Towards the Synthesis of Novel Chelates for Technetium-99m Imaging

By

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Declaration of Originality

The work reported in this thesis was completed between October 2009 and September 2013 at the Department of Chemistry, Imperial College London or GE Healthcare, Amersham. The work reported is entirely my own, unless otherwise stated through cited reference or acknowledgement and has never been previously submitted for a degree at this or any other university.

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Abstract

This thesis details the synthesis of tetradaentate ligand systems for use with technetium-99m with a focus on sulphur donors. The synthesis of a series of S₄ tetradaentate ligands is detailed (Chapter 3). The ligands with general formula Me₂PS(CH₂)ₓS(CH₂)ₓS(CH₂)ₓPSMe₂ where n = 2 – 4 (3.1 – 3.3). The ligands were reacted with technetium-99m, [ReO₂(py)₄]Cl and [ReOCl₃(PPh₃)₂] unfortunately evidence for complexation was not obtained. In order to gain an understanding of the coordination chemistry of the ligands 3.1 – 3.3 were successfully complexed to Cu(I), Ag(I) and Pd(II) centres, the compounds and structures are discussed in chapter 3.

The synthesis of ligands containing 1-methyl-2H-imidazole-2-thione units, which act as S donors is featured in chapter 4. Challenges met during the synthesis of the S₄ and N₂S₂ ligands are discussed. P₂S₂ (4.12 and 4.16) ligands were synthesised by the reaction of the imidazole unit with 1,3-propanebis(phenyldihydroxymethylphosphine) dichloride. This led to the subsequent synthesis of an analogous P₂O₂ (4.17) ligand using 1-ethyl-2H-imidazolin-2-one. The P₂S₂ and P₂O₂ chelates were reacted with PdCl₂ to produce Palladium(II) complexes. Reactions with [ReOCl₃(PPh₃)₂] were also completed and although pure samples were not isolated, there is evidence that [ReO₂L]⁺ complexes were synthesised.

The synthesis of a tetradaentate phosphine oxime (P₂N₂) ligand system is the focus of chapter 5. The synthetic challenges encountered during the proposed synthesis are detailed along with alternative synthetic routes. The synthesis of analogous P₂N₂ compounds is also reported. Whilst evidence for the target chelate (5.2) was obtained its synthesis could not be fully confirmed.
# Table of Contents

Declaration.................................................................................................................... 2

Abstract......................................................................................................................... 3

Acknowledgements........................................................................................................ 8

Abbreviations................................................................................................................. 9

1.0 Introduction............................................................................................................... 13
  1.1 Technetium............................................................................................................. 14
  1.2 Chemistry of Rhenium and Technetium................................................................. 16
    1.2.1 Binary Compounds......................................................................................... 17
    1.2.2 Oxidation States............................................................................................ 18
  1.3 Technetium Complexes......................................................................................... 20
    1.3.1 With Bidentate Ligands................................................................................ 20
    1.3.2 With Tridentate Ligands................................................................................ 22
    1.3.3 With Tetradeinate Ligands............................................................................. 24
    1.3.4 Organometallic Complexes............................................................................ 29
  1.4 Technetium-99m as an Imaging Agent................................................................. 33
    1.4.1 Production of Technetium-99m...................................................................... 34
    1.4.2 Imaging Technetium-99m............................................................................. 35
    1.4.3 Kit Formulations............................................................................................ 36
  1.5 The Place of Technetium-99m in Nuclear Imaging............................................ 39
  1.6 References............................................................................................................. 41

2.0 Thesis Justification and Rationale............................................................................ 45
  2.1 Challenges and Opportunities in \(^{99m}\text{Tc}\) Chemistry.................................. 46
  2.2 Project Aims and Objectives................................................................................ 46
  2.3 Relevant Literature............................................................................................... 50
    2.3.1 Thioether Bridged Systems with Tc(V) and Re(V)............................... 50
3.0 Synthesis and Characterisation of Tetradeutate Ligands Incorporating the Thiophosphoryl Donors

3.1 Chapter Aims and Overview
3.2 Introduction
3.3 Ligand Synthesis
3.4 Reaction with Technetium-99m and Rhenium
   3.4.1 Rhenium Complexes
   3.4.2 Technetium-99m Complexes
3.5 Metal Complexes
   3.5.1 Copper(I) Complexes
   3.5.2 Silver(I) Complexes
   3.5.3 Palladium(II) Complexes
   3.5.4 Comparison of X-ray Crystal Structures
   3.5.5 Can the Rhenium and Technetium-99m results be explained?
3.6 Conclusion
3.7 Experimental
   3.7.1 Synthesis of Starting Materials
   3.7.2 General Synthesis of 3.1 – 3.3
   3.7.3 General Reaction Conditions for the Synthesis of Re(V) Complexes
   3.7.4 General Reaction Conditions for the Synthesis of $^{99m}$Tc Complexes
   3.7.5 General Synthesis of 3.6 – 3.8
   3.7.6 General Synthesis of 3.9 – 3.11
   3.7.7 General Synthesis of 3.12 3.13
3.8 References

4.0 Towards the Synthesis of Tetradeutate Ligands Containing the Mercaptoimidazole Moiety

4.1 Chapter Aims and Overview
4.2 Introduction ........................................................................................................ 124

4.3 Synthesis of Compound 4.Y .............................................................................. 128
   4.3.1 Attempted Synthesis of 4.Y .......................................................................... 128
   4.3.2 Synthesis of 1-hydroxymethyl-2-methylimidazole-2-thione....................... 135
   4.3.3 Synthesis of 1-chloromethyl-3-methylimidazole-2-thione hydrochloride........ 138

4.4 Reactions Towards the Synthesis of 4.9 and 4.10 ........................................ 141
   4.4.1 Attempted Synthesis of 4.9 ........................................................................... 142
   4.4.2 Attempted Synthesis of 4.10 ...................................................................... 145

4.5 Synthesis of 4.12 and Analogous Ligands ......................................................... 147
   4.5.1 Synthesis of 1,3-bis(phenylbishydroxymethylphosphonium)propane dichloride..148
   4.5.2 Synthesis of Bisphosphine Bisimidazole Tetradentate Ligand Systems......... 150
   4.5.3 Complexation of 4.12, 4.16 and 4.17 with Palladium(II) .............. 156
   4.5.4 Complexation of 4.12, 4.16 and 4.17 with Rhenium(V) ... 158

4.6 Conclusion ........................................................................................................... 161

4.7 Experimental ...................................................................................................... 163
   4.7.1 Synthesis of Starting Materials ................................................................... 164
   4.7.2 Attempted Synthesis of 4.2 – 4.6 ................................................................. 165
   4.7.3 Synthesis of 4.7 – 4.9 .................................................................................. 166
   4.7.4 Synthesis of 4.11 – 4.18 .............................................................................. 169
   4.7.5 General Synthesis of 4.19 – 4.21 ................................................................. 172
   4.7.6 General Synthesis of 4.22 – 4.24 ................................................................. 173
   4.7.7 General Synthesis of 4.25 – 4.27 ................................................................. 175

4.8 References .......................................................................................................... 176

5.0 Synthesis of a Tetradentate Phosphine Oxime Ligand System............178

   5.1 Chapter Aims and Overview ........................................................................... 179
   5.2 Introduction ....................................................................................................... 180
   5.3 Investigation of Proposed Ligand System ....................................................... 182
      5.3.1 Reactions of 1,3-bis(phenylphosphino)propane with chloro-butane compounds ........................................................................................................ 185
5.3.2 Reaction of 1,3-bis(phenylphosphino)propane and 2-bromo-2-methylbutane

5.4 Attempted Synthesis of Tetradentate Phosphine Oxime Ligands

5.4.1 Reaction of 1-chloro-2-propanone oxime and 1,3-bis(phenylphosphino)propane

5.4.2 Reaction of 5.8 and 1,3-bis(phenylphosphino)propane

5.5 Towards the Synthesis of 5.2

5.5.1 Proposed Synthesis of 5.2

5.5.2 Attempted Oxidation of 5.2

5.6 Conclusion

5.7 Experimental

5.7.1 General Synthesis of Phosphine Compounds

5.7.2 Synthesis of Nitroso Compounds

5.8 References

6.0 Conclusions and Future Work

6.1 The synthesis of a ligand system containing the thiophosphoryl moiety

6.2 The synthesis of tetradentate ligands containing the mercaptoimidazole unit

6.3 Attempted synthesis of a tetradentate phosphine oxime ligand

6.4 References

7.0 Appendices

7.1 X-ray Crystal data for 3.2

7.2 X-ray Crystal data for 3.6

7.3 X-ray Crystal data for 3.8

7.4 X-ray Crystal data for 3.12

7.5 X-ray Crystal data for 3.13

7.6 X-ray Crystal data for 4.11
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Simon, how to thank you? I could say a lot or a little but maybe all that should be said is, the Kracken is dead, thank you for dealing with a monster. I love you.
Abbreviations

$^{11}\text{C}$ Carbon-11

$^{13}\text{C}\{^1\text{H}\}$ NMR Carbon-13 Proton Decoupled Nuclear Magnetic Resonance

$^{18}\text{F}$ Fluorine-18

$^{31}\text{P}\{^1\text{H}\}$ NMR Phosphorus-31 Proton Decoupled Nuclear Magnetic Resonance

5-HT1A 5-hydroxytryptamine1A

$^{64}\text{Cu}$ Copper-64

$^{68}\text{Ga}$ Gallium-68

$^{99m}\text{Tc}$ Technetium-99m

$^\circ\text{C}$ Degrees Celsius

$\alpha$ alpha Radiation

$\beta$ beta Radiation

$\gamma$ gamma Radiation

$\delta$ Chemical Shift

$d$ Deuterium

$n$ Neutron

$p$ Proton

$a$ annum

acac Acetylacetone

BBB Blood Brain Barrier

bdt 1,2-Benzenedithiol

Bu Butyl

$t^{\text{Bu}}$ Tere-butyl

Bz Benzyl

$\text{CDCl}_3$ Deuterated Chloroform

COD Cyclooctadiene

COE Cyclooctene

Cp Cyclopentadienyl

d Doublet
DBU  1,8-diazabicyclo[5.4.0]undec-7-ene
DCM  Dichloromethane
DMSO Dimethylsulfoxide
dppe 1,3-bis(diphenylphosphino)ethane
dppp 1,3-bis(diphenylphosphino)propane
ECD  Ethylene dicysteinediester
Et  Ethyl
EtOAc  Ethyl acetate
EtOH  Ethanol
ES MS  Electrospray Mass Spectrometry
HMPAO  Hexamethylpropyleneamineoxime
HPLC  High Performance Liquid Chromatography
Hz  Hertz
J  Coupling Constant
Lipp  Dilithium 1,3-bis(phenylphosphino)propane
LSIMS  Liquid Secondary Ion Mass Spectrometry
m  Multiplet
m  Meta
MALDI  Matrix Assisted Laser Desorption Ionisation
Me  Methyl
MeCN  Acetonitrile
MEK  Methyleneethyketone
MeOH  Methanol
MDP  Methylenediphosphonate
mL  Millilitre
MMI  1-methyl-2H-imidazole-2-thione
mmol  Millimol
NCS  Isothiocyanate
NMR  Nuclear Magnetic Resonance
\( O \) Ortho
\( P \) Para
PET Positron Emission Tomography
Ph Phenyl
ppm Parts Per Million
PPh\(_3\) Triphenylphosphine
POPh\(_3\) Triphenylphosphine oxide
PMT Photon Multiplier Tube
PnAO Propylene Amine Oxime
PSMA Prostate Specific Membrane Antigen
py Pyridine
q Quartet
SPECT Single Photon Emission Computed Tomography
T Temperature
t Triplet
tacn 1,4,7-triazacyclononane
TEA Triethylamine
TLC Thin Layer Chromatography
TFA Trifluoroacetic Acid
THF Tetrahydrofuran
TOF Time of Flight
TPP Triphenylphosphonium
‘If we knew what we were doing, it would not be called research, would it?’

Albert Einstein
Chapter 1: Introduction
1.0 Introduction

This thesis describes the development of novel ligands for technetium-99m. The results section is separated into three chapters. Each one is reported in a dissertation format and contains a short introduction which details the pertinent literature and aims of that piece of work. The results are discussed along with a conclusion and the experimental details are reported at the end of each chapter. The final chapter of the thesis provides an overall project conclusion and discusses scope for future work.

The introduction compiled here gives a general overview of the literature of technetium including its discovery, fundamental and coordination chemistry. Nuclear imaging and important $^{99m}$Tc radiotracers are also discussed. The second chapter within this thesis outlines the objectives of the project and features some relevant literature.

1.1 Technetium

The early history of technetium is littered with false discovery claims. Throughout the 1800’s several reports of element 43 were published although all were disputed and none confirmed.$^1$ One of the more significant false claims came from Noddack et al.$^2$ who reported the discovery of masurium and rhenium. Masurium was thought to be element 43, however repeat investigation did not produce success, resulting in much scientific controversy.$^3,^4$ Whilst Noddack et al.$^5$ defended their work and produced rhenium in relatively large quantities, the claim for the discovery of element 43 was never verified.$^1$ Eventually the first man made element was detected in 1937 with the use of a cyclotron. Perrier and Segré irradiated molybdenum with deuterons resulting in radioactivity attributed to the technetium isotopes $^{97m}$Tc and $^{95m}$Tc.$^6$ Named after the Greek word τεχνητός meaning artificial, there are now many known isotopes of element 43, a selection of which are shown in Table 1-1.
All known isotopes of technetium are radioactive; $^{98}\text{Tc}$ has the longest half-life at 4.2 Ma and is used to explain the lack of primordial technetium in the Earth’s crust which was formed approximately 4.4 billion years ago.\textsuperscript{7} Non-primordial technetium has been observed, and $^{99}\text{Tc}$, which has a half-life of $2.13 \times 10^5$ years, is present in the Earth’s crust. This has been isolated from samples of pitchblende, and the presence of $^{99}\text{Tc}$ is due to the spontaneous fission of $^{238}\text{U}$.\textsuperscript{8} The source of $^{99}\text{Tc}$ was determined from the observed $^{99}\text{Tc}/^{238}\text{U}$ ratio being similar to that observed for the $^{99}\text{Mo}/^{238}\text{U}$ ratio. Table 1-1 shows some technetium isotopes, how they are produced, their half-lives and type of decay.

Technetium-99 is a weak $\beta^-$ emitter, the only one to be obtained in gram quantities, and it is isolated from spent nuclear fuel.\textsuperscript{9} During the fission of $^{235}\text{U}$ several different technetium isotopes are thought to be produced however, those with short half-lives decay before waste separation begins. Of the longer lived isotopes ($^{97}\text{Tc}$, $^{98}\text{Tc}$ and $^{99}\text{Tc}$) it is technetium-99 which is principally isolated. This is due to the high fission yield of $^{99}\text{Tc}$ (6.13 atom %) when compared to $^{97}\text{Tc}$ and $^{98}\text{Tc}$ (8.7 $10^{-7}$ atom %).\textsuperscript{9} Through the PUREX process it was the isolation of technetium-99 in gram quantities that allowed for the chemistry of the transition metal to be studied.
Chapter 1

1.2 Chemistry of Technetium and Rhenium

Technetium is a transition metal belonging to group 7, its properties are closer to those of rhenium than manganese and this is due to the lanthanide contraction. Tc and Re have similar atomic radii (136 pm and 137 pm respectively) whilst manganese is smaller at 127 pm. It is important to compare and contrast the chemistry of rhenium and technetium as many researchers use ‘cold’ rhenium to synthesise, manipulate and characterise complexes before producing similar complexes with radioactive technetium.
1.2.1 Binary Compounds

When both metals are fully oxidised as $M^{7+}$ they form heptaoxides ($M_2O_7$). These oxides are water soluble and dissolve to give perrhenic and pertechnic acids. The two oxides are structurally different, where rhenium heptaoxide is a polymeric layered structure with half the Re atoms tetrahedrally coordinated and the other half in an octahedral geometry, whilst the technetium heptaoxide remains monomeric. It is interesting to note that when in the form of perrhenate ([ReO$_4$]$^-$), the compound does not exhibit any anti-corrosion properties, whereas the analogous Tc compound pertechnetate acts as an excellent inhibitor. It has been reported that carbon steel could be protected by TcO$_4^-$ at concentrations of 5 – 50 ppm$^{10}$ i.e. ten times less than that required for CrO$_4^{2-}$. The obvious drawback of using pertechnetate is the radioactivity of the isotope. This has meant its use as a corrosion inhibitor can only be considered for use in closed systems and it was proposed for use in steam generating nuclear reactors.

Both metals also form the dioxides MO$_2$ which have distorted rutile structures containing M-M bonds. Rhenium has a higher tendency to form M-M bonds than technetium. For this reason many rhenium oxides are reported which do not have fully characterised technetium analogues, for example ReO$_3$, Re$_2$O$_3$.xH$_2$O and Re$_2$O$_5$.\textsuperscript{11}

Like the heptaoxides, heptasulfides ($M_2S_7$) of both metals have been reported, which decompose to MS$_2$ when heated. Crystals of MSe$_2$ and MTe$_2$ have been formed by heating the elements in a quartz tube to $\sim$1000$^\circ$C.\textsuperscript{12} Many halide complexes have been reported for both metals including TcCl$_4$, TcF$_6$, Re$_3$I$_9$ and ReF$_7$. The rhenium heptafluoride is one of only two heptafluorides reported, the other being iodine heptafluoride.\textsuperscript{13}

Binary compounds with phosphides and arsenides are also of note. Whilst TcP$_4$, Tc$_2$P$_3$ and Tc$_3$As are shown to be isostructural to the analogous rhenium compounds, the structure of Tc$_3$P resembles MnP$_3$, CrP$_3$ and NiP$_3$.\textsuperscript{14,15} The basic chemistry presented here gives an idea of the
metal’s accessible oxidation states. It also shows that while many aspects of Tc and Re chemistry are similar there are differences between the two.

1.2.2 Oxidation states

Technetium has an electronic configuration of 1s\(^2\)2s\(^2\)2p\(^6\)3s\(^2\)3p\(^6\)3d\(^10\)4s\(^2\)4p\(^6\)4d\(^6\)5S\(^1\) and has oxidation states varying from +7 to -1 and coordination numbers of 4 to 9. Some examples of compounds in several of these oxidation states are detailed in this section.

The two lowest oxidation states (M(-I) and M(0)) of Tc and Re are mainly carbonyl complexes with the \(\pi\)-acceptor ligand stabilising the metal centre i.e \([\text{M(CO)}_5]^-\) where M = Mn, Tc and Re.\(^{14}\) One of the most relevant oxidation states of both technetium and rhenium within the nuclear imaging field is M(I). The \([\text{M(CO)}_3]^{+}\) core has been extensively investigated and this is discussed further in section 1.3.4. The most common geometry of the M(I) oxidation state is octahedral and a wide range of complexes with various donor groups including isonitrile,\(^{15}\) phosphine\(^{16}\) and nitrogen\(^{17}\) have been synthesised.

Compounds with oxidation states II, III and IV are all reported with mixed ligand systems. Whilst octahedral appears to be the most common geometry, others have been observed, including trigonal bipyramidal and trigonal prismatic. Table 1-2 shows a few examples of complexes with Tc(II), Tc(III) or Tc(IV) cores.
<table>
<thead>
<tr>
<th>Complex</th>
<th>Oxidation state</th>
<th>Coordination number</th>
<th>Geometry</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Tc(NCS)$_2$(dppe)$_2$]</td>
<td>II</td>
<td>6</td>
<td>Octahedral</td>
<td>Libson et al $^{18}$</td>
</tr>
<tr>
<td>[TcCl$_2$(py)$_4$]</td>
<td>II</td>
<td>6</td>
<td>Octahedral</td>
<td>Barrera et al $^{17}$</td>
</tr>
<tr>
<td>[Tc(acac)$_3$]</td>
<td>III</td>
<td>6</td>
<td>Octahedral</td>
<td>Hasimoto et al $^{19}$</td>
</tr>
<tr>
<td>[TcCl(Cp)$_2$]</td>
<td>III</td>
<td>-</td>
<td>-</td>
<td>Apostolidis et al $^{20}$</td>
</tr>
<tr>
<td>[TcCl(NNC$_6$H$_4$Cl)$_2$(PPh$_3$)$_2$]</td>
<td>III</td>
<td>5</td>
<td>Trigonal bipyramidal</td>
<td>Nicholson et al $^{21}$</td>
</tr>
<tr>
<td>[TcCl$_4$(PET)$_3$]</td>
<td>IV</td>
<td>6</td>
<td>Octahedral</td>
<td>Rochon et al $^{22}$</td>
</tr>
<tr>
<td>[Tc$_2$(bdt)$_4$]</td>
<td>IV</td>
<td>6</td>
<td>Trigonal prismatic</td>
<td>Colmanet et al $^{23}$</td>
</tr>
</tbody>
</table>

Table 1-2: Examples of Tc complexes in oxidation states II, III and IV, with the coordination number and geometry. Dppe = 1,2-bis(diphenylphosphino)ethane, py = pyridine, acac = acetylacetone, Cp = cyclopentadienyl, bdt = 1,2-benzenedithiol

Although a varied range of geometries, coordination numbers and donor atoms are observed very few radiotracers have been produced from these oxidation states. It is the M(V) core that is the most prevalent throughout technetium chemistry and is utilised in many of the radiotracers that are discussed further in section 1.3.

The M(V) oxidation state is important for both metals and both form several important cores; the oxo cores [MO]$^{3+}$, [MO$_2$]$^{2+}$ and the nitride core [MN]$^{2+}$, that tend to dictate the chemistry in this oxidation state. Complexes which contain the [MO]$^{3+}$ and [MN]$^{2+}$ cores usually have a square pyramidal geometry, whilst those with the [MO$_2$]$^{2+}$ core have octahedral geometry.

Complexes in the higher oxidation states VI and VII are generally stabilised by imido or nitrido groups which act as strong electron donors. There is very little chemistry known of Tc(VII) complexes with those reported being stabilised by the [TcO$_3$]$^{2+}$ core.$^{24,25}$ Na[TcO$_4$] is used as a Tc(VII) imaging agent and other compounds have been shown to act as oxidising agents but there is very little scope for use due to the radioactivity of the metal centre.$^{26}$ More compounds are observed for Tc(VI) with several di-techtanium species reported.$^{27,28}$
1.3 Technetium complexes

Whilst it has been highlighted that technetium forms a diverse range of compounds in a number of different oxidation states, the field of nuclear imaging is dominated by Tc complexes in the +5 and +1 oxidation state. In the Tc(V) state many of the complexes formed contain the \([\text{TcO}^3]\) core due to its stability and accessibility from the \(\text{TcO}_4^–\) parent compound. Compounds with the \([\text{TcO}]^{3+}\) or \([\text{TcN}]^{2+}\) cores tend to have a square pyramidal geometry with the oxygen or nitrogen atom at the apex. In some cases octahedral geometry has also been observed, usually with a halide occupying the position \(\text{trans}\) to the apex, octahedral geometry is observed in the \([\text{TcO}_2]^–\) core. Although the \([\text{TcO}]^{3+}\) core is prevalent in technetium-99m chemistry, there are many Tc complexes that do not contain these cores but are of significant interest. This section will discuss a range of technetium complexes, structures and chemistry. The structural information highlighted in the following sections has been obtained from studies using the longer lived technetium-99 isotope.

1.3.1 With bidentate ligands

In transition metal chemistry, bidentate ligands have played an important role in understanding the coordination chemistry of the transition metals. Many of these metal complexes have found applications in catalysis.\(^{29-31}\) During the 1980’s a number of technetium crystal structures were reported with a large variation of ligands. Many of these structures contain bidentate coordinating ligands with different combinations of donor atoms, some examples are shown in Figure 1-1. These examples all have an octahedral geometry with the complexes in Figure 1-1a\(^{32}\) and Figure 1-1b\(^{33}\) containing Tc(III) whilst Figure 1-1c\(^{34}\) shows the \([\text{TcO}]^{3+}\) with a coordinated chloride ion. The analogous rhenium complex to that shown in Figure 1-1c was also synthesised by Luo \textit{et al}\(^{34}\) using the starting material \([\text{ReOCl}_3(\text{PPh}_3)_2]\).
One of the most important technetium-99m complexes with a bidentate ligand is Myoview™ also known as $^{99m}$Tc-tetrofosmin (Figure 1-2). With the dioxo-core and two bidentate phosphine ligands the myocardial perfusion agent has an octahedral geometry and an overall +1 charge. Many myocardial imaging tracers are positively charged, as this increases the specificity of the pharmaceutical. This is caused by the biological tendency of cationic species, for example alkali metals and organics to concentrate within the walls of the heart.

These examples show the variety of donor atoms which can coordinate to technetium. This offers a way to control the properties of the ligand by changing the R groups of two or more heteroatoms. It also introduces further opportunities to link a biomolecule to the metal centre.

1.3.2 With tridentate ligands

Tridentate ligands coordinated to Tc have been used in the complexation of the Tc(CO)$_3$ core which is discussed further in section 1.3.4. There are also examples with the [TcO]$_3^{3+}$ and
[TcN]$^{2+}$ cores. In most cases an additional ligand is required to complete the coordination sphere of the metal centre, and when a mono-dentate ligand is used for this purpose it is known as a [3+1] system. Many complexes have been synthesised and characterised using this system (Figure 1-3).

Figure 1-3a shows a mixed NS donor ligand system combined with a monodentate thiol. The series of ligands published by Pirmettis et al.\textsuperscript{36} contained a range of substituents at the N position and made use of various monodentate thiols. During synthesis two isomers were produced, and depending on how the N donor coordinates, the substituents on the side arm are positioned in either a syn or anti-isomer with respect to the mono-oxo core. In the syn-isomer X-ray crystal structures show complexes to have a trigonal bipyramidal geometry, whilst the anti-isomers show the more common square based pyramidal geometry.

![Figure 1-3: Complexes with the [3+1] ligand system, a) published by Pirmettis et al., b) and c) complexes with biologically relevant mono-dentate ligands published by Fernandes et al.\textsuperscript{37,38}](image)

Figure 1-3b\textsuperscript{37} shows a complex where the monodentate thiol ligand contains a 5-HT$_{1A}$ (5-hydroxytryptamine$_{1A}$) receptor binding moiety. The 5-HT$_{1A}$ receptors are part of the serotonin receptors within the brain and a series of these complexes were synthesised using different binding ligands. Biodistribution studies however showed that none of the complexes produced
were capable of crossing the blood brain barrier, a vital quality for the imaging of serotonin receptors.

The structure of Figure 1-3c\textsuperscript{38} is one example of three compounds considered in biodistribution and stability studies for the labelling of peptides. Different dipeptides were coordinated to Re and Tc centres through the monodentate thiol. The dipeptides glycine-glycine, alanine-glycine and phenylalanine-glycine were tested and it transpired that they were susceptible to ligand exchange with biological compounds containing the thiol moiety. This is well documented\textsuperscript{39} for compounds of this type and has been the main challenge for researchers investigating the [3+1] system. In order to avoid this issue the [3+2] system (Figure 1-4) has been investigated where a bidentate ligand is utilized to fill the coordination sphere of the metal centre and enhance the chemical and biological stability of the resultant technetium complex. Figure 1-4a\textsuperscript{40} and Figure 1-4b\textsuperscript{41} show rhenium complexes with the [3+2] ligand system, where a variety of different donor atoms have been used. With rhenium in an octahedral geometry, the complexes are more stable to ligand exchange than those utilising the [3+1] system.

A recent paper published by Mathur et al\textsuperscript{42} reports the structure of a [TcN]\textsuperscript{2+} complex with a tri-dentate PNP ligand (Figure 1-4c). The coordination sphere is filled with a bidentate sanazole analogue for potential use in hypoxia imaging. Biological studies showed that the complex had a low uptake in tumour cells when compared to [\textsuperscript{18}F] fluromisonidazole\textsuperscript{43}, which is currently used in a clinical setting. It was postulated that the result was due to the fast clearance of the compound from the blood.
Figure 1-4: Complexes with the [3+2] ligand system a) published by Nock et al. 40, b) published by Bolzati et al. 41, c) published by Mathur et al. 42 and d) published by Braband et al. 44

Figure 1-4d 44 shows the reaction scheme for the synthesis of a hypoxia agent where \([\text{TcO}_3(\text{tacl})]^+\) (tacl is 1,4,7-triazacyclononane) is the starting material and the reaction proceeds by the cycloaddition of the corresponding alkene to two oxygen atoms. The reaction was shown to be versatile by the synthesis of complexes with other biologically relevant compounds coordinated including a glucose analogue. X-ray crystallography data shows the metal centre in a distorted octahedral geometry. This reaction route provides an interesting new route into the [3+2] ligand system with technetium-99m.

1.3.3 With tetradeutate ligands

The vast majority of technetium complexes reported make use of tetradeutate ligands, which typically tend to be coordinated to a \([\text{TcO}_3]^3+, [\text{TcN}]^{2+}\) or \([\text{TcO}_2]^+\) core with technetium in the +5 oxidation state. A large proportion of technetium(V) complexes were reported during the 1980’s and 1990’s and there are many well-known and exploited tetradeutate ligand motifs, several of which are used in a clinical environment. Ligand sets that have been investigated include \(\text{N}_4, 45 \text{N}_2\text{S}_2, 46 \text{N}_3\text{S}, 47 \text{N}_3\text{P}, 48 \text{S}_3\text{P} 49\). One of the main issues encountered with the \(\text{N}_4\text{S}_4\).
ligand sets is the formation of isomers which occurs upon complexation, potentially leading to compounds with different pharmacokinetic properties. Figure 1-5 shows two technetium species featuring the N₄ amine oxime ligands.

![Figure 1-5: Structures of a) Tc-PNAO (propylene amine oxime) published by Troutner et al. and b) Tc-HMPAO published by Neirinckx et al.](image)

A larger variety of amine oxime ligands have been developed and consequently there are many examples of these chelates with Tc(V) in the literature. The flexibility of the synthesis of these amine oxime ligands has meant that the properties of the resultant imaging agents can be finely tuned by derivatisation of the ligand framework. This was exemplified during the development of ⁹⁹ᵐTc-HMPAO (Figure 1-5b). Troutner et al. initially produced ⁹⁹ᵐTc-PnAO (Figure 1-5a) as a potential brain imaging agent. The complex was found to diffuse at a high rate across the blood brain barrier (BBB) in both directions. This somewhat limited the use of ⁹⁹ᵐTc-PnAO as a brain imaging agent, since the complex was not retained within the brain for a long enough period of time for an accurate image to be obtained. For a material to pass through the BBB it must be a non-ionised lipophilic compound.

A large series of complexes were then investigated with the aim of finding a more suitable brain imaging agent. Modification of the PnAO framework eventually led to the synthesis of ⁹⁹ᵐTc-d,l-hexamethylpropyleneamineoxime (HMPAO). It was postulated that upon passing through the BBB the ⁹⁹ᵐTc-HMPAO converts into a hydrophilic species and this resulted in
retention of the compound within the brain. It was also shown that the meso compound of $^{99m}$Tc-HMPAO undergoes the same transition but at a much slower rate. This complex can therefore diffuse out through the BBB and the images that are produced are not as clear.\textsuperscript{54}

Technetium complexes with amine oxime ligands are still under investigation\textsuperscript{55} with novel complexes even now, being synthesised.\textsuperscript{56} Different cores ([TcO$_2$]$^+$\textsuperscript{57}, [TcN]$^{2+}$\textsuperscript{58,59}) are also reported within this prolific ligand system. It is therefore of note that rhenium analogues have not been isolated or reported. Since many technetium compounds are reported alongside the rhenium analogues it could be assumed that unsuccessful attempts have been made to synthesise the rhenium compounds. So despite many similarities between the two metals there are also differences which should be considered.

Since the development of $^{99m}$Tc-HMPAO several other brain imaging agents have been investigated. One of these is $^{99m}$Tc-O-$\textit{l,l}$, ethylene dicysteinediester (ECD),\textsuperscript{60} illustrated in Figure 1-6a which has been used as a cerebral perfusion imaging agent. This complex was shown to be chemically stable and have a fast clearance rate. In the same way as $^{99m}$Tc-HMPAO, the compound converts to a polar species which cannot exit through the BBB. It is suggested that $^{99m}$Tc-$\textit{l,l}$-ECD is converted to a polar monoester-monoacid species that is retained by the brain. It was also observed that the enantiomer $^{99m}$Tc-$\textit{d,d}$-ECD was taken up by the brain but there was little retention; this infers that the transformation process is an enzyme mediated stereospecific reaction.\textsuperscript{61}
Figure 1-6: Structure of a) $^{99m}\text{Tc-}l,l-$ECD published by Leveille et al $^{60}$ and b) $[^{99m}\text{Tc-MAG3}]^{2+}$ published by Fritzberg et al $^{62}$

Figure 1-6b shows $[^{99m}\text{TcO(MAG}_3\text{)}]^2$ a renal imaging agent. $^{62}$ In this case the use of the N$_3$S ligand removes the production of different isomers resulting in the formation of one complex. There are many other complexes with this type of ligand that contain various donor atoms, backbones and substituents. The majority of which have square based pyramidal geometry with the $[\text{TcO}]^{3+}$ core. $^{63, 64}$

The incorporation of biomolecules into radiotracers is of great importance as the production of targeted imaging agents is the wider aim within the field. Figure 1-7 shows technetium complexes which have been designed to mimic spiperone using the integrated approach. This method replaces part of a high affinity receptor ligand by a metal chelate. The whole metal complex must imitate the high affinity receptor molecule, and generally this presents the need for synthetically challenging complexes.
Spiperone is an inhibitor for dopamine D2 receptors, and it was shown that the molecules (Figure 1-7b and Figure 1-7c) retained a high affinity for the receptors but membrane permeability became a problem resulting in low brain uptake. However, high uptake was observed in other receptor-rich organs suggesting that with further modification to increase brain uptake this molecule could be an interesting brain imaging agent.\textsuperscript{65-67} Figure 1-8a published by Kothari \textit{et al}.\textsuperscript{68} shows how biomolecules can be coordinated to the metal centre in another way. The N\textsubscript{2}P\textsubscript{2} bifunctional chelate complexed to the [TcO\textsubscript{2}]\textsuperscript{+} core contains a pendant arm with a COOH group available for conjugation to biologically relevant compounds.

Figure 1-8: a) a N\textsubscript{2}P\textsubscript{2}-BFCA published by Kothari \textit{et al}.\textsuperscript{68} and b) an alternative ligand complexed to the \[\text{Tc(CO)}_{3}\]\textsuperscript{+} core published by Kannan \textit{et al}.\textsuperscript{69}, M = Tc and Re

Figure 1-7: a) The structure of spiperone, b) \textsuperscript{99m}Tc-BUP-BAT and c) \textsuperscript{99m}Tc-BP-BAT both published by Samnick \textit{et al}.\textsuperscript{65}
The water soluble ligand (Figure 1-8a) was complexed to $^{99m}$Tc within 10 minutes at room temperature and was shown to be stable \textit{in vivo}. It is interesting that a ligand reported recently\textsuperscript{69} (Figure 1-8b) also contains a phosphine with pendant hydroxymethyl substituents, it is however complexed to the tricarbonyl core.

\textbf{1.3.4 Technetium(I) complexes}

In recent years technetium-99m in the +1 oxidation state has been come of great interest with the technetium tricarbonyl core extensively studied. However a good example of a $^{99m}$Tc(I) complex from the radio-pharmaceuticals field is Cardiolite® also known as Tc-sestamibi \textsuperscript{70} (Figure 1-9). Cardiolite® is a cationic species used for myocardial and tumour imaging. Other complexes with isonitrile ligands have been synthesised\textsuperscript{71} however, Tc-sestamibi remains the most well studied and the only clinically available isonitrile complex with technetium.

![Figure 1-9: Structure of Cardiolite® also known as Tc-sestamibi](image)

The $[\text{Tc(CO)}_3]^+$ also contains technetium-99m in the +1 oxidation state when the tricarbonyl core is capped by a tridentate ligand, the resulting octahedral complex can become very stable shielding the metal centre from oxidation and ligand exchange.\textsuperscript{72} The precursor $[\text{Tc(H}_2\text{O)}_3(\text{CO})_3]^+$ can be prepared using $\text{K}_2[\text{H}_3\text{BCO}_2]$ as the \textit{in situ} reducing agent and CO source.\textsuperscript{73} The use of $\text{K}_2[\text{H}_3\text{BCO}_2]$ led to the production of Tc-carbonyl pre-prepared kits, where the addition of pertechnetate to the freeze-dried reactants results in the synthesis of
[Tc(OH$_2$)$_3$(CO)$_3$]$^+$. This is subsequently reacted in a second step which exchanges the water molecules for the desired ligand.

The [Tc(CO)$_3$]$^+$ core has been thoroughly investigated over the last 15 years, and there are examples of both bidentate and tridentate ligands. When bidentate chelates are used a monodentate ligand is required to complete the co-ordination spheres e.g. H$_2$O, halide ions or small molecules have been employed for this reason. Figure 1-10a $^{74}$ shows a complex where a bromide ion fills the final co-ordination site of the metal centre. If base is utilized during the reaction synthesis, the ligand becomes tridentate with an oxygen donor replacing the bromide ion.

![Figure 1-10: Examples of M(CO)$_3$ core complexes with bidentate ligands where M = Re or Tc a) published by Makris et al $^{74}$, b) published by Barbazán et al $^{75}$, c) published by Kożmiński et al $^{76}$, and d) published by Zobi et al $^{77}$](image)

Figure 1-10b $^{75}$ is a second example of a halide ion used to fill the coordination sphere, whilst Figure 1-10c$^{76}$ employs a water molecule for this role. Figure 1-10d $^{77}$ shows an example of an amino acid and a nucleobase as the co-ordinating ligand for the [Re(CO)$_3$] core. Serine acts as
the bidentate chelate and guanine as the monodentate ligand with the aim of mimicking the total structure of guanosine.

![Diagram](image)

Figure 1-11: Complexes with tridentate ligands where M = Re or Tc a) published by Mylonas et al\textsuperscript{78}, b) published by Mundwiler et al\textsuperscript{79} and c) structures related by pH published by Bottorff et al\textsuperscript{80}

Figure 1-11 shows three examples of simple tridentate ligands complexed to the Re or Tc tricarbonyl core. Figure 1-11c\textsuperscript{80} is interesting as a change in the pH of the reaction solution results in internal ligand exchange between the carboxylate and triazole moieties. At acidic pH the carboxylic acid is protonated and the triazole is coordinated to the metal centre whilst at basic pH the carboxylate is deprotonated and coordinated to the metal centre. Each example in Figure 1-11 exhibits potential for further modification of the ligands with targeted biomolecules for the production radiotracers. This has already been extensively investigated with the \textit{fac}-[Tc(CO)\textsubscript{3}]\textsuperscript{+} core labelling biomolecules and two recent examples from the literature are shown in Figure 1-12.
Figure 1-12a shows a structure published by Moura et al.\textsuperscript{81} and is one in a series of tricarbonyl complexes linked to triphenylphosphonium (TPP). The use of TPP as a mitochondrial imaging agent is well documented,\textsuperscript{82,83} and the biological data reported showed the $^{99m}$Tc complexes to accrue in tumour cells. Uptake was observed throughout the different cell lines studied. Of the complexes studied Figure 1-12a presented high mitochondria affinity and was shown to preferentially accumulate in tumour mitochondria compared to normal cells.

Figure 1-12: Targeted tricarbonyl complexes where M = Re and Tc, a) mitochondria imaging agent published by Moura et al.\textsuperscript{81} and b) a complex targeted to PSMA (prostate specific membrane antigen) for imaging of prostate cancer published by Lu et al.\textsuperscript{84}

Figure 1-12b shows a complex published by Lu et al.\textsuperscript{84} which investigated the rhenium complexes for binding to PSMA (prostate specific membrane antigen) for the imaging of prostate cancer. The complexes were shown to have a moderate affinity to PSMA and the technetium analogues were isolated with a radiochemical purity of > 95%. Further in vivo studies of these complexes have not yet been completed.
Figure 1-13: Tropane analogues a) TRODAT-1 published by Kung et al \(^{50}\) and b) TROTEC-1 published by Hoepping et al \(^{85}\)

An interesting comparison of the \([\text{TcO}]^{2+}\) and \([\text{Tc(CO)}_3]^{+}\) cores can be made when considering tropane analogues which are used to target DAT, a dopamine transporter molecule. TRODAT-1 (Figure 1-13a) \(^{50}\) which has a \(\text{N}_2\text{S}_2\) ligand system, has been used for the study of dopamine transporter effects in depression, post-traumatic stress disorder and Parkinson’s disease. The equivalent complex using the tricarbonyl core is known as TROTEC-1. Both complexes present high affinities for the target molecule; however TROTEC has not been studied as extensively as TRODAT. The use of the \(\text{Tc}\)-tricarbonyl core has in recent years become an expanding field and at the moment a large proportion of technetium-99m research involves this motif.

1.4 Technetium-99m as an Imaging Agent

As mentioned previously the two most common technetium isotopes are \(^{99}\text{Tc}\) and the metastable nuclide \(^{99m}\text{Tc}\). In general, the ground state isotope is studied for structural analysis along with rhenium in order to define the \(^{99m}\text{Tc}\) complexes that are produced. Technetium-99m is widely used in nuclear imaging as a SPECT (single photon emission computed tomography) agent. This section provides an overview of the production of the technetium-99m radioisotope \(^{99}\text{Mo}\), examples of \(^{99m}\text{Tc}\) tracers which have been translated into the clinic and a summary of how images are acquired.
1.4.1 Production of Technetium-99m

Figure 1-14 shows a decay schematic for $^{99}$Mo which decays to $^{99m}$Tc by the emission of a $\beta^-$ particle, shown in transition 1 to 2. $^{99m}$Tc with a half-life of 6 hours decays to $^{99g}$Tc with the emission of a $\gamma$-ray at 140 keV, it is from the detection of this gamma ray that an image is produced. The ground state has a long half-life but as a weak $\beta^-$ emitter (present at the tracer level) poses no additional risk to the patient or surroundings. Technetium-99m is used in ~ 80 % of SPECT scans in the clinical environment.

