Application of Asymmetric C-H Activation to the Synthesis of Planar Chiral Catalysts and Ligands.

Synthesis and Application Metallocene Based Palladacycles.

By Ketan Mahesh Panchal
4583922

Doctoral Thesis

Submitted in partial fulfilment of the requirement for the award of

Doctor of Philosophy

The University of East Anglia

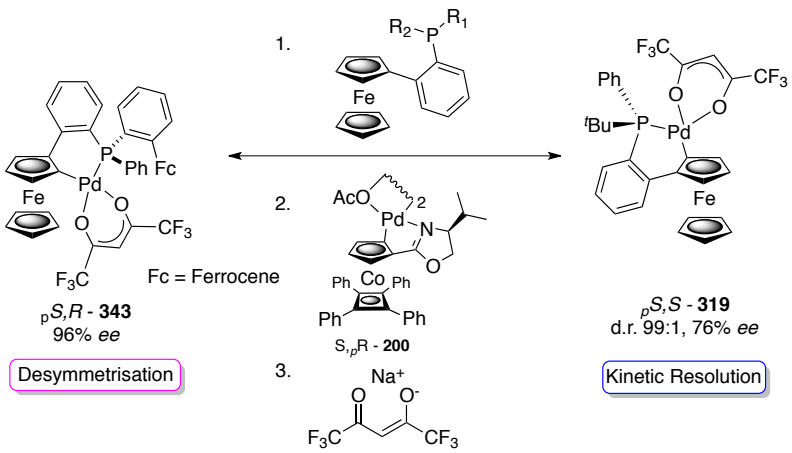
Department of Chemistry

September 2014

Contents Page

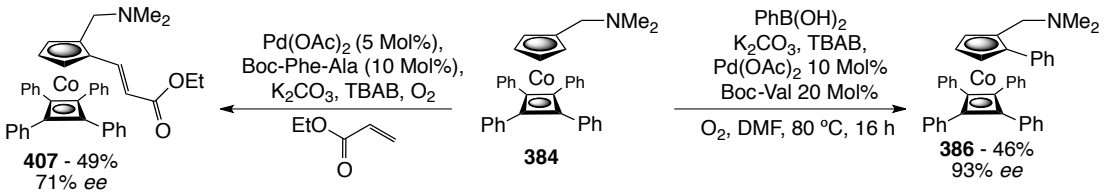
Abstract

The synthesis and application of ferrocene-based palladacycles has been at the forefront of catalysis for a number of years. The use of C-H activation to synthesise such compounds has been a relatively new development. The work within this thesis attempts to develop on known protocols devised by Richards *et al.* for the generation of enantioenriched planar chiral palladacycles.[1] The first of which includes the synthesis and application of symmetrical and non-symmetrical phosphines, and in this work the latter have been transformed into a diastereomerically pure enantiomerically enriched palladacycle *via* a transcyclopalladation (**Scheme I**).



Scheme I. Transcyclopalladation of P-chiral phosphines.

Compound **343** was generated as a diastereomerically pure palladacycle in 96% *ee*, and the kinetic resolution of the phosphine pre-courser to **319** afforded a d.r. of 99:1 and a 76% *ee*. Finally, methods developed by Shu Li-You and Wu have been extended to a cobalt sandwich complex affording novel bi-substituted ligands (**Scheme II**).[2]



Scheme II. Synthesis of novel cobalt sandwich containing bi-substituted ligands.

[1] Roca. F. X, Motevalli. M, Richards. C. J, *J. Am. Chem. Soc.* 127, **2005**, 2388

[2] Pi. C, Li. Y, Cui. X, Wu. Y, *Chem. Sci.* 4, **2013**, 2675-2679; Goa. D. W, Shi. Y. C, You. Shu-Li, *J. Am. Chem. Soc.* 135, **2013**, 86-89.

Acknowledgments

First and foremost, I would like to say that this would not have been possible without the continuing support of the Bank of Mum & Dad, especially its two long-suffering shareholders, to whom I owe a great deal of debt. I must also thank my sister Rina for her support and wisdom. I must also thank my uncle Yogesh 'Be Professional' Luhar for some inspirational words during the challenging times.

Many thanks are owed to my supervisor Dr Chris Richards for obtaining the funding for my position, and then taking me on as a student. His seemingly limitless patience, advice and guidance have been gratefully received, and his appetite for a decent curry has the made the lab great place to work. I wish the 'Gaffer' all the best in the future. I would also like to thank the INTEREGG for the funding.

I have had the opportunity to meet some fantastic people whilst at UEA and I sincerely apologise if I have missed anyone out. Many thanks must go to the those who have inhabited it over the years, Dr Lydia Sosa-Vargas, Paulina 'Polish Maffia' Glowacka, Doyle 'maybe' Cassar, 'Ian 'Ket you're a ****' Strutt, Mark 'Ket, get back in defence' Walton, James 'what happened to the fire extinguisher, Ket?' Goillau, Julie 'duck salad' Doulcet, Oliver 'Palpy' McGaw, Ross 'turn that s**t off, Ket' Arthurs, Sarah 'Fired' Delf, Fran 'cat lady' Kinsey, Ryan 'I've got a fatal nut allergy but I love bakewell tarts' Tinson, César 'Fisher' Hurtado, Small Mini Eggs, Dr Chris 'pussyole' Schubert, Dr David Day, Dr Fabrice Bisaro, and finally I would like to thank Prof. Phillip Page for allowing me to come to his Christmas parties and summer barbecues.

A special mention must be given to the highly educated people who have dedicated their time to proof read my thesis; Dr Ken Hamilton, Dr Chris 'Purp' Pearce, Dr Chris 'nostrils' Bartlett, and Dr Eamonn Sucllion.

Outside the four walls of the chemistry department, there are many people who have stuck with me whilst completing this Ph.D. and I am thankful for their support. Special thanks must be given to Emma Walton for putting up with me whilst writing up and being patient with my ridiculous working schedule. Although, I have rarely seen them

throughout this chapter in my life, the small amount out time I have spent with these people has been a massive help, Dev Solanki, Vinny Hughes and, Ryan Lee, thank you.

During this Ph.D. one quote has stuck with me and has carried me through the challenging times and I must thank its author, a Mr Neil Quinn.

'*Success is measured not so much by the position that one has reached in life, as by the obstacles one has overcome*.'

Neil Quinn, **2014**

Abbreviations

Å	Angstrom
AcAc	acetylacetonate
Anal.	elemental analysis
APCI	atmospheric pressure chemical ionisation
app.	apparent
Ar	Aromatic
Atm	Atmosphere
br	Broad
Bu	Butyl
BINAP	2,2'-bis(diphenylphosphino)-1,1'binapthyl
BINOL	1,1'-bi-2-naphthol
c	cyclo
^{o}C	Celsius
ca.	*circa*
Cat.	Catalytic
Calc	Calculated
conv.	Conversion
COP	(η^5-(*S*)-2-(4 Methylethyl) oxazolinylcyclopentadienyl)-(η^4-tetraphenylcyclobutadiene)cobalt
COP-OAc	Di-μ-acetatobis[(η^5-(*S*)-($_p$*R*)-2-(2'-(4' methylethyl)oxazolinyl) cyclopentadienyl, 1-C, 3'-N)(η^4-tetraphenylcyclobutadiene) cobalt]dipalladium
COP-Cl	Di-μ-chlorobis[(η^5-(*S*)-($_p$*R*)-2-(2'-(4'-methylethyl)

	oxazolinyl)cyclopentadienyl, 1-C, 3'-N)(η^4-tetraphenylcyclobutadiene)cobalt] dipalladium
cy	Cyclohexyl
Cp	η^5-cyclopentadienyl
Cp*	pentamethyl η^5-cyclopentadienyl
δ	chemical shift
d	doublet
d.e.	diastereomeric excess
d.r.	diastereomeric ratio
dba	dibenzylideneacetone
DCM	dichloromethane
d	doublet
dd	doublet of doublets
ddd	doublet of doublet of doublets
decomp.	decomposition
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIBAL-H	diisobutylaluminium
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
dppb	1,4 -bis(diphenylphosphino)butane
dppf	1,1'-bis(diphenylphosphino)ferrocene
dt	doublet of triplets
dtt	doublet of triplet of triplets
Δ	heat
E	Configurational stereochemistry based on Cahn Ingold Prelog priority rules
E^+	electrophile
e.e.	enantiomeric excess

eq.	equivalents
equiv.	equivalents
ES	electrospray
Et	ethyl
FAB	fast atom bombardment
Fc	ferrocene
FT-IR	fourier transform infra red spectroscopy
g	gram
G.C.	gas chromatography
h	hours
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HfAcAc	hexafluoro acetylacetonate
Hz	Hertz
IPA	*iso*-propyl alcohol
IR	infra red
λ	wavelength
J	coupling constant
LDA	lithium diisopropylamide
L	litre
L	ligand
L_n	number of ligands
Lit	literature
m	multiplet
mg	milligram
mL	millilitre
min	minutes(s)
m	*meta*
Me	methyl
mol	Mole
mmol	Millimole(s)

M.p.	melting point
MS	mass spectrometry
m/z	mass to charge ratio
NacNac	1,3-diketimines
N	normal
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NMR	nuclear magnetic resonance
NOE	Nuclear Overhauser Effect
Nuc	Nucleophile
OAc	Acetate
[O]	Oxidation
OTf	trimethanesulphonate
p	*para*
pent	pentet
Ph	phenyl
ppm	parts per million
Pr	propyl
py	pyridine
[R]	reduction
$_{p}$R	planar chiral (*R*) stereochemistry
$_{p}$S	planar chiral (*S*) stereochemistry
q	quartet
R	Absolute (*R*) stereochemistry based on Cahn Ingold Prelog priority rule
R_a	Axially chiral (*R*) stereochemistry
rac	racemic
rt	room temperature
s	Singlet
S	Absolute (*S*) stereochemistry based on Cahn Ingold Prelog priority rule

sat.	saturated
S_a	Axially chiral (*S*) stereochemistry
t	tertiary
t	triplet
tert	tertiary
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
Tol	tolyl
Vol.	Volume
Z	Configurational stereochemistry based on Cahn Ingold Prelog priority rules.
(*)	Relative stereochemistry
(+)	Rotates plane polarised light clockwise
(-)	Rotates plane polarised light anti clockwise

Chapter 1

An Introduction to the Synthesis and Application of Palladium and Associated Ligands to Asymmetric Catalysis.

1.0 – General Introduction

Metal-based catalysis within organic synthesis has grown significantly in a relatively short period of time, and one reason for this is the emergence of enantiomerically enriched catalysts which have the ability to transfer chiral information from catalyst to substrate. One of the key tools in this transformation is the ligand. These are bound to the metal and can have a vast array of effects on the property and function of metal centre involved in any catalytic transformation. The body of text below is an introduction to the areas that underpin the research undertaken. It is key to understanding the function and theory behind palladium and its affinity towards phosphorus-based ligands, which have so much control over its reactivity. Another key area is the relatively new field of C-H activation and how this can generate new and active palladium species to then be reacted further. Finally, the two above mentioned topics are now brought together and applied to the generation of planar chiral metallocene based palladacycles, as well as their function within organic transformations from the Overman Rearrangement to the Suzuki cross-coupling.

1.1 - Application of Palladium.

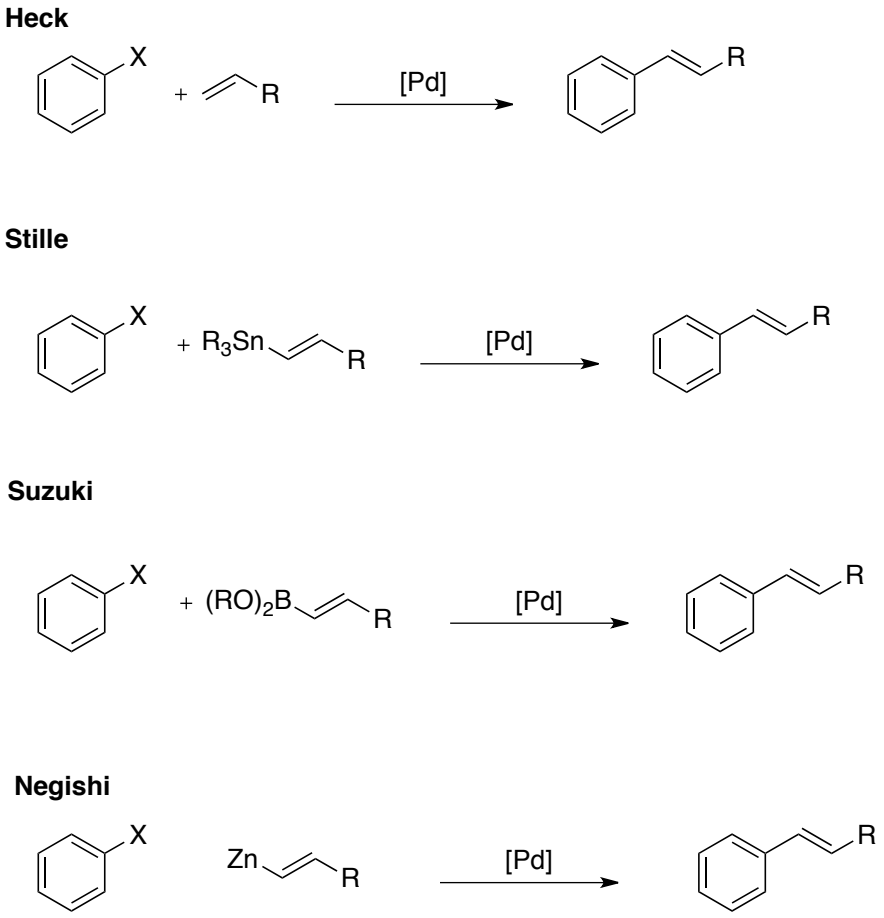
Palladium is arguably the most versatile and ubiquitous metal in modern organic synthesis.[1] Palladium mediated processes have become essential tools, necessary for the synthesis of natural products, polymers, agrochemicals and pharmaceuticals. This is due to the ability of palladium to participate in catalytic transformations as well as its high functional group tolerance. Many areas in synthetic organic chemistry have been affected by this versatile transition metal, which has fundamentally changed the way that a retrosynthetic analysis can be carried out.[2]

Palladium is a relatively cheap when compared to rhodium but not iron or ruthenium, and very little is needed for catalytic processes in many cases in comparison to ruthenium, platinum and osmium. Palladium can also be used in the pharmaceutical industry but there are toxicity issues and strict limitations. The numerous industrial processes that it has been incorporated into demonstrate the importance of palladium catalysts. In recent communications it is suggested that activation barriers present for changes in oxidation states are much smaller than previously anticipated, reinforcing positive outcomes of using palladium ligand complexes. In comparison, platinum experiences greater barriers to both redox and ligand substitution reactions, rendering it less effective in this context.

Palladium can be used to conduct countless transformations with organic molecules. In fact, there are a number of well-known named reactions that employ this particular transition metal, including the Heck, Suzuki, Stille as well as many others. In addition to coupling reactions, palladium can also catalyse hydrogenation; hydrogenolysis; carbonylation; formation of C-C, C-O, C-N and C-S bonds; cycloisomerizations and finally, pericyclic reactions. Palladium-based methods often proceed under mild conditions affording high yields, with excellent levels of stereo, regio and chemoselectivity.[3]

Advanced palladium chemistry started in the early 1960's, and in 2010, in a culmination of this body of research, Heck, Negishi and Suzuki won the Nobel Prize for their work on palladium catalysed reactions within organic synthesis. Palladium is versatile compared to

other transition metals commonly used in organic synthesis. There are a variety of methods available as well as a high tolerance of functional groups. Protecting groups allow modifications to be made while preventing unwanted reactions, maintaining crucial functionality and stereochemistry. However, precautions are still needed, as some palladium complexes are sensitive to oxygen, moisture and acids. Examples of coupling reactions are outlined in **Scheme 1**.



Scheme 1. Generic representation of famous palladium mediated coupling reactions.

1.2 - Palladium$^{(0)}$ and Palladium$^{(II)}$

1.2 - Oxidation States.

Palladium can exist in a number of different oxidations states. Organic methods are dominated by the use of $Pd^{(0)}$ and $Pd^{(II)}$, although the utility of $Pd^{(IV)}$ has been of increasing interest. The remaining oxidation state, $Pd^{(III)}$ are yet to find many practical applications, and their observation remains rare. The increased stability of the even numbered oxidation states can be rationalised by the low tendency of palladium to undergo one-electron or radical processes, it readily participates in two electron oxidation or reduction processes. The ability of palladium to undergo facile and reversible two electron operations has contributed to its versatility in catalysis reactions, since each oxidation state can yield different chemistry (**Table 1**). Reactions such as cross-couplings and olefin hydrogenations are common to the $Pd^{(0)}$ platform, while transformations such as alcohol oxidation can be achieved by using $Pd^{(II)}$.[4]

$Pd^{(0)}$	$Pd^{(II)}$
Cross-Couplings	Wacker Process
Allylic Alkylation	Cycloisomerization
Hydrogenation	Alcohol Oxidation
Hydrogenolysis	Allylic Oxidation
Carbonylation	Allylic Rearrangement

Table 1. Palladium processes.

1.3 - Reactivity.

The bulk of organopalladium literature is centred on the use of $Pd^{(0)}$ and $Pd^{(II)}$. Many reports do not clearly delineate the active catalyst (e.g. $Pd^{(II)}$ precatalyst can be used to generate $Pd^{(0)}$ *in situ*). In general, palladium catalysed reactions proceed through a simplified catalytic cycle, which is represented in **Figure 1**. $Pd^{(0)}$ can undergo either oxidation or oxidative addition, which will afford a $Pd^{(II)}$ complex. This $Pd^{(II)}$ complex can

generate new $Pd^{(II)}$ complexes *via* processes such as carbometallation, *β*-hydride elimination, transmetallation, ligand substitution, insertion or palladation. Finally, reductive elimination converts the $Pd^{(II)}$ complex back to $Pd^{(0)}$. This mechanistic understanding, combined with the ability of ligands and reaction parameters to modulate the reactivity of palladium, has allowed for a substantial amount of rational design in this field.

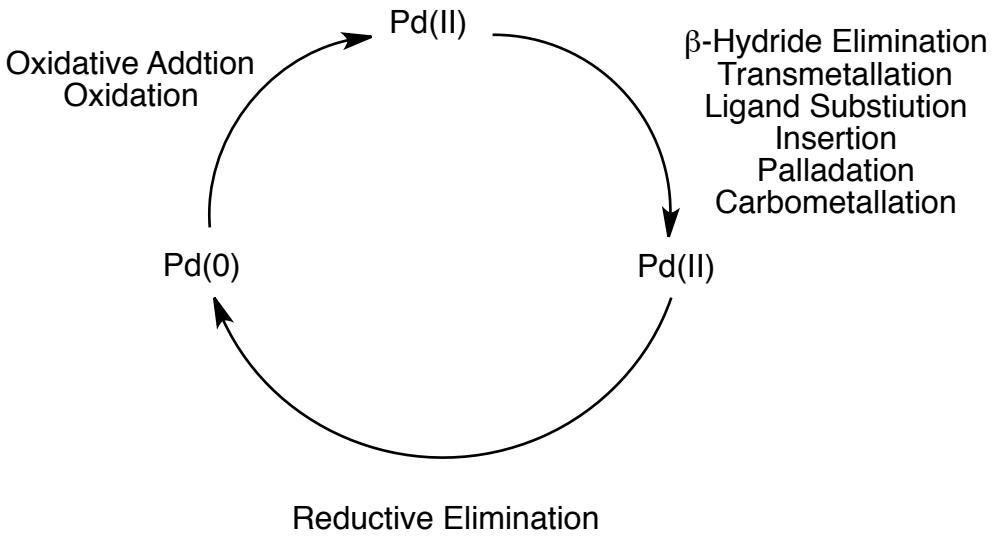


Figure 1. Schematic representation of palladium mediated catalytic cycle.

1.4 - Phosphines as Ligands.

1.4.1 – Known Ligands.

Bosnich and his group were early pioneers of the application of phosphines in asymmetric metal based catalysis, and this has now been brought into the modern era by chemists such as Stephen Buchwald.[5,6]

There are three main types of organophosphorus compounds, those containing P-R bonds (R = alkyl/aryl), those with P-ER linkage (E = heteroatoms such as O/N, R = alkyl/aryl), and those containing a combination of the two. A smaller but related group of secondary (R_2PH) and primary (RPH_2) phosphines are also known, but their use is largely limited to precursors to tertiary phosphines. Halo-containing phosphines have also been extensively studied, again largely as starting materials for the formation of PR_3 compounds, often *via*

their reaction with Grignard or organolithium reagents, but also as ligands in their own right.

The ability to modify the properties of phosphorus(III) compounds has resulted in their use in a large number of diverse applications,[7] and their synthesis/coordination chemistry has been subject to numerous reviews.[8,9,10] Typically, $P^{(III)}$ compounds are air/moisture sensitive and are often malodorous.

Phosphines and related trivalent phosphorus ligands are among the most important ancillary ligands in homogeneous catalysis, perhaps in all of organometallic chemistry. All of the transition metals, particularly late transition metals, form complexes with trivalent compounds of phosphorus. The soft donor matches well with soft low valent metals, and the substituents on the phosphorus atom can dramatically affect their properties and the reactivity of the metal centre. There are a vast number of known transition metal complexes containing phosphine ligands, which have been used in many ways in metal catalysis. Tertiary phosphine and related ligands are shown in **Figure 2.**[11]

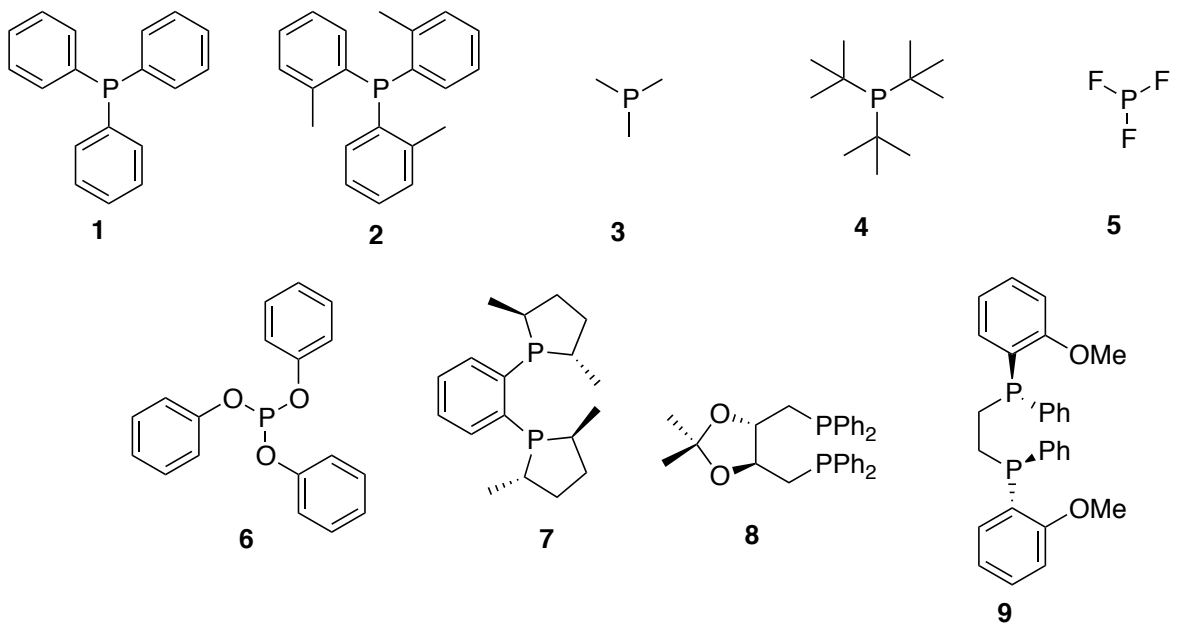
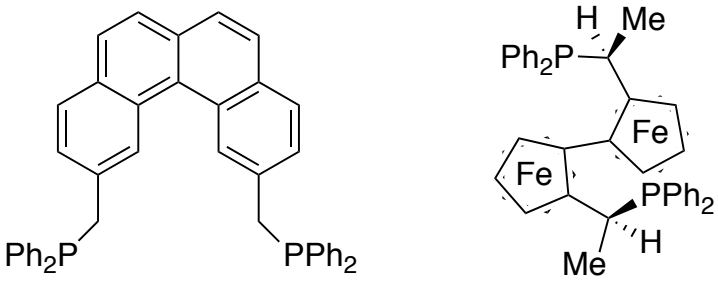


Figure 2. Representative common and historically important monophosphine and biphosphines.

1.4.2 – Bonding Properties.

PR_3 compounds are σ-donors, due to the lone pair of electrons, and π-acceptors. For the majority of phosphines, especially those that contain groups with a positive inductive effect, σ-donation is the dominant effect. Phosphines that contain P-OR or P-NR_2 are generally better π-acceptors than aryl/alkyl analogues, and as a result $R_nP(ER_x)_{3-n}$ (n = 0-2, E = O, x = 1, E = N, x = 2) compounds have been extensively studied, as a way of tailoring the steric and electronic properties of phosphine ligands.

In contrast to carbon monoxide as a ligand, dative ligands, including phosphines, can be tethered to another donor atom that binds the metal through more than one donor site. Ligands containing two, three, or four donor atoms are often called bidentate, tridentate, and tetradentate. These ligands bind metals in what is called a chelating fashion and, as a group, are often called chelating ligands. Phosphorus donors are most often combined with another phosphorus donor to create symmetric, dissymmetric and C_2-symmetric bidentate ligands. However, unsymmetrical bisphosphine ligands are becoming more common, and many ligands combine a phosphorus donor with another neutral donor, such as a nitrogen heterocycle, to form an unsymmetrical, neutral, bidentate ligand. The tether length of most chelating ligands is short enough to enforce a *cis* disposition of the two donor atoms. Certain bidentate phosphine ligands have been designed to ensure or encourage the two phosphines donors to bind in *trans* orientation, as seen in **Figure 3**.[12,13,14]



11 **12**

Figure 3. Two ligands designed to enforce *trans* geometries.

The phosphine-metal-phosphine angle enforced by the backbone of a bidentate ligand can strongly affect the reactivity of a complex containing a chelating ligand in both

catalytic and stoichiometric reactions. Casey and Whiteker have defined a range of angles that a series of chelating ligands prefer to adopt and have termed this the 'bite angle'. Some prefer to bind to a metal with a ligand bite angle less than 90°.[15] This ligand creates complexes that are stable with two donor atoms bound *cis* to each other in an octahedral or square planar geometry, or bound with one of the donors in the axial and one in the equatorial position of a trigonal bipyramidal. Other chelating ligands prefer to bind to a metal with angles closer to 120 °. These ligands prefer to bind, for example, to two equatorial positions of trigonal bipyramidal geometry.[16]

Free trialkylphosphines have similar basicities to the corresponding amines. The pK_a of HP^+Et_3 in DMSO is 9.1, while the pK_a of HN^+Et_3 is 9. However most transition metals are much softer acids and they will, therefore prefer to bind more strongly to the soft phosphorus in a phosphine than to the harder nitrogen in an amine.[17,18]

1.4.3 – Metal-Phosphine Interactions.

The large size of the phosphorus atom makes the metal-phosphine distance longer than the metal-nitrogen distance and the steric effects of the substituents in analogous nitrogen and phosphorus ligands are less pronounced for the phosphorus compounds. Thus, tertiary phosphines usually bind to transition metals with much higher affinity than tertiary amines. Phosphines are more susceptible to oxidation than amines because $P^{(V)}$ is a stable oxidation state. Some phosphines are air sensitive and must be handled under an inert atmosphere. Many alkylphosphines are sensitive but arylphosphines and phosphites, which are less electron rich in comparison to alkyl phosphines, are less sensitive or indefinitely stable to air.[19,20]

The barrier to the inversion at phosphorus is much higher than the barrier to inversion at nitrogen and typically ranges from 29 – 35 kcal/mol.[21,22] Amines containing three different substituents will consist of a racemic mixture in solution, while phosphines containing three different substituents can be prepared in an optically active form. Such phosphines can be resolved and stored indefinitely as single enantiomers. A chiral phosphorus compound was the first ligand that generated an enantioselective catalyst for

hydrogenation.[23] The development of P-chiral ligands has experienced a renaissance in recent years.[24]

Trialkylphosphine ligands bind to transition metals predominantly by Lewis acid-base interactions. The soft diffuse loan pair serves as a strong Lewis base to the soft transition metal Lewis acid. In contrast to many other dative ligands, monophosphines bind to a single metal centre in almost all cases.[25] Trialkylphosphines are the strongest electron doners of the dative phosphorus ligands, whereas arylphosphines are the weakest. This trend is observed, in part, because the greater *s*-character of the sp^2 hybridised orbital of the aryl group makes it a weaker electron donor in comparison to an sp^3 alkyl group. Phosphites, which contain three alkoxy groups at phosphorus, are weaker electron donors than phosphines because inductive electron withdrawal by the alkoxy groups.

1.4.4 – Orbital Overlap Theory.

Tertiary phosphines and phosphites can also serve as π-acceptors. These ligands were once thought to stabilise transition metal alkyl derivatives through $d\pi$-$d\pi$ back bonding in which filled metal *d*-orbitals overlap with the vacant *d*-orbitals of the phosphorus. However, more recent studies on the potential of phosphines and phosphites to act as π acceptors have indicated that the acceptor orbital is a hybrid of the P-Xσ^* orbitals and the phosphorus *d*-orbital with the dominant component being the P-Xσ^*.[26,27] The orbitals resulting from combining the P-Xσ^* and phosphorus d-orbitals, and the symmetry of these back bonding interactions are shown in **Figure 4**.

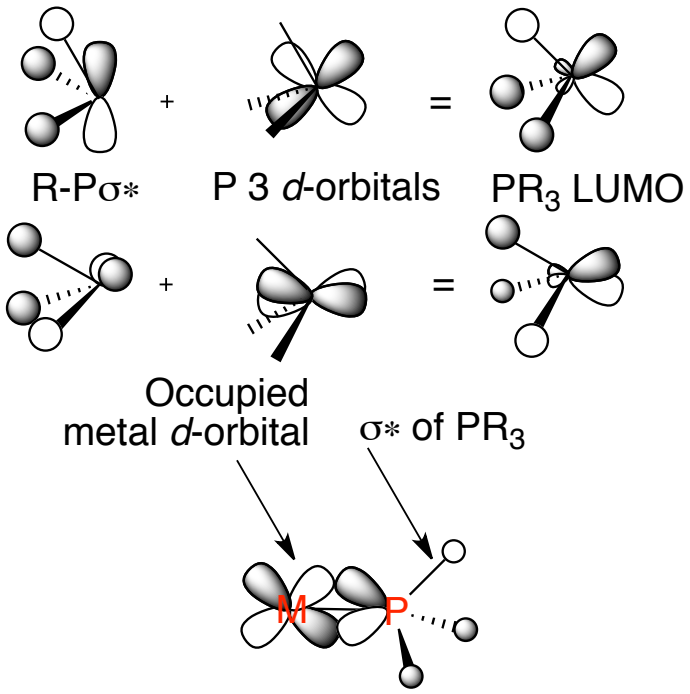


Figure 4. Mixing of σ*-orbitals in $P^{(III)}$ ligands with the phosphorus d-orbital and the symmetry of orbital interactions in metal-phosphine backbonding.

The view in the figure above has been widely accepted until several reports were published that proposed that anti-bonding P-R orbitals can act as the accepting orbitals without requiring the direct participation of the phosphorus 3d orbitals. These reports contained *ab initio* studies on PR_3 compounds,[28] and metal-PR_3 complexes,[29] and showed that while 3d orbitals play some part in π-back bonding, it occurs through the formation of hybridised orbitals with anti-bonding P-R orbitals. Anti-bonding P-R orbitals are still able to participate in *π*-back bonding in the absence of 3d orbitals though the effect is reinforced by the presence of the 3d orbitals.[30]

The *π*-accepting ability has been shown by comparing structural data on pairs of phosphine and phosphite compounds with the same ligand geometry using two different oxidation states. If the ligand were a simple *σ*-donor, then the M-P bond would be shorter in the complex containing the metal in the higher oxidation state. This was rationalised by weaker donation of electron density from the metal into the *σ**-orbital within the compound in the higher oxidation state.[31,32]

The magnitude of that donation depends on the substituents at phosphorus because the electronegativity of the group affects the energy of the P-C σ^*-orbitals. Harvey *et al.* provides a scale of the π-accepting abilities of different ligands.[33] This scale, resulting from a natural bond orbital analysis, sets the π-accepting ability of CO at 100. Although these numbers are generated from somewhat arbitrary weighing of data from calculations of different compounds, they do illustrate the relative π-accepting ability of different phosphorus ligands to CO and amine-based ligands (**Figure 5**).

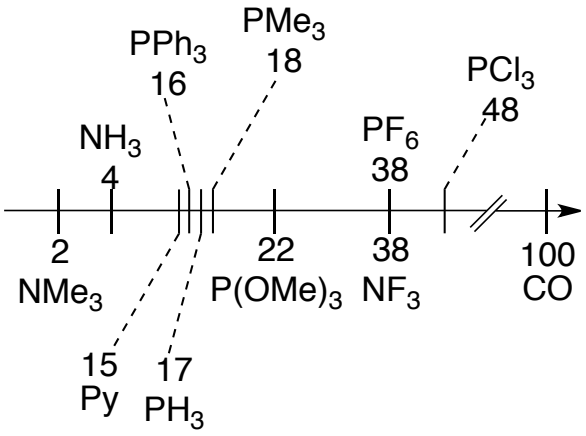


Figure 5. Calculated π-acceptor index for P- and N- based ligands, relative to CO, determined by a natural bond orbital (NBO) analysis.[25]

1.4.5 – Steric Properties of Phosphines.

The steric properties of phosphorus ligands have been exploited many times to control the reactivity of organometallic compounds in both stoichiometric and catalytic chemistry. Thus, much effort has been spent on quantifying the steric properties of phosphine ligands. Tolman can be credited with an early systematic treatment of the steric properties of phosphorus ligands. Tolman devised a structural parameter he called cone angle, which is the angle defined by the outer edge of the substituents at phosphorus and the metal centre of a space-filling model.[34]

This work was accurate enough before computer modeling and computational energy minimisation procedures. Two significant drawbacks to the cone angle parameter should be noted. First, the angle depends on conformation. The cone angle is based on the

conformation that is least hindered, and can vary significantly from one structure to another. Second, the proper definition of the cone angle of an unsymmetrical ligand is less straightforward. An average of the cone angles for the symmetric phosphines, weighted for the number of substituents, was originally used. A range of cone angles better describes these steric properties.

Phosphines and related $P^{(III)}$ compounds typically serve as ancillary ligands, but the dissociation of the ligand is crucial to the reactivity. Tolman correlated the ligand cone angle with the equilibrium for dissociation from NiL_4 compounds. The extent of the ligand association in these chemical complexes and in related palladium complexes increases in the order $PMe_3 < PMe_2Ph < PMePh_2 < PEt_3 < PPh_3 < PPr^i_3 < PCy_3 < PPhBu^t_2$. These steric and electronic properties of phosphines also affect the overall geometry of a complex. Bulky phosphines tend to bind *trans* to one another, and the presence of several bulky phosphines in the same coordination sphere can cause deviations from the idealised coordination geometry.[35]

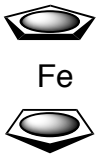
1.4.6 – NMR Properties of Phosphines.

Another advantage in using phosphine based ligands is that ^{31}P is NMR active. The ^{31}P nucleus has a spin of a 1/2 and it is 100% abundant. The ^{31}P NMR shifts depend on several parameters and predictions of ^{31}P NMR of complexes of phosphines and related ligands are tenuous. Chemical shift data is useful as a fingerprint, and the chemical shifts of phosphites, phosphinites, halophosphines, and phosphines fall in distinct regions. This allows any change to be identified and analysed easily. ^{31}P NMR data is a useful NMR handle and can be used to monitor a reaction, or even determine the identity of intermediates.

2.0 - Ferrocene.

Bis(cyclopentadienyl)iron, $[Fe(\eta^5\text{-}C_5H_5)_2]$, or ferrocene, (**Figure 6**) was discovered in 1951. It was reported by Kealy and Pauson as the product of the reaction between both

cyclopentadienyl magnesium bromide in benzene and anhydrous iron$^{(III)}$chloride in ether.[36] The reaction was expected to yield fulvalene but instead gave orange crystals containing Fe^{II}, analysing for $C_{10}H_{10}Fe$. An independent synthesis of the same compound was reported in a paper submitted earlier but published later by Miller, Tebboth and Tremaine.[37] The initial structural formulation was $[Fe(\eta^1\text{-}C_5H_5)_2]$, however the correct nature of this material was soon established by Wilkinson.[38] It was the first example of a class of compounds that became known as metallocenes for which G. Wilkinson and E. O. Fischer shared the 1973 Nobel Prize.



13

Figure 6. Ferrocene

Ferrocene is an orange, air stable crystalline solid. It is soluble in common organic solvents (*e.g*. Et_2O, CH_2Cl_2, petroleum ether) and insoluble in aqueous solvents (*e.g*. H_2O, acidic and basic aqueous solutions). The X-ray crystal structure analysis of ferrocene shows that the cyclopentadienyl rings are parallel to each other, with all carbon - carbon bonds being of equal lengths, and all carbon atoms being equidistant from the metal centre. The chemical behaviour of ferrocene is similar to that of other aromatic compounds. It readily undergoes electrophilic substitution reactions and, in comparison to benzene, the ferrocene rings are far more reactive to the magnitude of 10^6. This is due to the six π-electrons of the aromatic cyclopentadienyl rings being distributed over five carbon centres instead of six; and it is also partly due to the polarisable d-electrons of the iron atom being in close proximity to the carbon centres and therefore they help to stabilise the formation of a positive charge during an electrophilic addition type reaction.

3.0 – Properties of Functionalised Ferrocene Derivatives.

3.1 - Planar Chirality

Like other metallocenes, ferrocene displays planar chirality when two or more different substituents are attached to one of the rings. When this is the case the mirror images are non-super imposable, and the compounds are consequently chiral.

The first compound of this type to be prepared was 1,1'-dimethylferrocene-3-carboxylic acid,[39] in which both enantiomers were obtained by resolution of the racemate with cinchonidine and quinidine.[40] It was suggested that this isomerism could be called "planar chirality" since it occurs on a plane.[41]

Assignment of chirality was first coined by Schlögl and later described by Wagner and Hermann. [42,43] The observer regards the molecule from the side of the ring to be assigned (known as the 'top' or 'upper' ring). The substituents are then analysed for priority according to the Cahn-Ingold-Prelog rules. If the direction of the path from the substituent with the highest priority to that with next highest priority is clockwise, the chirality descriptor is (*R*), otherwise it is (*S*). In order to show clearly that chirality descriptor belongs to an element of planar chirality it can be denoted as ($_pR$) or ($_pS$) respectively (**Figure 7**).

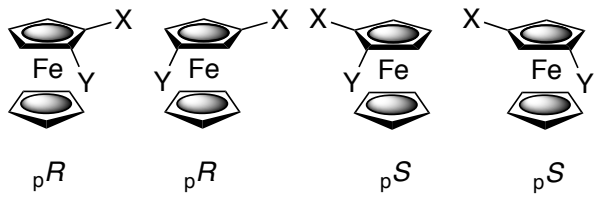


Figure 7. Assignment of chirality on ferrocenes.

(X has higher priority than Y according to Cahn-Ingold-Prelog rules)

The need to obtain chiral ligands and auxiliaries for use in asymmetric organic synthesis has become increasingly important. Since the isolation of the first planar chiral compound, many different methods have been established to synthesise such complexes in various ways.

3.2 – Structural Properties of Ferrocene

Since the discovery of ferrocene, its fascinating structure has captured the imagination of chemists and it is among the most important structural motifs in organometallic chemistry, materials science and catalysis.[44] Ferrocene as a ligand is unique because of its combination of flexibility, redox activity and conformational control; it has all the properties required to be a suitable ligand for a number of applications in metal-catalysed processes (**Figure 8**).

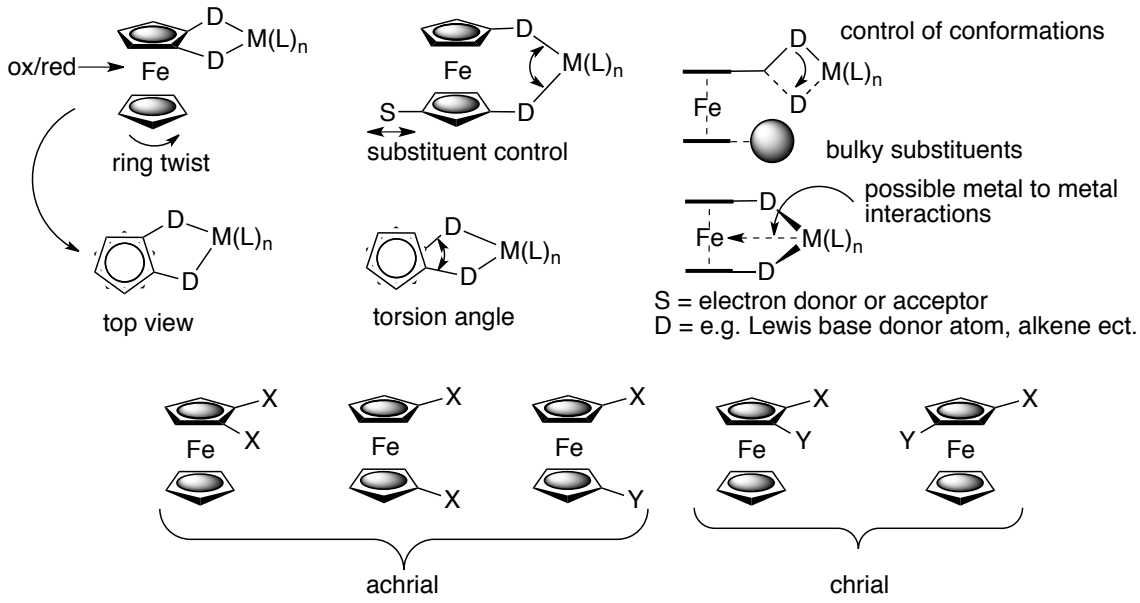
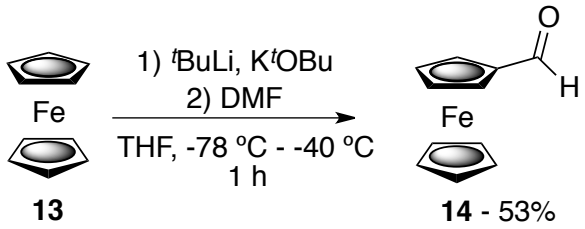


Figure 8. Ferrocene as a ligand.

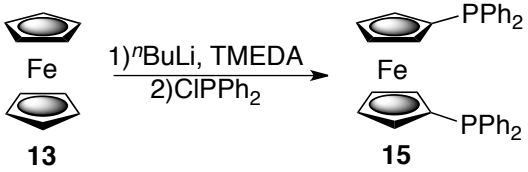
3.3 – Synthesis of Substituted Ferrocene Moieties.

The preparation of ferrocenyllithium reagents are relatively straightforward and may be carried out on scales ranging from a few grams to many kilograms. The method of monolithiation is well described but is used less as it often affords the 1-1'-dilithiated complex. The use of *tert*-butyllithium or *n*-butyllithium in THF with ferrocene to prepare lithioferrocene from THF has been described.[45] However, these syntheses were later superseded by preparations of *tert*-butyllithium and potassium *tert*-butoxide used as a superbase (**Scheme 2**).



Scheme 2. Synthesis of ferrocene carboxaldehyde (14) *via* a superbase mediated monolithiation.

Ferrocene has ideal properties such as thermal stability and high tolerance to oxygen and many other reagents. Its behaviour as an electrophile in an aromatic substitution reaction, its facile lithiation and di-lithiation at the 1,1' position, and the high electron density of the cyclopentadienyl rings resulting in stabilization of carbocations at the alpha position are all key chemical properties that provide practical approaches to functionalised ferrocenes. The best known ferrocene based ligand, 1,1'-bis(diphenylphosphino)ferrocene or dppf (**Scheme 3**), was first described in 1965. It was synthesised *via* a di-lithiation with *n*-butyllithium, and TMEDA, and trapping of the organo-lithium species with chlorodiphenylphosphine.[46]



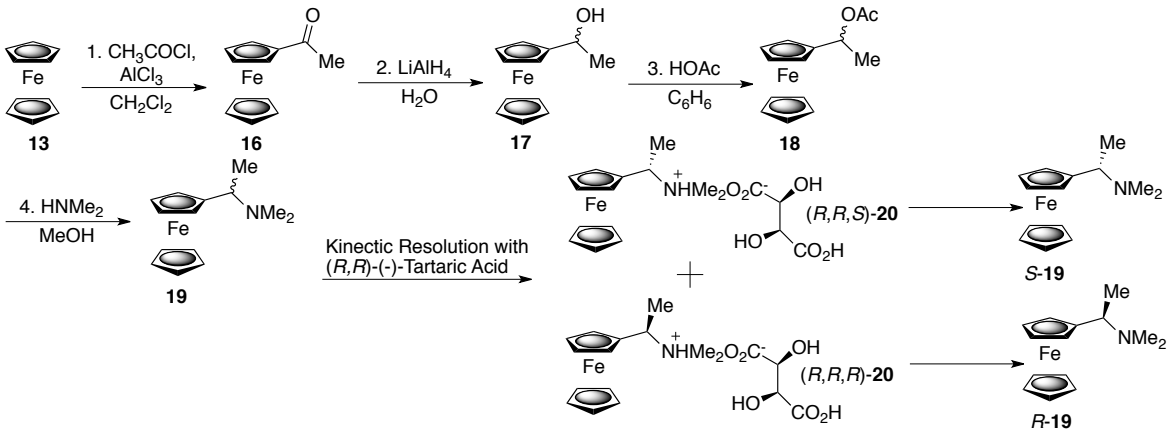
Scheme 3. Synthesis of 1,1'bis(diphenylphosphino)ferrocene).

The lithiation of such ferrocene containing compounds is well documented within the literature and is said to be a facile process, resulting in many synthetically useful derivatives.[47,48,49]

3.4 – Synthesis and resolution of Ugi's amine.

The pioneering work by Ugi *et al.* on functionalisation of enantiopure *N,N*-dimethyl-1-ferrocenethylamine, where planar chirality is introduced into the ferrocene backbone by

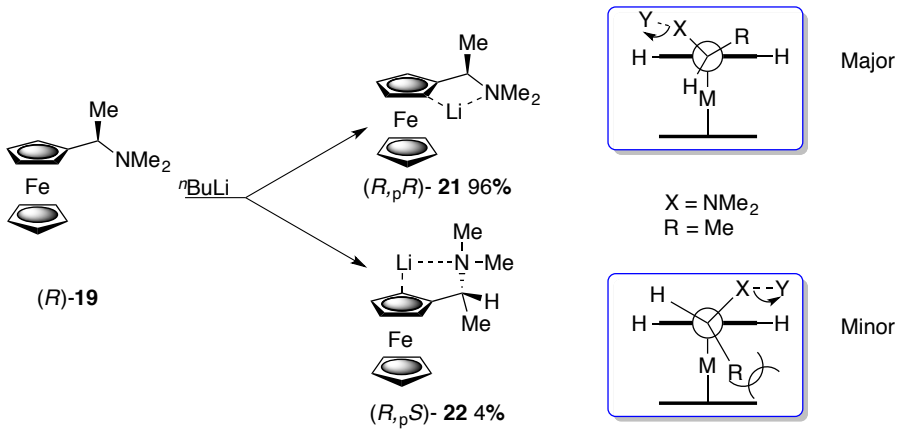
a diastereoselective lithiation and subsequent trapping with an electrophile, has been adopted as the standard protocol for the preparation of many planar chiral derivatives (**Scheme 4**).



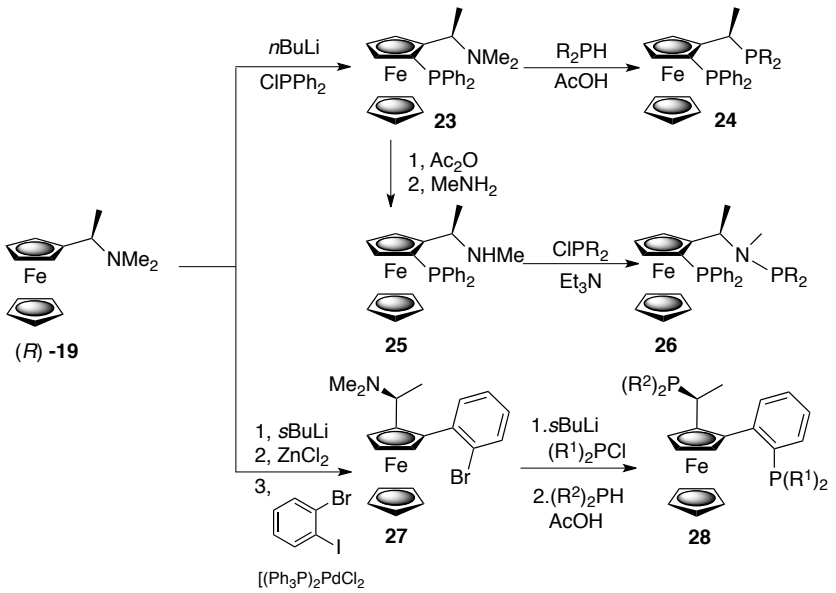
Scheme 4. Synthesis of *R* and *S* enantiomers of Ugi's Amine.

3.5 – Highly Diastereoselective Lithiation of Ugi's Amine and Synthesis of Planar Chiral P,N-Ligands.

In 1974, M. Hayashi and K. Kumada achieved the highly diastereoselective lithiation of *N,N*–dimethyl-1-ferrocenethylamine, and further reaction with electrophilic phosphorous led to the first examples of enantiopure planar chiral ferrocenyl phosphine ligands. Ugi's amine directs lithiation to the pro-$_p$*R* position selectively because the alternate conformation in which the amine is pointed towards the pro-$_p$*S* hydrogen is disfavoured by collision of the α-methyl group with the lower unsubstituted cyclopentadienyl ring. This was a major scientific break through as a series of high profile chiral ferrocene ligands were then developed (**Scheme 5**).[50]



Scheme 5. A suitably located donor atom one of the cyclopentadienyl rings directs the lithiation to the adjacent position.



Scheme 6. Examples of synthesis of 1,2-disubstituted ferrocene ligands from Ugi's amine.

The **Figure 9** below shows an array of other phosphine based ligands, which can be generated by implementation of a diastereoselective lithiation of Ugi's amine, trapping with the appropriate electrophile, and for manipulation where appropriate.

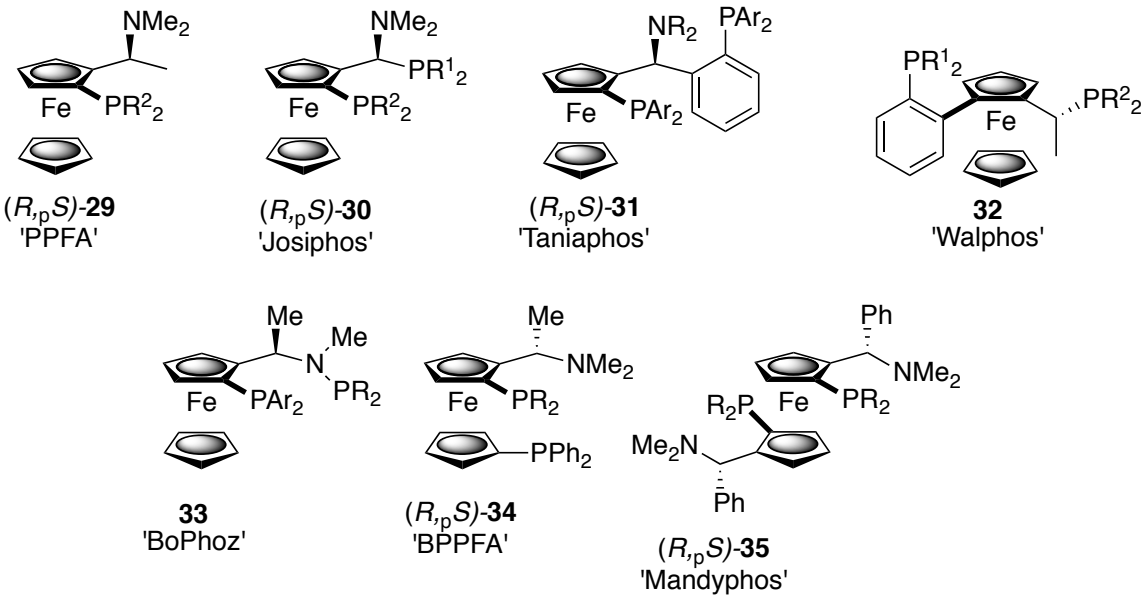
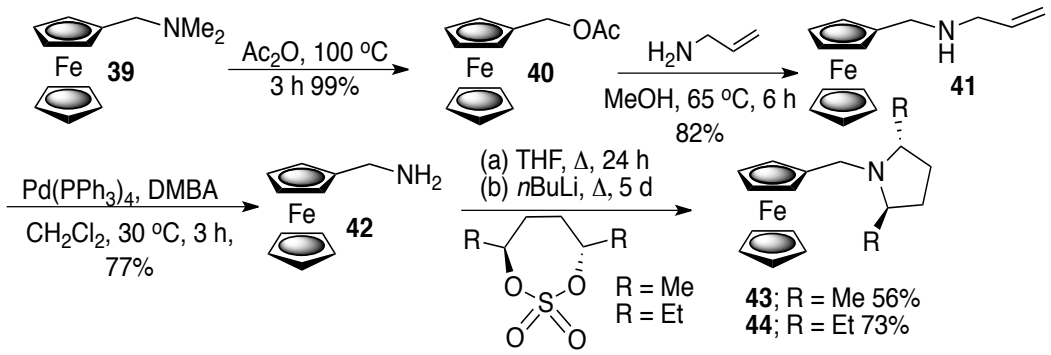


Figure 9. Examples of well known chiral ferrocenyl phosphine ligands.

6.1 – Further Examples of the Asymmetric Lithiation of Ferrocene.

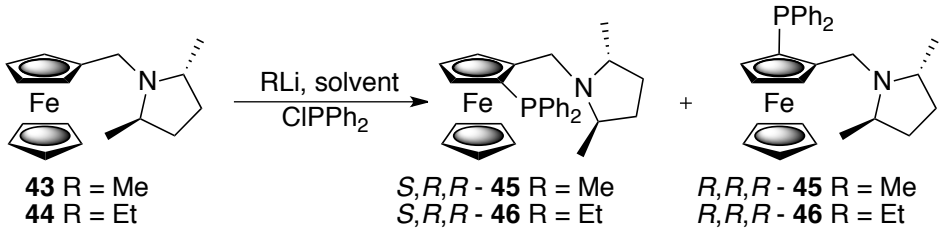
(2*R*,5*R*)-2,5-Dialkyl-1-(ferrocenylmethyl)pyrrolidines **43** and **44** were synthesised to study their ability to direct a diastereoselective metallation as a potential route to amine based ferrocenylphosphine ligands that possess both planar chirality and carbon based stereogenic centres (**Scheme 7**).



Scheme 7. Synthesis of pyrrolidines 43 and 44.

The directed diastereoselective *ortho*-lithiation of *trans*-(2*R*,5*R*)-2,5-dialkyl-1-(ferrocenylmethyl)pyrrolidines **43** and **44** and subsequent treatment with chlorodiphenylphosphine was investigated. The process was found to be sensitive to the

2,5-dialkyl substitutions. The use of *n*-butyllithium in either ether or hexane, at -78 °C or ambient temperature, failed to give the desired result. Changing to *sec*-butyllithium in ether gave a yield of 65% in 80% *d.e.* which was then purified to >100:1 after a single recrystallisation (**Scheme 8**).[51]



Scheme 8. Diastereoselective lithiation of pyrrolidines 43 and 44

Amine	RLi	Temp (°C)	Time (h)	Yield (%)	d.e. (%)[d]
43	^{n}BuLi[a]	-78	1	-	-
43	^{n}BuLi[a]	25	1	-	-
43	^{s}BuLi[b]	25	1	65	80[c]
43	^{s}BuLi[b]	25	5	37	80
43	^{s}BuLi[b]	0	1	20	90
43	^{t}BuLi[b]	25	1	30	82
43	^{t}BuLi[b]	0	1	10	90
44	^{t}BuLi[b]	25	1	10	78[c]

[a] Hexane or Et_2O as solvent. [b] Et_2O as solvent. [c] >100:1 after a single recrystallization from EtOH. [d] *S, R, R* = major product

Table 2. Diastereoselectivity of *ortho*-lithiation of *trans*-(2*R*,5*R*)-2,5-dialkyl-1-(ferrocenylmethyl)pyrrolidines 43 and 44

This is the first reported example of a diastereoselective *ortho*-metallation directed by a *trans*-(2*R*,5*R*)-2,5-dialkyl substituted pyrrolidine nitrogen atom. It is clear that there is a subtle interplay between the steric bulk of the alkyl lithium reagent and that of the 2,5-dialkyl group. The more hindered 2,5-diethyl-substituted pyrrolidine afforded the product in low yield with both *sec* or *tert*-butyllithium. The less sterically hindered 2,5-dimethyl-substiuted pyrrolidine gives the desired product with both *sec*- and *tert*-butyllithium, although the latter proceeds with a poor yield as shown in **Table 2**.

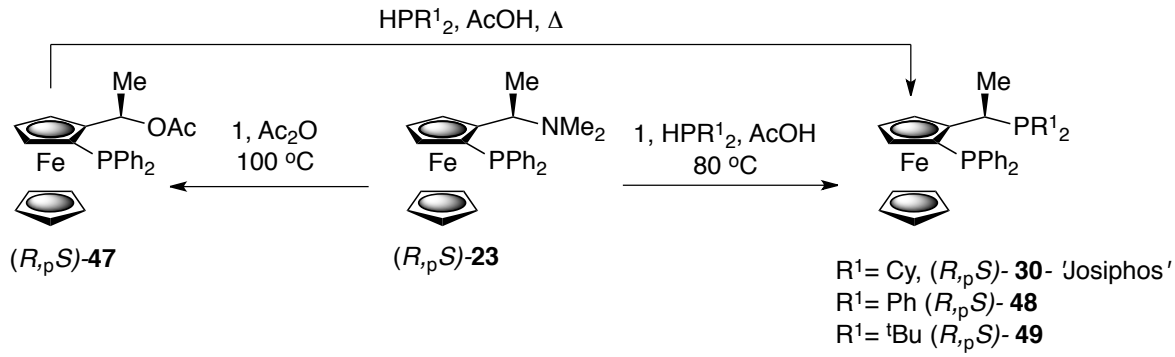
The major product was assigned (*S*) planar chirality, which was suggested by comparison of its optical rotation with known ferrocenyl compounds. It was proposed that (*S*)-planar chirality is preferred due to the orientation of the pyrrolidinyl methyl groups and their interaction with the incoming lithiating reagent.[52,53]

4.0 - Nitrogen – Phosphorus Exchange.

4.0 – Application of Nitrogen – Phosphorus Exchange in Ligand Synthesis.

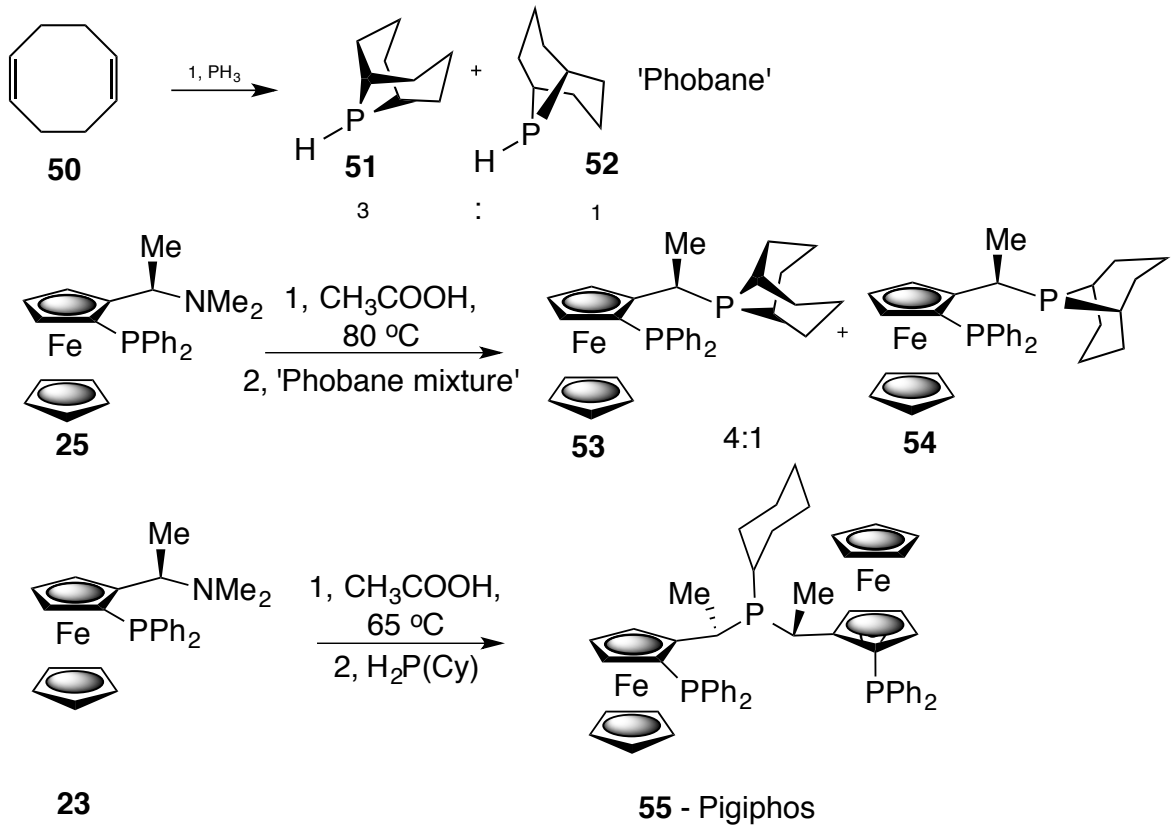
Nitrogen/phosphorus exchange (**Scheme 9**) was shown to allow the synthesis of a diverse range of planar chiral metallocenes with varying electronic and steric properties.

For example, by heating to 80 °C in glacial acetic acid in the presence of a secondary phosphine, the aforementioned ($R_{,p}S$)-**30**, 'Josiphos' can be synthesised.[54,55]



Scheme 9. Synthesis of ferrocenylphosphine ligands.

Substitution of the amine by a phosphorus group, which is not a diaryl-phosphine, was demonstrated by using 9-phospha-9H-bicyclo[3.3.1]nonane, known commercially known as phobane, with the principle benefit being that it has less steric bulk compared dicyclohexylphosphine. Furthermore it offers the advantage of being much less air sensitive, as a solid, and more convenient to work with than simple dialkylphosphines. Phophane is synthesised by a reaction between 1,5-cyclooctadiene with phosphine, generating a 2:1 mixture of major [3.3.1] and minor [4.2.1] regio-isomers (**Scheme 10**). [56]



Scheme 10. Examples of 1,2-unsymmetrical ferrocene ligands, derived from an amine-phosphorus exchange.

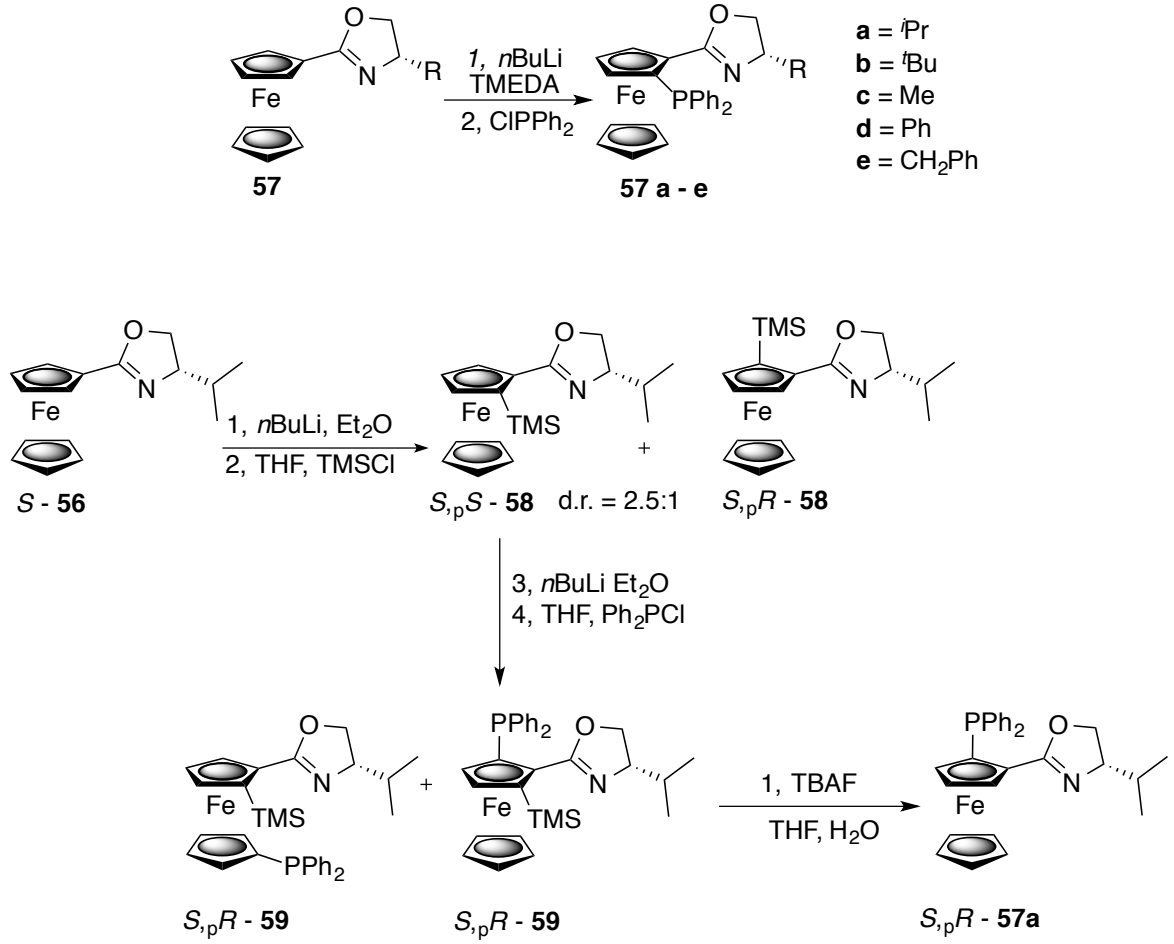
Scheme 10 also illustrates the synthesis of the 'Phobyphos' ligands **53** & **54** and the chiral tridentate *bis*ferrocenyl ligand, 'Pigiphos' **55**. This ligand proved that the amine group can be substituted with a cyclohexylphosphine group with retention of configuration.[57]

5.0 - Ferrocene Oxazolines.

5.0 – Synthesis and application of ferrocene oxazolines.

Following on from the great interest of chiral oxazolines in asymmetric catalysis, the ferrocenyl phosphine-oxazolines, readily prepared by *ortho* lithiation of ferrocenyl oxazolines, are an important type of P,N ligands. The modular approach in their synthesis has allowed the preparation of a great number of ligands, covering a wide range of steric and electronic properties at the phosphane and oxazoline moieties. A number of groups have shown that *ortho*-lithiation of 2-ferrocenyloxazolines and *in situ* quenching with

chlorodiphenylphosphine provides highly selective access to enantiopure *(S,$_p$S)*-α-phosphino substituted 2-ferrocenyloxazolines derivatives (**Scheme 11**).[58,59,60]

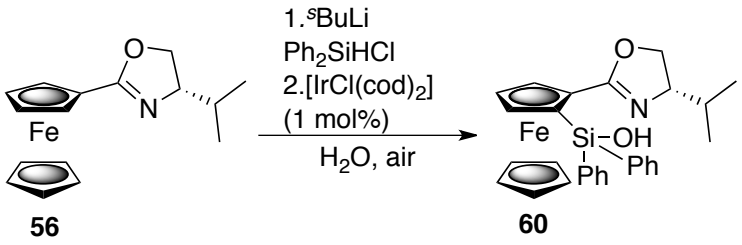


Scheme 11. Synthesis of 2-ferroceneoxazoline derivatives *via* an *ortho*-lithiation protocol

The corresponding (*S,$_p$R*)-diastereoisomer can be obtained through the introduction of TMS blocking group, lithiation, quenching with $ClPPh_2$ and subsequent deprotection with TBAF.[18,61]

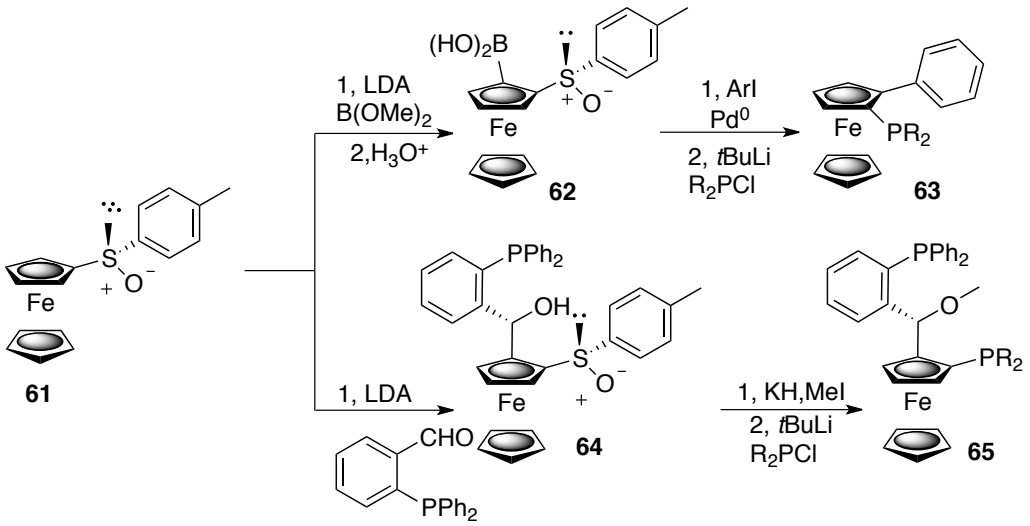
5.1 – Synthesis of Organosilicon and Sulfoxide ligands.

The ferrocene oxazoline moiety has also been used to make analogous corresponding organosilicon ligands as reported by Bolm *et al.* [62]



Scheme 12. Recent example of a 1,2 disubstituted ferrocene ligand prepared by *α* - lithiation of a chiral oxazoline.

In an extension to the *N,N*-dimethyl-1-ferrocenethylamine and ferrocene oxazoline ligands, sulfoxide ligands have also been prepared but this is not normally part of the ligand and is used as handle for further modifications and functional group manipulation. The sulfoxide approach has significantly enlarged the possibilities for preparing structurally diverse 1,2-disubstituted ferrocenes, including ligands with planar chirality. In this method, after a diastereoselective *α*-metallation/functionalisation step, the sulfonated *α*-directing group can be reduced to a metal coordinating thioether.[63] It can also act as a removable group *via* a *tert*-butyllithium mediated C-S bond cleavage and further reaction of the resulting ferrocenyllithium with an electrophile (**Scheme 13**).[64]



Scheme 13. Sulfoxide-mediated synthesis of 1,2-disubstiuted ferrocene ligands

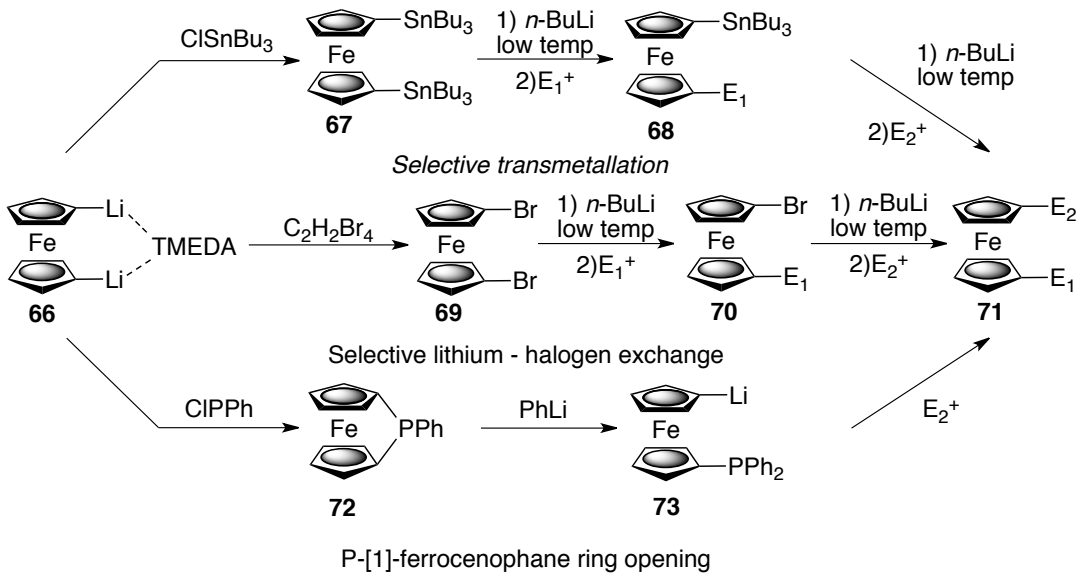
The use of an external source of chirality for the enantioselective *ortho*-lithiation of prochiral ferrocenes bearing a directing functionality constitutes another interesting

conceptual alternative for the preparation of planar-chiral ferrocenes. Deprotonation with a combination of lithium and (−)-sparteine or (1*R*,2*R*)-*N*,*N*,*N*',*N*'-tetramethyl cyclohexanediamine, as well as the use of chiral lithium amide bases has been reported.[65, 66, 67] The (−)-sparteine mediated directed *ortho*-lithiation of tertiary ferrocenecarboxamides has proved to be very effective. However, to date this strategy has found little application in the preparation of ferrocene ligands for asymmetric catalysis. The majority of methods for generating planar chirality are based on chiral *ortho*-directing groups, therefore the majority of chiral ferrocene ligands have both central and planar chirality. In some cases it has been proved that both chiral elements act synergistically (matched combination), which may be essential for achieving a high asymmetric induction.[68] However, there are a growing number of ferrocene ligands with planar chirality that provide excellent enantioselectivities in a variety of reactions, thus showing the key asymmetric role exerted by this stereogenic element.

6.0 - Synthetic Routes to 1,1'-Unsymmetrical Ferrocenes.

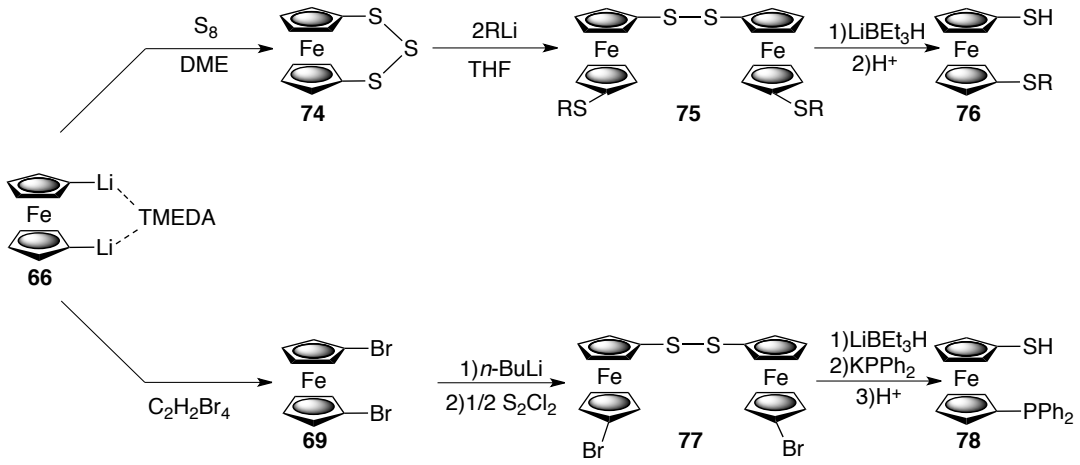
6.1 – Synthesis of 1,1'-Ferrocenes.

Controlled 1,1'-dilithiation of ferrocene by ^{n}BuLi in the presence of the chelating diamine TMEDA is the usual method by which substituents are introduced to the 1 and 1' positions. Three main synthetic methods that have been developed for the synthesis of 1,1'-unsymmetrical ligands are shown in **Scheme 14**. Cullen first utilised ring opening of 1-phenyl-1-phospha-[1]-ferrophane **72** to synthesise unsymmetrical bis(phosphine)ferrocene derivatives.[69]



Scheme 14. Synthetic routes 1,1'-unsymmetrical ferrocene ligands.

