UNIVERSITY OF ZULULAND

SYNTHESIS AND CATALYTIC EVALUATION OF CHIRAL FERROCENYL P^P AND P^N PALLADIUM(II) COMPLEXES

By

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201000941

Submitted to the

Faculty of Science and Agriculture

in fulfilment of the requirements for the degree of

Master of Science

in the

Department of Chemistry

at the

University of Zululand

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November 2013

DECLARATION

I, Siphamandla Cecil Masikane, declare that the work presented in this Masters degree is, to the best of my knowledge, my own work. It has not been submitted to any academic institutions for a degree award. Sources of information used have been acknowledged using appropriate referencing methods.

Signature: …….

ACKNOWLEDGEMENTS

My sincere gratitude goes to my supervisors, Dr. Tebogo Segapelo and Prof. Neerish Revaprasadu, for granting me the opportunity to further my studies in the research work hereby presented in this dissertation. Many thanks for their guidance, support and encouragement.

The financial support received from the National Research Foundation and the host, University of Zululand, has played a vital role towards completion of this project, and for that I am humbly grateful.

Special thanks go to the NMR spectroscopy technician at the University of KwaZulu Natal (Westville Campus), Dilip Jagjivan, for the analyses. I would also like to acknowledge the mass spectrometry unit at the University of Stellenbosch for the Gas Chromatography analyses.

Fellow research students and the staff members in the Department of Chemistry at the University of Zululand KwaDlangezwa Campus are also acknowledged for their academic and moral support.

Lastly, my profound appreciation goes to my parents, Mr. Thulasizwe Masikane and Mrs Jabulile Masikane, and also my brothers, Ntuthuko, Muziwenhlanhla and Philani. I would not have made it thus far without your encouragement, endless love and full. This dissertation is dedicated to you.

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List of abbreviations

THF	Tetrahydrofuran
DCM	Dichloromethane (CH_2Cl_2)
pz	Pyrazolyl
Cp	Cyclopentadienyl
Me	Methyl
Ph	Phenyl
*t*Bu	Tertiary butyl
Li	Lithium
RT	Room temperature
°C	Degrees Celsius
min	Minutes
h	Hour/s
FT-IR	Fourier Transform Infrared
^{1}H NMR	Proton Nuclear Magnetic Resonance
^{31}P NMR	Phosphorus Nuclear Magnetic Resonance
GC	Gas chromatography
MS	Mass spectrometry
FID	Flame ionisation detector
MSD	Mass selective detector
ESI	Electron spray ionisation
cm^{-1}	Reciprocal centimetre

s	Singlet
d	Doublet
t	Triplet
q	Quartet
m	Multiplet
J	Coupling constant
Hz	Hertz
mol	Mole
g	Gram
mg	Microgram
mL	Millilitre
M	Molar
eq.	equivalents
TON	Turnover number

List of formulas

$MgSO_4$	Magnesium sulphate
$PdCl_2$	Palladium(II) dichloride
$PdCl_2(NCMe)_2$	Palladium(II) dichloride acetonitrile
nBuLi	Butyl lithium
$ClPPh_2$	Chlorodiphenylphosphine
$AlCl_3$	Aluminium chloride
AcCl	Acetyl chloride
AcOH	Acetic acid
$tBuO^-K^+$	Potassium tertiary butoxide
HBF_4	Tetrafluoroboric acid
$SOCl_2$	Thionyl chloride
NaOH	Sodium hydroxide
Et_3N	Triethylamine
$LiPPh_2$	Lithium diphenylphosphine

ABSTRACT

Chapter 2 outlines initial attempts made to synthesize analogues of the P,N-type chiral ligands (η^5-C_5H_5)Fe(η^5-C_5H_3-PPh_2)C*H(OH)(3,5-R_2pz) R = H **SPNa** and R = Me **SPNb** first prepared by Togni, and the P,P-type chiral ligands (η^5-C_5H_5)Fe(η^5-C_5H_3-PR_2)C*H(OH)(PPh_2) R = Ph **SPPa**, R = *i*-Pr **SPPb** of the Josiphos family. In these ligands, the methyl group on the stereogenic carbon is replaced with a hydroxyl group.

The preparation of **SPNa** and **SPNb** included the use of the scaffolds (η^5-C_5H_5)Fe(η^5-C_5H_4)(CO)(3,5-R_2pz) R = H **3a** and R = Me **3b** which were prepared from the reaction of ferrocenoyl chloride with appropriate pyrazolyl moieties. It was unfortunately discovered that neither **3a** nor **3b** could be reduced to the corresponding alcohol derivatives (η^5-C_5H_5)Fe(η^5-C_5H_4C*H(OH)(3,5-R_2pz) R = H **3-OHa** and R = Me **3-OHb** which were the required intermediates towards the preparation of **SPNa** and **SPNb**.

The preparation of **SPPa** and **SPPb** used the scaffold (η^5-C_5H_5)Fe(η^5-C_5H_4)(CO)(PPh_2) **4** which was prepared similarly to ligands **3a** and **3b** using lithium diphenylphosphine. Disappointingly, scaffold **4** was obtained in yields less than 10%. Furthermore, it could also not be reduced to the required intermediate (η^5-C_5H_5)Fe(η^5-C_5H_4)C*H(OH)(PPh_2) **4-OH** as it was the case for **3a** and **3b**.

The alternative scaffolds (η^5-C_5H_5)Fe(η^5-C_5H_4-COMe) **5** and (η^5-C_5H_5)Fe(η^5-C_5H_4-PPh_2) **7** were then synthesized. Compound **5** could be reduced to (η^5-C_5H_5)Fe(η^5-C_5H_4) C*H(OH)(Me) **5-OH** which was subsequently used to prepare the ligand intermediates (η^5-C_5H_5)Fe(η^5-C_5H_4)C*H(3,5-R_2pz)(Me) where R = H **6a** and R = Me **6b** by a substitution reaction with appropriate pyrazolyl moieties. The lithiatiation of **6b** followed by the reaction with chlorodiphenylphosphine yielded the chiral ligand (η^5-C_5H_5)Fe(η^5-C_5H_3-PPh_2)C*H(3,5-Me_2pz)(Me) **LPNb**.

Friedel-Crafts acetylation of **7** with acetyl chloride afforded a heteroannular intermediate (η^5-C_5H_4-PPh_2)Fe(η^5-C_5H_4-COMe) **8** instead of the desired homoannular intermediate.

* This indicates that the carbon atom is a chiral centre.

This intermediate could be reduced to (η^5-C_5H_4-PPh_2)Fe(η^5-C_5H_4)C*H(OH)(Me) **8-OH** which was then used as a starting material in the attempts to synthesize heteroannulated analogues of the alternative P,N and P,P-type ligands proposed previously. Decomposed products were obtained when substitutions with pyrazolyl and diphenylphosphino moieties were attempted. Palladium(II) complexes of the ligands **6a**, **6b** and **LPNb** were then prepared using $PdCl_2(NCMe)_2$ as the metal precursor, while the one for **7** was prepared using $PdCl_2$ as the metal precursor.

In Chapter 3, the prepared complexes [$PdCl_2${(η^5-C_5H_5)Fe(η^5-C_5H_4)C*H(3,5-R_2pz)(Me)}$_2$] R = H **CNa** and R = Me **CNb**, [$PdCl_2$(η^5-C_5H_5)Fe(η^5-C_5H_3- PPh_2)C*H(3,5-Me_2pz)(Me)] **CPNb** and **[**$PdCl_2${(η^5-C_5H_5)Fe(η^5-C_5H_4-PPh_2)}$_2$] **CP1** were catalytically evaluated in a Suzuki-Miyaura coupling reaction of phenylboronic acid with iodobenzene to obtain biphenyl as the product. Interestingly, **CNb** could catalyse this reaction to give yields of at least 50% at 30 °C. However, the best yields were obtained when the temperature is doubled, using 2 M sodium hydroxide as the base in tetrahydrofuran. From the tested complexes, **CNa** and **CP1** gave maximum conversions of over 90%, although the former achieved these conversions in half the time.

CHAPTER 1

THE CHEMISTRY OF PHOSPHINE COMPOUNDS AND THEIR USE IN COUPLING REACTIONS: A LITERATURE REVIEW

Introduction

1.1 Phosphine compounds: an overview

Phosphines fall under the organophosphorus group of the chemical formula, PR_3, where R groups are organic substituents, Figure 1.1. The earliest form of phosphine is PH_3, it was once mistaken for being a gaseous form of phosphorus element until in 1789 when Lavoisier showed that it is actually a compound.[1] The first PH_3 complex was made by Fischer *et al*.[2] However, it was observed that PH_3 has problems associated with high toxicity, flammability and low affinity towards transition metal compounds.[3]

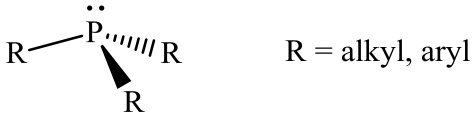


Figure 1.1: Compound structure of organophosphorus group, phosphine.

The chemical behaviour of phosphines enables them to be used as both reagents in chemical reactions as well as ligands in complexes. Their use as successful ligands dates back to the 1960's on the work that was done by Wilkinson *et al.*[4] What makes phosphines interesting is the lone pair of electrons of phosphorus which is readily available for co-ordination with metal centres.

Phosphines exhibit both σ-donor and π-acceptor character. They are usually stronger σ-donors and weaker π-acceptors; and this effect can be boosted by using R groups which are electron-donating or suppressed by using R groups which are electron-withdrawing. However, it is this π-acceptor character (*i.e.* dπ-σ* back-bonding of the soft phosphorus

[1] A.L. de Lavoisier, *Traité élémentaire de Chimie, présenté dans un ordre nouveau, et d'aprè les découvertes moderns,* Cuchet, Paris, **1789**.
[2] E.O. Fischer, E. Louis, W. Bathelt, E. Moser, J. Müller, *J. Organomet. Chem.* 14 (**1968**) P9.
[3] C. Dreher, M. Zabel, M. Bodensteiner, M. Scheer, *Organometallics* 29 (**2010**) 5187.
[4] J.A. Osborn, F.H. Jardine, J.F. Young, G. Wilkinson, *J. Chem. Soc.* A (**1966**) 1711.

donor atom) which plays a role or makes it possible for these ligands to stabilise metal centres of low oxidation states in a complex.[5]

Not only can phosphine ligands can be utilised for manipulation of the electronic properties of the co-ordination compound (complex), but also their steric properties can be turned to influence the alkalinity. Phosphines are prone to oxidation because they are nucleophilic in nature. They also behave as bases, their base strength seems to trail along the trend: $PR_3 > HPR_2 > H_2PR > H_3P$ (tertiary alkyl substituted phosphine > secondary alkyl substituted phosphine > primary alky substituted phosphine > phosphine); as a result of the magnitude and nature of the alkyl R groups. An increase in bulkiness (measured by the cone angle, θ) of the phosphine ligand results in an increase in degree of dissociation, Figure 1.2; this is one of the requirements responsible for the acceleration of the *oxidative addition* step which is a key-step in most catalytic cycles.

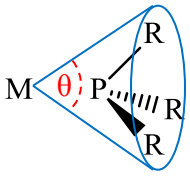


Figure 1.2: Cone angle measurements on phosphine complexes.[6]

Phosphines can be synthesised to serve a specific role or function of choice. They can be modified into ligands that can assume different types of coordination modes with transition metals, Figure 1.3.

[5] (a) Z. Freixa, P.W.N.M. van Leeuwen, *Dalton Trans.* (**2003**) 1890. (b) L. Mahalakshmi, D. Stalke, *Struct. Bond.* 103 (**2002**) 88.
[6] C.A. Tolman, *Chem. Rev.* 77 (**1977**) 313.

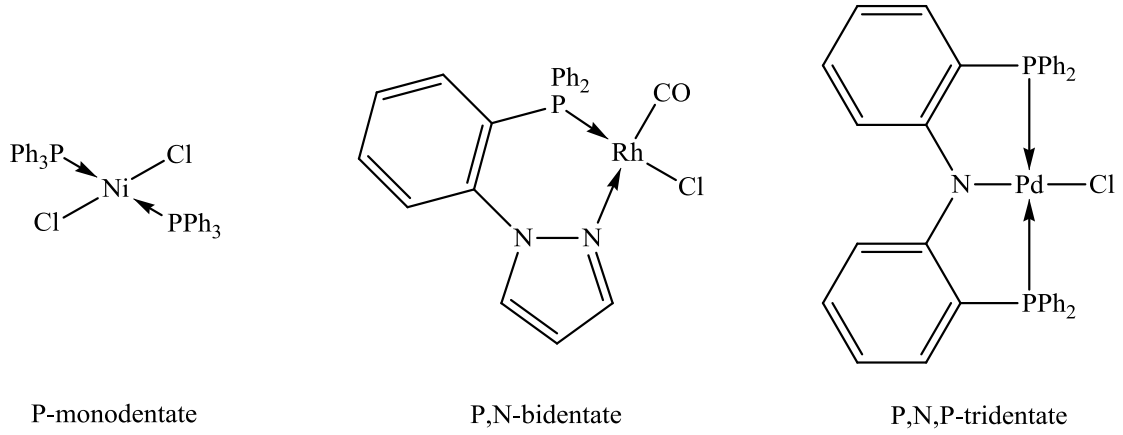


Figure 1.3: Structure of phosphine ligands with different coordination modes

Introducing other properties such as chirality on phosphine ligands broadens the scope of their applications; (*S*)-ethyl-2-[bis(diphenylphosphino)amino]propanoate (*s-alap*) prepared by Payne *et al.*[7] has a *chiral* centre directly bonded to the nitrogen donor atom, Figure 1.4. Chirality on this ligand enabled the corresponding metal complex (catalyst) to be identified as a suitable candidate in asymmetric reactions.

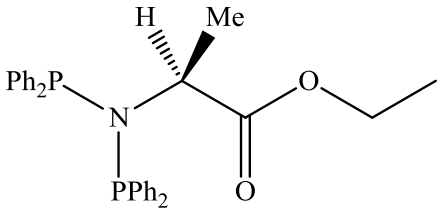
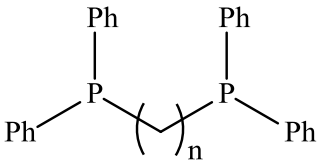
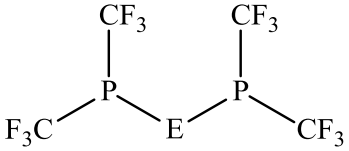


Figure 1.4: Chemical structure of s-alap

The common phosphine ligands are those containing carbon backbones, and have been synthesised and utilised in a range of reactions. However, over the years, these backbones have been modified to incorporate other groups or heteroatoms, Figure 1.5. Such groups or heteroatoms are either bonded directly to the phosphorus atom or to alkyl substituents on the phosphorus atom.

[7] N.C. Payne, D.W. Stephan, *J. Organomet. Chem.* 221 (**1981**) 203.





n = 1, Bis-diphenylphosphino methane (dppm)
n = 2, 1,2-Bis-diphenylphosphino ethane (dppe)
n = 3, 1,3-Bis-diphenylphosphino propane (dppp)

E = O, S or Se

Figure 1.5: Chemical structure of a heteroatom bridged phosphine.

Different backbones bring about significant electronic and characteristic influence on the function and stability of the complex when used as a catalyst. The most common heteroatom backbones and bridges are those containing nitrogen (N), oxygen (O), sulfur (S) and selenium (Se). The effects of these heteroatoms and bridges on the coordination chemistry and reactivity of their complexes has been studied. [8]

Phosphine ligands have been successfully synthesised and used for more than four decades, and are still being used in many reactions. The progress made in developing new phosphine ligands has increased dramatically since then. Despite the astonishing properties and characteristics of the vast number of phosphine ligands; their synthesis can be, however, carried out with ease or difficulty depending on the method of preparation.

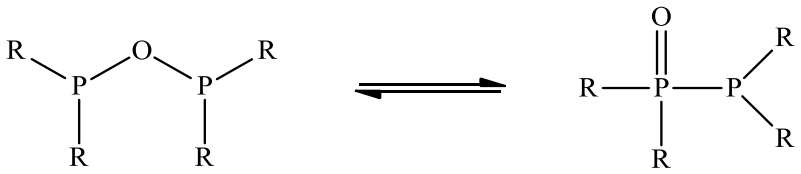
1.1.1 Advantages and problems encountered in preparing phosphine ligands

There are known issues pertaining to the preparation of phosphines and related compounds. The most encountered problem is their stability which would require the use of glove boxes in reactions to avoid high amounts of oxidized product as well as specialised storage techniques. There is also an issue with costly reaction protocols which tend to be time consuming and consequently result to yields of the expected products when proper precautions are ignored. This seriously affects the use of such compounds as

[8] (a) For N: D.S. Payne, A.P. Walker, *J. Chem. Soc.* Sect. C (**1966**) 498. (b) For O: T. Appleby, J. D. Woollins, *Coord. Chem. Rev.* 235 (**2002**) 125. (c) For S and Se: A. Burg, K. Gosling, *J. Am. Chem. Soc.* 87 (**1965**) 2113.

ligands for industrial applications because up-scaling then becomes a problem. There are also other sophisticated problems that are unique to different synthetic routes; like the problem of racemisation which occurs during attack by $LiPR_2$ in synthesis of aromatic aliphatic chiral phosphines.[9]

Another common problem in phosphine ligands which are anchored on backbones containing other heteroatoms is the Michaelis-Arbuzov rearrangement[10], Scheme 1.1, and also disproportionation of the phosphine ligands which renders them unstable, this is common in phosphine ligands containing S, Se and O backbones.



Scheme 1.1: Michaelis-Arbuzov rearrangement on disphosphine ligands with O-backbone.

Other complex challenges are side-reactions that produce undesirable by-products together with targeted ligands. This results in difficulties when the pure ligands have to be isolated from the mixture. For phosphine ligands that will be used in catalysis, it is of crucial importance that the solvents (chemicals) used in preparing them are dry, as the vapour or water molecules could compromise the efficiency and activity of the compounds when used as catalysts.

[9] J.M. Longmire, X. Zhang, *Tetrahedron Lett*. 38 (**1997**) 1725.
[10] (a) A. Arbuzov, J. Russ, *Phys. Chem. Soc*. 38 (**1906**) 687. (b) A. Arbuzov, *Chem. Zentr*. *II* (**1906**) 1693.

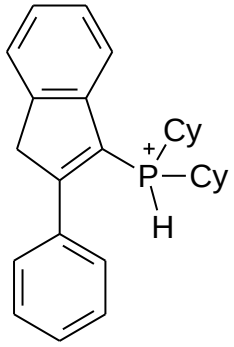


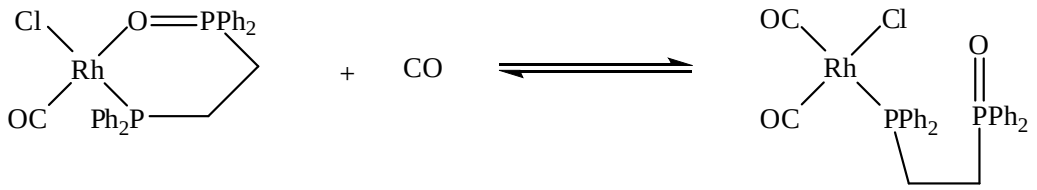
Figure 1.6: Structure of 2-phenylindene phosphonium salt

Amongst the many applications in which phosphine ligands are used, homogeneous catalysis stands out as one area where they have been extensively utilised.[11] For this purpose, phosphine ligands can easily be tailored to be soluble in either organic or aqueous media, by functionalising them with appropriate groups as indicated earlier. This is quite useful as it might be useful at recovering the phosphine ligand-bearing catalyst where organic compounds are the products. Some phosphine ligands can be converted to salts. For example, 2-phenylindene phosphonium salt has been shown to be air and moisture stable as a salt and can be stored over long periods, Figure 1.6.[12]

1.1.2 Preparations of phosphine ligands bearing other donor atoms

As mentioned earlier, the most common donor atoms incorporated with phosphines are N, S and Se. These atoms on the phosphine ligands may be attached on the phosphorus or to the alky group which is directly bonded to the phosphorus. These kinds of ligands can be synthesized with existing methods of synthesis: ordinary chemical reaction, condensation, metathesis, etc.

[11] (a) P. Espinet, K. Soulantica, *Coord. Chem.. Rev*. 193-195 (**1999**) 541-551; (b) A. Fihri, P. Meunier, J. Hierso, *Coord. Chem. Rev*. 251 (**2007**) 2023-2053
[12] M.R. Netherton, G.F. Fu, *Org. Lett.* 3 (**2001**) 4295



Scheme 1.2: Hemilabile behaviour of P,O donor ligand**.**

Incorporating phosphine ligands with other donor atoms which are comparatively softer (e.g. O, S, Se) than phosphorus atom, automatically renders the ligand to be hemilabile as the bonding abilities of the metal-phosphorus and metal-less softer donor atoms are quite different. This difference in bonding makes it possible for the ligand in the metal complex to create/generate "vacant site" at the metal centre; which is of crucial importance in catalytic reactions. An example of such a phenomenon is depicted in Scheme 1.2.[13] Since O is a "hard" donor, the resulting metal-oxygen bond is weak and prone to dissociation due to absence of dπ-back bonding in comparison to a metal-phosphorus bond.

1.1.3 Preparation of phosphine bearing metal complexes

Metal complexes may be used for various purposes which may range from clinical use to industrial use.[14] As already mentioned, ligands play a crucial role in fine-tuning the metal centre for a specific task; *i.e.* the activity of the metal centre (due to its vacant sites) depends on the electronic effects (bonding character) brought about by the ligands. Physical properties such as steric effects of the ligands should also not be ignored, as they enhance the reactivity of the complex by varying the "bite-angle" and also the dissociation rate (*i.e.* the larger the phosphine ligand, the faster the dissociation rate, the

[13] D.K. Dutta, B. Deb, *Coord. Chem. Rev*. 255 (2011) 1689.

[14] (a) P.C.A Bruijnincx, P.J. Sadler, *Chem. Biol*. 12 (**2008**) 197; (b) Y. Tong, J.J.R. F. Silva, A.J.L. Pombeiro, G.Wagner, R. Herrmann, *J. Organomet. Chem*. 552 (**1998**) 17; (c) H. Bjelosevic, C. Spégel, Å.S. Snygg, L. Gorton, S.K.C. Elmroth, T. Persson, *Tetrahedron* 62 (**2006**) 4519.

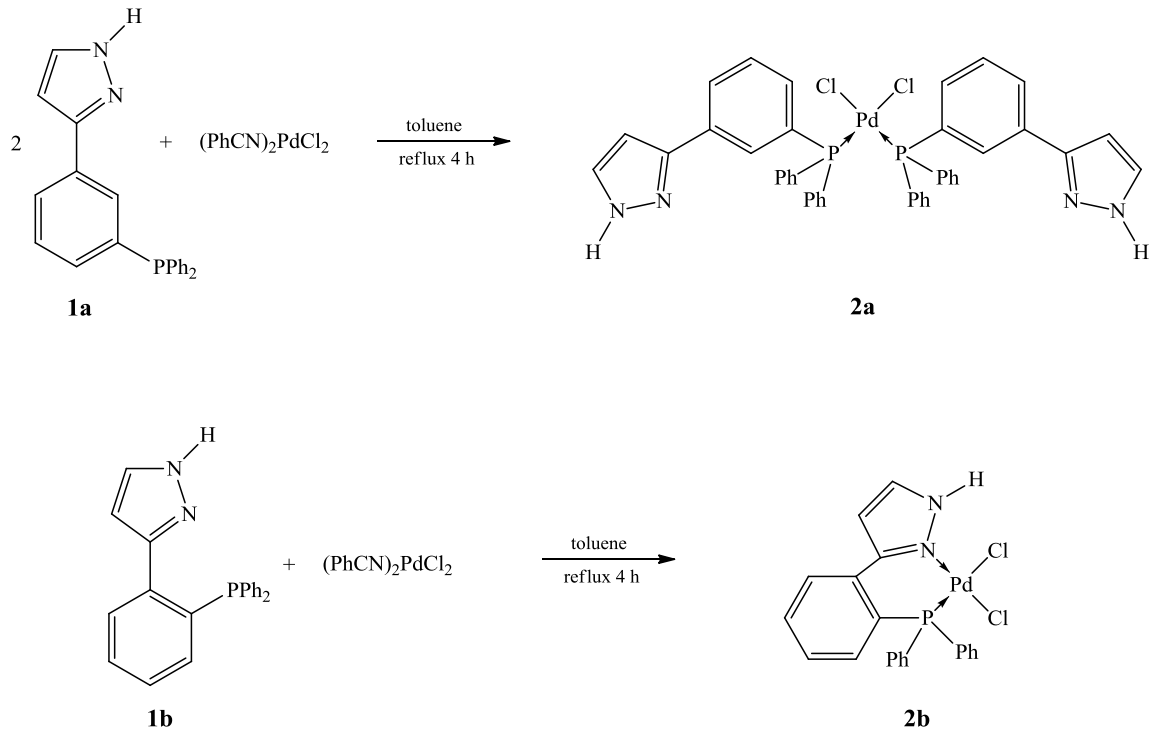
more reactive the complex).[15] The metal centre also plays a crucial role as it influences the configuration/geometry of the resulting complex.

Metal complexes bearing phosphine ligands have received a lot of attention in catalysis and medicinal research sector, due to their remarkable properties. As a result, there are certain specifications required for such complexes, these include solubility in polar and ionic solvents as well as lability in biological media, stability and flexibility of the activated complex enhanced by its ligands in catalytic reactions. This is the reason why phosphine ligands have been used as reliable candidates to tune the complex to match the requirements above. It should also be noted that factors such as choice of starting materials, solvent media and reaction conditions affect the metal complex formed.

1.1.3.1 Nature of phosphine ligands and the types of metals used on complexations.

In the work done by Y. Sun *et al.*[16] revealed that the regioisomers of the ligands (**1a** and **1b**) below yielded different complexes when reacted with $[(PhCN)_2PdCl_2]$, under similar reaction conditions, Scheme 1.3. The products **2a** and **2b** precipitated as yellow crystalline solids; with comparable yields of 71% and 73%, respectively. Both complexes have a square planar configuration as expected from a d^8 metal ion. This work showed how what the nature of ligands and atoms responsible for coordination can influence the complexes produced.

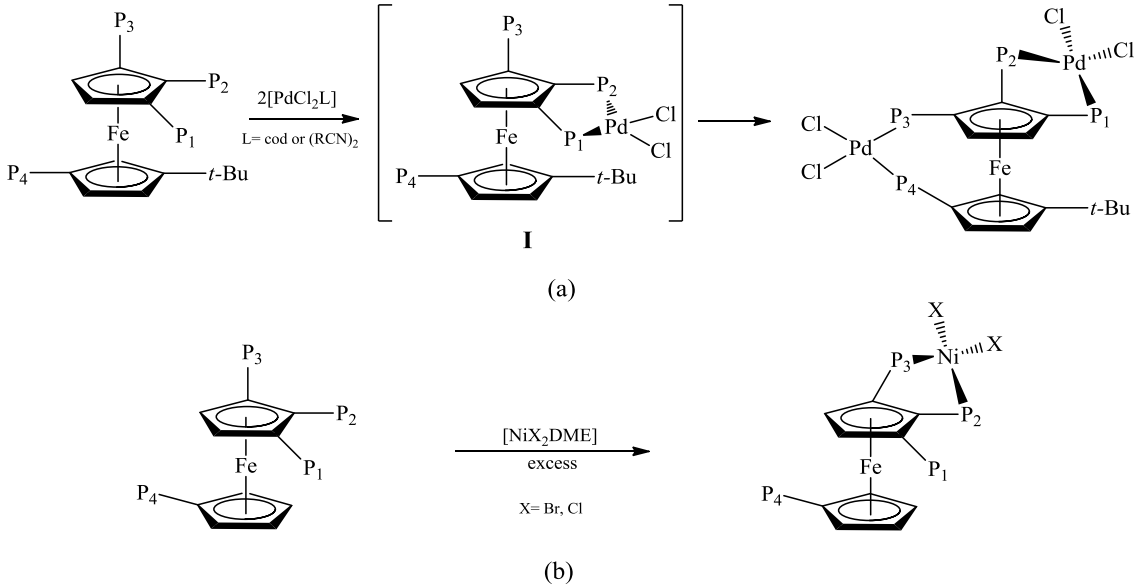
[15] (a) M.-N. Birkholz (née Gensow), Z. Freixa, P.W.N.M. van Leeuwen, *Chem. Soc. Rev.* 38 (**2009**) 1099. (b) C.A. Christoph, H. Plenio, *Chem. Soc. Rev.* 39 (**2010**) 694. (c) L. Xue, Z. Lin, *Chem. Soc. Rev.* 39 (**2010**) 1692.
[16] Y. Sun, A. Hienzsch, J. Grasser, E. Herdtweck, W. R. Thiel, *J. Organomet. Chem.* 691 (**2006**) 294.



Scheme 1.3: Synthesis of Pd complexes using isomers under similar reaction conditions

The following examples showcase how a substituent on the ligand backbone can influence the type of complex formed. Based on their study on synthesis of the Pd and Ni complexes (Scheme 1.4 (a) and (b), respectively), D.A. Thomas *et al.*[17] observed that the formation of a dinuclear metal complex from two equivalents of Pd metal source was due to steric hindrance at complex **I**; as a result of the presence of the bulky group (*t*-Bu). However, in the Ni complex, even when the excess of Ni metal was used, the formation of a mononuclear metal complex still formed due to an absence of the *t*-Bu group that assists in locking the Cp rings in place to favour dinuclear metal complex formation. Thus the nature of a ligand plays a major role in orientation and coordination modes of the resulting complexes.

[17] D.A. Thomas, V.V. Ivanov, I.R. Butler, P.N. Horton, P. Meunier, J.C. Hierso, *Inorg. Chem*. 47 (**2008**) 1607.



Scheme 1.4: Synthesis of (a) dinuclear Pd and (b) mononuclear Ni complexes

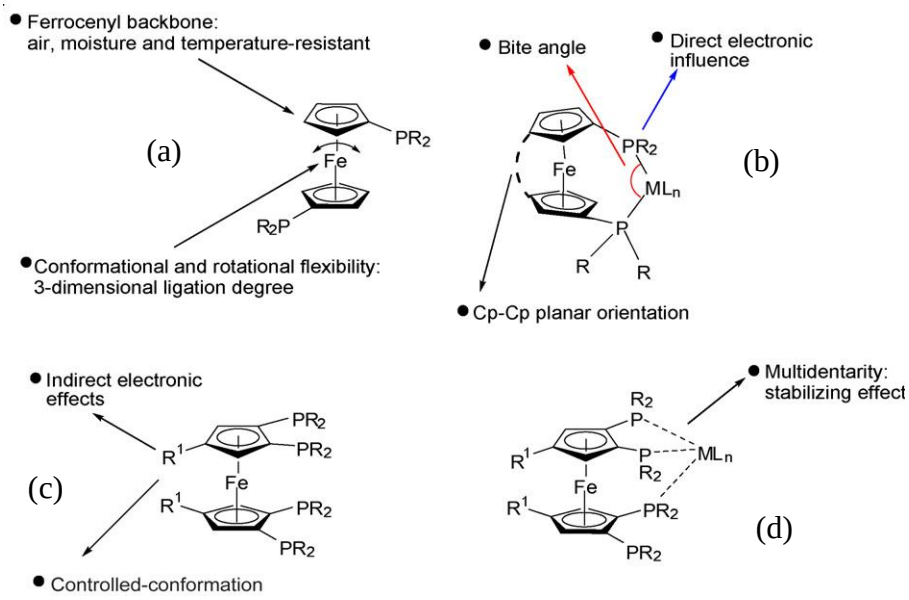
1.1.3.2 Advantages and disadvantages of using such metal complexes in organic transformations

The degree of reactivity and rate of performance of the metal complexes are greatly influenced by both the physical and properties of the ligands incorporated in them.[15] In this regard, ferrocenylphosphine ligands have mostly been exploited in the preparation of most of these metal complexes, due to their flexible physical and electronic properties which can be tuned, depending on their applications.

Of utmost importance, is that all the physical properties that exist on such complexes are interrelated (*i.e.* greatly affect each other which in turn render the complex to behave in a specific manner). In ferrocenyl derivatives, these physical features are: bite angle, conformational and rotational flexibility, orientation of the cyclopentadienyl (Cp) rings, direct and indirect electronic effects by functional groups as well as the denticity of the complex.

One advantage of such complexes is the bite angle (an angle made by a metal centre and adjacent phosphorus atoms). The bite angle on these complexes can be easily

manipulated by various ways, in order to either enhance or inhibit the reactivity in catalytic reactions. Heyashi *et al.*[18] discovered experimentally that an increase in bite angle resulted in an increase in activity and reactivity; based on their Kumada coupling reactions of *sec*-butyl magnesium chloride with bromobenzene using [$PdCl_2(PPh_3)_2$], [$PdCl_2$(dppe)], [$PdCl_2$(dppp)] and [$PdCl_2$(dppf)] where ligand dppf-complex had a large P-Pd-P bite angle. Dierkes and van Leeuwen[19] later revealed that the bite angle is related to the rate of specific reactions; they discovered that smaller bite angles favour oxidative addition because of an increase in electron density on the metal centre, whilst larger bite angles favour reductive elimination because of a decrease in electron density on the metal centre.[20] In this way, it is evident that it is possible to manipulate the reaction to a specific route; but also to the end product of choice. Bite angle can be increased by opening the torsion angle (an angle between two planes, where Cp rings lie) along the Cp-Fe-Cp axis, by means of rotational flexibility, Scheme 1.5 (a). Another successful approach would be opening the angle between the Cp ring planes, by means of Cp-Cp plane orientation, Scheme 1.5 (b).

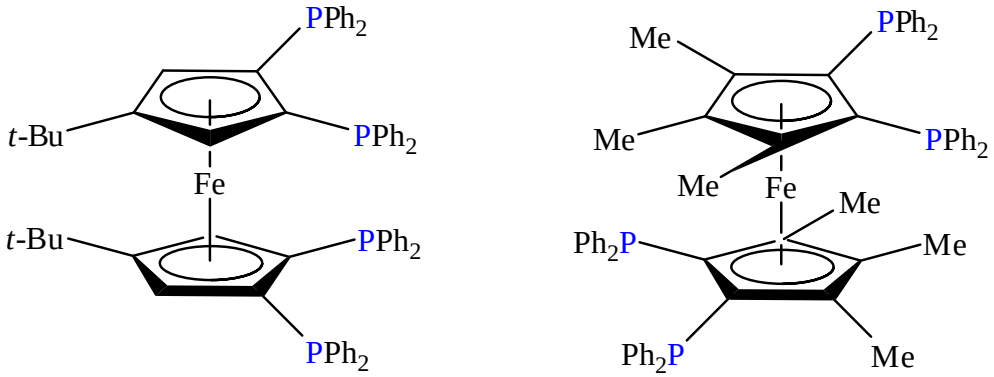


Scheme 1.5: Factors affecting activity and efficiency of ferrocenylphosphine ligands-containing complexes**.**

[18] T. Heyashi, M. Konishi, Y. Korobi, M. Kumada, T. Higuchi, K. Hirotsu, *J. Am. Chem. Soc*. 106 (**1984**) 158.
[19] P. Dierkes, P.W.N.M. van Leeuwen, *J. Chem. Soc. Dalton Trans.* (**1999**) 1519.
[20] C. Amatore, G. Broeker, A. Jutand, F. Khalil, *J. Am. Chem. Soc*. 119 (**1997**) 5176.

Another advantage in using such complexes is the indirect electronic influence of the substituents attached on the Cp ring, Scheme 1.5 (c), and a direct electronic influence of the substituents on the phosphorus, Scheme 1.5 (b); which stabilises the metal centre at low oxidation states; which fluctuate throughout the three fundamental catalytic step cycles (oxidative addition, transmetalation and reductive elimination).[21]

The ferrocenyl backbone itself contributes to the efficiency of the complex in reactions. Ferrocenyl backbone is stable in to air, moisture and can withstand high temperatures; rendering the ligand to be stable and assures that it does not disintegrate during catalytic reactions. Another interesting phenomenon on this ferrocenyl backbone is the ability to block the conformation by restricting the rotation of the Cp rings using bulky substituents directly attached to the Cp rings so as to achieve a steric barrier.[22] Blocked and unblocked conformations have different catalytic performances due to the positioning of the phosphorus donor atoms. Hierso *et al.*[23] revealed interesting experimental findings on the influence of blocked-conformation [Figure 1.7, Fc(P)$_4$^{t}Bu] on catalytic activity in a Heck and Suzuki catalytic reactions.



Fc(P)$_4$*t*-Bu Fc(P)$_4$Me

Figure 1.7: Blocked [Fc(P)$_4$*t*-Bu] and unblocked [Fc(P)$_4$Me] -conformation on typical ferrocenyl phosphine ligands.

[21] A. Fihri, P. Meunier, J.C. Hierso, *Coord. Chem. Rev*. 251 (**2007**) 2047.
[22] V.V. Ivanov, J.C. Hierso, R. Amardeil, P. Meunier, *Organometallics* 25 (**2006**) 989.
[23] J.C. Hierso, A. Fihri, R. Amardeil, P. Meunier, H. Doucet, M. Santelli, B. Donnadieu, *Organometallics* 22 (**2003**) 4490.

1.1.4 The incorporation of the ferrocene backbone

1.1.4.1 Ferrocenyl phosphine ligands

The discovery of sandwich structured ferrocene and later its derivatization during the early 1950s[24] led to a new powerful class of chiral and nonchiral organophosphine ligands which heralded a new era of organometallic chemistry.[25] The chiral ferrocenyl phosphine ligands have been successfully utilised and recognised as reliable and most efficient candidates in asymmetric catalysis (metal-catalysed organic reactions) owing to the following relevant characteristics: (i) They are usually robust, stable and isolation of their stereoisomers is often achievable without problems; (ii) They are versatile in a sense that they exist in a large number of them can be prepared by varying electronic and steric properties yet sharing the same primary structure or backbone; and (iii) They readily form complexes with different metals and oxidation states. A few industrial processes have used asymmetric catalysis in producing large quantities of optically pure products, using only minimal amounts of chiral ligands.[26]

1.1.4.1.1 Chirality in ferrocenyl phosphine ligands

Asymmetric catalysis occurs due to the transfer of chiral information from the catalyst to a prochiral substrate, yielding enantio or diastereo pure compound. There are different types of chirality that exist, arising from how they are induced on the compound as well as their structural orientation with respect to the catalyst backbone.

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[24] (a) T. J. Kelly, P. L. Pauson, *Nature* 168 (**1951**) 1039. (b) G. B. Kauffman, *J. Chem. Educ.* 60 (**1983**) 185.

[25] (a) J. W. Irvine, G. Wilkinson, *Science* 113 (**1961**) 742. (b) G. Wilkinson, J. *Organomet. Chem.* 100 (**1975**) 273.

[26] (a) J. Crosby, *Tetrahedron* 47 (**1991**) 4789. (b) S.C. Stinson, *Chem. News Eng*. 21 **(1998**) 83. (c) A. Richards, R. McCague, *Chem. Ind. June* 2 (**1997**) 422. (d) H.U. Blaser, F. Spindler, *Top. Catal*. 4 (**1997**) 275. (e) S.C. Stinson, *Chem. Eng. News* 41 (**1999**) 101. (f) S.C. Stinson, *Chem. Eng. News* 43 (**2000**) 55. (g) S.C. Stinson, *Chem. Eng. News* 40 (**2001**) 79. (h) H.U. Blaser, B. Pugin, F. Spindler, in: B. Cornils, W.A. Herrmann (Eds.), *Applied Homogeneous Catalysis by Organometallic Complexes*, VCH, Weinheim, **1996**. (i) R.A. Sheldon, *Chirotechnology*, Marcel Dekker Inc., New York, NY, **1993**. (j) A.N. Collins, G.N. Sheldrake, J. Crosby (Eds.), *Chirality in Industry*, Wiley, New York, NY, **1992**. (k) H.U. Blaser, *Chem. Commun*. (**2003**) 293.

Planar chirality[27] in a ferrocene molecule is induced by breaking its plane of symmetry by introducing two or more substituents on one Cp ring, by means of electrophilic substitution reactions. The ferrocene compound (Figure 1.8), synthesised and isolated by Thomson[28] is not only the first chiral ferrocene compound made but also the first ferrocene compound with planar chirality. An advantage associated with planar chirality is that is does not undergo racemisation.

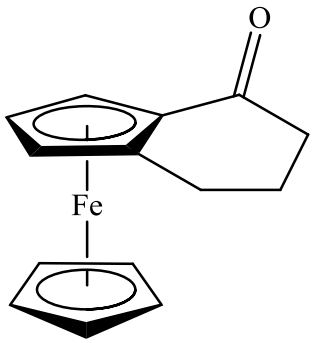
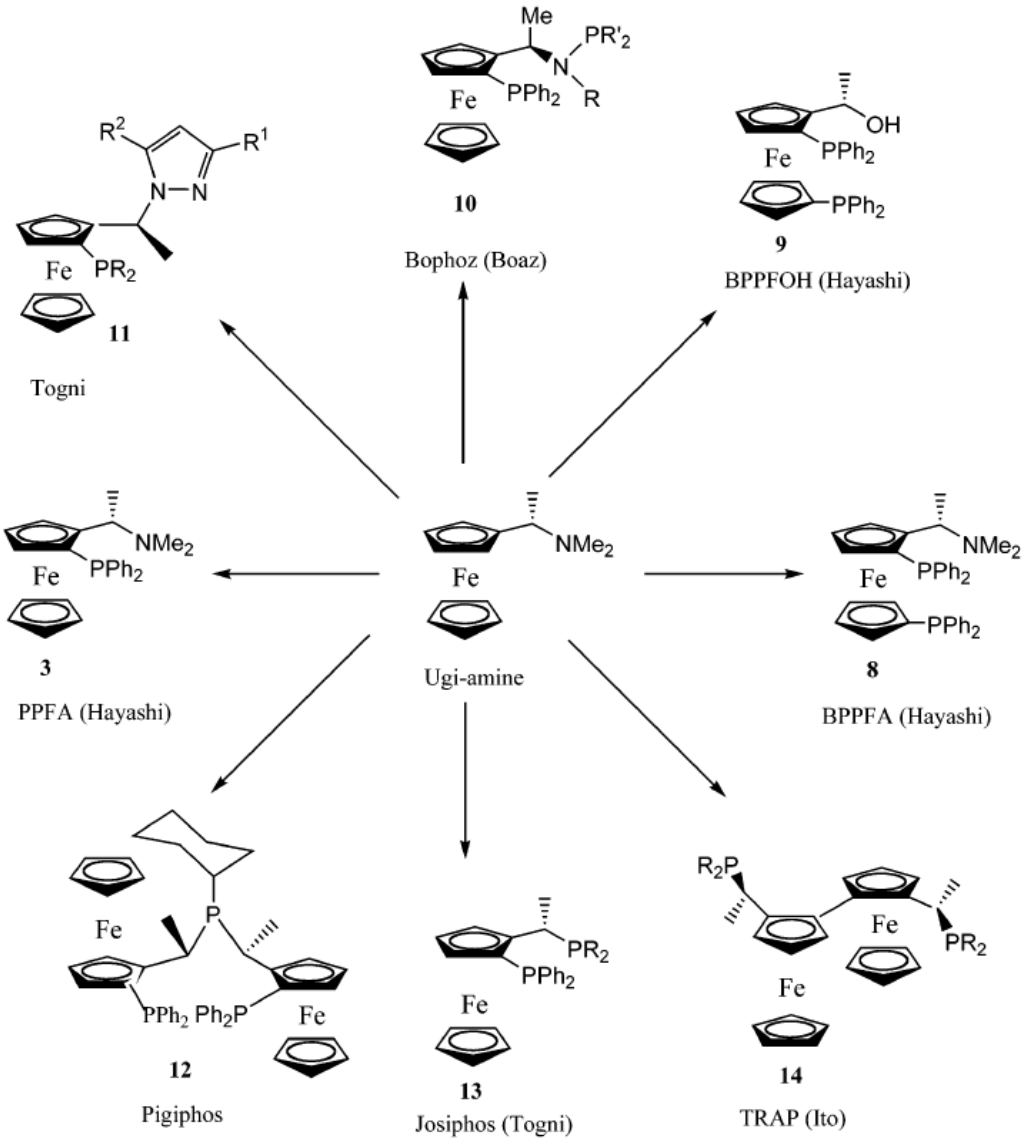


Figure 1.8: Chiral ferrocene ligand bearing *planar chirality*

Lateral/central chirality in a ferrocene compound is induced by introducing a unit which has a chiral centre, on a Cp. A classic example of this kind of chirality is an Ugi-amine compound[29] which has been used successfully as a starting material for the preparation of other chiral compounds, Scheme 1.6.

