) before the addition of hydrochloric acid in order to remove any water present in the reaction mixture. Unfortunately, in this case, the imidazolium salt 18 was again not pure enough for the subsequent reaction, and its instability on silica and on alumina made its purification unsuccessful. Different methods of recrystallization were attempted without success.

An alternative to this could be to replace the counter anion with a larger anion such as BF$_4^-$, TfO$^-$ or BPh$_4^-$, which could aid crystallization.

![Chemical structure](image)

*Reagents and conditions: (i) (HCOH)$_n$, HX, toluene.*

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction conditions</th>
<th>Salt</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50 °C then addition of HBF$_4$ at r.t. then r.t. for 40 h</td>
<td>Traces</td>
</tr>
<tr>
<td>2</td>
<td>Addition of HBF$_4$ at r.t. then 120 °C Dean-Stark for 24 h</td>
<td>Traces</td>
</tr>
<tr>
<td>3</td>
<td>50 °C then addition of HOTf at r.t. then r.t. for 48 h</td>
<td>Traces</td>
</tr>
<tr>
<td>4</td>
<td>50 °C then addition of HOTf at -20 °C then r.t. for 6 days</td>
<td>Traces</td>
</tr>
</tbody>
</table>

*Table 11: Attempts to synthesize the imidazolium salts 19 and 20.*

The first attempt was performed using tetrafluoroboric acid instead of hydrochloric acid as shown in Table 11. After 40 hours reaction time (Entry 1, Table 11), a black solid was isolated, and $^1$H NMR spectroscopy showed this to be a
complex mixture of unidentified products containing a small amount of the imidazolium salt 19 (signals at 10.02 ppm and 8.33 ppm (DMSO-d$_6$) corresponding at the protons on the imidazolium moiety). The use of a Dean-Stark trap was also investigated (Entry 2, Table 11), which again afforded traces of the desired imidazolium salt 19.

The reaction was also carried out using triflic acid instead of hydrochloric acid or tetrafluoroboric acid. In this case, even if the addition of the acid was performed at room temperature (Entry 3, Table 11) or at $-20\, ^\circ\mathrm{C}$ (Entry 4, Table 11), the reaction did not occur cleanly and only traces of the expected imidazolium salt 20 were detected (signals at 9.0 ppm and 7.8 ppm corresponding at the protons on the imidazolium moiety).

![Chemical structures](image)

Reagents and conditions: (i) NaBPh$_4$, ethanol, acetonitrile, r.t., 5 min.

**Scheme 12:** Attempted synthesis of imidazolium salt 21.

A further attempt was made with BPh$_4^-$ by treating the imidazolium salt 18 with sodium tetraphenylborate in a mixture of ethanol and acetonitrile (Scheme 12), but in this case no trace of the expected product 21 was detected (or the starting material). Only sodium tetraphenylborate along with a mixture of products, which probably correspond to the decomposition of the starting material, were observed in the $^1\mathrm{H}$ NMR spectrum.

In 1999 Arduengo and co-workers reported a method to synthesize IPrHCl 16 starting from its corresponding diazabutadiene 1 with chloromethylethyl ether in tetrahydrofuran by either heating at 40 $^\circ\mathrm{C}$ or using molecular sieves.$^7$
**Reagents and conditions:** (i) chloromethylethyl ether.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction conditions</th>
<th>Imidazolium salt 18</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF, H₂O, 40 °C for 18 h then r.t. for 3 days</td>
<td>Traces</td>
</tr>
<tr>
<td>2</td>
<td>THF, Molecular sieves, r.t., 7 days</td>
<td>No trace</td>
</tr>
</tbody>
</table>

**Table 12:** Attempts to synthesize the imidazolium salts 18.

This new method was then applied to the diazabutadiene 2 and the reaction was carried out at 40 °C (Entry 1, Table 12) or using molecular sieves (Entry 2, Table 12). Only when the reaction was conducted in tetrahydrofuran in the presence of few drops of water were traces of the desired imidazolium salt 18 observed (signals at 9.4 ppm and 8.3 ppm (CDCl₃) corresponding at the protons on the imidazolium moiety).

Recently enantiomerically pure imidazolium triflates have been prepared from bisoxazolines using silver triflate in combination with chloromethyl pivalate (Scheme 13) in good yield.¹⁵

**Scheme 13:** Synthesis of enantiomerically pure imidazolium triflate.
Treatment of the 1,4-bis-(2-methylthiophenyl) diazabutadiene 2 with silver triflate and chloromethyl pivalate according to the method describe by Lehmann and co-workers at room temperature for 11 days (Scheme 14) afforded traces of the expected imidazolium salt 20. Unfortunately, in our case, the corresponding imidazolium salt was not obtained pure, and purification by column chromatography was impossible due to its instability on silica and alumina. Attempts to recrystallize 20 using different solvents were unsuccessful.

**2.3.3 Synthesis of 1,3-bis-(2-hydroxyphenyl) imidazolium salts 22 and 23**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction conditions</th>
<th>Imidazolium salt</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100 °C then addition of HCl at 40 °C, then r.t. for 4 days</td>
<td>Traces</td>
</tr>
<tr>
<td>2</td>
<td>100 °C then addition of HCl at 40 °C then 120 °C Dean-</td>
<td>Traces</td>
</tr>
<tr>
<td></td>
<td>Stark overnight</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>100 °C then addition of HBF₄ at r.t. then r.t. for 4 days</td>
<td>Traces</td>
</tr>
<tr>
<td>4</td>
<td>addition of HBF₄ at r.t. then 120 °C Dean-Stark overnight</td>
<td>Traces</td>
</tr>
</tbody>
</table>

*Table 13: Attempts to synthesise the imidazolium salts 22 and 23.*
When the diazabutadiene 9 was treated with paraformaldehyde and hydrochloric acid or tetrafluoroboric acid at room temperature for 4 days or at 100 °C using a Dean-Stark trap overnight (Table 13), the reaction was not clean, and only traces of the imidazolium salt 22 and 23 were observed. The fact that the solid obtained was only soluble in ethanol and unstable on silica or alumina made purification difficult.

A reason for this lack of success could be attributed to the presence of the free hydroxy group. An alternative to this could be to protect the free hydroxy group, but unfortunately all attempts to protect the diazabutadiene 9 with tosyl chloride or iodomethane failed (see section 2.2).

**Conclusion of section 2.3**

Synthesis of IPrHCl and IPrHBF₄ has been reproduced based on the procedure described by Huang and Nolan. From 1,4-bis-(2-methylthiophenyl) diazabutadiene 2, attempts have been made to obtain the corresponding imidazolium salts by different methods. Unfortunately, none of them have been successful, and only impure corresponding imidazolium salt has been obtained. Concerning the synthesis of the 1,4-bis-(2-hydroxyphenyl) imidazolium salt, only traces of it have been detected.

**2.4 Attempted synthesis of 1,3-bis substituted saturated imidazolium salt**

On the basis of the results obtained concerning the synthesis of the imidazolium salt 18, derived from the 1,4-bis-(2-methylthiophenyl) diazabutadiene 2, we decided to investigate the synthesis of the imidazolium salt derivative from the \(N,N\)-bis-(2-methylthiophenyl)-ethane-1,2-diamine 24.

In 2001, the Hartwig group reported that \(N,N\)′-diisopinocampheylimidazolinium tetrafluoroborate could be synthesized by reduction of the corresponding diazabutadiene with sodium triacetoxyborohydride in dichloromethane followed by cyclization using triethyl orthoformate and ammonium tetrafluoroborate (Scheme 15).
Reagents and conditions: (i) NaBH(OAc)$_3$, DCM, r.t., 24 h, 50%, (ii) NH$_4$BF$_4$, triethyl orthoformate, 120 °C, 2 h, 64%.

Scheme 15: Synthesis of $N,N'$-diisopinocampheylimidazolinium tetrafluoroborate

First, the synthesis of the $N,N$-bis-(2-methylthiophenyl)-ethane-1,2-diamine 24 was carried out using different conditions as shown in Table 14.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction conditions</th>
<th>Diamine 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaBH(OAc)$_3$, DCM, r.t., 2 days</td>
<td>26%</td>
</tr>
<tr>
<td>2</td>
<td>NaBH(OAc)$_3$, DCM, reflux, 2 days</td>
<td>30%</td>
</tr>
<tr>
<td>3</td>
<td>NaBH$_4$, DCM/MeOH 1/1, r.t., 36 h</td>
<td>95%</td>
</tr>
</tbody>
</table>

Table 14: Attempts to synthesize the diamine 24.

Treatment of the diazabutadiene 2 with sodium triacetoxyborohydride in dichloromethane at room temperature following Hartwig's method for 2 days (Entry 1, Table 14) give a yellow solid identified by $^1$H NMR spectroscopy as a mixture
containing the desired product 24 along with some starting material. The desired product 24 was isolated by column chromatography (dichloromethane/light petroleum 2/1) as light brown solid. The yield after chromatography was 26%. The low yield was probably due to the poor solubility of the starting material in dichloromethane at room temperature.

The same reaction was then performed under reflux (Entry 2, Table 14), and 30% of the desired diamine 24 was isolated after column chromatography. However, when the reduction of the diazabutadiene 2 was carried out using sodium borohydride in a mixture of dichloromethane/methanol 1/1 (Entry 3, Table 14), the desired pure product 24 was obtained pure in 95% yield.

\[
\begin{align*}
\text{Reagents and conditions: (i) NH}_4\text{BF}_4, \text{ triethyl orthoformate, 120 °C, 3 h.}
\end{align*}
\]

**Scheme 16: Attempt to synthesize the salt 25.**

Treatment of the diamine 24 with 1 equivalent of ammonium tetrafluoroborate in 1 equivalent of triethyl orthoformate at 120°C for 3 hours (Scheme 16) gave a brown oil. $^1$H NMR spectroscopy of the resulting oil did not show any signal around 9-10 ppm corresponding to the acidic proton on the imidazolinium moiety. A mixture containing starting material and unidentified products in a ratio of 1:2 was observed.

**Conclusion of section 2.4**

 Attempts to synthesize saturated imidazolium salt in a two steps processes starting from a 1,2-diamine were carried out. However, the cyclization in the second step failed.
2.5 Synthesis of N-heterocyclic carbene

Functionalized carbenes can be synthesized under basic conditions according to different methods described in the literature. This procedure consists of the deprotonation of the acidic proton in the imidazolium moiety with different types of bases such as n-butyllithium, sodium hydride, potassium hydride, or potassium tert-butoxide in different solvents.

2.5.1 Attempted synthesis of the 1,3-bis-(2,6-diisopropylphenyl) imidazol-2-ylidene 26

Faust and Göbelt have shown recently that the deprotonation of a dialkynyl imidazolium salt with n-butyllithium in tetrahydrofuran at -78 °C affords the corresponding carbene (Scheme 17). In the case of the use of potassium tert-butoxide, sodium or potassium hydride in either tetrahydrofuran or dimethyl sulphoxide, only decomposition products were observed even at temperatures as low as -100 °C.

![Scheme 17: Synthesis of 4,5-dialkynyl imidazol-2-ylidene by deprotonation of the corresponding imidazolium salt with n-butyllithium.](image)

Reagents and conditions: (i) n-BuLi, THF, -78 °C.

Scheme 17: Synthesis of 4,5-dialkynyl imidazol-2-ylidene by deprotonation of the corresponding imidazolium salt with n-butyllithium.
Following the procedure described by Faust and Göbelt, 1 equivalent of 1,4-bis-(2,6-diisopropylphenyl) imidazolium chloride 16 was treated with 1 equivalent of n-butyllithium at -78 °C in tetrahydrofuran for 10 minutes (Entry 1, Table 15) using a Schlenk line. After evaporation of the solvent, a brown solid was obtained which was recrystallized from dichloromethane under an atmosphere of nitrogen. After 1 day crystals appeared. Unfortunately these crystals were identified by ¹H NMR spectroscopy as the pure imidazolium chloride 16.

In 1999, Arduengo et al. described the synthesis of the 1,3-bis-(2,6-diisopropylphenyl) imidazol-2-ylidene 26 by deprotonation of the corresponding imidazolium chloride salt 16 with 1.06 equivalents of potassium tert-butoxide in tetrahydrofuran at room temperature.⁷

This procedure was then reproduced under the same conditions (Entry 2, Table 15). Unfortunately crystallization of the carbene 26 failed, and the ¹H NMR spectrum of the oil obtained after evaporation of the solvent showed a mixture of starting material and diisopropylaniline in a ratio 1:4.

This reaction was tried several times under the same reaction conditions and each time the same results were obtained.

### Table 15: Attempts to synthesize the carbene 26.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base (equivalents)</th>
<th>Temperature</th>
<th>Solvent</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n-BuLi (1.0)</td>
<td>-78 °C</td>
<td>THF</td>
<td>17</td>
</tr>
<tr>
<td>2</td>
<td>t-BuOK (1.06)</td>
<td>r.t.</td>
<td>THF</td>
<td>16 +</td>
</tr>
</tbody>
</table>

Diisopropylaniline 1:4
It is well known that carbenes are particularly unstable, so a possible reason for this lack of success concerning the reproduction of the synthesis of the carbene 26 could be that the atmosphere under which isolation of the carbene has been synthesized was not sufficiently inert.

2.5.2 Attempted synthesis of the 1,4-bis-(2-methylthiophenyl) imidazol-2-ylidene 27

![Reaction scheme]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base (equivalents)</th>
<th>Temperature</th>
<th>Solvent</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n-BuLi (1.1)</td>
<td>-78 °C</td>
<td>THF</td>
<td>Unidentified products</td>
</tr>
<tr>
<td>2</td>
<td>t-BuOK (1.5)</td>
<td>r.t.</td>
<td>THF</td>
<td>Starting material</td>
</tr>
<tr>
<td>3</td>
<td>t-BuOK (2.5)</td>
<td>r.t.</td>
<td>THF</td>
<td>Unidentified products</td>
</tr>
</tbody>
</table>

Table 16: Attempts to synthesise the carbene 27

The procedure of Faust and Gőbelt was applied to the 1,4-bis-(2-methylthiophenyl) imidazolium chloride 18 (Entry 1, Table 16). In this case, 1.1 equivalents of n-butyllithium (2.5 M in hexane) was used. The $^1$H and $^{13}$C NMR spectra of the brown solid obtained showed the same result as for the attempted synthesis of carbene 26, i.e. no trace of the desired carbene 27. The $^{13}$C spectrum of this type of carbene should show a resonance around 210-220 ppm for the carbene centre. In our case, no peak in that area was observed.

Further attempts were performed following the procedure described by Arduengo. When 1.5 equivalents of potassium tert-butoxide were used (Entry 2, Table 16), lots of starting material remained after 3 hours. The same reaction was then
performed using 2.5 equivalents of base (Entry 3, Table 16) in this case, no starting material was detected as well as no trace of the carbene 27. The $^{13}$C spectrum of the crude reaction mixture confirmed this by the fact that no resonance around 210-220 ppm was observed.

One explanation for this could be that the carbene 27 is too unstable to be isolated, but again the lack of an inert atmosphere could be responsible. The fact that the starting material was not used in 100% pure form could be a contributing factor.

**Conclusion of section 2.5**

In conclusion, the attempted synthesis of two carbene ligands were performed by deprotonation of the corresponding imidazolium salt using different bases, but unfortunately we were unable to isolate either of them.

On the basis of these results, the synthesis of carbene complexes where the carbene would be generated in situ was investigated.

**2.6 Synthesis of complex 28, 29, 30, 31**

Functionalized carbene complexes can be synthesized in two ways. The first method consists of the reaction of an imidazolium salt with a metal complex containing a ligand which functions as the base required for the carbene formation.\[^{3,19a,22,23,24}\] The second consists of deprotonation of an imidazolium salt followed by reaction of the isolated carbene with a metal.\[^{19a-e,25,26}\] The latter method can also be performed by generating the carbene in situ without trying to isolate it.\[^{27}\]

Most of the attempts performed followed the second procedure by generating the carbene in situ. One attempt was made following the first method.
2.6.1 Attempted synthesis of nickel and palladium carbene complexes derivatives from IPrHCl 16 and IPrBF₄ 17

When the imidazolium salt 16 or 17 was deprotonated using n-BuLi or t-BuOK to generate the corresponding carbene 26 (Entry 1 and 2, Table 17), followed by reaction with nickel chloride, no trace of the desired complex 28 was observed. The $^{13}$C NMR spectrum did not show any resonance around 165-175 ppm, which is the typical resonance area for a carbene centre bonded to a metal.

In the case where n-butyllithium was used as a base (Entry 1, Table 17), recrystallization from dichloromethane gave only the pure imidazolium salt.

An attempt was performed using palladium acetate as the metal source (Entry 3, Table 17), which contains basic ligands that could function as the base required for the carbene formation. Unfortunately, refluxing the imidazolium salt 16 with palladium acetate in acetonitrile for 16 hours did not afford any trace of the desired palladium complex 29, instead a mixture of unidentified compounds was obtained.

Table 17: Attempts to synthesize the carbene complexes 28 and 29

<table>
<thead>
<tr>
<th>Entry</th>
<th>Metal source</th>
<th>Base/amount</th>
<th>Reaction conditions$^{a,b}$</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NiCl₂</td>
<td>n-BuLi/1 eq.</td>
<td>THF/10/18</td>
<td>Unidentified products</td>
</tr>
<tr>
<td>2</td>
<td>NiCl₂</td>
<td>t-BuOK/2 eq.</td>
<td>DCM/80/3</td>
<td>Unidentified products</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OAc)$_2$</td>
<td>None</td>
<td>CH$_3$CN/16</td>
<td>Unidentified products</td>
</tr>
</tbody>
</table>

$^a$: Solvent/time of deprotonation (min)/time of reaction with the metal (h).

$^b$: All the reactions with n-BuLi were performed at −78 °C, all the reactions with t-BuOK at room temperature.
2.6.2 Attempted synthesis of nickel and palladium carbene complexes derivatives from the imidazolium salt 18

![Diagram of imidazolium salt 18 and metal complexes 30 and 31]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Metal source</th>
<th>Base/amount</th>
<th>Reaction conditions$^{a,b}$</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NiCl$_2$</td>
<td>n-BuLi/1.1 eq.</td>
<td>THF/10/18</td>
<td>Unidentified products</td>
</tr>
<tr>
<td>2</td>
<td>NiCl$_2$</td>
<td>t-BuOK/2.5 eq.</td>
<td>THF/5/1</td>
<td>Unidentified products</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OAc)$_2$</td>
<td>NaH/1.5 eq.</td>
<td>THF/5/5</td>
<td>Decomposition</td>
</tr>
<tr>
<td>4</td>
<td>NiCl$_2$</td>
<td>K$_2$CO$_3$</td>
<td>DCM/0/48</td>
<td>Unidentified products</td>
</tr>
<tr>
<td>5</td>
<td>Pd(OAc)$_2$</td>
<td>None</td>
<td>CH$_3$CN/16</td>
<td>Unidentified products</td>
</tr>
</tbody>
</table>

$^{a}$ Solvent/time of deprotonation (min)/time of reaction with the metal (h).
$^{b}$ All the reactions with BuLi were performed at –78 °C.

Table 18: Attempts to synthesize the carbene complexes 30 and 31

Attempts to synthesize the nickel or palladium carbene complex derived from 1,4-bis-(2-methylthiophenyl) imidazolium chloride 18 were performed using several different bases including inorganic or organic bases.

In all cases (Table 18), no trace of the desired complexes 30 or 31 was observed.

The use of sodium hydride, (Entry 3, Table 18) even when using only 1 equivalent, led to decomposition of the starting material. Indeed, the $^1$H NMR spectrum of this attempt shows the presence of peaks in the alkene area, which are probably due to the decomposition of the imidazolium salt.

An attempt was made using potassium carbonate (Entry 4, Table 18), and after 2 days starting material remained.

A last attempt was performed without added base using a metal complex containing basic ligands (Entry 5, Table 18). After heating the reaction mixture under
reflux in acetonitrile for 16 hours a black solid was obtained. Unfortunately, its insolubility in most deuteriated solvents made it impossible to obtain a \(^1\)H NMR spectrum. Different methods of recrystallization were tried without success.

**Conclusion of section 2.6**

Formation of carbene complexes either by deprotonation of the imidazolium salt followed by reaction of the generated carbene with a metal or by using a metal complex containing basic ligands which should function as a base required for the carbene formation have not been successful.

**2.7 Conclusion**

Several amines were condensed with glyoxal following either the method described by Huang and Nolan or modified reaction conditions to obtain the corresponding diazabutadiene. Only two of them were successful.

Cyclizations of the diazabutadiene obtained using different methods have been tried. Only the synthesis of IPrHCl and IPrBF\(_4\) gave some positive results.

Concerning the synthesis of saturated imidazolium salt, all attempts failed.

Finally, the synthesis of carbene and metal complexes was performed but has been unsuccessful.
3.1 Introduction

In this section, the synthesis of enantiomerically pure tricyclic saturated imidazolium salts (Figure 5) and the subsequent investigation of such salts in catalytic processes are discussed.

![Figure 5: Enantiomerically pure tricyclic saturated imidazolium salt.](image)

In 1996, Hermann and co-workers showed that the use of the ligand depicted in Figure 6 in the rhodium-catalysed hydrosilylation of acetophenone gave only modest enantioselectivities.28

![Figure 6: Ligand used in the rhodium-catalysed hydrosilylation of acetophenone.](image)

Very recently, Hartwig and co-workers have described the synthesis of three enantiomerically pure saturated imidazolium salts (Figure 7).16 When applied to the palladium catalysed asymmetric synthesis of a range of oxindoles, encouraging enantioselectivities were observed (40-76% ee).16
Figure 7: Enantiomerically pure saturated imidazolium salts synthesized by Hartwig and co-workers.

The idea of utilizing a tricyclic ring system would be to restrict the free rotation around the carbon nitrogen bonds present in the imidazolium salts discussed in Chapter 2. This factor is presumed to contribute to the modest enantioselectivities observed in catalytic processes using these ligand systems. The increased rigidity of the tricyclic ring systems should reduce the number of degrees of freedom present in conventional chiral saturated imidazol-2-ylidene ligands and therefore increase the enantioselectivity.

A possible retrosynthetic pathway (Scheme 18) envisaged the formation of the (A) and (C) rings first and then subsequent cyclization to form the imidazole ring (B). In the case of this synthetic pathway, the product would be a saturated imidazolium salt.

Scheme 18: A possible retrosynthetic pathway.
There is literature precedence for the formation of imidazolium salts from acyclic ethylene diamines by the reaction with triethyl orthoformate and ammonium tetrafluoroborate.\(^4\)

It has been shown in the literature that 2,2'-bipyridine can be reduced to 2,2'-bipiperidine in excellent yield. Krumholz and co-workers reported that treating 2,2'-bipyridine with metallic sodium in ethanol resulted in the isolation of 2,2'-bipiperidine in good yield.\(^29\) Later Yoshikawa and co-workers repeated this work and separated the meso and racemic forms of 2,2'-bipiperidine\(^{30}\) via the hydrochloride salt of the diamine. In addition, they resolved the racemic form by complexation with \([\text{Co(NO}_2)_6]\)\(^{3^2}\). It has also been shown that 2,2'-bipyridine can be hydrogenated in the presence of platinum oxide to give 2,2'-bipiperidine.\(^3^1\)

Functionalized tricyclic imidazolium salts can be prepared in two steps starting from 2,2'-bipyridine derivatives. The first step is a reduction by hydrogenation to afford the corresponding 2,2'-bipiperidine derivative which is then cyclized (Scheme 19) with ammonium tetrafluoroborate in neat triethyl orthoformate to give the corresponding tricyclic saturated imidazolium salt.

\begin{align*}
\textbf{Reagents and conditions:} (i) \text{H}_2 (10 \text{ psi}), \text{PtO}_2, \text{AcOH}, \text{r.t.}, \quad \text{(ii) NH}_4\text{BF}_4, (\text{EtO})_3\text{CH}, 70 \, ^\circ\text{C}, 3 \, \text{h.}
\end{align*}

**Scheme 19:** Proposed method to synthesize tricyclic imidazolium salts.
3.2 Preparation of diamines via different methods

3.2.1 Hydrogenation

3.2.1.1 Synthesis of 6,6'-dimethyl-2,2'-bipiperidine 40

![Chemical structure diagram]

Reagents and conditions: (i) NiCl₂·6H₂O, PPh₃, Zn, DMF, 50 °C, 4 h, 93%, (ii) PtO₂, H₂ (40 psi), AcOH, r.t., 10 days, 94%.

Scheme 20: Synthesis of the bipiperidine 40.

Treatment of the commercially available 6-bromo-2-methyl pyridine with NiCl₂·6H₂O in N,N-dimethylformamide in the presence of triphenylphosphine and zinc powder at 50 °C for 4 hours gave the desired 6,6'-dimethyl-2,2'-bipyridine 39 in 93% yield (Scheme 20). Reduction of the bipyridine 39 under an atmosphere of hydrogen in the presence of a catalytic amount of platinum oxide resulted in the isolation of 6,6'-dimethyl-2,2'-bipiperidine 40 in excellent yield. The reaction was monitored by ¹H NMR spectroscopy, which showed the gradual disappearance of the aromatic signals accompanied by the appearance of aliphatic signals. Interestingly, no intermediate imine or alkene signals were observed, suggesting that the reaction proceeds by a concerted mechanism.

Examination of the ¹³C NMR spectrum showed the product to be made up of a mixture of three isomers (1:7:22). At this stage, it was impossible to determinate which isomers were formed among the 10 possible.

Alexakis and co-workers have reported a method to separate meso and (±)-diphenyl ethylene diamine (Figure 8) as well as (+) and (-)-diphenyl ethylene diamine, by first treating the crude mixture with racemic tartaric acid in ethanol, which, after neutralized the precipitated ammonium salt with aqueous sodium hydroxide, produced then the (±)-diphenyl ethylene diamine. Then, treating the (±)-
diamine with (+) or (-)-tartaric acid to isolate either the (+) or (-)-diphenyl ethylene diamine.

![Diphenyl Ethylene Diamine Structures](image)

**Figure 8:** *meso* and (±)-diphenyl ethylene diamine.

This method was applied to the bipiperidine 40, but unfortunately this method did not afford a good separation of the *meso* and racemic forms. In order to understand what was happening during the resolution, an attempt was repeated with isolation of the white precipitate. $^{13}$C NMR spectroscopy of this salt showed that complexation did occur between the bipiperidine 40 and the tartaric acid (as shown by the shift of the carbon signals of the bipiperidine 40 in the $^{13}$C NMR spectrum).

Another group has also reported the resolution of different diamines using tartaric acid but utilising different reaction conditions (methanol, acetic acid). $^{34}$ This method was applied to the bipiperidine 40 but unfortunately did not afford the pure racemic form.

It has been shown in the literature that racemic 2,2'-bipiperidine and the *meso* form have been separated through the dihydrochloride salt of the diamine. $^{30}$ In addition, the racemic form has been resolved by complexation with [Co(NO$_2$)$_6$]$^3$.

![Reagents and Conditions](image)

*Reagents and conditions:* (i) HCl, EtOH 95%, r.t., (ii) NaOH, 93%.

**Scheme 21:** Separation of the bipiperidine 40 through its hydrochloric salt.
The crude bipiperidine 40 was thus treated with an excess of hydrochloric acid (Scheme 21). After evaporation of the volatile components, the salt was recrystallized from 95% ethanol, and some colourless crystals were obtained. $^{13}$C NMR spectrum of these crystals showed the presence of only 6 signals, which indicated that a single isomer had been isolated. Treatment of the hydrochloric salt 41 with an aqueous solution of sodium hydroxide gave a light yellow oil identified by $^{13}$C NMR spectroscopy as one single isomer of the free bipiperidine 40. The oil crystallized on standing to give colourless crystals. X-Ray analysis (Appendix 2) of those crystals showed the isomer to be the meso form (Figure 9).

Comparison of the $^{13}$C NMR spectrum of the meso bipiperidine 40 with the $^{13}$C NMR spectrum of the crude bipiperidine 40, after hydrogenation, showed that the hydrogenation gave mainly the meso-bipiperidine 40.

Figure 9: meso-6,6'-dimethyl-2,2'-bipiperidine 40 suggested by X-Ray analysis.

3.2.1.2 Synthesis of bidecahydroquinoline 42

Reagents and conditions: (i) PtO$_2$, H$_2$ (40 psi), AcOH, r.t., 18 days, 96%.

Scheme 22: Synthesis of the bidecahydroquinoline 42.
Commercially available 2,2'-biquinoline was subjected to the same hydrogenation conditions, and, in that case after 18 days, bidecahydroquinoline 42 was isolated in 96% yield (Scheme 22). As for the preceding reaction no intermediate imine or alkene signals were observed by ^1H NMR spectroscopy.

Examination of the ^13C NMR spectrum showed the presence of a complex mixture of different isomers. At this stage, it was impossible to determinate which isomers were formed among the different possible.

\[ \text{Reagents and conditions: (i) HCl, EtOH 95%, r.t.} \]

Scheme 23: Separation of the bipiperidine 42 through his hydrochloric salt.

Treatment of the bipiperidine 42 with an excess of hydrochloric acid and recrystallization from 95% ethanol (Scheme 23) afforded colourless crystals. The ^13C NMR spectrum of these crystals in D$_2$O showed 9 signals, which indicates that only one of the isomers had been isolated. Conversion to the free bipiperidine 42 could not be attempted due to the small amount of crystals obtained. Even leaving the mother liquor several months to crystallize did not afford more salt.

3.2.1.3 Synthesis of 6,6'-bis(1-methoxy-2,2'-dimethylpropyl)-2,2'-bipiperidine 49

Bolm and co-workers have reported the enantioselective synthesis of 6,6'-bis-(1-methoxy-2,2'-dimethylpropyl)-2,2'-bipyridine 46 for application as a chiral ligand.\textsuperscript{35} We were interested in the synthesis and subsequent hydrogenation of this compound, hoping that the alcohol may direct the hydrogenation and give some
stereoselectivity. Even if no selectivity were observed, we would still isolate an imidazolium tetrafluoroborate salt with chiral appendages present. Initially, we followed the work of Bolm to generate racemic 6,6'-bis-(1-methoxy-2,2'-dimethylpropyl)-2,2'-bipyridine 46 (Scheme 24).

\[
\begin{align*}
\text{Br} & \quad \text{Br} \\
\text{(i)} & \quad \text{Br} & \quad \text{Br} \\
\text{N} & \quad \text{Br} & \quad \text{N} \\
\text{(ii)} & \quad \text{Br} & \quad \text{N} \\
\text{(±)-44} & \quad \text{OH} & \quad \text{(i)} \\
\text{(±)-45} & \quad \text{OMe} & \quad \text{(ii)} \\
\text{meso and (±)-46} & \quad \text{OMe} & \quad \text{MeO}
\end{align*}
\]

Reagents and conditions: (i) n-BuLi, pivalaldehyde, Et₂O, –78 °C→r.t., 2 h, 88%, (ii) NaH, MeI, THF, 0 °C, 1.5 h, 97%, (iii) NiCl₂·6H₂O, PPh₃, Zn, DMF, 70 °C, 3 h, 56%.

Scheme 24: Synthesis of the (±)-2,2'-bipyridine 46.