In 1992, Adeleke implemented the selective transmetallation of 1,1'-bis(tri-*n*-butylstannyl)ferrocene **67** at low temperatures using ^{n}BuLi followed by the addition of an electrophile.[70] The selective lithium halogen exchange of 1,1'-dibromoferrocene **69** was first developed by Dong *et al.* in 1994,[71] to synthesise a variety of unsymmetrical ferrocene derivatives in high yield. An alternative route to sulfur containing unsymmetrical ferrocenes has been developed by Dong *et al. via* a di(ferrocenyl)disulfide intermediate as shown below (**Scheme 15**).



Scheme 15. Synthetic route to sulfur-containing ferrocene ligands *via* disulfides.

6.2 - P/P Ligands

The first unsymmetrical 1,1'-P/P ferrocene derivatives, 1-(diphenylphosphino)-1-(di-*tert*-butylphosphino)ferrocene **79** and 1-(diphenylphosphino)-1-(diisopropylphosphino)ferrocene **80** were synthesised by Cullen *et al.* in 1985 *via* P-[1]-ferrocenophane ring opening (**Figure 10**).[72,73]

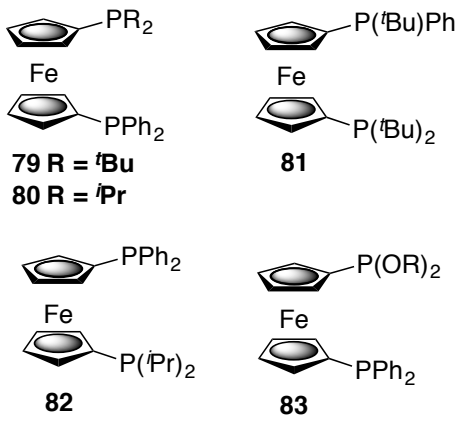
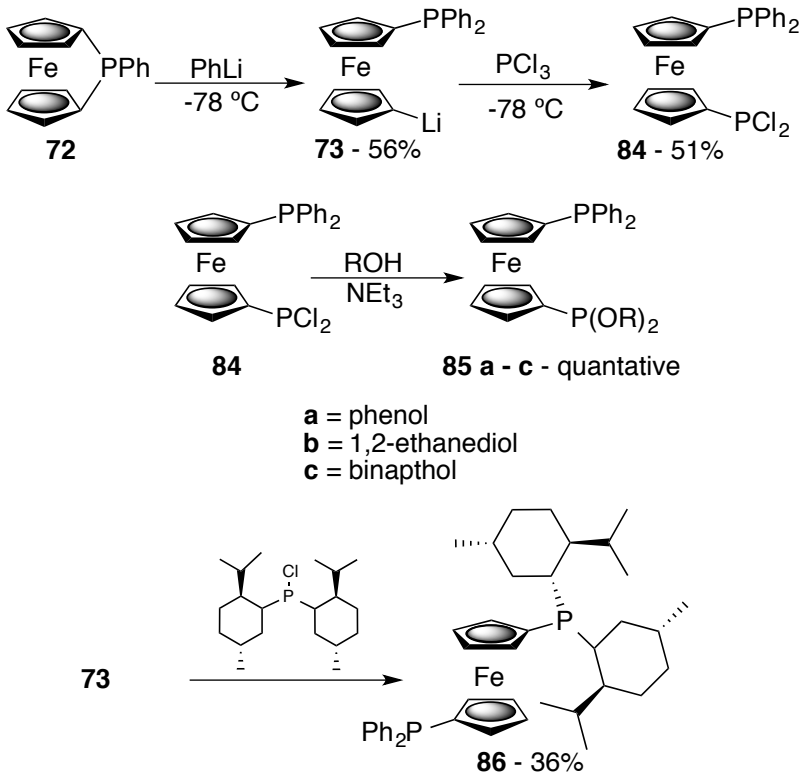


Figure 10. Unsymmetrical 1,1'-P/P ligands.

Reaction between P-[1]-ferrocenophane **72** with *tert*-butyllithium, provides unsymmetrical ligands such as **81** which contains an asymmetrically substituted phosphine.[74] Boyes found that a palladium (II) complex of **80** was found to be a reasonable catalyst precursor for a Heck coupling of iodobenzene with methyl acrylate.[75] It should also be noted that although **80** performed better than dppf, disoppf (**82**) was a superior ligand to both, indicating that the unsymmetrical nature of the ligand was not the most important factor. Compound **80** has also been synthesised *via* a selective lithium halogen exchange by Dong *et al.*[76] 1,1'-Unsymmetrical phosphine-phosphinite derivatives **83** have been synthesised by Broussier *via* ring opening of (1,1'-ferrocene-diyl)phenyphosphine with phenyllithium followed by addition of PCl_3. The resulting dichlorophosphine was reacted with various alcohols in the presence of NEt_3 to form the phosphine-phosphonite ligand.[77]

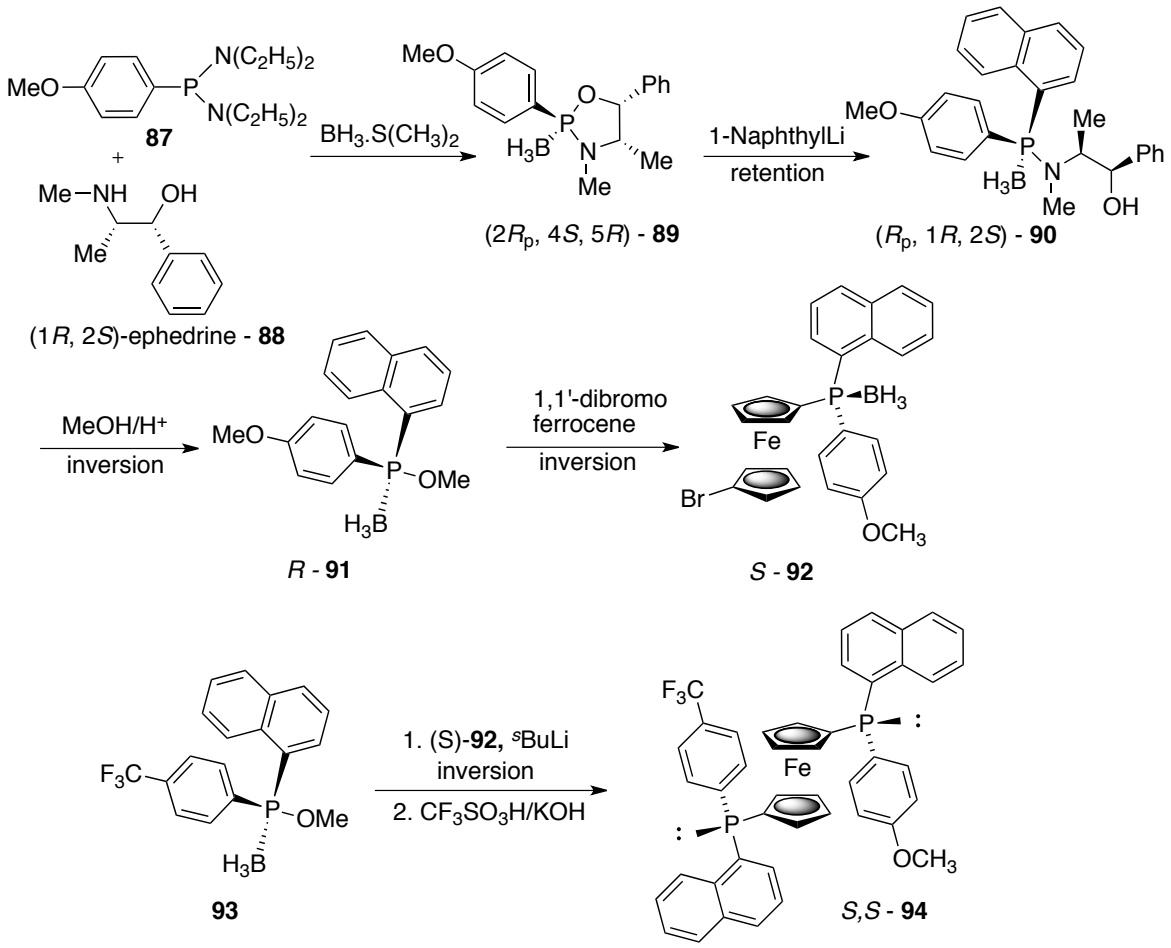
Ferrocenyl diphosphines have been synthesised as shown in **Scheme 16**, in which the chirality is derived from the optically active (1*R*,3*R*,4*S*)-menthyl substituents, by selective lithium halogen exchange and P-[1]-ferrocenophane ring opening.[78]



Scheme 16. Synthesis of unsymmetrical ferrocenyl diphosphines.

A rhodium complex of **86**, which was generated *in situ,* was used as an asymmetric hydrogenation catalyst giving high yields but only moderate enantiomeric excess. The nickel catalysed Grignard of 1-phenylmagnesium chloride with vinyl bromide was also investigated but **86** produced only a low *ee*.

The P-chiral diphosphine **94**, was synthesised *via* selective lithium halogen exchange prior to a lengthy chiral phosphine synthesis (**Scheme 17**).[79,80]



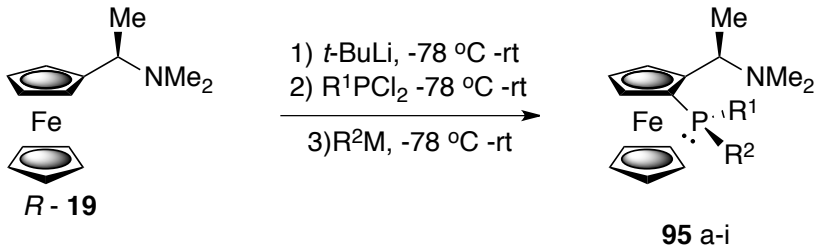
Scheme 17. Synthesis of P-chiral ligand 87.

Nucleophilic attack of 1-naphthyllithium delivered the ring opening of phosphorus amide borane **89** in good yields, followed by acidic methanolysis of the phosphorus amide to afford the configurationally inverted phosphinite borane **91**.[81] Following the lithiation of 1,2-dibromoferrocene and addition of R-**91** afforded **92**, which was then reacted again with *sec*-butyllithium and trifluoroanalogue **93** to give ligand **94** in 70% yield.[82]

6.3 – P-Chiral Ferrocene Based Planar Chiral Ligands.

Almost all of the documented ferrocene-based planar chiral phosphine ligands are synthesised by chiral group-directed diastereoselective α-lithiation or enantioselective lithiation followed by reaction with a mono chlorophosphine. Ferrocene based P-chiral

phosphines could be synthesised by reaction of a dichlorophosphine with a chiral lithiated ferrocene followed by the addition of second organometallic reagent. Below is the first example of the highly stereoselective and modular synthesis of ferrocene based P-chiral ligands using this simple and straightforward strategy. Enantiopure *N,N*-dimethyl-1-ferrocenylethylaime (Ugi's Amine) is readily available and provides a suitable starting material. The amine was lithiated with ^{t}BuLi, followed by reaction with $PhPCl_2$ and then reacted with *ortho*-anisyllithium to afford a single diastereoisomer, which was confirmed by ^{1}H and ^{31}P NMR, as shown in Table 3. This new synthetic methodology is highly modular, and using different chlorophosphine and organometallic reagents, gave a variety of ferrocene-based P-chiral phosphines, each as a single diastereoisomer in high yield. Replacement of the lithium reagent with the corresponding Grignard reagents gave similar results. The two diastereomers with opposite configuration at the phosphorus can be prepared by exchanging R^1 and R^2 in R^1PCl and R^2M. The absolute configuration of each compound in this series was inferred from the established stereochemistry of **95a** which was determined by X-ray diffraction. (**Scheme 18**, **Table 3**).



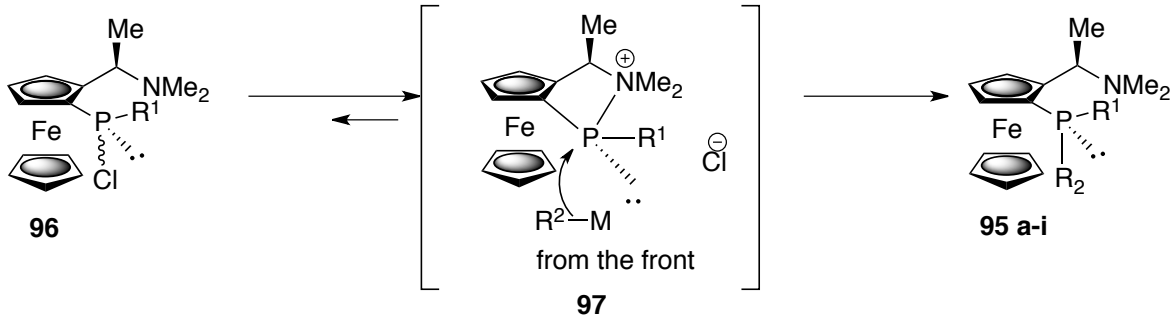
Scheme 18. Synthesis of Ferrocene-Based P-Chiral Phosphines

Entry	R^1	R^2	M	Yield (%)	Product	Configuration
1	Ph	*o*-An	Li	91	**95**a	(R_C,S_{Fc},S_p)
2	Ph	1-Np	Li	89	**95**b	(R_C,S_{Fc},S_p)
3	Ph	1-Np	MgBr	83	**95**b	(R_C,S_{Fc},S_p)
4[a]	1-Np	Ph		78	**95**c	(R_C,S_{Fc},R_p)
5	Ph	2-Np	MgBr	87	**95**d	(R_C,S_{Fc},S_p)
6	Ph	2-BiPh	Li	94	**95**e	(R_C,S_{Fc},S_p)
7	Cy	Ph	MgBr	95	**95**f	(R_C,S_{Fc},S_p)
8	Ph	Cy	MgCl	92	**95**g	(R_C,S_{Fc},R_p)
9	Ph	Me	MgBr	89	**95**h	(R_C,S_{Fc},R_p)
10	*t*-Bu	Me	Li	86	**95**i	(R_C,S_{Fc},R_p)

[a] (R_C,S_{Fc},R_p)- **95c** was prepared from (R_C,S_{Fc},S_p)-**95b** crystallisation induced asymmetric transformation.

Table 3. Synthesis of Ferrocene-Based P-Chiral Phosphines.

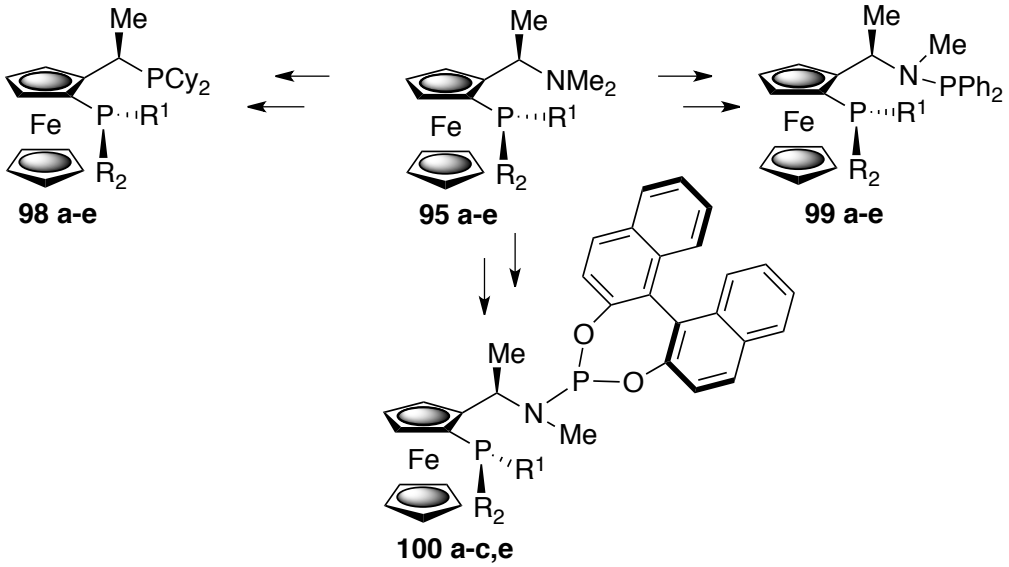
The stereochemistry and high diastereoselectivity of this reaction can be explained by the reaction mechanism shown below (**Scheme 19**). A five-membered cyclic quaternary ammonium salt intermediate, **97**, is formed and then the organometallic compound attacks from the front to give the product.



Scheme 19. Frontal attack of the organometallic reagent to afford the corresponding P-chiral product.

The reaction pathway from **96** to **97** is the step in which the chirality is established. Compound **97** is useful as a starting point for expanding the range of the novel

compounds of potential utility. Several new families of ferrocene-based phosphine ligands, combining phosphorus chirality, and other chiralities, as exemplified by the P-chiral phosphine-amino-phosphine ligands **99 a-e**, P-chiral phosphine-phosphoramidite ligands **100 a**,**b**,**d** and P-chiral 1,3-bisphosphine ligands **98 a-e** (**Scheme 20**) can be prepared easily. It should be noted that epimerization at the phosphorus stereocentre occurred when transformations were performed at elevated temperatures. Fortunately, most of the transformations can be carried out at room temperature, with no evidence of any epimerization.[83]



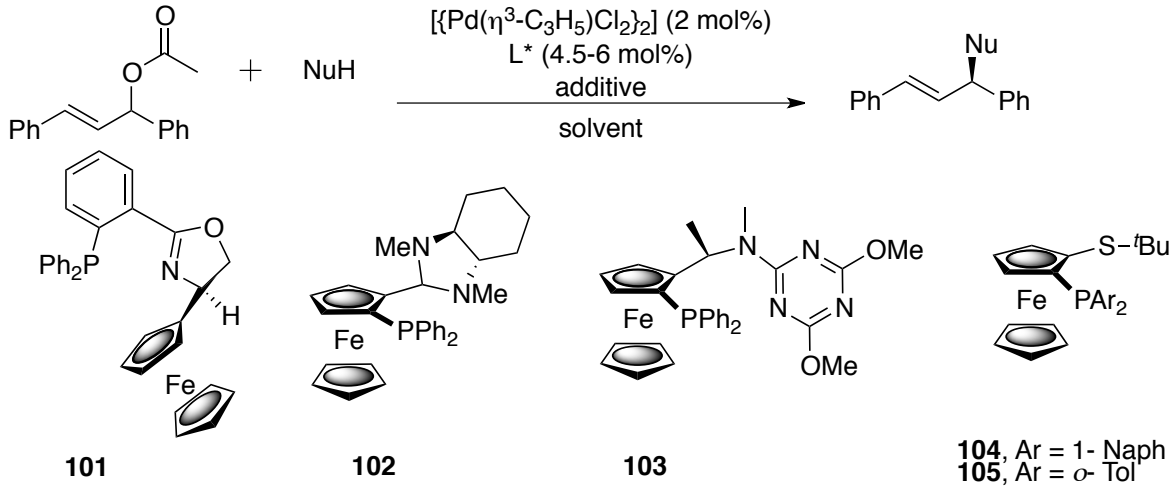
Scheme 20. Novel route into P-chiral phospho-amino based ligands.

7.0 - Application of Ferrocene based ligands: Asymmetric Metal-catalysed coupling reactions.

7.1 – Application to an Allylic Alkylation

The Pd-catalysed asymmetric allylic alkylation reaction of 1,3-diphenylpropenyl acetate with a soft nucleophile has become a standard model reaction for the screening of newly designed ligand structures. Unfortunately, most of the ferrocene-based chiral ligands appear to be confined to this particular reaction, since only in very few cases have their application to more challenging substrates have been demonstrated. The scheme below

is an example of how ferrocene-base ligands have been applied to this reaction. Manyano and co-workers have found that the Phox ligand **101**, with a ferrocenyl group at C4 of the oxazoline ring, led to 99.6% *ee* in allylic alkylation of 1,3-diphenylallyl acetate with dimethyl malonate.[84] Jin and co-workers, using the phosphinoimidazolidine **102,** achieved up to 99% *ee* in this transformation after exploring several phosphine – heteroaryl amine ligands.[85] The phosphine – trizine ligand has also been successfully applied to the aforementioned reaction by Zheng *et al.*[86] The novel P,S ligands with the structure 1-phosphino-2-sulfenylferrocene are also very effective in this transformation. The ligands **104** and **105** with sterically demanding groups at both the sulfur and phosphorus coordinating groups led to an enantioselectivity of 99.5%.[87]



Scheme 21. Ferrocene ligands in the asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate.

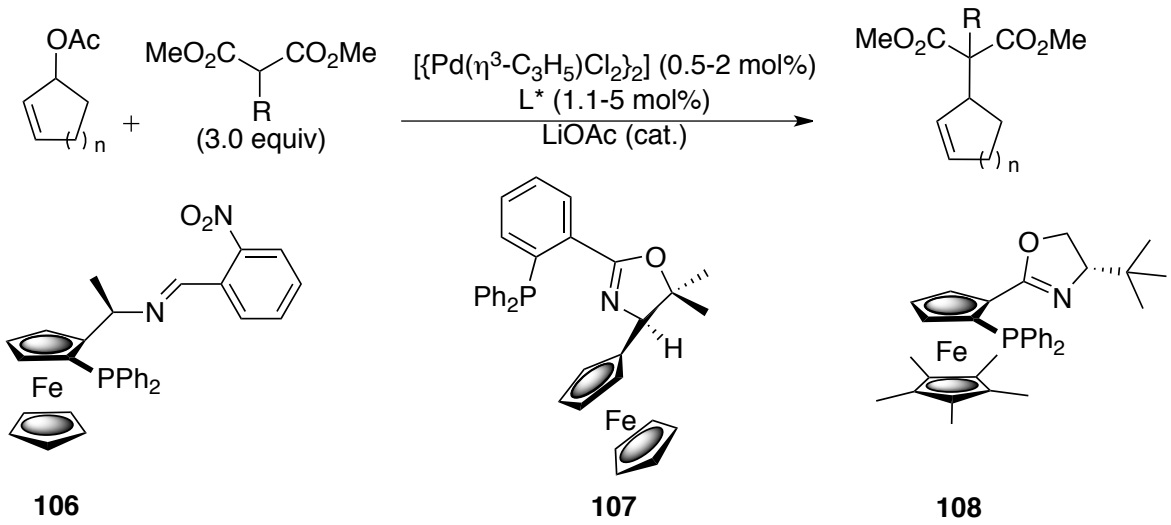
Entry	NuH	Conditions	L*	Yield [%]	*ee* [%] (*S*)
1	$CH_2(CO_2Me)_2$	CH_2Cl_2, rt[a]	**101**	63	99.6
2	$CH_2(CO_2Me)_2$	C_6H_6, rt[a]	**102**	99	99.6
3	$CH_2(CO_2Me)_2$	CH_2Cl_2, 10 °C[b]	**103**	93	99.0
4	$BnNH_2$	THF, rt	**104**	82	99.5
5	$BnNH_2$	THF, rt	**105**	93	99.5

[a] (3.0 equiv; bis(trimethylsilyl)acetamide), LiOAc (cat.). [b] (3.0 equiv), KOAc (cat.).

Table 4. Ferrocene ligands in the asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate.

7.2 - Application to an Allylic Alkylation of a Cyclic Substrate.

With few exceptions, most ligands that perform well with the 1,3-diphenylallyl systems led to particularly poor results with more synthetically valuable substrates, such as cycloalkenyl esters or unsymmetrical allylic substrates. Ferrocene-based ligands have induced enantiomeric excesses of > 80% in the reaction of cyclic substrates. Zheng *et al.*[88] have evaluated their family of ferrocenyl phosphine-imine ligands in the asymmetric allylic alkylation reaction of 2-cycloalkenyl esters with diethyl malonate. Their best results were obtained with the *meta*-nitrophenyl imine **106** (**Scheme 22**). This provided the substitution products of cyclopentenyl, cyclohexenyl, and cycloheptenyl substrates with up to 89% *ee* (**Table 5**). Moyano found that the Phox ligand **107**, analogous to **101** but with a geminal dimethyl group at the C5 position of the oxazoline ring, led to a significant enantioselectivity in the asymmetric allylic alkylation reaction of dimethyl malonate with 2-cyclohexenyl acetate, while ligand **101** provided the product in only 11% *ee*. It was hypothesised that the geminal dimethyl group in **107** restricts the conformational mobility of the ligand, the ferrocene moiety becoming orientated towards the π-allyl complex. A sterically demanding class of planar chiral Phox ligands, possessing a pentamethylferrocene backbone have recently been developed by Helmchen *et al.*[89] Ligand **108** with matched planar and central chirality has provided excellent yields and enantioselectivities in the Pd-catalysed allylic alkylation of cycloalkenyl acetates with dimethyl sodiomalonate using 1 mol% of catalyst.



106 **107** **108**

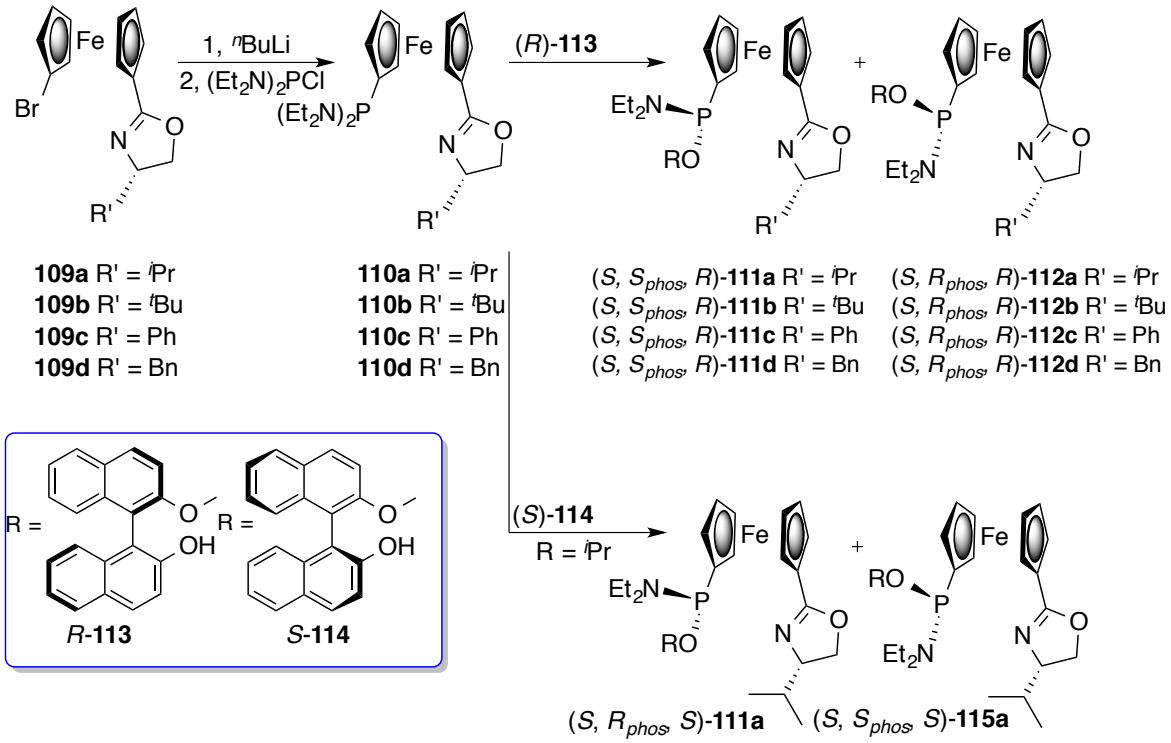
Scheme 22. Ferrocene ligands in the asymmetric allylic alkylation of cyclic substrates .

Entry	*n*	R	Solvent, T [°C]	L*	Yield [%]	Config.	*ee* [%]
1	1	H	Toluene, rt	**106**	89	(*R*)	82
2	2	Me	Toluene, rt	**106**	78	(*R*)	81
3	3	H	Toluene, rt	**106**	95	(*R*)	89
4	2	H	THF, rt	**107**	60	(*S*)	58
5	1	H	THF, -30	**108**	96	(*R*)	92
6	2	H	THF, rt	**108**	92	(*R*)	84
7	3	H	THF, rt	**108**	93	(*R*)	94

Table 5. Ferrocene ligands in the asymmetric allylic alkylation of cyclic substrates.

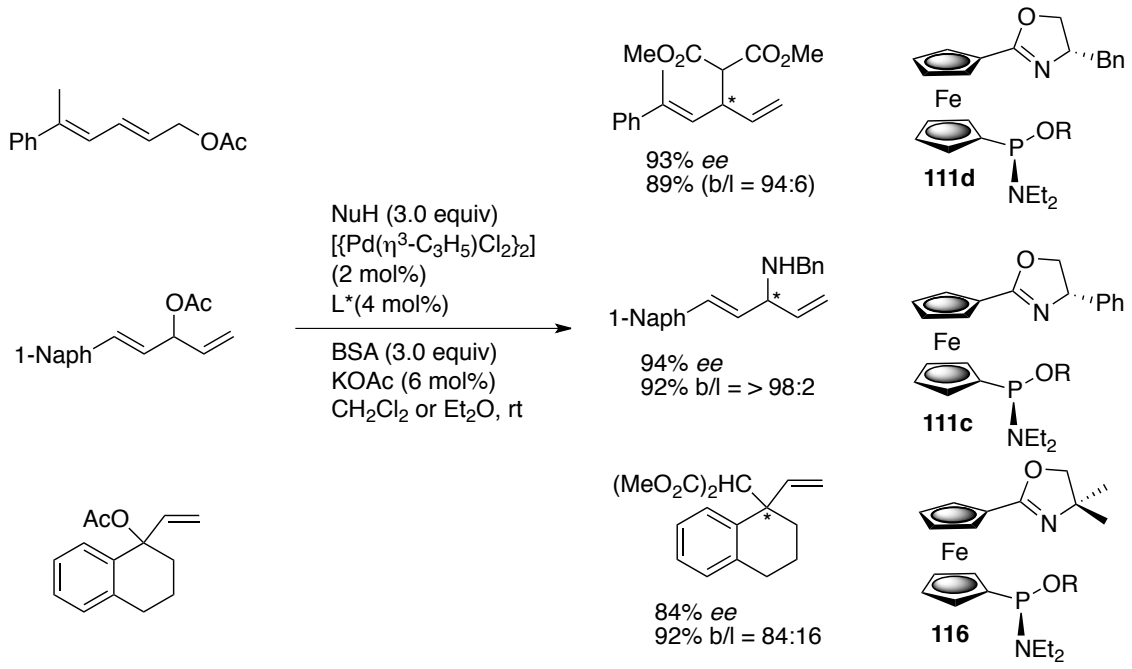
7.3 – Nitrogen/Phosphorus Based Ligand for Application to the Allylic Alkylation.

The research groups of Hou and Dai have devoted a continuous effort to developing new methodologies of asymmetric allylic alkylation with chiral ferrocene based ligands.[90] In 2001 they reported outstanding results in the asymmetric allylic alkylation of model substituted allylic acetates using newly designed chiral *P,N*-1,1'-disubstituted ferrocene bearing a chirogenic phosphorus atom bonded to a key BINOL derived unit (**Scheme 23**).[91]



Scheme 23. Synthesis of *P,N*-1,1'-disubstited ferrocenes.

The above ferrocene based *P,N*-ligands have also been applied to Pd-catalysed allylic amination reactions, a more challenging but useful reaction to synthesise allylic amines. Ligands **111d** and **111c** were more recently found to efficiently promote the allylic alkylation and amination of dienyl esters. In the reaction with dimethyl malonate, linear substrates gave better regio- and enantio- selectivities with **111d**, while branched allyl acetates provided the best results in the amination with benzylamine with ligand **111c**. The construction of chiral carbon quaternary stereocentres by enantioselective nucleophilic addition on the geminal disubstituted terminus of the palladium π-allyl species, which is especially challenging because of significant steric hindrance, has also been realised in the presence of the ligand **116** (**Scheme 24**).

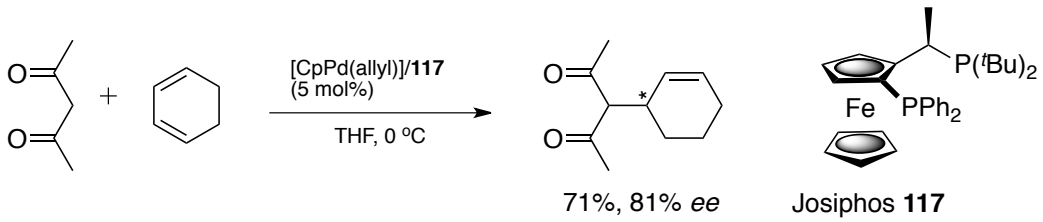


R = (*R*)-2-(2'-hydroxy-1,1'-binaphthyl)

Scheme 24. Asymmetric allylic alkylation of unsymmetrical acyclic allylic substrates; (absolute stereochemistry not determined).

7.4 - Further Asymmetric Processes Involving Chiral Palladium Intermediates.

From a mechanistic point of view the palladium catalysed addition of stabilised nucleophiles to conjugated dienes is closely related to the allylic substitution process, except for the fact that in the former the allylpalladium intermediate is formed by insertion of a chiral hydride palladium intermediate into the diene unit. This approach neither requires a leaving group nor an external base. The first intramolecular enantioselective version of this reaction was achieved by Hartwig and co-workers in 2004 using as chiral catalysts the combination of [CpPd(allyl)], as a precursor to Pd^0 and application of the *tert*-butyl Josiphos ligand, **109**.[92] The reaction of 2,4-pentadione with 1,3-cyclohexadiene occurred with 5 mol% catalyst to give the addition product in good yield and enantioselectivity (**Scheme 25**). The addition of prochiral carbon pronucleophiles to acyclic dienes was also investigating as an alternative for asymmetric addition, but lower enantioselectivities were obtained.

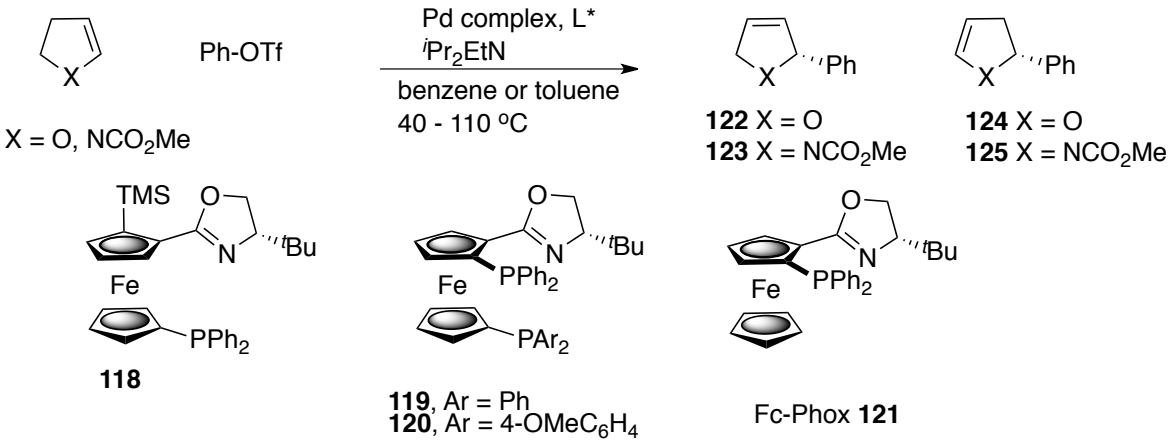


Scheme 25. Josiphos/Pd-catalysed asymmetric nucleophilic addition to conjugated dienes (stereochemistry not determined.)

Asymmetric Cross Coupling Reactions.

8.0 – Application of Ferrocene Based Ligands to an Asymmetric Heck Cross-Coupling.

High enantioselectivities have been documented in both intermolecular and intramolecular variants of the catalytic asymmetric Heck reaction, with BINAP and Phox ligands being the most proficient.[93] The reaction of dihydrofuran with aryl or alkenyl triflates has become a standard test reaction for screening new ligands. As an extension of the initial success with 1,1'-*P*,*N*-ferrocenyl phosphinooxazoline ligands **118**, Hou *et al.*[94] have reported that the 1,1'-diphosphine-2-oxazoline ferrocene **119** provides high regio and enantioselectivity in the intermolecular Heck phenylation of 2,3-dihydrofuran, as shown in the table below (**Scheme 26**).



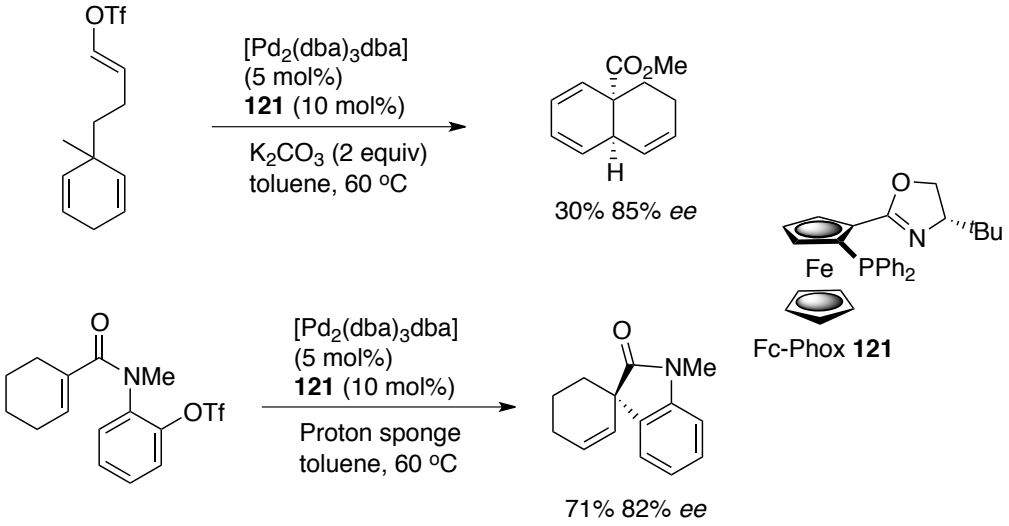
Scheme 26. Asymmetric intermolecular Heck reaction.

Entry	X	Pd complex (mol %)	L* (Mol%)	3,4-alkene/ 2,3-alkene	Yield [%]	*ee* [%] (*R*)
1	O	$[Pd_2(dba)_3.dba]$ (3)	**118**(6)	< 98:2	75	92
2	O	$Pd(OAc)_2$ (1.5)	**119** (3)	95:5	85	97
3	NR	$Pd(OAc)_2$ (5)	**119** (5)	95:5	68	98
4	O	$[Pd_2(dba)_3.dba]$ (1.5)[b]	**120** (3)	95:5	-	-
5	O	$[Pd_2(dba)_3.dba]$ (3)	**121** (6)	8:92	52	99

Table 6. Asymmetric intermolecular Heck reaction.

A dramatic variation of the selectivity was found, depending on the palladium source, solvent, and the electronic nature of the phosphines units. Thus, the best regioselectivity was observed when $[Pd_2(dba)_3.dba]$ was used instead of $Pd(OAc)_2$ (**entry 4**) , especially in combination with electron-rich phosphines such as **120**. It was hypothesised that when $Pd(OAc)_2$ is used as the palladium source, the nucleophilicity of the acetate anions with regard to the palladium atom facilitates the dissociation of the metal-olefin complex to give **122** and **123**.

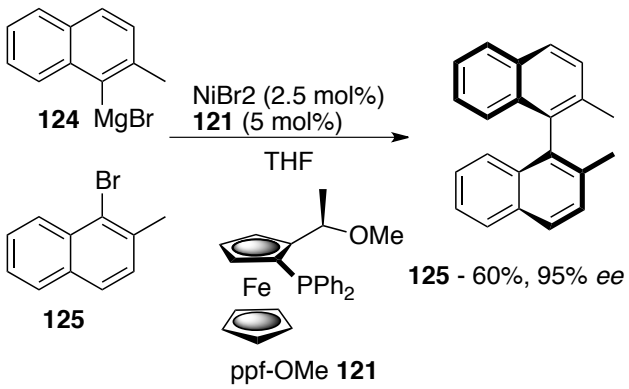
The efficacy of 1,2-Fc-Phox was demonstrated in inter- and intramolecular Heck reactions [95, 96] The bulky *tert*-butyl-substituted ligand **121** provided very high enantioselectivity in the phenylation of 2,3-dihydrofuran, but with low selectivity and reactivity. Ligand **121** afforded up to 85% *ee* in the intramolecular Heck reaction to form spirocyclic lactams and *cis*-decalins (**Scheme 27**). In both the intermolcular and intramolecular variants, higher reactivity of the ^{t}Bu-substituted ligand **121** over the corresponding ^{i}Pr derivative was observed.[97]



Scheme 27. Asymmetric intramolecular Heck reactions.

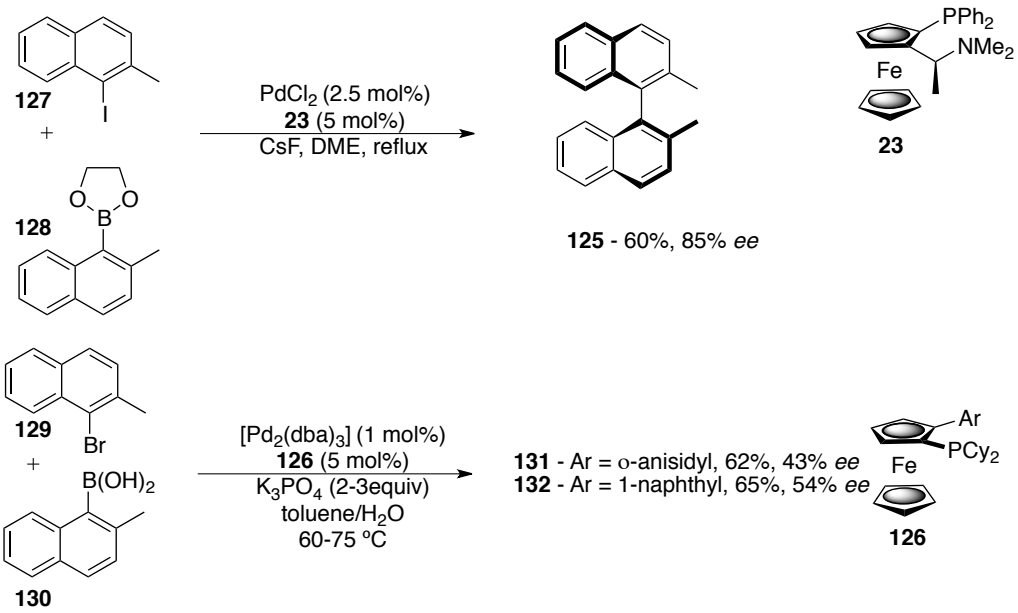
9.1 - Application of Ferrocene Based Ligands to Asymmetric Suzuki Cross-Coupling

The direct asymmetric construction of C-C biaryl bonds from chiral substrates still remains challenging, because of the inherent difficulty in coupling together two sterically hindered arenes. Hayashi, Ito and Kumada reported the first highly atropenantioselective cross-coupling of aryl halides with aryl Grignard reagents using $NiBr_2$ and the planar chiral ferrocenyl phosphine **122**, providing axially chiral binapthalenes as shown in the scheme below (**Scheme 28**).[98]



Scheme 28. Atropopenatioselective Kumada cross-coupling reaction

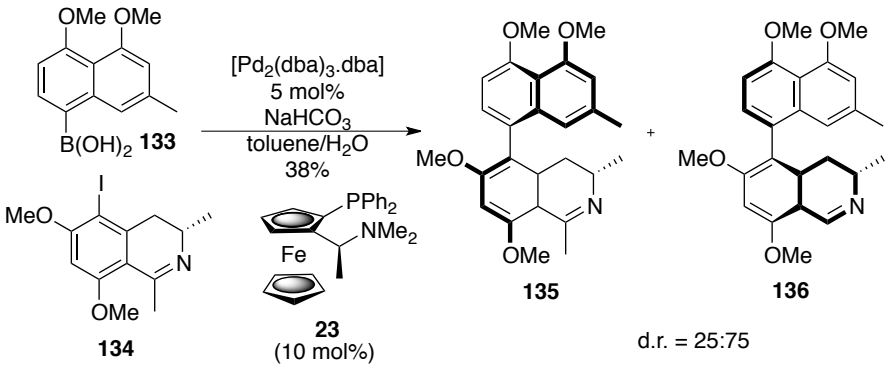
This work triggered subsequent developments in enantioselective biaryl coupling.[99] The Suzuki-Miyaura cross-coupling has emerged as one of the most used methods for the construction of C-C bonds due to its versatility and relatively high environmental friendliness.[100] Cammidge *et al.* showed that the Suzuki cross-coupling of 1-iodo-2-methylnaphthalene with the 2-methyl-1-naphthyl boronic ester **125** provided the C_2-symmetric binaphthalene **125** in the presence of ligand **23**.[101,102] Ligand **121** afforded much lower enantioselectivities, which is in contrast to the results described for the Kumada coupling, in which the ligand **23** failed to promote any coupling. It was proposed the stronger donor character of the NMe_2 group compared to the OMe group facilitates coordination to the boron atom. Other ferrocene based P,P-ligands proved ineffective, which concurs with other research that shows P,N-ligands are optimal in this transformation (**Scheme 29**).



Scheme 29. Atropenantioselective Suzuki cross-coupling reactions.

Newly developed aryl ferrocenyl electron-rich phosphine ligands such as **126** have been applied in the Pd-catalysed synthesis of the binaphthyl compound **125** as shown in the scheme above. The enantioselective activity depends on the aryl substituent of **126**. Ligand **23** has been used as a chiral ligand to improve the diastereoselectivity in the coupling between a chiral 5-iodoisoquinoline and a naphthylboronic acid for the synthesis of the antileishmanial alkaloids ancistroealanie A **135**[103] by using (*S*,$_p$*R*)-ppfa, **23** an

atropoisomeric ratio of 75:25 was observed in favour of **136**, as shown in **Scheme 30**, a preference opposite to that obtained with an achiral catalyst. The enantiomer of the ligand (*S,pR*)-PPFA provided negligible preference for one of the diastereomers (d.r. 51:49).

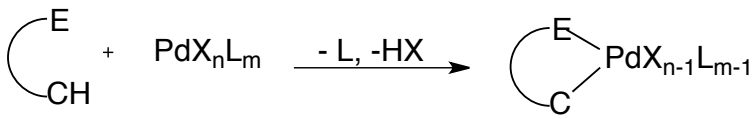


Scheme 30. Diastereoselective Suzuki cross-coupling.

Introduction to Palladacycles.

9.0 – Introduction.

Direct C-H bond activation of alkenes and arenes is a highly attractive strategy for the insertion of functionality into hydrocarbons. It is important to gain an understanding of the intermediate steps of metal mediated C-H activation. A versatile methodology to control the activity of the metal centre, to accomplish C-H bond activation, relies on the ability of an intramolecular heteroatom lone pair to bind reversibly to a metal centre. This facilitates metallation, and simultaneously directs the regioselectivity of this reaction. This process is conceptually related to a directed *ortho*-metallation. This produces a palladacycle where the palladium–heteroatom bond is thermodynamically stable (**Scheme 31**).



Scheme 31. Generic scheme for a cyclopalladation reaction.

The metal-carbon bond is significantly stabilised through chelation as compared to unsupported Pd-C bonds. This increases the stability of the organopalladium product, allowing comprehensive analysis of the properties and reactivity of this important class of compounds. The vast majority of cyclometallating ligands serve as mono anionic *E,C*-bidentate 4e donor or as a pincer type *E,C,E*-tridentate 6e-donors. The most common are nitrogen, phosphorus and sulfur containing groups such as amine, imines, phosphines, phosphinites, phosphites and thioethers.

9.1 – Palladacycles.

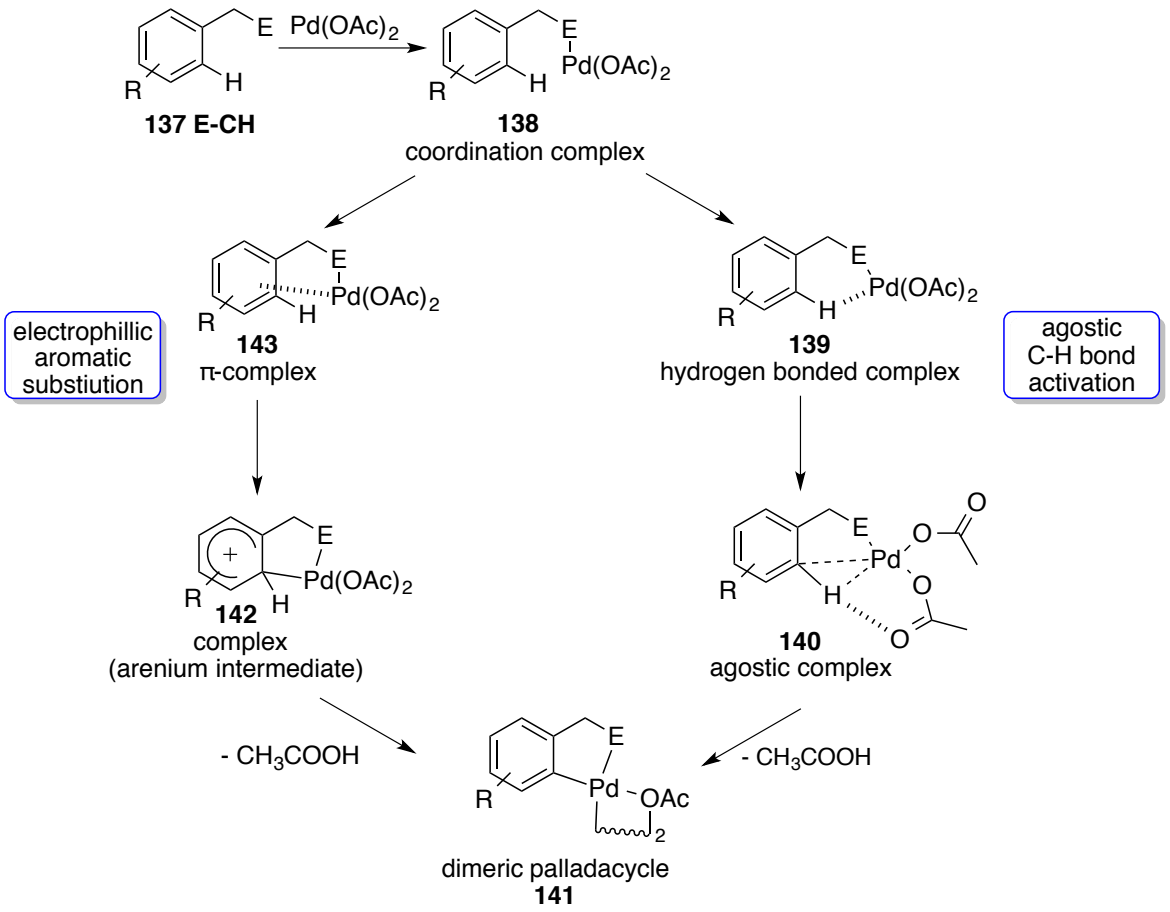
Palladacycles consisting of a formally neutral 4e-donor, such as bidentate N,C-amino carbanion or P,C-phosphino carbanion ligands, have been prepared *via* C-H bond activation. The wide scope of this reaction with respect to donor groups emphasises the potential of the cyclopalladation reaction in synthesis. Cyclopalladation *via* C-H bond activation may be considered as a template process that is typically reliant on the intramolecular availability of coordinating heteroatoms. Preliminary bonding of the heteroatom to the palladium centre arranges the metal centre and the C-H bond in a confined structural motif. Heteroatom assisted reorganisation of the reactive components is particularly pronounced within pincer type structures.

Cyclometallation is strongly preferred if five membered rings are formed, though different ring sizes have also been isolated. The geometry allows for the most ideal accommodation of the 90^{o} bond angle of the square planar palladium (II), and the 109-120^{o} angles of the mostly sp^3 and sp^2 hybridised ligand atoms in the metallocycle. This preference for five membered palladacycles allows one to predict the C-H bond that is likely to be activated in a given ligand. This strong directing effect of the heteroatom in cyclopalladation provides a rational method for the selective activation of unactivated C-H bond.

9.2 - Activation of Aryl C-H bonds.

Early investigations showed that the reaction rates correlate well with the electron donating ability of the substituents on the arene, this close analogy to aromatic

electrophilic substitution promoted the formulation of a related mechanism for cyclopalladation. This mechanism involves initial heteroatom coordination to the centre (E), followed by the formation of a π-complex, which subsequently rearranges into an arenium intermediate, known also as a σ-complex. This complex finally undergoes proton abstraction to give the cyclopalladated product (**Scheme 32**).[104]



Scheme 32. The two hypothesised pathways for C-H activation.

Recent theoretical calculations on the cyclopalladation of dimethylbenzylamine with palladium acetate point to a reaction profile which include an agostic interaction as a key structural feature in the reaction pathway. The six-member transition state **139**, involving a hydrogen-palladium interaction, has been found to initiate the C-H activation process. Displacement of one oxygen donor of the η^2-bound acetate by the C-H bond appears to be the rate-determining step and leads to an agostic intermediate, **140**. Subsequent reaction to the palladacycle was calculated to proceed with virtually no

activation energy. The acetate is thought to play a dual role in this processes, acting as ligands for the palladium and simultaneously, as an intramolecular base for deprotonation.[105]

9.3 - Donor Groups.

The donor group is pivotal for determining the regioselectivity of cyclopalladation and for initiating the C-H activation process. Further reaction is generally assumed to occur upon dissociation of one donor site and formation of a coordinately unsaturated 14e-electron species $[Pd(OAc)_2(E\text{-}CH)]$ **138**. An important parameter of cyclometallation is therefore the strength of the Pd-E bond. Strong bonding promotes the formation of the coordination complex $[Pd(OAc)_2(E\text{-}CH)]$, though it will be detrimental to ligand dissociation to afford the reactive species **138**.

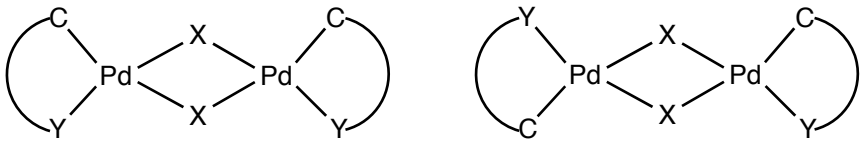
In amine coordination, the steric shielding of the nitrogen lone pair by the substituents is a crucial parameter. As a consequence of the Thorpe-Ingold effect, dialkyl substitution of the amine promotes cyclometallation, though metal coordination is typically observed only for small substituents such as in NMe_2. Larger groups coordinate palladium only when their rotational degree of freedom is restricted, for example, cyclic amines such as pyrrolidine or piperidine. In contrast, primary benzylamines are less easily cyclometallated. Cyclopalladation of phosphine and phosphite analogues *via* C-H activation was first reported in the mid-1970s.[106]

Phosphines have been observed to undergo internal metallations only with difficulty as compared with the amine analogues. The phosphine-palladium bond is significantly stronger than the palladium-nitrogen bond, thus stabilising the coordination complex. High temperatures, paired with longer reaction times, are required for successful palladation. The presence of two bulky substituents on the phosphine facilitates metallation considerably. The increase in the palladium-phosphine bond strength due to the basicity of phosphines is compensated by the steric influence of the bulky groups. This finding led to the development of the, 'gem-di-*tert*-butyl effect' which is found in the cyclometallation of phosphines. It was found that the palladium-phosphine bond was

weakened when the donor group had sterically demanding substituents on the phosphorus, causing the pyramidal geometry around phosphorus to significantly distort at the expense of the palladium-phosphines bond strength.[107]

9.4 - Types of Palladacycles.

Palladacycles can be divided into two types: anionic four-electron donor or six-electron donor. The former usually exists as a halogen or acetate bridged dimer, in one of two geometric isomers, *cisoid* and *transoid* configuration (**Figure 11**).



cisoid-palladacycle *transoid*-palladacycle

Figure 11. Schematic representation of *cis*oid and *trans*oid-palladacycles.

Four electron donor palladacycles can be neutral (**146**),[108] bis-cyclopalladated[109] (**147**), monomeric (**148**)[110], cationic (**149**),[111] or anionic (**150**)[112]depending on the nature of the other X ligands, as shown in the figure below. The most common palladacycles are derived from tertiary amines and imines and are usually five- or six- membered rings. Cyclopalladated complexes derived from primary amines are rare. The metallated ring of a four-electron donor type of palladacycle can vary between three and eleven membered. Three- and four- membered palladacycles are not usually stable, and examples of isolated and well-characterised compounds are very rare (**Figure 12**).

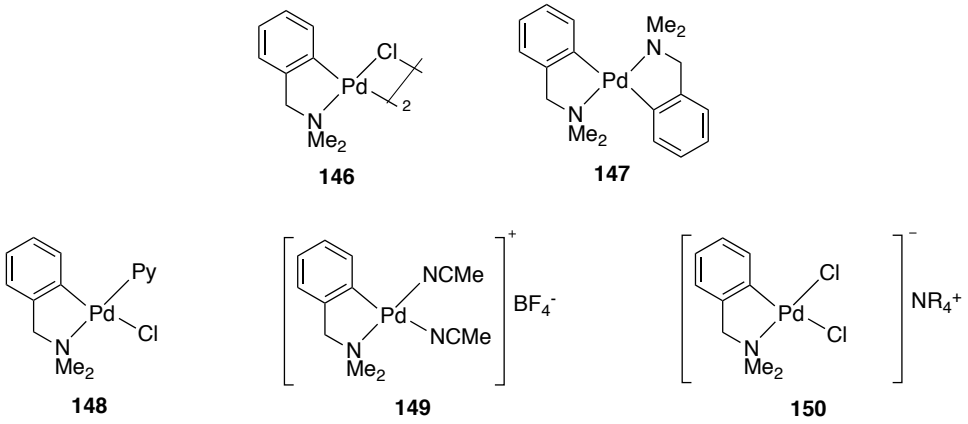


Figure 12. Examples of neutral (dimer, monomer, and bis-cyclopalladated), cationic and anionic 4-electron type palladacycles.

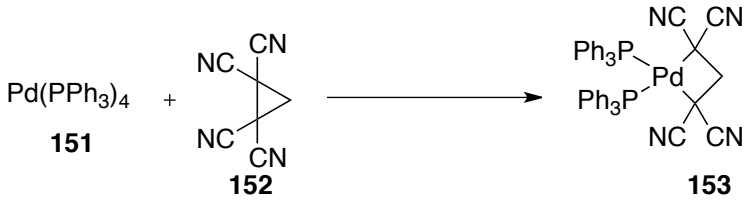
9.5 - Method of Preparation.

There are several methods available for the generation of the palladacycles such as the aforementioned C-H activation protocol, oxidative addition, transmetallation, and nucleophilic addition onto an unsaturated bond. Often a five or six membered chelate ring is formed as a result of the formation of a stable palladium carbon bond, assisted by coordination of the two-electron donor group.

9.6 – Oxidative Addition.

This is the method used to generate cyclopalladated complexes that are not usually accessible by direct C-H bond activation.

Oxidative addition involves the addition of carbon-carbon bond of cyclopropane to a transition metal leading to metallacyclic complexes. This method is suitable for palladium insertion into a cyclopropane bearing electron withdrawing substituents. Lenarda *et al.* prepared palladacyclobutanes starting with tetracyanocyclopropane and *tetrakis* (triphenylphosphine)palladium(0) as shown in **Scheme 33**. The palladium species inserts into the carbon-carbon bond of cyclopropane bearing electron-withdrawing substituents.[113]



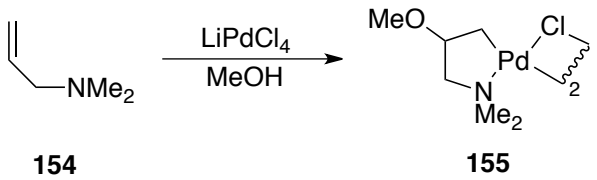
Scheme 33. Synthesis of 153 *via* the oxidative addition of palladium.

9.7 – Transmetallation

Transmetallation involves in most cases the use of organolithium or organomercury compounds as transmetallating agents and is often used to achieve bis-cyclopalladation. Similar to the oxidative addition methodology, the transmetallation method can be used to generate complexes that are not accessible by the standard C-H activation protocol (**Scheme 35**).

9.8 – Nucleophilic Addition onto an Unsaturated Bond

The regiospecific carbopalladation of allylic amines by stabilised enolates or carbanions and $LiPdCl_4$ provides a stable five-membered cyclopalladated complex (**Scheme 34**).[114]

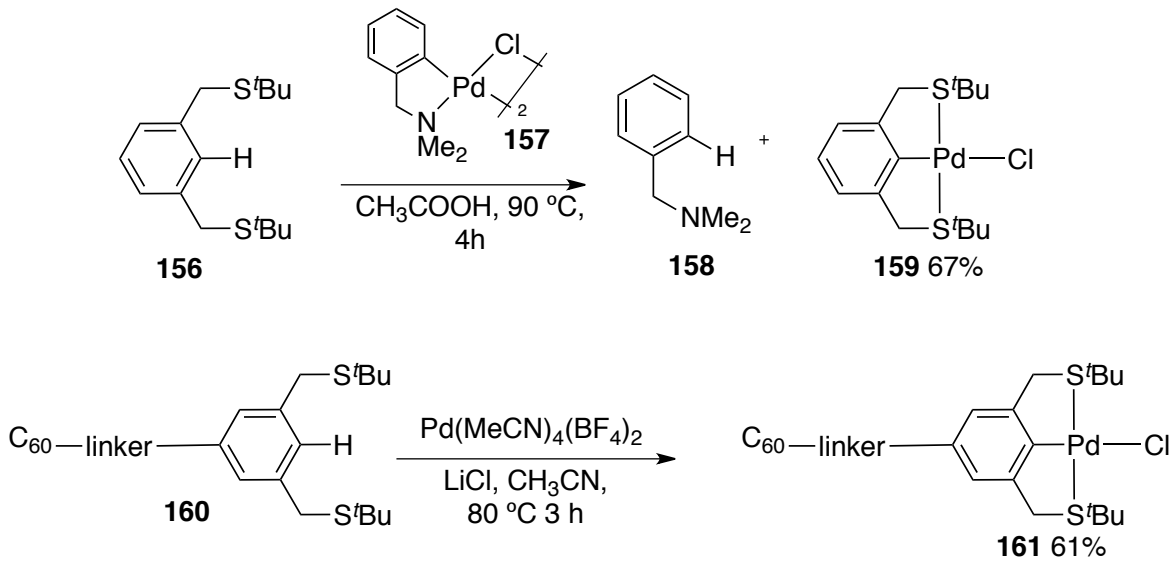


Scheme 34. Application of a nucleophilic addition methodology.

The reaction proceeds *via* external nucleophilic addition of the alkoxy anion onto the allylamine coordinated to the metal centre through the carbon-carbon double bond, and the nitrogen lone pair, to produce a thermodynamically stable five-membered cyclopalladated complexes.[115]

9.9 - C-H Activation.

The direct chelation assisted palladation of C-H bonds is the most simple and direct method for the construction of palladacycles, often termed *ortho*-palladation.[116] Common palladation agents include tetrachloropalladate salts coupled with a base, often the first method of choice due to their ease of use,[117] or palladium acetate in acetic acid or benzene. A ligand exchange process can also be employed utilising another palladacycle, which is also known as transcyclopalladation.[118] For example, in the synthesis of **159**, employing tetrachloropalladate salts was unsuccessful and a low 10% yield was obtained with $Pd(OAc)_2$ in acetic acid, whereas a transcyclopalladation protocol gave the product in > 90% yield (**Scheme 35**).[119] The addition of acetic acid to **157** will form the acetate-bridged palladacycle, which can aid in the initial deprotonation of **156**. The mechanism is very similar to that show in **Scheme 32** where an agostic intermediate is formed similar to **140**, which undergoes a concerted metalation deprotonation step, affording the corresponding palladacycle. For the reaction to proceed with relative success, the affinity for palladium must be greater in the product than in the starting material. In this case, sulfur has a higher affinity for palladium than nitrogen, therefore the equilibrium is shifted to the right, giving the product. The cationic $Pd(NCMe)]_4(BF_4)_2$ compound can also be employed as a palladium transfer agent, and has been used for the generation of SCS pincer palladacycles attached to C_{60}.[120] Detailed thermodynamic and kinetic investigations clearly show that the transcyclopalladation reaction takes place due to acidolysis of the starting palladacycle in acetic acid. $Pd^{(II)}$ is released by the ligand and the more thermodynamically stable palladacycle, in this case **159**, is formed.[121]



Scheme 35. Synthesis of SCS pincer complexes.

10.0 - Chiral Cyclopalladated Compounds

Chiral cyclopalladated compounds that exist in enantioenriched form may be subdivided into many different classes, and a discussion of the different types of chirality is presented in the figure below. One class of chiral cyclopalladated compounds are those that feature a stereogenic carbon atom directly σ-bonded to the metal, as seen in compound **162** below. In compound **163** the stereogenic centre directly bound to the palladium is an asymmetrically substituted donor group such as an amine, phosphine, or thioether. In compound **164** the stereogenic centre is not directly bound to the metal, but is located in the metallated ligand; this type of complex is often conformationally very stable and has the most widespread applications. Planar chirality is exhibited by molecules **165** and **166** usually courtesy of a ferrocenyl or η^6-chromium carbonyl moiety. This type of complex is becoming more popular and has many applications in asymmetric synthesis (**Figure 13**).[122]

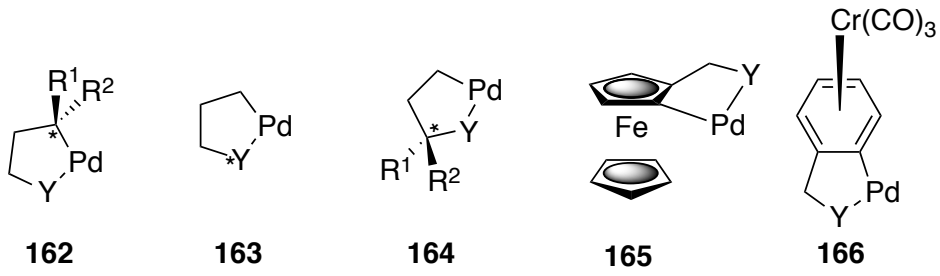


Figure 13. Schematic representation of chirality exhibited by cyclopalladated compounds.

Planar chiral complexes typically contain a metallocene or chromium carbonyl moiety. (**Figure 14**). Direct C–H bond activation is a general route to racemic planar chiral palladacycles illustrated by **167**[123], **168**[124] and **169**. The resulting complexes are obtained in enantiopure form by a standard resolution technique such as derivatisation with amino acids *S*-proline (**167**) or *S*-leucine (**168**), the method of which is outlined in **Section 11.2**. Diastereoisomers can be separated by crystallisation or chromatography, followed by re-generation of the chiral palladacycle by treatment with acid. The absolute configuration of the metallocycles may be determined by X-ray crystallography.

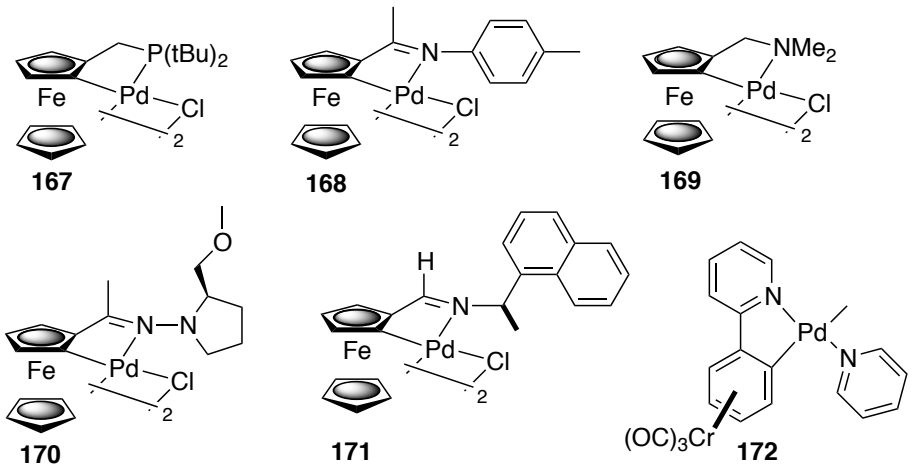


Figure 14. Planar chiral palladacycles

11.0 - Asymmetric Synthesis of Metallocene based palladacycles.

Three general methods for asymmetric C-H activation have been reported- i) enantioselective deprotonation using a chiral base, ii) the use of a chiral directing group, and iii) asymmetric ligand exchange. Under the hypothesis that carboxylate bases are directly involved in the generation of planar chirality with $Pd^{(II)}$ salts for the C-H activation of ferrocenyl derivatives, Sokolov devised an ingenious enantioselective version using chiral bases, which under optimal pH conditions afforded *ee*s of up to 90%. Enantioenriched palladacycles such as **169** were synthesised using Na_2PdCl_4 in the presence of the chiral base *N*-acetyl-(*S*)-valine, which effected the enantioselective deprotonation of the starting ferrocenylamine later discussed in **Section 11.8**.[125] For the synthesis of palladacycles **170**[126] and **171**[127] a chiral motif was attached to the ferrocene *via* the condensation of a ferrocenyl aldehyde/ketone with a chiral amine, and the C-H activation process was observed to proceed with moderate diastereoselectivity.

Bridged palladacycles can exist as mixtures of *cis*/*trans* isomers with respect to the orientation of the two bidentate C-X ligands about the $Pd_2(\mu\text{-}L)_2$ core. As a consequence there are six possible stereoisomers for a bridged planar chiral palladacycle that is not enantiopure, as shown in **Figure 15**, but normally one of the two geometrical isomers, usually the *trans*, is formed exclusively, simplifying the analysis of these compounds.

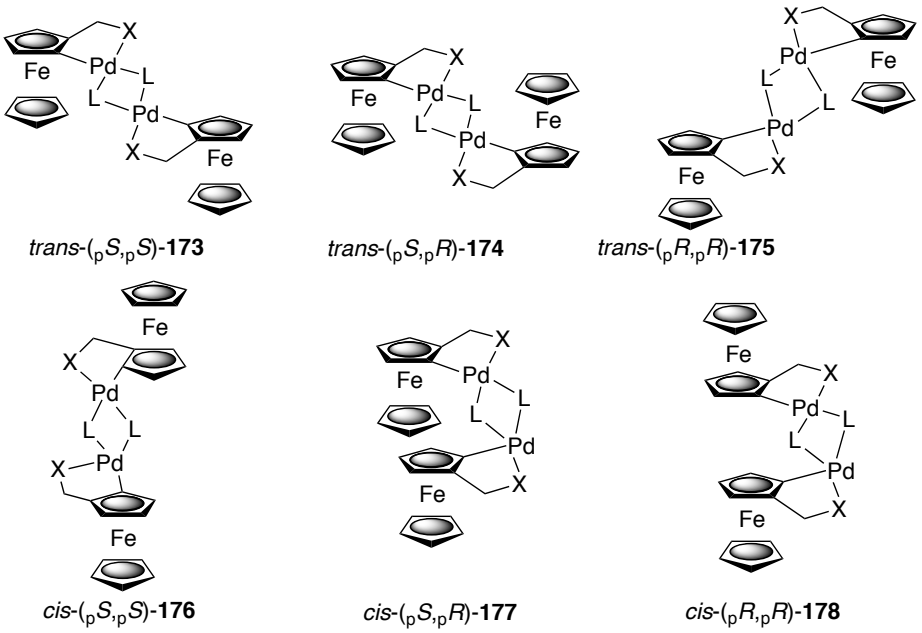
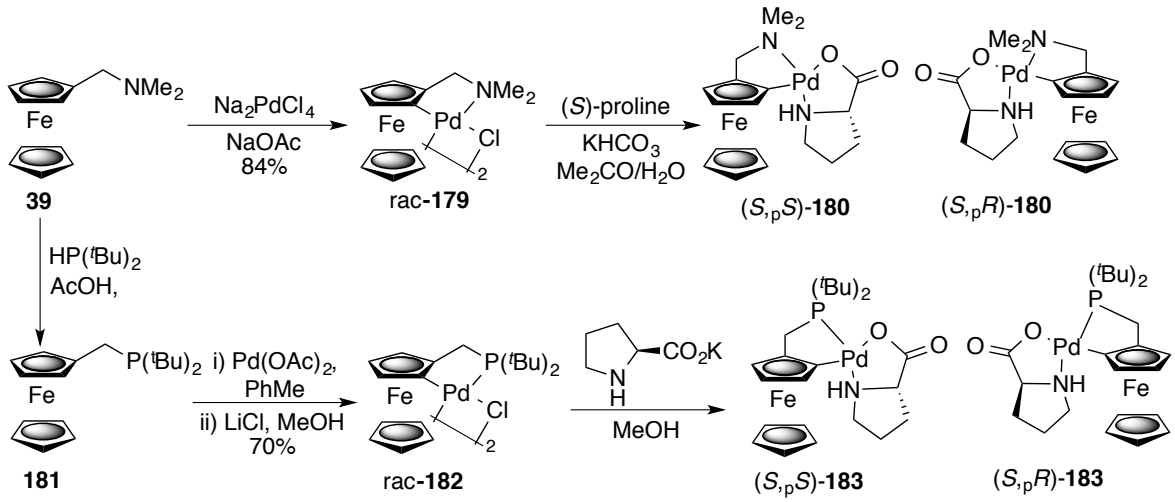


Figure 15. Possible stereoisomers for a bridged planar chiral palladacycle.

The acetate-bridged palladacycles will readily transform into the chloride on addition of sodium chloride; the reverse reaction requires the addition of silver acetate.

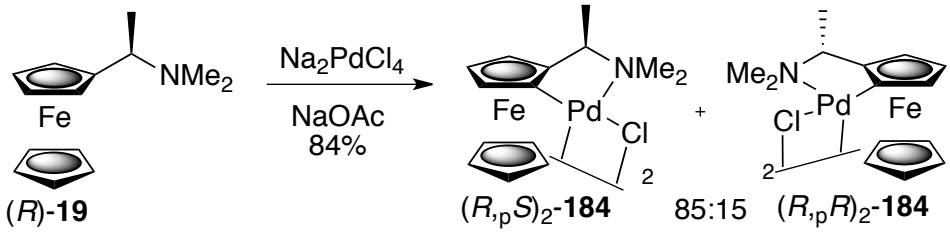
11.1 – Resolution of Chiral Ferrocene Containing Palladacycles.

There are a number of examples of the resolution of planar chiral metallocycles by reaction with an amino acid, followed by a separation of the resulting diastereoisomers. This was first demonstrated with rac-**170** to which (*S*)-proline and potassium hydrogen carbonate were used to make the desired derivatives followed by fractional crystallisation to give both (*S*,$_p$*S*)-**180** and (*S*,$_p$*R*)-**180**.[128] In the same way palladation of **181** was followed by resolution of the resulting phosphapalladacycle **182** by combining extraction and fractional crystallisation to separate (*S*,$_p$*S*)-**183** and (*S*,$_p$*R*)-**183**.[129]



Scheme 36. Amino acid mediated separation of phospho and amino-based palladacycles

The analogous palladation of *R*-**19** gives $(R,_pS)_2$-**184** and $(R,_pR)_2$-**184** with a d.r. of 85:15 (**Scheme 37**).[130] It was later reported that only a single diastereoisomer precipitated from the reaction mixture, but the 85:15 selectivity has also been independently verified.[131,132]

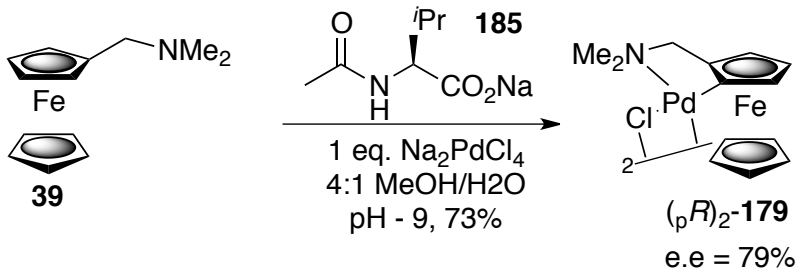


Scheme 37. Diastereoselective palladation of Ugi's amine.

11.2 – Amino Acid Mediated Enantioselective Palladation.