Figure 1-15 shows a picture of a DRYTEC generator which is produced by GE Healthcare.

In the 1950’s, research at the Brookhaven National Laboratory USA led to the development of the $^{99}$Mo/$^{99m}$Tc generators. The parent isotope ($^{99}$Mo) obtained from the nuclear fission of $^{235}$U, is loaded onto an alumina column and as the isotope decays technetium-99m is eluted with a high radiochemical purity using saline solution as pertechnetate ($^{99m}$TcO$_4^-$). Figure 1-15 shows a picture of a DRYTEC generator which is produced by GE Healthcare.

34
generators are compact and easy to handle which is ideal for the clinical setting. In recent years, due to ageing nuclear reactors and unscheduled shutdowns, a worldwide molybdenum-99 shortage has occurred. Leading to the investigation of efficient routes of technetium-99m production from a cyclotron.\textsuperscript{88,89}

![Figure 1-15: Picture of a DRYTEC $^{99}$Mo/$^{99m}$Tc generator produced by GE Healthcare, taken from the GE Healthcare website $^{90}$](image)

### 1.4.2 Imaging Technetium-99m

There are two types of nuclear imaging technique PET (positron emission tomography) and SPECT (single photon emission computed tomography), the difference between the two techniques is the mode of isotope decay. In the case of PET, isotopes decay by the emission of a positron which then undergoes an annihilation reaction and from this two gamma rays are emitted, these are detected and an image is produced. SPECT isotopes decay by the emission of a single gamma ray in order to determine the location of the radiotracer, collimators are used to filter out a high number of the $\gamma$-rays emitted. Only those with certain incidence angles are detected and multiplied in the PMT (photon multiplier tube). For the production of 3D images, the gamma camera must be rotated around the patient increasing the scan times required. Figure 1-16 shows a schematic of how a SPECT image is acquired.
1.4.3 Kit formulations

In 1964 the first report of a brain scan with $^{99m}$TeO$_4^-$ was published.\cite{87} Since then several radiotracers have been approved for use in a clinical setting, some of which have been discussed in previous sections. The development of pre-formulated kits has ensured the ease of use in a clinical environment.

The ready-to-use kits usually contain the compounds required for complex synthesis, for example reducing agent, ligand and buffer. Normally packed and sealed under N$_2$, the kits are often stored at temperatures of between 2 – 8° to ensure a long shelf-life. Table 1-3 shows information regarding the kit formulation of six clinically approved radiopharmaceuticals. The structure of each complex is reported along with kit reactants, conditions for labelling, stability and purity. This information was obtained from the International Atomic Energy Agency technical report number 466.\cite{92} In some cases very few reagents are present in the kit (Tc-MDP
and Tc-HMPAO) with only the ligand, reducing agent and buffer present. It is interesting to note that Tc-HMPAO is only stable for 30 mins post labelling; and so this requires the patient to be scanned almost immediately post injection. The production of other complexes requires the use of a co-ligand, this is used to stabilise the $[\text{TcO}]^{3+}$ core upon reduction allowing time for the ligand to coordinate to the metal centre (Tc-MAG$_3$ and Tc-ECD). Co-ligands currently used include gluconate, tartrate and mannitol. MDP can also be used as a co-ligand and is present in some pre-formulated kits which are used for research purposes. It is notable that the thiol protected ligand Bz-MAG$_3$ is the reagent used for the synthesis of Tc-MAG$_3$. The thiol is deprotected under the reaction conditions resulting in the active ligand.

It is interesting to consider the radio-labelling conditions of Tc-Sestamibi which undergoes trans-metallation from the analogous copper(I) complex. The reagent tetrakis(2-methoxy-2-methylpropyl-1-isocyanide)copper(I) tetrafluoroborate is stable under the kit conditions. However upon the addition of $^{99m}$TcO$_4^-$, which is reduced to $^{99m}$Tc(I) using SnCl$_2$, the ligand coordinates to the radionuclide. Additional reactants may be added to formulations to improve the shelf life of kits used for radiolabelling. For example sulphosalicylate salt is present in the Tc-tetrofosmin kit to stabilise the phosphine, which is sensitive to oxidation. During radio-labelling the salt dissociates allowing tetrofosmin to complex the $[^{99m}\text{TcO}_2]^{3+}$ core.

In each case, it typically takes 20 minutes to complete labelling with a high radiochemical purity. The radio-labelling of these complexes requires very few manipulations, all of which can be carried out in a vial which is shielded using a small lead container. Generally in the kit formulation the ligand will be present in large excess and this can become unfavourable when a potentially expensive biomolecule is attached.
<table>
<thead>
<tr>
<th>Name</th>
<th>Structure</th>
<th>Kit contents</th>
<th>Amount of pertechnetate added</th>
<th>Labelling conditions</th>
<th>Stable for</th>
<th>Radiochemical purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{99m}$Tc-MDP</td>
<td><img src="image" alt="Structure" /></td>
<td>MDP 10 mg SnCl$_2$.2H$_2$O 1 mg Ascorbic acid 2 mg</td>
<td>4 ml TcO$_4^-$ in saline</td>
<td>Stir 1 min Use after 5 min</td>
<td>6 h</td>
<td>&gt;95 %</td>
</tr>
<tr>
<td>$^{99m}$Tc-MAG3</td>
<td><img src="image" alt="Structure" /></td>
<td>Bz-MAG$_3$ 1 mg Na$_2$glucoheptonate 20 mg Na$_2$tartrate 40 mg Lactose 20 mg SnCl$_2$.2H$_2$O 1 mg</td>
<td>3 ml TcO$_4^-$ in saline</td>
<td>Stir 1 min Stand 5 min Heat at 100°C 15 min</td>
<td>6 h</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>$^{99m}$Tc-ECD</td>
<td><img src="image" alt="Structure" /></td>
<td>A: ECD 1 mg SnCl$_2$.2H$_2$O 80μg Na$_2$EDTA 0.3mg Mannitol 20 mg B: 1ml 0.02M phosphate buffer pH 7.5 - 8</td>
<td>3 ml TcO$_4^-$ in saline</td>
<td>Stand 30 min</td>
<td>4 h</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>$^{99m}$Tc-HMPAO</td>
<td><img src="image" alt="Structure" /></td>
<td>d,l-HMPAO 1 mg SnCl$_2$.2H$_2$O 0.08 mg NaCl 40 mg</td>
<td>4 ml TcO$_4^-$ in saline</td>
<td>Stir 1 min</td>
<td>30 min</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>$^{99m}$Tc-Sestamibi</td>
<td><img src="image" alt="Structure" /></td>
<td>[Cu(CNCH$_2$CMe$_2$OCH$_3$)$_4$]$^+$ 1 mg SnCl$_2$.2H$_2$O 0.075 mg L-cysteine hydrochloride 1 mg NaCitrate 2.6 mg d-mannitol 20 mg</td>
<td>5 ml TcO$_4^-$ in saline</td>
<td>Stir 1 min Heat at 100°C 12 min</td>
<td>6 h</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>$^{99m}$Tc-tetrofosmin</td>
<td><img src="image" alt="Structure" /></td>
<td>Tetrofosmin sulphosalicylate 0.25 mg SnCl$_2$.2H$_2$O 50 μg Na d-gluconate 1 mg NaHCO$_3$ 1.8 mg</td>
<td>5 ml TcO$_4^-$ in saline</td>
<td>Mix well and use after 15 min</td>
<td>12 h</td>
<td>&gt;90%</td>
</tr>
</tbody>
</table>

Table 1-3: Kit formulation reactants and condition of use for six commercially available $^{99m}$Tc pharmaceuticals, information taken from IAEA report 466
1.5 The Place of Technetium-99m in Nuclear Imaging

As mentioned before there are two types of nuclear imaging i.e. PET and SPECT which are defined by the type of isotope used i.e. a positron or photon emitter. Table 1-4 compares some of the most commonly used isotopes within biomedical and molecular imaging.

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Decay type</th>
<th>Imaging type</th>
<th>Production</th>
<th>Half-life</th>
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<tbody>
<tr>
<td>$^{99m}$Tc</td>
<td>$\gamma$</td>
<td>SPECT</td>
<td>$^{99}$Mo/$^{99m}$Tc generator</td>
<td>6 h</td>
</tr>
<tr>
<td>$^{11}$C</td>
<td>$\beta^+$</td>
<td>PET</td>
<td>Cyclotron</td>
<td>20 h</td>
</tr>
<tr>
<td>$^{18}$F</td>
<td>$\beta^+$</td>
<td>PET</td>
<td>Cyclotron</td>
<td>110 min</td>
</tr>
<tr>
<td>$^{64}$Cu</td>
<td>$\beta^+$</td>
<td>PET</td>
<td>Cyclotron</td>
<td>12 h</td>
</tr>
<tr>
<td>$^{68}$Ga</td>
<td>$\beta^+$</td>
<td>PET</td>
<td>$^{68}$Ge/$^{68}$Ga generator</td>
<td>68 min</td>
</tr>
<tr>
<td>$^{123}$I</td>
<td>$\gamma$</td>
<td>SPECT</td>
<td>Cyclotron</td>
<td>13.2 h</td>
</tr>
<tr>
<td>$^{111}$In</td>
<td>$\gamma$</td>
<td>SPECT</td>
<td>Cyclotron</td>
<td>2.8 days</td>
</tr>
</tbody>
</table>

Table 1-4: Comparison of isotopes used for nuclear imaging, decay type, production and half-life are detailed

The main problem radiochemists face in this field is how to synthesise and purify a radio-tracer within the time constraints (governed by the isotopes’ half-life), that has high specificity for a target and can be cleared readily through the human system. This is made more complicated by the chemical composition of the isotope: carbon-11 is produced in the form of $^{11}$CO$_2$ which is then converted into the desired tracer. Recent developments in carbon-11 and fluorine-18 radio-chemistry have led to much interest in the field. These isotopes are also of interest as they are biologically compatible i.e. the addition of a CO, $[\text{CH}_3]^+$ or F$^-$ group to a known drug or targeting biomolecule would not be expected to alter the biology of the molecule significantly. Contrast this with the addition of a transition metal to a biomolecule and the situation becomes more problematic. This is one of the major difficulties within technetium-99m chemistry.

Figure 1-17 shows a graph which details the number of papers published between 1990 and 2012 for radioisotopes used within nuclear imaging. Five isotopes were considered, $^{99m}$Tc being the isotope this thesis is concerned with, $^{11}$C and $^{18}$F as they are biologically compatible
and two other transition metals $^{64}$Cu and $^{68}$Ga, which have been of interest recently. The search results were limited to include journal papers which were relevant to the imaging field.

![Graph showing the number of papers published between 1990 and 2012 for the radio nuclides $^{99m}$Tc, $^{18}$F, $^{11}$C, $^{64}$Cu, $^{68}$Ga. The search parameters were refined to only show papers relevant to the nuclear imaging field.](image)

In the last few years the number of papers concerning $^{64}$Cu, $^{68}$Ga and $^{11}$C has risen. Probably most strikingly though is the rise of papers published on $^{18}$F which since 2000 has seen a year on year increase in publications. With ‘bench’ top cyclotrons currently being engineered and increased academic and industrial attention on $^{11}$C and $^{18}$F the clinical use of radionuclides looks to be changing.

Currently however, technetium-99m is a key component within nuclear imaging as the ‘workhorse’ of the field, with the metal centre remaining a more available alternative to more bio-compatible PET agents. It is interesting that over the past 20 years the number of papers published regarding technetium-99m has stayed constant at around the 500 paper per year mark. Indicating the continued search for technetium-99m radiotracers remains ongoing.
1.6 References

90. www.gedrytec.com
Chapter 2: Thesis Justification and Rationale
2.0 Thesis Justification and Rationale

This chapter aims to give a more concise introduction to the work reported in this thesis. An outline of the major project objectives are presented, along with the relevant literature in order to contextualise the work.

2.1 Challenges and Opportunities in $^{99m}$Tc Chemistry

The importance of technetium-99m within the nuclear imaging field is clear (Figure 1-17) and the metal nuclide will continue to be used in a clinical environment for the foreseeable future. The development of novel chelates which can form stable $^{99m}$Tc complexes in a high radiochemical yield and at a range of conditions is one of the main challenges within the field. Ligands which can be radiolabelled at a range of pHs and temperatures would lead to a flexibility regarding the use of biomolecules which may require specific conditions.

The emphasis of this work was to address the challenges and opportunities identified here by developing chelates which could label technetium-99m efficiently over a wide range of conditions.

2.2 Project Aims and Objectives

Chapter 1 demonstrated the diversity of technetium chemistry and showed examples of the wide range of ligands which form stable metal complexes. The focus of this thesis was to develop and synthesise the tetradentate ligand systems for the formation of technetium complexes containing the $[\text{TcO}]^{3+}$, $[\text{TcO}_2]^+$ or $[\text{TcN}]^{2+}$ cores. Figure 2-1 is a schematic which illustrates the various ways the amine oxime chelate could be altered.
This is a joint project with GE Healthcare. Their recent focus has featured the use of biomolecules with amine oxime or tetra-amine ligands. The ligands were complexed to technetium-99m under slightly basic conditions (approximately pH 9.5), and a selection of the target biomolecules were shown to be sensitive at this pH. This led to the use of bisamine dithiol ligands which label at lower pH (between 4 – 7) however, the use of thiol donors added further complications during ligand synthesis. Notably the stability of the thiol may become an issue, as the formation of disulphide linkages can cause long term storage problems in terms of the kit formulation. Protecting groups have been used to solve this problem, for example in the case of MAG$_3$ the pre-formulated kit contains a ligand precursor (Bz-MAG$_3$) where the thiol group is protected by a benzyl moiety. Deprotection occurs under the reaction conditions and leads to the synthesis of the [TcMAG$_3$] complex.\textsuperscript{1,9} Whilst this solution is applicable in some cases, when biomolecules are introduced the deprotection step may have an adverse effect. As such, alternative sulphur donors were proposed and are investigated in this thesis and chelates with S$_4$, N$_2$S$_2$ and P$_2$S$_2$ being the main focus.
The reactivity of the thiol groups has also led to the use of protecting groups during synthesis i.e. S-benzyl-L-cysteine is reacted with 1,2-dichloroethane to afford the l-l-ECD derivative in Figure 2-2. The compound is then deprotected with liquid ammonia before esterification. The synthesis of the ligand in Figure 2-3c uses the trityl protecting group, and the compound was subsequently deprotected using TFA prior to complexation. Whilst the use of protecting groups allows for synthetic problems to be overcome, the deprotection step may cause complications if a biomolecule is tethered to the ligand.

As mentioned above the use of chelates containing thiol moieties are interesting due to the range of pHs labelling can occur at (pH 4 – 7) and the potential compatibility with a range of biomolecules, however the chemistry can be challenging. So it was proposed that alternative stable sulphur donors could lead to chelates with similar labelling properties to the bisamine dithiol ligands and be compatible with a large range of biomolecules. From this a major theme of this project arose, with a future objective of producing a chelate system which could be
linked to any required biomolecule, labelled at low concentration and under a range of conditions.

Modification of the amine oxime ligand to produce chelates which can label at a range of pHs is also proposed. The use of amine groups as the bridging donor atoms is well documented and as discussed in the introduction, several commercial imaging agents contain a diamine bridge including MAG3,\textsuperscript{1} ECD\textsuperscript{2} and HMPAO.\textsuperscript{3} Figure 2-3 shows three examples of technetium complexes where the diamine bridge has been used in combination with other nitrogen, sulfur and phosphine donors to produce tetra-dentate chelates. Whilst there are many instances of bridging amine groups, there are fewer examples of alternatives. Consequently a project aim was formed and it was considered interesting to investigate different moieties i.e. thioether and phosphine groups, with the aim of producing ligands which could label technetium-99m at a wide range of pHs. A comparison with the analogous diamine chelate could then be made. The use of thioether and phosphine bridging groups is a common theme throughout this thesis. For this reason, the current literature pertaining to thioether and phosphine-bridged tetra-dentate ligands for technetium-99m is detailed in the following section.

The use of mixed donor ligands with technetium-99m is well-established, with several reported complexes containing N\textsubscript{x},S\textsubscript{4-x} ligands.\textsuperscript{7,8} The combination of nitrogen and sulfur donors and in particular, thiol groups has led to the synthesis of a wide range of technetium complexes including the commercially used \textsuperscript{99m}Tc-\textsuperscript{l-l-ECD} and \textsuperscript{[99mTcO(MAG\textsubscript{3})]}\textsuperscript{2} which were discussed in Chapter 1.\textsuperscript{1,2}

The two main aims of thesis can be defined as:

- An investigation of different bridging donor atoms for technetium-99m. Producing tetra-dentate chelates with thioether and phosphine bridges for comparison with the analogous amine compounds.
• A search for a stable sulphur donor. Identifying suitable sulphur donor moieties and incorporating those into a tetra-dentate ligand system for use with technetium-99m.

2.3 Relevant Literature

This section details the pertinent literature regarding thioether- and phosphine-bridged systems with technetium-99m and rhenium. Section 2.3.2 also features the kit formulation of Myoview™, the bi-dentate phosphine ligand is discussed as a precedent for the use of air-sensitive ligands with technetium-99m.

2.3.1 Thioether-bridged systems with Tc(V) or Re(V)

The literature contains examples of rhenium(V) and technetium(V) complexes with thioether ligands, a selection of which are featured here. Reisgys et al 11 report the synthesis of [ReOCl₃L] complexes where L = RS(CH₂)₂SR and R = Et, Bu, CH₂Ph (Figure 2-4). In these complexes the metal centre is present as the [ReO]³⁺ core with rhenium in the +5 oxidation state. Similar ligands have also been complexed to the rhenium tricarbonyl core. 12

Figure 2-4: A series of [ReOCl₃L] complexes with thioether ligands published by Reisgys et al 11

Figure 2-5 shows three examples of mixed donor ligand systems containing the thioether moiety. 13-15 The soft thioether is combined with strong σ-donors such as amines and phosphines. Figure 2-5a shows a tetra-dentate ligand which has been bound to the rhenium and technetium-99m mono oxo cores [MO]³⁺, and reported in yields of 60-65 % for the rhenium complexes. 14 Upon complexation to the metal cores the amine groups deprotonate to give the ligand a -2 charge. The remaining charge from the metal centre is balanced by a coordinated chloride ion giving the complex an octahedral geometry.
Figure 2-5: Examples of Tc$^{99m}$ complexes with thioether ligands: a) published by Dhara et al$^{14}$ where $n = 0$ and 1, b) published by Smith et al$^{13}$ where $n = 1$ and 2 and, c) published by Tisato et al$^{16}$

Figure 2-5b shows another tetra-dentate ligand system which has been complexed to the rhenium di-oxo core. The analogous technetium-99m complexes have been thoroughly investigated for use as biologically targeted nuclear imaging agents.$^{13,17,18}$ This system has also been adapted by the addition of only one phosphine arm to the dithiol precursor, providing a tridentate ligand which is also compatible with rhenium and technetium tricarbonyl cores.$^{19}$

Figure 2-5c is a [TcN]$^{2+}$ complex with a PSP ligand which was used to investigate the stereochemistry of the complex.

Although the soft thioether moiety may not provide ideal σ-donors for ‘hard’ rhenium(V) and technetium-99m(V) centres, there is literature evidence of complexes containing the moiety. It appears that the right combination of donor groups can produce an appropriate ligand system for technetium-99m. The next section discusses the use of phosphine ligands with Tc(V) and Re(V) along with the protocol used to produce Myoview$^{TM}$ in a pre-prepared kit formulation.

2.3.2 Phosphine bridged systems with Tc(V) or Re(V)

There are several reports of multi-dentate ligands containing phosphine donor atoms coordinated to technetium-99m. However the majority of these are bi-dentate chelates with substantially fewer tri- and tetra-dentate compounds in the literature. Figure 2-6 shows two complexes with bi-dentate ligands and Figure 2-6b shows the commercially available Myoview$^{TM}$ where two ligands are complexed to the [TcO$_2$]$^+$ core. As mentioned in the
introduction, Myoview™ is prepared using a pre-formulated kit. In this case the phosphine ligand is air sensitive and is stabilised by the use of the sulphosalicylate salt. This dissociates during production to yield the technetium complex (Myoview™) and disodium sulphosalicylate. This indicates that the use of air-sensitive ligands in radiopharmaceutical kits is feasible.

Figure 2-6: Technetium-99m complexes with bi-dentate phosphine ligands a) published by Glavan et al. and b) published by Kelly et al. 

Figure 2-7 shows two examples of tetra-dentate ligand systems containing phosphine donor atoms coordinated to Tc(V). A range of different ligand structures are presented including the tripodal ligand shown in Figure 2-7b. The schematic shown in Figure 2-7c was used to search the literature for a tetra-dentate ligand system which uses the phosphine moiety as bridging donor atoms. Interestingly no ‘hits’ were obtained, indicating that the use of phosphine donors with technetium-99m has not been fully explored.

Figure 2-7: Technetium-99m complexes with tetra-dentate ligand systems which contain phosphine donors; a) published by Tisato et al. and b) published by Dilworth et al. and c) the schematic of a structural search where R = any alkyl or aryl group, Y = 0 – 4 carbon chain and X = any heteroatom.
2.4 Thesis Synopsis

This section details a brief outline of each chapter. Chapter 3 features the synthesis and characterisation of a $S_4$ tetra-dentate ligand system containing the thiophosphoryl moiety. This moiety was investigated as a stable thiol analogue. The ligands synthesised contain a thioether bridge of varying lengths and were reacted with rhenium and technetium-99m. Complexes with Re(V) and Tc(V) cores could not be produced, however, in order to understand the coordination chemistry of the ligands, complexes with transition metal centres including Ag(I), Cu(I) and Pd(II) were synthesised. The results and structures obtained are detailed.

![Chapter 3](image1)

![Chapter 4](image2)

![Chapter 5](image3)

Figure 2-8: Target structures of the tetra-dentate ligands proposed in Chapters 3 – 5, where $n = 1, 2$ and 3, $X = S, NH$ or $PPh$

Chapter 4 is intended to combine the main aims of the Thesis, i.e. the search for a stable thiol moiety and a comparison of different donor atoms. Issues were encountered during the synthesis of the tetra-dentate ligand systems where $X = S$ or NH. A variety of conditions and reagents were used and are discussed within the chapter. Synthesis of the ligand where $X = PPh$ is presented along with a series of analogous compounds. Complexation of the tetra-dentate compounds with Pd(II) and Re(V) centres was carried out and these results are also detailed.

The aim of the final results chapter is to synthesise a ligand which could be compared to the amine oxime chelate by using phosphine donors instead of the amine moieties. The proposed reaction scheme was unsuccessful, this lead to an investigation of an alternative synthetic route.
The results of this are reported and the data obtained are discussed. The final chapter within this Thesis provides some conclusions and details ideas for future work to be completed.

2.5 References

Chapter 3: Synthesis and Characterisation of Tetradentate Ligands Incorporating Thiophosphoryl Donors
3.0 Synthesis and Characterisation of Tetradaentate Ligands Incorporating Thiophosphoryl Donors

3.1 Chapter Aims and Overview

In the search for stable thio donors the thiophosphoryl moiety was thought to be of interest. A series of tetradaentate ligands were designed and it was proposed that the use of dimethylvinylphosphine sulphide would incorporate the thiophosphoryl moiety into the system. The ligands reported here contain a thioether bridge, with the general formula (CH$_3$)$_2$PS(CH$_2$)$_n$S(CH$_2$)$_2$PS(CH$_3$)$_2$ (n = 2 (3.1), 3 (3.2), 4 (3.3)).

![Structures of 3.1 - 3.3](image)

Compounds 3.1 – 3.3 were reacted with the rhenium cores [ReO]$^{3+}$, [ReO$_2$]$^+$ and technetium-99m. However, neither rhenium nor technetium-99m complexes were produced. The results obtained from the attempted complexation reactions are detailed in section 3.4. In an attempt to explain the results obtained and gain an understanding of the coordination behaviour of the ligands, 3.1 – 3.3 were reacted with palladium(II) chloride, tetrakis(acetonitrile)copper(I) tetrafluoroborate and silver(I) hexafluorophosphate. The resulting complexes are described and an explanation regarding the rhenium and technetium results is proposed.
3.2 Introduction

The use of thioether donors as part of tetra-dentate ligand systems for use with technetium-99m has been discussed in the previous chapter, this introduction will focus on ligand systems containing thiophosphoryl moieties. The literature shows that chelates with thiophosphoryl donors have been used to complex transition metal centres which have been used in catalysis. For example, pincer type ligands have been synthesised as mono- and bis-chalcogenide compounds. Montag et al.\(^2\) published the reaction of the rhodium precursor [Rh(COE)\(_2\) (acetone)\(_2\)]\(\text{BF}_4\) (COE = cyclooctene) with the ligand in Figure 3-2a. This resulted in the exclusive C-C oxidative addition of the ligand to the metal forming an octahedral rhodium centre with a bidentate ketol molecule. The SCS ligand was shown to coordinate in the equatorial plane and whilst the methyl moiety coordinated axially.\(^2\)

Figure 3-2: Structural representations of a) a thiophosphoryl SCS ligand and complex published by Montag et al.\(^2\) and, b) a mixed bidentate PS ligand, published by Saikia et al.\(^3\)

Figure 3-2b shows an example of a mono-chalcogenide compound which has been complexed to palladium via the phosphine and thiophosphoryl groups. The complex was shown to be
active in Suzuki-Miyaura cross-coupling reactions with various aryl bromides and aryl boronic acids.\textsuperscript{3} Two types of ligand structure were tested, both were synthesised as the diphosphines and the mono thiophosphoryl analogue. The ligands were reacted with Pd(II), forming compounds with the general formula [PdCl\textsubscript{2}L]. All the complexes tested were shown to have a higher catalytic activity than the control experiment with PdCl\textsubscript{2}. Complexes with the phosphine ligands showed a higher activity than those formed with the thiophosphoryl analogues. Interestingly, during the recycling experiments complexes containing the phosphine ligands were shown to have a decreased catalytic activity on the second run, whilst complexes containing the thiophosphoryl ligand showed little change in catalytic activity. In this case, the use of the thiophosphoryl moiety appears to stabilise the complex so that the catalytic activity remains consistent. In general, it can be considered that inclusion of a thiophosphoryl moiety stabilises the phosphines to oxidation, this can subsequently result in stable complexes. This allows for easier manipulation of the compounds which can then be used in a wider range of experimental conditions, supporting the proposed use of thiophosphoryl donors as stable thiol analogues.

The literature also shows evidence of rhenium and technetium complexes with thiophosphoryl ligands. The tridentate ligand 2,6-bis(diphenylphosphinosulfide)pyridine\textsuperscript{4} has been synthesised and complexed to the rhenium(I) tricarbonyl core. The ligand, which contains two thiophosphoryl moieties was expected to bind in a bidentate mode but instead acts as a tridentate ligand (Figure 3-3).
More interestingly, the coordination of thiophosphoryl groups to Tc(V) are also reported. The literature reports the complexation of the bidentate ligand \(\{N(SPPh_2)_2\}\) with both the \([\text{TcN}]^{2+}\) and the \([\text{TcO}]^{3+}\) cores.\(^6\,^7\) Figure 3-4 shows structure of \([\text{TcN}\{N(SPPh_2)_2\}]\),\(^6\) and \([\text{TcO}\{N(SPPh_2)_2\}OEt]\)\(^7\) where two ligands are coordinated through the thiophosphoryl moieties to the technetium-99m core. The examples detailed here provide evidence of rhenium and technetium core coordinated to thiophosphoryl moieties.

Some linear examples of ligands containing the thiophosphoryl moiety are shown in Figure 3-5, whilst coordination properties of cyclic ligands have also been investigated.\(^8\) Figure 3-5a\(^9\) shows a tripodal type ligand which has been used as a precursor for the reduced phosphine ligand obtained by reduction with LiAlH\(_4\). Figure 3-5b is an example of one in a series of bis-thiophosphoryl bis-thioether ligands published by Genge et al that can act as tetra-dentate chelates to transition metal centres, including Pd(II), Pt(II), Cu(I), Ag(I) and Au(I).\(^10\,^11\)
Figure 3-5: Examples of published compounds containing thiophosphoryl moieties\textsuperscript{9,10,12}

Figure 3-5c published by Griffiths \textit{et al} \textsuperscript{12} as part of a range of phosphorus containing multidentate ligands, dimethylvinylphosphine sulphide was used as the main precursor during synthesis. The publication also details the synthesis of the ligand shown in Figure 3-6, 3.1 (Figure 3-8) was produced as a by-product during the synthesis.

Figure 3-6: Structure of 2-(2-dimethylphosphinothioylethylsulfanyl)-ethanethiol

This literature evidence shows that mixed donor thioether thiophosphoryl ligands have previously been synthesised and complexed to a range of transition metals but not rhenium or technetium. The combination of thioether and thiophosphoryl moieties within the same ligand motif is of interest due to the potential use of radiolabelling across a range of pH. As discussed in the introduction, mixed donor ligands have been used extensively for technetium-99m complexes.\textsuperscript{13-15} It was subsequently proposed that a series of tetradentate ligands with bis-thioether dithiophosphoryl donors could be suitable for rhenium and technetium cores [MO]\textsuperscript{3+}, [MO\textsubscript{2}]\textsuperscript{+}, [MN]\textsuperscript{2+}, with the potential for further investigation of the ligand system by changing the thioether groups to amine and phosphine moieties.

3.3 Ligand Synthesis

Dimethylvinylphosphine sulfide has been used as a starting material for many phosphine-based compounds.\textsuperscript{9} To ease synthetic procedures this air-stable thiophosphoryl can be used under
aerobic conditions. Following manipulations, the thiophosphoryl can then be reduced using LiAlH₄ to the corresponding phosphine. Figure 3-7 shows the reaction scheme used for the synthesis of dimethylvinylphosphine sulfide. Initially the literature procedures were followed for the synthesis of tetramethyldiphosphine disulphide,¹⁶ dimethylthiophosphinic bromide¹⁷ and dimethylvinylphosphine sulphide⁹ (Figure 3-7) however, issues were encountered during the synthesis of dimethylthiophosphinic bromide.

![Reaction scheme for the synthesis of dimethylvinylphosphine sulfide](image)

**Figure 3-7: Reaction scheme for the synthesis of dimethylvinylphosphine sulfide**

The synthesis reported by Schmutzler¹⁷ in 1970 uses carbon tetrachloride as the solvent and the product is isolated by distillation of the solvent via a Vigreux column. This method resulted in the loss of yield due to the azeotropic nature of the product in carbon tetrachloride. The availability of the solvent was also problematic and led to the use of DCM as the solvent instead. This meant that dimethylthiophosphinic bromide could be isolated by removal of the solvent *in vacuo* without significant loss of yield. Synthesis of tetramethyldiphosphine disulfide and dimethylvinylphosphine sulfide proceeded according to the literature methods reported. All steps for the synthesis of dimethylvinylphosphine sulfide could be completed consecutively within one day. It was often convenient to then use the compound *in situ* for the synthesis of 3.1 – 3.3 (Figure 3-9) as the reaction proceeded overnight and the product could be isolated the next day.
Figure 3-8: Structure of 2-(2-dimethylphosphinothioylethylsulfanyl)-ethanethiol and 3.1 both previously published by Griffiths et al., and the structures of 3.2 and 3.3 which have not been previously reported.

Compounds 3.1 - 3.3 (Figure 3-8) were synthesised by nucleophilic addition of the appropriate deprotonated di-thiol to dimethylvinyl phosphinesulphide in ethanol, from which the product precipitated as a white solid. Griffiths et al reported the synthesis of 2-(2-dimethylphosphinothioylethylsulfanyl)-ethanethiol\textsuperscript{12} (Figure 3-8), producing 3.1 as a by-product. This reaction procedure was used as a template for the synthesis of 3.1 - 3.3. Sodium ethoxide is used to produce the disodium thiolate salt prior to the reaction. Figure 3-9 shows the reaction scheme for the synthesis of 3.1 – 3.3 where 3.1 has been previously reported by Griffiths et al.\textsuperscript{12}

Figure 3-9: General reaction scheme for the synthesis of 3.1 - 3.3, \( n = 0 - 2 \)

The chain length of the carbon backbone was altered so that the ideal length for rhenium and technetium complexes could be determined by examining the rates and stability of complexation. Figure 3-10 shows a basic schematic of a tetra-dentate ligand coordinating to a metal centre. The diagram shows that three rings are formed during coordination (i, ii, iii), and in this scheme all of the rings formed are 6-membered. Changing the backbone of 3.1 - 3.3 will
alter the size of ring ii in any complexes that are produced. A metal centre may have a preferred 
ring size which could increase the probability of complexation and the stability of the complex. 
This may be dependent on the size and charge of the metal ion. Rhenium and technetium have 
a series of oxo and nitrido cores with different charges; for example [MO]^{3+}, [MO_2]^+, [MN]^{2+}. 
If a pattern could be established for the different cores and the preferred ring sizes the 
information could be used to design the next series of ligands.

![Figure 3-10: Schematic of a tetra-dentate ligand coordinating to a metal centre](image)

3.1 - 3.3 were purified by washing with ethanol and diethylether to afford white powders. 
Characterisation was completed by NMR spectroscopy, mass spectrometry, elemental analysis 
and IR spectroscopy. The NMR spectral data shows that the phosphorus environments of 3.1 - 
3.3 are similar to that of 2-(2-dimethylphosphino thioylethylsulfanyl) ethanethiol, which has a 
^{31}P\{^{1}H\} NMR spectrum signal of 36.0 ppm as reported by Griffiths et al.\textsuperscript{12} 3.1 - 3.3 all showed 
comparable ^{31}P\{^{1}H\} NMR spectra with singlet shifts at ~ 36 ppm. For 3.1 - 3.3 the P=S bond 
can be observed in the IR spectrum at ~ 630 cm\textsuperscript{-1}. 
The diffusion of hexane into a DCM solution of 3.2 yielded colourless crystals of X-ray quality. The crystal structure (Figure 3-11) shows that two different conformers are observed in 3.2. The main difference between the conformers is around the two C6 bond angles. The C5A-C6A-C7A angle is 110.23(13)° and the C5B-C6B-C7B angle is 113.01(15)°, the C6-C5-S4 angle is the same in both conformers at 115.32(11)° and 115.43(12)° however the C6-C7-S8 differs between the conformers. C6A-C7A-S8A has an angle of 109.02(11)° and the C6B-C7B-S8B angle is 113.05(12)°. All other bond angles are comparable between the two conformers. The bond length of the P=S bond is shown to be 1.97 Å in both conformations. Upon synthesis of 3.1 – 3.3 reactions with Re(V) and 99mTc were completed, the next section details the results obtained.

3.4 Reactions with Rhenium and Technetium

As previously mentioned rhenium is often used as a technetium-99m analogue as the metals have comparable size (due to the lanthanide contraction) and a similar chemical nature. Many chelates are shown to coordinate to both metal centres with similar coordination chemistry and
this allows for the structures of the complexes to be defined. However there are a few examples, most notably amine oxime chelates where the X-ray structure of the Re analogues has not been obtained.\textsuperscript{19-21}

### 3.4.1 Rhenium Complexes

Attempts to make the Re(V) di-oxo (or mono-oxo) complexes were unsuccessful. Initially it was envisaged that the ligands would complex to the di-oxo [ReO\textsubscript{2}]\textsuperscript{+} core more readily due to the smaller charge on the core when compared to the mono-oxo [ReO]\textsuperscript{3+} core. This was due to the nature of the neutral ligands, since the charge on a complex would be governed by the rhenium core. For this reason, the first reactions were completed using the rhenium precursor [ReO\textsubscript{2}(py)\textsubscript{4}]Cl which has previously been shown to form complexes with tetra-dentate ligand systems.\textsuperscript{22} Figure 3-12 shows the reaction conditions used for the attempted synthesis.

![Figure 3-12: Synthetic scheme for the reaction of 3.1 - 3.3 (n = 0, 1, 2) and [ReO\textsubscript{2}(py)\textsubscript{4}]Cl to synthesise 3.4](image)

Table 3-1 shows the set of reactions completed with the [ReO\textsubscript{2}]\textsuperscript{+} core, in which several solvents were tested allowing for a range of reflux temperatures to be trialled. The reactions were monitored by \textsuperscript{31}P\{\textsuperscript{1}H\} NMR spectroscopy. Samples were taken every 6 hours for the first day and then every 24 hours for 1 week. The \textsuperscript{31}P\{\textsuperscript{1}H\} NMR spectra were found to be unchanged after 6 hours, Table 3-1 reports the results obtained at 12 hours.
<table>
<thead>
<tr>
<th>Precursor</th>
<th>Ligand</th>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>Observations at 12 hours upon cooling of sample</th>
<th>$^{31}\text{P}$${^1\text{H}}$ solution NMR spectrum after 12 hours (ppm)</th>
<th>$^{31}\text{P}$${^1\text{H}}$ solid NMR spectrum after 12 hours (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$[\text{ReO}_2(\text{py})_4]\text{Cl}_3$</td>
<td>3.1 C$_2$ backbone</td>
<td>DCM</td>
<td>39</td>
<td>Orange solution</td>
<td>36.1</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MeCN</td>
<td>82</td>
<td>Red solution, dark precipitate</td>
<td>36.4</td>
<td>No Signal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MeOH</td>
<td>64</td>
<td>Orange solution, cream and red precipitate</td>
<td>No Signal</td>
<td>38.48</td>
</tr>
<tr>
<td>Toluene</td>
<td></td>
<td></td>
<td>110</td>
<td>Black solution, and precipitate</td>
<td>36.9</td>
<td>36.33</td>
</tr>
<tr>
<td>$[\text{ReO}_2(\text{py})_4]\text{Cl}_3$</td>
<td>3.2 C$_3$ backbone</td>
<td>DCM</td>
<td>39</td>
<td>Orange solution</td>
<td>36.1</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MeCN</td>
<td>82</td>
<td>Brown solution and precipitate</td>
<td>36.5</td>
<td>37.12</td>
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<td></td>
<td></td>
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<td>64</td>
<td>Orange solution, cream precipitate</td>
<td>No signal</td>
<td>36.43</td>
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<td>56</td>
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<td>N/A</td>
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<tr>
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<td></td>
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<td>Black solution and precipitate</td>
<td>36.8</td>
<td>No signal</td>
</tr>
<tr>
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<td>MeCN</td>
<td>82</td>
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<td>37.0</td>
<td>N/A</td>
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<tr>
<td>Toluene</td>
<td></td>
<td></td>
<td>110</td>
<td>Black solution and precipitate</td>
<td>36.1</td>
<td>No signal</td>
</tr>
</tbody>
</table>

Table 3-1: The different solvents used and the result obtained from each completed reaction

In all reactions the continued presence of the starting ligand at ~ 36 ppm suggested that complexation was not occurring. Formation of a black precipitate was observed in some reactions and it appeared to form upon heating to reflux at temperatures >85°C possibly indicating that the rhenium starting material was decomposing. When methanol was used as
the solvent, it appears that the ligand precipitated out of solution upon cooling, which was expected as 3.1 - 3.3 are not soluble in methanol.

Analysis of the data shown in Table 3-1 led to the conclusion that the rhenium precursor [ReO$_2$(py)$_4$]Cl was not the best choice for the successful complexation of 3.1 - 3.3. For this reason reactions with [ReOCl$_3$(PPh$_3$)$_2$] were attempted. This rhenium compound contains the [ReO]$^{3+}$ core but it has also been reported that complexes with the [ReO$_2$]$^+$ core have been synthesised from this starting material.$^{23,24}$ The conditions used for the reaction of [ReOCl$_3$(PPh$_3$)$_2$] and 3.1 - 3.3 are shown in Figure 3-13. Unfortunately the same result was obtained for each of the three ligands so only the result from the reaction of 3.2 is detailed here.

The rhenium precursor is only partially soluble in most organic solvents so a series of different solvents were tested (Table 3-2) and ethanol was chosen as the most suitable solvent as it partially dissolved the precursor and the ligand at reflux temperatures.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>3.2 solubility</th>
<th>[ReOCl$_3$(PPh$_3$)$_2$] Solubility</th>
<th>Reaction result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toluene</td>
<td>Poor</td>
<td>Poor</td>
<td>No reaction</td>
</tr>
<tr>
<td>Acetone</td>
<td>Good</td>
<td>Fair</td>
<td>No reaction</td>
</tr>
<tr>
<td>DCM</td>
<td>Good</td>
<td>Poor</td>
<td>No reaction</td>
</tr>
<tr>
<td>MeCN</td>
<td>Poor</td>
<td>Fair</td>
<td>No reaction</td>
</tr>
<tr>
<td>EtOH</td>
<td>Poor</td>
<td>Fair</td>
<td>Decomposition of rhenium material</td>
</tr>
</tbody>
</table>

Table 3-2: The solubility of 3.2 and [ReOCl$_3$(PPh$_3$)$_2$] in the solvents tested and the reaction result observed

The reaction between 3.2 and [ReOCl$_3$(PPh$_3$)$_2$] was completed in ethanol and heated at 85°C over two days. Upon cooling a green solution and a light brown precipitate were observed. The $^{31}$P{$^1$H} NMR spectrum (Figure 3-14) of the solution obtained from the reaction of 3.2 with [ReOCl$_3$(PPh$_3$)$_2$] in ethanol shows two phosphorus signals, one at 37.66 ppm and the other at
25.5 ppm. The peak at 37.7 ppm corresponds to the signal from the free ligand. The signal of the rhenium precursor (-19 ppm) is not observed. Had the ligand complexed to the rhenium-oxo core a signal corresponding to triphenylphosphine at -5 ppm would be expected in the $^{31}$P{$^1$H} NMR spectrum. However, no signal is observed at this shift in either the $^{31}$P{$^1$H} NMR spectra of the isolated solid or solution. The signal at 25.5 ppm can be assigned to oxidised triphenylphosphine which has a signal at ~27 ppm in CDCl$_3$. The $^{31}$P{$^1$H} NMR spectrum of the cream brown solid obtained is similar to that seen in Figure 3-14 suggesting again that the free ligand and triphenylphosphine oxide are present. This data suggests that there is no complex formation and that the rhenium precursor may decompose under these conditions.