Monolithiation of commercially available 2,6-dibromopyridine with n-butyllithium in ether followed by trapping with pivalaldehyde gave (±)-1-(6-bromopyridin-2-yl)-2,2-dimethylpropanol 44 in 88% yield after recrystallization from light petroleum (Scheme 24). Protection of the alcohol using sodium hydride and iodomethane in tetrahydrofuran at 0 °C gave (±)-(1-(6-bromopyridin-2-yl)-2,2-dimethylpropyl) methyl ether 45 in good yield (97%). Nickel(0)-mediated homocoupling of 45 was performed in N,N-dimethylformamide in the presence of triphenylphosphine and zinc. After 3 hours at 70 °C, a mixture of meso and (±)-6,6'-bis-(1-methoxy-2,2'-dimethylpropyl)-2,2'-bipyridine 46 was obtained in 56% yield.
Reagents and conditions: (i) 1) n-BuLi, pivalonitrile, Et₂O, –78 °C→r.t., 1 h, 2) 2N H₂SO₄, 60 °C, 2 h, 88%, (ii) 1) (+)-(Ipc)₂BCl, r.t., 2 days, 2) diethanolamine, Et₂O, r.t., 3.5 h, 32%, (iii) NaH, MeI, THF, 0 °C, 1.5 h, 84%, (iv) NiCl₂·6H₂O, PPh₃, Zn, DMF, 70 °C, 3 h, 55%.

Scheme 25: Synthesis of the (S,S)-2,2'-bipyridine 46.

The 2,6-disubstituted compound 47 was synthesized in 88% yield by metal-halogen exchange of the commercially available 2,6-dibromopyridine with n-butyllithium in ether followed by treatment with pivalonitrile (Scheme 25).

Asymmetric reduction was performed using (+)-(Ipc)₂BCl. The optical purity of the product was determined by ¹H NMR spectroscopy of the camphanate derived from 44 and (1S)-camphanoyl chloride. In this case, the enantiomeric excess of the bromopyridyl alcohol (S)-44 was ≥92%.

Isopinocampheol 48 (Figure 10) was identified as a major by-product of the asymmetric reduction using (Ipc)₂BCl. By-product 48 was separated from the product mixture by careful chromatography. Since 48 was not present in the reducing reagent (¹H NMR analysis), it may have been formed by air oxidation during the workup which involved the addition of diethanolamine/ether for borane removal. In the crude product mixture, the amount of 48 appeared to increase upon standing in air. Additional 48 was formed during the chromatographic purification of the desired alcohol (S)-44.
Protection of the alcohol (S)-44 using sodium hydride and iodomethane in tetrahydrofuran at 0 °C gave (S)-[1-(6-bromopyridin-2-yl)-2,2-dimethylpropyl] methyl ether 45 in good yield. Nickel(0)-mediated homocoupling of (S)-45 was performed in N,N-dimethylformamide in the presence of triphenylphosphine and zinc. After 3 hours at 70 °C, (S,S)-6,6’-bis(1-methoxy-2,2’-dimethylpropyl)-2,2’-bipyridine 46 was obtained in 55% yield.

Reagents and conditions: (i) PtO₂, H₂ (40 psi), AcOH, r.t., 14 days.

Scheme 26: Synthesis of the (S,S)-2,2’-bipiperidine 49.

(S,S)-6,6’-Bis(1-methoxy-2,2’-dimethylpropyl)-2,2’-bipyridine 46 was then hydrogenated using platinum oxide as catalyst in acetic acid under 40 psi at room temperature (Scheme 26). Unfortunately in this case, after 14 days, only the unreacted starting material was recovered.

Conclusion of section 3.2.1

Attempts to reduce three different 2,2’-bipyridine derivatives by hydrogenation have been carried out. Two of them gave the desired bipiperidines. Several methods to resolve these were investigated, but did not afford good
separation. In the case of 6,6'-dimethyl-2,2'-bipiperidine 40, the resolution showed that the hydrogenation mainly afforded the meso isomer.

3.2.2 Reduction of bipyridine \(N,N'\)-dioxide derivatives

Recently, Zacharie and co-workers have developed an efficient, mild procedure for the reduction of pyridine \(N\)-oxide to piperidine (Scheme 27). This is accomplished by catalytic transfer hydrogenation with ammonium formate as the hydrogen source in the presence of palladium on carbon. The reaction is carried out in methanolic solution overnight at room temperature. The procedure is simple and does not require special apparatus, hydrogen atmosphere, or harsh conditions. The work-up is easy, requiring only filtration of catalyst followed by removal of the solvent. A variety of pyridines, quinolines and isoquinolines were converted into their piperidine derivatives. The authors observed that several reducible functionalities such as methoxycarbonyl, carboxyl, amino, hydroxy and amides are unaffected with this reagent system.\(^{36}\)

\[
\text{Reagents and conditions: (i) HCOONH}_4, 10\% \text{ Pd/C, MeOH, r.t., 16 h, 87\%}.
\]

**Scheme 27:** Reduction of quinoline \(N\)-oxide to tetrahydroquinoline.
3.2.2.1 Synthesis of 2,2'-bipyridine-\textit{N},\textit{N}'-dioxide derivatives

![Chemical structure of 2,2'-bipyridine-\textit{N},\textit{N}'-dioxide derivatives](image)

Reagents and conditions: (i) \textit{m}-CPBA, DCM, 0 °C, 2 h, 63%.

Scheme 28: Oxidation of the commercially available 2,2'-biquinoline.

Oxidation of the commercially available 2,2'-biquinoline was carried out using \textit{m}-chloroperoxybenzoic acid in dichloromethane at 0 °C for 2 hours (Scheme 28). After purification by column chromatography using ethyl acetate/methanol 10/1 as eluent, the pure 2,2'-biquinoline-\textit{N},\textit{N}'-dioxide 50 was isolated in 63% yield.

![Chemical structure of 6,6'-dimethyl-2,2'-bipyridine 39 and 2,2'-biquinoline-\textit{N},\textit{N}'-dioxide 50](image)

Reagents and conditions: (i) \textit{m}-CPBA, DCM, 0 °C, overnight.

Scheme 29: Oxidation of 6,6'-dimethyl-2,2'-bipyridine 39.

The same oxidation was applied to the 6,6'-dimethyl-2,2'-bipyridine 39 (Scheme 29). Unfortunately, in this case a complex mixture of unidentified products was obtained. This reaction was carried out twice and each time gave the same result.
3.2.2.2 Reduction of 2,2'-biquinoline-\(N,N'\)-dioxide 50

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction conditions</th>
<th>Products observed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HCOONH(_4), 10% Pd/C, MeOH, r.t., 19 h</td>
<td>50 + unidentified products</td>
</tr>
<tr>
<td>2</td>
<td>HCOONH(_4), 10% Pd/C, MeOH, reflux, 19 h</td>
<td>50 + unidentified products</td>
</tr>
</tbody>
</table>

Table 19: Reduction of 2,2'-biquinoline-\(N,N'\)-dioxide 50.

Zacharie’s method was applied to the 2,2'-biquinoline-\(N,N'\)-dioxide 50 but even when the reaction was carried out at room temperature (Entry 1, Table 19) or at reflux (Entry 2, Table 19) a complex mixture containing traces of unreacted starting material and unidentified products was obtained. In each case, observation of the desired product 52 was difficult even by comparison with the \(^1\)H and \(^{13}\)C NMR spectrum with the known compound 52.\(^{37}\) Attempts to isolate the different products by column chromatography failed.

In the light of these results, this method was abandoned.

Conclusion of section 3.2.2

Reduction of 2,2'-biquinoline-\(N,N'\)-dioxide 50 was investigated using ammonium formate in the presence of palladium on carbon following Zacharie’s method.\(^{36}\) Unfortunately, this new method of reduction did not afford the desired bipiperidine 52.\(^{37}\) 2,2'-Biquinoline-\(N,N'\)-dioxide 50 has been synthesized using \(m\)-chloroperoxybenzoic acid in 63% yield. Using the same oxidant for the synthesis of 6,6'-dimethyl-2,2'-
bipyridine-$N,N'$-dioxide 51 failed. Other oxidants were not investigated. A new method of reduction was thus required to access bipiperidine derivatives.

3.2.3 Reduction of quaternized bipyridine derivatives

The most common method to reduce a pyridine to its corresponding piperidine is a four step synthesis (Scheme 30).38

![Scheme 30: Method to reduce pyridine to piperidine.](image)

*Reagents and conditions: (i) R-X, (ii) NaBH₄ or LAH, (iii) H₂.*

This method involves first the quaternization of the nitrogen atom of the pyridine with an alkyl group to give a pyridinium salt. This salt can then be reduced to its $N$-alkyl-1,2,3,6-tetrahydropyridine using sodium borohydride or lithium aluminium hydride. A subsequent hydrogenation will afford an $N$-alkylpiperidine, which can be dealkylated to give the desired piperidine.
3.2.3.1 Synthesis of 6,6'-dimethyl-2,2'-bipiperidine 40 by reduction of the corresponding pyridinium salt

3.2.3.1.1 Quaternization of the nitrogen of 6,6'-dimethyl-2,2'-bipyrine 39

![Chemical structures](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents</th>
<th>Reaction conditions</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeI</td>
<td>DCM, reflux, overnight then r.t., 21 days</td>
<td>39 + 8% 57</td>
</tr>
<tr>
<td>2</td>
<td>MeI</td>
<td>Neat, r.t., 2 days</td>
<td>39 + traces of 57</td>
</tr>
<tr>
<td>3</td>
<td>Me₂SO₄</td>
<td>188 °C, 1 h⁹⁹</td>
<td>Traces of 54</td>
</tr>
<tr>
<td>4</td>
<td>Me₂SO₄</td>
<td>188 °C, 1 h then KPF₆⁴⁰</td>
<td>62% 55</td>
</tr>
<tr>
<td>5</td>
<td>TMSOTf</td>
<td>DCM, 0 °C→r.t., overnight</td>
<td>39</td>
</tr>
</tbody>
</table>

Table 20: Quaternization of the nitrogen atom of 6,6'-dimethyl-2,2'-bipyridine 39.

First, methylation of the 6,6'-dimethyl-2,2'-bipyridine 39 was carried out using either iodomethane or dimethyl sulphate (Table 20). In the case where iodomethane was used as methylating agent either at reflux in dichloromethane (Entry 1, Table 20) or neat at room temperature (Entry 2, Table 20), the starting material was the main recovered product. In both cases, traces of 1,6,6'-trimethyl-2,2'-bipyridinium iodide 57 were obtained.

When dimethyl sulphate was used, exchange of the counter-anion CH₃SO₄⁻ by PF₆⁻ was necessary to isolate the desired 1,1',6,6'-tetramethyl-2,2'-bipyridinium hexafluorophosphate 55 in 62% yield (Entry 4, Table 20).⁴⁰ If the exchange of counter-anion was not made (Entry 3, Table 20) a green solid was obtained which
turned into a black oily residue upon contact with air. The $^1$H spectrum of this residue showed traces of the desired salt 54 along with some unidentified products, probably derived from decomposition of the desired salt 54.

Knowing that the methyl group on the nitrogen could be difficult to remove, an attempt was carried out using trimethylsilyl triflate as the alkylating agent (Entry 5, Table 20). Unfortunately, in this case only the starting material was recovered.

3.2.3.1.2 Reduction of the 1,1',6,6'-tetramethyl-2,2'-bipyridinium salt 55


circle.png

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents</th>
<th>Reaction conditions</th>
<th>Observed products</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaBH₄</td>
<td>MeOH, r.t., 2 days</td>
<td>Unidentified products</td>
</tr>
<tr>
<td>2</td>
<td>LAH</td>
<td>THF, r.t., 2 days</td>
<td>55 + mixture of alkene and alkane</td>
</tr>
</tbody>
</table>

Table 21: Reduction of the 1,1',6,6'-tetramethyl-2,2'-bipyridinium salt 55.

Attempts to reduce the salt 55 have been made using both sodium borohydride and lithium aluminium hydride (Table 21). Using sodium borohydride in methanol at room temperature for two days (Entry 1, Table 21) gave a mixture of unidentified products. Attempts to isolate the different products by column chromatography were carried out but were unsuccessful due to the fact that the crude mixture stuck on the base line of the TLC, when either silica or alumina was used.

Reduction of the salt 55 using lithium aluminium hydride gave a mixture made of aromatic, alkene and alkane products according to the $^1$H NMR spectrum. Once again isolation of the different products by column chromatography was a problem due to the polarity of the mixture.
3.2.3.2 Synthesis of 1,2,3,4,1',2',3',4'-octahydro-2,2'-biquinoline 52 by reduction of the corresponding biquinolinium salt

3.2.3.2.1 Quaternization of the nitrogen of 2,2'-biquinoline

As for the methylation of the 6,6'-dimethyl-2,2'-bipyridine 39 (see section 3.2.3.1.1), iodomethane and dimethyl sulphate were tried as methylaing agents for 2,2'-biquinoline. When iodomethane was used in dichloromethane (Entry 1, Table 22) or neat (Entry 2, Table 22), only the unreacted starting material was recovered. However, using dimethyl sulphate at 188 °C (Entry 3, Table 22) gave after one hour the corresponding salt 61 in 93% yield. 39

Again, aware of the possible difficulty of removal of the methyl group on the nitrogen, attempts were carried out using trimethylsilyl triflate or benzyl bromide as alkylating agents. Unfortunately, the use of trimethylsilyl triflate at room temperature in dichloromethane (Entry 4, Table 22) or benzyl bromide at reflux in acetonitrile (Entry...
5, Table 22) or neat at 150 °C (Entry 6, Table 22) did not afford any trace of the corresponding salt 62 or 63 respectively. In all these cases, the unreacted starting material was recovered.

3.2.3.2 Reduction of 1,1'-dimethyl-2,2'-biquinolinium dimethylsulphate 61

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents</th>
<th>Reaction conditions</th>
<th>Observed products</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaBH4</td>
<td>MeOH, r.t., 2 days</td>
<td>61 + 64 (1:3) + 65 (traces)</td>
</tr>
<tr>
<td>2</td>
<td>NaBH4</td>
<td>EtOHaq., r.t., 2 days</td>
<td>64 + 65 (1:5)</td>
</tr>
<tr>
<td>3</td>
<td>LAH</td>
<td>THF, r.t., overnight</td>
<td>85% 64</td>
</tr>
</tbody>
</table>

Table 23: Reduction of 1,1'-dimethyl-2,2'-biquinolinium dimethylsulphate 61.

Reduction of the salt 61 using sodium borohydride (Entry 1 and 2, Table 23) gave a mixture of starting material, 1,1'-dimethyl-1,4,1',4'-tetrahydro-2,2'-biquinoline 64 and 1,1'-dimethyl-1,2,3,4,1',2',3',4'-octahydro-2,2'-biquinoline 65. Using an aqueous solution of ethanol as solvent instead of dry methanol at room temperature afforded after two days a complete conversion of the salt 61 (Entry 2, Table 23). In this case, column chromatography of the crude mixture using light petroleum/dichloromethane 7/3 as eluent allowed the isolation of 22% of 1,1'-dimethyl-1,2,3,4,1',2',3',4'-octahydro-2,2'-biquinoline 65 as a purple oil containing two isomers according to the $^{13}$C NMR spectrum. Standing this purple oil at room temperature for a few days led to the formation of one colourless crystal which was
identified by X-Ray (Appendix 3) as the meso isomer (Figure 11). Attempts to separate the two different isomers by column chromatography failed.

Interestingly, reduction of the salt 61 using lithium aluminium hydride in tetrahydrofuran at room temperature gave after two days 85% of 1,1'-dimethyl-1,4,1',4'-tetrahydro-2,2'-biquinoline 64, sufficiently pure to be used in the next hydrogenation step. However, attempted purification by column chromatography was carried out and showed an instability of compound 64 to silica gel. $^1$H NMR spectroscopy of compound 64, after one week, showed that it had decomposed.

Figure 11: meso-65 suggested by X-Ray analysis.
3.2.3.2.3 Reduction by hydrogenation of 1,1'-dimethyl-1,4,1',4'-tetrahydro-2,2'-biquinoline 64

![Chemical structures](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction conditions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H₂, Pd/C, EtOAc, r.t., 2 days</td>
<td>64</td>
</tr>
<tr>
<td>2</td>
<td>H₂, PtO₂, NH₄OH, MeOH, r.t., overnight⁴¹</td>
<td>Quantitative 65</td>
</tr>
</tbody>
</table>

Table 24: Hydrogenation of 1,1'-dimethyl-1,4,1',4'-tetrahydro-2,2'-biquinoline 64.

Hydrogenation of 1,1'-dimethyl-1,4,1',4'-tetrahydro-2,2'-biquinoline 64 in the presence of palladium on carbon in ethyl acetate at room temperature for two days (Entry 1, Table 24) resulted in the isolation of unreacted starting material.

However, hydrogenating 1,1'-dimethyl-1,4,1',4'-tetrahydro-2,2'-biquinoline 64 in the presence of platinum oxide as catalyst in methanol with a few drops of a solution of aqueous ammonia at room temperature overnight (Entry 2, Table 24) gave the desired 1,1'-dimethyl-1,2,3,4,1',2',3',4'-octahydro-2,2'-biquinoline 65 quantitatively. Again, the ¹³C NMR spectrum of the purple oil showed the presence of two isomers.

3.2.3.2.4 Demethylation of 64 and 65

In 1997, Olofson and co-workers reported a mild procedure for the N-dealkylation of tertiary amines using various chloroformates such as vinylchloroformate, benzylchloroformate or phenylchloroformate (Scheme 31).⁴² This method relies on the exchange of the methyl group by another group which is actually more easy to remove.
Reagents and conditions: (i) Voc-Cl, 1,2-dichloroethane, reflux, 92%, (ii) HCl (excess), Et₂O, EtOH, 50 °C, 98%.

**Scheme 31:** Demethylation using vinylchloroformate.

In 1995, Ferguson's group used this method in the synthesis of the alkaloid anatoxin-A (Scheme 32).

Reagents and conditions: (i) Voc-Cl, K₂CO₃, dichloromethane, reflux, 95%, (ii) HCl (excess), Et₂O, EtOH, 50 °C, 75%.

**Scheme 32:** Synthesis of the alkaloid anatoxin-A.
This method was applied to the 1,1′-dimethyl-1,4,1′,4′-tetrahydro-2,2′-biquinoline 64.

![Diagram of compounds 64 and 66-67]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Reaction conditions</th>
<th>Observed products</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BnOC(O)Cl</td>
<td>DCE, K₂CO₃, reflux, overnight</td>
<td>64 + BnCl</td>
</tr>
<tr>
<td>2</td>
<td>PhOC(O)Cl</td>
<td>DCE, reflux, overnight</td>
<td>64 + PhOC(O)Cl + unidentified product</td>
</tr>
<tr>
<td>3</td>
<td>PhOC(O)Cl</td>
<td>DCE, K₂CO₃, reflux, overnight</td>
<td>No more N-Me</td>
</tr>
</tbody>
</table>

Table 25: Demethylation of 1,1′-dimethyl-1,4,1′,4′-tetrahydro-2,2′-biquinoline 64.

Exchange of the methyl group on the nitrogen of 1,1′-dimethyl-1,4,1′,4′-tetrahydro-2,2′-biquinoline 64 by a different group which would be more easy to remove was attempted using different chloroformates including benzylchloroformate or phenylchloroformate (Table 25).

First, benzylchloroformate was used in the presence of potassium carbonate at reflux overnight (Entry 1, Table 25), but under these reaction conditions no exchange occurred. Instead, a mixture of starting material along with benzyl chloride was recovered. The formation of the benzyl chloride can be explained by the following mechanism, shown in Scheme 33.
Scheme 33: Possible mechanism for the formation of benzyl chloride.

In order to avoid the formation of such side-product, phenylchloroformate was used instead. When phenylchloroformate was used in 1,2-dichloroethane at reflux overnight (Entry 2, Table 25) a mixture of starting material, phenylchloroformate and traces of an unidentified product were obtained.

A last attempt was made under the same reaction conditions, but this time in the presence of potassium carbonate (Entry 3, Table 25). In this case, the \(^1\)H NMR spectrum of the crude mixture was complex, revealing no peaks corresponding to the N-methyl group. Isolation of the different products by column chromatography using dichloromethane as eluent did not afford the desired product 67.

In view of these results, we decided to attempt demethylation of the 1,1'-dimethyl-1,2,3,4,1',2',3',4'-octahydro-2,2'-biquinoline 65 (Scheme 34).

\[
\text{Reagents and conditions: (i) PhOC(O)Cl, K_2CO_3, 1,2-dichloroethane, reflux, 6 days.}
\]

Scheme 34: Demethylation of 1,1'-dimethyl-1,2,3,4,1',2',3',4'-octahydro-2,2'-biquinoline 65.
Following the method used for 1,1'-dimethyl-1,4,1',4'-tetrahydro-2,2'-biquinoline 64, 1,1'-dimethyl-1,2,3,4,1',2',3',4'-octahydro-2,2'-biquinoline 65 was treated with phenylchloroformate in 1,2-dichloroethane in the presence of potassium carbonate at reflux for 6 days (Scheme 34). Unfortunately, in this case, no trace of the desired product 68 was observed. Only starting material along with phenylchloroformate was recovered.

In 1964, Bartlett et al. reported the oxidative demethylation of some ajmaline derivatives using lead tetraacetate (Scheme 35).

\[
\text{Reagents and conditions: (i) Pb(OAc)}_4, \text{ benzene, r.t., 20 min.}
\]

**Scheme 35:** Oxidative demethylation of an ajmaline derivative.

This method was then applied to the 1,1'-dimethyl-1,2,3,4,1',2',3',4'-octahydro-2,2'-biquinoline 65 (Scheme 36).

\[
\text{Reagents and conditions: (i) Pb(OAc)}_4, \text{ toluene, r.t., overnight.}
\]

**Scheme 36:** Oxidative demethylation of 1,1'-dimethyl-1,2,3,4,1',2',3',4'-octahydro-2,2'-biquinoline 65.

In this case, the $^1$H NMR spectrum of the resulting dark-red residue revealed no peaks corresponding to the N-Me group, but column chromatography
of the crude mixture did not give the desired product 69. Instead a mixture of unidentified products was obtained.

3.2.3.3 Synthesis of \((S,S)\)-6,6'-bis-(1-methoxy-2,2'-dimethylpropyl)-2,2'-bipiperidine 49 by reduction of the corresponding bipyridinium salt

![Chemical structure](image)

\[(S,S)-46\] \(\xrightarrow{X}\) \(\text{Observed products} \]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction conditions</th>
<th>Observed products</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{Me}_2\text{SO}_4, 188 \degree C, 1 \text{ h})</td>
<td>Decomposition</td>
</tr>
<tr>
<td>2</td>
<td>1) (\text{Me}_2\text{SO}_4, 150 \degree C, 1 \text{ h}), 2) (\text{KPF}_6)</td>
<td>Decomposition</td>
</tr>
</tbody>
</table>

Table 26: Quaternization of the nitrogen atom of the \((S,S)\)-2,2'-pyridine derivative 46.

Up to this point, our attempts to quaternize the 6,6'-dimethyl-2,2'-bipiperidine 39 and the commercially available 2,2'-biquinoline had been successful only when dimethyl sulphate was used. This method was then applied to the chiral 2,2'-bipyridine 46 either at 188 °C for 1 hour (Entry 1, Table 26) or at 150 °C for 1 hour, followed by exchange of the counter-anion \(\text{CH}_3\text{SO}_4^-\) by \(\text{PF}_6^-\) (Entry 2, Table 26). Unfortunately, in both cases only decomposition of the starting material was observed.

Knowing that the alkylation of the 6,6'-dimethyl-2,2'-bipyridine 39 or 2,2'-biquinoline has failed using iodomethane, trimethylsilyl triflate or benzyl bromide, these reagents were not tried on the chiral 2,2'-bipyridine 46. Instead it was decided to test a new method of reduction using lithium triethylborohydride (Super-Hydride®).
Conclusion of section 3.2.3

In this section, reduction of N,N'-alkyl-2,2'-bipyridinium salts using sodium borohydride or lithium aluminium hydride was investigated. First, the synthesis of N,N'-alkyl-2,2'-bipyridinium salts was carried out using different alkylating reagents such as idomethane, dimethyl sulphate, trimethylsilyl triflate and benzyl bromide. Only dimethyl sulphate was reactive enough to give the 1,1',6,6'-tetramethyl-2,2'-bipyridinium salt 55 and the 1,1'-dimethyl-2,2'-biquinolinium salt 61. Unfortunately, using dimethyl sulphate with the chiral 2,2'-bipyridine 46 afforded only decomposition of the starting material.

Reduction of the salts 55 and 61 with sodium borohydride or lithium aluminium hydride was only successful with 1,1'-dimethyl-2,2'-biquinolinium salt 61. In this case, using sodium borohydride gave 22% of 1,1'-dimethyl-1,2,3,4,1',2',3',4'-octahydro-2,2'-biquinoline 65 and lithium aluminium hydride gave 85% of 1,1'-dimethyl-1,4,1',4'-tetrahydro-2,2'-biquinoline 64. Hydrogenation of the 1,1'-dimethyl-1,4,1',4'-tetrahydro-2,2'-biquinoline 64 gave quantitatively the 1,1'-dimethyl-1,2,3,4,1',2',3',4'-octahydro-2,2'-biquinoline 65.

Demethylation was investigated on the 1,1'-dimethyl-1,4,1',4'-tetrahydro-2,2'-biquinoline 64 and the 1,1'-dimethyl-1,2,3,4,1',2',3',4'-octahydro-2,2'-biquinoline 65, either by exchange of the methyl group with an alkylformate which is more easily removed, or by oxidative reduction using lead tetraacetate. Unfortunately, the desired demethylated products were not isolated.

3.2.4 Reduction using Super-Hydride®

In 1993, Blough and Carroll reported the reduction of quinolines and pyridines to give 1,2,3,4-tetrahydroquinolines and piperidines respectively using lithium triethylborohydride (Scheme 37).45
Reagents and conditions: (i) LiBHEt₃ (3.0 eq), THF, r.t., 81%.

**Scheme 37:** Reduction of pyridine using lithium triethylborohydride.

This group explored the mechanism of the reduction of isoquinolines and pyridines with lithium triethylborodeuteride (Super-Deuteride®). These mechanistic experiments conducted in the reduction of pyridines suggested that hydride initially adds at C-2 (Scheme 38). This intermediate then tautomerizes, allowing 1,4-hydride addition at C-4. The second intermediate can also tautomerize, which allows the final equivalent of hydride to add at C-6.

**Scheme 38:** Mechanism of the reaction of pyridine with Super-Hydride®.
3.2.4.1 Reduction of the 6,6'-dimethyl-2,2'-bipyridine 39 using Super-Hydride®

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction conditions</th>
<th>Observed products</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.4 eq LiBHEt₃, r.t., overnight then 50 °C, 90 min</td>
<td>39 + 15% 72</td>
</tr>
<tr>
<td></td>
<td>1) 4.4 eq LiBHEt₃, -78 °C → 0 °C, overnight, 2)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>4.4 eq LiBHEt₃, r.t., 1 day, 3) 4.4 eq LiBHEt₃, r.t., 1 day</td>
<td>39 + traces 72</td>
</tr>
<tr>
<td></td>
<td>4) 4.4 eq LiBHEt₃, r.t., 1 day</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1) 8 eq LiBHEt₃, 50 °C, 4 days, 2) 8 eq LiBHEt₃, 50 °C, overnight</td>
<td>27% 72</td>
</tr>
</tbody>
</table>

Table 27: Reduction of the 6,6'-dimethyl-2,2'-bipyridine 39 using Super-Hydride®.

The reduction method using lithium triethylborohydride was first applied to the 6,6'-dimethyl-2,2'-bipyridine 39 (Table 27). When 4.4 equivalents of lithium triethylborohydride were added to a solution of 6,6'-dimethyl-2,2'-bipyridine 39 in tetrahydrofuran at room temperature, and the mixture allowed to stand overnight (Entry 1, Table 27), the reaction did not reach completion. The reaction mixture was then heated at 50 °C, but after 90 minutes no progression could be observed by TLC (methanol). ¹H NMR spectroscopy of the oil obtained after work-up showed the presence of starting material along with some unidentified products. Column chromatography of the crude oil allowed isolation of 15% of 6,6'-dimethyl-1,2,3,4,5,6-hexahydro-2,2'-bipyrene 72 and some unreacted starting material (conversion 40%) and some unidentified products, which did not correspond to the desired bipiperidine 40 by comparison of the ¹³C NMR spectrum.
The reduction at lower temperature was then investigated (Entry 2, Table 27) and in this case the conversion was even worse. 4.4 Equivalents of lithium triethylborohydride were added to the reaction mixture, which was stirred overnight at room temperature. This last procedure was repeated three times, and in this case after work-up the crude mixture was identified as a mixture containing mostly unreacted starting material and traces of 6,6'-dimethyl-1,2,3,4,5,6-hexahydro-2,2'-bipyrine 72.

Finally, investigation at higher temperature was carried out by heating a solution of 6,6'-dimethyl-2,2'-bipyridine 39 and 8.8 equivalents of lithium borohydride in tetrahydrofuran at 50 °C for 4 days, then stirring overnight after adding an other 8.8 equivalents of lithium borohydride in order to bring the reaction to completion. In this case, the ¹H NMR spectrum of the orange oil showed a mixture containing the 6,6'-dimethyl-1,2,3,4,5,6-hexahydro-2,2'-bipyrine 72 along with some unidentified products. Column chromatography of the crude oil allowed isolation of 35% of 6,6'-dimethyl-1,2,3,4,5,6-hexahydro-2,2'-bipyrine 72 and some unidentified products. Comparison of the ¹³C NMR spectra with ¹³C NMR spectrum of the unresolved 6,6'dimethyl-2,2'-bipiperidine 40 revealed that no trace of the desired bipiperidine 40 could be observed.

Reagents and conditions: (i) 1) LiBHEt₃ (8.0 eq), THF, 50 °C., 4 days, 2) LiBHEt₃ (8.0 eq), 50 °C, overnight.

Scheme 39: Reduction of 6,6'-dimethyl-1,2,3,4,5,6-hexahydro-2,2'-bipyrine 72 using lithium triethylborohydride.

Reduction of 6,6'-dimethyl-1,2,3,4,5,6-hexahydro-2,2'-bipyrine 72 using lithium triethylborohydride was then carried out in the hope of reducing the second ring to isolate the desired 6,6'-dimethyl-2,2'-bipiperidine 40 (Scheme 39). Unfortunately, under these reaction conditions the unreacted starting material was recovered.
3.2.4.2 Reduction of 2,2'-biquinoline using lithium triethylborohydride

Reagents and conditions: (i) \( \text{LiBHEt}_3 \) (8.0 eq), THF, 50 °C, 4 days, 2) \( \text{LiBHEt}_3 \) (8.0 eq), 50 °C, overnight.

Scheme 40: Reduction of 2,2'-biquinoline using lithium triethylborohydride.

The commercially available 2,2'-biquinoline was subjected to the same lithium triethylborohydride reduction. After 5 days and a total of 16 equivalents of lithium borohydride added, a mixture was obtained identified by \(^1\text{H}\) NMR spectroscopy as a complex mixture containing some unreacted starting material along with some unidentified products. Observation of the desired product 52 was difficult even by comparison with the \(^1\text{H}\) and \(^{13}\text{C}\) NMR spectrum with the known compound 52.\(^{37}\) Attempts to isolate the different products by column chromatography were not successful.

3.2.4.3 Reduction of (S,S)-6,6'-bis-(1-methoxy-2,2'-dimethylpropyl)-2,2'-bipyridine 46 with lithium triethylborohydride

Reagents and conditions: (i) \( \text{LiBHEt}_3 \) (8.0 eq), THF, 50 °C, 4 days, 2) \( \text{LiBHEt}_3 \) (8.0 eq), 50 °C, overnight.

Scheme 41: Reduction of (S,S)-2,2'-bipyridine 46 using lithium triethylborohydride.
The reduction of \((S,S)-6,6'\text{-bis-(1-methoxy-2,2'-dimethylpropyl)-2,2'\text{-bipyridine}}\) 46 using lithium triethylborohydride under the same reaction conditions used previously did not afford the desired \((S,S)-2,2'\text{-bipiperidine}}\) 49. The unreacted starting material was the only material recovered. An explanation for the inertness of \((S,S)-2,2'\text{-bipyridine}}\) 46 to Super-Hydride\(^\circ\) could be the steric hindrance of this \((S,S)-2,2'\text{-bipyridine}}\) 46.