Rather than employing a ferrocene substituted chiral auxiliary to control diastereoselective metallation, an alternative is the use of a chiral metal reagent to effect the enantioselective synthesis of the planar chiral metallacycle. To date, three examples of this strategy have been reported; all employ a stoichiometric chiral source, which is not incorporated into the resulting palladacycle. Recognition of the importance of acetate in the palladation of *N*,*N*-dimethylaminomethylferrocene **39**, led to the use in its stead of the sodium salt of (*S*)-*N*-acetylvaline **185** (**Scheme 41**).[133] This resulted in the partially

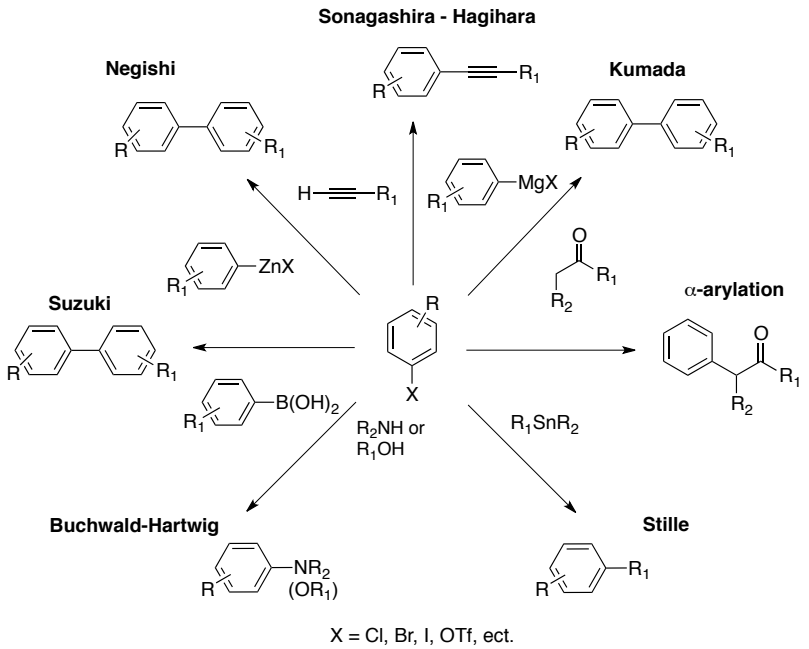
enantioselective formation of $(_pR)_2$-**179**, the yield and *e.e.* being dependent on the pH of the reaction, the optimum value for the latter being between 8-10 for maximum enantioselectivity.



Scheme 38. Enantioselective palladation of *N*,*N* dimethylaminomethylferrocene

12.0 - Application of palladacycles in asymmetric catalysis.

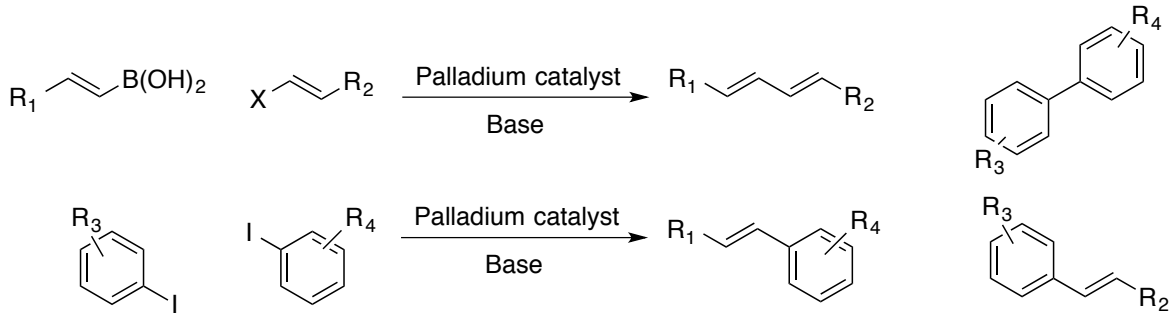
Palladacyclic intermediates play an important role in transformations leading to complex molecular architecture. Intramolecular cross-coupling reactions are powerful tools for the synthesis of various heterocycles and carbocycles, which involve palladacycle intermediates**. Scheme 39** outlines a range of cross-coupling reactions that palladacycles can mediate.



Scheme 39. Catalytic C-C and C-N coupling reactions promoted by palladacycles

12.1 – Suzuki Cross-Coupling.

The coupling of organoboron reagents has become one of the most commonly used coupling processes. Organoboron regents are less toxic than organotin reagents and tend to undergo coupling reactions in the presence of a variety of functional groups. Neutral organoboron reagents do not undergo metal cataysed cross-coupling without an additive. Suzuki showed that addition of a hard base such as hydroxide or fluoride enables the organoboron reagents to undergo cross-coupling by generating a four-coordinate anionic organoboron reagent that transfers the organic group from the boron to the metal. This process is now referred to as the "Suzuki coupling" (**Scheme 40**).[134]

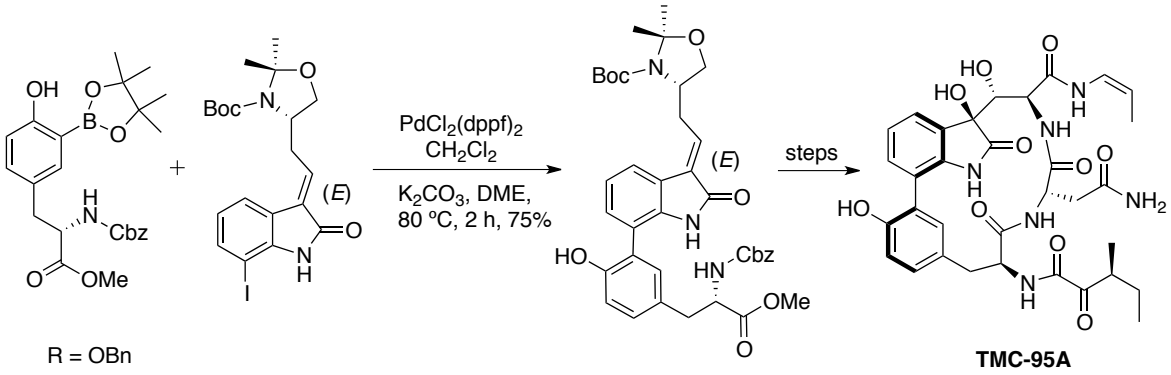


Scheme 40. Schematic representation the Suzuki coupling reactions.

The palladium catalysts which are traditionally employed include $Pd(PPh_3)_4$ or mixtures of triarylphosphines and appropriate $Pd^{(II)}$ or $Pd^{(0)}$ precursors such as palladium acetate or dipalladiumtris(dibenzylideneacetone), respectively. As the electrophilic coupling partners, aryl halides are most often used but halide surrogates such as aryl triflates and aryl diazonium salts can be employed. Aryl chlorides are the most accessible in terms of both cost and commercial availability, but they are also the least easily used since the high C-Cl bond strength compared with C-Br and C-I disfavors oxidative addition, the first step in the catalytic cycle, and makes the coupling of such substrates much more challenging.[135]

The Suzuki reaction has matured into a very powerful technique for the formation of new carbon-carbon bonds and is routinely used in research and development in

pharmaceutical discovery labs. For example, it has been applied industrially to the production of TMC-95A by S.J. Danishefsky *et al.* where the biaryl moiety of the compound was assembled in good yield by the cross-coupling of an aryl iodide and an aryl boron intermediate (**Scheme 41**).[136]



Scheme 41. The application of the Suzuki cross-coupling in the total synthesis of TMC-95A.

The scope of the Suzuki reaction for synthetic organic applications has been covered in several reviews such as those by Kashinath and Miyaura.[137,138] Efficient palladium catalysts for Suzuki cross-couplings have been reported by Buchwald (aryldialkylphosphines),[139] Fu (trialkylphosphines),[140] Nolan (*N*-hetereocyclic carbenes),[141] Bedford (palladacycles)[142] and others who wanted to couple deactivated or hindered chloro-arenes and chloro-alkyls under mild conditions. These recent developments in the ligands and catalysts employed have broadened the application of Suzuki cross-coupling enormously, so that the scope of the reaction partners is not restricted to aryls, but includes alkyls, and alkynyls.

12.2 – Mechanism of the Suzuki Cross-Coupling

The mechanism of the Suzuki cross-coupling is analogous to the standard cross-coupling reaction and has four distinct steps: **1**) oxidative addition of an organic halide to the $Pd^{(0)}$ species to form $Pd^{(II)}$; **2**) exchange of the anion attached to the palladium for the anion of the base (metathesis); **3**) transmetallation between $Pd^{(II)}$ and the aryl borate complex; and **4**) reductive elimination to form the C-C bond and regeneration of the $Pd^{(0)}$ species.

Although organoboronic acids do not transmetallate to the $Pd^{(II)}$ complexes, the corresponding ate-complexes readily undergo transmetallation. The quaternisation of the boron atom with an anion increases the nucleophilicity of the alkyl group and therefore accelerates its transfer to the palladium in the transmetallation step. Very bulky and electron-rich ligands, such as, $P(^tBu)_3$ increase the reactivity of otherwise unreactive aryl chlorides by accelerating the rate of the oxidative addition step.

12.3 - Palladacycles in Suzuki Cross-Couplings.

The growth in the use of palladacycles as precatalysts in the Suzuki cross-coupling reaction has been driven by two main factors (**Figure 16**). The first is that they can often be used in very low loadings, which is important because the use of palladium catalysed coupling in the production of fine chemicals and pharmaceuticals can be hampered by the need to remove heavy metal contamination down to ppm levels. Therefore, catalysts that show good activity at very low loadings reduce the need for subsequent removal of palladium. The second factor is that relatively simple modifications to the precatalysts can give excellent activity with challenging substrates such as aryl chlorides.

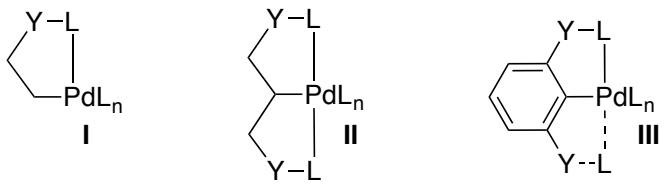
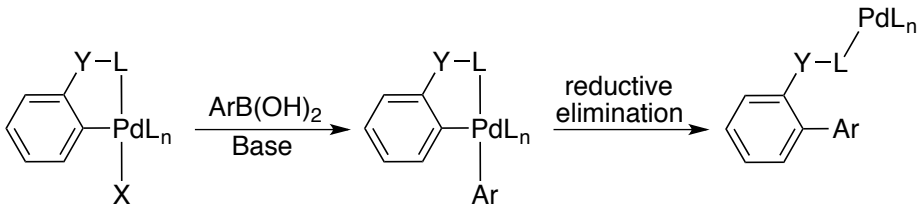


Figure 16. Generic structures of palladacycles (I) and pincer complexes (II,III)

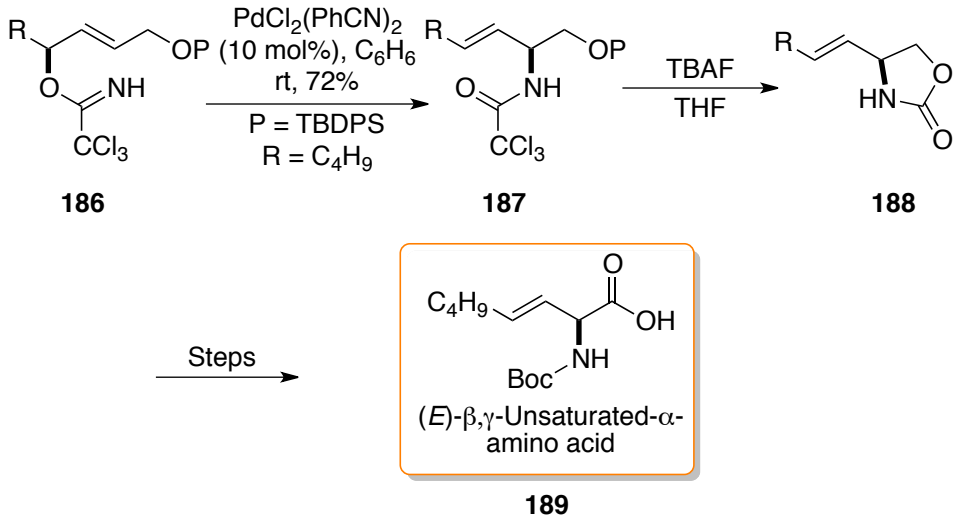
Much of the success enjoyed by palladacycles in the Suzuki reaction is down to the fact that they act as well defined, easily handled, stable precursor to highly active $Pd^{(0)}$ catalysts. The conversion of the palladacyclic precatalyst into highly active $Pd^{(0)}$ species typically involves their reaction with arylboronic acids, followed by reductive elimination of the resultant aryl-ligated palladacycle (**Scheme 42**).[143]



Scheme 42. Arylboronic acid mediated reduction of $Pd^{(II)}$ palladacycle precatalyst to active $Pd^{(0)}$ species.

12.4 - Further Application of Palladacycles $Pd^{(II)}$ to the Allylic Imidate Rearrangement

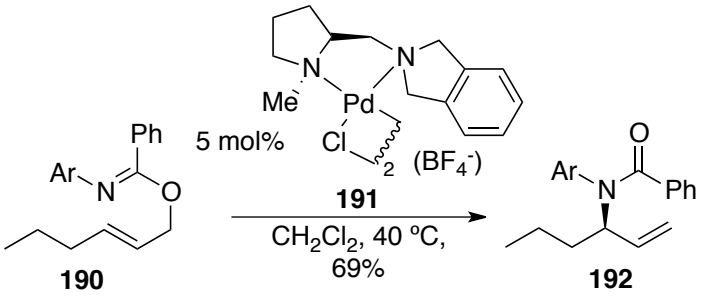
In recent years the allylic imidate rearrangement has become an important tool for organic synthesis (**Scheme 43**).



Scheme 43. Synthesis of chiral unsaturated amino acids *via* the Overman rearrangement

The transition metal catalysed Overman rearrangement allows the reaction to take place at room temperature, so thermally sensitive substrates can be used. Mehmandoust *et al.* applied this to the synthesis of enantiomerically pure (*E*)-β,γ-unsaturated α-amino acids, which are potent enzyme inhibitors. [144] This work led to the exploration of an asymmetric

Overman rearrangement, and in early work catalyst (**191**) was found to be effective, providing 69% yield and 55% *ee* for the conversion of *N*-(4-trifluoromethylphenyl)benzimidate into (*R*)-(*E*)-N-(4-trifluoromethylphenyl)benzamide.[145]



Scheme 44. One of the first catalysts developed for enantioselective allylic imidate rearrangement.

When planar chirality was introduced with ferrocenyl amine complex (**184**), a significant improvement in enantioselectivity was observed when compared to the non-planar chiral analogue **183** (14% *ee*). Using 5 mol% of ($R_{,p}S$)$_2$-**184** with (*E*)-hex-2-en-1-yl N-phenylbenzimidate gave *R*-**192** in 67% *ee* without any by-products arising from imidate ionisation. [146]

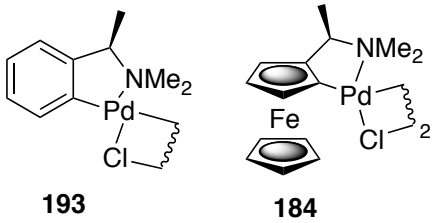
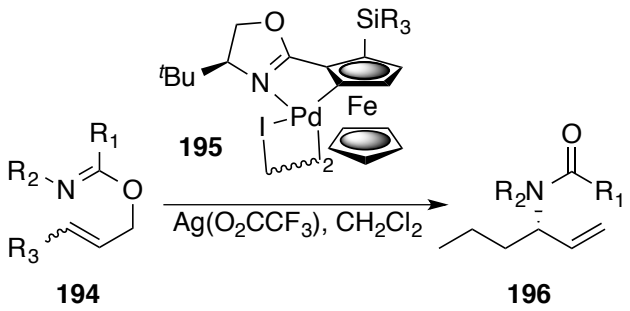


Figure 17. Catalysts developed for the improvement of enantioselective allylic imidate rearrangement.

When the halogen bridging ligand was changed to trifluoroacetate, the results further improved to give a 61% *ee* and an essentially quantitative yield of 98% with (*E*)-hex-2-en-1-yl-N-(4-(trifluoromethyl)phenyl)benzimidate as the rearrangement substrate.

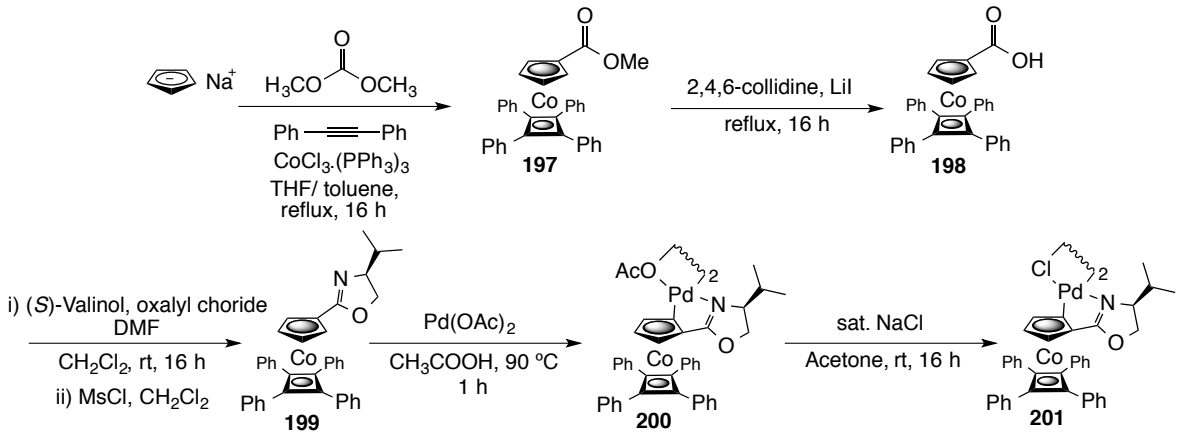
12.5 – Synthesis and application of cobalt oxazoline palladacycles.

The success of the ferrocene-based palladacylces resulted in further investigations into the use of ferrocenyloxaoline based systems.[147] These palladacycle catalysts promote the enantioselective rearrangement of (*Z*)-imidates such as (*Z*)-allylic-(*N*)-(4-methoxyphenyl) benzimidate to give the corresponding amide in 90% yield and 97% *ee* (**Scheme 45**).



Scheme 45. Allylic imidate rearrangement using ferrocene based palladacycle

The synthesis of COP-X was reported by the Richards group as part of a program investigating derivatives of (η^5-C_5H_5)($\eta^{4-}$$C_4Ph_4$)-Co complexes (**Scheme 46**).[148]

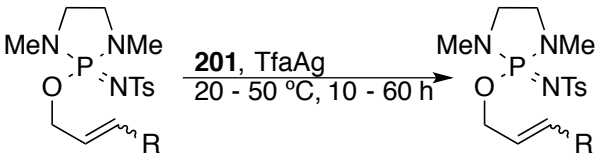


Scheme 46. Diastereoselective synthesis of Cobalt Oxazoline Palladacycles

A major breakthrough in the allylic imidate rearrangement was the discovery that the palladacycle COP-Cl (**201**), which is readily derived from (**199**) *via* diastereoselective palladation and ligand exchange, gives high enantioselectivities for the rearrangement of both *E* and *Z*- trifluoroacetimidates. [148] The advantage of this particular palladacycle is the fact that it does not need activation by the addition of one equivalent of silver trifluoroacetate. Following the development of COP-Cl for the trifluoroacetimidate rearrangement, a report by Anderson and Overman showed that it was also able to rearrange trichloroacetimidates with high enantioselectivities.[149] The current and most effective use of this metallocene-based catalyst is for the asymmetric allylic imidate rearrangement.

12.6 - Oxa-Claisen Rearrangements.

In recent years, asymmetric versions of other [3,3]-sigmatropic rearrangements have attracted much attention. The aza-phospha-oxa-Cope rearrangement is closely related to the Overman rearrangement with the only difference being that pentavalent phosphorus derivatives are used instead of acyl groups for the protection of the amino group. The choice of these unusual protecting groups is based on the fact that the transformation of the $P^{(V)}$=N bond into the $P^{(V)}$=O bond is thermodynamically favourable. (Alkyoxy)iminodiazaphospholidines were chosen as substrate. The best result in the asymmetric version of the rearrangement of these compounds into *N*-tosylallylamines was obtained with the use of a COP-type palladacycle with a trifluoroacetate bridge, generated *in situ* from the corresponding chloride bridged palladacycle by treatment with silver trifluoroacetate. This catalytic system was studied in the reactions of alkyl-subsituted substrates with unbranched groups. There is an inverse dependence of the results of the reaction on the geometry of the substrates compared to that typical of the Overman rearrangement. Thus the reaction rate of *Z* substrates is substantially lower than that of their *E* analogues, and the enantioselectivity is lower. For example, the chemical yields of the allylamine derivatives in the reaction of the *E* and *Z* isomers where R = Et, are 43% and 97% respectively; the *ee* values are 84% and 92% for the *S* and *R* enantiomers, respectively (**Scheme 47**).



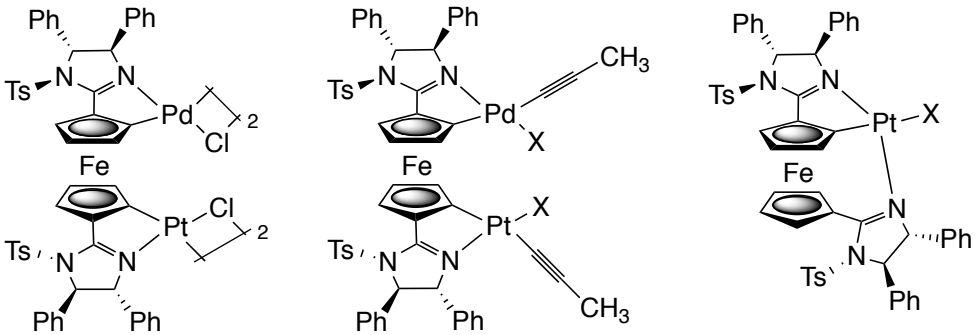
16% - 97%, 82% - 96% *ee*

R = Me, Et, ^{n}Pr, CH_2OTBS (TBS = *tert*-butyldimethylsilyl)

Scheme 47. Catalytic [3,3]-rearrangement of allyloxyiminodiazaphospholidines

12.7 – Synthesis of 1,1'-Palladacycles

It has recently been reported that planar chiral ferrocene bisimidazoline bispalladacycles act as highly enantioselective homobimetallic catalysts in a range of different reactions such as the enantioselective [3,3]-rearrangement of allylic imidates or Michael additions of various nucleophiles to enones.[150] For the 1,4-addition of α-cyanoacetates to enones, detailed kinetic studies have provided strong evidence for the intramolecular cooperation of both metals by the simultaneous activation of both substrates. The first diastereoselective cycloplatination of enantiomerically pure ferrocene derivatives using the ferrocenebisimidazoline ligand for the synthesis of the systems are shown in the figure below. The resulting platinum complex **206** gave only poor results in the allylic imidate rearrangement (**Figure 18**).



204-[FBIP-Cl]$_2$ **205**-[FBIP-X]$_2$ **206**

Figure 18. Planar chiral bis-palladacycle precatalyst [FBIP-Cl]2, the activated monomeric catalysts FBIP-X (X– is an anionic ligand), and monoplatinacycle 206.

On the other hand, it enabled the first enantioselective intramolecular Friedel-Crafts alkylations of indoles with internal olefins that are not activated by a π-acceptor substituent. This application represents the first reported enantioselective reaction catalysed by a platinacycle. Both $Pd^{(II)}$ and $Pt^{(II)}$ are known to serve as carbophilic Lewis acids capable of activating olefins as electrophiles for a large number of atom and step - economic processes, but they generally offer a complementary reactivity profile. Ligand exchange processes are usually much slower for $Pt^{(II)}$ in comparison to $Pd^{(II)}$, often resulting in a slow catalytic process. Another dissimilarity is given by the reactivity of the σ-alkyl-metal intermediates formed by attack of suitable nucleophiles at π-olefin complexes. Alkyl-$Pd^{(II)}$ complexes display a comparatively high tendency to undergo a β-hydride elimination while, their alkyl-$Pt^{(II)}$ counterparts prefer to undergo protonolysis and a β-hydride elimination pathway is usually significantly slower.[151,152]

12.8 – Summary

The majority of the work carried out using palladacycles in asymmetric catalysis is based around utilisation of palladium in its fixed oxidation state, maintaining the intrinsic structure of the palladacycle during a given chemical transformation. The up coming work within this thesis is focused around the generation and application of palladacycles in their Pd^{II}-Pd^{0} oxidation state

Chapter 2

Synthesis of Ferrocene Based Phosphines.

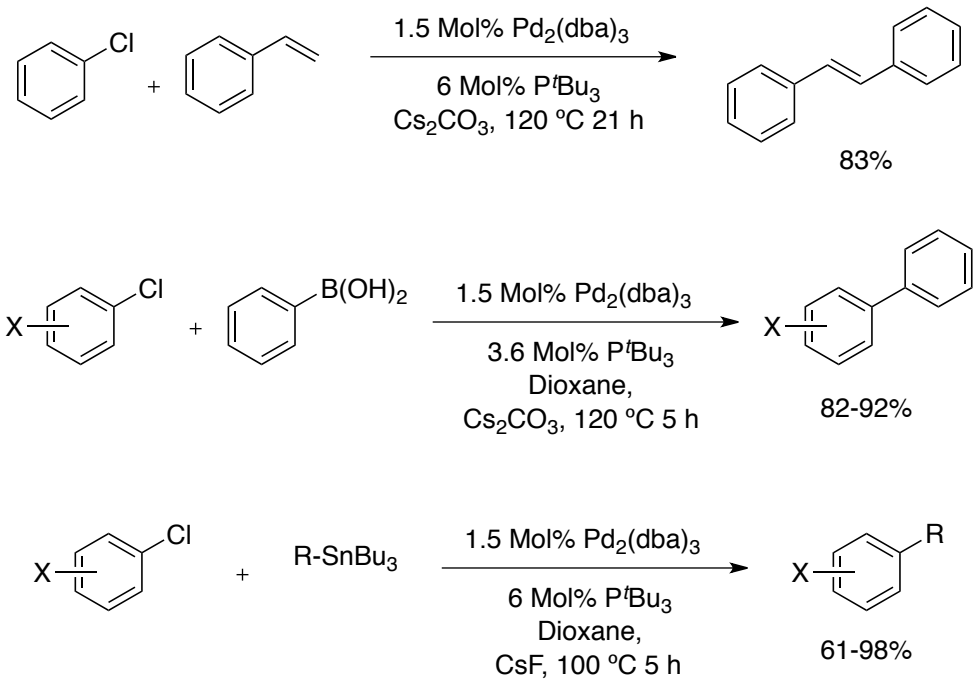
13.0 – Introduction.

As mentioned in **Chapter 1**, the Suzuki cross-coupling reaction plays an integral part in many total syntheses.[153] The development of new and selective organic transformations has led to great improvements in the production of chemical substances since the emergence of the Suzuki cross-coupling reaction. The pharmaceutical and fine chemical industries are experiencing continuous demand for new methods for the synthesis of organic compounds.

This chapter starts with a brief introduction, detailing the recent developments in the synthesis of phosphine-based ligands for application into a Suzuki cross coupling reaction. As mentioned earlier, recent developments in bond forming reactions have involved the use of bulky electron rich phosphine ligands. One of the main areas of interest is to improve the activity of such ligands, and to generate a new class of ligands where the chirality is stored at the heteroatom centre. Another area of interest is improving the activity of these systems so that cheaper, more readily available and lower molecular weight substrates can be used. For these new carbon-carbon bond-forming reactions the choice of ligand is crucial, and by fine-tuning the ligand, the new bonds can be formed in high yield using an array of palladium catalysts.

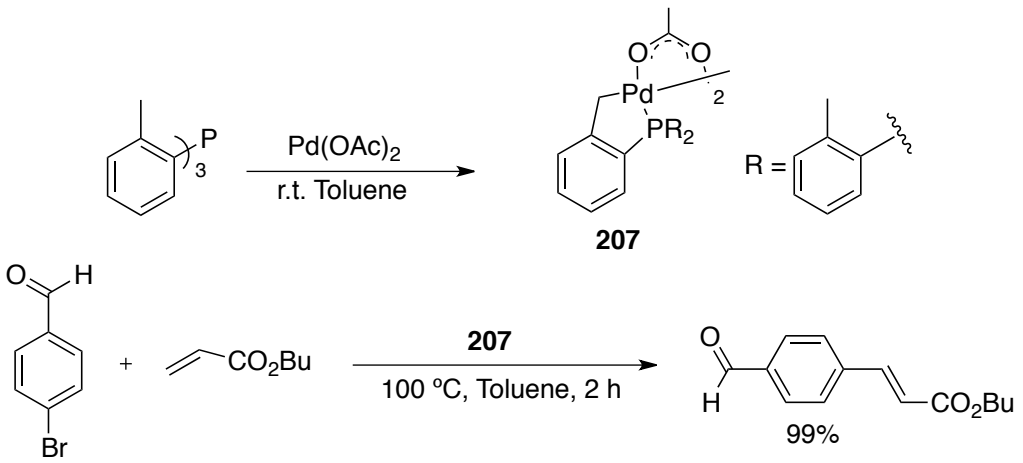
An important property of a phosphine ligand is its electron density, which is governed by the substituents attached to the phosphorus atom. One of the more reactive catalysts reported to date uses the bulky, electron rich ligand, tri-*tert* butyl phosphine. This ligand

can be introduced into various palladium mediated coupling reactions, for example, it has been used in Heck, Suzuki and Stille cross coupling reactions (**Scheme 48**).[154,155,156]



Scheme 48. Implementation of $P(^tBu)_3$ as a ligand in various palladium mediated coupling reactions.

This type of coupling reaction can also be promoted by palladacyclic precatalysts, for example palladacycle **190**, developed by Herrmann *et al.,* is an excellent precatalyst for the Heck vinylation of aryl bromides (**Scheme 49**).[157]



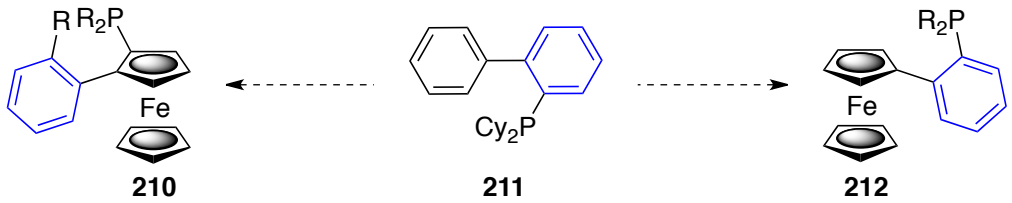
Scheme 49. Implementation of Herrman's palladacycle.

The Hermann group have previously carried out much work related to phosphine cone angles and phosphine ligand electron densities, and it has been established that electron rich P^tBu_3 and PCy_3, combined with their relatively large cone angles make them very good for palladium mediated cross coupling reactions. Similar phosphine ligands developed by Buchwald *et al.* have shown the best combination of phosphine basicity and optimum cone angle.[158] Ligand **208** in combination with palladium acetate has been shown to be highly active in Suzuki couplings with various aryl halides (**Figure 19**).

208 **209**

Figure 19. Buchwald's biaryl ligands

In order to change the properties of the ligand and to introduce more steric bulk around the phosphorus atom, a ferrocene moiety was incorporated. As mentioned in **Chapter 1**, ferrocene is a very versatile sandwich complex that can exhibit 1,1- substitution and 1,1'-substitution reactions. A generic scheme for the incorporation of ferrocene is detailed in (**Scheme 50**).



210 **211** **212**

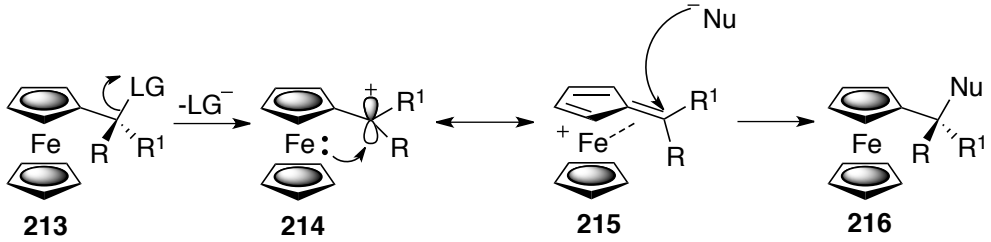
Scheme 50. Initial design model for ferrocene substituted phosphine ligands

13.1 – Advantages for the incorporation of ferrocene.

The incorporation of ferrocene has many potential advantages including the following;

- The ferrocene is bulkier than the phenyl ring, the ligands would have larger cone angles and consequently this should accelerate the rate of reductive elimination.[159]

- It is known that the oxidative addition step to palladium is promoted by electron rich phosphine ligands.[160]
- The presence of the ferrocene and its recognised ability to stabilise an adjacent positive charge may impart favourable electronic properties. This has been demonstrated by the isolation of ferrocenylcarbenium ions, intermediates in stereospecific substitution reactions alpha to ferrocene (**Scheme 51**).[161]



Scheme 51. S_N1 type elimination and formation of the ferroceneylcarbenium ion in stereospecific substitution reactions.

It has been discussed that π-coordination between $Pd^{(0)}$ and the π-systems of the *ortho*-aromatic groups on the ligands may play an important role in the Suzuki catalytic cycle. The isolation of an η^2-aryl $Pd^{(0)}$ complex from a phenanthracene based ligand, and the possible intermediacy of a similar species in the catalytic cycle of the Suzuki coupling have been reported.[162] A Cα-Pd species and the possible significance of this in the catalytic cycle have also been discussed (**Figure 20**).[163]

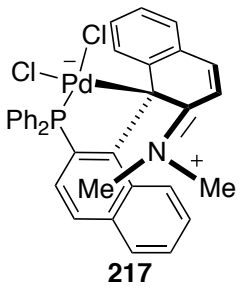


Figure 20. Isolated C_α-Pd Complex.

Therefore it is postulated that besides bulkiness and electron-richness, an important factor that imparts a high catalytic performance on dialkyl biphenylphosphanes is that the π-systems of the *ortho*-aromatic groups on the ligand interacts with the Pd centre (**Figure 21**).

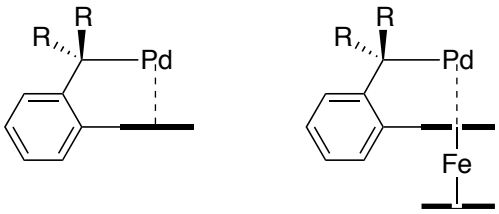
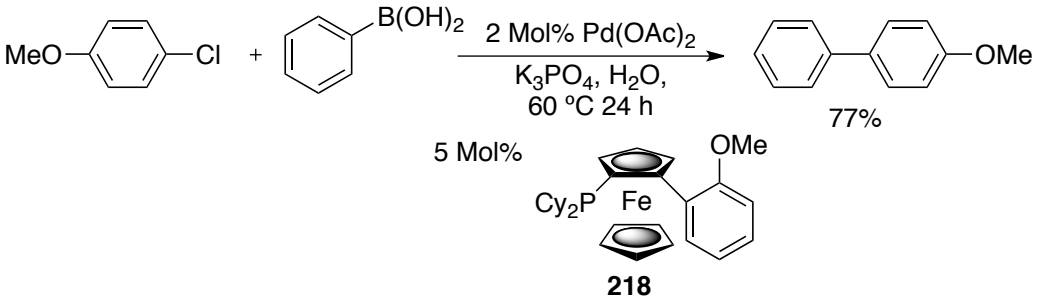


Figure 21. Schematic representation of metal-π electron interaction.

This property would be modified with the cyclopentadienyl ring of ferrocene because of its intrinsic electron rich nature. An illustration of this is the predisposition of this metallocene to undergo electrophilic aromatic substitution.[164,165]

Such ferrocene substituted ligands have received a great deal of attention in recent years. Johannsen *et al.* displayed this fact very elegantly in the cross-coupling outlined in **Scheme 52**, utilising activated and non-activated aryl chlorides.

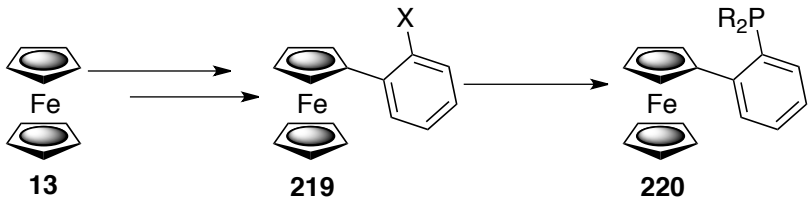


Scheme 52. Suzuki cross-coupling using the Johannsen ligand 218.

Ligand **218** and many others in this class have shown a great deal of activity in Suzuki coupling, but they fail to catalyse the reaction of non-activated aryl chlorides at room temperature. The Buchwald ligands **208** and **209** have overcome this issue. With this in mind it was envisaged that we must combine the two concepts and design a new class of ferrocene substituted phosphine ligands.

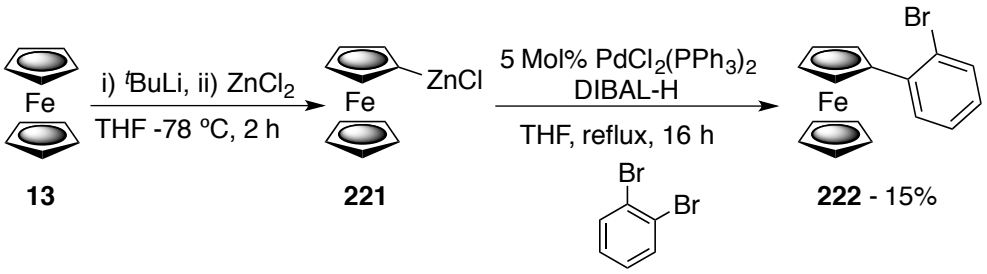
13.2 - Synthesis of ferrocene substituted phosphine ligands.

A relatively facile synthetic protocol was hypothesised for the synthesis of biaryl-phosphine ligands (**Scheme 53**).



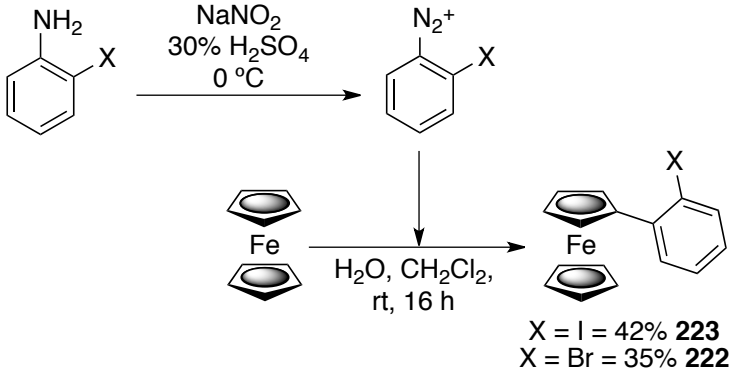
Scheme 53. Generic Scheme for the synthesis of ferrocene substituted phosphine ligands.

Previous work in the lab generated **222** *via* a Negishi coupling following the lithiation of the cyclopentadienyl ring and transmetallation with $ZnCl_2$ (**Scheme 54**).[166]



Scheme 54. Synthesis of Bromophenyl ferrocene using a Neghishi cross-coupling protocol.

Use of the Kagan lithiation protocol, in which ^{t}BuLi in THF at -78 ^{o}C, was added, and subsequent transmetallation with anhydrous zinc chloride, was followed by the addition of a palladium catalyst generated *in situ* from DIBAL-H reduction of $PdCl_2(PPh_3)_2$. Addition of 1,2-dibromobenzene, afforded **222** in 15% yield on a 10-gram scale (**Scheme 54**). [167,168] There are many disadvantages in employing such a low yielding reaction at the start of the ligand synthesis. The starting materials are relatively expensive and the reaction is very air and moisture sensitive, leading to great difficulties when scale up is required. An alternative procedure was found in the literature using a diazonium salt, where the bromo[169] and iodophenyl ferrocene could be synthesised (**Scheme 55**).[170]

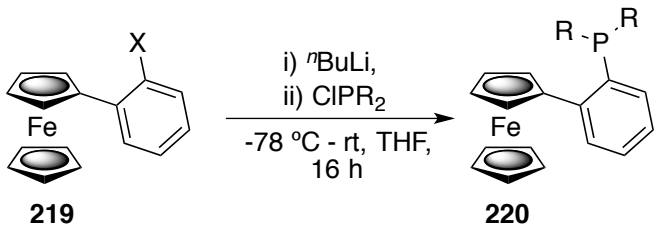


Scheme 55. Implementation of Sander's protocol for the synthesis of bromo/iodophenylferrocene.

The diazonium salt was synthesised from bromoaniline by reaction with sodium nitrite in 30% sulfuric acid at 0 °C. Sulfamic acid is then added to destroy any excess sodium nitrite, evolving nitric oxide, as a brown toxic gas. The solution is allowed to stir for 2 hours, then sodium acetate and ferrocene in dichloromethane were added. The resulting mixture was left to stir overnight at room temperature. 2-Bromoaniline gave compound **222** in 35% yield and 2-iodoaniline gave compound **223** in 42% yield after purification *via* flash chromatography.

In comparison with the palladium mediated coupling, the method by Sanders avoids the use of dry solvents and the use of the extremely pyrophoric organometallic base, *tert*-butyllithium. The reaction can be scaled up to 50 g.

These reagents were then readily converted to a range of symmetrical phosphine ligands, *via* a lithium-halogen exchange with *n*-butyllithium and subsequent nucleophilic attack on a range of disubstituted chlorophosphines (**Scheme 56**).



Scheme 56. Synthesis of symmetrical ferrocene substituted phosphines.

Compound	R =	^{31}P Chemical Shift (ppm)	% Yield
224	Ph	-11.63	76
225	Cy	-11.81	71
226	^{i}Pr	-3.77	93
227	^{t}Bu	+18.17	15

Table 7. Synthesis of phosphino ferrocene derivatives.

Bromo-halogen exchange on **222** or **223** at -78 ^{o}C and subsequent addition of $ClPR_2$ at room temperature, and column chromatography, afforded the corresponding complexes in good yield. This was a very versatile protocol, allowing for the synthesis of diaryl and dialkyl phosphine ligands. The aforementioned ligands were synthesised in moderate yield and their identification in crude phosphorus NMR spectra proved to be very straightforward. The table above outlines the relevant chemical shifts and the yields of the ligands that were synthesised. Compounds **224** and **225** have been previously reported by the Richards group and compounds **226** and **227** are known to be novel ferrocene containing ligands. Starting with the diphenyl substituted phosphine ligand **224**; the ^{31}P chemical shift came at -11.63 ppm, which was very characteristic for similar compounds.[171] It was possible to monitor the reaction by ^{31}P NMR and check for any oxidation to the corresponding phosphine oxide because this has a characteristic signal at 31.09 ppm. With respect to the ^{1}H NMR, the ferrocene peaks have a unique splitting pattern. The unsubstituted cyclopentadienyl ring was shown to be a characteristic singlet at 4.07 ppm, and in the product, the α and β protons shift to 4.42 and 4.18 respectively. The aromatic region can be somewhat complicated, but a doublet of doublet of doublets (ddd) at 7.94 ppm is a strong indicator of the formation of the product. The proton at the 6-postion of the aromatic ring is shifted downfield due to an anisotropic affect from iron. The ring sits at an angle with respect to the flat cyclopentadienyl ring, and its interaction with the ferrocene core deshields this proton, in turn, shifting it downfield. This effect is only seen when a bulky substituent is at the 2-postion. It is not as pronounced in

bromophenyl ferrocene but is evident in iodophenyl ferrocene (7.83 ppm) versus a double doublets at 7.64 ppm for **222**. The X-ray structure of **225** clearly displays this.

The diisopropyl substituted phosphine ligand gave the best yield, although the yields of the ligands were dependent on the age of the bottle of the chlorophosphine and butyllithium. In terms of the NMR spectra the major difference came when analysing the isopropyl groups attached to the phosphorus. The isopropyl groups were split into a doublet of doublets with the first coupling constant being the largest at 14 Hz, due to coupling from phosphorus. The second coupling constant was 7 Hz. The two methyl groups of an isopropyl group are diastereotopic resulting in two sets of signals. Upon palladation of **226** this is increased to four sets of double doublets displaying ^{3}JH-H and ^{3}JP-H coupling. This observation will also be apparent with **224** and **225**, but the simplicity of the spectra derived from the diisopropylphosphino derivative is especially useful.

Compound **227** was only generated in a very low yield due to its high sensitivity to air and oxidation on silica gel during its purification. *In situ* borane protection was attempted but this also led to further decomposition. All solvents were thoroughly degassed and dried but this did not improve the yield. The highly electron rich di-*tert*-butyl phosphine ligand is very susceptible to oxidation, but if the ligand could be isolated and protected, *in situ* deprotection and ligation to a palladium source may give a very active ligand. It is also likely that the ^{31}P NMR chemical shift of ligand **227** is not only a function of its electron richness but also the steric hindrance of both *tert*-butyl groups.

A trend can be established in relation to the electron richness or deficiency of phosphines and their relative ^{31}P chemical shifts. As phosphines become more electron rich their chemical shift can be seen to move upfield and *vice versa*. This can be seen when comparing **224** and **227** where the chemical shifts are -11.63 ppm and +18.17 ppm, respectively.

The behavior of phosphines as ligands is dependent on the electron donating and electron accepting properties of the phosphorus atom and of the steric effects of the substituents. As mentioned before, to quantify these electronic and steric effects, many ligand parameters have been proposed.[172] The early parameters introduced by Tolmann *et al.* in 1977, are cone angle, θ, and the electronic parameter, χ.[173] These properties have been used in many structure-activity relationships of coordination and organometallic compounds containing phosphine ligands. One of the key areas of analysis is the nature of

the metal-phosphine bond, particularly its separation into σ and π electronic and steric components. This is a classic controversy in coordination chemistry.[174]

The interpretation of the NMR chemical shift values for elements other than hydrogen is known to be difficult. For phosphorus derivatives several factors have been proposed. Three factors, two electronic and one steric, seemed to be the most important: the distribution of electron density in the σ bond between phosphorus and its substituent; the extent to which phosphorus participates in π bonding, and bond angles around the phosphorus.[175] For phosphines, the electronegativity of substituents on phosphorus and the angles between them are very important variables determining ^{31}P NMR chemical shifts and coupling constants.

Sales reported that ^{31}P NMR chemical shifts can be predicted on the basis of molecular structure alone. Similar studies of simple phosphine derivatives, such as oxides (OPR_3), sulphides (SPR_3), and phosphites ($P(OR)_3$), for example, can give information about what kind of descriptors can play an important role in the prediction of ^{31}P NMR chemical shifts.

The crystal structures of **224** and **225** was previously obtained by another member of the group and in both cases it was confirmed that the phosphorous lone-pair is orientated towards one of the alpha-carbons of the substituted cyclopentadienyl ring of ferrocene (**Figure 22**). Further analysis of **224** showed that the phenyl-ferrocenyl dihedral angle was 34.7^{o} and this increased in **225** to 52.1^{o} to avoid an unfavourable interaction between ferrocene and a cyclohexyl group.[171]

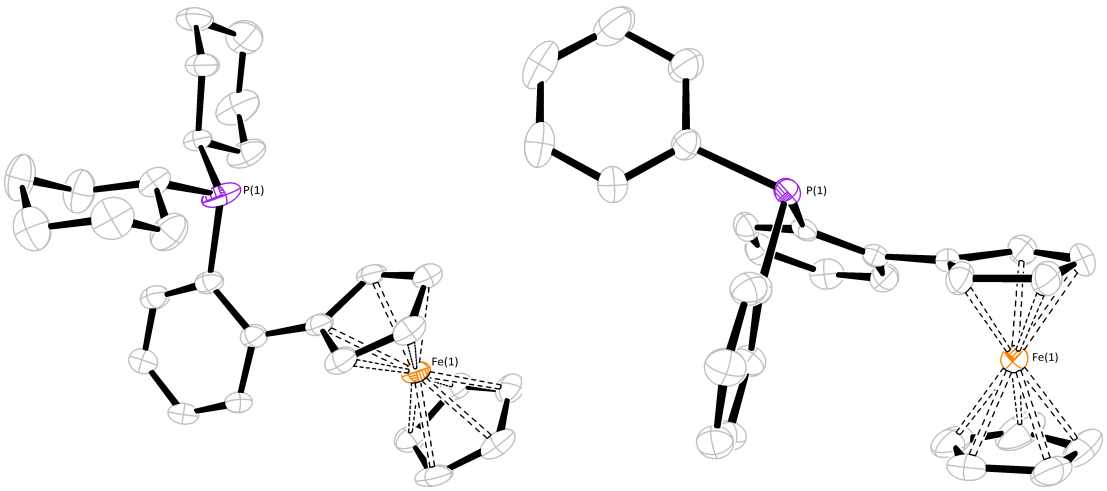
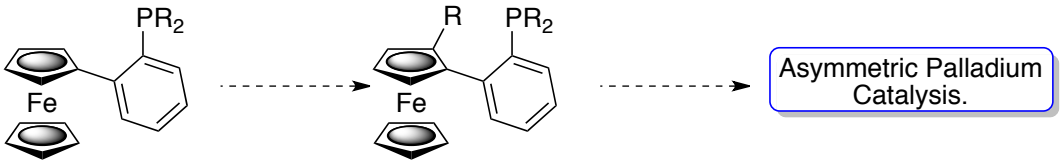


Figure 22. ORTEP representation of compound 224 & 225. Hydrogen atoms, solvent molecules and minor disordered components have been removed for clarity. Displacement ellipsoids are drawn at 50% probability level.[181]

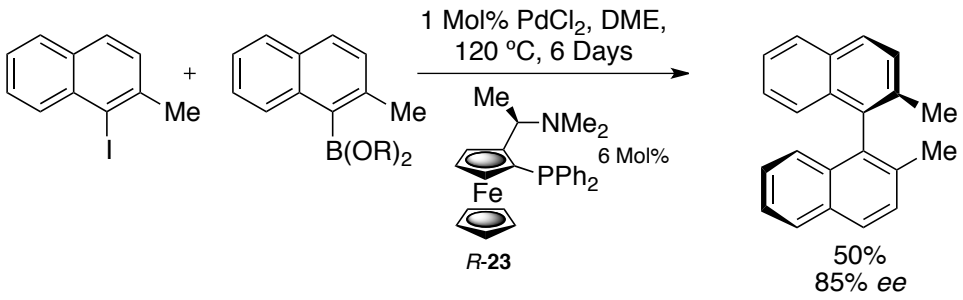
13.3 - Application of Planar Chiral 2-Phosphinophenylferrocene ligands.

The aforementioned mono-dentate symmetrical phosphine ligands have been successfully utilised to a range of Suzuki cross coupling reactions as outlined in a paper by Richards *et al.*[166] An extension of this methodology is the synthesis of related planar chiral mono-dentate or bi-dentate ligands, where R can be a phosphine or amine moiety, in order to introduce chirality into subsequent cross-coupling reactions (**Scheme 57**).



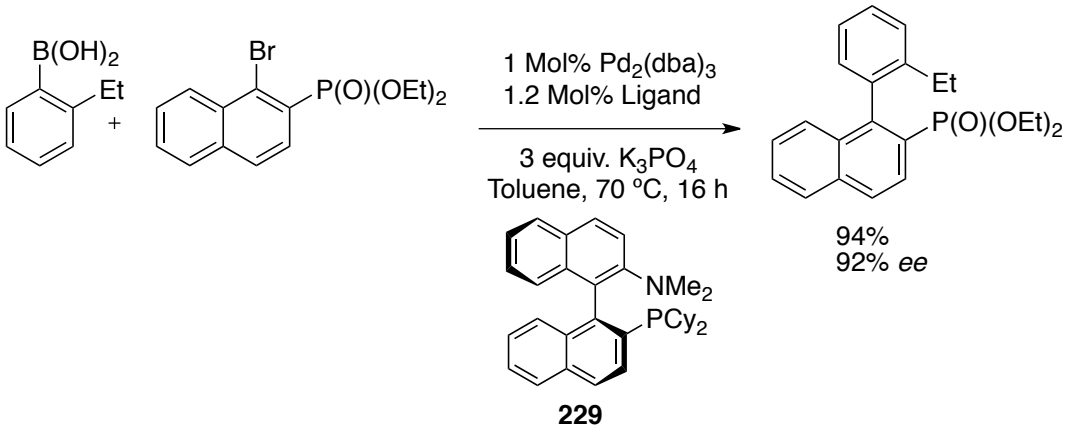
Scheme 57. Synthesis of planar chiral phosphine ligands.

The first reported asymmetric Suzuki cross coupling was published by Cammidge *et al.*[176] Planar chiral ligand **23**, a derivative of Ugi's amine was used in the synthesis of axially chiral biaryls *via* a Suzuki cross coupling in 50% yield at 85% *ee* (**Scheme 58**).[177]



Scheme 58. Suzuki Cross-coupling implemented by Cammidge *et al.*

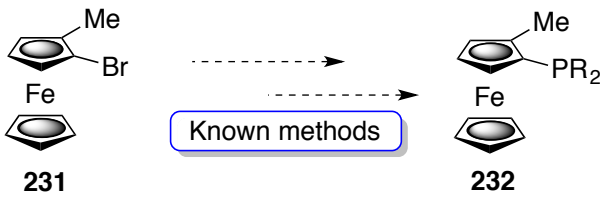
Buchwald *et al.* utilised an electron rich phosphine ligand to afford a range of axially chiral biaryl compounds *via* the Suzuki cross-coupling (**Scheme 59**). [178]



Scheme 59. Application of binaphthyl-phosphines ligands

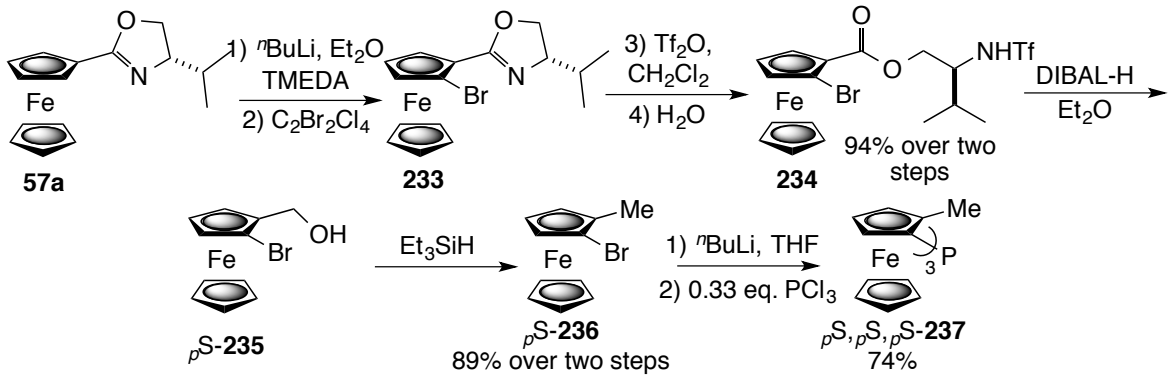
13.4 - 1,2-substiuted planar chiral ferrocenyl phosphine ligands.

Previous work within the group has concentrated on the lithiation of ferrocenyloxazolines, generating new planar chiral compounds *via* a diastereoselective lithiation. Richards *et al.* have extended this methodology to the synthesis of ferrocene based phosphine ligands (**Scheme 60**).



Scheme 60. Synthesis of planar chiral ferrocene ligands.

After a great deal of work this approach was successfully completed by two members within the Richards group, cumulating in the generation of **TomPhos**, a novel, C_3-symmetrical tri-ferrocenyl phosphine ligand (**Scheme 61**).[179]



Scheme 61. Stereoselective synthesis of TomPhos from ferroceneoxazoline.

Triarylphosphines may be synthesised by the addition of aryllithium precursors to phosphorus trichloride. A stereoselective synthesis of **TomPhos** using this method requires access to enantiomerically pure 2-lithio-1-methylferrocene. The addition of butyllithium to ferroceneoxazoline in the presence of TMEDA followed by the addition of dibromotetrachloromethane led to the formation of the bromoferroceneoxazoline.[180] Ring opening *via* the addition of triflic anhydride, followed by the addition of water gave compound **234**. DIBAL-H reduction of the ester gave the corresponding alcohol, which was completely converted to ($_p$S)-1-bromomethylferrocene by further reduction with two equivalents of triethylsilane in TFA. Bromine-lithium exchange was followed by the addition of PCl_3, warming of the reaction mixture to room temperature and subsequent isolation of **TomPhos** as a yellow crystalline solid.

13.5 - Application to 2-Phosphinophenylferrocene Ligands.

13.5.1 – Project Aims.

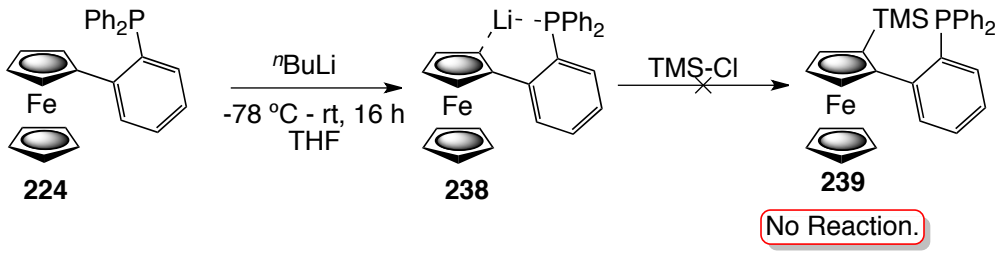
The aims of this section of the thesis was to devsive a range of protocols which would:

I. To synthesise a range of new planar chiral ligands using a lithiation protocol previously carried out within the group starting from **224**.

II. To synthesise a range of chiral at phosphorus ferrocenenyl ligands starting from bromophenyl ferrocene.

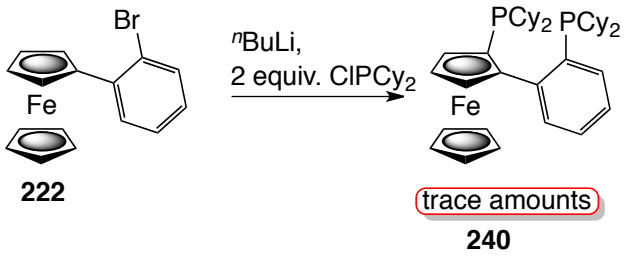
III. Finally, the development a novel catalytic protocol using Ullamn type chemistry and palladium mediated phosphine-borane coupling in order to synthesise the aforementioned P-chiral monodentate phosphine ligands.

The initial aim of this project was to devise a facile protocol for the synthesis of bi-substituted planar chiral phosphine based ferrocene ligands derived from complexes **224**-**226**. The initial protocol used the application of a standard lithiation protocol with *n*-butyllithium and quenching with TMS-Cl (**Scheme 62**).



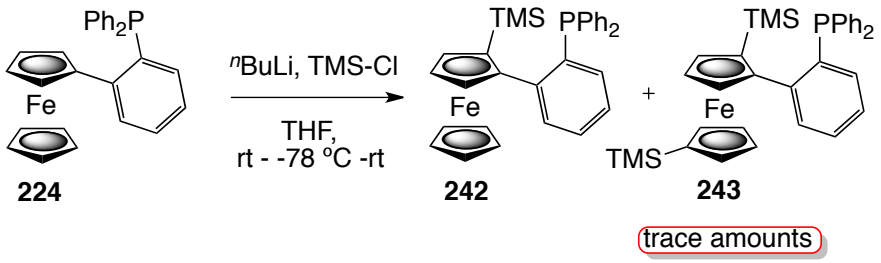
Scheme 62. Attempted synthesis of planar chiral phosphine ligands.

Previous members in the Richards group were able to synthesise a similar compound by changing the electrophile to $ClPCy_2$ a reaction presumably passing through intermediate ligand **238** (**Scheme 63**).



Scheme 63. Generation of a novel planar chiral phosphine bi-dentate ligand.

As shown in the scheme above, the ligand is a dicyclohexyl phosphine derivative and this ligand was only synthesised in a trace amount. It does, however, prove that such reactions can take place.[181] Many reactions were carried out to repeat this body of work and to consolidate the hypothesised intermediate but most resulted in decomposed material or led to oxidation of the phosphine (**Scheme 64**, **Table 8**). The phosphorus atom on compound **224** was seen to be less prone to oxidation and, therefore, this was used for subsequent reactions.



Scheme 64. Attempted lithiation of 224

Run	Temp of BuLi addition (^{o}C)	Electrophile	Solvent	*n*/*s*/*t*-BuLi	Outcome.	Isolation of **423 (%)**
1	-78	TMS-Cl	THF	*n*BuLi	Oxidation	34
2	-30	TMS-Cl	THF	*n*BuLi	Oxidation	48
3	-10	TMS-Cl	THF	*n*BuLi	Oxidation	55
4	0	TMS-Cl	THF	*n*BuLi	Oxidation	65
5	rt	TMS-Cl	THF	*n*BuLi	Trace amounts	N/A
6	-78	TMS-Cl	THF	*t*BuLi	Decomp	N/A
7	-78	TMS-Cl	THF	sBuLi	Decomp	N/A
8[a]	-78	TMS-OTf	THF	*n*BuLi	Decomp	N/A
9	-78	TMS-OTf	Ether	*n*BuLi	Oxidation	42
10	0	TMS-OTf	Ether	*n*BuLi	Oxidation	39
11	-78	TMS-Cl	Ether	*n*BuLi	Oxidation	57
12	0	TMS-Cl	Ether	*n*BuLi	Oxidation	65

a. Reaction with TMS-OTf in THF with *n*BuLi led to complete decomposition and polymerisation of THF into a solid deposit in the reaction vessel.

Table 8. Attempted synthesis of 242.

As shown in **Table 8** most attempts oxidised the phosphine and a change in the organometallic base used led to decomposition of the starting material. The electrophile was changed to TMS-OTf but this led to polymerization and decomposition of the starting material. It is thought that the addition of TMS-OTf in the presence of *n*BuLi and THF led to ring opening and subsequent polymerisation of the solvent. Further attempts at purification did not give any insight into what was occurring. Using **225** and **226**, led to oxidation or decomposition upon attempting the same chemistry. From closer analysis of the NMR data, it can be seen that the addition of butyllithium at room temperature, stirring for an hour, cooling to -78 ^{o}C followed by the addition of TMS-Cl led, to the formation of 2 new compounds in trace amounts, which could only be separated by

preparative TLC. This method was not taken any further as only a low yield could be obtained. Compound **242** shows the classic splitting pattern for a 1,2-disubstituted ferrocene moiety where the three-cyclopentadienyl protons are clearly seen in the spectra as well as the C_5H_5 moiety (**Figure 23, Table 8**).

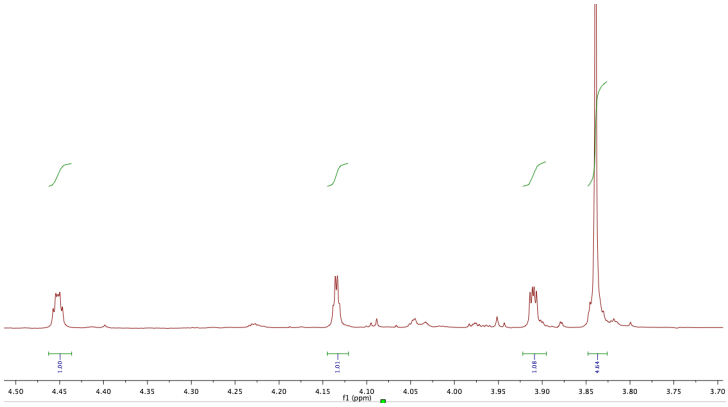


Figure 23. NMR of the cyclopentadienyl region of 242.

The formation of **243** is linked to the temperature of the addition of butyllithium. It was found that lithiation at room temperature lithiated the bottom cyclopentadienyl ring of 224 and, therefore, leading to the formation of **243**. The NMR is very indicative of the presence of the product and the cyclopentadienyl region is again, very diagnostic, due to 7 diastereotopic signals, as shown in (**Figure 24**).

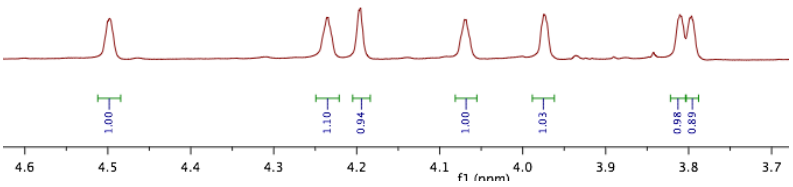
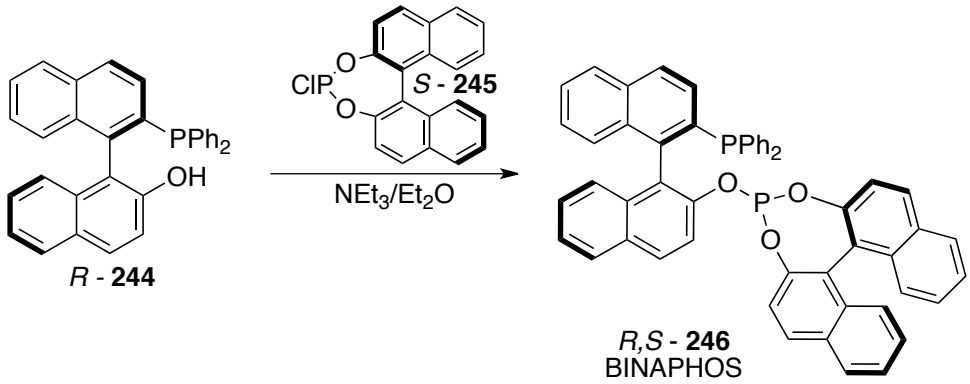


Figure 24. Cyclopentadienyl region of 243.

13.6 - Further Synthesis of 2-Phosphinophenylferrocene Ligands.

It was important to attempt the synthesis of a range of phosphorous-based ligands to quantify and analyse their effect on palladium mediated cross-coupling reactions. With much evidence to suggest that **224,** and other similar dialkyl analogues, are efficient and highly active ligands, other diaryl and dialkyl ligands were anticipated to have similar or greater activity.

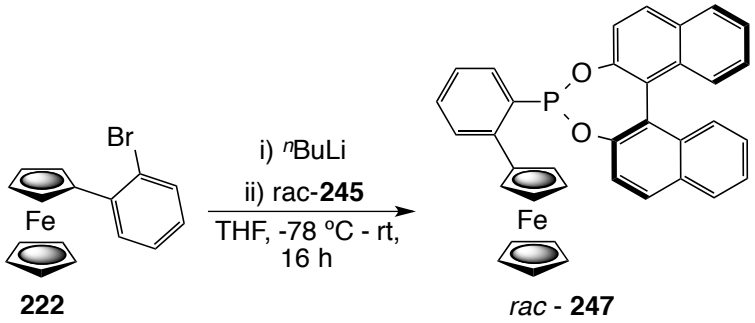
Takaya *et al.* developed a new class of chiral phosphine-phosphite ligands for rhodium and platinum mediated highly enantioselective asymmetric hydroformylation (**Scheme 65**).[182]



Scheme 65. Synthesis of *R,S*-BINAPHOS 246.

As shown in **Scheme 65**, **245** is utilised as a chiral electrophile affording diastereomerically pure **246**. This compound was then complexed with either rhodium or platinum and applied to a range of asymmetric hydroformylations.

It was postulated that binaphthyl derivative **245** could be applied to a phenyl ferrocene species, thus giving a new chiral element around the phosphorous atom. The compound in question can be synthesised from BINOL, and in the first instance racemic BINOL was used, with rac-**245** generated by heating racemic BINOL in a closed vessel at 90 ^{o}C in neat PCl_3 for 16 hours. The excess PCl_3 was removed *via* an azeotropic distillation with toluene and the product was freeze dried in the presence of benzene in liquid nitrogen affording *rac*-**245** in 96% yield. The compound was highly air sensitive and prone to oxidation, and could not be purified with flash chromatography, but the ^{31}P NMR peak +174 ppm showed the presence of the product, which matched with the quoted literature value. This was then used with a lithiated ferrocene species as shown in **Scheme 66**.

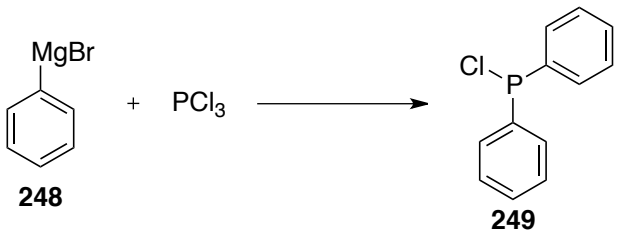


Scheme 66. Attempted synthesis of 247.

Closer inspection of the NMR data resulted in the conclusion that the reaction did not proceed as expected. Only starting material and reduced product, phenyl ferrocene could be isolated. The formation of phenyl ferrocene shows that it is not the lithiation step that is issue. Instead the nucleophilic attack into the phosphorus-chlorine bond is the limiting factor. It maybe that the steric bulk of the lithiated ferrocene species combined with that of **226** caused the product not to form. After the addition of the phosphite-chloride, the reaction was warmed to room temperature and refluxed for 16 hours but still no product was isolated. All solvents were thoroughly degassed and dried, as **245** is prone to oxidation but this also made no difference.

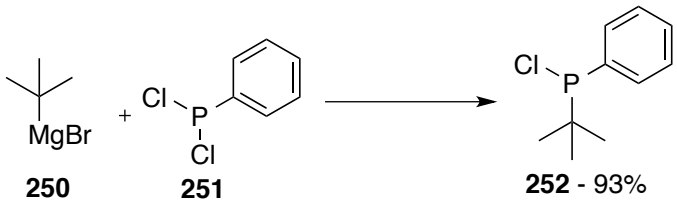
13.7 - Attempted Synthesis of Phosphine Chlorides.

Although diphenylphosphine chloride, dicyclohexylphosphine chloride and diisopropylphosphine chloride are commercially available, the latter two are rather expensive and it was important to devise a facile and efficient protocol to generate such compounds in high quantities in order to synthesise the relevant ligands. The first attempted synthetic protocol was the application of a Grignard reagent with PCl_3 (**Scheme 67**).



Scheme 67. Attempted synthesis of diphenylphosphine chloride.

The synthesis of diphenylphosphine chloride has been well documented and is relatively straightforward.[183] Repetition of this procedure with cyclohexyl- and isopropyl- Grignard reagents did not give the desired phosphine chlorides. Predominantly oxidation was observed which was evident by the formation of a white solid upon attempted purification. A range of different Grignard reagents were tried but *tert*-butylphenylphosphine chloride (**252**) was the only successfully isolated compound, which gave a ^{31}P NMR peak at 107.64 ppm (**Scheme 68**).



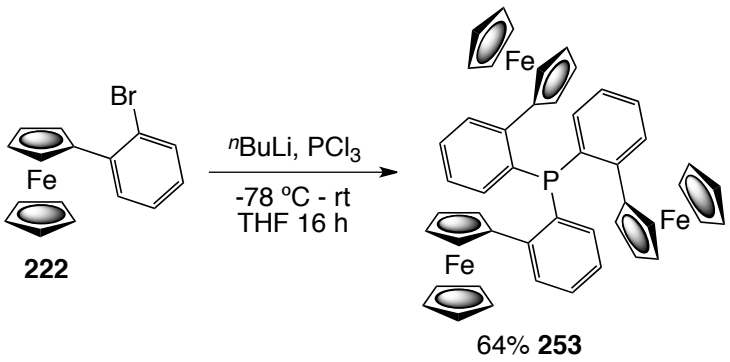
Scheme 68. Synthesis of 252.

As shown in **Scheme 68** the starting phosphine chloride was changed to dichlorophenylphosphine and *tert*-butyl Grignard was added. Although the synthesis was somewhat time consuming and technically quite arduous, it did afford the desired compound in high yield.

The reaction only worked with *tert*-butyl magnesium bromide due to the fact that the steric hindrance of the *tert*-butyl group only allowed for mono addition at the phosphorus centre.

14.0 - Synthesis of Sterically Bulky Ferrocenyl Phosphines.

A development on this synthetic protocol is the synthesis of new sterically bulky phenylphosphino ferrocene derivatives. Using methods related to **Scheme 68**, a lithiated phenyl ferrocene species was reacted with PCl_3 to afford a new sterically hindered phosphine ligand (**Scheme 69**).



Scheme 69. Synthesis of KetPhos, 253.

Compound **253**, or **KetPhos**, is a novel, sterically bulky triaryl phosphine ligand. Its synthesis is relatively trivial in comparison with the aforementioned **TomPhos** due to it not being planar chiral. This substrate is prochiral and shows the potential to be diastereoselectively functionalised using a range of C-H activation protocols. Addition of butyllithium to bromophenylferrocene followed by 0.33 equivalents of PCl_3 afforded **253** in 64% yield. The ^{31}P NMR signal is considerably up field in comparison to the other phosphines mentioned and comes at -23.56 ppm, which is likely to be a function of the steric bulk around the phosphorus atom. X-ray crystal structure analysis confirmed the identity of **253** and highlighted some unique aspects, which have not been seen in any related ligands (**Figure 25**).

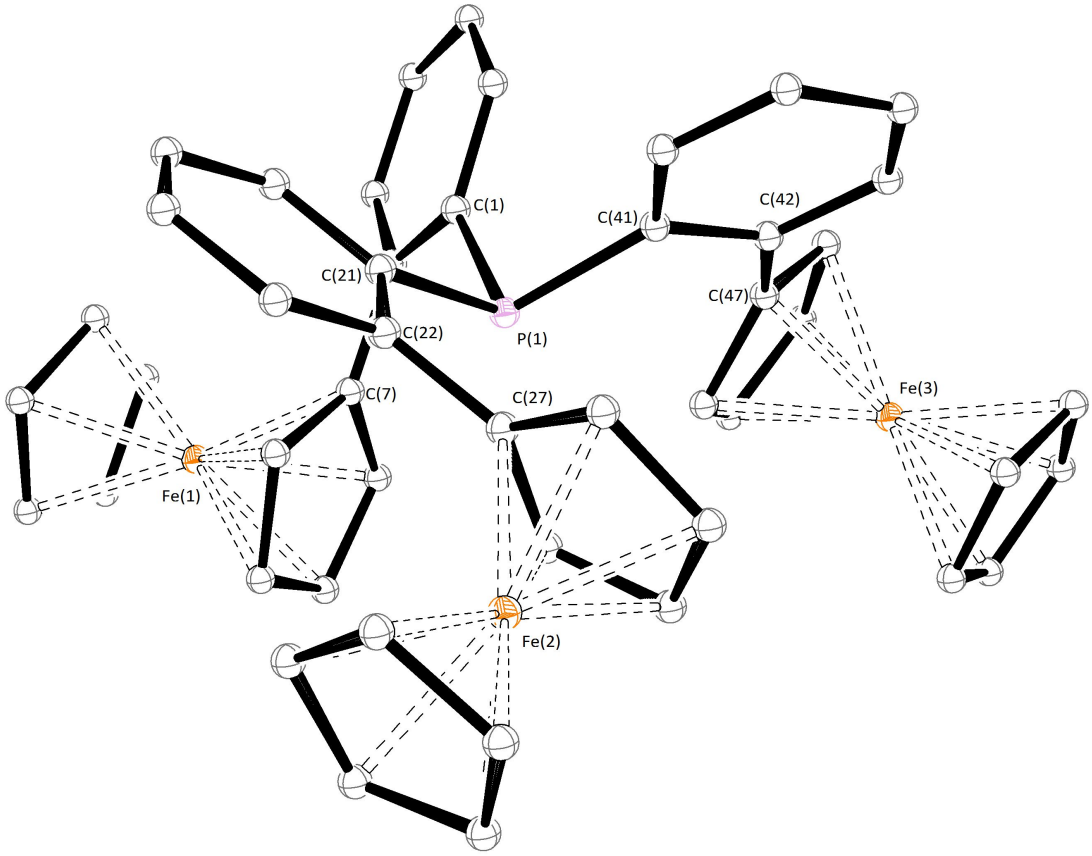


Figure 25. ORTEP representation of compound 253. Hydrogen atoms, solvent molecules and minor disordered components have been removed for clarity. Displacement ellipsoids are drawn at 50% probability level. Principal bond lengths [Å] include: C(2)-C(7) 1.483, P(1)-C(1) 1.844, P(1)-C(21) 1.845, P(1)-C(41) 1.844. Principle torsion angles [°] include: C(51)-C(47)-C(42)-C(41) 138.13, C(41)-P(1)-C(21)-C(22) -74.03, C(22)-C(21)-P(1)-C(1) -178.00

In the solid state the phosphine ligand exhibits C_1-symmetry due to the fact that all the ferrocene moieties do not orientate themselves in the same way due to the crystal packing. Fc(1) and Fc(3) are seen to be parallel to one another but Fc(2) is perpendicular to Fc(3) (**Figure 26**).