Figure 3-13: Conditions used in the reaction of 3.2 with [ReOCl$_3$(PPh$_3$)$_2$] in the attempted synthesis of 3.5
The reaction was repeated but heated at 65°C, both 3.2 and [ReOCl₃(PPh₃)₂] partially dissolved at this temperature. The reaction was monitored by $^{31}$P{¹H} NMR spectroscopy and Figure 3-15 shows the spectrum obtained after 24 hours. A sample was taken from the reaction, and the solvent was removed in vacuo to afford a green solid which was re-dissolved in CDCl₃.

The spectrum shows 6 signals, 3 of which can be assigned, as shown in Table 3-3.
Figure 3-15: $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum of the solution in CDCl$_3$ from the attempted synthesis of 3.5 obtained after 24 hours

<table>
<thead>
<tr>
<th>Signal (ppm)</th>
<th>43.3</th>
<th>36.0</th>
<th>29.2</th>
<th>-5.4</th>
<th>-9.3</th>
<th>-19.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assignment</td>
<td>Unknown</td>
<td>3.2</td>
<td>Unknown</td>
<td>PPh$_3$</td>
<td>Unknown</td>
<td>[ReOCl$_3$(PPh$_3$)$_2$]</td>
</tr>
</tbody>
</table>

Table 3-3: The assignment of the signals from the $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum in Figure 3-15

The unknown signals at 43.3 ppm, 29.2 ppm, -9.3 ppm were considered as potential complexes. However, it was thought that the $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum of 3.5 would have a shift downfield from the signal of the free ligand at ~36 ppm. For this reason the signal at 43.3 ppm was assigned as a potential rhenium complex with 3.2. Although the signals at 29.2 ppm and -9.3 cannot be conclusively identified the signal at 29.2 ppm was thought to be triphenylphosphine oxide or coordinated triphenyl phosphine oxide. Whilst the signal at -9.3 ppm was thought that it was due to a rhenium complex similar to the starting material [ReOCl$_3$(PPh$_3$)$_2$] for example [ReO(OEt)Cl$_2$(PPh$_3$)$_2$].
It was proposed that complexation was occurring at a slow rate due to the observation of both starting materials in the $^{31}$P{$^1$H}NMR spectrum, and for this reason the reaction was left to heat for a further 96 hours with samples taken every 24 h. However, the $^{31}$P{$^1$H} NMR spectrum remained unchanged after 48 hours. Figure 3-16 shows the $^{31}$P{$^1$H} NMR spectrum obtained after 48 hours, it shows 4 signals, corresponding to PPh$_3$, OPPh$_3$, 3.2 and an unknown species at 43.33 ppm. The lack of a signal at -9.29 ppm suggests that it may have been due to an intermediate rhenium complex formed during decomposition.

![Figure 3-16: $^{31}$P{$^1$H} NMR spectrum of the solution in CDCl$_3$ from the attempted synthesis of 3.5 obtained after 48 hours](image)

The rhenium precursor is not observed in the spectrum suggesting that it had decomposed. A sample of the crude product was submitted for mass spectrometry, in the hope that a rhenium complex could be observed. The mass spectrometry data obtained shows several peaks, unfortunately the expected mass for 3.5 (Figure 3-17c) which is [550]$^{3+}$ was not present at 183 m/z. With peaks corresponding to PPh$_3$ (263 m/z) and OPPh$_3$ (279 m/z). Figure 3-17a-e shows
a series of proposed structures that were considered to be viable from the reaction conditions used. This includes complexes with the rhenium di-oxo core (Figure 3-17a, 3.4), coordinated chloride ions (Figure 3-17b and Figure 3-17d) and a dimer (Figure 3-17e). From the $^{31}$P{$^{1}$H} NMR spectrum we can postulate that it is unlikely that any PPh$_3$ ligand is bound to the rhenium core. It would be expected that a signal from any remaining coordinated PPh$_3$ ligands would have a similar shift to those observed in the rhenium starting material at -19 ppm.

Unfortunately, none of the combinations of ligand, halogen, triphenylphosphine or [ReO]$^{3+}$ could be found to fit the mass spectrometry data. The reaction was repeated and the same result obtained. Without any evidence for a rhenium complex the reactions were deemed unsuccessful and no further rhenium complexation experiments were attempted. The next section details the reactions of 3.2 with technetium-99m.

**3.4.2 Technetium-99m Complexes**

It is well-known that the amine oxime technetium chelate has not been complexed to rhenium cores, suggesting that ligands do not always react in the same way with rhenium and technetium-99m. For this reason a series of complexation reactions were attempted to assess
how the ligands would react with technetium-99m. Since many ligands used to complex $^{99m}$Tc contain a C3 backbone it was thought that 3.2 (Figure 3-18) would be the best compound to complete the initial screening with.

![Figure 3-18: Structure of 3.2](image)

As discussed in the introduction, when technetium-99m complexes are synthesised within a clinical setting, a freeze-dried kit is used. The kit contains the ligand, a reducing agent, a buffer and in some cases, a co-ligand is used to aid complexation. To this mixture saline is added followed by pertechnetate in saline which comes from the Mo$^{99}$/Tc$^{99m}$ generator. Commercially available freeze-dried kits are optimised for individual ligands. There are however, kits available for use in a research setting which can allow for the assessment of potential ligands. Initially a methylene diphosphonate (MDP) kit was used. MDP acts as a co-ligand and the kit includes tin(II) chloride as the reducing agent and a buffer at pH 9-10. This formulation has previously been used to produce Tc(V) complexes including the amine oxime and tetra-amine systems and was the first method used in the attempted complexation of 3.2 and technetium-99m. Analysis of the reaction mixture was completed using both HPLC and TLC. Under reverse phase HPLC conditions the starting material pertechnetate is eluted in the void volume whilst TLC techniques were also used to identify other known species. For example, a mixture containing pertechnetate and the precursor technetium gluconate will show 100% integration at the solvent front when saline is used as the mobile phase. However, if methyl ethyl ketone (MEK) is used as the solvent, the TLC will show signals at the solvent front (pertechnetate) and at the base line (technetium gluconate).
Chapter 3

Table 3-4 shows the reaction conditions used for the attempted complexation of 3.2 with technetium-99m. The first two complexation attempts were undertaken with pre-prepared freeze-dried kits, an MDP kit and a gluconate kit were used. To the freeze-dried mixtures, saline, 3.2 and $[\text{Tc}^{99m}\text{O}_4]^{-}$ from the generator were added, the reactions were then left for 30 minutes before analysis by HPLC and TLC. Neither of the attempts with the freeze-dried kits resulted in complex formation and only pertechnetate was observed in the HPLC and TLC analyses.

<table>
<thead>
<tr>
<th>Experiment Code</th>
<th>Reducing agent</th>
<th>Co-ligand</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDP kit GE001</td>
<td>SnCl₂</td>
<td>MDP</td>
<td>9.2</td>
</tr>
<tr>
<td>Gluconate Kit GE002</td>
<td>SnCl₂</td>
<td>Sodium gluconate</td>
<td>9.2</td>
</tr>
<tr>
<td>GE003</td>
<td>SnCl₂</td>
<td>Sodium gluconate</td>
<td>7.0</td>
</tr>
<tr>
<td>GE004</td>
<td>SnCl₂</td>
<td>Sodium gluconate</td>
<td>9.2</td>
</tr>
<tr>
<td>GE005</td>
<td>SnCl₂</td>
<td>Potassium hydrogen tartrate</td>
<td>7.0</td>
</tr>
<tr>
<td>GE006</td>
<td>SnCl₂</td>
<td>Potassium hydrogen tartrate</td>
<td>9.2</td>
</tr>
</tbody>
</table>

Table 3-4: Conditions used in reactions GE001 - 005 for the complexation of 3.2 with technetium-99m

Since the pre-prepared kits did not produce complexation the rest of the reactions were prepared by hand. Tin(II) chloride was the reducing agent used in the reactions as it is the most common reductant for pertechnetate.\textsuperscript{26-28} Tin(II) chloride was dissolved in a 0.01M HCl solution and was degassed by bubbling N\textsubscript{2} before use. The co-ligand and pH were altered in an attempt to complex technetium-99m with 3.2. In an N\textsubscript{2} sealed vial the buffer, co-ligand and 3.2 were mixed before $[\text{Tc}^{99m}\text{O}_4]^{-}$ was added this was followed immediately by the reducing agent.

Reactions GE004 - 6 did not result in complex formation and HPLC and TLC analysis showed only pertechnetate to be present in all reactions. The most promising result was obtained from
GE003, with gluconate acting as the co-ligand and the pH at 7.0. Figure 3-19 shows the HPLC trace of the solution. The radioactivity trace shows pertechnetate in the void volume and a separate species at around 26 minutes.

Figure 3-19: HPLC trace of the mixture from reaction SHGE003, where gluconate was the co-ligand and the pH was at 7.0

Initially this was considered to be a [Tc$^{99m}$3.2] complex, however the radio-TLC analysis completed suggested that pertechnetate and technetium gluconate were present. To verify the presence of a [Tc$^{99m}$3.2] complex and not technetium gluconate, a control reaction was completed (GE007). The control was a repeat of GE003 without the addition of 3.2. This reaction was then analysed by HPLC, Figure 3-20 shows the trace obtained.
Pertechnetate is observed within the void volume and a second radioactive species is observed at 26 minutes. This suggests that the species present at 26 minutes is not a [Tc\textsuperscript{99m}3.2] complex but a technetium gluconate compound. This result meant that from reactions GE001 - 007 a technetium complex with 3.2 had not been formed. In a further attempt to synthesise a [Tc\textsuperscript{99m}3.2] complex, the reactions GE001 - 006 were repeated with heating at 70°C for 20 minutes. The same result was obtained and the complexation of 3.2 with technetium-99m had not occurred. The initial screening of 3.2 with technetium-99m was shown to be unsuccessful, with HPLC and TLC analysis showing only [Tc\textsuperscript{99m}O\textsubscript{4}]\textsuperscript{+} or [Tc\textsuperscript{99m}gluconate] species present. Due to the results reported here no further technetium-99m reactions were completed using 3.1 – 3.3.
In an attempt to understand the coordination chemistry, 3.1 - 3.3 were complexed to a range of transition metal centres. It was thought that an awareness of the coordination and binding modes of 3.1 - 3.3 might lead to an explanation of the results obtained, thus the ligands were reacted with copper, silver, and palladium centres.

3.5 Metal Complexes

This section reports the complexes synthesised from the coordination of 3.1 - 3.3 to various metal centres. The X-ray crystal structures of the complexes are detailed within this section along with some relevant data.

3.5.1 Copper Complexes

[Cu(3.1)]BF$_4$ (3.6) was synthesised from the reaction of tetrakis(acetonitrile)copper(I) tetrafluoroborate$^{29}$ and 3.1 (Figure 3-21). The product was isolated by concentration of the solvent in vacuo to ~5 ml and addition of diethylether to afford a white solid, which was further washed with diethylether. The $^{31}$P{$^1$H} NMR spectrum of the dried product showed a single peak at 38.7 ppm, shifted ~3 ppm downfield compared to the starting ligand, 3.1. Characterisation and purity of 3.6 was determined using NMR spectrometry, mass spectrometry and elemental analysis, the product was isolated with a yield of 54 %.

![Reaction conditions used to synthesise 3.6](image)

Diffusion of diethyl ether into an acetonitrile solution of 3.6 afforded colourless crystals suitable for structural X-ray analysis. The structure (Figure 3-22) shows the copper centre in a
distorted tetrahedral environment. The angles around the metal centre for a tetrahedral complex are expected to be $109.5^\circ$ however the structure shows angles varying between $91.70(2)^\circ$ (for S5-Cu-S8) and $126.57(3)^\circ$ (for S1-Cu-S8). Since Cu(I) is a d$^{10}$ metal centre, the distortion observed is not caused by electronic effects but may be due to the steric constraints caused by the small bite angle of the -S(CH$_2$)S- bridge.

Figure 3-22: Ball and stick representation of the X-ray crystal structure of 3.6, with the counter ion and hydrogen atoms omitted for clarity

A similar series of ligands which contain phenyl groups instead of methyl groups as the phosphine substituents (Figure 3-23a) have previously been complexed to copper(I) centres.$^{11}$ The work published by Genge et al $^{11}$ details the crystal structure of a Cu(I) complex with a ligand containing a propane bridge between the two thioether moieties and phenyl substituents on the phosphines. This shows the copper centre to be in a distorted tetrahedral geometry, however the angles ($99.2^\circ$ - $118.6^\circ$)$^{11}$ observed are not as distorted as those seen in 3.6. This could be due to the addition of the extra CH$_2$ linker group in the bridge between the two
thioether groups, allowing a larger bite angle to the metal centre. The crystal structure of a selenophosphoryl analogue is also reported. The ligand (Figure 3-23b) contains an ethane bridging unit, this allows for a comparison of the corresponding copper(I) complex with 3.6. The X-ray crystal structure reported shows the equivalent E-Cu-E angle in the complex of the selenide analogue to be 92.5° (E = Se) supporting the conclusion that the steric constraints of the ligand have resulted in the distorted tetrahedral geometry.

The structure of 3.6 shows the ligand acting as a tetra-dentate chelate and coordinating through the two thioether and two phosphine sulphide donors. The structure shows that the two CuSPC₂S six-membered rings within the complex have different conformations. The S₁/S₅ ring has a chair conformation while the S₈/S₁₂ ring has a twist-boat conformation. The length of the P=S bond increased by ~ 0.2 Å from the starting ligand bond length of 1.97 Å. The lengthening of the P=S bond upon complexation is expected due to back-bonding from the metal centre. This should be observed in the IR spectrum of the complex with the P=S stretch shifting to lower wave numbers. The ligand P=S stretch is observed at 634 cm⁻¹ but unfortunately the range of the spectrometer does not go below 600 cm⁻¹ so the P=S stretch in the complexes cannot be reported.

The same reaction was completed using identical conditions (Figure 3-21) with the other two ligands (3.2 and 3.3). Figure 3-24 shows the proposed structure of 3.7, the ³¹P{¹H} NMR spectrum shows a similar shift i.e. 39.2 ppm to the one observed for 3.6. Mass spectrometry and elemental analysis confirmed the formula of 3.7 to be [CuC₁₁H₂₆SnP₂]BF₄. The structure
of 3.7 was expected to be very similar to 3.6 with the complex in a tetrahedral geometry and the ligand acting as a tetra-dentate chelator. This conclusion is supported by previously reported Cu(I) complexes with similar ligands where there are phenyl substituents on the phosphine units instead of methyl groups.\textsuperscript{11}

![Figure 3-24: Structure of 3.7](image)

Cyclic voltammetry of 3.7 was completed to examine whether any redox activity could be observed. The ligand is able to coordinate in a square planar geometry (discussed in section 3.5.3) as well as the tetrahedral geometry observed for the copper (I) centres, so it may be flexible enough to also stabilise a Cu(II) centre. Figure 3-25 shows the scan obtained from the cyclic voltammetry of 3.7. Oxidation of the Cu(I) centre to Cu(II) can clearly be seen but no reduction is observed. This suggests that once the copper centre is oxidised the complex decomposes so that no reduction occurs.
Figure 3-25: Cyclic voltammogram of 3.7, a 5 mM solution was prepared in dry degassed MeCN containing 20 equivalents of electrolyte (Bu$_4$N$^+$PF$_6^-$) with a Pt working electrode (0.05 mm) and a silver wire reference electrode.

Analysis of the reaction between tetrakis(acetonitrile)copper(I) tetrafluoroborate and 3.3 proved to be more complicated than initially thought. It was assumed that the structure of 3.8 (Figure 3-26) would be similar to those observed for 3.6 (n = 1) and 3.7 (n = 2) however, the data obtained has not proved conclusive. Accurate mass spectrometry data showed a molecular ion peak at 424.9753 m/z. This corresponds to the formula [Cu(3.3)]$^+$ which has a calculated mass of 424.9845 m/z. The $^{31}$P{$^1$H} NMR spectrum shows a singlet at 39.30 ppm comparable to that observed in the spectra of 3.6 and 3.7, and this along with the accurate mass spectrometry data suggests the successful synthesis of the complex shown in Figure 3-26.

![Figure 3-26: Proposed structure for 3.8 (n = 3)](image-url)
Colourless crystals of 3.8 suitable for X-ray analysis were obtained from the diffusion of diethyl ether into a solution of 3.8 in acetonitrile. The crystal structure was expected to show the proposed structure (Figure 3-26) however, a polymeric structure was obtained from the X-ray analysis. A single unit of the structure can be seen in Figure 3-27, it contains two Cu(I) centres, a ligand and two acetonitrile molecules.

![Figure 3-27: Ball and stick representation of the X-ray crystal structure of 3.8 with the counter ions and hydrogen atoms omitted for clarity](image)

The polymeric structure is an extended 2D sheet polymer with a 2:1 copper to ligand ratio, each copper atom is observed in a distorted tetrahedral environment. Disorder is observed along the butane bridging group between the two thioether moieties making S5 and S10 non-equivalent. The ligand acts as a bi-dentate chelate for two metal centres with the thiophosphoryl units bridging to another metal centre. The bridging of the S1 centre is asymmetric and the bond length of Cu-S1, the thiophosphoryl incorporated within the 6-membered ring, is 2.3492(9) Å whilst the bond length of Cu-S1B, the thiophosphoryl outside of the 6-membered ring, is 2.3718(9) Å, 0.02 Å longer. The final coordination environment is filled with an acetonitrile molecule.
Figure 3-28: Ball and stick representation of the X-ray crystal structure of the extended array of 3.8 with the counter ions and hydrogen atoms omitted for clarity.

To determine whether similar compounds had been reported a literature search was completed. Figure 3-29 shows the two molecule fragments which the search was based on, the bridge was defined as \(-\text{S(CH}_2\text{)}_4\text{S}^-\). Several structures that contain the fragment Figure 3-29a are reported, and most of these complexes have a Cu(II) metal centre\(^{30-33}\) to which the two thioether moieties are coordinated. A Cu(I) complex with a tetradentate \(\text{N}_2\text{S}_2\) ligand featuring a butane bridge (Figure 3-30a) was synthesised from electrolysis of the equivalent Cu(II) complex\(^{34}\) but unfortunately no structural data are available for comparison.

![Figure 3-29: Structure fragments used to search the electronic databases](image)

a) \(\text{S}^-\text{CuS}^-\)   b) \(\text{CuS-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-S}^-\text{Cu}\)
In the search for Figure 3-29b, a series of dimeric Cu(I) complexes were found, and dimeric Cu(II) complexes with a butane bridge have also been reported. Figure 3-30b shows the structure of a N₂S₂ macrocyclic ligand which was coordinated to a Cu(I) centre. The ligand contains a butane bridge between two thioether moieties, and the paper by Taylor et al reports that a monomeric Cu(I) compound was not formed via this ligand.

Two different compounds were isolated from the synthesis, a dimeric molecule [Cu(I)S₂BuNPr(MeCN)]₂ and a polymeric one. The crystal structure of the polymeric form (Figure 3-31) shows the core structure N,N,S-(endo)-S-(exo)(7,8,16,17-bisbenzo-10,14-diaza-1,6-dithiacyclotheptadeca-9,14-diene) copper(I) tetrafluoroborate. The ligand coordinates through the two N donors and one S donor, the other thioether moiety coordinates to a different Cu(I) centre. The lack of literature evidence for a monomeric Cu(I) species with a S(CH₂)₄S bridge suggests that monomeric complexes with this bridge may have formation or stability issues.
The elemental analysis data obtained for 3.8 did not support the formula of the polymeric compound, which was found from the crystal structure or the formula of the monomeric species. The reaction was repeated with the stoichiometry altered to encourage formation of the polymer i.e. instead of a 1:1 reaction ratio a 2:1 metal:ligand ratio was used. A reaction using an excess of ligand was also completed to try and force formation of the monomer. Unfortunately, the elemental analysis data that was obtained from these reactions did not correspond to the calculated percentages. Table 3-5 shows the different elemental analysis results obtained from repeat reactions trying to synthesise 3.8. The samples were all washed with DCM to remove any excess ligand and recrystallised using diethyl ether and acetonitrile.
Chapter 3

<table>
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<th></th>
<th>Calculate For the monomer</th>
<th>Calculated For the polymer</th>
<th>Observed for A Initial reaction</th>
<th>Observed for B 2:1 Metal:ligand ratio used</th>
<th>Observed for C Excess ligand used</th>
<th>Observed for D Repeat of B</th>
</tr>
</thead>
<tbody>
<tr>
<td>C%</td>
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<td>0.59</td>
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</tr>
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</table>

Table 3-5: Table of the elemental analysis data obtained for 2.6. Calculated 1: Monomeric species [CuC₂H₃S₄P₂]BF₄, Calculated 2: Polymeric species [Cu₂C₂H₃S₄P₂(MeCN)₂][BF₄]₂, Sample A initial synthesis, recrystallisation produced crystal structure, Sample B Metal:ligand ratio changed 2:1 used, Sample C excess ligand used, Sample D repeat reaction B.

From the table it can be seen that the experimental values are very different to those calculated for both the monomeric and polymeric species. Whilst the data obtained for sample A is closest to the calculated percentages of the polymer, all of the experimental data reported is below the expected values. Unfortunately solvent does not account for the difference in the calculated and experimental values for sample A. The data show that the samples are impure, and suggests that several species may be present within the samples. A dimeric structure such as that observed by Taylor et al. may be present along with the polymeric species.

The reaction was repeated using DCM as the solvent instead of MeCN to determine whether using a coordinating solvent was detrimental to the synthesis of the monomeric species. The elemental analysis data obtained for the isolated product was comparable to that observed for A in Table 3-5. From this it can be concluded that within the different species present any coordinated acetonitrile units are molecules which have not been displaced by 3.3 from the tetrakis(acetonitrile) copper(I) starting material.

The \(^{31}\text{P}\{\text{^1H}\}\) NMR spectrum (Figure 3-32) of 3.8 shows a singlet at 39.3 ppm indicating that only one phosphorus environment is present. This would suggest that all phosphine sulfide moieties are coordinated to a metal centre. If there were phosphine sulfide groups not
Chapter 3

coordinating to the Cu(I) centre a second peak would be observed in the $^{31}$P$\{^1$H$\}$ NMR spectrum which would have a shift similar to that observed for the free ligand at ~36 ppm.

Figure 3-32: $^{31}$P$\{^1$H$\}$ NMR spectrum of 3.8 in d3-MeCN

The $^{31}$P$\{^1$H$\}$ NMR spectrum shows that within the sample all of the phosphine sulfide moieties are coordinated to a Cu(I) centre. The X-ray crystal structure obtained shows a polymeric species has formed either under the reaction conditions or during recrystallization, suggesting the product to be unstable. Despite attempts to produce a pure sample elemental analysis data shows that the products obtained were not pure and may have several species present. It is speculated that other species within the samples may be dimers or trimers but unfortunately this cannot be proven with the data presented here.

The information gathered from the copper complexes shows the different coordination modes of 3.1 -3.3. The X-ray crystal structures show that the ligands can act as bi- and tetra-dentate chelates and that the phosphine sulphide moiety can act a bridging donor. The data presented
here also suggests that 3.3 which has a C4 carbon backbone may produce less stable Cu complexes than 3.1 (C2 backbone) and 3.2 (C3 backbone).

### 3.5.2 Silver(I) Complexes

Silver(I) has an effective ionic radii of 100 pm whilst the equivalent copper(I) radii is 60 pm,\(^{37}\) thus comparison between the complexes of the two metals would be interesting. For this reason the same reaction was repeated, but changing the metal centre from copper to silver using the starting material silver hexafluorophosphate. The reaction conditions (Figure 3-33) were kept the same in each reaction, and 3.9 - 3.11 were isolated as white precipitates by vacuum filtration. As with some other silver complexes, the compounds synthesised were light sensitive and decomposed slowly when exposed.

![Reaction Scheme](image)

**Figure 3-33: General reaction scheme used for the synthesis of 3.9**

Figure 3-34 shows the \(^{31}\)P{\(^1\)H} NMR spectrum of 3.9 (Figure 3-33), and shows a single peak at 44.96 ppm, shifted downfield by approximately 8 ppm from the starting ligand 3.1, and a septet at -144.36 ppm, indicative of the PF\(_6\) counter ion. This suggested that complexation had occurred, however no coupling between the phosphorus and silver centres is observed. Silver isotopes (Ag\(^{107}\) and Ag\(^{109}\)) have NMR active nuclei with spin \(\frac{1}{2}\). The literature supports this finding, as Ag(I) thiophosphoryl complexes do not usually exhibit any observable coupling.\(^{38-41}\) The difficulty in studying Ag\(^{107}\) and Ag\(^{109}\) using NMR spectroscopy is due to the low gyromagnetic ratios of the two isotopes. This leads to long spin-lattice relaxation (T\(_1\)) times and poor sensitivity.\(^{42,43}\) In Ag(I) phosphine complexes, coupling can be observed but signals
may be broad, with resolution of the signal possibly being achieved by obtaining the $^{31}$P{$^1$H} NMR spectra at low temperatures.$^{44,45}$

Mass spectrometry and elemental analysis were used to confirm the formula of 3.9 as [Ag(C$_{10}$H$_{24}$S$_4$P$_2$)]PF$_6$. The proposed structure is shown in Figure 3-33. It is proposed that the silver(I) compounds would have a similar structure to the copper complexes with the ligand acting as a tetra-dentate chelate and the metal centre in a tetrahedral geometry.

![Figure 3-34: $^{31}$P{$^1$H} NMR spectrum of 3.9 in d3-MeCN](image)

3.10 and 3.11 were synthesised and fully characterised in the same way as 3.9. The proposed structures determined from the data obtained are shown in Figure 3-35. The $^{31}$P{$^1$H} NMR spectrum of 3.10 shows a singlet peak at 44.96 ppm and the septime indicative of the PF$_6$ counter ion. Mass spectrometry and elemental analysis confirmed the expected formula of 3.10 to be [Ag(C$_{11}$H$_{26}$S$_4$P$_2$)]PF$_6$. 
X-ray crystal structures of 3.9 – 3.11 have not been obtained for the silver(I) complexes reported here. Genge et al.\textsuperscript{11} report silver(I) complexes with similar ligands (Figure 3-23) and the complexes reported are shown to have tetrahedral geometry.\textsuperscript{11} For this reason 3.9 and 3.10 are expected to have similar structures to those reported, Figure 3-36 shows the silver(I) complex with a ligand similar to 3.1.

The $^{31}$P{^1}H NMR spectrum of 3.11 shows a singlet at 43.8 ppm and a signal which is assigned to the counter ion. 3.8 (the copper (I) complex with 3.3) was thought to be a mixture of several compounds including the polymeric form, so there was concern that 3.11 may also be a mixture of products. However, the elemental analysis obtained for 3.11 supports synthesis of the compound with the formula [Ag(C_{12}H_{28}S_{4}P_{2})]PF_{6}. This, along with the NMR spectra and mass spectrometry data suggest that the monomeric form has been isolated. The larger ionic radius of silver(I) when compared to copper(I) may provide an explanation for this. As noted at the beginning of this section, silver(I) with a coordination number of four has an effective ionic radii of 100 pm whereas the equivalent radius for copper(I) is 60 pm. Whilst 3.3 with a C\textsubscript{4} carbon backbone appeared to be too flexible to form a monomeric species with a copper(I)
centre it seems that the larger silver(I) centre is able to stabilise the more flexible 7 membered ring which forms upon complexation with 3.3.

3.5.3 Palladium(II) Complexes

With tetradeutate ligands, palladium(II) tends to form +2 square planar complexes thus 3.1 - 3.3 were reacted with palladium(II) chloride to investigate the flexibility of the ligand. The copper and silver complexes have shown that the ligands can co-ordinate in a tetrahedral fashion and can act as tetra-dentate, bi-dentate or bridging chelates. Figure 3-37 shows the reaction conditions used to synthesise 3.12. In similar reaction systems silver(I) hexafluorophosphate can be used as a reactant, however with this ligand system [AgL]+ complexes could be produced. As a result thallium(I) hexafluorophosphate was used as a non-coordinating reactant.

![Diagram of reaction scheme used for the synthesis of 3.12](image)

**Figure 3-37: Reaction scheme used for the synthesis of 3.12**

Synthesis of 3.12 was confirmed by NMR spectroscopy, mass spectrometry and elemental analysis. The $^{31}$P{$^{1}$H} NMR spectrum shows the product peak as a singlet at 44.6 ppm and a septet at -144.2 ppm which corresponds to the PF$_6$ counter ion. The $^{1}$H NMR spectrum shows the broad multiplet signals which were assigned to CH$_2$ groups in the backbone. The signal broadening indicates that in solution ‘flipping’ of the rings surrounding the metal centre occurs.

Yellow crystals suitable for X-ray structural analysis were isolated by slow diffusion of diethyl ether into a solution of 3.12 in acetonitrile. The crystal structure (Figure 3-38) of 3.12 shows that, as expected, the ligand coordinates as a tetra-dentate chelate to a square planar
palladium(II) centre. The ideal bond angles of a square planar complex are 90° and 180°. The bond angles measured from the X-ray crystal structure of 3.12 are between 88.19(3)° – 93.86(3)° and 172.40(3)° – 176.50(3)° showing that the structure is distorted from the ideal geometry.

Figure 3-38: Ball and stick representation of the X-ray crystal structure of 3.12 with the counter ions and hydrogen atoms omitted for clarity

In compound 3.6, where 3.1 acts as a tetra-dentate chelate for a Cu(I) centre, the Cu-S bond lengths have no discernable pattern. In 3.12, the Pd-S bond lengths show a clear pattern, the internal thioether units give Pd-S bond lengths of 2.2940(8) and 2.2880(8) Å while the terminal thiophosphoryl units have longer Pd-S bond lengths of 2.3412(9) and 2.3338(9) Å. The P=S bond length is increased by ~0.3 Å to 2.0176(13) Å from the original starting ligand bond length of 1.9684(5) Å. Unlike the copper complex, where the two CuSPC$_2$S six-membered rings are in different conformation, in 3.12 the two PdSPC$_2$S six-membered rings have the same chair shaped conformation.
The same reaction conditions (Figure 3-37) were used for the synthesis of 3.13, however due to availability TiOTf was used instead of TIPF₆. Synthesis of 3.13 was confirmed by NMR spectroscopy, mass spectrometry and elemental analysis. The $^{31}$P{$^\text{1H}$} NMR spectrum shows a single peak at 46.2 ppm, comparable to that seen in 3.12. The $^\text{1H}$ NMR spectrum also shows broadening of the backbone CH₂ signals indicating flexibility of the rings surrounding the metal centre. The crystal structure of 3.13 is shown in Figure 3-39. As expected, the structure is similar to that observed in 3.12 with the ligand acting as a tetradentate chelate binding to palladium in a square planar geometry. As in the structure of 3.12, the bond angles are distorted from the ideal square planar geometry, with the measured values ranging from 85.81(3)° – 92.62(3)° and 167.72(3)° - 172.50(3)°. Unlike in the structure of 3.12, all 4 of the Pd-S bonds have a similar length ranging from 2.3147(7) – 2.3315(8) Å.

Figure 3-39: Ball and stick representation of the X-ray crystal structure of 3.13 with counter ions and hydrogen atoms omitted for clarity
Figure 3-40 shows similar chelates that have been complexed to Pd(II) and Pt(II) metal centres by Connolly et al.\textsuperscript{10} Unfortunately no X-ray crystal data is reported for the Pd(II) and Pt(II) complexes so no structural comparison can be made between the reported complexes\textsuperscript{10} and those in this thesis.

![Figure 3-40: Chelates used to complex Pd(II) and Pt(II) metal centres where E = S, Se, as published by Connolly et al.\textsuperscript{10}](image)

Interestingly, the reaction of 3.3 with PdCl\textsubscript{2} did not result in complex formation. A brown precipitate was isolated from the reaction and showed no signals within the \textsuperscript{31}P\{\textsuperscript{1}H\} NMR spectrum. The reaction was repeated several times however the same result was obtained through each repeat. The lack of a signal in the \textsuperscript{31}P\{\textsuperscript{1}H\} NMR spectrum suggests that 3.3 has not complexed to the palladium(II) centre. This indicates that no polymerisation or dimerisation has occurred, unlike the copper(I) reaction with 3.3 which produced a mixture of polymeric and dimeric species. The unsuccessful reaction of 3.3 with PdCl\textsubscript{2} may be explained by the ionic radius of Pd(II) which is 64 pm with a coordination number of four. Similar to that observed for copper(I) it appears that the C\textsubscript{4} backbone of 3.3 may be too flexible for these (Cu(I) and Pd(II)) smaller metal centres.

![Figure 3-41: Conditions used in the unsuccessful reaction of 3.3 with PdCl\textsubscript{2}](image)
The literature shows a few examples of palladium(II) complexes with \(-\text{S(CH}_2\text{)}_4\text{S}\)- bridges. Figure 3-42 shows three of these ligands. The \(S_4\) tetra-dentate chelate (Figure 3-42a) has been reported to complex to Pd(II) and Pt(II) centres by Hartley et al.\(^{46}\) The published data shows that the complex is isolated as a monomeric species. To distinguish between the dimeric and monomeric forms where the anions are uncoordinated the concentration dependence of the conductivities was measured. The Debye-Hückel equation was used to identify the ratio of electrolytes i.e. 1:2 in the monomeric form and 1:4 in the dimeric form.

\textbf{Figure 3-42: Ligands with a S(CH}_2\text{)}_4\text{S bridge that have previously been complexed to Pd(II) metal centres}\(^{46-48}\)

The \(S_3\) chelate (Figure 3-42b) was shown by Giesbrecht et al.\(^{47}\) to coordinate through two of the thioether donor atoms with coordinating anions filling the coordination sphere. Complexation of the bidentate chelate (Figure 3-42c) to Pd(II) is reported by Levason et al.\(^{48}\) where two ligand units coordinate to the metal centre. In all three cases the palladium(II) precursor \([\text{Pd(MeCN)}_4][\text{X}]_2\) was synthesised before addition of the ligand. This method was attempted but unfortunately the same result was obtained and the desired compound shown in Figure 3-41 was not isolated.

The information obtained from palladium complexes \textbf{3.12 and 3.13} shows that \textbf{3.1} and \textbf{3.2} can act as tetradeinate chelates in a square planar geometry. This structural data suggests that chelates \textbf{3.1} and \textbf{3.2} should be able to coordinate to Re or \(^{99m}\text{Tc}\) cores in a square-based pyramidal or octahedral geometry with the chelate binding in the equatorial plane. The X-ray crystal structures are used to postulate an explanation for the rhenium and technetium results.
in section 3.5.5 whilst the next section makes a comparison of the four crystal structures obtained.

### 3.5.4 Comparison of X-ray crystal structures

Figure 3-46 to Figure 3-48 show the X-ray crystal structures discussed in the previous sections, here a comparison of some interesting bond lengths and angles is made. Table 3-6 shows the M-S and S=P bond lengths of the thiophosphoryl moieties in 3.6, 3.8, 3.12 and 3.13, whilst Figure 3-43 shows a schematic detailing the notation which is used to discuss the relevant bond lengths and angles that are noted here. The crystal structure of 3.2 (Section 3.3) shows the P=S bond length to be 1.9684(5) Å. The data presented in Table 3-6 shows that in all complexes the P=S bond is longer than in 3.2, this is as expected and is likely due to π back bonding from the metal centre.

![Schematic showing the notation used for the discussion within the section](image-url)

**Figure 3-43: Schematic showing the notation used for the discussion within the section**
<table>
<thead>
<tr>
<th>Bond</th>
<th>Thiophosphoryl 1 (Å)</th>
<th>Thiophosphoryl 2 (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Compound</strong></td>
<td>M-S1</td>
<td>S1=P2</td>
</tr>
<tr>
<td>3.6</td>
<td>[Cu(3.1)]BF₂</td>
<td>2.2988(7)</td>
</tr>
<tr>
<td>3.8</td>
<td><a href="BF%E2%82%84">Cu₂(3.3)MeCN₂</a>₂</td>
<td>2.3492(9)</td>
</tr>
<tr>
<td>3.12</td>
<td><a href="PF%E2%82%86">Pd(3.1)</a>₂</td>
<td>2.3412(9)</td>
</tr>
<tr>
<td>3.13</td>
<td><a href="PF%E2%82%86">Pd(3.2)</a>₂</td>
<td>2.3315(8)</td>
</tr>
</tbody>
</table>

Table 3-6: The M-S and S-P bond lengths of the thiophosphoryl moieties in 3.6, 3.8, 3.12 and 3.13

It is interesting to note that the P=S bond of 3.2 is visible in the IR spectrum at 627 cm⁻¹ however, the P=S bond is no longer observed upon complexation. Since the spectrometer does not go below 600 cm⁻¹ this suggests that the P=S bond frequency has shifted below this, indicating that the bond has lengthened. This has been confirmed by the structural data obtained.

<table>
<thead>
<tr>
<th>Bond</th>
<th>Thioether 1 i.e M-S5 (Å)</th>
<th>Thioether 2 i.e. M-S8/9/10(Å)</th>
<th>Thiophosphoryl 1 i.e. M-S1 (Å)</th>
<th>Thiophosphoryl 2 i.e. M-S12/13 (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Compound</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.6</td>
<td>[Cu(3.1)]BF₂</td>
<td>2.3224(7)</td>
<td>2.3803(7)</td>
<td>2.2988(7)</td>
</tr>
<tr>
<td>3.8</td>
<td><a href="BF%E2%82%84">Cu₂(3.3)MeCN₂</a>₂</td>
<td>2.3817(16)</td>
<td>2.3114(16)</td>
<td>2.3492(9)</td>
</tr>
<tr>
<td>3.12</td>
<td><a href="PF%E2%82%86">Pd(3.1)</a>₂</td>
<td>2.2880(8)</td>
<td>2.2940(8)</td>
<td>2.3412(9)</td>
</tr>
<tr>
<td>3.13</td>
<td><a href="PF%E2%82%86">Pd(3.2)</a>₂</td>
<td>2.3218(7)</td>
<td>2.3147(7)</td>
<td>2.3315(8)</td>
</tr>
</tbody>
</table>

Table 3-7: The bond lengths of the M-S bonds in 3.6, 3.8, 3.12 and 3.13
Table 3-7 shows the bond lengths of the four metal-sulfur bonds in 3.6, 3.8, 3.12 and 3.13. Interestingly for 3.6 and 3.8 there does not appear to be an observable pattern, although possibly less surprising for 3.8 since the bond length of thiophosphoryl 2 is indicative of the bridging thiophosphoryl moiety to a second Cu centre. A more distinct pattern can be observed for the palladium(II) complex 3.12, with both M-S thioether bonds of similar length and shorter than the two M-S thiophosphoryl bonds. In the case of 3.13 all four M-S bonds appear to be of a more similar length. The data here does not point towards any obvious trends either between the ligands or the metal centres.

Table 3-8 details the bond angles around the metal centres; the measured bond angle is reported alongside the distortion from the ideal angle. This was obtained by calculating the difference between the measured bond angle and the ideal angle; this is also presented as a percentage distortion. The total complex distortion has also been calculated; although not intended to give an accurate representation it is interesting to note an average overall distortion given in numerical form. The total complex distortion was calculated by summing the distortion from the ideal angle in degrees and averaging this over the number of angles. 3.8 is slightly more complicated due to the flexibility of the C₄ carbon backbone which causes disorder throughout the polymer, for this reason S5 and S10 are non-equivalent. Therefore, two total complex distortions are noted, one concerning the Cu(I) centre bound to S5 and the other with Cu(I) bound to S10.

