Reactions of N-sulfonylpyrroles yielding metal complexes with potential anti-cancer activity

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January 2008

Declaration

I declare that the work presented in this thesis was carried out exclusively by myself under the supervision of Dr A Dinsmore and Professor J P Michael. It is being submitted for the degree of Master of Science in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination in any other University.

_W. Nxumalo__
(Signature of candidate)

15th day of _May_2008

Abstract

The dissertation describes the synthesis of sulfonylimine ligands from *N*-sulfonylpyrrole. These ligands form metal complexes with various transition metals and are to be tested for activity against cancer cells. The introductory chapter sets the scene by describing transition metals in existing therapy and current investigations on transition metals in therapy. It also covers current methodology for deprotonation of *N*-sulfonylpyrrole leading to carbon-carbon bond formation.

The second chapter describes the experimental work performed in this project. A synthetic route towards sulfonylimine ligands, 4-methyl-*N*-[phenyl(1*H*-pyrrol-2yl)methylene]benzenesulfonamide **15** and *N*-[phenyl(1*H*-pyrrol-2yl)methylene]benzenesulfonamide **6**, is described. The mechanism for the 1,4-migration of the sulfonyl group was investigated in a crossover experiment and was found to occur via an *intra* molecular shift.

The sulfonylimine ligands were complexed with late transition metals from the first row (cobalt(II), nickel(II), copper (I), copper(II) and zinc(II)), second row (palladium(II) and silver(I))and third row (platinum(II)), and were submitted for testing against cancer cells. The first row transition metal complexes did not show activity against HeLa cancer cells, while in the second row, activity was observed for the silver complexes. The third row metal complex also showed anti-cancer activity.

Previously reported methodology employing Grignard reagent and catalytic amine base to deprotonate *N*-sulfonylpyrrole and quenching with electrophiles was extended to indole, imidazole and benzimidazole ring systems. Results obtained were comparable to those reported using lithium bases. Addition of lithium chloride to the Grignard reagent reduces the mole equivalent of the reagent required for deprotonation.

A comparison between the arylsulfonyl and dimethylsulfamoyl protecting groups in pyrrole and imidazole showed that arylsulfonyl are better protecting groups for pyrrole, while dimethylsulfamoyl is a better protecting group for imidazole.

All synthesized organic structures were characterized by NMR spectral data, mass spectrometry and melting points where applicable. The synthesized metal complexes were characterized by mass spectroscopy, infrared spectroscopy and X-ray crystallography where applicable.

Dedication

This thesis is dedicated to my family and friend

my late Father Sonto

my mother Rose

my brothers Nyiko, Conrald, Newton and Brian

my nephews Luther and Sonto

my niece Xiluva and Nhlalala

my late friend Mluleki Sithoza

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List of abbreviations

ESI	Electrospray ionization
FAB	Fast atom bombardment
IR	Infrared
NMR	Nuclear magnetic resonance
DCM	Dichloromethane
DMF	*N*,*N*-Dimethylformamide
THF	Tetrahydrofuran
DA	Diisopropylamine
DBU	1,8-Diazabyicyclo[5.4.0]undec-7-ene
LDA	Lithium diisopropylamide
TMP	2,2,6,6-Tetramethylpiperidine
TMS	Trimethylsilyl
TPP	Triphenylphosphine
Ar	Aryl
Bu	Butyl
^{i}Pr	Isopropyl
Bn	Benzyl
Ac	Acetyl
Et	Ethyl
Me	Methyl
Ph	Phenyl

Chapter 1

Introduction

Chapter 1: Introduction

1.1 Background on transition metals in biological systems

Transition metals play essential roles in the functioning of physiological life. They participate in important biological functions, e.g. iron (Fe) in hemoglobin, cobalt (Co) in vitamin B12, molybdenum (Mo) in the molybdenum cofactor (Moco)[1], just to mention a few. Deficiency in these essential transition metals leads to serious illness and in some cases death. Not all transition metals, however, are used biologically. This is due to their bioavailability; nature appears to prefer metals that are easily obtained from the soil.

Transition metals that are bioavailable include manganese (Mn), iron (Fe), cobalt (Co), copper (Cu), zinc (Zn) and the second row metal molybdenum (Mo)[2]. Much research is currently focused on making complexes which contain these essential transition metals and testing their activity against various diseases. The research involves collaboration of various disciplines in the field of science e.g. chemistry and biochemistry.

A brief overview containing current transition metals in therapy and current investigations of transition metals in therapy is given below.

1.2 Background on transition metals in therapy

1.2.1 Existing transition metal-based therapy

Transition metals that are not bioavailable have also been investigated for activity against various diseases. The most useful complex is without doubt cisplatin **1**, discovered in the 1960s[3], used in the treatment of cancer. The complex contains a platinum metal bonded to two nitrogen ligands and two chlorine ligands. The mode of action of cisplatin is believed to involve the binding of the complex into the two DNA strands, blocking

replication and transcription of nucleic acids into proteins. It has also been shown to trigger programmed cell death (apoptosis)[1]. Other findings in this research show that the platinum complex binds to one DNA strand and causes distortion that results in cell death[4-6].

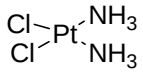
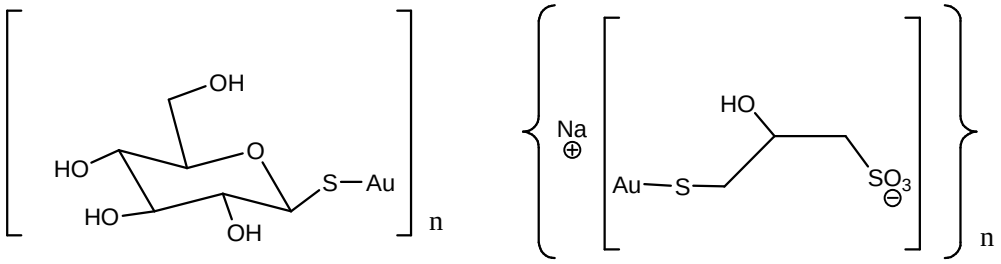


Figure 1. Cisplatin (1)

Cisplatin is currently being used for the treatment of cancer, and has shown high activity against various cancer cell lines. The IC_{50} value, the concentration of a drug required to kill 50% of infected cells, is below 5 μM in most cell lines. The drug **1** has shown side effects such as nephrotoxicity, neurotoxicity, vomiting and nausea. Other cancer cell lines are resistant to cisplatin[7-8]. These limitations have led to research into finding drugs that are as active as, or more active than, cisplatin but with fewer side effects.

Gold compounds have also been used in therapy. The use of gold in medicine can be dated back to 2500 B.C.[9-10] where it has been used to treat leprosy, epilepsy and other diseases.

In 1928 gold-thiolate drugs (Figure 2) found their use in the treatment of rheumatoid arthritis (RA) and even today they are still used[9]. These drugs contain gold in its +1 oxidation state and act as anti-inflammatory agents. However, they have been shown to have severe side effects and are only used as a last line of defense. Treatment of RA in the early stages usually involves more conventional organic drugs known as non-steroid anti-inflammatory agents (NSAIDs) and corticosteroids. The NSAIDs drugs act by blocking cyclooxygenase enzymes, COX-1 and COX-2, and in turn block prostaglandins generated by the COX enzymes. The prostaglandins are important mediators for both pain and inflammation[9]. The corticosteroids act as anti-inflammatory and immunoregulatory agents.



aurothioglucose

sodium aurothiopropanol sulphonate

Figure 2. Gold-thiolate drugs

1.2.1 Current investigations into transition metals as therapeutic agents

Much research is currently focused on making transition metal complexes that contain both the bioavailable and non-bioavailable transition metals and many publications have shown some of these complexes to have some biological activity.

Cobalt complexes have shown anti-malarial effects[11] where they target the plasmodium parasite. The activity of the compounds was comparable to that of the currently used drug, amodiaquine, at similar concentrations (Figure 3 a). These studies were *in vitro* studies and only show the toxicity to the parasite not the host. No further biological testing information was reported. Other studies have shown cobalt complexes to have anti-bacterial activity which is also comparable to the presently available drug, imipenium[12]. These results were also done *in* v*itro* and there is no mention of further biological testing on these compounds (Figure 3 b). Cobalt is a redox active metal where the +2 and +3 oxidation states are most common.

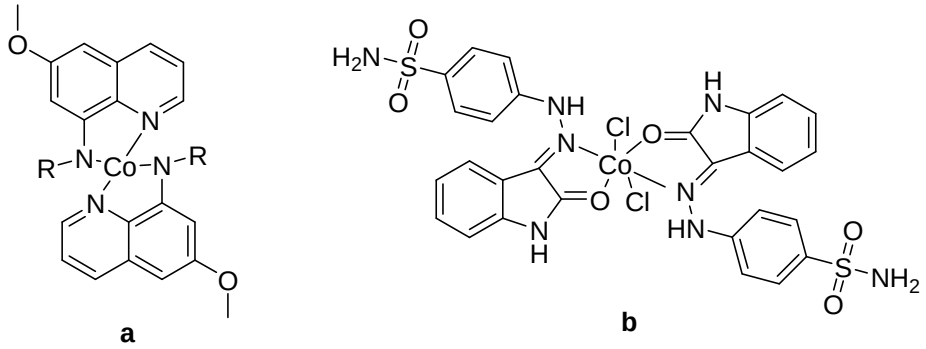


Figure 3. An example of cobalt complexes used in anti-malaria (a) and anti-bacteria (b) studies.

Molybdenum complexes (e.g. Figure 4) have shown anti-cancer activity[13] against the cell line, V79 Chinese hamster lung cells. These complexes were used to study the relationship between cellular uptake and toxicity and were only performed *in vitro*. Unlike most transition metals in biological systems, Mo has a high oxidation state of +6 and a high coordination number.

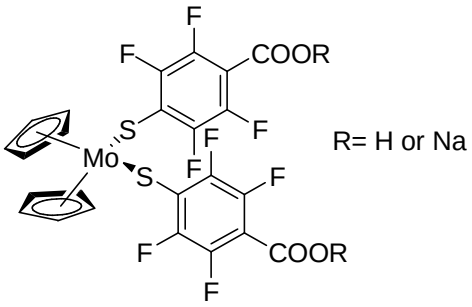


Figure 4. An example of a molebdenum complex used in an anti-cancer study.

A number of synthetic copper complexes have been shown to have anti-malarial activity[11], anti-cancer activity[14-15], nuclease activity[16], anti-inflammatory activity in rheumatoid arthritis[17], and they also catalyse several reactions, such as nitration of aromatic compounds, which are usually catalysed by the enzyme superoxide dismutase[18]. The mode of action of these complexes is unclear and both oxidation states of the metal, i.e. +1 and +2, are used. Promising results have been observed from both oxidation states. These reported results were performed *in vitro* and there appear to be no further mention of other biological testing.

Zinc complexes have been shown to bind strongly to an HIV receptor CXCR4, used for membrane fusion, and hence inhibit the spread of the virus[19]. The complexes were shown to be ten times more active than the metal-free ligand, showing the importance of the metal (Figure 5). Other zinc complexes have been shown to have anti-malarial activity[11] and also anti-bacterial activity[12] in similar studies to those of cobalt.

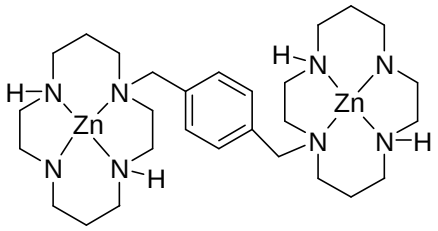


Figure 5. An example of a Zn complex used in an anti-HIV study.

Many platinum-containing complexes (e.g. Figure 6) have since been synthesized, after cisplatin, and some have shown promising results [7, 20-22]. The focus has been in trying to incorporate ligands that are similar to those in biological systems and also less toxic. Other platinum complexes have been shown to have anti-HIV activity[23]. Complexes containing metals that are isoelectronic to platinum(II), i.e. palladium(II) and gold(III) have also been investigated for their activity against cancer.

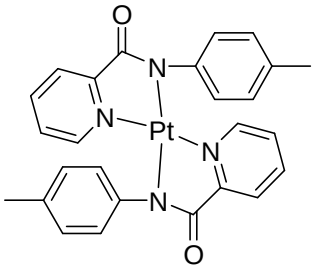


Figure 6. An example of a platinum complex used in an anti-cancer study.

Palladium complexes (e.g. Figure 7) have shown anti-cancer activity similar to their platinum counterparts[7,23] and in some cases have been more active than cisplatin[24]. Pd(II) is a d^8 ion which has square planar geometry around the metal, similar to Pt(II). In catalysis the processes catalysed by platinum can also be catalysed by palladium and in some cases palladium is better[25].

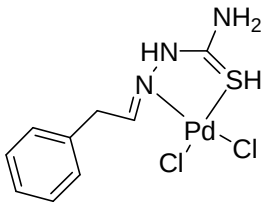


Figure 7. An example of a palladium complex used in an anti-cancer study.

Gold complexes (e.g. Figure 8) have also shown anti-cancer activity but, interestingly, both oxidation states of gold, i.e. +1 and +3 have shown activity[23- 30]. The different oxidation states of the gold metal have been shown to direct the metal to different target areas, Au(I) complexes have been shown to interact strongly with the mitochondria, while Au(III) has been shown to interact with the DNA with a mechanism suggested to be related to that of cisplatin the platinum complexes[31].

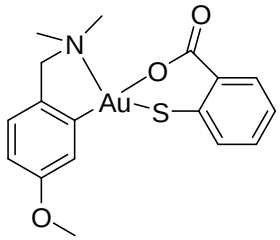


Figure 8. An example of a gold complex used in an anti-cancer study.

The use of silver in medicine has been known for some time. For example, silver nitrate ($AgNO_3$) has been used as an anti-microbial agent since the 1800s. Silver complexes have also shown anti-cancer[19, 31-32] and anti-malarial activity[11], and in other experiments silver complexes were more active when compared to the platinum and palladium complexes. Nickel complexes have also shown significant activity against certain cancer cell lines[33-34].

1.2.3 Toxicity

Although some transition metal complexes have shown activity against several diseases, most of the results obtained were from *in vitro* studies. This type of study involves only affected cells and no information about healthy cells can be obtained. When *in vivo* or

clinical tests are performed, most of the metal complexes have been shown to be toxic to healthy cells and thus not effective for the treatment of a particular disease. In most cases, the infected cells and the normal cells are very similar i.e. they have similar DNA, protein, RNA structure and other molecules essential for the functioning of the cells[1]. The difference between healthy cells and infected cells is usually the disruption of one pathway which leads to overproduction or underproduction of certain molecules which result in disease. Cancer cells have been shown to be more metabolically active than normal cells and this result in cancer cells replicating faster than normal cells and spreading over a large area in the body[1].

It is important to have compounds that are selective for only the infected cells but not the healthy ones. This helps in minimizing side effects. The way of achieving this goal is to identify the major difference between the normal and infected cell, then target those specific areas in the cell. Cisplatin targets the DNA of the cancer cells since they replicate faster than normal cells and hence minimize the spread of the cancer cells[35]. It should be noted that the mode of action of most of these metal complexes is not known and thus it is difficult to make target-specific metal complexes.

Transition metals in their free ion form are toxic and not target-specific. They also have a high risk of being excreted by the kidneys before they can be absorbed by the cells. Other metal salts e.g. $Au(CN)_2^-$ are insoluble and have to be administered orally. One way of making soluble target-specific metal complexes is by ligand design.

1.3 Background on ligand design

Designing a ligand is one of the challenging parts of drug design since many variables are involved. These variables include polarity, size, shape and metal binding ability and strength. The polarity of the ligand must be able to allow the metal complex to be soluble in the host medium, which is aqueous and also be able to interact with the cell membrane which is mainly hydrophobic[1, 36]. Once the drug is on the membrane it should be able pass through into the cell or it must interact with the membrane receptors and induce

other physiological pathways. This requires the metal complex to have polar groups that can interact with the aqueous medium and also non-polar groups to interact with the hydrophobic portion of the cell membrane[36].

The balance between the polar and non-polar properties of the molecule is measured by the log p value (equation 1), which measures the concentration of the molecule in the organic phase versus the aqueous phase[36]. This is obtained by dissolving a known amount of the compound in a solvent mixture of water and octanol, shaking the mixture and measuring the concentration in both phases.

$$\log p = \frac{\text{Concentration of compound in octanol}}{\text{Concentration of compound in aqueous solution}} \qquad (1)$$

The higher the value of log p, the more non-polar the compound will be, and vice versa. It has been shown that compounds with a high log p value are more biologically active than those with lower values[36]. This may be due to the compounds(low log p) being too polar and not being able to pass through the membrane, resulting in their excretion by the kidneys[1, 36]. The range of log p value shown to be effective is between +1 and +5. Above +5, the molecule is very non-polar and not soluble in the aqueous medium but gets absorbed by the fat tissues instead. This results in the molecule not reaching its target and subsequently getting excreted without performing its intended function[36].

The size of the molecule must not be too large since this tends to increase the number of polar groups attached on the molecule. The molecular weight of the molecule should be less than 500 g/mol, but this value is difficult to obtain with metal complexes since metals have high coordination number and require more than one ligand. Transition metals also have high molecular weights per atom which results in the overall complex being heavy. If the complex has a high molecular weight then it should also have a high log p value to make the complex less polar[36].

The shape of the ligand plays a very important role in making the molecule target-specific since a target area requires specific geometry of substrates. Drugs targeting the DNA are planar and disrupt the DNA replication by intercalating with the double strand. Proteins usually require a 3-D structure to bind in their active site and hence the molecules need not to be planar but must have a size similar to those that naturally bind the active site of the protein[36]. Metal complexes are usually too large to compete for the active site of proteins and they probably target areas away from or near the active site and modify activity by an allosteric mechanism[1].

The ability of the ligand to bind the metal and form a stable complex is extremely important and will determine if the complex will survive in biological solution, which contains a large pool of molecules capable of complexing metals. The molecules include the amino acids, nucleotides and carbohydrates which contain OH, NH and SH groups that can coordinate with metals[1, 2 ,36]. It is extremely important to design ligands that will form strong interactions with metals when compared to interactions with other biological ligands. A strong metal-ligand interaction ensures that the complex will have a high binding constant. This is usually achieved by using appropriate chelating ligands chosen on the basis of hard-soft acid-base (HSAB) theory.

Chelating ligands have two or more donor atoms in the molecule, which can bind the metal ion at the same time[2]. This is very useful since it reduces the number of molecules coordinating to the metal centre. Chelating ligands have been shown to form stable complexes with metals when compared to non-chelating ligands. This is due to less repulsion around the metal since the number of molecules around the metal centre is reduced. Also of importance are the kinetics of formation of the metal-chelate complex, which are usually fast compared with a non-chelate-metal complex[2].

The hard-soft acid-base (HSAB) theory states that soft metals (Lewis acids) will form strong interactions with soft ligand donors (Lewis bases), and likewise hard metals with hard ligand donors[2]. Soft metals and ligand donors are those with a polarisable electron density cloud around the nucleus, while hard metals and ligand donors have an

unpolarised electron cloud. Hard metals are found in the top and left of the periodic table and metals become softer when moving to the left and bottom of the periodic table. High oxidation states favour hard metals while soft are favoured by low oxidation states.

Hard donor ligands are often those with oxygen donor groups and their strength increases with the negative charge on the oxygen, and also fluorine and chlorine. Soft donor ligands are those with phosphorus, bromine, iodine and in rare cases carbon ligands. Other donor atoms such as nitrogen and sulfur have been shown to be intermediate in their bonding strength. They form stable complexes with both the hard and soft metals[2].

Most of the transition metals being investigated for biological activity are those found in the right and bottom of the periodic table, hence they are soft or slightly soft in nature. Most of the ligands designed for complexing these metals are chelating and contains intermediate to soft donor ligands depending on the nature of the metal. Most of these ligands contain at least one nitrogen donor atom and in other cases all the donor atoms are nitrogen atoms.

Very soft metals such as gold(I), silver(I) and copper(I) are usually complexed with soft donor ligands containing nitrogen, sulfur or phosphorus atoms[4, 23, 24, 27, 28 and 29]. The slightly soft metals such as Pt(II), Pd(II), Ni(II), Cu(II), Zn(II), Co(II) and Au(III) form strong interactions with nitrogen and sulfur donor atoms, but in some cases oxygen donor atoms can be used[11, 29, 31-32].

Many synthetic transition metal complexes are being investigated for their anti-cancer activity, but synthesizing a particular molecule with specific target areas is very difficult since the causes of cancer are very diverse and hence there are many target areas involved[1, 37-38].

1.4 Background on cancer

Cancer is a disease caused by cells with uncontrollable cell growth[37]. This uncontrollable growth is caused mainly by two factors, i.e., cells not responding to growth factors, and overproduction or underproduction of various proteins responsible for growth regulation. Growth factors (GFs) are molecules which send signal to cells to start or stop cell division and also to undergo programmed cell death (a process known as apoptosis) when the cells are damaged or old[1, 37 -38]. These GFs ranges from small organic molecules to small peptide molecules such as hormones.

When cells overproduce proteins responsible for cell division, e.g. DNA polymerase, the DNA of the cell will continuously replicate and this will lead to uncontrollable cell division. Other proteins that can be overproduced are those that signal the start of cell division. Underproduction of proteins that stop cell division or induce apoptosis also results in uncontrollable cell division or growth[38].

More than 90% of all cancer is caused by the damage to the cell DNA, which is responsible for the production of all proteins in the cell[39]. Damage to the DNA is caused by mutations and cleavage of DNA fragments. Mutations can arise from a change of one nucleotide to another, e.g. guanine (G) to thymine (T), or cytosine (C) to uracil (U). They can also occur due to the translocation between chromosomes. The resulting mutations result in a change in the genes responsible for protein coding and synthesis, resulting in modified proteins being produced. These modified proteins may perform different functions compared to the normal ones and, in the worst cases, change the cell from being normal to a cancer cell[37-39].

DNA damages occur naturally and can also be induced by environmental factors known as carcinogens, which are:

(i) Physical agents (radiation),

(ii) Chemical agents (organic compounds), and

(iii) Infectious agents (viruses).

Radiations, e.g. X-rays, have been shown to cleave DNA, and when DNA repair occurs, mutations are likely to occur. In other cases the DNA is not repaired and as a result other proteins are no longer produced. Chemical agents cause mutations by altering the DNA sequence where one nucleotide is replaced by another. In other cases, the nucleotide is methylated and is no longer recognized by the replicating enzymes, resulting in loss of protein production[40]. The role of viruses in the cause of cancer is not fully known but it is believed that the virus DNA gets incorporated into the host DNA and in other cases the virus produces proteins that inhibit apoptosis[38].

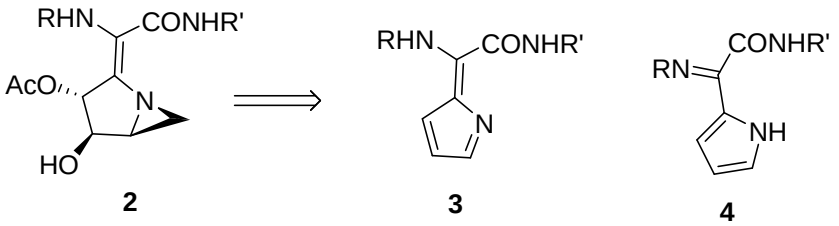
DNA from natural cells has been shown to undergo mutations even when not exposed to environmental factors causing cancer. The history of cancer has been known since humans first learnt to record their activities[38] but it used to be an old-age disease. As humans grown old, the rate of DNA mutations increases, since their DNA has replicated so many times. The rate of mutation for normal cells, however, is very low compared to cells exposed to carcinogens[40]. High occurrence of cancer in human is also observed in infants since their cells replicate faster than adult cells thus high rate of mutations is possible.