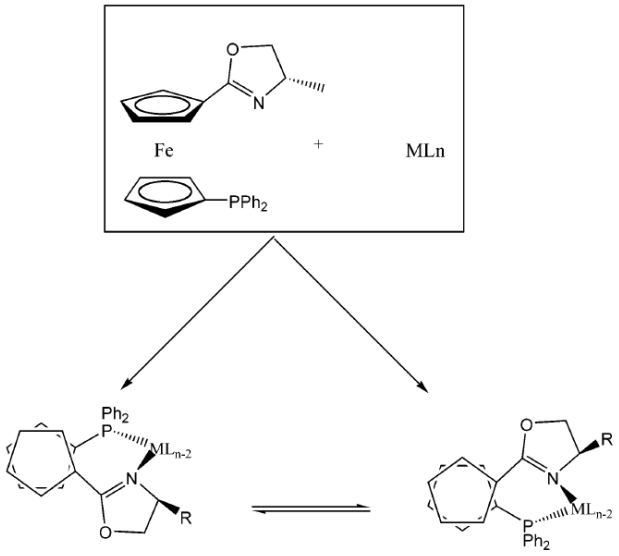
[27] R. S. Cahn, C. Ingold, V. Prelog, *Angew. Chem., Int. Ed. Engl.* 4 (**1966**) 385.
[28] J. B. Thomson, *Tetrahedron Lett.* 1 (**1959**) 26.
[29] (a) D.Marquarding, H. Klusacek, G. Gokel, P. Hoffmann, I. Ugi, *J. Am. Chem. Soc.* 92 (**1970**) 5389.
(b) G. Gokel, D. Marquarding, I. Ugi, *J. Org. Chem.* 37 (**1972**) 3052.



Scheme 1.6: Chiral ferrocenyl phosphine ligands prepared from Ugi-amine ligand.[30b]

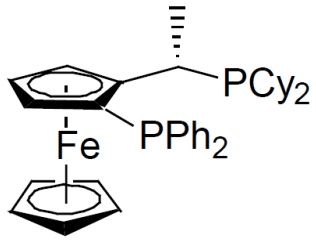
Axial chirality is a rare chirality that occurs when 1,1'-disubstituted ferrocenes coordinate to a metal to form *rotamers*, Scheme 1.7.[30]

[30] (a)W.-P. Deng, S.-L. You, L.-X. Dai, Y.-H. Yu, W. Xia, J. Sun, *J. Am. Chem. Soc.* 123 (**2001**) 6508. (b) T.J. Colacot, *Chem. Rev.* 103 (**2003**) 3101.



Scheme 1.7: Demonstration of *axial chirality* in ferrocenyl phosphine-metal complex system.[30]

There are instances where an asymmetric catalyst would contain more than one type of chirality, e.g. a Kumada and Hayashi PPFA-type ligand has both *planar* and *central chirality*, Scheme 1.6, ligand **3**. *Planar* and *central chirality* combination is very common in ferrocenyl phosphine asymmetric catalysts. However, as expected, the type of chirality influences the products. Planar chirality has, on several occasions been reported to show a significant effect on enantioselectivity.[31]



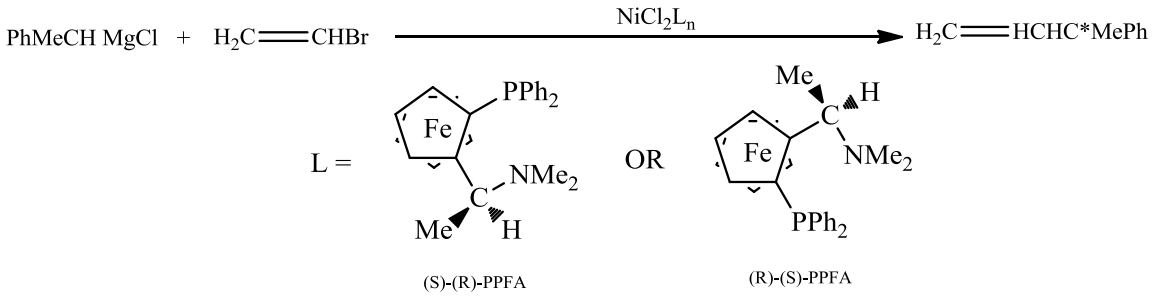
(*R*)-(*S*)-*Josiphos*

Figure 1.9: Structural representation of a *Josiphos* ligand

[31] (a) W.Zhang, T. Shimanuki, T. Kida, Y. Nakatusuji, I. Ikeda, *J. Org. Chem.* 64 (**1999**) 6247. (b) R. Shintani, M. M.-L. Lo, G. C. Fu, *Org. Lett.* 2 (**2000**) 3695. (c) O. G. Mancheño, J. Priego, S. Cabrera, R. G. Arraya´s, T. Llamas, C. Carretero, *J. Org. Chem.* 68 (**2003**) 3679

The simplest nomenclature was proposed by Schlögl[32] where the molecule is viewed from the C_5 axis (directed towards the observer) of the most substituted Cp ring. The priority in chirality nomenclature follows the trend *central* > *axial* > *planar*. An example would be a (*R*)-(*S*)-*Josipho* ligand (Figure 1.9) prepared by Togni *et al.*,[33] whereby the *R* configuration is due to decreasing priority of substituents bonded to the chiral centre, and the following *S* configuration is due to decreasing priority of substituents on the top Cp ring.

The synthesis of the first *planar* and *central chiral* ferrocenyl phosphine ligand PPFA (Scheme 1.10, ligand **3**) was reported by Hayashi and Kumada during the mid-1970s.[34] It was synthesised by diastereoselective ortho-lithiation of Ugi-amine, followed by reaction with an electrophile, Ph_2PCl. They tested the ligand on asymmetric coupling reaction named after them (Asymmetric Kumada-Hayashi Coupling, Scheme 1.8).[35]



Scheme 1.8: The original Asymmetric Kumada-Hayashi Coupling reaction.

Scheme 1.6 summarises the most known breakthroughs in chiral ferrocenyl phosphine ligands from the pioneering work of successful researchers in this field; such as Hayashi, Kumada, Ugi and Togni, amongst others.

[32] (a) K. J. Schlögl, *Organomet. Chem.* 300 (**1986**) 219. (b) K. Schlögl, *Topics Stereochem.* 1 (**1967**) 39.
[33] A. Togni, C. Breutel, A. Schnyder, F. Spindler, H. Landert, A. Tijani, *J. Am. Chem. Soc.* 116 (**1994**) 4062.
[34] T. Hayashi, K. Yamamoto, M. Kumada, *Tetrahedron Lett*. 15 (**1974**) 4405.
[35] (a) T. Hayashi, In *Ferrocenes*; A. Togni, T. Hayashi, Eds.; VCH: Weinheim, **1995**; pp 105.
(b) T. Hayashi, M. Konishi, Y. Okamoto, K. Kabeta, M. Kumada, *J. Org. Chem*. 51 (**1986**) 3772.

1.1.4.2 Ferrocenyl pyrazole compounds.

Pyrazoles are well known heterocyclic compounds that have been widely employed in a preparation of biologically active compounds for use in pharmaceutical and agrochemical research areas.[36] They are versatile, easily prepared/derivatized and in most cases, are robust bridging ligands that have various coordination modes with metal ions as a result of moderate structural rigidity and two readily available nitrogen donor atoms.[37]

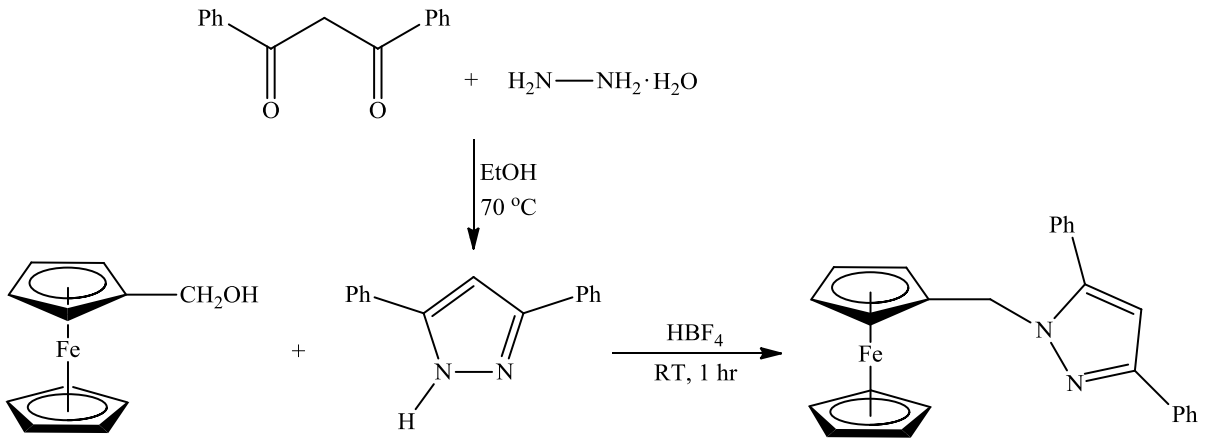
Ferrocenyl compounds incorporating aromatic heterocyclic moieties such as pyrazoles have shown to have interesting electrochemical behaviour that has been extensively exploited in various research areas.[38] The reversible redox reaction between Fe(II) and Fe(III) is a key property that has led ferrocene derivatives into potential applications such as electronic[39], electrochemical[40] and optical applications[41].

Incorporating pyrazoles with ferrocenyl compounds results in electron-transfer systems that are known to allow ferrocene to electronically communicate with a coordinated metal centre through π-conjugated systems on pyrazoles.[42] The resulting physical and chemical properties of these ferrocenylpyrazole compounds have been exploited in homogeneous catalysis and biological applications.[43]

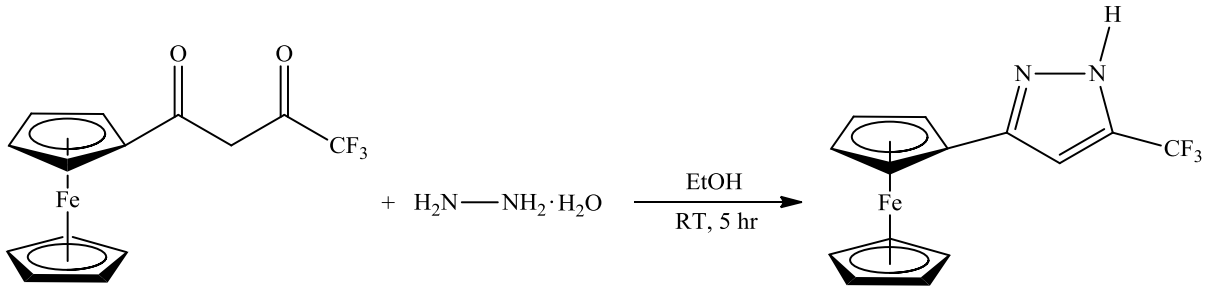
There are two routes that are used in the preparation of ferrocenylpyrazoles, they differ in the manner in which pyrazole is introduced/anchored on the ferrocene backbone. In one, pyrazole is firstly prepared using classical methods of synthesis followed by nucleophilic

[36] A.N. Rodionov, A.A. Simenel, A.A. Korlyukov, V.V. Kachala, S.M. Peregudova, K.Y. Zherebker, E.Y. Osipova, *J. Organomet. Chem.* 696 (**2011**) 2108.
[37] (a) N. Burzlaff, I. Hegelmann, B. Weibert, *J. Organomet. Chem.* 626 (**2001**) 16. (b) F. Meyer, *Eur. J. Inorg. Chem.* (**2006**) 3789. (c) M.A. Halcrow, *Dalton Trans.* (**2009**) 2059.
[38] L.-F. Tang, W.-L. Jia, Z.-H. Wang, J.-F. Chai, J.-T. Wang, *J. Organomet. Chem.* 637-639 (**2001**) 209.
[39] V. Mereacre, M. Nakano, J. Gomez-Segura, I. Imaz, C. Sporer, K. Wurst, J. Veciana, C. Turta, D. Ruiz-Molina, P. Jaitner, *Inorg. Chem.* 45 (**2006**) 10443.
[40] (a) V.N. Nemykin, G.T. Rohde, C.D. Berrett, R.G. Hadt, C. Bizzarri, P. Galooni. B. Floris, I. Nowik, R.H. Herber, A.G. Marrani, R. Zanoni, N.M. Loim, *J. Am. Chem. Soc.* 131 (**2009**) 14969. (b) D.A. Boyd, R.J. Crutchley, P.E. Fanwick, T. Ren, *Inorg. Chem.* 49 (**2010**) 1322.
[41] (a) X.-Y. Wang, Z.-X. Deng, B.-K. Jin, Y.-P. Tian, X.-Q. Lin, *Spectrochim. Acta. Part A* 58 (**2002**) 3113. (b) X.-Y. Wang, Z.-X. Deng, B.-K. Jin, Y.-P. Tian, X.-Q. Lin, *Electrochim. Acta.* 47 (**2002**) 1537.
[42] Q. Zhang, W.-L. Song, A.M. Showkot Hossain, Z.-D. Liu, G.-J. Hu, Y.-P. Tian, J.-Y. Wu, B.-K. Jin, H.-P. Zhou, J.-X. Yang, S.-Y. Zhang, *Dalton Trans.* 40 (**2011**) 3510.
[43] C. López, A. González, R. Bosque, P.K. Basu, M. Font-Bardía, T. Calvet, *RSC Advances* 2 (**2012**) 1986.

substitution on the ferrocenyl scaffold, Scheme 1.9.[43] In the other, the pyrazole moiety is synthesized directly on the ferrocenyl scaffold, Scheme 1.10.[42]



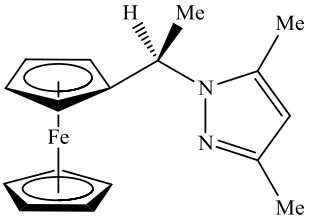
Scheme 1.9: Preparation of 1-ferrocenylmethyl-3,5-diphenylpyrazole using a previously prepared 3,5-diphenylpyrazole.



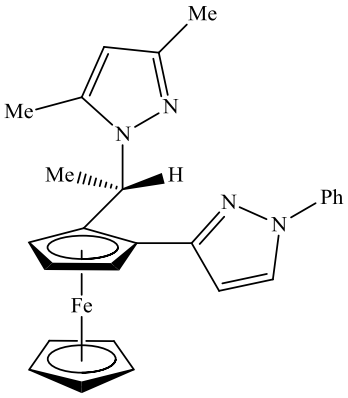
Scheme 1.10: Preparation of 2-(5-trifluoromethyl-3-ferrocenyl) pyrazole from a 5-(1,2,3-trifluoromethyl-2,4-dione) ferrocene scaffold.

Apart from introducing substituents on pyrazole with the aim of tuning electronic and steric properties of the overall ferrocenyl ligand system, other properties such as chirality can be incorporated into this system thereby enhancing the efficiency in specific reactions. Examples of ferrocenylpyrazole compounds endowed with chirality are: ferrocenyl(ethyl)-*1N*-(3,5-dimethyl)pyrazole equipped with axial chirality prepared by

Simenel *et al.*[44] and dipyrazole derivative of Josiphos equipped with both axial and planar chirality prepared by Togni and co-workers[45], Scheme 1.11.



Ferrocenyl(ethyl)-1*N*-(3,5-dimethyl)pyrazole

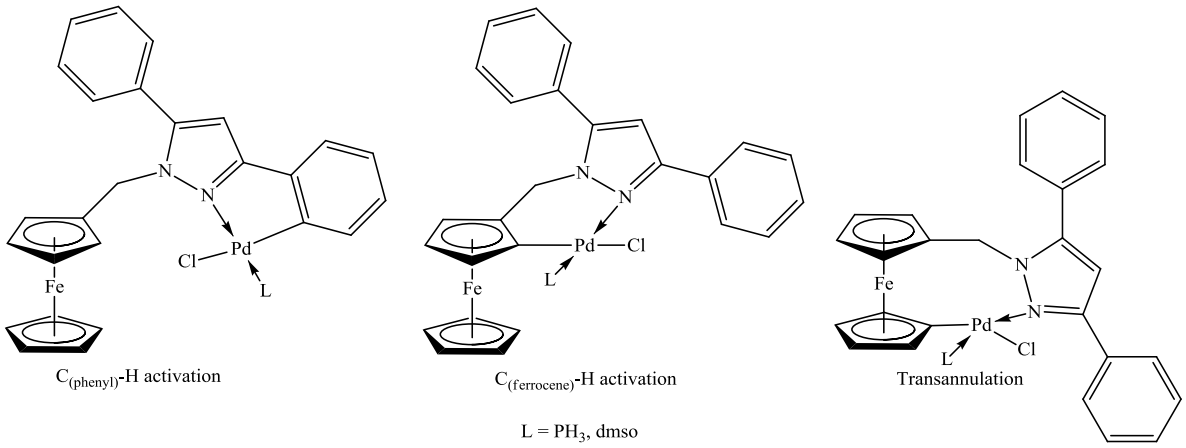


1-{(*R*)-1-[(*S*)-2-{3-(1-phenyl)-1*H*-pyrazolyl}ferrocenyl]ethyl}-3,5-dimethyl-1*H*-pyrazole

Scheme 1.11: Ferrocenyl ligands with different chiralities.

There has been a slow progress in using ferrocenylpyrazole ligands in palladium-catalysed reactions, mainly pure organic pyrazole ligands have been intensively studied instead.[46] Possible explanation to this is that most ferrocenylpyrazole-palladium complexes are sensitive to the type of palladium metal precursor used to prepare them and they have limited or no catalytic activity due to instability in solution.[45] However, they show interesting coordination modes under different conditions which broaden their efficiency in other various applications, Scheme 1.12.[42]

[44] A.A. Simenel, Y.V. Kuzmenko, E.A. Morozova, M.M. Ilyin, I.F. Gun'ko, L.V. Snegur, *J. Organomet. Chem.* 688 (**2003**) 140.
[45] U. Burckhardt, D. Drommi, A. Togni, *Inorg. Chim. Acta* 296 (**1999**) 185.
[46] (a) M. Bovens, A. Togni, L.M. Venanzi, *J. Organomet. Chem.* 451 (**1993)** C28. (b) K. Li, M.S. Mohlala, T.V. Segapelo, P.M. Shumbula, I.A. Guzei, J. Darkwa, *Polyhedron* 21 (**2008**) 1017. (c) D. Peral, F. Gómez-Villarraga, X. Sala, J. Pons, J.C. Bayón, J. Ros, M. Guerrero, L. Vendier, P. Lecante, J. García-Antón, K. Philippot, *Catal. Sci. Technol.* 3 (**2013**) 475.



Scheme 1.12: Different coordination modes of 1-ferrocenylmethyl-3,5-diphenylpyrazole Pd complexes.

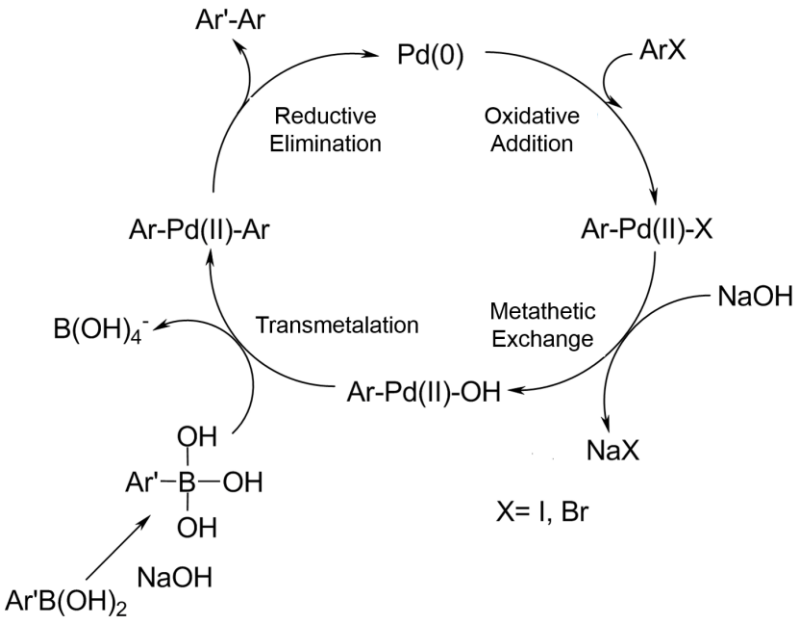
1.2 Carbon-carbon coupling reactions

Research in catalysis has revolutionised both industry and research in academia throughout the years; by transforming difficult and/or near-impossible reactions to successful and routine reactions. Catalysis over the years focused on finding solutions to promote and/or speed up the rate of product formation. It also looks at alternative routes that would improve the yield of the product at a relatively cheaper, cleaner and faster way while also attempting to minimise unwanted products from forming. Organic transformations, usually involving the use of transition-metal catalysts, is the well-researched area in catalysis.[27, 47, 48] An example of organic transformations is *coupling reactions*, which generally focus on carbon-carbon bond formations; high energy is required for such bonds to form, hence the use of catalysts. Heck and Suzuki coupling reactions are the most common. They are simple to carry out and therefore ideal for testing new or modified ligands.

[47] A. Suzuki, *Pure and Appl. Chem.* 63 (**1991**) 419.
[48] N. Miyaura, K. Yamada, A. Suzuki, *Tetrahedron Lett.* 36 (**1979**) 3437.

1.2.1 Suzuki coupling reaction

Suzuki reactions[49] are similar to Heck reactions[50] but the major difference lies in the nature of the aryl moiety and that it is widely used for aryl-aryl coupling reactions. Suzuki coupling reactions also have two additional steps. These steps are: metathetic exchange and transmetalation, Scheme 1.13. The metathetic exchange step is a molecular process where two substrates exchange. In the transmetalation step, two metal centres exchange their ligands.



Scheme 1.13: A typical example of Suzuki coupling reaction

In the Suzuki coupling reaction, reduction of the complex and oxidative addition of an aryl halide occurs similarly to the Heck reactions. After the oxidative addition step, metathetic exchange between the complex and NaOH occurs (*i.e.* the –OH exchanges places with –X). Transmetalation between an aryl boronic acid and the complex follows, which produces a complex that accommodates two aryl groups from different sources and a ligand. Reductive elimination then occurs, regenerating the complex (catalyst) which is then ready for a new catalytic cycle.

[49] N. Miyaura, K. Yamada, A. Suzuki, *Tetrahedron Lett.* 36 (**1979**) 3437.
[50] R. F. Heck, J. P. Nolley, *J. Org. Chem.* 37 (**1966**) 2320.

1.3 Rationale and motivation of the study

The reactivity and efficiency of all the above mentioned chiral ferrocenyl phosphine ligands do not solely rely on their characteristics but also on the type of substrate, reaction parameters and the nature of additives or catalyst supports. These ligands are extremely important as they provide opportunities for improving and developing fine, pure products that range from industrial to clinical use. It is for this reason that industries and/or companies own and fund a lot of research projects in this field. These ligands are clearly precious and powerful. However, they are expensive hence more research effort is focused in finding cost-effective alternative methods of synthesising these highly efficient ligands.

A strategy for this study involves the use of starting materials that are readily accessible and easy to prepare. These will be used as scaffolds for the preparation of compounds.

The project aims to:

(i) Synthesize and characterize cheaper ligand scaffolds that could be used as templates to prepare chiral diphosphine (homoleptic) and mixed chiral phosphine (heteroleptic) ligands. Methods of synthesis and characterisation of the scaffolds and ligands have been outlined in the Methodology section.

(ii) Compare and evaluate stability and reactivity of the prepared ligands when reacted with different metals to form metal complexes. Stability refers to the decomposition or breaking down of ligands due to the chemical environment and presence of other chemical species (that might want to attach to the ligand or extract a substituent(s) from the ligand). The reactivity (reaction kinetics) is related to the orientation of the ligand as well as the nature of the metal since these two depict the resulting orientation of the complex due to factors like steric effects. Metal centres usually used with this kind of ligands are Platinum group (*i.e.* Nickel, Palladium and Platinum) due to their catalytic properties.

(iii) Evaluate the performance or effectiveness of the metal complexes in organic transformation such as the Heck and Suzuki coupling reactions. The performance of the complexes in a catalytic reaction is associated with its life span during the reaction cycle. Also, reaction parameters such as reaction time and the amount of material needed give information about the performance of the complexes. Determination of the performance of the complex is purely for comparison purposes and will be compared to existing complexes of this nature, especially those with industrial applications.

CHAPTER 2

SYNTHESIS AND CHARACTERISATION OF PYRAZOLE AND PHOSPHINE-CONTAINING FERROCENYL LIGANDS AND THEIR PALLADIUM COMPLEXES

2.1 Introduction

Phosphine compounds such as triphenylphosphine (PPh_3) has been exploited as a ligand in a majority of Pd and Ni catalysed coupling reactions since the late 1970s.[51] Kumada and Hayashi[52] were the first to anchor the phosphine group on the Ugi-amine[53] ferrocenyl backbone, Figure 2.1. The ligand **PPFA** is endowed with chirality which they hoped would improve the stereoselectivity while the bulkiness from the phosphine moiety would improve the efficiency of the ligand when used in coupling reactions.

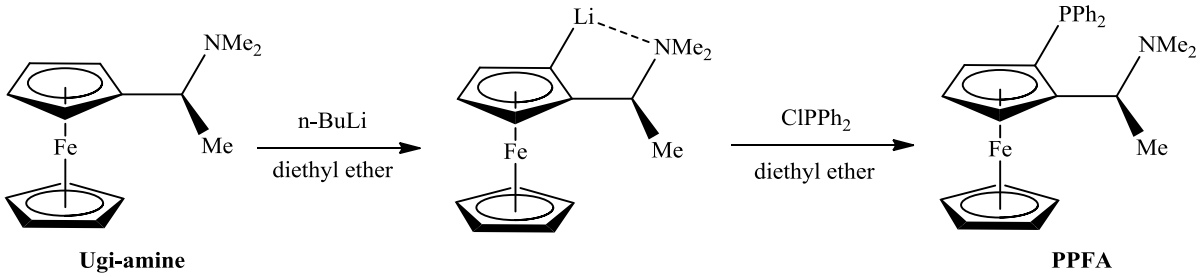


Figure 2.1: A typical preparation of the chiral **PPFA** ligand

It was Ugi and co-workers[53a] who had earlier demonstrated that the asymmetric ortho-lithiation of Ugi-amine could be achieved using n-BuLi. Kumada and Hayashi[52] took it further by reacting the lithiated species with a phosphine electrophile to obtain **PPFA** ligand. They were the first group to synthesize this class of chiral ferrocenyl ligands and subsequently applying them in asymmetric catalysis.[54] The **PPFA** ligand was used to obtain experimental data that emphasized the importance of having planar chirality and how it affects the performance of the ligand.[55]

Cammidge *et al.*[56] later showed the versatility of the ligand by using it as a catalyst in a Pd catalysed Suzuki coupling reaction of binaphthalene derivatives. Other derivatives of **PPFA** have been prepared, such as ***BoPhoz***, Figure 2.2 which have been reported to form complexes with

[51] (a) N. Miyaura, K. Yamada, A. Suzuki, *Tetrahedron Lett.* 36 (**1979**) 3440. (b) N. Miyaura, T, Yanagi, A. Suzuki, *Synthetic Commun.* 11 (**1981**) 514. (c) N. Miyaura, K. Yamada, H. Suginome, A. Suzuki, *J. Am. Chem. Soc.* 107 (**1985**) 973.

[52] T. Hayashi, T. Mise, M. Fukushima, M. Kagotani, N. Nagashima, Y. Humada, A. Matsumoto, S. Kawakami, M. Konishi, K. Yamamoto, M. Kumada, *Bull. Chem. Soc. Jpn.* 53 (**1980**) 1138.

[53] (a) D.Marquarding, H. Klusacek, G. Gokel, P. Hoffmann, I. Ugi, *J. Am. Chem. Soc*. 92 (**1970**) 5389. (b) G. Gokel, D. Marquarding, I. Ugi, *J. Org. Chem.* 37 (**1972**) 3052.

[54] (a) T. Hayashi, M. Konishi, M. Fukushima, T. Mise, M. Kagotani, M. Tajika, M. Kumada, *J. Am. Chem. Soc.* 104 (**1982**) 180. (b) T. Hayashi, M. Konishi, Y, Okamoto, K. Kabeta, M. Kumada, *J. Org. Chem.* 51 (**1986**) 3772.

[55] M. Uemera, H. Nishimura, T. Hayashi, *Tetrahedron Lett.* 34 (**1993**) 107.

[56] A.N. Cammidge, K. Crepy, *Chem. Comm.* (**2000**) 1723.

rhodium(I) where the ligand binds through the phosphorus atom of the phosphine anchored on the cyclopentadienyl ring and the phosphorus atom of the phosphine attached on the amine to form a seven-membered chelate ring. [57]

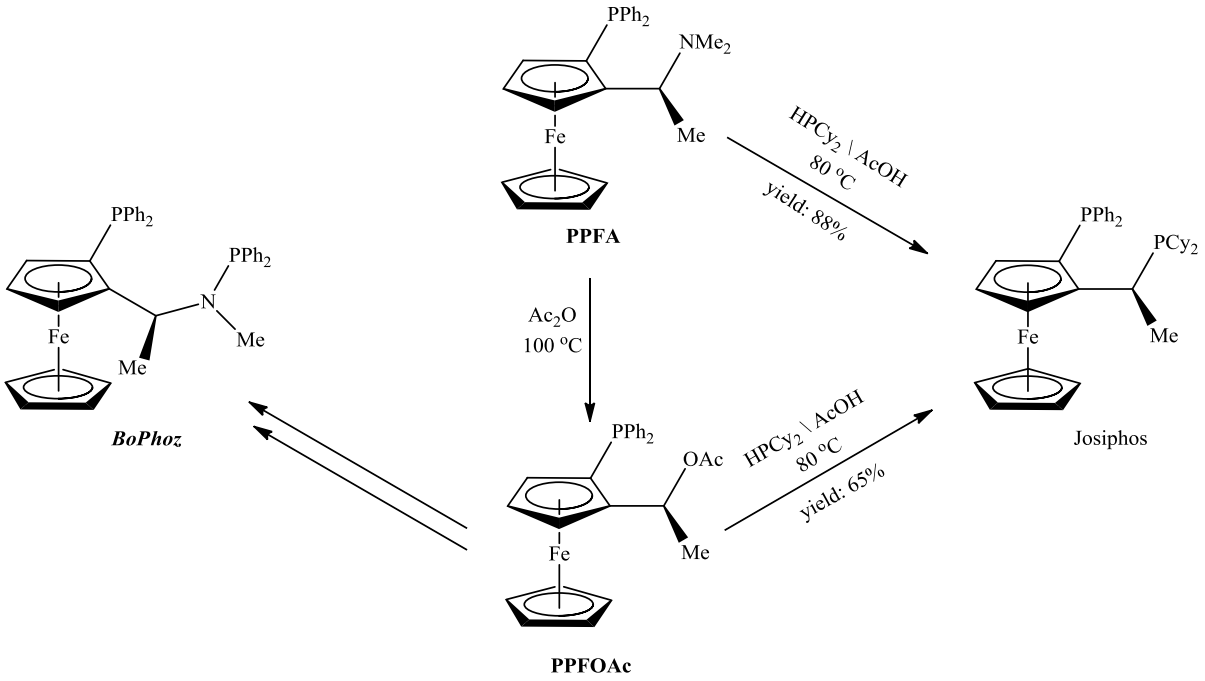


Figure 2.2: The typical preparation of **Josiphos** from **PPFA** and **PPFOAc**.

Togni and co-workers functionalised the **PPFA** ligand *via* nucleophilic substitution of the amino group with other phosphine derivatives thus obtaining diphosphino ferrocene ligands,[58] the acetate derivative **PPFOAc** was also used in place of **PPFA**, although low yields were obtained, Figure 2.2.[59] This class of ligands were named Josiphos, after Josi Puleo, the technician who was the first to prepare them.[60] These ligands were used in the industrial scale preparation of *(S)*-metolachlor,[61] *d*-(+)-biotin[62] and (+)-*cis* methyl dihydrojasmonate[63] and were found to have high turnover numbers and stereoselectivity.

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[57] R.C.J. Atkinson, V.C. Gibson, N.J. Long, *Chem. Soc. Rev.* 33 (**2004**) 318.
[58] A. Togni, C. Breutel, A. Schnyder, F. Spindler, H. Landert, A. Tijani, *J. Am. Chem. Soc.* 116 (**1994**) 4063.
[59] A. Togni C. Breutel, M.C. Soares, N. Zanetti, T. Gerfin, V. Gramlich, F. Spindler, G. Rihs, *Inorg. Chim. Acta.* 222 (**1994**) 213.
[60] H. Blaser, W. Brieden, B. Purgin, F. Spindler, M. Studer, A. Togni, *Top. Catal.* 19 (**2002**) 5.
[61] H.U. Blaser, H.P. Buser, K. Coers, R. Hanreich, H.P. Jalett, E. Jelsch, B. Pugin, H.D. Schneider, F. Spindler, A. Wegmann, *Chimia* 53 (**1999**) 275.
[62] J. McGarrity, F. Spindler, R. Fuchs, M. Eyer, EP 624 587 (**1994**). R. Imwinkelried, *Chimia* 51 (**1997**) 300.
[63] D. Dobbs, K. Vanhessche, V. Rautenstrauch, WO 98/52 687 (**1997**), D.A. Dobbs, K.P.M. Vanhessche, E. Brazi, V. Rautenstrauch, J.-Y. Lenoir, J.-P. Genet, J. Wiles, S.H. Bergens, *Angew. Chem. Int. Ed.* 39 (**2000**) 1992.

Many of these ligands were patented and are sold commercially by the Swiss company, Solvias.

Following the extensive work on the preparation of Josiphos derivatives, Togni and co-workers also reported the preparation of the chiral P,N-ferrocenyl ligands using **PPFA** as a starting material and pyrazoles as nitrogen-donor moieties.[64] They were prepared using the same reaction protocols used in the preparation of Josiphos, Figure 2.3. These types of ligands allowed manipulation of electronic and steric properties using appropriate substituents on the heterocyclic pyrazole system which improves efficiency and stability of the overall ligand. As a result, they showed highest enantioselectivities and pronounced stereoselectivity on Rh-catalysed hydroboration of styrene with catecholborane. They were also used in other Pd and Rh-catalysed reactions.[65]

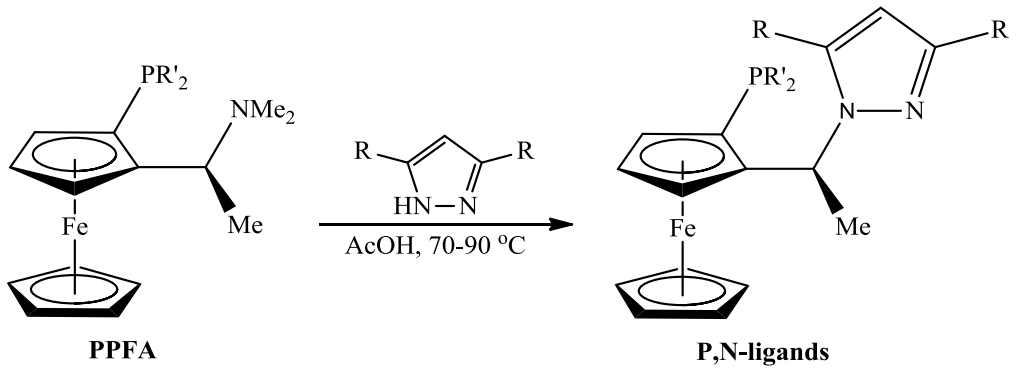


Figure 2.3: The preparation of chiral P,N-ligands.

As much as the Josiphos and P,N-ligands developed by Togni are desirable for use in many catalytic reactions due to their high efficiency, the major drawback lies in their common synthetic protocol which rely on the use of the commercially available but expensive Ugi-amine as starting material. This calls for alternative methods and/or other ligands that can be prepared from cheaper materials while trying to maintain the high efficiency of the final ligands.

There are several literature reports that collectively provide necessary information on overcoming this drawback. In fact, two reaction protocols that produce ferrocenyl azolyl ligands bearing axial chirality without the use of the Ugi-amine have been reported.

[64] (a)A. Schnyder, L. Hintermann, A. Togni, *Angew. Chem.* 107 (**1995**) 996; *Angew. Chem. Int. Ed. Engl.* 34 (**1995**) 931. (c) U. Burckhardt, L. Hintermann, A. Schnyder, A. Togni, *Organometallics* 14 (**1995**) 5420.
[65] R.C.J. Atkinson, V.C. Gibson, N.J. Long, *Chem. Soc. Rev.* 33 (**2004**) 320, and reference therein.

Simenel *et al.*[66] showed that the nucleophilic substitution of the OH group on the ferrocenyl ethanol with azoles can be achieved in five minutes to afford very good to quantitative yields of ferrocenyl azoles, with the aid of tetrafluoroboric acid (HBF_4) as catalyst, Figure 2.4. Interestingly, Seo *et al.*[67] later showed that the same substitution reaction can occur on the ferrocenyl ethanol with imidazoles by using glacial acetic acid (AcOH) as a solvent. The glacial acetic acid converts the ferrocenyl ethanol into the intermediate bearing the acetate (OAc) group which is a good leaving group.

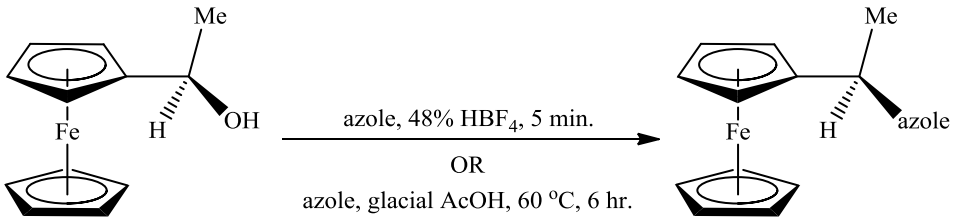


Figure 2.4: The preparation of chiral ferrocenyl azoles by Simenel *et al.* and Seo *et al.*

Ueberbacher *et al.*[68] also demonstrated the stereoselective *ortho*-lithiation and a subsequent electrophilic substitution of the cheaper ferrocenyl ethanol scaffold with appropriate electrophiles to yield a compound with the same configuration found on P,N-ligands, Figure 2.5. The lithiation mechanism resembles that of the Ugi-amine. Therefore, carefully combining and modifying the reaction protocols by either Simenel *et al.* or Seo *et al.* with that of Ueberbacher *et al.* might be an alternative method for the preparation of P,N-ligands.

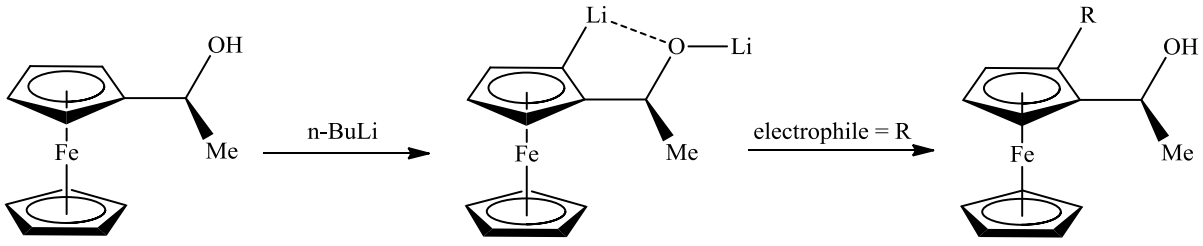


Figure 2.5: The preparation of 1-PPh_2-2-ethanoyl ferrocene from ferrocenyl ethanol.

[66] A.A. Simenel, Y.V. Kuzmenko, E.A. Morozova, M.M. Ilyin, I.F. Gun'ko, L.V. Snegur, *J. Organomet. Chem.* 688 (**2003**) 140.
[67] H. Seo, B.Y. Kim, J.H. Lee, H.-J. Park, S.U. Son, Y.K. Chung, *Organometallics* 22 (**2003**) 4788.
[68] B.J. Ueberbacher, H. Griengl, H. Weber, *Chem. Comm.* (**2008**) 3287.

It is clear all the reactions mentioned above utilize ferrocenyl ethanol as the crucial primary starting material; even the laboratory preparation of the Ugi-amine makes use of it as the starting material.[69] Ferrocenyl ethanol can be prepared in bulk amounts from cheaper methods which basically involve the reduction of acetylferrocene. Vitride,[69] borane-oxazaborolidine systems[70] and classical reducing agents such as sodium borohydride ($NaBH_4$) and lithium aluminium hydride ($LiAlH_4$) are examples of the reducing agents that have been used to obtain ferrocenyl ethanol from acetylferrocene.

Acetylferrocene can be prepared from ferrocene using various synthetic protocol that include acetylation with acetic anhydride,[71] Friedel-Crafts acetylation using acetyl chloride,[72] acylation with a $2CH_3COOH{\cdot}BF_3$ complex[73] in acidic conditions and acylation *via* an electrochemical process.[74] The first two techniques are the most common to synthetic chemists because they make use of readily available cheap starting materials and simple reaction protocols.