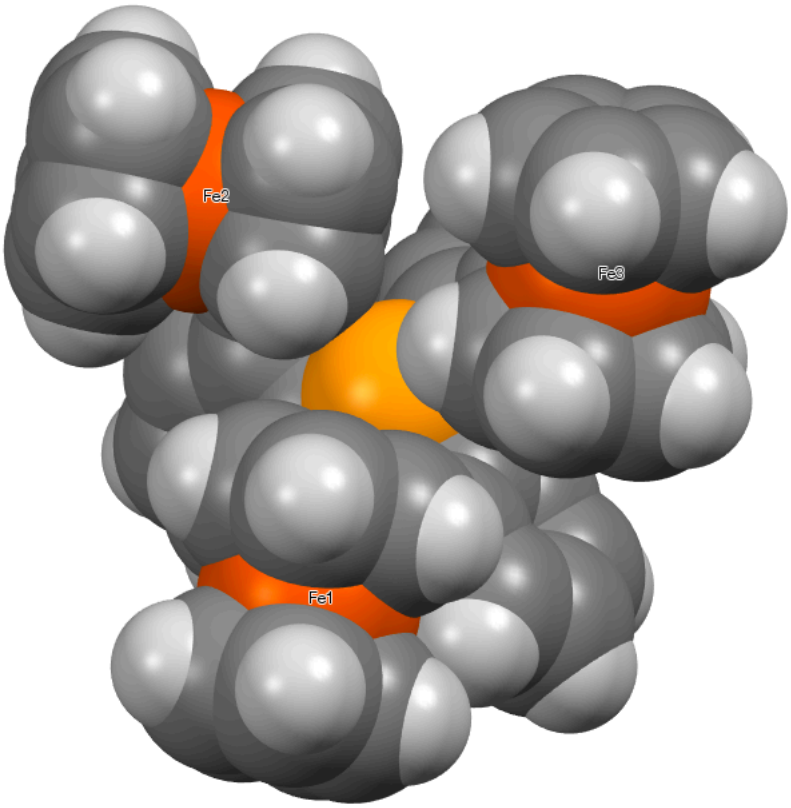
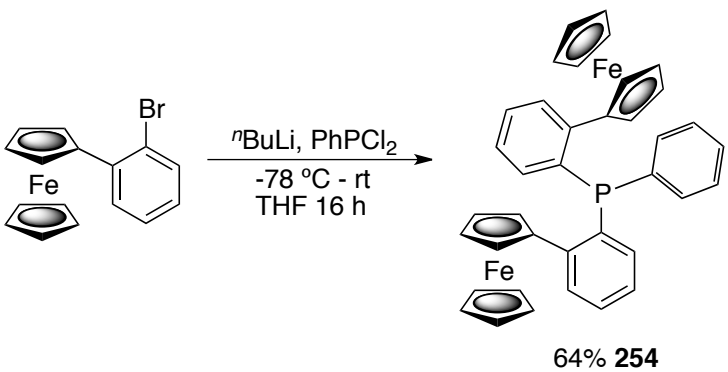


Figure 26. Space filling representation of KetPhos.

In solution it is anticipated that **Ketphos** is C_3-symmetrical and, therefore, is also chiral as it exhibits properties of propeller chirality. A sample was submitted for HPLC analysis but only one peak was seen, showing the barrier to inversion to be very low.[184] Closely linked to the synthesis of compound **253** is compound **254** which can be readily synthesised from dichlorophenylphosphine, *n*-butyllithium and **222** (**Scheme 70**).

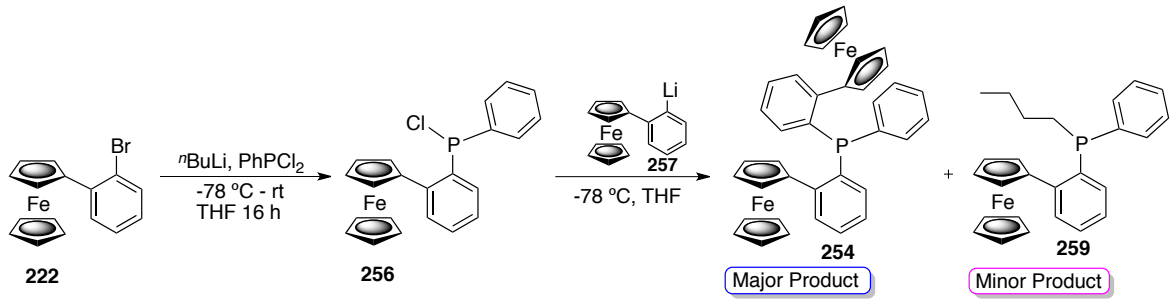
14.1 – Synthesis of a Di-ferrocenylphosphine Ligand, MudzPhos.



Scheme 70. Synthesis of MudzPhos (254).

The synthesis of **254** followed closely a publication by John Whitall *et al.* [185] in which it was envisioned that ferrocene-based P-chiral phosphines could be synthesised by reacting dichlorophosphine with a chiral lithiated ferrocene species, followed by a second organometallic reagent. They have reported the first example of highly stereoselective and modular synthesis of ferrocene-based P-chiral phosphine ligands using this simple and straightforward strategy (**Scheme 18**).[185]

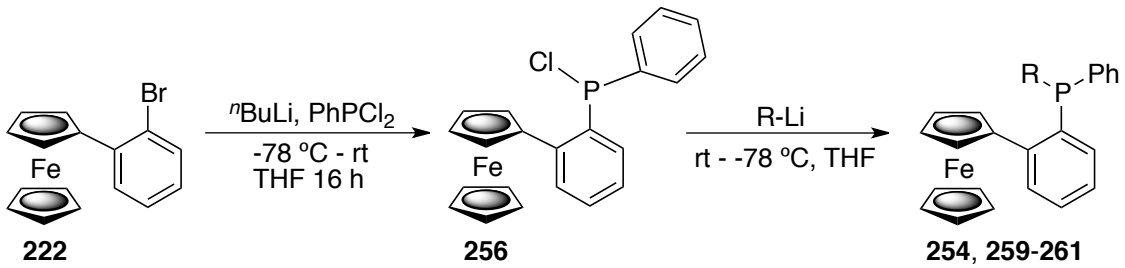
A key aspect in this body of work is the temperature of addition of the organometallic reagent. It is predicted that the phosphine must travel through a phosphine-chloride intermediate followed by a second nucleophilic attack from another lithiated species (**Scheme 71**).



Scheme 71. Reaction pathway for the synthesis of 254.

This reaction cannot be carried out a 'one-pot' system. With respect to the dichlorophenylphosphine, half an equivalent of bromophenylferrocene and half an equivalent of butyllithium were combined in THF at -78 ^{o}C. With respect to bromophenyl ferrocene, one equivalent of dichlorophenylphosphine was added. This was allowed to warm to room temperature, favouring the formation of **256**. This was cooled to -78 ^{o}C and another equivalent of lithiated phenylferrocene was added *via* a cannula to the flask containing **256**. Only this method of addition would favour the formation of **254**. The major product of the 'one-pot' synthesis was **259**. The one pot synthesis involved the addition of 1 equivalent of *n*BuLi, followed by the addition of dichlorophenylphosphine and allowing this to warm to room temperature. Before addition of the final equivalent of *n*BuLi the reaction was cooled back down to -78 ^{o}C. The formation of **259** opened up a whole new methodology for the synthesis of P-chiral ferrocenyl ligands. Using this methodology *n*-butyl(phenyl)-phosphinophenylferrocene, methyl(phenyl)-

phosphinophenylferrocene and *ortho*-tolyl(phenyl)-phosphinophenylferrocene were generated (**Scheme 72, Table 9**).



Scheme 72. Synthesis of P-chiral ligands using stepwise addition of the relevant organolithium reagent .

Run	R-Li	Number	^{31}P NMR	Yield %
1	Fc-Ph-Li	[b]**254**	-17.95	67%
2	^{n}BuLi	[a]**259**	-23.43	76%
3	^{s}BuLi	N/A	N/A	Decomposition
4	^{t}BuLi	N/A	N/A	Decomposition
5	Me-Li	[b]**261**	-33.95	32%
6	LDA	N/A	N/A	Decomposition
7	*ortho*-tolyl	[b]**260**	-19.65	29%

a) synthesised using the 'one pot' methodology. b) synthesised using a stepwise addition of nucleophile

Table 9. Synthesis of P-chiral ligands.

In runs **5** and **7,** the yields of the desired phosphines are relatively low when compared to runs **1** and **2**. At first, this was put down to the decomposition of the starting organolithium reagent but even when new bottles of regents were used with dry solvents, and under strictly anhydrous conditions the yield still did not increase. This shows that butyllithium exhibits a greater level of nucleophilicity, therefore, reacting with intermediate **256** before the other organolithium reagent. The corresponding Grignard reagents were formed but this did not improve the yield.

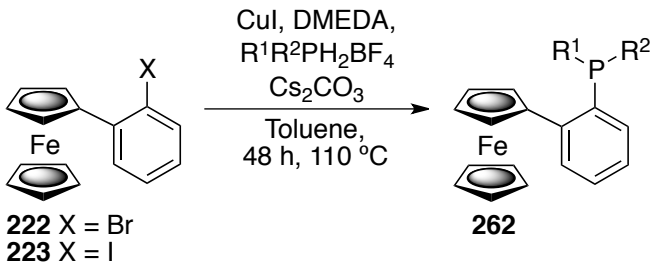
In runs **4** and **6** *tert*-butyllithium and lithium diisopropyl amine were used respectively to form a *tert*-butyl substituted phosphine and a novel diisopropyl amine substituted

phosphine. The lack of reaction and decomposition of starting material suggested that the increase in steric bulk of both nucleophiles slowed the rate of attack and their increased basicity led to decomposition of the starting material. Finally, *sec*-butyllithium was employed for run **3**. The addition of this particular organometallic reagent adds another level of complexity to the synthesis of the intended phosphine. The extra chiral centre alpha to phosphorous may lead to further complication in subsequent palladation reactions. The success of this reaction was of great interest but unfortunately no addition occurred and no new ^{31}P signals could be seen in the NMR spectrum.

14.2 - Attempted Catalytic Synthesis of Novel P-Chiral Phosphines.

The above-mentioned mode of synthesis does give rise to a new library of P-chiral phosphine ligands but the method is somewhat limited. It was key to devise another efficient, high yielding and dynamic protocol in order to synthesise such ligands. A cross coupling methodology was implemented, the first of which is a variation of a Ullman type phosphine-borate, copper mediated cross-coupling. Venkataraman *et al.* reported a range of copper catalysed cross-coupling reactions for the formation of unsymmetrical phosphines. [186]

These methods have demonstrated increased functional group tolerance and improvement over the traditional Ullmann-type reaction conditions. In addition, there exists an economic attractiveness to the development of copper-based methods, since they are the methods of choice for large and industrial scale reactions. As mentioned in the publication by Venkataraman, bromo-substituted aryl groups were not good candidates for this reaction, therefore iodophenylferrocene was employed in place of the more widely used bromophenylferrocene (**Scheme 73**, **Table 10**).

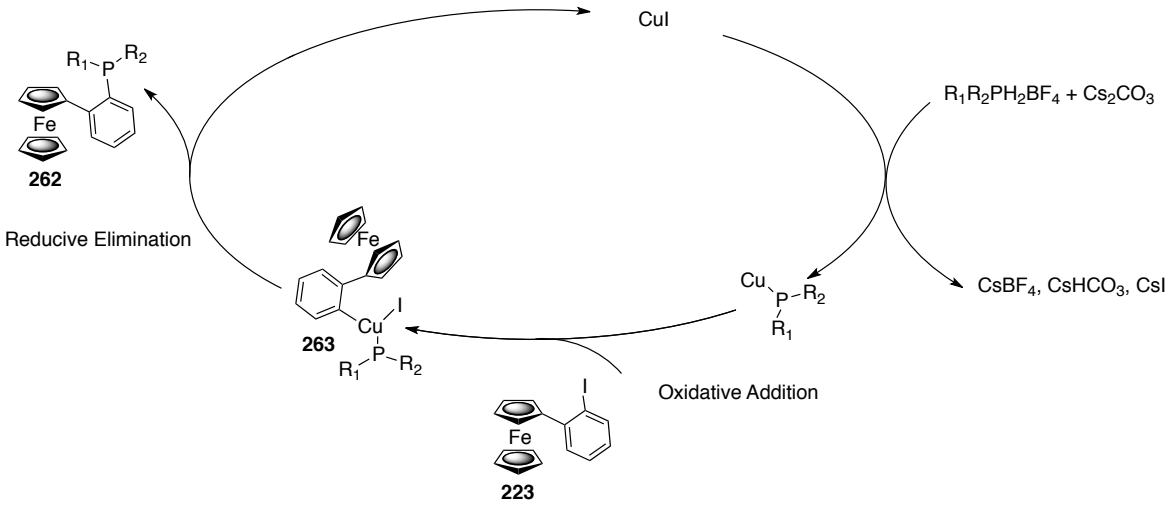


Scheme 73. Attempted copper mediated catalytic synthesis of P-chiral phosphines.

Run	Halogen (X)	Catalyst	Ligand	Solvent	Time	Temp	Base (5 equiv)	R'R"PH_2BF_4 (1.88 equiv)	Yield
1	Br	CuI 12.5 mol%	DMEDA 20 mol%	Toluene	27 h	110 °C	Cs_2CO_3	$(Cy)_2PH_2BF_4$	0
2	I	CuI 12.5 mol%	DMEDA 20 mol%	Toluene	36 h	110 °C	Cs_2CO_3	$(Cy)_2PH_2BF_4$	11%
3	I	CuI 20 mol%	DMEDA 100 mol %	Toluene	48 h	110 °C	Cs_2CO_3	*tert*-$BuPhPH_2BF_4$	23%
4	I	CuI 20 mol%	DMEDA 80 mol %	Toluene	72 h	110 °C	Cs_2CO_3	*tert*-$BuPhPH_2BF_4$	10 %

Table 10. Attempted copper mediated catalytic synthesis of P-chiral phosphines

In all of the above reactions, the base which was used was Cs_2CO_3, as this is the most active in the work carried out by Venkataraman and Buchwald *et al.*[187] In both papers a phosphine is used but as shown in the table above a phosphine tetrafluoroborate salt is used. This protects the phosphine from oxidation and simplifies the storage and manipulation of the compound. This will undergo an *in situ* deprotonation in order to enter the copper mediated catalytic cycle (**Scheme 74**).



Scheme 74. Catalytic cycle of the Ullmann cross-coupling

In run **1**, bromophenyl ferrocene (**222**) was used with the coupling partner dicyclohexylphosphonium tetrafluoroborate. The reason for this was that if the reaction

was successful it was possible to identify the compound from known ^{31}P NMR data. Under conditions previously used by Buchwald, there was no sign of the presence of product, only starting material and a small quantity of reduced phenyl ferrocene. The unreacted bromophenylferrocene shows that the catalytic cycle is stopping at the first hurdle, the compound is not undergoing oxidative addition with CuP(R_1R_2). The aryl halide was changed to the more active iodophenylferrocene (**run 2**) and under the same conditions 11% of the product was observed with many more new ^{31}P NMR peaks indicating several by-products. The formation of the product was confirmed by ^{31}P NMR signal at -12.8 ppm which showed the reaction was working, and manipulation in the conditions may afford the desired compound in greater yield. It is also known that the coupling of dialkylphosphines is more challenging when compared to diaryl counterparts.

The coupling partner was then changed to *tert*-butylphenylphosphonium tetrafluoroborate (**run 3**). As seen in the table, the copper loading was increased to 20 mol% and the ligand increased to 1 equivalent. The change in conditions resulted in a yield of 23%, which is still not a suitable yield for the beginning of a ligand synthesis.

The ^{31}P NMR spectrum showed a singlet peak at 5.6 ppm and oxidation of this phosphine gave a signal at 43.3 ppm. The compounds corresponding to the peaks at -5.6, -14.2 and +47.3 could not be isolated. One of the main issues with this run is the formation of the reduced phenyl ferrocene. A longer reaction time was used (**run 4**) but this did not yield a better result.

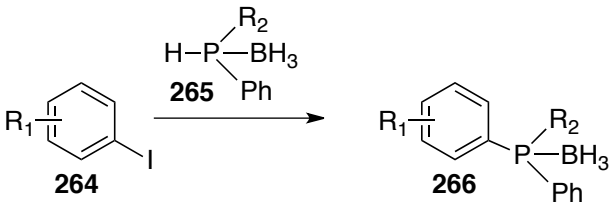
There are many reasons why this reaction did not proceed with the intended success. It is well documented that aryl iodides are far more sensitive to decomposition and reduction when compared to aryl bromides. Iodophenyl ferrocene was stored strictly under inert anhydrous conditions and away from any light to avoid this from happening. Buchwald *et al.* states that the reaction is sensitive to steric bulk in the aryl iodide and resulted in a large quantity of reduced arene, and our results are consistent with this statement. Increasing the ratio of phosphine to iodide did not yield a complete reaction.[187] The addition of chelating ligand *N,N*'-dimethylethylenediamine did not enhance the efficiency of the copper-catalysed phosphination.

The electronic and steric properties of the phosphines are important to the success of this reaction. Diarylphosphines are more active and it seems that the steric demands of the phosphines rather than the aryl halide determines the rate and efficacy of this

transformation. The only development that can be suggested is to use one equivalent of copper and ligand as there is a close relationship between the copper loading and the generation of the desired product.

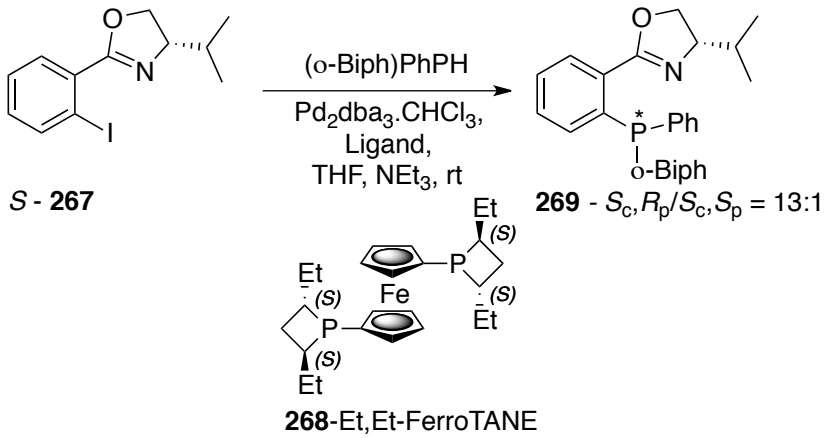
14.2 - Palladium Mediated Phosphine Borane Coupling.

The formation of C-P bonds has been achieved by the palladium-catalysed reaction of secondary phosphine oxides with aryl triflates. If the phosphine rather than the phosphine oxide is desired, either Ni or Pd catalysis is employed with R_2PH as the nucleophile.[188] Work by Imamoto *et al.* established conditions for the catalytic synthesis of triarylphosphines-boranes (**Scheme 75**).[189]



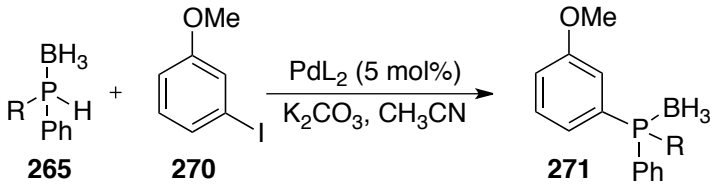
Scheme 75. Synthesis of borane protected triarylphosphines.

This work was further developed by Helmchen *et al.* in the asymmetric synthesis of phosphino oxazoline ligands.[190] Their synthesis was accomplished by nucleophilic or electrophilic substitutions with phosphides or phosphorus halides, respectively. Palladium mediated C-P bond formation was then employed to carry out the same functionalization (**Scheme 76**).



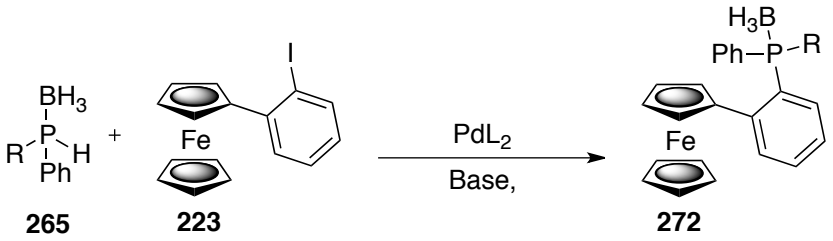
Scheme 76. Synthesis of PHOX ligands.

Gaumont *et al.* have been involved in C-P bond forming reactions by using either the hydrophosphination or metal catalysed cross-coupling reactions. In the latter case, an examination of the catalytic cycle of palladium mediated cross-coupling reactions between aryl iodides and diphenylphosphine – borane has been explored.[191] This work has now progressed to an enantioselective version of this reaction using simple unhindered racemic secondary phosphine-boranes and a range of chiral catalysts (**Scheme 77**).



Scheme 77. Palladium mediated coupling of phosphine-boranes.

This body of work, linked to the aforementioned copper mediated C-P formation, is a very efficient route to novel P-chiral ferrocenyl ligands. A generic protocol was devised and formation of the desired synthetic targets were attempted with the manipulation of certain conditions and reaction parameters (**Scheme 78**, **Table 11**).



Scheme 78. Palladium mediated P-chiral phosphine synthesis.

Run	Catalyst	Ligand	Base	Time	Solvent	Temperature	R'R''PHBH$_3$	Yield
1	Pd(OAc)$_2$ 5 mol%	(±)-BINAP 10 mol%	K_2CO_3	24 h	MeCN	60 °C	*tert*-BuPhPHBH$_3$	10%
2	Pd(OAc)$_2$ 5 mol%	(±)-BINAP 10 mol%	K_2CO_3	24 h	MeCN	60 °C	MePhPHBH$_3$	0
3	Pd(OAc)$_2$ 5 mol%	(±)-BINAP 10 mol%	K_2CO_3	36 h	Toluene	110 °C	*tert*-BuPhPHBH$_3$	9%
4	Pd(OAc)$_2$ 5 mol%	Autocat* 10 mol%	K_2CO_3	36 h	Toluene	110 °C	*tert*-BuPhPHBH$_3$	13%
5	Pddppf.CH_2Cl_2 10 mol%	N/A	Cs_2CO_3	48 h	Toluene	110 °C	*tert*-BuPhPHBH$_3$	8%
6	Pddppf.CH_2Cl_2 10 mol%	N/A	K_2CO_3	48 h	Toluene	110 °C	*tert*-BuPhPHBH$_3$	13%
7	Pd(OAc)$_2$ 10 mol%	Dppf 20 mol%	Cs_2CO_3	48 h	Toluene	110 °C	*tert*-BuPhPHBH$_3$	6%
8	Pd(OAc)$_2$ 10 mol%	Dppf 20 mol%	K_2CO_3	48 h	Toluene	110 °C	*tert*-BuPhPHBH$_3$	11%
9	Pd(OAc)$_2$ 10 mol%	Autocat* 10 mol%	Cs_2CO_3	48 h	Toluene	110 °C	*tert*-BuPhPHBH$_3$	7%

Table 11. Palladium mediated P-chiral phosphine synthesis

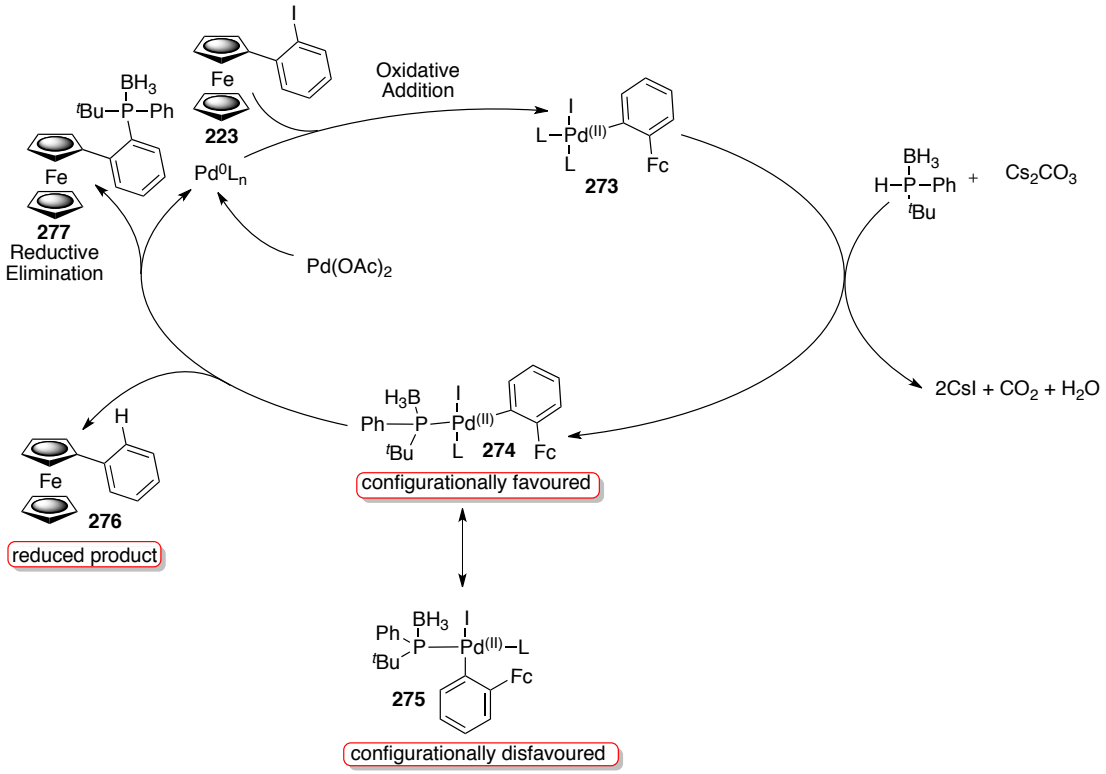
The modes of analysis for these reactions mirrored that of the copper mediated coupling and the intended synthetic target was the *tert*-butylphenyl-substituted phosphine **277**. Taking into consideration of the steric bulk of iodophenylferrocene, in **run 1**, BINAP was combined with Pd(OAc)$_2$ along with potassium carbonate, in acetonitrile at 60 °C for 24 hours. As stated in the paper by Gaumont,[191] the rate-determining step was the reductive elimination; therefore, a ligand with a greater bite angle was selected, which would favor this step. Thus, the application of BINAP to this reaction along with Pd(OAc)$_2$ which was used over Pd_2dba_3 due to the formation of a side product. After purification only 10% of the desired product was isolated and the other major products were starting material and reduced phenylferrocene. To ensure the coupling of relatively bulky sterically hindered

phosphine borane was not the issue, the phosphine borane complex was changed to methylphenylphosphine-borane and under the same conditions did not yield any product. In **run 3**, the solvent was changed to toluene and the time of reaction increased to 36 hours but this only gave an unsatisfactory yield of 9%. To rule out any issues of ligand ligation and formation of an *in situ* Pd^0 species, an auto catalyst methodology was implemented. This is where the phosphine-borane complex is added to palladium acetate in toluene and stirred forming a Pd^0 species with the coupling partner, but this did not improve the yield. A range of palladium sources, bases and ligands were used to increase the yield but no change gave an increased yield.

There are many reasons why this reaction did not work in high yield. For simplicity, it can be put down to the steric bulk of the phenylferrocenyl group coupling with the relatively sterically hindered *tert*-butylphenyl phosphineborane complex, or the issues could be more complex than first thought.

Work by Stawinski *et al.* highlights some key aspects of C-P bond forming reactions such as the identity of the palladium ligand used, and identifying certain areas of the catalytic cycle which can be seen as problematic. Their paper suggests that the palladium source is an integral part of this reaction and the most commonly used palladium sources are $Pd(PPh_3)_4$, Pd_2dba_3, $Pd(OAc)_2$ and $PdCl_2$. The former two are preformed Pd^0 species, whereas the others are palladium(II) salts, which must be reduced prior to entering a catalytic cycle. They came to the conclusion that $Pd(OAc)_2$ is the most active form of palladium in these types of reactions.

Stawinski *et al.* also carried out a body of work which detailed the mechanism of key steps within the C-P bond forming catalytic cycle. Their work focused in the coupling of H-phosphonate diesters, and many of the aspects and theory can be applied to the coupling of phosphine-boranes with aryl halides.



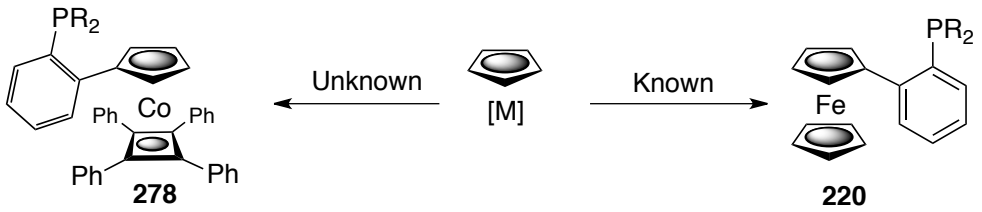
Scheme 79. Catalytic cycle of C-P bond forming reaction (Fc = ferrocene).

Most mechanistic studies have focused on oxidative addition, a common step for a variety of important heteroatom cross coupling reactions. The reductive elimination step in C-P bond forming reactions has received less attention.[192,193] It is assumed that, similarly to the palladium-catalysed C-C bond formation, that *cis* arrangement of the eliminated groups, secured by bidentate ligands, facilitates carbon-phosphorus bond formation. This is the key issue with the above-mentioned body of work as it is theorised that both the iodophenylferrocene and *tert*-butylphenyl phosphine borane are adding onto the palladium co-ordination sphere but are unable to be rearranged into a *cis* configuration in order to undergo the reductive elimination (**Scheme 79**). This is

consolidated by the formation of phenylferrocene and palladium-phosphine-borane complex, which are identifiable by ^{31}P NMR.

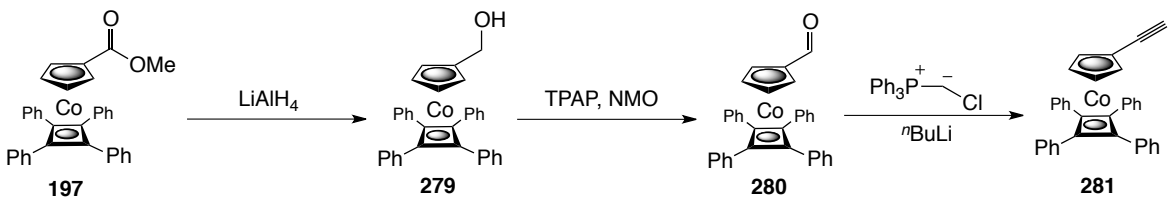
14.3 - Synthesis of Cobalt Sandwich Complex Based Phosphine Ligands.

The synthesis of ferrocene based phosphine ligands has been well documented but synthesis with a cobalt-based analogue is still seen as a synthetic challenge (**Scheme 80**).



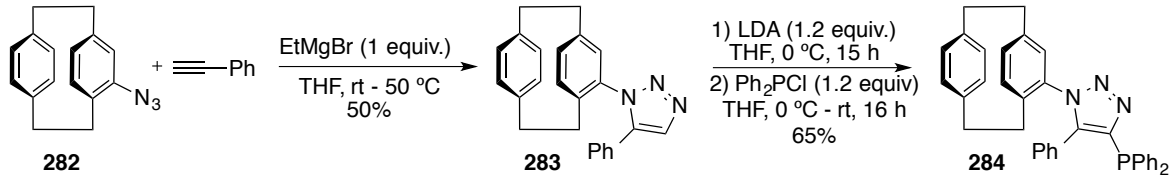
Scheme 80. Generic cobalt sandwich complex to mirror known phosphinophenyl ferrocene ligands.

The highly deactivated cyclopentadienyl ring in the cobalt sandwich complex makes it very difficult to functionalise. Superbase lithiation and toxic mercury chemistry are but a few of the methods of derivatisation but these only afford the desired compounds in very low yield. Richards *et al.* has devised a methodology of functionalising other cobalt sandwich complex derivatives starting from methyl ester **197**, which can be synthesised from $CoCl(PPh_3)_3$, dimethylcarbonate and sodium cyclopentadiene. This is the starting block for the majority of cobalt based sandwich complexes, and in this case reduction of the ester to alcohol **279**, oxidation with catalytic tetrapropylammonium perruthenate and *N*-methylmorpholine-*N*-oxide cleanly afforded aldehyde **280**. This was then transformed to alkyne **281** *via* the implementation of a Corey-Fuchs methodology (**Scheme 81**).



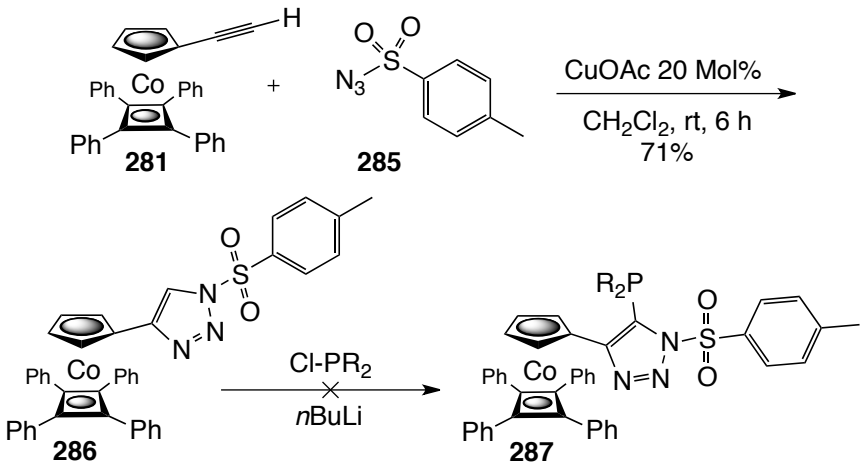
Scheme 81. Synthesis of compound 281.

In work by Bräse *et al.* a lithiation was carried out on paracyclophane tethered triazole and quenched with a chloro-phosphine to afford a new range of paracyclophane based phosphine ligands such as **284** (**Scheme 82**).[194]



Scheme 82. Synthesis of clickphos type ligand.

This can also be applied to **281** where it was reacted with tosyl azide at room temperature in dichloromethane to to afford triazole **286** and with the aim of generating **287** (**Scheme 83**).



Scheme 83. Attempted synthesis of 264.

Addition of LDA or butyllithium with diphenyl or dicyclohexyl chlorophosphine led to decomposition. This work was not investigated any further as the formation of alkyne **259** was very time consuming and further derivatisation of the phosphine ligand could cause further issues. If the phosphine were to be palladated there may be competing reactions between the phosphine and triazole nitrogen.

14.4 - Conclusion

Phosphines **224**, and **225** have already been reported within our lab and to add to this known methodology phosphines **227** and **226** have been synthesised (**Figure 27**).[166]

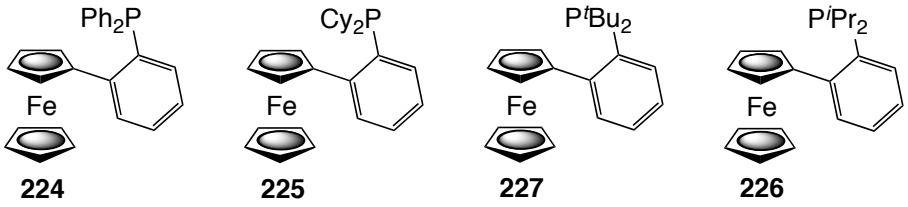


Figure 27. Synthesised symmetrical phosphine ligands.

The application of $PhPCl_2$ has allowed the synthesis of new chiral racemic and achiral phosphine ligands, giving the possibility for the synthesis of many novel phosphine ligands (**Figure 28**).

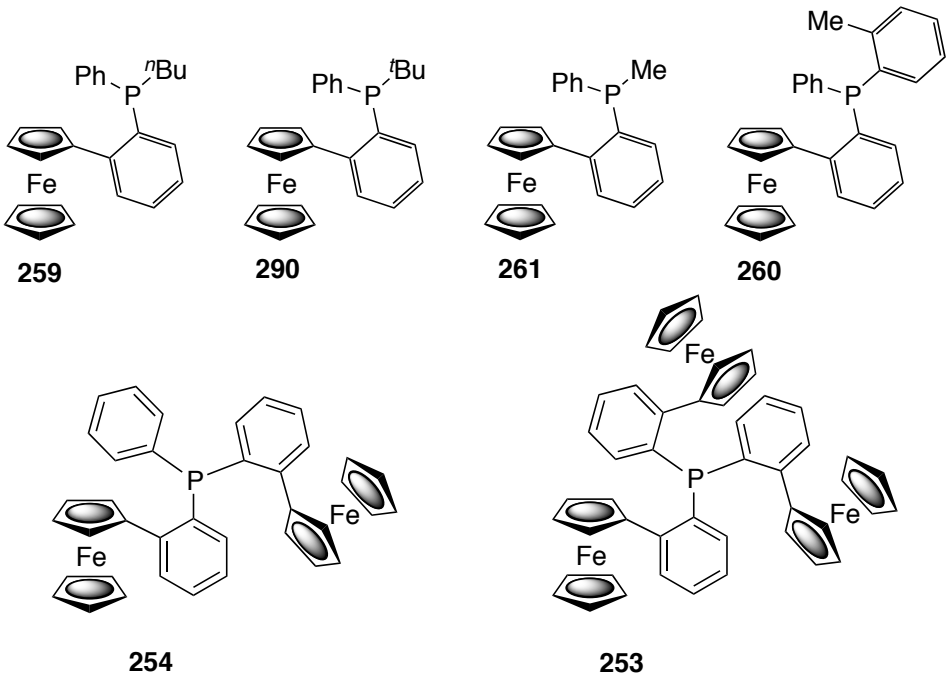


Figure 28. Synthesis of novel P-Chiral phosphine ligands.

The synthesis of **253**, a bulky phosphine ligand holds the potential for this to be functionalised to give a novel chiral ligand, which could possibly hold similar properties to the aforementioned **TomPhos**. The advantage of **KetPhos** (**253**) is that it has a very short

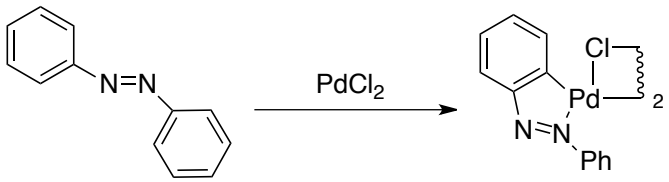
synthesis from relatively cheap and widely available starting materials. Applications of **Ketphos** may lead to its use as a frustrated lewis pair with a range of boron containing reagents.

Chapter 3

Synthesis and Application of Ferrocenyl-Phosphine Palladacycles.

15.0 – Introduction to the Synthesis of Palladacycles.

Palladacycles are a class of organometallic complexes in which the palladium atom is contained within a ring, and these have proven to be efficient catalyst precursors for many C-C and C-heteroatom bond-forming reactions. The first palladacycle was reported in 1965 when A. C. Cope published the carbopalladation of azobenzene with $PdCl_2$ to generate **292** (**Scheme 84**).[195]



291 **292**

Scheme 84. The first reported palladation of azobenzene by Cope.

Since this discovery, palladacyclic catalysts have been successfully employed as pre-catalyst and intermediates in the Heck, Suzuki and Buchwald – Hartwig aminations as well as many other palladium mediated cross-coupling reactions.[196, 197] The use of palladacycles as catalyst precursors is relatively recent, with the first application being reported in 1980 with the hydrogenation of C=C bonds by cyclopalladated triphenyl phosphite, followed by the use of cyclopalladated azobenzene, hydrazobenzene or *N,N*-dimethylbenzylamine in the selective reduction of aromatic compounds, nitro-alkenes, nitriles, alkynes, alkenes and aromatic carbonyl compounds.[198]

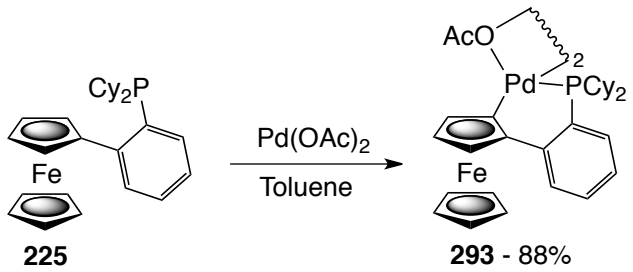
It is generally accepted that in the Suzuki cross-coupling reactions, palladacycles are reduced to $Pd^{(0)}$, which is the entry point into the catalytic cycle. Hartwig *et al.* have suggested that $Pd^{(0)}$ is the active metal for these reactions, outlining two possible

mechanisms for the reduction of palladium on palladacycles, both suggesting the destruction of the cycle.[199] However, there is still much speculation over the mechanism for these reactions. Work published by Shaw suggests other pathways that preserve the palladacycle, as does a recent paper by Buchwald.[200,201,202]

Despite uncertainty over how palladacycles act, palladacycle chemistry is an exciting area of research and they are omnipresent in catalytic transformations. Palladacyclic intermediates play an important role in cascade transformations leading to complex molecular architectures. [203] **Chapter 2** has outlined the synthesis and potential applications of palladacycles, including work previously carried out in the group on the synthesis of ferrocene-based phospapalladacycles. In this work this is extended to a new class of P-chiral phosphines. An attempt to simultaneously control the diastereoselectivity and enantioselectivity was attempted. Preliminary test on their catalytic activity has also been investigating.

15.1 - Synthesis of Ferrocene Based Phosphopalladacycles.

Repeated synthesis of ferrocene-based phosphopalladacycles afforded the diphenyl- and dicyclohexyl- ferrocene-derived phosphine ligands (**Scheme 85**).[166]



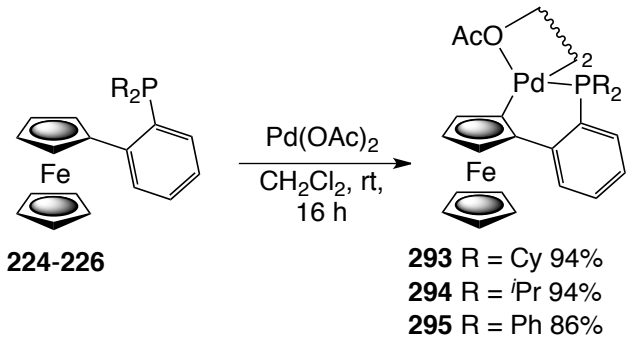
225 **293** - 88%

Scheme 85. Synthesis of a dicyclohexylphosphine palladacycles.

The dicyclohexyl derivative **225** was added to toluene at room temperature with 1 equivalent of $Pd(OAc)_2$ and afforded the corresponding palladacycle in 88% yield. Analysis of the ^{31}P NMR showed the appearance of a new peak at 45.1 ppm, indicating the ligation of the phosphine to the metal, with remaining starting material at -11.7 ppm (**Scheme 85**). Analysis of the ^{1}H NMR did not show the classic 2-2-5 pattern but 1-1-1-5 where one

cyclopentadienyl proton had been replaced by a carbon-palladium bond. Proof of formation of the product was further consolidated by appearance of the methyl of the acetate ligand at 2.16 ppm. The ^{1}H NMR spectrum clearly shows the emergence of a new ferrocene-containing compound and splitting and shifting of the cyclopentadienyl protons, which also indicate the insertion of palladium onto the cyclopentadienyl ring. The formation of a side product in this reaction led to a change in solvent and this will be discussed further in **Section 15.2**.

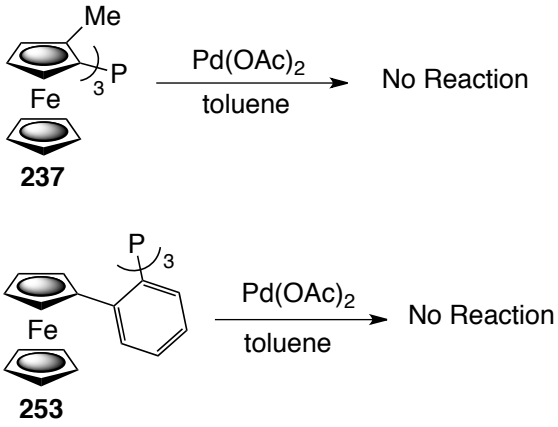
The same protocol led to the synthesis of diphenyl and diisopropyl substituted phosphopalladacycles in high yield (**Scheme 86**).



Scheme 86. Synthesis of diisopropyl and diphenylphosphine derived phosphopalladacycles

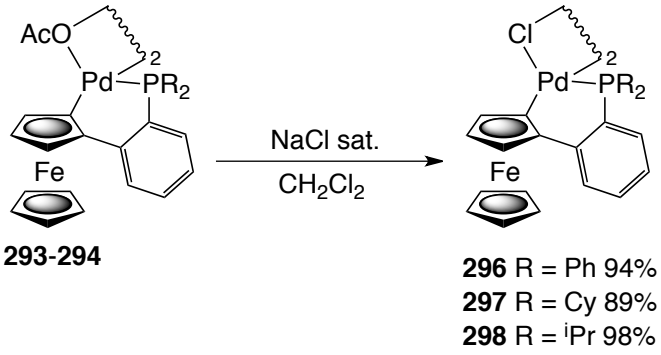
Unfortunately **227** could not be palladated due to its extreme sensitivity to oxygen and only the phosphine oxide could be isolated.

Previous members from our group had attempted the palladation of **TomPhos** (**237**) but this did not yield a positive result as upon heating with palladium acetate, only palladium black was observed and one new peak in the crude ^{31}P NMR specra, which did not correspond to a palladacycle. The same conditions were applied to **KetPhos** (**253**) and a similar outcome was observed. Addition of palladium acetate did not yield a palladacycle (**Scheme 87**).



Scheme 87. Attempted palladation of KetPhos.

The acetate-bridged dimers mentioned earlier can be cleanly converted into a chloride-bridged dimer by stirring in brine and removal of solvent *in vacuo*. The transformation to the chloride bridged dimer brought to light novel characteristics of palladacycle dimers (**Scheme 88**).



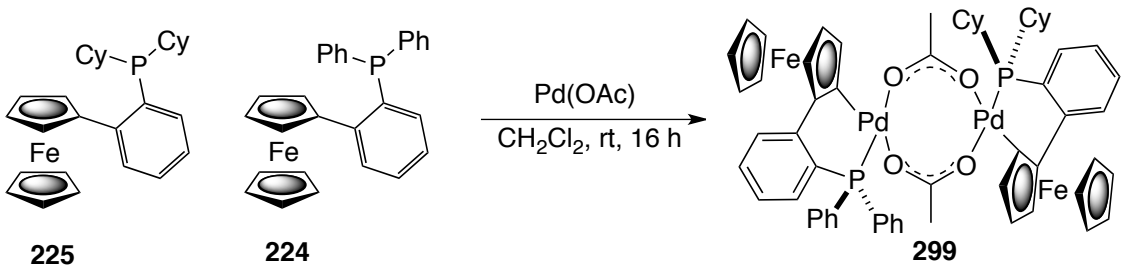
Scheme 88. Facile ligand exchange to a chloride bridged dimer.

Dimeric planar chiral chloride-bridged palladacycles have the potential to exist as a mixture of isomers due the element of planar chirality, and the *cis* or *trans* orientation of the two bidentate ligands about the Pd_2Cl_2 core. A racemic complex could give rise to $_pR^*/_pR^*$-*trans*, $_pR^*/_pR^*$-*cis*, $_pR^*/_pS^*$-*trans* and $_pR^*/_pS^*$-*cis* isomers. Previous work by Richards *et al.* outlined the enantioselective synthesis of the diphenyl and dicyclohexyl substituted palladacycles, and it was observed to be a mixture of *cis* and *trans* isomers with respect to the $Pd_2(\mu\text{-}Cl)_2$ core.[171] Identification of four signals in the ^{31}P NMR spectra of the racemic chloride-bridged dimers can be accredited to the additional stereochemically mixed $_pR^*/_pS^*$-*trans* and $_pR^*/_pS^*$-*cis* isomers. In the acetate analogue only one sharp singlet can be seen in the ^{31}P NMR indicating a single species, which is

consolidated by ^{1}H and ^{13}C NMR data. There are three possible explanations for the simplicity of the ^{31}P spectra of the acetate bridged ligands compared to the chloride-bridged ligands:

I. Signal coincidence for each isomer, which would appear unlikely as this would have to be the case for every compound formed (**293-295**).
II. Complete chirality self-recognition in a *cis* or *trans* acetate bridged dimer, where little self-recognition is found in the corresponding chloride-bridged dimers.
III. Finally, and the most likely of reasons, is that in solution the dimeric acetate bridged palladacycles are in fact monomeric. Dimer-monomer interconversion has been previously quoted with weakly coordinating acetate ligands in other known phosphopalladacycles. [204]

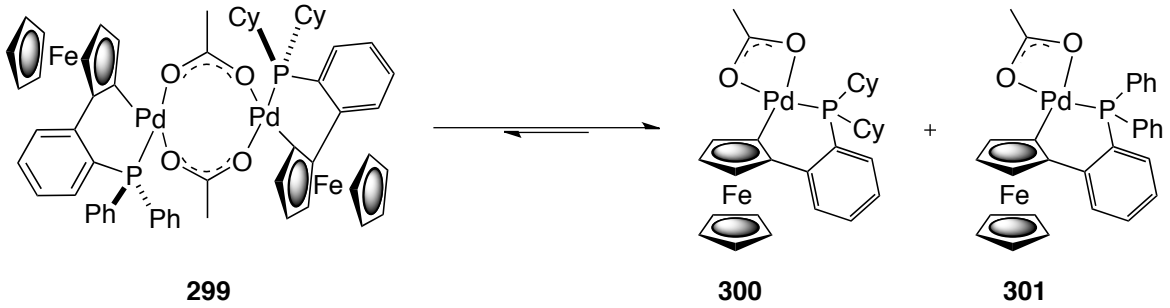
To further prove the monomeric nature of acetate-bridged phosphopalladacycles in solution, the formation of a mixed palladacycle was attempted. Ligands **224** and **225** (0.5 equivalents) with palladium acetate (1 equivalent) and subjected to previously reported conditions (**Scheme 89**).



Scheme 89. Synthesis of mixed palladacycle 299.

^{31}P NMR spectroscopy showed the formation of both the **293** and **295** and the vastly different rates of reaction of **224** and **225**. It was hypothesised that a mixed palladacycle would form if a new ^{31}P NMR peak would be seen. In practice this was not the case and this experiment was repeated with isopropyl ligand **226** and cyclohexyl ligand due to their similar rates of reaction, but this did not give a new ^{31}P signal in the resultant NMR

spectrum. The lack of formation of the mixed palladacycle can be ascribed to the formation of a monomeric species in solution. In the solid state, the complex exists as a dimer as confirmed by X-ray data, but in solution this is in equilibrium with a monomeric acetate bridged palladacycle (**Scheme 90**).

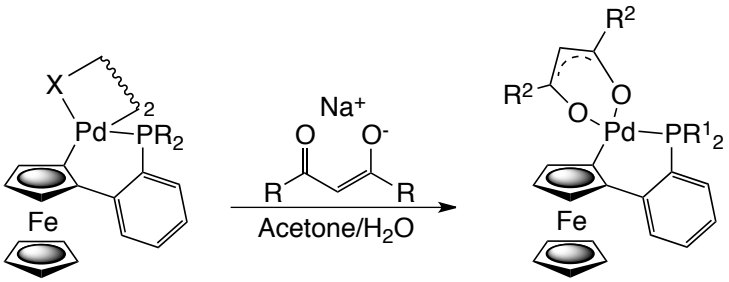


299 **300** **301**

Scheme 90. Hypothesised monomeric palladacycle formation.

In addition, the solution ($CHCl_3$) IR spectrum of the cyclohexyl substituted palladacycle (**293**) gave ν(CO) signals at 1486 and 1448 cm^{-1}, consistent with a bidentate acetate ligand in a monomeric structure.[205] These values contrast to the corresponding signals observed at 1571 and 1405 cm^{-1} in the solid state (ATR) IR spectrum, consistent with an acetate-bridged dimeric structure. All planar chiral acetate-bridged palladacycles for which the X-ray crystal structure has been determined are dimers, specifically *trans*-dimers.[206]

For ease of characterisation and purification the chloride and acetate bridged dimers can be transformed into acetylacetonate or hexafluoroacetylacetonate monomers (**Scheme 91**).



X = OAc, **293-295**
X = Cl, **296-298**

$R_2 = CF_3$, $R_2 = CH_3$,
R_1 = Ph, **302** R_1 = Ph, **305**
R_1 = Cy, **303** R_1 = Cy, **306**
R_1 = ^{i}Pr, **304** R_1 = ^{i}Pr, **307**

Scheme 91. Ligand exchange to monomeric acac/hfacac derivatives.

The acetate or the chloride-bridged dimers can be transformed to their corresponding monomer *via* addition of sodium hexafluoroacetylacetonate or sodium acetylacetonate in a solution of acetone and water. The crude product is then filtered through silica to yield an air stable solid. Again, these compounds are easily identified with ^{1}H NMR, as the acac proton is seen at 6-6.5 ppm depending on the substituent attached to the phosphorus. The acac adducts are crystalline and can be submitted for X-ray analysis. The acac substituted diisopropyl phosphopalladacycles obtained in this work, show that the 6 membered palladacycle ring contains a near tetrahedral phosphorus atom with *pseudo*-equatorial and *pseudo*-axial isopropyl or cyclohexyl substituents (**Figure 29**). The orientation of the large *pseudo*-axial substituent away from the ferrocene twists the palladium containing square-plane towards the metallocene, as revealed by the X-ray structure of (**307**) where O(31)-Pd-C1-C(5) is calculated to have an angle of -35.0^{o}. The palladium-oxygen bond length is [O(32)-Pd = 2.093 Å] indicating that the *trans* influence of the anionic carbon ligand of the palladacycle is similar to the dialkyl phosphorus component. This is in contrast to the significantly longer Pd-O bond *trans* to carbon, indicative of a larger *trans* influence, in nitrogen based planar chiral palladacycles containing a hexafluoro acetylacetonate ligand (**Figure 29**).

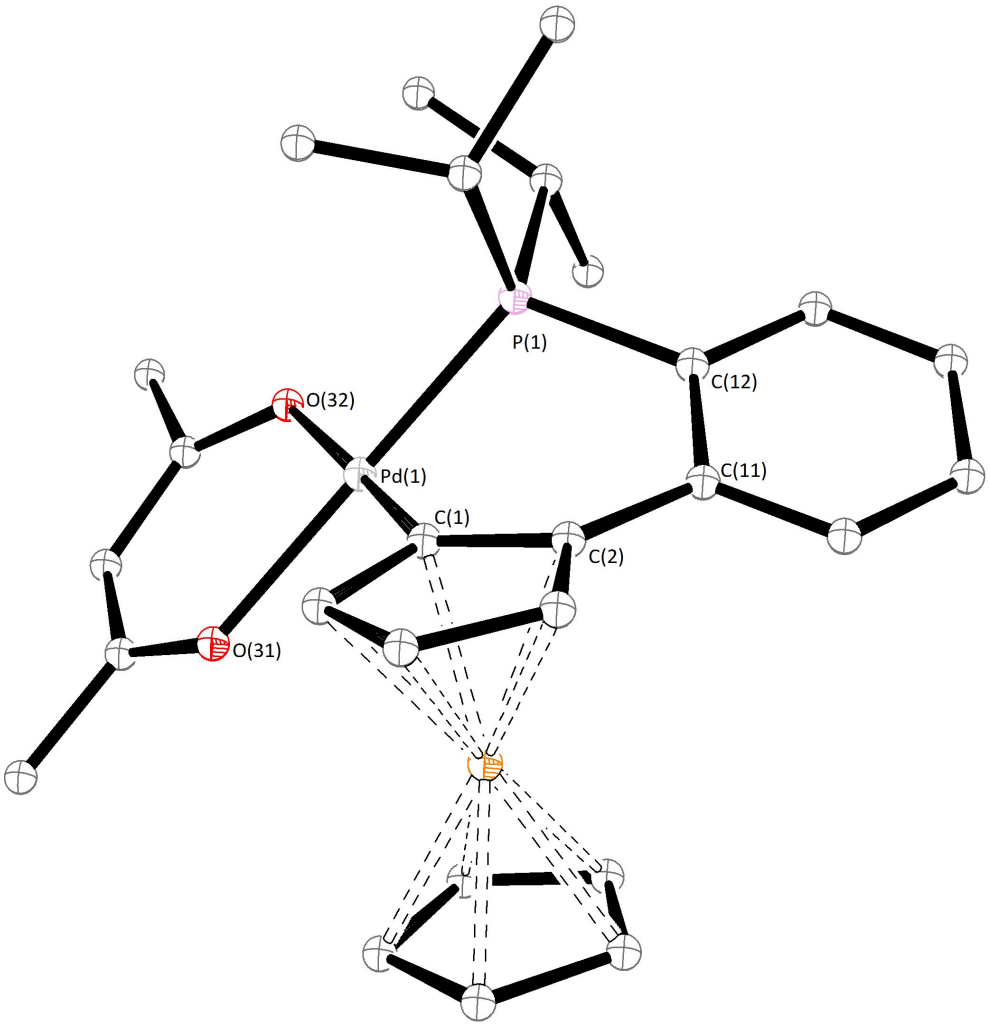


Figure 29. ORTEP representation of compound 307. Hydrogen atoms, solvent molecules and minor disordered components have been removed for clarity. Displacement ellipsoids are drawn at 50% probability level. Principal bond lengths [Å] include: Pd(1)-C(1) 1.988(6), Pd(1)-P(1) 2.2070(16), Pd(1)-O(31) 2.089(5), Pd(1)-O(32) 2.093(5). Principal angles [°] include: O(31)-Pd(1)-O(32) 89.07(19), C(1)-Pd(1)-P(1) 81.75(19). Principal torsion angles [°] include: O(31)-Pd(1)-C(1)-C(5) -35.0(5), C(3)-C(2)-C(11)-C(16) 25.9(10).

Finally, a notable feature of the ^{1}H NMR spectra of the diisopropylphosphino palladacycles **294**, **304** and **307** are the four sets of double doublets resulting from the four diastereotopic methyl groups in each complex (the spectrum of chloride-bridged palladacycle **298** is complicated further by this being a mixture of isomers). In all of the planar chiral palladacycles the two R substituents are diastereotopic, and the two methyl groups of an isopropyl group are also diastereotopic resulting in four clearly differentiated sets of signals displaying ^{3}JH-H and ^{3}JP-H coupling. The ^{1}H NMR spectrum of

the precursor phosphine **226** contains just two sets of double doublets as previously discussed, and a similar differentiation is also observed in the ^{13}C NMR spectra. These differences provide a convenient indicator for the presence of planar chirality, and as such are anticipated to be of use in aiding the identification of complexes derived from the phosphapalladacycles described. This property is also applicable to the cyclohexyl derivative, but the simplicity of the spectra derived from phosphine **226** is especially useful (**Figure 30**).

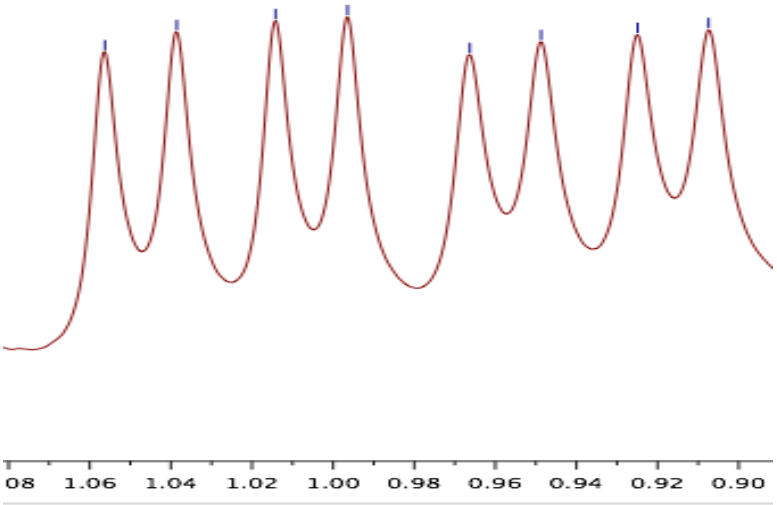


Figure 30. ^{1}H NMR of palladacycle 226

15.2 - Formation of an Unknown Compound.

The palladation reactions outlined in **Scheme 85** also resulted in the formation of a by-product. In the case of the dicyclohexyl ligand (**225**) the formation of this additional compound was very prevalent and a cause for concern. The issue only became apparent when an excess of palladium acetate was used. At higher metal to ligand ratios the expected palladacycle (**293**) was not observed but the precipitation of an orange solid occurred. Upon addition of another equivalent of the ligand the unknown complex reacted further and formed the corresponding palladacycle. This palladium-containing

compound proved to be difficult to characterise. **Figure 31** shows the ^{31}P NMR spectra where 2 equivalents of palladium acetate are added to both **224** and **225**.

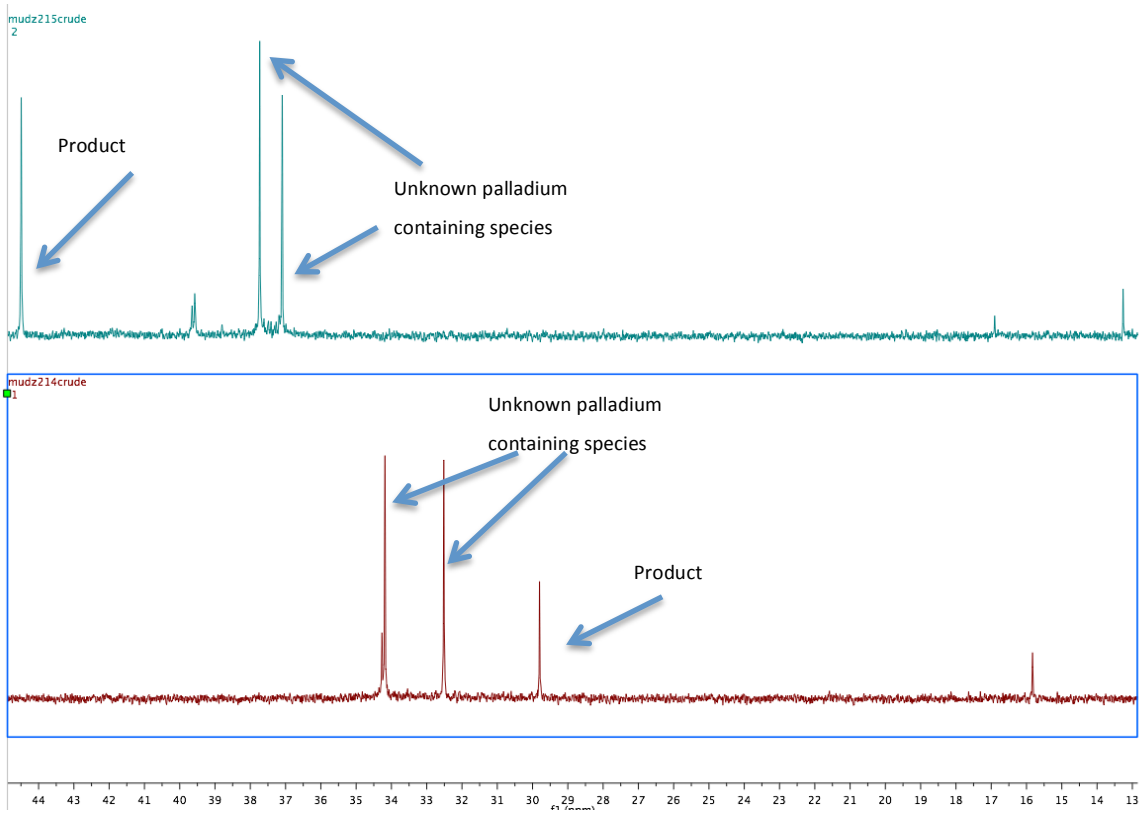
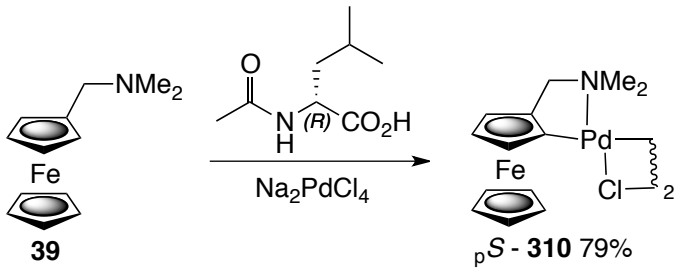


Figure 31. ^{31}P NMR of an 2:1 ratio $Pd(OAc)_2$ (bottom-PPh_2, top-PCy_2)

Palladacycles (**295**) and (**293**) appear on the ^{31}P NMR spectra at 29.7 ppm and 45.1 ppm respectively and it is clear to see the appearance of new peaks in both cases. It is hypothesised that when the reaction is carried out in toluene, a C-H activation occurs with the solvent, leading to a new palladium species, but without further work and isolation of the unknown intermediate it is difficult to give a definitive answer to the identity of the compound. Carrying out all palladations in dichloromethane at room temperature solved this problem and also supports the suggestion that the unknown compound is reacting with toluene.

15.3 - Synthesis of Enantioenriched Phosphopalladacycles.

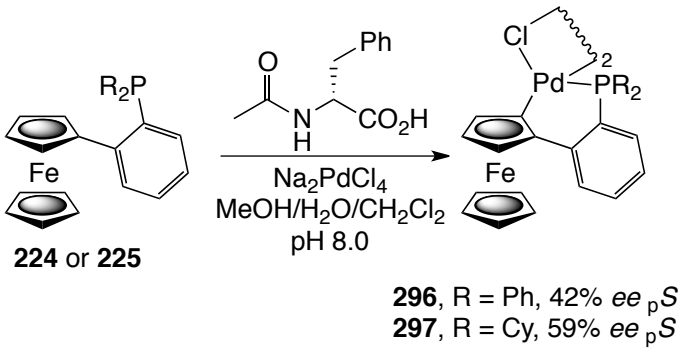
As mentioned earlier, the synthesis of racemic phosphopalladacycles has been documented. The next challenge was the synthesis of such palladacycles in their enantioenriched form. The majority of enantioenriched planar chiral palladacycles are synthesised by resolution or by the use of a chiral auxiliary to control a diastereoselective palladation. Examples of enantioselective palladations within the literature are rare, but in 1979 Sokolov *et al.* [207] described the reaction of dimethylaminomethylferrocene (**39**) with sodium tetrachloropalladate in the presence of one equivalent of *N*-acetylleucine, which resulted in the isolation of palladacycle **310** in 79% yield (**Scheme 92**).



Scheme 92. Original synthesis of a planar chiral palladacycles implemented by Sokolov *et al.*

There has been a recent emergence of interest in transition metal catalysed C-H activation and its applications to the synthesis of novel chiral metallocenes by enantioselective functionalisation. In order to synthesise enantioenriched phosphopalladacycles the above protocol has been applied previously in the group to a variety of ferrocenyl phosphine-based ligands. [166]

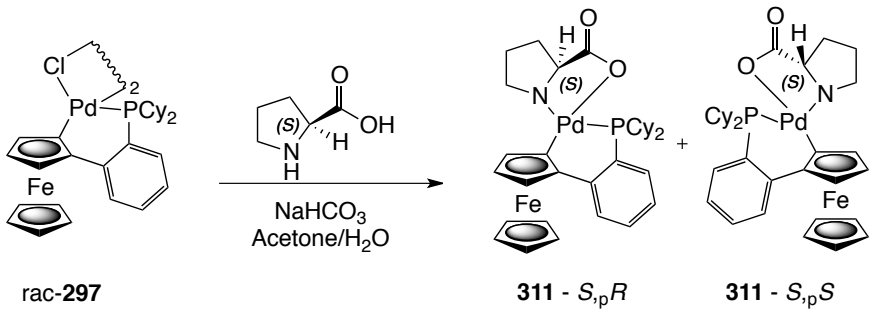
Prochiral phosphines were dissolved in a solution of methanol and dichloromethane. To this was added an aqueous solution of *N*-acetyl-phenylalanine, and sodium tetrachloropalladate and the pH of this solution was adjusted to 8 with a solution of sodium hydroxide. Richards *et al.* screened various *N*-protected ligands and the best results in terms of enantioselectivity and yield was with *N*-acetyl-phenylalanine (**Scheme 93**). [221]



Scheme 93. Amino acid mediated enantioselective palladation.

After manipulation of the conditions, the enantioselectivity of **297** was increased to 65% *ee* by adding two equivalents of the *N*-acetylphenyl alanine.

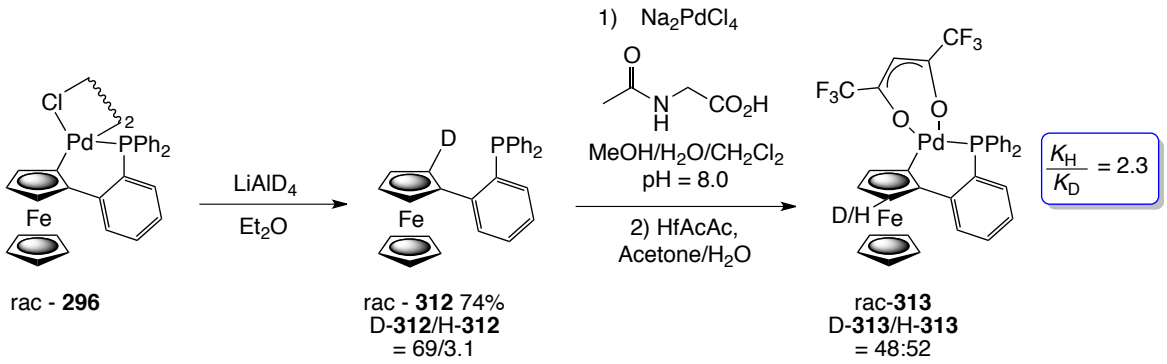
In the original Sokolov publication the enantioselectivity of the enantioenriched palladacycle ascertained from dimethylaminomethylferrocene was determined *via* polarimetry. The Richards group devised a more accurate method by reacting a racemic phosphine based ligand with (*S*)-proline that gives (*S*,$_p$*S*)-**311** and its diastereoisomer (*S*,$_p$*R*)-**311** with well separated methyl and cyclopentadienyl singlets in the resulting proton NMR (**Scheme 94**).



Scheme 94. Synthesis of proline derived diastereomers in order to calculate enantioselectivity.

The enantioselectivities observed for the palladation of **224** and **225**, and the requirement for a stoichiometric quantity of *N*-acyl protected amino acid ligand indicate that these reactions proceed through a palladium-carboxylate species in which the ligand is involved in the palladium-carbon bond forming step. An electrophilic aromatic substitution pathway has been postulated as the mechanism of palladation reactions on

related aryl substrates, and ferrocenyl substrates also undergo such reactions, for example, the Friedel Crafts acylation.

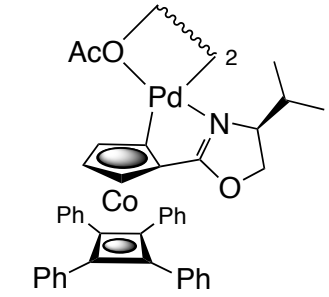


Scheme 95. Determination of intramolecular isotope effect of chiral carboxylate mediated enantioselective palladation reactions.

An alternative concerted metallation–deprotonation pathway has also been postulated. This has been used to describe the acceleration of palladation and other metallation reactions in the presence of carboxylate ligands. A number of palladium-catalysed direct arylation reactions have displayed intramolecular isotope effects (K_H/K_D) between 3.5 and 6.5.[208, 209] These values are inconsistent with an electrophilic aromatic substitution pathway for the introduction of palladium and point towards a concerted metallation deprotonation pathway (**Scheme 95**). To determine the intramolecular isotope effect of *N*-acetyl amino acid mediated palladations, racemic **296** was reacted with lithium aluminum deuteride, resulting in the isolation of **312** with 69% deuteride incorporation, as determined by ^{1}H NMR. Palladation in the prescence of N-acetylglycine followed by conversion to the hfacac monomer (**313**) and ^{1}H NMR analysis showed that 48% deuterium incorporation at the 3 position of the palladacycle. The calculated ration of 2.3 showed that the involvement of the C-H bond cleavage in the rate determining step, and the outcome is consistent with the participation of the carboxylate in the CMD pathway.

15.4 – Transcyclopalladation.

Another method for the synthesis of enantioenriched planar chiral phosphopalladacycles is to implement a transcyclopalladation protocol with the palladium transfer agent COP-OAc (**Figure 32**).



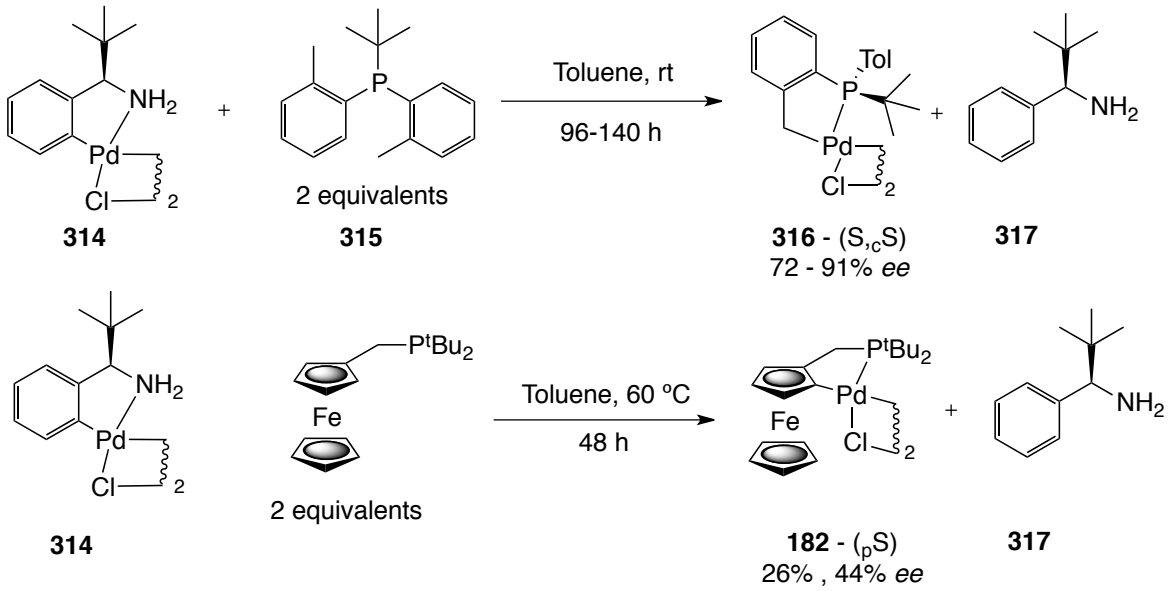
COP-OAc, $_{p}R,S$ - **200**

Figure 32. COP-OAc.

Transcyclometallations have been used to synthesise a range of enantiomerically-enriched metallocycles with a high conversion rate. Two main considerations are required when devising a successful transcyclopalladation methodology.[171] The first is that an aprotic medium is necessary for the retention of the starting homochiral palladacycle in the chelated state during C-H bond activation. When reactions are carried out in acetic acid the palladium is released into the reaction medium and cannot be classed as an intrinsic intermolecular palladium transfer reaction. Hence this is not strictly a transcyclopalladation. The second factor is the relative affinity of the hetero-atom to palladium. There must be a shift in the equilibrium for the palladium transfer to take place. For example the starting palladacycle must be chelated to nitrogen and the resulting palladacycle must contain a palladium-phosphorus bond due to the greater bond strength and affinity of palladium for phosphorous.

Dunina *et al.* recently reported the first asymmetric transcyclopalladation. [210] The reaction between *tert*-butyldi(*o*-tolyl)phosphine **315** and cyclopalladated (*R*)-α-*tert*-butylbenzylamine **314** yielded the optically active phosphopalladacycles **316** with good to excellent enantiomeric excesses and yields. Unfortunately, due to reactivity problems and

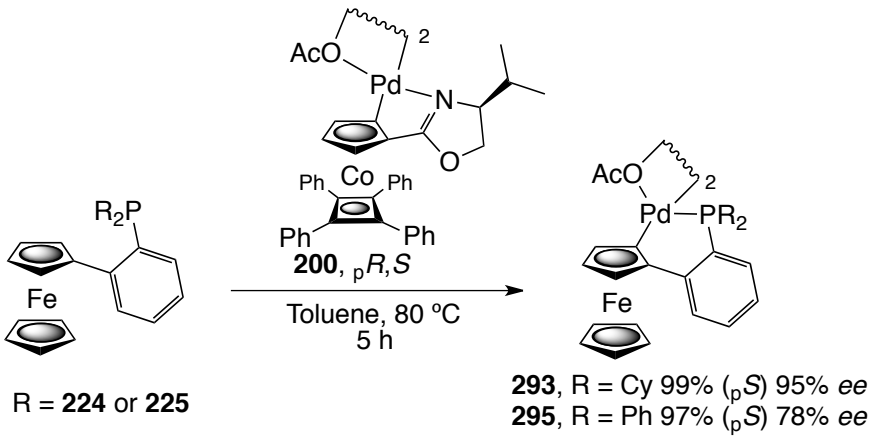
selectivity, they could not obtain similar results with di-*tert*-butylferrocenylmethylphosphine **182** as substrate (**Scheme 96**).



Scheme 96. Earliest example of an asymmetric Transcyclopalladation

15.5 - Application of COP-OAc (200) to Transcyclopalladation.

In view of the liability of ferrocene substrates **224** and **225** towards a palladation, and the high enantioselectivity exhibited by **200** in catalysis, Richards decided to explore the reaction between these metallocenes as a means of achieving highly enantioselective synthesis of planar chiral phosphopalladacycles (**Scheme 97**). [211,171]



Scheme 97. Transcyclopalladation with COP-OAc.