**Conclusion of section 3.2.4**

Studies of the reduction of 3 different bipyridines derivatives with Super-Hydride\(^\circ\) have been investigated. Unfortunately, in all cases no traces of the desired bipiperidine derivatives were observed. Concerning the 6,6'-dimethyl-2,2'-bipyridine 39, the only product isolated was the 6,6'-dimethyl-1,2,3,4,5,6-hexahydro-2,2'-bipyryine 72. In the case of the 2,2'-biquinoline, isolation of the numerous obtained products failed. Finally, the \((S,S)-2,2'\text{-bipiperidine}}\) 46 was observed to be inert to Super-Hydride\(^\circ\).

### 3.3 Synthesis of different tricyclic saturated imidazolium salts

**3.3.1 Synthesis of the imidazolium salt derivative 73 from 6,6'-dimethyl-2,2'-bipiperidine 40**

\[
\begin{align*}
\text{40} & \quad \overset{(i)}{\longrightarrow} \quad \text{73} \\
\text{Reagents and conditions: } (i) \text{NH}_4\text{BF}_4, \text{CH(OEt)}_3, 120 ^\circ\text{C}, 3 \text{ h}, 95\%.
\end{align*}
\]

**Scheme 42:** Synthesis of the imidazolium salt 73.

Cyclization of the 2,2'-bipiperidine 40 (mixture of 3 different isomers) using ammonium tetrafluoroborate in triethyl orthoformate at 120 °C for 3 hours (Scheme
42) gave a light yellow solid in 95% yield corresponding to the imidazolium salt 73. According to $^{13}$C NMR spectroscopy, three different isomers were obtained (1:3:8). Recrystallization from dichloromethane gave colourless needles identified by $^{13}$C NMR spectroscopy as one single isomer. X-ray (Appendix 4) of these needles showed that this isomer is the meso one (Figure 12).

Figure 12: X-ray of the meso imidazolium salt 73.
Comparison of the $^{13}$C NMR spectrum of the *meso* compound with the $^{13}$C NMR of the crude material containing all three isomers showed that the major compound is the *meso*.

![Diagram of meso-40 and meso-73](image)

*Reagents and conditions:* (i) $\text{NH}_3\text{BF}_4$, $\text{CH}(\text{OE})_3$, 120 °C, 3 h, 99%.

**Scheme 43:** Synthesis of the *meso*-imidazolium salt 73.

Cyclization of the *meso*-2,2'-bipiperidine 40 following the same previous method gave a colourless solid in good yield identified by $^{13}$C NMR spectroscopy as the *meso*-imidazolium salt 73.

### 3.3.2 Synthesis of the imidazolium salt derivative 74 from bidecahydroquinoline 42

![Diagram of 42 and 74](image)

*Reagents and conditions:* (i) $\text{NH}_3\text{BF}_4$, $\text{CH}(\text{OE})_3$, 120 °C, 3 h, 88%.

**Scheme 44:** Synthesis of the imidazolium salt 74.

The diamine 42 (mixture of all the different isomers) was cyclized using the same method as for the cyclization of the bipiperidine 40, and the salt 74 was obtained in 88% yield. The $^{13}$C NMR spectrum of this salt showed a mixture of 7 different
isomers, of which only three are major (1:1:1:3:5:9). Recrystallization from ethyl acetate gave colourless needles identified by $^{13}$C NMR spectroscopy as a mixture of all the 7 isomers of the cyclic compound.

**Conclusion of section 3.3**

Syntheses of two tricyclic saturated imidazolium salts 73 and 74 have been carried out by cyclization of the corresponding bipiperidines 40 and 42 respectively using ammonium tetrafluoroborate in triethyl orthoformate. These reactions were performed on the unseparated bipiperidines and gave the corresponding imidazolium salts as mixtures of isomers. Recrystallization of the 6,6'-dimethyl-2,2'-imidazolium salt 73 in dichloromethane gave a single isomer identified as the *meso* one. Cyclization of the *meso*-6,6'-dimethyl-2,2'-bipiperidine 40 under the same reaction conditions afforded exclusively the *meso*-imidazolium salt 73 in excellent yield.

### 3.4 Suzuki cross-coupling

Knowing that the critical step in the synthesis of carbene-complexes is the deprotonation of the imidazolium salt, we decided to test the different imidazolium salts obtained in Suzuki cross-couplings of 4-chlorotoluene with phenylboronic acid. In this case, according to the yield of the coupling, we should get an idea of which carbene complex has been actually formed *in situ* and which one is the best for this reaction. Nolan and co-workers have shown recently that the coupling of 4-chlorotoluene and phenylboronic acid (1.5 equiv) in the presence of 1.5 mol% of Pd$_2$(dba)$_3$, 3.0 mol% of the carbene IMes, and Cs$_2$CO$_3$ in dioxane at 80 °C proceeded to give 4-phenyltoluene in 59% isolated yield.$^{46,47,48}$ Since imidazol-2-ylidene carbenes are considerably less stable to air and moisture than the corresponding imidazolium salts, to avoid the preparation and isolation of the carbene IMes (Figure 13), they developed a protocol in which the carbene ligand is generated *in situ* from the corresponding imidazolium salt. In that case, when the coupling reaction was performed with IMesHCl under the same general conditions, the product 4-phenyltoluene was isolated in 96% yield (Scheme 45).
Figure 13: Carbene IMes

Reagents and conditions: (i) Pd$_2$(dba)$_3$ (1.5 mol%), IMesHCl (3.0 mol%), Cs$_2$CO$_3$ (2.0 eq), dioxane, 80 °C, 1.5 h, 96%.

Scheme 45: Suzuki cross-coupling reaction of 4-chlorotoluene and phenylboronic acid

We repeated this reaction with the different imidazolium salts already synthesized. The results of these reactions are summarized in Table 28.
In the case where no ligand was used (Entry 1, Table 28) only a poor yield was obtained. The poor result for the ligand 75 (Entry 3, Table 28) was expected due to the fact that the structure of this ligand is not bulky, and this would affect the formation of the carbene and probably make it less stable. In the case where a methyl group is present (ligand 73)(Entry 4, Table 28), the carbene should be more stable and the reaction indeed gives better results (42%). The different isomers of ligand 73 were not separated at this stage, so perhaps using a single isomer could give a better result. Unfortunately, performing the reaction using meso-73 afforded only 14% of the 4-
phenyltoluene. Finally, using the ligand 74 gave a really poor yield, possibly due to the bulkiness of the ligand or to the fact that the salt was used as a mixture of different isomers. In the cases where poor yields were obtained it is difficult to tell if this was due to the ligand used not being good enough for this reaction or due to the complex being too unstable under the reaction conditions.

Conclusion of section 3.4

The different imidazolium salts obtained were tested in the Suzuki cross-coupling of the 4-chlorotoluene with phenylboronic acid. The best result (42%) was obtained for the ligand 73 where the different isomers were not separated. Unfortunately when meso-73 was used the reaction afforded only 14% of 4-phenyltoluene.

3.5 Conclusion

Several methods to reduce three different 2,2'-bipyridine derivatives have been tried. Only reduction by hydrogenation was successful, for two of the substrates. Unfortunately, among the methods tried to separate the isomers, none afforded a good separation.

Synthesis of two tricyclic saturated imidazolium salts has been carried out by cyclization of the corresponding bipiperidines using ammonium tetrafluoroborate in triethyl orthoformate.

Finally, the Suzuki cross coupling of 4-chlorotoluene with phenylboronic acid was investigated in the presence of the different imidazolium salts prepared.

3.6 Future work

Recently, Legault and Charette have reported a novel and highly regioselective approach to 2,6-disubstituted tetrahydropyridines from 2-substituted pyridinium moieties using N-benzoyliminopyridinium ylides (Scheme 46).49
Reagents and conditions: (i) 1) RMgX, DCM, r.t., 40 min, 2) NaBH₄, AcOH, – 78 °C, 90 min.

Scheme 46: Formation of 2,6-disubstituted-1,2,5,6-tetrahydropyridines.

This methodology consists of the addition of Grignard reagent to a N-benzoyliminopyridinium ylide. The addition proceeds smoothly at room temperature within 40 minutes. Because the corresponding dihydropyridines obtained were found to be unstable, they were reduced in situ with sodium borohydride in acetic acid to afford the 2,6-disubstituted-1,2,5,6-tetrahydropyridines in good yields. Several Grignard reagents were added to the 2-methyl-N-benzoyliminopyridinium ylide and the results are summarized in Table 29.49

<table>
<thead>
<tr>
<th>Entry</th>
<th>RMgX</th>
<th>Cis/trans (a)</th>
<th>Yield (%) (b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeMgBr</td>
<td>69/31</td>
<td>86</td>
</tr>
<tr>
<td>2</td>
<td>n-PrMgCl</td>
<td>81/19</td>
<td>85(61)</td>
</tr>
<tr>
<td>3</td>
<td>i-PrMgBr</td>
<td>&gt; 95/5</td>
<td>84(84)</td>
</tr>
</tbody>
</table>

(a): Ratio were determined by ¹H NMR.  
(b): Combined yields of the two diastereomers. Isolated yield of the cis isomer is shown in parentheses.

Table 29: Results of the formation of 2,6-disubstituted-1,2,5,6-tetrahydropyridines.

Legault and Charette showed that, in all cases, the regioselectivity was complete, favouring the 1,2-adduct. Following the addition, the resulting dihydropyridines were reduced to afford the 2,6-disubstituted-1,2,5,6-tetrahydropyridines, favouring the cis isomer in moderate to excellent diastereoselectivities and in high yields.49

This new methodology could be a useful alternative for the synthesis of 2,6-bipiperidine (Scheme 47).
Reagents and conditions: (i) 1) DCM, r.t., 40 min, 2) NaBH₄, AcOH, −78 °C, 90 min, (ii) H₂, (iii) Ni Raney, (iv) Resolution, (v) NH₄BF₄, CH(OEt)₃, 120 °C, 3 h.

Scheme 47: Proposed new synthesis of 2,6-bipiperidine.
Chapter 4: Experimental Detail

4.1 General experimental detail

$^1$H NMR spectra were measured at 250.13 MHz or at 400.13 MHz using a Bruker AC 250 spectrometer or a Bruker DPX 400 MHz spectrometer respectively. Chemical shift, $\delta$, values are given in ppm and coupling constants $J$ in Hertz.

$^{13}$C NMR spectra were recorded on a Bruker DPX 400 instrument operating at 100.62 MHz unless otherwise stated.

All NMR spectra were recorded using tetramethylsilane (TMS) as the internal reference in CDCl$_3$ unless otherwise stated.

IR spectra were determined using a Perkin Elmer FT-IR Paragon 1000 spectrometer as thin film unless otherwise stated. All the infrared spectra were recorded in the range 4000 to 600 cm$^{-1}$.

Mass spectra were recorded on Jeol-SX102 instrument and GC-MS on a Fisons GC 8000 series (AS 800).

Elemental analysis was performed on a Perkin Elmer 2400 CHN Elemental Analyser.

Melting points were measured using a Bibby stuart scientific SMP3 melting point instrument and are uncorrected.

Optical rotation values were measured with an Optical Activity PolAAr 2001 instrument, operating at $\lambda = 589$ nm, corresponding to the sodium line, (D), at the temperatures indicated. The solutions for these measurements were prepared in volumetric flasks for maximum accuracy of the volume of the solvent used.

Thin Layer Chromatography (TLC) using silica gel as the adsorbent was carried out with aluminium backed plates coated with silica gel (Merck Kiesel 60).
containing fluoresces (F₂₅₄) and thin layer chromatography using alumina as the adsorbent was carried out with aluminium backed plates coated with aluminium oxide (Merck 15, type T).

**Column chromatography** using silica gel was carried out with Merck Kiesel gel 60 H silica.

**Solvents** were distilled before use. Petroleum ether (b.p. 40-60 °C) and ethyl acetate were distilled from anhydrous calcium chloride. Dichloromethane was distilled from phosphorus pentoxide. Tetrahydrofuran and diethyl ether were freshly distilled over the sodium-benzophenone radical anion under an atmosphere of nitrogen. Toluene was distilled from calcium hydride.

All reactions were performed using dry glassware and under an atmosphere of nitrogen. Deuteriated solutions of diazabutadienes were dried through magnesium sulphate before recording ¹H or ¹³C spectra. All carbene and metal-complex reactions were carried out in Schlenk glassware and using a Schlenk line.
4.2 Experimental data for Chapter 2
4.2.1 Experimental data for section 2.2

1,4-Bis-(2,6-diisopropylphenyl) diazabutadiene

An aqueous solution of glyoxal (3.2 mL, 28 mmol, 40% in water) was added to a solution of 2,6-diisopropylaniline (10 g, 56.5 mmol) in absolute ethanol (50 mL). A few drops of formic acid were added as catalyst. The colour of the reaction mixture turned from yellow to brown and a yellow precipitate appeared after a few hours. The reaction mixture was stirred for 2 days and the yellow solid was collected by filtration (8.39 g, 80%), identified as the desired product 1, m.p. 72-73 °C (lit.\textsuperscript{6,7} 71-73 °C); $\nu_{\text{max}}$ (film)/cm$^{-1}$ 3062 (sp$^2$ C-H), 1627 (C=N), 818-758 (Ar substitution); $\delta_H$ 1.23 (24H, d, $J$ 6.7, CH$_3$, H-8,8',9,9',11,11',12,12'), 2.96 (4H, sept., $J$ 6.7, CH(CH$_3$)$_2$, H-7,7',10,10'), 7.05-7.27 (6H, m, ArH, H-3,3',4,4',5,5'), 8.12 (2H, s, NCH, H-13,14); $\delta_C$ 23.4 (CH$_3$, C-8,8',9,9',11,11',12,12'), 28.1 (CH(CH$_3$)$_2$, C-7,7',10,10'), 123.2 (CH Ar, C-3,3',5,5'), 125.1 (CH Ar, C-4,4'), 136.7 (C$_{\text{quat.}}$ Ar, C-2,2',6,6'), 148.0 (C$_{\text{quat.}}$ Ar, C-1,1'), 163.1 (NCHCHN, C-13,14); $m/z$ 377.2958 C$_{26}$H$_{36}$N$_2$ (MH$^+$) requires 377.2957.
1,4-Bis-(2-methylthiophenyl) diazabutadiene 2

\[
\begin{align*}
\text{NH}_2 & \quad \rightarrow \\
\text{SMe} & \quad \text{SMe}
\end{align*}
\]

2-(Methylthio)aniline (4.6 mL, 36 mmol) was added to an aqueous solution of glyoxal (2 mL, 18 mmol, 40% in water) in absolute ethanol (32 mL) at room temperature. A few drops of formic acid were added as catalyst. An orange solution was obtained and a solid began to appear after a few hours of stirring. Stirring was continued for 48 hours and the precipitated solid was collected by filtration. Recrystallization from hot toluene gave the desired compound 2 (3.98 g, 74%) as yellow needles, m.p. 220 °C (lit.\textsuperscript{3} 227-228 °C); \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 3050 (sp\(^2\) C-H), 1457 (C=N), 848-721 (Ar substitution); \(\delta_H\) 2.49 (6H, s, CH\(_3\), H-8,8'), 7.07-7.33 (8H, m, ArH, H-2,2',3,3',4,4',5,5'), 8.42 (2H, s, HCN, H-9,10); \(\delta_C\) 14.9 (CH\(_3\), C-8,8'), 117.3 (C\(_{\text{quat.}}\) Ar, C-6,6'), 124.8 (CH Ar, C-5,5'), 125.3 (CH Ar, C-4,4'), 128.3 (CH Ar, C-3,3'), 135.8 (CH Ar, C-2,2'), 147.3 (C\(_{\text{quat.}}\) Ar, C-1,1'), 159.6 (NCHCHN, C-9,10); \(m/z\) 300.0747 \(C_{16}H_{16}N_2S_2\) (M\(^+\)) requires 300.0755.

1,4-Bis-(2-pyridine) diazabutadiene 3

\[
\begin{align*}
\text{NH}_2 & \quad \rightarrow \\
\text{N} & \quad \text{N}
\end{align*}
\]

Table 1, Entry 1: Room temperature for 3 days then reflux overnight

An aqueous solution of glyoxal (0.6 mL, 5.3 mmol, 40% in water) was added to a solution of 2-aminopyridine (1 g, 10.6 mmol) in absolute ethanol (9.5 mL). A few drops of formic acid were added as catalyst. The colour of the reaction mixture turned
from pink to black. The progress of the reaction was monitored by TLC in ethanol. After 3 days no precipitate appeared and lots of starting material remain. The mixture was then heated at reflux overnight. Ethanol was then removed under reduced pressure and a black solid was obtained. The resulting solid was identified by $^1$H NMR spectroscopy as a complex mixture containing the desired product 3 (40% conversion), which could be recognised by a signal at 8.44 ppm corresponding to the azomethine protons along with some starting material and unidentified products. The yield was not determined.

**Table 1**, Entry 2: Room temperature for 6 days

An aqueous solution of glyoxal (0.3 mL, 2.7 mmol, 40% in water) was added to a solution of 2-aminopyridine (0.5 g, 5.3 mmol) in absolute ethanol (5 mL). A few drops of formic acid were added as catalyst. The colour of the reaction mixture turned from pink to black. The progress of the reaction was monitored by TLC in ethanol. After 6 days no precipitate appeared and no starting material remained. Ethanol was then removed under reduced pressure and a black solid was obtained. The resulting solid was identified by $^1$H NMR spectroscopy as a complex mixture containing the desired product 3, which could be recognised by a signal at 8.44 ppm corresponding to the azomethine protons along with some unidentified products. Attempt to isolate the different products by column chromatography failed.

**Table 1**, Entry 3: Reaction without solvent without acid

2-Aminopyridine (0.2 g, 2.1 mmol) in solid form was added to an aqueous solution of glyoxal (0.15 g, 1.05 mmol, 40% in water) at 0 °C. After 30 minutes, the reaction mixture was allowed to warm up to room temperature and a few drops of dichloromethane were added. After 1 day, the colour of the reaction mixture turned from pink to black. The progress of the reaction was monitored by $^1$H NMR spectroscopy. After 11 days no precipitate appeared and $^1$H NMR spectroscopy showed a complex mixture of starting material and unidentified products. No trace of the desired product 3 was observed.
1,4-Bis-(2-methoxyethyl) diazabutadiene 4

Table 2, Entry 1: Use of formic acid at room temperature

An aqueous solution of glyoxal (0.65 mL, 5.8 mmol, 40% in water) was added to a solution of 2-methoxyethylamine (0.86 g, 11.5 mmol) in absolute ethanol (11 mL). A few drops of formic acid were added as catalyst. After 5 days no starting material remained. The ethanol was evaporated and an orange oil was obtained. The resulting oil was identified by $^1$H NMR spectroscopy as a complex mixture containing a small amount of the desired product 4, which could be recognised by a signal at 8.6 ppm corresponding to the protons on the diazabutadiene moiety. Column chromatography of the crude mixture did not give the desired product 4. Instead a complex mixture of products was obtained. These were not identified.

Table 2, Entry 2: Use of hydrochloric acid at room temperature

An aqueous solution of glyoxal (0.2 mL, 1.8 mmol, 40% in water) was added to a solution of 2-methoxyethylamine (0.26 g, 3.5 mmol) in absolute ethanol (3.5 mL). A few drops of hydrochloric acid (4 M in dioxane) were added as catalyst and after 20 hours no starting material remained. Ethanol was evaporated and an orange oil was obtained. The resulting oil was shown by $^1$H NMR spectroscopy to a complex mixture containing no trace of the desired product 4.

Table 2, Entry 3: Use of hydrochloric acid at 0 °C

An aqueous solution of glyoxal (0.2 mL, 1.8 mmol, 40% in water) was added to a solution of 2-methoxyethylamine (0.26 g, 3.5 mmol) in absolute ethanol (3.5 mL). The reaction mixture was cooled down to 0 °C and a few drops of hydrochloric acid (4 M in dioxane) were added as catalyst. After 20 hours no starting material remained.
by TLC. Ethanol was then evaporated and an orange oil was obtained. The resulting oil was shown by $^1$H NMR spectroscopy to be a complex mixture containing no trace of the desired product 4.

Table 2, Entry 4: Use of molecular sieves

An aqueous solution of glyoxal (0.2 mL, 1.8 mmol, 40% in water) was added to a solution of 2-methoxyethylamine (0.26 g, 3.5 mmol) in absolute ethanol (3.5 mL) with molecular sieves. After 20 hours no starting material remained. Ethanol was then evaporated and an orange oil was obtained. The resulting oil was shown by $^1$H NMR spectroscopy to be a complex mixture containing no trace of the desired product 4.

Table 2, Entry 5: Use of formic acid at 0 °C

An aqueous solution of glyoxal (0.4 mL, 3.4 mmol, 40% in water) was added to a solution of 2-methoxyethylamine (0.51 g, 6.8 mmol) in absolute ethanol (6 mL) at 0 °C. The reaction mixture was kept at 0 °C. Then a few drops of formic acid were added as catalyst. After 2 days no starting material remained. The ethanol was then evaporated and an orange oil was obtained. The resulting oil was identified by $^1$H NMR spectroscopy as a complex mixture containing the desired product 4, which could be recognised by a signal at 8.6 ppm corresponding to the azomethine protons. The yield was not determined.

Table 2, Entry 6: Reaction without solvent with formic acid

An aqueous solution of glyoxal (0.13 mL, 1.2 mmol, 40% in water) was added to 2-methoxyethylamine (0.17 g, 2.3 mmol). A few drops of formic acid were added as catalyst. After 2 days a brown mixture was obtained, then a few drops of dichloromethane were added and the organic layer was washed three times with water, then dried over magnesium sulphate. Evaporation of the solvent gave an oil. The resulting oil was identified by $^1$H NMR spectroscopy as a complex mixture containing a small amount of the desired product 4, which could be recognised by a signal at 8.6 ppm corresponding to the azomethine protons. The yield was not determined.
2-((tert-butyldimethylsilyloxy) ethyl amine 5

![Chemical structure of 2-(tert-butyldimethylsilyloxy) ethyl amine 5]

Triethylamine (0.5 mL, 3.6 mmol) was added dropwise to a solution of ethanolamine (0.2 g, 3.3 mmol) in dichloromethane (6 mL). The mixture was stirred for a few minutes, then tert-butyldimethylsilyl chloride (0.54 g, 3.6 mmol) and 4-dimethylaminopyridine (0.04 g, 0.3 mmol) were added in solid form. The solution was stirred overnight. Water (10 mL) was added and the mixture was stirred for 10 minutes. The organic layer was extracted 3 times with water and once with brine, then dried over magnesium sulphate. Evaporation of the solvent gave the desired product 5 (0.51 g, 89%) as a light yellow oil, \( \nu_{\text{max}}(\text{film})/\text{cm}^{-1} \) 3360, 3276 (NH\(_2\)), 1104 (Si-O), 836, 777 (Si(R)\(_3\)); \( \delta_H \) 0.70 (6H, s, CH\(_3\), H-6,7), 0.90 (9H, s, (CH\(_3\)\(_3\)), H-9,10,11), 1.67 (2H, s, NH\(_2\)), 2.79 (2H, s broad, CH\(_2\)N, H-2), 3.63 (2H, t, \( J \approx 5.3 \), CH\(_2\)O, H-3); \( \delta_C \) -5.3 (CH\(_3\), C-6,7), 18.3 (C (CH\(_3\)\(_3\), C-8), 25.9 ((CH\(_3\)\(_3\)), C-9,10,11), 44.2 (CH\(_2\)N, C-2), 65.2 (CH\(_2\)O, C-3).

**Attempted synthesis of 1,4-bis-[2-(tert-butyldimethylsilyloxy)ethyl]diazabutadiene 6**

![Chemical structures of 2-(tert-butyldimethylsilyloxy) ethyl amine 5 and 1,4-bis-[2-(tert-butyldimethylsilyloxy)ethyl]diazabutadiene 6]

**Table 3, Entry 1: Reaction in ethanol**

An aqueous solution of glyoxal (0.07 mL, 0.6 mmol, 40% in water) was added dropwise to a solution of 2-(tert-butyldimethylsilyloxy) ethyl amine 5 (0.21 g, 1.2 mmol) in absolute ethanol (4 mL). After 2 days no starting material remained.
Evaporation of the solvent gave an orange oil shown by $^1$H NMR spectroscopy to be a complex mixture containing no trace of the desired product 6.

Table 3, Entry 2: Reaction without solvent

An aqueous solution of glyoxal (0.03 mL, 0.3 mmol, 40% in water) was added dropwise to 2-($tert$-butyldimethylsilyloxy) ethyl amine 5 (0.1 mg, 0.6 mmol). After 2 days no starting material remained. Evaporation of the volatile gave an orange oil shown by $^1$H NMR spectroscopy to be a complex mixture containing no trace of the desired product 6.

$N$-[2-(phenyloxy)ethyl]formamide 8

![Chemical structure of N-[2-(phenyloxy)ethyl]formamide 8]

An aqueous solution of glyoxal (0.8 mmol, 0.09 mL, 40% in water) was added dropwise to a solution of 2-phenoxyethylamine (0.21 g, 1.5 mmol) in absolute ethanol (4 mL). A few drops of formic acid were added as catalyst. After 2 days no starting material remained. Evaporation of the solvent gave an orange oil. Crystallization of the crude oil from hot toluene gave the $N$-[2-(phenyloxy)ethyl]formamide 8 (0.79 g, 35%) as light yellow crystals, m.p. 72-73 °C; Found: C, 65.69; H, 6.86; N, 8.10. C$_9$H$_{11}$NO$_2$ requires C, 65.44; H, 6.71; N, 8.48; $\nu$$_{\text{max}}$(film)/cm$^{-1}$ 3235 (NH), 3053 (sp$^2$ C-H), 2880 (sp$^3$ C-H), 1644 (C=N), 751-689 (Ar substitution); $\delta$$_H$ 3.70 (2H, q, J 4.8 and 10, CH$_2$N, H-3), 4.04 (2H, t, J 4.8, CH$_2$O, H-4), 6.25 (1H, s, NH, H-2, D$_2$O shake), 6.87-6.90 (2H, m, ArH, H-8,10), 6.95-6.99 (1H, m, ArH, H-9), 7.26-7.30 (2H, m, ArH, H-7,11), 8.20 (1H, s broad, C(=O)H, H-1); $\delta_C$ 31.3 (CH$_2$N, C-3), 66.8 (CH$_2$O, C-4), 114.8 (CH Ar, C-8,10), 121.7 (CH Ar, C-9), 129.9 (CH Ar, C-7,11), 158.7 (C$_{\text{quat}}$. Ar, C-6), 161.7 (C=O); m/z 165.0778 C$_9$H$_{11}$NO$_2$ (M$^+$) requires 165.0790. X-Ray see Appendix 1.
1,4-Bis-(2-hydroxyphenyl) diazabutadiene 9

An aqueous solution of glyoxal (0.95 mL, 9.2 mmol, 40% in water) was added dropwise to a solution of 2-aminophenol (2 g, 18.3 mmol) in absolute ethanol (50 mL). A few drops of formic acid were added as catalyst. A white precipitate appeared after a few hours. The reaction mixture was stirred for 3 days and the white solid was collected by filtration (1.68 g, 73%), m.p. 219 °C (decomp.); Found: C, 69.86; H, 4.81; N, 11.56. C_{14}H_{12}N_{2}O_{2} requires C, 69.99; H, 5.03; N, 11.66; m/z 240.0899 C_{14}H_{12}N_{2}O_{2} (M^+) requires 240.0898.

Open form 9: δ_{H} 4.88 (2H, s, OH), 5.32 (2H, d, J 3.7, HCN, H-7,8), 6.69 (2H, dd, J 1.2 and 7.7, ArH, H-3,3'), 6.74-6.85 (6H, m, ArH, H-4,4',5,5',6,6'); δ_{C} 75.9 (HCN, C-7,8), 114.9 (CH Ar, C-3,3'), 117.1 (CH Ar, C-5,5'), 120.6 (CH Ar, C-6,6'), 122.1 (CH Ar C-4,4'), 128.5 (C_{quat.} Ar, C-1,1'), 141.5 (C_{quat.} Ar, C-2,2').

Cyclic form 10: δ_{H} (DMSO-d_{6}) 5.27 (2H, d, J 4.2, CH, NHCHO, H-7,7'), 6.58-6.77 (8H, m, ArH, H-2,2',3,3',4,4',5,5'); 7.32 (2H, d, J 4.2, NH, D_{2}O shake); δ_{C} 75.6 (CH, C-7,7'), 114.5 (CH Ar, C-2,2'), 116.4 (CH Ar, C-5,5'), 119.0 (CH Ar, C-4,4'), 121.7 (CH Ar, C-3,3'), 130.5 (C_{quat.} Ar, C-1,1'), 141.6 (C_{quat.} Ar, C-6,6').
Attempted synthesis of 1,4-bis-(2-p-toluene sulfonyl acid phenyl ester) diazabutadiene 12

![Chemical Structures of 9 and 12](image)

**Table 4, Entry 1: Using sodium hydride and diethyl ether**

Sodium hydride (0.04 g, 1.0 mmol, 60\% in oil) was added to a solution of 1,4-bis-(2-hydroxyphenyl) diazabutadiene 9 (0.1 g, 0.4 mmol) in diethyl ether (5 mL). The reaction was stirred and p-toluene sulfonyl chloride (0.18 g, 1.0 mmol) was added in solid form. After 4 days, the mixture was evaporated. A white-yellow solid was obtained and shown by $^1\text{H NMR}$ spectroscopy to be a complex mixture. The mixture was subjected to a column chromatography, using ethyl acetate/petroleum ether 2/8 as eluent to give three different fractions (p-toluene sulfonyl chloride, starting material, unidentified products) containing no trace of the desired product 12.

**Table 4, Entry 2: Using triethylamine and dichloromethane**

Triethylamine (0.2 mL, 1.4 mmol) was added dropwise to a solution of 1,4-bis-(2-hydroxyphenyl) diazabutadiene 9 (0.15 g, 0.6 mmol) in dichloromethane (10 mL). The mixture was stirred for a few minutes then p-toluene sulfonyl chloride (0.27 g, 1.4 mmol) and 4-dimethylaminopyridine (0.007 g, 0.06 mmol) was added in solid form. The solution was stirred for 2 days. Water (10 mL) was added and the mixture was stirred for 10 minutes. The organic layer was extracted 3 times with water and once with brine, then dried over magnesium sulphate. Evaporation of the solvent gave an orange solid-oil shown by $^1\text{H NMR}$ spectroscopy to be a mixture containing traces of the starting material, traces of p-toluene sulfonyl chloride and an unidentified product, which was not the desired product 12 according to GC/MS.
Table 4, Entry 3: Using sodium hydride and dichloromethane

Sodium hydride (0.04 g, 1.0 mmol, 60% in oil) was added to a solution of 1,4-bis-(2-hydroxyphenyl) diazabutadiene 9 (0.1 g, 0.4 mmol) in dichloromethane (5 mL). The colour of the reaction turned pink and after a few minutes p-toluene sulfonyl chloride (0.18 g, 1.0 mmol) was added. After 3 days the reaction mixture was filtered and evaporation of the filtrate gave a yellow solid shown by $^1$H NMR spectroscopy to be a mixture containing traces of the starting material, traces of $p$-toluene sulfonyl chloride and an unidentified product, which was not the desired product 12 according to GC/MS.