Since most metal-complexes are too large to mimic molecules binding to the active site of enzymes, their target area is mainly on the DNA. These molecules need to be planar for them to be effective since they should intercalate with the DNA strands and stop DNA replication. Planar metal complexes must have a square planar geometry in the metal centre, as well as planar ligands. Planar ligands are made from aromatic compounds and since coordinating atoms are required, heteroaromatic compounds are usually used.

1.5 Introduction to this project

1.5.1 Synthesis of *N*-phenylsulfonylimine ligands

The *N*-phenylsulfonylimine ligands were synthesized in our laboratory by Patil and Mandy[41] in an effort to generate precursors for azinomycin synthesis. The most demanding step in azinomycin synthesis is the generation of a densely functionalized pyrolidine-aziridine ring system[42], which has been previously synthesized from carbohydrate precursors. An alternative disconnection of the pyrolidine ring **2** leads to azafulvene synthon **3** or its tautomeric form of pyrrole **4** (Scheme 1).

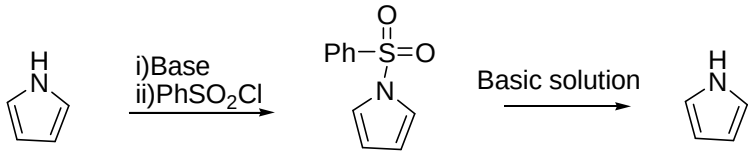


Scheme 1.

Azafulvenes are intermediates in a number of reactions but they are highly reactive molecules[43-45]. They undergo rapid dimerisation[43,44] and also react with various nucleophiles[42]. Azafulvene species are formed from electron rich pyrrole molecules[43-45]. Introducing an electron-withdrawing group (EWG) into a pyrrole ring, on the nitrogen atom, suppresses the formation of azafulvene[42]. This has led to exploration into using electron deficient pyrrole systems as alternative to azafulvenes.

The EWG chosen in our laboratory was the phenylsulfonyl group, which also has an additional advantage of being a directing *ortho* metallation (DOM) group. Phenylsulfonyl chloride, source of the phenylsulfonyl group, is crystalline in nature, and this crystallinity is usually transferred to molecules bearing the sulfonyl group. The sulfonyl group can be introduced into a pyrrole, in a presence of base (Scheme 2), to give *N*-phenylsulfonylpyrrole **5**. Itahara *et al.*[46] made use of sodium hydride in DMF, Gaare *et al.*[47] made use of LDA, Ottoni *et al.*[48] made use of potassium hydroxide and Anderson[49],

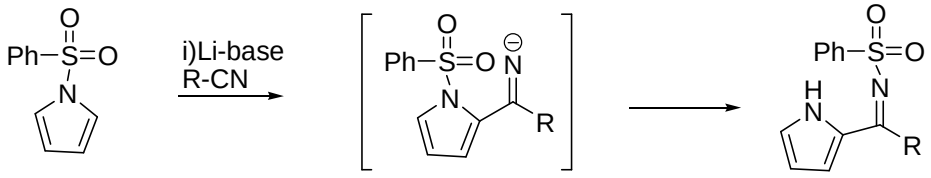
Artico[50] and Zelikin[51] all made use of sodium hydroxide under varying conditions. The sulfonyl group can be easily removed under basic hydrolytic conditions (Scheme 2) with sodium hydroxide[52], sodium methoxide[53], and potassium hydroxide[49] or potassium carbonate[54].



5

Scheme 2.

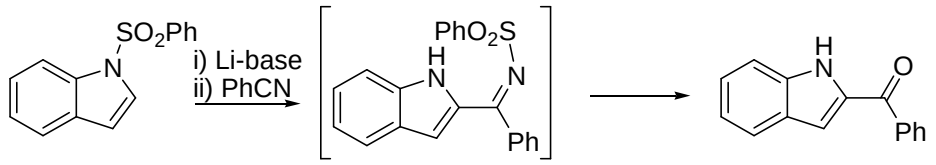
Dinsmore *et al.*[55] explored the functionalization of pyrrole **5** using magnesiation conditions, where the pyrrole was deprotonated at the 2-position and various electrophiles were introduced. Patil and Mandy[41] made use of lithium bases to deprotonate pyrrole **5** and various electrophiles were introduced, but of importance were the nitrile electrophiles as they give products that could be potential precursors to azinomycin synthesis. Unexpectedly, these workers found that nitrile electrophiles allows a 1,4-migration of the sulfonyl group, believed to occur via *intra*-molecular process, from the pyrrole into the imine (Scheme 3) and thus make products similar to **4**.



Scheme 3.

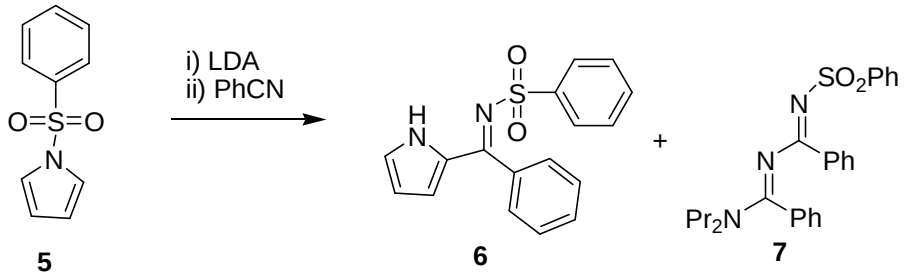
The 1,4-migration was first observed from the reaction of lithiated *N*-phenylsulfonylindole with benzonitrile, where 2-ketoindole was isolated. The product is believed to have occurred from the hydrolysis of the imine (not isolated or characterized) into a ketone, following the 1,4-migration (Scheme 4). Unlike the indole reaction, Patil

and Mandy[41] found that the hydrolysis step does not occur with pyrrole when subjected to similar conditions as indole.



Scheme 4.

In an attempt to generate methodology for making **4**, lithiated pyrrole **5** was reacted with benzonitrile to give the *N*-phenylsulfonylimine **6** and an amidine product **7** (Scheme 5). The formation of the amidine product involves an *inter*-molecular step whereby the sulfonyl group is transferred from the sulfonylpyrrole **2.** These results suggests that the rates of *intra*- and *inter*-molecular steps might be comparable, and also the 1,4-migrartion of the sulfonyl group might proceed via the suggested *intra*-molecular shift and also via the *inter*-molecular shift.



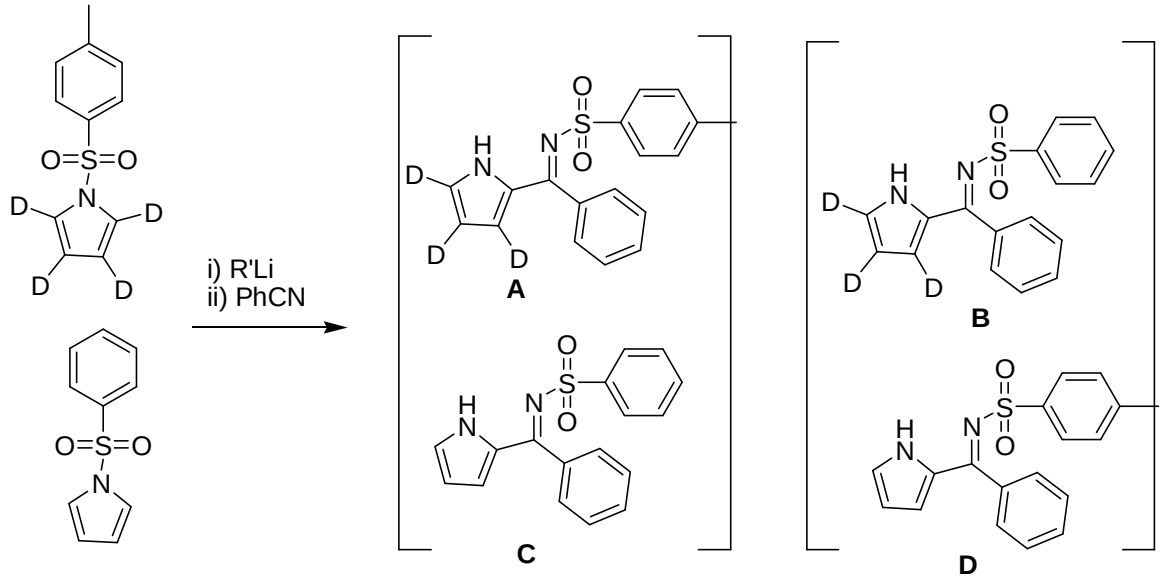
5 **6** **7**

Scheme 5.

1.5.2 Crossover experiment

To investigate the 1,4-migration of the sulfonyl, an experiment which involved mixing a lithiated sulfonyl pyrrole **5** and a lithiated substituted *N*-toluenesulfonylpyrrole, then quenching with benzonitrile (Scheme 6), was attempted. In their attempt, Patil and Mandy[41] tried to substitute the pyrrole hydrogen of *N*-toluenesulfonylpyrrole **8,** with deuterium. Their hypothesis was as follows: exclusive production of products designated

A and **C** will support the intramolecular shift while if in addition to **A** and **C**, products **B** and **D** are detected**,** then the intermolecular mechanism will be taking place as well. Due to the inability to label the pyrrole ring appropriately, the crossover experiment was not performed. A successful completion of such a crossover experiment is described in this thesis.



Scheme 6.

1.5.3 Metal Complexes

The *N*-phenylsulfonylimine **6** was investigated for its ability to complex metal ions via its two nitrogen atoms, thus acting as a bidentate ligand. Complexes with copper(II) **9,** copper(I) **10** and palladium(II) **11** (Figure 9) were synthesized by Patil and Mandy[41]. These complexes were tested for anti-cancer activity and promising results were observed, where IC_{50} values were below 10 µM in *in vitro* assays.

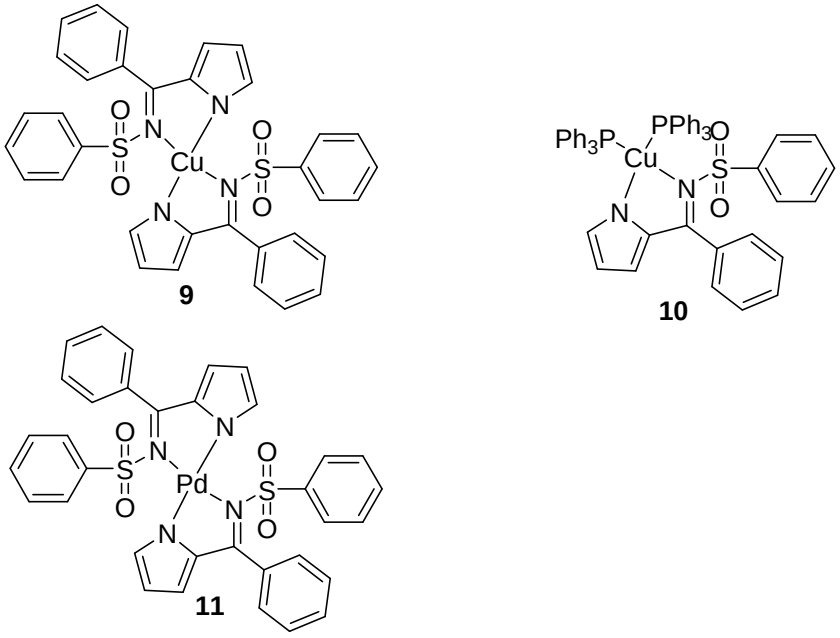


Figure 9. Metal complexes previously synthesized in our laboratory.

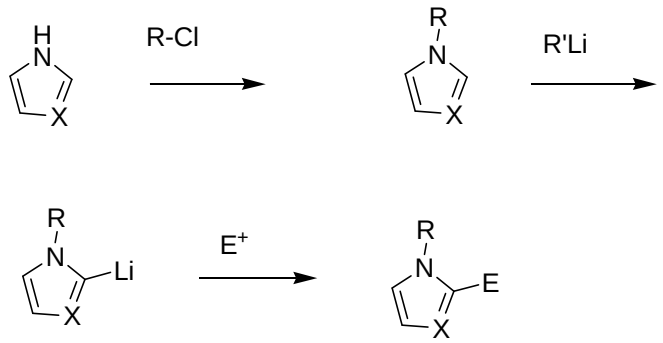
The less soft metals, i.e. Cu (II) and Pd (II) were chelated with two ligands while the more soft metal contains one chelate ligand and two soft phosphine ligands. Complex **10** was more active than **9,** indicating that the phosphine ligands may enhance the activity of the complex. The complexes are prepared by treating pyrrole **6** and a metal salt in a presence of a base. The palladium complex **11** was also tested for catalytic activity in the Heck-type coupling reaction between iodobenzene and an activated sulfonylpyrrole. No activity was observed as only the starting materials were recovered without any trace of products.

1.5.4 Magnesium amide bases in C-C bond formation

N-Heterocyclic compounds, e.g. pyrrole, indole, imidazole, pyridine, are very important in organic synthesis, where they serve as starting materials. These compounds are able to form a carbon-carbon bond, which is one of the most important steps in organic synthesis[56]. A popular way of making a C-C bond is by nucleophilic electrophilic reaction. The N-heterocyclic compounds contain acidic protons that can be extracted by a

base and generate a nucleophilic carbon that can then react with an electrophilic carbon making a C-C bond.

Although N-heterocyclic compounds may have acidic protons, their pk_as are high such that normal bases can not deprotonate them. Very strong bases are used to deprotonate these compounds, and the most commonly used bases are the lithium bases R-Li (R= alkyl or amide)[43]. Many lithiation reactions have been performed on pyrrole[56-60], indole[56, 60] and imidazole[56, 61-62], with subsequent quenching with electrophiles resulting in a C-C bond formation. The heterocyclic compounds are first protected at the nitrogen atom to remove the more acidic N-H proton thus leaving the acidic C-H proton available for deprotonation (Scheme 7).

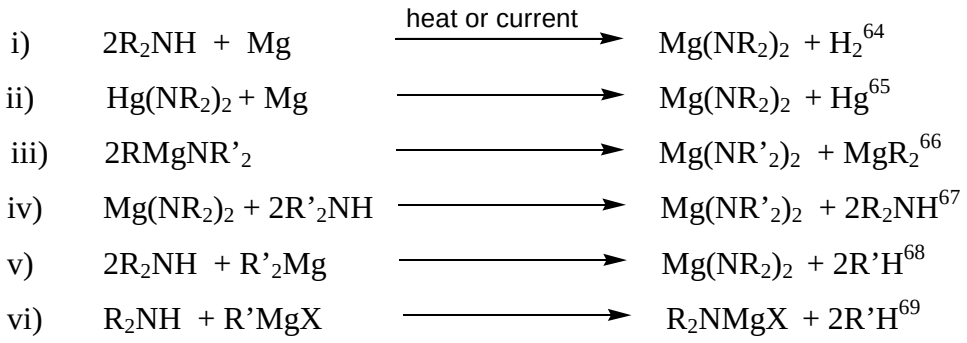


Scheme 7. X=H, pyrrole; X=N, imidazole, R = protecting group and R'= alkyl

Organolithium bases react irreversibly with many electrophiles and as a result they are very unstable. They react with moisture forming LiOH and RH and at this stage the base is no longer effective. Their storage requires inert atmosphere and low temperatures. Their reactions also require very low temperatures, e.g. –78 °C, since the reactions are very exothermic. Low temperatures also help in reducing the number of side reactions that can occur since these bases can also react with other functional groups present in the molecule, leading to undesired products. An alternative to using lithium bases is the use of magnesium bases.

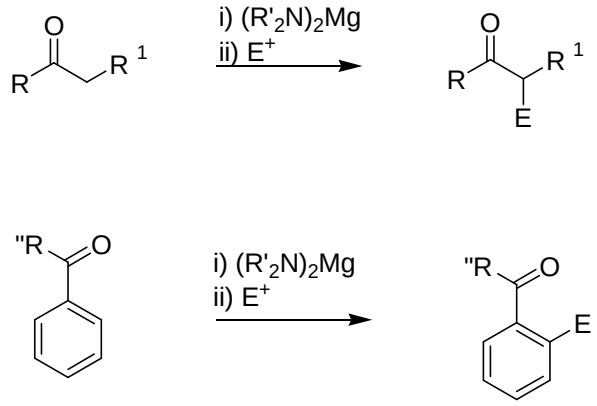
Magnesium is mainly used as a constituent of Grignard reagents, RMgX (R= alkyl, aryl, ect.; X = Cl, Br), and these reagents are widely used in C-C bond formation reactions[63].

These reagents contain a carbon metal bond which is a good nucleophile for C-C bond formation but, unlike lithium reagents, they are not good bases for deprotonating heterocyclic compounds. Grignard reagents are usually converted into amides or bisamides (Scheme 8), which are good bases for deprotonating acidic protons on a carbon. Various methods used are shown below



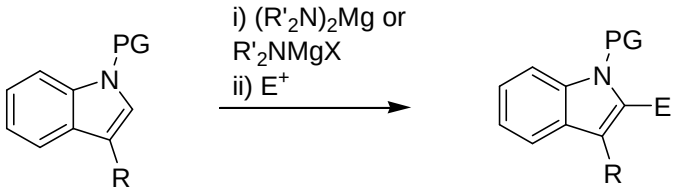
Scheme 8.

The bis(amides) have been shown to deprotonate acidic protons from ketones and also from benzene rings without reacting with the functional groups present (Scheme 5), showing greater functional group tolerance than lithium reagents[70- 75].



Scheme 9.

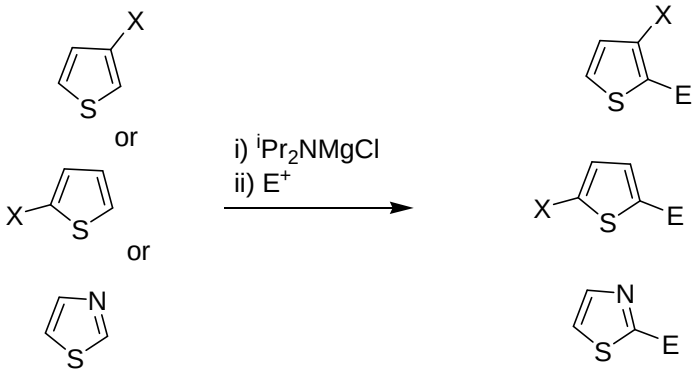
Work by Kondo *et al.* showed that in addition to magnesium bis(amide) bases, magnesium amides (known as Hauser bases) can be used to deprotonate heterocyclic protons[76-77]. N-protected indoles, which are reactive at the 3-position, were deprotonated exclusively at the 2-position using diisopropylaminomagnesium chloride ($^{i}Pr_2NMgCl$) **12**, and quenched with different electrophiles[76] (Scheme 10).



PG= SO_2Ph or Boc
R = H, Me, CO_2Me or CN
E = I, CO_2Me, Ph or $CH_2CH{=}CH$
R'= ^{i}Pr
X=Br

Scheme 10.

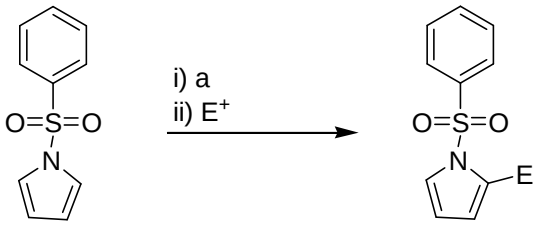
Thiophenes and thiazoles, containing functional groups, were also deprotonated at the 2-position using **12**[77] (Scheme 11). These reactions, unlike lithium reactions, were performed at ambient temperature and the yields obtained were comparable.



X= CO_2Et, H

Scheme 11.

By realizing that the active species in deprotonation is the magnesium amide species, Dinsmore *et al*., successfully used diisopropylamine in catalytic amounts with respect to the Grignard reagent[55]. *N*-Phenylsulfonylpyrrole **5** was deprotonated at the 2-position using this method, and different electrophiles were introduced in moderate to good yields (Scheme 12).



a = 2.5eq. ^{i}PrMgCl / 5 mol% (^{i}Pr)$_2$NH
E= I, alkyl, aryl, SiMe$_3$ and heteroaryl

Scheme 12.

The downfall of using Hauser bases is the formation of dimers, where there is bridging in the chlorides. This was determined from the crystal structure, determined by Power, of [(Me$_3$Si)$_2$NMgCl.(Et$_2$O)]$_2$ (Figure 10)[78]. A large excess of the base, as high as 3[55], is used as a result of this dimer formation.

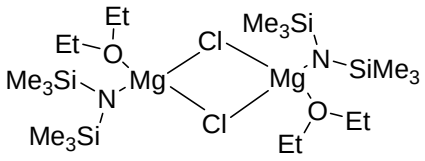
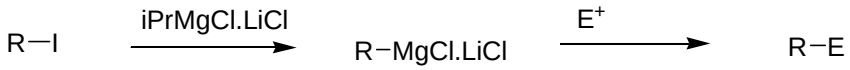


Figure 10.

In an attempt to reduce the base equivalent amount, Knochel *et al*., very recently found that adding lithium chloride (LiCl) to the Grignard reagent isopropylmagnesium chloride (^{i}PrMgCl) **13**, reduces the amount of the reagent required in a reaction[79-81]. The new Grignard reagent isopropylmagnesium chloride-lithium chloride (^{i}PrMgCl.LiCl) **14,** has been shown to be superior to **13** in I/Mg exchange reactions (Scheme 13). The LiCl is

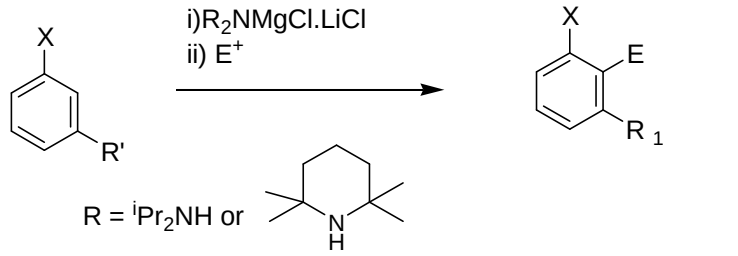
believed to prevent dimer formation and thus providing monomers of the Grignard species[81].



R= alkyl, aryl and heteroaryl

Scheme 13.

Hauser bases containing lithium chloride have also been prepared with a general formula, $R_2NMgCl.LiCl$[82-83]. These bases were shown to be superior to normal Hauser bases and lithium bases in that they required fewer equivalents of base (1.1 eq.) and their yields were generally higher. These bases were used in the deprotonation of benzene substrates bearing different functional groups[82] (Scheme 14), and also with several heterocyclic compounds[83]. These bases are used at ambient temperatures and can tolerate a wide range of functional groups.



R' = CO_2Et ; X = Cl, OH, CO_2NMe_2, $CO_2C(CH_3)_3$, Boc

Scheme 14.

The drawbacks in using these new Grignard reagent is that they are not atom economic. Equivalent amount of LiCl, Mg and TMP are required to prepare the base and thus the cost of preparing these bases is high.

1. 6 Aims of this project.