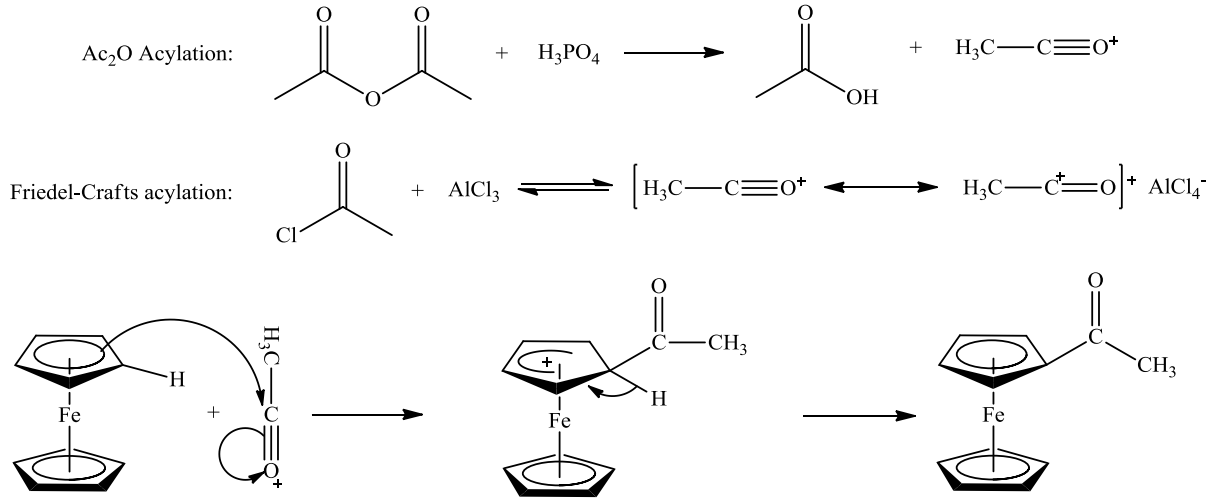


Figure 2.6: The acetylation reaction mechanisms of ferrocene.

Acetylation with acetic anhydride is the cheapest technique and employs a milder H_3PO_4 acid catalyst, which is responsible for the generation of the acylium ion (CH_3CO^+) active species,

[69] H. Blaser, W. Brieden, B. Purgin, F. Spindler, M. Studer, A. Togni, *Top. Catal.* 19 (**2002**) 7.
[70] J. Wright, L. Frambes, P. Reeves, *J. Organomet. Chem.* 476 (**1994**) 215.
[71] (a) V. Weinmayr, *J. Am. Chem. Soc.* 77 (**1955**) 3010. (b) P.L. Pauson, *Q. Rev. Chem. Soc.* 9 (**1955**) 409, and reference therein.
[72] G.D. Broadhead, J.M. Osgerby, P.L. Pauson, *J. Chem. Soc.* (**1958**) 653.
[73] S.P. Gubin, I.P. Shepilov, A.N. Nesmeyanov, *B. Acad. Sci. USSR. Ch.* 15 (**1966**) 363.
[74] M.D. Vukićević,Z.R. Ratković, A.V. Teodorović, G.S. Stojanović, R.D. Vukićević, *Tetrahedron* 58 (**2002**) 9001.

Figure 2.6. The reaction protocols are designed to obtain acetylferrocene at highest yields within a short period of time. However, prolonged reaction times and high temperatures lead to the decomposition of the product into a tarred material.

The Friedel-Crafts acetylation route is cleaner and the yields are consistently higher but long reaction times that extend to a couple of hours are required. The active species in this reaction is the $CH_3CO^+AlCl_4^-$ complex which is very reactive compared to the acylium ion due to the electronic influence by the aluminium metal centre. The products can be purified in a similar way for H_3PO_4 acid catalysed acylation using either column chromatography or by recrystallizing from hot hexane. Generally, yields of pure acetylferrocene of over 80% are obtained.[75]

The importance of using $AlCl_3$ as Lewis acid in the reaction was demonstrated in an experiment by Vukićević *et al.*[76] where $AlCl_3$ was generated *in situ* under electrochemical conditions. The main idea was to rather generate the participating reactants (acetyl chloride and $AlCl_3$) than using the commercially available ones. Acetyl chloride was prepared from the chlorination of acetic acid by PCl_3; $AlCl_3$ was obtained from the electron-potential oxidation of the Al anode in an electrolyte solution of tetraethylammonium chloride in dichloromethane at 50 mA. Prolonged electrolysis afforded maximum yields of 73% at 4.5 F/mol. However, extreme prolonged electrolysis resulted in a decrease in formation of acetylferrocene but with an increase in undesired products (diacetyl ferrocene and other unidentified products), Figure 2.7.

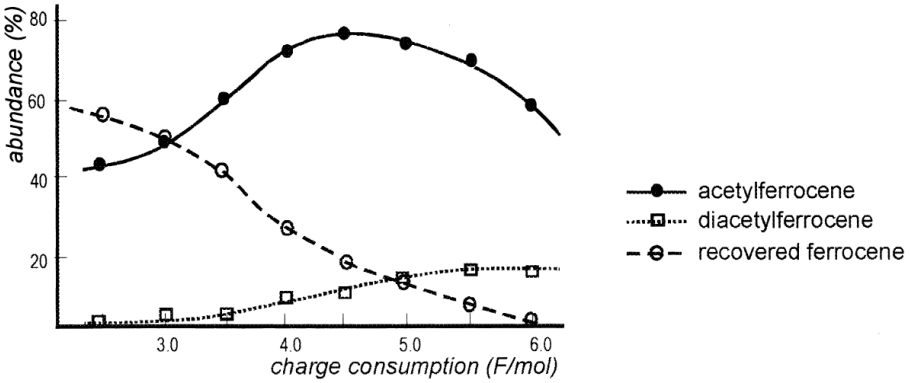


Figure 2.7: Product distribution by electrochemical acetylation of ferrocene.[76]

[75] G.D. Broadhead, J.M. Osgerby, P.L. Pauson, *J. Chem. Soc.* (**1958**) 653.
[76] M.D. Vukićević,Z.R. Ratković, A.V. Teodorović, G.S. Stojanović, R.D. Vukićević, *Tetrahedron* 58 (**2002**) 9001.

Another disadvantage is that it takes more than five hours (excluding work-up) to produce maximum yields of acetyl ferrocene. When the Al electrode setup was replaced with commercial $AlCl_3$, maximum yields of 88% were obtained.

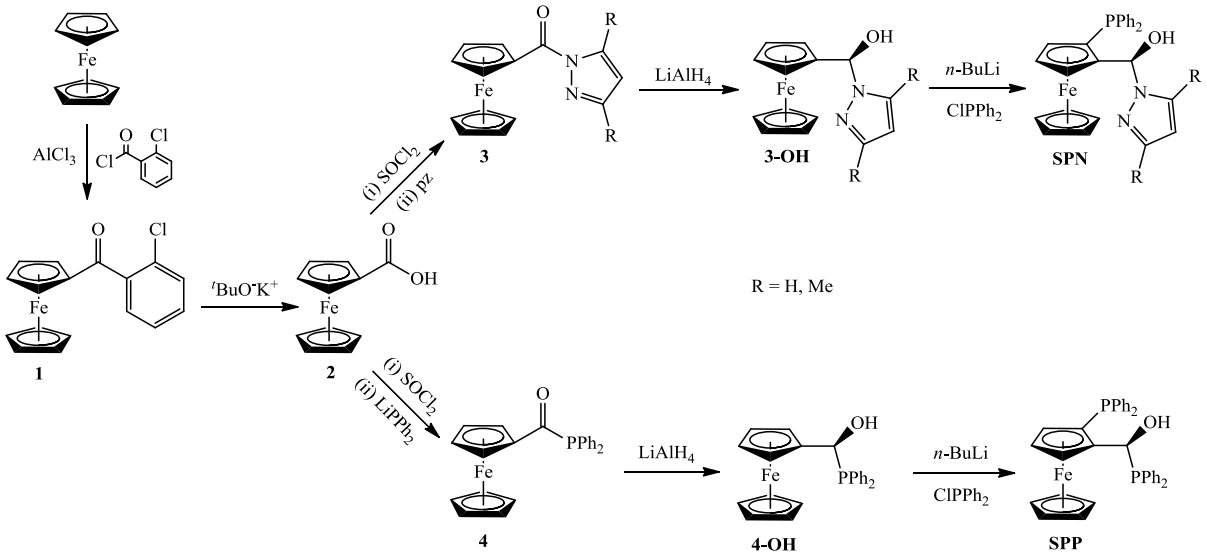
In this chapter the use of 2-chlorobenzoylferrocene and acetylferrocene as prochiral starting materials are explored in preparing bidentate chiral P^P and P^N ligands.

2.2 Results and Discussion

2.2.1 Ligands and their scaffolds

2.2.1.1 Preparation of ferrocenyl compounds bearing planar chirality

The preparation of compound **1** was carried out using Friedel-Crafts acetylation method, Scheme 2.1. The product was obtained in yields of about 75% and can be used without further purification. The typical ^1H NMR spectrum of compound **1** shows a multiplet peak appearing at 7.49 ppm due to protons of the phenyl ring, Figure 2.8 (i). The remaining peaks appearing at the range between 4 ppm and 5 ppm are typical of the protons of the unsubstituted [(a)] and substituted [(b) and (c)] Cp rings. The compound is also easily characterisable by IR stretching frequency of the $\upsilon_{(CO)}$ band at 1680 cm^{-1}, Figure 2.9.



Scheme 2.1: Proposed route for the preparation of P^N and P^P ligands.

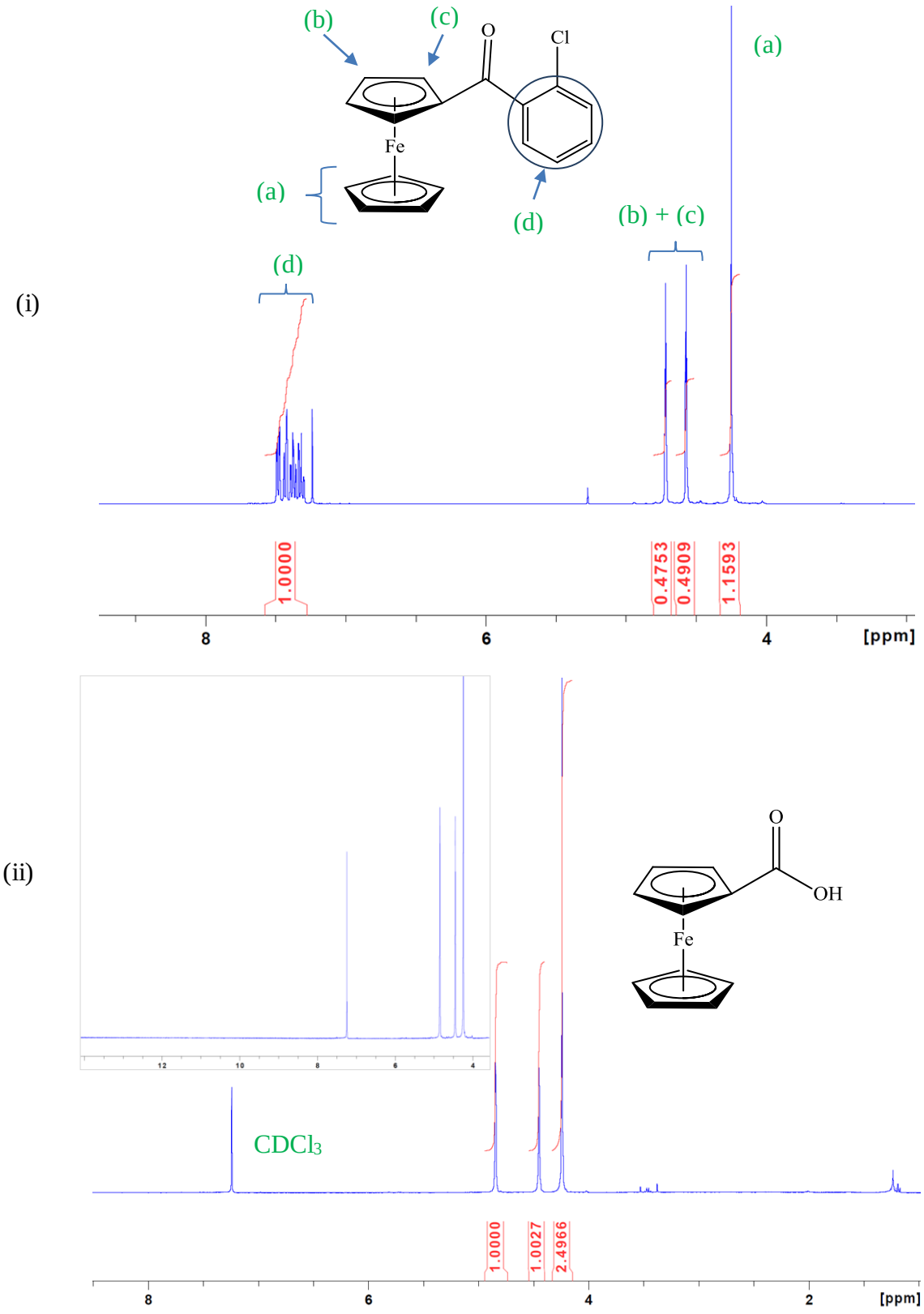


Figure 2.8: The ^{1}H NMR spectra of (i) **1** and (ii) **2**, spectrum cut since no peak observed above 8 ppm (see insert).

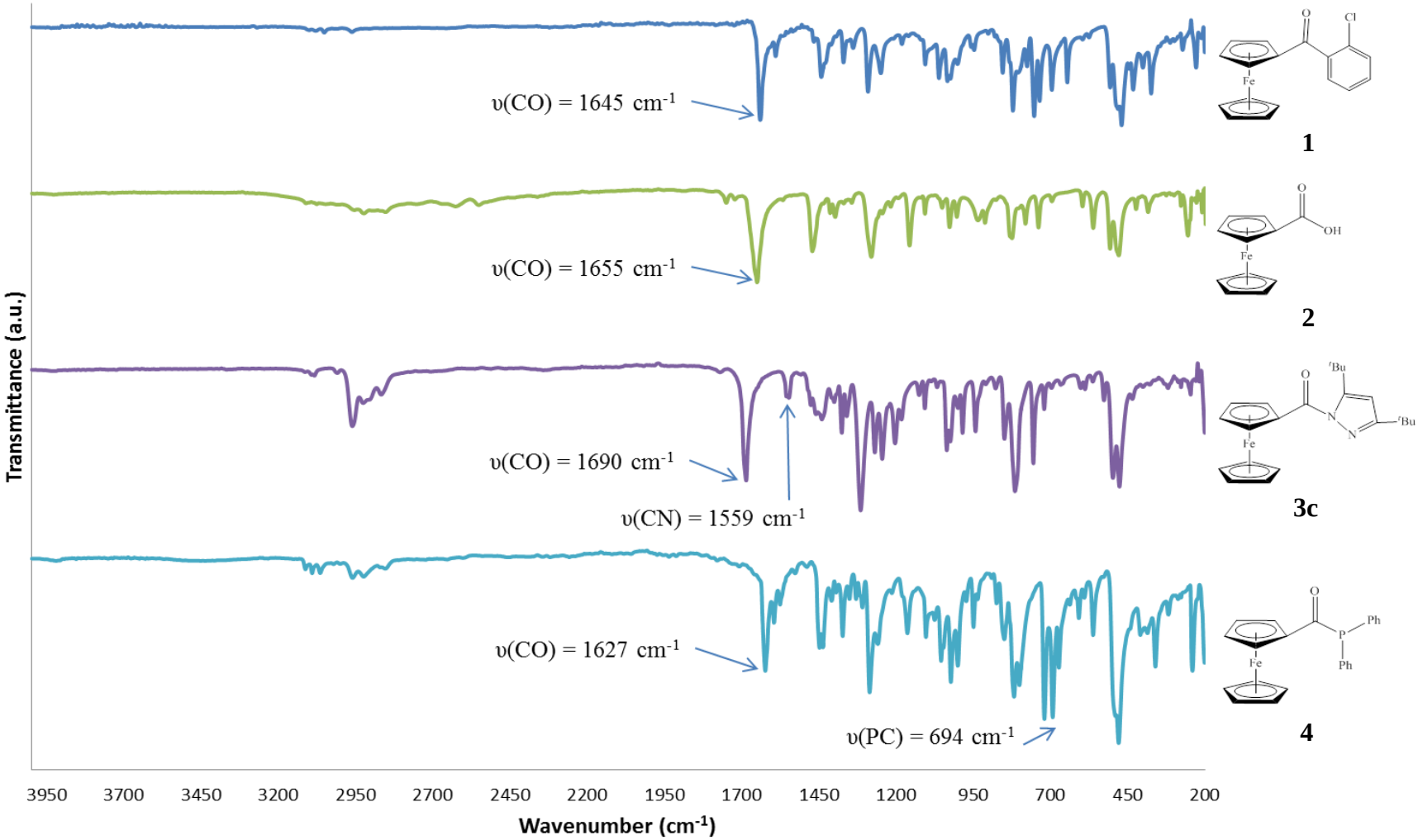


Figure 2.9: The comparative FT-IR spectra of **1**, **2**, **3c** and **4**.

The carboxylic acid **2** is formed from **1** by the cleavage of the bond between the carbonyl and the 2-chlorobenzene moiety in **1** using potassium *tert*-butoxide. An advantage of this method is that the yellow product is precipitated out from the aqueous phase and no further purification is required. Yields as high as 76% were obtained; which are higher than those obtained from other conventional methods.[77] Interestingly, no reaction took place when the non-chlorinated benzoylferrocene derivative was used under similar conditions indicating that the electron withdrawing chloride atom attached on the phenyl ring in **1** plays a significant role towards the conversion of 2-chlorobenzoyl ferrocene **1** into a carboxylic acid **2**.

Using the NMR, the conversion of **1** into a carboxylic acid compound **2** was confirmed by the disappearance of the multiplet peak observed at 7.49 ppm in **1** indicating that the chlorobenzyl moiety has been cleaved, Figure 2.8. However, the peak corresponding to the hydroxyl group of the carboxylic acid moiety was not observed as expected between 10 ppm and 12 ppm, Figure 2.8- (ii) insert. This is similar to the observation made on its FT-IR spectrum where the $\upsilon_{(OH)}$ band of the carboxylic functionality was absent. Further confirmation for formation of **2** was obtained from mass spectrometry where a molecular ion peak corresponding to **2** was obtained at *m/z* = 230, Figure 2.10.

Ferrocene carboxylic acid, **2**, was prepared with the intention of using it as a prochiral backbone for synthesizing P^N and P^P ferrocenyl compounds bearing both axial and central chirality. Pyrazoles and diphenylphosphines were chosen as nitrogen and phosphorus donor moieties to be anchored on ferrocenoyl chloride prepared *in situ* from **2**. Anchoring of pyrazoles on a bisferrocenoyl chloride intermediate has previously been published by Herrick *et al.*[78] using simple pyrazole and 3,5-dimethylpyrazole to prepare 1,1'-disubstituted analogues of **3a** and **3b**, respectively. The current preparation of the monosubstituted derivatives was carried out with slight modification to their procedure. The compounds were obtained as red coloured oils with yields of between 52% and 59% for **3a** and **3b** respectively, whereas the yields ranging between 57 and 70% were obtained for the disubstituted analogues which were obtained as red solids. The additional derivative of 3,5-di-*tert*-butylpyrazole (**3c**) was also prepared in 63% yield and it was obtained as a red solid.

[77] R.A. Benkeser, D. Goggin, G. Schroll; *J. Am. Chem. Soc.* 76 (**1964**) 4025.
[78] R.S. Herrick, B.R. Franklin, C.J. Ziegler, A. Çetin, *Inorg. Chem. Comm.* 12 (**2009**) 1210.

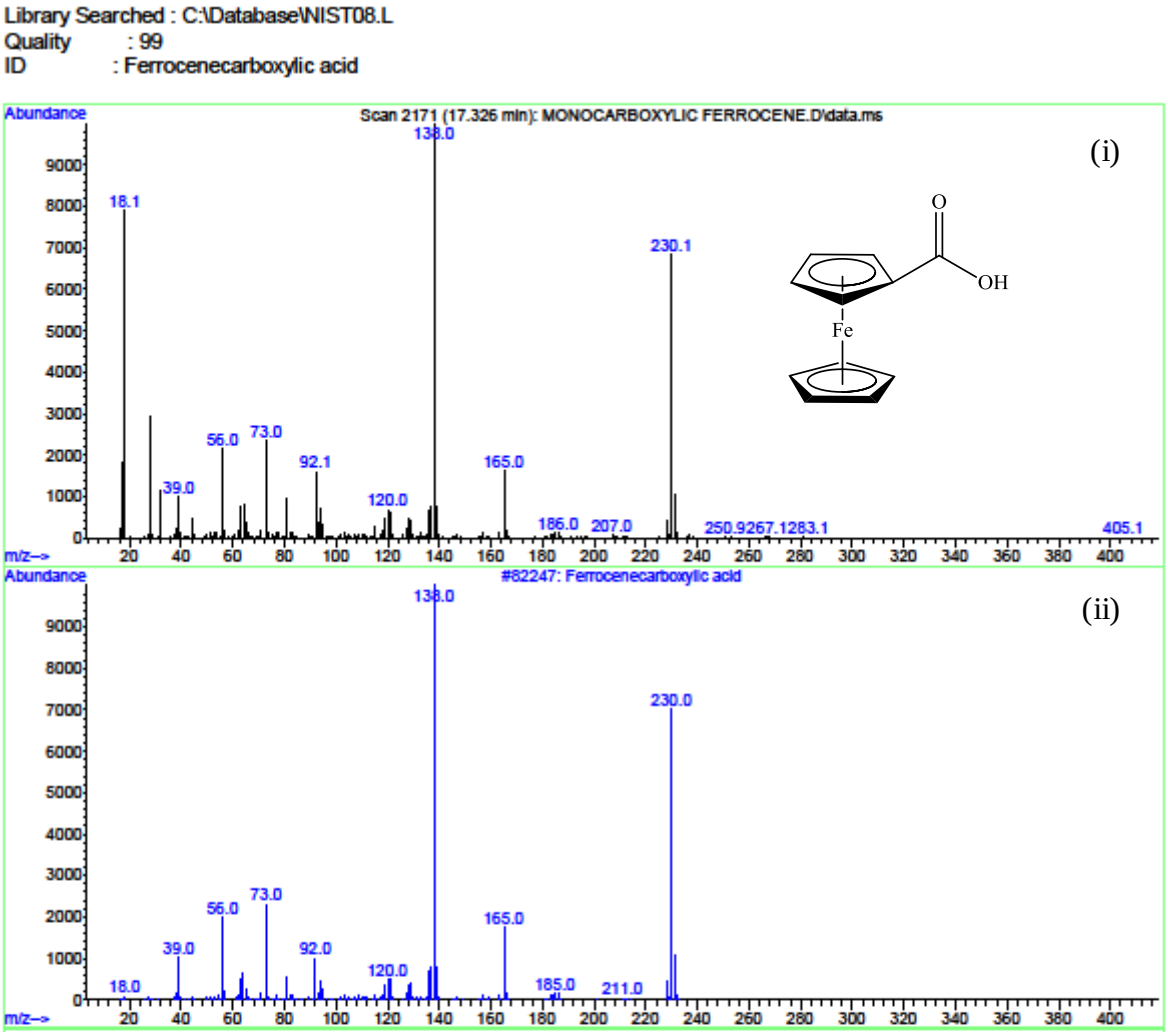


Figure 2.10: (i) GC mass spectrum of **2**. (ii) GC mass spectrum of **2** from the library software.

Since the prepared **3a** and **3b** compounds are mono-substituted versions of the ones prepared by Herrick *et al.*[78]; similarities in the analysis data was expected. The FT-IR frequencies of the carbonyl peaks appearing at $\upsilon_{(CO)}$ = 1680 cm^{-1} for **3a** and $\upsilon_{(CO)}$ = 1681 cm^{-1} for **3b** fall within the range of 1670 – 1690 cm^{-1} reported by Herrick *et al.* Evidence pointing out to the successful incorporation of the pyrazolyl moiety was provided by the presence of the $\upsilon_{(CN)}$ band that arises due to the carbon-nitrogen bond in the pyrazole at 1533 cm^{-1} for **3a** and 1580 cm^{-1} for **3b**.

The preparation of ferrocene carboxypyrazole **3c** from a bulkier 3,5-di^{t}butylpyrazole compared to the simple and 3,5-dimethylpyrazole by Herrick *et al.*[78] was confirmed by a major increase in $\upsilon_{(CO)}$ frequency by 35 cm^{-1} units on the carbonyl peak. The frequency of the carbon-nitrogen stretching bond which is normally expected to appear within the range 1500-1600 cm^{-1} was found at 1559 cm^{-1}.

The ^{1}H NMR data of the di-substituted compounds assisted in the interpretation of the mono-substituted ones. It was clear from the similarities in the chemical shifts that the mono-substituted compounds **3a** and **3b** were successfully prepared, Table 2.1. For **3c**, the two singlets appearing at 1.33 ppm and 1.46 ppm are due to the *tert*-butyl protons, and the singlet appearing at 6.12 ppm is due to the proton attached on the pyrazolyl ring, Figure 2.11.

Table 2.1: ^{1}H NMR data comparison of mono- and di-substituted ferrocene carboxypyrazole.

Derivative	**Component**	**Di-substituted by Herrick *et al.* (ppm)**	**Mono-substituted (ppm)**
Simple pyrazole	H-pz	8.27	8.34
		7.59	7.74
		6.37	6.43
	β-η^5-C_5H_4	5.44	5.54
	α-η^5-C_5H_4	4.56	4.59
	η^5-C_5H_5	-	4.21
3,5-dimethylpyrazole	H-pz	5.91	5.98
	β-η^5-C_5H_4	5.43	5.36
	α-η^5-C_5H_4	4.51	4.54
	η^5-C_5H_5	-	4.18
	Me-pz	2.51	2.58
		2.20	2.27

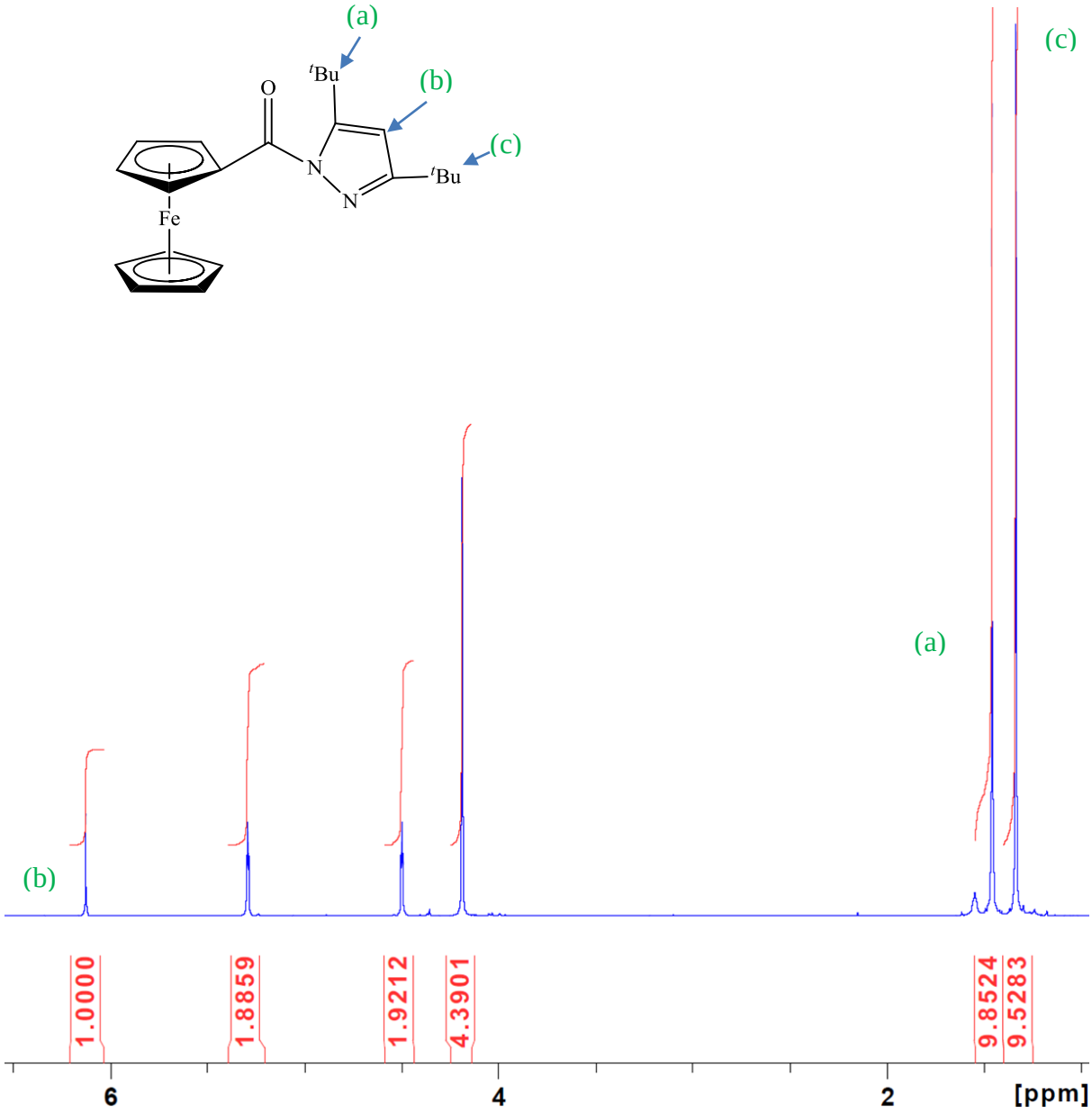


Figure 2.11: A typical ^{1}H NMR spectrum of ferrocene carboxy(3,5-di^{t}butylpyrazole) **3c**.

Compound **4** was prepared from the reaction between $LiPPh_2$ and ferrocenoyl chloride. Both reactants are separately prepared *in situ*, the former from the lithiation of PPh_3 with lithium wire while the latter is prepared from chlorination of **2**. Ferrocenoyl chloride is added into the $LiPPh_2$ reaction to avoid air and moisture exposure to lithiated products which are prone to oxidation. Major problems that were encountered during its preparation were:

- **The work-up protocols**

  The *in situ* generation of $LiPPh_2$ and ferrocenoyl chloride is a major contributor of impurities which had to be dealt with in a complex manner. Failure to address this issue prior to purification by column chromatography led to the clogging of the column by what appeared to be a white paste of unknown chemical composition. It was observed that the white substance formed when the sample was exposed to air, or when aqueous solutions or solvent mixture with a large polarity difference (e.g. hexane:ethyl acetate mixture) were used. To prevent or minimise the clogging problem, minimum amount of saturated $NaHCO_3$ and brine aqueous solutions were incorporated in the work-up protocols; the extraction of the white substance is improved. The disadvantage of using water for washing and large amounts of aqueous solutions was that it led to formation of large amounts of oxidized product.

- **Purification**

  It was however discovered that to obtain a pure product, flash chromatography was not enough. Dissolving the oily product in acetone followed by slow evaporation at low temperatures in the fridge afforded a red crystalline material which was of better quality.

The substitution with a diphenylphosphine moiety in ferrocenoyl chloride was confirmed by the appearance of the $\upsilon_{(CO)}$ band in the FT-IR spectrum of **4** at 1627 cm^{-1} while the $\upsilon_{(PC)}$ band typical of phosphorus-carbon stretching band appears at 694 cm^{-1}.

The ^{31}P NMR spectrum of **4** was used to identify the components present in the sample instead of the ^{1}H NMR spectrum, which only gave broad peaks as a result of fluxionality. The product peak is observed at 21.4 ppm while the phosphorus peak in the $LiPPh_2$ starting material is normally observed at -23 ppm.[79] There was also traces of oxidized PPh_3 which is observed at 29.1 ppm,[80] Figure 2.12.

[79] A.-M. Larsonneur, R. Choukroun, J.-C. Daran, T. Cuenca, J.C. Flores, P. Royo, *J. Organomet. Chem.* 444 (**1993**) 85.
[80] C.R. Hilliard, N. Bhuvanesh, J.A. Gladysz, J. Blümel, *Dalton Trans.* 41 (**2012**) 1742.

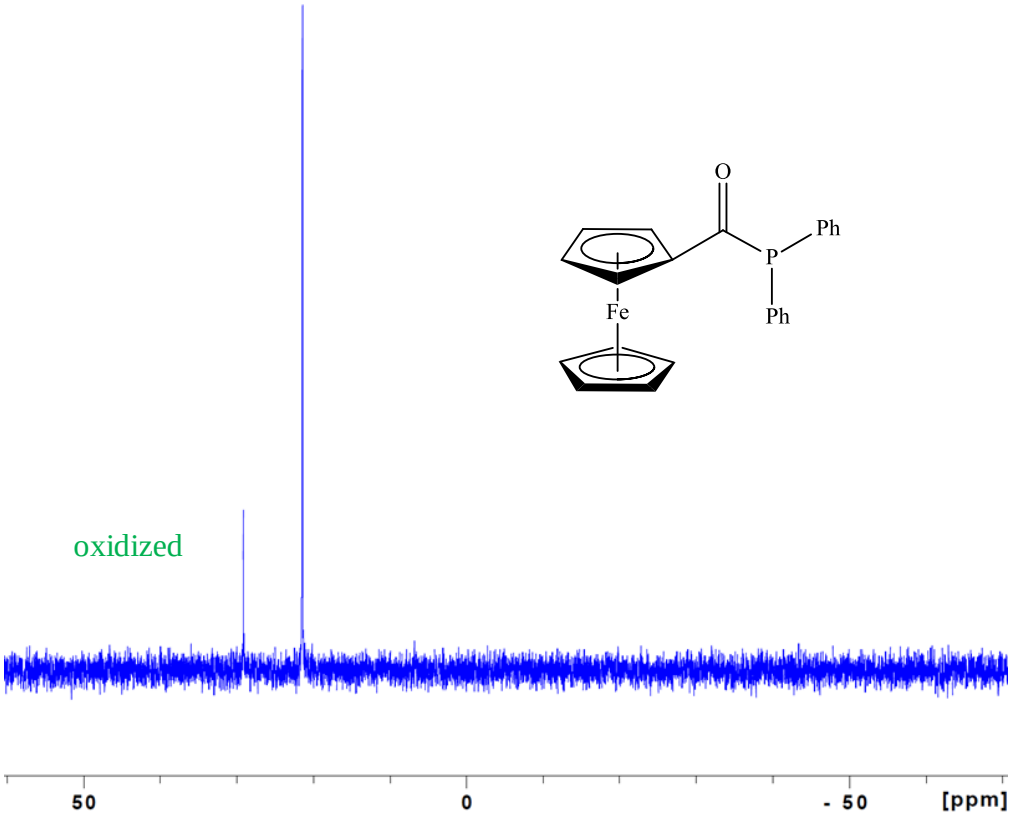


Figure 2.12: The ^{31}P NMR spectrum of **4**

The preparation of **3a-c** and **4** was aimed at preparing prochiral compounds which once reduced to form **3-OH** and **4-OH** respectively, could be used to anchor another donor moiety on the ortho position of the same cyclopentadienyl ring. It has been reported in the literature that the presence of hydroxyl group on the stereogenic carbon helps facilitate this process.[68]

Unfortunately, neither of the potential prochiral compound could be reduced into their corresponding alcohols using common reducing agents such as a powerful $LiAlH_4$ and a moderate $NaBH_4$. Attempted reduction of **3a-c** using both reducing agents led to the cleavage of the pyrazolyl moiety from the ferrocenoyl backbone, whereas using **4** no reaction took place at all.

Due to the problems encountered in reducing **3a-c** and **4**, the desired chiral P^N and P^P ligands could not be prepared. An alternative route in preparing similar type of ligands was devised where the carbonyl linker in **3** was replaced with a substituted methylene linker derived from

acetylferrocene, whereas in an alternative for **4** the carbonyl linker was completely removed, Figure 2.13.

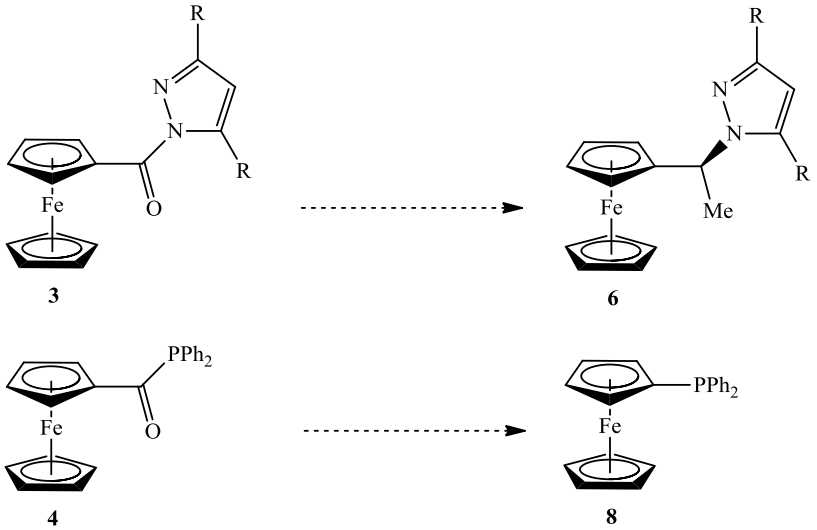
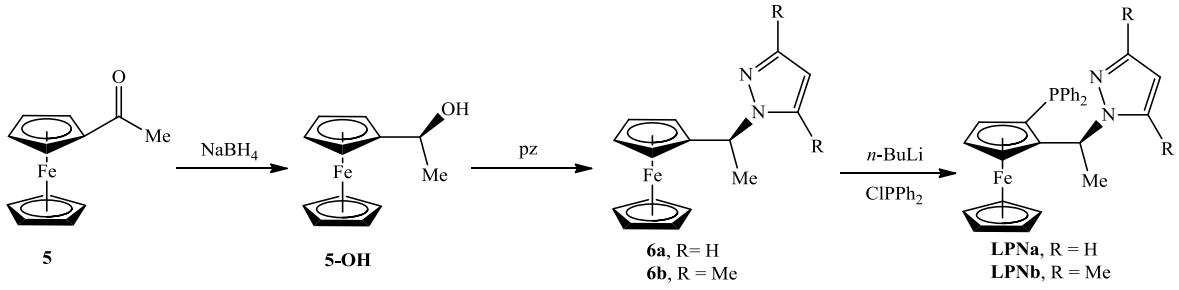


Figure 2.13: Modifications to the linker in the ligands.

2.2.1.2 **Preparation of chiral ferrocenyl compounds:** alternative route

2.2.1.2.1 Syntheses using the acetylferrocene scaffold

The pyrazole containing monosubstituted ferrocene compounds were prepared from acetylferrocene, **5**, Scheme 2.2. After careful consideration, the system that employs acetic anhydride and phosphoric acid for the preparation of **5** was chosen amongst others previously mentioned because it is practically cheap, easy to carry out and can be repeated many times because of the shorter reaction times required. Another advantage was that the unreacted ferrocene from the acetylation reactions could easily be recovered and reused.



Scheme 2.2: Reaction scheme for the preparation of **LPN**.

Reduction of **5** to 1-ferrocenyl ethanol **5-OH** was carried out using both mild and strong reducing agents, $NaBH_4$ and $LiAlH_4$ respectively. Both reducing agents achieve conversions that are almost quantitative (>98%), however $NaBH_4$ was a preferred choice over a $LiAlH_4$ system because of its easy work-up procedure. The conversion of the acetylated compound **5** to the corresponding alcohol **5-OH** is confirmed by the disappearance of the $\upsilon_{(CO)}$ band at 1652 cm^{-1} and the appearance of the $\upsilon_{(OH)}$ band at 3235 cm^{-1} is observed, Figure 2.14.

The use of ^1H NMR spectroscopy confirmed that **5-OH** was prepared successfully owing to the appearance of a quartet at 4.54 ppm due to the methine proton on the stereogenic carbon which then results in the splitting and shifting of the methyl group appearing at 2.37 ppm in **5**, into a doublet at 1.42 ppm, Figure 2.15.

Ferrocenyl(ethyl)pyrazole compounds **6a** and **6b** were prepared from **5-OH**, using a modified reported procedure by Simenel *et al.*[66] The hydroxide group in **5-OH** is substituted by a pyrazole using tetrafluoroboric acid (HBF_4) as a catalyst and the substitution reaction is complete in less than 5 min; within the first minute, the reaction colour changes from yellow to greenish-brown thus indicating that the reaction was occurring. The blue aqueous layer obtained during the work-up implies that ferrocenium ions have formed as a result of attack by the acid.[81] Ferrocenium ion formed using this procedure was considerably less since the desired compounds were obtained in good yields (above 80%). The disappearance of the OH stretching frequency and the subsequent appearance of the $\upsilon_{(CN)}$ band at 1509 cm^{-1} for **6a** and 1550 cm^{-1} for **6b** confirm that the substitution had occurred.

From the ^1H NMR spectra, the additional singlets appearing at 7.46 ppm, 6.16 ppm and 7.26 ppm in **6a** correspond to the protons on the third, fourth and fifth positions of the pyrazole ring, Figure 2.16. A singlet appearing at 5.71 ppm and two others at 2.19 and 2.16 ppm in **6b** correspond to a proton on the fourth position on the pyrazole ring and a pair of methyl protons attached on the pyrazole, Figure 2.16. This serves as further evidence that substitution of pyrazoles on the stereogenic centre had indeed occurred. For the ESI mass spectra of **6a** and **6b**, see Appendix Figure A3.

[81] M. Rausch, *Can. J. Chem.* 41 (**1963**) 1304.