From the percentage distortion it can be seen that the two copper complexes have the highest percentage distortion at individual angles, with 3.6 containing two angles distorted from the ideal by ~16 % whilst 3.8 contains three angles with distortion of about ~12 %. However the total complex distortion for both copper(I) centres is low when compared to the Pd(II) complexes. The palladium(II) complexes are seen to have lower percentage distortions across individual angles, however in 2.10 only one angle is larger than the ideal with three of the other
angles being acute. This has led to a fairly large total distortion parameter of -1.89. 3.13, with two angles larger than the ideal value has a larger distortion parameter than that seen for 3.12, this was unexpected. It was initially thought that the smaller bite angle of ligand 3.1, when compared to 3.2, due to the length of the carbon backbone, may have caused the distortion observed in 3.12 however when considering 3.13 this appears to not be the case. Palladium(II) square planar complexes are d8 therefore, the distortion observed is unlikely to be due to crystal field splitting effects.
<table>
<thead>
<tr>
<th>Compound</th>
<th>Bond notation</th>
<th>Angle (°)</th>
<th>Distortion from ideal angle (°)</th>
<th>Percentage distortion from ideal angle (%)</th>
<th>Total complex distortion ( \Sigma )distortion from ideal angle/num er of angles</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3.6 [Cu(3.1)]BF₂</strong></td>
<td>S1-Cu-S5</td>
<td>109.24(3)</td>
<td>-0.25</td>
<td>0.23</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td>S1-Cu-S12</td>
<td>105.11(2)</td>
<td>-4.39</td>
<td>4.01</td>
<td></td>
</tr>
<tr>
<td></td>
<td>S5-Cu-S12</td>
<td>118.73(3)</td>
<td>9.23</td>
<td>8.43</td>
<td></td>
</tr>
<tr>
<td></td>
<td>S1-Cu-S8</td>
<td>126.57(3)</td>
<td>17.07</td>
<td>15.59</td>
<td></td>
</tr>
<tr>
<td></td>
<td>S5-Cu-S8</td>
<td>91.70(2)</td>
<td>-17.80</td>
<td>16.26</td>
<td></td>
</tr>
<tr>
<td></td>
<td>S12-Cu-S8</td>
<td>106.32(2)</td>
<td>-3.18</td>
<td>2.90</td>
<td></td>
</tr>
<tr>
<td><strong>3.8 [Cu₂(3.3)MeCN₂] (BF₄)₂</strong></td>
<td>S1-Cu-S5</td>
<td>95.09(5)</td>
<td>-14.41</td>
<td>13.16</td>
<td>0.79</td>
</tr>
<tr>
<td></td>
<td>S1B-Cu-S5</td>
<td>116.26(5)</td>
<td>6.76</td>
<td>6.17</td>
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</tr>
<tr>
<td></td>
<td>N20-Cu1-S5</td>
<td>97.25(10)</td>
<td>-12.25</td>
<td>11.19</td>
<td></td>
</tr>
<tr>
<td></td>
<td>S1B-Cu-N20</td>
<td>119.48(9)</td>
<td>9.98</td>
<td>9.11</td>
<td></td>
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<tr>
<td></td>
<td>S1B-Cu-S1B</td>
<td>119.16(2)</td>
<td>9.66</td>
<td>8.82</td>
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<tr>
<td></td>
<td>S1-Cu-N20</td>
<td>105.01(9)</td>
<td>-4.49</td>
<td>4.10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C10-Cu-N20</td>
<td>107.50(10)</td>
<td>-2.00</td>
<td>1.83</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>S10-Cu-S1</td>
<td>107.80(5)</td>
<td>-1.70</td>
<td>1.55</td>
<td></td>
</tr>
<tr>
<td></td>
<td>S10-Cu-S1B</td>
<td>96.56(5)</td>
<td>-12.94</td>
<td>11.82</td>
<td></td>
</tr>
<tr>
<td><strong>3.12 <a href="PF%E2%82%86">Pd(3.1)</a>₂</strong></td>
<td>S5-Pd-S8</td>
<td>88.86(3)</td>
<td>-1.14</td>
<td>1.27</td>
<td>-1.89</td>
</tr>
<tr>
<td></td>
<td>S5-Pd-S12</td>
<td>172.40(3)</td>
<td>-7.60</td>
<td>4.22</td>
<td></td>
</tr>
<tr>
<td></td>
<td>S8-Pd-S12</td>
<td>93.86(3)</td>
<td>3.86</td>
<td>4.29</td>
<td></td>
</tr>
<tr>
<td></td>
<td>S5-Pd-S1</td>
<td>88.19(3)</td>
<td>-1.81</td>
<td>2.01</td>
<td></td>
</tr>
<tr>
<td></td>
<td>S8-Pd-S1</td>
<td>176.50(3)</td>
<td>-3.50</td>
<td>1.94</td>
<td></td>
</tr>
<tr>
<td></td>
<td>S12-Pd-S1</td>
<td>88.83(3)</td>
<td>-1.17</td>
<td>1.30</td>
<td></td>
</tr>
<tr>
<td><strong>3.13 <a href="PF%E2%82%86">Pd(3.2)</a>₂</strong></td>
<td>S9-Pd-S13</td>
<td>91.37(3)</td>
<td>1.37</td>
<td>1.52</td>
<td>-3.55</td>
</tr>
<tr>
<td></td>
<td>S9-Pd-S5</td>
<td>88.67(3)</td>
<td>-1.33</td>
<td>1.48</td>
<td></td>
</tr>
<tr>
<td></td>
<td>S13-Pd-S5</td>
<td>167.72(3)</td>
<td>-12.28</td>
<td>6.82</td>
<td></td>
</tr>
<tr>
<td></td>
<td>S9-Pd-S1</td>
<td>172.50(3)</td>
<td>-7.50</td>
<td>4.17</td>
<td></td>
</tr>
<tr>
<td></td>
<td>S13-Pd-S1</td>
<td>85.81(3)</td>
<td>-4.19</td>
<td>4.66</td>
<td></td>
</tr>
<tr>
<td></td>
<td>S5-Pd-S1</td>
<td>92.62(3)</td>
<td>2.62</td>
<td>2.91</td>
<td></td>
</tr>
</tbody>
</table>

Table 3-8: The bond angles around the metal centre, the distortion from the ideal angle, percentage distortion from the ideal angle, and the total complex distortion as an average over all angles present, for 3.6, 3.8, 3.12 and 3.13
Since the total distortion is an average over the whole molecule it is not the most reliable parameter to consider. Instead the more telling data is the difference between the measured angle and the ideal angle of that geometry; in the case of 3.13, the ideal square planar geometry would have angles of 90° and 180°. In 3.13 the two 180° angles are 167° and 172°, this appears to give rise to the high total complex distortion. Figure 3-44a shows a schematic of the query used to search the CCDC database for similar Pd(II) complexes. Analysis of the search results showed that the angles observed in 3.13 are comparable to other complexes within the literature.\(^1,49,50\) Figure 3-44b shows an example of one complex with angles of 170° and 166° which are comparable to those seen in 3.13. It is postulated that the large distortion observed for 3.13 is due to the way 3.2 wraps around the metal centre. Figure 3-44c shows the space filled crystal structure of 3.13, the structure appears to show the ligand coordinating on one side of the Pd(II) centre, possibly causing the distortion observed.
Figure 3-47: Ball and stick representation of the X-ray crystal structure of 3.6 with the ring size noted. The counter ion and hydrogen atoms are omitted for clarity.

Figure 3-48: Ball and stick representation of the X-ray crystal structure of 3.12 with the ring size noted. The counter ion and hydrogen atoms are omitted for clarity.

Figure 3-45: Ball and stick representation of the X-ray crystal structure of 3.13 with the ring size noted. The counter ion and hydrogen atoms are omitted for clarity.

Figure 3-46: Ball and stick representation of the X-ray crystal structure of 3.8 with the ring size noted. The counter ion and hydrogen atoms are omitted for clarity.
### 3.5.5 Can the rhenium and technetium results be explained?

As previously discussed there is literature evidence for the coordination of thioether and thiophosphoryl moieties to rhenium and technetium metal centres. However the combination of four ‘soft’ sulphur donors and the high metal oxidation state may not be ideal. From the literature gathered it was thought that 3.1 - 3.3 may have the potential to form complexes with rhenium and technetium.

In several rhenium and technetium-99m complexes where a tetra-dentate chelate coordinates to a metal core ([MO]^{3+}, [MN]^{2+}, [MO_2]^{+}), the resulting complex geometry can be square based pyramidal or octahedral. The geometry of the complex can be influenced by the charge of the ligand and the charge on the metal core. Since the ligands reported here (3.1 - 3.3) are neutral and do not have a site for deprotonation the charge of any rhenium or technetium complexes synthesised would be governed by the charge of the metal core. For this reason it was thought that the core most likely to complex 3.1 - 3.3 would be [MO_2]^{+}. This would give the complexes a +1 charge and octahedral geometry.

Table 3-9 shows the atomic radii of the metal centres discussed in this chapter, copper(I), silver(I), palladium(II), rhenium(V) and technetium(V). The metal centres all have similar atomic radii (except silver (I)). The similarity of the Pd(II), Re(V) and Tc(V) atomic radii allows for a structural analysis of 3.12 and 3.13 to be comparable to the expected complexes of rhenium(V) and technetium(V).

<table>
<thead>
<tr>
<th>Metal</th>
<th>Cu(I)</th>
<th>Ag(I)</th>
<th>Pd(II)</th>
<th>Re(V)</th>
<th>Tc(V)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geometry</td>
<td>Tetrahedral</td>
<td>Tetrahedral</td>
<td>Square Planar</td>
<td>Octahedral</td>
<td>Octahedral</td>
</tr>
<tr>
<td>Effective Ionic Radii (pm)^37</td>
<td>60</td>
<td>100</td>
<td>64</td>
<td>58</td>
<td>60</td>
</tr>
</tbody>
</table>

*Table 3-9: The effective ionic radii of Cu(I), Ag(I), Pd(II), Re(V) and Tc(V)*
The crystal structures of $\text{3.12}$ and $\text{3.13}$ offer a good opportunity to visualise how $\text{3.1}$ and $\text{3.2}$ may co-ordinate to rhenium and technetium-$99m$ centres. The orientation of $\text{3.1}$ and $\text{3.2}$ around the metal centre can be observed though the space-filled structures of $\text{3.12}$ and $\text{3.13}$ (Figure 3-49). The space-filled structures show that the phosphine methyl groups are orientated towards the metal centre enclosing one face of the palladium(II) centre.

Assuming that $\text{3.1}$ and $\text{3.2}$ would coordinate to rhenium and technetium in the same way allows for a comparison with the metal cores. With one face of the metal centre ‘capped’ by $\text{3.1}$ and $\text{3.2}$, it is unlikely that a $[\text{MO}_2]^+$ core could be accommodated. Figure 3-50 shows the space-filled X-ray crystal structure of $\text{trans-bis(1,2-bis(dimethylphosphino)ethane-P,P')-dioxo-rhenium(V)}$ published by Engelbrecht et al. This shows the $[\text{ReO}_2]^+$ core and gives an impression of the space required. By comparing this space-filled structure to those in Figure 3-49 it can be proposed that rhenium and technetium complexes with the di-oxo core $[\text{MO}_2]^+$ were not synthesised due to the steric constraints of the $\text{3.1}$ and $\text{3.2}$ around the metal.

With only one face of the metal centre ‘capped’ it is suggested that coordination at $[\text{ReO}]^{3+}$ would not be limited by this factor. Unfortunately as discussed, complexes were not successfully synthesised with this core. It is reasoned that this is due to the high charge on the core. It has been shown that in some cases a chloride ion (or other anion) can coordinate to the rhenium centre, creating an octahedral complex and lowering the overall charge.
Unfortunately this is an unlikely possibility here due to the steric constraints imposed by the ligand.

![Space filled X-ray crystal structure of trans-bis(1,2-bis(dimethylphosphino)ethane-P,P')-dioxo-rhenium(V) hexafluorophosphate dihydrate](image)

**Figure 3-50: Space filled X-ray crystal structure of trans-bis(1,2-bis(dimethylphosphino)ethane-P,P')-dioxo-rhenium(V) hexafluorophosphate dihydrate**

Whilst it is postulated that the coordination of the ligand may have had an effect on the outcome of the rhenium and technetium reactions the donor atoms can also be considered as a factor. As mentioned in previous chapters thioether groups are soft $\sigma$ donors and when combined with other ‘harder’ groups can coordinate to Re(V) and Tc(V). However, in this case it may be that the blend of thioether and thiophosphoryl groups may not be suitable for the hard metal cores. To further investigate the use of the thiophosphoryl moiety as a stable thiol analogue chelates that combine this group with amine and phosphine donors should be produced. The ligands here may also be of use with Re(I) or Tc(I) tricarbonyl cores.

### 3.6 Conclusion

Dimethylvinyl sulphide has been used to synthesise bis-thioether bis-thiophosphoryl ligands (3.1 – 3.3) with varying carbon backbone lengths. These have been shown to be tetra-dentate chelates which are also reported to act as bi-dentate and bridging donors. 3.1 - 3.3 have been complexed to different metal centres to show the ligand in different coordination modes.
Reactions of 3.1 - 3.3 with rhenium precursors [ReO$_2$(py)$_4$]Cl and [ReOCl$_3$(PPh$_3$)$_2$] were completed using a series of different conditions. $^{31}$P{$^1$H} NMR spectra suggest possible complexation, mass spectrometry data show no evidence of a [ReO$_n$] complex and unfortunately complexes could not be isolated. Technetium-99m reactions with 3.2 were also completed; initially pre-made freeze-dried kits were used with little success. Reactions were then completed with a reductant, co-ligand and buffer, to test different conditions. Unfortunately technetium-99m complexes were not synthesised, with unreacted [99mTcO$_4^-$] isolated in each reaction.

It was shown here that complexes with copper(I) (3.6 - 3.8) possess a tetrahedral geometry. The reaction between copper(I) and 3.3 resulted in complex 3.8. The NMR spectra and mass spectrometry data of 3.8 suggested a monomeric structure however X-ray crystal analysis has indicated a polymeric structure. The elemental analysis obtained showed that 3.8 was not isolated as a pure sample and after several repeat reactions it was concluded that 3.8 was a mixture of monomer, dimer and polymer units.

The silver(I) complexes (3.9 - 3.11) synthesised are proposed to have a tetrahedral geometry similar to that observed for 3.6. Elemental analysis shows that 3.9 - 3.11 were isolated as pure samples. Interestingly the reaction of silver(I) and 3.3 to synthesise 3.11 does not result in a polymeric complex like 3.8, but a monomeric complex similar to 3.6. Palladium(II) complexes (3.12 and 3.13) are shown by X-ray crystal structure analysis to have a square planar geometry, whilst the reaction of 3.3 with PdCl$_2$ did not yield the desired product.
It is proposed that these results can be explained by the increasing carbon backbone of the ligands and the effective ionic radii of the metal centres investigated. Silver(I) has a larger ionic radii of ~40 pm than copper(I) and palladium(II). The reactions of 3.3 with the smaller metal centres resulted in multiple species of polymeric or dimeric form (copper(I)) or an unsuccessful reaction (palladium(II)) whilst the reaction with silver(I) the larger metal centre, resulted in the isolation of a monomeric complex. This suggests that 3.3 with the longest carbon backbone (C₄) may be too flexible for the metal centres and the formation of the 7-membered ring during complexation is not stable. The literature evidence supports this proposal in the case of copper(I) with no monomeric species containing 7-membered rings with thioether donors observed, however these have been noted for palladium(II).

The X-ray crystal structures of 3.12 and 3.13 were used to visualise how the compounds 3.1 and 3.2 would coordinate around a metal centre. This led to a postulated reason for the rhenium and technetium results and the combination of donors, i.e. the ‘soft’ thioether moiety, the sterics of the ligand upon complexation and the charge of the metal centre are offered as an explanation.
3.7 Experimental

All reactions and manipulations were carried out under anaerobic conditions unless otherwise stated. All starting materials were of reagent grade, were purchased from Sigma Aldrich and used without further purification. Tetrakis(acetonitrile)copper(I) tetrafluoroborate was synthesised according to the literature procedure.\textsuperscript{29} \textsuperscript{1}H, \textsuperscript{31}P\{\textsuperscript{1}H\}, \textsuperscript{13}C\{\textsuperscript{1}H\} NMR spectra were recorded on a Bruker AV 400 MHz spectrometer. ESI mass spectra were recorded on a Micromass LCT Premier spectrometer by John Barton or Lisa Haigh. Elemental analyses were completed by Stephen Boyer at the Science Centre, London Metropolitan University. Single crystal X-ray analysis was completed by Dr Andrew White at Imperial College London. Electrochemistry was completed by Shuoren Du of Imperial College London with a 5 mM solution of the substrate was prepared in dry degassed DCM containing 20 equivalents of electrolyte (tetrabutylammonium hexafluorophosphate). The working electrode was a circular platinum disc 0.05 mm in diameter. The counter electrode was a platinum coil 1 mm in diameter and the reference electrode was a silver wire 1 mm in diameter. The cyclic voltammograms were measured using a MacLab potentiostat and analyzed using Gamary Workshop software at scan rates between 100 and 5000 mV/s.

3.7.1 Synthesis of starting materials

Literature methods were followed and referenced, unless there was a modification of the reported protocol.

**Tetramethyldiphosphine disulfide\textsuperscript{16}**

\[
\begin{array}{c}
\text{S} \\
\text{P-P} \\
\text{S} \\
\end{array}
\]

Starting with thiophosphoryl chloride (4.35 mL) yielded 3.11 g, 78 %. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}, ppm): \(\delta\) 2.01 (sextet, CH\textsubscript{3}). \textsuperscript{31}P\{\textsuperscript{1}H\} NMR (162 MHz, CDCl\textsubscript{3}, ppm): \(\delta\) 35.2 (s, P=S). LSIMS MS (+): 187 \textit{m/z} [M]\textsuperscript{+}. Elemental analysis for Me\textsubscript{2}PSPSMe\textsubscript{2} experimental (calculated) %: C, 25.93 (25.81); H, 6.63 (6.50).
Dimethylvinylphosphine sulfide\textsuperscript{9,17}

Bromine in dry DCM (4.0 mL, 0.65 M, 2.6 mmol) was added dropwise to a cooled solution of tetramethyldiphosphine disulfide (0.50 g, 2.7 mmol) in dry DCM. The reaction was left to stir for a further hour before the solvent was removed \textit{in vacuo}. Dry THF was then added to dissolve the residue and the solution was cooled to 0°C and vinylmagnesium bromide (5.3 mL, 5.3 mmol, 1M) was added dropwise. The reaction mixture was warmed to room temperature and left to stir for 1 hour before the solvent was removed \textit{in vacuo}. The residue was then dissolved in degassed Et\textsubscript{2}O (10 mL) and the reaction quenched with degassed H\textsubscript{2}O (10 mL). The organic layer was removed and the aqueous layer was then washed with degassed Et\textsubscript{2}O (6 x 5 mL), dried of MgSO\textsubscript{4} and the solvent removed \textit{in vacuo} to afford the product as a white powder. Yield 0.52 g, 81 %. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}, ppm): δ 1.80 (d, \textit{J}_{PH} = 12.8 Hz, 6H, C\textsubscript{H}\textsubscript{3}), 6.18 (m, 1H, C\textsubscript{H}), 6.40 (m, 2H, C\textsubscript{H}\textsubscript{2}). \textsuperscript{31}P \{\textsuperscript{1}H\} NMR (162 MHz, CDCl\textsubscript{3}, ppm): δ 29.2 (s, P=S).

\textbf{Rhenium oxotrichlorobis(triphenylphosphine)}\textsuperscript{54}

\begin{center}
\begin{align*}
\text{Ph}_3\text{P} & \quad \text{\textsuperscript{O}Cl} \\
\text{\textsuperscript{Cl}} & \quad \text{ReCl} \\
\text{\textsuperscript{Cl}} & \quad \text{\textsuperscript{Cl}PPh}_3 \\
\end{align*}
\end{center}

Starting with Re\textsubscript{2}O\textsubscript{7} (0.75 g, 1.54 mmol) yielded 2.16 g, 84 %. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}, ppm): δ 6.96 (m, Ph). \textsuperscript{31}P \{\textsuperscript{1}H\} NMR (162 MHz, CDCl\textsubscript{3}, ppm): δ -19.08 (s, PPh\textsubscript{3}).

Elemental analysis for ReOCl\textsubscript{3}(PPh\textsubscript{3})\textsubscript{2} experimental (calculated) %: C, 52.0 (51.9); H, 3.6 (3.6).

\textbf{Rhenium nitridodichlorobis(triphenylphosphine)}\textsuperscript{55}

\begin{center}
\begin{align*}
\text{Ph}_3\text{P} & \quad \text{\textsuperscript{N}Cl} \\
\text{\textsuperscript{Cl}} & \quad \text{ReCl} \\
\text{\textsuperscript{Cl}} & \quad \text{\textsuperscript{Cl}PPh}_3 \\
\end{align*}
\end{center}

Starting with rhenium oxotrichlorobis(triphenylphosphine) (2.0 g, 2.40 mmol) yielded 1.32 g, 69 %. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}, ppm): δ 6.96 (m, Ph). \textsuperscript{31}P \{\textsuperscript{1}H\} NMR (162 MHz, CDCl\textsubscript{3}, ppm): δ 24.2 (s, PPh\textsubscript{3}). Elemental analysis for ReNCl\textsubscript{2}(PPh\textsubscript{3})\textsubscript{2} experimental (calculated) %: C, 54.4 (54.3); H, 3.6 (3.8); N, 1.8 (1.8).
Rhenium dioxotetrapyridinechloride\textsuperscript{56}

Starting with rhenium oxotrichlorobis(triphenylphosphine) (1.0 g, 1.20 mmol)
yielded 0.44 g, 64 %. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}, ppm): \(\delta\) 9.05 (m, 9H, py); 8.43 (m, 8H, py); 7.75 (m, 5H, py). Electrospray MS (+): 535.12 \(m/z\) [M]\textsuperscript{+}. Elemental analysis for [ReO\textsubscript{2}(py)\textsubscript{4}]Cl experimental (calculated) %: C, 41.9 (42.1); H, 3.7 (3.5); N, 9.7 (9.8).

3.7.2 General synthesis of 3.1 – 3.3

The dithiol (1.66 mmol) was added to an EtOH solution of degassed sodium ethoxide (5.35 ml, 3.32 mmol, 0.62 M) in EtOH (5 mL). The solution was left to stir for 1 hour then added to dimethylvinylphosphine sulphide (0.4 g, 3.32 mmol) in degassed EtOH (10 ml). The reaction was left to stir overnight. A white precipitate formed in this time which was isolated by vacuum filtration and washed with diethyl ether.

3.1, ((CH\textsubscript{3})\textsubscript{2}PSCH\textsubscript{2}CH\textsubscript{2}SCH\textsubscript{2})

Starting with 1,2-ethanedithiol (0.17 mL, 1.66 mmol) yielded 0.25 g, 45 %. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}, ppm): \(\delta\) 2.94 (m, 4H, ((CH\textsubscript{3})\textsubscript{2}PSCH\textsubscript{2}CH\textsubscript{2}SCH\textsubscript{2}-)), 2.84 (s, 4H, ((CH\textsubscript{3})\textsubscript{2}PSCH\textsubscript{2}CH\textsubscript{2}SCH\textsubscript{2}-)), 2.19 (m, 4H, ((CH\textsubscript{3})\textsubscript{2}PSCH\textsubscript{2}CH\textsubscript{2}SCH\textsubscript{2}-)), 1.80 (d, \(J_{HP} = 12.8\) Hz, 12H, CH\textsubscript{3}). \textsuperscript{31}P \{\textsuperscript{1}H\} NMR (162 MHz, CDCl\textsubscript{3}, ppm): \(\delta\) 36.10 (s, P=S). \textsuperscript{13}C \{\textsuperscript{1}H\} NMR (100 MHz, CDCl\textsubscript{3}, ppm): \(\delta\) 34.78 ((CH\textsubscript{3})\textsubscript{2}PSCH\textsubscript{2}CH\textsubscript{2}SCH\textsubscript{2}-)), 34.28 ((CH\textsubscript{3})\textsubscript{2}PSCH\textsubscript{2}CH\textsubscript{2}SCH\textsubscript{2}-)), 31.94 ((CH\textsubscript{3})\textsubscript{2}PSCH\textsubscript{2}CH\textsubscript{2}SCH\textsubscript{2}-)), 25.09 ((CH\textsubscript{3})\textsubscript{2}PSCH\textsubscript{2}CH\textsubscript{2}SCH\textsubscript{2}-)), 21.21 (d, \(J_{CP} = 54.1\) Hz, CH\textsubscript{3}). Electrospray MS (+): 335 \(m/z\) [M]\textsuperscript{+}. IR spectrum (cm\textsuperscript{-1}): 2977 (CH\textsubscript{3} C-H stretch), 2843 (CH\textsubscript{2} C-H stretch), 2799 (CH\textsubscript{2} C-H stretch), 1428 (C-H bend), 1287, 1116, 979, 945, 928, 887, 744, 710 (CH\textsubscript{2}-S C-S stretch), 634 (P=S stretch). Elemental analysis for C\textsubscript{10}H\textsubscript{24}S\textsubscript{4}P\textsubscript{2} experimental (calculated) %: C, 35.83 (35.91); H, 7.36 (7.23).
3.2, \((\text{CH}_3)_2\text{PSCH}_2\text{CH}_2\text{SCH}_2\text{CH}_2\) \_2\text{CH}_2

Starting with 1,3-propanedithiol (0.19 mL, 1.66 mmol) yielded 0.19 g, 33 %. \(^1\text{H} \text{NMR} (400 \text{ MHz, CDCl}_3, \text{ ppm}): \delta 2.89 \text{ (m, 4H, ((CH}_3)_2\text{PSCH}_2\text{CH}_2\text{SCH}_2\text{CH}_2\text{CH}_2))}, 2.71 \text{ (t, }3J_{\text{HH}} = 6.5 \text{ Hz, 4H, ((CH}_3)_2\text{PSCH}_2\text{CH}_2\text{SCH}_2\text{CH}_2\text{CH}_2))}, 2.18 \text{ (m, 4H, ((CH}_3)_2\text{PSCH}_2\text{CH}_2\text{SCH}_2\text{CH}_2\text{CH}_2))}, 1.94 \text{ (p, 2H, ((CH}_3)_2\text{PSCH}_2\text{CH}_2\text{SCH}_2\text{CH}_2\text{CH}_2))}, 1.79 \text{ (d, }2J_{\text{HP}} = 12.8 \text{ Hz, 12H, CH}_3\text{)}. \(^3\text{P} \quad ^1\text{H} \text{NMR} (162 \text{ MHz, CDCl}_3, \text{ ppm}): \delta 35.01 \text{ (s, P=S)}\).

\(^{13}\text{C} \quad ^1\text{H} \text{NMR} (100 \text{ MHz, CDCl}_3, \text{ ppm}): \delta 34.62 \text{ (((((\text{CH}_3)_2\text{PSCH}_2\text{CH}_2\text{SCH}_2\text{CH}_2\text{CH}_2))))}, 34.09 \text{ (((((\text{CH}_3)_2\text{PSCH}_2\text{CH}_2\text{SCH}_2\text{CH}_2\text{CH}_2))))}, 31.78 \text{ (((((\text{CH}_3)_2\text{PSCH}_2\text{CH}_2\text{SCH}_2\text{CH}_2\text{CH}_2))))}, 27.93 \text{ (((((\text{CH}_3)_2\text{PSCH}_2\text{CH}_2\text{SCH}_2\text{CH}_2\text{CH}_2))))}, 25.09 \text{ (((((\text{CH}_3)_2\text{PSCH}_2\text{CH}_2\text{SCH}_2\text{CH}_2\text{CH}_2))))}, 21.07 \text{ (d, }J_{\text{CP}} = 54.4 \text{ Hz, CH}_3\text{)} \text{ Electrospray MS (+): 349 m/z [M]}. \text{ IR Spectrum (cm}^{-1}): 2898 \text{ (CH}_3\text{ C-H stretch), 2832 \text{ (CH}_2\text{ C-H stretch), 2765 \text{ (CH}_2\text{ C-H stretch), 1418 \text{ (C-H bend), 1288, 1274, 1115, 946, 903, 864, 747, 711 \text{ (CH}_2\text{-S C-S stretch), 627 \text{ (P=S stretch). Elemental analysis for C}_{11}\text{H}_{26}\text{S}_4\text{P}_2 experimental (calculated) %: C, 37.81 (37.93); H, 7.40 (7.53).}

3.3, \((\text{CH}_3)_2\text{PSCH}_2\text{CH}_2\text{SCH}_2\text{CH}_2\text{-})_2

Starting with 1,4-butandithiol (0.21 mL, 1.66 mmol) yielded 0.22 g, 37 %. \(^1\text{H} \text{NMR} (400 \text{ MHz, CDCl}_3, \text{ ppm}): \delta 2.87 \text{ (m, 4H, ((CH}_3)_2\text{PSCH}_2\text{CH}_2\text{SCH}_2\text{CH}_2\text{-})_2))}, 2.61 \text{ (m, 4H, ((CH}_3)_2\text{PSCH}_2\text{CH}_2\text{SCH}_2\text{CH}_2\text{-})_2))}, 2.18 \text{ (m, 4H, ((CH}_3)_2\text{PSCH}_2\text{CH}_2\text{SCH}_2\text{CH}_2\text{-})_2))}, 1.79 \text{ (d, }2J_{\text{HP}} = 12.8 \text{ Hz, 12H, CH}_3\text{)). 1.74 \text{ (m, 4H, ((CH}_3)_2\text{PSCH}_2\text{CH}_2\text{SCH}_2\text{CH}_2\text{-})_2))}, 2.17 \text{ (d, }J_{\text{CP}} = 53.8 \text{ Hz, CH}_3\text{). Electrospray MS (+): 363 m/z [M]}. \text{ IR spectrum (cm}^{-1}): 2964 \text{ (CH}_3\text{ C-H stretch), 2914 \text{ (CH}_2\text{ C-H stretch), 2876 \text{ (CH}_2\text{ C-H stretch), 1410 \text{ (C-H bend), 1288, 1278, 1115, 1018.}}

112
947, 872, 746, 711 (CH$_2$-S C-S stretch), 630 (P=S stretch). Elemental analysis for C$_{12}$H$_{28}$S$_4$P$_2$ experimental (calculated) %: C, 39.93 (39.77); H, 7.79 (7.79).

### 3.7.3 General reaction conditions for the attempted synthesis of rhenium(V) complexes

3.4 and 3.5: Rhenium dioxotetrapyridinechloride or rhenium oxotrichlorobis(triphenylphosphine) was dissolved in dry solvent and 3.2 added. The mixture was heated to reflux temperatures. Upon cooling if a precipitate was present it was isolated by vacuum filtration and the remaining solvent was removed in vacuo. If no precipitate was present the solution was concentrated in vacuo. The precipitate and filtrate were treated as crude products and standard analysis was obtained for each reaction.

### 3.7.4 General reaction conditions for the synthesis of technetium(V) complexes

HPLC analysis was completed on a phenomenex Luna C18 column 150 x 4.6 mm. Using 50 mM ammonium acetate in water as mobile phase A and acetonitrile as mobile phase B. The gradient of mobile phase B was increased from 25 % to 85 % over 20 minutes. TLC analysis was completed using on Whatman grade 3 Chr paper strips as the static phase and solvent including MEK, saline and acetone were used as the mobile phase.

**Kit synthesis, (GE001 and GE002):** To a freeze-dried GE premade kit (MDP kit, batch N°: 173/119-101, or Gluconate kit, Lot 2, 08/03/95) 3.2 (0.1 ml, 0.325 M solution in MeCN) was added. TcO$_4^-$ (0.1 ml, 264 MBq) in saline was added followed immediately by 0.4 ml saline. The reaction vessel was left for 20 mins before HPLC and TLC analysis.

**Synthesis of GE003 – GE006:** To the co-ligand (0.10 ml, 0.05M) in a P6 vial a buffer (0.50 ml, pH 7.0 (phosphate) or pH 9.2 (NaHPO$_4$/NaOH)) and saline (0.31 ml) were added. TcO$_4^-$ (0.1 ml) in saline was added followed immediately by SnCl$_2$ (0.15 ml, 0.6 mM) in HCl (0.01 M). The reaction vessel was left for 10 mins before the addition of 3.2 (0.1 ml, 0.33 M in MeCN) and then left for a further 20 mins. HPLC and TLC analysis were completed.
3.7.5 General synthesis of 3.6 – 3.8

The ligand (0.30 mmol) was added to dry MeCN under N₂ (50 ml), along with [Cu(MeCN)₄]BF₄ (0.30 mmol, 0.069 M in MeCN) and the reaction was heated to 50°C for 4 hours. The solvent was concentrated _in vacuo_ to 2 ml and diethyl ether (5 ml) was added to afford a white precipitate which was isolated by vacuum filtration. The resulting product was then stored under N₂.

3.6, [Cu(3.1)]BF₄

![Diagram of [Cu(3.1)]BF₄](image)

Starting with 3.1 (0.10 g, 0.29 mmol) yielded 0.08 g, 55 %. ¹H NMR (400 MHz, d³-MeCN, ppm): δ 3.07 (s, 4H, ((CH₃)₂PSCH₂CH₂SCH₂-)₂), 2.90 (m, 4H, ((CH₃)₂PSCH₂CH₂SCH₂-)₂), 2.29 (m, 4H, ((CH₃)₂PSCH₂CH₂SCH₂-)₂), 1.84 (d, ²J_HP = 13.2 Hz, CH₃, 12H). ³¹P {¹H} NMR (162 MHz, d³-MeCN, ppm): δ 38.66 (s, P=S). ¹³C {¹H} NMR (100 MHz, d³-MeCN, ppm): δ 33.31 ((((CH₃)₂PSCH₂CH₂SCH₂-)₂), 28.48 (((CH₃)₂PSCH₂CH₂SCH₂-)₂), 27.94 (((CH₃)₂PSCH₂CH₂SCH₂-)₂), 26.61 (((CH₃)₂PSCH₂CH₂SCH₂-)₂), 19.43 (d, ¹J_Pc = 54.3 Hz, CH₃). ESI MS [Cu(2.1)]⁺: 396.9478 m/z. Elemental analysis for [CuC₁₀H₂₄S₄P₂]BF₄ experimental (calculated) %: C, 24.80 (24.79); H, 5.02 (4.99).

3.7, [Cu(3.2)]BF₄

![Diagram of [Cu(3.2)]BF₄](image)

Starting with 3.2 (0.11 g, 0.31 mmol) yielded 0.09 g, 57 %. ¹H NMR (400 MHz, d³-MeCN, ppm): δ 3.09 (s, 4H, ((CH₃)₂PSCH₂CH₂SCH₂CH₂)₂), 2.89 (t, ²J_HP = 6.1 Hz, 4H, ((CH₃)₂PSCH₂CH₂SCH₂)₂ CH₂), 2.40 (m, 4H, ((CH₃)₂PSCH₂CH₂SCH₂)₂ CH₂), 2.09 (m, 2H, ((CH₃)₂PSCH₂CH₂SCH₂)₂ CH₂), 1.86 (d, ³J_HHH = 13.3 Hz, 12H, CH₃). ³¹P {¹H} NMR (162 MHz, d³-MeCN, ppm): δ 39.17 (s, P=S). ¹³C {¹H} NMR (100 MHz, d³-MeCN, ppm): δ 32.80 (((CH₃)₂PSCH₂CH₂SCH₂)₂CH₂), 30.85 (((CH₃)₂PSCH₂CH₂SCH₂)₂CH₂), 29.24 (((CH₃)₂PSCH₂CH₂SCH₂)₂CH₂), 27.60
Ligand (0.3 mmol) and AgPF₆ (0.3 mmol) were added to dry MeCN (50 ml) under N₂ and the reaction was stirred over 2 days. The solvent was concentrated in vacuo to 2 ml and diethyl ether (5 ml) added afford a white precipitate which was isolated by vacuum filtration. The resulting product was then stored under N₂.

3.9, [Ag(3.1)]PF₆

Starting with 3.1 (0.09 g, 0.32 mmol) yielded 0.06 g, 37 %. ¹H NMR (400 MHz, d³-MeCN, ppm): δ 3.09 (s, 4H, ((CH₃)₂PSCH₂CH₂SCH₂CH₂-)_₂), 2.93 (m, 4H, ((CH₃)₂PSCH₂CH₂SCH₂CH₂-)_₂), 2.37 (m, 4H, ((CH₃)₂PSCH₂CH₂SCH₂CH₂-)_₂), 1.98 (d, ³JHH = 13.2 Hz, 12H, CH₃). ³¹P {¹H} NMR (162 MHz, d³-MeCN, ppm): δ 43.64 (s, P=S), 144.86 (septet, PF₆). ¹³C {¹H} NMR (100 MHz, d³-MeCN, ppm): δ 30.92 ((CH₃)₂PSCH₂CH₂SCH₂CH₂-)_₂), 30.01 ((CH₃)₂PSCH₂CH₂SCH₂CH₂-)_₂, 29.49
(((CH₃)₂PSCH₂CH₂SCH₂-)₂), 25.45 (((CH₃)₂PSCH₂CH₂SCH₂-)₂), 20.45 (d, J_P= 55.5 Hz, CH₃). ESI MS [Ag(3.1)]⁺: 442.9288 m/z. Elemental analysis for [AgC₁₀H₂₄S₄P₂]PF₆ experimental (calculated) %: C, 20.56 (20.48); H, 4.04 (4.12).

3.10, [Ag(3.2)]PF₆

Starting with 3.2 (0.09 g, 0.25 mmol) yielded 0.10 g, 64 %. ¹H NMR [PF₆](400 MHz, d³-MeCN, ppm): δ 3.06 (m, 4H, ((CH₃)₂PSCH₂CH₂SCH₂)₂CH₂), 2.88 (t, J_H_H = 7.1 Hz, 4H, ((CH₃)₂PSCH₂CH₂SCH₂)₂CH₂), 2.45 (m, 4H, ((CH₃)₂PSCH₂CH₂SCH₂)₂CH₂), 2.07 (q, 2H, ((CH₃)₂PSCH₂CH₂SCH₂)₂CH₂), 1.93 (d, J_H_H = 13.2 Hz 12H, CH₃). ³¹P {¹H} NMR (162 MHz, d³-MeCN, ppm): δ 44.96 (s, P=S), -143.92 (septet, PF₆). ¹³C {¹H} NMR (100 MHz, d³-MeCN, ppm): δ 32.98 (((CH₃)₂PSCH₂CH₂SCH₂)₂CH₂), 32.49 (((CH₃)₂PSCH₂CH₂SCH₂)₂CH₂), 30.38 (((CH₃)₂PSCH₂CH₂SCH₂)₂CH₂), 28.97 (((CH₃)₂PSCH₂CH₂SCH₂)₂CH₂), 24.61 (((CH₃)₂PSCH₂CH₂SCH₂CH₂-)₂), 29.05 (d, J_P= 54.3 Hz, CH₃). ESI MS [Ag(3.2)]⁺: 456.9445 m/z. Elemental analysis for [AgC₁₁H₂₆S₄P₂]PF₆ experimental (calculated) %: C, 21.87 (22.00); H, 4.25 (4.36).

3.11, [Ag(3.3)]PF₆

Starting with 3.3 (0.11 g, 0.27 mmol) yielded 0.09 g, 56 %. ¹H NMR [PF₆](400 MHz, d³-MeCN, ppm): δ 3.00 (m, 4H, ((CH₃)₂PSCH₂CH₂SCH₂CH₂-)₂), 2.76 (m, 4H, ((CH₃)₂PSCH₂CH₂SCH₂CH₂-)₂), 2.40 (m, 4H, ((CH₃)₂PSCH₂CH₂SCH₂CH₂-)₂), 1.99 (d, J_H_H = 13.2 Hz, 12H, CH₃), 1.82 (m, 4H, ((CH₃)₂PSCH₂CH₂SCH₂CH₂-)₂). ³¹P {¹H} NMR (162 MHz, d³-MeCN, ppm) δ 43.77 (s, P=S), -144.43 (septet, PF₆). ¹³C {¹H} NMR (100 MHz, d³-MeCN, ppm): δ 32.12 (((CH₃)₂PSCH₂CH₂SCH₂CH₂-)₂), 31.72 (((CH₃)₂PSCH₂CH₂SCH₂CH₂-)₂), 31.22 (((CH₃)₂PSCH₂CH₂SCH₂CH₂-)₂), 27.93 (((CH₃)₂PSCH₂CH₂SCH₂CH₂-)₂), 25.61
Chapter 3

$(((\text{CH}_3)_2\text{PSCH}_2\text{CH}_2\text{SCH}_2\text{CH}_2-)_2)$, 19.23 (d, $^1J_{PC} = 53.7$ Hz, CH$_3$). ESI MS $[\text{Ag}(3.3)]^+$: 470.9593 m/z. Elemental analysis for $[\text{AgC}_{12}\text{H}_{28}\text{S}_4\text{P}_2]\text{PF}_6$ experimental (calculated) %: C, 23.62 (23.45); H, 4.72 (4.70).

3.7.7 General synthesis of 3.12 - 3.13

PdCl$_2$(0.2 g, 1.13 mmol), TlPF$_6$ (0.78 g, 2.23 mmol) and the ligand (1.13 mmol) were dissolved in MeCN (50 ml). The reaction was heated to reflux for 24 hours then cooled to room temperature. TlCl was removed by filtering through celite. The solvent was then concentrated in vacuo to 2 ml and diethyl ether (5 ml) added. The precipitate formed was isolated by vacuum filtration.

3.12, $[\text{Pd}(3.1)](\text{PF}_6)_2$

Starting with 3.1 (0.03 g, 0.09 mmol) yielded 0.05 g, 69 %. $^1$H NMR (400 MHz, d$_3$-MeCN, ppm): $\delta$ 3.22 (s, 4H, ((CH$_3$)$_2$PSCH$_2$CH$_2$SCH$_2$-)$_2$), 3.01 (m, 4H, ((CH$_3$)$_2$PSCH$_2$CH$_2$SCH$_2$-)$_2$), 2.16 (m, 4H, ((CH$_3$)$_2$PSCH$_2$CH$_2$SCH$_2$-)$_2$), 1.84 (d, $^2J_{HP} = 13.2$ Hz, 12H, CH$_3$). $^{31}$P{${}^1$H} NMR (162 MHz, d$_3$-MeCN, ppm): $\delta$ 44.64 (s, P=S), -144.22 (septet, PF$_6$). LSIMS $[\text{Pd}(3.1)]^+$: 439.1 m/z. Elemental analysis calculated for $[\text{PdC}_{10}\text{H}_{24}\text{S}_4\text{P}_2](\text{PF}_6)_2$ experimental (calculated) %: C, 16.53 (16.44); H, 3.29 (3.31).

3.13, $[\text{Pd}(3.2)](\text{PF}_6)_2$

Starting with 3.2 (0.04 g, 0.11 mmol) yielded 0.06 g, 81 %. $^1$H NMR (400 MHz, d$_3$-MeCN, ppm): $\delta$ 2.67 (s, 4H, ((CH$_3$)$_2$PSCH$_2$CH$_2$SCH$_2$-CH$_2$), 2.44 ppm (s, 4H, ((CH$_3$)$_2$PSCH$_2$CH$_2$SCH$_2$-CH$_2$), 2.11 (m, 4H, ((CH$_3$)$_2$PSCH$_2$CH$_2$SCH$_2$-CH$_2$), 1.97 (m, 2H, ((CH$_3$)$_2$PSCH$_2$CH$_2$SCH$_2$-CH$_2$), 1.89 (d, $^3J_{HH} = 13.2$ Hz, 12H, CH$_3$). $^{31}$P{${}^1$H} NMR (162 MHz, d$_3$-MeCN, ppm): $\delta$ 46.20 (s, -144.59
(septet). LSIMS MS \([\text{Pd}(3.2)]^+\): 454.6 m/z. Elemental analysis calculated for \([\text{PdC}_{11}\text{H}_{26}\text{S}_{4}\text{P}_{2}](\text{PF}_{6})_{2}\) experimental (calculated) %: C, 17.68 (17.73); H, 3.60 (3.52).