Phosphine **225** was heated to 80 °C with palladacycle **200** and monitored by ^{31}P NMR spectroscopy. Following conversion to the phosphopalladacycles (**293**), the free oxazoline and the chloride-bridged phosphopalladacycles were isolated *via* flash chromatography. In the case of the phosphopalladacycles, the ligand exchange is so facile that residual chloride found on silica gel transformed the palladacycle from acetate to chloride-bridged dimers.[171] Application of chloride bridged palladacycle **201** gave poor conversion but led to the isolation of a ferrocene-cobalt metallocene adduct, which corresponds to a related intermediate in the transcyclopalladation mechanism which is outlined in **Scheme 111** (**Figure 33**).[212]

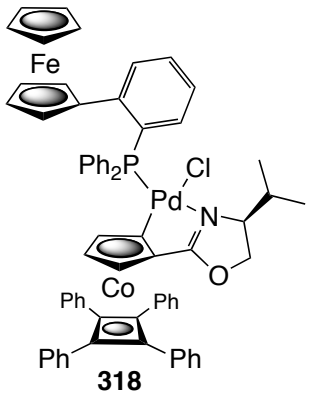
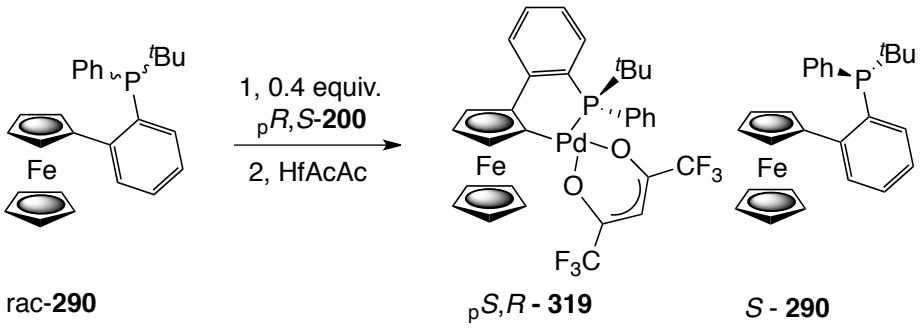


Figure 33. Ferrocene-cobalt metallocene adduct.

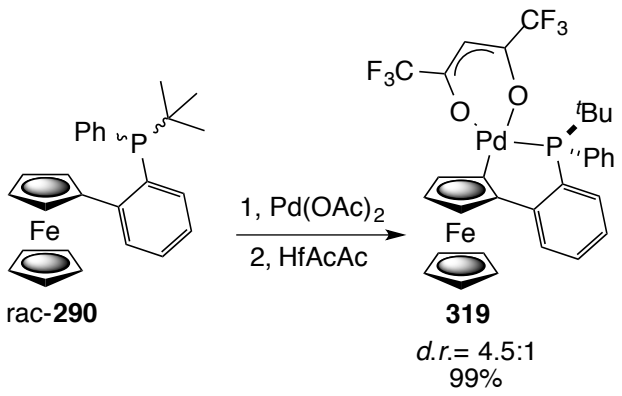
15.6 - Application of Transcyclopalladation to P-chiral Phosphines.

A development of this methodology is its application to P-chiral phosphines. The aim of this body of work is to control the diastereoselectivity and enantioselectivity of a transcyclopalladation affording novel diastereomerically enantiomerically enriched phosphopalladacycles. It was envisaged that the transcyclopalladation methodology could be applied in a kinetic resolution protocol (**Scheme 98**).



Scheme 98. Proposed transcyclopalladation of P-chiral ligand 290

Racemic palladation of rac-**290** with palladium acetate and formation of hfacac monomer in dichloromethane gave an initial diastereoselectivity of 4.5:1. Calculation of d.r. that was carried out *via* ^{1}H integration of the hfacac proton signals or by integration of CF_3 in the ^{19}F NMR. The former was the method of choice (**Scheme 99**, **Figure 34**).



Scheme 99. Racemic palladation of 290.

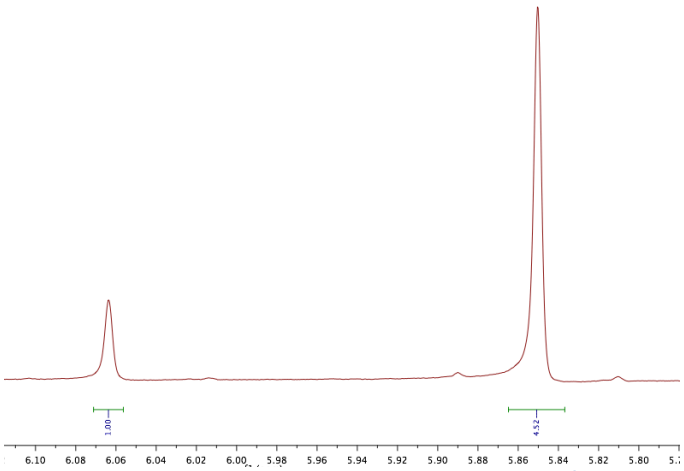


Figure 34. Calculation of diastereoselectivity from ^{1}H NMR of 319.

In order to produce a diastereomerically pure racemic palladacycle it was predicted that a lower temperature and longer reaction time would allow the palladation to be more selective. Therefore, the reaction was repeated at 0 ^{o}C and the reaction time was increased to 48 hours, but this did not have the desired effect. Infact, this caused the selectivity of the palladation to drop, lowering the diastereoselectivity to 2:1.

Both diastereoisomers were very difficult to separate *via* flash chromatography and their separation also proved arduous on preparative thin layer flash chromatography plates. Numerous attempts of recrystallisations also did not yield diastereomerically pure racemic palladacycles.

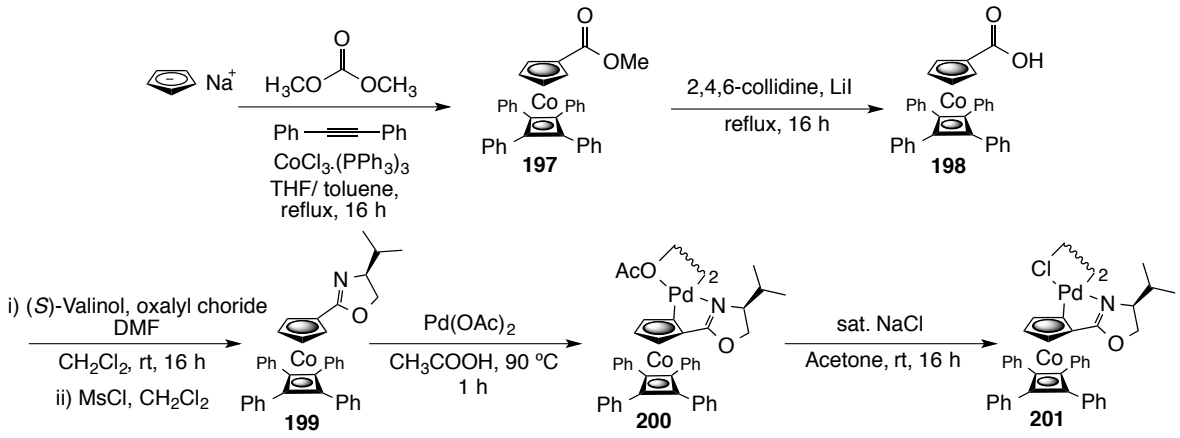
15.7 - Kinetic Resolution of P-chiral Phosphines.

The kinetic resolution of phosphine **290** with **200** has the potential to produce an enantiomerically enriched, diastereomerically pure P-chiral phosphopalladacycle and to recover the enantiomerically pure starting material (**Scheme 98**).

In accordance to the literature it was predicted that the stereoselectively of the transcyclopalladation would follow literature trends, therefore, $_{p}$*R*,*S*-**200** was anticipated to give the $_{p}$*S* palladacycle.[171] In terms of the diastereoselectivity and chirality around the phosphorus, it was hypothesised that the bulky *tert*-butyl group would lie in a *pseudo*-axial position around the 5 membered Pd-P ring therefore leaving the *S* enantiomer of the starting material.

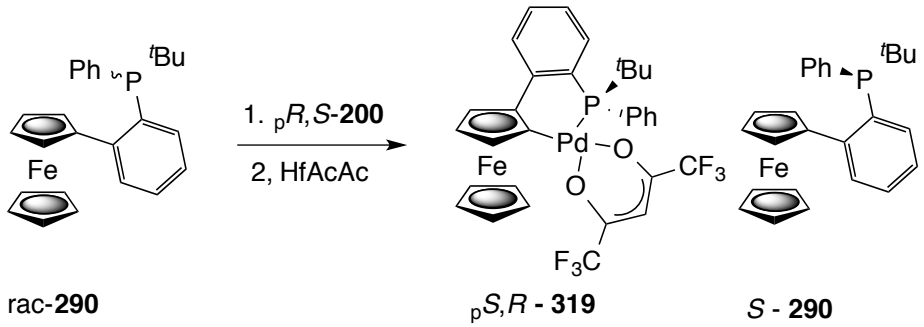
The synthesis of **200** was carried out in accordance to a literature procedure and has previously been outlined in **Scheme 46**. The synthesis of **199** is a modification of the procedure by Richards *et al.* The procedure has been altered to include large-scale preparation of the cobalt oxazoline. Starting from sodium cyclopentadiene and dimethylcarbonate the methyl ester substituted cyclopentadienyl ring was formed *in situ* and reacted with cobalt chloride *tris*-triphenylphosphine to give **197** as a yellow solid. Following titration from hexane and, in modification of the quoted method, purification *via* flash chromatography, gave pure **197** in 90% yield. Nucleophilic conditions, rather than hydrolytic conditions were used to cleave the methyl ester to the corresponding acid **198.** Again, flash chromatography yielded the acid in 80% yield. Subsequent formation of the acid chloride with oxalyl chloride and catalytic quantity of dimethylformamide, and

reaction with a solution of (*S*)–valinol, triethylamine followed by mesyl chloride mediated cyclisation gave **199**. Purification *via* flash chromatography and recrystallisation from acetonitrile and hexane afforded **199** in 81% yield. Compound **199** can be easily transformed to its corresponding palladacycle by heating to 90 °C for 2 hours where a single diastereoisomer precipitates out of solution. Vacuum filtration afforded the acetate-bridged palladacycles in 72% yield. Compound **200** can be transformed into **201** by stirring in saturated NaCl in acetone and water (**Scheme 100**).



Scheme 100. Synthesis and ligand exchange of cobalt sandwich complex containing palladacycles

The first transcyclopalladation run was carried out mirroring the conditions from the publication by Richards *et al.*, at 80 °C for 5 hours, using 40 mol% of **200** as the palladium transfer agent.[213] After removing the solvent *in vacuo*, dissolving in acetone and water and addition of sodium hexafluoroacetylacetonate, to form the corresponding hfacac monomer, a diastereoselectivity of 6:1 was obtained. Reducing the temperature to 40 °C and increasing the reaction time to 16 hours gave a single diastereoisomer (**Scheme 101**, **Table 12**).



Scheme 101. Transcyclopalladation of P-chiral phosphine 290.

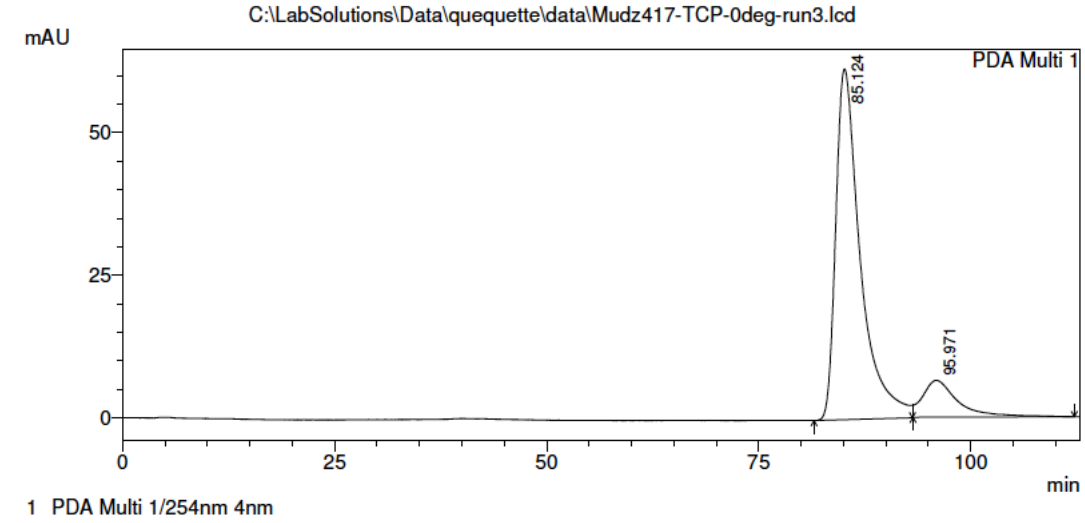
Run	Temperature	Solvent	Time	d.r.[a]	*e.e.* ($_pS$)	Yield (Pd-cycle)	COP-Loading
1	80 °C	Toluene	16 h	1:18	70%	26%	40 Mol%
2	80 °C	Toluene	16 h	1:16	86%	32%	40 Mol%
3	70 °C	Toluene	16 h	1:15	81%	36%	40 Mol%
4	40 °C	Toluene	16 h	1:99	79%	28%	40 Mol%
5	Room Temp	Toluene	64 h	1:7	67%	32%	40 Mol%
6	0 °C	Toluene	96 h	1:2	66%	14%	40 Mol%
7	40 °C	Toluene	64 h	1:99	73%	34%	40 Mol%
8	40 °C	Toluene	48 h	1:99	76%	32%	40 Mol%
9	40 °C	Toluene	48 h	1:99	45%	24%	30 Mol%
10	40 °C	Toluene	48 h	1:99	58%	41%	50 Mol%
11	40 °C	Benzene	48 h	1:99	48%	26%	40 Mol%
12	40 °C	Dichloromethane	48 h	1:99	47%	30%	40 Mol%
13	80 °C	Toluene	16 h	1:6	89%	54%	100 Mol%

a) major diastereoisomer being $_pS,R$-**319.** b) *e.e.* determined by chiral HPLC.

Table 12. Optimisation of transcyclopalladation conditions.

It is clear to see from **Table 12** that there is an increase of diastereoselectivity when the temperature is dropped but the opposite effect is observed when transcyclopalladations are carried out at temperatures below 40 °C (**runs 5&6, Table 12**). Changing the solvent does not have an effect on enantioselectivity or diastereoselectivity. It is also clear to see that there is not a correlation between diastereoselectivity and enantioselectivity with respect to temperature. It might be expected that an increase in temperature would decrease the diastereoselectivity as well as the enantioselectivity, thus, making the whole process less selective. When comparing **run 2** (16:1 d.r., 86% *ee*) and **run 4** (99:1 d.r., 79% *ee*) it might be expected that the run which was carried out at a lower temperature would

have the greater enantioselectivity. The reason for this trend is unknown but it sheds light on the fact that the intrinsic process is more complex than first predicted. Another challenge seen with this body of work was the actual calculation of enantiomeric excess of the resulting palladacycle. After many HPLC runs, numerous changes of chiral columns (ChiralPak® IA, IC and OD) and changing of the parameters, baseline separation was still not observed (**Figure 35**).



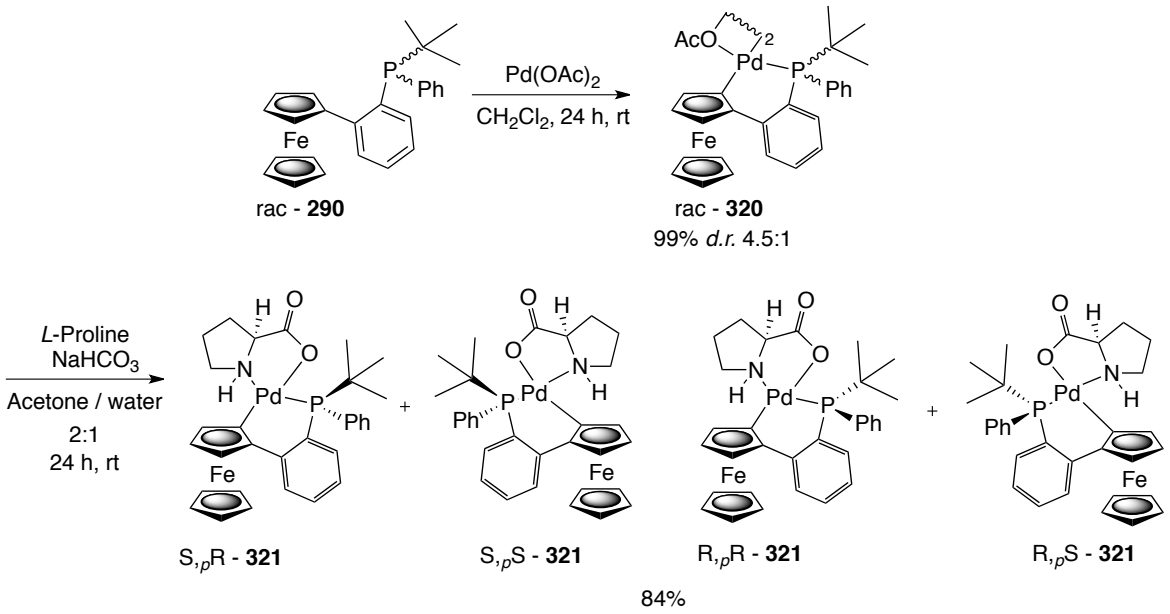
Quantitative Results

PDA

ID#	Name	Ret. Time	Area	Height	Conc.
1	RT85.124	85.124	12393194	61522	86.859
2	RT95.971	95.971	1874989	6456	13.141

Figure 35. HPLC trace of run 7 (Table 12).

The attempt generation of the proline adducts were attempted but this led to other complications (**Scheme 102**). The enantioselectivity was calculated using ^{31}P NMR spectroscopy on the crude reaction mixture as any purification *via* flash chromatography could result in further resolution. In the ^{31}P NMR, 4 peaks were to be expected for each of the adducts, but many more peaks were observed. There is precedent for another kinetic resolution to take place during the ligand exchange. Unfortunately, it is extremely difficult to calculate an accurate *d.e.* and therefore *e.e*. from the crude NMR due to the fact that when the proline adducts are formed the nitrogen from the proline can sit either in a *cis* or *trans* conformation giving the predicted *S*,$_p$*S*, *S*,$_p$*R*, *R*,$_p$*R*, *R*,$_p$*S* compounds as *cis* or *trans* isomers.

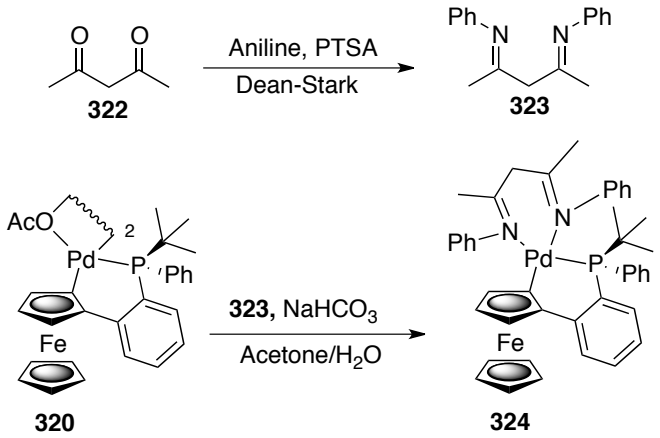


Scheme 102. Synthesis of proline adducts from a racemic palladation of 290.

This procedure was not taken any further due to the unforeseen complications of the aforementioned potential kinetic resolution.

16.0 – Attempted Synthesis of a NacNAc Monomer.

In a final attempt to synthesise a monomeric palladacycle, which would be resistant to decomposition when run through a chiral column, it was decided to use the NacNac ligand. NacNac is the name for a class of anionic bidentate ligands. 1,3-Diketimines are often referred to as "HNacNac", a modification of the abbreviation Hacac used for 1,3-diketones. These species can exist as a mixture of tautomers (**Scheme 103**).



Scheme 103. Synthesis of NacNac monomer 324.

Acetylacetone was heated at reflux in toluene under Dean-Stark conditions with aniline to give compound **323**. This was taken and reacted with rac-**320** with Na_2CO_3**,** and upon analysis of the ^{31}P NMR, there was no evidence of a new palladacycle and further analysis showed decomposition of starting material. The corresponding acetylacetone (acac) ligands was synthesised but did not give the desired baseline separation on any HPLC runs.

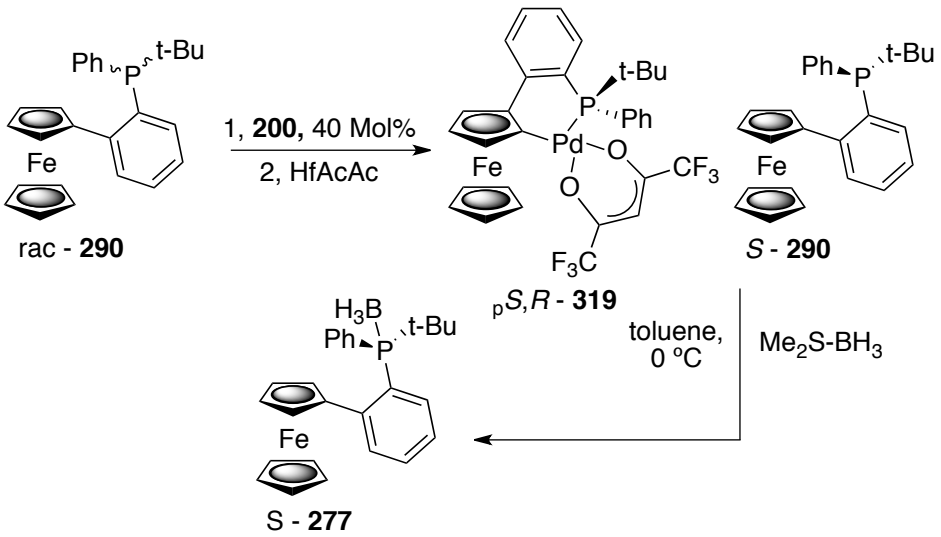
16.1 - Isolation of the Enantioenriched Phosphine From a Transcyclopalladation.

As mentioned earlier, in order to implement a successful kinetic resolution one must ideally be able to isolate the slower reacting enantiomer and to ascertain its enantioselectivity. Within this body of work this was far from trivial. The resulting phosphine was relatively air stable but all transcyclopalladations were carried out in dry, thoroughly degassed solvents. When isolating phosphine (**290**) a number of problems were encountered, the first of which was oxidation, and the R_f of the free phosphine was very similar to that of monomeric palladacycle (**319**), which made the rapid isolation of both compounds very arduous.

16.2 - Formation of Phosphine Borane Adducts.

The first method of getting round this problem was to synthesise the phosphine borane adduct of phosphine (**290**) in order to prevent oxidation. Burg *et al.* reported the first

synthesis of a phosphine-borane complex and this method has been utilised for the preparation of a wide range of phosphine borane complexes.[214] It was further shown that phosphine borane complexes are very stable, showing inertness to oxygen, moisture and most acids. This has been attributed to the fact that P-B and the B-H bonds seem to have low polarity and polarisability. Furthermore it was shown that tertiary phosphine boron compounds have a high thermal stability, which seems to be further enhanced by the number of the aromatic groups bound to the phosphorus. Various methods have been developed for the protection of phosphines with borane. Amongst them some of the most frequently used methods include the use of BH_3.THF and BH_3.SMe_2. It is also well known in the literature that deprotection is relatively facile using DABCO and no stereochemical information is lost during this process (**Scheme 104**).[215]



Scheme 104. Attempted isolation of borane adduct 277.

The crude mixture from a transcyclopalladation was cooled to 0 ^{o}C and an excess of boron-dimethylsulphide complex was added and allowed to stir for one hour. The solvent was then removed in vacuo after which acetone, water and the hfacac salt were added in order to synthesise the monomeric palladacycle (**319**). The formation of borane adduct (**277**) was monitored by ^{31}P and ^{11}B NMR. When phosphine **290** as a single entity is complexed with boron-dimethylsulphide the reaction goes to completion giving the borane adduct in high yield showing peaks at 35.3 ppm (^{31}P) and 42.3 (^{11}B). A change in the ^{31}P chemical shift was observed with respect to the free phosphine. This diagnostic

shift was accompanied by the formation of a broad signal, the result of P-B spin coupling and line broadening due to the quadrupole of the boron nucleus. When the reaction is carried out after a transcyclopalladation run, the formation of an unknown borane adduct is seen in the proton NMR. It is clear to see that phenylferrocene is present within this sample, and ^{31}P NMR shows no phosphine present. The ^{1}H NMR also shows the signals for another ferrocene containing compound and a broad triplet, which may result from the incorporation of BH_3 (**Figure 36**).

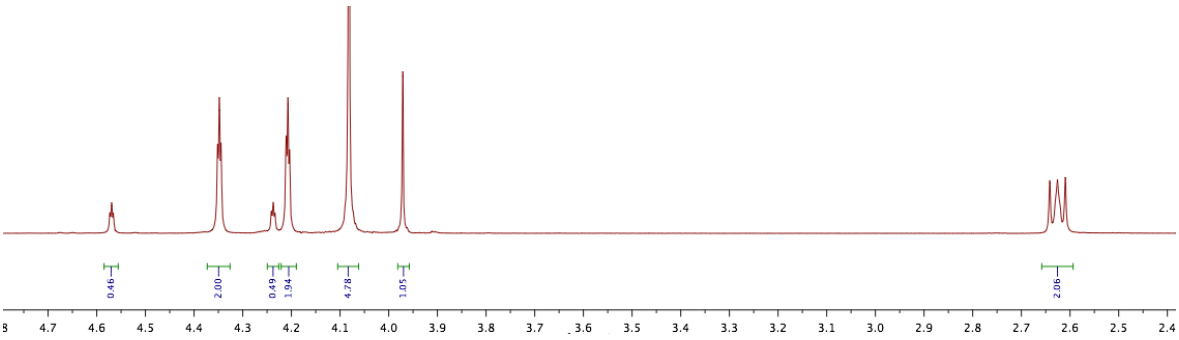


Figure 36. Formation of an unknown borane-containing compound

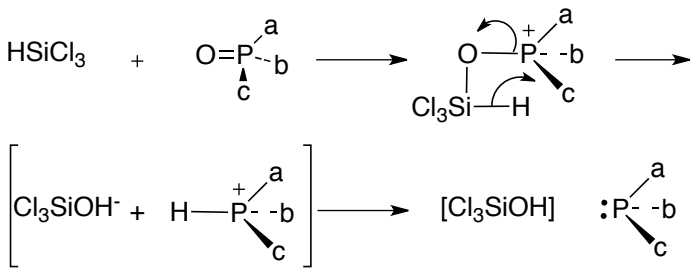
It was hypothesised that the formation of the compound may be leading to erosion or enhancement of the enantioselectivity of the starting material after transcyclopalladation; therefore an alternative route for protection was employed.

16.3 - Formation of Phosphine Oxide and Sulphides.

Another method of phosphine protection is to synthesise the corresponding phosphine oxide or sulphide. Their deprotection using a range of chlorosilane derivatives can conserve or invert the stereochemistry at the phosphorus centre. The original publication by Mislow *et al.*, further consolidation by Krenske, indicates that depending on the whether the oxide or sulfide is formed, the consequent reduction will go with retention of stereochemistry or inversion of stereochemistry, respectively. [216,217]

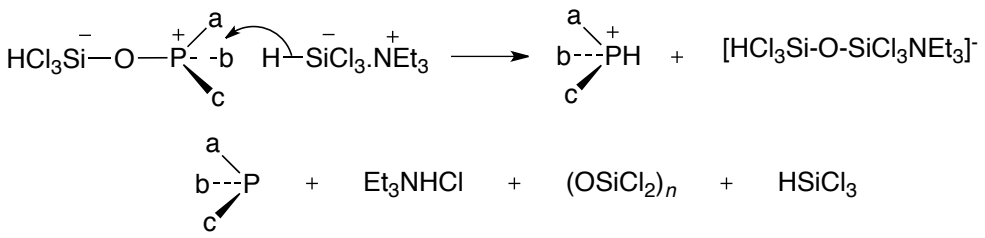
16.4 - Reduction of Phosphine Oxides.

The reduction of P-chiral phosphine oxides with trichlorosilane can afford the corresponding phosphine with net retention of configuration and high optical yield. Horner and Balzer observed that in the presence of triethylamine, acyclic tertiary phosphine oxides can be reduced to the phosphine with inversion of stereochemistry, whereas the presence of pyridine and *N*,*N*-diethylaniline resulted in retention of stereochemistry. [218] The retention of configuration can be rationalised by the complexation of a silane derivative and an intramolecular hydride transfer (**Scheme 105**).



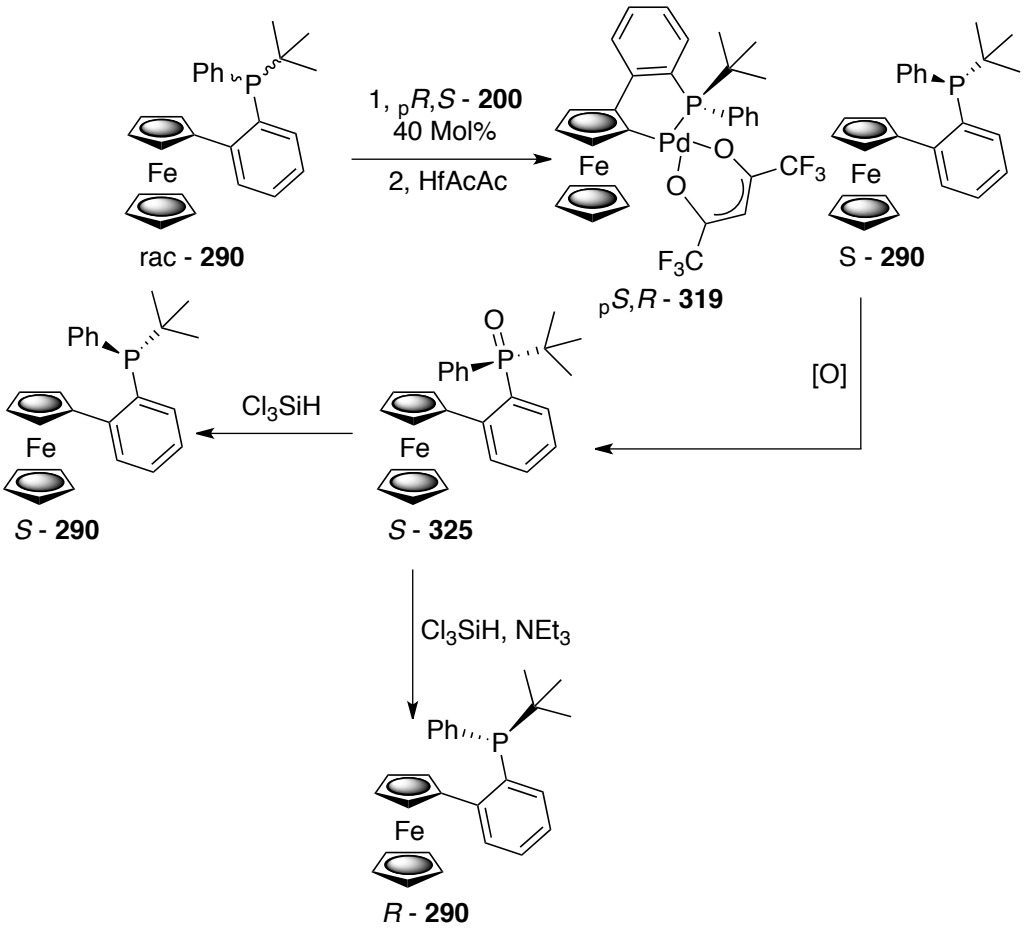
Scheme 105. Reduction of a phosphine oxide with the retention of stereochemistry.

To rationalise the inversion of stereochemistry in the presence of triethylamine, it was suggested that complexation, similar to that outlined in **Scheme 105**, is followed by intermolecular hydride transfer from a 1:1 triethylamine-trichlorosilane complex is an S_N2 type process (**Scheme 106**).



Scheme 106. Inversion of stereochemistry in the reduction of a phosphine oxide in the presence of triethylamine.

The application of this method to a transcyclopalladation protocol is a very attractive methodology as the stereochemistry of the resulting phosphine can be controlled with the modes of base specific reductions previously described (**Scheme 107**).



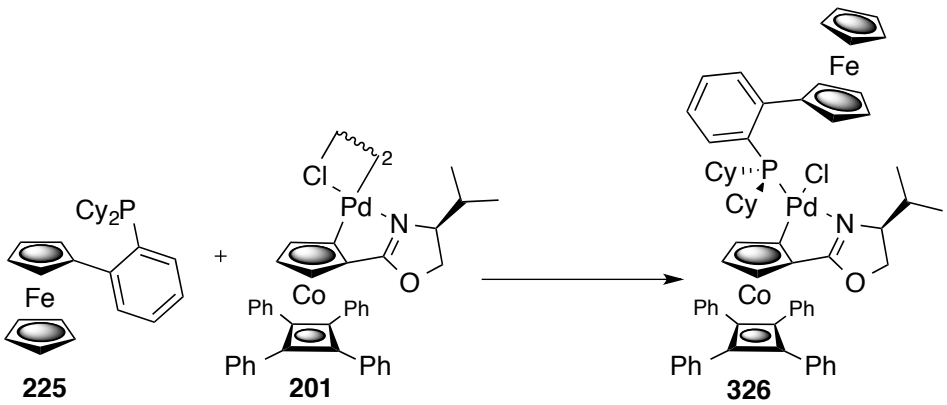
Scheme 107. Control of the stereochemical outcome of phosphine oxide 325 reduction to phosphine 290

It was envisaged that oxidation of the unreacted enantiomer would give the corresponding oxide. Oxidation of the free phosphine in dichloromethane with *m*CPBA gave oxide **325** in >90% yield which was confirmed by a chemical shift change in the ^{31}P NMR from 6.5 ppm to 42.54 ppm. When applied to a transcyclopalladation, after removal of toluene, addition of dichloromethane and *m*CPBA led to oxidation of phosphine as well as decomposition of the palladacycle and in some cases oxidation to the ferrocenium ion, which was identifiable by the solution turning green on numerous occasions. The stopper was removed and solution was refluxed in air but after 48 hours this only led to partial

oxidation. Similar work was implemented with the formation of the phosphine-sulfide adduct as this can also be reduced in the same manner. Oxidation using elemental sulfur in THF gave the corresponding phosphine-sulfide in 99% yield. Elizabeth Krenske describes reduction of a phosphine-sulphide with perchlorosilanes, but unfortunately the reduction led to further decomposition of the palladacycle.[219] The reason this was carried in 'one pot' manner was due to the fact that the free phosphine partially oxidised when exposed to the atmosphere therefore the *in situ* oxidation was attempted on the crude reaction mixture prior to separation.

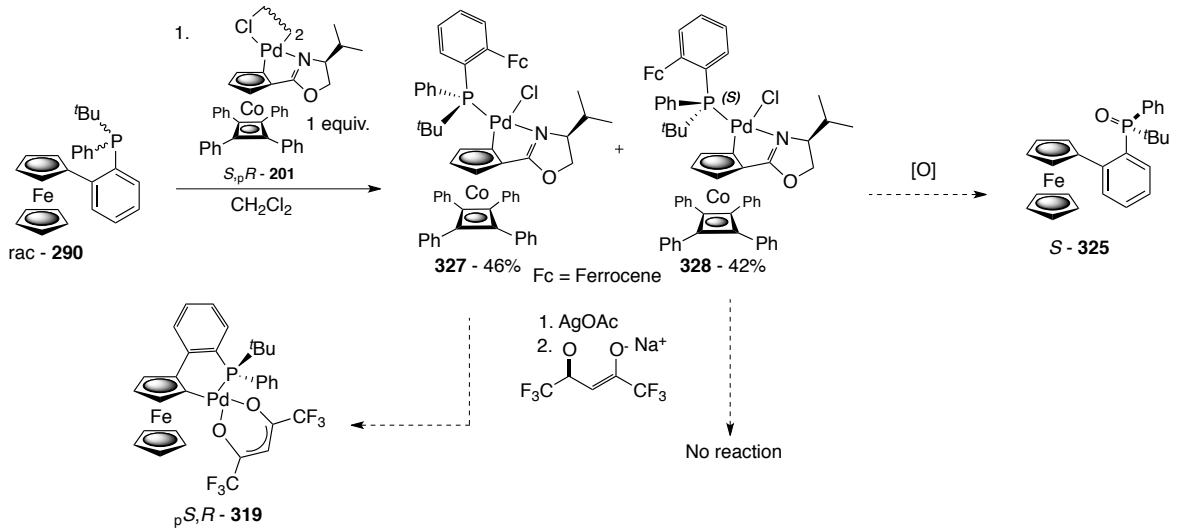
16.5 - Application of COP-Cl (201).

Previous members of the Richards group have documented that COP mediated transcyclopalladations travel through a cobalt-palladium-phosphine intermediate. The transcyclopalladation of cyclohexyl-substituted phosphine **225** with $_{p}$*R,S*-**201** does not give the predicted palladacycle because the acetate ligand is needed to aid in the deprotonation of the cyclopentadienyl ring, but it does form a palladium adduct which is identified in part by a ^{31}P NMR signal at 56.5 ppm (**Scheme 108**).[220]



Scheme 108. Synthesis of 326 with 201.

Addition of silver acetate will potentially afford the corresponding palladacycle following ligand exchange, and the free cobalt oxazoline. This methodology can also be applied to the diastereoselective synthesis of enantioenriched phosphopalladacycles (**Scheme 109**).



Scheme 109. Application of COP-Cl for the synthesis of enantioselective phosphopalladacycles.

It was predicted that, on addition of $_pR,S$-**201** to rac-**290**, diastereoisomers **327** and **328** would form, which could be separated by flash chromatography. Compound **327** would then be reacted with silver acetate in order to produce palladacycle **320** in its diastereomerically pure form, and subsequent hfacac formation would lead to $_pS,R$-**319.** The configuration of **328** would discourage palladation, and cleavage of the palladium phosphorus bond either by oxidation or addition or hfacac may lend to the enantioenriched free phosphine oxide (**325**). The synthesis of **327** was confirmed by proton and ^{31}P NMR but mass spectrometry data was inconclusive (**Figure 37**).

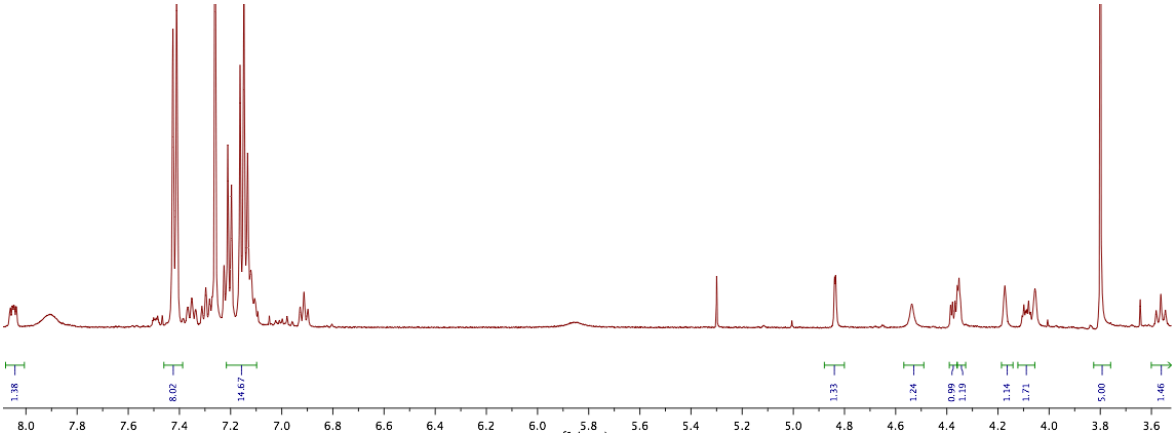
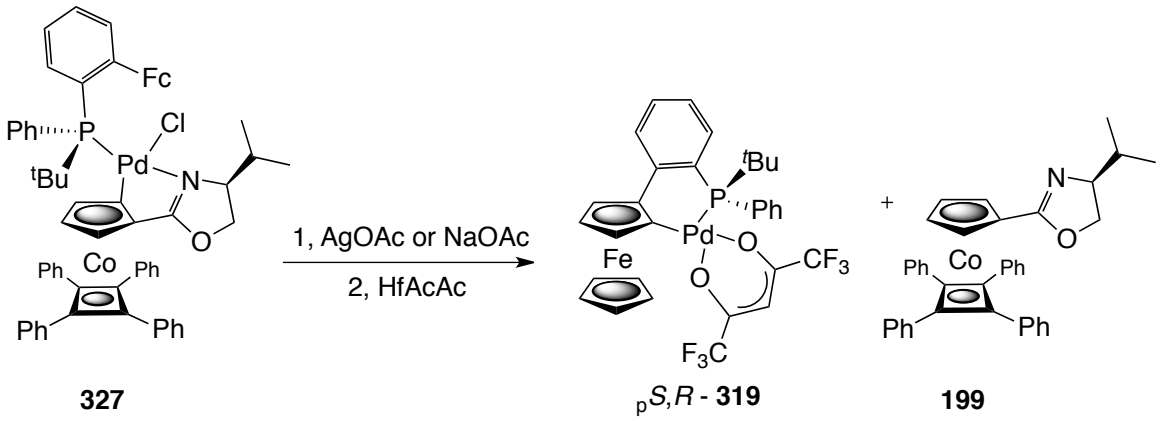


Figure 37. Identification of 327 *via* ^{1}H NMR.

Although mass spectrometry was inconclusive there is a great deal of evidence in ^{1}H and ^{31}P NMR spectroscopy for the formation of **327**:

I. Only one sharp singlet in ^{31}P NMR at 55.04, which is consistent with the formation of a palladium adduct and not a palladacycle.
II. Only 1 C_5H_5 peak showing the presence of one ferrocene containing species.
III. Positive identification of 7 cyclopentadienyl protons
IV. A cyclopentadienyl proton located on the cobalt metallocene section of the adduct is shifted downfield due to the phenyl ring situated on top of the cyclopentadienyl ring (ring current effect).
V. Finally as mentioned in **Chapter 2**, the observation of a doublet of doublet system at 8.05 ppm, due to proton 6 on the phenyl ring being effected by the anisotropic effect of iron due to the phenyl ring being perpendicular to the cyclopentadienyl ring of the ferrocene scaffold.

Adduct **327** was purified *via* flash chromatography in 46% yield. A range of methodologies and protocols were implemented to cleave the adduct giving the diastereomerically pure enantioenriched phosphopalladacycles (**Scheme 110**). The relative stereochemistry shown in **Scheme 110** is only a suggested configuration as attempts to recrystallise **327** were unsuccessful. This configuration was hypothesized due to the fact that it was envisioned that bulky *tert*-butyl group would orientate towards the back, far from the bulky ferrocenyl moiety.



327 $_pS,R$ - **319** **199**

Scheme 110. Attempted generation of $_pS,R$-319 from 327.

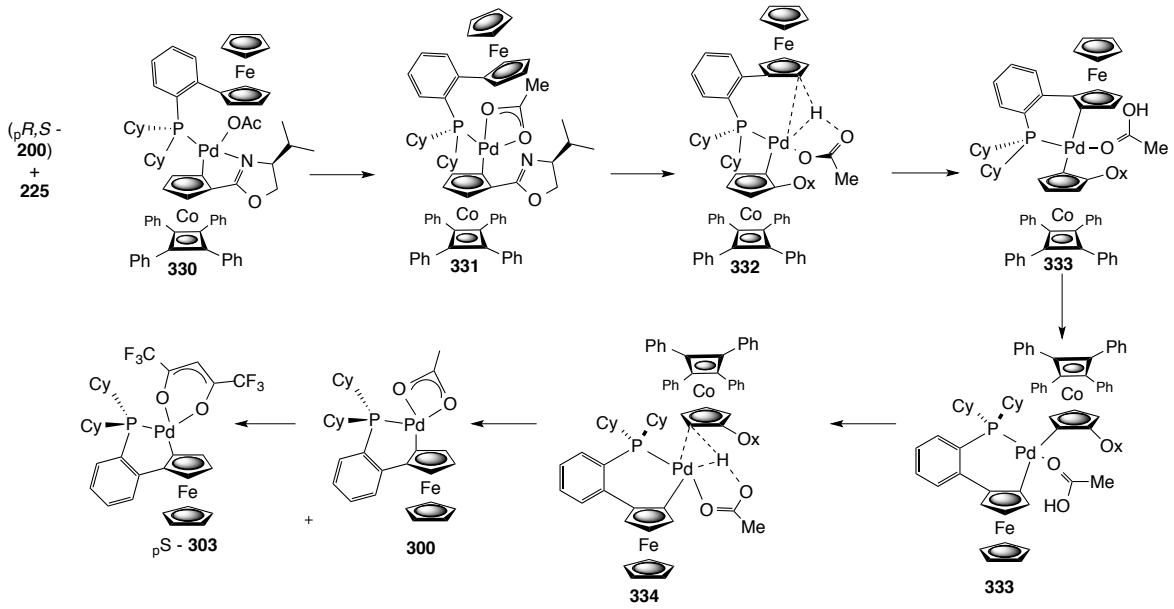
Run	Solvent	Temperature	AgOAc	NaOAc	Outcome
1	Dichloromethane	rt	1 equiv		Decomp
2	Dichloromethane	Reflux	1 equiv		Decomp
3	Dichloromethane	0 °C– rt	1 equiv		SM
4	Dichloromethane	rt		1 equiv	SM
5	Dichloromethane	Reflux		1 equiv	SM
6	Dichloromethane	0 °C– rt		1 equiv	SM
7	Acetone	rt	1 equiv		Decomp
8	Acetone	rt		1 equiv	Decomp
9	Acetone	40 °C	1 equiv		Decomp
10	Acetone	40 °C		1 equiv	Decomp
11	Toluene	rt	1 equiv		Decomp
12	Toluene	rt		1 equiv	Decomp

Table 13. Attempted generation of $_pS,R$-319 from 327

From **Table 13** above, it can be seen that the synthesis of **319** from **327** was not successful. Silver acetate and sodium acetate were employed in order to aid C-H activation to form the palladacycle but all attempts led to oxidation of the metallocene leading to a green precipitate.

16.6 - Enantioselective Transcyclopalladation Mechanism.

In 2005 Richards *et al.* described the application of cobalt oxazoline palladacycles **200** to the enantioselective transcyclopalladation of prochiral phosphine **225**. Heating of **200** and phosphine **225** in toluene for 5 hours led to the clean transfer of palladium, and following ligand exchange to the chloride dimer afforded the corresponding phosphopalladacycles in 95% *ee*. The driving force of the reaction is the greater bond strength of the synergistic palladium phosphorus bond of the product compared to the palladium nitrogen σ-bond of the starting material. The reaction is clearly controlled by the steric bulk of the starting palladacycle, with little positive or negative contribution from the oxazoline-based stereogenic centre.[221] Richards gives a detailed analysis of the transcyclometallation of a symmetrical tertiary phosphine (**Scheme 111**).

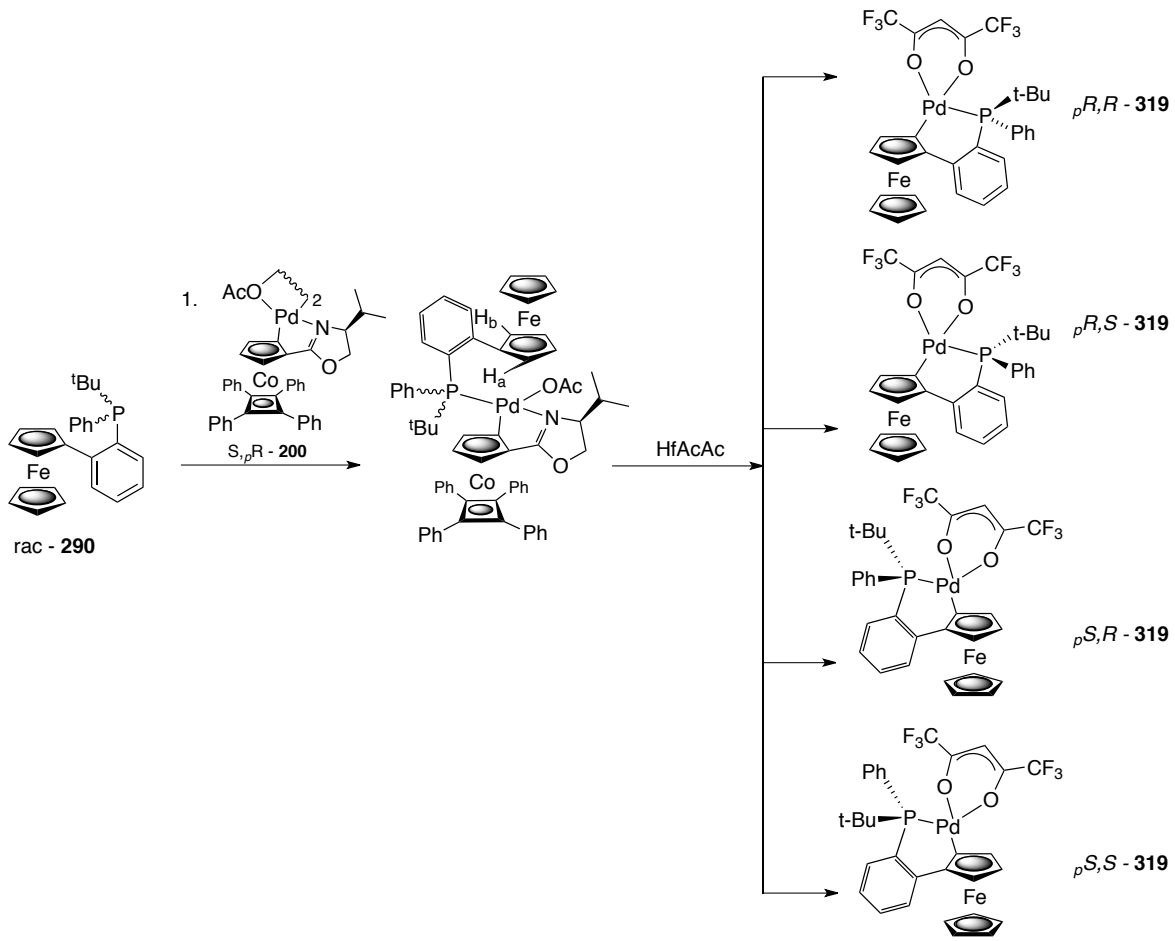


Scheme 111. Mechanism proposed by Richards *et al.* for the enantioselective transcyclopalladation of symmetrical tertiary phosphine.[222]

The reaction between dimeric ($_pR,S$)-**200** and phosphine **225** led to the formation of adduct **330**, which was identified by mass spectrometry and the *trans*-geometry of the phosphorus and nitrogen ligands is assigned by relation to other literature examples. An

η^2-acetate intermediate is formed by the displacement of the oxazoline ligand **331**. The approach of the ferrocene moiety from the opposite side to the bulky tetraphenyl cyclobutadiene moiety, and with palladium *exo* to ferrocene, accounts for the formation of the new ($_pS$)- configuration *via* **332** *via* a concerted metalation deprotonation step. The coordinate acetate ligand of intermediate **333** is known to participate in a retro concerted metallation deprotonation pathway *via* **334**, resulting in η^2-acetate **300**. Subsequent dimerisation and ligand exchange to the hfacac monomer afforded ($_pS$)-**303**.[222] When applied to a P-chiral phosphine the diastereoselectivity observed is due to the bulk of the palladium source. The mechanism of enantioselective C-H activation is very similar to that described by Richards *et al.* but when applied to a P-chiral phosphine there is a slight variance. [222]

There is the possibility of the formation of 4 compounds, both enantiomers and their diastereoisomers. One of the key factors which makes the implementation of the COP system into a transcyclopalladation protocol possible is the fact that **200** has the ability to distinguish selectively between prochiral H_a and H_b, depending on which enantiomer of **200** is utilised. In addition, it is possible to use this system to discriminate between enantiomers of a racemic P-chiral phosphine (**290**). In line with the current published data and known selectivity of the COP systems, it is predicted that when ($_pR,S$)-**200** is used for a transcyclopalladation on phosphine **290** and the major enantiomer and diastereoisomer will have the $_pS,S$ configuration (**Scheme 112**).



Scheme 112. Formation of possible stereoisomers from COP-OAc mediated transcyclopalladation.

The only way in which the absolute configuration could be proven is from an X-ray structure of the hfacac monomer of an enantioselective diastereoselective transcyclopalladation. Many attempts to grown a crystal failed but using a bi-phasic diffusion protocol using dichloromethane and hexane afforded what was first thought to be a crystal of hfacac monomer, but the resolved structure which came back was actually the unprecedented formation of a mixed cobalt-metallocene ferroenylphosphopalladacycle. The isolation of this structure suggests that the configuration in **Scheme 112** assigned to the major product is correct *i.e.* **Figure 38** has the predicted $_{p}S$ configuration and the bulky *tert*-butyl group is pointing up.

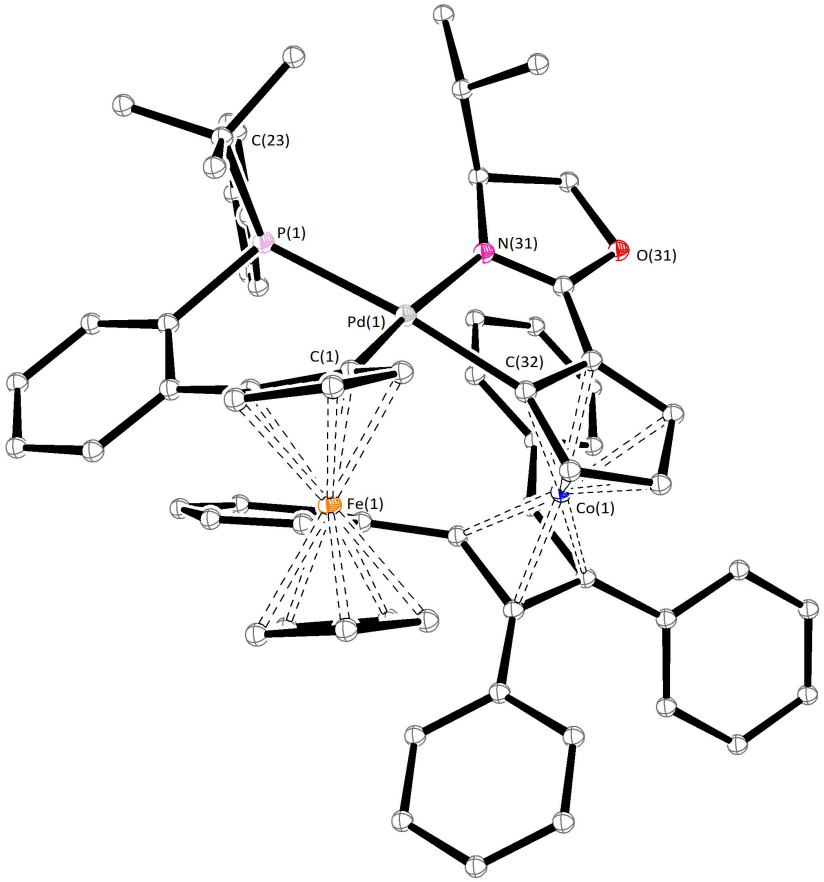
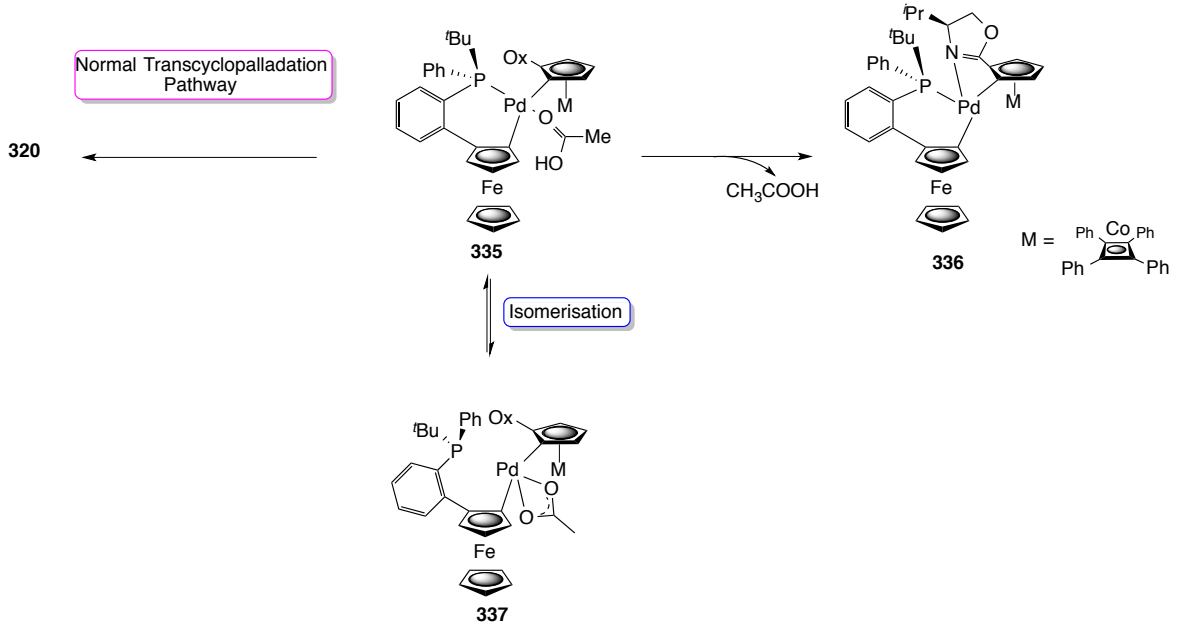


Figure 38. ORTEP representation of compound 336. Hydrogen atoms, solvent molecules and minor disordered components have been removed for clarity. Displacement ellipsoids are drawn at 50% probability level. Principle bond lengths [Å] include: Pd(1)-P(1) 2.534, N(31)-Pd(1) 2.210, C(1)-Pd(1) 2.008, C(32)-Pd(1) 2.055. Principal angles [°] include: C(32)-Pd(1)-C(1) 94.32, C(1)-Pd(1)-(P1) 86.02, P(1)-Pd(1)-N(31) 101.19, N(31)-Pd(1)-C(32) 79.39, C(17)-P(1)-C(23) 108.72, Pd(1)-P(1)-C(23) 123.06, Pd(1)-P(1)-C(17) 109.96.

In theory, this structure **336** can be formed but has never been seen in any of the trancyclopalladations protocols carried out by members of the Richards lab.[171] The formation of this compound sheds a degree of light on the inherent complexity of the transcyclopalladation process with P-chiral phosphines. **Scheme 112** outlined that the major enantiomer and diastereoisomer would be S_pS. Examination of the X-ray structure shows that the distorted palladium containing 6 membered ring has the *tert*-butyl group in an axial position, with the phenyl ring sitting in a *pseudo* equatorial orientation. One of the more intriguing aspects of this structure is that fact that both metallocene component are pointing towards one another. A theory for the formation of this

compound is that it is actually a by-product of the main process as outlined in (**Scheme 113**).



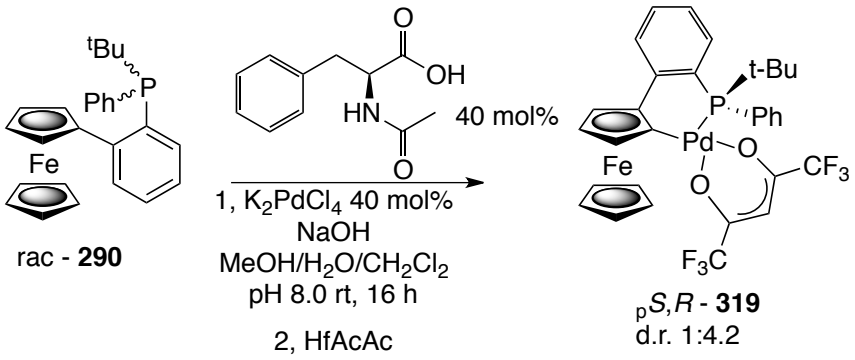
Scheme 113. Hypothesised synthesis of mixed palladacycle 335.

Rather than following the normal reaction pathway requiring a retro concerted metallation deprotonation, which would then lead to the acetate ligated phosphopalladacycles and free cobalt oxazoline ligand, there is a re-coordination of the oxazoline, and expulsion of acetic acid affording the double metallocene containing palladacycle. Religation of acetic acid in **335** can free the phosphine lone pair and allow for isomerisation. The planar chiral stereochemistry of the phosphopalladacycles component is in agreement with this model, being $_pS$. However, the geometry about the square planar palladium is *cis* with respect to the two carbons rather than *trans*. The phosphorus chirality is opposite to that expected from the kinetic resolution (i.e. the bigger group is pointing away from the ferrocene, this is opposite to what is seen in the transcyclopalladation of **MudzPhos**, which will be discussed later in this chapter).

An alternative explanation is that this is a product formed from the unreacted enantiomer of the phosphine, which is consolidated by the complexity of the ^{31}P NMR spectra of the crude reaction mixture. The enantiomer that does not lead to the final product and undergoes an alternative reaction by coordinating through the phosphorus *trans* to the

carbon of the cobalt oxazoline moiety, and then cyclopalladates to form the compound analysed by X-ray crystallography. This is not a complete analysis, but without further studies it is probably not possible to say much more.

The amino acid-mediated enantioselective transcyclopalladation was applied to this system and the diastereoselectivity observed is less than that found with cobalt-oxazoline palladacycles (**Scheme 114**).

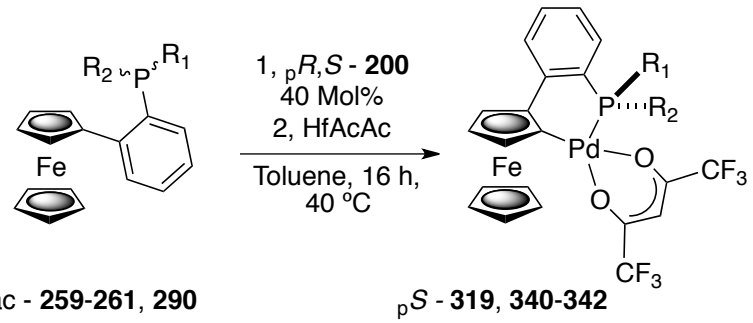


Scheme 114. Amino acid mediated enantioselective palladation of a rac-290

Richards also suggests how the enantioselectivity is controlled by the chirality and conformational properties of the coordinate amino acid-derived carboxylate ligand and on this basis the configuration of the major product is shown in **Scheme 115**.[221]

16.7 - Other Examples of Diastereoselectivity.

As previously mentioned COP-OAc **200** mediated transcyclopalladations are inherently very diastereoselective depending on the conditions used. Application of other P-chiral phosphines under the same conditions, were also examined (**Scheme 116**, **Table 14**, **Figure 39**).



rac - **259-261**, **290**

p*S* - **319**, **340-342**

Scheme 115. Diastereoselectivity of transcyclopalladations with a range of chiral phosphines.

Run	Compound	R_1	R_2	d.r.	Yield %	Corresponding ^{1}H NMR Spectra
1	**319**	*t*-butyl	phenyl	99:1	34	A
2	**340**	*n*-butyl	phenyl	1.83:1	29	D
3	**341**	methyl	phenyl	1.73:1	27	C
4	**342**	*σ*-tolyl	phenyl	1:2.82	32	B

Table 14. Diastereoselectivity of P-chiral phosphines.

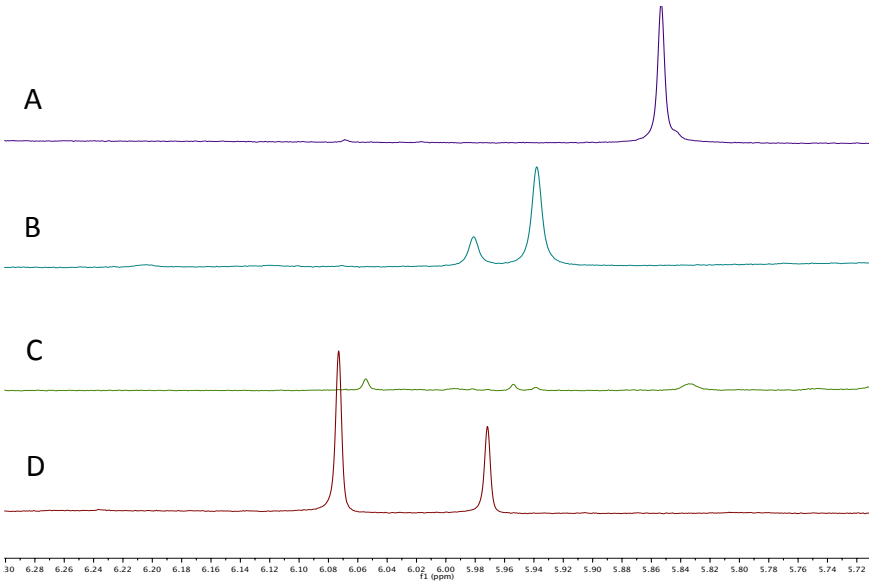


Figure 39. ^{1}H NMR showing the diastereoselectivity of selected P-Chiral phosphines in COP-Cl mediated transcyclopalladations.

It is clear from the NMR spectra above that stereochemistry at the chiral phosphorus is not only controlled by the transcyclopalladation but is a function of the steric bulk of the groups around the phosphorus. When comparing **340** and **342** the major and minor diastereoisomer switch their orientation.

16.8 - Initial Calculation of S-Value.

In 2001 a review by Jacobsen details that while under normal conditions, enantioselective reactions of prochiral substrates yield products of constant *ee*, the *ee* obtained in a kinetic resolution will change as a function of conversion.[223] With respect to preparative synthesis, the most attractive aspect of kinetic resolution is that the unreacted substrate can be recovered in high *ee* even if k_{rel} is not especially high simply by carrying the reaction out to a high enough conversion. The k_{rel} value determines the extent of the substrate conversion necessary to attain a target *ee*, but even a selectivity factor as low as 10 theoretically allows the isolation of unreacted substrate in 99% *ee* with 30% recovery. It is also quoted that *ee*s change as a function of conversion in standard kinetic resolutions, and k_{rel} values are generally considered to be more useful for evaluation and comparison of the efficacy of a kinetic resolution process.[223]

Applying this protocol to the enantioselective transcyclopalladation of a P-chiral phosphine proved to be far from simple. The first issue that arose was the real-time monitoring of conversion. This can be accurately carried out *via* ^{31}P NMR but closer analysis of the crude ^{31}P NMR showed, in addition to the formation of the product and the starting material left, the formation of unknown phosphorus species, oxidation products and formation of a phosphine-cobalt palladacycle adduct. The latter is an intermediate of transcyclopalladation identified before complete palladium transfer. Three individual transcyclopalladation runs were chosen and an initial selectivity factor was calculated using their ^{31}P NMR data. The enantioselectivities for each of the resulting palladacycle runs is known, therefore, conversion can be calculated from the integration of the peaks with respect to the starting material, as shown in **Table 15**. There are many other unknown ^{31}P NMR signals that have been taken into account when calculating the level of conversion.

Run	Temp	Prod	53.16 ppm	49.69 ppm	46.50 ppm	Oxide	40.59 ppm	35.78 ppm	29.41 ppm	SM	*ee*
1	0 °C	5%	0.1%	0.1%	5%	4%	6%	16%	0%	57%	66%
2	rt	11%	0.1%	0.1%	5%	4%	6%	16%	6%	52%	67%
3	40 °C	41%	0.1%	0.1%	8%	13%	4%	10%	13%	10%	73%

Table 15. Percentage conversion of transcyclopalladation runs at 0 °C, room temperature and 40 °C for 16 hours with 40 Mol% COP-OAc.

With respect to **run 3** if all the percentage values which are greater than 1 are added together except for the product. This value is 58% and can be taken as a crude estimation of the starting material left. Therefore, the remaining fraction can be taken as the level of conversion, and when this value is put into the equation shown in **Figure 40** the selectivity value is 10.8.

Run	Temp	SM	fraction remaining	*ee* of product	(1-C)*(1+ee)	(1-C)*(1-ee)	K_{rel}
1	0 °C	0.88	0.12	0.66	0.8008	0.9592	5.3
2	rt	0.89	0.11	0.67	0.8163	0.9637	5.5
3	40 °C	0.58	0.42	0.73	0.2734	0.8866	10.8

Table 16. Calculation of K_{rel}.

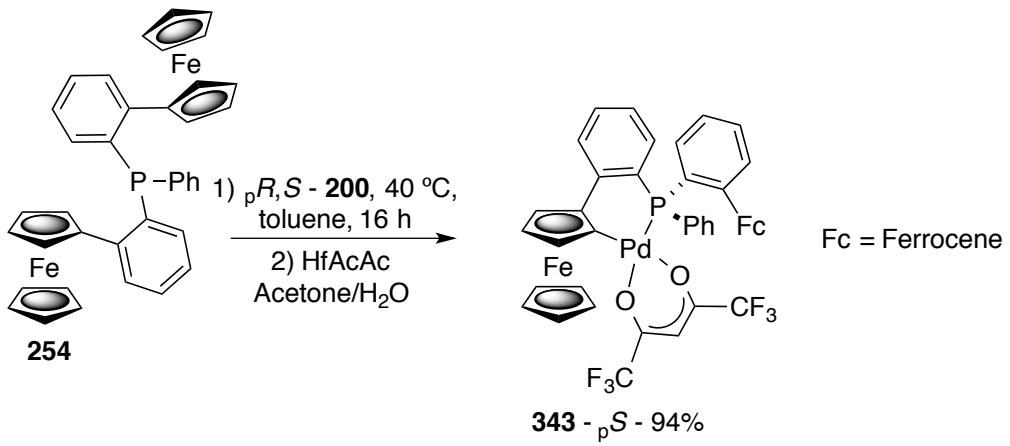
$$k_{rel} = \frac{\ln[1-c(1+ee)]}{\ln[1-c(1-ee)]}$$

Figure 40. Equation used for the calculation of k_{rel}.

It is clear to see from the data above the intrinsic process of a transcyclopalladation with COP-OAc on phosphine (**290**) is far more complex than first thought. Formation of unknown palladium ligated intermediates at 53.16, 49.69 and 46.50 makes it very difficult to accurately calculate a selectivity factor but a crude estimation can be calculated if the yield of palladacycle is taken as the conversion. The process has the potential to be selective, although diastereoselectivity must also be taken into account, which can be controlled *via* manipulation of the conditions employed.

16.9 - Desymmetrisation of 254 (MudzPhos)

The desymmetrisation of meso/prochiral compounds represents a powerful approach to asymmetric synthesis, and a number of enantioselective total syntheses have been based on this strategy.[224] Desymmetrisation is the loss of an element of symmetry which then results in the formation of a new stereogenic centre or element of chirality, and in order to produce an enantiomerically pure and diastereomerically pure phosphopalladacycle, a desymmetrisation protocol was implemented using bi-ferrocenylphosphine (**254**) (**Scheme 116**).



Scheme 116. Desymmetrization of 254 (MudzPhos).

The $_pR,S$-**200** mediated transcyclopalladation of ligand **254** and ligand exchange afforded the corresponding hfacac monomer in 95% yield and up to 96% *e.e.* which was determined by chiral HPLC. This method of synthesis of enantiomerically-enriched diastereomerically pure planar chiral phosphines was very attractive. When working with

a desymmetrisation, one does not have to worry about pushing to a set level of conversion to ascertain a given *ee*, as the starting material does not contain any chiral information. Hexane/dichloromethane mediated crystallisation afforded crystals, which could be then analysed by X-ray diffraction (**Figure 41**). This desymmetrisation protocol is very similar to the aforementioned kinetic resolution/transcyclopalladation, but instead of choosing between different enantiomers of a substrate, the COP-OAc chooses between two enantiotopic groups. The distinct advantage of a desymmetrisation is that the theoretical yield is 100%. Starting from bromophenylferrocene this process is only two steps from a diastereomerically pure enantiomerically enriched phosphopalladacycle, which installs two chiral centers in one step. The synthesis of the phosphine precursor is high yielding and can be scaled up to multi-gram quantities, and is resistant to oxidation. The kinetic resolution/transcyclopalladation of phosphine **290** turned out to be far from trivial and desymmetrisation is a simpler is a progression of that process. Palladation with palladium acetate in dichloromethane and subsequent ligand exchange to hfacac monomer also yielded a single diastereoisomer.

It was duly noted that in the kinetic resolution/transcyclopalladation of phosphine **290** the absolute configuration of palladacycle **319** is not know, but the formation of the bis-palladacycle can be taken as an accurate model of this process (**Figure 38**). The *tert*-butyl group is pointing away from the ferrocene and therefore in a *pseudo* axial position in the 6-membered palladacyclic ring. On closer analysis of the product of a COP-OAc mediated desymmetrisation of **MudzPhos** the non-palladated bulky phenyl-ferrocene moiety is actually in the opposite position. The less bulky phenyl group is *pseudo* axial and the bulky phenyl-ferrocene moiety is a *pseudo* equatorial position. Therefore, analysis of the structure concludes that this process will give the $_{p}S,R$ configuration when $_{p}R,S$-COP-OAc is used.

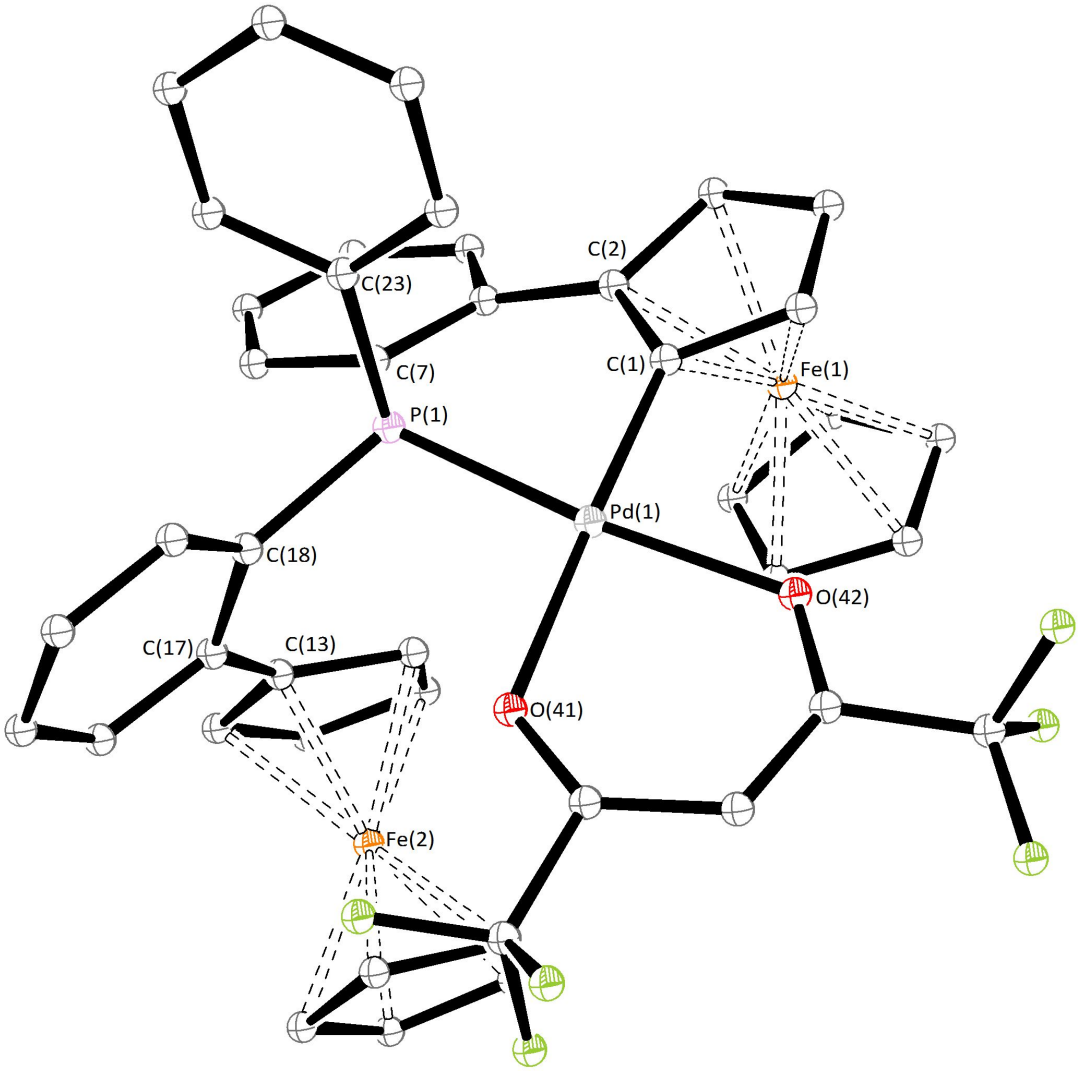


Figure 41. ORTEP representation of compound 343. Hydrogen atoms, solvent molecules and minor disordered components have been removed for clarity. Displacement ellipsoids are drawn at 50% probability level. Principal bond lengths [Å] include: Pd(1)-O(41) 2.151, Pd(1)-O(41) 2.117, Pd(1)-P(1) 2.207, Pd(1)-C(1) 1.988. Principle angles [°] O(41)-Pd(1)-P(1), P(1)-Pd(1)-C(1) 84.51, C(1)-Pd(1)-O(42) 91.12, O(42)-Pd(1)-(O41) 87.42, Pd(1)-P(1)-C(18) 110.83, Pd(1)-P(1)-C(23) 113.44, C(23)-P(1)-C(18) 104.42. Principal torsion angles [°] O(42)-Pd(1)-C(1)-C(5) -22.84, C(3)-C(2)-C(6)-C(7) -160.97, C(14)-C(13)-C(17)-C(18) -151.57.