The aims of the project are:

i) To investigate the mechanism behind the 1,4-migration of the sulfonyl group,

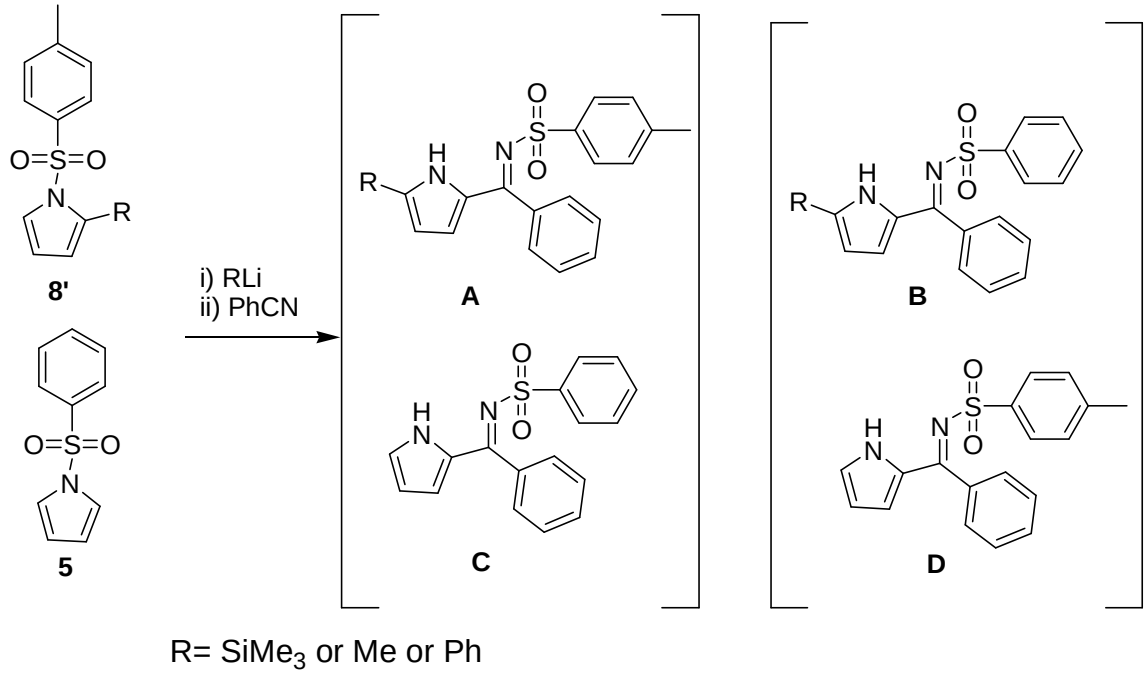
ii) To make more metal complexes using *N*-toluenesulfonylimine ligand and to test the complexes for anti-cancer activity,

iii) To extend the scope of magnesiation, developed by Dinsmore[55], to other N-heteraromatic compounds, and finally to try to improve the magnesiation conditions reported by Knochel[82-83], by making use of catalytic amine.

These aims are described in detail below.

1.6.1 Investigating the 1,4-migartion of the sulfonyl group

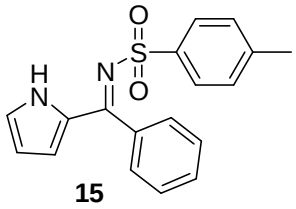
The approach in determining the mechanism was intended to be very similar to the one attempted by Patil and Mandy[41]. Instead of substituting the pyrrole protons with deuterium, a different substituent was to be introduced in the 2-position of *N*-toluenesulfonylpyrrole **8.** The substituent introduced must not be reactive under lithiating conditions, and a few that attracted our attention were the trimethylsilyl group ($SiMe_3$), the methyl group (Me) and the phenyl group. Once the 2-substituted pyrrole **8** has been made, it will be mixed with pyrrole **5**, lithiated, quenched with benzonitrile and the resulting products characterized (Scheme 15).



Scheme 15.

1.6.2 Metal complexes with *N*-toluenesulfonylimine ligands

We were interested in synthesizing metal complexes containing the chelate *N*-toluenesulfonylimine ligand **15** in order to test their activity against cancer cells. We were mostly interested in the late second and third row transition metals, i.e. Pt(II), Pd(II), Ag(I), and Au(III) since they have previously shown good activity against cancer cells. The first row transition metals, i.e. Co(II), Ni(II), Cu(I) and Cu(II), and Zn(II) were also considered in the study. The ligand **15** (Figure 11) is very similar to the phenylsulfonylimine ligand **6** with the only difference being the presence of toluyl instead of phenyl group. The ligand contains a sulfonamide portion which, for many years, has been used as an anti-bacterial drug[84].



15

Figure 11. **The sulfonylimine ligand to be used for complexation in this project.**

The initial approach will be to repeat the complexes made with ligand **6,** using ligand **15,** then after methodology has been established, more transition metal complexes will be synthesized. We aim to expand the range of these complexes by making Pt(II) **16**, Ag(I) 1**7**, Co(II) 1**8**, Ni(II) 1**9**, Zn(II) **20** and Au(III) 2**1**. We aim to chelate the soft Ag metal with one ligand and two phosphine ligands, while the rest we aim to chelate with two ligands (Figure 12).

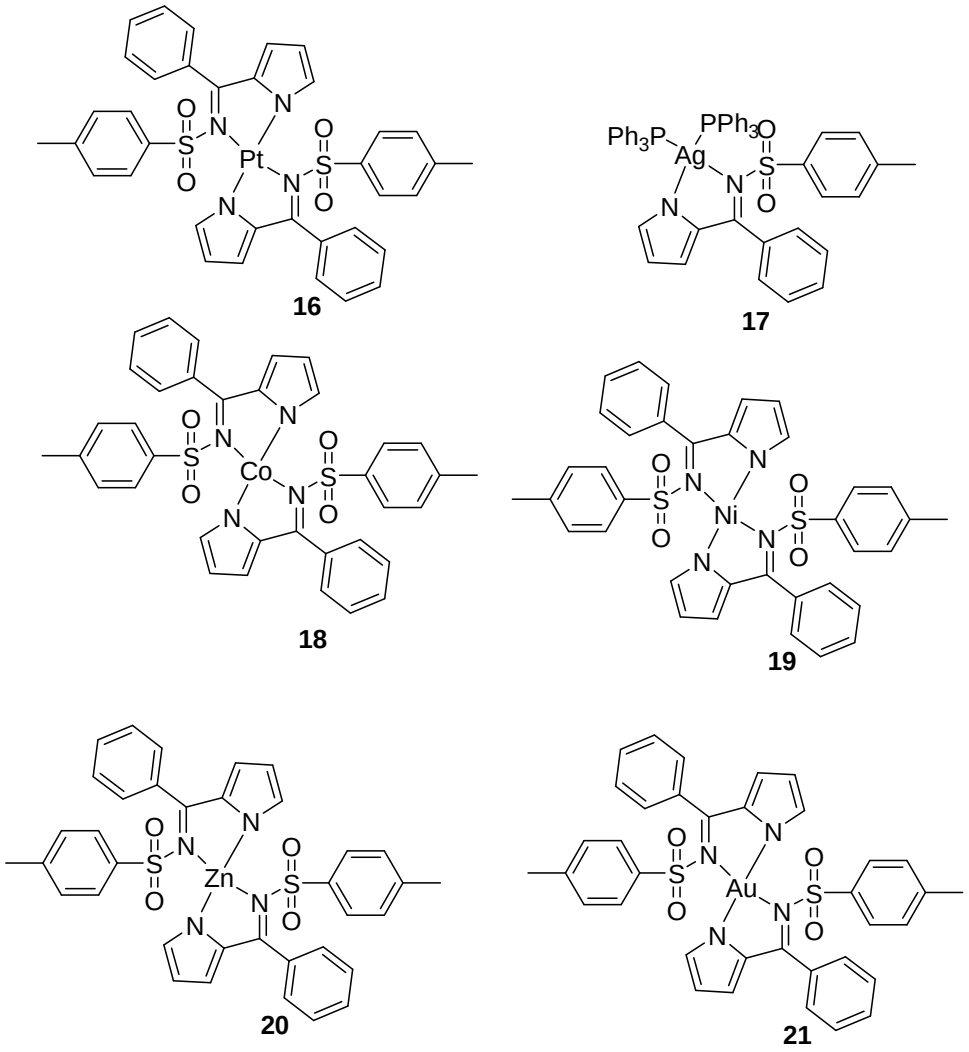


Figure 12. Metal complexes intended to be synthesized in this project.

1.6.3 Comparing the magnesiation conditions reported by Dinsmore[55] and Knochel[82-83]

Although these new generation Hauser bases (described in section 1.5.2) are very effective, the cost of making them is high. Equimolar amounts of LiCl, TMP or $^{i}Pr_2NH$ and ^{i}PrMgCl are needed. We aim to investigate whether LiCl and/or the amine bases can used in catalytic amounts, as described by Dinsmore *et al*.[55], and see if the same efficiency can be obtained. Our investigation will start using *N*-phenylsulfonylpyrrole **5**

as a substrate, comparing results to those from Dinsmore, then moving to other N-heterocyclic compounds, i.e., indole, imidazole, benzimidazole, quinoline and pyridine.

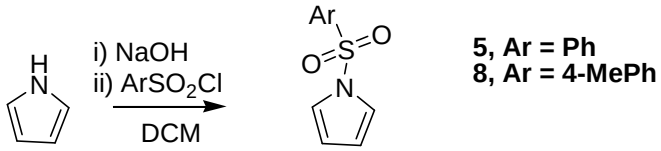
Chapter 2

Results and Discussion

Chapter 2: Results and Discussion

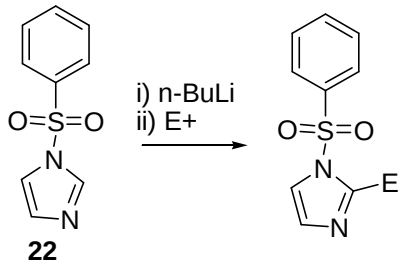
2.1.Ligand synthesis

We started by first preparing the *N*-protected pyrrole, using a variation of the method of Zelikin *et al*[51]. Adding pyrrole to a suspension of dichloromethane and sodium hydroxide then adding, dropwise, arylsulfonyl chloride to the mixture, stirring overnight at room temperature gave *N*-toluenesulfonylpyrrole **8** in 81% yield and *N*-phenylsulfonyl pyrrole **5** in 50% yield (Scheme 16). Spectroscopic data and melting points of our products were all consistent with those reported previously[41,51]. Later X-ray crystal structures of compounds derived from pyrrole **8** also confirmed the formation of the product **8** (see later).



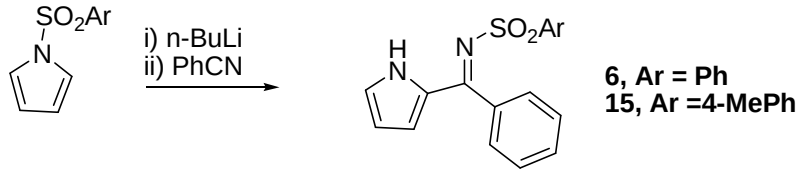
Scheme 16.

With the *N*-toluenesulfonylpyrrole **8** in hand, we then proceeded to the addition reaction with benzonitrile. The starting material requires deprotonation by means of very strong bases and our first choice was the lithium bases. Previous work by Patil and Mandy[41] employed lithiumdiisopropylamide (LDA) and lithium-tetramethylpiperidine (LiTMP) to deprotonate pyrrole **5** with subsequent quenching with benzonitrile to give the sulfonylimine **6**. Our attention was drawn to the mention of butyllithium as a base to deprotonate *N*-phenylsulfonylimidazole **22** at –20 °C (Scheme 17)[61]. We were interested in using butyllithium to deprotonate pyrroles **5** and **8** and compare the results with those from imidazole.



Scheme 17.

Treating pyrrole **8** with butyllithium and quenching with benzonitrile gave the desired product 4-methyl-*N*-[phenyl(1*H*-pyrrol-1yl)methylene]benzenesulfonamide **15** in 60% yield. Treating pyrrole **5** with *n*-BuLi and quenching with benzonitrile gave *N*-[phenyl(1*H*-pyrrrol-1yl)methylene]benzenesulfonamide **6** in 30% yield (Scheme 18). These results were similar to those reported by Patil and Mandy[41] and to our delight no side products resulting from the reaction of benzonitrile with butyllithium were observed. The amidine **7** (Chapter 1, section 1.5.1) was observed as a side product, resulting from the reaction of LDA and benzonitrile, by Patil and Mandy[41].

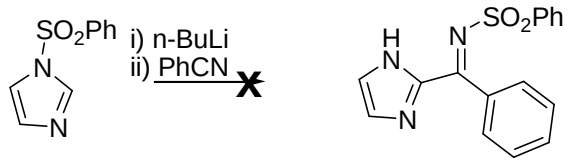


Scheme 18.

Mass spectroscopy showed the correct molecular ion [M^+ 324 for **6** and 310 for **15**] and the fragment ion [169 (M^+ - SO_2Ar] was observed for both products. This was also supported by ^1H NMR spectrum, in which a peak at 10.16, corresponding to an N-H peak was, observed. A crystal structure of **6** was obtained (Appendix 1), confirming the formation of the desired products.

With the idea of extending the sulfonyl transfer chemistry, we examined the possible reaction between lithiated imidazole **22** and benzonitrile (Scheme 19) but, to our disappointment, only the starting materials were obtained. The lithiation of **22** and

subsequent reaction with electrophiles, has been reported to be in low yields[61] and this could be the reason as to why no products were observed. The failure of imidazole **22** to react with benzonitrile meant that it could not be used in the study of the sulfonyl shift mechanism.

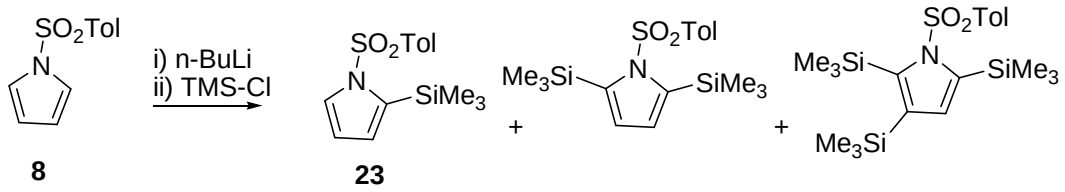


Scheme 19.

2.2 Crossover experiment

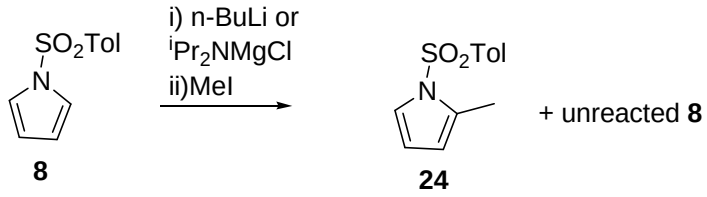
Having made the desired ligands, **6** and **15**, we then investigated the mechanism by which the sulfonyl group migrates. We were interested in making 2-substituted pyrrole, where the substituent placed must be able to tolerate harsh conditions, such as those of n-BuLi. The functional groups investigated were the trimethylsilyl (TMS), methyl (Me) and phenyl (Ph).

The first substituent to be investigated was the trimethylsilyl (Me_3Si) group, after it was shown to be stable under lithiating conditions[61]. Treating pyrrole **8** consecutively with *n*-BuLi and trimethylsilyl chloride (TMS-Cl) gave the 2-trimethylsilytoluenesufonylpyrrole **23,** but the product could not be separated from the disilylated and trisilylated product (Scheme 20). This was shown from mass spectrometry where peaks [M^+ 294.12 corresponding to **23**, 366.12 corresponding to disilylated product and 438.12 corresponding to trisilylated product] were observed on analysis of the crude product. Attempts to purify the products by chromatography and distillation failed to give **23** in a pure form.



Scheme 20.

We then attempted to make 2-methyltoluenesulfonylpyrrole **24** by treating **8** with n-BuLi and methyl iodide (MeI). The product was obtained in reasonable yield (75% from ^{1}H NMR spectroscopy) but it could not be separated from unreacted starting material regardless of the purification techniques (Scheme 21). The product and the starting material have the same R_f value in all solvents examined, thus chromatography could not separate them. Attempts to recrystallize the mixture failed to separate the compounds as crystals contained both compounds.



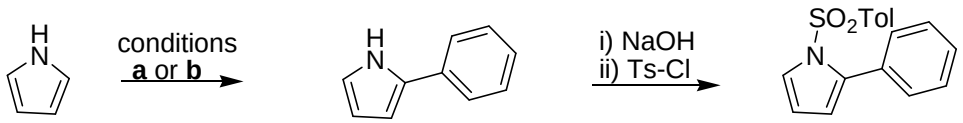
Scheme 21.

Treating **8** with ^{i}PrMgCl/ 5% $^{i}Pr_2$NH and MeI reduced the yield (15%) of **24** as shown by ^{1}H NMR spectroscopy (Scheme 21). This suggest that full deprotonation of **8** is required for the clean production of **24.** We then turned our attention to phenyl group as a marker on the pyrrole ring.

Three routes to a 2-phenylated sulfonylpyrrole were investigated and compared. These were either (i) an investigation of recently published novel, and very attractive methods to allow the regiospecific Pd-catalysed arylation of electron rich heterocycles and (ii) a

comparison of these with the Pd-catalysed phenylation of a magnesiated sulfonylpyrrole, methodology that was previously developed in our laboratory[55].

The first method was a modification of a method reported by Sames[85], in which the electron rich N-heterocyclic compounds i.e., pyrrole, indole and imidazole, were treated with catalytic tetrakis(triphenylphosphine)palladium [$Pd(Ph_3P)_4$] and MgO with refluxing in dioxane to afford 2-phenylated products in good yields. This method does not require an activated carbon, where in most cases a carbon-halogen bond is required for C-C bond coupling. When subjecting pyrrole **8** to the same conditions, no product was obtained. Our initial explanation was that free pyrrole is needed for these conditions since it is electron-rich. We then treated free pyrrole under the same conditions but only managed to get 3% yield of the product, 2-phenylpyrrole **25** (Scheme 22 condition a). It later emerged, following communications with the authors, that these reactions must be performed in a glove box under strictly anhydrous conditions for them to work.



25 **26**

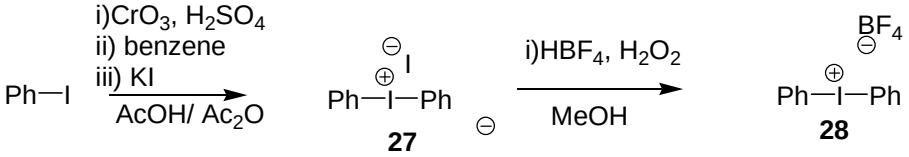
a = Ph-I , $Pd(Ph_3P)_4$, MgO, Dioxane/DMF (1:2)
b= $[Ph_2I]BF_4$, $PdCl_2$, AcOH

Scheme 22.

The second method is a two step reaction in which free pyrrole is first converted into 2-phenylpyrrole **25**, after which sulfonation would provide the desired pyrrole **26** (Scheme 22 condition b). This method also does not require an activated carbon site. The first example was reported by Sanford[86] who employed ambient conditions. $PdCl_2$ or $Pd(OAc)_2$, which are stable to air, are used instead of the air sensitive $Pd(Ph_3P)_4$. These Pd salts have an oxidation state of +2 and are suggested to undergo a +2/+4 oxidation change, unlike the 0/+2 oxidation state change that is involved in the coupling reactions[86,87]. The phenyl source diphenyliodonium-tetrafluoroborate $[Ph_2I]BF_4$ is different from the usual Ph-I or Ph-$B(OH)_2$. Ph_2I^+ is described as an oxidative source of

phenyl and it is suggested that it this allows the Pd to cycle between oxidation state 2 and 4 during the course of the catalytic reaction. The reactions are done at room temperature as compared to the first method, where high temperatures (~150 ^{o}C) are required

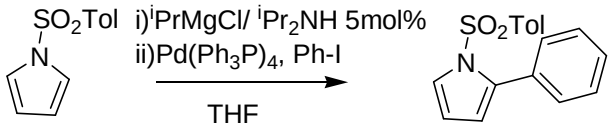
We began by preparing the phenyl source $[Ph_2I]BF_4$, which is made by the method of Skulski[88], using a one pot synthesis (Scheme 23). Iodobenzene is first oxidized by chromium trioxide (CrO_3) and sulfuric acid (H_2SO_4) in a solvent mixture of acetic acid (AcOH) and acetic anhydride (Ac_2O). Acidic coupling with benzene followed by washing with aqueous potassium iodide (KI) gave the diphenyliodonium iodide ($[Ph_2I]I$) **27** in 50% yield. The melting point of the solid (162-163 ^{o}C) and its mass spectrometry data [M^+ 281 corresponding to $(Ph_2I)^+$] were in agreement with the literature[88]. Treating pyrrole with **27** and $PdCl_2$ in AcOH yielded no product and this was due to the insolubility of **27** in AcOH. We then converted **27** into a more soluble diphenyliodonium tetrafluoroborate $[Ph_2I]BF_4$ **28,** by adding HBF_4 and H_2O_2 to **27** dissolved in methanol[89] (Scheme 23). The more soluble product **28** was obtained in 94% yield and its melting point (134 ^{o}C) was in agreement with literature[89].



Scheme 23.

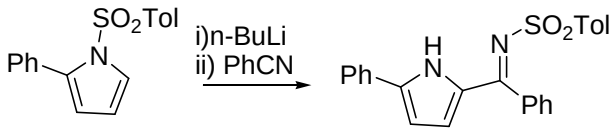
Treating pyrrole with **28** and $PdCl_2$ in AcOH gave **26** in 40% yield but it require a large ratio of pyrrole to **28** (10: 1) due to pyrrole having two reactive sites. Trace amounts of diphenylated pyrrole were also detected by mass spectrometry. When subjecting indole to the same conditions, the ratio of indole to **28** changes to (1: 2) since indole has only one reactive site in this reaction[86]. The requirement of a large excess of pyrrole means that starting with one gram of pyrrole will yield 84 mg of product and this is certainly not very economical.

The third method requires the activation of carbon but, unlike most activation where a carbon-halogen bond is required, the method uses a carbon-magnesium bond. This was first reported by Dinsmore *et al* [55], who showed that treating **5** with ^{i}PrMgCl/ 5% $^{i}Pr_2NH$ to deprotonate, followed by catalytic $Pd(Ph_3P)_4$ and iodobenzene permitted arylation to occur (Scheme 24). When treating **8** to the same conditions, **26** was obtained in 51% yield. The melting point (123-124 ^{o}C) and molecular mass ion spectrum [M^+ 298] were in agreement with literature values[90]. The reactions are done at room temperature and can also be extended to other *N*-heterocyclic compounds, to be discussed later. This method, when compared to above mentioned methods, is superior. It does not require a glove box and high temperatures as in method 1. The phenyl source is easily obtainable and it is not required in large excess as in method 2. By this method we were able to prepare gram quantities of pyrrole **26.**



Scheme 24.

Having made **26**, we then subjected it to the lithiating conditions used to make **6** and **15**, and to our delight, (*E*)-4-methyl-*N*-[phenyl(5-phenyl-1H-pyrrol-2-yl)methylene]benzenesulfonamide **29** was obtained in 36% yield (Scheme 25). The ^{1}H NMR spectrum showed the presence of two pyrrole C-H protons and also a peak at 10.81 belonging to NH. Mass spectrometry showed the correct parent peak [M^+ 400] and the fragmentation [245 (M^+- SO_2Tol)].