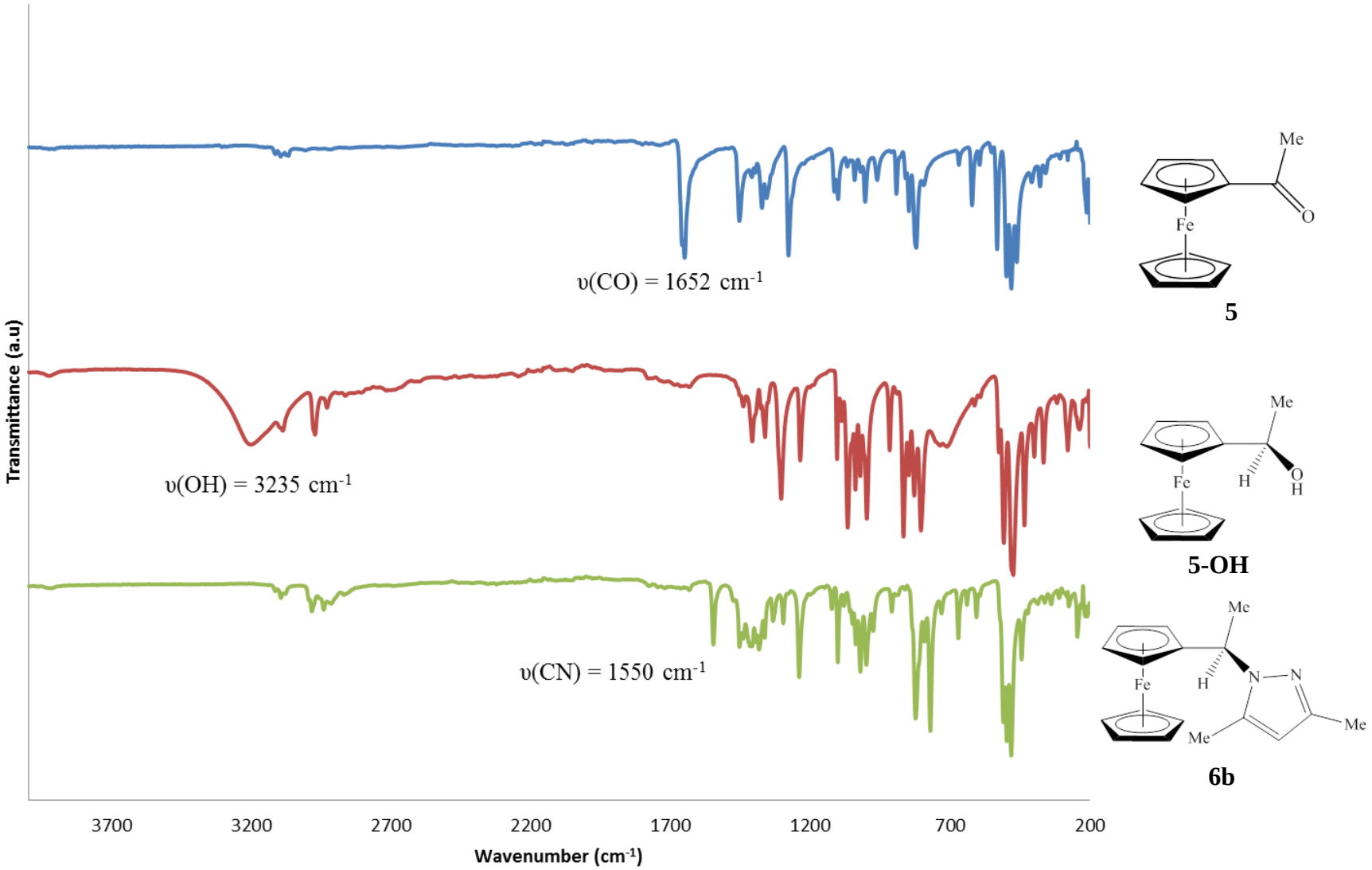
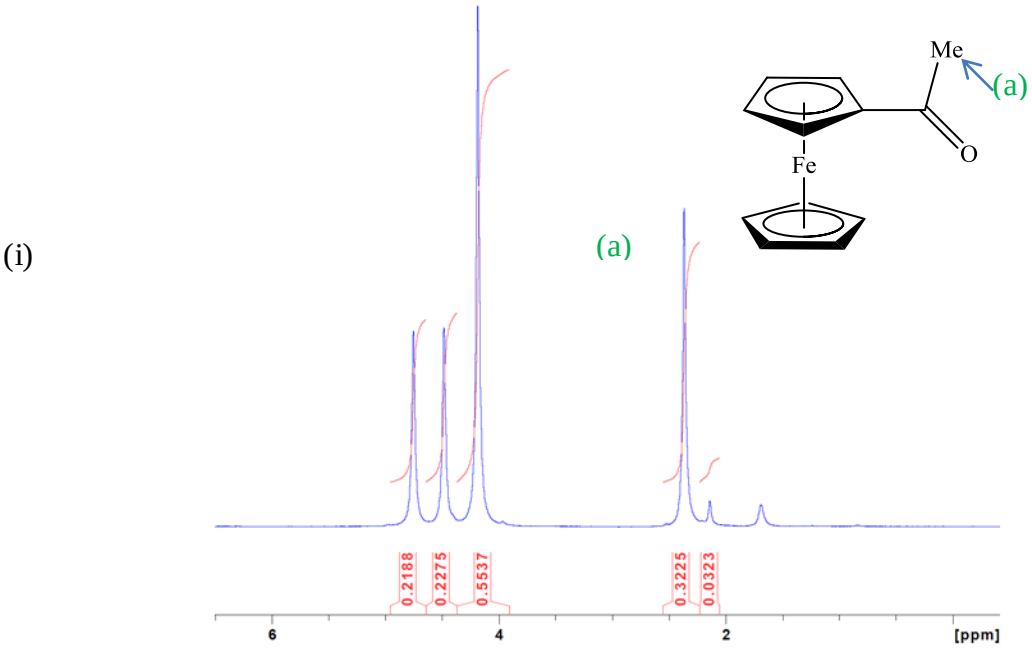


Figure 2.14: FT-IR spectra of **5**, **5-OH** and **6b**

(i)



(ii)

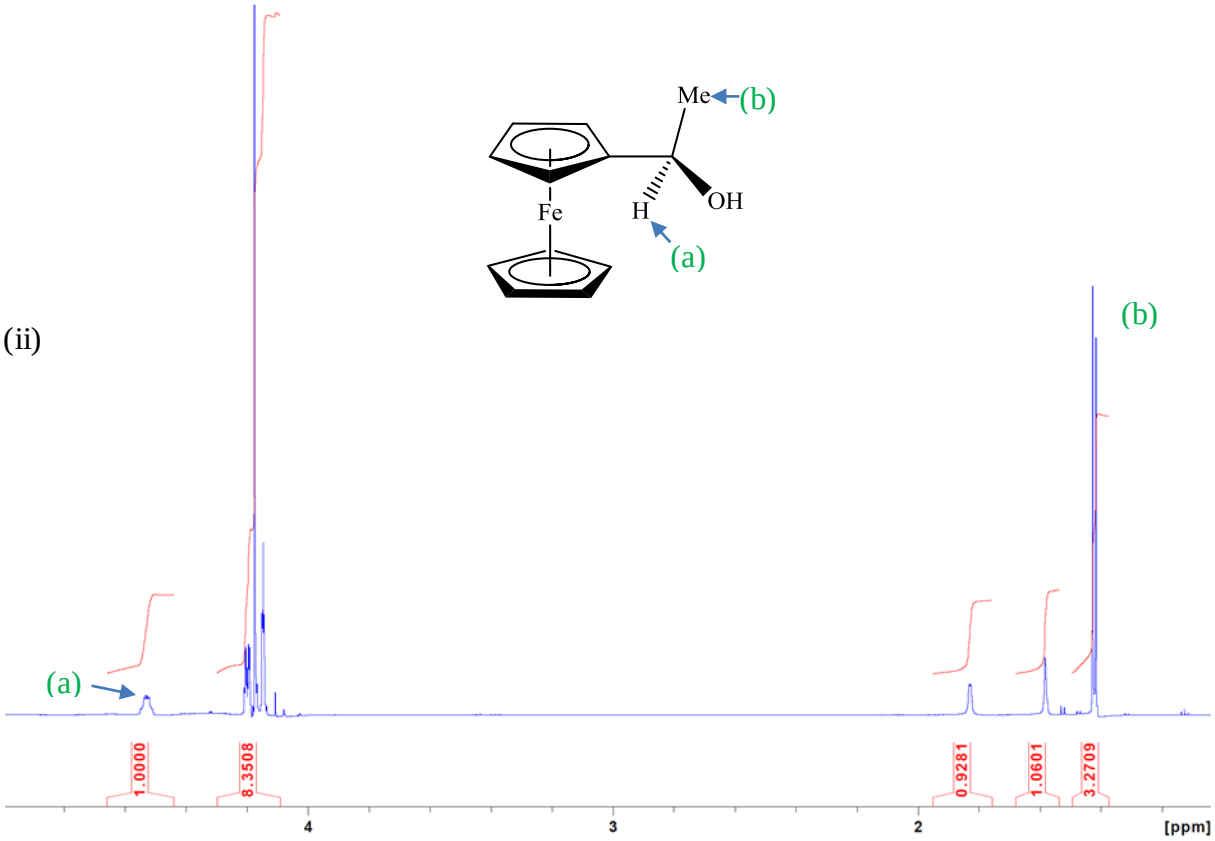


Figure 2.15: The ^{1}H NMR spectra of (i) **5** and (ii) **5-OH**.

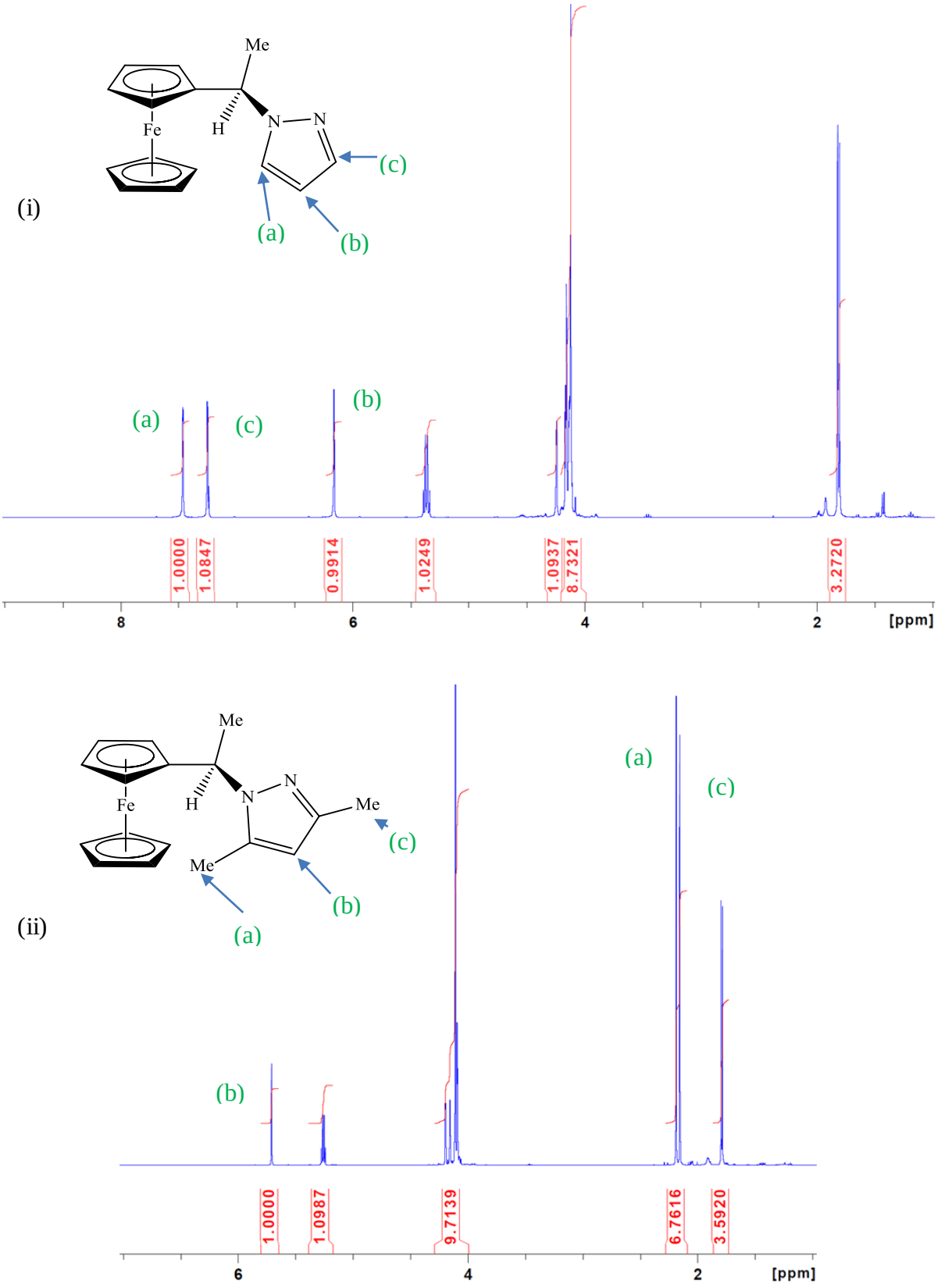
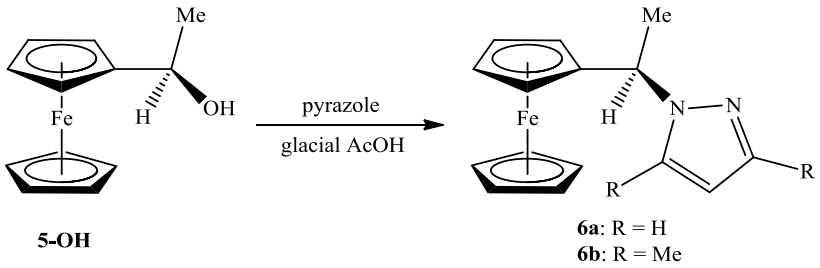


Figure 2.16: The ^{1}H NMR spectra of (i) **6a** and (ii) **6b**

An attempt to use a bulkier 3,5-diphenylpyrazole was carried out using the same procedure. The reaction proceeded in the same manner as observed in the preparation of **6a** and **6b**. However, the spectroscopic data obtained suggests that the substitution reaction had not occurred. This was unexpected since a similar ligand, with a methylene linker between ferrocene and 3,5-diphenylpyrazole moiety, has been prepared using a similar procedure.[82] It was concluded that the methyl moiety on the stereogenic carbon causes steric hindrance hence no reaction takes place.

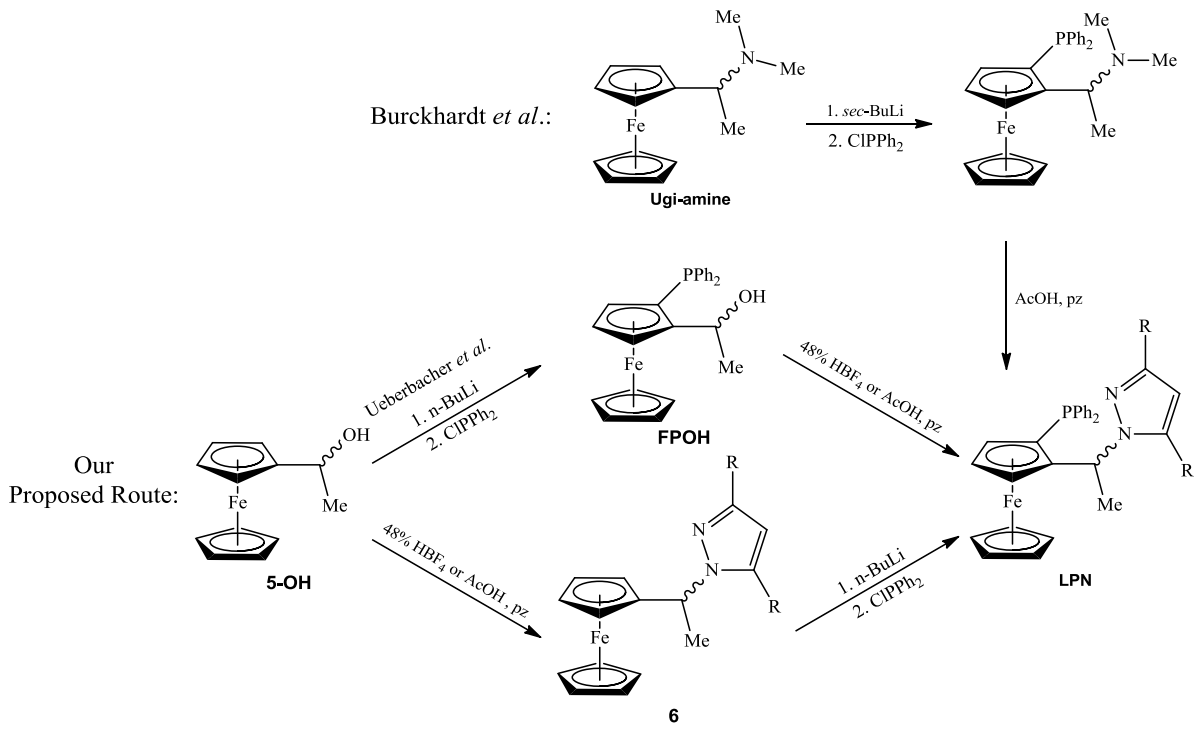
It is noteworthy that **6a** and **6b** can also be prepared using another modified procedure using the acetate intermediate,[67] Scheme 2.3. However, the procedure requires that the reaction be carried out for a minimum duration of six hours. Furthermore, the reaction requires heating and the yields are not better than those observed in the preferred method.



Scheme 2.3: Alternative method for the preparation of **6a** and **6b**.

The preparation of **LPN** compounds following the synthetic protocol by Burckhardt *et al.*[64c] makes use of the expensive Ugi amine scaffold, Scheme 2.4. Ueberbacher *et al.*[68] reported the use of a relatively cheaper scaffold **5-OH** which reacts in a similar way to the Ugi amine, the product **FPOH** adopted the same 1,2-disustituted configuration as that of the expected product, **LPN**. Since **LN1** compounds can be prepared from **5-OH** following the reaction protocol by either Simenel *et al.*[66] or Seo *et al.*[67] it was deemed theoretically possible to prepare **LPN** from **FPOH**. Furthermore, an opportunity to prepare **LPN** directly from the **LN1** compounds was identified; this would require anchoring a phosphine moiety as a last step in the preparation and therefore minimising the risk of oxidizing the phosphine moiety.

[82] C. López, A. González, R. Bosque, P.K. Basu, M. Font-Bardía, T. Calvet, *RSC Adv.* 2 (**2012**) 1986.



Scheme 2.4: The preparation of **LPN**

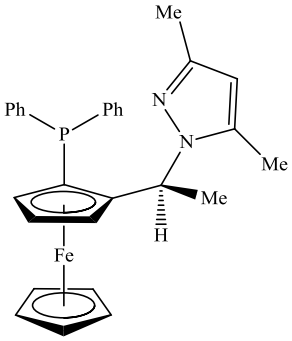
The two possible routes in Scheme 2.4 were put to test; the main focus was directed at anchoring the phosphine group at the ortho-position of the ferrocene backbone. Ueberbacher *et al.*[68] showed that **FPOH** is prepared at low temperatures using different solvents such as cyclohexane which has a high freezing point. It was however observed that the alcohol **5-OH** had poor solubility in cyclohexane at temperatures below 5 °C, fortunately this was not the case with **6a** and **6b**.

A red coloured solution is obtained during the reaction between *n*-BuLi with **6b** indicating that the lithiation had occurred; a turbid, orange coloured mixture formed immediately when **6a** was lithiated. It was also observed that the red colour of the solution slowly fades back to its original orange colour and a turbid mixture is formed when the reaction time exceeds two hours. Since a stabilising agents such as *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) was not used, it was assumed that this observation may possibly be due to short life span of lithiated intermediates. TMEDA is also used to activate *n*-BuLi but the ortho-directing group anchored on the ferrocenyl

scaffold is able to play a similar role, furthermore the combination of *n*-BuLi and TMEDA is known to favour dilithiation.[83] The reaction time was then reduced to a maximum of one hour, during which the solution was still red.

When the chlorodiphenylphosphine was added, the formation of the yellow turbid mixture signalled a substitution reaction taking place. Using thin-layer chromatography (TLC) it was established that a mixture of diethyl ether and hexane (volume ratio 3:1) was a good solvent mixture capable of separating the product **LPNb** from the crude product. Three orange bands were separated in a silica packed column. The first eluted band contained an unidentified compound whose ^{1}H and ^{31}P NMR spectroscopy data suggests that it contains a phosphine moiety. The FT-IR spectrum of the second band is superimposable to that of the starting material **6b**. The ^{1}H and ^{31}P NMR spectroscopy data of the third band corresponds to that of the expected product.[64c]

Table 2.2: ^{31}P and ^{1}H NMR spectroscopy data of **LPNb**.

Compound	Component	Togni and co-workers δ (ppm)	Obtained δ (ppm)
	^{31}P	-24.1	-23.8
	H-Ph	7.53 – 6.68	7.47 – 6.69
	-C<u>*H*</u>(pz)CH_3	5.58	5.60
	H-pz	5.06	5.04
	η^5-C_5H_3	4.80	4.84
	η^5-C_5H_3	4.36	4.35
	η^5-C_5H_5	4.05	4.03
	η^5-C_5H_3	3.73	3.72
	Me-pz	2.13	2.12
	Me-pz	1.95	1.95
	-CH(pz)C<u>*H*</u>$_3$	1.70	1.82

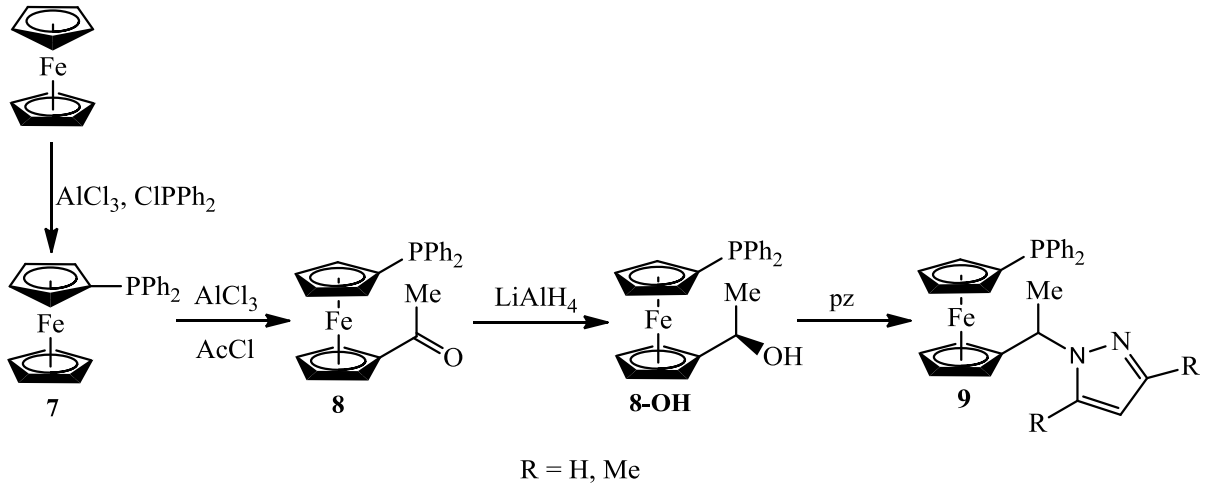
[83] R. Sanders, U.T. Mueller-Westerhoff, *J. Organomet. Chem.* 512 (**1996**) 219.

The NMR spectroscopy data obtained was compared to the results published by Togni and co-workers,[64c] as they were the first to prepare the **LPN** compounds. The findings were similar to the ones they obtained as shown in Table 2.2, and also Appendix Figure A4. This confirms that **LPNb** was indeed successfully prepared using different synthetic protocols.

The shifting of the υ(CN) band by 5 cm^{-1} from 1550 cm^{-1} in the starting material **6b** was a clear indication that a ferrocenyl scaffold had been modified to form **LPNb**, Figure 2.17. The observed major shift may imply that a modification had occurred at close vicinity of the pyrazole substituent. The appearance of the υ(CP) band at 696 cm^{-1} and the phenyl overtone bands appearing at the range between 1600 cm^{-1} and 2000 cm^{-1} confirm the presence of the diphenylphosphine moiety.

2.2.1.2.2 Syntheses using the ferrocenyl monophosphine scaffold

The preparation of monosubstituted ferrocenyldiphenylphosphine, **7**, was carried out *via* a typical Friedel-Crafts reaction using a cheaper $AlCl_3$ unlike the alternative route that proceeds *via* a lithiated ferrocene intermediate formed using an expensive *t*-BuLi[83] with potassium *tert*-butoxide used as a base, Scheme 2.5. Furthermore, in our preparation the carcinogenic benzene solvent was replaced with toluene. The product was characterised by elemental analysis, FT-IR, ^{1}H and ^{31}P NMR spectroscopy and mass spectrometry. For the NMR and mass spectrometry data of **7**, see Appendix Figure A6 and A7.



Scheme 2.5: Proposed route for the preparation of **9**.

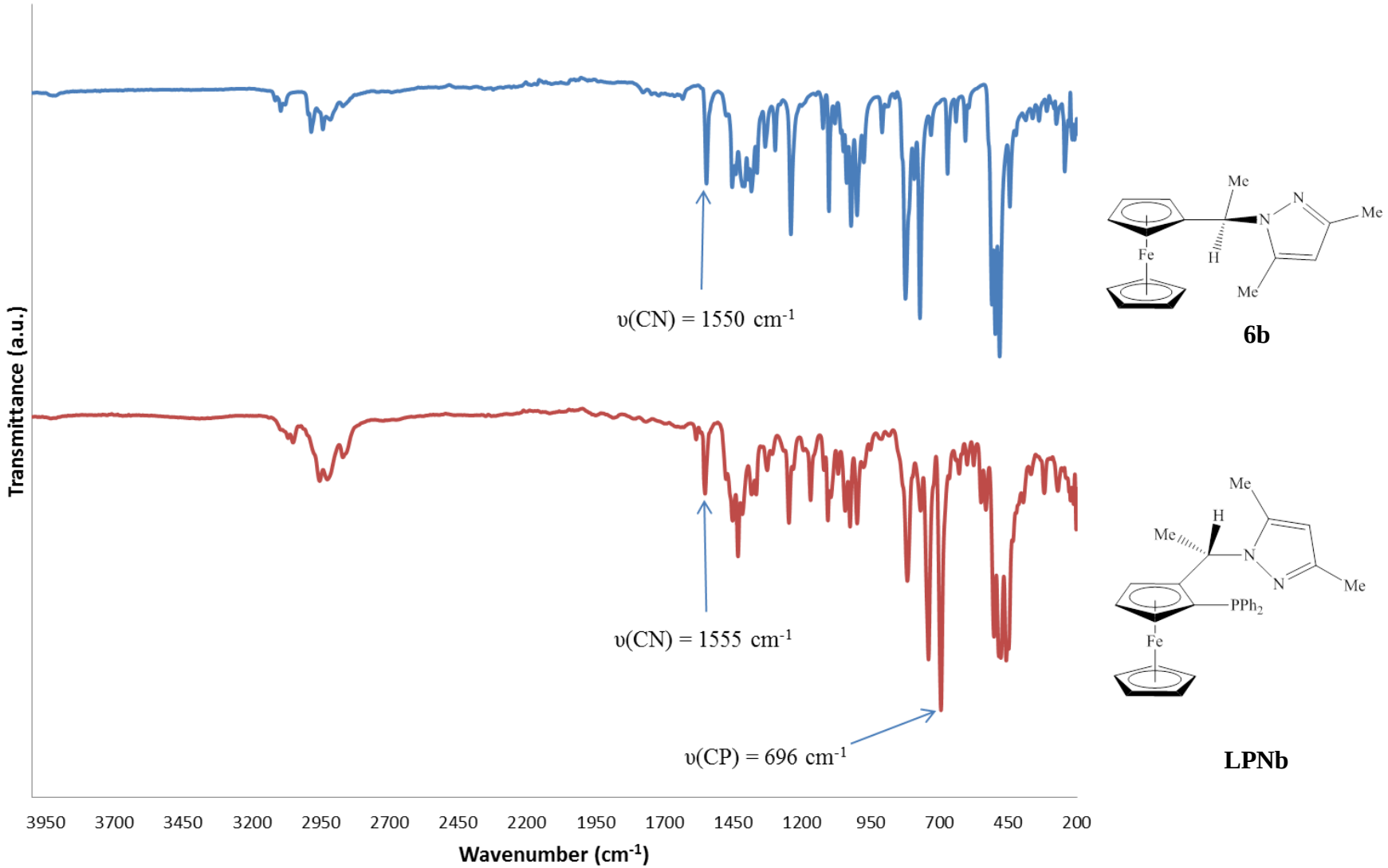
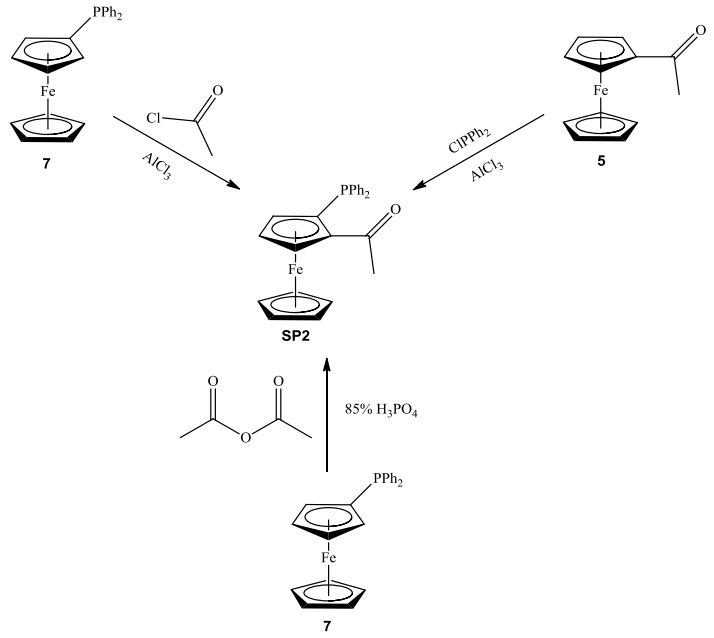


Figure 2.17: FT-IR spectra of **6b** and **LPNb**

The successful preparation of compound **7** led to an attempt to design an alternative synthetic protocol that would lead to the preparation of **LPN** compounds. This protocol would not involve the use of *n*-BuLi, it was also anticipated that a homoannular disubstituted ligand scaffold **SP2** would be formed instead, Scheme 2.6. To achieve this, reaction protocols for the preparation of acetylferrocene **5** and ferrocenyldiphenylphoshine **7** were combined.



Scheme 2.6: Proposed routes to the synthesis of 1-acetyl-2-diphenylphosphinoferrocene **SP2**.

The acetyl moiety was a preferred choice since it can be easily reduced thus introducing an additional central chirality to the molecule. There were three proposed routes that would lead to the preparation of the **SP2** scaffold, two of these showed no sign or reaction. The Friedel-Crafts acetylation of **7** with acetyl chloride was the only one to produce an acetylated product while no reaction occurred when acetic anhydride was used as an acetylating agent or when **5** was used as a starting material. It was expected that substitution would occur in the α- or β-positions of the substituted cyclopentadienyl (Cp) as in the phosphaferrocene reported by Mathey[84], Figure 2.18. However, upon characterisation of the acetylated product it became clear that the acetylated product was actually heteroannular and not homoannular as expected.

[84] F. Mathey, *J. Organomet. Chem.* 139 (**1977**) 82.

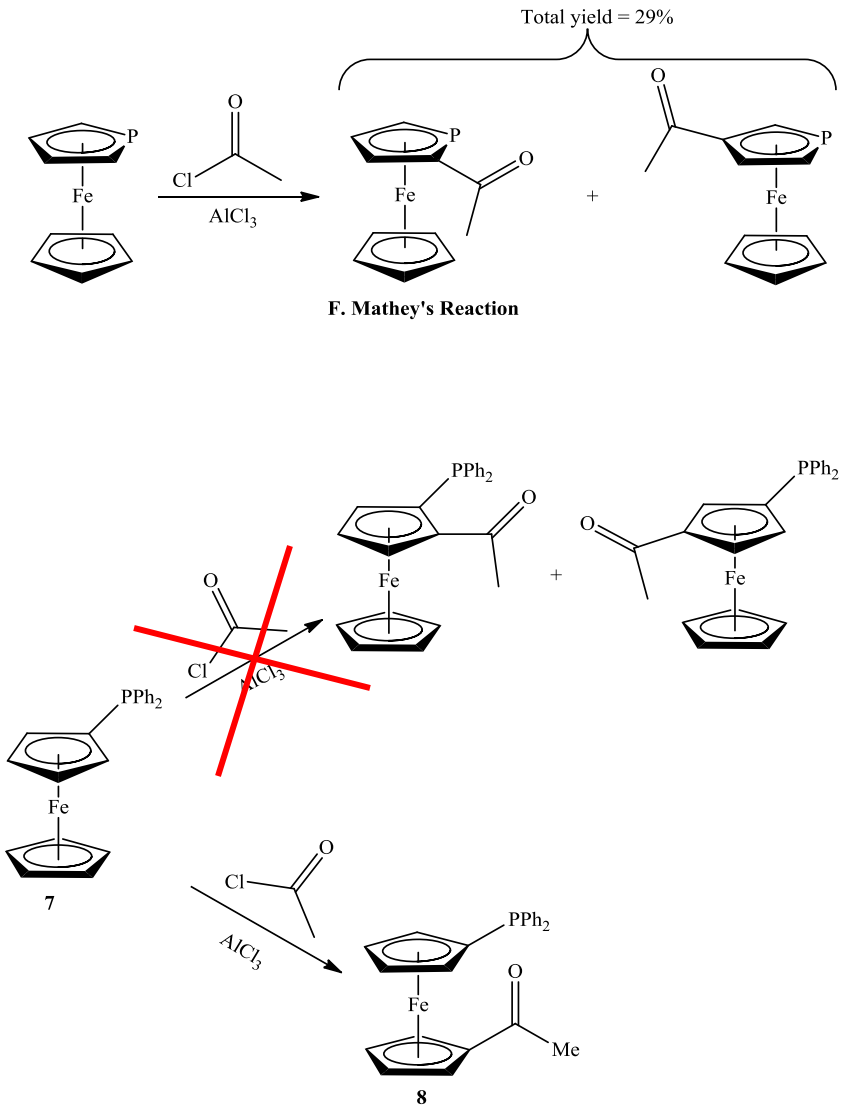


Figure 2.18: Preparation of **8** *via* Friedel-Crafts acetylation.

The presence of four equal cyclopentadienyl peaks at 4.65, 4.38, 4.35 and 4.10 ppm in the ^{1}H NMR spectrum of **8** suggests that a heteroannular, 1,1′-disubstituted product was obtained instead, Figure 2.19. The singlet appearing at 2.29 ppm is due to the protons of the methyl group attached to the carbonyl. The multiplet appearing at 7.34 ppm corresponds to the phenyl rings substituents on the phosphine. On the ^{31}P NMR spectrum the presence of the singlet that has shifted to -18.2 ppm from -16.5 ppm in **7** indicates that **8** was successfully prepared. The additional peak at 27.8 ppm is due the oxidized product. The intensities of the two peaks were carefully examined and it was concluded that a small amount of the product was oxidized. The oxidized product was not isolated, thus could not be identified.

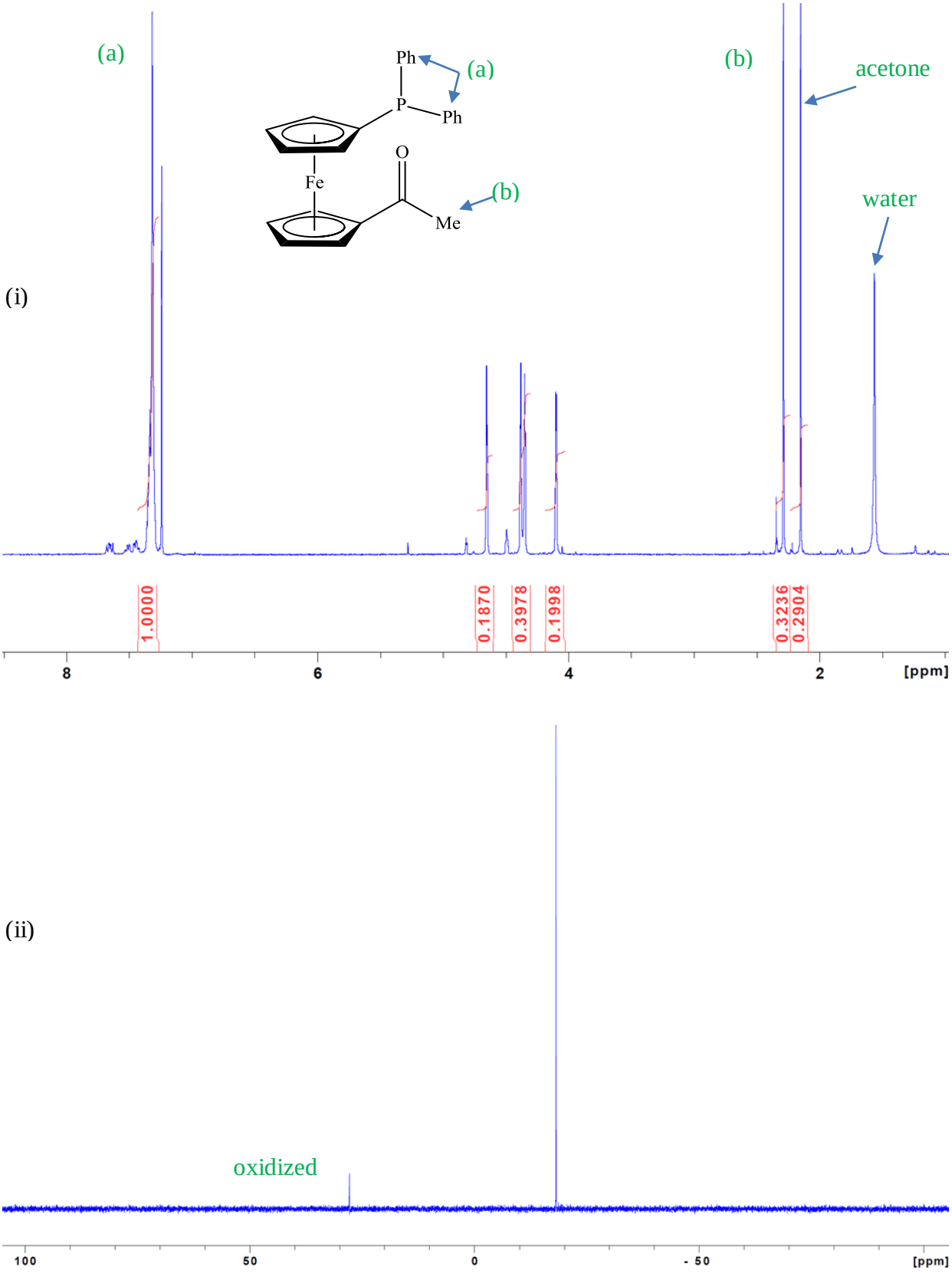


Figure 2.19: The (i) ^{1}H and (ii) ^{31}P NMR spectra of **8**

From mass spectrum, the presence of the molecular ion [M^+ + H] appearing at *m*/*z* = 413.1 corresponds to the expected product, Figure 2.20. This further suggests that the scaffold **8** could have been prepared successfully. Since the molecular ion is the base peak, this means the scaffold is thermally stable at higher temperatures before it undergoes fragmentation.

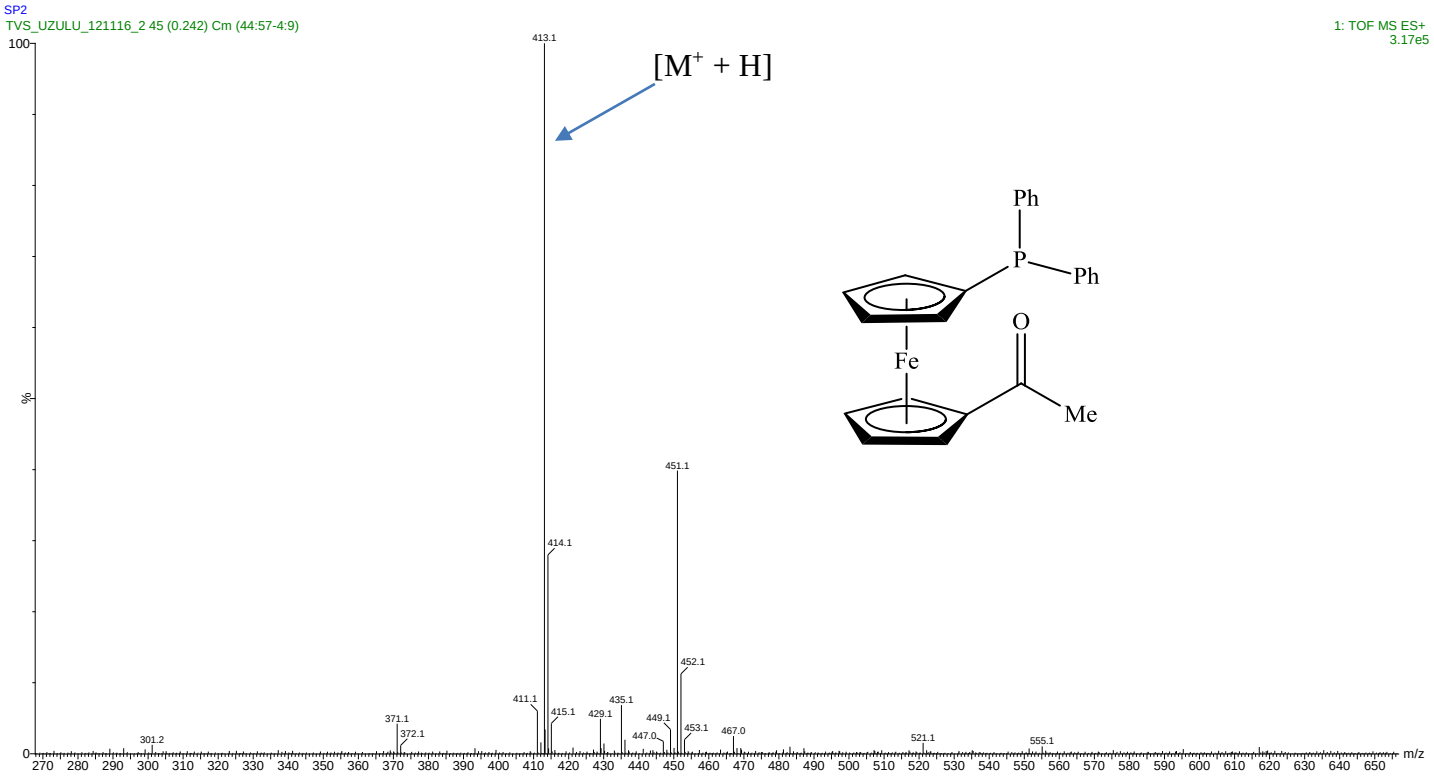


Figure 2.20: ESI mass spectra of **8**

The heteroannular scaffold, **8**, was obtained in reasonably good yields and could be reduced using only $NaBH_4$. The reduced scaffold was obtained as an oil unlike the ferrocenyl alcohol **5-OH** which was obtained as a solid. The replacement of the $\upsilon_{(CO)}$ band appearing at 1669 cm^{-1} in **8** by the $\upsilon_{(OH)}$ band at 3428 cm^{-1} on **8-OH** suggests successful reduction to an alcohol using $NaBH_4$, Figure 2.21. While there was an small shift in the $\upsilon_{(PC)}$ bands which appear at 697 cm^{-1} for both **8** and 696 cm^{-1} for **8-OH.** The presence of these bands was however further confirmation that the phosphine moiety was still attached to the ferrocenyl backbone. The establishment of the stereogenic centre in **8-OH** was confirmed by the presence of doublet at 1.35 ppm and a quartet at 4.46 ppm corresponding to protons of the methyl and methine groups respectively, Figure 2.22.