17.0 - Application of Palladacycles to Catalysis.

In the recent past Richards *et al.* have reported on ferrocene based ligands and application of these to Suzuki cross-coupling reactions.[225] Various observations have been made in connection in the high activity associated with ferrocene based phosphine ligands with palladium catalysis. These include comparison of steric and electronic properties of **225** to other phosphine based ligands. In view of the differences between a benzene ring and cyclopentadienyl rings of ferrocene, Richards reasoned that replacement of non-phosphorous substituted ring of **208** with ferrocene to give **225** would: **a**) generate a potentially highly active ligand for Suzuki cross-coupling and **b**) shed light on factors responsible for its activity (**Figure 42**).[226]

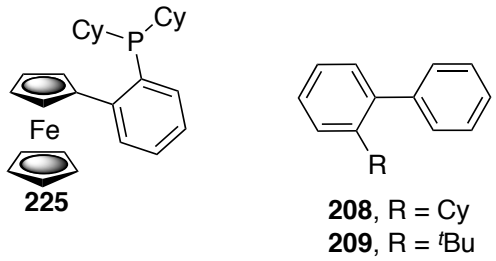
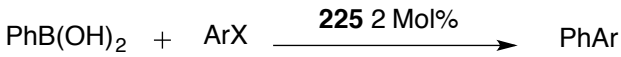


Figure 42. Ligands used in the Suzuki cross-coupling

The synthesis of ligands such as **225** and others related to it has been described in **Chapter 2**, and a great deal of work into the application of ligands such as these has already been published by Richards *et al.* In this work palladacycles (**293**) were tested in a range of coupling reactions with phenyl boronic acid employing palladium acetate with potassium fluoride in THF (**Scheme 117**, **Table 17**, **Figure 43**).[166]



Scheme 117. Suzuki cross-coupling with 225

Entry	ArX	Temperature	Conversion (%)[a]
1	**345**	rt	>95
2	**346**	rt	>95
3	**347**	rt	>95
4	**348**	rt	65
5	**349**	60 °C	83
6	**350**	60 °C	45
7	**351**	60 °C	>95
8	**352**	60 °C	>95

a) determined by ^{1}HNMR

Table 17. Suzuki cross-couplings with ligand 225.

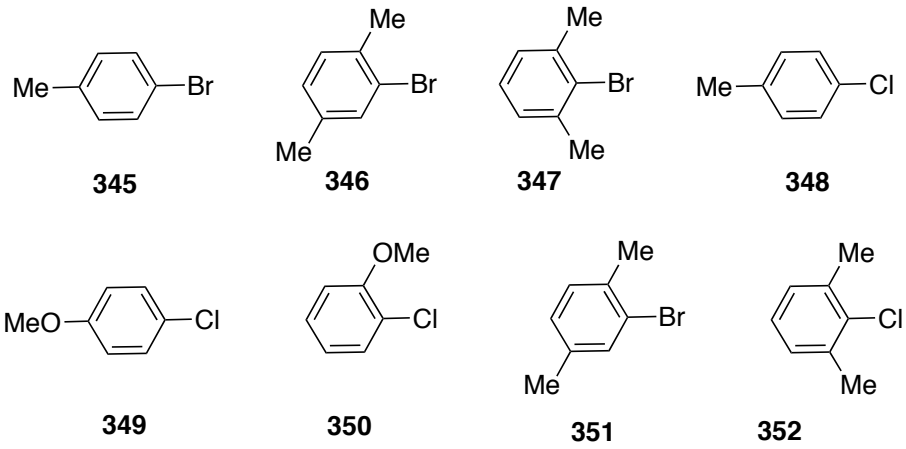
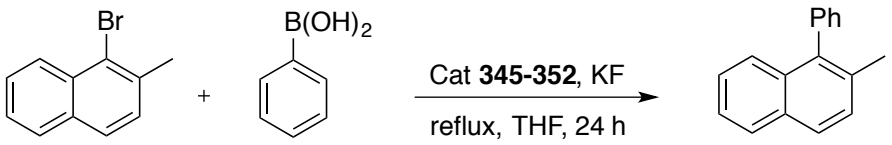


Figure 43. Substrates used for analysis of ligand 225 in the Suzuki cross-coupling.

Addition of ligand **225** gave excellent conversion to the corresponding product and the use of precatalyst **293** over **225** gave even better results.[166]

This earlier methodology was then extended in this work to test a range of preformed palladacycles in a Suzuki cross-coupling reaction (**Scheme 118**, **Figure 44**, **Table 17**).



Scheme 118. Effect of the palladacycle used in a representitive Suzuki cross-coupling.

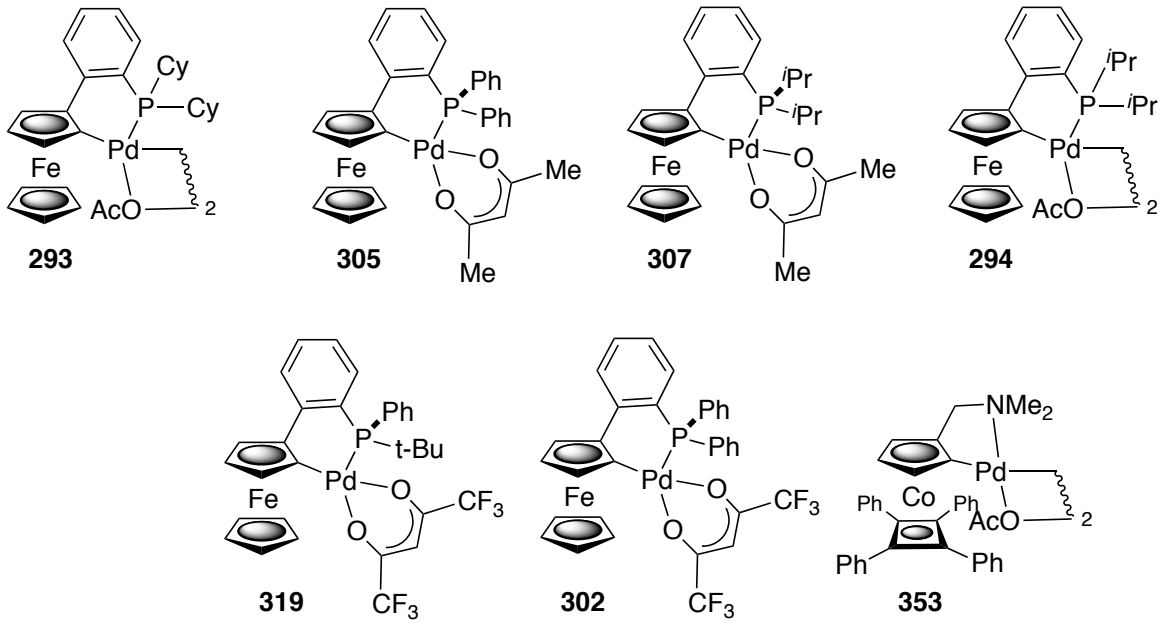


Figure 44. Palladacyclic precatalyst implemented into the Suzuki cross-coupling study

Entry	Catalyst	Yield (%)[b]
1	**293**	73
2	**305**	80
3	**307**	42
4	**294**	76
5	**319**	84
6	**302**	80
7	**353**	41
8	**353**[(a)]	45

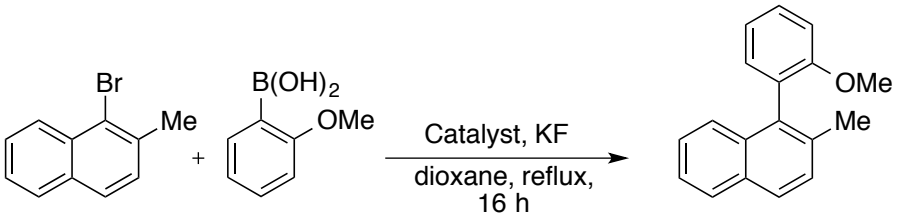
(a). addition of 10 Mol% of PPh_3 (b). determined by ^{1}HNMR

Table 18. Suzuki Cross-Coupling

All the palladacycles that were tested showed very good catalytic activity, giving the bi-aryl product in good yield. It is also known in the literature that amine based palladacycles do not show good activity in $Pd^{(II)}$ to $Pd^{(0)}$ systems. However, as shown in **Table 18** complex **353** in run 8 with 10 mol% of PPh_3 showed >40% conversion.

Another development of this topic was to test similar palladacycles in an asymmetric Suzuki cross-coupling, for two reasons: 1) to show if the palladacycles are active in a somewhat challenging cross-coupling, and 2) to test if there is any transfer of *ee* from the catalyst to the coupled product.

It is well documented that symmetrical phosphines cannot transfer any planar chirality from the catalyst to the product as dissociation of the C-Pd bond can lead to the loss of any chiral information. It is theorised that when using a chiral phosphorus species, the chirality stored at the phosphorus centre may lead to a degree of enantioselectivity in a cross-coupling reaction. This was then tested with the coupling of 1-bromo-2-methyl-napthalene and 2-methoxyphenylboronic acid in dioxane with potassium fluoride as a base. Catalyst runs were first carried out in THF and did not show any conversion, therefore, the solvent was changed to dioxane (**Scheme 119**, **Figure 44**, **Table 19**)



Scheme 119. The effect of palladacycles on a representative asymmetric Suzuki cross-coupling.

Entry	Catalyst	Conversion % (^{1}H NMR)
1	**307**	1
2	**304**	1
3	**294**	3
4	**298**	0.3
5	**296**	4
6	**295**	2.8
7	**293**	3.9
8	**297**	0.27
9	**353**	11
10	**354**	8
11	**319**	21

Table 19. The effect of palladacycles on the yield of an asymmetric Suzuki cross-coupling

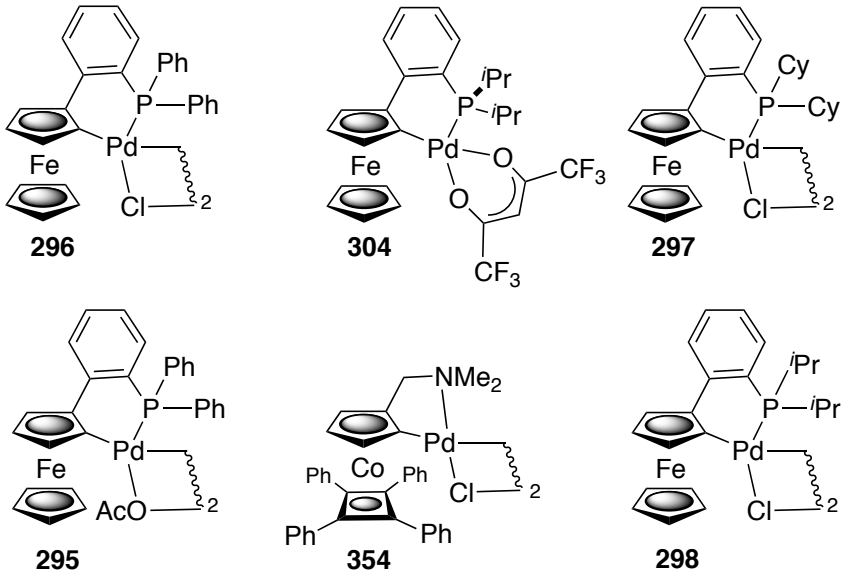


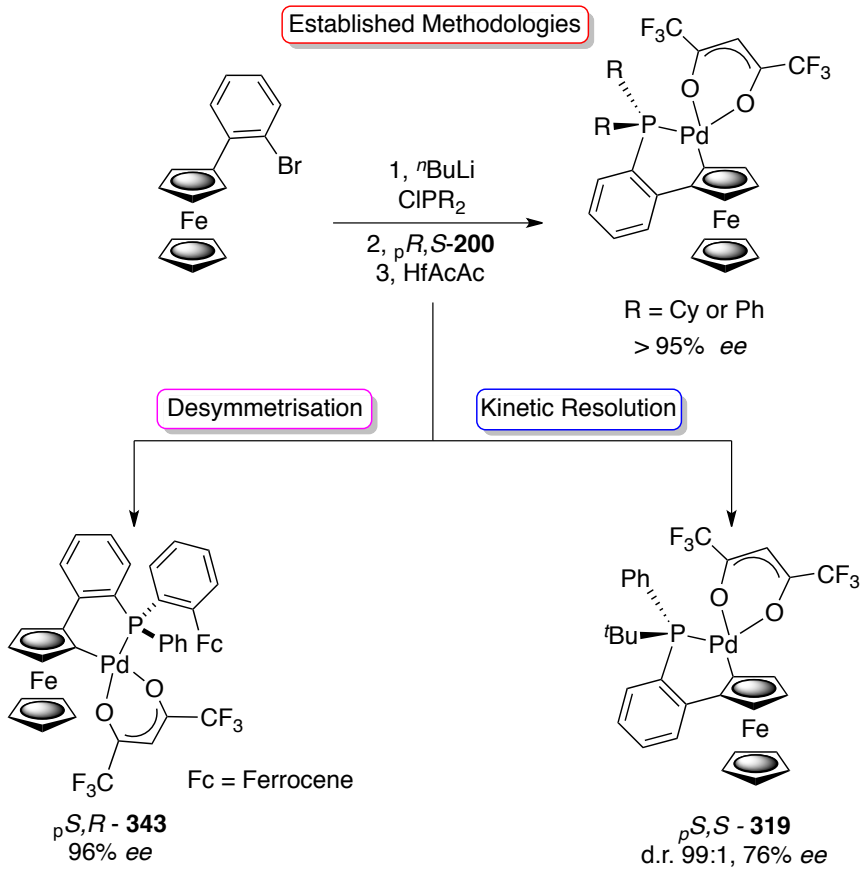
Figure 45. Palladacycles implemented into an asymmetric Suzuki cross-coupling.

As shown in the table above many attempts did not yield good levels of conversion but catalyst **319** did show a 21% conversion. However, the low level of conversion, whilst establishing that a planar chiral and chiral at phosphorous can catalyse the Suzuki cross-coupling reaction. The enantioselectivity of this process was not analysed as **319** used for this process was not enantioenriched.

17.0 - Conclusion.

The synthesis of palladacycles from phosphines has been developed by expanding procedures already present in the literature.[166] Racemic palladation with palladium acetate in dichloromethane afforded the corresponding palladacycles in high yield, avoiding the formation of an unknown palladium species. Facile ligand exchange has also led to the formation of new chloride, acac or hfacac bridged palladacycles. The existing protocol reported by Richards *et al.,* involving enantioselective transcyclopalladation, has been applied to a range of P-chiral phosphine ligands, giving rise to a novel class of enantioenriched diastereomerically pure phosphopalladacycles. The effect of substituents attached to the phosphine has also been analysed, showing that phosphine **290** is the most selective giving one diastereoisomer at 40 ^{o}C in toluene with 79% *ee*. This method was developed to include the desymmetrisation of symmetrical phosphine **254**, which

afforded palladacycle **343** in 96% *ee* as a single diastereoisomer. A promising result arose from the asymmetric Suzuki cross-coupling with P-chiral catalyst **319** giving 21% conversion (**Scheme 120**).



Scheme 120. Transcyclopalladation of a chiral and pro-chiral phosphine

Chapter 4

Attempted Synthesis of Planar Chiral Metallocenes via a C-H activation protocol

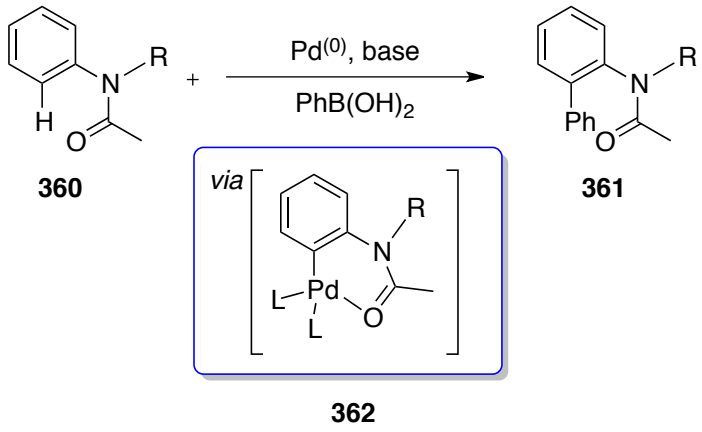
17.1 - Diastereoselective C-H Activation of Metallocenes.

C-C bond formation is an important process within organic synthesis and the Suzuki-Miyaura coupling is one of the most useful methods known which has been applied in the synthesis of many natural products, synthetic drugs and materials.[227] Recent advances in the field have allowed the use of relatively cheap starting materials including readily available organic chlorides, but an ideal and environmentally friendly method of constructing C-C bonds would be the direct functionalization of C-H bonds.[228]

Several efforts have been made to develop a transition metal catalyzed C-H functionalization and the direct arylation of aromatic C-H bonds have been developed with or without directing groups to construct a bi-aryl structural motif, which is an important scaffold in many pharmaceutical relevant and biologically active compounds.[229,230]

C-H bond activation can offer a direct route to C-M intermediates that are also accessible through oxidative addition of a low valent transition metal complex to organic halides. However, the direct activation of C-H bonds could lead to the same valuable products but avoid the requirement of the presence of halides in the starting material. This process can also be achieved using other methods but processes to form C-C bonds by Suzuki-Miyaura type coupling have been sparsely reported within the literature.[231] Yu. *et al.*[232] have reported the alkylation of sp^3 or sp^2 C-H bonds directed by pyridinyl and carboxylic groups, and Sames *et al.*[233] have reported the arylation of sp^3 C-H bonds catalyzed by ruthenium complexes with a boronic ester by using a heterocyclic directing group. These methods have now been extended to palladium mediated C-H bond activation affording highly regioselective *ortho*-arylation of aromatic C-H bond using a Suzuki-Miyaura type coupling with boronic acid directed by acetyl amino group. Yang *et al.* reported the highly

regioselective halogenation of acetanlides by using $Pd^{(II)}$ catalysed Suzuki-Miyaura type coupling under basic conditions. This can also be used in a C-H activation mediated Suzuki-Miyaura type coupling, which travels through a palladacycle intermediate (**Scheme 121**).

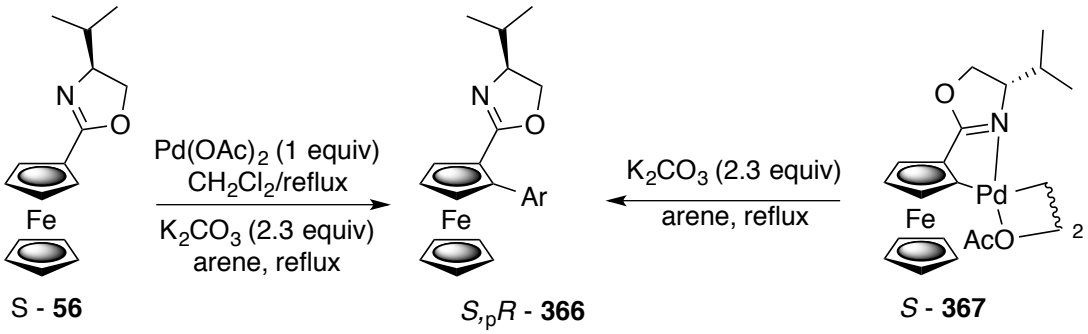


Scheme 121. Design of direct Suzuki-Miyaura coupling reaction with Pd-catalysed C-H bond activation

Palladacycle **362** can then undergo transmetallation with a range of boronic acids and, reductively eliminate to form a new C-C bond. This procedure has recently been extended to synthesise novel bi-substituted chiral metallocenes.

Ferrocene derivatives have been extensively used in homogenous catalysis, organic synthesis and materials and the facile synthesis of said compounds, exhibiting planar chirality are in great demand.[234] Shu-Li You envisaged that a directing group introduced to ferrocene would afford preferentially a proximal C-H activation on the cyclopentadienyl ring to initiate the coupling process, and possibly reduce the percentage of the homocoupling side product. You utilised a ferrocene oxazoline for this purpose due to its potential for wider applications within asymmetric catalysis.[235] This process was applicable to the highly diastereoselective synthesis of planar chiral ferrocenyl oxazoline derivatives. Heating **59** to reflux in benzene without any base did not lead to the formation of the product and addition of K_3PO_4 led to an 8% yield. Heating **59** to reflux in benzene with 1 equivalent of $Pd(OAc)_2$ led to the formation of the palladacycle intermediate in good yield. When this was subjected to the above condition the yield of the C-H coupled product increased to 69%, whereas without prior palladacycle formation the best yield attained was a mere 24%. You screened various coupling partners and it

was found that the protocol was resistant to range of arenes, giving a number of regioisomers depending on the arene used (**Table 20**, **Scheme 122**).



Scheme 122. Cross coupling reactions with Arenes.

Entry	Arene	Method	Temp ^{o}C	Time (h)	Yield (%)
1	Benzene	A	100	11	70
2	Toluene	A	100	24	44 (*m*/*p*: 2.7:1)
3[d]	Toluene		100	8	47 (*m*/*p*: 2.6:1)
4	Fluorobenzene	A	100	24	63 (*o*/*m*/*p*: 13.3:9:1)
5	^{t}Butylbenzene	C	100	48	32 (*m*/*p*: 1.7:1)
6	1,4-Dimethyoxybenzene	C	120	82	26
7	2,3-Benzofuran	B	100	51	37
8	Mesitylene	C	120	120	NR
9[e]	Pentafluorobenzene	C	120	40	complicated

[a] Methods : A **59** (0.3 mmol) and $Pd(OAc)_2$ (0.3 mmol) in arene (1.5 mL) were heated for 3 hours, then K_2CO_3 (0.69 mmol) was added. B: **59** and $Pd(OAc)_2$ in dichloromethane were refluxed for 3 hours; after removal of solvent, K_2CO_3 and arene was added and heated. C: **59**, $Pd(OAc)_2$ were heated in arene. [b]The temperature of the oil bath. [c]isolated yield based on recovered starting material. [d]Isolated dimer was used. [e]complex mixture was given.

Table 20. Cross coupling reactions with Arenes

Under optimised conditions, several other arenes have also been tested in the aforementioned cross-coupling reaction with **59**. When toluene was used, the isolated yield was 42% with a regiomeric ratio of 2.7:1 (*m*/*p*). When the isolated palladium dimer was used an identical result was observed. Fluorobenzene was also suitable for the cross-coupling and afforded 3 regioisomers 13.3:9:1 (*o*/*m*/*p*) in 63% yield. With respect to *tert*-butylbenzene, 32% yield of the mono-substituted and 6% of the bi-coupled product were

obtained. The lack of the *ortho* product here is due to the steric bulkiness of the *tert*-butyl group.

An intriguing feature of ferrocene derivatives is the introduction of planar chirality when two different groups are installed on the same cyclopentadienyl ring. Under the optimised conditions, the possibility to synthesise non-racemic planar chiral derivatives is potentially feasible by utilising enantiopure ferrocenyl oxazoline as a result of a diastereoselective palladation. Starting from ferrocenyl oxazoline, direct C-H bond activation of this compound afforded the corresponding coupled product in 24% yield (**Scheme 122**). This result was improved when the palladacycle dimer **367** was used in the presence of K_2CO_3. To synthesise the opposite diastereoisomers, ferroceneoxazoline was a lithiated and this was further reacted with TMS-Cl. The silyl-protected species was then subjected to the same C-H activation protocol and the subsequent deprotection with TBAF afforded the opposite diastereomer. Cross-coupling reactions with catalytic palladium acetate and an extra oxidant was also explored, but led to poor conversion.

17.1 – Enantioselective C-H Activation of Metallocenes, Application to the Suzuki Cross-Coupling.

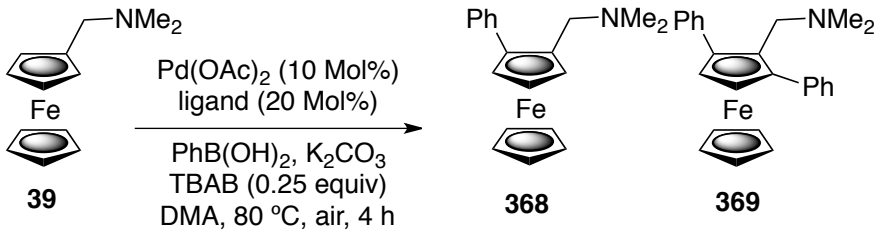
You *et al.* developed his application of a highly diastereoselective palladation of ferrocene oxazoline, and adapted methods from Sokolov and Richards, to successfully implement an enantioselective synthesis of planar chiral ferrocene ligands *via* palladium catalysed directed coupling of aryl boronic acids. [236]

The most widely used strategy is diastereoselective *ortho*-metalation induced by various chiral auxiliaries, where chirality must be pre-installed. [237] Snieckus and co-workers developed an enantioselective *ortho*-metalation of ferrocene derivatives with an external chiral base such as (-)-sparteine, which provides a straight forward route to planar chiral ferrocene derivatives. Recently, Ogasawara and co-workers reported an elegant method of the synthesis of planar chiral ferrocene through ring-closing metathesis. However, the catalytic enantioselective synthesis of planar chiral-ferrocenes still remains rare.

The highly challenging topic of catalytic enantioselective C-H activation has progressed rather slowly. Breakthroughs recently have been achieved by Yu and co-workers, who

discovered that chiral mono protected amino acids can serve as an effective ligand to facilitate enantioselective C-H activation of prochiral substrates.

Commercially available amino acid derivatives were found to be highly effective ligands for palladium catalysed direct C-H activation of ferrocene with boronic acids.[238] The conditions developed were relatively mild, general and afforded highly enantioselective ferrocene derivatives. Studies began with dimethylaminomethyl ferrocene as a substrate, utilising phenylboronic as the coupling partner, 10 mol% $Pd(OAc)_2$, K_2CO_3, *tetra*-butyl ammonium bromide (TBAB) in dimethylformamide, in the presence of air at 80 ^oC. This reaction proceeded to the desired product in 58% yield and 98% *ee*, which was determined by chiral HPLC, and the addition of TBAB improved the yield to 74% without effecting enantioselectivity (**Table 21**, **Scheme 123**).[236]



Scheme 123. Screening of protected amino acids.

Entry	Ligand	**368**/**369**[b]	Yield (%)[c]	*ee (%)*[d]
1[e]	Boc-*L*-Val-OH	42:1	58	97
2	Boc-*L*-Val-OH	8.3:1	74	98
3	Boc-*L*-Phe-OH	8.7:1	71	98
4	Boc-*L*-Abu-OH	10:1	64	94
5	Boc-*L*-Ala-OH	4.2:1	61	92
6	Boc-*L*-Leu-OH	20:1	51	96
7	Boc-*L*-Ile-OH	9.5:1	70	97
8	Boc-*L*-Tle-OH	9:1	75	98
9	Boc-*L*-Nva-OH	6.4:1	69	96
10	Boc-*L*-Phg-OH	6.5:1	48	81
11	Ac-*L*-Val-OH	10:1	60	88
12	Cbz-*L*-Val-OH	25:1	52	96
13	Fmoc-*L*-Val-OH	-	19[b]	-
14[f]	Boc-*L*-Val-OH	20:1	79	98
15[g]	Boc-*L*-Val-OH	50:1	59	97

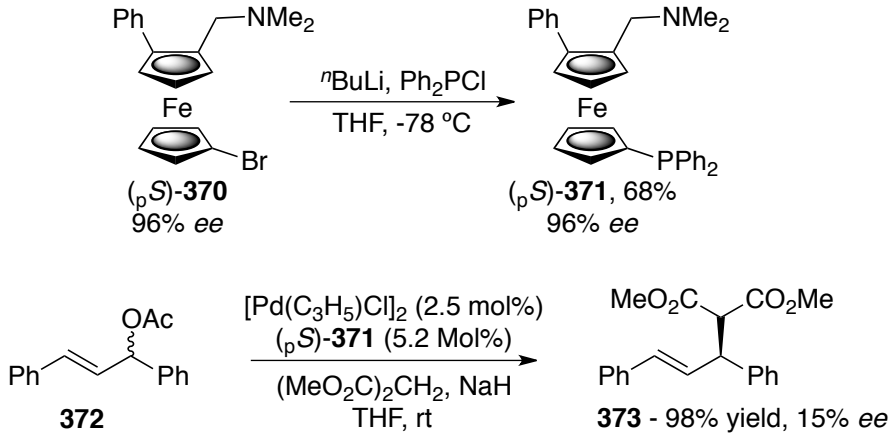
[a]Reaction conditions: **39** (0.2 mmol), $PhB(OH)_2$, $Pd(OAc)_2$ (10 mol%), ligand (20 mol%), K_2CO_3 and TBAB (0.25 equiv) in DMF at 80 °C in air. [b]Determined by ^1H NMR analysis with CH_2Br_2 as the internal standard. [c]Isolated yields. [d]Determined by HPLC analysis analysis. [e]Without TBAB. [f]At 60 °C. [g]At 40 °C.

Table 21. Screening of amino acids.

You screened many protected amino acid ligands and all entries gave the desired product in good yield and moderate to good enantioselectivity.[236] Boc-*L*-valine and Boc-*L*-*tert*-leucine proved to be the most efficient chiral ligand in terms of enantioselectivity and reactivity, giving the desired product in 74-75% yield and 98% *ee*. It was also found that the protecting group on the nitrogen of valine proved to have a dramatic impact on reactivity and enantioselectivity. Lowering the temperature to 60 °C slightly improved the yield to 79%. Notably, a kinetic resolution for the formation of the bi-phenylated product led to an increase in *ee*.

17.2 – Application of Planar Chiral Ferrocene Containing Metallocenes.

You also tested the practicality of the methodology and a relatively large-scale reaction was carried out. Amine **370** was synthesised on a 2 mmol scale without erosion in either the yield (73%) or enantioselectivity (98%). In further demonstration of the utility of this methodology, the planar chiral *P*,*N*-ligand **370** was prepared from **371** (96% *ee*). Lithiation with butyllithium followed by addition of chlorodiphenylphosphine to give **371** in 68% yield with 92% *ee*. This ligand has also been shown to catalyse an enantioselective allylic alkylation, giving the desired product in high yield (98%) but poor *ee* (15%) (**Scheme 124**).[236]



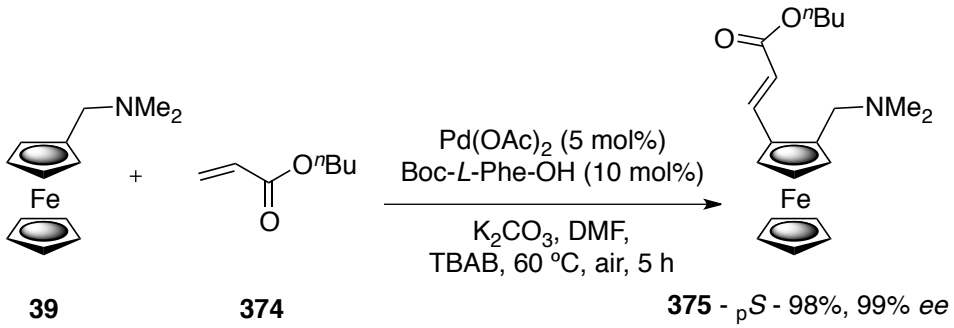
Scheme 124. Further derivatisation of 370 and application to asymmetric catalysis

In parallel to this work Wu *et al.* followed a similar pathway and subjected the reaction to Heck coupling conditions, which afforded some very promising results.[239]

Palladium catalysed reactions of Ar-H with olefins (dehydrogenation Heck reaction) has emerged as a powerful protocol for C-C bond formation over the recent years.[240] This strategy provides a more direct approach to build a carbogenic core of sophisticated molecules.

17.3 – Application of Heck Protocol for the Synthesis of Novel Planar Chiral Metallocenes.

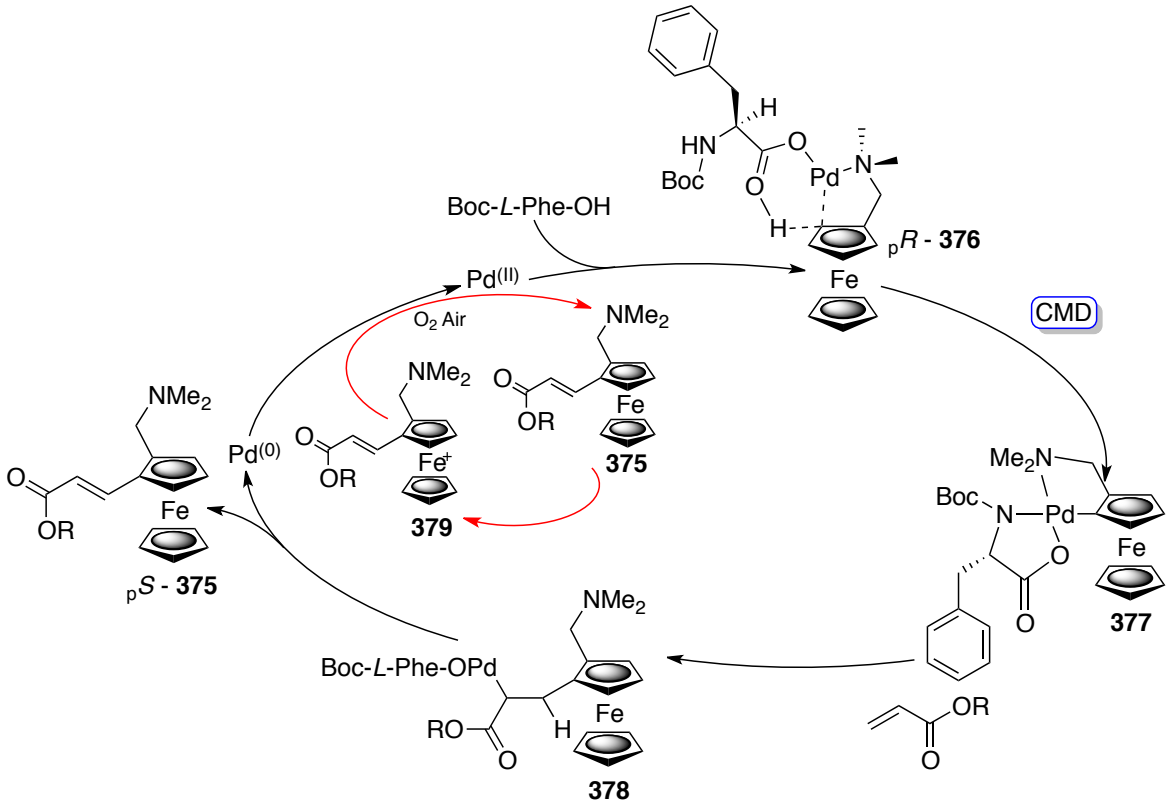
Dehydrogenitive Heck reactions occur with $Pd^{(II)}$ as a promoter and generate products and $Pd^{(0)}$. In most cases, and external oxidant is required to generate the active catalytic species $Pd^{(II)}$, which would require a stoichiometric amount of the oxidant and therefore reduce the overall greenness of the reaction.[241] The application of the N-O bond as both a directing group and internal oxidant, avoiding the use of an external oxidant and deprotection step, have been established. Yu *et al.*,[242] Hartwig *et al.*[243], Guimond *et al.*[244] reported other successful cases using entities in the dehydrogenitive coupling reaction. Internal oxidants generally require an additional step for implanting the oxidising directing group in the substrate. Wu *et al.* has recently reported a novel protocol to build ferrocene functionalised naphthalenes *via* palladium catalysed direct dehydrogenative annulations of *N*,*N*-dimethylaminomethyl ferrocene and internal alkynes.[245] In this catalytic process, the *N*,*N*-dimethylaminomethyl ferrocenium was generated *in situ* by atmospheric oxygen and this served as a terminal oxidant to generate the active $Pd^{(II)}$ species from reduced $Pd^{(0)}$ species. This has now been applied to the palladium-catalysed Heck reaction (**Scheme 125**).



39 **374** **375** - $_pS$ - 98%, 99% *ee*

Scheme 125. Application of mono-protected amino acid ligands to palladium mediated Heck cross coupling.

After screening many mono-protected amino acids it was found that Boc protected phenylalanine gave the best yield and the best enantioselectivity. Wu alludes to the fact that oxidation of the ferrocene moiety to ferrocenium is an integral part in the oxidation of palladium from $Pd^{(0)}$ to $Pd^{(II)}$ (**Scheme 126**).

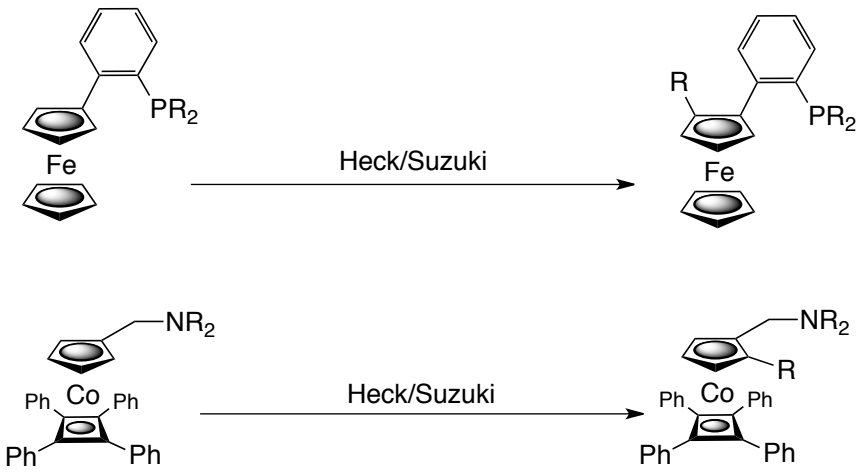


Scheme 126. Proposed mechanism for the Heck cross coupling using air.

Cyclopalladated *N*,*N*-dimethylaminomethylferrocene is formed *via* coordination of the palladium atom to nitrogen and subsequent enantioselective electrophilic attack at the 2-position, through intermediate **376**. The cyclopalladated complex coordinates with the alkene olefin followed by *syn* insertion and β-hydride elimination. Finally, $Pd^{(0)}$ is oxidised by *N*,*N*-dimethylaminomethyl ferrocenium to $Pd^{(II)}$, completing the catalytic cycle.

17.3.1 – Project aims.

The natural progression of this work is to implement both the Heck and Suzuki protocols to phosphino ferrocenes and cobalt metallocenes (**Scheme 127**). The aim is to produce a range of planar chiral amine and phosphine based metallocene ligands with the aforementioned methods by Yu and You. This will also be progressed to produce a class of bi-denate phosphine ligands.



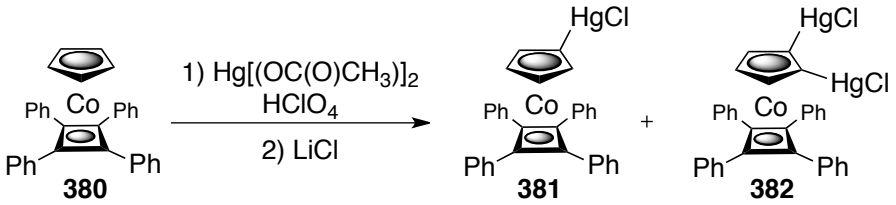
Scheme 127. Proposed novel C-H activation protocols.

In recent years Richards *et al.* has carried out a great deal of work on cobalt sandwich complexes from their synthesis to application. [246] Much work has been established on the synthesis and application of cobalt sandwich containing palladacycles but their functionalisation is far from trivial due to inactivity compared to ferrocene or other metallocene sandwich complexes. Their mono-functionalisation is well documented in a publication by Genetti and co-workers.[247]

17.4 - Synthesis of Novel Cobalt Sandwich Containing Complexes.

Although the concepts of aromaticity are still not well defined, ferrocene and related organometallic compounds are generally considered to be aromatic in that they resist ring addition reactions and undergo ring substitution reactions. Ferrocene is known to undergo various electrophilic substitution reactions such as Friedel-Crafts acylation,[248] alkylation, [249] formulation, [250] sulfonation, [251] and acetoxymercuration. [252] However, organocobalt compound π-cyclopentadieneyltetraphenylcyclobutadiene (**380**) was first prepared in 1961 by Nakamura and Hagihara,[253] and later by Wilkinson *et al.*[254] This compound possessed the necessary chemical stability and electronic configuration to undergo similar substitution reactions without appreciable concurrent decomposition under the reaction conditions involved. The most important ring substitution reaction of (**380**) in terms of developing the chemistry of this system has been the

acetoxymercuration. Treatment of **380** with mercuric acetate in dichloromethane containing perchloric acid, followed by the addition of lithium chloride, resulted in the formation of complexes **381** and **382**. This mercuration is a modification of the procedure described by Brown and co-workers.[255] Complex **381** has proved to be a valuable derivative, since a large number of new organometallic compounds can be derived from it (**Scheme 128**).



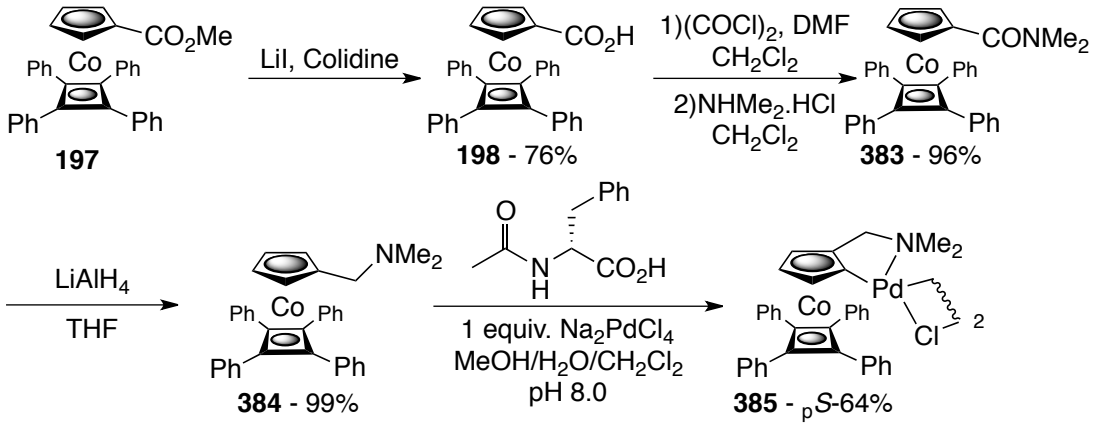
Scheme 128. Chloromercuration of 380.

From this publication and more recent bodies of work, the disubstitution of **380** is still a sought after methodology.

17.5 – Synthesis and Application of Cobalt Sandwich Complex Containing Amines.

In 2013 Richards *et al.* described the synthesis of a range of cobalt sandwich containing amines and their subsequent C-H activation to form a new class of aminopalladacycles and their application to the allylic imidate rearrangement. [256]

In these reactions the palladium-carbon bond in the palladacycle is maintained throughout the process. There are also numerous other examples of chiral palladacycle catalysed asymmetric transformation, which have been recently reported. As mentioned before, another application of palladacycles is the *in situ* generation of $Pd^{(0)}$, where the palladacycle is used as a pre-catalyst to another asymmetric transformation. The final and most relevant application of palladacycles is the development of an enantioselective C-H bond activation to afford planar chiral bi-substituted metallocene complexes (**Scheme 129**).

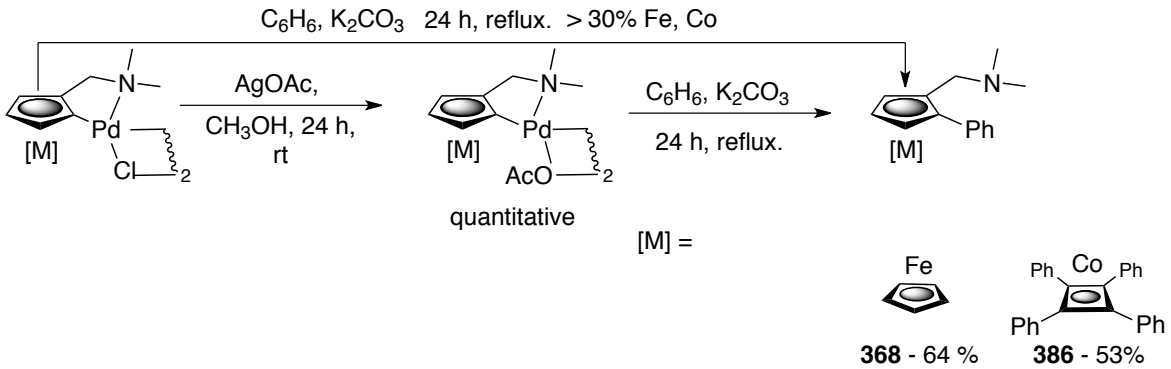


Scheme 129. Synthesis of palladacycle 385.

Amine **384**, a cobalt sandwich complex analogue of dimethylaminomethyl ferrocene, was first synthesied as previously reported from Mannich-type reaction of **380** with bis(dimethylamino)methane.[257] The low yielding of this reaction, typically 40%, led to the synthesis of acid **198**, which was converted to amide **383** and reduced by lithium aluminium hydride to **384** in good yield which is then palladated using known methodologies.[258] This work was first published by Richards *et al.* and was repeated in order to synthesise the starting material for the aforementioned C-H activation protocol.

17.6 – Mono and Di – C-H Activation of Amine 384.

Palladacycles derived from **384** were subjected to a double C-H activation protocol where it was heated to reflux refluxed in benzene to give the C-H coupled product in 53% yield (**Scheme 130**).[256]



Scheme 130. Attempted application of a double C-H activation.

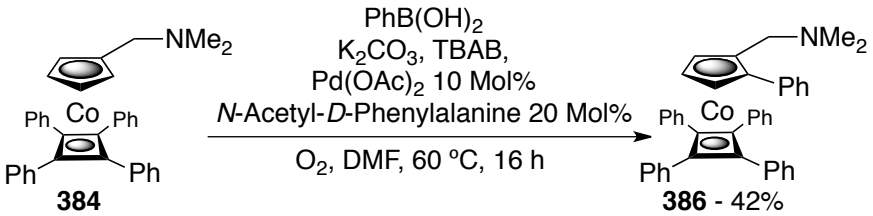
The acetate-bridged dimer is key to the success of this reaction as the acetate ligand is required to aid in the deprotonation of the arene. Reaction of the chloride bridged dimer, product of an enantioselective amino acid mediated palladation, with silver acetate gave quantitative conversion to acetate dimer and upon addition of potassium carbonate in benzene gave C-H coupled product in 53% yield. Reaction with chloride-bridged dimer only gave less than 30% yield. Both reactions use stoichiometric quantities of palladium and a catalytic protocol was sort after. Catalytic quantities of palladium acetate and amine **384** with a range of oxidants and potassium carbonate did not give the C-H coupled product in good yield. The yield closely resembled the quantity of palladium acetate used within the system indicating the lack of palladium turnover (**Table 22**).

Run	Pd loading	Oxidant	Yield
1	10 mol%	Benzoquinone	>10%
2	10 mol%	$Cu(OAc)_2$	>10%
3	10 mol%	O_2	15%
4	10 mol%	AgOAc	Decomposition

Table 22. Oxidant test.

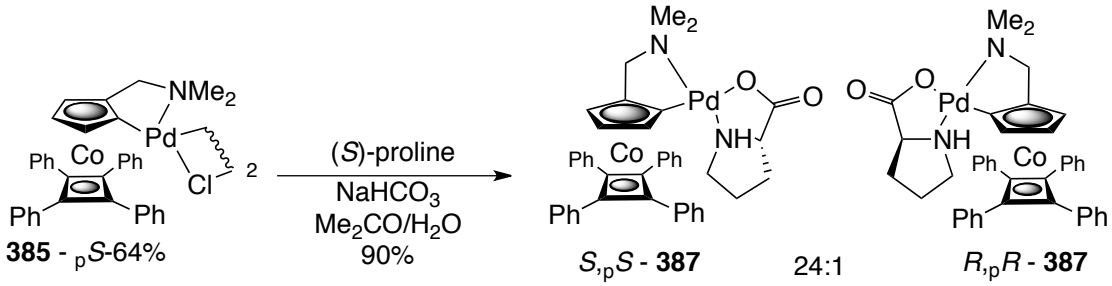
17.7 – Suzuki Cross-Coupling of Amine 384.

The natural progression of this work was to mirror the conditions used by You and implement an enantioselective Suzuki cross coupling (**Scheme 131**).



Scheme 131. Application of You's conditions.[236]

The absolute stereochemistry of this process is predicted to be $_pS$ on the basis of a recent publication by Richards *et al.* (**Scheme 132**).



Scheme 132. Proline derivatisation of 384.

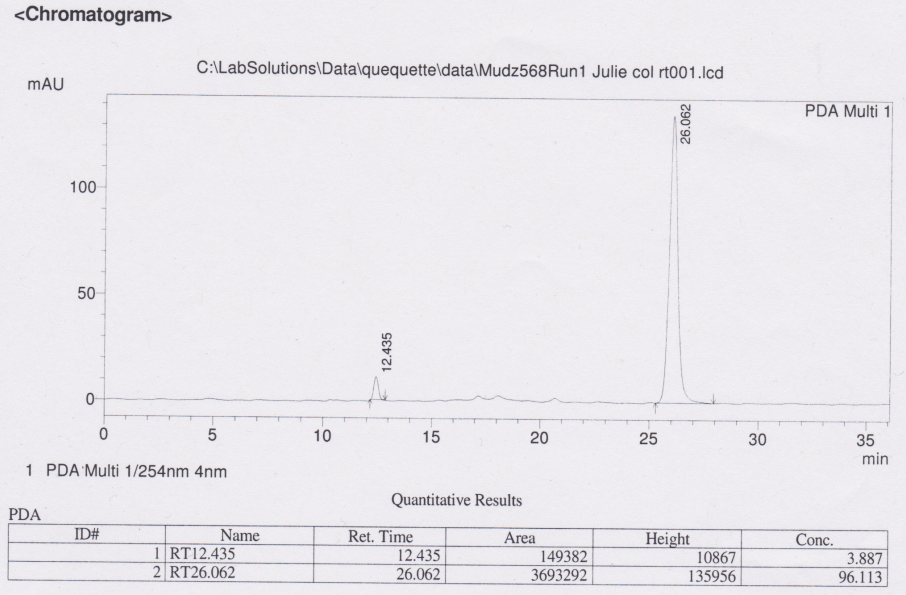
Formation of the proline adducts and recrystallisation from CH_2Cl_2/hexane of the proline adducts derived from an asymmetric palladation showed that the major diastereoisomer configuration of element of planar chirality was determined as $_pS$ by X-ray crystallography. Under this assumption it can be predicted that the absolute stereochemistry of this process must also be $_pS$ because of the intermediacy of a palladacycle

In light of the results by You,[236] only 4 amino acids were tested to see which would give the best selectivity and yield (**Table 23**).

Run	Ligand	Yield	*ee* ($_pS$)
1	Boc-valine	61%	93%
2	Boc-phenylalanine	54%	63%
3	*N*-Acetyl-valine	57%	68%
4	*N*-Acetyl-phenylalanine	42%	81%

Table 23. Ligand screening C-H activation.

Chiral HPLC analysis of phenylated product showed good separation of both enantiomers and the best selectivity came from Boc-valine (**run 1**, 93% *ee*) (**Figure 46**).



Quantitative Results

PDA

ID#	Name	Ret. Time	Area	Height	Conc.
1	RT12.435	12.435	149382	10867	3.887
2	RT26.062	26.062	3693292	135956	96.113

Figure 46. HPLC analysis of run 1.

Identification of the product was relatively straightforward as the hydrogens on the methylene group adjacent to the dimethylamino group are now diastereotopic and both protons spilt into doublets (3.03 (d, *J* = 13.2 Hz, 1H, CH_2), 2.67 (d, *J* = 13.1 Hz, 1H, CH_2)).

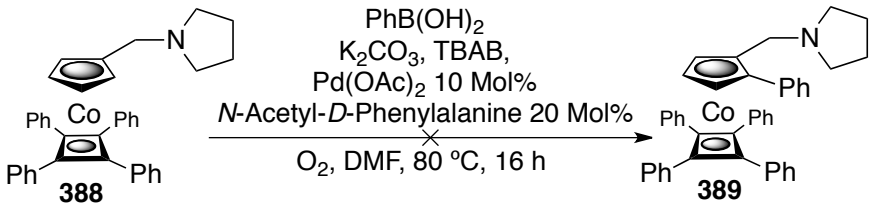
Boc-valine was chosen as one of the ligands because in the work carried out by You it was shown to give the best selectivity, and this was consolidated by our result. If the transformation does travel through a palladacycle intermediate the enantioselectivy of the run carried out with *N*-acetyl phenylalanine would match or be similar to that of the enantioselective palladation of **384** outlined previously by Richards *et al.*

The addition of TBAB to the reaction had no real effect on the enantioselectivity but did marginally increase the yield and gave cleaner conversion. Our results closely matched that of You, showing that Boc-protected ligands gave the best selectivity closely followed by N-acetylphenyl alanine.

When the reaction was carried out at lower temperatures there was an issue seen with solubility but with a temperature higher than 80 ^{o}C the reaction preceded with no major issues. It was also important to check the internal temperature of the reaction.

The pyrrolidine substituted analogue was also synthesised using methods quoted by Richards *et al.* and the application of the aforementioned enantioselective palladation protocol afforded the best selectivity (> 98% *ee*). When this was applied to You's C-H activation protocol it did not yield any desired product. [236] The NMR spectra was seen to

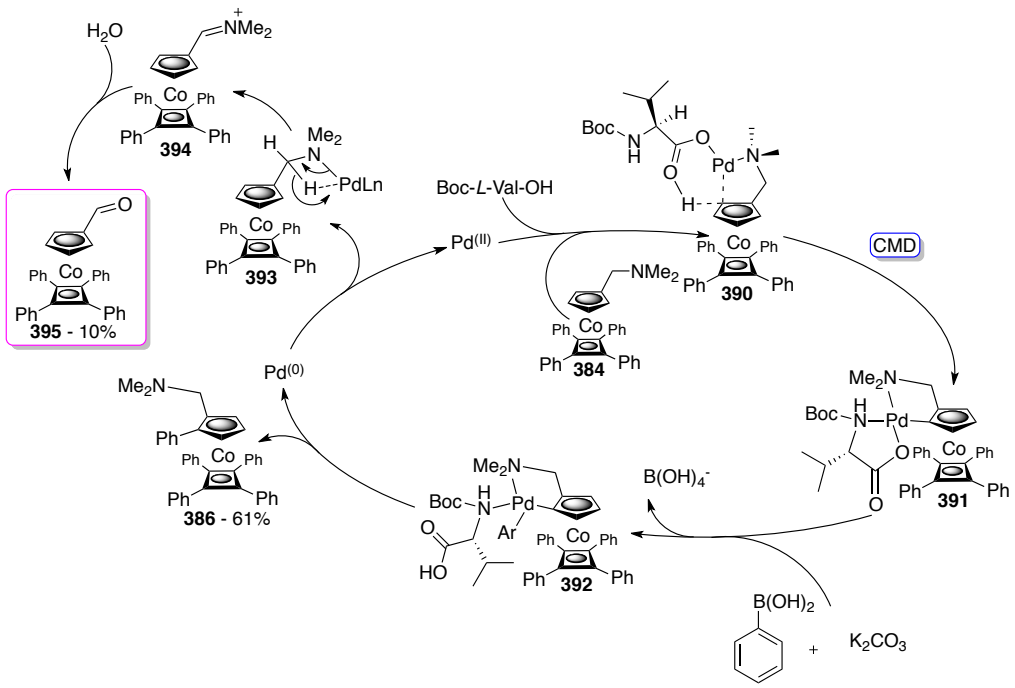
contain a complex mixture of compounds one if which was an aldehyde which may be formed by oxidation of the amine moiety (**Scheme 133**).



Scheme 133. Attempted application to 388.

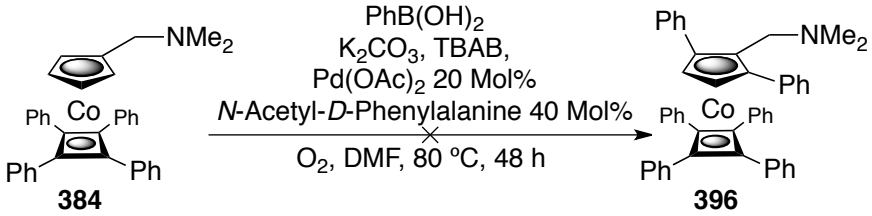
17.8 - Formation of a Secondary Aldehyde Species.

On repetition of the You methodology to *N*,*N*-dimethylaminomethylferrocene and cobalt complex **384** there was noticeable formation of an aldehyde at 9.95 ppm and 9.22 ppm, respectively, in the crude NMR and after flash chromatography. [236] It is hypothesised that formation of aldehyde **395** is due to secondary binding of palladium to the basic nitrogen, imine formation and attack of water, as the reaction is carried out in air (**Scheme 134**).



Scheme 134. Proposed pathway for aldehyde formation

Amine **384** undergoes a concerted metallation deprotonation step to insert palladium into the C-H bond *via* a chiral carboxylate intermediate. Phenyl boronic acid transmetallates on to the palladium, which is followed by reductive elimination to give the C-H coupled product. The yield of the reaction ranges from 50-60% and it is thought that secondary chelation of palladium to the starting material, followed by β-hydride elimination type process can lead to the *in situ* formation of imine **394** and attack of water leads to the formation of aldehyde **395**. The 10% yield obtained is related to the catalyst loading. Relating back to the work from You, [236] a kinetic resolution protocol takes place leading to bi-substituted metallocene but this is not the case when amine **384** is exposed to the same conditions. Increasing the palladium loading to 20 mol% with 5 equivalents of boronic acid did not give rise to compound **396** (**Scheme 135**).



Scheme 135. Attempted synthesis of 396

17.9 - Boronic Acid Screening.

A range of boronic acids were screened to ascertain the limitations and scope of the reaction (**Figure 47**, **Table 24**).

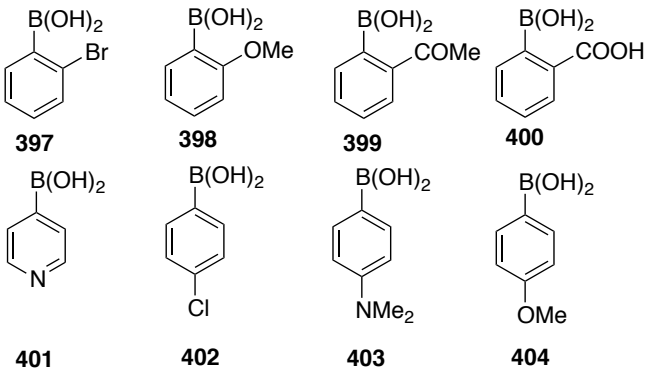


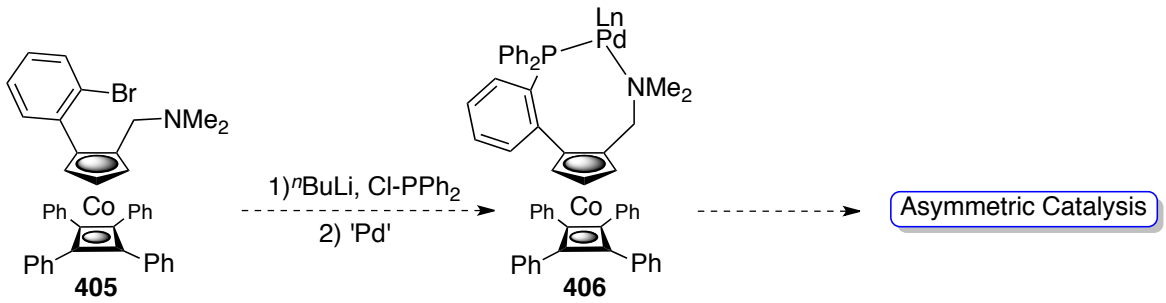
Figure 47. Screening of boronic acids.

Run	Boronic Acid	Result
1	**397**	Complex mixture
2	**398**	< 10% conversion[a]
3	**399**	< 10% conversion[a]
4	**400**	No reaction
5	**401**	No reaction
6	**402**	Complex mixture
7	**403**	No reaction
8	**404**	Complex mixture

[a] calculated from crude ^{1}H NMR.

Table 24. Screening of boronic acids

Compound **397** gave a complex mixture of products. It is possible for the bromine under go oxidative addition on to the palladium and, therefore, couple to the boronic acid. Boronic acid **397** was chosen because it is potentially possible to then lithiated the bromo compound and trap with an electrophile such as chlorodiphenylphosphine, affording phosphorus–nitrogen containing enantioenriched bi-dentate ligand (**Scheme 136**).

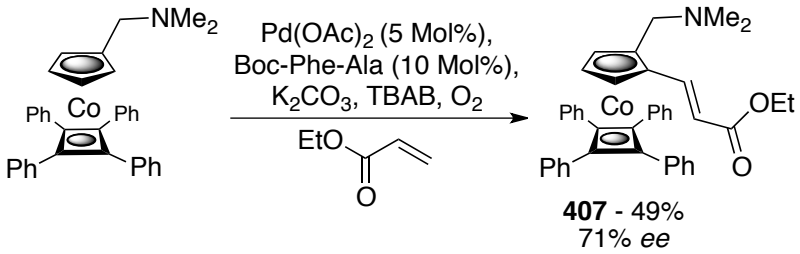


Scheme 136. Potential synthesis of a phosphorus – nitrogen containing enantioenriched bi-dentate ligand.

Compounds **398** and **399** showed trace amounts identifiable from ^{1}H NMR, and **400** and **401** showed no reaction and with respect to **401.** It is possible that secondary binding of the pyridine nitrogen to palladium forming a chelate could hinder the catalytic process.

18.0 - Application to Heck type C-H activation.

Compound **384** was also subjected to Heck type cross coupling conditions closely related to the work by Wu and co-workers. Amine **384**, catalytic quantity of palladium acetate, Boc-Phenyl-alanine, K_2CO_3, TBAB and DMF at 80 ^oC using O_2 (**Scheme 137**).

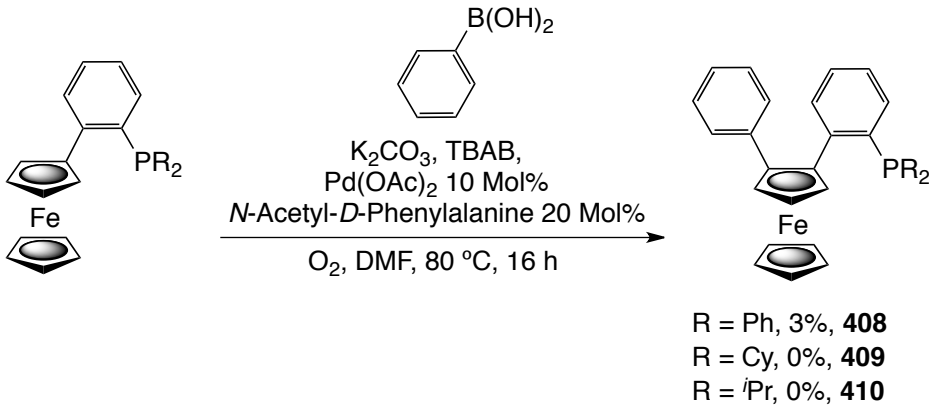


Scheme 137. Heck cross coupling of amine 384.

The reaction above gave **407** in 49% yield and 71% *ee* which was determined by chiral HPLC, but as mentioned earlier **395** was isolated in 10% yield as well as recovered starting material. This particular cross coupling sheds a degree of doubt over the findings by Wu *et al.* He indicated that the oxidation of ferrocene to the ferrocenium is an integral part of the process for the oxidation of palladium from $Pd^{(0)}$ to $Pd^{(II)}$. If this were the case the reaction would not work with its cobalt analogue **384** as this is prone to oxidation. You's group does also not mention this fact and oxidation of ferrocene to the ferrocenium is easy to identify due to the fact that the solution will turn green. Identification of the compound was consolidated by ^1H NMR due to the appearance of the alkene protons being shifted far down field at 7.14 (d, *J* = 15.8 Hz, 1H CH_2) and 5.74 (d, *J* = 15.7 Hz, 1H, CH_2). The same reaction was carried out using styrene in place of ethyl acrylate but no reaction was seen to take place.

18.1 – Ferrocenyl-Phosphine C-H Activation.

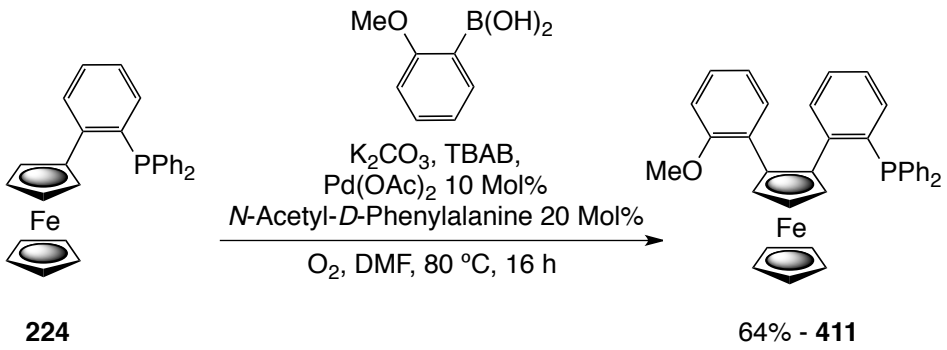
The aforementioned You[236] and Wu[239] methodology were applied to previously synthesised symmetrical and chiral phosphines to afford enantiomerically enriched planar chiral phosphine ligand, which could then be used in asymmetric catalysis (**Scheme 159**).



Scheme 138. Application of You conditions to symmetrical phosphines.

With respect to the formation of **409** and **410,** ^{31}P NMR showed the formation of a new palladium species and the only phosphine analogue to show successful C-H coupling was the diphenyl-substituted phosphine **408**. Crude ^{31}P NMR of the reaction mixture was very diagnostic and showed the formation of mono- and bis-substituted products.

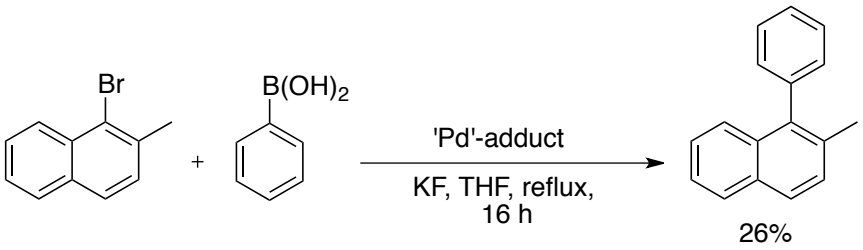
The phosphine precursor has a chemical shift of -12.25 ppm, the mono-substituted product is seen at -13.78 ppm and finally the di-substituted product at -15.29 ppm. This is a very promising result as it is possible that a kinetic resolution is taking place, similar to the results stated by You in their application of this protocol to *N*,*N*-dimethylaminomethyl ferrocene, therefore leading to a greater enantioselectivity of the **408**.[236] The main issue arose when attempting to purify and isolate both compounds. The R_f of the mono and di-substituted were very similar to that of starting material and the only way to obtain a clean sample was to use a preparative thin layer flash chromatography plate. The problem was over-come by using 2-methoxyphenylboronic acid (**Scheme 139**)



224 64% - **411**

Scheme 139. Application of 2-methoxyphenylboronic acid

Compound **411** was synthesised in 64% yield and it was noted that a change in the boronic acid stopped the formation of the di-substituted product. This reaction only worked with 64% yield once and repetition of conditions did not give the same outcome. Application of dicyclohexyl and diisopropyl phosphine analogues did not give any positive results. On repetition of the reaction it was noted from ^{31}P NMR that a palladium adduct was being formed and possibly stopping the completion of the reaction process. This theory was tested by applying the unknown palladium adduct into a Suzuki cross-coupling (**Scheme 140**).

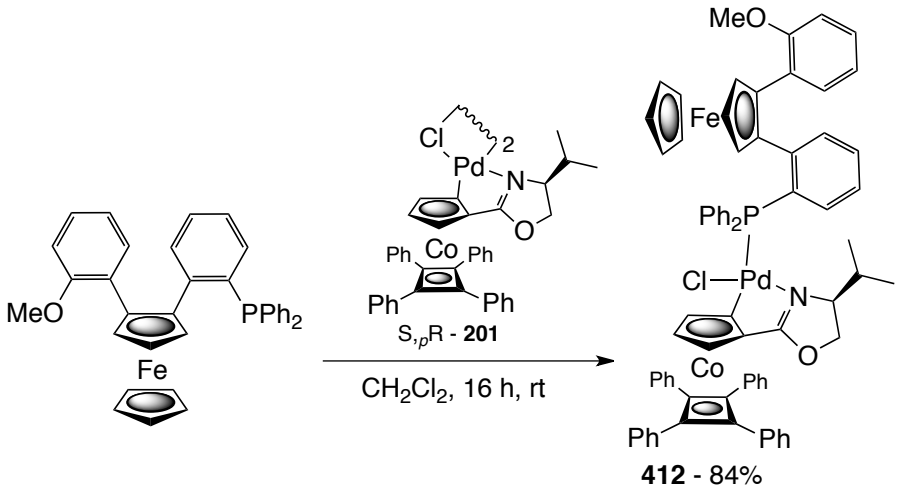


Scheme 140. Test reaction for the presence of an unknown palladium adduct.

The reaction worked in 26% yield proving the formation of an unknown palladium adduct and the C-H activation reaction was not going to completion.

18.2 - Initial Determination of Enantiomeric Excess.

Initial HPLC analysis of compound **411** did not yield any results due to lack of separation, therefore, a resolution by using COP-Cl, similar to the method used in **Chapter 3** was implemented (**Scheme 141**).

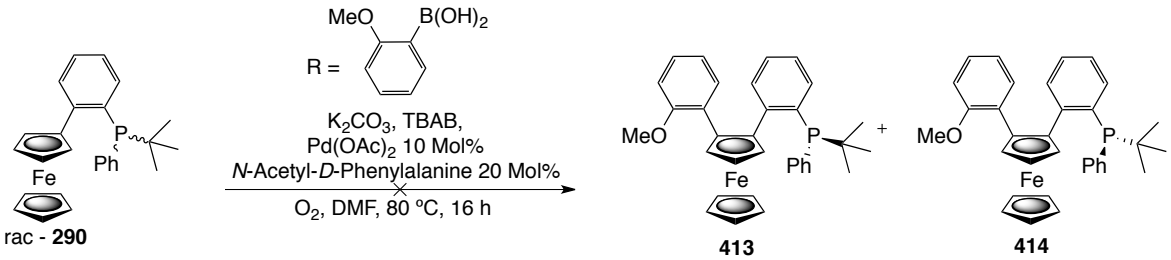


Scheme 141. Formation of adduct 412 for an initial calculation of *ee.*

This method of analysis proved inconclusive because the 64% yield of compound **411** could not be repeated therefore, attempts at enantioselectivity determination were not explored.

18.3 - Application to P-chiral Ferrocenyl Ligands.

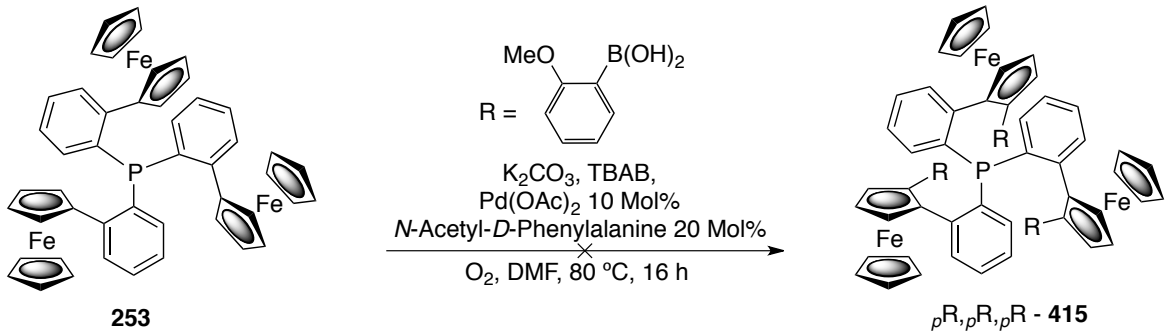
The application of the protocol to P-chiral ligands was a very sought after methodology as one would be able to measure the diastereoselectivity and enantioselectivity of the process. The aforementioned *tert*-butyl-phenyl ferrocene ligand was applied to You's methodology (**Scheme 142**).



Scheme 142. Application to a P-chiral phosphine ligand.

The reaction did not yield any product and it is theorised that the increased affinity of palladium to phosphorous stops the catalytic cycle and therefore no product is formed. This is consolidated by the formation of a palladium adduct at 48.50 ppm, the corresponding phosphine oxide at 40.72 ppm and starting material at 4.52 ppm.

Finally, the protocol was applied to **KetPhos** in order to synthesise a novel C_3-symmetrical enantiomerically enriched phosphine ligand similar to **TomPhos**. As mentioned in **Chapter 2**, the synthesis of **TomPhos**, starting from ferrocene oxazoline is a very arduous and complex synthesis. Application of the You protocol to **KetPhos**, could potentially produce similar ligand in only 2 steps (**Scheme 143**).

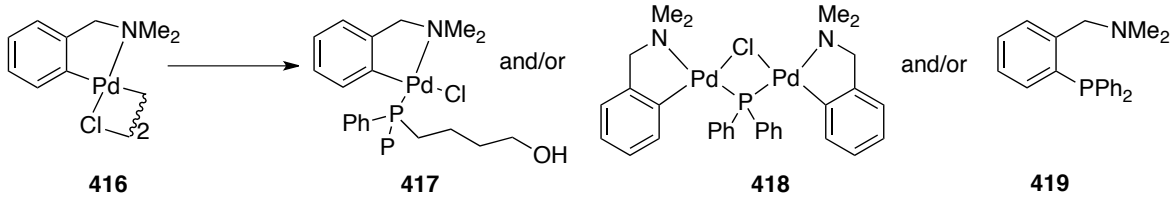


Scheme 143. Application to KetPhos.

It was thought that the chirality of the first addition will then control the of the subsequent 2nd and 3rd addition, therefore leading to *pR,pR,pR* product. This reaction did not work as the C-H activation process travels through a palladacycle intermediate and as stated in chapter 2, **KetPhos** did not form a palladacycle.

18.4 – Other Examples of Palladium Replacement, K-PPh_2 Addition.

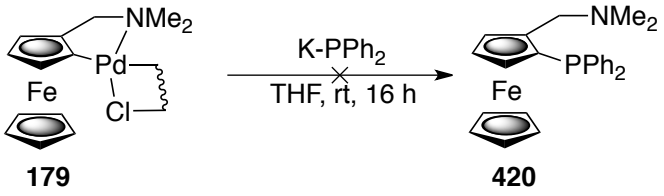
One of the most promising applications of cyclopalladated complexes and ligand transformations using reactions of the Pd-C bond.[259] The most studied reagents in the reactions are alkynyls, allenes, alkenes and carbon monoxide, although isocyanides, acyl halides, halogens and a few others have also been used. [260] Transformation of cyclopalladated complexes into aminophosphines, diphosphines and other related compounds containing PR_2 groups have also been explored. Sokolov *et al.*,[261,262] and Bolm *et al.*,[263] reveled that PPh_3 adducts of C,N-cyclopalladated complexes react with $LiPPh_2$ or $KPPh_2$ to yield aminophosphines and their $Pd^{(0)}$ complexes.[264] Complexes **417** and **419** were formed selectively by varying the structure of $LiPPh_2$ reagent, which was affected by the method of preparation, presence of bi-products, solvent polarity, concentration and age of phosphine reagent. Transformation of **416** upon the addition of the $LiPPh_2$ reagent was also sensitive to the addition order and reaction time. Changing to $KPPh_2$, due to the different coordination properties of potassium over lithium, replacing the latter with the former would control the reagents structure and therefore the reactivity. Monomeric, dimeric and polymeric structures have been reported for $LiPR_2$ reagents in solid state and solution; however, $KPPh_2$ solution is most likely to have a monomeric form, though other structures cannot be completely ruled out. Application of this protocol by Strepanova *et al.* on a *N*,*N*-dimethylbenzylamine derived palladacycle (**416**) in THF gave a range of compounds (**Scheme 144**).[264]



416 **417** **418** **419**

Scheme 144. Application of $KPPh_2$

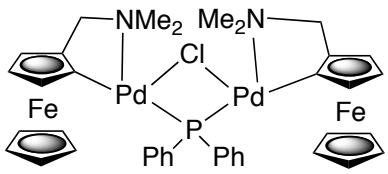
Application of this protocol to chloride bridged aminopalladacyle (**179**) did not afford the desired compound and a range of other phosphorous containing species were identifiable on analysis of crude ^{31}P NMR spectra (**Scheme 145**).