29

Scheme 25.

A crystal structure was also obtained, confirming that the correct product has been made (Figure 13, appendix 2). The crystal structure shows that **29** was obtained as a solvate solid with acetone. The results also show the geometry around the C=N bond to be *E*.

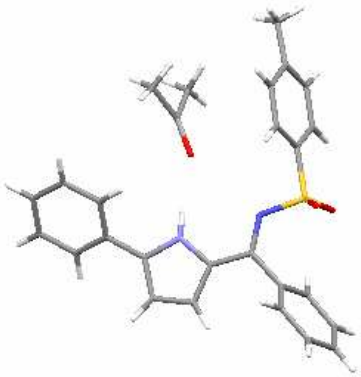
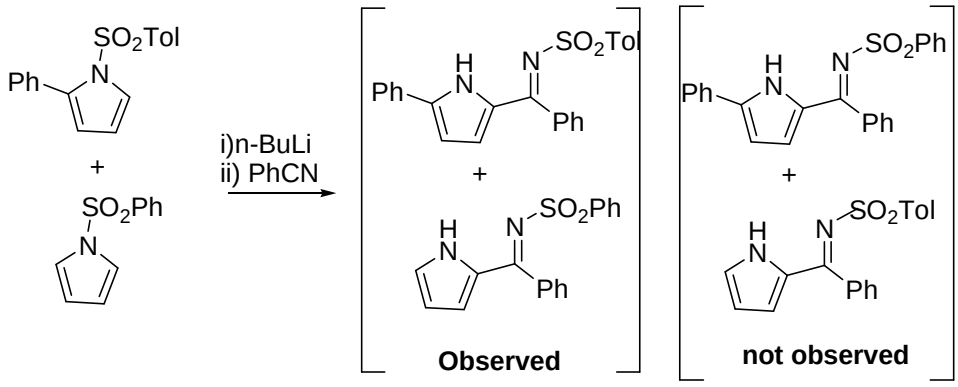
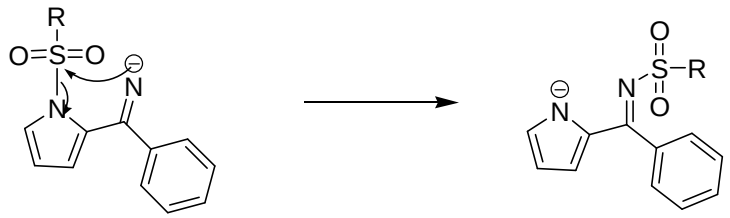


Figure 13. Crystal structure of the sulfonylimine 29.

With the required starting materials for a cross-over experiment and with three of the four expected products fully characterized, it was time to perform the experiment (Scheme 15, chapter 1). Treating **5** and **26,** in 1:1 ratio, with *n*-BuLi at –20 °C and benzonitrile gave two fractions after purification by chromatography and they were characterized by mass spectrometry (Scheme 26). The first fraction collected had a parent peak [M^+ 310 (60) which correspond to **6**], no peak at 324 corresponding to **15** was observed. The second fraction had a parent peak [M^+ 400 (65) corresponding to **29**]. No peak at 386 was observed and this led to the conclusion that the sulfonyl shift occurs mainly via the 1,4-intramolecular migration and the intermolecular migration can be neglected (Scheme 27).



Scheme 26.



Scheme 27.

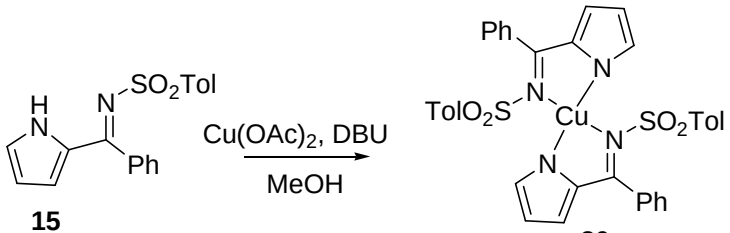
With the ligands synthesized and the mechanism of formation investigated, we then proceeded to making metal complexes.

2.3 Metal complexes

The first row transition metals were the ideal starting point since they are cheaper compared to the second and third row metals. The copper complexes were the first to be made since preparations of structurally related complexes (complexes **9** and **10**, Figure 9) have been reported by Patil and Mandy[41]. Patil reported the synthesis of copper(II) complex (**9**) and Mandy reported the synthesis of copper(I) complex (**10)**.

Copper(II) complex **30** was prepared by treating sulfonylimine **15** with copper(II)acetate, in the presence of the base DBU, and refluxing in methanol (Scheme 28). The product was obtained as dark green crystals which were not suitable for diffraction but were

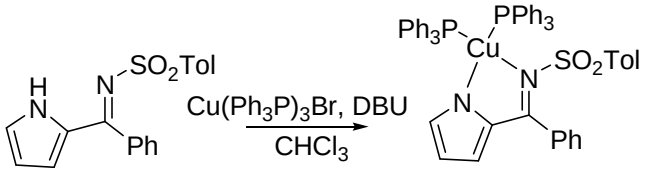
characterized by mass spectrometry and infrared spectroscopy (IR). NMR spectroscopy could not be used to characterize the complex since it contains a spin active d^9 metal. Mass spectrometry showed a parent peak at *m/z* 732 $[M + Na]^+$ and *m/z* 710 $[M + H]^+$ and fragmentations [347 and 324 corresponding to the ligand + Na^+ and ligand + H^+, respectively]. The IR spectrum showed the disappearance of the N-H stretch but no other obvious peak caused by the metal complexation could be observed. Elemental analysis data were also in agreement with the formation of the product.



15 **30**

Scheme 28.

Copper(I) complex **31** was prepared by treating sulfonylimine **15** with DBU and $CuBr(PPh_3)_3$ in chloroform (Scheme 29). The product was obtained as yellow crystals suitable for X-ray diffraction (Figure 14, appendix 3).



15 **31**

Scheme 29.

The complex has two triphenylphosphine ligands in addition to the chelating ligand **15.** The geometry around the copper atom is tetrahedral as expected for d^9 metal ions. The disappearance of the N-H proton was confirmed by ^1H NMR and IR spectroscopy. The mass spectrometry data were very interesting because the molecular ion peak $[M]^+$ was not observed either by FAB or ESI MS analysis. Peaks that were observed were *m/*z 587 $[M – ligand]^+$ i.e. $Cu(PPh_3)_2^+$ and *m/z* 325 $[CuPPh_3]^+$, and these peaks were obtained in both ESI and FAB. This can be explained by the HSAB theory[2] since Cu(I) is a soft

Lewis acid and phosphorus is a soft Lewis base compared to nitrogen. The Cu-P interactions will weaken the Cu-N bond causing the bond to break off easily. This was also observed with the silver (I) complexes, to be discussed later.

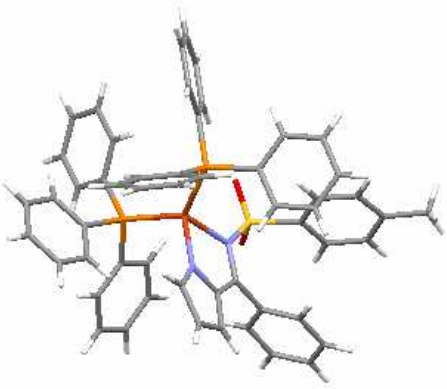
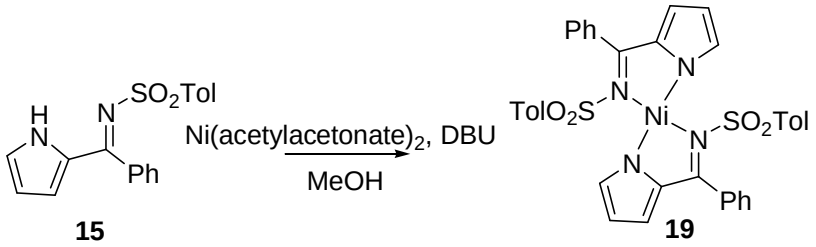


Figure 14. Crystal structure of the copper(I) complex.

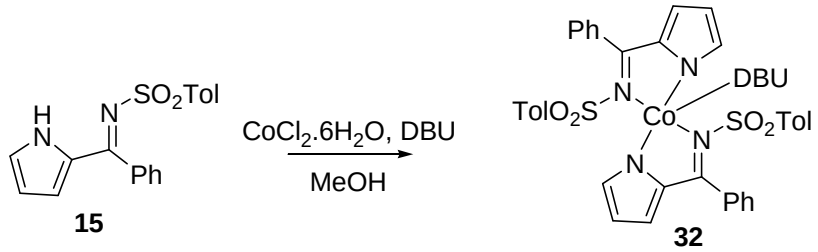
Synthesis of the nickel(II) complex **19** followed that for the preparation of **30**. Treating sulfonylimine **15** with DBU and nickel(II) chloride did not give the desired product even after increasing the reflux time. Replacing the $NiCl_2$ salt with the more reactive nickel(II) acetylacetonate gave the desired product as light green crystals (Scheme 30) which were not suitable for X-ray diffraction. ^{1}H NMR spectroscopy show that the complex is spin active, indicating that the geometry around the metal is tetrahedral instead of square planar as experienced by most d^8 metal ions[2]. Other studies of Ni, coordinated to four nitrogen atoms, have reported tetrahedral geometry around the metal centre[91]. Square planar complexes of Ni are favored by soft donor ligands, while tetrahedral is favored by intermediate to hard donor ligands[2]. IR spectroscopy showed the disappearance of the N-H stretch, while mass spectroscopy gave two parent peaks at *m/z* 727 $[M + Na]^+$ and *m/z* 705 $[M + H]^+$. A fragment peak at *m/z* 381 $[M – ligand]^+$ was also observed. From these results we concluded that the desired compound was made.



15 **19**

Scheme 30.

An attempt to make the Co complex **18** following the above procedure, and entailing treatment of sulfonylimine **15** with DBU and cobalt(II)chloride-hydrate ($CoCl_2.6H_2O$) gave an unexpected product, CoL_2DBU **31**, which in addition to the two chelating ligands around the metal, also include the base DBU coordinating the metal through nitrogen (Scheme 31).



15 **32**

Scheme 31.

A crystal structure of the compound was obtained (Figure 15, appendix 4), showing the two chelating ligands in an equatorial position and the DBU occupying the axial position. Mass spectrometry also gave a parent peak at *m/z* 858 $[M + H]^+$, confirming the formation of complex **32**. Attempts to make complex **18** by removing DBU gave no products, indicating the importance of a base in the reaction. The crystal structure shows that complex **32** was obtained as a solute with dichloromethane.

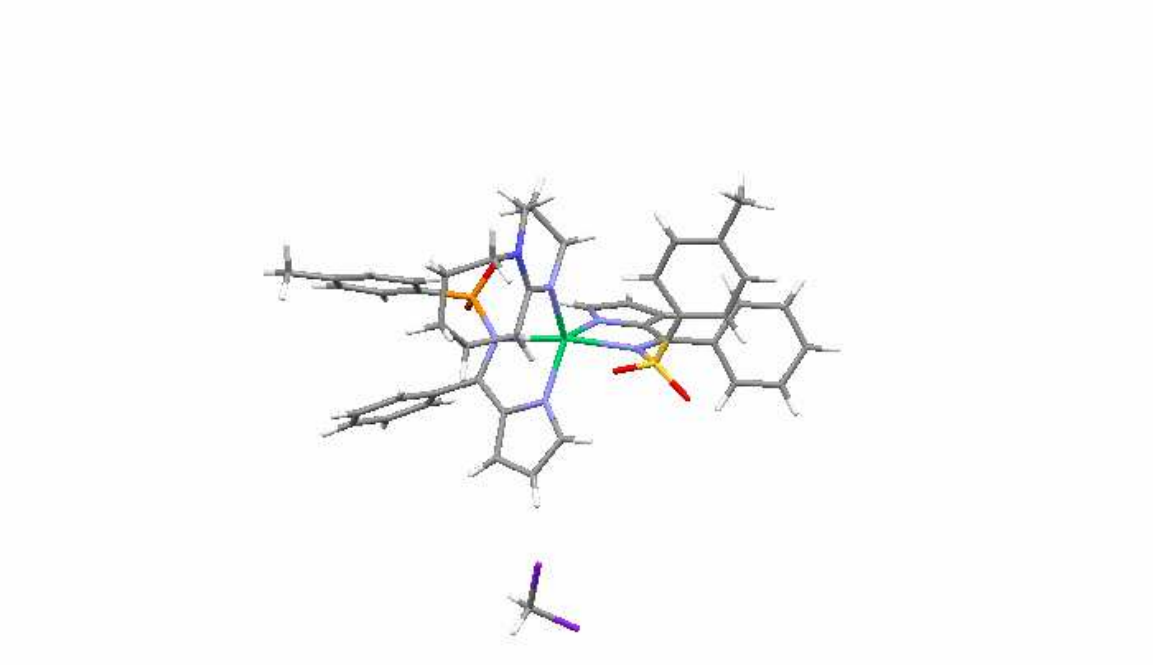


Figure 15. Crystal structure of cobalt(II) complex.

Similarly to the cobalt(II) complex, the intended zinc(II) complex **20** was never obtained after treating the ligand with DBU and zinc(II) chloride, ZnL_2DBU **33** (Figure 16) was obtained instead. Mass spectrometry gave the parent peak at *m/z* 863 $[M]^+$ and the fragments [711, 539 and 387 corresponding to ZnL_2, ZnLDBU and ZnL, respectively] were also observed. The isotopic distribution of the parent ion agreed with a simulated distribution. The IR spectrum showed the disappearance of the N-H bond.

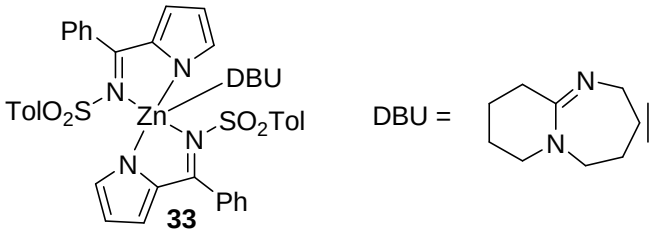
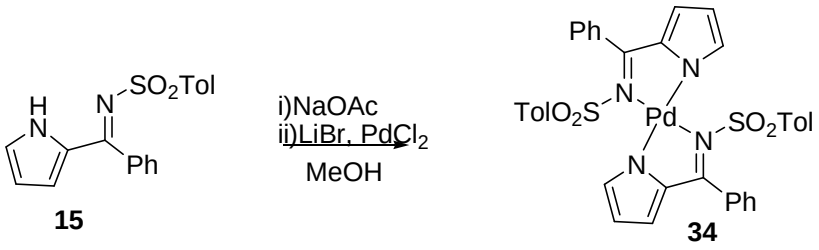


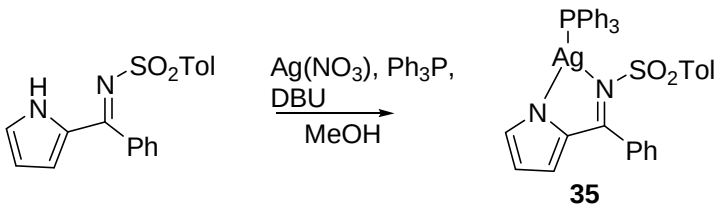
Figure 16. Line drawing structure of the zinc(II) complex.

Having investigated the late first row transition metals, we then investigated the ability of the ligands to coordinate to late second and third row transition metals i.e. Pd, Ag, Pt and Au. The Pd complex **34** was synthesized, using a variation of the method of Mandy[41], where the ligand **15** is treated with sodium acetate and $Li_2[PdCl_2Br_2]$ in methanol to give the product as a yellow solid. Attempts to recrystallize the solid were not successful as the compound was not soluble at room temperature in all solvents examined. Solubility was only observed in hot solvents but the product precipitated as small crystalline particles as soon as the solvent cooled down and as a result the crystal structure of the complex was not obtained. Mass spectrometry showed the parent peak at *m/z* 775 $[M + Na]^+$ and the IR spectrum showed the disappearance of the N-H peak, leading us to conclude the desired product had been formed (Scheme 32).



Scheme 32.

Attempts to make a silver complex containing only the chelate ligand were unsuccessful. When ligand **15** was treated with silver nitrate in methanol according to the method of Fenton[92] no product was obtained. We then reasoned that since Ag(I) is a soft metal an addition of a soft ligand might enhance the binding of the chelate ligand. We then treated **15** with DBU, silver nitrate and triphenylphosphine and refluxed in methanol hoping to make **17**, the analogue of the copper complex **10** and **31.** A different compound $AgLPPh_3$ **35** was formed instead of the desired product (Scheme 33).



Scheme 33.

The complex has the Ag metal with a coordination number of three, as shown by the crystal structure (Figure 17, appendix 5), where the chelate ligand is present with one triphenylphosphine. Metal complexes containing Ag with a coordination number of three have also been reported in the work of Fenton[92]. Mass spectrometry showed similar results to those obtained on the copper(I) complex **31**; the molecular ion peak was not observed but the fragment at *m/z* 369 $[AgPPh_3]^+$ was observed. Another interesting peak at *m/z* 633 $[Ag(PPh_3)_2]^+$ was also observed. ESI mass spectrometry studies on the complex, showed the presence of more additional species present in solution. In the negative mode a peak at *m/z* 755 $[AgL_2]^-$ was observed, while the positive mode gave peaks at *m/z* 1062, 631 and 369 which correspond to $Ag_2L(PPh_3)_2^+$, $Ag(PPh_3)_2^+$ and $AgPPh_3^+$, respectively. Again the HSAB theory supports the observations[2].

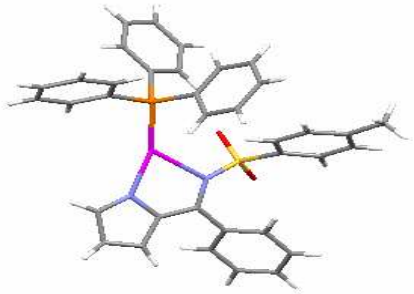
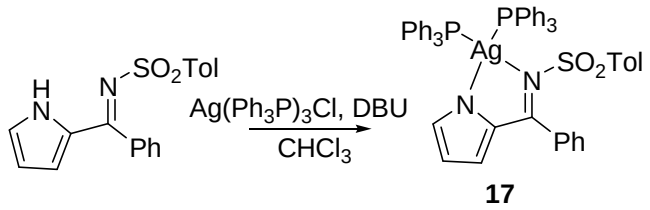


Figure 17. Crystal structure of the silver complex $AgL(PPh_3)$.

In an effort to increase the coordination number on the silver atom, we then decided to use similar conditions to those used in formation of the copper complex **31** i.e., by attaching phosphine ligands to the Ag metal before complexing the sulfonylimine ligand. We first prepared $Ag(PPh_3)_3Cl$ **36** using the method of Sanghani[93], in which AgCl is treated with triphenylphosphine in dichloromethane. The product was obtained as white crystalline solid and its melting point (185 °C) was consistent with the literature[93]. Treating ligand **15** with DBU and silver complex **36** in chloroform gave the desired product $AgL(PPh_3)_2$ **17** as a yellow solid (Scheme 34). Recrystallization from ethanol/DCM mixture gave crystals suitable for X-ray diffraction (Appendix 6). The structure is similar to the one obtained for the copper(I) complex **31** and the mass

spectrometry data has similar features to that of **31** and **35**. The molecular ion peak was not observed in the spectrum but fragments at *m/*z 631 and 369 corresponding to $[Ag(PPh_3)_2]^+$ and $[AgPPh_3]^+$ respectively, were observed.

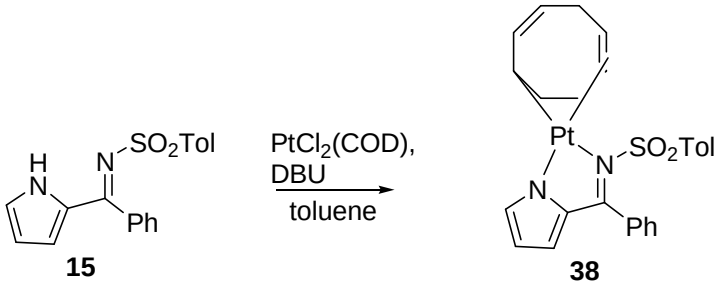


17

Scheme 34.

Moving down to the third row transition metals, we attempted to make PtL_2 **16** by modifying the method of Bhyrappa[94]. The platinum source was $PtCl_2$(cyclooctadiene) **37**, which has previously substituted its ligands for nitrogen ligands depending on the conditions. The complex **37** can substitute its cyclooctadiene (COD) ligand for two nitrogen ligands when refluxed with a ligand in toluene[95], and can substitute all its ligands for four nitrogen ligands when refluxed in DMF[94]. We then decided to try the second method as it was expected to introduce four nitrogen ligands, coming from two chelating ligands **15**.

Treating ligand **15** with DBU and **37** in refluxing DMF did not yield any product. This is possibly due to the nature of our ligand which is not macrocyclic, as in previous studies[93]. We then decided to try out the first method to see if different results could be obtained and to our delight, a product was obtained. The product obtained however, was not the desired product **16**. What we found was a platinum complex PtL(COD) **38**, containing one chelate ligand **15** and the COD ligand (Scheme 35). This was confirmed by the crystal structure (Figure 18, appendix 7). Neutral nitrogen ligands were used to substitute the COD ligand[95] and since our ligand **2** carries a negative charge, the chloride ligands are substituted first.



Scheme 35.

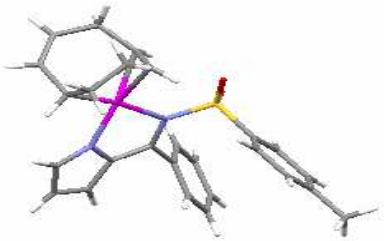


Figure 18. Crystal structure of the platinum(II) complex

The complex is neutral but since the ligand **15** carries a -1 charge, the COD ligand should also contribute a -1 charge. Crystal structure shows that the platinum has a sigma bond to a carbon and one double bond from COD has migrated to another carbon. This suggests that HCl is given off during the process in a mechanism still unknown. Mass spectrometry gave the parent peak at *m/*z 625 $[M]^+$ confirming the formation of complex **38.** Other sources of platinum such as $[PtCl_4]^{2-}$, which is an analogue of $[PdCl_2Br_2]^{2-}$, were not available to us and we could not make further attempts to synthesize the desired product **16**.

Attempts to make the gold complex **21** by treating ligand **15** with DBU and $[AuCl_4]^-$ were unsuccessful. When treating the gold salt with ligand **15** following the above

mentioned conditions a yellow oil was obtained but could not be characterized. No other gold salts we available to us thus no further experiments were carried.

2.3.2 Comparison of the metal complexes with literature precedent

We performed a Gmelin search to check for metal complexes with similar features to those synthesized. 4732 hits were found for copper(I) complexes with two chelate ligands, each having two nitrogen donor atoms, but no results were found for complexes with a sulfonyl-containing ligand. For the copper(I) complex, 527 hits were found for complexes with a bidentate ligand containing two nitrogen atoms and two triphenylphosphine units, but no hits were found for sulfonyl-containing ligands.

Five-coordinate complexes were found for searches performed on both the cobalt(II) and zinc(II), but few results were obtained when compared to six and four-coordinate complex. 17 hits were found for complexes with two bidentate ligands and an axial ligand, all having nitrogen donor ligands, for cobalt(II) while 50 hits were found for zinc(II) complexes. 1403 hits were found for cobalt(II) complexes coordinated to six nitrogen atoms, while 845 hits were found for zinc(II) complexes. No hits were found for complexes with a sulfonyl-containing ligand.