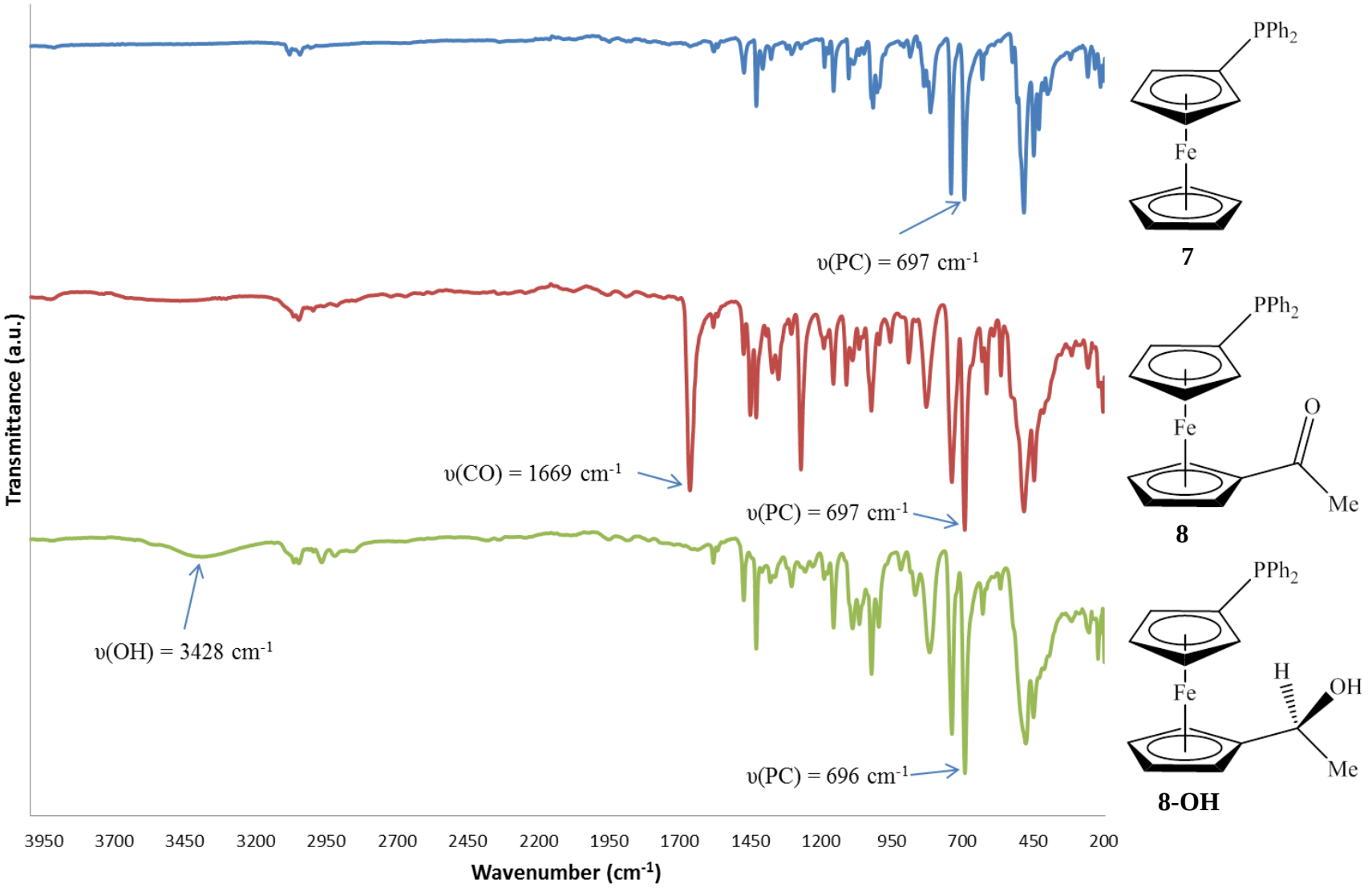


Figure 2.21: FT-IR spectra of **7**, **8** and crude **8-OH**

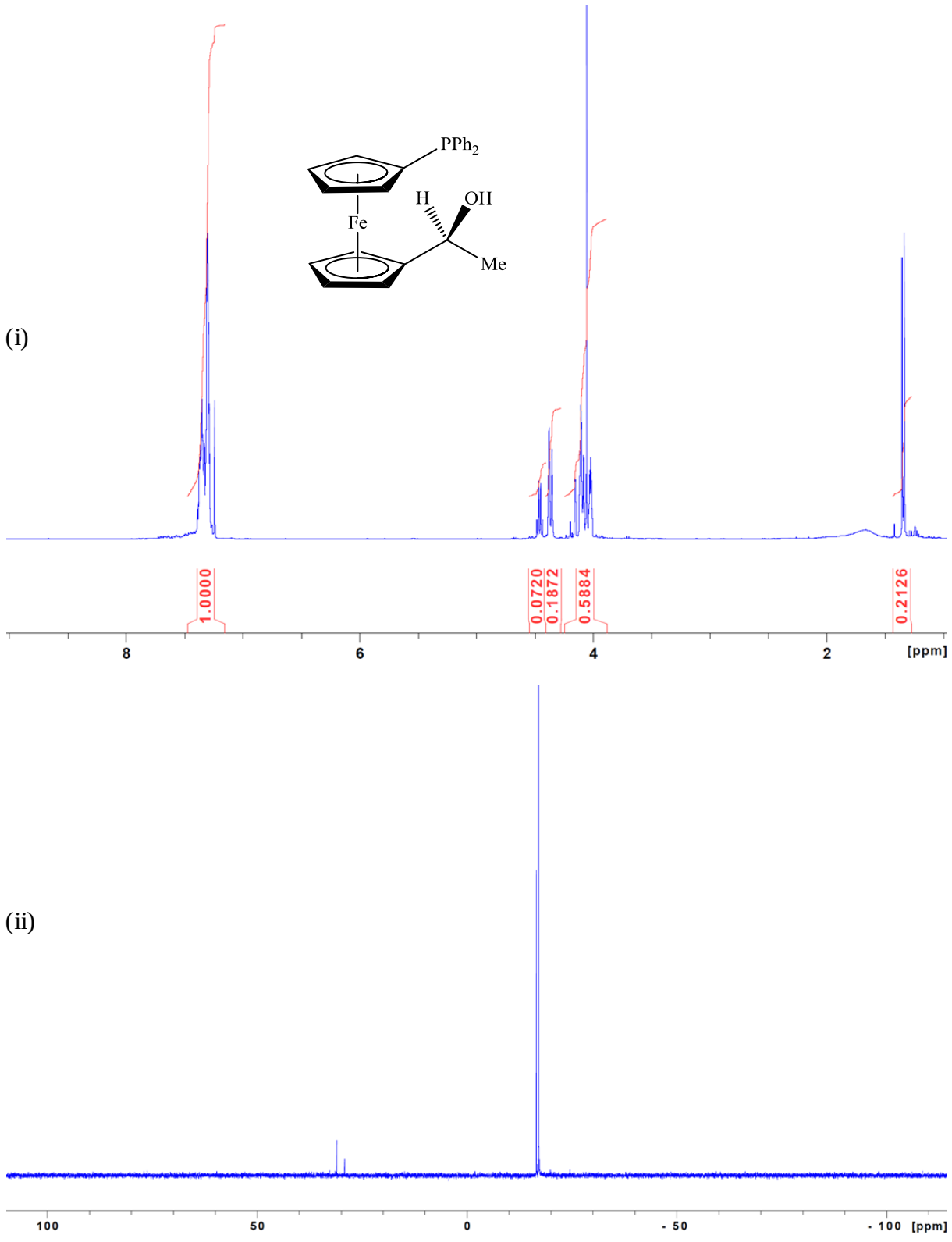


Figure 2.22: The (i) ^{1}H and (ii) ^{31}P NMR spectra of crude **8-OH**

Even though the formation of the heteroannular **8** was not expected, an opportunity to use this scaffold to prepare heteroleptic P^N and homoleptic P^P compounds endowed with axial and central chirality was identified, Figure 2.23. There are a lot of advantages in using **8** as the ligand scaffold, for example it is obtained as a solid which is moisture and air stable, and should the phosphorus atom centre be oxidized during one of the reaction steps (as evident in the ^{31}P NMR spectrum of **8**, Figure 2.19), it can be reduced back to its original state together with the acetyl group using reducing agents such as trichlorosilane[85] and diisobutylaluminium hydride (DIBAL-H).[86]

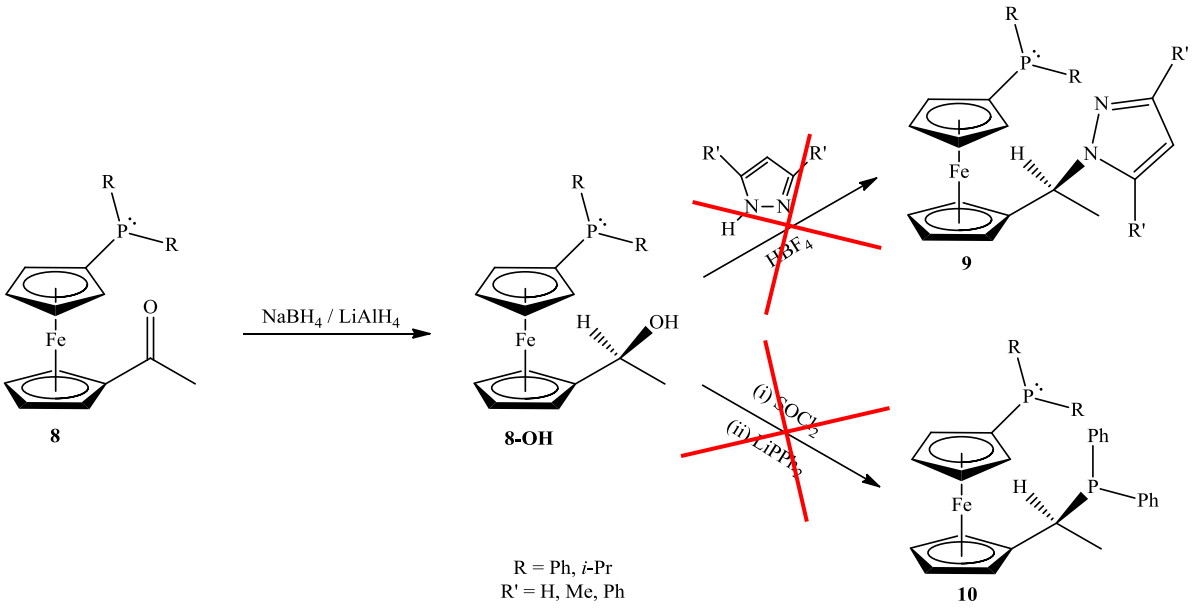


Figure 2.23: Proposed preparation of heteroleptic (P^N) and homoleptic (P^P) ferrocenyl phosphine ligands.

Substitution with the pyrazole moiety on **8-OH** should be possible since no problems were encountered when **6** compounds were prepared from ferrocenyl ethanol **5-OH**. It is also expected that the similar results would be observed, for example, quantitative yields of a product which is obtained analytically pure. Disappointingly, attempts to effect substitution reaction on the reduced derivative **8-OH** were unsuccessful.

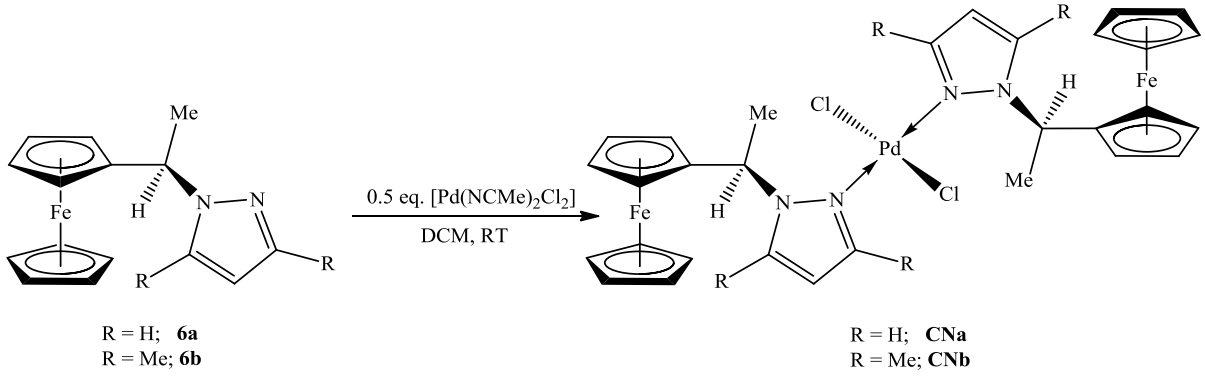
[85] (a) L.D. Quin, K.C. Caster, J.C. Kisalus. K.A. Mesch, *J. Am. Chem. Soc.* 106 (**1984**) 7029. (b) E.J. Enholm, J.P. Schulte II, *J. Org. Chem.* 64 (**1999**) 2610.

[86] C.A. Busacca, R. Raju, N. Grinberg, N. Haddad, P. James-Jones, H. Lee, J.C. Lorenz, A. Saha, C.H. Senanayake, *J. Org. Chem.* 73 (**2008**) 1531.

2.2.2 Palladium(II) Complexes

The preparation of most of the palladium(II) complexes was carried out using $[PdCl_2(NCMe)_2]$ as a metal precursor. The reactions were performed in dichloromethane (CH_2Cl_2) as a solvent at room temperature. The ligands **6a** and **6b** were complexed to $[PdCl_2(NCMe)_2]$ using a ligand to metal precursor ratio of 2:1 because of the monodentate nature of the ligands to produce **CNa** and **CNb** respectively, Scheme 2.7. Washing of the crude products with hot hexane afforded pure complexes in very good yields of 89% and 84% for **CNa** and **CNb**, respectively.

These complexes were obtained as light orange solids and showed good solubility in CH_2Cl_2 and warm THF. In instances where very pure complexes were required, recrystallisation was carried out using THF or a mixture of DCM and acetonitrile. It was observed after recrystallization, separation of the crystals from the mother liquor makes the crystals to crumble into a powdery form. This implies that the crystals are stabilised by hydrogen bonding with the solvent molecules. Recrystallization of **CNb** using a single solvent system can be achieved; THF forms crystals quicker than the dichloromethane and acetonitrile mixture. On the other hand, **CNa** failed to form crystals using common laboratory solvents.



Scheme 2.7: The preparation of **CNa** and **CNb** complexes

From the FT-IR spectroscopy results it was clear that complexes had formed. The $\upsilon_{(CN)}$ frequency increase to 1517 cm^{-1} in **CNa** complex from 1509 cm^{-1} in **6a** ligands was observed. A similar case was observed for **CNb**; an increase to 1556 cm^{-1} from 1550 cm^{-1} in 6**b**. This increase is mainly due to the electronic influence exerted by the Pd metal centre. A typical FT-IR spectra of the ligand and the corresponding complex is provided in Figure 2.24.

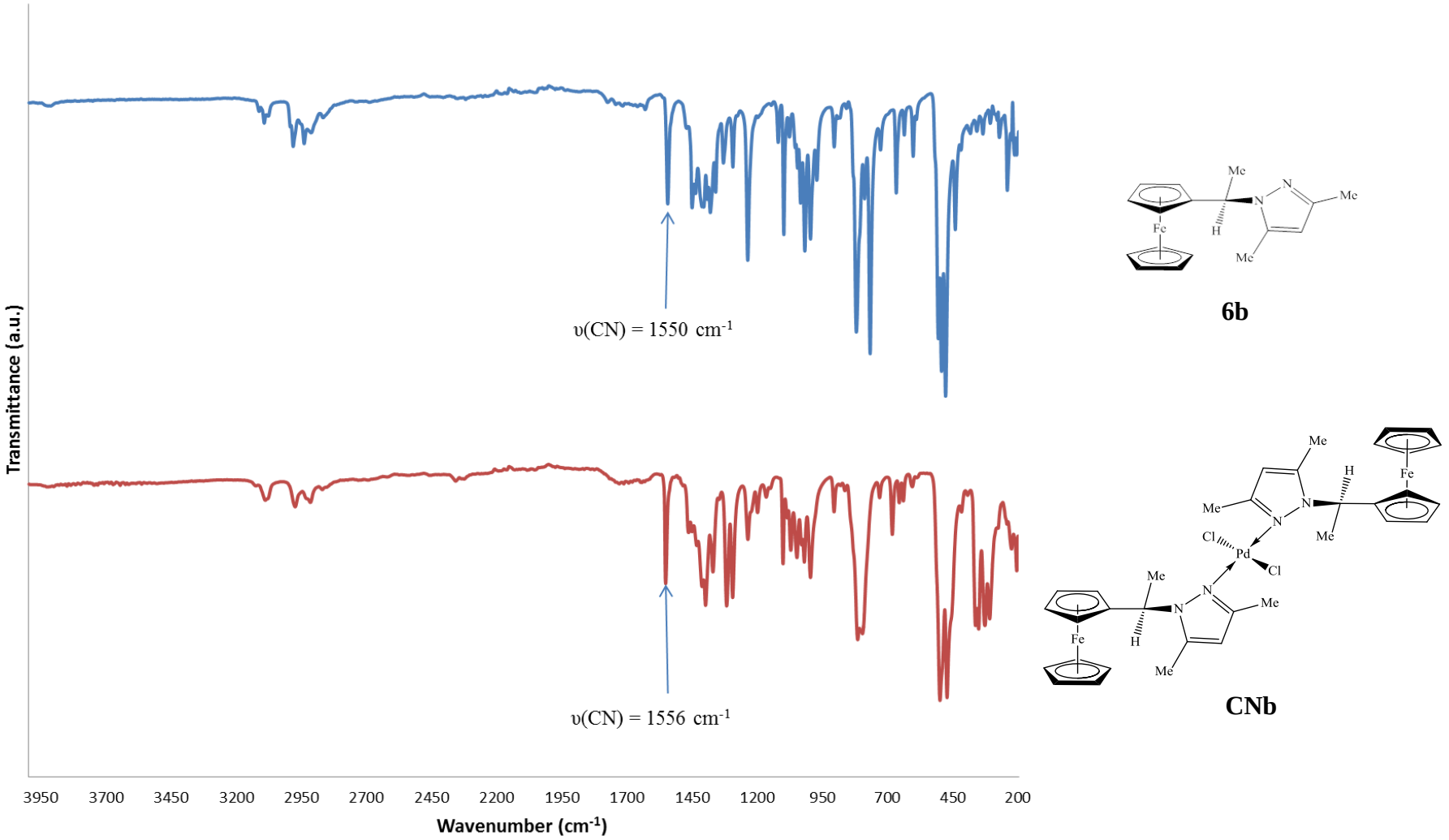


Figure 2.24: Typical comparative FT-IR spectra of the ligand (**6b**) and the corresponding complex (**CNb**).

Further evidence for the formation of the complexes was obtained from ^{1}H NMR spectroscopy, Figure 2.25. The presence of the quartet peaks at 7.79 and 7.92 ppm corresponding to the proton of the methine group in **CNa** and **CNb** respectively, shift downfield compared to 5.39 and 5.26 ppm in their respective ligands. Interestingly, a pair of doublets corresponding to the protons of the methyl on the stereogenic carbon in **CNa** were observed instead of a single doublet. The same was also observed for singlets corresponding to the α- and β-hydrogens on the substituted cyclopentadienyl rings in both **CNa** and C**Nb** where four peaks were observed instead of two peaks**.** This phenomenon is explained by the structural flexibility brought about by the stereogenic centre which consequently results in an unsymmetrical orientation of the ligand moieties in the complexes **CNa** and C**Nb**. The doublet appearing at 2.09 ppm corresponding to the methyl on the stereogenic centre in C**Nb** did not split in two doublets like in the case of **CNa** and it was spotted downfield compared to 1.80 ppm in **6b**.

There is a slight downfield shift for the proton attached to the fourth-position of the pyrazole substituents in **CNa** and C**Nb**. In the ^{1}H NMR spectrum of **CNa** the peak appearing at 6.24 ppm was observed at 6.16 ppm in the ligand while for **CNb** the appears at 5.77 compared to 5.71 ppm in the corresponding ligand. The remaining protons on the third and fifth position of the pyrazole in **CNa** appear at 7.17 ppm and 7.15 ppm. The two peaks appearing at 1.87 and 2.98 ppm in C**Nb** correspond to the methyl protons on the third and fifth positions which were observed at 2.16 and 2.19 ppm in **6b**. The observed shifts in the complexes are consistent with the expected complexation of ligands to the palladium centre.

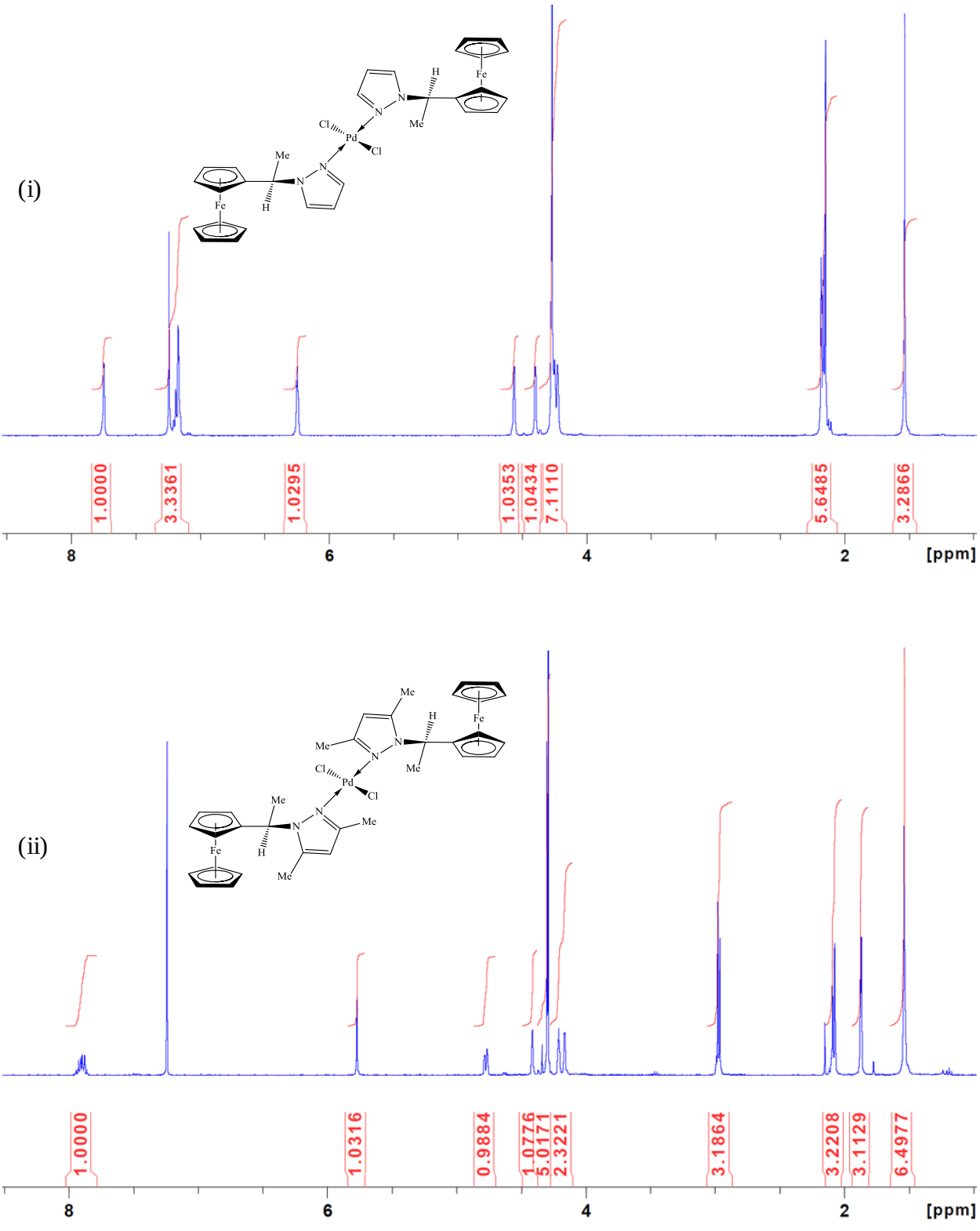
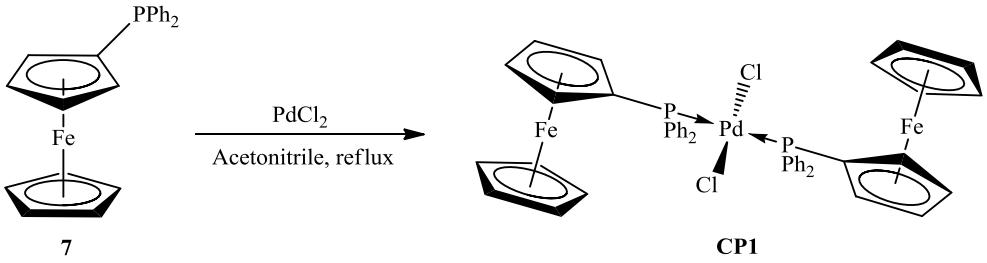


Figure 2.25: The comparative ^{1}H NMR spectra of (i) **CNa** and (ii) **CNb**

Attempts to prepare **CP1** following the same protocol yielded a product that showed indifferent solubility. This was overcome by preparing **CP1** using one-pot synthesis protocol, Scheme 2.8. In this one-pot synthesis reaction, it is assumed that $[PdCl_2(NCMe)_2]$ precursor is first formed *in situ* followed by complexation to the ligand used. The complex was obtained as a red coloured solid in moderate yields of 52% after it was washed with diethyl ether.



Scheme 2.8: Preparation of **CP1**.

The one pot synthesis method could possibly be extended to include the preparation of **CN1** complexes. However, since heating is involved this might lead to C-H activation thus producing cyclopalladated products. It is well documented that cyclometallation with ferrocenyl compounds bearing pyrazolyl[87] and phosphinyl[88] moieties are usually catalysed by either a base or an acid at various temperatures mostly using ethanol or toluene as a solvent. High temperatures alone do not have a significant effect towards cyclopalladation.

The data obtained from FT-IR and ^{1}H NMR spectroscopy was inconclusive. In the FT-IR spectrum, there was an small shift of the $\upsilon_{(PC)}$ band to 694 cm^{-1} in **CP1** from 697 cm^{-1} in **7**, Figure 2.26. In the ^{1}H NMR spectrum, there was only splitting of the phenyl protons into two multiplets and the shifting of the cyclopentadienyl protons of **CP1** compared to **7**, Figure 2.27. The ^{31}P NMR spectrum on the other hand was able to confirm that the complexation had occurred due to the presence of the phosphorus peak at 15.2 ppm which appears downfield compared to -16.5 ppm in ligand **7**.

[87] C. López, A. González, R. Bosque, P.K. Basu, M. Font-Bardía, T. Calvet, *RSC Advances* 2 (**2012**) 1986.
[88] J.-P. Djukik, A. Hijazi, H.D. Flack, G. Bernardinelli, *Chem. Soc. Rev.* 37 (**2008**) 411, and references therein.

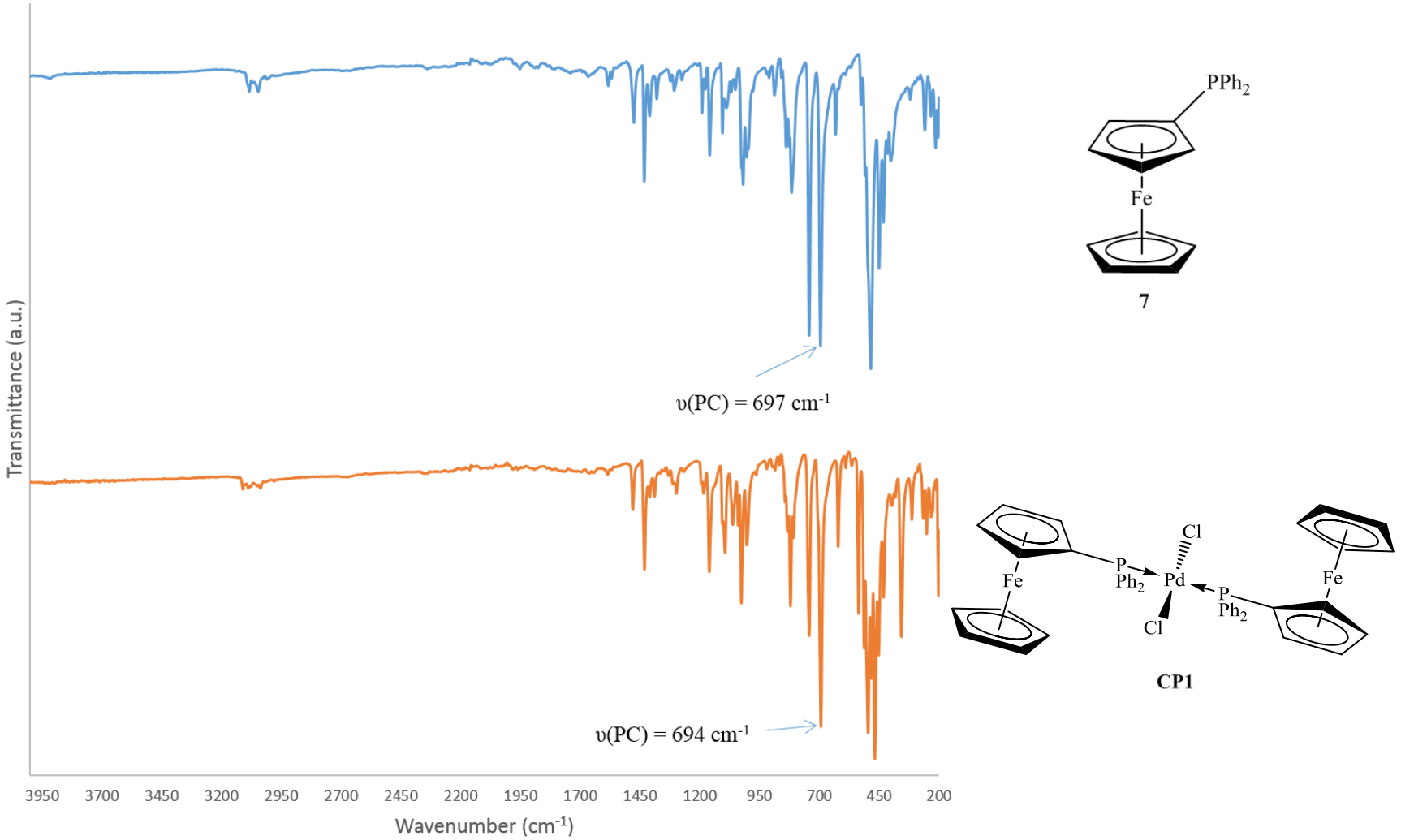
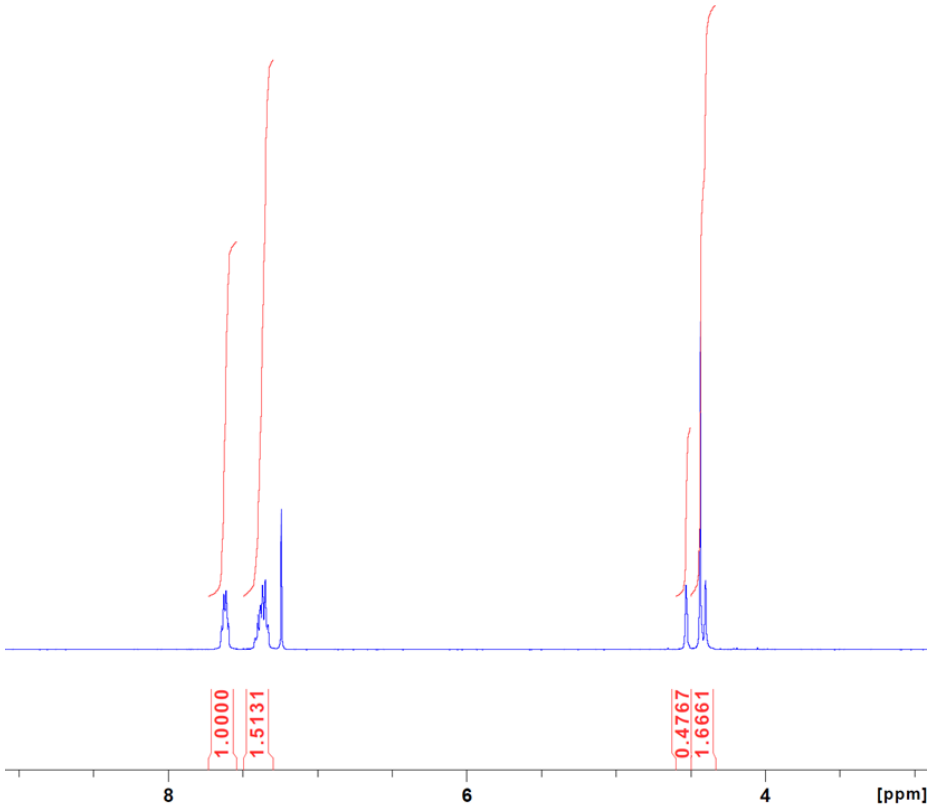


Figure 2.26: The FT-IR spectra of the ligand (**7**) and the corresponding complex (**CP1**).

(i)



(ii)

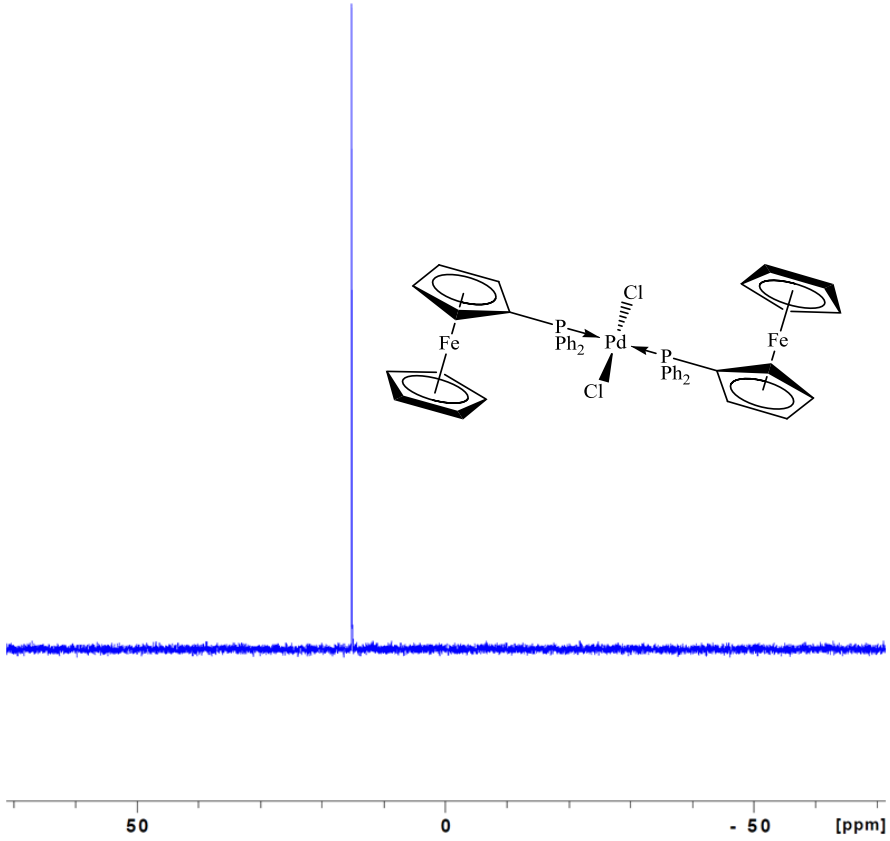
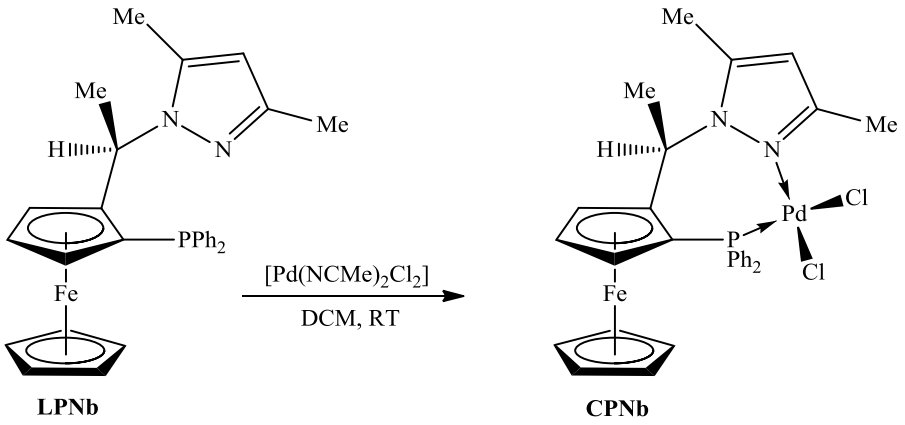


Figure 2.27: The (i) ^{1}H and (ii) ^{31}P NMR spectra of **CP1**.

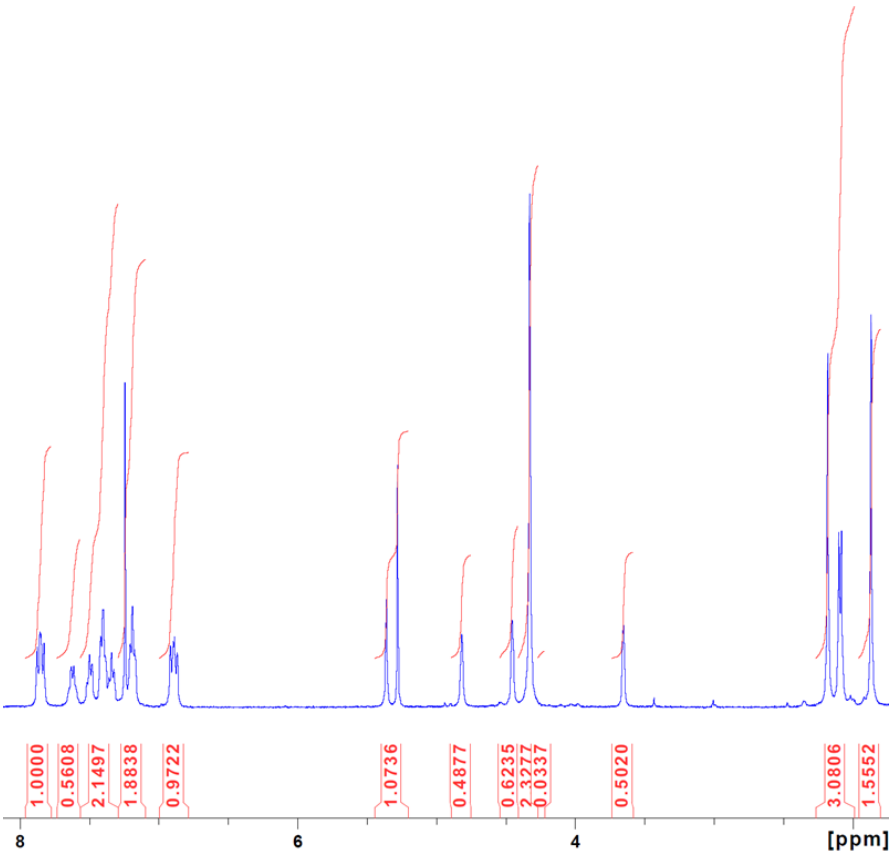
The preparation of **CPNb** compound was done using $[PdCl_2(NCMe)_2]$ and it behaved the same way as for **CN1** compounds, Scheme 2.9. The colour change from orange colour to red colour was an indication that complexation had occurred and the product was obtained in very good yields of 86% after washing with hot hexane. The ligand **LPNb** was used without further purification, that is, removal or reduction of the oxidized product. It was observed that this did not have any influence on the formation of **CPNb** since only one phosphorus peak was obtained and it appeared at 6.04 ppm compared to -23.8 ppm on the ligand **LPNb**, Figure 2.28. Further confirmation was obtained from ^{1}H NMR spectrum where the methine proton on the chiral centre appeared upfield (5.36 ppm in **CP1** compared to 5.60 ppm in **7**) and the methyl protons appear downfield (2.10 ppm in **CP1** compared to 1.82 ppm in **7**). Furthermore, the proton on the pyrazolyl ring and the protons on the phenyl rings appear downfield in **CP1** compared to the ligand **7**. There are also small shifts observed for the $\upsilon_{(CN)}$ and $\upsilon_{(PC)}$ bands on the comparative FT-IR spectra of **CP1** and **7**, Figure 2.29.



LPNb **CPNb**

Scheme 2.9: The preparation of **CPNb**

(i)



(ii)

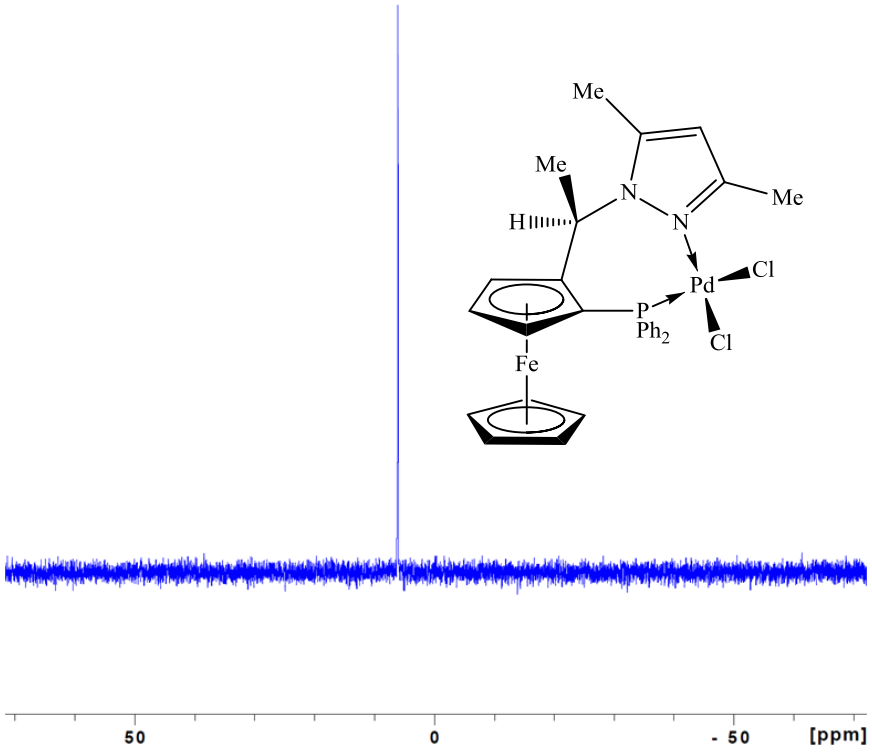


Figure 2.28: The (i) ^{1}H and (ii) ^{31}P NMR spectra of **CPNb**.