### 3.8 References


Chapter 4: Towards the Synthesis of Tetradentate Ligand Systems Containing the Mercaptoimidazole Moiety
4.0 Towards the Synthesis of Tetra-dentate Ligand Systems Containing the Mercaptoimidazole Moiety

4.1 Chapter Aims and Overview

This chapter features the attempted synthesis of tetra-dentate ligand systems, as illustrated in Figure 4-1, which shows the proposed reaction scheme and final ligand systems, where $X = S$, N or P. The overall aim of the work reported here was to investigate the use of the thione moiety as a stable thiol analogue. Therefore attempts were made to incorporate the 1-methyl-2H-imidazole-2-thione (4.1, Figure 4-2) unit into a tetra-dentate ligand. Modification of the bridging group (Figure 4-1) offered an interesting way to investigate the chelating ligand system and produce ligands with a combination of soft/soft ($X = S$) and soft/hard ($X = N$ or $P$) coordination sites.

The chemistry and coordination of MMI has been reported in the literature and is discussed in the introduction to this chapter however, the compound 4.Y has not been reported in the literature. Consequently section 4.2 focuses on the attempted synthesis of this compound, where $Y = a$ leaving group i.e. a halide or sulfonate moiety. This work led to the successful synthesis of the novel compound 1-hydroxymethyl-3-methylimidazole-2-thione (4.7, Figure 4-2), where $Y = OH$. 4.7 was subsequently reacted with thionyl chloride to afford of 1-chloromethyl-3-methylimidazole-2-thione hydrochloride (4.8, Figure 4-2).
Once 4.8 had been isolated it was thought that the tetra-dentate ligands could be synthesised via a reaction with the appropriate starting material i.e. 1,3-propanedithiol. However the poor solubility of 4.8 in all organic solvents had a detrimental effect on the outcome of these experiments. Section 4.4 details the attempted synthesis of 4.9 and 4.10 (Figure 4-2) via the reaction of 1,3-propanedithiol or 1,3-propanediamine with 4.8.

Whilst evidence for 4.9 was obtained by \(^1\)H NMR spectroscopy and mass spectrometry, a pure sample was not obtained in sufficient yield, and reactions with rhenium and 99m-technetium could not be attempted. Different literature methods were employed for the attempted synthesis of 4.10 and each reaction was analysed by \(^1\)H NMR spectroscopy and mass spectrometry. Unfortunately evidence for the formation of 4.10 was not obtained from the reaction detailed here.
At this point during the project it was considered prudent to move on from the proposed reaction scheme involving 4.8 and look for alternative synthetic routes. The search for another methodology led to the synthesis of 1,3-propanebis(phenyldihydroxymethylphosphine) dichloride (4.11). This phosphonium salt was then reacted with MMI and a series of analogous compounds to produce 4.12 and 4.16 (Figure 4-2). The synthesis of these ligands and subsequent complexation attempts are discussed in section 4.5.

### 4.2 Introduction

This section discusses the chemistry of MMI, related ligands and relevant transition metal complexes. Figure 4-3 shows the synthesis of MMI (4.1) via two different methods. The first (Figure 4-3a) published by Guizec et al. uses methyl imidazole and elemental sulphur whilst the second (Figure 4-3b) is an acid catalysed cyclisation reported in a patent by Katsura et al. Both methods were attempted however Figure 4-3a was used as the preferred synthetic route due to the yield obtained.

![Synthesis of 1-methyl-2H-imidazole-2-thione (3.1)](image)

**Figure 4-3: Synthesis of 1-methyl-2H-imidazole-2-thione (3.1) a) published by Guizec et al. and b) published by Katsura et al.**

Imidazole-2-thiones have two modes of coordination through the thione and amine moieties and as such can act as a mono-dentate or bi-dentate ligand. This is exemplified by Qin et al. who report ruthenium complexes using a MMI derivative, where the methyl group is replaced...
by a 4-methylphenyl unit. Two examples are shown in Figure 4-4. These compounds were part of a series which were investigated for the effect of photolysis on the oxidation state of the ruthenium centre. Figure 4-4a shows the imidazole derivative as a bi-dentate ligand, the chelate was deprotonated by NaOMe prior to complexation with Ru(II). Figure 4-4b shows the protonated ligand acting as a mono-dentate donor coordinating through the thione group.

Figure 4-4: Ruthenium complexes published by Qin et al 3 a) [RuH(κ^2-S,N-imt^{MPb})(CO)(PPh_3)_2] and b) [RuHCl(κ^1-S-Hint^{MPb})(CO)(PPh_3)_2] where Hint^{MPb} is the protonated imidazole ligand and imt is the deprotonated form

MMI itself has been previously complexed to transition metals including ruthenium, palladium, platinum, rhodium, cobalt, nickel and zinc. The redox behaviour of a variety of platinum complexes was investigated including [Pt(MMI)_4]Cl_2, redox compounds which exhibit DNA binding and have potential use as anti-tumour agents. MMI has also been incorporated into multi-dentate ligand systems including tripodal borates (Figure 4-5). Baba et al report the synthesis of Co(II) and Co(III) complexes with the HBMMI ligand. The complexes show the ligand acting as a bi-dentate and tri-dentate ligand depending on the oxidation state of the metal centre. The ligand, defined as a soft scorpionate compound has also been complexed to Sn, As and In centres.
Figure 4-5: Cobalt compounds with the tripodal B(MMI)$_3$ ligand published by Baba et al.

| a) [Co$^{II}$(HBMMI)$_3$] | b) [Co$^{III}$(HBMMI)$_3$]$^+$ |

Figure 4-6a shows a Re(V) complex with an MMI derivative and bis(2-mercaptoethyl)sulfide where R is a glycine dipeptide. As discussed in the introduction of this thesis, 3+1 complexes are vulnerable to the thiol groups in vivo, however the biological stability of this complex is not reported. This example shows the thiolate nature of the MMI unit with the secondary amine bearing a positive charge. Although the compound is shown to be stable in solution. Figure 4-6b shows a [ReO]$^{3+}$ complex with two methylmercaptobenzimidazole ligands with hydroxyl and chloride ions completing the coordination sphere.
Figure 4-6: a) a Re(V) 3+1 complex containing a MMI derivative published by Palma et al.\textsuperscript{16} and b) a Re(V) complex with methylmercaptobenzimidazole, hydroxyl and chloride ions fill the coordination sphere published by Gagieva et al.\textsuperscript{15}

A bidentate methyl mercaptoimidazole is shown in Figure 4-7 where two MMI molecules are connected by a methylene bridge. The bridge can link the imidazole rings through either the nitrogen or sulphur atoms giving two constitutional isomers which are reported in the literature.\textsuperscript{17} Complexes of 4.3N with Ni,\textsuperscript{18} Pb,\textsuperscript{19} Zn\textsuperscript{17} and half-sandwich complexes of Ir and Rh\textsuperscript{20} have been reported, in these compounds the thione groups coordinate to the metal centre.

In transition metal compounds with 4.3S it is the amine groups that can act as the donor moieties. 4.3S complexes with Zn,\textsuperscript{17} Sn,\textsuperscript{21} Ag\textsuperscript{22} and the rhenium tricarbonyl core\textsuperscript{23} have previously been published.

Figure 4-7: Structures of 4.3N and 4.3S

4.3N has also been complexed to the rhenium tricarbonyl core (Figure 4-8). Published by Maria et al.\textsuperscript{24} in the complex [Re(CO)\textsubscript{3}Br(4.3N)] (Figure 4-8a), the ancillary ligand (Br) was shown to be labile and easily replaced by coordinating solvent molecules. Altering the MMI bridging group from CH\textsubscript{2} to BH\textsubscript{2} allowed for stabilisation of the complex in coordinating solvents.
The literature describing MMI suggests that the thione group may be a soft donor moiety. When the MMI moiety is combined with hard donors the resulting ligands may be appropriate for Re(V) and Tc(V) cores. However if combined with other soft donors i.e. thio-ether groups it may allow for the complexation of rhenium and technetium centres in lower oxidation states.

4.3 Synthesis of compounds 4.Y

Figure 4-9 shows the proposed reaction scheme for the synthesis of the target ligands discussed within this chapter, where X = S, NH or PPh. This section discussed the synthesis of 4.Y, a MMI derivative bearing a leaving group. Different leaving groups were considered including halides and sulfonates, and these are reported here.

4.3.1 Attempted synthesis of 4.Y

The chemistry and coordination of methyl mercaptoimidazole has been widely studied however, the fragment 4.Y has not been reported in the literature. A search for a similar reaction motif was completed and Figure 4-10 shows the reaction conditions used for the synthesis of
7-methyl-2-propyl-3-(2-(tosyloxy)ethyl)-3H-benzimidazole-5-carboxylate published by Zhang et al.\textsuperscript{25} The scheme shows a benzimidazole derivative reacted with ethylene-1,2-ditosylate, with the product being purified by column chromatography.

![Synthesis of methyl 7-methyl-2-propyl-3-(2-(tosyloxy)ethyl)-3H-benzimidazole-5-carboxylate published by Zhang et al.\textsuperscript{25}}

Figure 4-10: Synthesis of methyl 7-methyl-2-propyl-3-(2-(tosyloxy)ethyl)-3H-benzimidazole-5-carboxylate published by Zhang et al.\textsuperscript{25}

Similar experimental procedure have been used to react mercaptoimidazole with methylene bis-tosylate (Figure 4-11). The starting materials were synthesised according to the relevant literature procedures\textsuperscript{1,26} and were isolated in high purity and good yields. It was mentioned in the introduction that \textit{4.1} can coordinate through both the amine and thio moieties. Due to this nature of \textit{4.1} it is expected that upon deprotonation the reaction mixture would be in equilibrium. Therefore it was envisaged that several different products may be produced, Figure 4-11 shows the potential products including three different dimeric species, the desired product \textit{4.2} and a by-product \textit{4.2S}. In an attempt to limit formation of dimeric products the reaction conditions were altered so that the synthesis of \textit{4.2} was favoured. This was completed by the slow addition of deprotonated \textit{4.1} (4.1-H) to an excess of methylene bis-tosylate in solution. Initially the reaction was completed using NaH as the base.
The product was dissolved in DCM and washed with water and brine, TLC analysis showed four products were present and purification was completed by column chromatography. Two of the products isolated were identified by TLC analysis as the starting materials, 4.1 and methylene bis-tosylate. The presence of sulfonate in the product was expected since an excess had been used during the reaction. However, evidence for 4.1 was not anticipated and, this suggested that the reaction had not proceeded to completion. The 1H NMR spectrum of the crude product shows the N-H signal from 4.1 clearly at 11.51 ppm.

Mass spectrometry of the crude product showed no evidence of the desired compound (4.2) but did suggest that a dimeric species was present with a molecular ion peak at 241 m/z. Figure 4-12 shows the 1H NMR spectrum. The signals observed for the CH2 linker are comparable to those reported in the literature for 4.3S not 4.3N at 4.64 ppm and 6.31 ppm respectively.27 This was unexpected as literature reports for the synthesis of 4.3S suggest more forcing reaction conditions are required when compared to 4.3N.27 Other fractions, isolated by column chromatography showed a mixture of products by 1H NMR spectroscopy, these were not identified.
Due to the presence of MMI in the product, the reaction was repeated over a longer time period and the progress was monitored by TLC analysis. After 2 days, 4.1 remained present in the reaction mixture, this led to the conclusion that NaH was not acting an effective base, possibly due to degradation of the sample. At this point it was deemed prudent to attempt the reaction with a different base and sodium hydroxide in ethanol was used to deprotonate 4.1. The same reaction conditions shown in Figure 4-11 were used. An aliquot was taken from the reaction and \(^1\)H NMR spectrometry and synthesis of 4.1-H was confirmed by the absence of the N-H signal. The deprotonated material was then isolated by removal of the solvent \textit{in vacuo}. The product was then dissolved in THF and added to a stirring solution of methylene bis-tosylate.

Mass spectrometry of the crude product showed evidence of synthesis of 4.2 or 4.2S as both have the same molecular weight, three spots were observed by TLC and the product was purified by column chromatography. Excess methylene bis-tosylate was isolated as the first
product and the second identified as the dimeric species (4.3N). The final product was isolated with a 44 % yield and although TLC analysis suggested a pure compound had been obtained, the \(^1\)H NMR spectrum suggests several products are present.

Further purification was attempted using recrystallization methods however a pure sample was not obtained. The same reaction was completed using methylene bis-mesylate with the aim of changing the solubility of the compound and obtaining a pure sample, Figure 4-14 shows the reaction conditions used. The mass spectrum shows the molecular ion peak at 223 m/z which corresponds to the desired product 4.4 or the by-product 4.4S. The crude material was purified by column chromatography and 3 fractions were isolated with one fraction identified as methylene bis-mesylate.

![Figure 4-13: Reaction conditions used for the synthesis of 4.4 and the potential by-products](image)

Mass spectrometry of the second product was completed and shows a dimeric product as the molecular ion species. The \(^1\)H NMR spectrum (Figure 4-14) of the compound which was isolated in a 27 % yield shows two sets of imidazole doublets, two singlet peaks corresponding to methyl groups are also observed. In the literature 4.3N and 4.3S are reported to have only
one set of imidazole signals, indicating the product may be \textbf{4.3NS}. Mass spectrometry was completed on the product and shows a dimeric product as the molecular ion species.

The third product was isolated with a yield of 14 \%, unfortunately the $^1$H NMR suggested the compound was impure with two products present. Mass spectrometry of the sample showed no evidence for \textbf{4.4} and no further purification was attempted. The mass spectrometry result obtained for the crude product does suggest the synthesis of \textbf{4.4} however it appears the product was unstable under the purification conditions.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{nmr_spectrum_4_3ns.png}
\caption{$^1$H NMR spectrum in CDCl$_3$ of the 4.3NS isolated from the reaction shown in Figure 4-14}
\end{figure}

At this point the use of methylene bis-sulfonate was reconsidered and it was thought that a methylene unit with two substituents of different reactivity may improve the outcome of the reaction and lead to the synthesis of \textbf{4.Y}. A paper published by Yan \textit{et al} $^{28}$ reported the synthesis of 3-(chloromethyl)-1-methylimidazolium bromide (Figure 4-15) using
chlorobromomethane, so for this reason chloroiodomethane was considered as an alternative reactant.

\[
\begin{align*}
\text{N} & \quad \text{N} \\
+ & \quad \text{Cl} \quad \text{Br} \\
\text{N} & \quad \text{N}^+ \quad \text{Cl} \\
\end{align*}
\]

Figure 4-15: Synthesis of 3-(chloromethyl)-1-methylimidazolium bromide published by Yan et al.

In the reaction published by Yan et al. 1-methylimidazole is added at a rate of 0.2 ml/h over 15 hours, thus limiting formation of the dimer to give a 9.5:1 product to dimer ratio. Using a syringe pump the same conditions were applied to the reaction shown in Figure 4-16. 4.1 was deprotonated using NaOH, and once the salt was isolated it was dissolved in dry THF before addition to chloroiodomethane. Due to the comparative reactivities it was thought that the iodide end of the methylene compound would react first to yield 4.6. It was also expected that several by-products could form, including the range of dimers and the equivalent 4.5 and 4.6 products where 4.1-H acts as a thiolate producing compounds similar to 4.4S.

The product was isolated as an orange solid. The \(^1\)H NMR spectrum of the crude product showed two products were present. 4.6 was not observed in mass spectrometry data however, the molecular ion mass at 254.9 m/z corresponds to 4.5, the dimer was also detected at 241.0 m/z. Purification of the product was attempted by column chromatography however the only compound isolated was 4.3. This result was obtained again upon repeating the reaction suggesting that 4.6 was decomposing on the column. The crude product was recrystallised.
several times but unfortunately a pure sample of 4.6 was not obtained. The next section discusses work completed in parallel with this purification and the synthesis of 1-hydroxymethyl-3-methylimidazole-2-thione which led to the purification of 4.6 being suspended.

### 4.3.2 Synthesis of 1-hydroxymethyl-3-methylimidazole-2-thione

This section features the synthesis of 4.7 (Figure 4-17) which was prepared as a precursor in the synthesis of 4.Y. A literature search for 4.7 showed the compound to be reported in a small number of patents\textsuperscript{29-32} from the 1980s which detail compounds for use in photographic solutions. Further analysis showed that a suitable synthetic route had not been reported.

![Figure 4-17: Structures of 4.Y and 1-hydroxymethyl-3-methylimidazole-2-thione (4.7)](image)

Figure 4-17: Structures of 4.Y and 1-hydroxymethyl-3-methylimidazole-2-thione (4.7)

Figure 4-18a shows reaction conditions used by Majumdar et al\textsuperscript{33} for the synthesis of 1-hydroxymethylimidazole, which is isolated without purification and in 85 % yield. It was thought that the same conditions could be applied to methyl mercaptoimidazole (Figure 4-18b) with the aim of synthesising 4.7. The reaction was completed and an oily product isolated. The \textsuperscript{1}H NMR spectrum of the crude product showed triethylamine was present. The product was then dissolved in DCM and washed with aqueous HCl, and a solid was obtained from the organic solvent. The \textsuperscript{1}H NMR spectrum showed that the methylene CH\textsubscript{2} protons were not observed (in the expected range of 5 - 6 ppm) and the broad singlet corresponding to the NH signal remained. From this the product was identified as the mercaptoimidazole starting material.
Figure 4-18: a) the reaction scheme for the synthesis of 1-hydroxymethylimidazole published by Majumdar et al.\(^{33}\) and b) the proposed reaction scheme for 4.7

The literature synthesis does not employ a solvent and requires the reaction mixture to be heated at 80°C until the paraformaldehyde has melted. Unlike imidazole, methyl mercaptoimidazole is a solid at room temperature, it was therefore considered practical to attempt the reaction in an appropriate solvent i.e. one in which 4.1 dissolved and could be heated at 80°C to react with paraformaldehyde. Both THF and acetonitrile were used, unfortunately the same result was obtained and 4.1 was isolated as the product. The reaction (Figure 4-19) was subsequently completed without a solvent or the addition of triethylamine (TEA). The mixture was heated at 90°C and both solids melted giving a thick viscous liquid which solidified with continued heating.

Figure 4-19: Reaction conditions for the synthesis of 4.7

The resulting solid was dissolved in DCM and filtered to remove any excess paraformaldehyde.

The methylene CH\(_2\) protons can be observed in the \(^1\)H NMR spectrum (Figure 4-20) at 5.43
ppm, the hydroxyl proton can also be identified by the broad singlet at 4.66 ppm. Synthesis of 4.7 was confirmed by mass spectrometry and elemental analysis, the product was isolated in a yield of 98%.

![Figure 4-20: ¹H NMR spectrum of 4.7 in CDCl₃](image)

It is interesting to note that if the reaction was cooled to room temperature prior to complete solidification, a mixture of 4.1 and 4.7 is observed in the ¹H NMR spectra. Additional paraformaldehyde can be added to the mixture which with further heating will continue to completion. The length of time the reaction requires is dependent on the amount of starting material used i.e. a longer period of heating is required for larger scale reactions. This is possibly due to the time needed to melt the reactants. The next section details reactions with 4.7.

4.3.3 Synthesis of 1-chloromethyl-3-methylimidazole-2-thione hydrochloride 4.8

Upon successful synthesis of 4.7, it was believed that the hydroxy moiety could be easily converted into an improved leaving group. Purification of the compounds in section 4.3.1 had
proved troublesome, so initial test reactions were completed with the aim of finding a system that would not require purification by column chromatography. Reactions were attempted with p-toluenesulfonyl chloride and the halogenation agent thionyl chloride. Figure 4-21 shows the two types of reaction condition used for the attempted synthesis of 4.2. Unfortunately the yields obtained were low with an average of 25% and 1H NMR spectroscopy showed several products were present. This reaction was therefore not investigated any further.

Figure 4-21: Reaction conditions used for the attempted synthesis of 4.2, 1) used DCM as the solvent and TEA as the base whilst 2) employed pyridine as the solvent and base

Thionyl chloride (SOCl₂) is commonly used to replace hydroxyl groups with a chloride moiety. Reactions using SOCl₂ have been shown to have high yields³⁴,³⁵ however, products are often used in situ.³⁶,³⁷ Figure 4-22 shows the reaction conditions used for the synthesis of 4.6. Upon addition of thionyl chloride a cream precipitate was observed. Once the reaction was complete excess SOCl₂ was removed by cannula filtration, the product was then washed with dry THF to ensure the complete removal of excess thionyl chloride.

Figure 4-22: Reaction conditions used for the attempted synthesis of 4.6

The isolated product was insoluble in common organic solvents but partially soluble in DMSO and soluble in H₂O. 1H NMR spectroscopy was completed in both solvents. The spectrum (Figure 4-23) in d₆-DMSO indicates that the reaction has occurred. The OH signal from 4.7 is
no longer present and the CH₂ protons have a downfield shift of 0.5 ppm. The ¹H NMR spectrum in D₂O shows decomposition of the product with the imidazole peaks present but several singlets observed around 5.5 ppm. This suggested that the product was moisture sensitive despite being air stable. Mass spectrometry data indicated the synthesis of 4.6 with a molecular ion mass of 163 m/z, however elemental analysis showed the product to be 4.8 the hydrochloride salt of 4.6. Literature analysis shows that the presence of the product as the hydrochloride salt was not unusual. Similar reactions of nitrogen heterocycles with thionyl chloride also produce products as a hydrochloride salt.38-40

![Figure 4-23: The structure and ¹H NMR spectrum of 4.8 in d6-DMSO](image)

In an attempt to improve the solubility of 4.8 the reaction shown in Figure 4-24 was completed. Unfortunately synthesis of the hydroxyl compound did not go to completion and before purification was attempted the project had moved forward and this system was not investigated further.
It was thought that the solubility of 4.8 would affect the next step in the ligand synthesis i.e. the reaction with 1,3-propanedithiol, 1,3-propanediamine or 1,3-bis(phenylphosphino)propane. Hydrochloride salts are not uncommon and have been used in the synthesis of more complex compounds.\textsuperscript{41-43} In many cases NEt\textsubscript{3} can be used to remove the HCl from the compound before further manipulation.\textsuperscript{44}

To ascertain if 4.6 could be isolated by removal of hydrochloride from 4.8, a few test reaction using NEt\textsubscript{3} were completed. Different solvents (EtOAc, DCM, THF, MeOH) were trialled with the expectation that the product 4.6 would be soluble in one. Unfortunately the reaction did not proceed as expected as 4.8 was isolated as the insoluble product in each experiment. A series of different organic bases were used including 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 1,8-bis(dimethylamino)naphthalene (proton sponge) but unfortunately these were also unsuccessful. 4.8 was isolated after each attempt and remained insoluble during each reaction. Despite this a series of experiments were designed with the aim of synthesising 4.9 and 4.10 and these are discussed within the next section.

4.4 Reactions towards the synthesis of 4.9 and 4.10

As reported in Chapter 3, 1,3-propanedithiol has been used to synthesise the ligands 3.1 – 3.3. As a result the synthesis of 4.9 appeared to be an appropriate starting point, it was then thought the same chemistry could be applied to the synthesis of 4.10.
4.4.1 Attempted synthesis of 4.9

Figure 4-25 shows the proposed reaction scheme for the synthesis of 4.9. There were several different factors to consider when designing the reaction including the solubility of 4.8, the type of base used and the deprotonation of the dithiol.

In the initial reactions a small excess of NaOEt in EtOH was used to deprotonate the 1,3-propanedithiol. This reaction mixture was then added to a stirred suspension of 4.8 and base (TEA or proton sponge). Upon addition of the di-sodium thiolate solution 4.8 immediately dissolved. Unfortunately it transpired that 4.8 was decomposing under these conditions. This was tested by the addition of NaOEt in EtOH to 4.8, resulting in the immediate dissolution of the salt. A ¹H NMR spectrum of the crude product, which was isolated by the removal of the solvent in vacuo, indicated decomposition of 4.8.

![Proposed reaction scheme for the synthesis of 4.9](image)

**Figure 4-25: Proposed reaction scheme for the synthesis of 4.9**

For this reason 1,3-propanethiolate sodium salt was isolated before use. Addition of NaOEt to the dithiol in THF or MeCN resulted in a cream precipitate which was isolated by vacuum filtration and identified as 1,3-propane di-sodium thiolate using ¹H NMR spectroscopy. This however did introduce other solubility problems e.g. the sodium salt was only soluble in EtOH or MeOH. Despite this a series of reactions were completed and a selection of these are shown in Table 4-1. A range of different solvents were used and the reactions were heated overnight. The crude products were analysed by mass spectrometry, but the mass of 4.9 at 361 m/z was not observed in any of the samples isolated.
Table 4-1: The series of conditions used in the reaction of 4.8 and 1,3-propanethiolate sodium salt

<table>
<thead>
<tr>
<th>Reaction N°</th>
<th>Solvent</th>
<th>Base</th>
<th>Temperature (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DCM</td>
<td>NEt₃</td>
<td>38</td>
</tr>
<tr>
<td>2</td>
<td>DCM</td>
<td>Proton sponge</td>
<td>38</td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>NEt₃</td>
<td>66</td>
</tr>
<tr>
<td>4</td>
<td>THF</td>
<td>Proton sponge</td>
<td>66</td>
</tr>
<tr>
<td>5</td>
<td>MeCN</td>
<td>NEt₃</td>
<td>82</td>
</tr>
<tr>
<td>6</td>
<td>MeCN</td>
<td>Proton sponge</td>
<td>82</td>
</tr>
<tr>
<td>7</td>
<td>MeOH</td>
<td>NEt₃</td>
<td>64</td>
</tr>
<tr>
<td>8</td>
<td>MeOH</td>
<td>Proton sponge</td>
<td>64</td>
</tr>
</tbody>
</table>

The main challenge with this reaction was the solubility of the starting materials. For this reason alternative reaction conditions were proposed (Figure 4-26). In this reaction the dithiol is not deprotonated prior to the reaction and the proton sponge base is used in a five-fold excess. As a strong base it was expected that the proton sponge would deprotonate the dithiol and remove the hydrochloride salt producing the neutral and more soluble 4.6.

Figure 4-26: Further reaction conditions proposed for the synthesis of 4.9

A series of solvents were used including DCM, THF, MeCN and MeOH. In all experiments complete dissolution of the reactants did not occur and in each case a mixture of different compounds was obtained comprising of the starting materials, along with a portion of decomposed 4.8. Mass spectrometry and ¹H NMR spectroscopy were used to analyse the crude materials. The most successful of these reactions was completed in THF. The product was extracted with DCM and washed with water and an aqueous HCl solution, removal of the
solvent afforded a cream solid in a poor yield of 8%. The $^1$H NMR spectrum is shown in Figure 4-27 and suggests the synthesis of 4.9. This is supported by mass spectrometry data which shows the molecular ion peak at 360 m/z. The $^1$H NMR spectrum shows that the sample is impure however, and due to the low yield further purification could not be completed on this sample. The reaction was repeated and left to react for a longer period of 48 hours, compared to the initial 12 hours, with the aim of increasing the yield. Unfortunately despite several attempts the synthesis of 4.9 was not reproducible via this method. Further attempts were made by altering the temperature and time of the reaction but without success.

Figure 4-27: $^1$H NMR spectrum of 4.9 in CDCl$_3$

At this point the synthesis of 4.9 was halted. It had been assumed that the synthesis of 4.9, from the reactions of 4.8 and 1,3-propanedithiol would lead to a set of reaction conditions that could
then be applied to the synthesis of other ligands i.e. 4.10 but unfortunately this was not the case.

4.4.2 Attempted synthesis of 4.10

The main issue encountered during the synthesis of 4.9 was the solubility of the starting material 4.8 however, a series of reactions were completed with the aim of synthesising 4.10 (Figure 4-28) and overcoming the solubility issues. A combination of literature conditions and methods previously employed in the attempted synthesis of 4.9 were used. Table 4-2 shows the conditions and the results obtained. The crude products were analysed by $^1$H NMR spectroscopy and mass spectrometry.

![Proposed reaction scheme for the synthesis of 4.10](https://via.placeholder.com/150)

**Figure 4-28: Proposed reaction scheme for the synthesis of 4.10**

From the table of results it can be seen that the main issue in this reaction is the insolubility of 4.8. As with the attempted synthesis of 4.9 the reaction appears not to proceed in a range of solvents. Several different bases were employed in an attempt to remove hydrochloride from 4.8 and produce compound 4.6 as a soluble reactant prior to the reaction with either 1,3-propanediamine or 1,3-propanedithiol. Unfortunately 4.6 was not obtained and 4.8 remained insoluble.
<table>
<thead>
<tr>
<th>Reaction N°</th>
<th>Reference</th>
<th>Solvent</th>
<th>Base</th>
<th>Result</th>
<th>Desired product present?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Abiraj et al 45</td>
<td>1,3-propanediamine</td>
<td>n/a</td>
<td>4.8 did not dissolve</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>n/a</td>
<td>1,3-propanediamine</td>
<td>NEt3</td>
<td>4.8 did not dissolve</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>n/a</td>
<td>1,3-propanediamine</td>
<td>Proton sponge</td>
<td>4.8 and proton sponge did not dissolve</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>Pandiyan et al 46</td>
<td>MeOH</td>
<td>KOH</td>
<td>4.8 dissolved however the bridging CH₂ groups are not observed in ¹H NMR spectra</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>Caro et al 47</td>
<td>THF</td>
<td>NEt³</td>
<td>4.8 did not dissolve</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>n/a</td>
<td>THF</td>
<td>Proton sponge</td>
<td>4.8 did not dissolve</td>
<td>No</td>
</tr>
</tbody>
</table>

Table 4-2: The series of conditions used in the reaction of 4.8 and 1,3-propanediamine

Considering the work completed and the results obtained alternative synthetic routes were investigated. For example the reaction scheme (Figure 4-29) combines the reported syntheses of 3-(chloromethyl)-1-methylimidazolium bromide^{28} and 1,1'-methylenebis(3-methyl-2H-imidazole-2-thione).^{48} As previously discussed in this chapter, 4.6 has been shown to be unstable under column chromatography conditions. For this reason the product from the second step of the reaction was not purified but used in situ. The ¹H NMR spectrum of crude 4.6 shows there are at least two different products present. Mass spectrometry of the crude material confirmed the presence of 4.6 before the second step was completed.
An initial test reaction was carried out using crude 4.6 and 1,3-propanediamine, with the reaction being heated at 50°C for 24 hours. The $^1$H NMR spectrum of the final product showed that 4.10 had not been synthesised with the bridging CH$_2$ signals not present in the spectrum and no evidence of the molecular ion mass of 326 m/z being observed in the mass spectrum.

Although the initial result obtained was not encouraging this method warranted further investigation, however due to time constraints this was not completed. Any future work completed in this section would focus on the synthesis of 4.9 and 4.10 via the synthetic route outlined in Figure 4-29.

**4.5 Synthesis of 4.12 and analogous ligands**

Due to the problems encountered in the previous section, the use of 4.8 in the synthetic route initially proposed (Figure 4-30) for the synthesis of 4.12 was no longer considered viable. For this reason alternative conditions were considered. This section details the synthesis of the tetra-dentate ligand 4.12 and its analogous compounds 4.16 and 4.17.

Figure 4-29: Alternative reaction scheme for the synthesis of 4.10
4.5.1 Synthesis of 1,3-bis(phenylbishydroxymethylphosphonium)propane dichloride

Previous work completed within the Long group had led to the synthesis of a series of alkyl (hydroxymethyl)phosphonium chloride salts which were treated with ammonium chloride to produce tripodal dialkyl phosphine ligands (Figure 4-31b).\textsuperscript{49} Formaldehyde and HCl was stirred with the appropriate phosphine to synthesise the phosphonium salts (Figure 4-31a) published by Fawcett \textit{et al.}\textsuperscript{50} The same reaction conditions were applied to 1,3-bis(phenylphosphino)propane (Figure 4-31c) to synthesise 1,3-bis(phenylbishydroxymethylphosphonium)propane dichloride (4.11).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure431.png}
\caption{a) Synthesis of bis(hydroxymethyl)phosphonium salts published by Fawcett \textit{et al.}\textsuperscript{50} where R = Ph or Cy; b) the synthesis of tripodal dialkyl phosphine ligands using bis(hydroxymethyl)phosphonium salts published by Miller \textit{et al.}\textsuperscript{48} where R = Ph, Cy or 'Bu; and c) the reaction scheme for the synthesis of 1,3-bis(phenylbishydroxymethylphosphonium)propane dichloride}
\end{figure}
4.11 was obtained by recrystallization from the reaction mixture using Et₂O. Large colourless crystals were then isolated by vacuum filtration in ~95 % yield. The $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum (Figure 4-33) shows a singlet peak at 22.52 ppm, and mass spectrometry and elemental analysis confirmed the synthesis of 4.11. Figure 4-32 shows the X-ray crystal structure obtained, the molecule has C2 symmetry through C(3). Table 4-3 gives some selected bond lengths and angles.

<table>
<thead>
<tr>
<th>Bond Lengths (Å)</th>
<th>Bond Angles (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P(1) – C(4)</td>
<td>1.792(3)</td>
</tr>
<tr>
<td>P(1) – C(2)</td>
<td>1.794(3)</td>
</tr>
<tr>
<td>P(1) – C(12)</td>
<td>1.815(4)</td>
</tr>
<tr>
<td>P(1) – C(10)</td>
<td>1.827(4)</td>
</tr>
<tr>
<td>C(10) – O(11)</td>
<td>1.404(4)</td>
</tr>
<tr>
<td>C(12) – O(13)</td>
<td>1.409(5)</td>
</tr>
<tr>
<td>C(4) – P(1) – C(2)</td>
<td>112.10(17)</td>
</tr>
<tr>
<td>C(4) – P(1) – C(12)</td>
<td>110.60(18)</td>
</tr>
<tr>
<td>C(2) – P(1) – C(12)</td>
<td>110.06(17)</td>
</tr>
<tr>
<td>C(4) – P(1) – C(10)</td>
<td>104.84(18)</td>
</tr>
<tr>
<td>C(2) – P(1) – C(10)</td>
<td>108.77(18)</td>
</tr>
</tbody>
</table>

Table 4-3: Selected bond lengths (Å) and angles (°) of 4.11

Figure 4-32: Crystal structure of 4.11
4.5.2 Synthesis of bisphosphine bisimidazole tetradentate ligand systems

Following the literature reaction conditions published by Miller et al.\textsuperscript{49} the reaction shown in Figure 4-34 was completed. The reaction was monitored by \(^{31}\text{P}\{^1\text{H}\}\) NMR spectroscopy and was deemed to be complete after 2 hours. The crude sample was isolated by removal of the solvent \textit{in vacuo}. The sample was shown to be unstable in solution, the \(^1\text{H}\) and \(^{31}\text{P}\{^1\text{H}\}\) NMR spectroscopy indicated the material to be decomposing to 1,3-bis(phenylphosphino)propane and 4.1.

![Figure 4-34: Reaction conditions used for the synthesis of 4.12](image-url)
The crude product was also shown to be air sensitive and would decompose over 2 – 4 hours upon exposure. An attempt to purify the product by column chromatography resulted in the isolation of 4.1, unfortunately no other products were obtained.

The product was soluble in Et₂O and purification of 4.12 was achieved by repeated washing of the crude sample with dry Et₂O. The pure product was subsequently isolated as a colourless oil and synthesis was confirmed by NMR spectroscopy, mass spectrometry and elemental analysis. The $^{31}$P{$^1$H} NMR spectrum (Figure 4-35) shows two singlets at -20.77 and -21.16 ppm, no other signals were observed in the spectrum.

![Figure 4-35: $^{31}$P{$^1$H} NMR spectrum of 4.12 in CDCl₃](image)

Two peaks are observed in the $^{31}$P{$^1$H} NMR spectrum due to the chiral nature of the phosphine and suggests the presence of the meso-compound and the racemic mixture in equal ratios. Figure 4-36 shows a representation of the meso-compound and the two enantiomers in the racemic mixture. Since the enantiomers are not distinguished by NMR spectroscopy only one
signal is observed for the racemic mixture whilst the meso-compound is distinguishable due to the different chemical and physical properties.

Figure 4-36: Representation of the meso-compound and the racemic mixture of 4.12

The successful synthesis of 4.12 led to a series of proposed ligands. It was thought that analogous compounds could be synthesised using the same reaction conditions with a range of different imidazole rings. The imidazole compound allows for a wide variety of compounds to be produced, for example the alkyl substituent at the tertiary amine can be changed (4.13), or other group 16 elements can be employed as the donor atom (4.14 and 4.15). Figure 4-37 shows the compounds which were synthesised as alternative reactants to 4.1.

Figure 4-37: Alternative imidazole rings used to synthesise tetra-dentate ligands analogous to 4.12, a) l-butyl-2H-imidazole-2-thione (4.13); b) l-methyl-2H-imidazole-2-selenone (4.15) both synthesised by the method published by Guziec et al.; and c) synthesis of 1-ethyl-imidazolin-2-one (4.14) reported in a patent by Higuchi et al.51
For the synthesis of 1-alkyl-imidazolin-2-ones the equivalent alkyl isocyanate is required.\textsuperscript{51} Due to the toxicity and a lack of availability of methyl isocyanate, 1-methyl-imidazolin-2-one was not synthesised and ethyl isocyanate was used to produce the corresponding imidazolin-2-one, \textit{4.14}. The synthesis of \textit{4.13} and \textit{4.15} was completed using the method published by Guziec \textit{et al.}\textsuperscript{1} \textit{4.13 }– \textit{4.15} were reacted with the phosphonium salt \textit{4.11} using the same reaction conditions shown in Figure 4-34, the products were isolated in the same way as \textit{4.12}. Figure 4-38 shows the structures of the compounds synthesised.

\begin{figure}[h]
\centering
\includegraphics[width=0.6\textwidth]{structures.png}
\caption{The structures of compounds 4.16 and 4.17 isolated from the reactions of 4.11 with 4.13 and 4.14}
\end{figure}

Compounds \textit{4.16} and \textit{4.17} were isolated as oils as was the case for \textit{4.12}. The characterisation data obtained (\textit{\textsuperscript{1}H}, \textit{\textsuperscript{13}C}{\textit{\textsuperscript{1}H}}, \textit{\textsuperscript{31}P}{\textit{\textsuperscript{1}H}} NMR spectra and mass spectrometry) indicated the successful synthesis of compounds \textit{4.16} and \textit{4.17}. However NMR spectroscopy and elemental analysis showed the samples to be impure, and it was thought the compound were decomposing in the same way as \textit{4.12}. Further attempts were made to purify the compounds but were unsuccessful. Table 4-4 details some pertinent characterisation data for \textit{4.12, 4.16} and \textit{4.17} including \textit{\textsuperscript{31}P}{\textit{\textsuperscript{1}H}} NMR spectra and mass spectrometry.
It is interesting that the reaction between 4.11 and the selenone imidazole ring (4.15) did not produce the expected tetra-dentate ligand but the bi-dentate compound (4.18) shown in Figure 4-39. An aliquot of the reaction mixture was taken and the $^{31}\!$P{\textsuperscript{1}H} NMR spectrum showed signals at 37.59 and 37.36 ppm, which suggested that the phosphine had oxidised. As a result, the reaction mixture was extracted with DCM and washed with HCl to remove excess triethylamine. A yellow oil was isolated and the structure of 4.18 was elucidated from the mass spectrometry data showing the molecular ion at 480.9561 \( m/z \) and the \textsuperscript{1}H NMR spectra (Figure 4-40), the signals are tabulated and assigned in Table 4-5. The result of this reaction indicated that 4.15 did not react in the same way as the other imidazole compounds and this reaction was not investigated further.

![Figure 4-39: Postulated structure of 4.18](image)
Since pure samples of 4.16 and 4.17 were not obtained an effort was made to synthesise the analogous selenophosphoryl compounds (Figure 4-41) in order to confirm the compounds had been produced. The selenophosphoryl analogue of 4.12 was also synthesised. The phosphine ligands were isolated as previously described, dissolved in DCM and elemental selenium was added, the mixture was then stirred for 2 hours and excess selenium removed by filtration. The solvent was then removed in vacuo. With the NH signal observed at ~ 11 ppm in the $^1$H NMR spectrum signals for 4.18.
spectra of the crude compounds the presence of the imidazole starting material was indicated. The pure product was extracted with Et₂O and in each case yielded a colourless oil.

![Structures of selenophosphoryl ligands](4.19-4.21)

**Figure 4-41: Structures of selenophosphoryl ligands 4.19 – 4.21**

Synthesis of the selenophosphoryl analogues was confirmed by \(^1\)H, \(^31\)P\{\(^1\)H\} and \(^{13}\)C\{\(^1\)H\} NMR spectra, mass spectrometry and elemental analysis. The isolation of 4.19 – 4.21 as pure samples indicates that as proposed, the compounds 4.12, 4.16 and 4.17 are synthesised by reaction of the appropriate imidazole with the phosphonium salt (4.11). As a result 4.12, 4.16 and 4.17 were reacted with palladium(II) and rhenium(V) centres, this is detailed within the next section.

### 4.5.3 Complexation of 4.12, 4.16 and 4.17 with palladium(II)

Figure 4-44 shows the proposed structures of the Pd(II) complexes with compounds 4.12, 4.16 and 4.17. Synthesis of the palladium(II) complexes was completed using the same reaction conditions (Figure 4-42) discussed in chapter 3. The complexes were isolated as solids ranging in colour from dark red (4.22) to yellow (4.24).