For the d^8 metal ions, four-coordinate complexes with two bidentate nitrogen ligands were very common. 3273 hits were found for nickel(II) while 389 hits were found for palladium(II). No hits were found for complexes with a sulfonyl containing ligand.

Silver(I) complexes with one bidentate nitrogen ligand and triphenylphosphine (TPP) unit(s) were found to be common. 33 hits were found for complexes having a bidentate ligand and two TPP units, while 166 hits were found for complexes having a bidentate ligand and one TPP unit. No hits were found for complexes with a sulfonyl containing ligand.

Only three hits were found for a platinum complex having a bidentate nitrogen ligand and a cyclooctadiene (COD) ligand. The loss of one hydrogen atom and a shift of one double bond in the COD ring are also observed in these three complexes. No hits were found for complexes with a sulfonyl containing ligand.

From the search results obtained, we observe that the complexes synthesized all posses similar features to those previously reported with the exception that the newly synthesized complexes contain a sulfonyl portion in their ligands.

2.4 *In vitro* studies of the metal complexes

The synthesized metal complexes were sent to Prof. C. Medlin's laboratory for screening against cancer cells. The *in vitro* cytotoxic properties of the metal complexes were assessed by measuring the effect on proliferation of the tumour cell line, human adenocarcinoma of the cervix (HeLa). The HeLa cell lines are the most sensitive cancer cells and are usually used as the start point in finding active compounds. Active compounds are those with IC_{50} (concentration resulting in 50% inhibition of tumour growth) less than 10 μM[36]. The active compounds are then screened against resistant cancer cell lines and if they are still active, they undergo *in vivo* studies to test their toxicity toward the host.

The metal complexes were incubated for seven days in the HeLa cells and the results are shown in table 1. The cell concentration was 5×10^2 cells per well, and the experiments were repeated three times for each compound.

Table 1. *In vitro* results for the metal complexes.

Drug	IC_{50} (µM)	± SEM	No exp done
$CuL(Ph_3P)_2$ **31**	Was not done***		
CuL_2 **30**	48.657	± 1.343	3
ZnL_2DBU **33**	44.82	± 2.539	3
CoL_2DBU **32**	17.855	± 1.47	3
NiL_2 **19**	>50		3
PdL_2 **34**	Was not done***		
PtL(COD) **38**	5.432	± 1.96	3
$AgL(Ph_3P)_2$ **17**	3.368	± 0.488	3
$AgL(Ph_3P)$ **35**	4.363	± 0.475	3
$Ag(Ph_3P)_3Cl$ **36**	1.187	± 0.023	3
cisplatin	0.852	± 0.117	3

*** Compounds did not dissolve in ethanol and could not be used in the study.

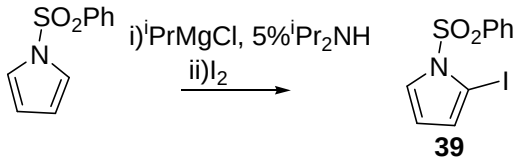
None of the first row transition metal complexes showed activity against the HeLa cell line with IC_{50} values all above 10 µM. The three silver compounds were all active with IC_{50} less than 5 µM with **36** being the most active with IC_{50} 1.187 µM. It appears from the results that the number of triphenylphosphines in the molecule enhances the activity of the compound. The complex **36** is the most active with three Ph_3P groups followed by **17** with two Ph_3P groups and finally **35** with just one Ph_3P group.

The platinum complex **38** was also active against the HeLa cell line but it had a high ± SEM value. The palladium complex was not soluble in ethanol as we experienced during the synthesis of the compound. What was surprising was the insolubility of the copper(I) complex which contains two triphenylphosphine units. We expected the Ph_3P group to enhance solubility of a compound, but this appears to have favoured solubility in non-polar solvents e.g. chloroform and DCM. The silver complexes containing the Ph_3P groups were all soluble in ethanol, suggesting that the metal ion might also have an influence on the solubility of a compound.

None of the active compounds were more active than cisplatin which has an IC_{50} 0.852 µM, but they will be investigated for activity against resistant cancer cell lines.

2.5 Magnesium amide bases in the synthesis of substituted N-heterocycles

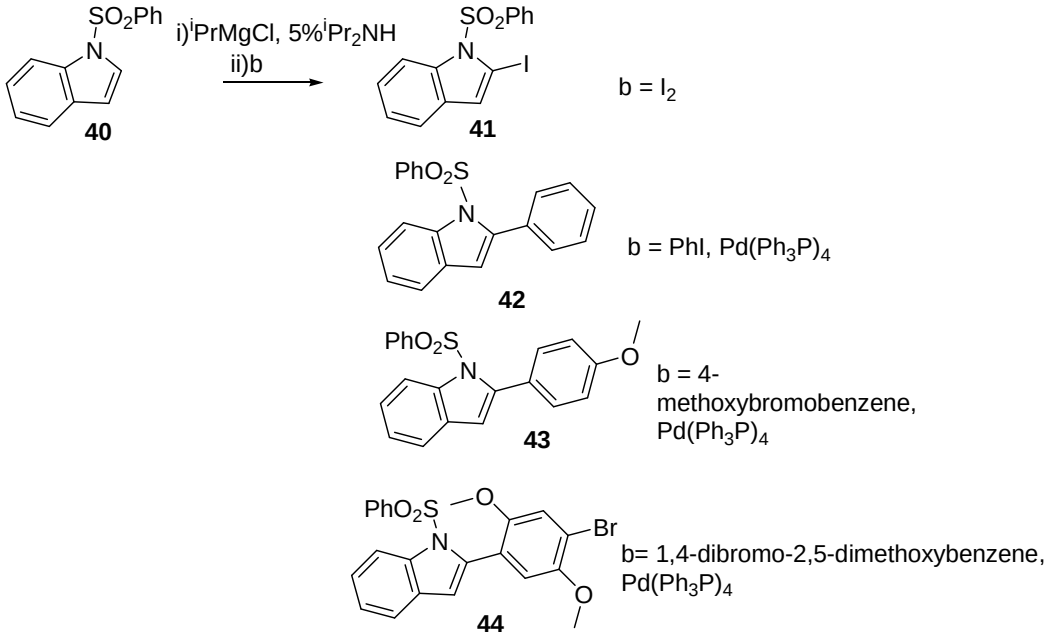
Our initial investigation was to extend the scope of the magnesiation protocol, using the method of Dinsmore *et al.*[55], from pyrrole to indole. We first prepared the Grignard reagent isopropylmagnesium chloride (^{i}PrMgCl) **15** by combining isopropyl chloride and magnesium in a 1.2: 1 ratio in tetrahydofuran (THF) at room temperature. The concentration of the base was determined by the method of Paquette[96], and found to be 0.9 M. We then repeated the magnesiation of *N*-phenylsulfonylpyrrole **5** by treating with ^{i}PrMgCl/ 5% $^{i}Pr_2NH$ and quenching with iodine (I_2) to afford 2-iodo-*N*-phenylsulfonylpyrrole **39** in 70% yield (Scheme 36).



39

Scheme 36.

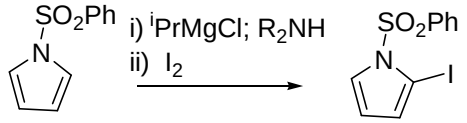
N-Phenylsulfonylindole **40** was subjected to the similar conditions and afforded 2-iodo-*N*-phenylsulfonylindole **41** in 75% yield. Having made the iodoindole **41**, we investigated the one-pot coupling reaction, in which **40** is treated with ^{i}PrMgCl/ 5% $^{i}Pr_2NH$ then $Pd(Ph_3)_4$ and arylhalide. Different 2-arylindoles were synthesized in this manner in a MSc work reported by Leboho[97] (Scheme 37). These results concluded that the method is compatible with indole.



Scheme 37.

We then reasoned that since tetramethylpiperidine (TMP) is much better than diisopropylamine in lithiation, using TMP in place of diisopropylamine (DA) may optimize this method. The number of equivalents of the Grignard may be reduced, the yields may increase and the reaction times may also be reduced. We began by repeating the preparation of iodosulfonylpyrrole **39** by modifying the general method by adding TMP in place of diisopropylamine. The product was obtained in less than 10% conversion, as shown from the ^{1}H NMR spectrum. This could due to TMP being more bulky compared to DA; and since the amine base is used in catalytic amounts, the rate of regenerating the magnesium amide base is slower in TMP than in diisopropylamine. Increasing the mol % of TMP and reducing the amount of base did lead to improved yields (Table 2). Results by Dinsmore, using equimolar amounts of DA and ^{i}PrMgCl in preparation of **39** gave a 55% yield[55], indicating that diisopropylamine is superior to TMP in magnesiation.

Table 2.



13 (mmol)	^{i}PrMgCl (mmol)	R_2NH (mmol)	Yield (%)
2.42	6.05 (2.5 eq.)	0.121 (5%) $^{i}Pr_2NH$ (18hrs)	70
2.49	6.08 (2.5 eq.)	0.123 (5%) TMP (18hrs)	9%[a]
2.49	2.904 (1.2 eq.)	2.904 (1.2 eq) TMP (4hrs)	39%[a]
2.42	3.63 (1.5 eq)	0.242 (10%) TMP (18hrs)	6%[a]

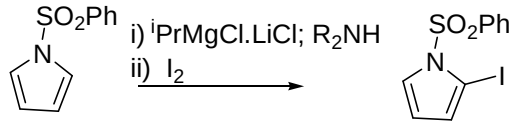
a= yields quoted from ^{1}H NMR

The work by Knochel[79-81] demonstrated a new generation of Hauser bases; $R_2NMgCl.LiCl$, and Grignard reagents; ^{i}PrMgCl.LiCl **14** to be superior to the previously reported species. We were interested in modifying the Hauser bases and attempted to use the amine in catalytic amounts, as reported by Dinsmore[55]. The initial step was preparing the Grignard reagent ^{i}PrMgCl.LiCl, using the method of Knochel[79-80], by which equimolar amounts of lithium chloride (LiCl) and magnesium (Mg) were mixed with excess isopropyl chloride in THF under argon. The concentration of the base was found to be 1.33 M, by the method of Paquette[96]. This is higher than the concentration of the first generation Grignard reagents, supporting the findings of Knochel that LiCl increases the solubility of the Grignard reagent in THF[80-81].

The initial investigation using ^{i}PrMgCl.LiCl **14** and catalytic amine, was the iodination of *N*-phenylsulfonylpyrrole **5.** Results were compared with those reported by Dinsmore[55]. We began by finding optimum conditions for magnesiation, starting with catalytic TMP. Using 1.5 equivalents of **14** and 10 mol% TMP gave the iodopyrrole **39** in 19% yield. Replacing TMP with diisopropylamine gave **39** in 65% yield. Because these results

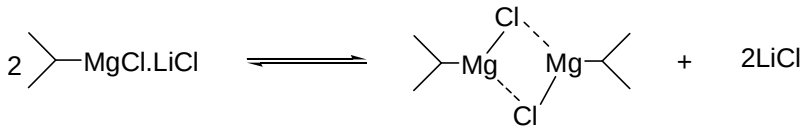
suggest that catalytic diisopropylamine is superior to TMP, further optimizing conditions were done using diisopropylamine. Reducing the mol% of diisopropylamine to 5 mol% gave **39** in 48% yield. When reducing the amount of Grignard reagent to 1.2 equivalents and keeping the amine at 10 mol%, gave **39** in 40% yield. Increasing the Grignard reagent to 1.8 equivalents and keeping the amine at 10 mol% gave **39** in 72% yield, which is comparable to results reported by Dinsmore[55] (Table 3).

Table 3.



^{i}PrMgCl.LiCl equivalent	Amine mol%	% yield
1.5	10 (TMP)	19
1.5	10 (Diisopropylamine)	65
1.2	5 (Diisopropylamine)	48
1.2	10 (Diisopropylamine)	40
1.8	10 (Diisopropylamine)	72

The downfall experienced with this method was the strength of the Grignard reagent with time. Repeating the above experiment with ^{i}PrMgCl.LiCl that was more than one week old gave yields lower than those initially obtained. Yields were reduced from 65% to 30% using conditions from entry 2 (Table 3) and from 48% to 18% from entry 3. When looking at the state of the Grignard reagent, we observed precipitates at the bottom of the flask. Initially it was assumed the base was decomposing but, when checking the concentration, it had not changed. We then concluded that the LiCl was precipitating from the solution, resulting in formation of magnesiated dimers (Scheme 38), hence the strength is reduced.



Scheme 38.

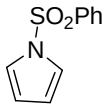
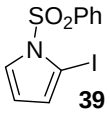
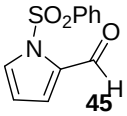
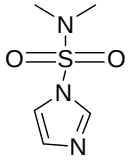
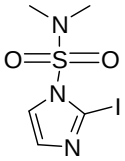
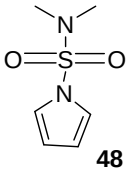
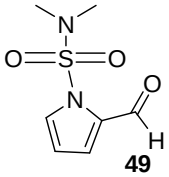
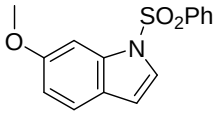
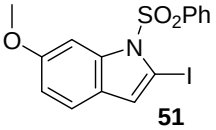
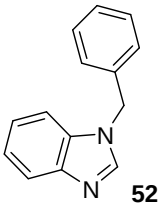
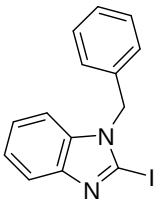
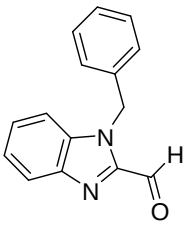
Stirring the solution for two hours before using the aged base solution gave improved results but could not reproduce the results obtained from a freshly prepared reagent. Yields improved from 30% to 53% (in entry 2) and from 18% to 40% (in entry 3) (Table 3). Although the previous studies showed the Grignard reagent and Hauser bases to be stable for over a month[79-80], our results show the best results are obtained using a freshly prepared reagent and yields drop as the Grignard reagent ages.

Different *N*-heterocyclic compounds were subjected to the optimum conditions, mentioned above, and then iodine and dimethylformide (DMF) were added as electrophiles (Table 4). Treating **5** with 1.8 eq. ^{i}PrMgCl.LiCl/ 10% $^{i}Pr_2NH$ and quenching with DMF, gave **45** in 60% yield (entry 1b) which is higher than the previously reported using the method of Dinsmore[55]. The spectroscopic data of the product were comparable to previously reported results.

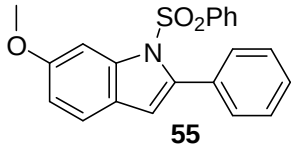
The iodoimidazole **47** was obtained from **46** in 78% yield (entry 2). Mass spectrometry gave the parent peak [M^+, 100] and the fragment [193 corresponding to the loss of –SO_2NMe_2]. ^{1}H NMR gave two imidazole protons, while ^{13}C NMR gave four carbon peaks corresponding to the desired product, thus we concluded that the desired product was formed.

The 2-formylpyrrole **49** was obtained in 31% yield (entry 3). The compound was obtained as oil, and this came as a surprise since the starting material **48** (its preparation to be discussed later) was a solid. Sulfonyl groups are known promote crystallization of many compounds. Mass spectrometry and NMR spectroscopy confirmed the formation of the product, however. A parent peak at *m/z* 202 $[M]^+$, three pyrrole protons together with an aldehyde proton, and six carbon peaks, led us to conclude the right product was made.

Table 4.

entry	substrate	electrophile	product	Yield (%)
1		a. I_2	 **39**	72
		b.DMF	 **45**	60
2	 **46**	I_2	 **47**	78
3	 **48**	DMF	 **49**	31
4	 **50**	I_2	 **51**	85
5	 **52**	a. I_2	 **53**	85
		b. DMF	 **54**	70

The iodoindole **51,** prepared from indole **50,** was obtained in 85% yield (entry 4) which is higher than the yield of iodoindole **41** obtained using the method of Dinsmore[55] (75%). Mass spectrometry gave the parent peak at *m/z* 412 $[M]^+$ and the fragment at *m/z* 271 $[M - SO_2Ph]^+$. ^1H NMR spectrum gave signals which integrated to the correct compound and lead us to conclude that the right molecule has been made. Treating indole **50** with 1.8 eq. $^iPrMgCl.LiCl$/ 10% $^iPr_2NH$ and adding catalytic $Pd(PPh_3)_4$ together with iodobenzene, gave the 2-phenylindole **55** in 60% yield (figure 19). The product was obtained as an oil even though it contains a sulfonyl group and the starting material **50** is a solid. A parent peak at *m/z* 363 $[M]^+$ is obtained from mass spectrometry. ^1H NMR spectrum gave a singlet at δ 6.48 ppm which correspond to the proton in the 3-position. These results led us to conclude that the desired product has been formed and that the new method can be used for one pot coupling reactions.



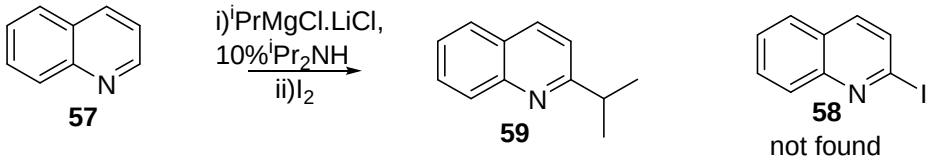
55

Figure 19.

Deprotonation of *N*-benzylbenzimidazole **52** has been reported[98-100], where lithium bases were employed. Treating **52** with 1.8 eq. $^iPrMgCl.LiCl$/ 10% $^iPr_2NH$ and quenching with I_2 gave the iodoproduct **53** in 85% yield, while quenching with DMF gave **54** in 75% yield. The spectroscopic data for both compounds were comparable with literature results, and also the melting points were in agreement with literature[98,100], leading to the conclusion that the right products were formed.

Knochel reported the deprotonation of 3-chloroquinoline **56**, at the 2 position[83]. We did not have **56** at our disposal so we used quinoline **57** instead. Treating **57** with $^iPrMgCl.LiCl$/ 10% $^iPr_2NH$ resulted in an immediate exothermic reaction and the flask had to be cooled down. Quenching with iodine did not the yield the 2-iodoquinoline **58** as expected. What was obtained was 2-isopropylquinoline **59** (Scheme 39). This was

confirmed by mass spectrometry which showed a parent peak at *m/z* 172 $[M + H]^+$. The ^1H NMR spectrum also showed the isopropyl protons.



Scheme 39.

This suggests that ^{i}PrMgCl.LiCl acted as a nucleophile in a similar manner observed from the Tschitschibabin reaction[101], where $NaNH_2$ acts as nucleophile toward quinoline to give 2-aminoquinoline **60** (Figure 20). Similar results were obtained with pyridine as the substrate, where 2-isopropylpyridine **61** was formed.

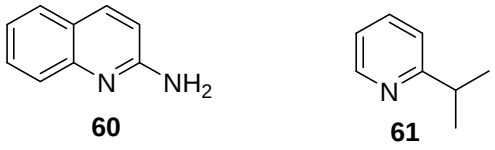
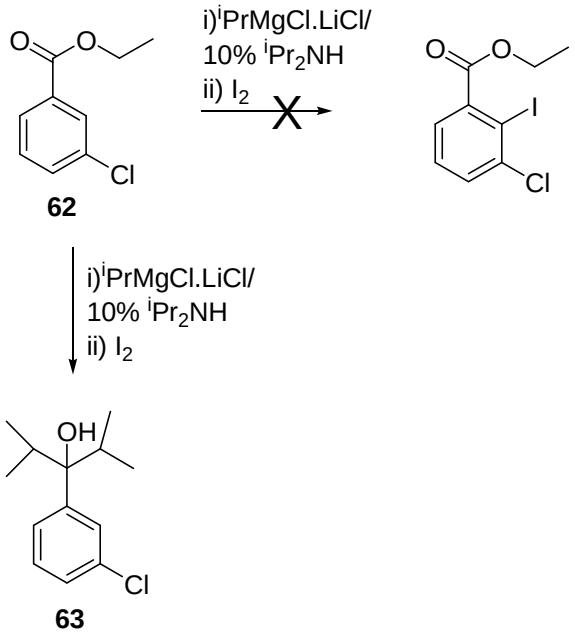


Figure 20.

Employing our method with the substituted benzene, ethyl-3-chlorobenzoate **62,** resulted in addition to the ester group, giving 3-(3-chlorophenyl)-2,4-dimethylpentan-3-ol **63,** instead of deprotonation at the 2-position (Scheme 40). This was confirmed by mass spectrometry where the parent peak at *m/z* 225$[M - H]^-$ was obtained when the instrument was run in negative ion mode.



Scheme 40.

These results suggest that the Grignard reagent is reactive toward electrophiles but not basic enough to deprotonate, and hence should be converted into the less reactive and more basic magnesium amide base.

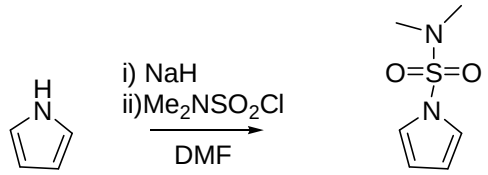
2.6 Sulfonyl protecting groups

Lastly we report differences between the two different sulfonyl protecting groups used in pyrrole and imidazole. The two were arylsulfonyl i.e., phenylsulfonyl and toluenesulfonyl, and *N*,*N*-dimethylsulfamoyl groups. The arylsulfonyl groups have been used extensively in pyrrole and indole protection[41,55,57,60,102], and good yields were obtained over a variety of reactions. These protecting groups however, reduce the reactivity of imidazole and thus are not used as protecting groups for imidazole. We also observed this in our experiment when trying to react benzonitrile with lithiated phenylsulfonylimidazole **22** and found no products.

The use of *N*,*N*-dimethylsulfamoyl protecting groups in pyrrole has been reported in substituted pyrrole[58-59]. Chadwick *et al.* showed the *N*,*N*-dimethylsulfamoyl to be better

protecting groups for imidazole[61]. The protecting group can be removed under basic conditions similar to those of removing arylsulfonyl protecting groups[49,52,61]. We were interested in introducing the *N*,*N*-dimethylsulfamoyl protecting group into a free pyrrole and perform similar reactions performed on the arylsulfonylpyrrole.

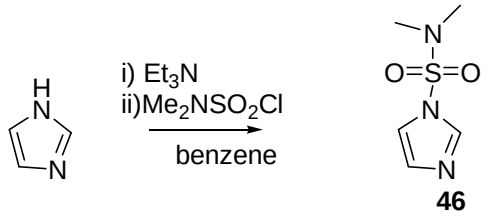
Preparation of the arylsulfonylpyrrole has already been reported in this chapter. The sulfamoylpyrrole **48** was prepared using the method of Wong *et al.*[103] who treated a disubstistuted pyrrole with sodium hydride followed by *N*,*N*-dimethylsulfamoyl chloride in DMF. We managed to get **48** in 99% yield using the method of Wong (Scheme 41). The ^{1}H NMR spectrum gave two signals in the aromatic region corresponding to the four protons but since the molecule is symmetrical, only two peaks are observed. Mass spectrometry gave the parent peak at *m/z* 174 $[M]^{+}$ and the fragment at *m/z* 108 which correspond to the $[N,N$-dimethylsulfamoyl$]^{+}$. These led us to conclude the desired compound was made. When trying methods used for arylsulfonyl protection, no products were obtained.