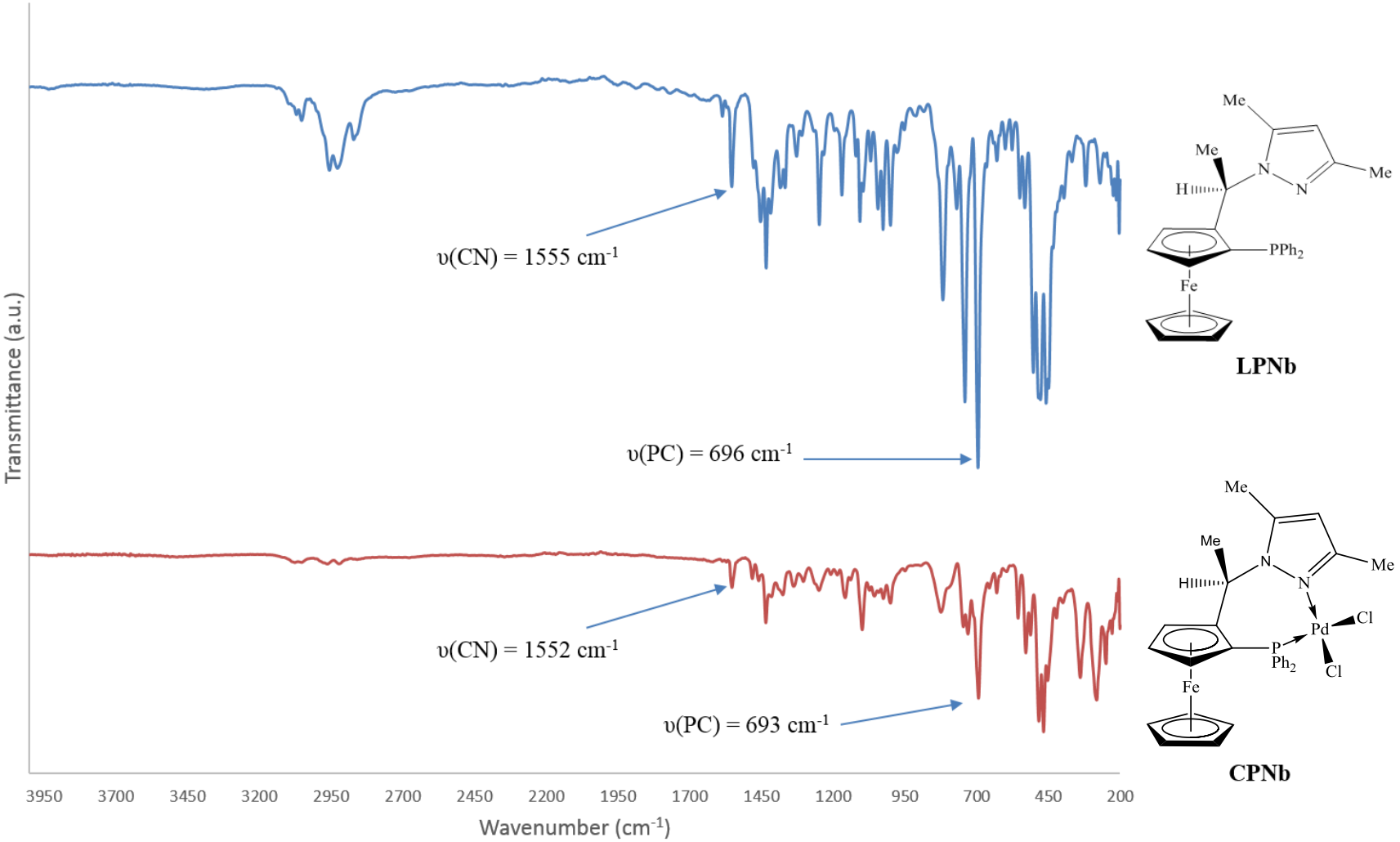


Figure 2.29: The FT-IR spectra of the ligand (**LPNb**) and the corresponding complex (**CPNb**).

2.3 Experimental.

2.3.1 Materials and Instrumentation.

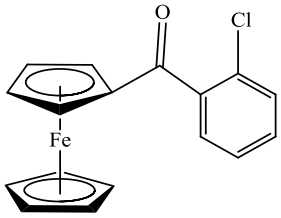
All reactions were carried out under inert nitrogen (N_2) atmosphere using standard Schlenk technique. Lithium wire, n-BuLi and pyrazole were purchased from Merck; the rest of the chemicals were purchased from Sigma-Aldrich and they were used as received. Starting materials such as 3,5-dimethylpyrazole,[89] 3,5-diphenylpyrazole,[90] 3,5-di-*tert*-butylpyrazole,[91] $HPPh_2$[92] and $PdCl_2(NCMe)_2$[93] were prepared using reported literature procedures. Cyclohexane, n-hexane, heptane, toluene and tetrahydrofuran (THF) were distilled over benzyl ketyl. Dichloromethane was distilled over P_2O_5. The dried solvents were stored over molecular sieves and used within five days.

FT-IR spectroscopy analyses were carried out in-house on a Bruker Tensor 27 FT-IR spectrometer using a standard ATR cell; the samples were analysed in their original form at the mid-IR range of 200 – 4000 cm^{-1}. Elemental analyses were also carried out in-house on a Perkin-Elmer 2400 Series II CHNS/O analyser. ^1H and ^{31}P $\{^1H\}$ NMR spectroscopy analyses of samples prepared in $CDCl_3$ were performed at the University of KwaZulu-Natal Westville campus (South Africa) on a Bruker Avance III 400 MHz and 600 MHz spectrometers. The residual peak of $CDCl_3$ at 7.24 ppm was used to reference ^1H chemical shifts. H_3PO_4 was used as an external reference for ^{31}P $\{^1H\}$ chemical shifts. Mass spectroscopy was performed at the University of Stellenbosch (South Africa) on a Waters Synapt G2 at a core voltage of 15 V, as well as in-house on a Agilent 7890A gas chromatograph fitted with a 5975C VL mass selective detector (MSD).

[89] R.V. Rothenburg, *Ber.* 27 (**1894**) 1097.
[90] N. Kitajima, K. Fujisawa, C. Fujimoto, Y. Morooka, S. Hashimoto, T. Kitagawa, K. Toriumi, K. Tatsumi, A. Nakamura, *J. Am. Chem. Soc.* 114 (**1992**) 1277.
[91] J. Alguero, E.G.R. Jacquier, *Bull. Soc. Chim. Fr.* 2 (**1968**) 707.
[92] D. Wittenberg, H. Gilman, *J. Org. Chem.* 23 (**1958**) 1065.
[93] G.K. Anderson, M. Lin, A. Sen, E. Gretz, *Inorg. Synth.* 28 (**1990**) 60.

2.3.2 Synthesis of ligand scaffolds and ligands

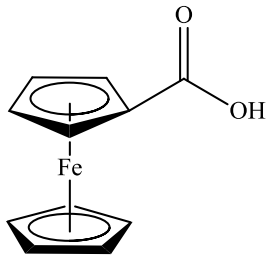
2.3.2.1 Preparation of 2-chlorobenzoyl ferrocene (**1**)



This was prepared using a modified literature procedure by Rausch *et al*.[94] Ferrocene (5.00 g, 26.9 mmol) was dissolved in dichloromethane (60 mL) and the resulting solution was cooled to 0 – 5 °C in an ice bath. To this solution, 2-chlorobenzoyl chloride (4.73 g, 3.42 mL, 26.9 mmol) was added followed by portion-wise addition of anhydrous $AlCl_3$ (3.65 g, 27.4 mmol). During the addition of anhydrous $AlCl_3$ the reaction colour changed from the original orange to dark blue. The reaction was stirred for 45 min at 0 – 5 °C and for 75 min at room temperature. The mixture was then transferred into a separating funnel containing ice-cold distilled water (100 mL) and the layers were separated. The remaining dark blue aqueous phase in the separating funnel was extracted with dichloromethane (3 x 20 mL). The combined red-coloured dichloromethane extracts were washed with distilled water (20 mL) and 10% NaOH solution (2 x 20 mL). The washed dichloromethane extracts were dried over anhydrous $MgSO_4$, filtered and the solvent was removed under reduced pressure producing deep red oil which solidified upon standing. The crude product was purified by column chromatography, hexane was used to elute unreacted ferrocene and dichloromethane to elute **1**. The solvent was evaporated and red crystalline solids of **1** were obtained. Yield = 6.55 g (75%). FT-IR: $\upsilon_{(CO)}$ = 1644 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.49 – 7.29 (m, 4H, -Ph), 4.72 (s, 2H, α-η^5-C_5H_4), 4.58 (s, 2H, β-η^5-C_5H_4), 4.25 (s, 5H, η^5-C_5H_5). Anal. Calc. for $C_{17}H_{13}OClFe$: C = 62.91%, H = 4.04%. Obtained: C = 62.28%, H = 3.97%. .

[94] M. Rausch, M. Vogel, H. Rosenberg, *J. Org. Chem.* 22 (**1957**) 905.

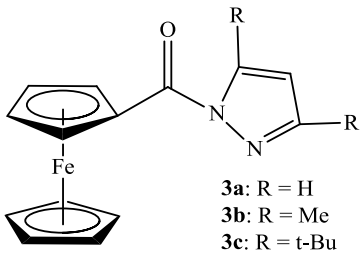
2.3.2.2 Preparation of ferrocenyl carboxylic acid (**2**)



This was prepared following a modified procedure by Reeves[95]. Potassium *tert*-butoxide (6.51 g, 58.0 mmol) was dissolved in 1,2-dimethoxyethane (50 mL). While stirring vigorously, distilled water (0.3 mL, 16.9 mmol) was added followed by **5** (4.57 g, 23.1 mmol) which was added as a solid. The reaction was then refluxed for an hour and the colour of the reaction mixture changed from the original red colour to tan. The mixture was then cooled to room temperature and poured into a separating funnel containing distilled water (150 mL). The resulting two-phase mixture was first washed with diethyl ether (3 x 30 mL) and was then back extracted with 10% NaOH solution (2 x 10 mL). The collected brown coloured aqueous extracts were acidified with concentrated HCl and the product **6** precipitated out as a yellow solid. The product was then filtered and air dried. Yield = 2.45 g (76%). FT-IR: $\upsilon_{(CO)}$ = 1652 cm^{-1}. Anal. Calc. for $C_{11}H_{10}O_2Fe$: C = 57.43%, H = 4.38%. Obtained: C = 57.31%, H = 4.35%. . ^1H NMR ($CDCl_3$): δ 4.84 (s, 2H, α-η^5-C_5H_4), 4.45 (s, 2H, β-η^5-C_5H_4), 4.24 (s, 5H, η^5-C_5H_5).

[95] P.C. Reeves, *Org. Synth.* 56 (**1977**) 28

2.3.2.3 Preparation of FcCO-*N*-pz (**3**)



These were prepared by using a modified procedure by Herrick *et al.*[78]

General Procedure

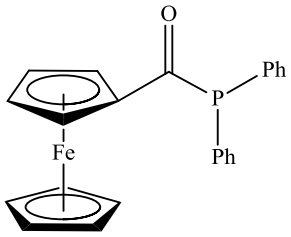
To **2** (1.00 g, 4.35 mmol) suspended in toluene (50 mL) was added triethylamine, Et_3N, (0.584 g, 800 μL, 5.77 mmol) followed by thionyl chloride, $SOCl_2$, (0.652 g, 400 μL, 5.48 mmol). The solution changed colour from yellow to red during the addition. It was refluxed for an hour, cooled to room temperature and filtered to remove the precipitate $Et_3N.HCl$ salt that had formed. The solvent was removed under reduced pressure and ferrocenoyl chloride was obtained as red oil. The red oil was re-dissolved in toluene, followed by another addition of Et_3N (598 mg, 819 μL, 5.91 mmol), and pyrazole (296 mg, 4.35 mmol). The resulting red solution was refluxed for an hour and was then cooled to room temperature, filtered and the filtrate was evaporated under reduced pressure. The product **3a** was obtained as a red oil. Yield = 638 mg, 52%. FT-IR: $\upsilon_{(CN)}$ = 1533 cm^{-1}. $\upsilon_{(CO)}$ = 1680 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.34 (s, 1H, H-pz), 7.74 (s, 1H, H-pz), 6.43 (s, 1H, H-pz), 5.45 (s, 2H, η^5-C_5H_4), 4.59 (s, 2H, η^5-C_5H_4), 4.21 (s, 5H, η^5-C_5H_5).

For **3b**: Using **2** (1.00 g, 4.35 mmol), 3,5-dimethylpyrazole (418 mg, 4.35 mmol) and Et_3N (598 mg, 819 μL, 5.91 mmol). The product **3b** was obtained as a red oil. Yield = 789 mg, 59%. FT-IR: $\upsilon_{(CN)}$ = 1580 cm^{-1}, $\upsilon_{(CO)}$ = 1681 cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.98 (s, 1H, H-pz), 5.36 (s, 2H, η^5-C_5H_4), 4.54 (s, 2H, η^5-C_5H_4), 4.18 (s, 5H, η^5-C_5H_5), 2.58 (s, 3H, Me-pz), 2.27 (s, 3H, Me-pz).

For **3c**: **2** (2.00 g, 8.69 mmol), 3,5-di-*tert*-butylpyrazole (1.36 g, 8.69 mmol) and Et_3N (949 mg, 1. 3 mL, 9.38 mmol) were used. The product was obtained as red solid. Yield = 2.15 g (63%). FT-IR: $\upsilon_{(CN)}$ = 1559 cm^{-1}, $\upsilon_{(CO)}$ = 1690 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.12 (s, 1H, pz), 5.29 (s, 2H, α-η^5-C_5H_4), 4.50 (s, 2H, β-η^5-C_5H_4), 4.19 (s, 5H, η^5-C_5H_5), 1.46 (s, 9H, ^{t}Bu-pz), 1.33 (s, 9H, *tert*-

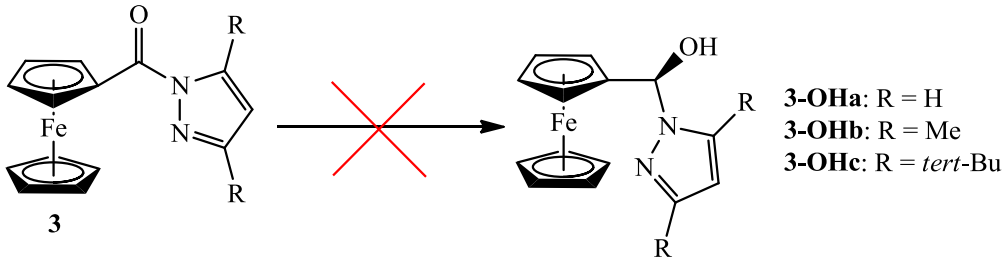
Bupz). MS (ESI): *m/z* 393.2 $[M + H]^+$. Anal. Calc. for $C_{22}H_{28}N_2OFe$: C = 67.35%, H = 7.19%, N = 7.14%. Obtained: C = 67.80%, H = 7.36%, N = 6.96%.

2.3.2.4 Preparation of ferrocenoyl diphenylphosphine (**4**)



Triphenylphosphine (4.77 g, 17.7 mmol) and lithium wire (0.185 g, 26.6 mmol) were dissolved in dry THF (60 mL). After an hour of stirring, the resulting deep red solution was cooled in an ice bath. Ferrocenoyl chloride prepared *in situ* from **2** (8.87 mmol) was dissolved in dry THF (~ 2mL) and was then added drop wise to the cooled reaction. The reaction was then removed from the ice bath after the addition was completed and stirring was continued for a further two hours at room temperature. After the specified time, distilled water (20 mL) was added to the reaction and the reaction mixture transferred into a separating funnel containing distilled water (100 mL). The red mixture was then extracted with diethyl ether (3 x 30 mL). The combined ethereal extracts were washed with a saturated solution of $NaHCO_3$ (3 x 30 mL), brine (3 x 30 mL) and distilled water (50 mL). The washed extracts were dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure. The red oil that was obtained was purified first by flash chromatography over silica using a mixture of hexane and diethyl ether (5:1). Recrystallization from acetone afforded analytically pure product as red crystals. Yield = 350 mg, 10%. FT-IR: $\upsilon_{(CO)}$ = 1627 cm^{-1}, $\upsilon_{(CP)}$ = 694 cm^{-1}. MS (ESI): *m/z* 399.2 $[M + H]^+$. ^{31}P $\{^1H\}$ NMR ($CDCl_3$): δ 21.43. Anal. Calc. for $C_{23}H_{19}OPFe$: C = 69.37%, H = 4.81%. Obtained: C = 69.22%, H = 4.90%.

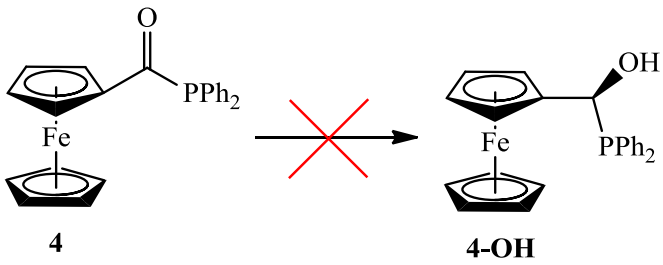
2.3.2.5 Attempted reduction of ferrocenoyl pyrazoles (**3-OH**)



General Procedure

Compound **3** (500 mg) was dissolved in diethyl ether (30 mL) in a Schlenk tube. Reducing agent $LiAlH_4$ (2 mole equivalence) was added portions-wise to the red coloured solution and the reaction was refluxed in a water bath. After an hour, the reaction was cooled to room temperature and hot distilled water (20 mL) was added dropwise to the yellow coloured mixture to destroy unreacted $LiAlH_4$. The mixture was transferred into a separating funnel and phases were separated. The organic phase was washed with room temperature distilled water (3 x 20 mL), dried over anhydrous $MgSO_4$ and evaporated under reduced pressure to obtain yellow-brown thin film. For **3-OHa**: Yield = 221 mg (44%), **3-OHb**: Yield = 258 (52%) and **3-OHc**: Yield = 496 mg (99%)

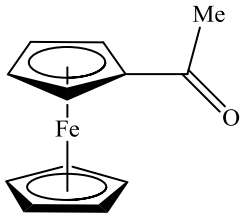
2.3.2.6 Attempted reduction of ferrocenoyl phosphine (**4-OH**)



This was attempted using similar reaction protocols for **3-OH** compounds in section 2.3.2.5.

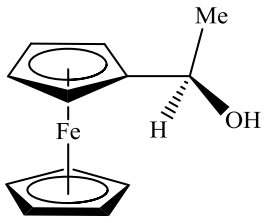
Compound **4** (100 mg, 0.251 mmol) and $LiAlH_4$ (19.0 mg, 0.502 mmol) were used. Yellow oil was obtained. Yield = 41 mg, (41%).

2.3.2.7 Preparation of acetyl ferrocene (**5**)



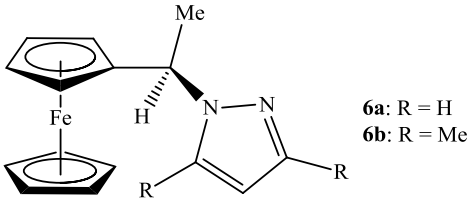
In a Schlenk tube immersed in an oil bath pre-set at 50 °C, ferrocene (4.00 g, 21.5 mmol) was suspended in neat acetic anhydride (40 mL) and stirred. To the mixture, 85% phosphoric acid (5 mL) was cautiously added dropwise over a 5 min period; during which ferrocene completely dissolved and the colour changed from orange to deep red. The reaction was refluxed for a further 5 min and was then left to cool to room temperature. The cooled deep red mixture was then transferred into crushed ice (200 g) and the resulting orange-brown mixture was stirred using a glass rod. The mixture was neutralised first with 30% NaOH (100 mL) followed by solid sodium bicarbonate and the pH was monitored using a red litmus paper. The neutralised mixture was allowed to stand for 10 min and was then filtered and air dried under suction. The orange-brown crude product was then purified by column chromatography over silica, n-hexane was used to elute unreacted ferrocene and dichloromethane to elute the product. The solvent was evaporated and acetyl ferrocene **1**, was obtained as red needle-shaped crystalline solids. Yield = 3.53 g (72%). FT-IR: $\upsilon_{(CO)}$ = 1650 cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.75 (s, 2H, α-η^5-C_5H_4), 4.48 (s, 2H, β-η^5-C_5H_4), 4.18 (s, 5H, η^5-C_5H_5), 2.37 (s, 3H, -CO<u>Me</u>). Anal. Calc. for $C_{12}H_{12}OFe$: C = 63.20%, H = 5.30%. Obtained: C = 63.41%, H = 5.29%.

2.3.2.8 Preparation of ferrocenyl ethanol (**5-OH**)



To a solution of **5** (2.04 g, 8.94 mmol) dissolved in a mixture of ethanol and water (30 mL : 1 mL) was added excess $NaBH_4$ (1.01 g, 26.8 mmol) dissolved in distilled water (8 mL). The reaction was refluxed for an hour during which the colour changed from red to yellow. The reaction was cooled to room temperature and then transferred into a separating funnel filled with distilled water (50 mL). The solution was extracted with diethyl ether (3 x 25 mL). The combined ethereal extracts were dried over anhydrous $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The product **5-OH**, was obtained as a brown oil which solidified overnight under reduced pressure to give a yellow solid. Yield = 2.02 g (98%). FT-IR: $\upsilon_{(OH)}$ = 3235 cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.49 (q, 1H, $^3J_{HH}$ = 3.6 Hz, -C<u>H</u>(OH)Me), 4.21 – 4.19 (s, 9H, 2x η^5-C_5H_4 and η^5-C_5H_5), 1.42 (d, 3H, $^3J_{HH}$ = 5.6 Hz, -CH(OH)<u>Me</u>). Anal. Calc. for $C_{12}H_{14}OFe$: C = 62.24%, H = 6.13%. Obtained: C = 62.65%, H = 5.94%.

2.3.2.9 Preparation of ferrocenyl(ethyl)pyrazoles (**6**)



These were prepared by following a modified procedure by Simenel *et al.*[66]

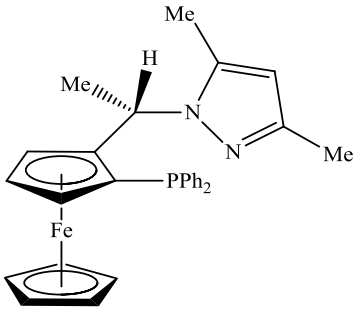
General procedure

In a two-neck flask, **5-OH** (600 mg, 2.61 mmol) was dissolved in dichloromethane (3 mL) producing a yellow solution. To this solution was then added pyrazole (178 mg, 2.61 mmol) and the reaction was stirred vigorously. Upon addition of 48% tetrafluoroboric acid (0.6 mL) the

reaction changed colour from yellow to greenish-brown. Stirring was continued for 5 min at room temperature. Cold distilled water (15 mL) and diethyl ether (15 ml) were added and the two-phase mixture was transferred into a separating funnel from which the faint blue aqueous phase was collected and discarded. The remaining yellow-gold organic phase was washed with cold distilled water (5 x 15 mL), dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. The product was obtained as yellow oil which solidified overnight under reduced pressure, producing **6a** as yellow solid. Yield = 678 mg (93%). FT-IR: $\upsilon_{(CN)}$ = 1509 cm^{-1}. MS (ESI): *m*/*z* 281.1 [M^+ + H]. ^{1}H NMR ($CDCl_3$): δ 7.46 (s, 1H, pz-H), 7.26 (s, 1H, pz-H), 6.16 (s, 1H, pz-H), 5.39 (q, 1H, $^3J_{HH}$ = 7 Hz, -CHpzMe), 4.12 (m, 9H, Fc), 1.81 (d, 3H, $^3J_{HH}$ = 7.0 Hz, -CHpzMe). Anal. Calc. for $C_{15}H_{16}N_2Fe$: C = 64.31%, H = 5.76%, N = 10.00%. Obtained: C = 63.77%, H = 5.56%, N = 9.56%.

For **6b**: Using **5-OH** (600 mg, 2.61 mmol) and 3,5-dimethylpyrazole (0.251 g, 2.61 mmol). The product was obtained as a yellow solid. Yield = 705 mg, (88%). FT-IR: $\upsilon_{(CN)}$ = 1550 cm^{-1}. MS (ESI): *m*/*z* 309.1 [M^+ + H]. ^{1}H NMR ($CDCl_3$): δ 5.71 (s, 1H, pz-H), 5.26 (q, 1H, $^3J_{HH}$ = 7.1 Hz, -CHpzMe), 4.19 (s, 2H, α-η^5-C_5H_4), 4.16 (s, 2H, β-η^5-C_5H_4), 4.11 (s, 5H, η^5-C_5H_5), 2.19 (s, 3H, pz-Me), 2.16 (s, 3H, Me-pz), 1.80 (d, 3H, $^3J_{HH}$ = 6.9 Hz, -CHpzMe). Anal. Calc. for $C_{17}H_{20}N_2Fe$: C = 66.25%, H = 6.84%, N = 9.09%. Obtained: C = 66.15%, H = 6.75%, N = 8.81%.

2.3.2.10 Preparation of 1-diphenylphosphine-2-ethlypyrazolyl ferrocene (**LPNb**)

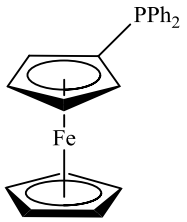


These were prepared by following a modified procedure reported by Ueberbacher *et al.*[68]

In a typical reaction, to a 0 – 5 °C cooled solution of **6b** (901 mg, 3.22 mmol) in dry cyclohexane (100 mL) was added drop wise using a syringe *n*-BuLi (2.8 mL, 6.44 mmol). The red slurry was stirred for an hour and then $ClPPh_2$ (1.42 g, 6.44 mmol) was added drop wise. The resulting

turbid yellow mixture was stirred further for an hour and was then allowed to warm up to room temperature for another hour. Ice cold distilled water (10 mL) was added to the mixture which was then transferred into a separating funnel. The organic phase was collected and thoroughly washed with a saturated $NaHCO_3$ solution (3 x 100 mL), brine (3 x 100 mL) and distilled water (100 mL). It was then dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure. The obtained orange oil was purified first by flash chromatography over silica using a mixture of diethyl ether and hexane (1:3). Several yellow bands were eluted and the last dark orange band was collected. The product was obtained as an orange solid from the last band and was recrystallized from hot ethanol to afford orange crystals. Yield = 667 mg (54 %). FT-IR: $\upsilon_{(CN)}$ = 1555 cm^{-1}, $\upsilon_{(CP)}$ = 696 cm^{-1}. $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ -23.8 (s). ^1H NMR ($CDCl_3$): δ 7.47 – 6.69 (m, 10H, Ph), 5.60 (m, 1H, -C<u>H</u>(pz)Me), 5.04 (s, 1H, H-pz), 4.84 (s, 1H, η^5-C_5H_3), 4.35 (s, 1H, η^5-C_5H_3), 4.03 (s, 5H, η^5-C_5H_5), 3.72 (s, 1H, η^5-C_5H_3), 2.12 (s, 3H, Me-pz), 1.95 (s, 3H, Me-pz), 1.82 (d, 3H, $^3J_{HH}$ = 6.5 Hz, -CHpz<u>Me</u>). Anal. Calc. for $C_{29}H_{29}N_2PFe$: C = 70.74 %, H = 5.94 %, N = 5.69 %; Obtained: C = 68.91 %, H = 6.39 %, N = 5.14 %.

2.3.2.11 Preparation of diphenylphosphino ferrocene (**7**)

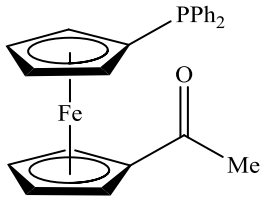


This was prepared following a modified procedure by Sollott *et al.*[96] In a two-neck flask, ferrocene (3.00 g, 16.1 mmol) and anhydrous $AlCl_3$ (2.15 g, 16.1 mmol) were suspended in dry hexane (50 mL). To this mixture, $ClPPh_2$ (3.56 g, 16.1 mmol) dissolved in dry hexane (5 mL) was added drop wise and the reaction was refluxed for 24 hours. The mixture was cooled to room temperature and the mother liquor (containing unreacted ferrocene) was decanted and stored. The remaining dark blue paste was washed with hot aliquots of hexane (100 mL in total) which were also collected and stored; these hexane washings combined with the mother liquor contained unreacted ferrocene. The remaining paste was then treated cautiously with copious

[96] G.P. Sollott, H.E. Mertwoy, S. Portnoy, J.L. Snead, *J. Org. Chem.* 28 (**1963**) 1091.

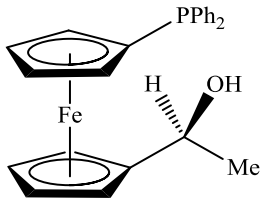
amount of hot water until the blue-coloured washings turned colourless. The remaining orange-brown solids were then extracted with hot toluene (150 mL), the insoluble brown material that was left behind was discarded. The toluene extracts were dried over anhydrous $MgSO_4$, filtered and evaporated once more. The resulting orange solids were extracted with boiling hexane (150 mL) and concentrated to dryness under reduced pressure. The product **7** was obtained as orange crystalline material which was recrystallized from hot ethanol giving yellow-gold needle-like crystals. Yield = 1.33 g (26%). FT-IR: $\upsilon_{(PC)}$ = 697 cm^{-1}. MS (ESI): *m/z* 371.1 $[M^+ + H]$. ^{31}P $\{^1H\}$ NMR ($CDCl_3$): δ -16.5(s). ^1H NMR ($CDCl_3$): δ 7.36 – 7.28 (m, 10H, Ph), 4.35 (s, 2H, α-η^5-C_5H_4), 4.08 (s, 2H, β-η^5-C_5H_4), 4.05 (s, 5H, η^5-C_5H_5). Anal. Calc. for $C_{22}H_{19}PFe$: C = 71.38 %, H = 5.17 %; Obtained: C = 71.47 %, H = 5.27 %.

2.3.2.12 Preparation of 1-diphenylphosphino-1´-acetyl ferrocene (**8**)



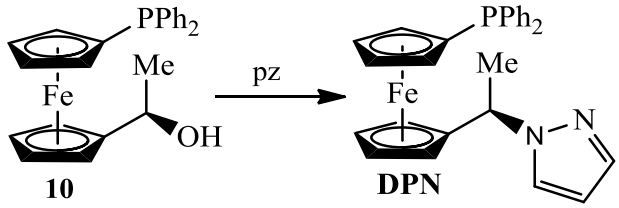
In a two-neck flask, **7** (201 mg, 6.28 mmol) was dissolved in CH_2Cl_2 (20 mL) and the solution was cooled to 0 – 5 °C. Then anhydrous $AlCl_3$ (86.7 mg, 18.8 mmol) and acetyl chloride (49.2 mg, 6.27 mmol) dissolved in CH_2Cl_2 (3 mL) were added. Stirring was continued for 30 min at 0 – 5 °C and for 2 hours at room temperature, during this period the reaction colour changed from the original yellow colour to violet. The solution was then transferred into a separating funnel containing distilled water (100 mL) and the two-phase mixture was extracted with dichloromethane (3 x 25 mL). The combined CH_2Cl_2 extracts were washed with 10% NaOH (2 x 50 mL), dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure. The product **8** was obtained as orange oil which eventually solidified. Yield = 0.153 g (60%). FT-IR: $\upsilon_{(CO)}$ = 1669 cm^{-1}, $\upsilon_{(PC)}$ = 697 cm^{-1}. MS (ESI): *m/z* 413.1 $[M + H]^+$. ^{31}P $\{^1H\}$ NMR ($CDCl_3$): δ -18.2 (s). ^1H NMR ($CDCl_3$): δ 7.30 (m, 10H, Ph), 4.65 – 4.09 (8H, Cp_2), 2.21 (s, 3H, Me). Anal. Calc. for $C_{24}H_{21}OPFe$: C = 69.92%, H = 5.13%; Obtained: C = 69.64%; H = 5.04%.

2.3.2.13 Preparation of 1-diphenylphosphino-1'-ethanoyl ferrocene (**8-OH**)



To a solution of **8** (482 mg, 1.19 mmol) dissolved in a mixture of ethanol and water (35 mL : 1 mL) was added $NaBH_4$ (900 mg, 2.38 mmol) dissolved in distilled water (2 mL). The reaction was refluxed for an hour. As the reaction progressed the colour changed from the original orange colour to pale yellow. The reaction was then cooled to room temperature and transferred into a separating funnel filled with distilled water (50 mL). The mixture was extracted with diethyl ether (3 x 25 mL). The combined ether extracts were dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure. The product **8-OH** was obtained as a yellow oil. Yield = 322 mg, 65%. FT-IR: $\upsilon_{(OH)}$ = 3428 cm^{-1}, $\upsilon_{(PC)}$ = 696 cm^{-1}. ^{31}P NMR ($CDCl_3$): δ -17.0 (s). ^1H NMR ($CDCl_3$): δ 7.37 – 7.28 (m, 10H, Ph), 4.46 (q, 1H, $^3J_{HH}$ = 6.4 Hz, -C<u>H</u>(pz)Me), 4.37 – 4.09 (8H, Cp_2), 1.35 (d, 3H, $^3J_{HH}$ = 6.4 Hz, -CH(pz)<u>Me</u>).

2.3.2.14 Attempted preparation of 1-ethylpyrazolyl-1'-diphenylphosphinoferrocene (**DPN**)

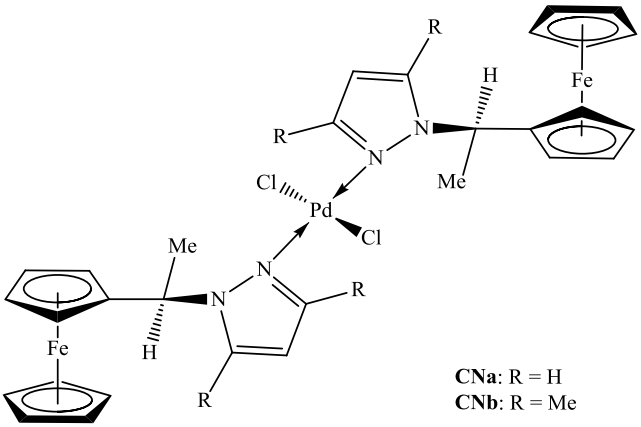


This was prepared using similar reaction protocols for **6** in section 2.3.2.9.

Compound **10** (322 mg, 0.777 mmol) and pyrazole (52.9 mg, 0.777 mmol) and 48% HBF_4 (0.14 mL) were used. The product **DPN** was obtained as a yellow oil. Yield = 286 mg (79%).

2.3.3 Synthesis of complexes

2.3.3.1 Preparation of $PdCl_2\{FcCH(pz)Me\}_2$ (**CN**)



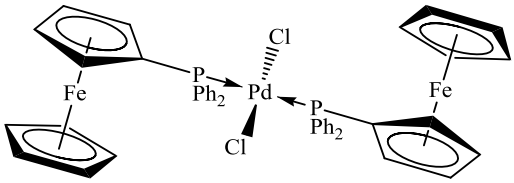
General procedure

To a two-neck flask charged with **6a** (253 mg, 0.904 mmol) and $[PdCl_2(NCMe)_2]$ (117 mg, 0.452 mmol) was added dry dichloromethane (15 mL) under nitrogen. The mixture was stirred vigorously for eight hours at room temperature and the colour changed from the original yellow to deep yellow. The mixture was filtered and the filtrate was evaporated under reduced pressure producing yellow oil. The oil solidified upon washing with diethyl ether (3 x 15 mL) to a yellow solid, which was the product **CNa**. Yield = 656 mg, (89%). FT-IR: $\upsilon_{(CN)}$ = 1516 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.75 (s, 2H, pz-H), 7.19 (s, 2H, -C<u>H</u>(pz)Me), 7.17 (s, 2H, pz-H), 6.24 (s, 2H, pz-H), 4.56 (s, 4H, α-η^5-C_5H_4), 4.40 (s, 4H, β-η^5-C_5H_4), 4.25 (s, 10H, η^5-C_5H_5), 2.18 (d, 6H, $^3J_{HH}$ = 7.0 Hz, -CH(pz)<u>Me</u>). Anal. Calc. for $C_{30}H_{32}N_4Cl_2Fe_2Pd$: C = 48.85%, H = 4.37%, N = 7.60%. Obtained: C = 48.52%, H = 4.34%, N = 7.17%.

For C**Nb**: **6b** (114 mg, 0.370 mmol) and $[PdCl_2(NCMe)_2]$ (40.8 mg, 0.185 mmol) were used. The yellow solid was recrystallized from dichloromethane and acetonitrile mixture to afford yellow crystals. Yield = 250 mg, (84%). FT-IR: $\upsilon_{(CN)}$ = 1516 cm^{-1}. MS (ESI): *m*/*z* 759.1 $[M - Cl]^+$. ^1H NMR ($CDCl_3$): δ 7.92 (q, 2H, $^3J_{HH}$ = 7.2 Hz, -C<u>H</u>(pz)Me), 5.77 (s, 2H, pz-H), 4.78 (s, 2H, (s, 4H, η^5-C_5H_4), 4.41 (s, 2H, η^5-C_5H_4), 4.30 (s, 10H, η^5-C_5H_5), 4.21 (s, 2H, η^5-C_5H_4), 4.16 (s, 2H, (s, 2H, η^5-C_5H_4), 2.98 (s, 6H, pz-Me), 2.09 (d, 6H, $^3J_{HH}$ = 7.2 Hz, -CHpz<u>Me</u>), 1.87 (s, 6H, pz-Me).

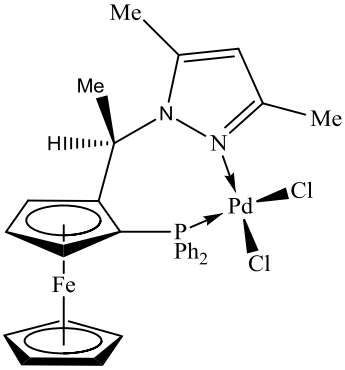
Anal. Calc. for $C_{34}H_{40}N_4Cl_2Fe_2Pd$: C = 51.45%, H = 5.08%, N = 7.06%. Obtained: C = 51.28%, H = 5.09%, N = 6.83%.

2.3.3.2 Preparation of $PdCl_2(FcPPh_2)_2$ (**CP1**)



In a preheated solution of **7** (230 mg, 0.0621 mmol) in acetonitrile (20 mL) at 70 °C was added $PdCl_2$ (53.1 mg, 0.0311 mmol). The resulting mixture was stirred vigorously for two hours during which the colour change from orange colour to red colour was observed. The mixture then was cooled to room temperature and the mother liquor was decanted. The retained maroon coloured product was dried in vacuum. Yield = 322 mg (56%). ^{31}P $\{^1H\}$ NMR ($CDCl_3$): δ 15.2 (s). ^1H NMR ($CDCl_3$): δ 7.64 – 7.33 (m, 20H, Ph), 4.53 (s, 4H, η^5-C_5H_4), 4.43 (s, 4H, β-η^5-C_5H_5), 4.40 (s, 10H, η^5-C_5H_4). Anal. Calc. for $C_{44}H_{38}P_2Fe_2PdCl_2$: C = 57.58 %, H = 4.17 %; Obtained: C = 57.68 %, H = 3.99 %.

2.3.3.3 Preparation of $PdCl_2$(1-aceto-2-diphenylphosphinoferrocene) (**CPNb**)



This were prepared following the same protocol as in **CN** compounds.

The ligand **LPNb** (250 mg, 0.0509 mmol), $[PdCl_2(NCMe)_2]$ (132 mg, 0.0509 mmol) and dry CH_2Cl_2 (50 mL) were used. The reaction was carried out for two hours and a colour change from orange colour to red colour was observed. The product was precipitated from hexane, filtered and dried under vaccum. Yield = 293 mg (86%). FT-IR: $\upsilon_{(CN)}$ = 1552 cm^{-1}, $\upsilon_{(CP)}$ = 693 cm^{-1}. ^{31}P

{^{1}H} NMR ($CDCl_3$): δ 6.04 (s). ^{1}H NMR ($CDCl_3$): δ 7.87 – 6.86 (m, 20H, Ph), 5.36 (s, 2H, -C<u>H</u>(pz)Me), 5.28 (s, 2H, H-pz), 4.81 (s, 2H, η^5-C_5H_3), 4.45 (s, 2H, η^5-C_5H_3), 4.33 (s, 5H, η^5-C_5H_5), 3.65 (s, 1H, η^5-C_5H_3), 2.18 (s, 3H, Me-pz), 2.10 (d, 3H, $^3J_{HH}$ = 7.3 Hz, -CHpz<u>Me</u>), 1.87 (s, 3H, Me-pz).

2.4 Conclusions

The scaffolds **3a** and **3b** were successfully prepared in good yields of 52% and 59%, respectively. On the other hand, the scaffold **4** was prepared, although disappointing yields of 10% were obtained. However, all these scaffolds could not be converted into the required intermediates that could have been used to prepare the desired **SPN** and **SPP** chiral ligands.

Alternative scaffolds **5** and **7** were also prepared successfully at yields of 72% and 26% respectively. The former was used to prepare the intermediates **5a** (which failed to produce the chiral ligand, **LPNa**) and **5b** (gave **LPNb** at good yields of 54% using cheaper methods, even though small amounts of the oxidised product was observed); the latter failed to produce the intermediate bearing planar chirality after Friedel-Crafts acetylation thus **LPP** could not be prepared. The heteroannular disubstitution on compound **8**, was confirmed by FT-IR and multi-nuclear NMR spectroscopy, GC mass spectrometry, and elemental analysis. It was reduced using mild conditions but the resulting compound, **8-OH**, gave unidentified decomposed products when substitution reaction with pyrazoles was attempted.

The compounds **LNa**, **LNb**, **7** and **LPNb** were successfully complexed with $PdCl_2$ and the corresponding complexes **CNa**, **CNb**, **CP1** and **CPNb** were obtained, respectively, at good yields between 56% and 89%. The first two complexes were prepared using as the metal precursor, while the others were prepared in a one-pot synthesis technique where it was assumed that $[PdCl_2(NCMe)_2]$ is formed *in situ*.