![Reaction conditions used for the synthesis of 4.22 (X = S and alkyl = Me), 4.23 (X = S and alkyl = Bu) and 4.24 (X = O and alkyl = Et)](4.22-4.24)

**Figure 4-42: Reaction conditions used for the synthesis of 4.22 (X = S and alkyl = Me), 4.23 (X = S and alkyl = Bu) and 4.24 (X = O and alkyl = Et)**
Recrystallisation of compounds 4.22 – 4.24 was completed using a series of different solvent combinations but unfortunately crystals of a high quality were not obtained. The complexes were characterised using NMR spectroscopy, mass spectrometry and elemental analysis. The $^{31}$P{$^{1}$H} NMR spectrum of 4.23 is shown in Figure 4-43, two signals are observed at ~ 8 ppm along with the septet at -144 ppm which corresponds to the PF$_6$ counter ion. The presence of two signals indicates that two complexes are present this shows that both the *meso*-and *rac*-compounds coordinate to the Pd(II) centre. This results in complexes which have the same formula but different physical and chemical properties.$^{52}$ The presence of two different complexes could be used to explain the lack of high quality X-ray crystals. Although X-ray crystal structures were not obtained the data suggests that the complexes were isolated as monomeric compounds.

![Figure 4-43: $^{31}$P{$^{1}$H} NMR spectrum of 4.23 in MeCN](image)
It can be proposed that 4.22 – 4.24 have a square planar geometry as is generally observed Pd(II) complexes. Figure 4-44 shows the proposed structure of complexes 4.22 – 4.24 these structures assume that the ligand coordinates as a thione moiety however, as mentioned the chelates may have some thiolate nature. This would result in different complex structures to those proposed. Figure 4-45 shows the proposed structure of 4.22 with the ligand coordinated in its thiolate form. Before the structures can be well defined further analysis is required.

The successful synthesis of 4.22 – 4.24 showed that compounds 4.12, 4.16 and 4.17 coordinate as tetradentate chelates. The ligands were then reacted with [ReOCl$_3$(PPh$_3$)$_2$] and [ReO$_2$(py)$_4$], the next section details the preliminary results obtained.

**4.5.4 Complexation of 4.12, 4.16 and 4.17 with rhenium(V)**

Compounds 4.12, 4.16 and 4.17 have been reacted with rhenium(V) and the initial results obtained are detailed here. Due to time constraints reactions with technetium-99m have not yet been completed but are currently under investigation at GE Healthcare. Figure 4-46 shows the two sets of reaction conditions used for the synthesis of 4.25 – 4.27. Since the chelates are
neutral, it was proposed that the [ReO₂]⁺ core would be preferred over the [ReO]³⁺ core due to the charge. Therefore reactions were initially completed using the [ReO₂(py)_4]Cl precursor, unfortunately the results obtained from these reactions were inconclusive and due to time constraints were not investigated further. 4.12, 4.16 and 4.17 were subsequently reacted with the [ReOCl₃(PPh₃)_2] precursor which has been shown to produce complexes with the [ReO₂]⁺ core.⁵³,⁵⁴

![Diagram](image)

**Figure 4-46**: The two sets of reaction conditions for the synthesis of 4.25 (X = S, alkyl = Me), 4.26 (X = S, alkyl = Bu), 4.27 (X = O, alkyl = Et).

The appropriate ligand was dissolved in dry toluene and [ReOCl₃(PPh₃)_2] added, the reaction was then heated to 80°C overnight. The products were then isolated by filtration as solids ranging in colour from light red (4.26) to purple (4.27). The crude materials were washed with DCM and any insoluble material removed by filtration. Mass spectrometry of the samples indicated the synthesis of [ReO₂L]⁺ compounds with the molecular ion observed, where L = 4.12, 4.16 or 4.17. Whilst the compounds were shown to be impure, the ³¹P{¹H} NMR spectra of 4.25 – 4.27 all showed similar signals present. Figure 4-48 shows the ³¹P{¹H} NMR of 4.26 and Table 4-6 proposes the assignment of the signals observed. It was thought that in the same way as the palladium(II) complexes the *meso* and *rac*-compounds would form two chemically different Re(V) complexes resulting in two similar ³¹P{¹H} NMR spectrum shifts. As a result of this, the signals at ~ 23 ppm have been assigned to the desired compound 4.26.
Figure 4-47: Proposed structures for compounds 4.25 – 4.27

Figure 4-48: $^{31}$P{$^1$H} NMR spectrum of 4.26 in MeCN

<table>
<thead>
<tr>
<th>$^{31}$P{$^1$H} shift</th>
<th>36.68</th>
<th>36.58</th>
<th>25.58</th>
<th>22.95</th>
<th>22.76</th>
<th>17.55</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assignment</td>
<td>Oxidised 4.16</td>
<td>Oxidised 4.16</td>
<td>OPPh$_3$</td>
<td>4.26</td>
<td>4.26</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

Table 4-6: $^{31}$P{$^1$H} NMR spectrum shifts of 4.26 and the proposed assignment

The presence of the oxidised ligand indicates that the reaction has not proceeded to completion and suggests the conditions used could be optimised. This and further purification is required before synthesis of complexes 4.25 – 4.27 can be confirmed. However evidence for compounds 4.25 – 4.27 in the mass spectrometry and the information obtained from the $^{31}$P{$^1$H} NMR
spectra do suggest the successful synthesis of the complexes. This is encouraging and the chelates 4.12, 4.16 and 4.17 necessitate further investigation.

4.6 Conclusions

The reaction initially proposed for the synthesis of compounds 4.9, 4.10 and 4.12 (Figure 4-49) did not prove to be as successful as originally thought. Synthetic problems were encountered while attempting the synthesis of 4.Y. However during this process the novel compounds 4.6 - 4.8 (Figure 4-50) were synthesised. 4.7 was synthesised from the reaction of l-methyl-2H-imidazole-2-thione and paraformaldehyde and was produced in yields of >90 %. The compound could potentially be used as a starting material for more complex molecules containing the thione moiety.

4.8 was synthesised from the reaction of 4.7 and thionyl chloride. Initially it was thought to be a useful starting material for the synthesis of the proposed tetra-dentate ligand systems. That said the solubility of the compound hampered subsequent reactions. The compound was insoluble in all organic solvents and in addition water sensitive. Despite evidence in the \(^1\)H NMR spectrum and mass spectrometry data suggesting the synthesis of 4.9, using 4.8 as a starting material, the reaction was unreproducible and a sample of high purity and formed in good yield could not be obtained. Optimum reaction conditions were not found during the
course of this project and as a result 4.9 and 4.10 were not synthesised or isolated using 4.8 as a starting material.

![Structures of compounds 4.6, 4.7, and 4.8](image)

**Figure 4-50: Structures of the compounds synthesised 4.6 – 4.8**

Alternative routes to the proposed tetra-dentate ligand system were considered. This led to the synthesis of the novel compound 1,3-bis(phenylbishydroxymethylphosphonium)propane dichloride (4.11) which was isolated in yields of > 90 %. The phosphonium salt was reacted with a series of imidazole rings to produce compounds 4.12, 4.16 and 4.17 (Figure 4-51). 4.12 was isolated as a pure sample unfortunately 4.16 and 4.17 were not. To prove synthesis of the ligands the selenophosphoryl analogues (4.19 – 4.21) were produced in good yield and high purity.

![Structures of compounds 4.12, 4.16, and 4.17](image)

**Figure 4-51: Structures of compounds 4.12, 4.16 and 4.17 synthesised from the reaction of 1,3-bis(phenylbishydroxymethylphosphonium)propane dichloride and various imidazole rings**

Compounds 4.12, 4.16 and 4.17 were reacted with Pd(II) and Re(V). Complexes 4.22 – 4.24 were isolated as coloured solids, the data indicate that the compounds act as tetradentate chelates. The meso- and rac-compounds both coordinate to the palladium(II) centre producing complexes with the same formula but different chemical and physical properties, the result of this is two signals observed in the $^{31}\text{P}^{'1}\text{H}$ NMR spectrum.
4.12, 4.16 and 4.17 were then reacted with [ReOCl₃(PPh₃)₂] and the preliminary results obtained are reported. Mass spectrometry shows evidence for [ReO₂]⁺ complexes 4.25 – 4.27, whilst the ³¹P{¹H} NMR spectrum shows the products to be impure and the two signals at ∼ 23 ppm are assigned to the Re(V) complexes. This shows that chelates 4.12, 4.16 and 4.17 warrant further investigation with Re(V) and technetium-99m.

4.7 Experimental

All reactions and manipulations were carried out under anaerobic conditions unless otherwise stated. All starting materials were of reagent grade, purchased from Sigma Aldrich and used without further purification. The equipment used has previously been stated and can be found in chapter 3, section 3.7. Mercaptoimidazole,¹ methylene bis-tosylate²⁶ and methylene bis-mesylate²⁶ were synthesised according to the literature procedure and the resulting ¹H NMR spectra, mass spectra and yields are reported here. 3-(Chloromethyl)-1-methylimidazolium bromide²⁸ was synthesised by Andreas Phanopoulos at Imperial College London. For the synthesis of the rhenium starting materials [ReOCl₃(PPh₃)₂] and [ReO(py)₄]Cl see chapter 3.
4.7.1 Synthesis of materials according to the literature procedure

The literature methods were followed and referenced, unless the protocol was modified.

**Methylene bis-mesylate**\(^{26}\): Using silver methanesulfonate (17.1 g, 84.6 mmol) yielded 5.50 g, 64 %. \(^1\)H NMR (400 MHz, CDCl\(_3\), ppm): δ 5.86 (s, 2H, CH\(_2\)), 3.20 (s, 6H, CH\(_3\)). ESI MS (+): 204 m/z [M]\(^+\).

**Methylene bis-tosylate**\(^{26}\): Using silver \(p\)-toluenesulfonate (14.2 g, 50.9 mmol) yielded 4.89 g, 54 %. \(^1\)H NMR (400 MHz, CDCl\(_3\), ppm): δ 7.62 (d, \(^3\)J\(_{HH}\) = 1.25 Hz, 4H, CH\(_2\)), 7.27 (d, \(^3\)J\(_{HH}\) = 1.25 Hz, 4H, CH\(_2\)), 5.83 (s, 2H, CH\(_2\)), 2.46 (s, 6H, CH\(_3\)). ESI MS (+): 357 m/z [M]\(^+\).

**1-Methyl-2H-imidazole-2-thione**\(^{1}\) (4.1): Using 1-methylimidazole (5.3 mL, 62.7 mmol) yielded 4.57 g, 64 %. \(^1\)H NMR (400 MHz, CDCl\(_3\), ppm): δ 12.01 (bs, 1H, NH), 6.71 (d, \(^3\)J\(_{HH}\) = 2.52 Hz, 1H, CH), 6.68 (d, \(^3\)J\(_{HH}\) = 2.53 Hz, 1H, CH), 3.58 (s, 3H, CH\(_3\)). \(^13\)C\{\(^1\)H\} NMR (100 MHz, CDCl\(_3\), ppm): δ 160.42 (C=S), 119.13 (CH), 114.26 (CH), 34.29 (CH\(_3\)). ESI MS (+): 115 m/z [M]\(^+\).

**1-Butyl-2H-imidazole-2-thione**\(^{1}\) (4.13): Using 1-butylimidazole (2.0 mL, 15.2 mmol) yielded 2.07 g, 87 %. \(^1\)H NMR (400 MHz, CDCl\(_3\), ppm): δ 12.06 (bs, 1H, NH), 6.71 (dd, \(^3\)J\(_{HH}\) = 18.8 Hz, 2H, CH\(_2\)), 3.00 (t, \(^3\)J\(_{HH}\) = 7.3, 2H, NCH\(_2\)), 1.75 (m, 2H, CH\(_2\)), 1.38 (m, 2H, CH\(_2\)), 0.95 (t, \(^3\)J\(_{HH}\) = 7.2 Hz, 3H, CH\(_3\)). \(^13\)C\{\(^1\)H\} NMR (100 MHz,CDCl\(_3\), ppm): δ 160.42 (C=S), 119.13 (CH), 114.26 (CH), 34.29 (CH\(_3\)). EI MS (+): 156 m/z [M]\(^+\). Elemental analysis calculated for C\(_7\)H\(_5\)N\(_2\)S experimental (calculated) %: C, 53.73 (53.84); H, 7.65 (7.75); N, 17.98 (17.94).

**1-Ethyl-2H-imidazol-2-one**\(^{51}\) (4.14): Using 1-(2,2-dimethoxyethyl)-3-ethylurea (3.14 g, 17.9 mmol) yielded 1.66 g, 83 %. \(^1\)H NMR (400 MHz, CDCl\(_3\), ppm): δ 10.81 (bs,
1H, N\textsubscript{H}), 6.32 (s, 1H, CH\textsubscript{2}), 6.21 (s, 1H, CH\textsubscript{2}), 3.79 (q, \textit{J}\textsubscript{HH} = 7.18 Hz, 2H, CH\textsubscript{2}), 1.31 (t, \textit{J}\textsubscript{HH} = 7.21 Hz, 3H, CH\textsubscript{3}). \textsuperscript{13}C\{\textsuperscript{1}H\} NMR (100 MHz, CDCl\textsubscript{3}, ppm): \textit{\delta} 154.61 (C=O), 110.61 (CH), 108.33 (CH), 37.90 (CH\textsubscript{2}), 14.85 (CH\textsubscript{3}). CI MS (+): 113 m/z [M]\textsuperscript{+}. Elemental analysis calculated for C\textsubscript{5}H\textsubscript{8}N\textsubscript{2}O experimental (calculated) %: C, 53.37 (53.54); H, 7.00 (7.19); N, 24.84 (24.99).

1-Methyl-2H-imidazole-2-selenone\textsuperscript{1} (4.15): Using 1-methylimidazole (4.5 mL, 53.4 mmol) yielded 5.51 g, 64 %. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}, ppm): \textit{\delta} 121.95 (bs, 1H, N\textsubscript{H}), 6.70 (dd, \textit{J}\textsubscript{HH} = 2.43 Hz, 2H, CH\textsubscript{2}), 3.67 (s, 3H, CH\textsubscript{3}). \textsuperscript{13}C\{\textsuperscript{1}H\} NMR (100 MHz, CDCl\textsubscript{3}, ppm): \textit{\delta} 147.33 (C=Se), 121.40 (CH), 119.15 (CH), 35.87 (CH\textsubscript{3}). ESI MS (+): 160 m/z [M]\textsuperscript{+}. 

4.7.2 Attempted synthesis of 4.2 – 4.6

Method 1: Methimidazole (0.33 g, 2.89 mmol) in dry THF (5 ml) was added dropwise to a stirred solution of NaOH (0.11 g, 2.89 mmol) in EtOH (20 ml) and left to stir for 1 hour before the solvent was removed \textit{in vacuo}. The residue was dissolved in dry THF (20 ml) and added dropwise to a stirred solution of methylene bis-tosylate (4.2), methylene bis-mesylate (4.4) or chloroiodomethane (4.5 + 4.6) (5.78 mmol) in dry THF (10 ml). The reaction heated at 50°C overnight, upon cooling the solvent was removed \textit{in vacuo} yielding a yellow solid. Purification was completed by column chromatography using silica as the stationary phase and a 50:50, Et\textsubscript{2}O / acetone mobile phase.

For 4.2: Product 1 – 4.1: \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}, ppm): \textit{\delta} 11.30 (bs, 1H, N\textsubscript{H}), 6.74 (d, \textit{J}\textsubscript{HH} = 2.49 Hz, 1H, CH\textsubscript{2}), 6.71 (d, \textit{J}\textsubscript{HH} = 2.49 Hz, 1H, CH\textsubscript{2}), 3.04 (s, 3H, CH\textsubscript{3}). ESI MS (+): 115 m/z [M]\textsuperscript{+}. Product 2 - methylene bis-tosylate: \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}, ppm): \textit{\delta} 7.85 (d, \textit{J}\textsubscript{HH} = 2.60 Hz, 4H, CH\textsubscript{2}), 7.13 (d, \textit{J}\textsubscript{HH} = 2.60 Hz, 4H, CH\textsubscript{2}), 6.01 (s, 2H, CH\textsubscript{2}), 2.39 (s, 6H, CH\textsubscript{3}). ESI MS (+): 357 m/z [M]\textsuperscript{+}. Product 3 – dimer (4.3S): \textsuperscript{1}H

164
NMR (400 MHz, CDCl$_3$, ppm): $\delta$ 7.09 (d, $^3J_{HH} = 2.39$ Hz, 1H, $CH$), 6.95 (d, $^3J_{HH} = 2.20$ Hz, 1H, $CH$), 4.62 (s, 2H, $CH_2$), 3.63 (s, 3H, $CH_3$). ESI MS (+): 241 [M]$^+$ Product 4 – unknown: $^1$H NMR (400 MHz, CDCl$_3$, ppm): $\delta$ 7.94 (d, $^3J_{HH} = 7.91$ Hz, 1H), 7.81 (d, $^3J_{HH} = 8.93$ Hz, 1H), 7.69 (s, 6H), 7.20 (d, $^3J_{HH} = 7.91$ Hz, 2H) 7.11 (s, 6H), 7.06 (d, $^3J_{HH} = 8.93$ Hz, 1H), 7.03 (d, $^3J_{HH} = 8.41$ Hz, 1H), 7.00 (d, $^3J_{HH} = 8.93$ Hz, 1H), 6.93 (s, 5H), 6.16 (s, 2H), 5.13 (s, 1H), 4.63 (s, 1H), 4.15 (s, 3H), 3.63 (s, 4H), 3.59 (s, 3H), 3.55 (s, 2H), 3.27 (s, 5H), 3.23 (s, 2H).

For 4.4: Product 1 - methylene bis-mesityle: $^1$H NMR (400 MHz, CDCl$_3$, ppm): $\delta$ 5.85 (s, 2H, $CH_2$), 3.19 (s, 6H C$H_3$). ESI MS (+): 204 m/z [M]$^+$. Product 2 – dimer (4.3N): $^1$H NMR (400 MHz, CDCl$_3$, ppm): $\delta$ 7.10 (d, $^3J_{HH} = 2.35$ Hz, 1H, $CH$), 6.97 (d, $^3J_{HH} = 2.50$ Hz, 1H, $CH$), 6.88 (d, $^3J_{HH} = 2.69$ Hz, 1H, $CH$), 6.60 (d, $^3J_{HH} = 2.35$ Hz, 1H, $CH$), 5.65 (s, 2H, $CH_2$), 3.60 (s, 3H, $CH_3$), 3.53 (s, 3H, $CH_3$). ESI MS (+): 241 m/z [M]$^+$. Product 4 – unknown: $^1$H NMR (400 MHz, CDCl$_3$, ppm): $\delta$ 7.34 (d, $^3J_{HH} = 2.77$ Hz, 3H), 7.28 (d, $^3J_{HH} = 2.77$ Hz, 3H), 6.73 (d, $^3J_{HH} = 4.85$ Hz 1H), 6.69 (d, $^3J_{HH} = 2.65$ Hz 1H), 5.48 (s, 0.3H), 3.88 (s, 8H), 3.74 (s, 0.5H), 3.60 (s, 3H), 3.43 (s, 8H).

For 4.5/4.6: Crude $^1$H NMR (400 MHz, CDCl$_3$, ppm): $\delta$ 7.22 (d, $^3J_{HH} = 2.77$ Hz, 1 H), 7.10 (d, $^3J_{HH} = 2.77$ Hz, 1H), 7.04 (d, $^3J_{HH} = 4.85$ Hz, 1H), 5.56 (dd, $^3J_{HH} = 3.28$ Hz, 1H), 4.63 (s, 1H), 4.61 (s, 2H), 4.37 (t, $^3J_{HH} = 4.79$ Hz, 0.5H), 4.37 (m, 2H), 4.06 (q, $^3J_{HH} = 5.72$ Hz, 4H), 3.88 (s, 3H), 3.73 (s, 1H), 3.63 (s, 4H). CI MS (+): 254 m/z [M]$^+$.

Method 2: To an ice cold solution of 4.7 (0.54 g, 4.7 mmol) in dry DCM (20 ml), dry NEt$_3$ (2.5 ml, 18 mmol) was added followed by the addition of p-toluenesulfonyl chloride (0.89 g, 4.7 mmol) portionwise. The reaction was warmed to rt and left to stir overnight, the solution was then washed with HCl (1 M, 3 x 10 ml) and water (3 x 10 ml).
For 4.2: Crude $^1$H NMR (400 MHz, CDCl$_3$, ppm): $\delta$ 8.09 (d, $^3J_{HH} = 2.08$ Hz, 1H), 7.86 (d, $^3J_{HH} = 2.08$ Hz, 2H), 7.46 (m, 3H), 7.38 (m, 4H), 7.25 (m, 3H), 7.18 (d, $^3J_{HH} = 2.00$ Hz, 2H), 6.69 (d, $^3J_{HH} = 2.38$ Hz 1H), 5.32 (s, 2H), 3.61 (s, 3H), 3.48 (s, 2H), 2.53 (s, 2H), 2.49 (m, 2H), 2.46 (d, $^3J_{HH} = 5.08$ Hz, 5H), 2.40 (s, 2H).

**Method 3:** As method 2, using pyridine as solvent and base

For 4.2: Crude $^1$H NMR (400 MHz, CDCl$_3$, ppm): $\delta$ 8.01 (d, $^3J_{HH} = 2.39$ Hz 1H), 7.84 (d, $^3J_{HH} = 2.39$ Hz, 1H), 7.77 (tt, $^3J_{HH} = 7.29$ Hz, 4H), 7.53 (d, $^3J_{HH} = 2.35$ Hz, 2H), 7.35 (m, 8H), 7.29 (d, $^3J_{HH} = 2.15$ Hz, 3H), 7.19 (d, $^3J_{HH} = 2.15$ Hz, 3H), 6.69 (d, $^3J_{HH} = 2.35$ Hz 1H), 3.79 (s, 3H), 3.69 (s, 2H), 3.48 (s, 2H), 2.42 (s, 6H).

**1-Chloromethyl-3-methylimidazole-2-thione (4.6)**

3-(Chloromethyl)-1-methylimidazolium bromide$^{28}$ (0.46 g, 2.2 mmol) was dissolved in MeOH, S$_8$ (0.07 g, 2.2 mmol) and K$_2$CO$_3$ (1.5 g, 11 mmol) were added and mixture was heated to reflux for 24 hours. The solvent was removed in vacuo and the residue washed with CHCl$_3$, the precipitate was removed by vacuum filtration. The solvent was then removed in vacuo yielding a light orange solid which was used in situ. Crude $^1$H NMR (400 MHz, CDCl$_3$, ppm): $\delta$ 7.63 (d, $^3J_{HH} = 2.5$, 1H), 6.85 (d, $^3J_{HH} = 2.4$, 2H), 6.73 (d, $^3J_{HH} = 2.4$ Hz, 2H), 6.62 (d, $^3J_{HH} = 2.5$ Hz, 1H), 6.34 (s, 1H), 5.45 (s, 4H), 3.71 (s, 1H), 3.65 (s, 6H), 3.60 (s, 3H), 3.41 (s, 6H).

**4.7.3 Synthesis of 4.7 – 4.9**

**1-Hydroxymethyl-3-methylimidazole-2-thione (4.7)**

Methimidazole (2.17 g, 17.81 mmol) and paraformaldehyde (0.57 g, 19 mmol) were stirred together and heated at 100°C. The mixture was heated until the reaction has solidified, the product was dissolved in DCM and the solvent was removed *in*
vacuo to afford a greyish solid. Yield 2.72 g, 98 %. $^1$H NMR (400 MHz, CDCl$_3$, ppm): $\delta$ 6.82 (d, $^3J_{HH} = 2.95$ Hz, 1H, CH), 6.70 (d, $^3J_{HH} = 2.91$ Hz, 1H, CH), 5.44 (s, 2H, CH$_2$), 4.59 (bs, 1H, OH), 3.63 (s, 3H, CH$_3$). $^{13}$C {$^1$H} NMR (100 MHz, CDCl$_3$, ppm): $\delta$ 161.80 (s, C=S), 118.07 (s, C=H), 116.69 (s, C=H), 71.44 (s, CH$_2$), 34.60 (s, CH$_3$). CI MS (+): 115 m/z [M$^+$]. Elemental analysis calculated for C$_5$H$_8$N$_2$SO experimental (calculated) %: C, 41.49 (41.66); H, 5.43 (5.59); N, 19.31 (19.44).

1-Chloromethyl-3-methylimidazole-2- thione hydrochloride (4.8)

To ice cold 4.7 (0.5 g, 3.47 mmol) thionyl chloride was added dropwise (5 ml). Once addition was completed the mixture was left to warm to room temperature and then heated to reflux for 1 hour. A cream precipitate formed which upon cooling was filtered via cannula, washed with dry THF or DCM and isolated by vacuum filtration. Yield 0.59 g, 87 %. $^1$H NMR (400 MHz, d$_6$-DMSO, ppm): $\delta$ 7.33 (d, $^3J_{HH} = 2.71$ Hz, 1H, CH), 7.23 (d, $^3J_{HH} = 2.71$ Hz, 1H, CH), 5.93 (s, 2H, CH$_2$), 3.48 (s, 3H, CH$_3$). CI MS (+): 163 m/z [M$^+$]. Elemental analysis calculated for C$_5$H$_8$N$_2$SCl$_2$ experimental (calculated) %: C, 30.13 (30.30); H, 3.87 (4.07); N, 13.75 (14.14).

(MeNCHCHCSNCH$_2$S)$_2$(CH$_2$)$_3$ (4.9)

To a suspension of 4.8 (0.24 g, 1.21 mmol) in dry THF (10 ml), 1,3-propane dithiol (50 µl, 0.5 mmol), and the proton sponge (PS) (0.54 g, 2.5 mmol) were added and the mixture was heated at 80°C overnight. DCM (15 ml) was added and sample was washed with water (3 x 5 ml) and aqueous HCl (3 x 5 ml, 1M), the organic layer was dried over MgSO$_4$, filtered and the solvent removed in vacuo to yield a cream solid. Yield 0.014 g, 7 %. Crude $^1$H NMR (400 MHz, CDCl$_3$, ppm): $\delta$ 7.97 (m, 16H, PS), 7.65 (m, 1H, PS), 6.87 (d, $^3J_{HH} = 2.7$ Hz, 2H, CH), 6.75 (d, $^3J_{HH} = 2.7$ Hz, 2H, CH), 5.86 (s, 4H, NCH$_2$S), 3.77 (t, 2H), 3.09 (s, 6H, CH$_3$), 3.42 (bs, 30H, PS), 3.16 (t, $^3J_{HH} = 3.11$ Hz 4H, SCH$_2$), 2.83
(m, 34H, PS), 2.77 (s, 13H), 2.67 (q, $^3J_{HH} = 6.18$ Hz, 6H), 2.32 (m 2H, CH$_2$), 2.03 (quintet, $^3J_{HH} = 6.22$ Hz, 4H), 1.88 (m, 2H), 1.40 (m, 2H). ESI MS (+): 360 m/z [M]$^+$. 

4.7.4 Synthesis of 4.11 – 4.18 

1,3-bis(phenylbishydroxymethylphosphonium)propane dichloride (4.11) 

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\text{To a stirred sample of 1,3-bis(phenylphosphino)propane (1.2 g, 4.62 mmol) degassed formaldehyde (2 ml, 23 mmol, 35 %) and conc HCl (0.8 ml, 9.2 mmol, 36 %) were added and the mixture was stirred for 2 hours. Et$_2$O was added to afford colourless crystals which were isolated by vacuum filtration. Yield 1.97 g, 94 %}. 

$^1$H NMR (400 MHz, D$_2$O, ppm): $\delta$ 7.70 (m, 6H, Ph), 7.58 (m, 4H, Ph), 4.70 (s, 8H, CH$_2$OH), 2.73 (m, 4H, PCH$_2$), 1.87 (quintet, 2H, PCH$_2$CH$_2$CH$_2$P). $^{31}$P{$^1$H} NMR (162 MHz, D$_2$O, ppm): $\delta$ 22.52 (s, P). $^{13}$C{$^1$H} NMR (100 MHz, D$_2$O, ppm): $\delta$ 135.42 (s, p-Ph), 132.34 (d, $^2J_{PC} = 3.3$ Hz, o-Ph), 132.30 (d, $^2J_{PC} = 3.9$ Hz, o-Ph), 130.25 (d, $^2J_{PC} = 5.7$ Hz, m-Ph), 130.18 (d, $^2J_{PC} = 5.6$ Hz, m-Ph), 112.73 (d, $^1J_{PC} = 13.3$ Hz, ipso-Ph), 52.21 (d, $^1J_{PC} = 17.3$ Hz, PCH$_2$OH), 17.03 (d, $^1J_{PC} = 16.59$ Hz, PCH$_2$), 16.41 (d, $^1J_{PC} = 16.59$ Hz, PCH$_2$), 14.55 (s, PCH$_2$CH$_2$CH$_2$P). CI MS (+): 205 m/z [C$_{19}$H$_{28}$P$_2$O$_4$Na]$^{2+}$. Elemental analysis for C$_{19}$H$_{28}$P$_2$O$_4$Cl$_2$ experimental (calculated) %: C, 50.46 (50.43); H, 6.36 (6.24). 

General synthesis of 4.12, 4.16 – 4.18 

To a solution of 4.11 (0.1 g, 0.22 mmol) in dry MeOH, NEt$_3$ (0.15 ml, 1.10 mmol) and the appropriate imidazole ring (0.44 mmol) were added, the reaction was heated to reflux for 2 hours. Upon cooling, the solvent was removed in vacuo and the product isolated was washed with dry Et$_2$O, filtered via cannula and the solvent removed, this was repeated three times.
(MeCHCHNCSNCH₂PPh₂)(CH₂)₃ (4.12)

Using 4.11 (0.11 g, 0.24 mmol) yielded 0.09 g, 72 %. ¹H NMR (400 MHz, CDCl₃, ppm): δ 7.48 (m, 4H, Ph), 7.34 (m, 6H, Ph), 6.66 (s, 4H, CH), 4.06 (m, 4H, PCH₂N), 3.58 (s, 6H, CH₃), 2.08 (m, 2H, PCH₂), 2.01 (m, 2H, PCH₂), 1.73 (m, 2H PCH₂CH₂CH₂P). ³¹P {¹H} NMR (162 MHz, CDCl₃, ppm): δ -20.96 (4.12), -21.44 (4.12). ¹³C {¹H} NMR (100 MHz, CDCl₃, ppm): δ 160.51 (s, C=S), 135.63 (s, 1JPC = 5.3 Hz, ipso-Ph), 135.51 (s, 3JPC = 1.3 Hz, o-Ph), 128.93 (t, 1JPC = 20.3 Hz, NCH₂P), 34.62 (s, CH₃). ¹H NMR (400 MHz, CDCl₃, ppm): δ 7.48 (m, 4H, Ph), 7.34 (m, 6H, Ph), 6.66 (s, 4H, CH), 4.06 (m, 4H, PC₂H₂N), 3.58 (s, 6H, CH₃), 2.08 (m, 2H, PC₂H₂), 2.01 (m, 2H, PC₂H₂). TOF ES MS (+): 513 m/z [M]+. Elemental analysis for C₂₅H₃₀N₄P₂S₂ experimental (calculated) %: C, 58.40 (58.58); H, 5.98 (5.90); N, 10.92 (10.94).

(BuCHCHNCSNCH₂PPh₂)(CH₂)₃ (4.16)

Using 4.11 (0.10 g, 0.22 mmol) yielded 0.109 g of impure 4.16. ¹H NMR (400 MHz, CDCl₃, ppm): δ 7.48 (m, 4H, Ph), 7.31 (m, 6H, Ph), 6.63 (m, 4H, CH), 4.04 (m, 4H, PCH₂N), 3.96 (m, 4H, NCH₂P), 2.04 (m, 2H, PCH₂), 1.96 (m, 2H, PCH₂), 1.72 (m, 6H, PCH₂CH₂CH₂P, NCH₂CH₂), 1.34 (m, 4H, CH₂CH₃) 0.92 (t, 6H, 3JHH = 7.41 Hz, CH₃). ³¹P {¹H} NMR (162 MHz, CDCl₃, ppm): δ -21.22, -21.73, -53.48. ¹³C {¹H} NMR (100 MHz, CDCl₃, ppm): δ 159.81 (s, C=S), 135.82 (s, 1JPC = 6.3 Hz, ipso-Ph), 135.69 (d, 1JPC = 6.6 Hz, ipso-Ph), 132.41 (d, 2JPC = 16.8 Hz, o-Ph), 128.85 (s, p-Ph), 128.49 (d, 3JPC = 6.3 Hz, m-Ph), 117.80 (s, CH), 114.31 (s, CH), 62.24 (d, 1JPC = 16.2 Hz, PCH₂N), 12.24 (d, 1JPC = 16.7 Hz, PCH₂N), 47.20 (s, NCH₂), 46.79 (s, NCH₂), 31.09 (s, NCH₂CH₂), 30.91 (s, NCH₂CH₂), 24.43 (t, 1JPC = 12.2 Hz, PCH₂), 22.30 (m, PCH₂CH₂CH₂P), 19.73 (s, CH₂CH₃), 15.24 (s, CH₃), 13.66 (s, CH₃). TOF ES MS (+): 619 m/z [MNa]+. Elemental analysis for C₃₁H₄₂N₄P₂S₂ experimental (calculated) %: C, 57.45 (62.39); H, 8.34 (7.09); N, 8.84 (9.39).
(EtCHCHNCONCH₂PPh)₂(CH₂)₃ (4.17)

Using 4.11 (0.11 g, 0.24 mmol) yielded 0.089 g of impure 4.17. ¹H NMR (400 MHz, CDCl₃, ppm): δ 10.57 (bs, 0.5H, NH, 4.13), 7.48 (m, 4H, ph), 7.34 (m, 6H, ph), 6.26 (d, 1H, 3JHH = 2.78 Hz, CH), 6.19 (d, 1H, 3JHH = 2.78 Hz, CH), 4.07 (m, 4H, PC₃H), 3.64 (m, 4H, NC₃H₂), 2.09 (m, 2H, PC₃H₂), 2.00 (m, 2H, PC₃H₂), 1.72 (m, 2H, PCH₂CH₂CH₂P), 1.28 (t, 6H, 3JHH = 6.97 Hz, C₃H₃). ³¹P{¹H} NMR (162 MHz, CDCl₃, ppm): δ -20.96, -21.47, -53.18. ¹³C{¹H} NMR (100 MHz, CDCl₃, ppm): δ 154.38 (s, C=O), 135.79 (d, JPC = 5.7 Hz, ipso-Ph), 135.66 (d, JPC = 5.1 Hz, ipso-Ph), 132.43 (d, JPC = 16.3 Hz, o-Ph), 128.89 (s, p-Ph), 128.54 (d, JPC = 6.8 Hz, m-Ph), 110.64 (s, CH), 108.30 (s, CH), 63.61 (d, JPC = 16.7 Hz, PCH₂N), 63.07 (d, JPC = 6.8 Hz, m-Ph), 37.80 (s, NCH₂CH₃), 24.34 (t, JPC = 10.7 Hz, PCH₂), 22.30 (m, PCH₂CH₂CH₂P), 14.80 (s, C₃H₃). TOF ES MS (+): 531 m/z [MNa]⁺. Elemental analysis for C₂₇H₃₄N₄P₂O₂ experimental (calculated) %: C, 56.50 (63.75); H, 4.63 (6.74); N, 5.80 (11.02).

(OHCH₂SePPh)₂(CH₂)₃ (4.18)

Using 4.15 (0.07 g, 0.46 mmol) yield 0.042 g, 39 %. ¹H NMR (400 MHz, CDCl₃, ppm): δ 7.88 (m, 4H, Ph), 7.50 (m, 6H, Ph), 4.09 (m, 4H, OHCH₂P), 3.49 (bs, 2H, OH), 2.47 (m, 4H, PCH₂CH₂CH₂P), 2.05 (m, 2H, PCH₂CH₂CH₂P). ³¹P{¹H} NMR (162 MHz, CDCl₃, ppm): δ 39.75 (JpSe = 705.16 Hz), 39.5 (JpSe = 701.83), 37.59, 37.36, 35.41 (JpSe = 705.16), 35.19 (JpSe = 701.83). ¹³C{¹H} NMR (100 MHz, CDCl₃, ppm): δ 132.44 (d, JPC = 8.5 Hz, o-Ph), 131.98 (d, JPC = 9.6 Hz, m-Ph), 128.91 (m, ipso-Ph), 127.66 (s, p-Ph), 127.01 (s, s-Ph) 63.61 (d, JPC = 16.7 Hz, OHCH₂P), 63.07 (d, JPC = 16.7, OHCH₂P), 28.19 (t, JPC = 42.6 Hz, CH₂) 28.05 (t, JPC = 42.6 Hz, CH₂), 17.47 (d, JPC = 14.8 Hz, CH₂). TOF ES MS (+): 480.9561 m/z [M⁺].

170
4.7.5 General synthesis of 4.19 – 4.21

To a solution of 4.12, 4.16 or 4.17 (0.2 mmol) in dry DCM (10 ml), elemental selenium (0.4 mmol) black was added and the mixture heated to reflux for 2 hours. Excess selenium was removed by filtration and the solvent removed in vacuo to yield a green/yellow oil.

(MeCHCHNCSNCH₂PSePh)₂(CH₃)₃ (4.19)

Using 4.12 (0.10 g, 0.19 mmol) yielded 0.09 g, 68 %. ¹H NMR (400 MHz, CDCl₃, ppm): δ 7.87 (m, 4H, ph), 7.46 (m, 6H, ph), 6.68 (m, 4H, CH), 4.10 (m, 4H, PCH₂N), 3.55 (s, 6H, CH₃), 2.55 (m, 2H, PCH₂), 2.39 (m, 2H, PCH₂), 2.03 (m, 2H PCH₂CH₂CH₂P). ³¹P {¹H} NMR (162 MHz, CDCl₃, ppm): δ 36.96 (s, ¹J₃P = 705.50 Hz), 36.87 (s, ¹J₃P = 703.62 Hz). ¹³C {¹H} NMR (100 MHz, CDCl₃, ppm): δ 160.16 (s, C=S), 132.27 (s, p-Ph), 131.93 (d, ³J₃PC = 8.6 Hz, m-Ph), 128.85 (d, ²J₃PC = 5.3 Hz, o-Ph), 128.73 (d, ¹J₃PC = 5.2 Hz, o-Ph), 127.90 (d, ¹J₃PC = 6.8 Hz, Ph P-C), 127.24 (d, ¹J₃PC = 6.8 Hz, Ph P-C), 119.30 (s, CH), 114.29 (s, CH), 63.19 (d, ¹J₃PC = 17.1 Hz, Ph₂N), 63.13 (d, ¹J₃PC = 17.8 Hz, PCH₂N), 34.68 (s, CH₃), 34.40 (s, CH₃), 28.44 (d, ¹J₃PC = 13.1 Hz, PCH₂), 28.13 (m, PCH₂CH₂CH₂P). MALDI TOF (+): 638.8 [M – S]⁺, 610.7 m/z [M – S₂]⁺. Elemental analysis for C₂₅H₃₀N₄P₂S₂Se₂ experimental (calculated) %: C, 44.43 (44.64); H, 4.54 (4.49); N, 8.39 (8.33).

(BuCHCHNCSNCH₂PSePh)₂(CH₃)₃ (4.20)

Using 4.16 (0.12 g, 0.20 mmol) yielded 0.10 g, 72 %. ¹H NMR (400 MHz, CDCl₃, ppm): δ 7.92 (m, 4H, ph), 7.48 (m, 6H, ph), 6.27 (m, 4H, CH), 4.14 (d, ²J₃PC = 18.27 Hz, 4H, PCH₂N), 3.63 (q, ³J₃HH = 7.69 Hz, 4H, NCH₂), 2.59 (m, 2H, PCH₂), 2.41 (m, 2H, PCH₂), 2.07 (m, 2H, PCH₂CH₂CH₂P), 1.26 (t, ³J₃HH = 7.20 Hz, 6H, CH₃). ³¹P {¹H} NMR (162 MHz, CDCl₃, ppm): δ 37.34 (¹J₃PSe = 703.12), 37.19 (¹J₃PSe = 704.19 Hz). ¹³C {¹H} NMR (100 MHz, CDCl₃, ppm): δ 160.51 (s, C=S), 135.63 (d, ¹J₃PC = 5.3
Hz, P-C), 135.51 (d, $^{1}J_{PC} = 5.3$ Hz, P-C), 132.41 (d, $^{2}J_{PC} = 17.3$ Hz, o-Ph), 128.93 (s, p-Ph), 128.55 (d, $^{3}J_{PC} = 6.1$ Hz, m-Ph), 119.11 (s, CH), 114.19 (s, CH), 62.21 (t, $^{1}J_{PC} = 20.3$ Hz, NCH$_{2}$P), 34.62 (s, CH$_{3}$), 34.33 (s, CH$_{3}$), 24.28 (t, $^{1}J_{PC} = 12.9$ Hz, PCH$_{2}$), 22.44 (q, $^{2}J_{PC} = 14.9$ Hz, PCH$_{2}$CH$_{2}$CH$_{2}$P). MALDI TOF (+): 757.5 m/z $[M]^+$. Elemental analysis for C$_{31}$H$_{42}$N$_{4}$P$_{2}$S$_{2}$Se$_{2}$ experimental (calculated) %: C, 49.00 (49.20); H, 5.70 (5.59); N, 7.56 (7.40).