48

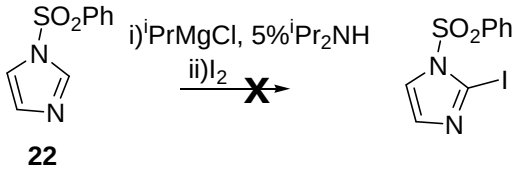
Scheme 41.

The sulfamoylimidazole **46** was prepared using the methods of Chadwick[61]. Imidazole is treated with triethylamine and *N*,*N*-dimethylsulfamoyl chloride in benzene at room temperature (Scheme 42). The product was obtained in 78% yield. Spectroscopic data and melting point were similar to previously published data.



Scheme 42.

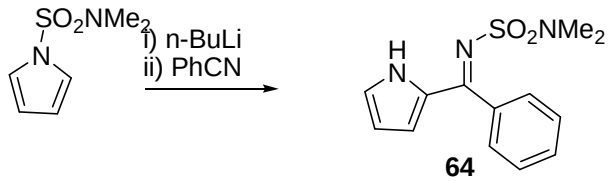
The first comparison of the different protecting groups was in the iodination reaction; arylsulfonylpyrrole **5** and **8** iodination yield was in the range of 60-75% (Scheme 36), while arylsulfonylimidazole **22** could not be iodated (Scheme 43). The second comparison is the addition of benzonitrile to the lithiated arylsulfonylheterocycle; the yields for benzonitrile addition to arylsulfonylpyrrole ranged from 30-60% (Scheme 18) while no products were found in the addition to arylsulfonylimidazole (Scheme 19). Arylsulfonylpyrrole was methylated while its imidazole analogue could not be. These results led us to conclude that arylsulfonyl protecting groups are suitable for pyrrole and not for imidazole.



Scheme 43.

Moving on to the *N*,*N*-dimethylsulfamoyl protecting group; the sulfamoylpyrrole **48** iodination was found to be 65% by ^{1}H NMR analysis while the iodination of sulfamoylimidazole **46** was 78%. Methylation of sulfamoylpyrrole was not observed, while that of sulfamoylimidazole occured in 71% yield. The methods used for methylation were reported by Chadwick *et al*. and his results[61] were comparable to those obtained in our laboratory. These results suggest the *N*,*N*-dimethylsulfamoyl protecting group is suitable for both the imidazole and pyrrole but, it favours imidazole over pyrrole.

From the above mentioned comparisons, both protecting groups are compatible with pyrrole but the arylsulfonyl protecting group is a better protecting group for pyrrole. The last reaction performed to support these observations was the benzonitrile addition to lithiated sulfamoylpyrrole **48**. The reaction was performed under similar conditions to those for arylsulfonylpyrrole (Scheme 18), treating **48** with butyllithium followed by benzonitrile gave the sulfamide **64** in 25% yield (Scheme 44).



64

Scheme 44.

^{1}H NMR spectrum showed three pyrrole protons and mass spectrometry gave the parent peak [M^{+} 277] and the fragment [169 corresponding to the loss of *N*,*N*-dimethylsulfamoyl]. These results led us to conclude that the correct molecule was made. We also concluded that arylsulfonyl chloride are better protecting groups for pyrrole when compared to *N*,*N*-dimethylsulfamoyl chloride.

2.7 Conclusion and Recommendations

In this dissertation, we were successful in achieving our aims. We started by investigating the 1,4-migration of the sulfonyl group during the synthesis of *N*-sulfonylimine ligands **6** and **15**. The investigation required the preparation of a 2-substituted *N*-toluenesulfonylpyrrole **8** which is mixed with *N*-phenylsulfonylpyrrole **5** in the crossover experiment. Attempts to make a silyl and methyl substituted pyrrole did not yield the desired products in pure form. We were successful in preparing 2-phenyl-*N*-toluenesulfonylpyrrole **26** in gram quantities using the method developed by Dinsmore e*t al*. Other methods investigated for the preparation of **26** either required the reaction to be performed in a glove box or required a large excess of starting material for the reaction to occur. We then concluded that the method developed by Dinsmore *et al*. is superior over

the current existing methods. When performing the crossover experiment, we found that the 1,4-migration of the sulfonyl group occurs via an intramolecular shift.

The *N*-toluenesulfonylimine ligand **15** was successfully complexed with various transition metals and the metal complexes formed were sent for testing against cancer cells. Although we intended that the metal ion should have a coordination number of four either by complexing two chelate ligands **15** or one chelate ligand with two triphenylphosphine units, as in the case for copper(I) and silver(I) metal ions, we observed metal complexes with coordination number of five, as in cobalt(II) **32** and zinc(II) **33**, where in addition to the two chelate ligands a DBU unit is coordinated to the metal. When preparing the silver complex, we discovered that depending on the source of triphenylphosphine (TPP), we can produce metal complexes with one TPP unit **35** and also with two TPP units **17**. The platinum complex **38** contains one chelate ligand **15** and a cyclooctadiene ligand as the second chelate ligand. The metal complexes that showed anti-cancer activity were the silver complexes and the platinum complex, and these complexes are currently undergoing further tests.

We extended the scope of magnesiation, developed for the deprotonation of sulfonylpyrrole by Dinsmore *et al.*, into sulfonylindole and found the method to work. Iodination of sulfonylindole was achieved in more than 70% yield, also the phenylation of sulfonylindole was achieved in more than 70% yield.

Finally we investigated the magnesiation methodology recently developed by Knochel *et al.* which used a combination of lithium chloride and Grignard reagent. We were interested in using catalytic amine base as opposed to the stochiometric amount required in the published report. We found that catalytic diisopropylamine was superior over tetramethylpiperidine, when using 10% mole equivalent, but found that the reaction time for deprotonation increases. The newly developed methodology was used to deprotonate *N*-sulfonylpyrrole, *N*-sulfonylindole, *N*-sulfonylimidazole and *N*-benzylbenzimidazole in moderate to good yields.

For future work we recommend the following;

- Solution studies on the complexes made, using UV-VIS and ESI mass spectrometry in trying to understand the stability and binding constants of the complexes in different media. This will be very important for the metal complexes which showed promising results as it might give insight on the mode of action of these compounds;
- Further testing on the metal complexes against other diseases such as HIV and malaria, and also investigating the mode of action of the compounds;
- Further investigation on the magnesiation methodology employing lithium chloride and catalytic amine and to try and use lithium chloride in catalytic amounts;
- The total synthesis of the densely functionalized pyrolidine-aziridine ring system **2** starting from *N*-sulfonylimine **4**. This will require changing the nitrile source from benzonitrile to cyano-*N*,*N*-dimethylformamide or its derivatives, when reacting lithiated *N*-sulfonylpyrrole with nitriles. If the synthesis of **2** is successful, the total synthesis of azinomycin can be attempted.

Chapter 3

Experimental

Chapter 3: Experimental

3.1 General

a) Purification of reagents and solvents

- THF and diethyl ether were distilled from sodium/benzophenone
- Dichloromethane and DMF were distilled from calcium hydride
- Benzene and toluene were distilled from sodium
- Hexane and ethyl acetate were distilled without addition of reagents

b) Spectroscopic and Physical data

- Melting points were obtained using a Reichert hot-stage microscope, and are uncorrected
- ^{1}H and ^{13}C NMR spectra were recorded at 300.139 MHz and 75.035 MHz, respectively, on Bruker Avance-300 spectrometer. Spectra were recorded in deuteriated chloroform ($CDCl_3$) unless otherwise specified. Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane as internal standard at zero ppm. The ^{1}H NMR chemical shifts are reported: value (number of hydrogens, description of signal, coupling constant(s) in hertz (Hz) where applicable, assignment) and the ^{13}C NMR chemical shifts are reported: value (assignment). Abbreviations used: s = singlet, d = doublet, t = triplet and m= multiplet.
- Infrared spectra were obtained on Bruker Tensor 27 spectrometer. Samples were placed on a diamond tip. The absorptions are reported on the wavenumber (cm^{-1}) scale, in the range 400 – 4000 cm^{-1}.
- High-resolution, low-resolution and fast atom bombardment (FAB) mass spectra were recorded on a VG70-SEQ instrument, electrospray ionization (ESI) mass spectra were recorded on a Thermo Fischer LXQ instrument. Data are quoted: *m/z* value (relative abundance). Samples ran on FAB were dissolved in a 3-nba matrix, while those in ESI were dissolved in a ethanol/water mixture.

- The crystal structure data sets was obtained on a Bruker SMART 1K CCD area detector diffractometer with graphite monochromator Mo K_α radiation (50 kV, 30 mA).

c) Nomenclature and numbering of compounds

The compounds prepared during the course of this project are named in the following experimental section according to systematic nomenclature. However, the numbering system used to illustrate the diagrams of these compounds is one adopted for convenience and is not meant to reflect systematic numbering of these compounds.

3.2 Synthetic procedures

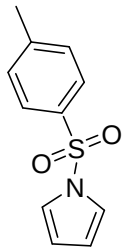
Isopropylmagnesium chloride (*i*PrMgCl) 13

A flame dried three neck round bottom flask containing Mg (4.89 g, 0.201 mol) pre-dried under high vacuum at 90 °C for 50 minutes, was fitted with a dropping funnel containing isopropyl chloride (30 ml, excess), reflux condenser, and 250 ml flask containing dry THF (200 ml) via a cannula. THF (50 ml) was transferred to the flask followed by isopropyl chloride (~6 ml) and few crystals of iodine. The flask was heated to initiate the reaction and placed in an ice-water bath once the reaction started. The remaining isopropyl chloride was added drop-wise at such a rate to maintain a gentle reflux and the resulting solution was stirred at room temperature until all Mg has reacted. The final solution was diluted with dry THF, allowed to settle and transferred into a dry Ar flushed flask via a cannula. The concentration of the solution was determined using the method of Paquette[83]. In a flame dried, one-neck round bottomed flask, menthol (0.312 g, 2 mmol) and 1,10-phenanthroline (4mg) were dissolved in dry THF and stirred for 2 minutes under Ar. The Grignard solution was added drop-wise via syringe until a distinct violet color persisted for longer than a minute. The concentration was found to be 0.91 M.

Isopropylmagnesium chloride- lithium chloride (*i*PrMgCl.LiCl) 14

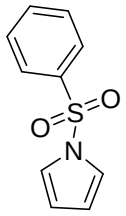
The base was prepared using the method of Knochel[67-68]. Mg (2.673 g, 110 mmol) and anhydrous LiCl (4.25 g, 100 mmol) were dried under high vacuum at 90 °C for 30 minutes. Isopropyl chloride (9.14 ml, 100 mmol) dissolved in dry THF (50 ml) was added slowly added into the flask along with few crystals of I_2 and the mixture stirred under Ar at room temperature. The reaction which starts within a few minutes was kept at room temperature and left stirring for 16 hours. The concentration was determined as mentioned above, and found to be 1.33 M.

***N*-Toluenesulfonylpyrrole 8**



In a flame dried flask, pyrrole (5 ml, 0.07 mol) and NaOH (8.4 g, 0.21 mol) were suspended in dry DCM (50 ml) and stirred at room temperature for 5 minutes to give a finely divided mixture. *p*-Toluenesulfonyl chloride (19 g, 0.1 mol), dissolved in DCM (40 ml), was added to the mixture, the flask was capped with a drying tube and stirred at room temperature for 48 hours. The reaction was quenched with water, the resulting solution extracted with DCM (3 × 50 ml), the combined organic layers washed with brine (15 ml), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure to give a brown solid which was purified by column chromatography, eluting with hexane / EtOAc (80 :20). *N*-Toluenesulfonylpyrrole was isolated as a brown-tan solid, (12.578 g, 81.3%); mp 93-95 °C (Lit[87]. 98-100^{o}C); ν_{max} (NaCl) /cm^{-1} 3054 (m), 1596 (m, C=N), 1455 (m), 1371 (m),1265 (s) and 1189 (m, -SO_2-); δ_H (300 MHz; $CDCl_3$; Me_4Si) 7.98 (2H, d, *J* 7.8, Ar-H), 7.29 (2H, d, *J* 7.3, Ar-H), 7.15 (2H, m, Pyrrole-H), 6.28 (2H, m, pyrrole-H) and 2.40 (3H, s, -Me); δ_C (75 MHz; $CDCl_3$) 142.9, 134.1, 127.9, 124.8, 118.7, 111.5 and 19.6; LREI *m/z* 221 (M^+, 100), 155 (32), 91 (71) and 65 (18).

***N*-Phenylsulfonylpyrrole 5**

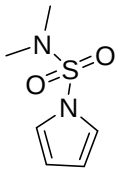


The above method was repeated using phenylsulfonyl chloride as an electrophile. After purification, N-phenylsulfonylpyrrole was isolated as a grey solid, (7.635 g, 50%); mp 82-84 ^{o}C (Lit[88]. 87-88 ^{o}C); ν_{max} (NaCl / cm^{-1}) 3054 (m), 1596 (m, C=N), 1455 (m), 1371 (m),1265 (s) and 1189 (m, -SO_2-); δ_H (75 MHz; $CDCl_3$; Me_4Si) 7.85 (2H, t, *J* 2.3, pyrrole -H), 7.57 (3H, m, Ar-H), 7.17 (2H, m, Ar-H), 6.30 (2H, t, *J* 2.3, pyrrole-H); δ_C (75 MHz; $CDCl_3$) 139.5, 134.2 , 129.8 , 127.14, 121.2 and 114; *m/z* 207 (M^+, 70), 141 (35), 115 (5), 77 (100) and 51 (16) (Found: 207.0343. $C_{10}H_9NSO_2$ requires 207.03540).

***N,N*-Dimethylsulfamoyl chloride**

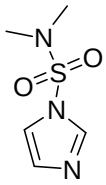
Using the variation to the methods of Hendrickson[89], *N,N*-dimethylamine hydrochloride (30 g, 0.369 mol) was added to a 250 ml r.b. flask. The flask was then placed in an ice-bath then sulfuryl chloride (SO_2Cl_2) (99.6 g, 0.729 mol) was added drop-wise over 5 minutes into the flask. The flask was then capped with a drying tube and gently refluxed for 24 hours. The excess SO_2Cl_2 was removed under reduced pressure then dry THF (45 ml) was added to precipitate the unreacted N,N-dimethylamine hydrochloride. The solution was filtered through a plug of celite, then THF removed under reduced pressure to give a clear oil which was purified by distillation to give the title compound as a clear oil (45.953 g, 89.6 %). b.p 54 ^{o}C at 2.8 mmHg (Lit.[89] 67 ^{o}C at 8 mmHg); δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.693 (6H, s, Me); δ_C (75 MHz; $CDCl_3$) 39.5914; (LREI) *m/z* 143.6 (M^+ , 50), 108.1 (100).

***N,N*-Dimethyl-1H-pyrrole-1-sulfonamide 48**



NaH (1.22 g, 0.05 mol) was suspended in DMF (20 ml) and placed in an ice bath. Pyrrole (2.63 ml, 0.0368 mol) was added drop-wise into the solution where a thick creamy solution formed. *N,N*-Dimethylsulfamoyl chloride (4.36 ml, 0.041mol) was added drop-wise at 0 ^{o}C over 5 minutes, then the resulting mixture was allowed to warm to room temperature and left stirring for 4 hours. DMF was removed under high vacuum. The resulting dark oil was partitioned between EtOAc/water (1: 1) (50 ml), the organic layer extracted, the aqueous layer washed twice more with EtOAc (20 ml). The combined organic layers were washed with brine (10 ml), dried over $MgSO_4$, and the solvent removed to give a dark oil which crystallized upon standing to give a black solid. The solid was then dissolved in DCM and filtered through silica plug to give *N,N*-Dimethyl-1H-pyrrole-1-sulfonamide **(**6.356 g, 99%) of a light brown solid. mp. 55 ºC; δ_H (300 MHz; $CDCl_3$; Me_4Si) 7.08 (2H, m, pyrrole H), 6.31 (2H, m, pyrrole H), 2.81 (6H, s, -Me); δ_C (75 MHz; $CDCl_3$) 124.1, 112.1, 38.6; LREI *m/z* 174 (M^+, 80), 108 (100), 68 (93).

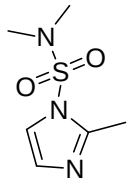
***N,N*-Dimethylimidazole-1-sulfonamide 46**



Using the method of Chadwick[48], imidazole (3.010 g, 0.0528 mol), triethylamine (6 ml, 0.043 mol) and *N,N*-dimethylsulfamoyl chloride (6 ml, 0.055 mol) were dissolved in benzene (40 ml) and stirred at room temperature for 20 hours. The mixture was filtered and the precipitate washed with benzene (2 x 15 ml). The filtrate and the washings were combined and the solvent removed under reduced pressure to give a clear oil which was dried under vacuum to give *N,N*-dimethylimidazole-1-sulfonamide (7.563 g, 78%) as a

white solid; mp 40-42˚C (lit.[48] 42-44˚C) ; ν_{max} (NaCl / cm^{-1}) 3127 (w), 1625.4 (w), 1391 (m)1153 (m, -SO_2-); δ_H (300 MHz; $CDCl_3$; Me_4Si) 7.92 (1H, s, imidazole-2-H), 7.27 (1H, s, imidazole-4-H), 7.16 (1H, s, imidazole-5-H) and 2.86 (6H, s, -Me); δ_C (75 MHz; $CDCl_3$) 137.1, 130.9, 118.1 and 38.5; LREI *m/z* 175 (M^+, 30), 108 (100), 69.2 (20).

_N,N_-Dimethyl-2-methylimidazole-1-sulfonamide[48]



Following the method of Chadwick[48], the sulfonamide **46** (0.5 g, 2.9 mmol) was dissolved in dry THF (10ml) and the solution cooled to -78 ^oC in a N_2/ acetone bath, n-BuLi (1.6 M, 2.19 ml, 3.5 mmol) was added and the resulting solution stirred for 15 minutes at -78˚C. The reaction was quenched with iodomethane (0.3 ml, 4.8 mmol). The stirring was continued at room temperature for 20 hours and the mixture was extracted with 2M HCl (5 x 12ml). The combined acidic solutions were washed once with Et_2O (10 ml) and basified with 10% NaOH solution. The solution was saturated with NaCl, extracted five times with chloroform (10 ml), the combined organic phase dried over $MgSO_4$ and the solvent removed to give *N*,*N*-dimethyl-2-methylimidazole-1-sulfonamide as a brown mobile oil (0.39 g , 71%). δ_H (300 MHz; $CDCl_3$; Me_4Si); 7.22 (1H, d, *J* 1.7 Hz, imidazole 4-H), 6.93 (1H, d, *J* 1.7 Hz, imidazole 5-H), 2.91(6H, s, NMe_2), 2.63 (3H, s, Me); δ_C (75 MHz; $CDCl_3$) 145.7, 130.5, 119.7, 38.2 and 15.3; LREI *m/z* 189.1 (M^+, 38), 108.1 (100), 83.2 (26) and 54.3 (9).

General Method for Magnesation

Method A[65]

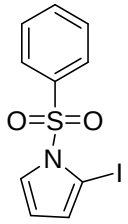
To *N*-toluenesulfonyl pyrrole **8** was added *i*PrMgCl (0.86 M, 2.5 eq. with respect to **8,** in THF) and $(iPr)_2NH$ (0.05 eq. with respect to **8**). The mixture was maintained at room

temperature under an argon atmosphere for 18 hours. An electrophile (2 eq. with respect to **8**) was added and the mixture was stirred at room temperature. The reaction was quenched by addition of saturated aqueous NH_4Cl (20 ml), and a saturated $Na_2S_2O_3$ solution (20 ml) in the case of I_2 as an electrophile. The mixture was extracted three times with EtOAc, the organic layer was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Further details are given for each individual preparation, described below.

Method B

To an *N*-heterocycle was added a solution of *i*PrMgCl.LiCl (1.11M, 1.8 eq. with respect to N-heterocycle, in THF) and $(i\text{Pr})_2\text{NH}$ (0.1 with respect to N-heterocycle). The mixture was stirred at room temperature under an argon atmosphere for 18 hours. An electrophile was added and the mixture was stirred at room temperature for 20 minutes. The reaction was quenched by addition of saturated aqueous NH_4Cl (20 ml), and a saturated $Na_2S_2O_3$ solution (20 ml) in the case of I_2 as an electrophile. The mixture was extracted three times with EtOAc, the organic layer was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure.

***2*-Iodo- *N*-Phenylsulfonylpyrrole 39**

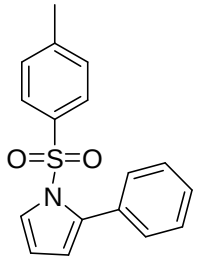


N-Phenylsulfonylpyrrole **5** (1.00 g, 4.82 mmol) was treated according to method A, with *i*PrMgCl (12.05 mmol, 14 ml, 2.5 eq.) and $(i\text{Pr})_2\text{NH}$ (28 µl, 0.2 mmol, 5 mol %). After standing at room temperature for 18 hours, the reaction was treated with I_2 (3.00 g, 12.0 mmol) followed by aqueous work-up and recrystallized from 96% EtOH to give *2*-iodo - *N*-phenylsulfonylpyrrole **39** (1.12 g, 70%) as brown crystals; mp. 96-98 (Lit.[65] 97-98)

δ_H (300 MHz; $CDCl_3$; Me_4Si) 7.91-7.94 (2H, m, Ar-H), 7.61-7.66 (1H, m, Ar-H), 7.59 (1H, dd, *J* 3.4 and 1.8, pyrrole-H), 7.50-7.56 (2H, m, Ar-H), 6.52 (1H, dd, *J* 3.4 and 1.8, pyrrole-H), and 6.27 (1H, apparent t, *J* 3.4, pyrrole-H); δ_C (75 MHz; $CDCl_3$) 147.5, 138.2, 134.2, 129.2, 128.1, 127.9, 126.7 and 114.6; HREI *m/z* 333 (M^+, 85), 207 (7), 192 (9), 141 (46) and 77 (100) (Found: 332.9392. $C_{10}H_8NO_2SI$ requires 332.9321).

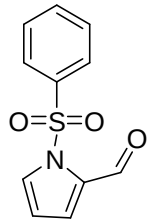
The reaction was also performed using method B and 2-iodo- *N*-phenylsulfonylpyrrole was obtained in 68% yield. Spectroscopic and physical properties obtained, were identical to those reported above.

***2*-Phenyl- *N*-toluenesulfonylpyrrole 26**



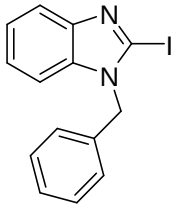
N-Toluenesulfonylpyrrole **8** (0.884 g, 3.98 mmol) was treated according to method A, with *i*PrMgCl (0.86 M, 9.95 mmol, 2.5 eq.) and $(i\text{Pr})_2NH$ (28 µl, 0.2 mmol, 5 mol %). Iodobenzene (0.89 ml, 7.96 mmol) and $Pd(Ph_3P)_4$ (0.231 g, 0.2 mmol). After stirring at room temperature for 48 hours, the reaction was partitioned between EtOAc (50 ml) and sat. aq. NH_4Cl (50 ml), the organic phase separated, the aqueous phase washed further with EtOAc. The combined organic phase were dried over $MgSO_4$ and the solvent removed under reduced pressure to give a brown oil which was further purified by column chromatography on silica gel, eluting with dichloromethane / hexane (1:4) to yield the title compound as a brown solid (600 mg, 51%) mp. 122 ˚ C (Lit. 123-124 ˚C)[77] δ_H (300 MHz; $CDCl_3$; Me_4Si) 7.05-7.44 (10H, m, 9Ar-H and 1 pyrrole-H), 6.30 (1H, apparent t, *J* 3.3, pyrrole-H), 6.15 (1H, apparent dd, *J* 1.8 and 3.3, pyrrole-H) and 2.35 (3H, s, Me); δ_C (75 MHz; $CDCl_3$) 145.0, 136.4, 136.0, 131.7, 131.3, 129.7, 128.6, 127.7, 127.5, 124.5, 116.1, 112.4 and 21.9; HREI *m/z* 297.08 (M^+, 100).