CHAPTER 3

THE CATALYTIC EVALUATION OF PYRAZOLE AND PHOSPHINE-CONTAINING FERROCENYL PALLADIUM COMPLEXES ON THE SUZUKI-MIYAURA COUPLING REACTION

3.1 Introduction

Cross coupling reactions, responsible for the formation of C-X bonds (where X = C, N, S, O and P) which cannot be formed under normal reaction conditions,[97] have been the centre of attention for many decades as a result of having solved synthetic problems experienced by organic chemists in both academia and pharmaceutical or chemical processing industries.[98]

Grignard reagents were once identified as good nucleophiles for use in cross-coupling reactions, this prompted a discovery of many other organometallic reagents. [99-100] Negishi reported the use of other organometallic reagents such as organoaluminium[101a], zinc[101b] and zirconium[101c] in palladium catalysed cross-coupling reactions; a sequel to the work firstly demonstrated by Murahashi[102] using Grignard reagents. Organosilicon, lithiums, stannanes were also later used, amongst others.[103]

Organoboron compounds, on the other hand, have received a lot of attention because they are easily accessible, they can accommodate different functional groups (such as alkyls, acids, and esters, etc) and hence their electronic properties can also be easily tuned. Even though the overall organoboron compound is electrophilic, the organic substituents are weakly nucleophilic and as a result their use in ionic reactions is limited. However, the nucleophilicity can be increased by the coordination of the negatively charged base on a boron atom.[101]

Organoboron compounds are commercially available but they can also be prepared in good yields in a typical laboratory. Reports on their synthesis from a range of reaction protocols that include the use of magnesium or organolithium reagents, hydroboration of alkenes and alkynes, and haloboration of terminal alkynes.[103] Organoboronic acids have been the preferred choice for

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[97] M.-N. Birkholz (née Gensow), Z. Freixa, P.W.N.M. Leeuwen, *Chem. Soc. Rev.* 38 (**2009**) 853, and references therein.
[98] (a) T.J. Colacot, *Platinum Metals Rev.* 45 (**2001**) 22. (b) H. Blaser, W. Brieden, B. Purgin, F. Spindler, M. Studer, A. Togni, *Topics in Catalysis* 19 (**2002**) 3. (c) L. Xue, Z. Lin, *Chem. Soc. Rev.* 39 (**2010**) 1692.
[99] K. Tamao, K. Sumitani, M. Kumada, *J. Am. Chem. Soc.* 94 (1972) 4374. K. Tamao, Y. Kiso, K. Sumitani, M. Kumada, *J. Am. Chem. Soc.* 94 (1972) 9268.
[100] R.J.P. Corriu, J.P. Masse, *J. Chem. Soc., Chem. Commun.* (**1972**) 144.
[101] (a) E. Negishi, S. Baba, *J. Chem. Soc., Chem. Commun.* (**1976**) 596. (b) E. Negishi, A.O. King, N. Okukado, *J. Org. Chem.* 42 (**1977**) 1821. (c) E. Negishi, D.E. Van Horn, *J. Am. Chem. Soc.* 99 (**1977**) 3168.
[102] M. Yamamura, I. Moritani, S. Murahashi, *J. Organomet. Chem.* 91 (1975) C39.
[103] N. Miyaura, A. Suzuki, *Chem. Rev.* 95 (**1995**) 2457, and references therein.

use in cross-coupling reactions over the past years due to their thermal stability and inertness to water and air.[103]

In a typical palladium catalysed cycle for cross-coupling reactions, the organometallic reagent would exchange ligands with intermediate complex **A** thus forming intermediate complex **B** without any change in configuration, a process commonly known as *transmetalation*, Figure 3.1. The presence of these intermediates in cross-coupling reactions has been extensively studied by isolation and spectroscopic techniques.[104]

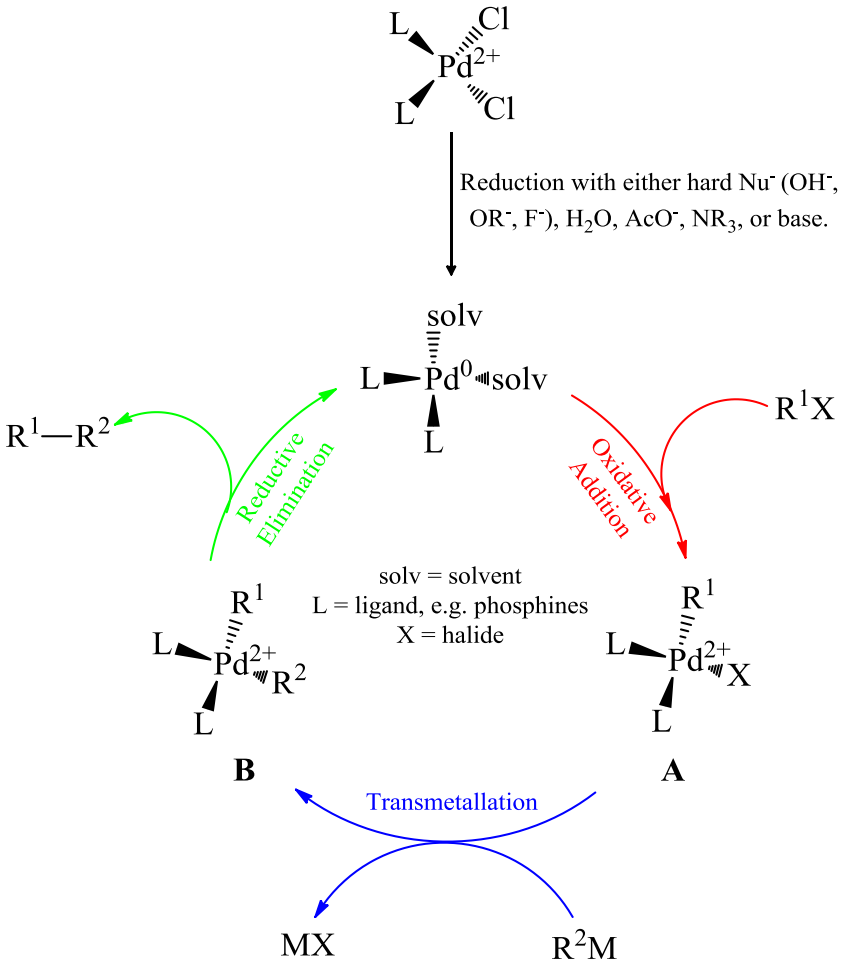


Figure 3.1: A typical catalytic cycle for cross-coupling reaction with organometallic compounds.[103, 105]

[104] A.O. Aliprantis, J.W. Canary, *J. Am. Chem. Soc.* 116 (**1994**) 6985.
[105] A.N. Trzeciak, J.J. Ziółkowski, *Coord. Chem. Rev.* 249 (**2005**) 2308; *Coord. Chem. Chem.* 251 (**2007**) 1281.

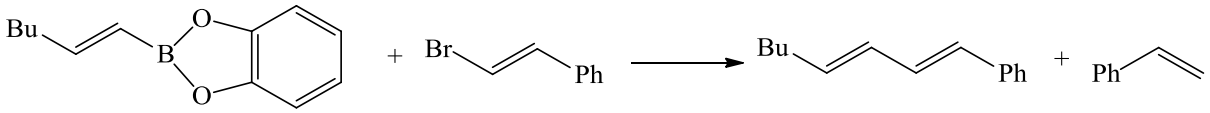
Regardless of the weak nucleophilicity of the organic substituents, organoboron compounds are reactive towards transmetalation with other metals. There are a number of reports that have confirmed a successful transmetalation of organoboron compounds with metal halides such as those containing Mg(II), Al(III), Zn(II), Ag(I) and Cu(I).[103] This is also observed for Pd(II) complexes with selective coupling of iodobenzene and 1-alkenyl group from the lithium 1-hexynyl(tributyl)borate compound being an earliest example.[106] It was noted that activation of organoboron compounds required a suitable base which was essential in promoting the reactions to occur at optimum levels.[107]

Oxidative addition is a key step in the above catalytic cycle; however, the oxidative addition step has very slow kinetics and is thus considered to be a rate-determining step. For this reason, a type of organohalide reagent used is of crucial importance e.g. alkyl halides having a β-hydrogen are hardly ever used following unsupported suspicions of competing with the β-hydride elimination step (detachment of the coupled product from the intermediate complex **B**).[103] The relative reactivity of R^2X towards oxidative addition increases in the order: X = Cl << Br < OTf < I. However, the introduction of the electron-withdrawing groups along the proximity of the aryl and 1-alkenyl halides e.g. 3-chloroenone enhances the reactivity towards oxidative addition step.[103]

Reductive elimination occurs on the *cis*-configuration on the intermediate complex **B**. In the case where a *trans*-configuration is obtained; the complex would isomerize to the corresponding *cis*-configuration prior to the elimination process.[103] Depending on the nature of the coupled product formed, normally the rate at which reductive elimination occurs decreases in the order: diaryl > (alkyl)aryl > dipropyl > diethyl > dimethylpalladium(II) intermediate complex **B**. Alkyl-alkyl coupling occurs *via* a dissociative mechanism of the intermediate complex **B**; reaction depends upon the rate at which the phosphine ligand dissociates to form a three-coordinated complex. Therefore, the product formation is inhibited by the presence of excess phosphine ligands in a catalytic system.[103] Dissociation proceeds easily in the order: dppe << PEt_3 < PEt_2Ph < $PMePh_2$ < $PEtPh_2$ < PPh_3.

[106] E. Negishi, *Aspects of Mechanism and Organometallic Chemistry*; J.H. Brewster, Ed.; Plenum Press; New York, **1978**; p 285.
[107] (a) A. Suzuki, *Acc. Chem. Res.* 15 (**1982**) 178. (b) N. Miyaura, A. Suzuki, *J. Synth. Org. Chem. Jpn.* 46 (**1988**) 848. (c) A. Suzuki, *Pure Appl. Chem.* 66 (**1994**) 213.

Miyaura and Suzuki stated that the transmetalation step strongly depends on the properties of the coupling reactants and the reaction parameters used in coupling reactions.[103] They also discovered that the organoboron compounds are inert towards organopalladium(II) halides and therefore it is highly unlikely that the latter will take part in the catalytic cycle. However, organoboranes appear to be reactive with organomercurials under neutral conditions.[108] The incorporation of a suitable base has been proven to have made a remarkable improvement on transmetalation rates.[103]



1 **2** **3** **4**

Scheme 3.1: Cross-coupling of (*E*)-1-Hexenyl-1,3,2-benzodioxaborole (**1**) with (*E*)-*β*-Styryl Bromide (**2**).

Based on the data collected by Miyaura and Suzuki[109], it was evident that the yield of the desired diene product obtained from the coupling of (*E*)-1-Hexenyl-1,3,2-benzodioxaborole with (*E*)-*β*-Styryl bromide, Scheme 3.1, was improved when strong bases like NaOEt and NaOH are used instead of weak ones like KOAc and Et_3N. They also noted that the choice of the solvent also plays a crucial role; reactions conducted in benzene gave higher yields compared to THF. However, the yields of THF-based reactions could be improved by increasing the amount of the catalyst used and the reaction time. The key observation was that no reaction occurs in both benzene and THF in the absence of a base, this was further confirmation that the base also plays a crucial role in the reaction.

[108] (a) J.B. Honeycutt, J.M. Riddle, *J. Am. Chem. Soc*. 82 (**1960**) 3051. (b) R.C. Larock, *J. Organomet. Chem.* 72 (**1974**) 35.
[109] (a) N. Miyaura, K. Yamada, H. Suginome, A. Suzuki, *J. Am. Chem. Soc.* 107 (**1985**) 973. (b) N. Miyaura, K. Yamada, A. Suzuki, *Tetrahedron Lett.* 36 (**1979**) 3440.

3.1.1 Preparation of biphenyls by coupling reactions with phenylboron derivatives

Biphenyls have attracted a lot of attention in various fields of research. They have been useful in biological applications as chromophores for photoremovable protecting group,[110] in electronic applications as cheaper organic-based light emitting diodes,[111] in the renewable energy applications as organic dyes for dye-sensitized solar cells,[112] and in homogeneous catalysis as backbone for ligands,[113] amongst other fields of research and applications. As a result, cross-coupling reactions have been the key methods of synthesizing derivatives of biphenyls.

The earliest publication on the preparation of biphenyls dates back to as early as 1866.[114a] Their preparation was from phenyldiazonium salts[114] and this was the method of choice for more than five decades. A great achievement over this period was the discovery that benzene could be used as both a solvent and a secondary source of the phenyl,[114b-c] Figure 3.2. The use of these diazonium salts to prepare biaryls was however not desirable because their corresponding dry oxides (active form towards coupling reactions) were highly explosive during decomposition and the yields were generally low.[114c] Even when these oxides were prepared *in situ*, without a need for isolation, the explosions could not be prevented. Some oxides such as *p*-toluene diazo oxide would explode while on the filter paper after the filtration process. Some reactions produced milder explosions when they were conducted under cooler reaction conditions.

[110] A. Specht, F. Bolze, L. Donato, C. Herbivo, S. Charon, D. Warther, S. Gug, J.-F. Nicoud, M. Goeldner, *Photochem. Photobiol. Sci.* 11 (**2012**).
[111] J. Kwon, J.-P. Hong, S. Lee, J.-I. Hong, *New J. Chem.* DOI: 10.1039/c3nj00295k
[112] P. Gao, Y.J. Kim, T.W. Holcombe, M.K. Nazeeruddin, M. Grätzel, *J. Mater. Chem. A.* 1 (**2013**) 5535.
[113] K. Aikawa, K. Mikami, *Chem. Comm.* 48 (**2012**) 11050.
[114] (a) P. Griess, Liebigs Ann. Chem. 137 (**1866**) 84. (b) R. Möhlau, R. Berger, *Ber.* 26 (**1893**) 1995. (c) M. Gomberg, W.E. Bachmann, *J. Am. Chem. Soc.* 46 (**1924**) 2340.

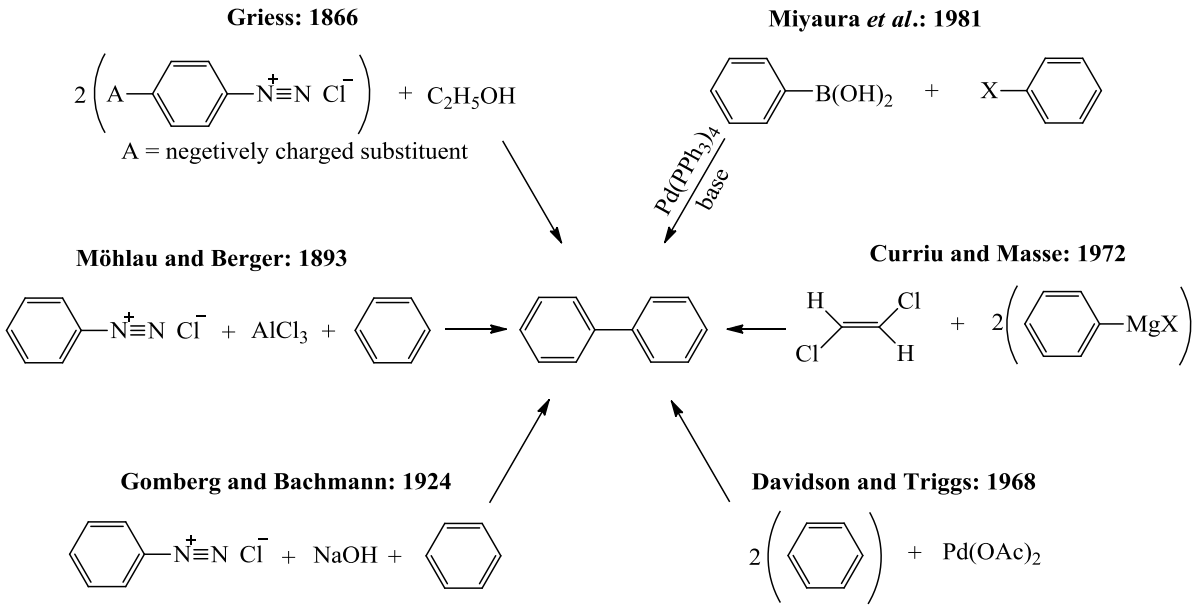


Figure 3.2: Previous reports on the preparation of biphenyls from a range of reactions.

In 1968, Davidson and Triggs[115] observed that benzene coordinated to the $Pd(OAc)_2$ and thermal decomposition of the resulting complex gave biphenyls, amongst other products. In this kind of reactions, formation of aryl-metal complexes are catalysed by acids which increase the electrophilic strength of the metals towards phenyls and aryls in general, depending on the metal salt used. Gold(III) also behaves in a similar way to Pd(II) whereas Hg(II) and Tl(III) give stable arylcomplexes thus no biphenyl compounds formation is observed. In contrast, the study showed that only the metal ions with d^8 and d^{10} electron configurations in low valencies are reactive towards basic donors such as benzene. However, the corresponding π complexes of the d^8 metal ions are unstable while for the d^{10} metal ions are stable. Further supporting evidence was obtained from a d^6 Rh(III) which failed to react with benzene yet a d^{10} Ag(I) managed to form highly stable benzene complex.

[115] J.M. Davidson, C. Triggs, *J. Chem. Soc. (A).* (**1968**) 1326.

The preparation of biphenyl by the activation of phenyl Grignard reagents with transition metal complexes was reported by Curriu and Masse[116] in 1972. Other biaryls were also prepared using the same reaction conditions.

After their pioneering work on the Pd-catalysed cross-coupling of alkenylboranes with organic halides under basic conditions, Miyaura *et al*.[117] published yet another set of results in 1981 which mainly focused on the coupling of phenylboronic acid with halobenzenes thus producing biphenyls and their derivatives. Since then, this coupling reaction which today is known as the Suzuki-Miyaura coupling reaction, is the most preferred by scientists when they have to evaluate the efficiency of their new and/or improved palladium catalysts. What makes this reaction attractive to researchers is that a variety of substrates to be used are readily accessible at a reasonable cost, they can be stored easily due to their high stability and the reactions are straight forward as a result they are easy to carry out.

The coupling reaction proposed by Miyaura and Suzuki seemed more practical and easier to carry out when compared to the rest of the previously mentioned routes. Over the years, increases in the modified versions of this reaction have been reported in an attempt to optimise the yield of the products obtained. There are so many variables that can be changed in order to find a most efficient catalytic system. Variables such as, the nature of the halide and the reaction time play a major role but the key factor is the type of catalyst that is used.[97]

[116] R.J.P. Corriu, J.P. Masse, *J. Chem. Soc., Chem. Commun.* (**1972**) 144.
[117] N. Miyaura, T, Yanagi, A. Suzuki, *Synthetic Commun.* 11 (**1981**) 514.

3.2 Experimental

3.2.1 Materials and Instrumentation

Suzuki coupling reactions were done under inert N_2 atmosphere using a two-neck flask. Phenylboronic acid, iodobenzene and triethylamine were purchased from Sigma-Aldrich. Mesitylene, which was used as an internal standard, was purchased from Riedel-de Haën. All the chemicals were used as received. Tetrahydrofuran and toluene were distilled from benzyl ketyl.

The progress of the reactions was monitored in-house using a Agilent 6850 gas chromatograph fitted with a flame ionisation detector (FID). The coupled products were also analysed in-house on a Agilent 7890A gas chromatograph fitted with a 5975C VL mass selective detector (MSD). For both chromatographs, the same column and similar parameters were used. The type of column installed on both GC systems was a HP-5, 5% phenyl methyl siloxane with dimensions: 30 m x 250 μm x 0.25 μm. Helium was used as a carrier gas at a flow rate of 1 mL/min on the GC/FID and 0.7 mL/min on the GC/MS. Injection source and detector temperatures were both set at 250 °C. The initial oven temperature at 60 °C was held constant for 2 min then ramped-up to the final temperature at 300 °C, at a rate of 10 °C/min.

3.3 General Procedure for Suzuki coupling reactions

A modified procedure by Miyaura *et al.*[117] was followed.

A two-neck flask equipped with a reflux condenser was charged with a complex (0.0318 mmol), iodobenzene (3.18 mmol) and THF (25 mL); the mixture was stirred at room temperature for 30 min. Phenylboronic acid (3.50 mmol) and a base (2 M, 3.2 mL, 6.40 mmol) were added and the reaction flask was immersed in an oil bath preheated to a required temperature. Samples were then withdrawn at different time intervals and analysed.

3.4 Results and Discussion

The layout of the GC/MS chromatogram obtained was similar to that one of the GC/FID therefore the compounds were easily identified from the pre-installed library database, Figure 3.3. The four peaks observed after 5 min retention time were identified as mesitylene, iodobenzene (Figure 3.4 a), biphenyl (Figure 3.4 b) and triphenylboroxine, listed in the order they appear on the chromatogram.

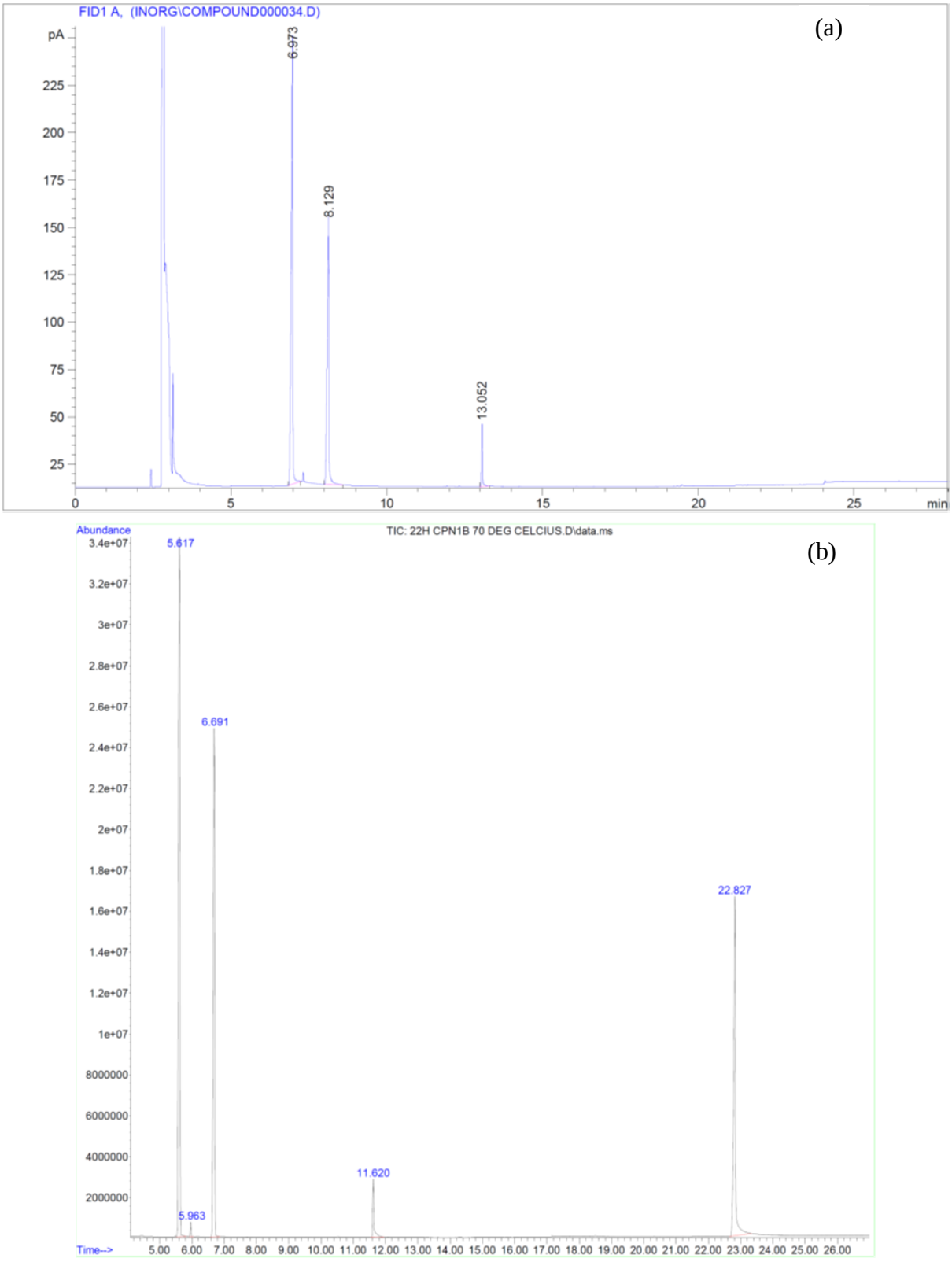


Figure 3.3: Typical GC chromatograms obtained by (a) FID and (b) MSD.

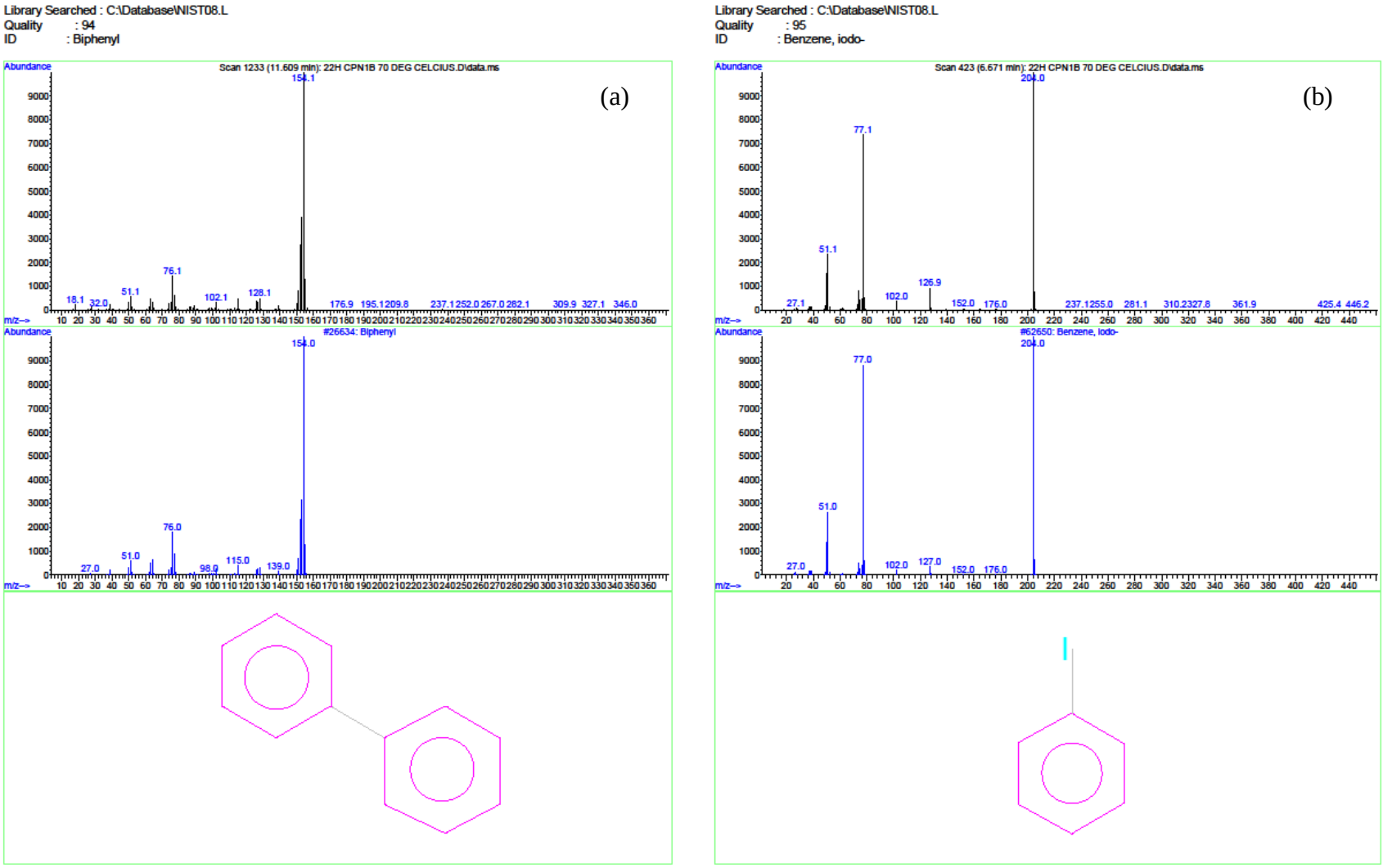


Figure 3.4: Identification of (a) iodobenzene, the reactant and (b) biphenyl coupled product by MS from the NIST library.

Mesitylene was used as an internal standard that assists in correcting the amounts of iodobenzene consumed and biphenyl formed from collected samples at different time intervals. This method is an alternative to a more complex and time consuming calibration technique using standard solutions of biphenyl.

There were a couple of observations made as a result of varying parameters such as the type of solvent, different temperature settings and the type of base known to have major influence on the coupling reactions.

Choosing a proper solvent for use in coupling reactions is of crucial importance. The main focus is on the solubility of the participating species at different temperature settings. It was observed that when using a high boiling solvent, toluene, the complexes were partially soluble and further decomposed on further heating without any coupling reaction taking place and thus no biphenyl products were formed. The desired product was obtained when a low boiling solvent, THF, was used. The product was obtained when both **CPNb** and **CNb** were used as catalyst precursors. The change in colour from yellow colour to deep red was a typical indicator that the reaction was in progress; this was not the case with toluene.

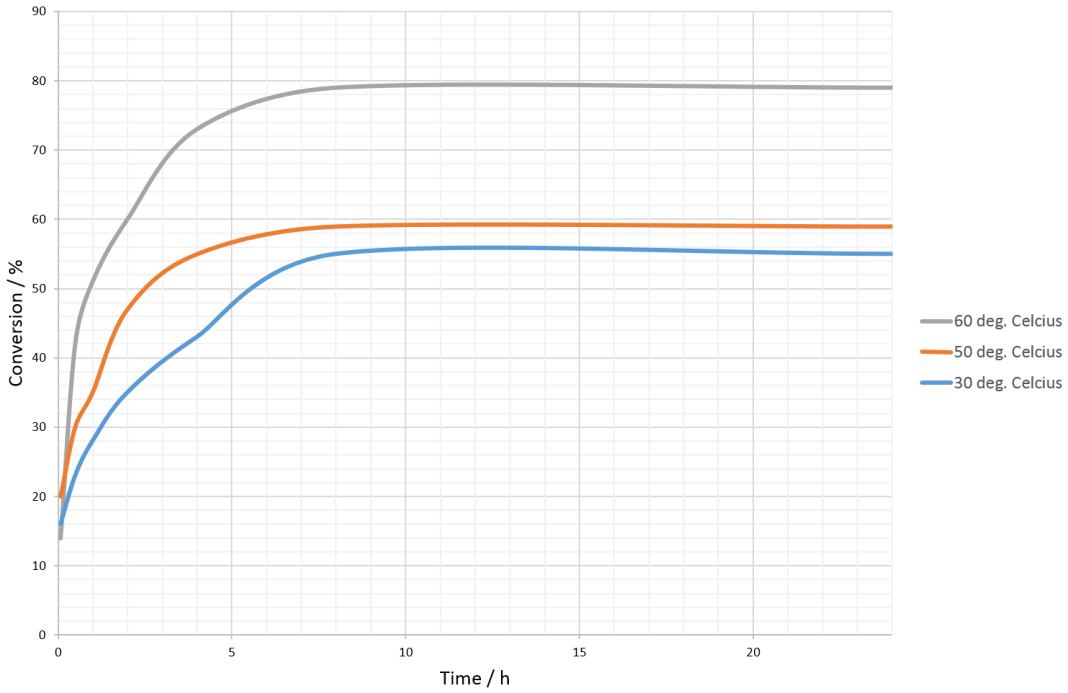


Figure 3.5: Line graph representation of the reaction profile for the NaOH and **CNb** system under temperature variations.

Temperature is a parameter that can be used to improve the catalytic cycle by improving solubility and activation energy required by the participating species. While using THF, it was observed that temperature variations affected the kinetics of the coupling reaction, Figure 3.5 and 3.6. An increase in temperature resulted in an increase in both the rate and total conversions towards the formation of biphenyl product. The catalyst seemed to easily survive the change in temperature, since milder temperatures were used in this study. About 55% conversion was obtained at 30 °C, and this increased to 79% conversion when the temperature was doubled to 60 °C. From the plot of variation of temperature over time it became clear that the maximum conversions were obtained within the first 8 h, after which they yields were invariably the same.

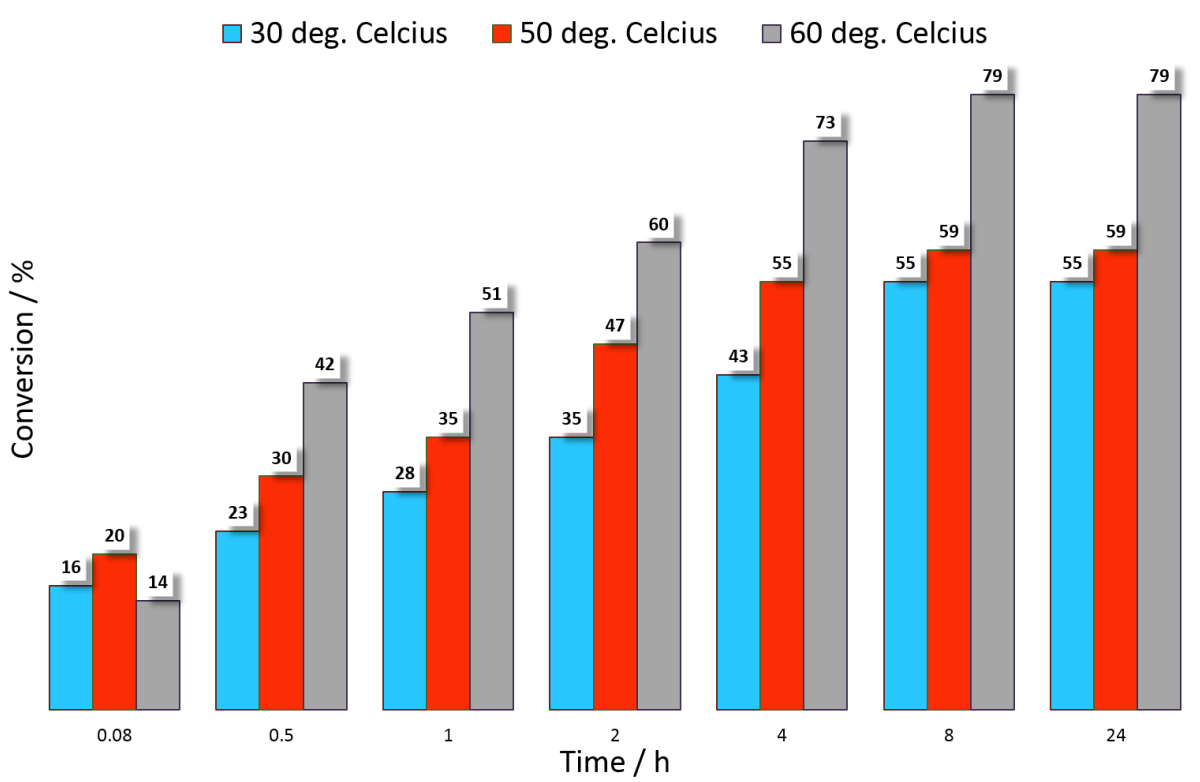


Figure 3.6: Bar graph representation of the reaction profile for the NaOH and **CNb** system under temperature variations.

Table 3.1: Catalytic evaluation of complexes using Suzuki-Miyuara coupling reaction.

Entry	Catalyst	Base	Time [h]	Conversion [%]	TOF [h^{-1}]
1	CPNb	Et_3N	6	11	1.83
2	CPNb	Et_3N^a	30	11	0.367
3	CNb	Et_3N	8	14	1.75
4	CPNb	Na_2CO_3	8	26	3.25
5	CNb	Na_2CO_3	12	18	1.50
6	CPNb	NaOH	8	72	9.00
7	CNb	NaOH	8	79	9.88
8	CP1	NaOH	8	90	11.2
9	CNa	NaOH	4	90	22.5

All reactions were done in THF at 60 °C using 3.18 mmol of iodobenzene, 10% excess of phenylboronic acid, 1 mole % of catalysts and 6.40 mmol of bases. [a]3 mole equivalence with respect to iodobenzene was used.

It was also observed that different types of bases give different yields of the biphenyl product. Weak bases gave low conversions while a strong base gave high conversions, Table 3.1. This trend is consistent with the literature reports,[109] the weak Lewis base (Et_3N) and alkali metal base (Na_2CO_3) gave conversions below 20% for both **CPNb** and **CNb**, Entry 1-5. Na_2CO_3 has been successfully used with other catalytic systems,[118] but was found not to be suitable for the production of biphenyl using our catalyst systems and even others in the literature such as $Pd(PPh_3)_4$.[117] The strong alkali metal base (NaOH) gave good conversions that were above 70% for both catalysts, Entry 6-7.

For the remaining catalysts, NaOH was used as a base and the temperature in the studies was maintained at 60 °C.

Good conversions of 79% were obtained for **CNb** as a result of using hard nitrogen donor pyrazole ligands. On the other hand, excellent conversions of 90% were obtained for **CP1** since

[118] A. Suzuki, *J. Organomet. Chem.* 576 (**1999**) 147-168.

it contains soft phosphorus donor ligands whose phenyl substituents on the phosphine impart steric factors that also improve the catalytic efficiency of the complex, Entry 8. It was then expected that since **CPNb** contained both the nitrogen and phosphorus donors from both **CNb** and **CP1** (Figure 3.7), it would have hybrid properties, thus counteracting the shortcomings experienced by the individual complexes. This complex also has a *cis* disposition of the chlorides while the other two have chlorides in a *trans* orientation.

It is also noteworthy that **CPNb** has two additional properties which have received a lot of attention in other catalytic studies. These properties are, (1) planar chirality which in combination with axial chirality have been reported to influence the stereoselectivity of the coupled products especially in asymmetric catalysis,[119] and (2) a bidentate configuration resulting in a strained seven membered chelate ring system[120] to the metal centre which would increasing the kinetics of the catalytic reaction.

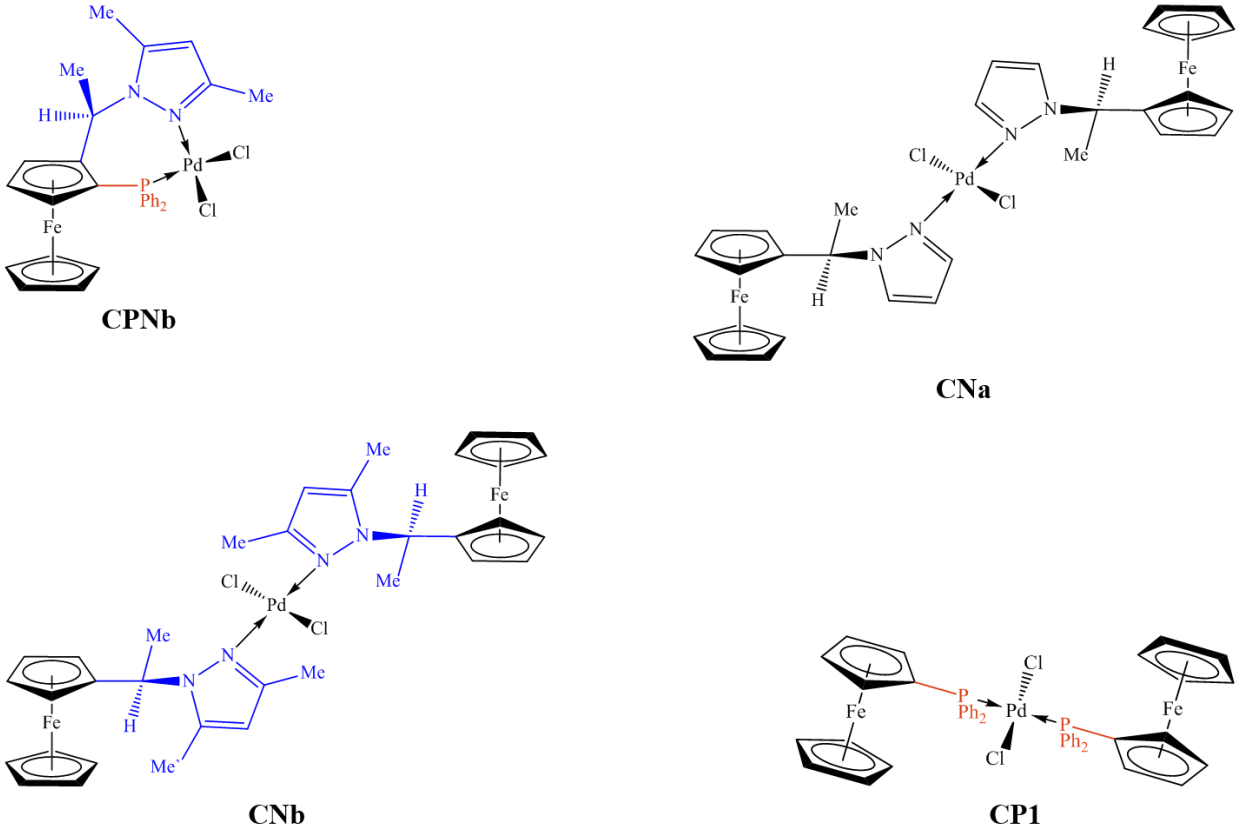


Figure 3.7: Complexes used as catalyst precursors for the cross coupling reactions.

[119] L.-X. Dai, T. Tu, S.-L. You, W.-P. Deng, X.-L. Hou, *Acc. Chem. Res.* 36 (**2003**) 660
[120] R.C.J. Atkinson, V.C. Gibson, N.J. Long, *Chem. Soc. Rev.* 33 (**2004**) 318 – 319.

Despite all its extra feature, **CPNb** did not show the reactivity that was better than any of the other catalysts; the highest yield obtained was a conversions of 72%, which was lower relative to **CNb** and **CP1**, Figure 3.8. It was expected that the reactivity would be between those displayed by the other two complexes. Thus, reactivity was expected to increase in the order: N-Pd-N < N-Pd-P < P-Pd-P.