2-aminophenyl-4-toluene sulfonate 11$^{50,51}$

![Chemical structure](image)

Triethylamine (0.28 mL, 2.0 mmol) was added dropwise to a solution of 2-aminophenol (0.2 g, 1.8 mmol) in dichloromethane (10 mL). After a few minutes, $p$-toluene sulfonyl chloride (0.38 g, 2.0 mmol) was added in solid form. The solution was stirred overnight. The organic layer was extracted 3 times with water, then dried over magnesium sulphate. Evaporation of the solvent gave the desired product 11 (0.45 g, 93%) as a light pink solid, m.p. 97-98 °C (lit.$^{50}$ 98.5 °C, lit.$^{51}$ 99-100 °C); $\nu_{\text{max}}$(film)/cm$^{-1}$ 3475, 3387 (NH$_2$), 3065 (sp$^2$ C-H), 1366, 1180 (O-SO$_2$), 1194, 1091 (C-O), 880-660 (Ar substitution); $\delta_H$ 2.44 (3H, s, CH$_3$, H-15), 4.06 (2H, s, NH$_2$, D$_2$O shake), 6.62 (1H, dd, J 1.6 and 8.0, ArH, H-2), 6.79 (2H, dd, J 1.2 and 8.0, ArH, H-4,5), 7.02 (1H, dd, J 1.6 and 8.0, ArH, H-3), 7.31 (2H, d, J 8.0, ArH tosyl, H-10,14), 7.78 (2H, d, J 8.0, ArH tosyl, H-11,13); $\delta_C$ 22.1 (CH$_3$, C-15), 118.0 (CH Ar, C-2), 125.
119.2 (CH Ar, C-5), 123.3 (CH Ar, C-4), 128.2 (CH Ar, C-3), 128.9 (CH Ar tosyl, C-10,14), 130.2 (CH Ar tosyl, C-11,13), 132.9 (C quat. Ar, C-1), 137.6 (C quat. Ar tosyl, C-9), 139.3 (C quat. Ar tosyl, C-12), 146.0 (C quat. Ar, C-6); m/z 263.0620 C_{13}H_{13}N_{03}S (M^+) requires 263.0616.

**Attempted synthesis of 1,4-bis-(2-p-toluene sulfonic acid phenyl ester) diazabutadiene 12**

Table 5, Entry 1: Reaction in ethanol with formic acid

An aqueous solution of glyoxal (0.02 mL, 0.2 mmol, 40% in water) was added dropwise to a solution of p-toluene sulfonic acid 2-amino-phenyl ester 11 (0.1 g, 0.4 mmol) in absolute ethanol (5 mL). A few drops of formic acid were added as catalyst and a white precipitate appeared after a few hours. The reaction mixture was stirred for 2 days. The white solid was collected by filtration and the filtrate evaporated under reduced pressure. $^1$H NMR spectroscopy of the white solid and the filtrate showed no trace of the desired diazabutadiene 12 (confirmed by mass and elemental analysis). Only traces of the starting material along with an unidentified product were observed.

Table 5, Entry 2: Reaction without formic acid and without solvent

*p*-toluene sulfonic acid 2-amino-phenyl ester 11 (0.5 g, 1.9 mmol) in solid form was added to an aqueous solution of glyoxal (0.06 g, 1.0 mmol, 40% in water) at 0 °C. After 30 minutes, the reaction mixture was allowed to warm up to room temperature and a few drops of dichloromethane were added. After 1 day, the colour of the reaction mixture turned from light red to dark red. The progress of the reaction was monitored by $^1$H NMR spectroscopy. After 11 days no precipitate appeared and $^1$H NMR spectroscopy showed a complex mixture of starting material as the major compound. No trace of the desired product 12 was observed.
1,4-Bis-(2-methoxyphenyl) diazabutadiene 13

Table 6, Entry 1: Using triethylamine and iodomethane

Triethylamine (0.12 mL, 0.8 mmol) was added dropwise to a solution of 1,4-bis-(2-hydroxyphenyl) diazabutadiene 9 (0.1 g, 0.4 mmol) in dichloromethane (5 mL) at 0 °C. After 10 minutes, iodomethane (0.05 mL, 0.8 mmol) was added drop by drop. After 1 day, water was added and the organic layer was washed 3 times with water and once with brine, then dried over magnesium sulphate and filtered. Evaporation of the solvent gave a white solid identified by \(^1\)H NMR spectroscopy as the unreacted starting material 9.

Table 6, Entry 2: Using potassium tert-butoxide and iodomethane

Potassium tert-butoxide (0.11 g, 1.0 mmol) was added in solid form to a solution of 1,4-bis-(2-hydroxyphenyl) diazabutadiene 9 (0.1 g, 0.4 mmol) in dichloromethane (10 mL). The colour of the reaction turned brown and after 10 minutes iodomethane (0.05 mL, 0.8 mmol) was added drop by drop. After a few hours, a precipitate appeared. The mixture was stirred overnight then filtered to give a light yellow solid identified by \(^1\)H NMR spectroscopy as the unreacted starting material 9.

Table 6, Entry 3: Using potassium carbonate and iodomethane

Potassium carbonate (0.13 g, 0.9 mmol) was added in solid form to a solution of 1,4-bis-(2-hydroxyphenyl) diazabutadiene 9 (0.1 g, 0.4 mmol) in acetone (10 mL). After 15 minutes, iodomethane (0.06 mL, 0.9 mmol) was added drop by drop. The solution was heated to reflux for 6 hours. After the solution was cooled to room temperature, water was added and the organic layer was washed 3 times with water and once with brine, then dried over magnesium sulphate and filtered. Evaporation of the solvent
gave a light yellow solid identified by $^1$H NMR spectroscopy as the unreacted starting material 9.

**Table 6, Entry 4: Using sodium hydride and iodomethane**

Sodium hydride (0.09 g, 3.0 mmol, 60% in oil) was added in solid form to a solution of 1,4-bis-(2-hydroxyphenyl) diazabutadiene 9 (0.2 g, 0.8 mmol) in tetrahydrofuran (10 mL) at 0 °C. After 30 minutes, iodomethane (0.23 mL, 3.7 mmol) was added drop by drop. The solution was stirred at 0 °C for 24 hours. After the solution was warmed to room temperature, water was added and the aqueous layer was extracted 3 times with diethyl ether, then dried over magnesium sulphate and filtered. Evaporation of the solvent gave a red-orange solid shown by $^1$H NMR spectroscopy to be a complex mixture, which looked like a decomposition of the starting material 9.

**Table 6, Entry 5: Using caesium carbonate and dimethyl sulphate**

Caesium carbonate (2.57 g, 7.9 mmol) was added in solid form to a solution of 1,4-bis-(2-hydroxyphenyl) diazabutadiene 9 (0.5 g, 2.1 mmol) in dichloromethane (10 mL). After 30 minutes, dimethyl sulphate (0.75 mL, 7.9 mmol) was added drop by drop. The solution was stirred at room temperature for 48 hours. The reaction mixture was then washed twice with water and brine. The organic layers were combined, dried over magnesium sulphate and filtered. Evaporation of the solvent gave a brown solid identified by $^1$H NMR spectroscopy as the unreacted starting material 9.

**Table 6, Entry 6: Using n-butyllithium and methyl triflate**

A solution of $n$-butyllithium (1.8 mL, 4.6 mmol, 2.5 M in hexane) was added dropwise to a solution of 1,4-bis-(2-hydroxyphenyl) diazabutadiene 9 (0.5 g, 0.2 mmol) in tetrahydrofuran (10 mL) at $-78$ °C and stirred 30 minutes at this temperature. Methyl triflate (0.49 mL, 4.4 mmol) was then added dropwise and the mixture was stirred at $-78$ °C for 5 hours. The reaction was quenched by addition of water and then allowed to warm up to room temperature. All the volatile were evaporated under reduced pressure and the resultant residue dissolved in ethyl acetate and then washed with water and brine. The organic layers were combined and dried
over magnesium sulphate. Evaporation of ethyl acetate gave a brown residue shown by $^1$H NMR spectroscopy to be a complex mixture containing traces of the starting material along with some unidentified products. No trace of the desired diazabutadiene 13 was detected.

Table 7, Entry 1: Reaction in ethanol with formic acid

An aqueous solution of glyoxal (0.54 mL, 4.7 mmol, 40% in water) was added dropwise to a solution of 2-methoxyaniline (1.16 g, 9.4 mmol) in absolute ethanol (10 mL). After 14 days some starting material remained. Evaporation of the ethanol under reduced pressure gave a red-brown oil. The $^1$H NMR spectrum of the crude oil showed a complex mixture containing some starting material along with some unidentified products.

Table 7, Entry 2: Reaction in dichloromethane without formic acid

2-Methoxyaniline (0.2 g, 1.6 mmol) was added dropwise to an aqueous solution of glyoxal (0.12 g, 0.8 mmol, 40% in water) at 0 °C. After 30 minutes, a brown precipitate appeared. A few drops of dichloromethane were added which dissolved the precipitate and the reaction mixture was then allowed to warm up to room temperature. The progress of the reaction was monitored by $^1$H NMR spectroscopy. After 11 days no precipitate reappeared and the solvent was evaporated. $^1$H NMR spectroscopy of the resultant dark-red residue showed a complex mixture containing some starting material along with some unidentified products.

Table 7, Entry 3: Reaction in water without formic acid

2-Methoxyaniline (0.5 g, 4.0 mmol) was added dropwise to an aqueous solution of glyoxal (0.29 g, 2.0 mmol, 40% in water) at 0 °C. After 30 minutes, a brown gummy
solid appeared and a few drops of pure water were added and the reaction mixture was allowed to warm up to room temperature. The progress of the reaction was monitored by $^1$H NMR spectroscopy. After 14 days, $^1$H NMR spectrum of the brown solid showed a mixture of the desired diazabutadiene 13 (signal at 8.54 ppm corresponding to the azomethine protons) along with the unreacted starting material. Attempts to isolate the product 13 by recrystallization failed. The yield was not determined.

2-(tert-Butyldimethylsilyloxy)aniline 14

![Diagram of 2-(tert-Butyldimethylsilyloxy)aniline 14]

Triethylamine (0.84 mL, 6.0 mmol) was added dropwise to a solution of 2-aminophenol (0.6 g, 5.5 mmol) in dichloromethane (30 mL). The mixture was stirred for a few minutes then tert-butyldimethylsilyl chloride (0.91 g, 6.0 mmol) and 4-dimethylaminopyridine (0.067 g, 0.54 mmol) were added in solid form. The solution was stirred overnight. Water (30 mL) was then added and the mixture was stirred for 10 minutes. The organic layer was extracted 3 times with water and once with brine, then dried over magnesium sulphate. After removal of solvent, the residue was subjected to column chromatography, using ethyl acetate/petroleum ether 1/1 as eluent to give the desired product 15 (0.98 g, 93%) as an orange oil, $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$ 3471, 3375 (NH$_2$), 3052 (sp$^2$ C-H), 1033 (Si-O), 832, 782 (Si(R)$_3$); $\delta$H 0.28 (6H, s, CH$_3$, H-9,10), 1.06 (9H, s, (CH$_3$)$_3$, H-12,13,14), 3.72 (2H, s, NH$_2$, D$_2$O shake), 6.62-6.77 (4H, m, ArH, H-3,4,5,6); $\delta$C – 4.2 (CH$_3$, C-9,10), 18.2 (C (CH$_3$)$_3$, C-11), 25.8 (CH(CH$_3$)$_3$, C-12,13,14), 115.6 (CH Ar, C-6), 118.4 (CH Ar, C-4), 118.5 (CH Ar, C-3), 121.8 (CH Ar, C-5), 138.2 (Cquat. Ar, C-6), 142.9 (Cquat. Ar, C-2); m/z 224.1467 C$_{12}$H$_{21}$NOSi (MH$^+$) requires 224.1471.
1,4-Bis-[2-(tert-butyldimethylsilyloxy)phenyl] diazabutadiene 15

\[
\begin{align*}
\text{NH}_2 
\end{align*}
\]

\[
\begin{align*}
\text{OR} 
\end{align*}
\]

Table 8, Entry 1: Use of ethanol

An aqueous solution of glyoxal (0.52 mmol, 0.05 mL, 40% in water) was added dropwise to a solution of 2-(tert-butyldimethylsilyloxy)aniline 14 (0.2 g, 1.0 mmol) in ethanol (10 mL). The reaction mixture was stirred at room temperature and after 1 day, a brown precipitate appeared. After 2 days, the precipitate was isolated by filtration and the filtrate evaporated. The solid and the filtrate were both shown by $^1$H NMR spectroscopy to be a complex mixture containing no trace of the desired diazabutadiene 15.

Table 8, Entry 2: Use of ethanol and molecular sieves at room temperature

An aqueous solution of glyoxal (0.28 mmol, 0.03 mL, 40% in water) was added to a 25 mL round-bottom flask containing molecular sieves and a solution of 2-(tert-butyldimethylsilyloxy)aniline 14 (0.11 g, 0.56 mmol) in absolute ethanol (5 mL). After 5 days ethanol was evaporated and an orange oil was obtained. The oil was identified by $^1$H NMR spectroscopy as a complex mixture containing traces of the desired product 15 (which could be recognised by a signal at 8.36 ppm corresponding to the azomethine protons) along with some starting material. The yield was not determined.

Table 8, Entry 3: Use of dichloromethane

An aqueous solution of glyoxal (0.16 g, 1.1 mmol, 40% in water) was added dropwise to 2-(tert-butyldimethylsilyloxy)aniline 14 (0.5 g, 2.2 mmol) at 0 °C. The reaction mixture was stirred and after 1 hour a toffee-solid appeared. A few drops of
dichloromethane were added which dissolved the precipitate and the reaction mixture was allowed to warm up to room temperature. After 13 days, no precipitate reappeared and evaporation of the solvent gave an orange oil identified by $^1$H NMR as a mixture containing traces of the desired product 15 (which could be recognised by a signal at 8.36 ppm corresponding to the azomethine protons) along with some starting material. The yield was not determined.

Table 8, Entry 4: Use of pure water

2-(tert-Butyldimethylsilyloxy)aniline 14 (0.2 g, 0.89 mmol) was added in solid form to an aqueous solution of glyoxal (0.65 g, 0.45 mmol, 40% in water) at 0 °C was added. The reaction mixture was stirred and after 30 minutes a brown gummy solid appeared. A few drops of pure water were added and the reaction mixture was allowed to warm up to room temperature. The progress of the reaction was monitored by $^1$H NMR spectroscopy. After 6 days, $^1$H NMR spectrum of the brown solid showed a mixture of the desired diazabutadiene 15 (signal at 8.36 ppm corresponding to the azomethine protons) along with the unreacted starting material 14. Attempts to isolate the product 15 by recrystallization failed. The yield was not determined.

4.2.2 Experimental data for section 2.3

1,3-Bis-(2,6-diisopropylphenyl) imidazolium chloride 16 (IPrHCl)$^7$

![Diagram](image)

Table 9, Entry 1:

Paraformaldehyde (0.48 g, 15.9 mmol) was added in solid form to a solution of 1,4-bis-(2,6-diisopropylphenyl) diazabutadiene 1 (6 g, 15.9 mmol) in toluene (120 mL). The reaction mixture was heated to 100 °C until most of the paraformaldehyde was
dissolved. It was then cooled to 40 °C and hydrochloric acid (4 mL, 15.9 mmol, 4 M in dioxane) was syringed in. The colour of the reaction mixture turned brown and a white precipitate appeared after a few hours. It was then stirred at room temperature for 36 hours. The off-white precipitate was collected by filtration and washed with tetrahydrofuran to give the desired product 16 (2.91 g, 43%) as a colourless solid, m.p. 274 °C (lit., 7 > 255 °C); Found: C, 76.10; H, 8.69; N, 6.50. C_{27}H_{37}ClN_2 requires C, 76.29; H, 8.77; N, 6.59; δ_H 1.25 (12H, d, J 6.9, CH_3, H-8,9,11,12), 1.29 (12H, d, J 6.9, CH_3, H-8',9',11',12'), 2.45 (4H, sept., J 6.9, CH(CH_3)_2, H-7,7',10,10'), 7.35 (4H, d, J 7.6, ArH, H-3,3',5,5'), 7.57 (2H, t, J 7.6, ArH, H-4,4'), 8.14 (2H, s, NCH, H-14,15), 10.11 (1H, s, NCHN, H-16); δ_C 23.7 (CH_3, C-8,9,11,12), 24.8 (CH_3, C-8',9',11',12'), 29.2 (CH(CH_3)_2, C-7,7',10,10'), 124.8 (CH Ar, C-3,3',5,5'), 126.8 (CH Ar, C-4,4'), 129.9 (C_{quat Ar}, C-1,1'), 132.2 (NCHCHN, C-14,15), 138.7 (NCH, C-16), 145.1 (C_{quat Ar}, C-2,2',6,6'); m/z 389.2958 C_{27}H_{37}N_2 (cation) requires 389.2957.

1,3-Bis-(2,6-diisopropylphenyl) imidazolium tetrafluoroborate 17 (IPrHBF_4)

Table 9, Entry 2:

Paraformaldehyde (0.4 g, 13.3 mmol) was added in solid form to a solution of 1,4-bis-(2,6-diisopropylphenyl) diazabutadiene 1 (5 g, 13.3 mmol) in toluene (100 mL). The reaction mixture was heated to 100 °C until most of the paraformaldehyde was dissolved. It was then cooled to 40 °C and tetrafluoroboric acid (1.8 mL, 24.6 mmol, 54% in diethyl ether) was syringed in. The colour of the reaction mixture turned purple and a purple precipitate appeared after a few hours. It was then stirred at room temperature for 90 hours. The precipitate was collected by filtration and recrystallized.
from dichloromethane then washed with ethyl acetate to afford the pure imidazolium salt 17 (5.6 g, 88%) as light purple needles, m.p. 263 °C; Found: C, 67.78; H, 7.84; N, 5.84. C$_{27}$H$_{37}$BF$_4$N$_2$ requires C, 68.07; H, 7.83; N, 5.88; $\delta$$_H$ (DMSO-d$_6$) 1.17 (12H, d, J 6.7, CH$_3$, H-8,9,11,12), 1.27 (12H, d, J 6.7, CH$_3$, H-8',9',11',12'), 2.36 (4H, sept., J 6.7, CH(CH$_3$)$_2$, H-7,7',10,10'), 7.54 (4H, d, J 7.7, ArH, H-3,3',5,5'), 7.70 (2H, t, J 7.7, ArH, H-4,4'), 8.56 (2H, s, NCH, H-14,15), 10.16 (1H, s, NCHN, H-16); $\delta$$_C$ (DMSO-d$_6$) 25.7 (CH$_3$, C-8,9,11,12), 26.7 (CH$_3$, C-8',9',11',12'), 31.2 (CH(CH$_3$)$_2$, C-7,7',10,10'), 127.2 (CH Ar, C-3,3',5,5'), 128.8 (CH Ar, C-4,4'), 132.6 (C$_{quat}$. Ar, C-1,1'), 134.4 (NCCN, C-14,15), 141.8 (NCN, C-16), 147.4 (C$_{quat}$. Ar, C-2,2',6,6'); m/z 389.2958 C$_{27}$H$_{37}$N$_2$ (cation) requires 389.2957.

1,3-Bis-(2-methylthiophenyl) imidazolium chloride 18

![Chemical Structure](image)

Table 10, Entry 1:

Paraformaldehyde (0.15 g, 5 mmol) was added in solid form to a solution of 1,4-bis-(2-methylthiophenyl) diazabutadiene 2 (1.5 g, 5 mmol) in toluene (38 mL). The reaction mixture was heated to 100 °C until most of the paraformaldehyde was dissolved. It was then cooled to 40 °C and hydrochloric acid (1.3 mL, 5 mmol, 4 M in dioxane) was syringed in. The colour of the reaction mixture turned black and a black precipitate appeared after a few hours. It was then stirred at room temperature for 36 hours. The black precipitate was collected by filtration and identified by $^1$H NMR spectroscopy as a complex mixture containing traces of the desired product 18, which could be recognized by a signal at 9.85 ppm and 8.30 ppm corresponding to the protons on the imidazolium moiety.
Table 10, Entry 2:

Paraformaldehyde (0.08 g, 2.7 mmol) was added in solid form to a solution of 1,4-bis-(2-methylthiophenyl) diazabutadiene 2 (0.8 g, 2.7 mmol) in dry toluene (40 mL). The reaction mixture was heated to 50 °C until most of the paraformaldehyde was dissolved. It was then cooled to room temperature and hydrochloric acid (0.67 mL, 2.7 mmol, 4 M in dioxane) was added drop by drop. The colour of the reaction mixture turned from orange to black and a black precipitate appeared after a few hours. It was then stirred at room temperature for 48 hours. The black precipitate was then collected by filtration and identified by $^1$H NMR spectroscopy as the desired product 18 albeit impure, which could be recognised by a signal at 9.85 ppm and at 8.30 ppm corresponding to the protons on the imidazolium moiety. Recrystallization from dichloromethane/light petroleum gave the desired imidazolium salt 18 cleaner but still impure (0.511 g, 55%) as a black solid, m.p. 200-201 °C; $\delta_H$ 2.51 (6H, s, CH$_3$, H-8,8'), 7.30-7.70 (8H, m, ArH, H-2,3,4,5,2',3',4',5'), 8.30 (2H, s, NCH, H-10,11), 9.85 (1H, s, NCHN, H-9); $\delta_C$ 16.1 (CH$_3$, C-8,8'), 124.3 (CH Ar, C-3,3'), 126.9 (CH Ar, C-5,5'), 127.6 (CH Ar, C-4,4'), 131.7 (CH Ar, C-2,2'), 132.4 (C$_{quat}$ Ar, C-1,1'), 133.1 (NCCN, C-10,11), 135.1 (C$_{quat}$ Ar, C-6,6'), 138.4 (NCN, C-9); m/z 313.0833 C$_{17}$H$_{17}$N$_2$ (cation) requires 313.0833.

Table 10, Entry 3: Using Dean-Stark conditions

Paraformaldehyde (0.52 g, 1.7 mmol) was added in solid form to a solution of 1,4-bis-(2-methylthiophenyl) diazabutadiene 2 (0.52 g, 1.7 mmol) in dry toluene (20 mL). The reaction mixture was heated to 120 °C for 4 hours using Dean-Stark apparatus. It was then cooled to room temperature and hydrochloric acid (0.43 mL, 1.7 mmol, 4 M in dioxane) was added drop by drop. The colour of the reaction mixture turned from yellow to black. The reaction mixture was heated at 70 °C overnight and stirred at room temperature for 36 hours. The black precipitate formed was then collected by filtration (0.43 g, 71%) and identified by $^1$H NMR spectroscopy (DMSO-d$_6$) as the desired product 18 although impure, which could be recognised by a signal at 10.02 ppm and at 8.33 ppm corresponding at the protons on the imidazolium moiety.
1,3-Bis-(2-methylthiophenyl) imidazolium tetrafluoroborate 19

![Chemical structure of 19](image)

Table 11, Entry 1:

Paraformaldehyde (0.08 g, 2.7 mmol) was added in solid form to a solution of 1,4-bis-(2-methylthiophenyl) diazabutadiene 2 (0.8 g, 2.7 mmol) in dry toluene (40 mL). The reaction mixture was heated to 50 °C until most of the paraformaldehyde was dissolved. It was then cooled to room temperature and tetrafluoroboric acid (0.37 mL, 2.7 mmol, 54% in diethyl ether) was added drop by drop. The colour of the reaction mixture turned orange to black and a black precipitate appeared after a few hours. It was then stirred at room temperature for 40 hours. The black precipitate was collected by filtration and a black solid ("toffee") was obtained. The black solid was identified by $^1$H NMR spectroscopy (DMSO-d$_6$) as a complex mixture containing the desired product 19, which could be recognised by a signal at 10.02 ppm and at 8.33 ppm corresponding to the protons on the imidazolium moiety. The yield was not determined.

Table 11, Entry 2: Using Dean-Stark conditions

Paraformaldehyde (0.02 g, 0.67 mmol) in solid form then tetrafluoroboric acid (0.09 mL, 2.7 mmol, 54% in diethyl ether) dropwise, were added to a solution of 1,4-bis-(2-methylthiophenyl) diazabutadiene 2 (0.2 g, 0.67 mmol) in dry toluene (25 mL). The reaction mixture was then heated at 120 °C using a Dean-Stark for 24 hours. A black precipitate was collected by filtration and identified by $^1$H NMR spectroscopy (DMSO-d$_6$) as a complex mixture containing the desired product 19 impure, which could be recognised by a signal at 10.02 ppm and at 8.33 ppm corresponding to the protons on the imidazolium moiety. The yield was not determined.
1,3-Bis-(2-methylthiophenyl) imidazolium triflate 20

\[ \text{N} \text{N} \text{SMe MeS} \quad \text{2} \quad \xrightarrow{\text{OTI}} \quad \text{N} \text{N} \text{SMe MeS} \quad \text{20} \]

Table 11, Entry 3: Addition of triflic acid at room temperature

Paraformaldehyde (0.01 g, 0.33 mmol) was added in solid form to a solution of 1,4-bis-(2-methylthiophenyl) diazabutadiene 2 (0.1 g, 0.33 mmol) in dry toluene (5 mL). The reaction mixture was heated to 50 °C until most of the paraformaldehyde was dissolved. It was then cooled to room temperature and triflic acid (0.03 mL, 0.33 mmol, 98%) was added drop by drop. The colour of the reaction mixture turned from orange to black and a black precipitate appeared after a few hours. It was then stirred at room temperature for 48 hours. The black precipitate was collected by filtration and a black solid ("toffee") was obtained. The black solid was shown by $^1$H NMR spectroscopy to be a complex mixture of unidentified products containing traces of the desired imidazolium salt 20, which could be recognised by a signal at 9.0 ppm and at 7.8 ppm corresponding to the protons on the imidazolium moiety. The yield was not determined.

Table 11, Entry 4: Addition of triflic acid at −20 °C

Paraformaldehyde (0.01 g, 0.33 mmol) was added in solid form to a solution of 1,4-bis-(2-methylthiophenyl) diazabutadiene 2 (0.1 g, 0.33 mmol) in dry toluene (5 mL). The reaction mixture was heated to 50 °C until most of the paraformaldehyde was dissolved. It was then cooled to −20 °C and triflic acid (0.03 mL, 0.33 mmol, 98%) was added drop by drop. Then, the reaction was left to warm up to room temperature. The colour of the reaction mixture turned from orange to black and a black precipitate appeared after a few hours. It was then stirred at room temperature for 6 days. The black precipitate was collected by filtration and a black solid ("toffee") was obtained. The black solid was shown by $^1$H NMR spectroscopy to be a complex mixture containing traces of the desired product 20, which could be recognised by a signal at
9.0 ppm and at 7.8 ppm corresponding to the protons on the imidazolium moiety. Attempt to isolate the product 20 by column chromatography failed.

**Attempted synthesis of 1,3-bis-(2-methylthiophenyl) imidazolium tetraphenylborate 21**

![Chemical structure of 1,3-bis-(2-methylthiophenyl) imidazolium chloride 18 and sodium tetraphenylborate 21](image)

A solution of sodium tetraphenylborate (0.22 g, 0.64 mmol, 99%) in acetonitrile (5 drops) was added to a solution of 1,4-bis-(2-methylthiophenyl) imidazolium chloride 18 (0.2 g, 0.57 mmol) in a mixture of ethanol (3 mL) and acetonitrile (10 drops). The reaction mixture was stirred for 5 minutes then ethanol and acetonitrile were removed under reduced pressure. The residue was dissolved in ethanol and water was added. The precipitate was collected by filtration then washed with ethanol and diethyl ether. The solid was shown by $^1$H NMR spectroscopy to be a complex mixture containing a majority of sodium tetraphenylborate. No trace of the desired product 21 as well as the starting material was detected.

**Imidazolium chloride 18 using chloromethyl ethyl ether**

![Chemical structure of 1,4-bis-(2-methylthiophenyl) diazabutadiene 2 and 1,3-bis-(2-methylthiophenyl) imidazolium chloride 18](image)

**Table 12, Entry 1: Reaction at 40 °C in presence of water**

A solution of 1,4-bis-(2-methylthiophenyl) diazabutadiene 2 (0.1 g, 0.34 mmol) in tetrahydrofuran (10 mL) was added to a solution of chloromethyl ethyl ether (0.03 g,
0.36 mmol, 95%) in tetrahydrofuran (2 mL). Two drops of water were added and the mixture was heated at 40 °C for 18 hours. The mixture was then allowed to cool at room temperature and stirred at this temperature. After 3 days, evaporation of the solvent under reduced pressure gave an orange oil identified by $^1$H NMR spectroscopy as a complex mixture containing traces of the desired product 18 (signals at 9.4 ppm and 8.3 ppm (CDCl$_3$) correspond to the protons on the imidazolium moiety) along with some starting material and unidentified products.

Table 12, Entry 2: Reaction at room temperature with molecular sieves

A solution of 1,4-bis-(2-methylthiophenyl) diazabutadiene 2 (0.1 g, 0.34 mmol) in tetrahydrofuran (10 mL) was added to a solution of chloromethyl ethyl ether (0.03 g, 0.36 mmol, 95%) in tetrahydrofuran (2 mL) and molecular sieves. The reaction mixture was stirred at room temperature. A yellow precipitate appeared after a few hours. After 7 days, the precipitate was collected by filtration and identified by $^1$H NMR spectroscopy as the starting material. $^1$H NMR of the filtrate showed no signal corresponding to the expected imidazolium salt 18.

Imidazolium triflate 20 using silver triflate and chloromethyl pivalate

Chloromethyl pivalate (0.13 mL, 0.93 mmol) was added to a mixture of 1,4-bis-(2-methylthiophenyl) diazabutadiene 2 (0.2 g, 0.68 mmol) and silver triflate (0.20 g, 0.8 mmol) in dichloromethane (40 mL). The reaction mixture was kept under nitrogen in the dark. After 11 days, $^1$H NMR spectroscopy of the crude reaction showed a mixture of the desired product 20 (signal at 9.0 ppm and at 7.8 ppm corresponding to the
protons on the imidazolium moiety) along with some chloromethyl pivalate. Attempts to recrystallize it failed.

1,3-Bis-(2-hydroxyphenyl) imidazolium chloride 22 and tetrafluoroborate 23

![Chemical structure](image)

Table 13, Entry 1: Using hydrochloric acid and room temperature for 4 days

Paraformaldehyde (0.03 g, 0.83 mmol) was added in solid form to a solution of 1,4-bis-(2-hydroxyphenyl) diazabutadiene 9 (0.2 g, 0.83 mmol) in dry toluene (10 mL). The reaction mixture was heated to 100 °C until most of the paraformaldehyde was dissolved. It was then cooled to 40 °C and hydrochloric acid (0.21 mL, 0.83 mmol, 4 M in dioxane) was added drop by drop. The colour of the reaction mixture turned white to black and a black precipitate appeared after a few hours. It was then stirred at room temperature for 4 days. The black precipitate was collected by filtration and identified by $^1$H NMR spectroscopy as a complex mixture containing traces of the desired product 22, which could be recognised by a signal at 9.86 ppm and at 8.23 ppm (DMSO-d$_6$) corresponding to the protons on the imidazolium moiety. The yield was not determined.

Table 13, Entry 2: Using hydrochloric acid and Dean-Stark conditions

Paraformaldehyde (0.01 g, 0.4 mmol) was added in solid form to a solution of 1,4-bis-(2-hydroxyphenyl) diazabutadiene 9 (0.1 g, 0.4 mmol) in dry toluene (10 mL). The reaction mixture was heated to 100 °C until most of the paraformaldehyde was dissolved. It was then cooled to 40 °C and hydrochloric acid (0.1 mL, 0.4 mmol, 4 M in dioxane) was added drop by drop. The reaction mixture was heated at 120 °C using
Dean-Stark conditions overnight. A black precipitate was collected by filtration and identified by $^1$H NMR spectroscopy as a complex mixture containing the desired product 22, which could be recognised by a signal at 9.86 ppm and at 8.23 ppm (DMSO-$d_6$) corresponding to the protons on the imidazolium moiety. The yield was not determined.