N-Phenylsulfonylpyrrole-2-carbaldehyde 45



N-Phenylsulfonylpyrrole (2.42 mmol, 0.50 g) was treated according to method B with *i*PrMgCl.LiCl (4.356 mmol, 3.92 ml, 1.8 eq) and $(i\text{Pr})_2\text{NH}$ (0.242 mmol, 34 µl, 10 mol%). DMF (6 mmol, 0.31 ml) was added and the solution stirred for 30 min. The aqueous work-up gave a brown oil which was purified with column chromatography on silica gel using 20% EtOAc: hexane as eluent to give *N*-phenylsulfonylpyrrole-*2*-carbaldehyde (0.344 g, 60%) as an off-white solid; mp 77-78 ºC (Lit[90]., mp. 78-79 ºC); δ_H (300 MHz; $CDCl_3$; Me_4Si) 9.96 (1H, s, CHO), 7.94-7.91 (2H, m, Ar-H), 7.67-7.46 (4H, m, pyrrole-H and Ar-C), 7.18 (1H, dd, *J* 3.4 and 1.7, pyrrole-H) and 6.43 (1H, apparent t, *J* 3.4, pyrrole-H); δ_C (75 MHz; $CDCl_3$) 179.2 (CHO), 138.6, 134.9, 133.9, 129.8, 127.8, 125.2 and 112.9; HREI *m/z* 235.03 (M^+, 100).

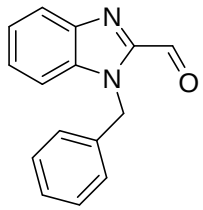
***1*-Benzyl-2-iodo-1*H*-benzo[*d*]imidazole 53**



N-Benzylbenzimidazole (2.42 mmol, 0.503 g) was treated according to method B with *i*PrMgCl.LiCl (4.356 mmol, 3.92 ml, 1.8eq) and $(i\text{Pr})_2\text{NH}$ (0.242 mmol, 34 µl, 10 mol%). I_2 (6 mmol, 1.50 g) was added and the solution stirred for 10 min. The aqueous work-up gave a brown solid which was purified with column chromatography on silica gel using 20% EtOAc: hexane as eluent to give *1*-benzyl-*2*-iodo-1*H*-benzo[*d*]imidazole (0.686 g, 85%) as a white solid; mp 118-119 ºC (Lit.[84] 118-120 ºC); δ_H (300 MHz; $CDCl_3$; Me_4Si)

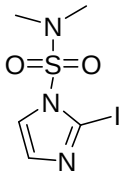
7.75 (1H, t, *J* 3.0, benzimidazole-H), 7.32-7.13 (8H, m, benzimidazole-H and Ar-H), 5.38 (2H, s, -CH_2-); LREI *m/z* 334.8 (M + H, 15), 333.8 (M^+, 100), 207 (25).

_1_-benzyl-1_H_-benzo[_d_]imidazole-_2_-carbaldehyde 54



N-Benzylbenzimidazole (2.42 mmol, 0.503 g) was treated according to method B with iPrMgCl.LiCl (4.356 mmol, 3.92 ml, 1.8 eq) and (iPr)$_2$NH (0.242 mmol, 34 µl, 10 mol%). DMF (6 mmol, 0.31 ml) was added and the solution stirred for 30 min. The aqueous work-up gave a brown oil which was purified with column chromatography on silica gel using 20% EtOAc in hexane as eluent to give *1*-benzyl-1*H*-benzo[*d*]imidazole-*2*-carbaldehyde (0.406 g, 70%) as a white-yellow solid; mp 104-105 ^{o}C (lit.[86] 105-107 ^{o}C); δ_H (300 MHz; $CDCl_3$; Me_4Si) 10.141 (1H, s, CHO), 7.95 (1H,t , *J* 3.0, benzimidazole-H), 7.44-7.15 (8H, m, benzimidazole-H and Ar-H), 5.85 (2H, s, -CH_2-); δ_C (75 MHz; $CDCl_3$) 184.9 (CHO), 145.9, 142.9, 136.6, 136.0, 128.9, 128.0, 127.1, 126.937, 124.2, 122.5, 111.4 and 48.0; HREI *m/z* 236.09 (M^+, 100).

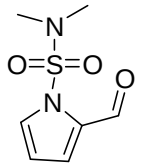
_2_-Iodo-_N,N_-dimethyl-1_H_-imidazole-_1_-sulfonamide 47



N,*N*-Dimethylimidazole-*1*-sulfonamide (2.42 mmol, 0.420 g) was treated according to method B with *i*PrMgCl.LiCl (4.356 mmol, 3.92 ml, 1.8eq) and (iPr)$_2$NH (0.242 mmol, 34 µl, 10 mol%) and left stirring at room temperature for 18 hrs. I_2 (6.0 mmol, 1.50 g) was added and the solution stirred for 10 min. The aqueous work-up gave a dark brown oil which was purified with column chromatography on silica gel using 20% EtOAc: Hexane as eluent to give *2*-iodo-*N*,*N*-dimethyl-1*H*-imidazole-*1*-sulfonamide (0.568 g, 78%) as brown oil. δ_H (300 MHz; $CDCl_3$; Me_4Si) 7.45 (1H, d, *J* 1.8, imidazole-H), 7.05

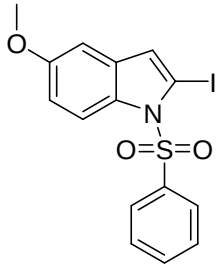
(1H, d, *J* 1.8, imidazole-H), 2.98 (6H, s, -Me); δ_C (75 MHz; $CDCl_3$) 131.2, 123.5, 83.2 and 37.8; LREI *m/z* 301.9 (M + H, 5), 300.9 (M^+, 100), 193.9 (29).(Found 300.9376: $C_5H_8N_3SO_2I$ requires 300.9382).

***2*-Formyl-*N*,*N*-dimethylpyrrole-1-sulfonamide 49**



N,*N*-Dimethyl-1*H*-pyrrole-1-sulfonamide (2.42 mmol, 0.417 g) was treated according to method B with *i*PrMgCl.LiCl (4.356 mmol, 3.92 ml, 1.8eq) and $(i\text{Pr})_2\text{NH}$ (0.242 mmol, 34 µl, 10 mol%) and left stirring at room temperature for 18 hrs. DMF (6 mmol, 0.31 ml) was added and the solution stirred for 30 min. The aqueous work-up gave a brown oil which was purified with column chromatography on silica gel using 40% EtOAc in hexane as eluent to give *2*-formyl-*N*,*N*-dimethylpyrrole-*1*-sulfonamide (0.151 g, 31%) as a brown oil. V_{max} 1665 (CHO), 1421 (C=O), 1379, 1249 and 1153 (-SO_2-); δ_H (300 MHz; $CDCl_3$; Me_4Si) 10.06 (1H, s, CHO), 7.40 (1H, apparent t, *J* 1.7, pyrrole-H), 7.27-7.23 (1H, m, pyrrole-H), 6.39 (1H, apparent t, *J* 3.3, pyrrole-H) and 2.87 (6H, s, -Me); δ_C (75 MHz; $CDCl_3$) 179.9 (CHO), 133.9, 129.9, 122.5, 111.4 and 38.2; *m/z* HREI 202.0408 (M^+, 100) (Found 202.0408: $C_7H_{10}O_3N_2S$ requires 202.0412).

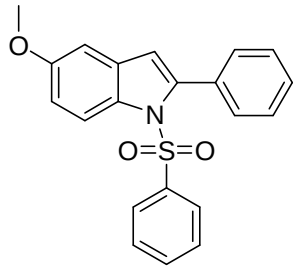
***2*-Iodo-5-methoxy-*1*phenylsulfonyl-1*H*-indole 51**



5-Methoxy-*1*-phenylsulfonyl-1*H*-indole (2.42 mmol, 0.695 g) was treated according to method B with *i*PrMgCl.LiCl (4.356 mmol, 3.92 ml, 1.8eq) and $(i\text{Pr})_2\text{NH}$ (0.242 mmol, 34 µl, 10 mol%) and left stirring at room temperature for 18 hrs. I_2 (6 mmol, 1.5 g) was added and the solution stirred for 10 min. The aqueous work-up gave a dark brown oil

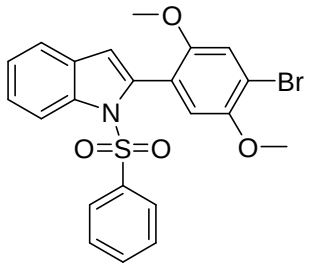
which was purified with column chromatography on silica gel using 10% EtOAc in hexane as eluent to give *2*-iodo-*5*-methoxy-1-phenylsulfonyl-1*H*-indole (0.849 g, 85%) as a brown solid; mp. 122-124˚C; δ_H (300 MHz; $CDCl_3$; Me_4Si) 8.18 (1H, d, *J* 8.2, Ar-H), 7.87 (2H, d, *J* 7.9, Ar-H), 7.55-7.53 (1H, m, indole-H), 7.46-7.41 (2H, m, Ar-H), 6.93-6.85 (3H, m, indole-H) and 3.83 (3H, s, -OMe); δ_C (75 MHz; $CDCl_3$) 156.9, 138.5, 134.4, 133.7, 133.1, 129.5, 127.5, 124.8, 116.8, 114.2, 102.4 and 56.0; LREI *m/z* 414.8 (M + H, 12), 412.8 (M^+, 79), 271.8 (100) and 228.8 (10) (Found 412.9585: $C_{15}H_{12}NO_3SI$ requires 412.9582).

5-Methoxy-2-phenyl-1-phenylsulfonyl-1*H*-indole 55



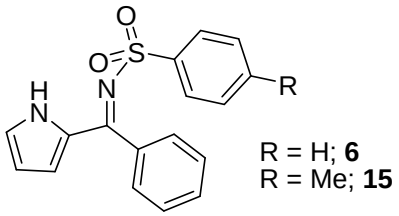
5-Methoxy-1-phenylsulfonyl-1*H*-indole (2.42 mmol, 0.695 g) was treated according to method B with *i*PrMgCl.LiCl (4.356 mmol, 3.92 ml, 1.8eq) and $(i\text{Pr})_2NH$ (0.242 mmol, 34 µl, 10 mol%) and left stirring at room temperature for 18 hrs. The reaction was treated with iodobenzene (0.49 ml, 4.356 mmol) and $Pd(Ph_3P)_4$ (231.16 mg, 0.2 mmol). After stirring at room temperature for 48 hours, the reaction was partitioned between EtOAc (50 ml) and sat. aq. NH_4Cl (50 ml), the organic phase separated, the aqueous phase washed further with EtOAc (25 ml). The combined organic phase were dried over $MgSO_4$ and the solvent removed under reduced pressure to give a brown oil which was further purified by column chromatography on silica gel, eluting with dichloromethane / hexane (1:4) to yield the title compound as a brown oil (0.527 g, 60%); δ_H (300 MHz; $CDCl_3$; Me_4Si) 8.19 (1H, d, *J* 9, Ar-H), 7.51-7.24 (10H, m, Ar-H and indole-H), 6.96 (1H, dd, *J* 2.4 and 9, indole-H), 6.88 (1H, d, *J* 2.4, indole-H), 6.48 (1H, s, indole-H) and 3.814 (3H, s, -OMe); δ_C (75 MHz; $CDCl_3$) 157.1, 143.0, 137.2, 133.4, 132.8, 132.3, 131.7, 130.2, 128.7, 128.5, 127.5, 126.7, 117.7, 113.9, 113.5, 103.2 and 55.6; HREI *m/z* 363.09 (Found 363.0924: $C_{21}H_{17}O_3NS$ requires 363.0929).

2-(4-Bromo-2,5-dimethoxyphenyl)-1-phenylsulfonyl-1*H*-indole 44



1-Phenylsulfonyl-1*H*-indole (2.42 mmol, 0.622 g) was treated according to method A with *i*PrMgCl (6.05 mmol, 2.5 eq.) and (*i*Pr)$_2$NH (28 µl, 0.2 mmol, 5 mol %). After standing at room temperature for 18 hours, the reaction was treated with 1,4-dibromo -2,5-dimethoxybenzene (4.356 mmol, 1.280g) and Pd(Ph$_3$P)$_4$ (231.16 mg, 0.2 mmol). After stirring at room temperature for 48 hours, the reaction was partitioned between EtOAc (50 ml) and sat. aq. NH$_4$Cl (50 ml), the organic phase separated, the aqueous phase washed further with EtOAc. The combined organic phase were dried over MgSO$_4$ and the solvent removed under reduced pressure to give a brown oil which was further purified by column chromatography on silica gel, eluting with EtOAc / hexane (1:5) to yield the title compound as a brown solid (0.706 g, 62%) mp. 181-183˚C; δ_H (300 MHz; CDCl$_3$; Me$_4$Si) 8.24 (1H, d, *J* 8.4, Ar-H), 7.51 -7.25 (8H, m, Ar-H and indole-H), 7.13 (1H, s, Ar-H), 6.78 (1H, s, Ar-H), 6.58 (1H, s, indole-H), 3.82 (3H, s, -OMe) and 3.68 (3H, s, -OMe); δ_C (75 MHz; CDCl$_3$) 153.1, 149.6, 139.0, 137.9, 137.0, 133.8, 130.4, 129.0, 127.1, 125.2, 124.3, 121.5, 121.3, 116.7, 116.5, 116.1, 113.5, 113.3, 57.4 and 56.5 ; HREI *m/z* 471.01 (Found 471.0151: C$_{22}$H$_{18}$O$_4$NBrS requires 471.0139).

4-Methyl-N-[phenyl(1*H*-pyrrol-2yl)methylene]benzenesulfonamide 15



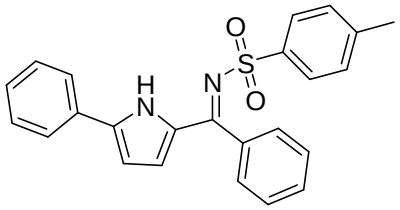
Using variation methods to Mandy and Patil[42], *N*-toluenesulfonylpyrrole **8** (1.004g, 0.0046 mol) was dissolved in dry THF (20 ml), the flask was cooled to –20 °C in N$_2$/

acetone bath. n-BuLi (1.6 M, 3.25 ml, 0.0052 mol, 1.2 eq) was added and the solution stirred at –20ºC for 20 minutes. Benzonitrile (0.6 ml, 0.0055 mol) was added and the final solution was allowed to warm to room temperature and stirred for 17 hours. The reaction was quenched with saturated NH_4Cl solution, and extracted with EtOAc (2 × 20 ml). The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent removed under reduced pressure to give a brown oil, which was further purified by column chromatography, eluting with hexane / EtOAc (80 : 20) to give the title compound (0.894 g, 60%)**;** mp 110-113˚C; ν_{max} (NaCl / cm^{-1}) 3358 (m, N-H), 3058 (m), 1595 (w, C=N), 1545 (s) and 1197 (s, -SO_2); δ_H (300 MHz; $CDCl_3$; Me_4Si) 10.16 (1H, broad s, -NH), 7.75 (2H, d, *J* 7.846, Ar-H), 7.52-7.36 (5H, m, Ar-H), 7.26-7.21 (4H, m, Ar-H), 6.48 (1H, m, pyrrole-H), 6.30 (1H, m, pyrrole-H) and 2.43 (3H, s, -Me); δ_C (75 MHz; $CDCl_3$) 142.0, 137.9, 131.1**,** 129.6, 126.6, 126.1, 111.2 and 20.6**;** HREI *m/z* 324 (M^+, 37), 259 (70), 169 (100), 157 (24), 91 (42) and 77 (31) (Found 324.09237. $C_{18}H_{16}O_2N_2S$ requires 324.09325).

N-[Phenyl(1*H*-Pyrrol-2yl)methylene]benzenesulfonamide 6

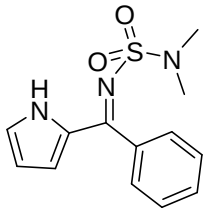
Repeating the above procedure with *N*-phenylsulfonylpyrrole **5** gave the title compound **6** (0.423 g, 30%) ; mp 145-148˚C; ν_{max} (NaCl / cm^{-1}) 3428 (m, N-H), 3055 (m), 1544 (s) and 1156 (s); δ_H (300 MHz; $CDCl_3$; Me_4Si) 10.16 (1H, broad s, -NH), 7.99-7.82 (2H, m, pyrrole-H), 7.70-7.38 (8H, m, Ar-H), 7.25 (2H, m, Ar-H), 6.51 (1H, m, pyrrole-H), 6.33 (1H, m, pyrrole-H); δ_C (75 MHz; $CDCl_3$) 141.8, 132, 130.7, 129.6, 129.3, 128.6, 128.0, 127.7 and 112.3; HREI *m/z* 31.01003 (M^+, 46), 249.1169 (10), 169.0698 (100) and 77.03945 (38) (Found 310.01003, $C_{17}H_{14}N_2O_2S$ requires 310.0776).

(*E*)-4-Methyl-N-[phenyl(5-phenyl-1*H*-pyrrol-2-yl)methylene]benzenesulfonamide 29



2-Phenyl-N-tolueneulfonylpyrrole **26** (420 mg, 1.4 mmol) was dissolved in dry THF (5ml), the flask was cooled to –20 °C, in N_2/ acetone bath, n-BuLi (1.1 ml, 1.69 mmol) was added and the solution stirred at –20 °C for 30 minutes. Benzonitrile (1.69 mmol, 0.19 ml) was added and the final solution was allowed to warm to room temperature and stirred for 2 hours. The reaction was quenched with saturated NH_4Cl solution, and extracted with EtOAc (2 × 20 ml). The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent removed under reduced pressure to give a brown oil, which was further purified by column chromatography, eluting with hexane / EtOAc (80 : 20) to give (200 mg, 36%) of the title compound. Mp. 114˚C δ_H (300 MHz; $CDCl_3$; Me_4Si) 10.80 (1H ,broad s, NH), 7.71 (4H,dd, *J* 17.31 and 7.32,p-Tol-H), 7.35-7.52 (8H, m, Ar-H), 7.21-7.26 (2H, m, Ar-H), 6.61 (1H, apparent t, *J* 3.3, pyrrole-H) 6.54 (1H, m, pyrrole-H), 2.41 (3H,s,me); δ_C (75 MHz; $CDCl_3$) 143.4, 142.8, 139.3, 131.0, 130.6, 129.9, 128.0, 127.5, 125.9, 110.5, 21.9; HREI *m/z* 400.13245 (M^+,80), 245.11597 (100), 218.98562 (62) and 115.02906 (58) (Found 400.13245: $C_{24}H_{20}N_2O_2S$ requires 400.1245).

***N*,*N*-Dimethyl-*N*'-[phenyl(1H-pyrrol-2yl)methylene]sulfamide 64**



N,*N*-Dimethyl-1*H*-pyrrole-1-sulfonamide **48** (2.9 mmol, 0.501 g) was lithiated as mentioned above for the preparation of **15**, using n-BuLi (3.45 mmol, 2.2 ml) at –20 °C and stirred for 30 minutes before the addition of benzonitrile (3.45 mmol, 0.35 ml). The

final solution was allowed to warm to room temperature and left stirring for 2 hours. The usual aqueous work-up gave a dark oil which was purified by column chromatography using 20% EtOAc: hexane as eluent to give the title compound (0.202 g, 25%) as a brown solid; mp. 106-108 °C; δ_H (300 MHz; $CDCl_3$; Me_4Si) 7.60-7.41 (5H, m, Ar-H), 7.20 (1H, m, pyrrole-H), 6.50 (1H, m, pyrrole-H), 6.31 (1H, m, pyrrole-H) and 2.90 (6H, s, -Me); δ_C (75 MHz; $CDCl_3$) 130.8, 129.1, 128.6, 128.3, 127.4, 111.7 and 38.9; HREI *m/z* 278.18047 ($M + H^+$, 8), 277.177 (M^+, 40), 169.121 (100) and 77.053 (21) (Found 277.17715: $C_{13}H_{15}N_3O_2S$ requires 277.0885).

Crossover experiment

In a flame dried flask, 2-phenyl-*N*-tolueneulfonylpyrrole **26** (210 mg;0.7 mmol) and *N*-phenylsulfonyl pyrrole **5** (144.9 mg; 0.7 mmol) were dissolved in dry THF (5 ml). The flask was cooled to –20 °C, in N_2/ acetone bath, n-BuLi (1.1 ml, 1.69 mmol) was added and the solution stirred at –20 °C for 30 minutes. Benzonitrile (1.69 mmol, 0.19 ml) was added and the final solution was allowed to warm to room temperature and stirred for 2 hours. The reaction was quenched with saturated NH_4Cl solution, and extracted with EtOAc (2 × 20 ml). The combined organic layers washed with brine, dried over $MgSO_4$ and the solvent removed under reduced pressure to give a brown oil which was purified by chromatography using 10% EtOAc in hexane as eluent. Two fractions were collected and characterized by high resolution MS which showed the presence of (*E*)-4-methyl-N-[phenyl(5-Phenyl-1*H*-pyrrol-2-yl)methylene]benzenesulfonamide and *N*-[phenyl(1H-pyrrol-2yl)methylene]benzenesulfonamide as the products of the addition reaction.

Metal Complexes

Ligand 1 = deprotonated *4*-methyl-*N*-[phenyl(1H-pyrrol-2yl)methylene]benzenesulfonamide

$CuL(P(Ph)_3)_2$ 31

Ligand 1 (0.100 g, 0.301 mmol) and $CuBr(P(Ph)_3)_3$ (0.263 g, 0.301 mmol) were dissolved in chloroform (20 ml)and stirred for 2 minutes. DBU (45 µl, 0.301 mmol) was added to the solution by syringe and the resulting solution, which turned from light brown to dark brown, was left stirring at room temperature for 30 minutes. The reaction was quenched with sat. $NHCO_3$, washed with DCM, the organic layer dried over $MgSO_4$. The solvent was removed to give a dark brown oil which was dissolved in DCM: hexane (1: 1, 10 ml) to precipitate yellow crystals (160 mg, 58%) suitable for X-Ray diffraction. (See Appendix 3 for structure); mp.(dec.) 193-195ºC; ν_{max} 3053 (w), 1522 (s), 1481 (s, C=N), 1463 (s), 1433 (s), 1413(s), 1361 (s), 1297 (s), 1267 (vs), 1195 (w, -SO_2-), 1143 (vs); δ_H (300 MHz; $CDCl_3$; Me_4Si) 7.39-7.16 (31H, m, $P(Ph)_3$ and pyrrole-H), 7.04 (3H, t, J 7.8, Ar-H), 6.87 (2H, d, 7.5, Ar-H), 6.50-6.40 (4H, m, Ar-H), 6.23 (1H, apparent d, J 3.4, pyrrole-H), 5.29 (1H, m, pyrrole-H) and 2.17 (3H, s, -Me); Anal. Calcd. for $C_{54}H_{45}CuN_2O_2P_2S$: C, 71.15; H, 4.98; N, 3.07; S, 3.52. Found: C, 69.56; H, 5.14; N, 3.03; S 3.70. FAB *m/z* 587.4 (M minus L)$^+$ (15), 325.2 (15), 262.2 (25); ESI 587.25 (100)

CuL_2 30

Ligand 1(0.200 g, 0.617 mmol) and $Cu(OAc)_2$ (56.11 mg, 0.3085 mmol) were dissolved in methanol (10 ml) and stirred for 2 minutes, DBU (90 µl, 0.617 mmol) was added to the solution which was then refluxed for 2 hours. The solution was then allowed to cool to room temperature whereafter precipitation occurred. The precipitates were filtered, washed with methanol (5ml) and allowed to dry to afford dark green crystals (75 mg, 34%). mp.(dec.) >250 °C; ν_{max} 1596 (w), 1541 (vs), 1490 (s, -C=N), 1470 (w), 1443 (w), 1405 (s), 1369 (vs), 1317 (s), 1283 (vs), 1219 (s), 1201 (vs, -SO_2-), 1182 (s), 1151 (vs), 1108 (s) 1044 (vs), 1005 (s); *m/z* ESI *732*.13 (M + Na^+, 10), 710.08 (M + H^+, 12), 347.12 (L + Na^+, 100) and 325.03 (L + H^+).