179 **420**

Scheme 145. $KPPh_2$ addition to 179.

It is clear to see from the ^{31}P NMR data that there are a number compounds and formation of the desired product was not as clean as first envisioned. The formation of a palladium adduct (**421**), which gave a signal at 30.02 ppm in ^{31}P NMR spectra. This is very similar to the ^{31}P NMR signal for **418**. When this data is compared to the ferrocene analogue a major peak can be seen at 29.9 ppm, which indicates the formation of a palladium adduct shown in **Figure 48**.[264]



421

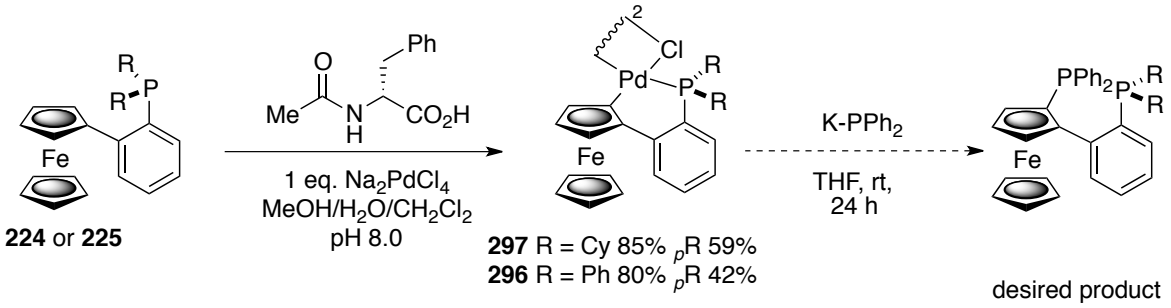
Figure 48. Formation of palladium amine adduct

This methodology was also repeated with *N*,*N*-dimethyl cobalt sandwich complex analogue of (**384**) but this also did not give the desired product.

18.5 – Application to Phosphopalladacycles.

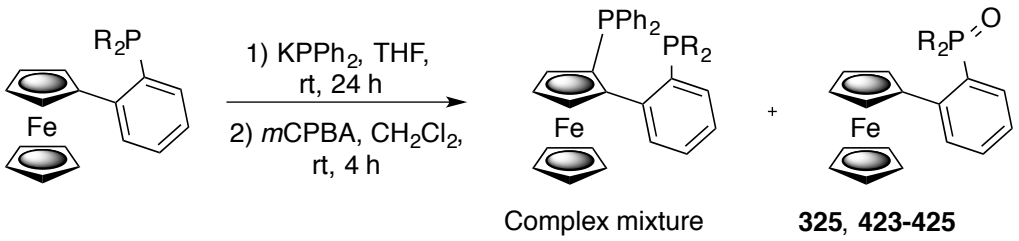
Finally, this methodology was also applied to a range of previously synthesised phosphopalladacycles, containing a range of phosphine analogues, bridged by acetate and chloride (**Scheme 146**). This would be a novel route into a range of bi-dentate phosphorous ligands which could potentially be applied to a variety of $Pd^{(II)}$-$Pd^{(0)}$ catalysed transformations. Another advantage of using this methodology is that the

enantioselective synthesis has already been established, therefore, leading to a new range of enantiomerically enriched planar chiral bidentate ligands (**Scheme 146**).



Scheme 146. Synthesis of an enantiomerically enriched bi-dentate ligand

The aforementioned methodology was applied to a range of phosphines and in all of these cases no product was isolated. It was theorised that after the addition and possible reductive elimination, the palladium is re-ligating to both phosphines and forming a palladium(0) species, which was very difficult to isolate and identify. Changing the phosphine did not make any difference to the outcome (**Scheme 147**, **Table 25**).



Scheme 147. Attempted cleavage of palladium phosphine adduct.

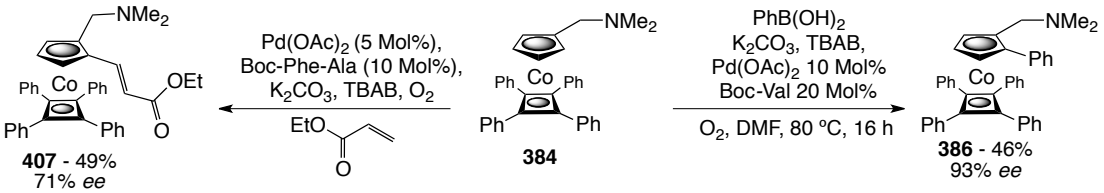
Run	R =	Outcome	Phosphine Oxide
1	Ph	Complex mixture	**423**
2	Cy	Complex mixture	**424**
3	^{i}Pr	Complex mixture	**425**
4	^{t}Bu(Ph)	Complex mixture	**325**

Table 25. Attempted bi-dentate ligand synthesis.

It was clear to see from crude ^{31}P NMR data that a palladium adduct was being formed. Attempted oxidation with *m*CPBA of the phosphine in order to cleave any palladium adduct only resulted in the formation of the corresponding phosphine oxide of the starting monophosphine and no sign of any C-H coupled product.

18.6 - Conclusion.

In conclusion the synthesis of novel di-substituted planar chiral amine based ligands has now been established, developing on methods reported by You[236] and Wu.[239] The successful Heck coupling, affording novel acrylate moieties give another reactive handle to further modifies the cobalt sandwich complexes (**Scheme 148**). With respect to C-H activation of phosphines, the synthesis of a novel set of ligands has not been established and development of more applicable reaction conditions may afford the desired compounds. Initial adduct formation with COP-Cl shows the reaction is selective and di-substitution can also lead to an increase in enantioselectivity but the reaction only worked once and is somewhat capricious.



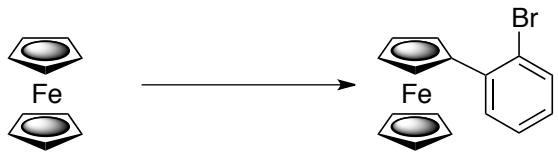
Scheme 148. Synthesis of novel cobalt metallocene bi-substituted ligands.

Experimental

General Methods

Thin layer chromatography (TLC) was performed on Merck Silica Gel 60 F254 and was visualized with UV light, iodine or potassium permanganate stain. NMR spectra were measured in $CDCl_3$ solution at 500 or 400 MHz for ^{1}H and 126 or 100 MHz for ^{13}C. The residual solvent protons (^{1}H) or the solvent carbons (^{13}C) were used as internal standards for chemical shift determinations. IR spectra were recorded on a Fourier transform interferometer; only diagnostic and/or intense peaks are reported. Melting points were measured in a melting point apparatus and are uncorrected. HPLC data was recorded using Hitachi Elite LaChrom software fitted with a L2400 UV detector, L2300 column oven, L2200 autosampler, L2130 pump and a DICEL CHIRAL CEL OD and DICEL CHIRAL CEL IA column. All reagents and solvents were purchased from commercial sources and were purified using standard methods where required. Toluene and THF were dried over sodium and benzophenone ketal. dichloromethane was dried over CaH_2. Chloroform was dried over 4 Å molecular sieves and stored under nitrogen. The petroleum ether used refers to that fraction boiling in the range of 40 – 60 ^{o}C. *N*-Butyllithium was purchased from Aldrich and titrated with diphenylacetic acid. All commercial products were used without further purification. Thin layer chromatography was performed with Keiselgel 60 F254 aluminium sheets and analysis of the plates was done with an UV lamp 254/365 nm and with I_2 on silica. Silica gel 60 (230-400 mesh ASTM) was used as stationary phase for all column/flash chromatography unless otherwise stated.

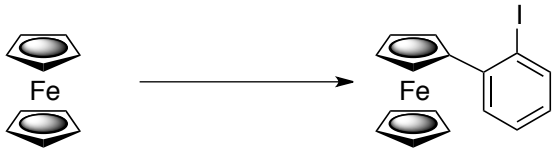
Synthesis of 2-bromophenylferrocene.[170]



13 **222**

A 1L round bottomed flask containing a stirrer bar was charged with 2-bromoaniline (18.56 g, 0.108 mol) and 30% sulphuric acid (200 mL). The mixture was cooled in an ice-bath for 30 minutes and then sodium nitrite (14.88 g, 0.216 mol) was slowly added, ensuring that the temperature of the reaction mixture remained below 5 ^{o}C. On completion of the addition the solution was stirred in an ice-bath for a further hour. The sulfamic acid (10.48 g, 0.108 mol) was added and stirring continued in the ice-bath for 30 minutes. To the resulting solution of the diazonium salt was added a solution of sodium acetate (61.20 g, 0.746 mol) in distilled water (120 mL), followed by a solution of ferrocene (20.00 g, 0.108 mol) in dichloromethane (120 mL). The resulting biphasic mixture was stirred vigorously at room temperature for 15 hours. The two layers were separated and the aqueous layer washed with dichloromethane (4 x 20 mL). The organic layers were combined, dried (Na_2SO_4), filtered and the solvent removed in vacuo to give a dark orange residue. Column chromatography (40-60 petroleum ether) gave recovered ferrocene (8.88 g, 44%) and 2 (12.76 g, 35%) as a dark orange crystalline solid. Mp 67-69 °C (lit. 68-69 °C); IR ν_{max}/cm^{-1} (Film) 1585 (C=C); Anal. Calcd. for $C_{16}H_{13}BrFe$: C, 56.35; H, 3.84. Found: C, 56.31; H 3.81. ^{1}H NMR ($CDCl_3$) δ 4.05 (5H, s, C_5H_5), 4.22 (2H, t, *J* = 2.0, Fc-β), 4.63 (2H, t, *J* =1.7, Fc-α), 6.94 (1H, td, *J* = 7.67, 1.73, H4), 7.15 (1H, td, *J* = 7.6, 1.00, H5), 7.44 (1H, td, *J* 7.9, 1.00, H3), 7.64 (1H, dd, *J* = 7.9, 1.73, H6); $^{13}C\{^{1}H\}$ ($CDCl_3$) δ 68.4 (s, Fc-β), 69.8 (s, C_5H_5), 70.4 (s, Fc-α), 86.4 (s, Fc-*ipso*), 122.7 (s, Ar), 127.0 (s, Ar), 127.6 (s, Ar), 132.3 (s, Ar), 133.7 (s, Ar), 139.1 (s, Ar).); *m/z* (ES+) 342.0 340.0 ($M^{+}H$, 75% 85%); HRMS (FAB) $M^{+}H$ $C_{16}H_{13}BrFe$ requires 339.9545 found 339.9549.

Synthesis of 2-Iodophenylferrocene.[170]



13 **223**

2-Iodoaniline (1.315 g, 0.006 mol) was dissolved in the minimum amount of 30% sulphuric acid (w/w). Once totally dissolved, the solution was cooled to 0 ^{o}C. Sodium nitrite (0.85 g, 0.0123 mol) was then carefully added ensuring the temperature did not rise above 5 ^{o}C and allowed to stir for 2 hours. Sulphamic acid (0.599 g, 0.006 mol) was added to the reaction mixture and stirred for another hour. Ferrocene (1.149 g, 0.006 mol) was dissolved in dichloromethane (20 mL) and added to a solution of sodium acetate (3.542 g, 0.045 mol) in water. This mixture was then added to the diazonium ion formed previously and stirred overnight. The organic layer was extracted with dichloromethane and neutralized with *sat.* $NaHCO_3$. This was then dried over $MgSO_4$ and solvent removed in vacuo. The crude product was the purified using flash chromatography on silica gel using hexane and ethyl acetate (95:5) to give *title compound* as a red oil in 42% yield; IR ν_{max}/cm^{-1} (Film) 2159 (C=C)' ^{1}H NMR (δ 400 MHz, $CDCl_3$) δ 4.18 (5H, s, C_5H_5), 4.33 (2H, t, *J* = 1.9 Hz, Fc-α), 4.64 (2H, t, *J* = 1.9 Hz, Fc- β), 6.91 (1H, ddd, *J* = 7.9, 7.3, 1.7 Hz, H5), 7.33 (1H, td, *J* = 7.5, 1.3 Hz, H3), 7.83 (2H, td, *J* = 7.8, 1.5 Hz, H6&H4); ^{13}C {^{1}H} ($CDCl_3$) δ 68.1 (s, Fc- β), 69.9 (s, C_5H_5), 71.0 (s, Fc- α), 84.2 (s, Fc-*ispo*), 127.6 (s, C4), 127.8 (s, C5), 129.4 (s, C6), 132.1 (s, C3), 139.9, (s-*ipso*); *m/z* (ES+); HRMS (FAB) $M^{+}H$ $C_{16}H_{13}IFe$ requires 388.9490 found 388.9477.

Synthesis of 2-(dicyclohexylphosphino)phenylferrocene.[166]

222 **225**

A solution of *n*-BuLi in hexane (0.63 mL, 1.46 mmol) was added slowly to 2-bromophenylferrocene (0.471 g, 1.38 mmol) in dry THF (6 mL) at -78 ^{o}C. The stirred solution was maintained at -78 °C for 1 h. Chlorodicyclohexylphosphine (0.44 mL, 2.0 mmol) was added to the reaction mixture which was allowed to warm to room temperature and stirred for a further 2 hours. The mixture was quenched with water and extracted with dichloromethane (2 x 10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude product was purified by column chromatography on silica gel (25% ethyl acetate/40-60 petroleum ether) to give 2-(dicyclohexylphosphino)phenylferrocene as a bright orange oil which crystallised on standing (0.447 g, 71 %). Mp 127-129 °C; Anal. Calcd. for $C_{28}H_{35}FeP$: C, 73.36; H, 7.70. Found: C, 73.56; H 7.76. δ ^{1}H NMR ($CDCl_3$) 0.81-1.20 (10H, m, P-*Cy*$_2$), 1.42-1.69 (12H, m, P-*Cy*$_2$), 4.06 (5H, s, -C_5H_5), 4.20 (2H, t, *J* = 1.7, Fc-β), 4.48 (2H, t, *J* = 1.5, Fc-α), 7.12 (1H, t, *J* = 7.1, H4), 7.24 (1H, t, *J* = 7.4, H5), 7.33 (1H, d, *J* = 7.4, H3), 7.85 (1H, dd, *J* = 7.7, 3.48, H6); ^{13}C{^{1}H} NMR ($CDCl_3$) δ 26.5 (s, Cy), 27.2 (d, *J* = 3.1, Cy), 27.4 (d, *J* = 6.2, Cy), 29.4 (d, *J* = 9.3, Cy), 30.4 (d, *J* = 16.5, Cy), 34.8 (d, *J* = 14.4, Cy), 67.5 (s, Fc-β), 69.4 (s, *C*$_5$H$_5$), 72.3 (d, *J* = 10.3, Fc-α), 89.1 (d, *J* = 7.2, Fc-*ipso*), 125.4 (s, *C*4), 127.8 (s, C5), 131.9 (d, *J* = 5.2, C6), 132.3 (s, C3), 134.9 (d, *J* = 22.7, C2), 146.0 (d, *J* = 24.8, Ph-*ipso*); ^{31}P{^{1}H} NMR ($CDCl_3$) δ -11.8 (-*P*Cy$_2$); *m/z* (ES+) 459.4 (M^+, 64%), 263.2 (M^+-PCy_2, 100%); HRMS (FAB) M^+H $C_{28}H_{35}FeP$ requires 459.1899, found 459.1902.

Synthesis of 2-(diisopropylphosphino)phenylferrocene.[211]

222 **226**

A solution of *n*-BuLi (0.56 mL, 1.02 mmol) was slowly added to 2-bromophenylferrocene (0.30 g, 0.879 mmol) in dry THF (5 mL) at -78 ^{o}C. The solution was allowed to stir for 1 hour at the same temperature. Chlorodiisopropylphosphine (0.209 mL, 1.3185 mmol) dropwise and the reaction mixture was allowed to warm to room temperature and stirred overnight. The mixture was quenched with distilled water then extracted with Et_2O, washed with brine and dried over $MgSO_4$. Crude product was purified by column chromatography (hexane 98% / EtOAc 2%) and gave the product 2-(Diisopropylphosphino)-phenylferrocene (0.309 g, 93%) as an orange oil. IR $\boldsymbol{\nu}_{max}$/cm^{-1} (Film) 1495 (C=C), 2946 (C-H); ^{1}H NMR (δ 400 MHz, $CDCl_3$) 0.89 (6H, dd, J = 11.9, 6.9), 0.99 (6H, dd, J = 14.3, 7.0), 1.85-1.92 (2H, m), 4.15 (5H, s), 4.30 (2H, t, J = 1.9), 4.60 (2H, t, J = 1.6), 7.22 (1H, td, J = 7.4, 1.4), 7.34, (1H, td, J = 7.2, 0.9), 7.41 (1H, dt, J = 7.7, 2.0), 7.96 (1H, ddd, J = 7.8, 3.7, 1.4); ^{13}C NMR (δ 126 MHz, $CDCl_3$) 19.7 (d, J = 11), 20.2 (d, J = 19), 24.6 (d, J = 14), 67.6, 69.5, 72.4, 89.1 (d, J = 7), 125.5, 127.9, 131.9 (d, J = 5), 132.1, 135.3 (d, J = 23), 145.87 (d, J = 25); ^{31}P NMR (δ 202 MHz, $CDCl_3$) -3.8; HRMS (ES) MH+ $C_{22}H_{28}FeP$ requires 379.1272, found 379.1276.

Synthesis of 2-(di-*tert*-butylphosphino)phenylferrocene

222 **227**

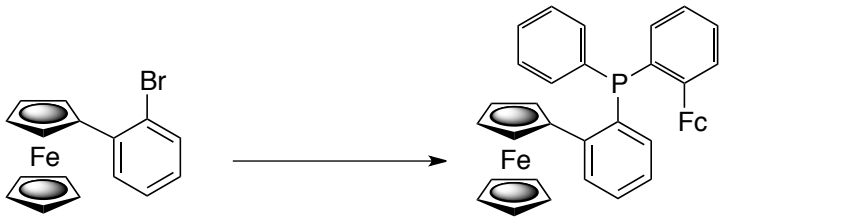
A solution of *n*-BuLi (1.5 mL, 4.0 mmol) was slowly added to 2-bromophenylferrocene (1.00 g, 2.9 mmol) in dry THF (5 mL) at -78 ^{o}C. The solution was allowed to stir for 1 hour at the same temperature. Chloro di-*tert*-butylphosphine (0.61 mL, 3.48 mmol) dropwise and the reaction mixture was allowed to warm to room temperature and stirred overnight. The mixture was quenched with distilled water then extracted with Et_2O, washed with brine and dried over $MgSO_4$. Crude product was purified by column chromatography on silica gel (hexane 95% / EtOAc 5%) and gave the product 2-(Diisopropylphosphino)-phenylferrocene (0.176 g, 15%) as an orange oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (ddd, *J* = 7.8, 3.9, 1.4 Hz, 1H, Ar), 7.72 (dt, *J* = 7.7, 1.6 Hz, 1H, Ar), 7.34 (dddd, *J* = 7.9, 7.3, 1.5, 0.7 Hz, 1H, Ar), 7.18 (td, *J* = 7.5, 1.5 Hz, 1H, Ar), 4.55 (q, *J* = 1.7 Hz, 2H, Cp), 4.26 (t, *J* = 2.1 Hz, 2H, Cp), 4.14 (s, 4H, C_5H_5), 1.10 (d, *J* = 11.6 Hz, 18H, ^{t}Bu); ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.8 (d, *J* = 29.4 Hz, Ar), 136.7 (Ar), 136.4 (Ar), 135.2 (d, *J* = 2.9 Hz, Ar), 132.3 (d, *J* = 6.3 Hz, Ar), 127.9 (Ar), 124.5 (Cp), 89.9 (d, *J* = 8.5 Hz, Cp), 72.8 (Cp), 72.8 (Cp), 69.3 (C_5H_5), 67.1 (Cp), 32.6 (d, *J* = 25.7 Hz, ^{t}Bu), 30.8 (^{t}Bu), 30.7 (^{t}Bu);^{31}P NMR (202 MHz, $CDCl_3$) δ 18.2 *P*(^{t}Bu)$_2$.

Synthesis of 2-(diphenylphosphino)phenylferrocene.[166]

222 **224**

A solution of *n*-BuLi in hexanes (1.36 mL, 3.38 mmol) was added slowly to a solution of 2-bromophenylferrocene (1.00 g, 2.93 mmol) in dry THF (30 mL) at -78 ^{o}C. The stirred solution was maintained at -78 ^{o}C for 1.5 h. Chlorodiphenylphosphine (0.76 mL, 4.2 mmol) was added to the reaction mixture which was then allowed to warm to room temperature and stirred for a further 2 hours. The mixture was quenched with water and extracted with dichloromethane (2 x 10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude product was purified by column chromatography (10% ethyl acetate/40-60 petroleum ether) to give 2-(diphenylphosphino)phenylferrocene as deep red crystals (1.00 g, 76 %); Mp 79-80 °C; Anal. Calcd. for $C_{28}H_{23}FeP$: C, 75.31; H, 5.31. Found: C, 75.35; H 5.19. ^{1}H NMR ($CDCl_3$) δ 4.07 (5H, s, -C_5H_5), 4.18 (2H, t, *J* = 0.4, Fc-β), 4.42 (2H, q, *J* = 0.4, Fc-α), 6.83 (1H, ddd, *J* = 1.9, 1.06, 0.31, Ar-H), 7.11 (1H, td, *J* = 1.9, 0.31, Ar-H) 7.17-7.37 (11H, m), 7.94 (1H, ddd, *J* = 1.9, 1.06 0.31, Ar-H); ^{13}C{^{1}H} ($CDCl_3$) δ 68.2 (Fc-β), 69.7 (C_5H_5), 71.3 (d, *J* = 8.3, Fc-α), 87.9 (d, *J* = 8.3, Fc-*ipso*), 126.4 (Ar-C4), 128.4 (Ar-C5), 128.5 (Ph-*para*), 128.6 (Ph-*meta*), 131.50 (d, *J* = 5.2, Ar-C6), 134.05 (d, *J* = 19.7, Ph-*ortho*), 134.07 (Ar-C3), 135.72 (d, *J* = 15.4, Ar-C2), 138.1 (d, *J* = 12.4, Ar), 144.6 (d, *J* = 25.9, Ar-*ipso*); ^{31}P{^{1}H} NMR ($CDCl_3$) δ -11.6 (-*P*Ph_2); *m/z* (EI) 447.2 (M^+H, 50%), 263.1 (M^+-PPh_2, 70%), HRMS (FAB) M^+H monomer $C_{28}H_{23}FeP$ requires 447.0960, found 447.0960.

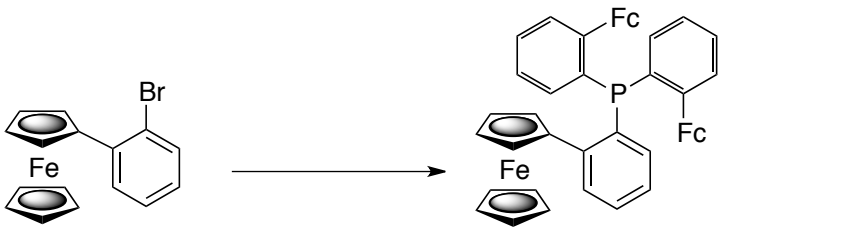
Synthesis of bis(2-phenylferrocenyl)(phenyl)phosphine (MudzPhos).



222 **254**

In two separate reaction vessels a solution of ^{n}BuLi (0.234 mL, 0.73 mmol) was slowly added to 2-bromophenylferrocene (250 mg, 0.73 mmol) in dry THF (5 mL) at -78 ^{o}C. To one of the vessels $PhPCl_2$ (0.0994 mL, 0.73 mmol) was added dropwise and the reaction mixture was allowed to warm to room temperature, stirred for one hour and cooled back to -78 ^{o}C. The lithiated ferrocene species in the other vessel was added to the other *via* a cannula. The solution was warmed to room temperature and stirred for 16 hours and quenched with distilled water then extracted with Et_2O, washed with brine and dried over $MgSO_4$. The crude product was purified by column chromatography (hexane 95% / EtOAc 5%) and gave the product **MudPhos** (0.588 g 64%) as an orange solid. MP 181-186 ^{o}C; IR V_{max}/cm^{-1} (Film) 1585.00 (C=C), 1433.21 (C-H).; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (ddd, *J* = 7.8, 4.3, 1.2 Hz, 2H, Ar-H), 7.32 (td, *J* = 7.7, 1.3 Hz, 2H, Ar-H), 7.28 (d, *J* = 5.7 Hz, 3H, Ar-H), 7.10 (td, *J* = 7.6, 1.3 Hz, 2H, Ar-H), 6.82 (ddd, *J* = 7.7, 3.8, 1.3 Hz, 2H, Ar-H), 4.30 (ddd, *J* = 3.7, 2.4, 1.2 Hz, 4H, Cp-α), 4.10 (dt, *J* = 2.6, 1.2 Hz, 4H Cp-β), 4.03 (s, 10H, $2xC_5H_5$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.1 (d, *J* = 26.5 Hz, Ar), 138.3 (d, *J* = 13.6 Hz, Ar), 136.8 (d, *J* = 17.4 Hz, Ar), 133.7 (d, *J* = 11.3 Hz, Ar), 133.1 (d, *J* = 10.1 Hz, Ar), 132.8 (d, *J* = 9.3 Hz, Ar), 131.4 (d, *J* = 5.4 Hz, Ar), 130.7 (d, *J* = 2.7 Hz, Ar), 128.3 (d, *J* = 6.3 Hz, Ar), 128.1 (Ar), 126.2 (Ar), 125.5 (d, *J* = 12.7 Hz, Ar), 87.9 (d, *J* = 7.3 Hz, Cp), 71.9 (d, *J* = 45.18, Cp) 71.2 (d, *J* = 9.0 Hz, Cp), 70.9 (d, *J* = 9.0 Hz, Cp), 69.5 ($2xC_5H_5$), 68.0 (d, *J* = 23.4 Hz, Cp); ^{31}P NMR (202 MHz, $CDCl_3$) δ -18.0 (*P*(Ph)PhFc); HRMS (FTMS + p APCI) $M^{+}H$ $C_{38}H_{32}F_2P$ requires 631.0934 found 631.0946

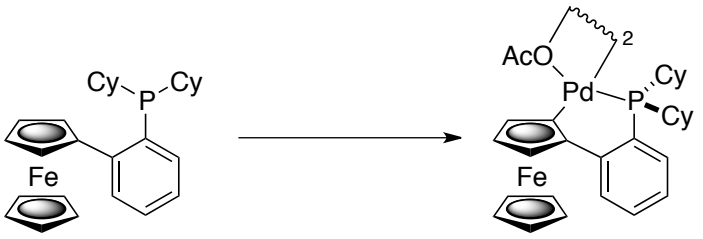
Synthesis of tris(2-phenylferroceneyl)phosphine (KetPhos).



222 **253**

A solution of ^{n}BuLi (1.5 mL, 4.0 mmol) was slowly added to 2-bromophenylferrocene (1.00 g, 2.9 mmol) in dry THF (5 mL) at -78 ^{o}C. The solution was allowed to stir for 1 hour at the same temperature. PCl_3 (0.084 mL, 0.96 mmol) was added dropwise and the reaction mixture was allowed to warm to room temperature and stirred overnight. The mixture was quenched with distilled water then extracted with Et_2O, washed with brine and dried over $MgSO_4$. Crude product was purified by column chromatography (hexane 90% / EtOAc 10%) and gave the product **KetPhos** (1.51 g, 64%) as an orange solid. Mp 290-292 ^{o}C; IR V_{max}/cm^{-1} (Film) 1596.00 (C=C), 1485.50 (C-H) V_{max}/cm^{-1} (Film) 2957.09 (C-H), 1584.90 (C=C), 1122.02 (P-Ar); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (ddd, *J* = 7.8, 4.3, 1.3 Hz, 1H, Ar), 7.28 (dd, *J* = 7.5, 1.4 Hz, 1H, Ar), 7.06 (td, *J* = 7.5, 1.4 Hz, 1H, Ar), 6.78 (ddd, *J* = 7.7, 3.4, 1.4 Hz, 1H, Ar), 4.30 - 4.19 (m, 2H, Cp), 4.04 (t, *J* = 1.9 Hz, 2H, Cp), 4.01 (s, 5H, C_5H_5); ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.0 (Ar), 143.8 (Ar), 137.20 (d, *J* = 20.2 Hz, Ar), 134.6 (Ar), 131.3 (d, *J* = 4.7 Hz, Ar), 127.8 (Ar), 126.04 (Cp), 87.8 (d, *J* = 7.3 Hz, Cp), 71.0 (Cp), 70.9 (Cp), 69.4 (C_5H_5), 67.8 (Cp); ^{31}P NMR (202 MHz, $CDCl_3$) δ (*P*Ar_2) -23.6; HRMS (FTMS + p APCI) $M^{+}H$ $C_{48}H_{40}Fe_3P$ requires 815.0910 found 815.0935

***Rac*-di-μ-aceto-bis[2-(dicyclohexylphosphino)phenylferrocene-C,P]dipalladium (Method 1).**[166]



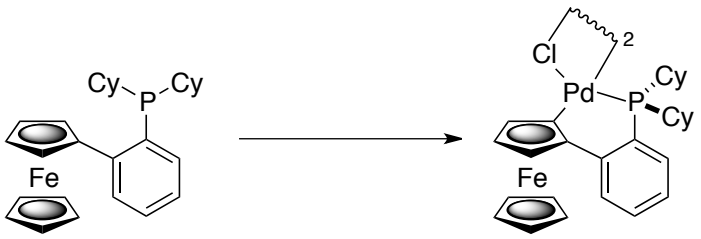
225 **293**

A solution of 2-(dicyclohexylphosphino)phenylferrocene (1.00 g, 2.18 mmol), $Pd(OAc)_2$ (0.49 g, 2.18 mmol) in toluene (75 mL) was stirred at room temperature for 1 hour. The resulting clear bright orange solution was filtered through a plug of SiO_2 (4 g), washed with dichloromethane (20 mL). The solvent was removed *in vacuo* to give the palladacycle as a deep orange powder (1.14 g, 88%). Mp 215 °C; Anal. Calcd. for $C_{60}H_{74}Fe_2O_4P_2Pd_2$: C, 57.85; H, 5.99%. Found C, 58.00; H, 5.75%; IR (NaCl) ν_{max}/cm^{-1} 1573.6 (-CO); ^{1}H NMR ($CDCl_3$) δ 0.78-2.04 (P-*Cy*$_2$), 2.13 (H_2O coordinated), 2.17 (-C*H*$_3$), 4.13 (10H, s, -C_5H_5), 4.38 (2H, t, *J* = 2.4, Fc), 4.56 (2H, br t, Fc), 4.75 (2H, br t, Fc), 7.17 (2H, t, *J* = 7.4, H4), 7.33 (2H, t, *J* = 8.5, H3), 7.38 (2H, t, *J* = 8.6, Ar), 7.62 (2H, dd, *J* = 7.9, 3.97, H6); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 24.4 (s, *C*H_2), 25.9 (d, *J* = 10.2, *C*H_2), 26.2 (d, *J* = 2.0, *C*H_2), 27.0 (d, *J* = 30.7, *C*H_2), 26.9 (d, *J* = 3.0, *C*H_2), 27.1 (s, *C*H_2), 27.9 (d, *J* = 4.0, *C*H), 28.8 (s, *C*H_2), 29.8 (s, *C*H_2), 31.1 (s, *C*H_2), 33.0 (d, *J* = 28.6, *C*H_2), 37.7 (d, *J* = 27.6, *C*H_2), 66.9 (Fc), 70.2 (Fc), 70.6 (*C*$_5$H$_5$), 73.5 (s, Fc), 79.0 (d, *J* = 19.45, Fc), 81.4 (d, *J* = 13.3, Fc), 116.5 (d, *J* = 51.1, Ar), 124.5 (d, *J* = 8.1, Ar), 127.0 (d, *J* = 8.9, Ar), 130.2 (s, Ar), 131.0 (s, Ar), 149.3 (d, *J* = 11.2, Ar-*ipso*) 188.7 (CO); $^{31}P\{^1H\}$ NMR ($CDCl_3$) δ 45.0 (-Pd*P*Cy_2); *m/z* (FAB) 1198 (M^+-AcO 3%), 622 (½M*,* 6%), 457 (100 %).

Method 2

A solution of 2-(dicyclohexylphosphino)phenylferrocene (1.00 g, 2.18 mmol), $Pd(OAc)_2$ (0.49 g, 2.18 mmol) in dichloromethane (10 mL) was stirred at room temperature for 24 hours. The solvent was removed in vacuo to afford title compound as an orange solid (1.27 g, 2.049 mmol, 94%); Mp 215 °C; Anal. Calcd. for $C_{60}H_{74}Fe_2O_4P_2Pd_2$: C, 57.85; H, 5.99%. Found C, 58.00; H, 5.75%; IR (NaCl) ν_{max}/cm^{-1} 1573.6 (-CO); ^1H NMR ($CDCl_3$) δ 0.78-2.04 (P-*Cy*$_2$), 2.13 (H_2O coordinated), 2.17 (-C*H*$_3$), 4.13 (10H, s, -C_5H_5), 4.38 (2H, t, *J* = 2.4, Fc), 4.56 (2H, br t, Fc), 4.75 (2H, br t, Fc), 7.17 (2H, t, *J* = 7.4, H4), 7.33 (2H, t, *J* = 8.5, H3), 7.38 (2H, t, *J* = 8.6, Ar), 7.62 (2H, dd, *J* = 7.9, 3.97, H6); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 24.4 (s, *C*H_2), 25.9 (d, *J* = 10.2, *C*H_2), 26.2 (d, *J* = 2.0, *C*H_2), 27.0 (d, *J* = 30.7, *C*H_2), 26.9 (d, *J* = 3.0, *C*H_2), 27.1 (s, *C*H_2), 27.9 (d, *J* = 4.0, *C*H), 28.8 (s, *C*H_2), 29.8 (s, *C*H_2), 31.1 (s, *C*H_2), 33.0 (d, *J* = 28.6, *C*H_2), 37.7 (d, *J* = 27.6, *C*H_2), 66.9 (Fc), 70.2 (Fc), 70.6 (*C*$_5$H$_5$), 73.5 (s, Fc), 79.0 (d, *J* = 19.45, Fc), 81.4 (d, *J* = 13.3, Fc), 116.5 (d, *J* = 51.1, Ar), 124.5 (d, *J* = 8.1, Ar), 127.0 (d, *J* = 8.9, Ar), 130.2 (s, Ar), 131.0 (s, Ar), 149.3 (d, *J* = 11.2, Ar-*ipso*) 188.7 (CO); $^{31}P\{^1H\}$ NMR ($CDCl_3$) δ 45.0 (-Pd*P*Cy$_2$); *m/z* (FAB) 1198 (M^+-AcO 3%), 622 (½M*,* 6%), 457 (100 %).

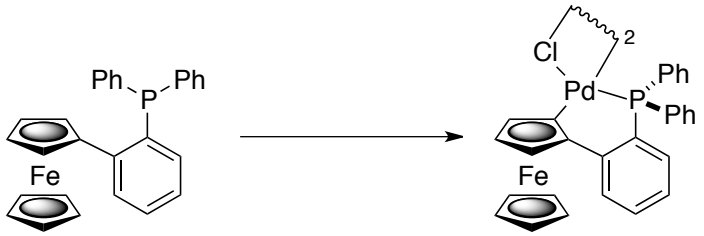
Synthesis of *rac*-di-*μ*-chloro-bis[2-(dicyclohexylphosphino)phenylferrocene-C,P]dipalladium by direct palladation.



225 **297**

2-(Dicyclohexylphosphino)phenylferrocene (200 mg, 0.438 mmol) was dissolved in dry toluene (10 mL) for 15 minutes under argon. $PdCl_2$ (46.64 mg, 0.438) was added, and the solution was warmed to 60 ^{o}C for 16 hours, the consumption of the ligand was monitored using ^{31}P NMR. Toluene was removed *in vacuo* and the reaction mixture was dissolved the minimum amount of dichloromethane and purified using neutral alumina (5 g) and the solvent removed *in vacuo* giving palladacycle as a dark orange powder (110.33 mg, 42%). Mp 208-215 ^{o}C (decomp.); Anal. Calcd. for $C_{56}H_{66}Cl_2Fe_2P_2Pd_2$: C, 56.21; H, 5.56; Found: C, 55.10; H, 5.90%; ^{1}H NMR ($CDCl_3$) δ 0.83-2.27 (44H, m, Cy), 4.16 (10H, br s, C_5H_5), 4.25 (1H, br s, Fc-*H*), 4.40 (1H, br s, Fc-*H*), 4.61 (1H, br s, Fc-*H*), 4.70 (1H, br s, Fc-*H*), 4.83 (2H, br s, Fc-*H*), 7.15 (2H, t, *J* = 7.6, Ar), 7.35 (2H, t, *J* = 7.3, Ar) 7.41 (2H, t, *J* = 7.5, Ar), 7.55 (2H, dd, *J* = 7.7, 3.43, Ar); ^{13}C{^{1}H} NMR ($CDCl_3$) δ 26.0 - 26.3 (m, Cy_2), 27.0 - 28.0 (m, Cy), 29.1 - 29.8 (m, Cy), 34.07 (d, *J* = 34.0, *C*y), 38.8 (d, *J* = 30.0, *C*y), 39.0(d, *J* = 28.0, *C*y), 66.6 (Fc), 67.2 (Fc), 69.0 (Fc), 69.7 (Fc), 70.5 (Fc), 70.8 (Fc), 71.1 (Fc), 80.2 (d, *J* = 21.7, Fc), 83.6 (d, *J* = 8.3, Fc), 120.0 (d, *J* = 47.7, Ar-*ipso*), 120.2 (d, *J* = 49.8, Ar-*ipso*), 120.3 (d, *J* = 48.7, Ar-*ipso*), 120.4 (d, *J* = 47.7, Ar-*ipso*), 124.3 (d, *J* = 6.2, Ar), 126.1 (Ar), 126.26 (Ar), 127.9 (d, *J* = 7.7, Ar), 128.4 (Ar), 128.49 (Ar), 129.2 (Ar), 129.7- 129.4 (m, Ar), 130.4- 130.4 (m, Ar), 149.4 - 149.6 (br s, Ar-*ipso*); ^{31}P{^{1}H} NMR ($CDCl_3$) δ 39.0, 39.7, 39.9 (3:2:1.5 ratio) (-Pd*P*Cy_2); *m/z* (ESI) 1154 (M+ dimer -Cl -½H_2O, 22%), 564.2 (M^+monomer-Cl 10%).

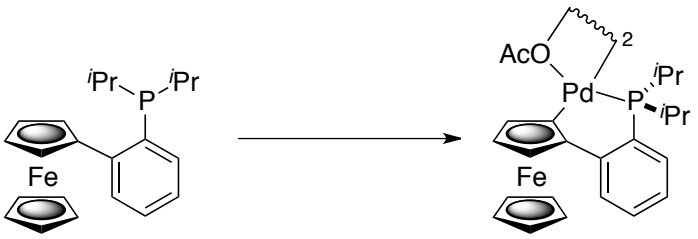
Synthesis of *rac*-di-*μ*-chloro-bis[2-(phenylphosphino)phenylferrocene-C,P]dipalladium by direct palladation.



224 **296**

2-(Diphenylphosphino)phenylferrocene (300 mg, 0.672 mmol) was dissolved in dry toluene (10 mL) for 15 minutes under argon. $PdCl_2$ (119.19 mg, 0.672) was added, and the solution was warmed to 60 ^{o}C for 16 hours, the consumption of the ligand was monitored using ^{31}P NMR. Toluene was removed *in vacuo* and the reaction mixture was dissolved the minimum amount of dichloromethane and purified using neutral alumina (5 g) and the solvent removed *in vacuo* giving palladacycle as a dark orange powder (142.7mg, 36%). Mp 198-200 ^{o}C; Anal. Calcd. for $C_{56}H_{44}Cl_2Fe_2P_2Pd_2$: C, 57.28; H, 3.78; Found: C, 56.24; H, 4.25; ^{1}H NMR ($CDCl_3$) δ 4.03 (10H, brs, C_5H_5), 4.30 (1H, brs, Fc-*H*), 4.62 (2H, brs, Fc-*H*), 4.59 (1H, brs, Fc-*H*), 4.75 (1H, brs, Fc-*H*), 4.85 (1H, brs, Fc-*H*), 6.72 (2H, t, *J* = 7.6, Ar), 7.12 (2H, t, *J* = 6.1, Ar), 7.19-7.54 (24H, brs, Ar); ^{13}C{^{1}H} NMR ($CDCl_3$) δ 65.9 (Fc), 66.0 (Fc), 68.5 (Fc), 69.6 (Fc), 69.7 (Fc), 69.9 (C_5H_5), 70.0 (C_5H_5), 70.1 (C_5H_5), 74.8 (Fc), 75.2 (Fc), 75.3 (Fc), 78.6 (t, *J* = 25.6, Fc- *ipso*), 84.5 (br s, Fc), 119.9 (d, *J* = 59.7, Ar), 120.3 (d, *J* = 61.7, Ar), 123.5 (br s, Ar), 126.5 (br t, Ar), 126.8 (d, *J* = 11.6, Ar), 127.1 - 127.4 (m, Ph), 128.7 (d, *J* = 16.2, Ph), 128.8 (d, *J* = 21.4, Ph), 129.2 (d, *J* = 4.8, Ph), 129.2 (br s, Ph), 129.38 (s, Ph), 129.6 (Ar), 129.7 (Ph), 130.0 (Ar), 131.0(br s, Ph), 131.2 (br s, Ph), 132.9 - 133.3 (br s, Ph), 147.7 (d, *J* = 16.6, Ph), 147.7 (d, *J* = 15.9, Ph); ^{31}P{^{1}H} NMR ($CDCl_3$) δ 32.8 (-Pd*P*Ph_2); *m/z* (ESI) 1174.1 (M^+-H, 1%), 1137.1 (M^+-Cl, 2%), 1105.2 (M^+-2Cl, 1%), 551.1 (½M^+ monomer - Cl, 40%), 445 (½M^+ monomer, 100%).

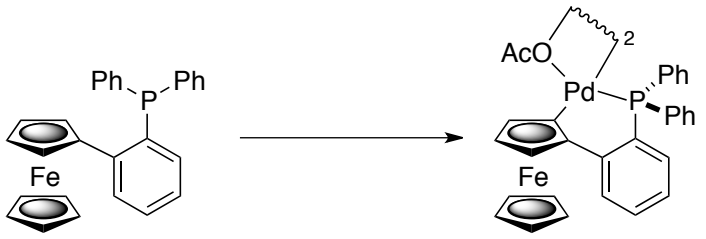
***Rac*-di-μ-aceto-bis[2-(diisopropylphosphino)phenylferrocene-C,P]dipalladium**



226 **294**

A schlenk tube was charged with 2-(diisopropylphosphino)-phenylferrocene (1.22 g, 3.75 mmol), $Pd(OAc)_2$ (0.724 g, 3.75 mmol) and dissolved in dichloromethane (20 mL). The reaction mixture was stirred overnight and the solvent removed *in vacuo*, yielding the palladacycle as a bright orange power (3.406 g, 94% yield). Mp 144 – 146 ^{o}C; IR ν_{max}/cm^{-1} (Film) 1573.78 (C=O), 1485.52 (C=C); ^{1}H NMR (δ 400 MHz, CDCl3), 0.87 (6H, dd, J = 17.3, 7.1), 1.00 (6H, dd, J = 15.5, 7.1), 1.40 (6H, dd, J = 7.0, 3.3), 1.44 (6H, dd, J = 7.0, 4.2), 2.13 (6H, s), 2.13-2.20 (2H,m), 2.63-2.73 (2H, m), 4.15 (10H, s), 4.40 (2H, brs), 4.55 (2H, brs), 4.75 (2H, brs), 7.18 (2H, tt, J = 7.5, 1.6), 7.31 (2H, td, J = 7.8, 1.4), 7.39 (2H, tt, J = 7.81.4), 7.63 (2H, ddd, J = 8.0, 3.9, 1.2); ^{13}C NMR (δ 101 MHz, $CDCl_3$) 17.3 (d, J = 4.1), 18.3 (d, J = 2.6), 19.4 (d, J = 3.4), 19.5, 23.1 (d, J = 29.1), 24.5, 29.1 (d, J = 30.0), 67.2 (d, J = 2.5). 70.6, 73.6 (d, J = 1.5), 77.7, 79.8 (d, J = 20.2), 82.2 (d, J = 14.1), 117.4 (d, J = 50.5), 124.9 (d, J = 7.6), 127.4 (d, J = 8.1), 130.3 (d, J = 2.7), 131.4 (d, J = 2.3), 149.4 (d, J = 11.3) (C-O not observerd); ^{31}P NMR (δ 162 MHz, $CDCl_3$) 53.1.

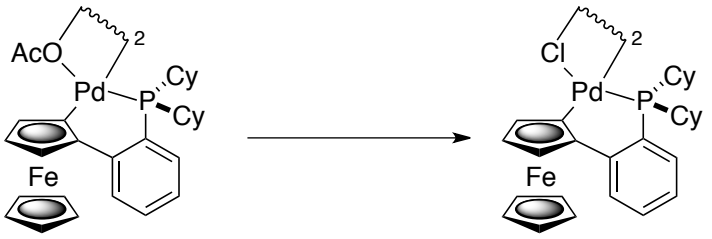
***Rac*-di-μ-aceto-bis[2-(diphenylylphosphino)-phenylferrocene-C,P]dipalladium**



224 **295**

A solution of 2-(diphenyllphosphino)phenylferrocene (1.56 g, 2.78 mmol), $Pd(OAc)_2$ (0.626 g, 2.78 mmol) in dichloromethane (10 mL) was stirred at room temperature for 3 hours. The solvent was removed *in vacuo* to give the palladacycle as dark red crystals (0.729 g, 86%). Mp 218-223 (decomp.) ^{o}C; Anal. Calcd. for $C_{60}H_{52}Fe_2O_4P_2Pd_2$: C, 58.90; H, 4.28; Found: C, 57.55; H, 4.18; IR (NaCl) ν_{max}/cm^{-1} 1680.5 (-CO); ^{1}H NMR ($CDCl_3$) δ (271.6 MHz, $CDCl_3$) 2.33 (6H, s, COCH_3), 4.01 (10H, s, C_5H_5), 4.21 (2H, brs, Fc), 4.28 (2H, t, *J* = 3.5, Fc), 4.61 (2H, t, *J* = 3.6, Fc), 7.13-7.46 (14H, m, Ar); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$) δ 24.8 (s, CH_3), 66.0(s, Fc), 69.9 (s, Fc), 70.6 (s, C_5H_5), 75.9 (s, Fc), 79.7 (d, *J* = 22.82, Fc), 83.5 (d, *J* = 13.49, Fc), 120.3 (d, *J* = 59.13, Ar), 124.5 (d, *J* = 8.30, Ar), 127.2 (d, *J* = 9.34, Ar), 128.1 (d, *J* = 10.90, Ph), 128.5 (d, *J* = 11.41, Ph), 129.7 (d, *J* = 35.31, Ph), 130.2 (s, Ar), 130.0 (d, *J* = 39.17, Ph), 130.8 (s, Ph), 131.1 (s, Ar), 133.0 (s, Ph), 134.4 (d, *J* = 7.36, Ph), 134.6 (d, *J* = 6.79, Ph), 149.1 (d, *J* = 14.52, Ar-*ipso*) 178.2 (*C*O); $^{31}P\{^{1}H\}$ NMR ($CDCl_3$) δ 29.8 (-Pd*P*Ph_2); *m/z* (ESI) 610.1 (M^+ monomer 1%), 551.1 (M^+ monomer -AcO, 45%).

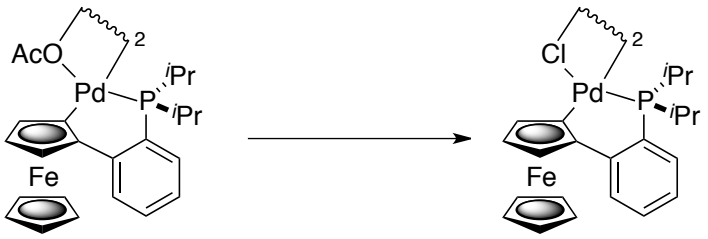
***Rac*-di-μ-chloro-bis[2-(dicyclohexylphosphino)-phenylferrocene-C,P]dipalladium**



293 **296**

To a solution of *rac*-di-μ-aceto-bis[2-(dicyclohexylphosphino)-phenylferrocene-C,P]dipalladium (0.500 g, 0.401 mmol) in dichloromethane (45 mL) and acetone (45mL) was added a solution of saturated aqueous sodium chloride (50 mL). The heterogeneous mixture was stirred at room temperature for 30 minutes, after which time the organic layer was separated, washed with water (2 x 100 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give as a dark orange powder (0.430 g, 89% yield). Mp 208-215 ^{o}C (decomp.); Anal. Calcd. for $C_{56}H_{66}Cl_2Fe_2P_2Pd_2$: C, 56.21; H, 5.56; Found: C, 55.10; H, 5.90%; ^{1}H NMR ($CDCl_3$) δ 0.83-2.27 (44H, m, Cy), 4.16 (10H, br s, C_5H_5), 4.25 (1H, br s, Fc-*H*), 4.40 (1H, br s, Fc-*H*), 4.61 (1H, br s, Fc-*H*), 4.70 (1H, br s, Fc-*H*), 4.83 (2H, br s, Fc-*H*), 7.15 (2H, t, *J* = 7.6, Ar), 7.35 (2H, t, *J* = 7.3, Ar) 7.41 (2H, t, *J* = 7.5, Ar), 7.55 (2H, dd, *J* = 7.7, 3.43, Ar); ^{13}C NMR ($CDCl_3$) δ 26 - 26.3 (m, Cy_2), 27.0 - 28.0 (m, Cy), 29.1 - 29.8 (m, Cy), 34.1 (d, *J* = 34.0, *C*y), 38.8 (d, *J* = 30.0, *C*y), 39.0 (d, *J* = 28.0, *C*y), 66.6 (Fc), 67.22 (Fc), 69.0 (Fc), 69.7 (Fc), 70.5 (Fc), 70.8 (Fc), 71.1 (Fc), 80.2 (d, *J* = 21.7, Fc), 83.6 (d, *J* = 8.3, Fc), 120.0 (d, *J* = 47.7, Ar-*ipso*), 120.2 (d, *J* = 49.8, Ar-*ipso*), 120.3 (d, *J* = 48.7, Ar-*ipso*), 120.4 (d, *J* = 47.7, Ar-*ipso*), 124.3 (d, *J* = 6.2, Ar), 126.1 (Ar), 126.3 (Ar), 127.9 (d, *J* = 7.7, Ar), 128.4 (Ar), 128.5 (Ar), 129.2 (Ar), 129.7- 129.7 (m, Ar), 130.4- 130.4 (m, Ar), 149.4 - 149.6 (br s, Ar-*ipso*); ^{31}P{^{1}H} NMR ($CDCl_3$) δ 39.0, 39.7, 39.9 (3:2:1.5 ratio) (-Pd*P*Cy_2); *m/z* (ESI) 1154 (M+ dimer - Cl -½H_2O, 22%), 564.2 (M^{+}monomer-Cl 10%).

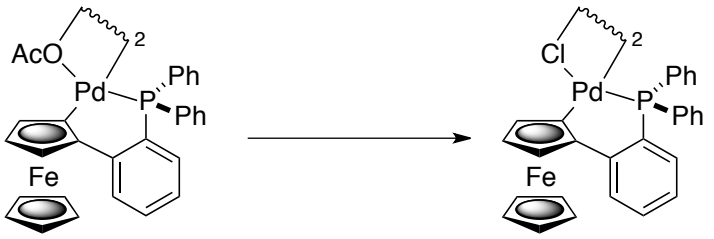
***Rac*-di-μ-chloro-bis[2-(diisopropylphosphino)-phenylferrocene-C,P]dipalladium**



294 **298**

A round bottom flask was charged with *Rac*-di-μ-aceto-bis[2-(diisopropylphosphino)-phenylferrocene-C,P]dipalladium (50 mg, 0.051 mmol) in dichloromethane (4 mL) and brine (3 mL). The mixture stirred overnight, extracted with dichloromethane (10 mL) and dried over $MgSO_4$. Solvent was remove under *vacuo* giving a red/orange powder (47 mg, 98%) Mp 175 – 179 ^{o}C; IR $\boldsymbol{\nu}_{max}$/cm^{-1} (Film) 1588.71 (C=C); ^{1}H NMR (δ 400 MHz, $CDCl_3$), 1.02 (24H, ddd, *J* = 17.7, 10.8, 7.2 Hz, *iPr*-CH_3), 1.20 (2H, dt, *J* = 15.1, 7.4 Hz, *iPr*-CH_3), 1.89 (2H, hept, *J* = 6.7 Hz, *iPr*-CH), 4.20 (10H, s, Fc-C_5H_5), 4.39 (2H, m, Fc-H), 4.44 (2H, m, Fc-H), 4.64 (2H, d, *J* = 2.4 Hz, Fc-H), 7.14-7.19 (2H, m), 7.35-7.40 (4H, m), 7.66 (2H, dd, J = 8.0, 3.5); ^{13}C NMR (δ 101 MHz, $CDCl_3$) 18.3 (d, *J* = 3.1 Hz), 18.6 (d, *J* = 7.2 Hz), 18.7 (d, *J* = 8.6 Hz), 19.7 (d, *J* = 3.4 Hz), 23.3 (d, *J* = 26.4 Hz), 29.8 (d, *J* = 29.7 Hz), 67.1 (t, *J* = 3.7 Hz), 69.7, 70.7, 71.1, 72.0, 83.8 (d, *J* = 8.4 Hz), 120.7 (d, *J* = 47.8 Hz), 124.4 (d, *J* = 7.2 Hz), 127.9 (t, *J* = 8.4 Hz), 129.3 (d, *J* = 4.5 Hz), 130.4 (dd, *J* = 6.2, 2.3 Hz), 149.1; ^{31}P NMR (δ 162 MHz, $CDCl_3$) 48.40, 47.8, 47.3, 47.1 (1: 0.88: 0.62: 0.28 ratio) (-*P*(^{i}Pr)$_2$).

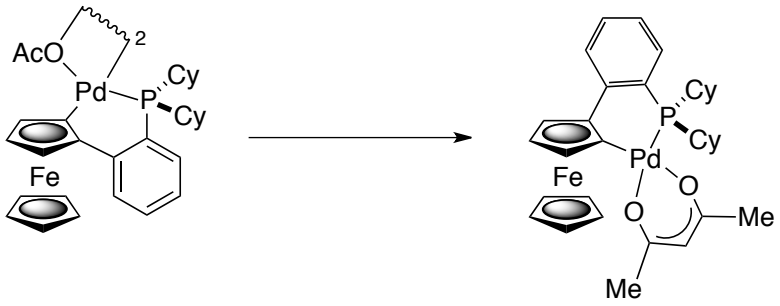
***Rac*-di-μ-chloro-bis[2-(diphenylphosphino)-phenylferrocene-C,P]dipalladium**



295 **296**

To a solution of *rac*-di-μ-aceto-bis[2-(diphenylphosphino)phenylferrocene-C,P]dipalladium (0.180 g, 0.15 mmol) in dichloromethane (12 mL) and acetone (5mL) was added a solution of saturated aqueous sodium chloride (20 mL). The heterogeneous mixture was stirred at room temperature for 30 minutes, after which time the organic layer was separated, washed with water (2 x 20 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give **296** as a dark orange powder (0.172 g, 94% yield). Mp 198-200 $^{\circ}$C; Anal. Calcd. for $C_{56}H_{44}Cl_2Fe_2P_2Pd_2$: C, 57.28; H, 3.78; Found: C, 56.24; H, 4.25; ^{1}H NMR ($CDCl_3$) δ 4.03 (10H, brs, C_5H_5), 4.30 (1H, brs, Fc-*H*), 4.62 (2H, brs, Fc-*H*), 4.59 (1H, brs, Fc-*H*), 4.75 (1H, brs, Fc-*H*), 4.85 (1H, brs, Fc-*H*), 6.72 (2H, t, *J* = 7.6, Ar), 7.12 (2H, t, *J* = 6.1, Ar), 7.19-7.54 (24H, brs, Ar); ^{13}C{^{1}H} NMR ($CDCl_3$) δ 66.0 (Fc), 66.0 (Fc), 68.5 (Fc), 69.6 (Fc), 69.74 (Fc), 69.9 (C_5H_5), 70.0 (C_5H_5), 70.1 (C_5H_5), 74.8 (Fc), 75.2 (Fc), 75.3 (Fc), 78.6 (t, *J* = 25.6, Fc- *ipso*), 84.5 (br s, Fc), 119.9 (d, *J* = 59.7, Ar), 120.3 (d, *J* = 61.7, Ar), 123.5 (br s, Ar), 126.5 (br t, Ar), 126.8 (d, *J* = 11.6, Ar), 127.0 - 127.4 (m, Ph), 128.7 (d, *J* = 16.2, Ph), 128.8 (d, *J* = 21.4, Ph), 129.1 (d, *J* = 4.8, Ph), 129.2 (br s, Ph), 129.4 (s, Ph), 129.6 (Ar), 129.7 (Ph), 130.0 (Ar), 131.0 (br s, Ph), 131.2 (br s, Ph), 132.9 - 133.3 (br s, Ph), 147.7 (d, *J* = 16.6, Ph), 147.8 (d, *J* = 15.9, Ph); ^{31}P{^{1}H} NMR ($CDCl_3$) δ 32.8 (-Pd*P*Ph$_2$); *m/z* (ESI) 1174.1 (M^+-H, 1%), 1137.1 (M^+-Cl, 2%), 1105.2 (M^+-2Cl, 1%), 551.1 (½M^+ monomer - Cl, 40%), 445 (½M^+ monomer, 100%).

Synthesis of *Rac*-acetylacetonate[2-(dicyclohexylphosphino)-phenylferrocene-C,P]dipalladium.



293 **306**

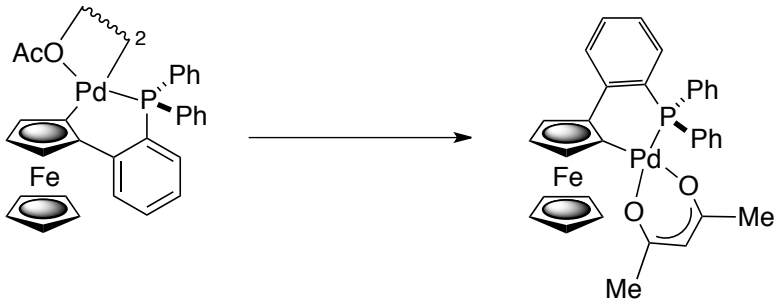
Method 1

A round bottom flask was charged with rac-di-μ-chloro-bis[2-dicyclohexylphosphino)-phenylferrocene-C,P]dipalladium (0.150 g, 0.125 mmol, sodiumacetylacetonate monohydrate (0.069 g, 0.492 mmol), acetone (10 mL) and water (6 mL). The mixture was allowed to stir overnight allowing the formation of a precipitate. The reaction mixture was then filtered through a sinter funnel; the resulting cake was washed with water (10 mL) and dried in an evacuated desiccator for 48 hours to generate a light orange powder. Further purified by silica filtration with dichloromethane (10 mL) to give title compound (0.166 g, 0.244 mmol, 97%). Mp 114 – 118 ^{o}C (Found: C 55.35%; H 5.78% $C_{33}H_{41}FeO_2PPd$ requires C, 60.24; 6.23%); IR ν_{max}/cm^{-1} (NaCl) 1741 (CO); ^{1}H NMR (δ 271.6 MHz, $CDCl_3$); 0.82 – 1.49 (12H, m, PCy_2), 1.56 – 1.75 (10H, m, PCy_2), 1.92 (3H, s, CH_3), 2.08 (2H, s, CH_2), 2.16 (3H, s, CH_3), 4.03 (s, C_5H_5), 4.40 (1H, t, *J* = 2.50 Hz, Fc-H), 4.64 (1H, t, *J* = 2.23 Hz, Fc-H), 4.82 (1H, t, *J* = 1.74 Hz, Fc-H), 5.53 (1H, s, CH), 7.15 (1H, tt, *J* = 7.47 Hz, 1.66 Hz, Ar), 7.36 (2H, m, Ar), 7.64 (1H, ddd, *J* = 4.24, 1.36); ^{13}C {^{1}H} NMR (δ 67.90, $CDCl_3$); 26.2 (d, *J* = 31.1 Hz Cy[CH_2]), 26.8 – 27.7 (m, Cy_2), 29.1 (d, *J* = 57.06 Hz, CH_2), 32.1 (d, *J* = 27.0 Hz, CH_2), 37.8 (d, *J* = 29.05 Hz, CH_2), 67.5 (s, CH), 70.2 (s, C_5H_5), 74.3 (s, CH), 79.3 (d, *J* = 16.59 Hz, Fc-*β*), 80.5 (d, J = 18.68 Hz, Fc-*α*), 99.2 (s, Fc-*ipso*), 119.2 (Ar), 124.02 (brs, Ar), 129.97 (d, *J* = 38.39 Hz, Ar), 150.0 (d, *J* = 11.41 Hz, Ar), 186.2 (s, C-O), 187.34 (s, C-O); ^{31}P {^{1}H} NMR (δ 109.3, $CDCl_3$) 36.9 (-Pd*P*Cy_2); *m/z* (EI) 662.1222 (M^+ - $C_{33}H_{41}O_2FePPd$ requires 662.1223), (M^+- 100%), 664.1 (86%), 666.1 (64%), 660.2 (45%).

Method 2

A 20 mL round bottom flask was charged with rac-di-μ-aceto-bis[2-(dicyclohexylphosphino)-phenylferrocene-C,P]dipalladium (0.250 g, 0.201 mmol), sodium acetylacetonate monohydrate (0.112 g, 0.804 mmol), acetone (16 mL) and water (8 mL). This was then allowed to stir overnight at room temperature until a precipitate was formed. The reaction mixture was then filtered on a sinter funnel; the resulting cake was washed with water (20 mL) and dried in an evacuated desiccator for 48 hours to generate a light orange powder. Further purified by silica filtration with dichloromethane (10 mL) to give title compound (0.264 g, 0.388 mmol, 97%). **Data as above**.

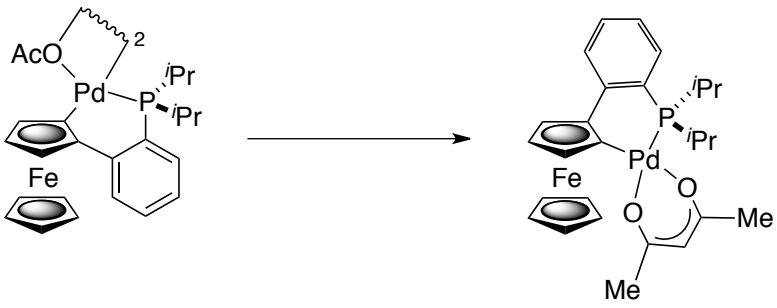
Synthesis of *Rac*-acetylacetonate[2-(diphenylphosphino)-phenylferrocene-C,P]dipalladium



295 **305**

A 20 mL round bottom flash was charged with rac-di-μ-aceto-bis[2-(diphenylphosphino)-phenylferrocene-C,P]dipalladium (0.025 g, 0.020 mmol, sodiumacetylacetonate monohydrate (0.1 g, 0.435 mmol), acetone (3 mL) and water (1.5 mL). This was then allowed to stir overnight at room temperature until a precipitate was formed. The reaction mixture was then filtered on a sinter funnel; the resulting cake was washed with water (10 mL) and dried in an evacuated desiccator for 48 hours to generate a light orange powder. Further purified by silica filtration with dichloromethane (10 mL) to give title compound (0.020 g, 0.026 mmol, 65%). Mp 89-90 ^{o}C; IR ν_{max}/cm^{-1} (NaCl) 1741(CO); ^{1}H NMR (δ 400 MHz, $CDCl_3$) 1.62 (3H, s, acac-CH_3), 2.09 (3H, s, acac-CH_3), 3.99 (5H, s, Fc-C_5H_5), 4.37 (1H, t, *J* = 2.3 Hz, Fc), 4.71 (1H, s, Fc), 4.88 (1H, s, Fc), 5.30 (1H, s, acac-CH), 6.93 – 6.87 (1H, m, Ar), 7.09 – 7.04 (1H, m, Ar), 7.27 (1H, d, *J* = 2.2 Hz, Ar), 7.29 (1H, dd, *J* = 2.1, 1.4 Hz, Ar), 7.32 (1H, dd, *J* = 3.4, 1.5 Hz, Ar), 7.36 (1H, t, *J* = 1.4 Hz, Ar), 7.40 (1H, dd, *J* = 2.5, 1.3 Hz, Ar), 7.43 – 7.41 (1H, m, Ar), 7.44 (1H, dd, *J* = 2.2, 1.4 Hz, Ar), 7.47 – 7.46 (m, 1H, Ar), 7.50 – 7.48 (1H, m, Ar), 7.53 – 7.50 (1H, m, Ar), 7.54 (1H, d, *J* = 1.5 Hz, Ar), 7.59 – 7.55 (1H, m, Ar), 7.67 (1H, dd, *J* = 7.4, 4.6 Hz, Ar), ^{13}C NMR (δ 126 MHz, $CDCl_3$) 27.7 (s, acac-CH_3), 29.8 (s, acac-CH_3) 67.0 (d, *J* = 1.2, Fc), 69.7 (s, Fc), 70.2 (s, Fc), 70.3 (s, Fc-C_5H_5), 73.9 (s, Fc), 77.7 (s, Fc), 80.3 (d, *J* = 21.8 Hz, Fc), 99.3 (s, acac-CH), 120.2 (d, *J* = 60.0 Hz, Ar), 124.4 (d, *J* = 8.5 Hz, Ar), 126.2 (d, *J* = 29.4 Hz, Ar), 127.3 (d, *J* = 9.0 Hz, Ar), 128.2 (d, *J* = 11.0 Hz, Ar), 128.3 (d, *J* = 11.4 Hz, Ar) 128.5 (s, Ar), 129.1 (s, Ar), 129.5 (s, Ar), 130.5 (d, *J* = 2.5 Hz, Ar), 130.6 (d, *J* = 2.6 Hz, Ar), 131.1 (d, *J* = 2.2 Hz, Ar), 131.2 (s, Ar), 131.7 (s, Ar), 132.8 (d, *J* = 4.2 Hz, Ar), 134.2 (d, *J* = 12.7 Hz, Ar), 134.6 (d, *J* = 11.3 Hz, Ar), 149.4 (d, *J* = 15.3 Hz, Ar), 187.0 (d, *J* = 0.9 Hz, CO), 187.9 (s, CO); ^{31}P NMR (δ 162 MHz, $CDCl_3$) 30.8 (s, *P*Ph_2). HRMS (FTMS + p APCI) $M^{+}H$ $C_{33}H_{30}FeO_2$ requires 651.0347 found 651.03

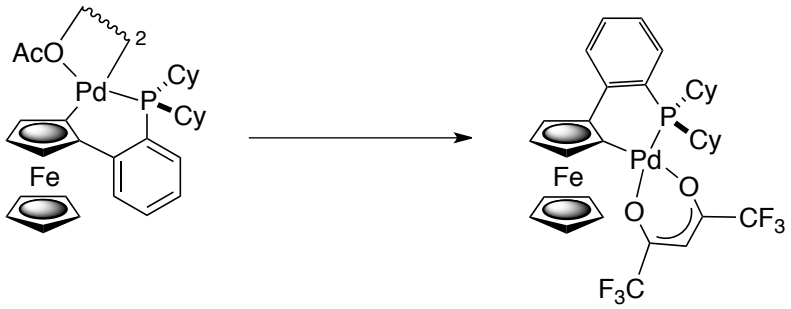
Synthesis of Acetylacetonate-*rac*-[2-(diisopropylphosphino)phenylferroceneC,P]Palladium



294 **307**

To a round bottom flask *Rac*-di-μ-aceto-bis[2-(diisopropylphosphino)-phenylferrocene-C,P]dipalladium (0.1 g, 0.103 mmol), sodium acetylacetonate hydrate (62 mg, 0.515 mmol), distilled water (6 mL) and acetone (12 mL). This was allowed to stir overnight, extracted with dichloromethane (2 x 20 mL) and dried over $MgSO_4$. The crude was purified *via* flash chromatography (hexane 15% / EtOAc 85%) to give the product as a dark orange solid (53 mg, 89%). Mp 163 – 165 ^{o}C; IR ν_{max}/cm^{-1} (Film) 1583.37 (C=O), 1451.01 (C=C); ^{1}H NMR (δ 400 MHz, $CDCl_3$) 0.93 (3H,dd, *J* = 16.1, 7.1 Hz, *iPr*-CH_3), 0.99 (3H, dd, *J* = 16.2, 7.1 Hz, *iPr*-CH_3), 1.49 (3H, dd, *J* = 7.1, 5.9 Hz, *iPr*-CH_3), 1.51 (3H, m, *iPr*-CH_3), 1.92 (3H, s, acac-CH_3), 1.97 (1H,dt, *J* = 9.0, 7.2 Hz, *iPr*-CH), 2.09 (1H, s, acac-CH_3), 2.91 (1H, dhept, *J* = 14.1, 7.1 Hz, *iPr*-CH), 4.06 (5H,s, Fc-C_5H_5), 4.20 (1H, s, acac-CH), 4.43 (1H,t, *J* = 2.4 Hz, Fc-H), 4.67 (1H, t, *J* = 1.8 Hz, Fc-H), 4.82 (1H, t, *J* = 1.8 Hz, Fc-H), 7.14 (1H, tt, *J* = 7.6, 1.5 Hz, Ar-H), 7.44 (2H,m, Ar-H), 7.66 (1H, ddd, *J* = 8.6, 3.5, 1.3 Hz, Ar-H); ^{13}C NMR (δ 101 MHz, $CDCl_3$) 17.7 (d, *J* = 3.4 Hz, *iPr*-CH_3), 18.4 (m, *iPr*-CH_3), 18.5 (s, acac-CH_3), 18.7 (s, acac-CH_3), 19.1 (s, *iPr*-CH_3), 21.7 (d, *J* = 26.9 Hz, *iPr*-CH), 27.8 (s, *iPr*-CH_3), 28.0 (d, *J* = 5.7 Hz, *iPr*-CH_3), 28.9 (d, *J* = 29.7 Hz, *iPr*-CH), 67.5 (d, *J* = 1.8 Hz, Fc-*ipso*), 70.3 (s, Fc-C_5H_5), 70.4 (s, Fc), 71.1 (s, Fc), 74.3 (s, Fc), 99.1 (s, CH-acac), 120.0 (d, *J* = 47.9 Hz, Ar-ipso), 124.1 (d, *J* = 7.1 Hz, Ar), 127.8 (d, *J* = 8.0 Hz, Ar), 129.5 (d, *J* = 2.4 Hz), 130.3 (d, *J* = 2.3 Hz, Ar) 149.8 (d, *J* = 11.9 Hz, Ar), 186.2 (s, CO), 187.3 (s, CO); ^{31}P NMR (162 MHz, $CDCl_3$) 44.8 (s, *P*(^{i}Pr)$_2$).

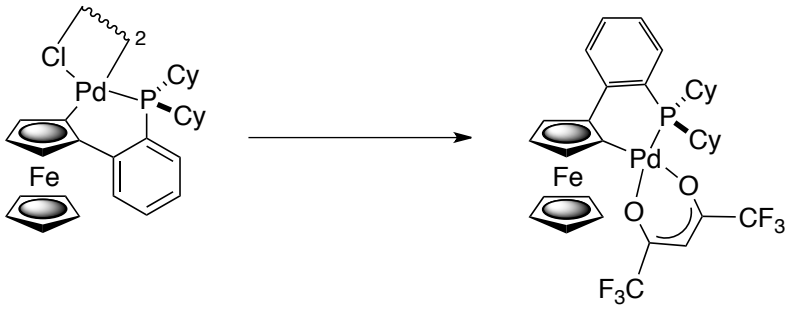
Synthesis of hexafluoroacetylacetonate-*rac*-[2-(dicyclohexylphosphino)-phenylferroceneC,P]palladium.



293 **303**

Rac-di-μ-aceto-bis[2-(dicyclohexylphosphino)-phenylferrocene-C,P]dipalladium (0.5 g, 0.401 mmol), sodium hexafluoroacetylacetonate (0.462 g, 8.6 mmol), 10 mL of acetone and 2 mL of water were allowed to stir for 16 hours at room temperature. The resulting solution was washed with water and extracted with dichloromethane (3x20 mL). The solvent was removed *in vacuo* and filtered through a plug of silica to afford the title compound as a bright orange solid (0.291 g, 94%). **Data as below**

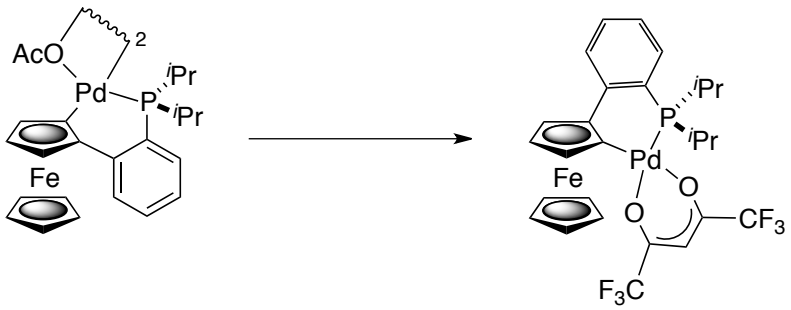
Hexafluoroacetylacetonate-*rac*-[2-(dicyclohexylphosphino)-phenylferroceneC,P] Palladium



297 **303**

A 25-mL round-bottomed flask equipped with a stirrer bar and charged with *rac*-di-*m*-chloro-bis[2-(dicyclohexylphosphino)-phenylferrocene-C,P]dipalladium (0.025 g, 0.020 mmol), sodium hexafluoroacetylacetonate (0.1 g, 0.43 mmol), 2 mL of acetone and 1 mL of water. The flask was covered with a stopper and stirred vigorously at room temperature until a precipitate is observed. The mixture was filtered and the filter cake is washed with water and then dried over in a vacuum dissecator for 12 hours to give 0.025 g (0.019 mmol 94%) of hexafluoroacetylacetonate-*rac*-[2-(dicyclohexylphosphino)-phenylferroceneC,P]palladium as an orange solid. Mp 160-165 ^{o}C; Anal. Calcd. for $C_{33}H_{35}F_6FeO_2PPd$: C, 51.42; H, 4.58; Found: C, 50.56; H, 4.59%; IR (NaCl) ν_{max}/cm^{-1} 1639.4, 1590.2, 1548.7 (C=O); ^{1}H NMR (δ 400 MHz, $CDCl_3$) δ 1.03-2.07 (22H, m, Cy), 3.65 (1H, s, Fc-C_5H_5), 4.03 (1H, s, Fc-H), 4.29 (1H, s, Fc-H), 5.60 (1H, s, acac-CH), 6.75 (1H, dd, *J* = 6.0, 2.2 Hz, Ar-H), 7.09 (1H, dd, *J* = 6.4, 3.2 Hz,), 7.54 (1H, dd, *J* = 6.4, 3.3 Hz, Ar-H), 7.62 (1H, dd, *J* = 8.0, 2.7 Hz,); ^{13}C NMR (δ 101 MHz, $CDCl_3$) 25.8 (d, *J* = 20.7 Hz, Cy), 26.7 (s, Cy), 27.0 (d, *J* = 1.9 Hz, Cy) 27.1 (s, Cy), 27.3 (d, *J* = 5.7 Hz, Cy), 27.4 (d, *J* = 5.0 Hz, Cy), 27.9 (s, Cy) 28.8 (s, Cy), 29.5 (s, Cy), 29.8 (d, *J* = 4.3 Hz, Cy), 32.7 (d, *J* = 27.2 Hz, Cy), 38.4 (d, *J* = 30.1 Hz, Cy), 66.6 (s, Fc), 67.8 (s, Fc), 69.0 (s, Fc), 69.7 (s, Fc), 71.8 (s, Fc-C_5H_5), 74.7 (s, Fc), 89.5 (s, hfacac-*C*H), 99.9 (s, CF_3), 100.9 (s, CF_3), 124.5 (d, *J* = 7.6 Hz, Ar), 126.9 (d, *J* = 12.6 Hz, Ar), 128.7 (d, *J* = 22.3 Hz, Ar), 133.5 (d, *J* = 58.4 Hz, Ar), 134.8 (d, *J* = 11.0 Hz, Ar), 138.4 (d, *J* = 40.7 Hz, Ar), 173.4 (s, CO), 174.5 (s, CO); ^{31}P NMR (δ 162 MHz, $CDCl_3$) 40.2 (s, *P*$(Cy)_2$); ^{19}F NMR (δ 376 MHz, $CDCl_3$) -75.6 (s, CF_3). -75.1 (s, CF_3); *m/z* (ES+) 769.9 (M^+, 100%), 457.1 (M^+-Pdhfacac, 55%); HRMS (FAB) M^+ $C_{29}H_{25}FeP$ requires 770.0658, found 770.0666.