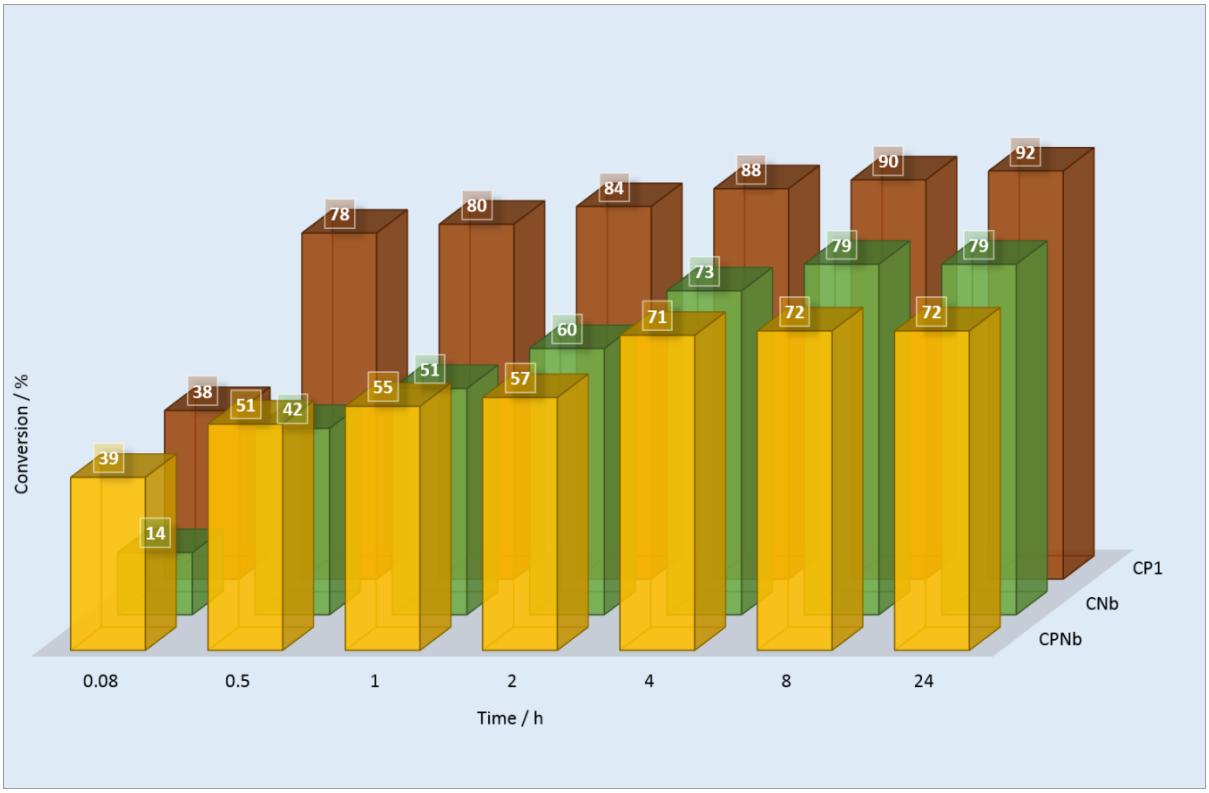


Figure 3.8: Reaction profiles obtained by GC for **CPNb**, **CNb** and **CP1**.

However, from the reaction profiles of the three catalysts it was noted that for the phosphine based catalyst derived from **CP1** the conversion was as high as 78% within the first 30 min. and only increased by a mere 14% over the following 23½ hours. The nitrogen based catalyst **CNb** produces a yield of 42% within the first 30 min. which then almost doubles to 79% over the next 7½ hours. The mixed donor catalyst shows a profile that is in-between the other two. It achieves a yield of 51% in the first 30min. then increases by almost one and half fold to 72% over the next

7½ hours. Disappointingly, **CNb** and **CPNb** do not show any reactivity beyond 8 hours suggesting that the catalysts is depleted. These findings reinforce the idea that the **LPNb** is a "multi-purpose" ligand since it has also been successfully used in other Pd[121] and Rh[122] catalysed organic transformation reactions.

Another interesting observation was made when the catalytic evaluation of **CNa** was compared to its derivative, **CNb**. The obtained data confirms the statements from literature that the catalytic efficiency of the complex is also affected by different substituents anchored on the pyrazolyl moiety thus tuning both its electronic and steric properties.[122a] It was found that the unsubstituted pyrazolyl moiety renders **CNa** to be highly reactive than the **CNb** which has methyl substituents on the pyrazolyl moiety; the former achieved 90% conversions in under 4 h, Table 3.1 Entry 9. Interestingly, **CNa** achieved a higher catalytic efficiency comparable to **CP1**, although the latter achieved the same conversion over 8 h. The observed activity of **CNa** could be attributed to its high solubility in THF as it was observed that it dissolves instantly at room temperature while with the other complexes needed to be heated to completely dissolve.

3.5 Conclusions

The complexes were succesfully evaluated in the Suzuki-Miyaura coupling reaction where biphenyl is the coupled product. The weak bases, Et_3N and Na_2CO_3, gave poor conversions which were typically below 14%, increasing the amount of base showed no improvements on the conversions. When the strong base, NaOH, was used, good conversions above 72% were obtained. It was also observed that the higher the temperature used, the better were yields obtained.

The main observation is that the mixed donor atoms system gave lower conversions compared to the unmixed counterparts.

[121] (a) A. Togni, U. Burckhardt, V. Gramlich, P.S. Pregosin, R. Salzmann, *J. Am. Chem. Soc.* 118 (**1996**) 1031. (b) G. Pioda, A. Togni, *Tetrahedron: Asymm.* 9 (**1998**) 3903.

[122] (a) A. Schnyder, L. Hintermann, A. Togni, *Angew. Chem.* 107 (**1995**) 996; *Angew. Chem., Int. Ed. Engl.* 34 (**1995**) 931. (b) A. Schnyder, A. Togni, U. Wiesli, *Organometallics* 16 (**1997**) 255.

Future outlook

Ideally, very good catalysts can catalyse the coupling of halogenated compounds which are deactivated; therefore, the prepared complexes would also be catalytically evaluated using bromo- and chlorobenzene compounds with different substituents, instead of highly reactive iodinated benzene compounds. It would also be worth investigating the influence that would arise from changing some components in these complexes, replacement of the ferrocene backbone with other metallocene backbones such as ruthenocene, the use of different metal precursors such as [PdClMe(COD)], etc.

An alternative cheaper method would have to be devised to successfully prepare **CPNa**. It would also be interesting to prepare 1,1'-disubstituted derivatives of **LN** compounds from 1,1'-acetylferrocene, and use them to prepare the corresponding derivatives of **LPN** compounds whose coordination modes would be investigated when complexed to different transition metals widely used in catalysis, Fig. 4.1. Preparation of achiral derivatives of **LN** compounds, with and without the linker, could be done thus assessing the role played by chirality in the preparation of biphenyl using the protocols discussed in Chapter 3, Fig. 4.2.

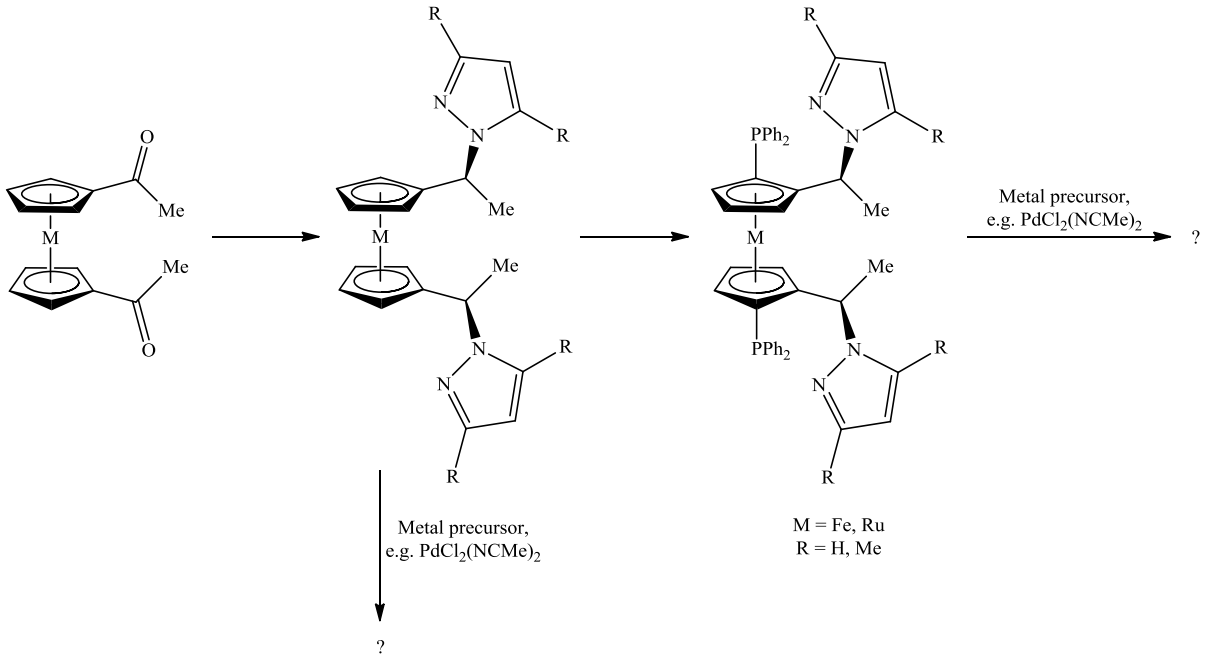


Fig. 4.1

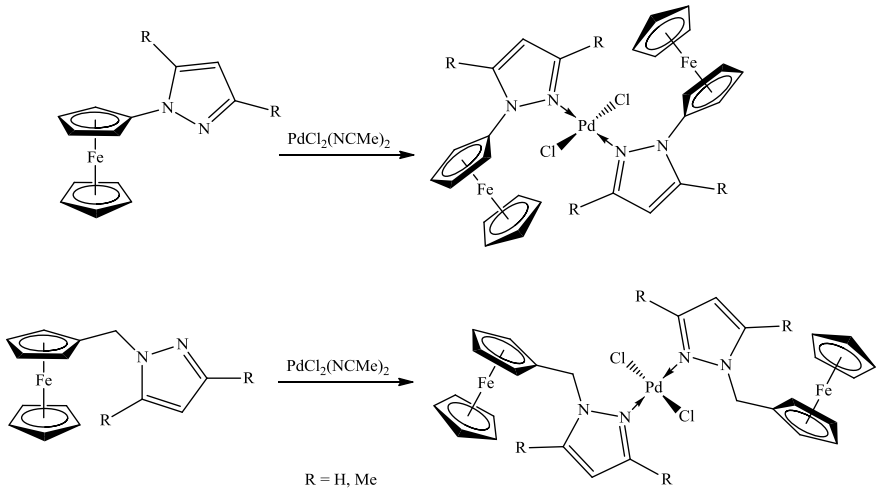


Fig. 4.2

Compounds **3a** and **3b** would be complexed with other metal precursors other than $[Mo(CO)_4(NHC_5H_{10})_2]$ which has been reported to rather exchange the pyrazolyl moiety of disubstituted derivatives with its piperidinyl moiety, instead of forming complexes.[123] An alternative method that may improve the yield of **4** would be tested, where *n*-BuLi and $ClPPh_2$ would be used instead of $LiPPh_2$ generated *in situ*, Fig. 4.3.

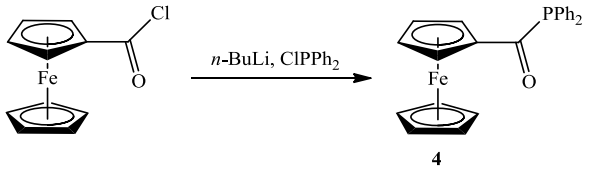


Fig. 4.3

Complexation of **8** and **8-OH** with Pd would be attempted and the corresponding complexes would be catalytically evaluated and compared to **CP1** and $[PdCl_2(dppf)]$, Fig. 4.4.

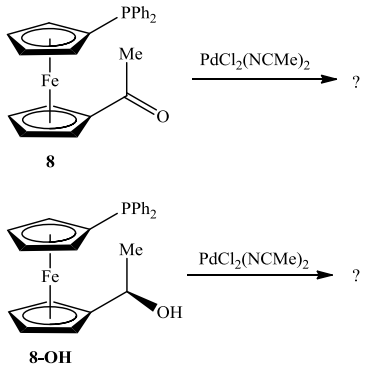


Fig. 4.4

[123] R.S. Herrick, B.R. Franklin, C.J. Ziegler, A. Çetin, *Inorg. Chem. Comm.* 12 (**2009**) 1210.

Appendix

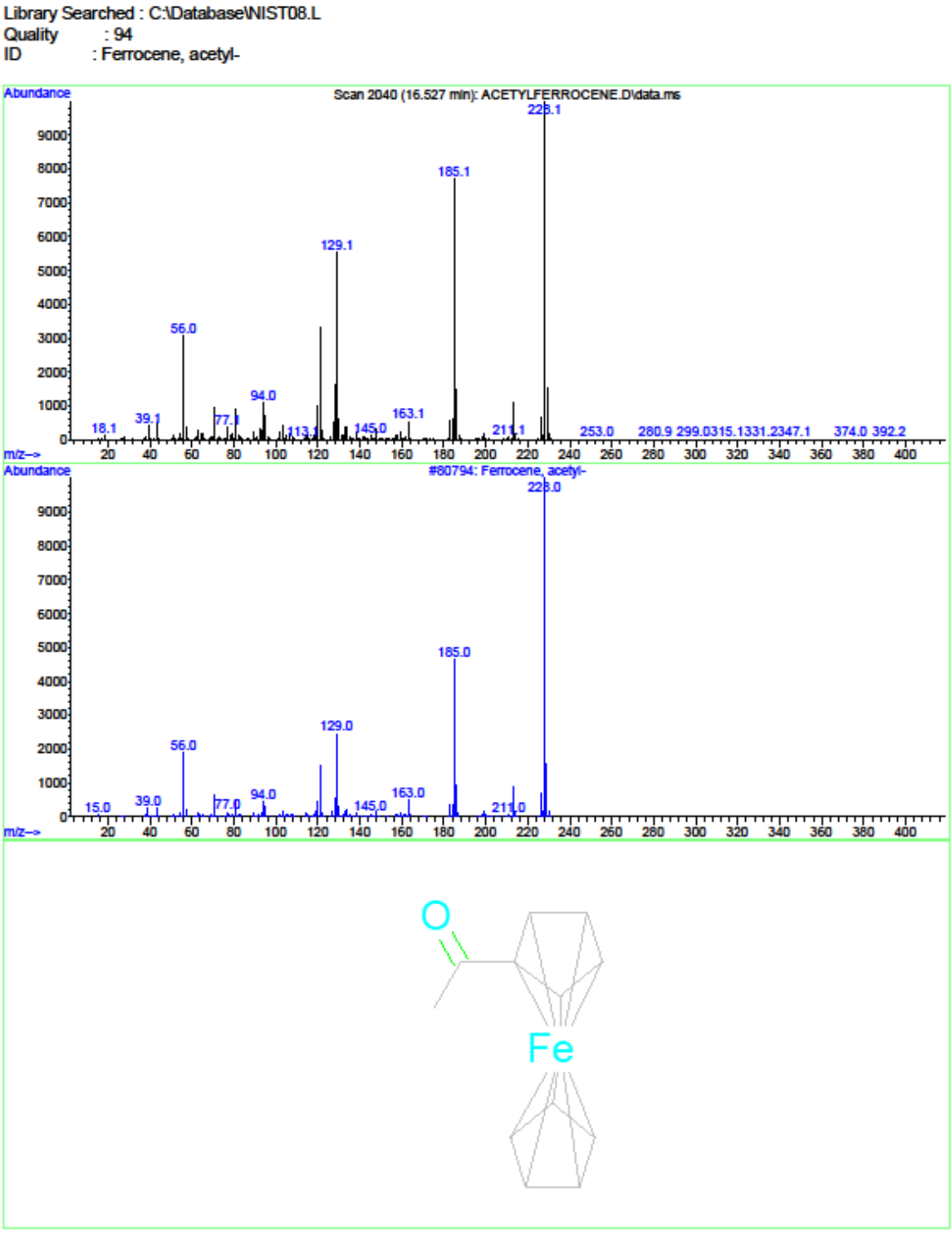


Figure A1: The prepared and library database mass spectra of acetylferrocene.

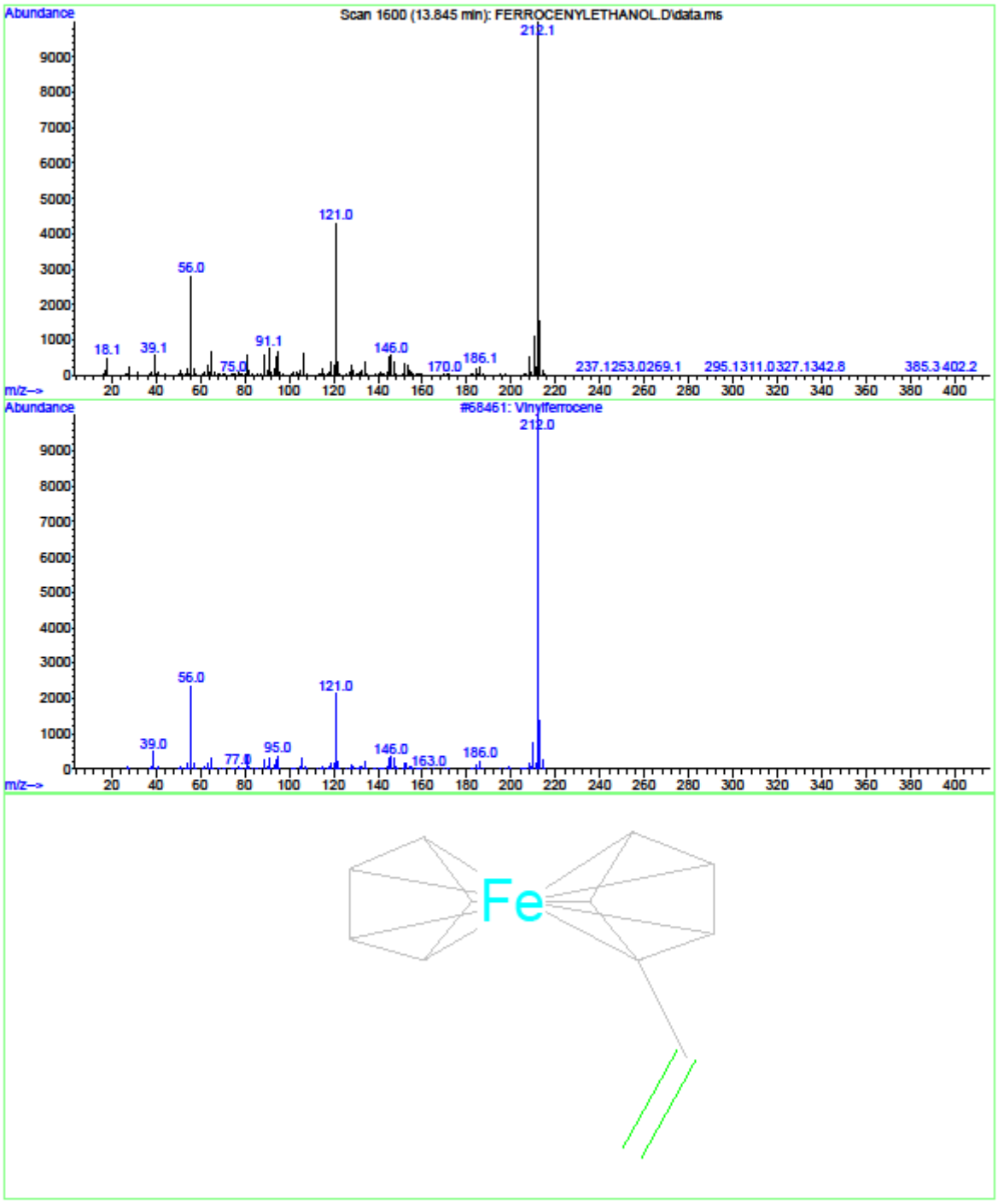
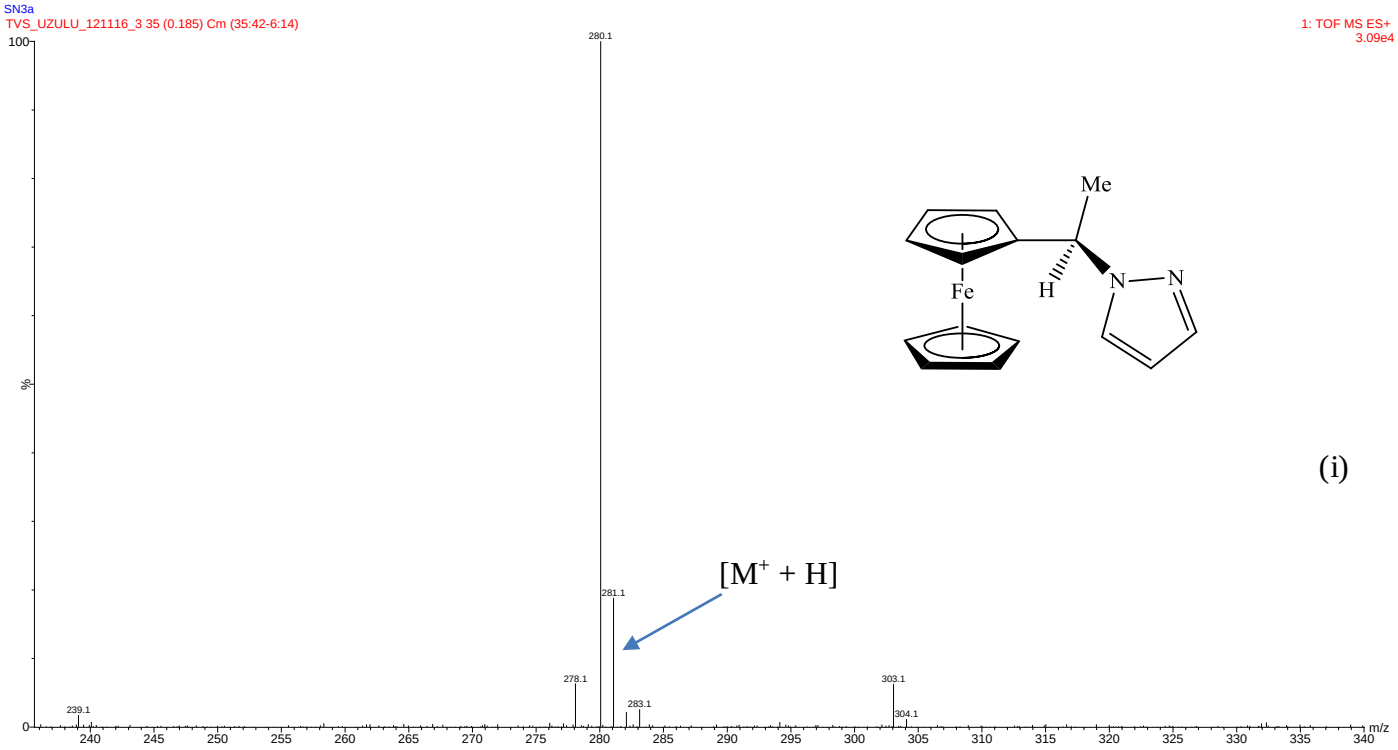


Figure A2: The MS analysis of **5-OH** and the subsequent library database comparison.



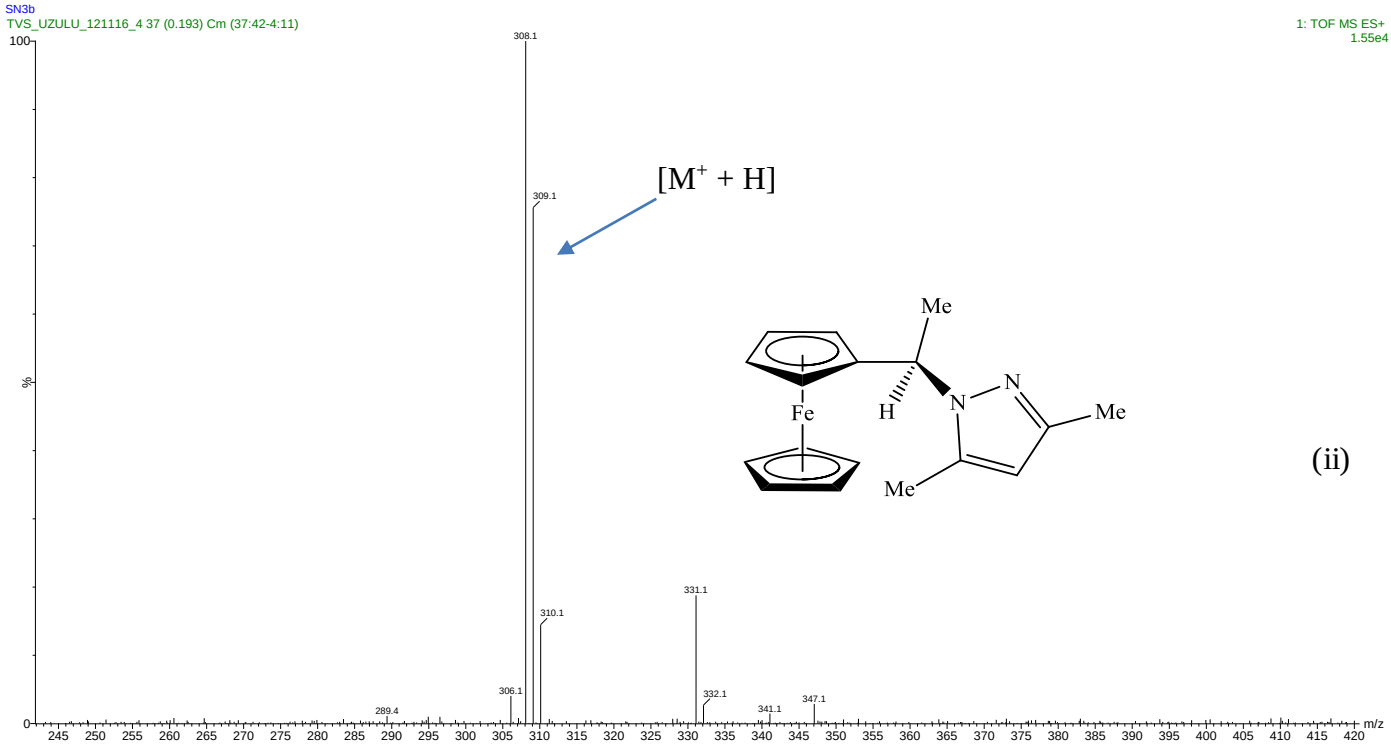


Figure A3: ESI mass spectra of (i) **6a** and (ii) **6b**.

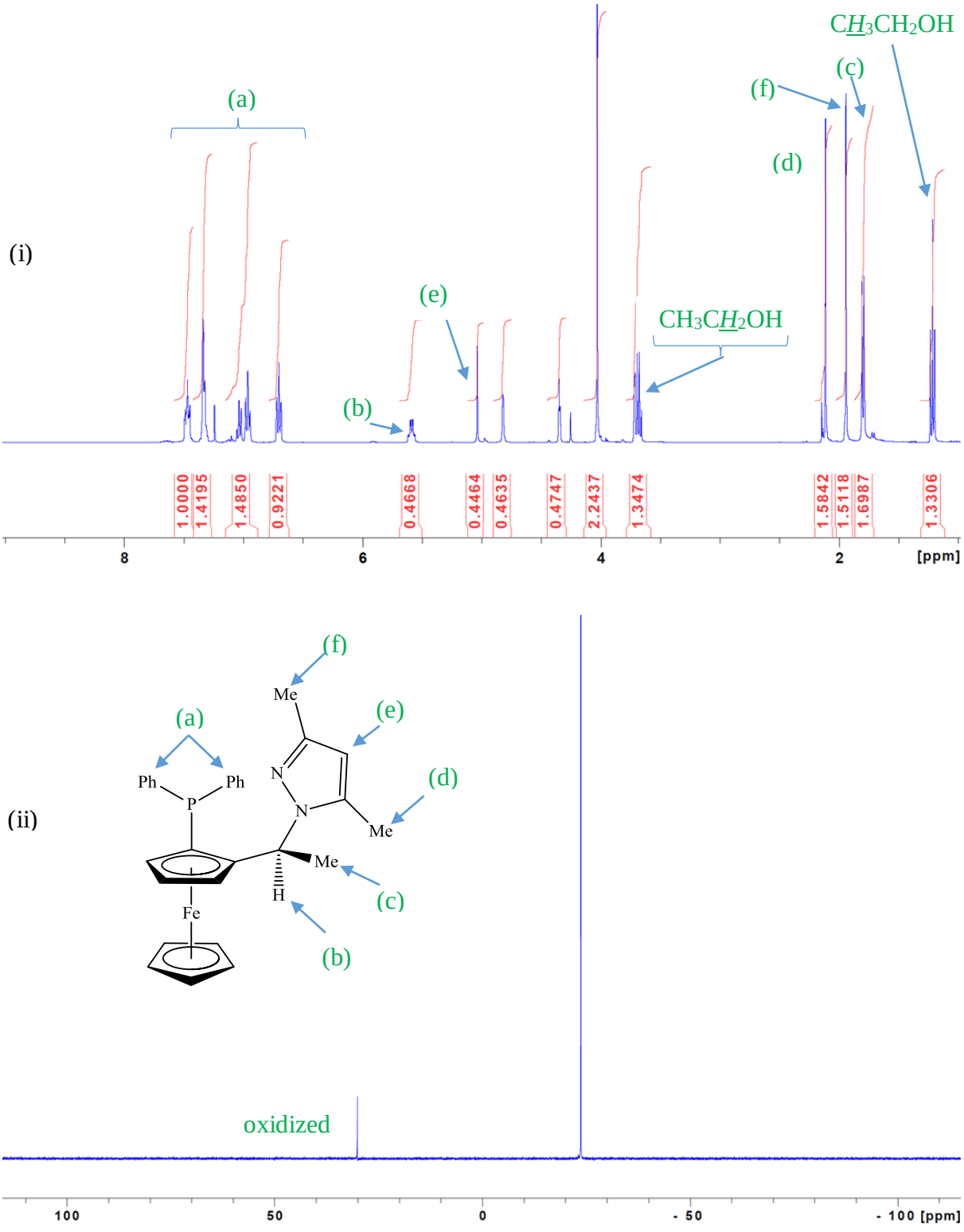


Figure A4: (i) ^{1}H NMR spectrum and (ii) ^{31}P NMR spectra of **LPNb**.

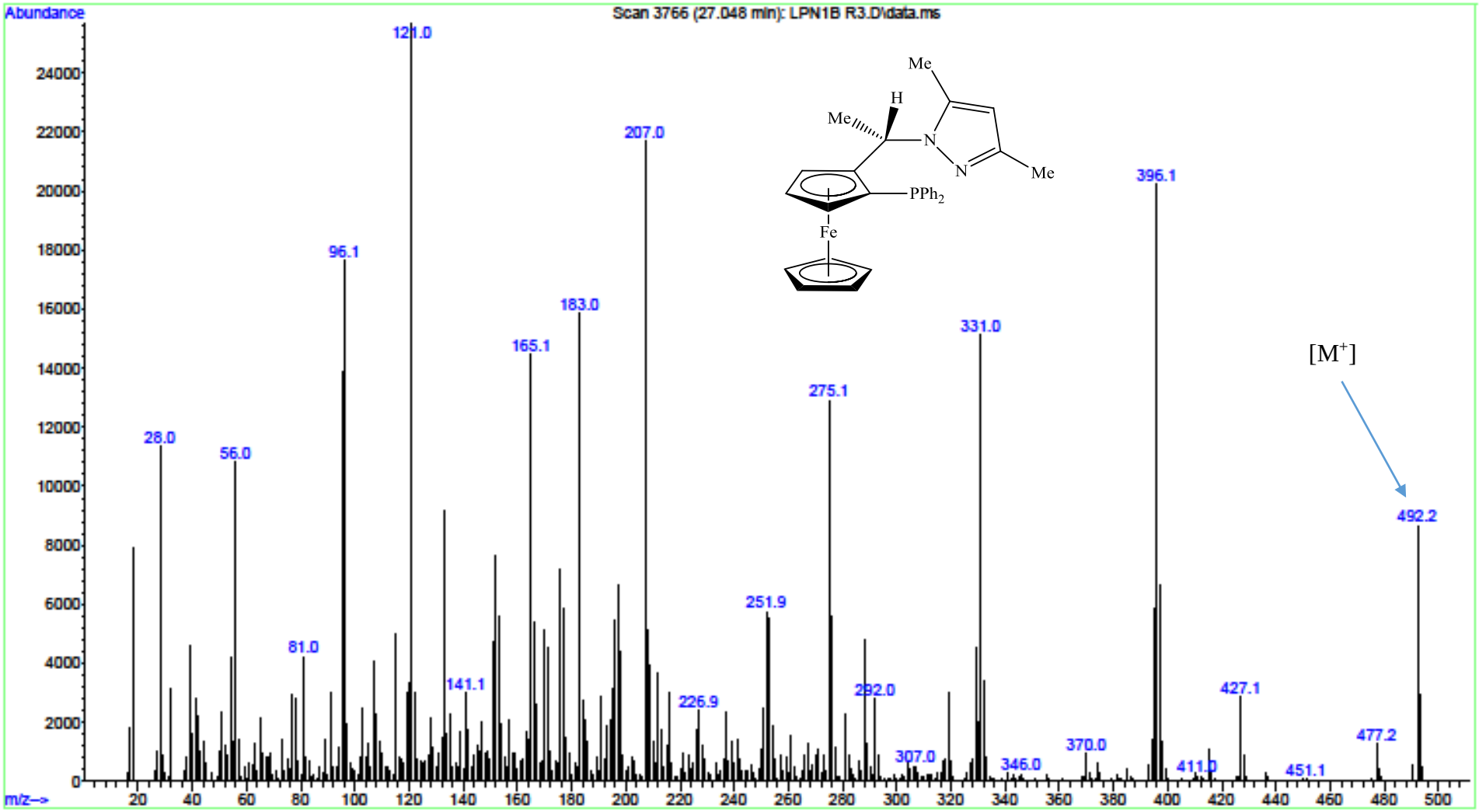
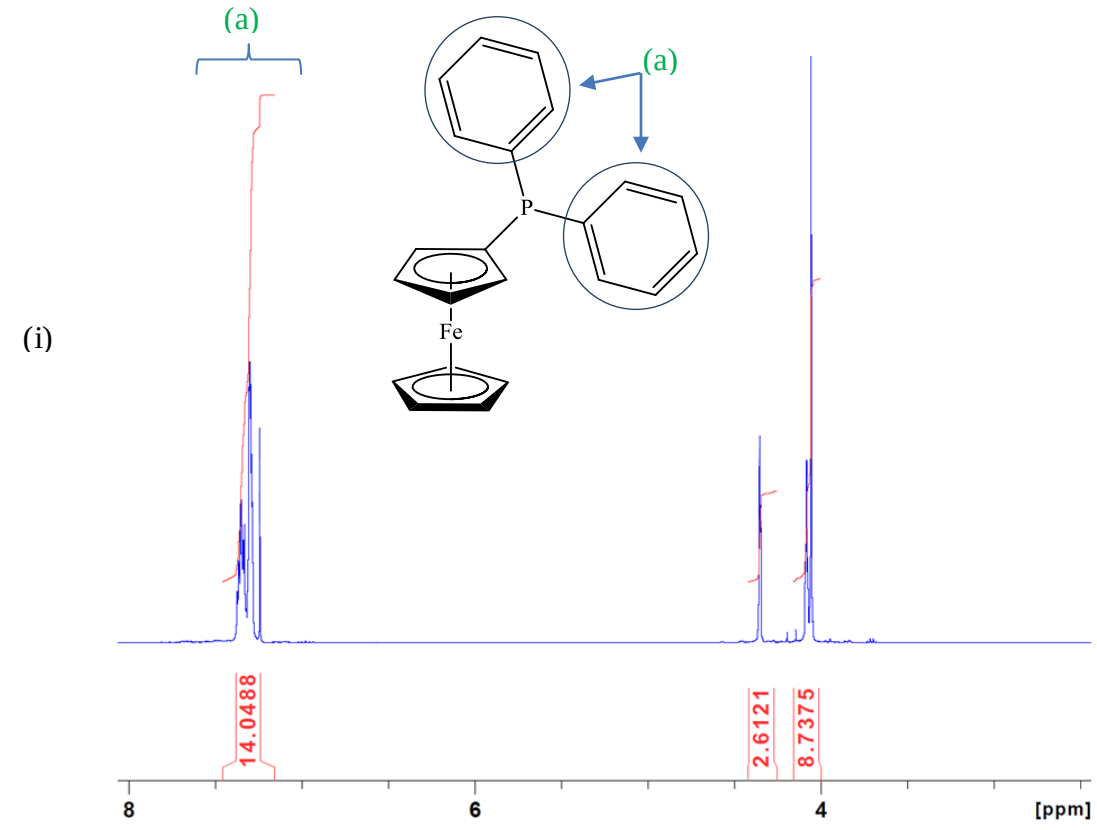


Figure A5: ES mass spectrum of **LPNb**.

(i)



(ii)

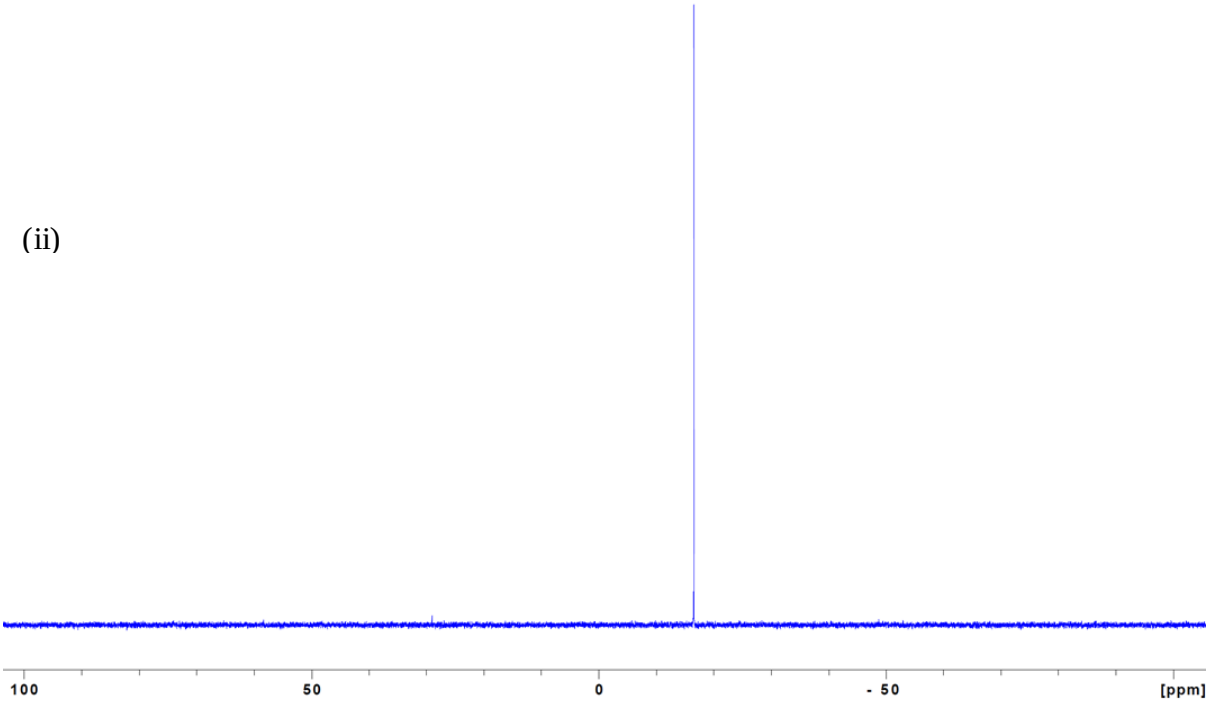


Figure A6: (i) ^{1}H NMR spectrum and (ii) ^{31}P NMR spectrum of **7**.

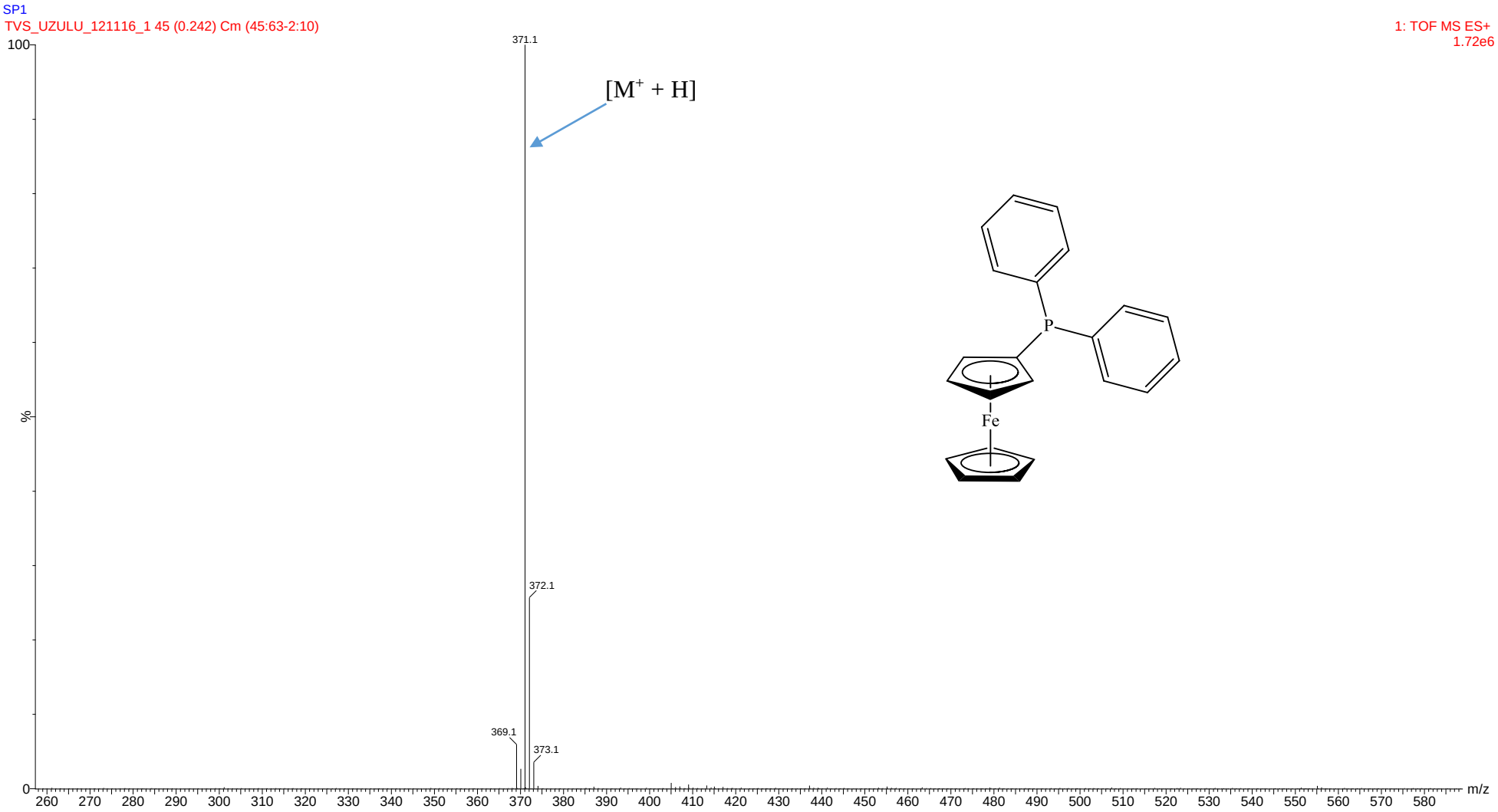


Figure A7: ESI mass spectrum of **7**.