Table 13, Entry 3: Using tetrafluoroboric acid and room temperature for 4 days

Paraformaldehyde (0.01 g, 0.38 mmol) was added in solid form to a solution of 1,4-bis-(2-hydroxyphenyl) diazabutadiene 9 (0.1 g, 0.38 mmol) in dry toluene (10 mL). The reaction mixture was heated to 100 °C until most of the paraformaldehyde was dissolved. It was then cooled to room temperature and tetrafluoroboric acid (0.05 mL, 0.38 mmol, 54% in diethyl ether) was added drop by drop. The colour of the reaction mixture turned from white to black and a black precipitate appeared after a few hours. It was then stirred at room temperature for 4 days. The black precipitate was collected by filtration identified by $^1$H NMR spectroscopy as a complex mixture containing traces of the desired product 23, which could be recognised by a signal at 9.86 ppm and at 8.23 ppm (DMSO-$d_6$) corresponding to the protons on the imidazolium moiety. The yield was not determined.

Table 13, Entry 4: Using tetrafluoroboric acid and Dean-Stark conditions

Paraformaldehyde (0.02 g, 0.76 mmol) in solid form and tetrafluoroboric acid (0.1 mL, 0.76 mmol, 54% in diethyl ether) dropwise were added to a solution of 1,4-bis-(2-hydroxyphenyl) diazabutadiene 9 (0.2 g, 0.76 mmol) in dry toluene (20 mL). The reaction mixture was then heated at 120 °C using Dean-Stark conditions overnight. A black precipitate was collected by filtration and identified by $^1$H NMR spectroscopy as a complex mixture containing the desired product 23 albeit impure, which could be recognised by a signal at 9.86 ppm and at 8.23 ppm (DMSO-$d_6$) corresponding to the protons on the imidazolium moiety. The yield was not determined.
4.2.3 Experimental data for section 2.4

*N,N*-Bis-(2-methylthiophenyl)-ethane-1,2-diamine 24

![Structure of N,N-Bis-(2-methylthiophenyl)-ethane-1,2-diamine 24]

Table 14, Entry 1: Using sodium triacetoxyborohydride at room temperature

Sodium triacetoxyborohydride (0.19 g, 0.83 mmol, 95%) was added in solid form to a solution of 1,4-bis-(2-methylthiophenyl) diazabutadiene 2 (0.1 g, 0.33 mmol) in dichloromethane (10 mL). The solution was stirred for 2 days. Then an aqueous solution of ammonium chloride (5 mL) was added and the aqueous layer was extracted 3 times with diethyl ether. The organic phases were combined and washed once with brine, then dried over magnesium sulphate. Evaporation of the solvent gave a yellow solid identified by $^1$H NMR spectroscopy as a mixture containing the desired product 24 along with some starting material (ratio 7:1). The resulting solid was subjected to column chromatography using dichloromethane/petroleum ether 2/1 as eluent to give the desired pure product 24 (0.026 g, 26%) as a light brown solid, m.p. 80-81 °C; δ$_H$ 2.30 (6H, s, CH$_3$, H-8,8'), 3.49 (4H, s, CH$_2$, H-10,11), 5.17 (2H, s broad, NH), 6.68 (4H, dd, J 1.28 and 8.04, ArH, H-2,2',4,4'), 7.20 (2H, dd, J 1.52 and 8.04, ArH, H-3,3'), 7.40 (2H, dd, J 1.48 and 8.04, ArH, H-5,5'); δ$_C$ 18.1 (SCH$_3$, C-8,8'), 42.9 (CH$_2$, C-10,11), 110.1 (CH Ar, C-2,2'), 117.4 (CH Ar, C-4,4'), 120.2 (C$_{quat}$. Ar, C-6,6'), 129.5 (CH Ar, C-3,3'), 134.2 (CH Ar, C-5,5'), 148.0 (C$_{quat}$. Ar, C-1,1'); m/z 304.1070 C$_{16}$H$_{20}$N$_2$S$_2$ (M$^+$) requires 304.1068.

Table 14, Entry 2: Using sodium triacetoxyborohydride at reflux

Sodium triacetoxyborohydride (0.19 g, 0.83 mmol, 95%) was added in solid form to a solution of 1,4-bis-(2-methylthiophenyl) diazabutadiene 2 (0.1 g, 0.33 mmol) in dichloromethane (20 mL). The solution was stirred for 2 days at reflux. Once the reaction mixture was cooled down, an aqueous solution of ammonium chloride (5 mL)
was added and the aqueous layer was extracted 3 times with diethyl ether. The organic phases were combined and washed once with brine, then dried over magnesium sulphate. Evaporation of the solvent gave a yellow solid identified by $^1$H NMR spectroscopy as a mixture containing the desired product 24 along with some starting material (ratio 2:1). The resulting solid was subjected to column chromatography, using dichloromethane/petroleum ether 2/1 as eluent to give the desired product 24 (0.03 g, 30%) as light brown solid. The spectral data were as above.

Table 14, Entry 3: Using sodium borohydride

Sodium borohydride (0.056 g, 1.5 mmol, 98%) was added in solid form portionwise to a solution of 1,4-bis-(2-methylthiophenyl) diazabutadiene 2 (0.1 g, 0.33 mmol) in dichloromethane (10 mL) and methanol (10 mL). The reaction mixture was stirred at room temperature for 36 hours. Then an aqueous solution of ammonium chloride (5 mL) was added and the aqueous layer was extracted 3 times with diethyl ether. The organic phases were combined and washed once with brine, then dried over magnesium sulphate. Evaporation of the solvent gave a light brown solid identified by $^1$H NMR spectroscopy as the desired product 24 (0.095 g, 95%). The spectral data were as above.

Attempted synthesis of 1,3-bis-(2-methylthiophenyl) imidazolinium tetrafluoroborate 25

![Diagram](image)

Ammonium tetrafluoroborate (0.07 g, 0.67 mmol) was added to a solution of $N,N$-bis-(2-methylthiophenyl)-ethane-1,2-diamine 24 (0.2 g, 0.67 mmol) in neat triethyl orthoformate (0.1 mL, 0.67 mmol). The reaction mixture was heated at 120 °C for 3
hours. The reaction mixture was then allowed to cool to room temperature and was left to stir at room temperature overnight. Removal the solvent under reduced pressure gave a brown oil shown by $^1$H NMR spectroscopy to be a mixture containing some starting material along with some unidentified products.

4.2.4 Experimental data for section 2.5

Attempted synthesis of 1,3-bis-(2,6-diisopropylphenyl) imidazol-2-ylidene 26

\[
\begin{align*}
16 &: X = Cl \\
17 &: X = BF_4 \\
26 &: 
\end{align*}
\]

Table 15, Entry 1: Use of $n$-butyllithium as a base.

Tetrahydrofuran (10 mL) was added to 1,4-bis-(2,6-diisopropylphenyl) imidazolium tetrafluoroborate 17 (0.12 g, 0.25 mmol) and the resulting suspension was cooled to –78 °C and stirred for 10 minutes. A solution of $n$-butyllithium (0.1 mL, 0.25 mmol, 2.5 M in hexane) was added drop by drop to the suspension. After stirring the mixture for 10 minutes, the mixture was allowed to warm to room temperature. All volatiles were then removed \textit{in vacuo}. The residue was dissolved into dichloromethane and the solvent volume decreased to one third and left to crystallize. After 24 hours, some white crystals appeared identified by $^1$H NMR spectroscopy as the imidazolium salt 17 pure. No trace of the expected carbene 26 was observed.

Table 15, Entry 2: Use of potassium tert-butoxide as a base

Tetrahydrofuran (5 mL) was added to 1,4-bis-(2,6-diisopropylphenyl) imidazolium chloride 16 (0.15 g, 0.36 mmol) and the resulting suspension was stirred for 15 minutes. Solid potassium tert-butoxide (0.044 g, 0.40 mmol) was then added to the
suspension at room temperature. After stirring the mixture for 20 minutes, all volatiles were removed in vacuo. The residue was extracted into warm toluene (60 °C) and filtered through celite. The solvent volume was decreased in vacuo to one third. After 2 days, a precipitate appeared and the toluene was removed by evaporation. An orange oil was obtained and shown by $^1$H NMR spectroscopy to be a mixture containing some starting material along with some diisopropylaniline in a 1:4 ratio.

**Attempted synthesis of 1,3-bis-(2-methylthiophenyl) imidazol-2-ylidene 27**

![Diagram showing the reaction and products](image)

**Table 16, Entry 1:** Use of n-butyllithium as a base.

Tetrahydrofuran (10 mL) was added to 1,4-bis-(2-methylthiophenyl) imidazolium chloride 18 (0.08 g, 0.23 mmol) and the resulting suspension was cooled to –78 °C and stirred for 10 minutes. A solution of n-butyllithium (0.1 mL, 0.25 mmol, 2.5 M in hexane) was added drop by drop to the suspension. After stirring the mixture for 10 minutes, the mixture was allowed to warm to room temperature. All volatiles were then removed in vacuo. A brown solid was obtained and shown by $^1$H NMR spectroscopy to be a mixture containing no trace of the desired product 27.

**Table 16, Entry 2:** Use of 1.5 equivalents of potassium tert-butoxide as a base

Tetrahydrofuran (10 mL) was added to 1,4-bis-(2-methylthiophenyl) imidazolium chloride 18 (0.051 g, 0.15 mmol) and the reaction mixture was stirred for 15 minutes. Solid potassium tert-butoxide (0.017 g, 0.15 mmol) was then added at room temperature. After stirring the mixture for 3 hours, tetrahydrofuran was removed in vacuo. A brown solid was obtained and shown by $^1$H and $^{13}$C NMR spectroscopy to be a complex mixture containing traces of the starting material.
Table 16, Entry 3: Use of 2.5 equivalents of potassium tert-butoxide as a base

Tetrahydrofuran (20 mL) was added to 1,4-bis-(2-methylthiophenyl) imidazolium chloride 18 (0.1 g, 0.29 mmol) and the reaction mixture was stirred for 15 minutes. Solid potassium tert-butoxide (0.085 g, 0.76 mmol) was then added at room temperature. After stirring the mixture for 3 hours, tetrahydrofuran was removed in vacuo. A brown solid was obtained and shown by \(^1\)H and \(^{13}\)C NMR spectroscopy to be a complex mixture containing no trace of the desired carbene 27.

4.2.5 Experimental data for section 2.6

Attempted synthesis of nickel and palladium carbene complexes 28 and 29 derivatives from IPrHCl and IPrBF\(_4\)

\[
\begin{align*}
16 & \quad X = \text{Cl} \\
17 & \quad X = \text{BF}_4 \\
28 & \quad M = \text{Ni} \\
29 & \quad M = \text{Pd}
\end{align*}
\]

Table 17, Entry 1: Using n-butyllithium and nickel chloride

A solution of 1,4-bis-(2,6-diisopropylphenyl) imidazolium tetrafluoroborate 17 (0.12 g, 0.25 mmol) in tetrahydrofuran (10 mL) was cooled to –78 °C and stirred for 10 minutes. A solution of n-butyllithium (0.1 mL, 0.25 mmol, 2.5 M in hexane) was added drop by drop to the suspension. After stirring the mixture for 10 minutes, a solution of nickel chloride (0.032 g, 0.25 mmol) in tetrahydrofuran (5 mL) was added drop by drop to the mixture. After 30 minutes, the reaction mixture was allowed to warm to room temperature and stirred overnight. The insoluble part was then filtered through celite and the filtrate evaporated. A brown solid was obtained which was recrystallized from dichloromethane to give some white crystals identified by \(^1\)H NMR as the pure imidazolium salt 17.
Table 17, Entry 2: Using potassium tert-butoxide and nickel chloride

A solution of 1,4-bis-(2,6-diisopropylphenyl) imidazolium tetrafluoroborate 17 (0.1 g, 0.21 mmol) in dichloromethane (10 mL) was stirred for 10 minutes. Potassium tert-butoxide (0.05 g, 0.42 mmol) in solid form was added to the suspension. After stirring the mixture for 80 minutes, solid nickel chloride (0.027 g, 0.21 mmol) was added to the mixture at room temperature. After 3 hours, TLC showed that no starting material remained so the mixture was then filtered through celite and the filtrate evaporated. A brown solid was obtained and shown by $^1$H and $^{13}$C NMR spectroscopy to be a mixture containing no trace of the desired nickel carbene complex 28.

Table 17, Entry 3: Using palladium acetate without base

A solution of 1,4-bis-(2,6-diisopropylphenyl) imidazolium chloride 16 (0.25 g, 0.58 mmol) and palladium acetate (0.13 g, 0.58 mmol) in acetonitrile (30 mL) was heated under reflux for 16 hours. The reaction mixture was then filtered through celite and the filtrate evaporated under reduced pressure. A black solid was obtained and shown by $^1$H and $^{13}$C NMR spectroscopy to be a mixture containing no trace of the desired palladium carbene complex 29.

Attempted synthesis of nickel and palladium carbene complexes 30 and 31 derivatives from the imidazolium salt 18.

Table 17, Entry 2: Using potassium tert-butoxide and nickel chloride

A solution of 1,4-bis-(2,6-diisopropylphenyl) imidazolium tetrafluoroborate 17 (0.1 g, 0.21 mmol) in dichloromethane (10 mL) was stirred for 10 minutes. Potassium tert-butoxide (0.05 g, 0.42 mmol) in solid form was added to the suspension. After stirring the mixture for 80 minutes, solid nickel chloride (0.027 g, 0.21 mmol) was added to the mixture at room temperature. After 3 hours, TLC showed that no starting material remained so the mixture was then filtered through celite and the filtrate evaporated. A brown solid was obtained and shown by $^1$H and $^{13}$C NMR spectroscopy to be a mixture containing no trace of the desired nickel carbene complex 28.

Table 17, Entry 3: Using palladium acetate without base

A solution of 1,4-bis-(2,6-diisopropylphenyl) imidazolium chloride 16 (0.25 g, 0.58 mmol) and palladium acetate (0.13 g, 0.58 mmol) in acetonitrile (30 mL) was heated under reflux for 16 hours. The reaction mixture was then filtered through celite and the filtrate evaporated under reduced pressure. A black solid was obtained and shown by $^1$H and $^{13}$C NMR spectroscopy to be a mixture containing no trace of the desired palladium carbene complex 29.

Attempted synthesis of nickel and palladium carbene complexes 30 and 31 derivatives from the imidazolium salt 18.

Table 18, Entry 1: Using $n$-butyllithium and nickel chloride

A solution of 1,4-bis-(2-methylthiophenyl) imidazolium chloride 18 (0.08 g, 0.23 mmol) in tetrahydrofuran (10 mL) was cooled to $-78$ °C and stirred for 10 minutes. A
solution of n-butyllithium (0.1 mL, 0.25 mmol, 2.5 M in hexane) was added drop by drop to the suspension. After stirring the mixture for 10 minutes, solid nickel chloride (0.03 g, 0.23 mmol) was added to the mixture. After 30 minutes the reaction mixture was allowed to warm to room temperature and stirred overnight. All volatiles were then removed in vacuo. $^{13}$C NMR spectrum of the resultant brown solid showed no signal around 165-175 ppm indicating that no trace of the expected complex 30 was obtained.

**Table 18, Entry 2: Using potassium tert-butoxide and nickel chloride**

A solution of 1,4-bis-(2-methylthiophenyl) imidazolium chloride 18 (0.1 g 0.29 mmol) in tetrahydrofuran (10 mL) was stirred for 15 minutes. Solid potassium tert-butoxide (0.085 g, 0.76 mmol) was added at room temperature. After stirring the mixture for 5 minutes, nickel chloride (0.045 g, 0.34 mmol) was added in solid form. The reaction was then left to stir for 1 hour and tetrahydrofuran was removed in vacuo. A brown solid was obtained and shown by $^1$H and $^{13}$C NMR spectroscopy to be a mixture containing no trace of the desired complex 30.

**Table 18, Entry 3: Using sodium hydride and palladium acetate**

A solution of 1,4-bis-(2-methylthiophenyl) imidazolium chloride 18 (0.1 g, 0.29 mmol) in tetrahydrofuran (20 mL) was stirred for 10 minutes. A suspension of sodium hydride (0.01 g, 0.43 mmol, 60% in oil) in tetrahydrofuran (5 mL) was added drop by drop to the suspension. After stirring the mixture for 5 minutes, a solution of palladium acetate (0.064 g, 0.29 mmol) in tetrahydrofuran (5 mL) was syringed into the mixture. After 5 hours the insoluble part was filtrated through celite and the filtrate evaporated. A black solid was obtained and shown by $^1$H and $^{13}$C NMR spectroscopy to be a mixture containing no trace of the desired palladium complex 31.

**Table 18, Entry 4: Using potassium carbonate and nickel chloride**

Solid nickel chloride (0.03 g, 0.23 mmol) was added to a solution of 1,4-bis-(2-methylthiophenyl) imidazolium chloride 18 (0.08 g, 0.23 mmol) in dichloromethane (20 mL). After a few minutes, a solution of potassium carbonate (0.14 g, 0.46 mmol)
in dichloromethane (10 mL) was added drop by drop to the mixture. The reaction was then left to stir for 2 days. After 2 days, some starting material remained, the base was eliminated by filtration and the filtrate evaporated. A brown solid was obtained and shown by $^1$H NMR spectroscopy to be a mixture containing some starting material and no trace of the desired complex 30.

Table 18, Entry 5: Using palladium acetate in acetonitrile

A solution of 1,4-bis- (2-methylthiophenyl) imidazolium chloride 18 (0.1 g, 0.29 mmol) and palladium acetate (0.065 g, 0.29 mmol) in dry acetonitrile (17 mL) was heated under reflux for 16 hours. The resultant mixture after 16 hours was filtered through celite and a black solid was obtained after evaporation of the filtrate under reduced pressure. No $^1$H NMR spectroscopy was performed on this solid due to its insolubility in different deuteriated solvents.

4.3 Experimental data for Chapter 3
4.3 1 Experimental data for section 3.2.1

6,6'-dimethyl-2,2'-bipyridine 39 

Zinc powder (0.12 g, 1.8 mmol) was added to a deep blue solution of nickel chloride hexahydrate (0.42 g, 1.8 mmol) and triphenylphosphine (1.8 g, 7.0 mmol) in dimethylformamide (9 mL) at 50 °C. After 1 hour, the colour of the reaction mixture has changed to red-brown. 2-bromo-6-methylpyridine (0.2 mL, 1.8 mmol) was added and the progress of the reaction monitored by TLC (ethyl acetate/dichloromethane 1/10). After 4 hours, the starting material had been consumed. The mixture was then poured into a dilute ammonia solution (36 mL) and extracted with chloroform. The organic layers were washed with water and dried over magnesium sulphate. Solvents
were removed under reduced pressure to give a brown solid which was purified by column chromatography (ethyl acetate/light petroleum 1/10) to give 6,6'-dimethyl-2,2'-dipyridine 39 (0.15 g, 93%) as a light brown solid, m.p. 89-90 °C (lit., 89-90 °C); Found: C, 78.14; H, 6.61; N, 15.29. C_{12}H_{12}N_{2} requires C, 78.23; H, 6.57; N, 15.21; δH 2.63 (6H, s, CH3, H-7,7'), 7.15 (2H, d, J 7.6, ArH, H-5,5'), 7.69 (2H, t, J 7.6, ArH, H-4,4'), 8.17 (2H, d, J 7.6, ArH, H-3,3'); δC 24.7 (CH3, C-7,7'), 118.2 (CH Ar, C-3,3'), 123.1 (CH Ar, C-5,5'), 137.0 (CH Ar, C-4,4'), 155.9 (Cquat. Ar, C-2,2'), 157.9 (Cquat. Ar, C-6,6'); m/z 184.1000 C_{12}H_{12}N_{2} requires 184.1000.

6,6'-Dimethyl-2,2'-bipiperidine 40

6,6'-Dimethyl-2,2'-bipyridine 39 (4 g, 21.7 mmol) was added to a solution of platinum oxide (0.4 g, 10% wt/wt) in acetic acid. The mixture was hydrogenated at 40 psi over 10 days. The catalyst was then removed by filtration and the filtrate basified with an aqueous solution of sodium hydroxide and extracted with diethyl ether. The combined organic layers were dried over magnesium sulphate and the solvent was removed under reduced pressure to give a yellow oil (3.97 g, 94%) identified by 1H and 13C NMR spectroscopy as a mixture of 3 different isomers of the desired compound 40.

Resolution of 6,6'-dimethyl-2,2'-bipiperidine 40

*General method using 1 equivalent of tartaric acid in ethanol*

Racemic, (+) or (-)-tartaric acid (0.39 g, 2.6 mmol) was added to a solution of the crude bipiperidine 40 (0.5 g, 2.6 mmol) in absolute ethanol (15 mL), and the heterogeneous mixture was stirred under reflux for 30 minutes. After cooling to room
temperature the precipitate was collected by filtration and washed twice with ethanol. The salt was poured into a mixture of an aqueous solution of sodium hydroxide (2.5 mL, 35%), water (8 mL) and diethyl ether (8 mL). After stirring for 30 minutes, the layers were separated, the aqueous phase extracted twice with diethyl ether, and the combined organic layers were dried over magnesium sulphate. The solvent was removed under reduced pressure to give a yellow oil identified by \(^1\)H NMR spectroscopy as the crude bipiperidine 40.

**General method using tartaric acid in methanol with acetic acid**

The crude bipiperidine 40 (0.5 g, 2.6 mmol) was dissolved in methanol (2 mL) and added slowly to a methanol (2 mL) solution of racemic tartaric acid (0.19 g, 1.3 mmol) at room temperature. After the solution clarified, acetic acid (0.13 mL, 2.3 mmol) was added. A few drops of diethyl ether were added to precipitate out the white powder. Water (1 mL) was added and the mixture was warmed to dissolve the precipitate. Upon standing at 0 °C overnight the tartrate salt was isolated. The tartrate salt was then dissolved in an aqueous solution of sodium hydroxide saturated with sodium chloride and extracted with diethyl ether. The combined organic layers were dried over magnesium sulphate and the solvent was removed under reduced pressure to give a yellow oil identified by \(^1\)H NMR spectroscopy as the crude bipiperidine 40.

**Resolution through the dihydrochloride salt**

An aqueous solution of the crude bipiperidine 40 (0.5 g, 2.6 mmol) was treated with an excess of hydrochloric acid and evaporated to dryness under reduced pressure. A suspension of the light brown mixture (0.96 g) in ethanol (6 mL, 95%) was heated to boiling point and then allowed to stand overnight at room temperature. After a few hours, crystals started to appear and were collected by filtration (0.34 g). These crystals were identified by \(^{13}\)C NMR spectroscopy as a single isomer (6 peaks). \(^{13}\)C NMR of the filtrate showed that some of the major isomer remained. The crystallization procedure was then repeated.

The crystals obtained (0.25 g, 0.93 mmol) were dissolved in an aqueous solution of sodium hydroxide and the aqueous phase was extracted with diethyl ether. The organic layers were dried over magnesium sulphate and the solvent evaporated to give
the *meso* isomer of the bipiperidine 40 (0.17 g, 93%) as a colourless oil which crystallized as a monohydrate, giving colourless crystals, \( v_{\text{max}}(\text{film})/\text{cm}^{-1} \) 3272 (N-H), 2927 (sp\(^3\) CH), 1376, 1123 (C-N); \( \delta_H \) 0.99-1.04 (2H, m, CH, H\textsubscript{ax}-5,5'), 1.06 (6H, d, \( J \) 6.4, CH\textsubscript{3}, H\textsubscript{eq}-7,7'), 1.09-1.20 (2H, m, CH\textsubscript{2}, H\textsubscript{ax}-3,3'), 1.29-1.33 (2H, m, CH\textsubscript{2}, H\textsubscript{ax}-4,4'), 1.55-1.64 (4H, m, CH\textsubscript{2}, H\textsubscript{eq}-3,3',4,4'), 1.77-1.81 (2H, m, CH\textsubscript{2}, H\textsubscript{eq}-4,4'); 2.42-2.48 (2H, m, CH, H\textsubscript{ax}-6,6'); \( \delta_C \) 23.4 (CH\textsubscript{3}, C-7,7'), 25.1 (CH\textsubscript{2}, C-4,4'), 28.4 (CH\textsubscript{2}, C-3,3'), 34.7 (CH\textsubscript{2}, C-5,5'), 52.9 (CH, C-6,6'), 62.3 (CH, C-2,2'); \( m/z \) 196.1943 C\textsubscript{12}H\textsubscript{24}N\textsubscript{2} (M\textsuperscript{+}) requires 196.1939. X-Ray see Appendix 2.

**Bidecahydroquinoline 42**

![Diagram of the bidecahydroquinoline 42 molecule]

2,2'-Biquinoline (2.5 g, 9.7 mmol) was added to a solution of platinum oxide (0.25 g, 10% wt/wt) in acetic acid. The mixture was hydrogenated at 40 psi over 18 days. The catalyst was then removed by filtration and the filtrate basified with an aqueous solution of sodium hydroxide and extracted with diethyl ether. The combined organic layers were dried over magnesium sulphate and the solvent was removed under reduced pressure to give a yellow-green oil (2.58 g, 96%) identified by \( ^1H \) and \( ^{13}C \) NMR spectroscopy as a mixture of different isomers of the desired compound 42. \( v_{\text{max}}(\text{film})/\text{cm}^{-1} \) 3311 (N-H), 2921 (sp\(^3\) CH), 1557, 1304, 1127 (C-N); \( m/z \) 276.2572 C\textsubscript{18}H\textsubscript{32}N\textsubscript{2} (M\textsuperscript{+}) requires 276.2565.

**Resolution of bidecahydroquinoline 42**

An aqueous solution of the crude bidecahydroquinoline 42 (0.3 g, 1.1 mmol) was treated with an excess of hydrochloric acid and evaporated to dryness under reduced
pressure. A suspension of the light brown mixture in 95% ethanol was heated to boiling point and then allowed to stand overnight at room temperature. After a few hours, crystals started to appear and were collected by filtration (0.1 g). These crystals were identified by $^{13}$C NMR spectroscopy as a single isomer. $^{13}$C NMR of the filtrate showed that some of the major isomer remained. The crystallization procedure was then repeated but did not afford any more of the desired product. Attempts to synthesize the free amine were not tried due to an insufficient amount of hydrochloric salt.

A solution of 2,6-dibromopyridine (1 g, 4.2 mmol) in diethyl ether (22 mL) was cooled to $-78 \, ^\circ\text{C}$, and the resulting suspension was treated with n-butyllithium (1.7 mL, 4.2 mmol, 2.5 M in n-hexane). The precipitate dissolved, and a clear yellow solution resulted. After stirring at this temperature for 75 minutes, pivalaldehyde (0.5 mL, 4.6 mmol) was added dropwise. The solution was stirred at $-78 \, ^\circ\text{C}$ for 2 hours and allowed to warm to room temperature over a period of 15 minutes. The mixture was acidified with dilute hydrochloric acid (10 mL) and then extracted 3 times with diethyl ether. The combined organic layers were washed once with brine and dried over magnesium sulphate. The solvent was removed under reduced pressure to give a crude product that crystallized after 2 hours. Recrystallization from light petroleum gave the desired compound (±)-44 (0.91 g, 88%) as colourless needles, m.p. 57-59°C (lit., 57-58°C); Found: C, 49.31; H, 5.74; N, 5.75. C$_{16}$H$_{14}$BrNO requires C, 49.20; H, 5.78; N, 5.74; $\delta$H 0.92 (9H, s, CH$_3$, H-10,11,12), 3.6 (1H, d, $J$ 7.6, OH, H-8), 4.33 (1H, d, $J$ 7.6, CHO$_2$, H-7), 7.18 (1H, d, $J$ 7.6, ArH, H-5), 7.38 (1H, dd, $J$ 7.6 and 0.8, ArH, H-3), 7.49 (1H, dd, $J$ 8 and 8, ArH, H-4); $\delta$C 26.0 (CH$_3$, C-10,11,12), 36.6 (C(CH$_3$)$_3$, 153
C-9), 80.7 (CHOH, C-7), 121.9 (CH Ar, C-3), 127.0 (CH Ar, C-5), 138.3 (CH Ar, C-4), 141.1 (Cquat. Ar, C-6), 162.4 (Cquat. Ar, C-2); m/z 243.0263 C16H14BrNO (M+) requires 243.0259.