NiL_2 19

Ligand 1 (0.400 g, 1.24 mmol) and Ni(acetylacetonate)$_2$ (0.159 g , 0.62 mmol) were dissolved in ethanol (10 ml), DBU (1.24 mmol, 180 µl) was added and the final solution was refluxed for 24 hours. The solution was allowed to cool to room temperature. The solvent was reduced to half its original volume and the solution was left in the fridge overnight whereafter precipitation occurred. The precipitates were filtered, washed with diethyl ether (10 ml), recrystallised from DCM: hexane mixture to give light green crystals (128 mg, 29%). mp.(dec) 149-151ºC; ν_{max} 1645 (s), 1580 (s), 1523 (m), 1487 (m, C=N), 1465 (m), 1443 (m), 1417 (s), 1366 (w), 1281 (s), 1196 (s, -SO_2-), 1148 (s), 1086 (s), 1034 (s); FAB *m/z* 727.2 (M + Na^+, 20), 705.2 (M + H^+), 381.1 (5), 325.1 (55).

CoL_2DBU 32

Ligand 1 (0.200 g, 0.617 mmol) and $CoCl_2.6H_2O$ (73.76 mg, 0.31 mmol) were dissolved in methanol (10 ml), DBU (90 µl, 0.617 mmol) was added to the solution which was refluxed for 24 hours and cooled to room temperature. The solvent was reduced to half and the solution was left in the fridge for 24 hours whereafter precipitation occurred. The precipitates were filtered off, washed with methanol (5 ml), then petroleum ether (10 ml) and left to dry in air to give a brown solid (160mg, 60%). The solid was recrystallised from DCM: EtOH mixture to afford dark crystals suitable for X-Ray diffraction (See appendix 4 for structure). mp.(dec) > 250ºC; ν_{max} 1599 (s), 1526 (s), 1489 (s, C=N), 1465 (s), 1429 (s), 1380 (s), 1312 (vs), 1273 (vs), 1214 (vs), 1194 (s, -$S0_2$), 1155 (vs), 1082 (s), 1042 (vs), 1003 (s); FAB *m/z* 858.2 (M + H^+, 5), 705.2 (8), 534.2 (36), 153.1 (100).

ZnL_2DBU 33

Ligand 1 (0.200 g, 0.617 mmol) and $ZnCl_2$ (42.16 mg, 0.31 mmol) were dissolved in methanol (10 ml). DBU (90 µl, 0.617 mmol) was added to the solution which was refluxed for 24 hours, then cooled to room temperature. The solvent was reduced to half

and the solution was left in the fridge for 24 hours whereafter precipitation occurred. The precipitates were filtered off, washed with methanol (5 ml), then petroleum ether (10 ml) and left to dry in air to give a brown solid (160mg, 60%). mp.(dec) 228-230º ; ν_{max} 1646 (w), 1599 (s), 1524 (s), 1490 (s, C=N), 1468 (s), 1432 (vs), 1379 (vs), 1310 (vs), 1276 (s), 1215 (vs), 1199 (s, -SO_2-), 1153 (vs), 1082 (s), 1042 (vs), 1003 (s); ESI *m/z* 733.48 (6), 711.17 (10), 603.22 (20), 347.10 (100); FAB 863.2 (M + H^+, 5), 711.2 (5), 539.2 (30), 387.1 (5), 325.1 (7), 153.2 (100).

AgLP(Ph)$_3$ 35

Ligand 1 (0.227 g, 0.855 mmol), silver nitrate (0.145 g, 0.855 mmol) and P(Ph)$_3$ (0.244 g, 0.885 mmol) were dissolved in ethanol (10 ml) and stirred for 2 minutes. DBU (0.855 mmol, 125 µl) was added to the solution, which was refluxed in the dark under Ar for 4 hours. The solution was allowed to cool to room temperature whereafter precipitation occurred. The precipitates were filtered, washed with EtOH (2 ml), diethyl ether (10 ml) and allowed to dry in air to give a dark green solid (340 mg, 61%) which was recrystallised in DMF-DCM mixture to give light green crystals suitable for X-Ray diffraction (See Appendix 5 for structure). mp.(dec.) 218-220 °C; ν_{max} 1738 (s), 1592 (w), 1435 (m), 1366 (s), 1229 (s), 1216 (s); δ_H (300 MHz; $CDCl_3$; Me_4Si) 7.64-7.14 (23H, m, PPh_3 and Ar-H), 6.84 (2H, d, *J* 7.8, Ar-H), 6.41-6.37 (2H, m, pyrrole-H) and 2.26 (3H, s,-Me); δ_C (75 MHz; $CDCl_3$) 168.4 , 145.6 , 142.1, 141.2, 140.3, 135.8, 134.6, 134.4, 131.9, 131.4, 131.1, 129.5, 129.4, 129.4, 128.9, 128.5, 127.5, 126.9, 116.9 and 21.8; Anal. Calcd for $C_{36}H_{30}AgN_2O_2PS$: C, 62.34; H, 4.36; N, 4.04; S, 4.62. Found: C, 59.93; H, 4.46; N, 4.05; S, 4.74.; *m/z* FAB 631.4 (100), 369.2 (70), 325.2 (40).

AgCl[P(Ph)$_3$]$_3$ 36

AgCl (1.49 g, 10 mmol) was suspended in DCM (140 ml) then P(Ph)$_3$ (10.97 g, 40 mmol) dissolved in DCM (40 ml) was added drop-wise into the solution. The final solution was stirred at room temperature for 2 hours, filtered, hexane added to the filtrate until the solution turned milky. The Ag complex precipitates out upon standing and was filtered,

washed with hexane and dried in air to give white crystals (7.52 g , 81%). m.p 185 ^{o}C (Lit. 185-187 ^{o}C)[80]

AgL[P(Ph)$_3$]$_2$ 17

Ligand 1 (0.277 g, 0.855 mmol) and AgCl[P(Ph)$_3$]$_3$ (0.795 g, 0.855 mmol) were dissolved in chloroform (20 ml), DBU (0.855 mmol, 0.125 µl) was added to the solution. The final solution was stirred at room temperature for 30 minutes, washed with sat. $NaHCO_3$ (10 ml) extracted with DCM (10 ml × 2), the combined organic layers were dried over Na_2SO_4, and the solvent removed to leave a dark brown oil. The oil was dissolved in DCM: hexane (1:4) where unreacted AgCl[P(Ph)$_3$]$_3$ was precipitated out as white solid (300 mg). The filtrate was again dissolved in DCM: Hexane mixture, at which point yellow precipitates (340 mg, 42%) were obtained. The solid was recrystallised from EtOH: DCM where crystals suitable for X-Ray diffraction were obtained (see appendix 6 for structure); mp. (dec) 226-230 °C; ν_{max} 1739 (s,br), 1597 (w), 1521 (s), 1480 (w, C=N), 1465 (s), 1433 (w), 1408 (s), 1371 (vs), 1323 (m), 1291 (s), 1265 (s), 1197 (s, -SO_2-), 1155 (s), 1141 (s), 1081 (s), 1048 (m)1031 (s); δ_H (300 MHz; $CDCl_3$; Me_4Si) 7.43-7.25 (33 H, m, PPh_3 and Ar-H), 7.13-6.91 (4H, m, Ar-H), 6.86 (2H, d, *J* 7.8, Ar-H), 6.64 (2H, d, *J* 7.8, Ar-H), 6.40 (1H, apparent d, *J* 3.9, pyrrole-H), 6.29- 6.28 (1H, m, pyrrole-H) and 2.20 (3H, s, -Me); FAB *m/z* 631.4 (M minus L)$^+$ (69), 369.2 (80), 262.2 (100); (Anal. calcd. for $C_{51}H_{45}AgN_2O_2P_2S$: C, 67.86; H, 4.75; N, 2.93; S, 3.35: Found C, 65.67; H, 4.82; N, 2.58, S, 2.95.

PdL$_2$ 34

Ligand 1 (0.2 g, 0.617 mmol) was dissolved in MeOH (10 ml). NaOAc (24 mg, 0.31 mmol) was added to the solution which was stirred for 5 minutes. In a separate flask, $PdCl_2$ (54.72 mg, 0.31 mmol) and LiBr (107.68 mg, 1.24 mmol) were dissolved in MeOH (2 ml) and stirred for 2 minutes before being transferred to the other flask. The final solution was stirred at 30ºC for 24 hours. Yellow precipitates, which started forming in the first hour, were collected by filtration, washed with methanol then petroleum ether to

give a yellow solid (140 mg); mp.(dec) >250 °C; ν_{max} 1595 (w), 1577 (w), 1547 (s), 1490 (w, C=N), 1444 (w), 1399 (s), 1365 (s), 1323 (s), 1293 (s), 1219 (w), 1196 (m, -SO_2), 1152 (s), 1084 (s), 1043 (s), 1010 (m); ESI *m/z* 775.1 (M + Na^+, 34), 347.11 (L + Na^+, 100), 325.08 (L + H^+, 5).

PtL(COD) 38

Ligand 1 (259.8 mg, 0.804 mmol) and $PtCl_2$(COD) (150 mg, 0.402 mmol) were dissolved Toluene (20 ml), DBU (117.6 µl, 0.804 mmol) was added and the resulting solution was refluxed under Ar for 12 hours. The solution was filtered, the solvent removed by evaporation and the resulting yellow oil was purified by column chromatography using 20% EtOAc in hexane as eluent. A bright yellow solid (156 mg) was obtained and recrystallised from DCM: EtOH mixture to give crystals suitable for X-Ray diffraction (see appendix 7 for structure); mp. (dec) 204-206 °C; ν_{max} 1597 (w), 1529 (s), 1491 (m, C=N). 1468 (m), 1406 (m), 1373 (s), 1322 (s), 1292 (s), 1250 (w), 1218 (w), 1197 (w, -SO_2), 1155 (s), 1080 (m), 1048 (s), 1016 (m); FAB *m/z* 625.4 (M^+, 62), 518.3 (5), 470.3 (25), 364.2 (12), 325.2 (25).

Chapter 4

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Chapter 4: References

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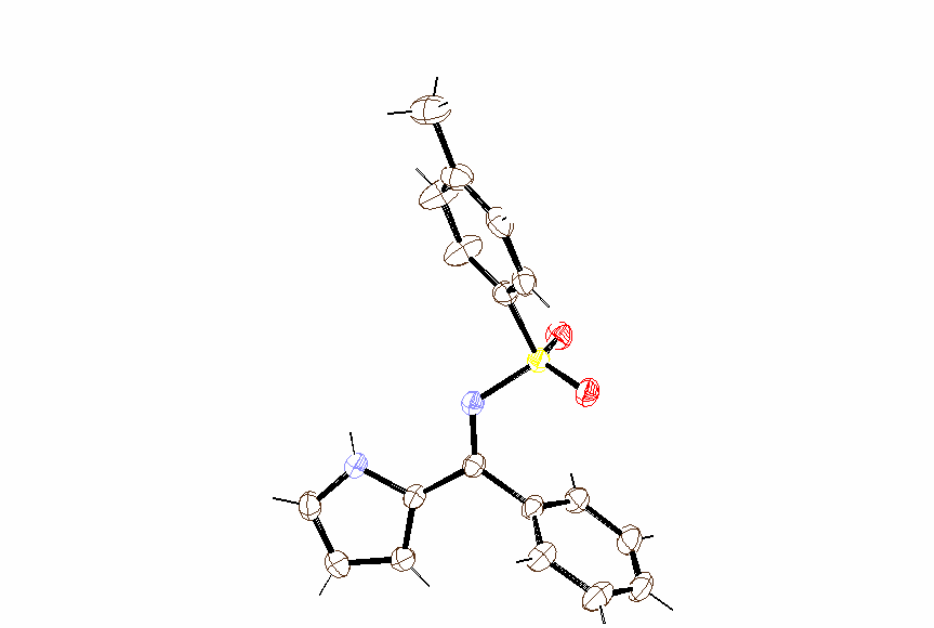
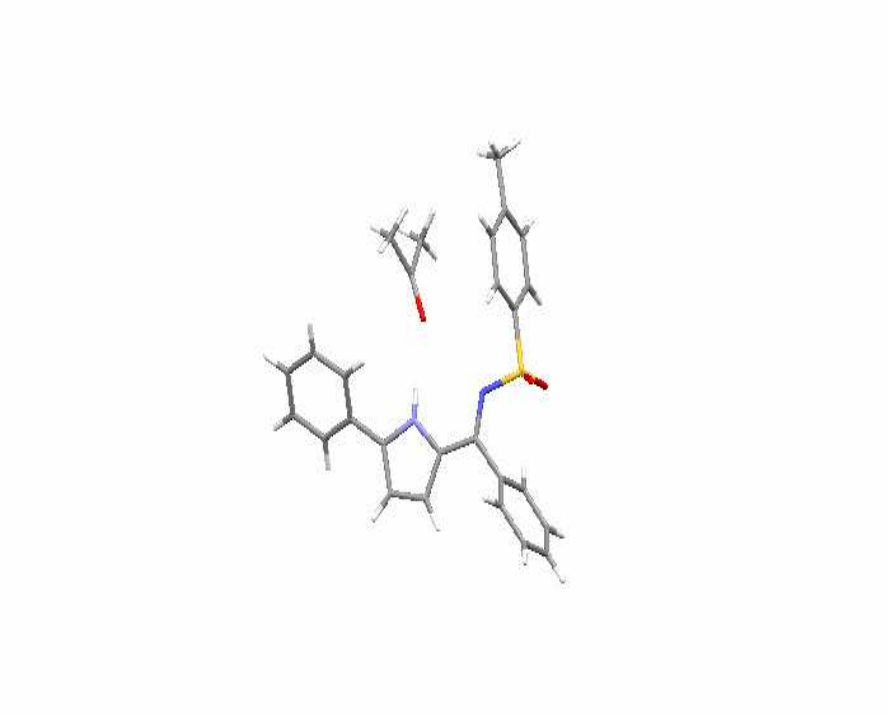
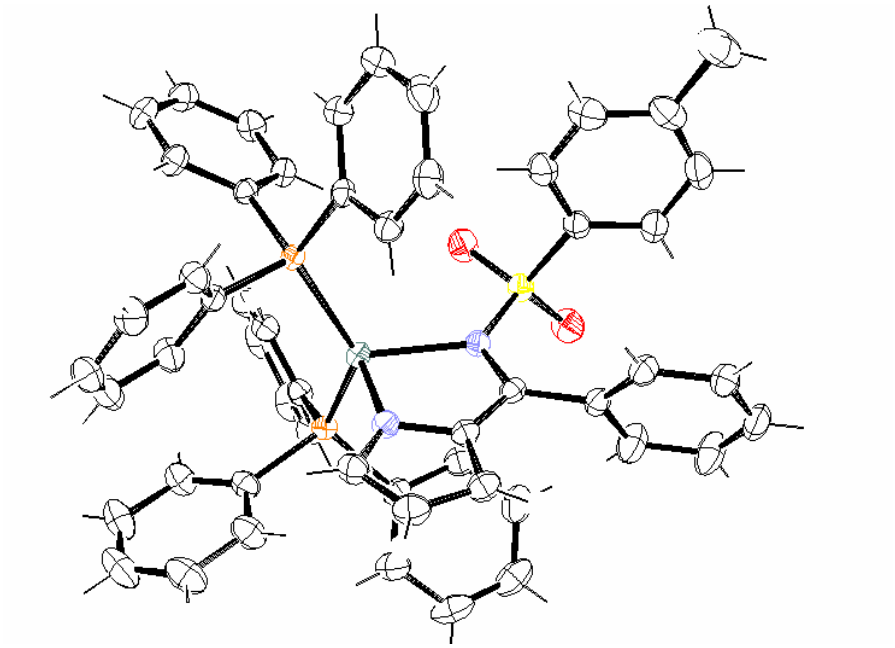
Appendices



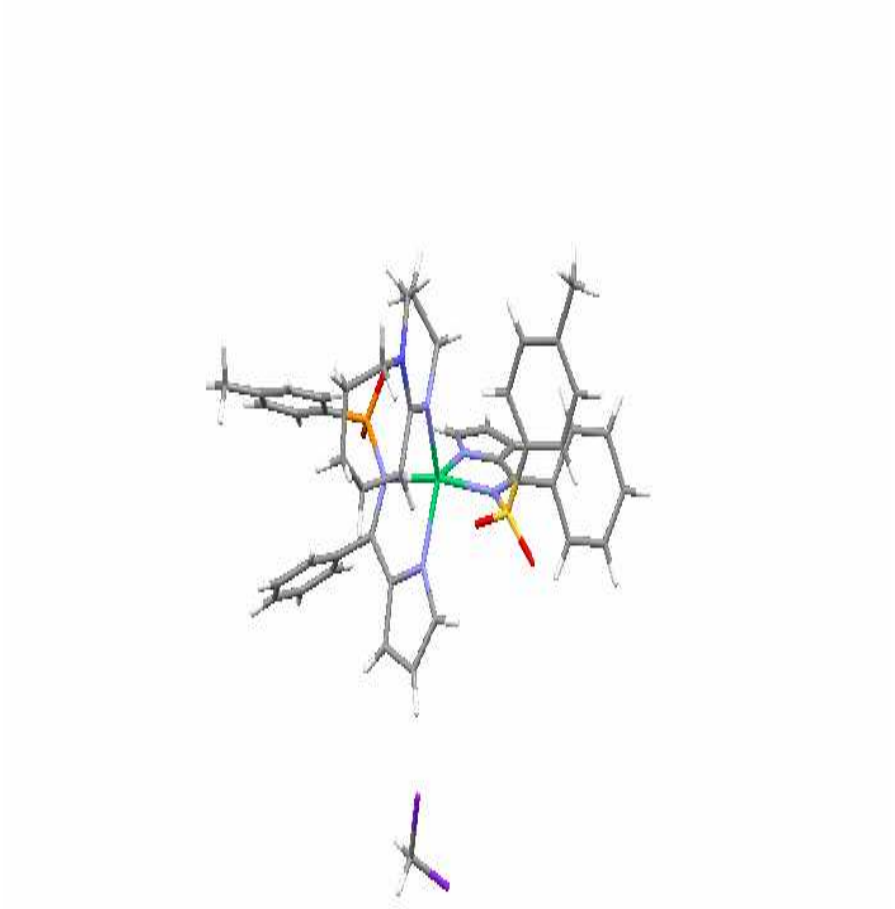
Appendix 1; Crystal structure of sulfonylimine **15**



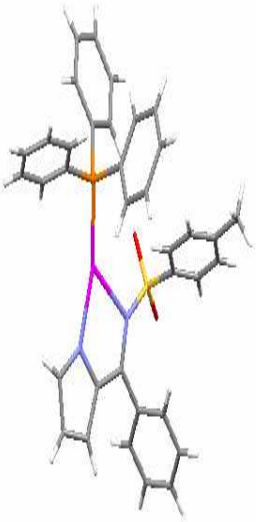
Appendix 2; Crystal structure of sulfonylimine **29**



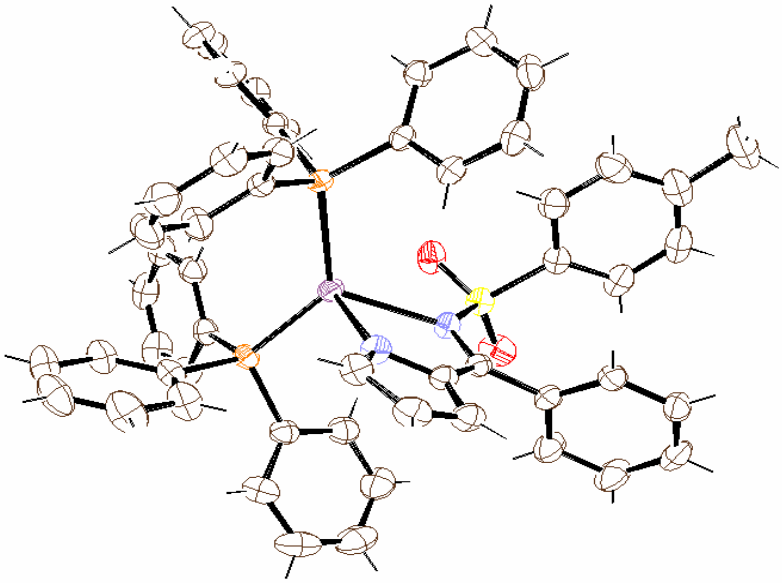
Appendix 3; Crystal structure of copper (I) complex **31**



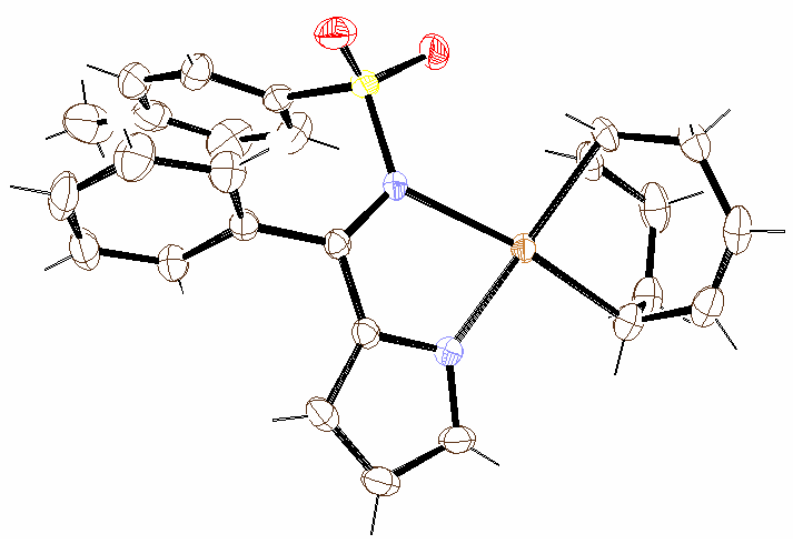
Appendix 4; Crystal structure of cobalt complex **32**



Appendix 5; Crystal structure of silver complex **35**



Appendix 6; Crystal structure of silver complex **17**



Appendix 7; Crystal structure of platinum complex **38**