(EtCHCHNCONCH$_{2}$PSePh)$_{2}$(CH$_{2}$)$_{3}$ (4.21)

Using 4.17 (0.09 g, 0.18 mmol) yielded 0.08 g, 66 %. $^{1}$H NMR (400 MHz, CDCl$_{3}$, ppm): $\delta$ 7.48 (m, 4H, ph), 7.34 (m, 6H, ph), 6.26 (d, 1H, $^{3}J_{HH} = 2.78$ Hz, C$_{H}$), 6.19 (d, 1H, $^{3}J_{HH} = 2.78$ Hz, CH), 4.07 (m, 4H, PC$_{H}$$_{2}$N), 3.64 (m, NC$_{H}$$_{2}$), 2.09 (m, 2H, PC$_{H}$$_{2}$), 2.00 (m, 2H, PCH$_{2}$), 1.72 (m, 2H, PCH$_{2}$CH$_{2}$CH$_{2}$P), 1.28 (t, 6H, $^{3}J_{HH} = 6.97$ Hz, CH$_{3}$). $^{31}$P$^{1}$H NMR (162 MHz, CDCl$_{3}$, ppm): $\delta$ 36.55 (s, $^{1}J_{PSe} = 703.44$ Hz), 36.50 (s, $^{1}J_{PSe} = 702.32$). $^{13}$C$^{1}$H NMR (100 MHz, CDCl$_{3}$, ppm): $\delta$ 154.38 (s, C=O), 135.79 (d, $^{1}J_{PC} = 5.7$ Hz, P-C), 135.66 (d, $^{1}J_{PC} = 5.1$ Hz, P-C), 132.43 (d, $^{2}J_{PC} = 16.3$ Hz, o-Ph), 128.89 (s, p-Ph), 128.54 (d, $^{3}J_{PC} = 6.8$ Hz, m-Ph), 110.64 (s, CH), 108.30 (s, CH), 62.34 (d, $^{1}J_{PC} = 15.09$ Hz, PCH$_{2}$N), 62.15 (d, $^{1}J_{PC} = 16.1$ Hz, PCH$_{2}$N), 37.80 (s, NCH$_{2}$CH$_{3}$), 24.34 (t, $^{1}J_{PC} = 10.7$ Hz, PCH$_{2}$), 22.30 (m, PCH$_{2}$CH$_{2}$CH$_{2}$P), 14.80 (s, CH$_{3}$). MALDI TOF (+): 668.9 m/z $[M]^+$. Elemental analysis for C$_{27}$H$_{34}$N$_{4}$P$_{2}$O$_{2}$Se$_{2}$ experimental (calculated) %: C, 48.30 (48.49); H, 5.26 (5.13); N, 8.47 (8.38).

4.7.6 General synthesis of 4.22 – 4.24

The tetradeutate ligand (4.12, 4.16 or 4.17) (0.15 mmol) was dissolved in dry MeCN (5 ml), PdCl$_{2}$ (0.15 mmol) and NaPF$_{6}$ (0.30 mmol) were added and the reaction mixture heated overnight. The solution was filtered through celite and the solvent removed in vacuo. The products were isolated as coloured solids.
[PdC₅H₃₀N₄P₂S₂][PF₆]₂ (4.22)

Using 4.12 (0.08 g, 0.15 mmol) yielded a dark red solid 0.087 g, 62 %.

¹H NMR (400 MHz, d⁴-MeCN, ppm): δ 7.90 (m, 4H, Ph), 7.49 (m, 6H, Ph), 7.18 (bs, 2H, CH), 7.08 (bs, 2H, CH), 4.71 (m, 4H, PCH₂N), 3.86 (s, 6H, CH₃), 2.51 (m, 2H, PCH₂), 1.64 (m, 2H, PCH₂), 1.26 (m, 2H PCH₂C₂H₂). ³¹P {¹H} NMR (162 MHz, d⁴-MeCN, ppm): δ 9.88, 8.11, -144.20 (PF₆). TOF ES MS (+): 311 m/z [M]²⁺. Elemental analysis for [PdC₅H₃₀N₄P₂S₂][PF₆]₂ experimental (calculated) %: C, 32.91 (33.04); H, 3.23 (3.33); N, 6.07 (6.17).

[PdC₃H₄²N₂P₂S₂][PF₆]₂ (4.23)

Using 4.16 (0.08 g, 0.13 mmol) yielded a yellow solid 0.109 g, 83 %.

¹H NMR (400 MHz, d⁴-MeCN, ppm): δ 7.90 (m, 4H, ph), 7.52 (m, 6H, ph), 7.30 (bs, 2H, CH), 7.19 (bs, 2H, CH), 4.87 (m, 4H, PCH₂N), 3.93 (m, 4H, NCH₂), 2.58 (m, 4H, PCH₂), 2.07 (m, 2H, PCH₂CH₂CH₂P), 1.67 (m, 4H, NCH₂CH₂) 1.26 (m, 4H, CH₂CH₃) 0.89 (t, ³JHH = 8.14 Hz, 6H, CH₃). ³¹P {¹H} NMR (162 MHz, d⁴-MeCN, ppm): δ 9.16, 7.74, -144.23 (PF₆). TOF ES MS (+): 353 m/z [M]²⁺. Elemental analysis for [PdC₃H₄²N₂P₂S₂][PF₆]₂ experimental (calculated) %: C, 37.31 (37.50); H, 4.13 (4.27); N, 5.43 (5.65).

[PdC₇H₃₄N₄P₂O₂][PF₆]₂ (4.24)

Using 4.17 (0.06 g, 0.13 mmol) yielded a orange solid, yield 0.089 g, 79 %. ¹H NMR (400 MHz, d⁴-MeCN, ppm): δ 7.93 (m, 4H, ph), 7.83 (m, 6H, ph), 7.54 (bs, 2H, CH), 7.42 (bs, 2H, CH), 4.65 (m, 4H, PCH₂N), 3.85 (bm, 4H, NCH₂), 2.34 (bs, 2H, PCH₂), 1.60 (bs, 2H, PCH₂), 1.20 (bs, 2H, PCH₂CH₂CH₂P), 0.87 (bs, 6H, CH₃). ³¹P {¹H} NMR (162 MHz, d⁴-MeCN, ppm): δ 15.64,
11.58, -144.58 (PF₆). TOF ES MS (+): 309 m/z [M]²⁺. Elemental analysis for [PdC₂₇H₃₄N₄P₂O₂][PF₆]₂ experimental (calculated) %: C, 35.72 (35.84); H, 3.68 (3.79); N, 6.19 (6.20).

4.7.7 General synthesis of 4.25 – 4.27

The tetradeutate ligand (4.12, 4.16 or 4.17) was dissolved in dry toluene (5 ml) and [ReOCl₃(PPh₃)₂] was added, the reaction mixture heated overnight at 80°C. A coloured solid precipitate, isolated by vacuum filtration and washed with toluene and diethyl ether.

**[ReO₂C₂₅H₃₀N₄P₂S₂]Cl (4.25)**

[Diagram]

Dark green solid. Crude ¹H NMR (400 MHz, MeCN-d₄, ppm): δ 7.85 (m), 7.53 (m), 7.36 (m), 6.92 (m), 4.72 (m), 4.33 (bs), 3.67 (bm), 3.50 (bm), 3.20 (bm), 2.14 (bs), 1.80 (m). ³¹P{¹H} NMR (162 MHz, MeCN-d₄, ppm): δ 36.67 (4.12O₂), 36.57 (4.12O₂), 25.57 (OPPh₃), 20.91 (4.25), 20.44 (4.25), 17.57. TOF ES MS (+): 732 m/z [M]⁺.

**[ReO₂C₃₁H₄₂N₄P₂S₂]Cl (4.26)**

[Diagram]

Light red solid. Crude ¹H NMR (400 MHz, MeCN-d₄, ppm): δ 7.91 (m), 7.80 (m), 7.52 (m), 7.41 (m), 4.68 (bm), 3.52 (bs), 2.51 (s), 1.58 (bs), 1.20 (m), 0.87 (bs). ³¹P{¹H} NMR (162 MHz, MeCN-d₄, ppm): δ 36.68 (4.16O₂), 36.58 (4.16O₂), 25.58 (OPPh₃), 22.95 (4.26), 22.76 (4.26), 17.55. TOF ES MS (+): 816 m/z [M]⁺.
\[ \text{ReO}_2 \text{C}_7 \text{H}_4 \text{N}_4 \text{P}_2 \text{O}_2 \text{Cl} \ (4.27) \]

Purple solid. Crude \(^1\text{H}\) NMR (400 MHz, MeCN-d4, ppm): \(\delta\) 8.19 (m), 7.91 (m), 7.53 (m), 7.37 (m), 4.73 (bm), 3.66 (bs), 3.06 (bs), 2.66 (bs), 2.31 (bs), 1.22 (m), 1.09 (m).

\[^{31}\text{P} \{^1\text{H}\} \text{ NMR (162 MHz, MeCN-d4, ppm): } \delta \ 36.70 \ (4.17 \text{O}_2), 36.61 \ (4.17 \text{O}_2), 25.59 \ (\text{OPPh}_3), 22.96 \ (4.27), 22.77(4.27), 17.55. \]

TOF ES MS (+): 728 m/z [M]+.

4.8 References


Chapter 5: Synthesis of a Tetradeutate Phosphine Oxime Ligand
5.0 Synthesis of a Tetradeptate Phosphine Oxime Ligand

5.1 Chapter Aims and Overview

This chapter details the attempted synthesis of the tetradeptate phosphine oxime ligand 5.2. It was proposed that the ligand would present an interesting analogue to the extensively studied amine oxime ligand system.\textsuperscript{1-3} The scheme shown in Figure 5-1 was initially proposed however, subsequent experiments showed that the reaction between the t-BuCl group and the phosphine was unfavourable.

\begin{center}
\includegraphics[width=0.8\textwidth]{figure5_1.png}
\end{center}

**Figure 5-1: Proposed reaction conditions to synthesise 5.2**

In order to understand the reaction a series of experiments were completed using secondary and primary alkyl halides. The compounds synthesised during this investigation are reported in section 5.3. These results led to the conclusion that ligands analogous to 5.2 could be produced using an alternative chloride starting material. For this reason the synthesis of 1-chloro-2-propanone oxime, 3-chlorobutan-2-one oxime and the subsequently unsuccessful reactions with 1,3-bis(phenylphosphino)propane are reported in section 5.4.

\begin{center}
\includegraphics[width=0.8\textwidth]{figure5_2.png}
\end{center}

**Figure 5-2: Conditions used for the proposed synthesis of 5.2**
Figure 5-2 shows the reaction conditions that were used for the proposed synthesis of 5.2. Section 5.5 features the characterisation data obtained from this reaction, which suggests evidence for and against the synthesis of 5.2. Attempts were made to prove the presence of the ligand by oxidising the phosphine atoms.

5.2 Introduction

The chemistry in this chapter attempts to incorporate the oxime moiety into a tetradeutate ligand to give a $P_2N_2$ donor set. Oxime moieties have been incorporated into a range of ligand systems which have varying donor atoms and denticity. Figure 5-1a shows a thioether oxime ligand analogous to the ligand proposed here (5.2). It was thought that this compound (Figure 5-1a) and the synthesis 5.2 would provide a way to investigate the use of different donor atoms with technetium-99m. Figure 5-3b also shows a thioether oxime ligand with (+)-3-carene substituents, where the ligand was complexed to Cu(II) and Pd(II) centres. Similar tetradeutate ligands with methyl substituents have also been reported and complexed to Cu(II) and Ni(II) centres.4,5 Figure 5-3c shows a bidentate phosphine oxime ligand bound to Rh(I) and Ir(I) COD. Interestingly the phosphine oxime ligand was synthesised from a dimeric phosphonium compound. Basic conditions were used to produce the corresponding phosphine aldehyde in situ which could then be complexed to the metal centres as a phosphine–enolate ligand. However, the addition of hydroxylamine or aniline results in a condensation reaction with the phosphine aldehyde, leading to the synthesis of phosphine-oxime or phosphine-imine complexes.
Figure 5-3: Oxime ligand complexes; a) a tetradentate thioether oxime complex, where M = Cu(II);4 b) a tetradentate thioether oxime complex, where M = Cu(II) and Pd(II) published by Kokina et al.;5 c) a bidentate phosphine oxime ligand, where M = Rh(I) and Ir(I) published by Park et al.7 and d) a pentadentate ligand, where M = Ni(II) published by Rosa et al.8

Figure 5-3d shows the pentadentate ligand to be fully coordinated to the Ni(II) centre, and the ligand was also shown to complex as a tri- or tetra-dentate ligand. The ligands show different donor set combinations with N₃, N₅S, N₅O and N₅OS all observed in Ni(II) or Zn(II) complexes. Whilst several different ligand motifs contain the oxime moiety, the amine oxime class of ligands has been studied extensively for use with technetium-99m (section 1.2.3).

Figure 5-4 shows two examples previously discussed. Amine oxime ligands have also been complexed to other transition metal centres including Ni(II)¹³, Co(III)¹⁴, Zn(II)¹⁵, Mn(III)¹³ and Pd(II).¹⁶
Synthesis of a tetradeinate phosphine-oxime ligand system would provide an interesting analogue to the amine oxime motif. \textbf{5.2} was the proposed target compound, however it was thought that an understanding of the ligand synthesis could lead to a wide range of potential chelating ligands.

\section*{5.3 Investigation of proposed ligand synthesis}

The literature shows that 1,3-bis(phenylphosphino)propane has previously been used to synthesise a range of phosphine ligands. King \textit{et al} \cite{17} used bidentate phosphines to produce a series of linear compounds while Brooks \textit{et al} \cite{18,19} have synthesised bis-phosphine heterocycles.

From the reported literature, the reaction scheme shown in Figure 5-5 was proposed.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{reaction_scheme.png}
\caption{Proposed reaction conditions to synthesise 5.2, from the reaction of 5.1 with 1,3-bis(phenylphosphino)propane}
\end{figure}

Figure 5-5 shows the reaction scheme used for the attempted synthesis of \textbf{5.2}. The tertiary chloro oxime compound (\textbf{5.1}) used was a mixture of two enantiomers and was obtained from
GE Healthcare. 1,3-Bis(phenylphosphino)propane was obtained from two different commercial sources throughout the course of the project, Strem chemicals and Alfa Aesar. \(^{31}\text{P}\{^1\text{H}\}\) NMR spectrum (Figure 5-6) of the commercial sample obtained from Alfa Aesar showed an impurity was present at -9.86 ppm, the same impurity was also present in the Strem sample. Unfortunately neither company was able to identify the source of the impurity and further analysis by \(^1\text{H}\) and \(^{13}\text{C}\{^1\text{H}\}\) NMR spectroscopy did not lead to an elucidation of the structure. Purification of the commercial 1,3-bis(phenylphosphino)propane was considered, this could be completed by vacuum distillation of the desired product (190°C/4.0 mmHg). However since there was no way to know at what temperature the impurity could be separated and in the initial test reactions the impurity appeared to have no effect on the reaction course, the purification of 1,3-bis(phenylphosphino)propane was not attempted.

![Figure 5-6: \(^{31}\text{P}\{^1\text{H}\}\) NMR spectrum of 1,3-bis(phenylphosphino)propane purchased from Alfa Aesar in CDCl\textsubscript{3}](image-url)
1,3-Bis(phenylphosphino)propane was dissolved in dry THF, upon addition of nBuLi the solution immediately turned yellow indicating deprotonation. The $^{31}$P{^1}H NMR spectrum of the deprotonated phosphine shows a singlet peak at -64.64 ppm, a shift of ~6 ppm upfield from 1,3-bis(phenylphosphino)propane and comparable to the reported literature shift of -63.0 ppm$^{19}$, the impurity is also present. Once full deprotonation was confirmed, 5.1 was dissolved in dry THF and added dropwise, no change in the reaction mixture was observed, though upon stirring overnight the colour had dissipated. The $^{31}$P{^1}H NMR spectrum of the crude product showed that only the phosphine starting material and the impurity were present.

Aguiar et al$^{21}$ reported the synthesis of lithium diphenylphosphide by the lithiation of triphenylphosphine with lithium metal. Phenyllithium is produced as a by-product during the reaction and consequently t-butyl chloride was added to the reaction mixture to react with the by-product. Figure 5-7 shows the reaction scheme reported, this appears to suggest that the reaction between t-butyl chloride and diphenylphosphide may not occur or is substantially slower than that between phenyllithium and tBuCl. When taking this and the proposed reaction scheme into account, it was concluded that if the reaction does take place it will be at a slower rate than expected. As a result of this, the reaction shown in Figure 5-5 was undertaken using harsher conditions.

![Figure 5-7: Reaction scheme proposed by Aguiar et al for the reaction of t-butyl chloride with phenyllithium$^{21}$](image)

The reaction was heated at reflux temperatures for varying amounts of time, unfortunately the same result was obtained and the starting material was isolated as the product in each case. This result suggests that the phosphine re-protonates over time, indicating the reaction of the
deprotonated phosphine with 5.1 does not proceed as expected. This conclusion led to a series of test reactions with the aim of synthesising an analogous compound to 5.2.

### 5.3.1 Reactions of 1,3-bis(phenylphosphino)propane with chloro-butane compounds

In order to confirm that the reaction was affected by the reactivity of the tertiary chloro moiety and not the nitroso group, the reaction in Figure 5-8 was proposed. 2-Chloro-2-methylbutane was used to mimic the reactivity of 5.1 without containing the nitroso moiety. Upon addition of 2-chloro-2-methylbutane to the deprotonated 1,3-bis(phenylphosphino)propane no colour change was observed indicating the reaction had not occurred.

![Figure 5-8](image)

**Figure 5-8: Conditions used for the reaction of 1,3-bis(phenylphosphino)propane and 2-chloro-2-methylbutane to synthesise 5.3**

The reaction was then heated to reflux temperatures overnight to give a colourless solution and the crude product was isolated by removal of the solvent *in vacuo*. The $^{31}$P{$^1$H} NMR spectrum of the crude product showed the starting material 1,3-bis(phenylphosphino)propane was present. A signal at -10 ppm was also observed and thought to be the impurity within the starting material. This result suggests that, as expected, the nitroso moiety in 5.1 is not affecting the reaction and that the result is due to the lack of reactivity of the tertiary chloride with lithiated phosphines.

Therefore other nitroso and oxime compounds were investigated and these are discussed in section 5.4. Firstly however, 1,3-bis(phenylphosphino)propane was reacted with 1-chlorobutane and 2-chlorobutane to confirm that 1,3-bis(phenylphosphino)propane would
react with primary and secondary chloro alkyls. Figure 5-9 shows the reaction of 1,3-bis(phenylphosphino)propane with 1-chlorobutane. To the yellow solution of the lithiated phosphine, 1-chlorobutane was added dropwise and the colour dissipated immediately.

Figure 5-9: Reaction conditions used for the synthesis of 5.4

The previously unreported product was isolated by extraction with dry hexane to give a colourless oil. Mass spectrometry data shows the molecular ion [M]⁺ of 5.4 at 373.27 m/z as well as fragments corresponding to the mono-phosphine oxidised ion [MO]⁺ and the di-phosphine oxidised ion [MO₂]⁺. As observed in chapter 4, two signals at -25.53 ppm and -25.58 ppm are observed in the ³¹P{¹H} NMR spectrum, showing the meso- and rac-compound in equal ratios. Figure 5-10 shows a representation of the meso-compound and the two enantiomers in the racemic mixture. Since the enantiomers are not distinguished by NMR spectroscopy only one signal is observed for the racemic mixture whilst the meso-compound is distinguishable due to the different chemical and physical properties.

Figure 5-10: Representation of the meso-compound and the racemic mixture
In a second test reaction 1,3-bis(phenylphosphino)propane was reacted with 2-chlorobutane to synthesise 5.5 (Figure 5-11). The product was isolated in the same way as 5.4 and obtained as a colourless oil. The $^{31}\text{P}\left\{^1\text{H}\right\}$ NMR spectrum shows 6 signals around -11 ppm. The number of signals observed is due to the isomers present in the sample. With four chiral centres in the molecule and the potential for 16 enantiomers, different sets of racemic mixtures and meso-compounds were expected. Synthesis of the novel compound 5.5 was confirmed by mass spectrometry and elemental analysis.

![Reaction conditions used for the synthesis of 5.5](image)

This reaction shows that 1,3-bis(phenylphosphino)propane reacts with 2-chlorobutane, a secondary chloro alkyl compound. From the successful synthesis of 5.4 and 5.5 it can be assumed that a primary or secondary chloro compound containing a nitroso compound would react with 1,3-bis(phenylphosphino)propane to synthesise compounds analogous to 5.2.

### 5.3.2 Reaction of 1,3-bis(phenylphosphino)propane and 2-bromo-2-methylbutane

The final reaction in this series was the reaction of 1,3-bis(phenylphosphino)propane and 2-bromo-2-methylbutane (Figure 5-12). By altering the halide from a chloro to a bromo moiety it was proposed that the halide moiety would be more reactive and therefore, synthesise the product, 5.3. Upon addition of 2-bromo-2-methylbutane to the reaction mixture, the yellow solution became colourless. The product was isolated in the same way as 5.4 and 5.5, and the $^{31}\text{P}\left\{^1\text{H}\right\}$ NMR spectrum (Figure 5-13) shows a large singlet peak at -7.85 ppm, a small singlet at -25.41 and a series of signals ~ -53 ppm which correspond to the phosphine starting material. The reaction was repeated using distilled 2-bromo-2-methylbutane with the aim of synthesising
the pure compound but unfortunately a small amount of 1,3-bis(phenylphosphino)propane was present in all samples isolated.

Figure 5-12: Reaction conditions for the synthesis of 5.3

The major product indicated by the signal at ~8 ppm observed in each reaction was initially thought to be related to the impurity seen in the starting phosphine material (Figure 5-6). It was assumed that the product 5.3 would also contain the meso- and rac-compounds as observed in the synthesis of 5.4 and 5.5. However the presence of the singlet in the $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum indicates this is not the case and the material may have been isolated as a racemate or a meso-compound but not a combination of both.

Figure 5-13: $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum of 5.3 in CDCl$_3$
Although mass spectrometry does not conclusively confirm synthesis of 5.3, it does suggest that the compound is present with a signal observed at 403 m/z, which could correspond to the molecular mass of 400 m/z, and the bis-oxidised species observed at 433 m/z. The $^1$H and $^{13}$C{$^1$H} NMR spectra were also thought to indicate synthesis of 5.3 but not confirm it. This inconclusive data led to an alternative synthetic route (Figure 5-14c) with the aim of identifying the species at ~8 ppm.

The lithiation of diphenylphosphinopropane (dppp) has previously been reported$^{22,23}$ and used in two different ways. Habeck et al $^{22}$ synthesised a tetra-dentate phosphine ligand (Figure 5-14a) and subsequently produced Fe(II) complexes. Yellow crystals of dilithium 1,3-bis(phenylphosphino)propane were isolated as a THF adduct prior to the reaction with 1-chloro-2-(diphenylphosphino)ethane. In contrast Chou et al $^{23}$ (Figure 5-14b) use the same method as Aguiar et al $^{21}$ and add t-butylchloride to the solution of dilithium 1,3-bis(phenylphosphino)propane in order to remove the byproduct phenyllithium from the reaction mixture. Methyl iodide is then added to synthesise 1,3-bis(methylphenylphosphino)propane.
Figure 5-14: a) Synthesis of a tetra-dentate phosphine ligand published by Habeck et al.\textsuperscript{22} where Lippp was isolated as yellow crystals prior to reaction; b) synthesis of 1,3-bis(methylphenylphosphino)propane published by Chou et al.\textsuperscript{23} where $t$-BuCl was used to remove phenyllithium from the mixture prior to reaction; c) proposed synthesis of 5.3

The reaction shown in Figure 5-14c was proposed as an alternative synthetic route. Dilithium 1,3-bis(phenylphosphino)propane was not isolated prior to the reaction but used \textit{in situ}. An aliquot of the reaction mixture was used to confirm synthesis of the lithiated phosphine using $^{31}$P\{\textsuperscript{1}H\} NMR spectroscopy, which showed full conversion with a singlet peak at -61.67 ppm. $t$BuCl was added before the addition of 2-bromo-2-methylbutane. The $^{31}$P\{\textsuperscript{1}H\} NMR spectrum showed that the product obtained was not pure, signals at -53 ppm correspond to 1,3-bis(phenylphosphino)propane indicating protonation of dilithium 1,3-bis(phenylphosphino)propane. However a singlet peak at -7.98 ppm does suggests the synthesis of the same compound seen in the $^{31}$P\{\textsuperscript{1}H\} NMR spectrum shown in Figure 5-13.

Whilst this reaction using DPPP appears to suggest that the species at -8 ppm is not the impurity observed in the 1,3-bis(phenylphosphino)propane starting, material evidence for the successful synthesis of \textbf{5.3} is not conclusive. It is of note that only one signal is present in the $^{31}$P\{\textsuperscript{1}H\}
NMR spectrum indicating that the expected meso-compound and racemate mixture have not been obtained.

Although the exact structure of 5.3 has not been previously presented in the literature, a similar compound, 1,3-bis(phenyl/butylphosphino)propane (Figure 5-15) has been synthesised by Brooks et al.\textsuperscript{19} The paper reports the synthesis of the compound from dilithium 1,3-bis(phenylphosphino)propane and tBuCl, the reported $^{31}$P\{$^1$H\} NMR spectrum shows two signals at 1.1 ppm and 7.5 ppm. The reaction was repeated but the compound could not be obtained a second time.

![Figure 5-15: Structure of 1,3-bis(phenyl/butylphosphino)propane](image)

Although the data reported here were inconclusive it suggested that 5.3 had been successfully synthesised. Subsequently it was proposed that the target ligand 5.2 could be synthesised using a bromo analogue of 5.1 and this reaction is discussed in section 5.5. The next section details the synthesis of primary and secondary oxime compounds and the successive reactions with 1,3-bis(phenylphosphino)propane, with the aim of synthesising tetra-dentate ligands analogous to 5.2.

### 5.4 Attempted synthesis of tetra-dentate phosphine oxime ligands

The reactions reported in the previous section lead to two different conclusions. Firstly that a primary or secondary chloro nitroso could be used to produce ligands analogous to 5.2, and secondly that the bromo analogue of 5.1 could be used to synthesise 5.2. Figure 5-16 shows the proposed compounds, however a literature search for the primary nitroso species did not reveal the ideal compound but did produce results for the related oxime species.
The search for the secondary nitroso compound did produce the desired compound however the synthetic details were inaccessible, but again the synthesis of the related oxime compound was obtained. Both oxime compounds have previously been reacted with 1,3-propanedithiol and 1,3-propanediamine to produce the tetra-dentate ligand systems shown in Figure 5-17. Considering this literature it was thought that the difference between the nitroso and oxime moieties would not have a significant affect on the proposed reaction with 1,3-bis(phenylphosphino)propane.

5.4.1 Reaction of 1-chloro-2-propanone oxime and 1,3-bis(phenylphosphino)propane
The oxime group has been incorporated into several different ligand motifs and 1-chloro-2-propanone oxime (5.6) has previously been used to synthesise a range of different ligand structures. Figure 5-18 shows a selection of published ligands, formed by using 1-chloro-2-propanone oxime. In the reported synthesis of these ligands the oxime starting material is not purified but used in situ.
Chapter 5

Figure 5-18: Examples of ligands synthesised using 1-chloro-2-propanone oxime a) published by Pavlishuk et al.; b) published by Prushan et al.; c) published by Methrubootham et al.

The synthesis of 1-chloro-2-propanone oxime (5.6) is shown in Figure 5-19 as reported by Pavlishuk et al. The $^1$H NMR spectrum of the compound was not detailed and the crude product was used without further purification. The synthesis of 5.6 was completed according to the literature procedure and yielded a straw yellow oil. Synthesis was monitored by mass spectrometry with the peak at 107 m/z corresponding to the molecular ion. However the $^1$H NMR of the crude product suggested several different products were present. Initially, a Kugelrhor distillation was completed and chloroacetone was successful removed from the crude product. However the compound was found to be temperature sensitive and the remaining material decomposed. Purification was also attempted by column chromatography using an ice-cold 1 % MeOH/DCM solvent system on alumina. The starting material chloroacetone was eluted first, unfortunately the remaining materials could not be separated. The $^1$H NMR spectrum (Figure 5-20) of the column purified product suggests several impurities are present. Although some signals can be assigned it was thought that the product may have decomposed on the column resulting in the impure fraction.

![Reaction scheme](image)

Figure 5-19: Reaction scheme for the synthesis of 5.6, 1-chloro-2-propanone oxime
The impure product 5.6 was reacted with 1,3-bis(phenylphosphino)propane (Figure 5-21) in a test reaction. Upon addition of 5.6 to the deprotonated phosphine the yellow mixture became blood-red, over a few minutes the colour faded back to yellow. The solvent was removed in vacuo and a sticky precipitate obtained. The $^{31}$P{$^{1}$H} NMR spectrum shows that both 1,3-bis(phenylphosphino)propane (-53 ppm) and the oxidised 1,3-bis(phenylphosphino)propane (27 ppm) are present. Oxidation of the phosphine is not observed in any of the other reactions completed. This, and the dramatic colour change which had not been previously observed before, suggested that the impure 5.6 was having an unexpected effect on the reaction. Further attempts to purify 5.6 were unsuccessful and resulted in temperature degradation of the product. The synthesis of 5.7 was discontinued at this point due to the lack of purity of 5.6 and instead the synthesis of 3-chlorobutan-2-one oxime was investigated with the aim of producing a pure starting material, as discussed in the next section.
5.4.2 Reaction of 5.8 and 1,3-bis(phenylphosphino)propane

Since 1,3-bis(phenylphosphino)propane reacted with 2-chlorobutane it was assumed that the analogous secondary chloro oxime would also react with the phosphine starting material. The same reaction conditions used for the synthesis of 5.6 were used to produce 3-chlorobutan-2-one oxime (Figure 5-22). The crude product was obtained as a dark brown oil, this was purified by flash column chromatography to give a colourless oil. Although 5.8 remained temperature sensitive, it did appear to be more stable than 5.6 and did not decompose during purification. The $^1$H NMR spectrum (Figure 5-23) shows two sets of signals and initially it was thought that the small impurity present was structurally related to 5.8.

![Figure 5-22: Reaction scheme used for the synthesis of 5.8](image)
Analysis of the $^{13}$C {$^1$H} NMR spectrum showed the two products to have very similar carbon environments. It was consequently proposed that the two products were geometric isomers caused by the lack of rotation around the C=N bond thus resulting in E and Z isomers (Figure 5-24). Whilst various oxime compounds are reported to form as a mixture of E and Z isomers this has not been reported for 3-chlorobutan-2-one oxime. The $^1$H and $^{13}$C {$^1$H} NMR data for 3-chlorobutan-2-one oxime does correspond to the major product observed in 5.8. As such, it was thought that the sample was a mixture of the geometric isomers but the compound was then reacted with 1,3-bis(phenylphosphino)propane (Figure 5-25).

![Figure 5-23: $^1$H NMR spectrum of 5.8 in CDCl₃](image)

![Figure 5-24: Structure of the E and Z isomers of 5.8](image)
Upon addition of **5.8** to the yellow solution of dilithium 1,3-bis(phenylphosphino)propane the solution changed colour and produced a white precipitate. The reaction was left to stir for a further hour before the solvent was removed *in vacuo* to afford a white solid. The $^{31}\text{P}_{\{^1\text{H}\}}$ NMR spectrum shows several signals present around 38 ppm. This shift appears to suggest that an oxidised product has been produced, and the shift does not correspond to oxidised 1,3-bis(phenylphosphino)propane which has a signal around 27 ppm. This suggests a reaction has occurred but that the product has oxidised during the course of the reaction.

![Figure 5-25: Reaction of 5.8 with 1,3-bis(phenylphosphino)propane to synthesise 5.9](image)

Mass spectrometry of the crude **5.9** does not show the expected mass of 431 m/z [M]$^+$ or the mass of oxidised compound at 478 m/z [MO$_2$]$^+$. Attempts were made to elucidate the structure of the compound isolated from the $^1\text{H}$ and $^{13}\text{C}_{\{^1\text{H}\}}$ NMR spectrum, however this was unsuccessful. Considering the reactions discussed in this chapter, oxidation of 1,3-bis(phenylphosphino)propane appears to be unique to the attempted synthesis of **5.7** and **5.9**, which suggests that the oxime moiety may be having an adverse effect on the reaction. It was thought that there would be very little difference between oxime and nitroso moieties, however based on the evidence this may have been the wrong conclusion. Figure 5-26 shows the structural differences between the two moieties.
In a small test reaction, \( n \text{BuLi} \) was dissolved in dry THF and 5.8 was added. The solution turned an orange colour immediately, after an hour of stirring the solvent was removed \textit{in vacuo} and the residue dissolved in deuterated THF. The \( ^1 \text{H} \) NMR spectrum obtained from the crude product does not show any signal indicative of 5.8, however several other signals which cannot be assigned are present. This suggests that 5.8 reacts with \( n \text{BuLi} \) in the reaction mixture and it is this side reaction that causes oxidation of the phosphine.

The use of the oxime moiety instead of the nitroso moiety appears to introduce an added complication that was not expected. Further investigation into the synthesis of 5.7 and 5.9 would have been interesting, however it was thought that the use of the oxime moiety would not lead to the synthesis of the desired tetra-dentate ligand motif.

### 5.5 Towards the synthesis of 5.2

This section details the two different synthetic routes used in the attempted synthesis of 5.2. Evidence for the successful synthesis of 5.2 is reported however the data remains inconclusive and the synthesis of 5.2 could not be confirmed.

#### 5.5.1 Proposed synthesis of 5.2

The reaction of 2-bromo-2-methylbutane and 1,3-bis(phenylphosphino)propane (section 5.3.2) was thought to produce the desired compound 5.3, but the characterisation data obtained did not fully confirm this. Nevertheless the reaction of 5.10 (Figure 5-27) with dilithium 1,3-bis(phenylphosphino)propane was proposed with the aim of synthesising the target ligand 5.2. Figure 5-27a shows the synthetic conditions published by Troutner \textit{et al.} \textsuperscript{25} for the synthesis of
2-chloro-2-methylbutane. By replacing conc. HCl with conc. HBr the unreported 2-bromo-2-methylbutane (5.10) can be synthesised (Figure 5-27b). The product precipitated from the reaction and was isolated as a white solid by vacuum filtration and washed with cold EtOH. As with 5.1 the product was temperature sensitive and was kept in a freezer.

![Chemical Structures](image)

Figure 5-27: a) Synthesis of 2-chloro-2-methyl-3-nitrosobutane (5.1) reported in the patent by Troutner et al and b) the proposed synthesis of 2-bromo-2-methyl-3-nitrosobutane (5.10)

The synthesis of 5.10 was confirmed by NMR spectroscopy and mass spectrometry, the $^1$H NMR spectrum (Figure 5-28) being similar to that obtained for 5.1. In the $^1$H NMR spectrum of 5.10, singlets at 1.87 and 1.84 ppm correspond to the two methyl substituents at the tertiary carbon centre, these signals are shifted by ~0.2 ppm downfield when compared to 5.1 due to the deshielding effect of the bromide group, an effect is also observed in the $^{13}$C{$^1$H} NMR spectrum.
Figure 5-28: $^1$H NMR spectrum of 5.10 in CDCl$_3$

From the synthesis of 5.10 the reactions shown in Figure 5-29 were proposed. It was thought that 5.2 could be produced via either route. Figure 5-29a illustrates the reaction of 5.10 with 1,3-bis(phenylphosphino)propane whilst Figure 5-29b shows the prior synthesis of Lippp from 1,3-bis(diphenylphosphino)propane. Initially, the reaction in Figure 5-29a was completed and the product isolated as a yellow oil.
Figure 5-29: Proposed reaction schemes for the synthesis of 5.2; a) the method used to synthesise 5.3 - 5.5; b) an alternative route to 5.2 using dppp as the starting material

Figure 5-30 shows the $^{31}$P{¹H} NMR spectrum of the product isolated from the Figure 5-29a. Signals at -54 ppm correspond to the phosphine starting material 1,3-bis(phenylphosphino)propane whilst the signal at -7.97 ppm was thought to suggest the presence of 5.2. The compound has the same shift as observed for 5.3. Whilst it was thought that the two compounds would have similar signals the exact shift was unexpected. In the same way as 5.3, the compound also has only one singlet peak, indicating that a mixture of enantiomers may be present, but that the mixture of meso- and rac-compounds seen during the synthesis of 5.4 and 5.5 are not observed in this sample.
The \(^1\)H NMR spectrum of the same sample does not show the expected signals. The broad undefined signals in the 0.5 – 2.5 ppm range could not be assigned and the \(^{13}\)C\(^{\{1\}H}\) NMR spectrum did not allow for characterisation of the compound. However, mass spectrometry data did indicate the presence of the oxidised ligand ([5.2O\(_2\)]\(^+\)) ion at 492 m/z. The reaction was repeated but the same inadequate data was observed. Due to this result, the proposed reaction in Figure 5-29b was attempted instead.

Figure 5-31 shows the \(^{31}\)P\(^{\{1\}H}\) NMR spectrum of the product isolated from the reaction shown in Figure 5-29b. The major product present at -7.91 ppm has a similar shift to that seen before. Signals at -53 ppm can be assigned to 1,3-bis(phenylphosphino)propane suggesting that there is moisture present in the sample of 5.10. The \(^1\)H NMR spectrum (Figure 5-32) of the product does not show the expected signals from the oxime moiety i.e. the CH\(_3\) groups at 1.8 and 1.5 ppm, which implies that the reaction may not have preceded as expected. However, mass spectrometry of the sample does show a small peak at 459 m/z which corresponds to the mass
of 5.2. Both reactions in Figure 5-29 were repeated however the results remained inconclusive.

Table 5-1 summarises the data obtained from both reactions.

![Figure 5-31: $^{31}$P{[H]} NMR spectrum of 5.2 from the Figure 5-29b reaction in CDCl$_3$](image-url)
Figure 5-32: $^1$H NMR spectrum of 5.2 from the Figure 5-29b reaction in CDCl$_3$

<table>
<thead>
<tr>
<th>Characterisation technique</th>
<th>Reaction Figure 5-29a</th>
<th>Reaction Figure 5-29b</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^1$H NMR spectra</td>
<td>Undefined aliphatic region</td>
<td>No observable CH$_3$ groups</td>
</tr>
<tr>
<td>$^{31}$P{$^1$H} NMR spectra</td>
<td>Singlet at -7.97 ppm</td>
<td>Singlet at -7.91 ppm</td>
</tr>
<tr>
<td>$^{13}$C{$^1$H} NMR spectra</td>
<td>Clear Ph signals, small indeterminate signals in aliphatic region</td>
<td>Clear Ph signals, small indeterminate signals in aliphatic region</td>
</tr>
<tr>
<td>Mass spectrometry</td>
<td>[MO$_2$]$^+$ observed at 492 m/z</td>
<td>[M]$^+$ observed at 459 m/z</td>
</tr>
</tbody>
</table>

Table 5-1: Summary of the characterisation data obtained from reactions shown in Figure 5-29a and Figure 5-29b

Without a pure sample and conclusive characterisation data, the synthesis of 5.2 cannot be deemed successful. The similarities between this data and that obtained for the synthesis of 5.3 using 2-methyl-2-bromobutane are troubling. If the $^{31}$P{$^1$H} NMR spectra is considered, the same signal at $\sim$ -8 ppm is observed from the two separate reaction routes for the synthesis of both 5.2 and 5.3. The phosphine environments of the two compounds are expected to be similar.
and the $^{31}\text{P}\{^1\text{H}\}$ NMR data supports this. However only one signal is observed, and this is unlike the data obtained for 5.4 which shows that the meso-compound and racemic mixture are present in the product. The mixture of enantiomers was expected, it is observed in the starting material 1,3-bis(phenylphosphino)propane and is reported in the literature.\textsuperscript{22} That the samples produced appear not to feature this mix of isomers is interesting and requires further investigation.

If the signal at -8 ppm in the $^{31}\text{P}\{^1\text{H}\}$ NMR spectra is assumed to be the desired product the remaining data can be explained by the lack of purity of the samples. The mass spectrometry data supports the synthesis of 5.2 whilst the $^1\text{H}$ and $^{13}\text{C}\{^1\text{H}\}$ NMR spectra are undefined due to the presence of other compounds.

Due to the questionable data, alternative ways to confirm the synthesis of 5.2 were considered. Initially oxidation of the phosphine atoms was completed, which would provide an air stable compound which could then be purified.

5.5.2 Attempted oxidation of 5.2

With the aim of confirming the synthesis of 5.2 the isolated product was dissolved in dry DCM and H$_2$O$_2$ used to oxidise the phosphine groups. Figure 5-33 shows the proposed structure, the $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum of the sticky solid isolated indicates the presence of several different products. This was supported by TLC analysis which showed 8 products to be present. Mass spectrometry of the sample was completed but did not show the desired mass at 491 m/z and for this reason purification was not attempted.
The use of selenium had been used in chapter 4 to produce stable selenophosphoryl analogues of the phosphine ligands. It was thought that using the same method, 5.12 could be synthesised and the structure determined, this in turn would confirm production of the desired phosphine oxime ligand 5.2. Figure 5-33 shows the proposed structure and the $^{31}\text{P} \{^1\text{H}\}$ NMR spectrum of the crude compound. The spectrum shows several products are present, this was also indicated by TLC analysis. Unfortunately no evidence for the synthesis of 5.12 was observed in the mass spectrometry data and purification was not attempted. The information obtained from these two reactions did not lead to the desired outcome and the synthesis of 5.2 was not confirmed via this route.