(±)-[1-(6-bromopyridin-2-yl)-2,2-dimethylpropyl] methyl ether 45

A solution of (±)-1-(6-bromopyridin-2-yl)-2,2-dimethyl propanol 44 (0.5 g, 2.1 mmol) in tetrahydrofuran (10 mL) was cooled to 0 °C, and sodium hydride (0.15 g, 3.7 mmol, 60% in oil) was added (gas evolution). After stirring at 0 °C for 40 minutes, the resulting suspension was treated with iodomethane (0.28 mL, 4.5 mmol). Stirring was continued for 90 minutes at this temperature, then the mixture was quenched with water (10 mL), and the layers were separated. The aqueous layer was extracted 3 times with diethyl ether, and the combined organic layers were dried over magnesium sulphate. The solvent was removed under reduced pressure to give the crude product, which was purified by column chromatography on silica using a mixture of light petroleum/ethyl acetate (30/1) as eluent to give (±)-[1-(6-bromopyridin-2-yl)-2,2-dimethylpropyl] methyl ether 45 (0.52 g, 97%) as a colourless oil, 35 δH 0.90 (9H, s, CH₃, H-10,11,12), 3.23 (3H, s, OCH₃, H-8), 3.95 (1H, s, CHOCH₃, H-7), 7.34 (1H, d, J 7.6, ArH, H-5), 7.37 (1H, d, J 8, ArH, H-3), 7.54 (1H, dd, J 7.6 and 7.6, ArH, H-4); δC 26.0 (CH₃, C-10,11,12), 35.7 (C(CH₃)₃, C-9), 57.9 (OCH₃, C-8), 92.0 (CHOCH₃, C-7), 120.7 (CH Ar, C-3), 126.4 (CH Ar, C-5), 138.1 (CH Ar, C-4), 140.6 (Cquat. Ar, C-6), 162.5 (Cquat. Ar, C-2); m/z 258.0499 C₁₁H₁₆BrNO (MH⁺) requires 258.0493.
A solution of nickel chloride hexahydrate (0.55 g, 2.3 mmol) in degassed N,N-dimethylformamide (10 mL) was heated at 72 °C (oil bath temperature), and triphenylphosphine (2.44 g, 9.3 mmol) was added to give a blue solution. Addition of zinc powder (0.17 g, 2.5 mmol) resulted in the formation of a dark red-brown mixture, which was stirred at this temperature for 1 hour. (±)-[1-(6-bromopyridin-2-yl)-2,2-dimethylpropyl] methyl ether 45 (0.5 g, 1.9 mmol) was added to this warm solution. After 3 hours at 70 °C, the mixture was allowed to cool to room temperature and an aqueous solution of ammonia (10 mL, 5%) was added to give a brown precipitate. The layers were separated, and the aqueous layer extracted four times with dichloromethane/diethyl ether (2/1). The combined organic layers were washed 3 times with water and once with brine. Drying over magnesium sulphate and removal of the solvent under reduced pressure gave an oil which solidified upon standing. The crude solid was purified by column chromatography (light petroleum/ethyl acetate: 50/1→10/1) on silica to give a mixture (1:1) of meso and (±)-6,6’-bis(1-methoxy-2,2’-dimethylpropyl)-2,2’-bipyridine 46 (0.39 g, 56%) as a white solid, m.p. 164°C (lit., 162-163°C); Found: C, 73.82; H, 8.87; N, 7.70. C_{22}H_{32}N_{2}O_{2} requires C, 74.12; H, 9.05; N, 7.86; δH 0.97 (18H, s, CH_{3}, H-10,11,12,10’,11’,12’), 3.28 (6H, s, OCH_{3}, H-8,8’), 4.05 (2H, s, CHOCH_{3}, H-7,7’), 7.37 (2H, dd, J 0.8 and 6.4, ArH, H-5,5’), 7.80 (2H, dd, J 7.6 and 7.6, ArH, H-4,4’), 8.24 (2H, dd, J 1.2 and 8, ArH, H-3,3’); δC 26.3 (CH_{3}, C-10,11,12,10’,11’,12’), 35.5 (C(CH_{3})_{3}, C-9,9’), 57.8 (OCH_{3}, C-8,8’), 92.8 (CHOCH_{3}, C-7,7’), 119.5 (CH Ar, C-5,5’), 121.6 (CH Ar, C-3,3’), 136.6 (CH Ar, C-4,4’), 155.1 (C quat. Ar, C-2,2’), 159.8 (C quat. Ar, C-6,6’); m/z 356.2470 C_{22}H_{32}N_{2}O_{2} (M^+) requires 356.2464.
1-(6-Bromopyridin-2-yl)-2,2-dimethylpropanone 54\textsuperscript{35}

\[
\begin{array}{c}
\text{Br} \quad \text{Br} \\
\text{N} \\
\end{array} \quad \rightarrow \quad \begin{array}{c}
\text{Br} \\
\text{N} \\
\text{Br} \\
\text{C} \\
\text{O} \\
\end{array}
\]

A suspension of 2,6-dibromopyridine (11.84 g, 50 mmol) in diethyl ether (200 mL) was cooled to –78 °C and treated with n-butyllithium (22 mL, 55 mmol, 2.5 M in n-hexane) over a period of 5 minutes. The precipitate dissolved and a clear yellow solution resulted. After stirring for 30 minutes at this temperature, pivalonitriile (6.6 mL, 60 mmol) was added. After stirring at –78 °C for 1 hour, the solution was allowed to reach room temperature (red mixture, formation of a precipitate) and sulphuric acid (180 mL, 2 N) was added, giving a clear yellow solution. The mixture was refluxed for 2 hours (oil bath temperature 60 °C), cooled to room temperature, and diluted with a few mL of diethyl ether. The layers were separated, and the aqueous layer was extracted 3 times with diethyl ether. The combined organic layers were washed with a saturated solution of sodium carbonate, and dried over magnesium sulphate. The solvent was removed under reduced pressure to give a yellow oil. Purification by Kugelrohr distillation (95-100 °C/0.04 mbar) gave the desired compound 47 (10.67 g, 88%) as a colourless oil,\textsuperscript{35} \(\delta_H\) 1.44 (9H, s, CH\textsubscript{3}, H-9,10,11), 7.58 (1H, dd, J 1.2 and 7.6, ArH, H-5), 7.68 (1H, dd, J 7.6 and 8, ArH, H-4), 7.88 (1H, dd, J 1.2 and 7.6, ArH, H-3); \(\delta_C\) 27.4 (CH\textsubscript{3}, C-9,10,11), 44.2 (C (CH\textsubscript{3})\textsubscript{3}, C-8), 122.5 (CH Ar, C-3), 130.5 (CH Ar, C-5), 139.0 (CH Ar, C-4), 139.6 (C\textsubscript{quat.} Ar, C-6), 154.6 (C\textsubscript{quat.} Ar, C-2), 204.8 (C=O, C-7); \(m/z\) 241.0104 C\textsubscript{10}H\textsubscript{12}BrNO (M\textsuperscript{+}) requires 241.0102.
(S)-1-(6-bromopyridin-2-yl)-2,2-dimethylpropanol 51

Solid (+)-(Ipc)₂BCl (4.7 g, 14.7 mmol) was rapidly stirred, and 1-(6-bromopyridin-2-yl)-2,2-dimethylpropanone 47 (3 g, 12.3 mmol) was added to give a yellow suspension. After stirring at room temperature for a few hours, the solid dissolved, and the mixture became viscous, stirring was continued for 2 days. Removal of the volatile compounds under reduced pressure (0.2 mbar, 4 hours) gave an oil which was dissolved in diethyl ether and treated with diethanolamine (4.1 g, 39.3 mmol) to give a white precipitate. After stirring for 3.5 hours, the solid was removed by filtration, and the filter cake washed with diethyl ether. Drying over magnesium sulphate and removal of the solvent under reduced pressure gave a yellow oil. Volatile products were separated by Kugelrohr distillation (0.2 mbar, 80 °C). The residue was purified by column chromatography on silica using a mixture of light petroleum/ethyl acetate (7/1) as eluent to give the desired product (S)-44 (0.96 g, 32%) as a colourless oil.³⁵ m.p. 57-59°C (lit., ³⁵ 57-58°C); [α]²⁰⁺ +17.9 (c 1.34, CH₃Cl); Found: C, 49.31; H, 5.74; N, 5.75. C₁₀H₁₄BrNO requires C, 49.20; H, 5.78; N, 5.74; δₜ 0.92 (9H, s, CH₃, H-10,11,12), 3.6 (1H, d, J 7.6, OH, H-8), 4.33 (1H, d, J 7.6, CHOH, H-7), 7.18 (1H, d, J 7.6, ArH, H-5), 7.38 (1H, dd, J 7.6 and 0.8, ArH, H-3), 7.49 (1H, dd, J 8 and 8, ArH, H-4); δC 26.0 (CH₃, C-10,11,12), 36.6 (C(CH₃)₃, C-9), 80.7 (CHOH, C-7), 121.9 (CH Ar, C-3), 127.0 (CH Ar, C-5), 138.3 (CH Ar, C-4), 141.1 (C₉₆ Ar, C-6), 162.4 (C₉₆ Ar, C-2); m/z 243.0263 C₁₀H₁₄BrNO (M⁺) requires 243.0259.

The enantiomeric excess was determined by ¹H NMR spectroscopy of the camphanates derived from (1S)-camphanoyl chloride.

Diastereisomer from (R)-44: δH = 5.56 (1H, s, CHC(CH₃)₃).

Diastereisomer from (S)-44: δH = 5.49 (1H, s, CHC(CH₃)₃).

Enantiomeric ratio: (S)-44: (R)-44 = 96:4.
Isopinocampheol 48 was isolated as a white solid by column chromatography on silica using a mixture of light petroleum/ethyl acetate (7/1) as eluent.\(^{35}\)

\[
\text{m.p. 55-56 °C; Found: C, 77.55; H, 11.68. } C_{10}H_{18}O \text{ requires C, 77.87; H, 11.76; } \delta_H \\
0.92 (3H, s, CH\text{, H-10 or H-11}), 1.14 (3H, d, J 7.4, CH\text{, H-8}), 1.22 (3H, s, CH\text{, H-10 or H-11}), 1.67-1.75 (1H, m, CH\text{, H-3}), 1.78-1.83 (2H, m, CH\text{, H-5}), 1.90-1.97 (2H, m, CH\text{, H-4,7}), 2.33-2.39 (1H, m, CH\text{, H-6}), 2.47-2.56 (1H, m, CH\text{, H-3}), 4.04-4.09 (1H, m, CH\text{, H-2}); \delta_C 20.7 (CH\text{, C-8}), 23.7 (CH\text{, C-10 or C-11}), 27.7 (CH\text{, C-10 or C-11}), 34.4 (CH\text{, C-5}), 38.1 (C_{\text{quat}}, C-9), 39.0 (CH\text{, C-3}), 41.8 (CH\text{, C-7}), 47.7 (CH\text{, C-4 or C-6}), 47.8 (CH\text{, C-4 or C-6}), 71.6 (CH\text{, C-2}); m/z 154.1361 C_{10}H_{18}O (M^+) \text{ requires 154.1358.}
\]

\text{Camphanate derived from (±)-44 and (S)-44}^{35}

A solution of (S)-1-(6-bromopyridin-2-y1)-2,2-dimethylpropanol 44 (0.24 g, 1 mmol) in dichloromethane (2.5 mL) and pyridine (0.5 mL) was cooled to 0 °C and treated with (1S)-camphanoyl chloride (0.26 g, 1.2 mmol) followed by a catalytic amount (0.01 g) of \(N,N\)-dimethylaminopyridine. After stirring at room temperature for 3 hours, the reaction mixture was quenched with a few mL of water. The layers were separated, and the aqueous layer was extracted three times with dichloromethane. The combined organic layers were washed with 2 N hydrochloric acid, a saturated aqueous
solution of sodium hydrogencarbonate and brine. After drying the organic phase over magnesium sulphate, the solvent was removed under reduced pressure to give a colourless solid (0.37 g). Recrystallization from cyclohexane gave a mixture of diastereomers (0.27 g, 64%). mp 156 °C (lit.,35 157-158 °C); Found: C, 56.69; H, 6.13; N, 3.20. C_{20}H_{26}BrN_{04} requires C, 56.61; H, 6.18; N, 3.30; m/z 424.1250 C_{20}H_{26}BrN_{04} (MH\textsuperscript{+}) requires 424.1123.

Diastereomer from (R)-44: δ\textsubscript{H} 0.99 (9H, s, C(CH\textsubscript{3})\textsubscript{3}, H-9,10,11), 1.05 (3H, s, CH\textsubscript{3}, H-camphanoyl), 1.07 (3H, s, CH\textsubscript{3}, H-camphanoyl), 1.14 (3H, s, CH\textsubscript{3}, H-camphanoyl), 1.66-1.75 (1H, m, CH\textsubscript{2}, H-camphanoyl), 1.90-1.99 (1H, m, CH\textsubscript{2}, H-camphanoyl), 2.00-2.10 (1H, m, CH\textsubscript{2}, H-camphanoyl), 2.42-2.53 (1H, m, CH\textsubscript{2}, H-camphanoyl), 5.56 (1H, s, CHC(CH\textsubscript{3})\textsubscript{3}, H-7), 7.25 (1H, d, J 0.7, ArH, H-5), 7.39 (1H, d, J 0.7, ArH, H-3), 7.51 (1H, dd, J 7.6 and 7.8, ArH, H-4).

Diastereomer from (S)-44: δ\textsubscript{H} 0.95 (3H, s, CH\textsubscript{3}, H-camphanoyl), 0.99 (9H, s, C(CH\textsubscript{3})\textsubscript{3}, H-9,10,11), 1.13 (3H, s, CH\textsubscript{3}, H-camphanoyl), 1.23 (3H, s, CH\textsubscript{3}, H-camphanoyl), 1.66-1.75 (1H, m, CH\textsubscript{2}, H-camphanoyl), 1.90-1.99 (1H, m, CH\textsubscript{2}, H-camphanoyl), 2.00-2.10 (1H, m, CH\textsubscript{2}, H-camphanoyl), 2.42-2.53 (1H, m, CH\textsubscript{2}, H-camphanoyl), 5.49 (1H, s, CHC(CH\textsubscript{3})\textsubscript{3}, H-7), 7.25 (1H, d, J 0.7, ArH, H-5), 7.39 (1H, d, J 0.7, ArH, H-3), 7.51 (1H, dd, J 7.6 and 7.8, ArH, H-4); δ\textsubscript{C} 9.7 (CH\textsubscript{3}, C-camphanoyl), 16.8 (CH\textsubscript{3}, 2 C-camphanoyl), 26.1 (CH\textsubscript{3}, C-9,10,11), 29.1 (CH\textsubscript{2}, C-camphanoyl), 30.72 (CH\textsubscript{2}, C-camphanoyl), 35.0 (CC(CH\textsubscript{3})\textsubscript{3}, C-8), 54.5 (C\textsubscript{quat.} camphanoyl), 54.9 (C\textsubscript{quat.} camphanoyl), 83.9 (CHO-camphanoyl, C-7), 91.2 (C\textsubscript{quat.} camphanoyl), 121.5 (CH Ar, C-3), 127.1 (CH Ar, C-5), 138.21 (CH Ar, C-4), 141.0 (C\textsubscript{quat.} Ar, C-6), 158.4 (C\textsubscript{quat.} camphanoyl), 166.7 (C\textsubscript{quat.} Ar, C-2), 178.3 (C\textsubscript{quat.} camphanoyl).

(S)-[1-(6-bromopyridin-2-yl)-2,2-dimethylpropyl] methyl ether 45\textsuperscript{35}
A solution of (S)-1-(6-bromopyridin-2-yl)-2,2-dimethylpropanol 44 (1 g, 4.1 mmol) in tetrahydrofuran (12 mL) was cooled to 0 °C, and sodium hydride (0.29 g, 7.4 mmol, 60% in oil) was added (gas evolution). After stirring at 0 °C for 40 minutes, the resulting suspension was treated with iodomethane (0.56 mL, 9 mmol). Stirring was continued for 90 minutes at this temperature, then the mixture was quenched with water, and the layers separated. The organic layer was extracted three times with diethyl ether, and the combined organic layers were dried over magnesium sulphate. The solvent was removed under reduced pressure to give the crude product, which was purified by column chromatography on silica using a mixture of light petroleum/ethyl acetate (1/9) as eluent to give the (S)-1-[1-(6-bromopyridin-2-yl)-2,2-dimethylpropyl] methyl ether 45 (0.89 g, 84%) as a colourless oil. \([\alpha]^{20}_D +16.8\) (c 1.28, CHCl₃); \(\delta_H\) 0.90 (9H, s, CH₃, H-10,11,12), 3.23 (3H, s, OCH₃, H-8), 3.95 (1H, s, CHOCH₃, H-7), 7.34 (1H, d, J 7.6, ArH, H-5), 7.37 (1H, d, J 8, ArH, H-3), 7.54 (1H, dd, J 7.6 and 7.6, ArH, H-4); \(\delta_C\) 26.0 (CH₃, C-10,11,12), 35.7 (C(CH₃)₃, C-9), 57.9 (OCH₃, C-8), 92.0 (CHOCH₃, C-7), 120.7 (CH Ar, C-3), 126.4 (CH Ar, C-5), 138.1 (CH Ar, C-4), 140.6 (C quat. Ar, C-6), 162.5 (C quat. Ar, C-2); \(m/z\) 258.0499 C₁₁H₁₆BrNO (MH⁺) requires 258.0493.

(S,S)-6,6'-bis(1-methoxy-2,2'-dimethylpropyl)-2,2'-bipyridine 46

![Structure of (S,S)-6,6'-bis(1-methoxy-2,2'-dimethylpropyl)-2,2'-bipyridine 46](image)

A solution of nickel chloride hexahydrate (0.77 g, 3.3 mmol) in degassed N,N-dimethylformamide (14 mL) was heated at 72 °C (oil bath temperature), and triphenylphosphine (3.41 g, 13.0 mmol) was added to give a blue solution. Addition of zinc powder (0.23 g, 3.52 mmol) resulted in the formation of a dark red-brown mixture, which was stirred at this temperature for 1 hour. (S)-1-[1-(6-bromopyridin-2-yl)-2,2-dimethylpropyl] methyl ether 45 (0.7 g, 2.7 mmol) was added to the warm solution. After 3 hours at 70 °C, the mixture was allowed to cool to room temperature.
and an aqueous solution of ammonia (14 mL, 5%) was added to give a brown precipitate. The layers were separated, and the aqueous layer was extracted four times with dichloromethane/diethyl ether (2/1). The combined organic layers were washed three times with water and once with brine. Drying over magnesium sulphate and removal of the solvent under reduced pressure gave an oil which solidified upon standing. The crude solid was purified by column chromatography (light petroleum/ethyle acetate: 50/1→10/1) on silica to give (S,S)-6,6'-bis(1-methoxy-2,2'-dimethylpropyl)-2,2'-bipyridine 46 (0.53 g, 55%) as a colourless solid. [α]D20 = 1.09 (c 1.09, CH3Cl); m.p. 164°C (lit.,35 162-163°C); Found: C, 73.82; H, 8.87; N, 7.70. C22H32N2O2 requires C, 74.12; H, 9.05; N, 7.86; δH 0.97 (18H, s, CH3, H-10,11,12,10',11',12'), 3.28 (6H, s, OCH3, H-8,8'), 4.05 (2H, s, CHOCH3, H-7,7'), 7.37 (2H, dd, J 0.8 and 6.4, ArH, H-5,5'), 7.80 (2H, dd, J 7.6 and 7.6, ArH, H-4,4'), 8.24 (2H, dd, J 1.2 and 8, ArH, H-3,3'); δC 26.3 (CH3, C-10,11,12,10',11',12'), 35.5 (C(CH3)3, C-9,9'), 57.8 (OCH3, C-8,8'), 92.8 (CHOCH3, C-7,7'), 119.5 (CH Ar, C-5,5'), 121.6 (CH Ar, C-3,3'), 136.6 (CH Ar, C-4,4'), 155.1 (Cquat. Ar, C-2,2'), 159.8 (Cquat. Ar, C-6,6'); m/z 356.2470 C22H32N2O2 (M+) requires 356.2464.

**Attempted synthesis of (S,S)-6,6'-bis(1-methoxy-2,2'-dimethylpropyl)-2,2'-bipiperidine 49**

(S,S)-6,6'-bis(1-methoxy-2,2'-dimethylpropyl)-2,2'-bipyridine 46 (0.17 g, 0.47 mmol) was added to a solution of platinum oxide (0.017 g, 10% wt/wt) in acetic acid. The mixture was hydrogenated at 40 psi over 14 days. The catalyst was then removed by filtration. The filtrate was basified with an aqueous solution of sodium hydroxide and extracted with diethyl ether. The combined organic layers were dried over magnesium sulphate and the solvent was removed under reduced pressure to give a colourless solid (0.17 g) identified by 1H and 13C NMR spectroscopy as the unreacted starting material (S,S)-46.
m-Chloroperoxybenzoic acid (5.38 g, 31.2 mmol, 50%) was added portionwise to a solution of 2,2'-biquinoline (2 g, 7.8 mmol) in dichloromethane (60 mL) at 0 °C and the mixture was stirred at room temperature overnight. The reaction mixture was washed three times successively with a saturated solution of sodium hydrogen carbonate and brine. After drying over magnesium sulphate, the solvent was evaporated under reduced pressure. The resulting solid was purified by column chromatography (ethyl acetate/methanol 10/1 as eluent) on silica to give 2,2'-biquinoline-N,N'-dioxide 50 (1.42 g, 63%) as an orange solid, m.p. 240 °C (decomp.); Found: C, 74.69; H, 4.05; N, 8.76. C_{18}H_{12}N_{2}O_{2} requires C, 74.99; H, 4.20; N, 9.72; ν_{max}(film)/cm^{-1} 3065 (sp^2 CH), 1596 (C=C), 1562 (C=N), 1523 (N=O), 1330 (C-N), 812-663 (Ar substitution); δ_{H} 7.69 (2H, t, J 7.2, ArH, H-9,9'), 7.78 (6H, t, J 7.2, ArH, H-6,6',7,7',8,8'), 7.91 (2H, t, J 7.2, ArH, H-4,4'), 8.83 (2H, t, J 7.2, ArH, H-3,3'); δ_{C} 120.2 (CH Ar, C-6,6' or C-7,7' or C-8,8'), 123.3 (CH Ar, C-6,6' or C-7,7' or C-8,8'), 124.7 (CH Ar, C-6,6' or C-7,7' or C-8,8'), 128.1 (CH Ar, C-3,3' or C-4,4' or C-9,9'), 129.3 (CH Ar, C-3,3' or C-4,4' or C-9,9'), 130.5 (CH Ar, C-3,3' or C-4,4' or C-9,9'), 139.0 (C_{quat}. Ar, C-2,2' or C-10,10'), 142.1 (C_{quat}. Ar, C-2,2' or C-10,10'), 147.3 (C_{quat}. Ar, C-5,5'); m/z 288.0896 C_{18}H_{12}N_{2}O_{2} (M^+) requires 288.0899.
Attempted synthesis of 6,6'-dimethyl-2,2'-bipyridine-N,N'-dioxide 51

\[
\text{N} \quad \text{O} \\
\text{O}
\]

\[\text{39} \quad \rightarrow \quad \text{O} \quad \text{N} \\
\text{O}
\]

\[\text{51}\]

\(m\)-Chloroperbenzoic acid (1.87 g, 5.4 mmol, 50%) was added portionwise to a solution of 6,6'-dimethyl-2,2'-bipyridine 39 (0.5 g, 2.7 mmol) in dichloromethane (20 mL) at 0 °C. The mixture was stirred at room temperature overnight. The reaction mixture was washed three times successively with a saturated solution of sodium hydrogencarbonate and brine. After drying over magnesium sulphate, the solvent was evaporated under reduced pressure. The resulting light yellow solid was shown by \(^1\)H NMR spectroscopy to be a complex mixture of unidentified products.

Attempted reduction of 2,2'-biquinoline N,N'-dioxide 50 using ammonium formate and palladium on carbon

\[
\text{N} \quad \text{O} \\
\text{O}
\]

\[\text{50} \quad \rightarrow \quad \text{X} \\
\text{52}
\]

Table 19, Entry 1: Room temperature

Dry ammonium formate (1.3 g, 20.5 mmol) was added to a solution of 2,2'-biquinoline-N,N'-dioxide 50 (0.3 g, 1 mmol) containing palladium on carbon 10% (0.11 g) in anhydrous methanol (11 mL) under an atmosphere of nitrogen. The reaction was allowed to stir at room temperature for 19 hours. The solution was then filtered and the solvent removed under reduced pressure to give a yellow solid shown by \(^1\)H NMR spectroscopy to be a complex mixture containing mainly starting material.
Table 19, Entry 2: Reflux

Dry ammonium formate (1.2 g, 19.2 mmol) was added to a solution of 2,2'-biquinoline-N,N'-dioxide 50 (0.26 g, 0.92 mmol) containing palladium on carbon 10% (0.26 g) in anhydrous methanol (18 mL) under an atmosphere of nitrogen. The reaction was allowed to stir at reflux for 19 hours. The solution was cooled to room temperature and filtered. The solvent was then removed under reduced pressure to give a yellow solid, which was shown by 1H NMR spectroscopy to be a complex mixture with unreacted starting material being the major compound. Attempts to isolate the products by column chromatography using light petroleum/ethyl acetate 50/1→10/1 as eluent failed.

4.3.3 Experimental data for section 3.2.3

Attempted synthesis of 1,1',6,6'-tetramethyl-2,2'-bipyridinium diiodide 53

![Chemical structure]

Table 20, Entry 1: Using iodomethane in dichloromethane

Iodomethane (1 mL, 16.3 mmol) was added dropwise to a solution of 6,6'-dimethyl-2,2'-bipyridine 39 (0.5 g, 2.7 mmol) in dichloromethane (5 mL). The reaction mixture was then heated under reflux for 24 hours. The progress of the reaction was followed by TLC (ethyl acetate/methanol 1/1). After 24 hours, TLC of the reaction mixture showed that some starting material remained. The reaction was then left to stir at room temperature for 3 weeks. All the volatile were removed under reduced pressure to give a light orange solid identified by 1H NMR spectroscopy as a mixture of starting material and 1,6,6'-trimethyl-2,2'-bipyridinium iodide 57. Recrystallization from cold
dichloromethane afford the pure 1,6,6'-trimethyl-2,2'-bipyridinium iodide 57 as colourless crystals (0.072 g, 8%).

**Table 20, Entry 2: Using iodomethane neat**

A solution of 6,6'-dimethyl-2,2'-bipyridine 39 (0.1 g, 0.54 mmol) in iodomethane (1 mL) was left stir at room temperature for 2 days. Evaporation of the volatile gave a light orange solid identified by $^1$H NMR spectroscopy as a mixture containing some starting material and traces of 1,6,6'-trimethyl-2,2'-bipyridinium iodide 57.

**1,6,6'-trimethyl-2,2'-bipyridinium iodide 57**

![Chemical structure of 1,6,6'-trimethyl-2,2'-bipyridinium iodide 57]

m.p. 229 °C (decomp.); Found: C, 47.67; H, 4.51; N, 8.44. C_{13}H_{15}IN_2 requires C, 47.87; H, 4.64; N, 8.59; $\delta_H$ 2.64 ($3H$, s, CH$_3$, H-7), 3.09 ($3H$, s, CH$_3$, H-14), 4.22 ($3H$, s, N-CH$_3$, H-15), 7.40 (1H, dd, $J$ 0.52 and 7.88, ArH, H-5), 7.84-7.92 (2H, m, ArH, H-12), 8.48 (1H, t, $J$ 7.88, ArH, H-11); $\delta_C$ 23.5 (CH$_3$, C-7), 24.5 (CH$_3$, C-14), 44.4 (CH$_3$, C-15), 123.8 (CH Ar, C-3), 125.5 (CH Ar, C-5), 127.9 (CH Ar, C-10), 129.9 (CH Ar, C-12), 138.4 (CH Ar, C-4), 144.8 (CH Ar, C-11), 150.0 (C$_{quat}$ Ar, C-13), 154.7 (C$_{quat}$ Ar, C-9), 157.0 (C$_{quat}$ Ar, C-2), 159.4 (C$_{quat}$ Ar, C-6); m/z 199.1203 C$_{13}$H$_{15}$N$_2$ (cation) requires 199.1205.
1,1',6,6'-tetramethyl-2,2'-bipyridinium dimethylsulphate 54

Table 20, Entry 3: Using dimethyl sulphate

6,6'-dimethyl-2,2'-bipyridine 39 (0.2 g, 1.1 mmol) was heated under reflux for 1 hour with dimethyl sulphate (2.8 mL). The mixture was then cooled to room temperature and poured into cold dry ethanol (30 mL). Filtration of the resultant precipitate gave a black oily residue, which was identified by $^1$H NMR spectroscopy as a complex mixture containing traces of the desired quaternary salt 54.

1,1',6,6'-tetramethyl-2,2'-bipyridinium hexafluorophosphate 55

Table 20, Entry 4: Using dimethyl sulphate and potassium hexafluorophosphate

A solution of 6,6'-dimethyl-2,2'-bipyridine 39 (0.2 g, 1.1 mmol) and dimethyl sulphate (2.8 mL) was heated to 188 °C for 1 hour. The mixture was cooled to room temperature and a mixture of water and diethyl ether (1/1) (5 mL) was added. The aqueous layer was separated to which aqueous potassium hexafluorophosphate (0.72 g, 3.9 mmol) was added. The resultant brown precipitate was filtered and identified by $^1$H NMR spectroscopy as the desired 1,1',6,6'-tetramethyl-2,2'-bipyridinium hexafluorophosphate 55 (0.34 g, 62%), m.p. 248 °C (decomp.); $v_{\text{max}}$(film)/cm$^{-1}$ 3101 (sp2 CH), 1623 (C=C), 1580 (C=N), 1093 (C-N), 821-668 (Ar substitution); $\delta_H$ 2.92
(6H, s, CH₃, H-7,7'), 3.93 (6H, s, N-CH₃, H-8,8'), 8.11 (2H, dd, J 1.2 and 7.6, ArH, H-3,3'), 8.35 (2H, dd, J 1.2 and 8.0, ArH, H-5,5'), 8.70 (2H, t, J 8.0, ArH, H-4,4'); δC 21.3 (CH₃, C-7,7'); 43.1 (CH₃, C-8,8'); 127.9 (CH Ar, C-3,3'); 131.5 (CH Ar, C-5,5'); 144.6 (Cquat. Ar, C-6,6'); 145.3 (CH Ar, C-4,4'); 159.4 (Cquat. Ar, C-2,2'); m/z 214.1473 C₁₄H₁₅N₂ (dication) requires 214.1470.

**Attempted synthesis of 6,6'-dimethyl-1,1'-trimethylsilyl-2,2'-bipyridinium triflate 56**

![Chemical structure](image)

**Table 20, Entry 5: Using trimethylsilyl triflate**

A solution of 6,6'-dimethyl-2,2'-bipyridine 39 (0.2 g, 1.1 mmol) in dichloromethane (3 mL) was cooled to 0 °C. Trimethylsilyl triflate (0.6 mL, 2.2 mmol) was then added dropwise. The reaction mixture was allowed to warm to room temperature and stirring was continued overnight. The mixture was then evaporated to dryness to give a colourless solid identified by ¹H NMR spectroscopy as the unreacted starting material 39.

**Reduction of 1,1',6,6'-tetramethyl-2,2'-bipyridinium hexafluorophosphate 55**

![Chemical structure](image)
**Table 21, Entry 1: Using sodium borohydride in methanol**

A solution of 1,1',6,6'-tetramethyl-2,2'-bipyridinium hexafluorophosphate 55 (0.2 g, 0.4 mmol) in aqueous methanol (3 mL) was added dropwise to a solution of sodium borohydride (0.046 g, 1.2 mmol, 98%) in aqueous methanol (10 mL) at 0 °C. The reaction mixture turned from yellow to red and to grey after 2 days. The solution was then acidified with hydrochloric acid concentrated and extracted with ethyl acetate. The organic layers were combined and dried over magnesium sulphate. Evaporation of the solvent under reduced pressure gave a yellow solid. $^1$H NMR spectroscopy showed a complex mixture of products, which was also the case after column chromatography. The products were not identified.

**Table 21, Entry 2: Using lithium aluminium hydride in tetrahydrofuran**

A solution of lithium aluminium hydride (0.65 mL, 0.65 mmol, 1 M in tetrahydrofuran) was added dropwise to a solution of 1,1',6,6'-tetramethyl-2,2'-bipyridinium hexafluorophosphate 55 (0.11 g, 0.22 mmol) in tetrahydrofuran (5 mL) at 0 °C. After 2 days, an aqueous solution of potassium sodium tartrate (5 mL) was added slowly and the solution was allowed to stir for 30 minutes. The reaction mixture was then extracted with ethyl acetate and the combined organic layers were dried over magnesium sulphate. Evaporation of the solvent gave a yellow solid, which was shown by $^1$H NMR spectroscopy to be a mixture of aromatic, alkenic and aliphatic compounds. These different products were not identified.

**Attempted synthesis of 1,1'-dimethyl-2,2'-biquinolinium diiodide 60**
Table 22, Entry 1: Using iodomethane in dichloromethane

Iodomethane (0.7 mL, 11.7 mmol) was added dropwise to a solution of 2,2'-biquinoline (0.5 g, 1.9 mmol) in dichloromethane (13 mL). The reaction mixture was then heated under reflux for 24 hours. The progress of the reaction was followed by TLC (dichloromethane/ethyl acetate 10/1). After 24 hours, TLC of the reaction mixture showed that some starting material remained. The reaction was then left at room temperature for 3 weeks. All the volatile were removed under reduced pressure to give a light orange solid identified by $^1$H NMR spectroscopy as the unreacted starting material.

Table 22, Entry 2: Using iodomethane neat

A solution of 2,2'-biquinoline (0.1 g, 0.4 mmol) in iodomethane (1 mL) was left stir at room temperature for 18 hours. Evaporation of the volatile under reduced pressure afforded a colourless solid identified by $^1$H NMR spectroscopy as the unreacted starting material.

1,1'-dimethyl-2,2'-biquinolinium dimethylsulphate 61$^{39}$

Table 22, Entry 3: Using dimethyl sulphate

2,2'-Biquinoline (0.5 g, 1.95 mmol) was heated under reflux for 1 hour with dimethyl sulphate (5 mL). The mixture was then cooled to room temperature. The solution was poured into cold dry ethanol (50 mL) and the solid which precipitated crystallized from aqueous ethanol to give the desired diquaternary salt 61$^{39}$ (0.93 g, 93%) as off-
white crystals, m.p. 133-134 °C; δ_H (D_2O) 3.56 (6H, s, N-CH_3, H-11,11'); 4.78 (6H, s, CH_3SO_4, H-12,12'); 8.18 (2H, dd, J 0.8 and 7.1, ArH, H-3,3'); 8.30 (2H, d, J 8.5, ArH, H-6,6'); 8.44 (2H, dd, J 1.5 and 7.0, ArH, H-7,7'); 8.53 (2H, d, J 8.3, ArH, H-5,5'); 8.59 (2H, d, J 9.1, ArH, H-8,8'); 9.45 (2H, d, J 8.4, ArH, H-4,4'); δ_C 43.1 (CH_3, C-11,11'); 55.6 (CH_3, C-12,12'); 119.3 (CH Ar, C-9,9'); 123.6 (CH Ar, C-7,7'); 131.2 (C_{quat. Ar}, C-5,5'); 131.6 (CH Ar, C-8,8'); 132.2 (CH Ar, C-6,6'); 138.9 (CH Ar, C-3,3'); 141.0 (C_{quat. Ar}, C-2,2'); 147.7 (C_{quat. Ar}, C-10,10'); 149.9 (CH Ar, C-4,4'); m/z 286.1469 C_{22}H_{24}N_{2} (dication) requires 286.1470.

The spectral data of 61 were identical to those in the literature.\(^{39}\)

**Attempted synthesis of 1,1'-bis-trimethylsilyl-2,2'-biquinolinium ditriflate 62**

![Chemical structure of 62](image)

**Table 22, Entry 4:** Using trimethylsilyl triflate

A solution of 2,2'-biquinoline (0.2 g, 0.78 mmol) in dichloromethane (2 mL) was cooled to 0 °C. Trimethylsilyl triflate (0.3 mL, 1.6 mmol) was then added dropwise and the reaction mixture was allowed to warm to room temperature and stir at this temperature overnight. The mixture was then evaporated to dryness to give a colourless solid identified by \(^1\)H NMR spectroscopy as the unreacted starting material.
Attempted synthesis of 1,1'-benzyl-2,2'-biquinolinium dibromide 63

\[
\begin{array}{c}
\text{N} & \text{N} \\
\text{N} & \text{N} \\
\end{array}
\xrightarrow{X} \begin{array}{c}
\text{N} \text{Bn} & \text{N} \\
\text{Bn} & \text{Bn} \\
\end{array}
\]

Table 22, Entry 5: Benzyl bromide in acetonitrile

Benzyl bromide (0.3 mL, 2.3 mmol) was added dropwise to a solution of 2,2'-biquinoline (0.2 g, 0.78 mmol) in acetonitrile (5 mL). The solution was then heated under reflux for 16 hours. On cooling to room temperature a white precipitate appeared, this was filtered and washed with cold acetonitrile. The white solid was identified by $^1$H NMR spectroscopy as the unreacted starting material.

Table 22, Entry 6: Benzyl bromide neat

A solution of 2,2'-biquinoline (0.15 g, 0.59 mmol) in benzyl bromide was heated at 150 °C overnight. The reaction mixture was allowed to cool to room temperature. Diethyl ether was then added to the mixture and a brown solid precipitated. Filtration of the mixture afforded a brown solid, which was identified by $^1$H NMR spectroscopy as the unreacted starting material.

Reduction of 1,1'-dimethyl-2,2'-biquinolinium dimethylsulphate 61

\[
\begin{array}{c}
\text{N} & \text{N} \\
\text{N} & \text{N} \\
\end{array}
\xrightarrow{2 \text{CH}_3\text{SO}_4}\begin{array}{c}
\text{N} & \text{N} \\
\text{N} & \text{N} \\
\end{array}
\]

\[
\begin{array}{c}
\text{N} & \text{N} \\
\text{N} & \text{N} \\
\end{array}
\]

\[
\begin{array}{c}
\text{N} & \text{N} \\
\text{N} & \text{N} \\
\end{array}
\]

171
Table 23, Entry 1: Using sodium borohydride in methanol

Sodium borohydride (0.03 g, 0.78 mmol, 98%) was added in solid form to a solution of 1,1'-dimethyl-2,2'-biquinolinium dimethylsulphate 61 (0.2 g, 0.4 mmol) in dry methanol (5 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature. After 2 days, the reaction mixture was acidified with hydrochloric acid, concentrated under reduced pressure and extracted with ethyl acetate. The organic layers were combined and dried over magnesium sulphate. Evaporation of the solvent in vacuo gave a red oil. 1H NMR spectroscopy of the crude mixture revealed sign of starting material, 1,1'-dimethyl-1,4,1',4'-tetrahydro-2,2'-biquinoline 64 (ratio: 1:3) and traces of 1,1'-dimethyl-1,2,3,4,1',2',3',4'-octahydro-2,2'-biquinoline 65. Attempts to isolate the different products by column chromatography failed.

Table 23, Entry 2: Using sodium borohydride in aqueous ethanol

A solution of 1,1'-dimethyl-2,2'-biquinolinium dimethylsulphate 61 (0.2 g, 0.39 mmol) in aqueous ethanol (3 mL) was added dropwise to a solution of sodium borohydride (0.045 g, 1.2 mmol, 98%) in aqueous ethanol (5 mL) at 0 °C. After 2 days, the solution was acidified with hydrochloric acid, concentrated under reduced pressure and extracted with ethyl acetate. The organic layers were combined and dried over magnesium sulphate. Removal of the solvent under reduced pressure gave a red-brown solid which was shown by 1H NMR spectroscopy to be a mixture of 1,1'-dimethyl-1,4,1',4'-tetrahydro-2,2'-biquinoline 64 and 1,1'-dimethyl-1,2,3,4,1',2',3',4'-octahydro-2,2'-biquinoline 65 in a 1:5 ratio. Column chromatography (light petroleum/dichloromethane 7/3) of the crude mixture gave 1,1'-dimethyl-1,2,3,4,1',2',3',4'-octahydro-2,2'-biquinolin 65 (0.025 g, 22%) as a light brown oil, ν_max(film)/cm\(^{-1}\) 3017 (sp\(^2\) CH), 2924 (sp\(^3\) CH), 1574 (C=C), 1076 (C-N), 832-668 (Ar substitution); δ_H 1.75-1.83 (4H, m, CH\(_2\), H-4,4'meso or H-4,4'trans), 1.92-1.98 (4H, m, CH\(_2\), H-4,4'meso or H-4,4'trans), 2.69-2.75 (4H, m, CH\(_2\), H-3,3'meso or H-3,3'trans), 2.77 (6H, s, N-CH\(_3\), H-11,11'meso or H-11,11'trans), 2.81-2.99 (4H, m, CH\(_2\), H-3,3'meso or H-3,3'trans), 3.04 (6H, s, N-CH\(_3\), H-11,11'meso or H-11,11'trans), 3.32-3.36 (2H, m, CH, H-2,2'meso or H-2,2'trans), 6.51-6.59 (2H, m, ArH, H-9,9'meso or H-9,9'trans), 6.59-6.64 (2H, m, ArH, H-7,7'meso or H-7,7'trans), 6.96-7.03 (2H, m, ArH, H-8,8'meso or H-8,8'trans), 7.07-
7.12 (2H, m, ArH, H-6,6'meso or H-6,6'trans); δc 21.9 (CH2, C-4,4'meso or C-4,4'trans), 22.6 (CH2, C-4,4'meso or C-4,4'trans), 23.4 (CH2, C-3,3'meso or C-3,3'trans), 24.2 (CH2, C-3,3'meso or C-3,3'trans), 40.1 (CH3, C-11,11'meso or C-11,11'trans), 41.6 (CH3, C-11,11'meso or C-11,11'trans), 60.3 (CH, C-2,2'meso or C-2,2'trans), 110.2 (CH Ar, C-9,9'meso or C-9,9'trans), 112.4 (CH Ar, C-9,9'meso or C-9,9'trans), 115.1 (CH Ar, C-7,7'meso or C-7,7'trans), 115.9 (CH Ar, C-7,7'meso or C-7,7'trans), 120.6 (C quat. Ar, C-5,5'meso or 5,5'trans), 122.1 (C quat. Ar, C-5,5'meso or 5,5'trans), 127.0 (CH Ar, C-8,8'meso or C-8,8'trans), 127.3 (CH Ar, C-8,8'meso or C-8,8'trans), 128.9 (CH Ar, C-6,6'meso or C-6,6'trans), 144.9 (C quat. Ar, C-10,10'meso or C-10,10'trans), 145.4 (C quat. Ar, C-10,10'meso or C-10,10'trans); m/z 292.2015 C20H24N2 requires 292.1939. For X-Ray of the meso isomer see Appendix 3.

Table 23, Entry 3: Using lithium aluminium hydride in tetrahydrofuran

Lithium aluminium hydride (0.47 g, 11.8 mmol) was added in solid form to a solution of 1,1'-dimethyl-2,2'-biquinolinium dimethylsulphate 61 (1 g, 1.9 mmol) in tetrahydrofuran (25 mL) at 0 °C. The reaction mixture was allowed to stir at room temperature overnight. An aqueous solution of potassium sodium tartrate (25 mL) was added slowly and the solution was allowed to stir for 30 minutes. The reaction mixture was extracted with ethyl acetate and the combined organic layers dried over magnesium sulphate. Evaporation of the solvent gave 1,1'-dimethyl-1,4,1',4'-tetrahydro-2,2'-biquinoline 64 (0.48 g, 85%) as a light brown solid. m.p. 102 °C (decomp.); Found: C, 83.65; H, 7.27; N, 9.92. C20H20N2 requires C, 83.30; H, 6.99; N, 9.71; vmax(film)/cm⁻¹ 3059 (sp² CH), 2899 (sp³ CH), 1576 (C=C), 1091 (C-N), 830-669 (Ar substitution); δH 2.88 (6H, s, N-CH3, H-11,11'), 3.49 (4H, d, J 4.1, CH2, H-4,4'), 4.85 (2H, t, J 4.2, CH, H-3,3'), 6.72 (2H, dd, J 0.9 and 7.4, ArH, H-9,9'), 6.86 (2H, J 1.2 and 7.4, ArH, H-7,7'), 6.98 (2H, dd, J 1.3 and 7.4, ArH, H-6,6'), 7.13 (2H, dd, J 1.6 and 7.4, ArH, H-8,8'); δc 27.9 (CH2, C-4,4'), 33.5 (CH3, C-11,11'), 100.5 (CH, C-3,3'), 111.9 (CH Ar, C-9,9'), 120.7 (CH Ar, C-7,7'), 122.7 (C quat. Ar, C-5,5'), 126.6 (CH Ar, C-8,8'), 128.3 (CH Ar, C-6,6'), 140.0 (C quat. Ar, C-10,10'), 143.1 (C quat., C-2,2'); m/z 288.1627 C20H20N2 (M⁺) requires 288.1626.
Hydrogenation of 1,1'-dimethyl-1,4,1',4'-tetrahydro-2,2'-biquinoline 64

Table 24, Entry 1: Using hydrogen and palladium on carbon

Palladium on carbon (0.02 g, 10% wt/wt) was added to a solution of 1,1'-dimethyl-1,4,1',4'-tetrahydro-2,2'-biquinoline 64 (0.2 g, 0.69 mmol) in ethyl acetate (5 mL). The reaction mixture was stirred under an atmosphere of hydrogen at room temperature overnight. After filtration of the catalyst through celite, the filtrate was evaporated to dryness under reduced pressure to give a brown residue identified by $^1$H NMR spectroscopy as the unreacted starting material 64.

Table 24, Entry 2: Using hydrogen and platinum oxide

Three drops of concentrated ammonium hydroxide solution were added to a solution of 1,1'-dimethyl-1,4,1',4'-tetrahydro-2,2'-biquinoline 64 (0.2 g, 0.69 mmol) in absolute methanol (50 mL). Adam's platinum oxide catalyst (0.099 g) was suspended in solution and the reaction shaken under hydrogen at room temperature and atmospheric pressure overnight. After filtration of the catalyst, the filtrate was evaporated to dryness under reduced pressure to give 1,1'-dimethyl-1,2,3,4,1',2',3',4'-octahydro-2,2'-biquinoline 65 (0.2 g, 100%) as a light brown oil. The spectral data were as above.
Attempted demethylation of the N of 1,1'-dimethyl-1,4,1',4'-tetrahydro-2,2'-biquinoline 64

![Chemical Figure]

Table 25, Entry 1: Using benzyl chloroformate (carbobenzoxy chloride) and potassium carbonate in 1,2-dichloroethane

Potassium carbonate (0.19 g, 1.4 mmol) was added in solid form to a solution of 1,1'-dimethyl-1,4,1',4'-tetrahydro-2,2'-biquinoline 64 (0.1 g, 0.35 mmol) in 1,2-dichloroethane (5 mL). Benzyl chloroformate (carbobenzoxy chloride) (0.2 mL, 1.4 mmol) was then added dropwise and the reaction mixture heated at reflux overnight. The reaction mixture was washed three times with water and the organic layers dried over magnesium sulphate. The solvents were removed under reduced pressure to give a purple oil, shown by \(^1\text{H}\) NMR spectroscopy to be a mixture of starting material 64 and benzyl chloride.

Table 25, Entry 2: Using phenyl chloroformate in 1,2-dichloroethane

Phenyl chloroformate (0.12 mL, 0.9 mmol) was added dropwise to a solution of 1,1'-dimethyl-1,4,1',4'-tetrahydro-2,2'-biquinoline 64 (0.1 g, 0.35 mmol) in 1,2-dichloroethane (5 mL) at 0 °C. The reaction mixture was then heated at 83 °C overnight. On cooling to room temperature, a brown precipitate appeared and evaporation of the filtrate under reduced pressure afforded a brown oil. \(^1\text{H}\) NMR spectroscopy of the brown solid and the brown oil showed that in both cases a complex mixture containing traces of the starting material 64, phenyl chloroformate and unidentified products.
Table 25, Entry 3: Using phenyl chloroformate and potassium carbonate in 1,2-dichloroethane

Solid potassium carbonate (0.125 g, 0.9 mmol) was added to a solution of 1,1'-dimethyl-1,4,1',4'-tetrahydro-2,2'-biquinoline 64 (0.1 g, 0.35 mmol) in 1,2-dichloroethane (5 mL) at 0 °C. Phenyl chloroformate (0.12 mL, 0.9 mmol) was added via syringe and the reaction mixture heated at reflux overnight. Removal of the solvent gave a black-green oil. $^1$H NMR spectroscopy of the crude mixture revealed that the peak corresponding to the N-Me were no longer present but column chromatography (dichloromethane) did not give the desired product. Instead a complex mixture of products was obtained. These were not identified.

Attempted demethylation of the N of 1,1'-dimethyl-1,2,3,4,1',2',3',4'-octahydro-2,2'-biquinoline 65

![Diagram]

Potassium carbonate (0.26 g, 1.9 mmol) was added in solid form to a solution of 1,1'-dimethyl-1,2,3,4,1',2',3',4'-octahydro-2,2'-biquinoline 65 (0.21 g, 0.72 mmol) in 1,2-dichloroethane (5 mL) at 0 °C. Phenyl chloroformate (0.19 mL, 1.5 mmol) was then added via syringe and the reaction mixture heated at reflux for 6 days. Once the unreacted potassium carbonate was filtered, the filtrate was evaporated under reduced pressure to give a blue oil shown by $^1$H NMR spectroscopy to be a mixture of unreacted starting material 65 and phenyl chloroformate.
Attempted synthesis of 3,4,3',4'-tetrahydro-2,2'-biquinoline 69

![Diagram of 3,4,3',4'-tetrahydro-2,2'-biquinoline 69](image)

Lead tetraacetate (1.4 g, 3.2 mmol) was added in solid form to a solution of 1,1'-dimethyl-1,2,3,4,1',2',3',4'-octahydro-2,2'-biquinolin 65 (0.11 g, 0.38 mmol) in toluene (6 mL) at room temperature. The reaction mixture was stirred at room temperature overnight, then filtered through celite. The filtrate was dried over magnesium sulphate and evaporated under reduced pressure to give a dark red residue. 

$^1$H NMR spectroscopy of the residue revealed that the peak corresponding to the N-Me no longer existed, but column chromatography (dichloromethane) did not afford the desired product 69. Instead a complex mixture of products was obtained. These were not identified.

Attempted synthesis of (S,S)-1,1'-dimethyl-6,6'-bis(1-methoxy-2,2'-dimethylpropyl)-2,2'-bipyridinium salts 70 and 71

![Diagram of (S,S)-1,1'-dimethyl-6,6'-bis(1-methoxy-2,2'-dimethylpropyl)-2,2'-bipyridinium salts 70 and 71](image)

Table 26, Entry 1: Using dimethyl sulphate at 188 °C

(S,S)-6,6'-bis(1-methoxy-2,2'-dimethylpropyl)-2,2'-bipyridine 46 (0.1 g, 0.28 mmol) was heated under reflux for 1 hour with dimethyl sulphate (0.7 mL). The mixture was then cooled to room temperature. The solution was poured into cold dry ethanol (7 mL) but no precipitate appeared. The ethanol was then removed under reduced pressure to give a green solid, which become gummy in air. $^1$H NMR spectroscopy of
the gummy solid showed a complex mixture corresponding to the decomposition of the starting material \((S,S)-46\).

**Table 26, Entry 2:** Using dimethyl sulphate at 150 °C and potassium hexafluorophosphate

A solution of \((S,S)-6,6'-\text{bis}(1\text{-methoxy-2,2'}\text{-dimethylpropyl})\text{-2,2'}\text{-bipyridine 46 (0.083 g, 0.23 mmol)}\) and dimethyl sulphate (0.6 mL) was heated at 150 °C for 3 hours. The mixture was cooled to room temperature and water/diethyl ether (1/1) (3 mL) was added. The aqueous layer was separated to which aqueous potassium hexafluorophosphate (0.15 g, 0.84 mmol) was added. The resultant green gummy precipitate was filtered and identified by \(^1\text{H}\) NMR spectroscopy as the decomposition of the starting material \((S,S)-46\).

4.3.4 Experimental data for section 3.2.4

Reduction of 6,6'-dimethyl-2,2'-bipyridine 39 with lithium triethylborohydride

Lithium triethylborohydride (2.4 mL, 2.4 mmol, 1.0 M in tetrahydrofuran) was added dropwise to a solution of 6,6'-dimethyl-2,2'-bipyridine 39 (0.1 g, 0.54 mmol) in tetrahydrofuran (5 mL) at room temperature. The reaction mixture turned yellow to reddish brown. The mixture was allowed to stir at room temperature overnight. TLC (methanol) of the mixture showed that some starting material remained. The mixture
was then heated at 50 °C for 90 minutes. TLC showed no further progress in the reaction. The reaction mixture was then quenched with methanol and the solution diluted with diethyl ether and 1N aqueous hydrochloric acid. Triethylborane was extracted with diethyl ether. The pH of the aqueous layer was adjusted to pH 8 and extracted with dichloromethane. The combined organic layers were dried over magnesium sulphate and concentrated under reduced pressure to give a yellow oil. The $^1$H NMR spectrum of the resultant oil revealed traces of starting material, with some unidentified products. Column chromatography of the crude oil using light petroleum/ethyl acetate 10/1 → methanol as eluent permitted the isolation of 15% of 6,6'-dimethyl-1,2,3,4,5,6-hexahydro-2,2'-bipyridine 72 as a light orange oil, some starting material and some unidentified products which did not correspond to the 6,6'-dimethyl-2,2'-bipiperidine 40.

Table 27, Entry 2:

Lithium triethylborohydride (2.4 mL, 2.4 mmol, 1.0 M in tetrahydrofuran) was added dropwise to a solution of 6,6'-dimethyl-2,2'-bipyridine 39 (0.1 g, 0.54 mmol) in tetrahydrofuran (5mL) at −78 °C. The mixture was stirred at this temperature for 4 hours and allowed to warm to 0 °C and stirred overnight. TLC (methanol) showed that some starting material remained, therefore further lithium triethylborohydride (4.4 equivalents, 2.4 mL, 2.4 mmol, 1.0 M in tetrahydrofuran) was added dropwise and the reaction stirred for 1 day at room temperature. The last procedure was repeated twice more in order to bring the reaction to completion. The reaction mixture was then quenched with methanol and the solution diluted with diethyl ether and 1N aqueous hydrochloric acid. Triethylborane was extracted with diethyl ether. The pH of the aqueous layer was adjusted to pH 8 and extracted with dichloromethane. The combined organic layers were dried over magnesium sulphate and concentrated under reduced pressure. The resultant yellow-orange oil was shown by $^1$H NMR spectroscopy to be a mixture containing some starting material and traces of 6,6'-dimethyl-1,2,3,4,5,6-hexahydro-2,2'-bipyridine 72.
Table 27, Entry 3:

Lithium triethylborohydride (2.4 mL, 2.4 mmol, 1.0 M in tetrahydrofuran) was added dropwise to a solution of 6,6'-dimethyl-2,2'-bipyridine 39 (0.2 g, 1.1 mmol) in tetrahydrofuran (5 mL) at room temperature. The mixture was heated at 50 °C for 4 days. TLC (methanol) showed that some starting material remained, therefore further lithium triethylborohydride (8 equivalents, 2.4 mL, 2.4 mmol, 1.0 M in tetrahydrofuran) was added dropwise and the reaction mixture heated at 50 °C overnight. The reaction mixture was then quenched with methanol and the solution diluted with diethyl ether and 1N aqueous hydrochloric acid. Triethylborane was extracted with diethyl ether. The pH of the aqueous layer was adjusted to pH 8 and extracted with dichloromethane. The combined organic layers were dried over magnesium sulphate and concentrated under reduced pressure. The resultant orange oil was shown by ¹H NMR spectroscopy to be a mixture containing 6,6'-dimethyl-2,2'-bipiperidine 40 along with some unidentified products. Column chromatography of the crude oil using light petroleum/ethyl acetate 5/5 → methanol allowed isolation of 35% of 6,6'-dimethyl-1,2,3,4,5,6-hexahydro-2,2'-bipyridine 72 as a light orange oil and some unidentified compounds which did not correspond to the 6,6'-dimethyl-2,2'-bipiperidine 40 by ¹³C comparison.

6,6'-dimethyl-1,2,3,4,5,6-hexahydro-2,2'-bipyridine 72

\[
\begin{align*}
6,6' &- \text{dimethyl-1,2,3,4,5,6-hexahydro-2,2'-bipyridine 72} \\
\end{align*}
\]

\[
\begin{align*}
\nu_{\text{max}}(\text{film})/\text{cm}^{-1} & = 3059 (s^2 \text{ CH}), 2925 (s^3 \text{ CH}), 1590 (C=C), 1114 (C-N), 880-668 (\text{Ar substitution}); \\
\delta_{\text{H}} & = 1.13 (3H, d, J 7.0, \text{ CH}_3, H-14), 1.16-1.20 (1H, m, \text{ CH}_2, H-5), 1.41-1.62 (2H, m, \text{ CH}_2, H-3,4), 1.63-1.72 (1H, m, \text{ CH}_2, H-5), 1.89-1.99 (2H, m, \text{ CH}_2, H-3,4), 2.52 (3H, s, \text{ CH}_3, H-7), 2.83-2.89 (1H, m, \text{ CH}_2, H-6), 3.16 (1H, s broad, NH, H-8), 3.78 (1H, dd, J 2.5 and 11.0, CH, H-2), 7.00 (1H, dd, J 0.4 and 7.6, ArH, H-12), 7.17 (1H, dd, J 0.4 and 7.7, ArH, H-10), 7.52 (1H, t, J 7.7, ArH, H-11); \\
\delta_{\text{C}} & = 22.7 (\text{CH}_3, \\
\end{align*}
\]
C-14), 24.4 (CH₃, C-7), 24.9 (CH₂, C-4), 31.8 (CH₂, C-3), 33.7 (CH₂, C-5), 52.7 (CH, C-6), 62.4 (CH, C-2), 117.3 (CH Ar, C-10), 121.6 (CH Ar, C-12), 136.8 (CH Ar, C-11), 157.5 (C quat. Ar, C-13), 162.2 (C quat. Ar, C-9); m/z 190.1469 C₁₂H₁₈N₂ (M⁺) requires 190.1470.

**Attempted reduction of 6,6'-dimethyl-1,2,3,4,5,6-hexahydro-2,2'-bipyridine 72 using lithium triethylborohydride at 50 °C**

![Diagram](image)

Lithium triethylborohydride (4 mL, 4 mmol, 1.0 M in tetrahydrofuran) was added dropwise to a solution of 6,6'-dimethyl-1,2,3,4,5,6-hexahydro-2,2'-bipyridine 72 (0.095 g, 0.5 mmol) in tetrahydrofuran (3 mL) at room temperature. The mixture was heated at 50 °C for 4 days. TLC (methanol) showed that some starting material remained, therefore further lithium triethylborohydride (8 equivalents, 4 mL, 4 mmol, 1.0 M in tetrahydrofuran) was added dropwise and the reaction mixture heated at 50 °C for 2 days. The reaction mixture was then quenched with methanol and the solution diluted with diethyl ether and 1N aqueous hydrochloric acid. Triethylborane was extracted with diethyl ether. The pH of the aqueous layer was adjusted to pH 8 and extracted with dichloromethane. The combined organic layers were dried over magnesium sulphate and concentrated under reduced pressure. The resultant yellow-orange oil was shown by ¹H NMR spectroscopy to be a mixture made mainly of unreacted starting material 72 and some unidentified products which did not correspond to the 6,6'-dimethyl-2,2'-bipiperidine 40 by ¹³C comparison.
Attempted reduction of 2,2'-biquinoline using lithium triethylborohydride at 50 °C

\[
\begin{align*}
\text{Lithium triethylborohydride (3.1 mL, 3.1 mmol, 1.0 M in tetrahydrofuran) was added} \\
dropwise to a solution of 2,2'-biquinoline (0.1 g, 0.39 mmol) in tetrahydrofuran (5 mL) at room temperature. The mixture was heated at 50 °C for 4 days. TLC (methanol) showed that some starting material remained, therefore further lithium triethylborohydride (8 equivalents, 3.1 mL, 3.1 mmol, 1.0 M in tetrahydrofuran) was added dropwise and the reaction mixture heated at 50 °C overnight. The reaction mixture was then quenched with methanol and the solution diluted with diethyl ether and 1N aqueous hydrochloric acid. Triethylborane was extracted with diethyl ether. The pH of the aqueous layer was adjusted to pH 8 and extracted with dichloromethane. The combined organic layers were dried over magnesium sulphate and concentrated under reduced pressure. The resultant orange oil was shown by \text{^1H NMR spectroscopy to be a complex mixture containing traces of starting material along with some unidentified products. Attempts to isolate the different products by column chromatography failed.}}
\end{align*}
\]

Attempted reduction of (S,S)-6,6'-bis(1-methoxy-2,2-dimethylpropyl)-2,2'-bipyridine 46 using lithium triethylborohydride at 50 °C

\[
\begin{align*}
\text{Lithium triethylborohydride (2.2 mL, 2.2 mmol, 1.0 M in tetrahydrofuran) was added} \\
dropwise to a solution of (S,S)-6,6'-bis(1-methoxy-2,2-dimethylpropyl)-2,2'-
\end{align*}
\]
bipyridine 46 (0.1 g, 0.28 mmol) in tetrahydrofuran (2 mL) at room temperature. The mixture was heated at 50 °C for 4 days. TLC (methanol) showed that some starting material remained, therefore further lithium triethylborohydride (8 equivalents, 2.2 mL, 2.2 mmol, 1.0 M in tetrahydrofuran) was added dropwise and the reaction mixture heated at 50 °C overnight. The reaction mixture was then quenched with methanol and the solution diluted with diethyl ether and 1N aqueous hydrochloric acid. Triethylborane was extracted with diethyl ether. The pH of the aqueous layer was adjusted to pH 8 and extracted with dichloromethane. The combined organic layers were dried over magnesium sulphate and concentrated under reduced pressure. The resultant orange oil was shown by ¹H NMR spectroscopy to be the unreacted starting material (S,S)-46.

4.3.5 Experimental data for section 3.3

Imidazolium salt derivative 73 from 6,6'-dimethyl-2,2'-bipiperidine 40

Ammonium tetrafluoroborate (0.28 g, 2.6 mmol) was added to a solution of 6,6'-dimethyl-2,2'-bipiperidine 40 (0.51 g, 2.6 mmol) in neat triethyl orthoformate (0.44 mL, 2.6 mmol). The reaction mixture was heated at 120 °C for 3 hours. The reaction mixture was allowed to cool to room temperature and was left to stir at room temperature overnight. Removal the solvent under reduced pressure gave the desired imidazolium salt 73 (three different isomers) (0.79 g, 95%). Recrystallization from dichloromethane gave some colourless needles corresponding to the meso compound. The yield after recrystallization was not determined, m.p. 85-86 °C; Found: C, 53.03; H, 7.67; N, 9.63. C₁₃H₂₃BF₄N₂ requires C, 53.08; H, 7.88; N, 9.52; ν_max(film)/cm⁻¹ 2941 (sp³ CH), 1656 (C=N), 1179 (C-N); m/z 207.1863 C₁₃H₂₃N₂ (cation) requires 207.1861.
Meso-imidazolium salt 73:

\[
\text{meso-40} \quad \rightarrow \quad \text{meso-73}
\]

Ammonium tetrafluoroborate (0.1 mg, 0.95 mmol) was added to a solution of meso-6,6'-dimethyl-2,2'-bipiperidine 40 (0.18 g, 0.95 mmol) in neat triethyl orthoformate (0.2 mL, 0.95 mmol). The reaction mixture was heated at 120 °C for 3 hours. The reaction mixture was allowed to cooled to room temperature and was left to stir at room temperature overnight. Removal the solvent under reduced pressure afforded the desired meso-imidazolium salt 73 (0.28 g, 99%). m.p. 85-86 °C; Found: C, 53.03; H, 7.67; N, 9.63. C_{13}H_{23}BF_{4}N_{2} requires C, 53.08; H, 7.88; N, 9.52; \nu_{\text{max}}(\text{film})/\text{cm}^{-1} 2941 (\text{sp}^{3} \text{CH}), 1656 (\text{C}=\text{N}), 1179 (\text{C}-\text{N}); \delta_{\text{H}} 1.34-1.41 (2H, m, CH_{2}, H_{ax}-5,5'), 1.49 (6H, d, J 6.4, CH_{3}, H_{eq}-7,7'), 1.54-1.67 (4H, m, CH_{2}, H_{ax}-3,3' and H_{ax}-4,4'), 1.75-1.83 (4H, m, CH_{2}, H_{eq}-3,3' and H_{eq}-5,5'), 1.93-1.98 (2H, m, CH_{2}, H_{eq}-4,4'), 3.46-3.54 (2H, m, CH, H_{ax}-6,6'), 4.18-4.21 (2H, m, CH, H_{ax}-2,2'), 7.65 (1H, s, NCHN, H-8); \delta_{C} 18.1 (\text{CH}_{3}, \text{C}-7,7'), 22.6 (\text{CH}_{2}, \text{C}-4,4'), 25.1 (\text{CH}_{2}, \text{C}-3,3'), 33.3 (\text{CH}_{2}, \text{C}-5,5'), 53.6 (\text{CH}, \text{C}-6,6'), 62.9 (\text{CH}, \text{C}-2,2'), 148.2 (\text{NCH}, \text{C}-8); m/z 207.1863 \text{ C}_{13}\text{H}_{23}\text{N}_{2} (\text{cation}) \text{ requires } 207.1861. \text{For X-Ray see Appendix 4.}

Imidazolium salt derivative 74 from bidecahydroquinoline 42

\[
\text{42} \quad \rightarrow \quad \text{74}
\]

Ammonium tetrafluoroborate (0.082 g, 0.78 mmol) was added to a solution of bidecahydroquinoline 50 (0.22 g, 0.78 mmol) in neat triethyl orthoformate (0.13 mL,
0.78 mmol). The reaction mixture was heated at 120 °C for 3 hours. The reaction mixture was allowed to cool to room temperature and was left to stir at room temperature overnight. Removal the solvent under reduced pressure gave the desired imidazolium salt 74 (0.26 g, 88%) as a orange brown solid. $^{13}$C NMR spectrum showed the presence of 7 different isomers, m.p. 130-131 °C; Found: C, 60.82; H, 8.12; N, 7.83. C$_{19}$H$_{31}$BF$_{4}$N$_{2}$ requires C, 60.97; H, 8.35; N, 7.48; $\nu_{max}(film)/cm^{-1}$ 2930 (sp$^3$ CH), 1634 (C=N), 1192 (C-N); m/z 287.2484 C$_{19}$H$_{31}$N$_{2}$ (cation) requires 287.2487.