5.6 Conclusion

The initial aim of this chapter was to synthesise the phosphine oxime ligand 5.2. The proposed reaction of 1,3-bis(phenylphosphino)propane with 2-chloro-2-methyl-3-nitrosobutane did not proceed as expected and the starting materials were isolated. The literature\textsuperscript{21,23} was found to support this result and tBuCl is reported not to react with lithiated phosphines. A series of experiments were subsequently planned to investigate the reaction. This lead to the successful synthesis of the novel compounds 5.4 and 5.5. Both products were isolated in yields of $\sim$ 70 % and were shown to be pure by NMR spectroscopy, mass spectrometry and elemental analysis. 5.4 with 2 chiral centres was isolated as the meso- and rac-compounds, whilst 5.5 with 4 chiral centres showed 6 signals suggesting several different meso- and rac-compounds were formed.
Since the phosphine starting material was shown to react with primary and secondary chloroalkyl compounds, it was proposed that ligands analogous to 5.2 could be synthesised. 1-Chloropropan-2-one oxime (5.6) and 3-chlorobutan-2-one oxime (5.8) were synthesised and reacted with 1,3-bis(phenylphosphino)propane to produce 5.7 and 5.9 respectively (Figure 5-35). The $^{31}$P{$^{1}$H} NMR spectra of the resulting products showed oxidised phosphine compounds and mass spectrometry did not show evidence for 5.7 or 5.9.

**Figure 5-35: Proposed ligands 5.7 and 5.9 from the reaction of 1,3-bis(phenylphosphino)propane and 5.6 or 5.8 respectively**

5.3 was believed to be synthesised from the reaction of 2-bromo-2-methylbutane and 1,3-bis(phenylphosphino)propane. The product was not isolated as a pure sample however, NMR spectroscopy and mass spectrometry data did suggest synthesis of the compound. It is notable that only one signal is observed in the $^{31}$P{$^{1}$H} NMR spectrum at -8 ppm suggesting that the mix of meso- and rac-compounds seen in 5.4 and 5.5 was not present in 5.3. It is also interesting that the same result was obtained using dppez as a starting material. It was thought that this
supported the synthesis of 5.3 and as such, the brominated analogue of 2-chloro-2-methyl-3-nitrosobutane was synthesised.

2-Bromo-2-methyl-3-nitrosobutane was reacted with 1,3-bis(phenylphosphino)propane with the aim of synthesising 5.2, the $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum shows one signal at -8 ppm. When all the data obtained was considered it was deemed inconclusive and the synthesis of 5.2 could not be confirmed. In an attempt to do this 5.2 was reacted with H$_2$O$_2$ and elemental selenium with the aim of producing the air-stable phosphine compounds 5.11 and 5.12. Unfortunately evidence for 5.11 and 5.12 was not obtained and the successful synthesis of 5.2 could not be established.

5.7 Experimental

All reactions and manipulations were carried out under anaerobic conditions unless otherwise stated. All starting materials were of reagent grade, purchased from Sigma Aldrich and used without further purification. The equipment used has previously been stated, and can be found in Chapter 3.

5.7.1 General synthesis of phosphine compounds

1,3-Bis(phenylphosphino)propane (0.11 g, 0.42 mmol) was placed in a Schlenk and dry THF (5 ml) added. The solution was cooled to -78°C and $n$BuLi (2.5 M, 0.33 ml, 0.84 mmol) added dropwise, the solution changed colour from colourless to yellow immediately. The mixture was allowed to warm to room temperature and the alkyl halide (0.84 mmol) dissolved in dry THF was added. Upon completion of the reaction, the solvent was removed in vacuo to give a white oily solid. The crude product was washed with dry hexane (~10 ml) and filtered via cannula. The solvent was removed from the solution in vacuo to give a colourless oil.
1,3-bis(phenylphosphino)propane (0.11 g, 0.42 mmol) yielded 0.14 g of crude 5.2. $^1$H NMR (400 MHz, CDCl$_3$, ppm): $\delta$ 7.45 (m, 10H, Ph), 7.23 (m, 10H, Ph), 4.39 (bs, 1H), 3.87 (bs, 1H), 2.28 (m, 2H), 2.13 (m, 3H), 1.91 (bs, 8H), 1.64 (bm, 5H), 1.30 (bs, 3H), 0.90 (m, 3H). $^{31}$P{$^1$H} NMR (162 MHz, CDCl$_3$, ppm): $\delta$ 26.81 (s), 25.76 (s), -7.96 (s), -33.35 (s), -49.69 (s), -53.21 (s), -53.70 (s). $^{13}$C{$^1$H} NMR (100 MHz, CDCl$_3$, ppm): $\delta$ 135.19 (d, $^2$J$_{PC}$ = 10.65 Hz, ipso-Ph), 133.69 (d, $^3$J$_{PC}$ = 15.77 Hz, m-Ph), 132.49 (m, Ph), 131.69 (m, Ph), 130.59 (m, Ph), 128.89 (d, $^2$J$_{PC}$ = 10.65 Hz, ipso-Ph), 128.40 (d, $^1$J$_{PC}$ = 5.49 Hz, m-Ph), 128.12 (s, p-Ph), 127.51 (s, p-Ph), 26.92 (t, $^2$J$_{PC}$ = 7.75 Hz), 24.50 (m), 1.04 (s). Electrospray MS (+): 459 m/z [M]$^+$, 492 m/z [M+2O]$^+$. 

1,3-bis(phenylphosphino)propane (0.11 g, 0.42 mmol) yielded 0.092 g of crude 5.3. $^1$H NMR (400 MHz, CDCl$_3$, ppm): $\delta$ 7.69 (m, 4H, Ph), 7.53 (m, 1H, Ph), 7.42 (m, 6H, Ph), 7.36 (m, 2H, Ph), 2.34 (m, 4H), 2.19 (m, 2H), 1.95 (m, 1H), 1.71 (m, 1H), 1.40 (m, 2H), 1.02 (m, 2H). $^{31}$P{$^1$H} NMR (162 MHz, CDCl$_3$, ppm): $\delta$ -7.85 (s), -25.41 (s), -53.15 (s), 54.00 (s). $^{13}$C{$^1$H} NMR (100 MHz, CDCl$_3$, ppm): $\delta$ 138.82 (t), 131.77 (t), 128.47 (s), 127.60 (s), 32.16 (s), 30.18 (d), 29.98 (d), 23.9 (s), 22.81 (s), 14.35 (d). TOF MS ES (+): 403.2353 [M]$^+$, 419.2300 [M+O]$^+$, 433.2463 [M+2O]$^+$. Elemental analysis for C$_{25}$H$_{38}$P$_2$ experimental (calculated): C, 60.70 (74.95); H, 7.11 (9.57).

1,3-bis(phenylphosphino)propane (0.11 g, 0.42 mmol) yielded 0.11 g, 77% of 5.4. $^1$H NMR (400 MHz, CDCl$_3$, ppm): $\delta$ 7.50 (m, Ph, 4H), 7.35 (m, Ph, 6H), 1.82 (m, BuPhPCH$_2$CH$_2$CH$_2$PPhBu, 4H), 1.69 (m, Ph, 6H), 1.82 (m, BuPhPCH$_2$CH$_2$CH$_2$PPhBu, 4H), 1.69 (m, Ph, 6H), 1.82 (m, BuPhPCH$_2$CH$_2$CH$_2$PPhBu, 4H), 1.69 (m,
PhCH₂CH₂CH₂CH₂P(CH₃)₃PPhCH₂CH₂CH₂CH₃, 4H), 1.51 (m, BuPhPCH₂CH₂CH₂PPhBu, 2H), 1.38 (m, PhCH₂CH₂CH₂CH₂P(CH₃)₃PPhCH₂CH₂CH₂CH₃, 4H), 1.31 (m, PhCH₂CH₂CH₂CH₂P(CH₃)₃PPhCH₂CH₂CH₂CH₃, 4H), 0.90 (m, CH₃, 6H) \(^{31}\)P \(^{1}\)H NMR (162 MHz, CDCl₃, ppm): δ -25.53, -25.58. \(^{13}\)C \(^{1}\)H NMR (100 MHz, CDCl₃, ppm): δ 138.76 (d, \(^{1}J_{PC} = 10.33\) Hz, ipso-Ph), 138.64 (d, \(^{1}J_{PC} = 10.33\) Hz, ipso-Ph), 132.26 (d, \(^{2}J_{PC} = 18.63\) Hz, m-Ph), 128.56 (s, \(p\)-Ph), 128.17 (d, \(^{3}J_{PC} = 5.84\), \(o\)-Ph), 29.83 (t, \(^{1}J_{PC} = 10.75\) Hz, PhBuPCH₂CH₂CH₂PPhBu), 29.84 (t, \(^{1}J_{PC} = 10.75\) Hz, PhBuPCH₂CH₂CH₂PPhBu), 28.08 (d, \(^{1}J_{PC} = 3.40\) Hz, CH₃CH₂CH₂CH₂PhP(CH₂)₃PPhCH₂CH₂CH₂CH₃), 27.97 (d, \(^{1}J_{PC} = 3.74\) Hz, CH₃CH₂CH₂CH₂PhP(CH₂)₃PPhCH₂CH₂CH₂CH₃), 27.71 (t, \(^{2}J_{PC} = 11.14\) Hz, CH₃CH₂CH₂CH₂PhP(CH₂)₃PPhCH₂CH₂CH₂CH₃), 24.26 (d, \(^{3}J_{PC} = 11.65\) Hz, CH₃CH₂CH₂CH₂PhP(CH₂)₃PPhCH₂CH₂CH₂CH₃), 22.33 (t, \(^{2}J_{PC} = 16.05\) Hz, PhBuPCH₂CH₂CH₂PPhBu), 13.81 (s, CH₃). Electrospray MS (+): 373.27 m/z [M]+, 389.42 m/z [M+O]+, 404.12 [M+2O]+. Elemental analysis for C₂₃H₄₄P₂ experimental (calculated): C, 74.16 (74.15); H, 8.98 (9.21).

CH₃CH₂CH₃PPh(CH₂)₃PPhCH₃CH₂CH₃ (5.5)

1,3-bis(phenylphosphino)propane (0.10 g, 0.38 mmol) yielded 0.097 g, 67% of 5.5. \(^{1}\)H NMR (400 MHz, CDCl₃, ppm): δ 7.50 (m, 4H, Ph), 7.33 (m, 6H, Ph), 1.93 (m, 4H, \(^{1}\)BuPhPCH₂CH₂CH₂PPhBu), 1.68 (m, 4H, CH₃CH₂CH₂CH₂PPh(CH₂)₃PPhCH₃CH₂CH₃), 1.49 (m, 2H, \(^{1}\)BuPhPCH₂CH₂CH₂PPhBu), 1.35 (m, 2H, CH₃CH₂CH₂CH₂PPh(CH₂)₃PPhCH₃CH₂CH₃), 1.03 (m, 6H, CH₃CH₂CH₂CH₃CH₂CH₃PPh(CH₂)₃PPhCH₃CH₂CH₃), 0.90 (m, 6H, CH₃CH₂CH₂CH₃CH₂CH₃PPh(CH₂)₃PPhCH₃CH₂CH₃) \(^{31}\)P \(^{1}\)H NMR (162 MHz, CDCl₃, ppm): δ -11.58, -11.65, -11.99, -12.05, -12.17, -12.22. \(^{13}\)C \(^{1}\)H NMR (100 MHz, CDCl₃, ppm): δ 136.94 (m, Ph P-C), 137.00 (t, \(^{1}J_{PC} = 15.75\) Hz, Ph P-C), 133.36 (m, \(m\)-Ph), 128.77 (s, \(p\)-Ph), 128.15 (m, \(o\)-Ph), 34.16 (m, CH₃CH₂CH₂CH₃CH₂CH₃PPh(CH₂)₃PPhCH₃CH₂CH₃), 26.89 (m,
\[^{1}\text{BuPh}\text{PCH}_2\text{CH}_2\text{CH}_2\text{PPh}^{i}\text{Bu}], \quad 26.36 \quad (d, \quad ^1J_{PC} = 14.21 \quad \text{Hz}, \quad \\
\text{CH}_3\text{CH}_2\text{CH}_3\text{CHPPh(CH}_2\text{)_3PPhCHCH}_3\text{CH}_2\text{CH}_3), \quad 23.09 \quad (m, \quad {^1}\text{BuPh}\text{PCH}_2\text{CH}_2\text{CH}_2\text{PPh}^{i}\text{Bu}), \\
15.53 \quad (m, \quad \text{CH}_3\text{CH}_2\text{CH}_3\text{CHPPh(CH}_2\text{)_3PPhCHCH}_3\text{CH}_2\text{CH}_3), \quad 12.23 \quad (m, \quad \\
\text{CH}_3\text{CH}_2\text{CH}_3\text{CHPPh(CH}_2\text{)_3PPhCHCH}_3\text{CH}_2\text{CH}_3).\text{ Electrospray MS (+): 373.22.10 m/z [M]^+, \quad \\
389.1898 m/z [M+O]^+, \quad 405.2098 [M+2O]^+. \text{ Elemental analysis for C}_{23}\text{H}_{34}\text{P}_2 \text{ experimental (calculated): C, 74.19 (74.15); H, 9.11 (9.21).}

5.7.2 Synthesis of Nitroso analogues

1-Chloropropan-2-one oxime (5.6)

Chloroacetone (1.0 ml, 12.4 mmol) was dissolved in Et\(_2\)O (10 ml), to this NH\(_2\)OH.HCl (0.87 g, 12.4 mmol) dissolved in H\(_2\)O (5 ml) was added dropwise. K\(_2\)CO\(_3\) (1.7 g) was dissolved in the minimum amount of H\(_2\)O and added to the reaction mixture over 30 min then left for a further 2 hours. The product was extracted with Et\(_2\)O (3 x 25 ml), dried over MgSO\(_4\) and the solvent removed in vacuo. A yellow oil was obtained. Crude yield 0.35 g. Relevant \(^1\)H NMR data (100 MHz, CDCl\(_3\), ppm): 4.09 (s, 2H, CH\(_2\)), 2.32 (s, 3H CH\(_3\)). CI MS [M]: 107 m/z.

3-Chlorobutan-2-one oxime (5.8)

Reaction as above, a brown oil was obtained and purified by column chromatography using silica and 1:1 hexane/EtOAc. Yield 0.98 g, 65 %. \(^1\)H NMR (400 MHz, CDCl\(_3\), ppm): 9.78 (bs, 1H, OH), 5.55 (q, 0.07 H, \(^3\)J\(_{HH}\) = 6.8 Hz), 4.64 (q, 1H, \(^3\)J\(_{HH}\) = 6.8 Hz, CH\(_2\)), 2.01 (s, 0.23H), 1.97 (s, 3H, CH\(_3\)), 1.63 (d, 3H, \(^3\)J\(_{HH}\) = 6.9 Hz, CH\(_3\)), 1.60 (d, 0.25, \(^3\)J\(_{HH}\) = 6.9). \(^{13}\)C \(^{1}\)H NMR (100 MHz, CDCl\(_3\), ppm): 157.99 (s, C\(_{\text{NOH}}\)), 157.41, 57.53 (s, CHCl\(_3\)), 47.86, 22.23 (s, CH\(_3\)), 21.52, 14.95, 9.86 (s, CH\(_3\)). CI MS [M]: 122 m/z.
2-Bromo-2-methyl-3-nitrosobutane (5.10)

2-methyl-2-butene (5 ml, 47.2 mmol) and \textit{iso}-pentynitrile (6.3 ml, 47.2 mmol) were mixed together with vigorous stirring and cooled to -30°C with a methanol/dry ice bath. cHCl (11 ml, 66 mmol) was added dropwise to the stirring mixture while the temperature was kept below -30°C. The mixture was left to stir for a further 2 hours during this time a white precipitate formed. The precipitate was isolated by vacuum filtration and washed with cold methanol. Yield 6.13 g, 73%. ¹H NMR (400 MHz, CDCl₃, ppm): 6.03 (q, \(J_{HH} = 6.6\) Hz, 1H, (CH₃)₂BrCCHCH₃NO), 1.87 (s, (CH₃)₂BrCCHCH₃NO), 1.84 (s, (CH₃)₂BrCCHCH₃NO), 1.54 (d, \(J_{HH} = 6.74\) Hz, (CH₃)₂BrCCHCH₃NO). ¹³C \{¹H\} NMR (100 MHz, CDCl₃, ppm): 67.54 (s, (CH₃)₂BrCCHCH₃NO), 63.85 (s, (CH₃)₂BrCCHCH₃NO), 30.81 (s, (CH₃)₂BrCCHCH₃NO), 30.49 (s, (CH₃)₂BrCCHCH₃NO), 14.15 (s, (CH₃)₂BrCCHCH₃NO). CI MS \[\text{M}^+\]: 179 m/z. Elemental analysis for C₅H₁₀NOBr.ETOH experimental (calculated): C, 37.45 (37.33); H, 7.01 (7.17); N, 5.98 (6.22).

5.8 References

Chapter 6: Conclusions and Future Work
6.0 Conclusions and Future Work

Whilst the three distinct pieces of work completed during this PhD have been concluded in the results chapters, this chapter summarises the results obtained and proposes some directions of future work. Some final remarks regarding the overall project are also discussed.

6.1 The synthesis of a ligand system containing the thiophosphoryl moiety

The aim of chapter 3 was to investigate the use of the thiophosphoryl moiety as a thiol analogue. The work reported features the synthesis of a tetradentate ligand system, and dimethylvinyl sulphide was used to synthesise the bis-thioether bis-thiophosphoryl compounds 3.1 – 3.3 (Figure 6-1). The ligands were reacted with technetium-99m, however analysis by HPLC and TLC showed that complexation had not occurred and \([^{99m}\text{TcO}_4]^{-}\) was isolated in each case. Reactions with \([\text{ReO}_2(\text{py})_4]\text{Cl}\) and \([\text{ReOCl}_3(\text{PPh}_3)_2]\) were also completed and whilst the \(^{31}\text{P}\{^1\text{H}\}\) NMR spectra suggested product formation however, no further evidence was obtained. To gain an understanding of the coordination chemistry of the ligands 3.1 – 3.3 were reacted with Pd(II), Ag(I) and Cu(I) metal centres.

![Compounds 3.1 – 3.3](image)

Figure 6-1: Compounds 3.1 – 3.3

Complexes 3.4 – 3.11 (Figure 6-2) were synthesised and showed the ligand’s ability to act as tetradeicate chelates. X-ray crystallography of the copper(I) complex 3.6 showed the ligand in
a tetrahedral geometry whilst the palladium(II) complexes 3.10 and 3.11 exhibited the ligand coordinated in a square planar geometry. The X-ray crystal structures of 3.10 and 3.11 were used to visualise how the compounds 3.1 and 3.2 could coordinate to a [MO₃] centre where M = ⁹⁹ᵐTc or Re. This led to postulations for the rhenium and technetium results and the lack of complexation, i.e. the ‘soft’ thioether moiety, the sterics of the ligand upon complexation and the charge of the metal centre.

![Structures of 3.6 - 3.7 and 3.9 - 3.11](image)

Figure 6-2: Structures of 3.6 - 3.7 and 3.9 - 3.11

In order to complete a full assessment of the thiophosphoryl moiety as a stable thiol analogue further investigation is required. Two different routes of study are proposed by synthesising analogues of compounds 3.1 – 3.3 i.e. the first alters the alkyl substituents on the phosphorus atoms and the second varies the ‘internal’ donor atoms. In the conclusion of this work, it is proposed that the sterics around the metal centre, caused by the coordination of the ligand, may be a factor in the technetium-99m and rhenium results. It is thought that by altering the substituents to bulkier alkyl groups the coordination of the ligand could be changed, which could potentially force the substituents away from the metal centre allowing for the complexation of a [MO₂]⁺ core, where M is ⁹⁹ᵐTc or Re. Figure 6-3 shows the proposed synthesis of a ligand analogous to 3.2 with iBu substituents instead of methyl groups. Synthesis of the starting thiophosphoryl bromide has previously been published by Kuchen *et al.* The same experimental conditions used to synthesise 3.2 could then be used to produce the proposed ligand. The inclusion of iBu groups may affect coordination of the ligand due to the
increased steric bulk. However assuming the ligand would coordinate in the same way as 3.2 the compound would provide an interesting way to investigate the proposed conclusion once coordinated to a Pd(II) centre.

**Figure 6-3: Proposed synthesis of a tetradentate ligand analogous to 3.2 with t-butyl substituents instead of methyl groups**

As well as investigating the use of the thiophosphoryl moiety, this would also be an interesting way to explore the use of thioether donors with rhenium and technetium-99m, assuming the use of the tBu groups works as expected and alters the way the ligand wraps around a metal centre. The successful synthesis of a $[\text{MO}_2]^+$ complex would lead to the conclusion that the sterics around the metal centre upon complexation were a key factor in the work reported in chapter 3. However if rhenium and technetium-99m complexes cannot be synthesised, it would suggest that the use of the thioether donors is the contributing factor.

To fulfil the aims of the chapter, the thiophosphoryl moiety needs to be investigated further, and altering the bridging donors to amine groups would be a useful route. As mentioned throughout this thesis, amine donors are known to coordinate to technetium-99m, and it is thought that this would provide an insightful way to explore the thiophosphoryl moiety. Figure 6-4a shows the reported synthesis of N, N'-(2'-dimethylphosphinothioethyl)-propylenediamine.\(^2\) With a known synthesis, amine analogues of 3.1 – 3.3 could be synthesised and reacted with rhenium and technetium-99m. The results obtained can be used to evaluate the use of the thiophosphoryl moiety as a stable thio alternative.
Depending on the results obtained, the analogous phosphine compounds could be synthesised and subsequently reacted with technetium-99m. Figure 6-4b shows the published synthesis of a phosphine analogue of 3.1. As well as investigating the thiophosphoryl moiety, the synthesis of amine and phosphine analogues would also offer a way to study the coordination of the ‘internal’ donor atoms with technetium.

6.2 The synthesis of tetradeutate ligands containing the mercaptoimidazole unit

The aim of chapter 4 was to investigate both the use of the thione moiety as a chalcogen donor for rhenium and different ‘internal’ donor atoms. Figure 6-5 shows the proposed reaction scheme for the synthesis of 4.9, 4.10 and 4.12. Whilst synthetic problems were encountered during the attempted synthesis of 4.Y, during the process novel compounds 4.6–4.8 (Figure 6-6) were produced.

Figure 6-5: Proposed reaction scheme for the synthesis of the tetra-dentate ligand systems where X = SH, NH₂ or PPhH in the starting material and S (4.9), NH (4.10) or PPh (4.12) in the product and Y = a leaving group
Unfortunately the synthesis of 4.9 and 4.10 could not be completed via the proposed route. An alternative method featured the synthesis of 1,3-bis(phenylbishydroxymethylphosphonium)propane dichloride (4.11), and the phosphonium salt was reacted with a series of imidazole rings to produce compounds 4.12, 4.16 and 4.17. Synthesis of the tetradentate ligands was confirmed by NMR spectroscopy and mass spectrometry, however only 4.12 was isolated as a pure compound. Synthesis of the ligands was confirmed by the isolation of selenophosphoryl analogues. The isolated chelates were subsequently reacted with PdCl₂ and the three complexes were isolated as coloured solids, with synthesis being confirmed by NMR spectroscopy and elemental analysis. Reactions of 4.12, 4.16 – 4.17 with ReOCl₃(PPh₃)₂ were also completed. Evidence for the synthesis of [ReO₂L]Cl complexes was observed in the ³¹P{¹H} NMR and mass spectra, but unfortunately due to time constraints pure complexes were not isolated.

![Figure 6-6: Structures of the compounds synthesised 4.6 – 4.8, 4.11 – 4.12 and 4.16 – 4.17](image)

Although complete characterisation of the rhenium complexes was not completed the data obtained suggests that these ligands should be investigated further for potential use with
technetium-99m. ReOCl$_3$(PPh$_3$)$_2$ which has been reported$^4$ to produce complexes with an [ReO$_2$]$^+$ core was shown to be compatible with the ligands reported in chapter 4 and led to the proposed synthesis of 4.25 – 4.27 (Figure 6-7). Reactions of 4.12, 4.16 - 4.17 with ReOCl$_3$(PPh$_3$)$_2$ and [ReO$_2$(py)$_4$]Cl should be repeated. Figure 6-7 shows the reaction conditions used and proposed structures for the crude rhenium complexes 4.25 – 4.27. Isolation of the pure compounds could lead to a well-defined structure intimating that analogous complexes with technetium-99m could be synthesised.

The reaction of ligands 4.12, 4.16 – 4.17 with [$^{99m}$TcO$_4$]$^-$ would initially be completed using pre-formulated kits, which have been discussed in chapter 3. These reactions are currently being undertaken at GE Healthcare. It is thought that the results obtained from these initial reactions will lead to further reaction conditions for the synthesis of technetium-99m complexes.

![Figure 6-7: Reaction conditions used for the synthesis of the crude compounds 4.25 – 4.27 and the proposed complex structures, where X = S (4.25 and 4.26) and O (4.27), R = Me (4.25), Et (4.27) and Bu (4.26)](image)

Whilst the tetradentate ligand systems containing ‘internal’ phosphine donors show promising results which require further study, synthesis of the other target ligands with amine and thioether donors could also be continued. The use of 4.8 as a starting material for the synthesis of 4.9 and 4.10 is documented in chapter 4, but the results indicate this synthetic route may not be viable. This has led to an alternative reaction scheme shown in Figure 6-8.
Figure 6-8: Alternative reaction conditions proposed for the synthesis of 4.9 and 4.10, where X = S (4.9) or NH (4.10)

The synthesis of 3-(chloromethyl)-1-methylimidazolium bromide has previously been reported by Yan et al. and can be combined with the reported method for the synthesis of 1,1'-methylenebis(3-methyl-2H-imidazole-2-thione) published by Williams et al. to produce 4.6. Since 4.6 has been shown to be unstable during purification, it is proposed that the compound is used in situ. It is thought that this reaction route would lead to the successful synthesis of 4.9 and 4.10, thus offering a way to study the thione moiety in a tetradequate ligand system with various bridging donor atoms.

6.3 Attempted synthesis of a tetradequate phosphine oxime ligand

The overall aim of chapter 5 was to synthesise a tetradequate phosphine oxime ligand (5.2), but unfortunately the proposed reaction of 1,3-bis(phenylphosphino)propane and 2-chloro-2-methyl-3-nitrosobutane did not proceed as expected. A series of experiments were completed to investigate the reaction, this led to the successful synthesis of the novel compounds 5.4 and 5.5. Unfortunately, a pure sample of 5.3 was not produced and synthesis could not be confirmed.
However since the phosphine starting material was shown to react with primary and secondary chloro alkyl compounds, it was proposed that ligands analogous to 5.2 could be synthesised. The attempted synthesis of ligands 5.7 and 5.9 (Figure 6-10) were completed using the appropriate oxime compound and 1,3-bis(phenylphosphino)propane. Unfortunately, the crude materials isolated were shown to contain a mixture of oxidised phosphine compounds. This indicated the oxime moiety was affecting the reaction and led to the synthesis of 2-bromo-2-methyl-3-nitrosobutane.

2-Bromo-2-methyl-3-nitrosobutane was reacted with 1,3-bis(phenylphosphino)propane with the aim of synthesising 5.2, the $^{31}$P{$^1$H} NMR spectrum shows one signal at -8 ppm. When all the data obtained was considered it was deemed inconclusive. In order to prove or disprove the synthesis of 5.2 the compound was reacted with elemental selenium to give the air stable selenophosphoryl compound 5.12. However several different compounds were observed in the $^{31}$P{$^1$H} NMR spectrum and attempts at purification were unsuccessful.
To fulfil the aim of this piece of work i.e. to compare the amine oxime ligand system with an analogous phosphine oxime system, the synthesis of a phosphine oxime compound is required. The synthetic routes reported in chapter 5 have been shown to be either unsuccessful or inconclusive in synthesising the target compounds. The issues encountered with the use of the oxime compounds (i.e. oxidation of the phosphine) and the tertiary halide starting materials (i.e. lack of reactivity or inconclusive results) have led to a possible alternative route. Figure 6-11 shows a proposed reaction scheme for a tetradeionate phosphine oxime ligand system.

![Proposed reaction scheme for the synthesis of a tetradeionate phosphine oxime ligand](image)

**Figure 6-11: Proposed reaction scheme for the synthesis of a tetradeionate phosphine oxime ligand**

It is proposed that the reaction conditions used to synthesise 2-bromo-2-methyl-3-nitrosobutane could be applied to the synthesis of 3-bromo-4-nitrosohexane, using 3-hexene as the starting material. It is thought that the use of 3-hexene to produce the secondary bromide would be more facile than using 1-pentene to produce a primary bromide compound. The successful synthesis of 3-bromo-4-nitrosohexane would allow for the synthesis of the tetradeionate ligand, but the phosphine oxime ligand with four chiral centres would be synthesised as a mixture of meso and racemic compounds. However, successful synthesis of the ligand and the subsequent rhenium and technetium-99m reactions would at least provide
information regarding complex formation. Successful complexation would then offer stimulus
to continue the synthesis of phosphine oxime ligands.

6.4 References

Chapter 7: Appendices
## 7.0 Appendices

### 7.1 X-ray crystal Structure of 3.2

Crystal data and structure refinement for 3.2

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<tr>
<td>Mean and maximum shift/error</td>
<td>0.000 and 0.001</td>
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Bond lengths [Å] and angles [°] for 3.2

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**Bond Angles (°):**

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C(2B)-C(3B)-S(4B)  107.95(10)
C(5B)-S(4B)-C(3B)  100.45(8)
C(6B)-C(5B)-S(4B)  115.32(11)
C(7B)-C(6B)-C(5B)  113.01(15)
C(6B)-C(7B)-S(8B)  113.05(12)
C(9B)-S(8B)-C(7B)  101.40(8)
C(10B)-C(9B)-S(8B)  115.21(11)
C(9B)-C(10B)-P(11B)  115.31(10)
C(15B)-P(11B)-C(14B)  104.31(9)
C(15B)-P(11B)-C(10B)  108.95(8)
C(14B)-P(11B)-C(10B)  103.96(8)
C(15B)-P(11B)-S(11B)  113.59(6)
C(14B)-P(11B)-S(11B)  112.92(7)
C(10B)-P(11B)-S(11B)  112.38(5)

7.2 X-ray crystal Structure of 3.6

Crystal data and structure refinement for 3.6
Identification code    NL1106
Formula    C_{10}H_{24}CuP_{2}S_{4}, BF_{4}
Formula weight    484.82
Temperature    173 K
Diffractometer, wavelength    OD Xcalibur 3, 0.71073 Å
Crystal system, space group    Monoclinic, P2(1)/c
Unit cell dimensions

\[
a = 13.0308(4) \text{ Å} \quad \alpha = 90^\circ \\
b = 14.2236(3) \text{ Å} \quad \beta = 107.943(3)^\circ \\
c = 11.0454(3) \text{ Å} \quad \gamma = 90^\circ
\]

Volume, Z    1947.64(10) Å³, 4
Density (calculated)    1.653 Mg/m³
Absorption coefficient    1.740 mm⁻¹
F(000)    992
Crystal colour / morphology    Colourless needles
Crystal size    0.35 x 0.07 x 0.02 mm³
θ range for data collection    3.30 to 29.36°
Index ranges    -18<=h<=11, -18<=k<=18, -15<=l<=14
Reflns collected / unique    9340 / 4504 [R(int) = 0.0254]
Reflns observed [F>4σ(F)]    3698
Absorption correction    Analytical
Max. and min. transmission    0.960 and 0.684
Refinement method    Full-matrix least-squares on F²
Data / restraints / parameters    4504 / 0 / 199
Goodness-of-fit on F²    1.048
Final R indices [F>4σ(F)]    R1 = 0.0336, wR2 = 0.0706
R indices (all data)    R1 = 0.0467, wR2 = 0.0747
Largest diff. peak, hole    0.761, -0.513 eÅ⁻³
Mean and maximum shift/error    0.000 and 0.001
Bond lengths [Å] and angles [°] for 3.6

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7.3 X-ray crystal Structure of 3.8

Crystal data and structure refinement for 3.8

Identification code NL1108
Formula C<sub>16</sub>H<sub>34</sub>Cu<sub>2</sub>N<sub>2</sub>P<sub>2</sub>S<sub>4</sub>, 2(BF<sub>4</sub>)
Formula weight 745.33
Temperature 173 K
Diffractometer, wavelength OD Xcalibur 3, 0.71073 Å
Crystal system, space group Monoclinic, P2(1)/n
Unit cell dimensions
\[ a = 11.6925(3) \text{ Å} \quad \alpha = 90^\circ \]
\[ b = 6.90571(15) \text{ Å} \quad \beta = 99.463(2)^\circ \]
\[ c = 18.2242(5) \text{ Å} \quad \gamma = 90^\circ \]
Volume, Z 1451.49(6) Å<sup>3</sup>, 2
Density (calculated) 1.705 Mg/m<sup>3</sup>
Absorption coefficient 1.926 mm<sup>-1</sup>
F(000) 756
Crystal colour / morphology Very pale yellow blocks
Crystal size 0.29 x 0.25 x 0.17 mm<sup>3</sup>
θ range for data collection 3.16 to 32.97°
Index ranges -16<=h<=16, -8<=k<=10, -23<=l<=26
Reflns collected / unique 14945 / 4917 [R(int) = 0.0202]
Reflns observed [F>4σ(F)] 4367
Absorption correction Analytical
Max. and min. transmission 0.784 and 0.686
Refinement method Full-matrix least-squares on F<sup>2</sup>
Data / restraints / parameters 4917 / 0 / 191
Goodness-of-fit on F<sup>2</sup> 1.294
Final R indices [F>4σ(F)]
\[ R1 = 0.0541, \ wR2 = 0.1144 \]
R indices (all data)
\[ R1 = 0.0611, \ wR2 = 0.1166 \]
Largest diff. peak, hole 0.819, -0.751 eÅ<sup>-3</sup>
Mean and maximum shift/error 0.000 and 0.001

Bond lengths [Å] and angles [°] for 3.8

[Cu(1)-N(20) 1.994(3)]
[Cu(1)-S(10)#1 2.3114(16)]
[Cu(1)-S(1)#2 2.3492(9)]
[Cu(1)-S(1) 2.3718(9)]
[Cu(1)-S(5) 2.3817(16)]
[S(1)-P(2) 2.0146(11)]
[S(1)-Cu(1)#3 2.3492(9)]
P(2)-C(12) 1.787(3)
P(2)-C(11) 1.789(3)
P(2)-C(3) 1.816(3)
C(3)-C(4) 1.520(5)
C(4)-S(10)#1 1.707(4)
C(4)-S(5) 1.932(4)
S(5)-C(6) 1.805(6)
C(6)-C(7) 1.517(9)
C(7)-C(8) 1.505(10)
C(8)-C(9) 1.515(9)
C(9)-S(10) 1.807(7)
S(10)-C(4)#1 1.707(4)
S(10)-Cu(1)#1 2.3114(16)
N(20)-C(21) 1.131(5)
C(21)-C(22) 1.459(5)
B(30)-F(33) 1.367(5)
B(30)-F(34) 1.367(5)
B(30)-F(31) 1.378(5)
B(30)-F(32) 1.387(5)
N(20)-Cu(1) 107.50(10)
N(20)-Cu(1)-S(1)#2 119.48(9)
S(10)#1-Cu(1)-S(1)#2 96.56(5)
N(20)-Cu(1)-S(1) 105.01(9)
S(10)#1-Cu(1)-S(1) 107.80(5)
S(1)#2-Cu(1)-S(1) 119.16(2)
N(20)-Cu(1)-S(5) 97.25(10)
S(10)#1-Cu(1)-S(5) 19.77(5)
S(1)#2-Cu(1)-S(5) 116.26(5)
S(1)-Cu(1)-S(5) 95.09(5)
P(2)-S(1)-Cu(1)#3 104.40(4)
P(2)-S(1)-Cu(1) 100.91(4)
Cu(1)#3-S(1)-Cu(1) 124.17(4)
C(12)-P(2)-C(11) 107.50(18)
C(12)-P(2)-C(3) 108.38(17)
C(11)-P(2)-C(3) 103.57(17)
C(12)-P(2)-S(1) 111.29(13)
C(11)-P(2)-S(1) 111.09(13)
C(3)-P(2)-S(1) 114.52(11)
C(4)-C(3)-P(2) 120.0(2)
C(3)-C(4)-S(10)#1 124.9(3)
C(3)-C(4)-S(5) 103.6(2)
C(6)-S(5)-C(4) 102.2(2)
C(6)-S(5)-Cu(1) 105.1(2)
C(4)-S(5)-Cu(1) 96.93(12)
C(7)-C(6)-S(5) 115.6(5)
C(8)-C(7)-C(6) 111.2(6)
C(7)-C(8)-C(9) 115.4(6)
C(8)-C(9)-S(10) 114.8(5)
C(4)#1-S(10)-C(9) 101.0(3)
7.4 X-ray crystal Structure of 3.12

Crystal data and structure refinement for 3.12

Identification code NL1103
Formula [C_{10}H_{24}PdP_{2}S_{4}](PF_{6})_{2}, C_{2}H_{3}N
Formula weight 771.87
Temperature 173 K
Diffractometer, wavelength OD Xcalibur PX Ultra, 1.54184 Å
Crystal system, space group Orthorhombic, Pbca
Unit cell dimensions
- a = 19.29036(15) Å, \( \alpha = 90^\circ \)
- b = 14.08150(12) Å, \( \beta = 90^\circ \)
- c = 20.69636(17) Å, \( \gamma = 90^\circ \)
Volume, Z 5621.90(8) Å³, 8
Density (calculated) 1.824 Mg/m³
Absorption coefficient 11.077 mm⁻¹
F(000) 3072
Crystal colour / morphology Yellow blocky needles
Crystal size 0.22 x 0.11 x 0.09 mm³
\( \theta \) range for data collection 4.27 to 72.45°
Index ranges -23<=h<=9, -17<=k<=17, -25<=l<=25
Reflns collected / unique 38404 / 5534 [R(int) = 0.0394]
Reflns observed [F>4σ(F)] 4763
Absorption correction Analytical
Max. and min. transmission 0.530 and 0.239
Refinement method Full-matrix least-squares on F²
Data / restraints / parameters 5534 / 768 / 367
Goodness-of-fit on F² 1.050
Final R indices [F>4σ(F)] R1 = 0.0321, wR2 = 0.0792
R indices (all data) R1 = 0.0391, wR2 = 0.0831
Extinction coefficient 0.000084(13)
Largest diff. peak, hole 0.577, -0.401 eÅ⁻³
Mean and maximum shift/error 0.000 and 0.001
### Bond lengths [Å] and angles [°] for 3.12

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<th>Length</th>
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7.5 X-ray crystal Structure of 3.13

Crystal data and structure refinement for 3.13
Identification code NL1301
Formula C₁₁H₂₆P₂PdS₄, 2(CF₃O₃S)
Formula weight 753.04
Temperature 173 K
Diffractometer, wavelength OD Xcalibur 3, 0.71073 Å
Crystal system, space group Monoclinic, P2(1)/n
Unit cell dimensions
\[ \begin{align*}
a &= 8.56323(18) \text{ Å} & \alpha &= 90^\circ \\
b &= 11.2334(3) \text{ Å} & \beta &= 91.3960(19)^\circ \\
c &= 27.5282(6) \text{ Å} & \gamma &= 90^\circ \\
\end{align*} \]
Volume, Z 2647.27(11) Å³, 4
Density (calculated) 1.889 Mg/m³
Absorption coefficient 1.366 mm⁻¹
F(000) 1512
Crystal colour / morphology Yellow thin plates
Crystal size 0.31 x 0.25 x 0.01 mm³
θ range for data collection 2.96 to 29.59°
Index ranges -8<=h<=11, -11<=k<=14, -38<=l<=30
Reflns collected / unique 20680 / 6382 [R(int) = 0.0287]
Reflns observed [F>4σ(F)] 5588
Absorption correction Analytical
Max. and min. transmission 0.979 and 0.705
Refinement method Full-matrix least-squares on F²
Data / restraints / parameters 6382 / 224 / 373
Goodness-of-fit on F² 1.146
Final R indices [F>4σ(F)] R1 = 0.0343, wR2 = 0.0642
R indices (all data) R1 = 0.0424, wR2 = 0.0667
Largest diff. peak, hole 0.955, -0.528 eÅ⁻³
Mean and maximum shift/error 0.000 and 0.002

Bond lengths [Å] and angles [°] for 3.13

\[ \begin{align*}
Pd-S(9) &= 2.3147(7) \\
Pd-S(13) &= 2.3157(7) \\
Pd-S(5) &= 2.3218(7) \\
Pd-S(1) &= 2.3315(8) \\
S(1)-P(2) &= 2.0097(11) \\
\end{align*} \]
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Chapter 7

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O(31')-S(30')-O(32') 118.2(12)
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7.6 X-ray crystal Structure of 4.11

Crystal data and structure refinement for 4.11

Identification code  NL1304
Formula  C_{19}H_{28}O_{4}P_{2}, 2(Cl)
Formula weight  453.25
Temperature  173 K
Diffractometer, wavelength  OD Xcalibur 3, 0.71073 Å
Crystal system, space group  Tetragonal, P4(3)2(1)2
Unit cell dimensions  
\[ a = 6.87609(13) \text{ Å} \quad \alpha = 90^\circ \]
\[ b = 6.87609(13) \text{ Å} \quad \beta = 90^\circ \]
\[ c = 44.8941(14) \text{ Å} \quad \gamma = 90^\circ \]
Volume, Z  2122.62(10) Å³, 4
Density (calculated)  1.418 Mg/m³
Absorption coefficient  0.479 mm⁻¹
F(000)  952
Crystal colour / morphology  Colourless blocks
Crystal size  0.33 x 0.28 x 0.23 mm³
θ range for data collection  3.26 to 27.67°
Index ranges  -8≤h≤8, -8≤k≤8, -56≤l≤54
Reflns collected / unique
Reflns observed [F>4σ(F)]
Absorption correction
Max. and min. transmission
Refinement method
Data / restraints / parameters
Goodness-of-fit on F^2
Final R indices [F>4σ(F)]
R indices (all data)
Absolute structure parameter
Largest diff. peak, hole
Mean and maximum shift/error

Bond lengths [Å] and angles [°] for 4.11

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Symmetry transformations used to generate equivalent atoms:
#1 -y,-x,-z+3/2