4.3.6 Experimental data for section 3.4

General method for Suzuki cross-coupling reaction:

1,4-Dioxane (3 mL), 4-chlorotoluene (1.0 mmol), phenylboronic acid (1.5 mmol) were added in turn to a Schlenk flask charged with Pd$_2$(dba)$_3$ (0.015 mmol), Ligand L (0.03 mmol), caesium carbonate (2.0 mmol) and a magnetic stirring bar. The Schlenk flask was placed in a 80 °C oil bath and stirred for 3 hours. The mixture was allowed to cool to room temperature and filtered through celite to give a residue which was purified by column chromatography (light petroleum) to give a colourless solid, m.p. 46 °C (lit.,$^{48}$ 44-47 °C); $\delta$H 2.38 (3H, s, CH$_3$, H-1), 7.23 (2H, d, J 8, ArH, H-3,3’), 7.28-7.32 (1H, m, ArH, H-9), 7.38-7.42 (2H, m, ArH, H-8,8’), 7.46-7.49 (2H, m, ArH, H-4,4’), 7.55-7.58 (2H, m, ArH, H-7,7’); $\delta$C 21.08 (CH$_3$, C-1), 127.0 (CH Ar, C-4,4’), 127.2 (CH Ar, C-7,7’), 128.7 (CH Ar, C-8,8’), 129.5 (CH Ar, C-3,3’), 137.0 (C$_{quat}$. Ar, C-5), 138.4 (C$_{quat}$. Ar, C-6), 141.2 (C$_{quat}$. Ar, C-2); m/z 168.0938 C$_{13}$H$_{12}$ requires 168.0939.
Chapter 5: Appendixes

The crystallographic data for the structures presented in the text are given in this section. Crystallographic analyses were carried out at Loughborough University by Dr M. R. J. Elsegood (N-[2-(phenyloxy)ethyl]formamide 8) Professor V. McKee (meso-6,6’-dimethyl-2,2’-bipiperidine 40, meso-1,1’-dimethyl-1,2,3,4,1’,2’,3’,4’-octahydro-2,2’-biquinoline 65, meso-imidazolium salt 73).

Appendix 1: N-[2-(phenyloxy)ethyl]formamide 8
Table 1. Crystal data and structure refinement for N-[2-(phenyloxy)ethyl]formamide 8.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical formula</td>
<td>C₉H₁₁NO₂</td>
</tr>
<tr>
<td>Formula weight</td>
<td>165.19</td>
</tr>
<tr>
<td>Temperature</td>
<td>150(2) K</td>
</tr>
<tr>
<td>Radiation, wavelength</td>
<td>MoKα, 0.71073 Å</td>
</tr>
<tr>
<td>Crystal system, space group</td>
<td>monoclinic, P2₁/c</td>
</tr>
<tr>
<td>Unit cell parameters</td>
<td>a = 17.53(3) Å, b = 5.6775(9) Å, c = 8.8852(13) Å</td>
</tr>
<tr>
<td>Cell volume</td>
<td>878.7(2) Å³</td>
</tr>
<tr>
<td>Z</td>
<td>4</td>
</tr>
<tr>
<td>Calculated density</td>
<td>1.249 g/cm³</td>
</tr>
<tr>
<td>Absorption coefficient μ</td>
<td>0.089 mm⁻¹</td>
</tr>
<tr>
<td>F(000)</td>
<td>352</td>
</tr>
<tr>
<td>Crystal colour and size</td>
<td>orange, 0.50 × 0.29 × 0.09 mm³</td>
</tr>
<tr>
<td>Reflections for cell refinement</td>
<td>3191 (θ range 2.34 to 28.11°)</td>
</tr>
<tr>
<td>Data collection method</td>
<td>Bruker SMART 1000 CCD diffractometer</td>
</tr>
<tr>
<td>ω rotation with narrow frames</td>
<td></td>
</tr>
<tr>
<td>θ range for data collection</td>
<td>2.34 to 28.89°</td>
</tr>
<tr>
<td>Index ranges</td>
<td>h -23 to 22, k -7 to 7, l -11 to 11</td>
</tr>
<tr>
<td>Completeness to θ = 26.00°</td>
<td>99.9 %</td>
</tr>
<tr>
<td>Intensity decay</td>
<td>0%</td>
</tr>
<tr>
<td>Reflections collected</td>
<td>7375</td>
</tr>
<tr>
<td>Independent reflections</td>
<td>2120 (R_{int} = 0.0181)</td>
</tr>
</tbody>
</table>
Reflections with $F^2 > 2\sigma$  \hspace{1cm} 1646
Absorption correction  \hspace{1cm} semi-empirical from equivalents
Min. and max. transmission  \hspace{1cm} 0.957 and 0.992
Structure solution  \hspace{1cm} direct methods
Refinement method  \hspace{1cm} Full-matrix least-squares on $F^2$
Weighting parameters a, b  \hspace{1cm} 0.0390, 0.2228
Data / restraints / parameters  \hspace{1cm} 2120 / 0 / 109
Final R indices [$F^2 > 2\sigma$]  \hspace{1cm} $R_1 = 0.0362$, $wR_2 = 0.0875$
R indices (all data)  \hspace{1cm} $R_1 = 0.0499$, $wR_2 = 0.0967$
Goodness-of-fit on $F^2$  \hspace{1cm} 1.024
Largest and mean shift/su  \hspace{1cm} 0.001 and 0.000
Largest diff. peak and hole  \hspace{1cm} 0.174 and $-0.156$ e Å$^{-3}$

Table 2. Atomic coordinates and equivalent isotropic displacement parameters (Å$^2$) for N-[2-(phenyloxy)ethyl]formamide 8. $U_{eq}$ is defined as one third of the trace of the orthogonalized $U_{ij}$ tensor.

<table>
<thead>
<tr>
<th></th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>$U_{eq}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>O(1)</td>
<td>0.92226(6)</td>
<td>-0.07851(15)</td>
<td>0.16013(9)</td>
<td>0.0466(3)</td>
</tr>
<tr>
<td>C(2)</td>
<td>0.92144(6)</td>
<td>-0.1932(2)</td>
<td>0.27731(12)</td>
<td>0.0317(2)</td>
</tr>
<tr>
<td>N(3)</td>
<td>0.90815(6)</td>
<td>-0.10719(17)</td>
<td>0.40963(10)</td>
<td>0.0348(2)</td>
</tr>
<tr>
<td>C(4)</td>
<td>0.89221(7)</td>
<td>0.1407(2)</td>
<td>0.43480(14)</td>
<td>0.0389(3)</td>
</tr>
<tr>
<td>C(5)</td>
<td>0.80976(7)</td>
<td>0.1847(2)</td>
<td>0.45854(13)</td>
<td>0.0371(3)</td>
</tr>
<tr>
<td>O(6)</td>
<td>0.79384(5)</td>
<td>0.04328(16)</td>
<td>0.58501(9)</td>
<td>0.0398(2)</td>
</tr>
<tr>
<td>C(7)</td>
<td>0.71900(7)</td>
<td>0.0321(2)</td>
<td>0.61710(13)</td>
<td>0.0344(3)</td>
</tr>
<tr>
<td>C(8)</td>
<td>0.70298(7)</td>
<td>-0.1413(2)</td>
<td>0.71907(14)</td>
<td>0.0411(3)</td>
</tr>
<tr>
<td>C(9)</td>
<td>0.62924(8)</td>
<td>-0.1648(2)</td>
<td>0.75925(16)</td>
<td>0.0482(3)</td>
</tr>
<tr>
<td>C(10)</td>
<td>0.57126(8)</td>
<td>-0.0158(3)</td>
<td>0.69797(17)</td>
<td>0.0510(4)</td>
</tr>
<tr>
<td>C(11)</td>
<td>0.58767(8)</td>
<td>0.1563(3)</td>
<td>0.59711(16)</td>
<td>0.0496(3)</td>
</tr>
<tr>
<td>C(12)</td>
<td>0.66121(7)</td>
<td>0.1831(2)</td>
<td>0.55555(14)</td>
<td>0.0413(3)</td>
</tr>
</tbody>
</table>
Table 3. Bond lengths [Å] and angles [°].

<table>
<thead>
<tr>
<th>Bond</th>
<th>Length [Å]</th>
<th>Bond</th>
<th>Length [Å]</th>
</tr>
</thead>
<tbody>
<tr>
<td>O(1)–C(2)</td>
<td>1.2294(13)</td>
<td>C(2)–N(3)</td>
<td>1.3180(14)</td>
</tr>
<tr>
<td>N(3)–C(4)</td>
<td>1.4571(15)</td>
<td>C(4)–C(5)</td>
<td>1.5051(17)</td>
</tr>
<tr>
<td>C(5)–O(6)</td>
<td>1.4339(14)</td>
<td>O(6)–C(7)</td>
<td>1.3755(14)</td>
</tr>
<tr>
<td>C(7)–C(8)</td>
<td>1.3881(17)</td>
<td>C(7)–C(12)</td>
<td>1.3908(16)</td>
</tr>
<tr>
<td>C(8)–C(9)</td>
<td>1.3860(18)</td>
<td>C(9)–C(10)</td>
<td>1.386(2)</td>
</tr>
<tr>
<td>C(10)–C(11)</td>
<td>1.378(2)</td>
<td>C(11)–C(12)</td>
<td>1.3892(18)</td>
</tr>
<tr>
<td>O(1)–C(2)–N(3)</td>
<td>125.41(11)</td>
<td>C(2)–N(3)–C(4)</td>
<td>123.44(10)</td>
</tr>
<tr>
<td>N(3)–C(4)–C(5)</td>
<td>112.69(10)</td>
<td>O(6)–C(5)–C(4)</td>
<td>106.99(9)</td>
</tr>
<tr>
<td>C(7)–O(6)–C(5)</td>
<td>117.59(9)</td>
<td>O(6)–C(7)–C(8)</td>
<td>115.87(10)</td>
</tr>
<tr>
<td>O(6)–C(7)–C(12)</td>
<td>124.04(11)</td>
<td>C(8)–C(7)–C(12)</td>
<td>120.09(11)</td>
</tr>
<tr>
<td>C(9)–C(8)–C(7)</td>
<td>120.01(12)</td>
<td>C(10)–C(9)–C(8)</td>
<td>120.27(13)</td>
</tr>
<tr>
<td>C(11)–C(10)–C(9)</td>
<td>119.38(13)</td>
<td>C(10)–C(11)–C(12)</td>
<td>121.26(12)</td>
</tr>
<tr>
<td>C(11)–C(12)–C(7)</td>
<td>119.00(12)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4. Anisotropic displacement parameters (Å²). The anisotropic displacement factor exponent takes the form: $\frac{-2\pi^2}{h^2a^*2U^{11} + ... + 2hka*b*U^{12}}$

<table>
<thead>
<tr>
<th></th>
<th>U^{11}</th>
<th>U^{22}</th>
<th>U^{33}</th>
<th>U^{23}</th>
<th>U^{13}</th>
<th>U^{12}</th>
</tr>
</thead>
<tbody>
<tr>
<td>O(1)</td>
<td>0.0800(7)</td>
<td>0.0334(4)</td>
<td>0.0283(4)</td>
<td>0.0017(3)</td>
<td>0.0144(4)</td>
<td>-0.0036(4)</td>
</tr>
<tr>
<td>C(2)</td>
<td>0.0371(6)</td>
<td>0.0279(5)</td>
<td>0.0306(5)</td>
<td>-0.0005(4)</td>
<td>0.0059(4)</td>
<td>-0.0013(4)</td>
</tr>
<tr>
<td>N(3)</td>
<td>0.0477(6)</td>
<td>0.0316(5)</td>
<td>0.0254(5)</td>
<td>0.0017(4)</td>
<td>0.0062(4)</td>
<td>-0.0021(4)</td>
</tr>
<tr>
<td>C(4)</td>
<td>0.0491(7)</td>
<td>0.0328(6)</td>
<td>0.0361(6)</td>
<td>-0.0073(5)</td>
<td>0.0106(5)</td>
<td>-0.0065(5)</td>
</tr>
<tr>
<td>C(5)</td>
<td>0.0457(7)</td>
<td>0.0335(6)</td>
<td>0.0316(6)</td>
<td>-0.0001(5)</td>
<td>0.0030(5)</td>
<td>-0.0014(5)</td>
</tr>
<tr>
<td>O(6)</td>
<td>0.0341(4)</td>
<td>0.0494(5)</td>
<td>0.0358(4)</td>
<td>0.0083(4)</td>
<td>0.0032(3)</td>
<td>0.0039(4)</td>
</tr>
<tr>
<td>C(7)</td>
<td>0.0338(6)</td>
<td>0.0352(6)</td>
<td>0.0334(6)</td>
<td>-0.0036(5)</td>
<td>-0.0004(4)</td>
<td>0.0000(5)</td>
</tr>
<tr>
<td>C(8)</td>
<td>0.0378(6)</td>
<td>0.0382(6)</td>
<td>0.0462(7)</td>
<td>0.0040(5)</td>
<td>0.0004(5)</td>
<td>0.0023(5)</td>
</tr>
<tr>
<td>C(9)</td>
<td>0.0446(7)</td>
<td>0.0465(7)</td>
<td>0.0538(8)</td>
<td>0.0055(6)</td>
<td>0.0065(6)</td>
<td>-0.0060(6)</td>
</tr>
<tr>
<td>C(10)</td>
<td>0.0333(7)</td>
<td>0.0598(9)</td>
<td>0.0600(9)</td>
<td>-0.0026(7)</td>
<td>0.0054(6)</td>
<td>-0.0029(6)</td>
</tr>
<tr>
<td>C(11)</td>
<td>0.0390(7)</td>
<td>0.0531(8)</td>
<td>0.0551(8)</td>
<td>-0.0002(6)</td>
<td>-0.0014(6)</td>
<td>0.0102(6)</td>
</tr>
<tr>
<td>C(12)</td>
<td>0.0416(7)</td>
<td>0.0395(7)</td>
<td>0.0420(7)</td>
<td>0.0025(5)</td>
<td>0.0008(5)</td>
<td>0.0047(5)</td>
</tr>
</tbody>
</table>

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Table 5. Hydrogen coordinates and isotropic displacement parameters (Å²).

<table>
<thead>
<tr>
<th></th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>U</th>
</tr>
</thead>
<tbody>
<tr>
<td>H(2)</td>
<td>0.9312</td>
<td>-0.3574</td>
<td>0.2720</td>
<td>0.038</td>
</tr>
<tr>
<td>H(3)</td>
<td>0.9090</td>
<td>-0.2046</td>
<td>0.4868</td>
<td>0.042</td>
</tr>
<tr>
<td>H(4A)</td>
<td>0.9048</td>
<td>0.2331</td>
<td>0.3464</td>
<td>0.047</td>
</tr>
<tr>
<td>H(4B)</td>
<td>0.9258</td>
<td>0.1966</td>
<td>0.5248</td>
<td>0.047</td>
</tr>
<tr>
<td>H(5A)</td>
<td>0.8017</td>
<td>0.3534</td>
<td>0.4799</td>
<td>0.044</td>
</tr>
<tr>
<td>H(5B)</td>
<td>0.7754</td>
<td>0.1401</td>
<td>0.3668</td>
<td>0.044</td>
</tr>
<tr>
<td>H(8)</td>
<td>0.7426</td>
<td>-0.2438</td>
<td>0.7613</td>
<td>0.049</td>
</tr>
<tr>
<td>H(9)</td>
<td>0.6184</td>
<td>-0.2836</td>
<td>0.8291</td>
<td>0.058</td>
</tr>
<tr>
<td>H(10)</td>
<td>0.5207</td>
<td>-0.0321</td>
<td>0.7252</td>
<td>0.061</td>
</tr>
<tr>
<td>H(11)</td>
<td>0.5479</td>
<td>0.2585</td>
<td>0.5552</td>
<td>0.059</td>
</tr>
<tr>
<td>H(12)</td>
<td>0.6719</td>
<td>0.3027</td>
<td>0.4861</td>
<td>0.050</td>
</tr>
</tbody>
</table>

Table 6. Torsion angles [°].

<table>
<thead>
<tr>
<th>Bond</th>
<th>Torsion Angle</th>
</tr>
</thead>
<tbody>
<tr>
<td>O(1)–C(2)–N(3)–C(4)</td>
<td>0.10(18)</td>
</tr>
<tr>
<td>N(3)–C(4)–C(5)–O(6)</td>
<td>57.40(12)</td>
</tr>
<tr>
<td>C(5)–O(6)–C(7)–C(8)</td>
<td>167.40(10)</td>
</tr>
<tr>
<td>O(6)–C(7)–C(8)–C(9)</td>
<td>179.50(11)</td>
</tr>
<tr>
<td>C(7)–C(8)–C(9)–C(10)</td>
<td>0.0(2)</td>
</tr>
<tr>
<td>C(9)–C(10)–C(11)–C(12)</td>
<td>0.1(2)</td>
</tr>
<tr>
<td>O(6)–C(7)–C(12)–C(11)</td>
<td>-179.54(11)</td>
</tr>
</tbody>
</table>

Table 7. Hydrogen bonds [Å and °].

<table>
<thead>
<tr>
<th>Bond</th>
<th>D–H...A</th>
<th>d(D–H)</th>
<th>d(H...A)</th>
<th>d(D...A)</th>
<th>&lt;(DHA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N(3)–H(3)...O(1')</td>
<td>0.88</td>
<td>1.96</td>
<td>2.8416(13)</td>
<td>174.1</td>
<td></td>
</tr>
</tbody>
</table>

Symmetry operations for equivalent atoms

' x, -y-1/2, z+1/2
Appendix 2: meso-6,6'–dimethyl-2,2'-bipiperidine 40
Normal data collection parameters etc. – summarized in table 1.
All non-hydrogen atoms were refined with anisotropic atomic displacement factors and hydrogen atoms attached to carbon were inserted at calculated positions using a riding model. Hydrogen atoms bonded to O or N were located from difference maps and not further refined.
The asymmetric unit contains two independent molecules (differing by rotation around the C6-C7 bond) and two water molecules. Hydrogen-bonding between the water and the amine groups form 2D sheets perpendicular to the a direction – which is why the crystals are thin plates.

Table 1. Crystal data and structure refinement for meso-6,6'-dimethyl-2,2'-bipiperidine 40.

<table>
<thead>
<tr>
<th>Empirical formula</th>
<th>C_{12}H_{26}N_{2}O</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formula weight</td>
<td>214.35</td>
</tr>
<tr>
<td>Temperature</td>
<td>150(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Triclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P-1</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 9.5109(9) Å</td>
</tr>
<tr>
<td>89.136(2)°.</td>
<td>α =</td>
</tr>
<tr>
<td></td>
<td>b = 11.7548(11) Å</td>
</tr>
<tr>
<td>83.480(2)°.</td>
<td>β =</td>
</tr>
<tr>
<td>87.571(2)°.</td>
<td>γ =</td>
</tr>
<tr>
<td>Volume</td>
<td>1321.8(2) Å³</td>
</tr>
<tr>
<td>Z</td>
<td>4</td>
</tr>
<tr>
<td>Density (calculated)</td>
<td>1.077 Mg/m³</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>0.068 mm⁻¹</td>
</tr>
<tr>
<td>F(000)</td>
<td>480</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.51 x 0.40 x 0.18 mm³</td>
</tr>
<tr>
<td>Theta range for data collection</td>
<td>1.72 to 25.00°</td>
</tr>
<tr>
<td>Index ranges</td>
<td>-11 &lt; =h&lt; =11, -13 &lt; =k&lt; =13, -</td>
</tr>
<tr>
<td>14 &lt; =l&lt; =14</td>
<td>Reflections collected</td>
</tr>
<tr>
<td>Independent reflections</td>
<td>4618 [R(int) = 0.0136]</td>
</tr>
<tr>
<td>Completeness to theta = 25.00°</td>
<td>99.4 %</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>Multiscan</td>
</tr>
<tr>
<td>Max. and min. transmission</td>
<td>1.00000 and 0.944521</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F²</td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
<td>4618 / 0 / 271</td>
</tr>
</tbody>
</table>
Goodness-of-fit on $F^2$

Final $R$ indices [$I > 2\sigma(I)$]

$R$ indices (all data)

Largest diff. peak and hole

1.047

$R_1 = 0.0393$, $wR_2 = 0.0992$

$R_1 = 0.0513$, $wR_2 = 0.1070$

0.256 and -0.163 eÅ$^{-3}$
Table 2. Atomic coordinates and equivalent isotropic displacement parameters (Å² x 10³) for meso-6,6'-dimethyl-2,2'-bipiperidine 40. Ueq is defined as one third of the trace of the orthogonalized $U_{ij}$ tensor.

<table>
<thead>
<tr>
<th></th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>Ueq</th>
</tr>
</thead>
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Table 6. Torsion angles [°].

C(6A)-N(1A)-C(2A)-C(1A) = -177.48(11)
C(6A)-N(1A)-C(2A)-C(3A) = 60.45(14)
N(1A)-C(2A)-C(3A)-C(4A) = -54.80(16)
C(1A)-C(2A)-C(3A)-C(4A) = -175.94(13)
C(2A)-C(3A)-C(4A)-C(5A) = 53.47(18)
C(3A)-C(4A)-C(5A)-C(6A) = -54.66(18)
C(2A)-N(1A)-C(6A)-C(5A) = -61.55(14)
C(2A)-N(1A)-C(6A)-C(7A) = 173.92(10)
C(4A)-C(5A)-C(6A)-N(1A) = 57.09(15)
C(4A)-C(5A)-C(6A)-C(7A) = 178.53(12)
N(1A)-C(6A)-C(7A)-N(2A) = 164.61(10)
C(5A)-C(6A)-C(7A)-N(2A) = 43.68(15)
N(1A)-C(6A)-C(7A)-C(8A) = -74.59(13)
C(5A)-C(6A)-C(7A)-C(8A) = 164.48(12)
N(2A)-C(7A)-C(8A)-C(9A) = -54.84(15)
C(6A)-C(7A)-C(8A)-C(9A) -176.67(11)
C(7A)-C(8A)-C(9A)-C(10A) 53.88(16)
C(8A)-C(9A)-C(10A)-C(11A) -54.81(16)
C(9A)-C(10A)-C(11A)-N(2A) 57.75(15)
C(9A)-C(10A)-C(11A)-C(12A) 178.64(12)
C(8A)-C(7A)-N(2A)-C(11A) 59.48(14)
C(6A)-C(7A)-N(2A)-C(11A) -177.70(10)
C(10A)-C(11A)-N(2A)-C(7A) -61.66(14)
C(12A)-C(11A)-N(2A)-C(7A) 175.33(12)
C(6B)-N(1B)-C(2B)-C(1B) -174.13(12)
C(6B)-N(1B)-C(2B)-C(3B) 62.89(13)
N(1B)-C(2B)-C(3B)-C(4B) -57.22(14)
C(1B)-C(2B)-C(3B)-C(4B) -178.26(12)
C(2B)-C(3B)-C(4B)-C(5B) 53.82(16)
C(3B)-C(4B)-C(5B)-C(6B) -53.95(16)
C(2B)-N(1B)-C(6B)-C(5B) -62.77(13)
C(2B)-N(1B)-C(6B)-C(7B) 171.99(10)
C(4B)-C(5B)-C(6B)-N(1B) 57.23(14)
C(4B)-C(5B)-C(6B)-C(7B) -178.33(11)
N(1B)-C(6B)-C(7B)-N(2B) -72.77(13)
N(1B)-C(6B)-C(7B)-C(8B) 164.72(11)
N(1B)-C(6B)-C(7B)-C(8B) 50.05(15)
C(5B)-C(6B)-C(7B)-C(8B) -72.46(14)
N(2B)-C(7B)-C(8B)-C(9B) -57.49(15)
C(6B)-C(7B)-C(8B)-C(9B) 178.78(11)
C(7B)-C(8B)-C(9B)-C(10B) 54.35(17)
C(8B)-C(9B)-C(10B)-C(11B) -53.48(17)
C(9B)-C(10B)-C(11B)-N(2B) 55.98(16)
C(9B)-C(10B)-C(11B)-C(12B) 177.89(13)
C(8B)-C(7B)-N(2B)-C(11B) 61.47(14)
C(6B)-C(7B)-N(2B)-C(11B) -172.34(10)
C(12B)-C(11B)-N(2B)-C(7B) 175.33(12)
C(10B)-C(11B)-N(2B)-C(7B) -60.89(14)
Table 7. Hydrogen bonds [Å and °].

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<th>D-H...A</th>
<th>d(D-H)</th>
<th>d(H...A)</th>
<th>d(D...A)</th>
<th>&lt;(DHA)</th>
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</thead>
<tbody>
<tr>
<td>N(1A)-H(1AN)...O(1W)#1</td>
<td>0.90</td>
<td>2.25</td>
<td>3.0888(14)</td>
<td>154.7</td>
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<tr>
<td>N(2B)-H(2BN)...O(2W)#2</td>
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<td>3.2003(16)</td>
<td>161.9</td>
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<tr>
<td>O(1W)-H(1WA)...N(1B)#3</td>
<td>0.90</td>
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<td>3.0089(15)</td>
<td>167.2</td>
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<tr>
<td>O(1W)-H(1WB)...N(1A)</td>
<td>0.92</td>
<td>1.97</td>
<td>2.8814(14)</td>
<td>170.2</td>
</tr>
<tr>
<td>O(2W)-H(2WA)...N(2A)</td>
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<td>2.08</td>
<td>2.9547(15)</td>
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<tr>
<td>O(2W)-H(2WB)...N(2B)</td>
<td>0.90</td>
<td>2.09</td>
<td>2.9314(15)</td>
<td>154.6</td>
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</tbody>
</table>

Symmetry transformations used to generate equivalent atoms:

#1 -x+1,-y+1,-z  #2 -x+1,-y,-z+1  #3 -x+1,-y+1,-z+1
Appendix 3: meso-1,1'-dimethyl-1,2,3,4,1',2',3',4'-octahydro-2,2'-biquinoline 65
Normal data collection etc.
Molecule is centrosymmetric. Some edge-to-face interactions in the packing.

Table 1. Crystal data and structure refinement for meso-1,1’-dimethyl-1,2,3,4,1’,2’,3’,4’-octahydro-2,2’-biquinoline 65.

<table>
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<th>Value</th>
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<td>Temperature</td>
<td>150(2) K</td>
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<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
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<tr>
<td>Crystal system</td>
<td>Monoclinic</td>
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<tr>
<td>Space group</td>
<td>P2(1)/n</td>
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<td>Unit cell dimensions</td>
<td></td>
</tr>
<tr>
<td>a</td>
<td>6.6923(7) Å</td>
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<tr>
<td>α</td>
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<tr>
<td>b</td>
<td>8.0736(8) Å</td>
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<tr>
<td>β</td>
<td>95.304(2)°</td>
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<tr>
<td>c</td>
<td>14.7877(15) Å</td>
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<tr>
<td>γ</td>
<td>90°</td>
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<td>Volume</td>
<td>795.57(14) Å</td>
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<tr>
<td>Z</td>
<td>2</td>
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<tr>
<td>Density (calculated)</td>
<td>1.221 Mg/m³</td>
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<tr>
<td>Absorption coefficient</td>
<td>0.071 mm⁻¹</td>
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<tr>
<td>F(000)</td>
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<tr>
<td>Crystal size</td>
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<tr>
<td>Crystal description</td>
<td>Colourless block</td>
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<tr>
<td>Theta range for data collection</td>
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<tr>
<td>Index ranges</td>
<td>-7&lt;=h&lt;=7, -9&lt;=k&lt;=9, -17&lt;=l&lt;=17</td>
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<td>Reflections collected</td>
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<td>Independent reflections</td>
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<td>Completeness to theta = 24.97°</td>
<td>99.9%</td>
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<tr>
<td>Absorption correction</td>
<td>Semi-empirical from equivalents</td>
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<tr>
<td>Max. and min. transmission</td>
<td>1.00000 and 0.838560</td>
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<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F²</td>
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<td>Data / restraints / parameters</td>
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<td>Goodness-of-fit on F²</td>
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<td>Final R indices [I&gt;2sigma(I)]</td>
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<td>R indices (all data)</td>
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<tr>
<td>Largest diff. peak and hole</td>
<td>0.336 and -0.275 e.Å⁻³</td>
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Table 2. Atomic coordinates ($x \times 10^4$) and equivalent isotropic displacement parameters ($\AA^2 \times 10^3$) for meso-1,1'-dimethyl-1,2,3,4,1',2',3',4'-octahydro-2,2'-biquinoline 65. U(eq) is defined as one third of the trace of the orthogonalized $U_{ij}$ tensor.

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Table 3. Bond lengths [Å] and angles [°].

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Table 4. Anisotropic displacement parameters ($\AA^2 \times 10^3$). The anisotropic displacement factor exponent takes the form: 

$$-2\pi^2[\ h^2 \ a^* a U_{11} + \ ... + 2h\ k\ a^* b^* U_{12} ]$$

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<th>$U_{33}$</th>
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Table 5. Hydrogen coordinates (x $10^4$) and isotropic displacement parameters ($\AA^2 x 10^{-3}$).

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Table 6. Torsion angles [°].

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<th>Torsion Angle</th>
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<tr>
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<td>-179.60(16)</td>
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<tr>
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<td>-56.80(19)</td>
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<td>68.1(2)</td>
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</table>

Symmetry transformations used to generate equivalent atoms: #1 -x,-y,-z+2
Appendix 4: meso-imidazolium salt 73
Table 1. Crystal data and structure refinement for meso-imidazolium salt 73.

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<td>Wavelength</td>
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<td>Space group</td>
<td>P2(1)2(1)2(1)</td>
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<tr>
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<tr>
<td></td>
<td>b = 10.3465(8) Å</td>
</tr>
<tr>
<td></td>
<td>c = 15.2951(11) Å</td>
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<tr>
<td></td>
<td>1475.78(19) Å</td>
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<tr>
<td>Density (calculated)</td>
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<tr>
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<td>Independent reflections</td>
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<td>Refinement method</td>
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</tr>
<tr>
<td>R indices (all data)</td>
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<td>Absolute structure parameter</td>
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<tr>
<td>Largest diff. peak and hole</td>
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Table 2. Atomic coordinates (x $10^4$) and equivalent isotropic displacement parameters (Å² $10^3$) for meso-imidazolium salt 73. U(eq) is defined as one third of the trace of the orthogonalized U_ij tensor.

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Table 3. Bond lengths [Å] and angles [°].

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Table 4. Anisotropic displacement parameters (Å² x 10³). The anisotropic displacement factor exponent takes the form: -2π²[\( h^2 a^* U_{11} + \ldots + 2hk a^* b^* U_{12} \)]

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<th>( U_{23} )</th>
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Table 5. Hydrogen coordinates ($x \times 10^4$) and isotropic displacement parameters ($\text{Å}^2 \times 10^3$).

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Table 6. Torsion angles [°].

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References