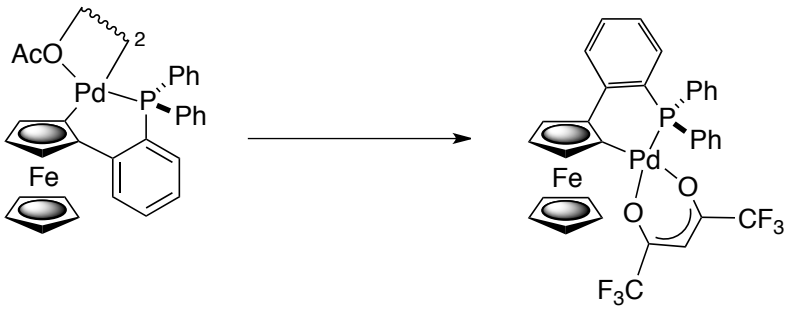
Synthesis of Hexafluoroacetylacetonate-*rac*-[2-(diisopropylphosphino)-phenylferroceneC,P]Palladium



294 **304**

To a round bottom flask *Rac*-di-μ-aceto-bis[2-(diisopropylphosphino)-phenylferrocene-C,P]dipalladium (0.1 g, 0.103 mmol), sodium hexafluoroacetylacetonate (0.118 g, 0.515 mmol), distilled water (6 mL) and acetone (12 mL). This was allowed to stir overnight, extracted with dichloromethane (2 x 20 mL) and dried over $MgSO_4$. The crude was purified *via* flash chromatography (hexane 5% / EtOAc 85%) to give the product as an orange solid (61 mg, 85%); Mp 184 – 186 ^{o}C; IR ν_{max}/cm^{-1} (Film) 1636.59 (C=O), 1550.80 (C=C); ^{1}H NMR (δ 400 MHz, $CDCl_3$) 1.01 (3H,dd, *J* = 16.6, 7.1 Hz, *iPr*-CH_3), 1.10 (3H,dd, *J* = 16.8, 7.1 Hz, *iPr*-CH_3), 1.42 (3H, dd, *J* = 7.0, 1.0 Hz, *iPr*-CH_3), 1.46 (3H,d, *J* = 7.0 Hz, *iPr*-CH_3), 2.07 (1H, app oct, J = 7.2Hz), 2.84 (1H, app oct, J = 7.0 Hz), 4.20 (5H, s, Fc-C_5H_5), 4.58 (1H, s, Fc-H), 4.87 (2H, d, *J* = 17.4 Hz, Fc-H), 7.13 (1H,m, Ar-H), 7.29 (3H, m, Ar-H); ^{13}C NMR (δ 101 MHz, $CDCl_3$) 17.0 (d, *J* = 3.1 Hz), 17.8 (m), 18.2, 18.5, 19.1, 21.5 (d, *J* = 27.8 Hz), 29.5 (d, *J* = 31.0 Hz), 67.8, 72.1, 74.7, 77.2, 89.3, 116.6, 118.3, 118.8, 124.5 (d, *J* = 7.6 Hz), 127.6 (d, *J* = 8.1 Hz), 129.3 (d, *J* = 3.0 Hz), 130.7 (d, *J* = 2.2 Hz), 149.2 (d, *J* = 11.6 Hz), 174.3, 174.7; ^{31}P NMR (δ 162 MHz, $CDCl_3$) 48.9 (s, -*P*(^{i}Pr)$_2$); ^{19}F NMR (δ 376 MHz, $CDCl_3$) -75.5 (s, -CF_3), -75.6 (s,-CF_3); HRMS (FTMS + p APCI) M^{+}H $C_{27}H_{28}F_6FeO_2PPd$ requires 691.0114 found 691.0131

Hexafluoroacetylacetonate-*rac*-[2-(diphenylphosphino)-phenylferrocene -C,P] palladium

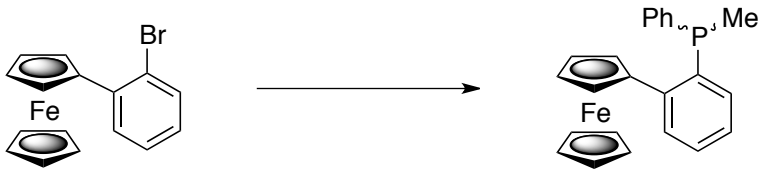


295 **302**

A 25-mL round-bottomed flask was equipped with a stir bar and charged with *Rac*-acetylacetonate[2-(diphenylphosphino)-phenylferrocene-C,P]dipalladium (0.025 g, 0.02 mmol), sodium hexafluoroacetylacetonate (0.1 g, 0.43 mmol), 2 mL of acetone and 1 mL of water. The flask was covered with a stopper and stirred vigorously at room temperature until a precipitate is observed. The mixture was filtered and the filter cake was washed with 10–20 mL of water and then dried over in a vacuum dissecator for 12 hours to provide 0.025 g (0.021 mmol 92.5%) of hexafluoroacetylacetonate-*rac*-[2-(diphenylphosphino)-phenylferrocene-C,P] palladium as an orange solid. Mp 140-145 ^{o}C, IR (NaCl) ν_{max}/cm^{-1} 1638.4, 1589.2, 1549.7 (C=O); ^{1}H NMR (δ 400 MHz, $CDCl_3$) 4.06 (1H, s, Fc-C_5H_5), 4.38 (1H, s, Fc), 4.70 (1H, s, Fc), 4.73 (1H, s, Fc), 5.95 (1H, s, hfacac-H), 6.85 (1H, ddd, *J* = 10.4, 7.8, 1.0 Hz, Ar-H), 7.02 (1H, td, *J* = 7.5, 1.2 Hz, Ar-H), 7.23 (1H, d, *J* = 2.5 Hz, Ar-H), 7.25 (1H, d, *J* = 2.3 Hz, Ar-H), 7.27 (1H, d, *J* = 2.4 Hz, Ar-H), 7.33 (1H, dd, *J* = 7.7, 2.5 Hz, Ar-H), 7.36 (1H, s, Ar-H), 7.37 (1H, d, *J* = 1.7 Hz, Ar-H), 7.42 (1H, d, *J* = 2.1 Hz, Ar-H), 7.43 (1H, s, Ar-H), 7.44 (1H, d, *J* = 1.4 Hz, Ar-H), 7.46 (1H, d, *J* = 2.5 Hz, Ar-H), 7.52 (1H, dd, *J* = 6.5, 3.3 Hz, Ar-H), 7.63 (1H, dd, *J* = 5.7, 3.3 Hz, Ar-H); ^{13}C NMR (δ 101 MHz, $CDCl_3$) 66.7 (s, Fc), 67.7 (s, Fc), 68.3 (s, Fc), 69.7 (s, Fc), 71.5 (s, Fc-C_5H_5), 74.0 (s, Fc), 89.6 (s, hfacac-CH), 119.5 (d, *J* = 63.4 Hz, Ar), 124.9 (d, *J* = 9.1 Hz, hfacac-CF_3), 126.1 (s, Ar), 126.3 (s, Ar), 127.3 (s, Ar), 127.4 (d, *J* = 9.1 Hz, hfacac-CF_3), 127.9 (s, Ar), 128.5 (d, *J* = 11.4 Hz, Ar), 128.7 (d, *J* = 11.8 Hz, Ar), 129.0 (s, Ar), 129.8 (s, Ar), 130.3 (s, Ar), 131.0 (s, Ar), 131.2 (dd, *J* = 4.8, 2.8 Hz, Ar), 131.6 (d, *J* = 2.2 Hz, Ar), 132.3 (d, *J* = 5.1 Hz, Ar) 132.6 (s, Ar), 133.2 (s, Ar) 134.1 (d, *J* = 7.7 Hz, Ar), 134.2 (d, *J* = 9.1 Hz, Ar), 175.2 (s, hfacac-CO), 175.5 (s, hfacac-CO); ^{31}P NMR (δ 162 MHz, $CDCl_3$) 32.4 (s, -*P*Ph_2); ^{19}F

NMR (δ 376 MHz, $CDCl_3$) -75.3 (s, CF_3), -76.0 (s, CF_3). HRMS (FTMS + p APCI) M^+H $C_{33}H_{24}F_6FeO_2PPd$ requires 758.9812 found 758.9799

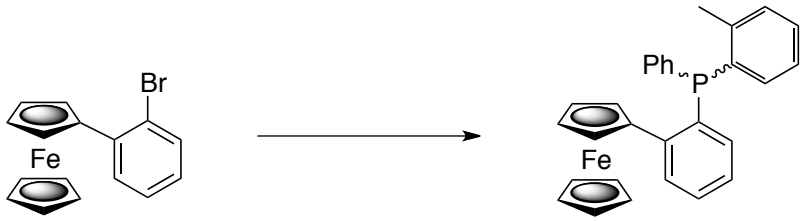
Synthesis of 2-((methyl)phenylphosphino)-phenylferrocene



222 **261**

A solution of bromophenyl ferrocene (500 mg, 1.466 mmol) in THF (10 mL) was cooled to -78 ^{o}C and ^{n}Buli (0.586 mL, 1.466 mmol) was added in one portion and allowed to stir for 1 hour. Dichlorophenylphosphine (0.198 mL, 1.466 mmol) was added and the resulting solution was allowed to warm to room temperature. This was stirred for 1 hour before cooling to -78 ^{o}C and methyllithium (1.82 mL, 2.932 mmol) was injected in, in one portion. The resulting mixture was allowed to stir for 16 hours. Upon completion water (1 mL) was added, washed with brine and extracted with diethylether (3 x 10 mL). This was dried over $MgSO_4$ and purified *via* flash chromatography (2% ethyl acetate, 98% hexane) to afford title compound as an orange oil (184 mg, 32%). V_{max}/cm^{-1} (Film) 2687.38 (C-H), 1459.82 (C=C), 1659.83 (C-C), 1416.58 (P-Ar); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (ddd, *J* = 7.9, 4.0, 1.3 Hz, 1H, Ar), 7.33 (ddd, *J* = 8.0, 6.9, 1.9 Hz, 1H, Ar), 7.27 (dd, *J* = 6.4, 3.1 Hz, 4H, Ar), 7.23 - 7.18 (m, 1H, Ar), 7.18 - 7.14 (m, 1H, Ar), 4.58 (dt, *J* = 2.5, 1.3 Hz, 1H, Cp), 4.46 (dt, *J* = 2.7, 1.5 Hz, 1H, Cp), 4.27 (td, *J* = 2.5, 1.3 Hz, 1H, Cp), 4.20 (td, *J* = 2.5, 1.3 Hz, 1H, Cp), 4.13 (s, 5H, C_5H_5), 1.40 (d, *J* = 4.8 Hz, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.7 (d, *J* = 24.6 Hz, Ar), 141.1 (d, *J* = 13.5 Hz, Ar), 138.8 (d, *J* = 17.4 Hz, Ar), 132.4 (Ar), 132.2 (Ar), 131.6 (d, *J* = 4.6 Hz, Ar), 131.1 (Ar), 128.3 (d, *J* = 5.8 Hz, Ar), 128.1 (Ar), 128.03 (Ar), 126.5 (Ar), 128.0 (Ar), 128.0 (Ar), 126.2 (Ar), 88.6 (d, *J* = 7.3 Hz, Cp), 71.6 (d, *J* = 7.2 Hz, Cp), 70.9 (d, *J* = 11.0 Hz, Cp), 69.6 (C_5H_5), 68.0 (Cp), 67.9 (Cp), 12.9 (d, *J* = 15.6 Hz, CH_3); ^{31}P NMR (202 MHz, $CDCl_3$) δ -33.22 (*P*(Me)Ph); HRMS (FTMS + p APCI) $M^{+}H$ $C_{23}H_{22}FeP$ requires 385.0803 found 385.0798

Synthesis of 2-((*ortho*-tolyl)phenylphosphino)-phenylferrocene

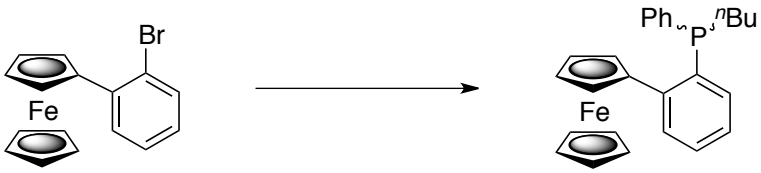


222 **260**

A solution of bromophenyl ferrocene (1 g, 2.93 mmol) in THF (10 mL) was cooled to -78 ^{o}C and ^{n}BuLi (1.17 mL, 2.93 mmol) was added in one portion and allowed to stir for 1 hour. Dichlorophenylphosphine (0.39 mL, 2.93 mmol) was added and the resulting solution was allowed to warm to room temperature. In a separate vessel, *ortho*-bromotoluene (0.352 mL, 2.93 mmol) was added to THF (5 mL) and cooled to -78 ^{o}C. ^{n}BuLi was added in 1 portion and the resulting solution was stirred for 1 hour. The lithiated bromophenyl ferrocene solution was cooled to -78 ^{o}C and the lithiated *ortho*-bromotoluene was added *via* a cannula at -78 ^{o}C. The resulting mixture was stirred at room temperature for 16 hours. Upon completion water (1 mL) was added, washed with brine and extracted with diethylether (3x10 mL). This was dried over $MgSO_4$ and purified *via* flash chromatography (2% ethyl acetate, 98% hexane) to afford title compound as an orange oil (316 mg, 29%). $\boldsymbol{\nu}_{max}$/cm^{-1} (Film) 2345.38 (C-H), 1567.92 (C=C), 1759.43 (C-C), 1316.58 (P-Ar); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (ddd, *J* = 7.8, 4.3, 1.4 Hz, 1H, Ar), 7.36 (dd, *J* = 7.5, 1.4 Hz, 1H, Ar), 7.32 (dddd, *J* = 4.3, 3.4, 2.4, 1.1 Hz, 3H, Ar), 7.24 (dd, *J* = 7.4, 1.3 Hz, 1H, Ar), 7.23 - 7.21 (m, 1H, Ar), 7.21 - 7.20 (m, 1H, Ar), 7.19 (q, *J* = 1.6, 1.2 Hz, 2H, Ar), 7.11 (td, *J* = 8.4, 7.6, 1.6 Hz, 2H, Ar), 6.81 (ddt, *J* = 7.4, 3.6, 1.6 Hz, 1H, Cp), 4.45 (dq, *J* = 2.5, 1.3 Hz, 1H, Cp), 4.37 (dq, *J* = 2.8, 1.4 Hz, 1H, Cp), 4.20 (td, *J* = 2.4, 1.3 Hz, 1H, Cp), 4.18 (td, *J* = 2.4, 1.3 Hz, 1H, Cp), 4.06 (s, 5H, C_5H_5), 2.29 (d, *J* = 1.0 Hz, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.7 (d, *J* = 26.8 Hz, Ar), 142.2 (Ar), 142.0 (Ar), 137.2 (Ar), 137.0 (d, *J* = 13.2 Hz, Ar), 135.1 (d, *J* = 15.5 Hz, Ar), 134.4 (Ar), 134.2 (d, *J* = 2.4 Hz, Ar), 133.3 (Ar), 132.4 (d, *J* = 9.3 Hz, Ar), 131.7 (d, *J* = 10.8 Hz, Ar), 131.4 (d, *J* = 5.5 Hz, Ar), 130.2 (d, *J* = 4.5 Hz, Ar), 126.4, 126.0 (Ar), 125.8 (d, *J* = 12.6 Hz, Ar), 125.0 (d, *J* = 12.8 Hz, Ar), 87.8 (d, *J* = 7.3 Hz, Cp), 71.4 (d, *J* = 7.7 Hz, Cp), 70.9 (d, *J* = 10.0 Hz Cp), 69.6 (C_5H_5), 68.2 (Cp), 68.1 (Cp), 21.4 (d, *J* = 21.0 Hz, CH_3); ^{31}P

NMR (202 MHz, $CDCl_3$) δ -19.7 (*P*(*ortho*-tolyl)(Ph); HRMS (FTMS + p APCI) M^+H $C_{29}H_{26}FeP$ requires 461.1116 found 461.1114

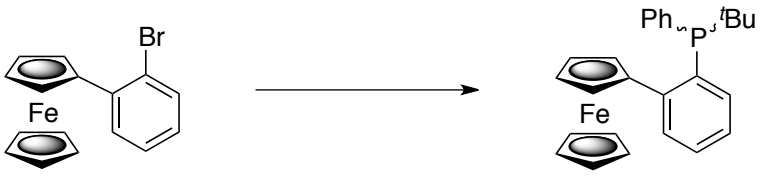
Synthesis of 2-((*n*-butyl)phenylphosphino)-phenylferrocene



222 **259**

To a solution of bromophenyl ferrocene (500 mg, 1.46 mmol) in THF (20 mL) ^{n}BuLi (0.93 mL, 1.46 mmol) was added at -78 ^{o}C and the resulting solution was allowed to stir for 1 hour. Dichlorophenylphosphine (0.187 mL, 1.46 mmol) was added in one portion and allowed to warm to room temperature. This was allowed to stir for 1 hour at room temperature and then cooled to -78 ^{o}C ^{n}BuLi (0.93 mL, 1.46 mmol) was added in one portion and the resulting mixture was allowed to warm to room temperature and stirred for 16 hours. Upon completion water (1 mL) was added, and the solution washed with brine and extracted with diethylether (3x10 mL). This was dried over $MgSO_4$ and purified *via* flash chromatography (5% ethyl acetate, 95% hexane) to afford title compound as an orange oil (473 mg, 76%); $\boldsymbol{\nu}_{max}/cm^{-1}$ (Film) 2876.38 (C-H), 1354.82 (C=C), 1579.83 (C-C), 1116.58 (P-Ar); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (ddt, *J* = 7.6, 3.8, 0.9 Hz, 1H), 7.35 - 7.30 (m, 1H, Ar), 7.29 - 7.24 (m, 5H, Ar), 7.23 - 7.18 (m, 2H, Ar), 4.56 (dq, *J* = 2.4, 1.2 Hz, 1H, Cp), 4.39 (dq, *J* = 2.8, 1.4 Hz, 1H, Cp), 4.26 (td, *J* = 2.4, 1.3 Hz, 1H, Cp), 4.18 (td, *J* = 2.4, 1.3 Hz, 1H, Cp), 4.11 (s, 5H, C_5H_5), 1.84 (ddd, *J* = 8.3, 6.5, 2.5 Hz, 2H, CH_2), 1.38 - 1.22 (m, 4H, $(CH_2)_2$), 0.81 (t, *J* = 7.0 Hz, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.2 (d, *J* = 23.8 Hz, Ar), 140.1 (d, *J* = 14.8 Hz, Ar), 137.6 (Ar), 137.5 (Ar), 132.9 (Ar), 132.8 (Ar), 131.7 (d, *J* = 5.2 Hz, Ar), 131.3 (Ar), 128.0 (Ar), 127.9 (Ar), 128.3 (d, *J* = 6.3 Hz, Ar), 128.1 (Ar), 128.0 (Ar), 126.4 (Ar), 88.6 (d, *J* = 6.7 Hz, Cp), 71.7 (d, *J* = 6.5 Hz, Cp), 71.1 (d, *J* = 11.6 Hz, Cp), 69.7 (d, *J* = 2.3 Hz, Cp), 69.6 (C_5H_5), 67.9 (d, *J* = 14.5 Hz, Cp), 28.3 (d, *J* = 17.1 Hz, CH_2), 28.0 (d, *J* = 12.9 Hz, CH_2), 24.4 (d, *J* = 12.9 Hz, CH_2), 13.9 (CH_3); ^{31}P NMR (202 MHz, $CDCl_3$) δ -23.4 (*P*(Ph)^{n}Bu); HRMS (FTMS + p APCI) $M^{+}H$ $C_{26}H_{28}FeP$ requires 427.1273 found 427.1276.

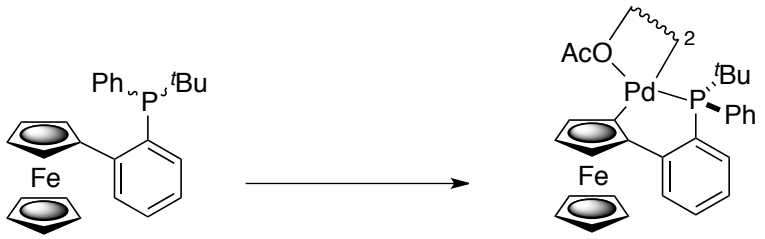
Synthesis of 2-((rac-*tert*-butyl)phenylphosphino)-phenylferrocene



222 **290**

Bromophenylferrocene (0.5 g, 1.466 mmol) was added to 10 mL of dry degassed tetrahydrofuran and cooled to -78 ^{o}C and allowed to stir for 1 hour. ^{n}BuLi (0.7 mL, 1.792 mmol) was added slowly and the reaction was allowed to stir for another hour. Chloro(*tert*-butyl)phenylphosphine was added and the reaction was warmed to room temperature and allowed to stir for 6 hours. The resulting solution was quenched with distilled water then extracted with Et_2O, washed with brine and dried over $MgSO_4$. The crude product was purified by column chromatography (hexane 75% / dichloromethane 25%) to give the title compound 2-((*tert*-butyl)phenylphosphino)-phenylferrocene (75%, 0.47 g, 1.103 mmol); ν_{max}/cm^{-1} (Film) 2895.98 (C-H), 1635.85 (C=C), 1585.81 (C-C), 1106.28 (P-Ar); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (1H, ddd, *J* = 7.7, 4.0, 1.4 Hz, Ar-H), 7.56 (1H, ddd, *J* = 7.7, 2.7, 1.4 Hz, Ar-H), 7.40 (1H, ddd, *J* = 6.2, 2.9, 1.2 Hz, Ar-H), 7.38 (1H, t, *J* = 1.6 Hz, Ar-H), 7.36 (1H, dd, *J* = 7.6, 1.4 Hz, Ar-H), 7.27 (2H, d, *J* = 0.9 Hz, Ar-H), 7.22 (1H, td, *J* = 7.5, 1.4 Hz, Ar-H), 4.55 (1H, dd, *J* = 2.4, 1.1 Hz, Cp-H), 4.38 (1H, tt, *J* = 2.3, 1.2 Hz, Cp-H), 4.24 (1H, td, *J* = 2.3, 1.2 Hz, Cp-H), 4.15 (1H, q, *J* = 1.2 Hz, Cp-H), 4.11 (5H,s, C_5H_5), 1.08 (9H, d, *J* = 12.5 Hz, ^{t}butyl). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.4 (d, *J* = 26.0 Hz, Ar), 138.7 (d, *J* = 20.4 Hz, Ar), 136.3 (d, *J* = 23.8 Hz, Ar), 135.5 (d, *J* = 19.1 Hz, Ar), 134.2 (d, *J* = 18.7 Hz, Ar), 134.0 (d, *J* = 18.2 Hz, Ar), 132.2 (d, *J* = 4.9 Hz, Ar), 131.9 (d, *J* = 6.7 Hz, Ar) 128.8 (Ar), 127.9 (d, *J* = 16.7 Hz, Ar), 127.8 (d, *J* = 5.6 Hz, Ar), 127.6 (Ar), 125.39 (Cp), 89.1 (d, *J* = 7.4 Hz, Cp), 72.0 (d, *J* = 6.3 Hz, Cp), 71.9 (d, *J* = 2.7 Hz, Cp), 69.4 (Cp-C_5H_5), 67.5 (d, *J* = 19.6 Hz, Cp), 28.8 (dd, *J* = 15.8, 12.2 Hz, CCH_3), 27.5 (d, *J* = 13.0 Hz, $^{t}BuCH_3$), 24.7 (d, *J* = 13.0 Hz, $^{t}BuCH_3$), 20.2 (d, *J* = 14.8 Hz, $^{t}BuCH_3$).^{31}P NMR (δ 202 MHz, $CDCl_3$) 6.1 (s, *P*(^{t}Bu)(Ph)) HRMS (FTMS + p APCI) $M^{+}H$ $C_{26}H_{28}FeP$ requires 427.1272 found 427.1277.

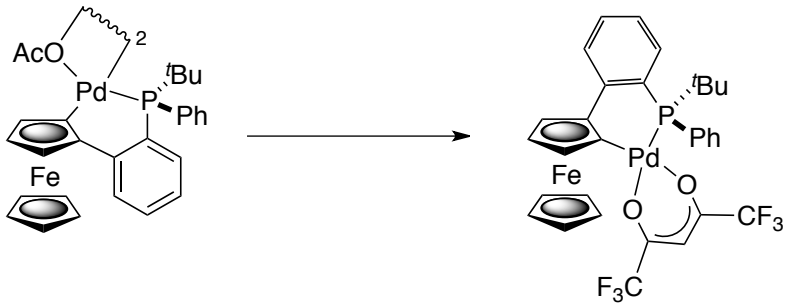
Synthesis of *Rac*-di-μ-aceto-bis[2-((*tert*-butyl)phenylphosphino)-phenylferrocene,P]dipalladium



290 **320**

A Schlenk tube was charged with 2-((*tert*-butyl)phenylphosphino)-phenylferrocene (100 mg, 0.23 mmol), $Pd(OAc)_2$ (52.52 mg, 0.23 mmol) and dissolved in dichloromethane (10 mL). The reaction mixture was allowed to stir overnight and solvent removed *in vacuo* to give title compound as a red oil. (134 mg, 99% yield). Product was identified by 31P NMR and carried on to the next step without any purification. MP 75-78 ^{o}C decomp; ν_{max}/cm^{-1} (Film) 3058.68 (C=C), 1638.11 (C-C), 1518.21 (C-H), 1149.51 (C-O)

Synthesis of hexafluoroacetylacetonate-*rac*-[2-((*tert*-butyl)phenylphosphino)-phenylferrocene,P]palladium.

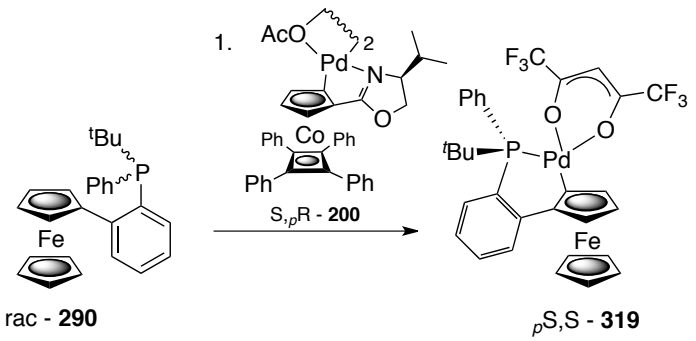


320 **319**

Major diastereoisomer.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (ddt, *J* = 10.9, 6.7, 1.6 Hz, 2H, Ar), 7.45 (d, *J* = 2.1 Hz, 1H, Ar), 7.44 (dd, *J* = 3.2, 1.9 Hz, 1H, Ar), 7.41 (dd, *J* = 4.8, 1.8 Hz, 1H, Ar), 7.40 (dd, *J* = 3.0, 1.7 Hz, 1H, Ar), 7.04 (dddd, *J* = 8.0, 7.1, 2.0, 1.1 Hz, 1H, Ar), 7.00 (ddd, *J* = 9.2, 7.8, 1.5 Hz, 1H, Ar), 5.93 (s, 1H, HfAcAc), 4.87 (s, 1H, Cp), 4.81 (s, 1H, Cp), 4.54 (d, *J* = 2.4 Hz, 1H, C_5H_5), 4.15 (s, 1H, Cp), 1.30 (d, *J* = 16.0 Hz, 9H, ^{t}Bu); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.1 (d, *J* = 10.6 Hz, CF_3), 174.8 (d, *J* = 10.8 Hz, CF_3), 150.2 (d, *J* = 13.7 Hz, CO), 148.5 (d, *J* = 10.7 Hz, CO), 143.4 (CH) 134.7 (d, *J* = 4.1 Hz, Ar), 134.5 (d, *J* = 11.5 Hz, Ar), 134.2 (d, *J* = 10.0 Hz, Ar), 134.0 (d, *J* = 3.6 Hz, Ar), 133.6 (d, *J* = 9.7 Hz, Ar), 131.3 (d, *J* = 2.5 Hz, Ar), 130.0 (d, *J* = 2.8 Hz, Ar), 128.2 (d, *J* = 10.1 Hz, Ar), 126.7 (d, *J* = 9.1 Hz, Ar), 124.2 (d, *J* = 8.1 Hz, Ar), 123.9 (d, *J* = 8.1 Hz, Ar), 118.4 (d, *J* = 55.4 Hz) (Cp), 89.5 (d, *J* = 17.4 Hz) (Cp), 89.1 (Cp), 74.1 (Cp), 70.7 (C_5H_5), 67.7, 66.74 (Cp), 35.6 (d, *J* = 29.4 Hz, $C(CH_3)_3$), 28.0 (d, *J* = 4.7 Hz, CH_3), 27.4 (d, *J* = 3.7 Hz, CH_3), 27.1 (d, *J* = 4.2 Hz, CH_3); ^{31}P NMR (202 MHz, $CDCl_3$) δ 53.3 (P(Ph)^{t}Bu); ^{19}F NMR (471 MHz, $CDCl_3$) δ -75.5 (CF_3), -76.2 (CF_3); (**minor**) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (td, *J* = 7.7, 1.2 Hz, 1H, Ar), 7.71 (ddd, *J* = 9.9, 8.2, 1.3 Hz, 1H, Ar), 7.35 (d, *J* = 7.6 Hz, 1H, Ar), 7.32 (d, *J* = 7.7 Hz, 1H, Ar), 7.21 (ddt, *J* = 7.3, 5.4, 1.7 Hz, 1H, Ar), 7.10 (dd, *J* = 8.3, 4.9 Hz, 2H, Ar), 6.94 (ddd, *J* = 8.2, 3.6, 1.3 Hz, 1H, Ar), 6.81 (dd, *J* = 8.1, 6.8 Hz, 1H, Ar), 6.14 (s, 1H, HfAcAc), 4.39 (s, 1H, Cp), 4.29 (s, 1H, Cp), 4.18 (s, 1H, Cp), 4.05 (s, 5H, C_5H_5), 1.17 (d, *J* = 14.8 Hz, 9H, ^{t}Bu); ^{31}P NMR (202 MHz, $CDCl_3$) δ 45.5 (P(Ph)^{t}Bu); ^{19}F NMR (471 MHz, $CDCl_3$) δ -75.4 (CF_3), -75.7 (CF_3).

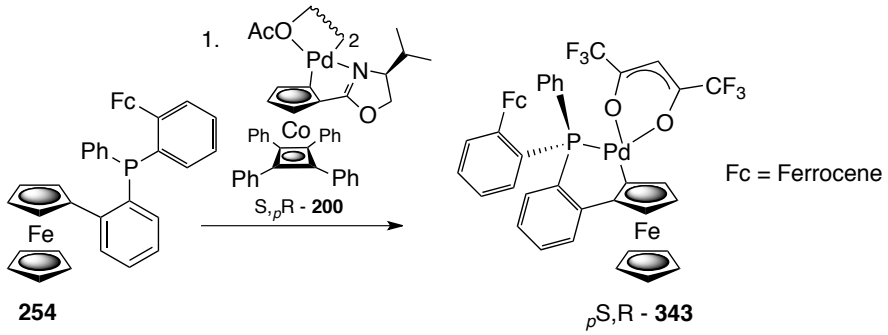
Synthesis of hexafluoroacetylacetonate-$_p$*S,S*-[2-((*tert*-butyl)phenylphosphino)-phenylferrocene,P]palladium.



A flame dried schlenk tube was charged with 2-((*tert*-butyl)phenylphosphino)-phenylferrocene (100 mg, 0.23 mmol), (η^5-(*S*)-2-(4-Methylethyl)oxazolinylcyclopentadienyl)-(η^4-tetraphenylcyclobutadiene)cobalt (73 mg, 40 Mol%) and degassed toluene (5 mL). The resulting solution was heated to 40 ^{o}C for 48 hours. The solvent was removed *in vacuo*, dissolved in acetone and sodium hexafluoroacetylacetonate (264 mg, 5 equiv.) was added and the resulting solution was stirred for a further 16 hours. The crude product was purified *via* flash chromatograph (95/5 hexane;ethyl acetate) to give the *title compound* as a red solid (58 mg, 34% yield) MP 75-78 ^{o}C ; IR ν_{max}/cm^{-1} (Film) 3058.68 (C=C), 1638.11 (C-C), 1518.21 (C-H), 1202.96 (P-Ar), 1149.51 (C-O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (ddt, *J* = 9.6, 6.6, 1.6 Hz, 1H, Ar), 7.62 (dd, *J* = 8.2, 4.9 Hz, 1H, Ar), 7.39 (dd, *J* = 7.7, 1.9 Hz, 1H, Ar), 7.36 (td, *J* = 3.1, 2.5, 1.3 Hz, 1H, Ar), 7.35 - 7.34 (m, 1H, Ar), 7.33 (dd, *J* = 1.8, 1.0 Hz, 1H, Ar), 7.31 (t, *J* = 1.6 Hz, 1H, Ar), 6.97 (dddd, *J* = 8.1, 7.1, 2.0, 1.2 Hz, 1H, Ar), 6.93 (ddd, *J* = 9.3, 7.8, 1.6 Hz, 1H, Ar), 5.85 (s, 1H, HfAcAc), 4.77 (t, *J* = 1.9 Hz, 1H, Cp), 4.70 (dt, *J* = 2.0, 0.9 Hz, 1H, Cp), 4.44 (t, *J* = 2.5 Hz, 1H, Cp), 4.05 (s, 5H, C_5H_5), 1.22 (d, *J* = 16.0 Hz, 9H, ^{t}Bu); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.2 (Ar), 150.1 (Ar), 134.0 (d, *J* = 3.4 Hz, Ar), 133.6 (d, *J* = 9.4 Hz, Ar), 131.3 (d, *J* = 2.3 Hz, Ar), 130.0 (d, *J* = 2.7 Hz, Ar), 130.0 (Ar), 129.59 (Ar), 129.0 (d, *J* = 24.0 Hz, Ar), 128.2 (d, *J* = 10.2 Hz, Ar), 127.7 (Ar), 127.69 (Ar), 126.7 (d, *J* = 9.1 Hz, Ar), 125.4 (AcAc), 123.9 (d, *J* = 8.4 Hz, Ar), 118.7 ((C-O)), 118.2 ((C-O)), 89.1 (hfacac), 73.9 (Cp), 70.7 (Cp), 70.3 (C_5H_5), 69.4 (Cp), 67.6 (Cp), 35.5 (d, *J* = 29.2 Hz, ^{t}Bu), 29.7 (s, ^{t}Bu), 28.8 (d, *J* = 15.5 Hz, ^{t}Bu), 28.0 (d, *J* = 4.7 Hz, ^{t}Bu); ^{31}P NMR (202 MHz, $CDCl_3$) δ 53.4 (*P*(Ph)^{t}Bu); ^{19}F NMR (471 MHz, $CDCl_3$) δ -75.5 (CF_3), -76.2 (CF_3); HRMS (FTMS + p APCI) $M^{+}H$ $C_{31}H_{27}F_6FeO_2PPd$ requires 737.0118 found

737.0125; The enantiomeric excess was determined by ChiralPak® OD (25 cm), Hexanes / IPA = 99.9 / 0.1, 0.1 mL/min, λ = 254 nm, t (major) = 85.12 min, t (minor) = 13.14 min.

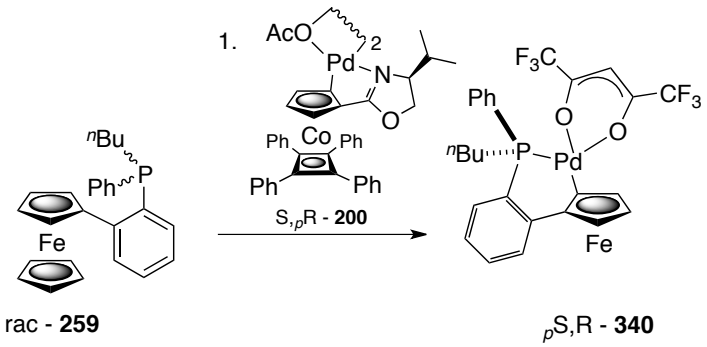
Synthesis of hexafluoroacetylacetonate-$_pS,R$-[2-((2-phenylferrocenyl)phenylphosphino)-phenylferrocene,P]palladium



A flame dried schlenk tube is charged with **MudzPhos** (300 mg, 0.476 mmol), (η^5-(*S*)-2-(4-Methylethyl)oxazolinylcyclopentadienyl)-(η^4-tetraphenylcyclobutadiene)cobalt (373.82 mg, 0.476 mmol) and degassed toluene (5 mL). The resulting solution was heated to 40 ^oC for 16 hours. The solvent is removed *in vacuo*, dissolved in acetone and sodium hexafluoroacetylacetonate (264 mg, 5 equiv.) was added and the resulting solution was stirred for a further 16 hours. The crude product was purified *via* flash chromatograph (95/5 hexane;ethyl acetate) to give the title compound as a red solid (400 mg, 89% yield); MP 231-235 ^oC; IR $\boldsymbol{\nu}_{max}/cm^{-1}$ (Film) 1588.68 (C=C), 1638.73 (C-C), 1518.21 (C-H), 866.44 (P-Ar), 1255.64 (C-O); ^1H NMR (500 MHz, $CDCl_3$) δ 8.12 (ddd, *J* = 8.0, 4.8, 1.3 Hz, 1H, Ar), 7.67 - 7.57 (m, 1H, Ar), 7.54 - 7.46 (m, 1H, Ar), 7.44 (tt, *J* = 7.7, 1.4 Hz, 1H, Ar), 7.37 - 7.30 (m, 2H, Ar), 7.30 - 7.26 (m, 2H, Ar), 7.14 - 7.07 (m, 2H, Ar), 7.01 (ddd, *J* = 10.8, 7.7, 1.4 Hz, 1H, Ar), 6.67 (ddd, *J* = 12.9, 7.9, 1.3 Hz, 1H, Ar), 5.89 (s, 1H, HfAcAc), 5.12 (dt, *J* = 2.6, 1.3 Hz, 1H, Cp), 4.70 (s, 1H, Cp), 4.48 (s, 1H, Cp), 4.38 (s, 2H, Cp), 4.25 (td, *J* = 2.5, 1.3 Hz, 1H, Cp), 4.20 (td, *J* = 2.5, 1.2 Hz, 1H, Cp), 4.16 (s, 5H, C_5H_5), 4.01 (s, 5H, C_5H_5);^{13}C NMR (126 MHz, $CDCl_3$) δ 175.0 (d, *J* = 3.3, CF_3), 174.7 (d, *J* = 3.2 Hz, CF_3), 147.2 (d, *J* = 13.9 Hz, Ar), 145.4 (d, *J* = 10.9 Hz, Ar), 134.5 (d, *J* = 7.3 Hz, Ar), 133.2 (d, *J* = 9.1 Hz, Ar), 132.0 (d, *J* = 5.1 Hz, Ar), 131.8 (Ar), 131.5 (d, *J* = 2.5 Hz, Ar), 131.3 (Ar), 131.0 (d, *J* = 2.7 Hz, Ar), 130.2 (d, *J* = 2.7 Hz, Ar), 129.1 (Ar), 128.7 (d, *J* = 11.8 Hz, Ar), 127.9 (d, *J* = 9.1 Hz, Ar), 125.6 (d, *J* = 9.3 Hz, Ar), 124.6 (d, *J* = 9.2 Hz, Ar), 124.5 (Ar), 124.1 (Ar), 121.0 (Ar), 120.5 (Ar), 119.1 (hfacac), 116.9 (hfacac), 89.2 (hfacac), 87.3 (d, *J* = 4.5 Hz, Cp), 73.7 (Cp), 72.9 (Cp), 70.9 (Cp), 70.5 (d, *J* = 2.5 Hz, Cp), 69.9 (2xC_5H_5), 69.5 (Cp), 68.6 (Cp), 68.1 (Cp);^{31}P NMR (202 MHz, $CDCl_3$) δ 32.3

(*P*(Pd)(Ph)(Ph-Fc));^{19}F NMR (471 MHz, $CDCl_3$) δ -75.3 (d, *J* = 4.6 Hz, CF_3), -75.5(d, *J* = 2.1 Hz, CF_3); HRMS (FTMS + p APCI) M^+H $C_{43}H_{32}F_6Fe_2O_2PPd$ requires 942.9787 found 942.9790; The enantiomeric excess was determined by ChiralPak® OD column (25 cm), hexanes / IPA = 97.5 / 2.5, 0.3 mL/min, λ = 254 nm, t (minor) = 14.06 min, t (major) = 15.76 min.

Synthesis of hexafluoroacetylacetonate-$_p$*S,R*[2-((*n*-butyl)phenylphosphino) phenylferrocene,P]palladium

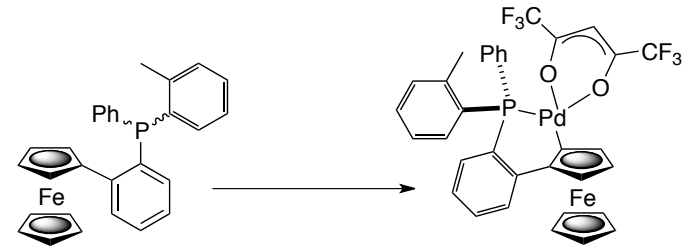


rac - **259** $_p$S,R - **340**

A flame dried schlenk tube is charged with 2-((*n*-butyl)phenylphosphine)-phenylferrocene (200 mg, 0.469 mmol), (η^5-(S)-2-(4-Methylethyl)oxazolinylcyclopentadienyl)-(η^4-tetraphenylcyclobutadiene)cobalt (147.3 mg, 40 Mol%) and degassed toluene (5 mL). The resulting solution was heated to 40 ^{o}C for 16 hours. The solvent was removed *in vacuo*, dissolved in acetone and sodium hexafluoroacetylacetonate (5 equiv.) was added and the resulting solution was stirred for a further 16 hours. The crude product is purified *via* flash chromatograph (98/2 hexane;ethyl acetate) to give the title compound as a red solid (102 mg, 29% yield); M.P. 84-86 ^{o}C IR ν_{max}/cm^{-1} (Film) 3108.69 (C=C), 1325.10 (C-C), 1512.72 (C-H), 1419.61 (C-O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 - 7.68 (m, 2H Ar), 7.68 - 7.64 (m, 1H, Ar), 7.51 (dd, *J* = 7.1, 1.9 Hz, 1H, Ar), 7.49 (dd, *J* = 2.5, 1.6 Hz, 1H, Ar), 7.48 - 7.46 (m, 2H, Ar), 7.46 - 7.44 (m, 1H, Ar), 7.42 (dt, *J* = 7.2, 1.4 Hz, 1H, Ar), 7.39 (d, *J* = 1.3 Hz, 1H, Ar), 7.38 (d, *J* = 1.6 Hz, 1H, Ar), 7.37 (d, *J* = 1.1 Hz, 1H, Ar), 7.35 (d, *J* = 1.6 Hz, 1H, Ar), 7.23 (dddd, *J* = 8.6, 7.0, 3.1, 1.6 Hz, 2H, Ar), 7.12 (tt, *J* = 7.5, 1.5 Hz, 1H, Ar), 7.07 - 6.98 (m, 1H, Ar), 6.14 (s, 1H, hfacac major), 6.04 (s, 1H, hfacac minor), 4.89 (t, *J* = 1.6 Hz, 1H, Cp, minor), 4.85 - 4.82 (m, 1H, Cp, minor), 4.73 (t, *J* = 1.8 Hz, 1H, Cp, major), 4.69 (t, *J* = 1.6 Hz, 1H, Cp, major), 4.47 (t, *J* = 2.5 Hz, 1H, Cp, minor), 4.41 (t, *J* = 2.4 Hz, 1H, Cp, major), 4.12 (s, 1H, Cp, major), 4.09 (s, 5H, C_5H_5 major), 4.00 (s, 1H, Cp, minor), 3.97 (s, 5H, C_5H_5, minor), 2.67 (dddd, *J* = 13.9, 12.2, 9.3, 4.2 Hz, 1H, *n*butyl), 2.45 (dddd, *J* = 16.2, 14.5, 10.1, 4.5 Hz, 1H, *n*butyl), 2.34 (tdd, *J* = 14.1, 12.1, 4.1 Hz, 3H, *n*butyl), 2.10 - 1.98 (m, 1H, *n*butyl), 1.83 - 1.72 (m, 2H, *n*butyl), 1.69 - 1.58 (m, 2H, *n*butyl), 1.35 (ddd, *J* = 13.0, 6.3, 2.3 Hz, 3H, *n*butyl), 0.95 (t, *J* = 7.3 Hz, 5H, *n*butyl). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.3 (CF_3), 176.0 (CF_3), 175.7 (CF_3), 175.5 (CF_3), 149.7 (C-O), 149.6 (C-O), 149.2 (C-O), 149.1 (C-

O), 133.4 (Ph), 133.0 (d, *J* = 10.5 Hz, Ph), 132.3 (d, *J* = 11.8 Hz, Ph), 131.9 (Ph), 131.6 (d, *J* = 3.7 Hz, Ph), 131.3 (d, *J* = 2.7 Hz, Ph), 130.9 (d, *J* = 3.4 Hz, Ph), 129.5 (d, *J* = 4.1 Hz, Ph), 129.3 (Ph), 129.1 (d, *J* = 11.3 Hz, Ph), 128.9 (d, *J* = 11.0 Hz, Ph), 128.3 (Ph), 128.2 (d, *J* = 8.7 Hz, Ph), 128.0 (Ph), 127.2 (d, *J* = 9.3 Hz, Ph), 133.0 (Ph), 126.8 (Ph), 126.4 (Ph), 125.4 (d, *J* = 8.7 Hz, Ph), 125.3 (d, *J* = 9.0 Hz, Ph), 119.1 (Ph), 118.1 (d, *J* = 60.4 Hz, Ph), 90.0 (hfacac major), 89.9 (hfacac minor), 81.4 (d, *J* = 12.9 Hz, major), 79.8 (d, *J* = 23.4 Hz, Cp minor), 74.0 (Cp major), 73.7 (Cp minor), 71.2 (Cp major), 70.9 (C_5H_5 major), 70.6 (C_5H_5 minor), 70.0 (Cp minor), 69.8 (Cp major), 68.4 (d, *J* = 4.3 Hz, Cp minor), 68.0 (Cp major), 66.9 (Cp minor), 28.4 (d, *J* = 34.0 Hz, *n*butyl), 27.7 (*n*butyl), 27.1 (*n*butyl), 24.9 (*n*butyl), 24.8 (*n*butyl), 24.6 (d, *J* = 3.3 Hz, *n*butyl), 24.3 (d, *J* = 16.3 Hz, *n*butyl), 14.0 (*n*butyl); ^{31}P NMR (202 MHz, $CDCl_3$) δ 27.8 (*P*(^{n}butyl)(Ph)Pd) minor, 26.0 (*P*(^{n}butyl)(Ph)Pd) major; ^{19}F NMR (471 MHz, $CDCl_3$) δ -74.0 (CF_3 minor), -74.0 (CF_3 major), -74.3 (CF_3 major), -74.5 (CF_3 minor); HRMS (FTMS + p APCI) M^+H $C_{31}H_{28}F_6O_2PPdFe$ requires 739.0117 found 739.0135.

Synthesis of hexafluoroacetylacetonate-*rac*-[2-((*σ*-tolyl)phenylphosphino) phenylferrocene,P]palladium

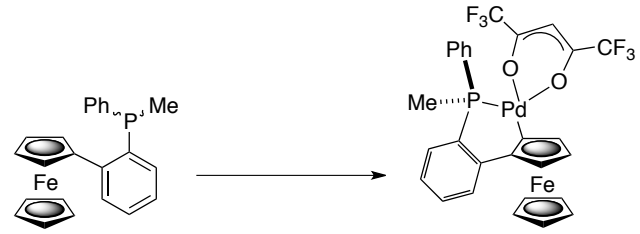


rac - **260** rac - **342**

A flame dried schlenk tube is charged with 2-((*σ*-tolyl)phenylphosphino)-phenylferrocene (80 mg, 0.185 mmol), $Pd(OAc)_2$ (41.47 mg, 0.185 mmol) and dichloromethane (5 mL). The resulting solution was allowed to stir at room temperature for 16 hours. The solvent is removed *in vacuo*, dissolved in acetone and sodium hexafluoroacetylacetonate (264 mg, 5 equiv.) was added and the resulting solution is stirred for a further 16 hours. The crude product is purified *via* flash chromatograph (97/3 hexane;ethyl acetate) to give the *title compound* as a red solid (129 mg, 91% yield) MP 68-70 ^{o}C; IR $\boldsymbol{\nu}_{max}$/cm^{-1} (Film) 3008.69 (C=C), 1659.81 (C-C), 1589.12 (C-H), 1222.97 (P-Ar), 1149.51 (C-O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (ddd, *J* = 8.0, 4.6, 1.1 Hz, 2H, Ar), 7.56 (tdd, *J* = 6.7, 2.4, 1.2 Hz, 2H, Ar), 7.48 - 7.47 (m, 2H, Ar), 7.46 - 7.43 (m, 1H, Ar), 7.42 (dq, *J* = 7.4, 1.3 Hz, 1H, Ar), 7.39 (dd, *J* = 2.1, 1.3 Hz, 1H, Ar), 7.36 (ddd, *J* = 7.1, 2.6, 1.3 Hz, 2H, Ar), 7.34 - 7.30 (m, 1H, Ar), 7.30 - 7.27 (m, 1H, Ar), 7.23 - 7.16 (m, 1H, Ar), 7.12 (tdd, *J* = 7.3, 2.1, 1.1 Hz, 2H, Ar), 7.08 (ddd, *J* = 7.4, 2.2, 1.3 Hz, 1H, Ar), 7.03 (dd, *J* = 7.6, 1.4 Hz, 1H, Ar), 7.01 (dd, *J* = 7.8, 1.4 Hz, 1H, Ar), 7.02 - 6.94 (m, 1H, Ar), 6.72 (ddd, *J* = 12.5, 7.8, 1.3 Hz, 1H, Ar), 6.64 (ddd, *J* = 11.0, 7.8, 1.3 Hz, 1H, Ar), 6.57 (ddd, *J* = 12.7, 7.8, 1.3 Hz, 1H, Ar), 6.06 (s, 1H, HfAcAc, minor), 6.02 (s, 1H, HfAcAc, major), 4.77 (dd, *J* = 2.0, 0.9 Hz, 1H, Cp, major), 4.76 (dq, *J* = 2.5, 0.6 Hz, 1H, Cp, minor), 4.74 (ddd, *J* = 2.2, 1.2, 0.7 Hz, 1H, Cp, major), 4.59 (ddd, *J* = 2.1, 1.3, 0.6 Hz, 1H, Cp, minor), 4.43 (t, *J* = 2.4 Hz, 1H, Cp, major), 4.36 (t, *J* = 2.4 Hz, 1H, Cp, minor), 4.11 (s, 5H, C_5H_5, major), 4.02 (s, 5H, C_5H_5, minor), 2.74 (s, 3H, CH_3, major), 2.59 (s, 3H, CH_3, minor); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.7 (q, *J* = 42.9, 34.1 Hz, CF_3), 149.1 (d, *J* = 13.8 Hz, Ar), 148.6 (Ar), 142.7 (d, *J* = 11.8 Hz, Ar), 142.5 (d, *J* = 12.8 Hz, Ar), 134.9 (d, *J* = 11.0 Hz, Ar), 133.7 (d, *J* = 7.3 Hz, Ar), 132.9 (d, *J* = 6.0 Hz, Ar), 132.0 (Ar), 132.01 (Ar), 132.0 (d, *J* = 3.0 Hz, Ar), 131.9 (Ar), 131.9 (Ar), 131.7 (Ar), 131.8 (Ar), 131.8 (Ar), 1316 (Ar), 131.6 (Ar),

131.5 (Ar), 131.5 (Ar), 131.5 (Ar), 131.7 (Ar), 131.4 (Ar), 130.0 (Ar), 129.5 (Ar), 129.2 (Ar), 129.0 (Ar), 129.0 (Ar), 128.9 (Ar), 128.7 (Ar), 128.2 (Ar), 128.0 (d, *J* = 9.2 Hz, Ar), 127.7 (d, *J* = 9.1 Hz, Ar), 126.9 (Ar), 126.6 (Ar), 126.4 (Ar), 126.2 (Ar) (d, *J* = 3.8 Hz, Ar), 126.1 (Ar), 126.0 (Ar), 125.9 (Ar), 125.5 (d, *J* = 9.2 Hz, Ar), 125.2 (d, *J* = 9.0 Hz, Ar), 120.5 (C-O), 120.0 (C-O), 118.9 (C-O), 118.4 (C-O), 89.8 (HfAcAc), 81.1 (Cp), 81.0 (Cp), 80.8 (Cp), 80.7 (Cp), 79.7 (Cp), 79.5 (Cp), 74.2 (Cp), 73.5 (Cp), 71.2 (Cp), 70.9 (C_5H_5), 70.8 (C_5H_5), 68.0 (d, *J* = 2.4 Hz, Cp), 67.2 (d, *J* = 1.7 Hz, Cp), 32.1 (s, CH_3), 30.1 (d, *J* = 5.4 Hz, CH_3); ^{31}P NMR (202 MHz, $CDCl_3$) δ 28.0 (*P*(σ-tolyl)Ph) major), 24.2 (*P*(σ-tolyl)Ph) minor); ^{19}F NMR (471 MHz, $CDCl_3$) δ -75.2 (CF_3, major), -75.3 (CF_3, minor), -76.2 (CF_3, major), -76.3 (CF_3, minor). HRMS (FTMS + p APCI) M^+H $C_{34}H_{26}F_6FeO_2PPd$ requires 773.9995 found 773.9868

Synthesis of hexafluoroacetylacetonate-*rac*-[2-((methyl)phenylphosphino) phenylferrocene,P]palladium

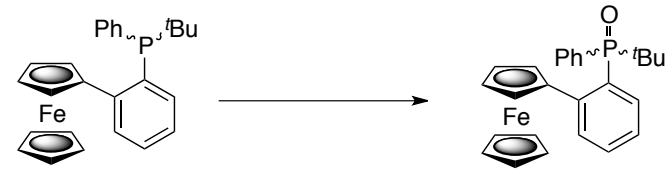


rac - **261** rac - **341**

A flame dried schlenk tube is charged with 2-((methyl)phenylphosphino)-phenylferrocene (105 mg, 0.273 mmol), $Pd(OAc)_2$ (61.28 mg, 0.273 mmol) and dichloromethane (5 mL). The resulting solution was allowed to stir at room temperature for 16 hours. The solvent was removed *in vacuo*, dissolved in acetone and sodium hexafluoroacetylacetonate (5 equiv.) was added and the resulting solution was stirred for a further 16 hours. The crude product was purified *via* flash chromatograph (99/1 hexane;ethyl acetate) to give the *title compound* as a red solid (165.3 mg, 87% yield) MP 60-62 ^{o}C; IR $\boldsymbol{\nu}_{max}$/cm^{-1} (Film) 3108.69 (C=C), 1666.06 (C-C), 1569.12 (C-H), 1322.47 (P-Ar), 1149.51 (C-O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (dd, *J* = 7.1, 4.7 Hz, 1H, Ar), 7.72 - 7.67 (m, 1H, Ar), 7.67 (d, *J* = 1.5 Hz, 1H, Ar), 7.69 - 7.63 (m, 1H, Ar), 7.60 - 7.54 (m, 1H, Ar), 7.54 (dd, *J* = 2.1, 1.3 Hz, 1H, Ar), 7.52 (dd, *J* = 2.5, 0.9 Hz, 1H, Ar), 7.51 (dd, *J* = 2.5, 1.6 Hz, 1H, Ar), 7.49 (dd, *J* = 2.6, 1.4 Hz, 1H, Ar), 7.46 (d, *J* = 2.4 Hz, 1H, Ar), 7.45 (t, *J* = 1.3 Hz, 1H, Ar), 7.44 - 7.36 (m, 1H, Ar), 7.37 (d, *J* = 1.6 Hz, 1H, Ar), 7.32 - 7.26 (m, 1H, Ar), 7.09 (tdd, *J* = 7.4, 2.1, 1.2 Hz, 1H, Ar), 6.93 (ddd, *J* = 11.0, 7.7, 1.4 Hz, 1H, Ar), 6.12 (s, 1H, HfAcAc, minor), 6.02 (s, 1H, HfAcAc, major), 4.93 - 4.78 (m, 1H, Cp, major), 4.76 - 4.72 (m, 1H, Cp, minor), 4.61 (s, 1H, Cp, minor), 4.51 (t, *J* = 2.4 Hz, 1H, Cp, major), 4.44 (s, 1H, Cp, minor), 4.09 (d, *J* = 1.6 Hz, 1H, Cp, major), 4.04 (s, 5H, C_5H_5, major), 4.00 (s, 5H, C_5H_5, minor), 2.17 (d, *J* = 11.6 Hz, 3H, CH_3, minor), 1.92 (d, *J* = 11.2 Hz, 3H, CH_3, major); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.4 (CF_3), 148.6 (Ar), 132.91 (d, *J* = 10.9 Hz, Ar), 131.9 (Ar), 131.5 (d, *J* = 2.8 Hz, Ar), 130.9 (d, *J* = 5.5 Hz, Ar), 129.1 (Ar), 129.0 (Ar), 128.9 (Ar), 128.7 (Ar), 127.3 (d, *J* = 9.2 Hz, Ar), 125.4 (d, *J* = 9.2 Hz, Ar), 121.6 (C-O), 121.1 (C-O), 89.9 (HfAcAc), 78.0 (Cp), 73.9 (Cp), 71.1 (Cp), 70.9 (C_5H_5, minor), 70.83 (C_5H_5, major), 70.1 (Cp), 67.3 (Cp), 15.1 (d, *J* = 36.8 Hz, CH_3); ^{31}P NMR (202 MHz, $CDCl_3$) δ 17.4 (*P*(CH_3)Ph), major), 17.0 (*P*(CH_3)Ph), minor); ^{19}F NMR (471 MHz, $CDCl_3$) δ -75.36 (CF_3,

minor) -75.4 (CF_3, major), -75.7 (CF_3, minor), -75.9 (CF_3, major);HRMS (FTMS + p APCI) M^+H $C_{28}H_{22}F_6FeO_2PPd$ requires 697.9673 found 697.9556

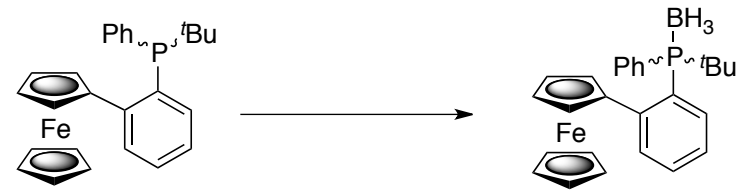
Synthesis of 2-((*tert*-butyl)phenylphosphineoxide)-phenylferrocene.



rac - **290** rac - **325**

A flask was charged with 2-((*tert*-butyl)phenylphosphino)-phenylferrocene (100 mg, 0.23 mmol) and *m*CPBA (80 mg, 2 equiv.). Dichloromethane (10 mL) was added and the resulting solution was allowed to stir for 5 hours, washed with water (10 mL) and extracted with dichloromethane (10 mL). The organic layer was then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was then further purified *via* flash chromatography (99:1 dichloromethane/methanol) to afford the *title compound* as red oil. (100 mg, 99% yield). IR ν_{max}/cm^{-1} (Film) 1586.29 (C=C), 1106.20 (P=O), 887.47 (C-H); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (dd, *J* = 7.9, 3.8 Hz, 1H, Ar), 7.98 (dd, *J* = 11.4, 7.8 Hz, 1H, Ar), 7.49 (t, *J* = 7.6 Hz, 1H, Ar), 7.32 (ddd, *J* = 9.1, 5.3, 2.1 Hz, 1H, Ar), 7.23 (dd, *J* = 11.5, 7.2 Hz, 3H, Ar), 7.11 (td, *J* = 7.6, 2.7 Hz, 2H, Ar), 5.13 (d, *J* = 2.7 Hz, 1H, Cp-H), 4.00 (s, 5H, C_5H_5), 3.90 (dt, *J* = 2.8, 1.6 Hz, 1H, Cp-H), 3.79 (t, *J* = 2.0 Hz, 1H, Cp-H), 3.71 (dt, *J* = 2.7, 1.5 Hz, 1H, Cp-H), 1.26 (d, *J* = 14.2 Hz, 9H, ^{t}Bu); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.5 (d, *J* = 6.4 Hz, Ar), 134.9 (d, *J* = 9.0 Hz, Ar), 131.9 (d, *J* = 8.5 Hz, Ar), 131.7 (Ar), 131.6 (Ar), 131.4 (Ar), 130.8 (d, *J* = 1.8 Hz, Ar), 130.5 - 130.2 (m, Ar), 130.2 (Ar), 128.2 (d, *J* = 10.3 Hz, Ar), 127.0 (d, *J* = 11.4 Hz, Ar), 124.9 (d, *J* = 11.6 Hz, Ar), 74.1 (Ar), 72.5 (Cp), 72.2 (Cp), 69.4 (C_5H_5), 67.4 (d, *J* = 22.4 Hz, Cp), 67.2 (Cp) , 66.5 (d, *J* = 22.5 Hz, Cp), 34.2 (d, *J* = 71.4 Hz, $C(CH_3)_3$), 26.3 (CH_3) , 18.7 (d, *J* = 5.5 Hz, CH_3), 13.7 (CH_3)^{31}P NMR (202 MHz, $CDCl_3$) δ 42.5 (O=*P*(^{t}Bu)Ph)

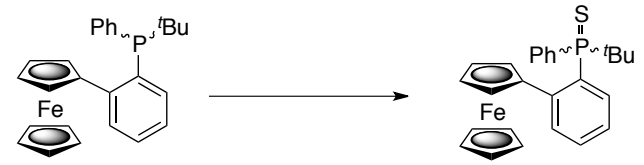
Synthesis of 2-((*tert*-butyl)phenylphosphineborane)-phenylferrocene.



rac - **290** rac - **277**

A flask was charged with 2-((*tert*-butyl)phenylphosphino)-phenylferrocene (200 mg, 0.46 mmol) and toluene (10 mL). The flask was then cooled to 0 ^{o}C and $BH_3.SMe_2$ (63 mg, 10 equiv.) was added. The resulting solution was allowed to warm to room temperature and stirred for 16 hours. The solvent was then removed *in vacuo* and filtered through a silica plug to afford the *title compound* as a red oil (195 mg, 95% yield); V_{max}/cm^{-1} (Film) 1589.86 (C=C), 1026.74 (P-Ar), 819.75 (C-H); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (ddd, *J* = 7.8, 3.8, 1.5 Hz, 1H, Ar), 7.90 (ddd, *J* = 10.6, 7.9, 1.4 Hz, 1H, Ar), 7.69 (ddd, *J* = 9.5, 6.8, 1.6 Hz, 1H, Ar), 7.49 (tdd, *J* = 7.8, 3.8, 2.4 Hz, 1H, Ar), 7.45 (tt, *J* = 7.8, 1.4 Hz, 2H, Ar), 7.37 - 7.30 (m, 3H, Ar), 7.22 (tt, *J* = 7.3, 1.5 Hz, 1H Ar), 7.13 - 7.06 (m, 2H, Ar), 4.63 (dd, *J* = 2.6, 1.3 Hz, 1H, Cp-H), 3.98 (s, 5H, C_5H_5), 3.92 (dd, *J* = 2.5, 1.3 Hz, 1H, Cp-H), 3.73 (dt, *J* = 2.5, 1.2 Hz, 1H, Cp-H), 3.64 (dt, *J* = 2.5, 1.3 Hz, 1H, Cp-H), 1.18 (d, *J* = 13.4 Hz, 9H, ^{t}Bu), 1.10 (d, *J* = 13.5 Hz, 3H, BH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.0 (d, *J* = 4.5 Hz Ar), 135.2 (d, *J* = 7.2 Hz Ar), 133.7 (d, *J* = 8.2 Hz Ar), 133.4 (Ar), 132.8 (d, *J* = 9.2 Hz Ar), 131.1 (d, *J* = 2.7 Hz Ar), 130.3 (d, *J* = 2.7 Hz Ar), 129.4 (d, *J* = 2.5 Hz Ar), 128.4 (d, *J* = 9.2 Hz Ar), 127.5 (d, *J* = 10.0 Hz Ar), 125.7 (d, *J* = 9.3 Hz, Ar), 90.0 (d, *J* = 2.8 Hz, Cp), 72.5 (Cp), 71.39 (Cp), 69.5 (C_5H_5), 67.5 (Cp), 67.0 (Cp), 32.7 (d, *J* = 30.6 Hz, $C(CH_3)_3$), 27.7 (d, *J* = 2.5 Hz, CH_3), 25.6 (d, *J* = 2.5 Hz, CH_3), 18.5 (d, *J* = 33.8 Hz, CH_3); ^{31}P NMR (202 MHz, $CDCl_3$) δ 35.2 (d, *J* = 67.1 Hz), 31.2 (h, *J* = 42.6, 38.3 Hz); ^{11}B NMR (160 MHz, $CDCl_3$) δ -42 (p, *J* = 87, 87.2 Hz).

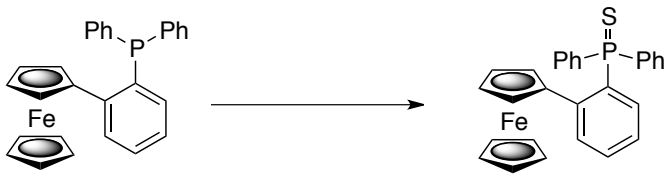
Synthesis of 2-((*tert*-butyl)phenylphosphinesulphide)-phenylferrocene



rac - **290** rac - **329**

A flask was charged with 2-((*tert*-butyl)phenylphosphino)-phenylferrocene (100 mg, 0.23 mmol) and elemental sulphur (73 mg, 10 equiv.) THF (10 mL) was added and the resulting solution was allowed to stir for 5 hours, washed with water (10 mL) and extracted with diethyl ether (10 mL). The organic layer was then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was then further purified *via* flash chromatography (95:5 hexane/ethyl acetate) to afford the *title compound* as a red oil. (100 mg, 99% yield). ν_{max}/cm^{-1} (Film) 1588.98 (C=C), 1461.44 (C-H); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ddd, *J* = 7.9, 4.5, 1.5 Hz, 1H, Ar), 7.99 (ddd, *J* = 12.3, 8.0, 1.4 Hz, 1H, Ar), 7.86 (ddt, *J* = 11.3, 6.7, 1.6 Hz, 1H, Ar), 7.48 - 7.44 (m, 2H, Ar), 7.33 (ddd, *J* = 7.1, 5.4, 1.5 Hz, 1H, Ar), 7.21 (ddt, *J* = 7.5, 5.9, 2.0 Hz, 1H, Ar), 7.10 (tdd, *J* = 7.3, 2.9, 1.1 Hz, 2H, Ar), 5.32 (dt, *J* = 2.6, 1.3 Hz, 1H, Cp), 3.97 (s, 5H, C_5H_5), 3.84 (dt, *J* = 2.6, 1.4 Hz, 1H, Cp), 3.70 (td, *J* = 2.5, 1.3 Hz, 1H, Cp), 3.66 (td, *J* = 2.5, 1.3 Hz, 1H, Cp), 1.27 (d, *J* = 15.9 Hz, 6H, ^{t}Bu), 1.16 (d, *J* = 15.9 Hz, 3H, ^{t}Bu); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.9 (d, *J* = 5.5 Hz, Ar), 135.5 (d, *J* = 9.2 Hz, Ar), 132.7 (d, *J* = 9.3 Hz, Ar), 132.3 (s Ar), 131.6 (d, *J* = 10.2 Hz, Ar), 131.3 (d, *J* = 2.7 Hz, Ar), 130.5 (d, *J* = 3.4 Hz, Ar), 130.2 (d, *J* = 2.7 Hz, Ar), 129.5 (s, Ar), 128.2 (d, *J* = 11.0 Hz, Ar), 127.1 (d, *J* = 11.9 Hz, Ar), 125.6 (d, *J* = 11.5 Hz, Ar), 89.2 (d, *J* = 3.9 Hz, Cp), 72.8 (Cp), 72.1 (Cp), 69.5 (C_5H_5), 67.4 (Cp), 67.0 (Cp), 37.5 (d, *J* = 50.1 Hz, $C(CH_3)_3$), 34.6 (d, *J* = 50.3 Hz, CH_3), 25.1 (d, *J* = 1.3 Hz, CH_3), 24.6 (d, *J* = 3.7 Hz, CH_3).^{31}P NMR (202 MHz, $CDCl_3$) δ 57.7 (S=*P*(^{t}Bu)Ph); HRMS (FTMS + p APCI) $M^{+}H$ $C_{26}H_{28}FePS$ requires 459.0993 found 459.0998

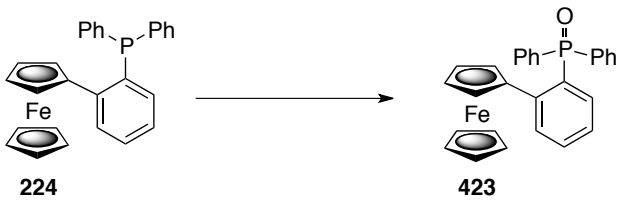
Synthesis of 2-(diphenylphosphinesulphide)phenylferrocene



224 **430**

A flask was charged with 2-(diphenylphosphino)phenylferrocene (100 mg, 0.22 mmol) and elemental sulphur (73 mg, 10 equiv.) THF (10 mL) was added and the resulting solution was allowed to stir for 5 hours, washed with water (10 mL) and extracted with diethyl ether (10 mL). The organic layer was then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was then further purified *via* flash chromatography (75:25 hexane/ethyl acetate) to afford the *title compound* as red oil. (100 mg, 99% yield); $\boldsymbol{\nu}_{max}/cm^{-1}$ (Film) 1673.25 (C=C), 1147.32 (P-Ar); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 8.0, 4.7 Hz, 1H, Ar), 7.83 (ddd, *J* = 12.7, 8.1, 1.6 Hz, 1H, Ar), 7.79 (t, *J* = 1.3 Hz, 1H, Ar), 7.77 (d, *J* = 1.5 Hz, 1H, Ar), 7.76 (d, *J* = 1.1 Hz, 1H, Ar), 7.75 (d, *J* = 1.5 Hz, 1H, Ar), 7.46 (ddddd, *J* = 11.6, 6.6, 4.9, 3.5, 2.2 Hz, 1H, Ar), 7.35 (td, *J* = 7.0, 1.6 Hz, 1H, Ar), 7.30 (d, *J* = 3.0 Hz, 1H, Ar), 7.29 (dd, *J* = 3.1, 1.4 Hz, 1H, Ar), 7.27 (dd, *J* = 2.9, 1.0 Hz, 1H, Ar), 7.16 (ddd, *J* = 8.7, 4.6, 2.1 Hz, 1H, Ar), 7.10 (ddd, *J* = 15.1, 7.9, 1.4 Hz, 1H, Ar), 4.69 (s, 2H, Cp), 4.06 (s, 5H, C_5H_5), 3.83 (s, 2H, Cp); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.7 (d, *J* = 7.6 Hz, Ar), 134.1 (d, *J* = 10.0 Hz, Ar), 133.9 (d, *J* = 12.5 Hz, Ar), 133.4 (Ar), 132.9 (Ar), 132.8 (Ar), 132.7 (Ar), 132.7 (Ar), 132.2 (Ar), 132.1 (d, *J* = 10.1 Hz, Ar), 131.5 (d, *J* = 2.8 Hz, Ar), 131.2 (d, *J* = 9.7 Hz, Ar), 131.0 (d, *J* = 2.9 Hz, Ar), 130.7 (d, *J* = 3.5 Hz, Ar), 128.7 (d, *J* = 11.9 Hz, Ar), 128.2 (Ar), 128.1 (Ar), 126.1 (d, *J* = 12.8 Hz, Ar), 119.5 (Ar), 115.9 (Ar), 88.6 (d, *J* = 4.6 Hz, Cp), 77. (Cp), 72.3 (Cp), 69.7 (C_5H_5), 67.8 (Cp); ^{31}P NMR (202 MHz, $CDCl_3$) δ 42.9 (S=*P*Ph_2); HRMS (FTMS + p APCI) M^+H $C_{28}H_{24}FePS$ requires 479.0680 found 479.0683.

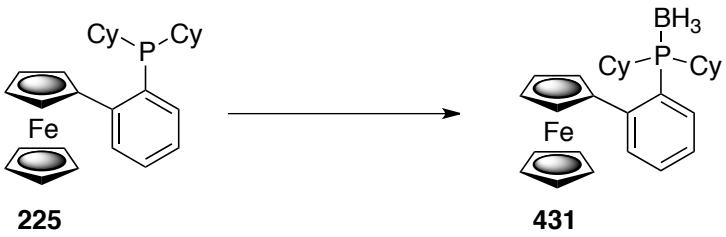
Synthesis of 2-(diphenylphosphineoxide)phenylferrocene.



224 **423**

A flask was charged with 2-diphenylphosphino-phenylferrocene (100 mg, 0.23 mmol) and *m*CPBA (80 mg, 2 equiv.). Dichloromethane (10 mL) was added and the resulting solution was allowed to stir for 5 hours, washed with water (10 mL) and extracted with dichloromethane (10 mL). The organic layer was then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was then further purified *via* flash chromatography (98:2 dichloromethane/methanol) to afford the *title compound* as a red oil. (100 mg, 99% yield); $\boldsymbol{\nu}_{max}/cm^{-1}$ (Film) 2835.92 (C-H), 1591.40 (C=C), 1265.13 (P=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, *J* = 7.7 Hz, 1H, Ar), 7.57 (d, *J* = 1.4 Hz, 1H, Ar), 7.57 - 7.55 (m, 1H, Ar), 7.51 (dt, *J* = 15.3, 1.5 Hz, 1H, Ar), 7.44 - 7.42 (m, 1H, Ar), 7.42 - 7.40 (m, 1H), 7.39 (d, *J* = 1.4 Hz, 1H, Ar), 7.38 (d, *J* = 1.4 Hz, 1H, Ar), 7.31 (td, *J* = 7.5, 2.9 Hz, 4H, Ar), 7.17 (tt, *J* = 6.5, 1.3 Hz, 1H, Ar), 7.09 (t, *J* = 6.6 Hz, 1H, Ar), 4.67 (s, 2H, Cp), 4.05 (s, 5H, C_5H_4), 3.88 (s, 2H, Cp); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.1 (Ar), 141.3 (Ar), 134.4 (d, *J* = 12.8 Hz, Ar), 133.2 (d, *J* = 10.1 Hz, Ar), 132.7 (Ar), 131.7 (Ar), 131.6 (Ar), 131.3 (Ar), 129.5 (Ar), 128.9 (Ar), 128.3 (Ar), 128.2 (Ar), 127.4 (Ar), 127.3 (Ar), 125.7 (d, *J* = 12.0 Hz, Ar), 119.7 (Cp), 115.8 (Cp), 87.6 (d, *J* = 4.0 Hz, Cp), 71.9 (Cp), 69.7 (C_5H_5), 68.08 (Cp); ^{31}P NMR (202 MHz, $CDCl_3$) δ 31.1 (O=*P*Ph_2); HRMS (FTMS + p APCI) M^+H $C_{28}H_{24}FePO$ requires 463.0906 found 463.0911.

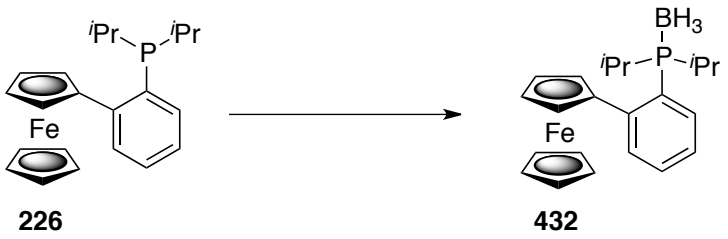
Synthesis of 2-((dicyclohexyl)phosphineborane)-phenylferrocene



225 **431**

A solution of boron-dimethylsulphide complex (3 drops) was added to 2-(dicyclohexylphosphino)phenylferrocene (50 mg 0.109 mmol) in degassed toluene (5 mL) and allowed to stir for 3 hours. The solvent was removed *in vacuo* and purified *via* flash chromatography to give the *title compound* as a bright orange oil (51 mg, 99%); $\boldsymbol{\nu}_{max}/cm^{-1}$ (Film) 2930.03 (C-H), 1649.06 (C=C), 1488.34 (C-C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (ddd, *J* = 7.7, 2.7, 1.4 Hz, 1H, Ar), 8.00 (ddd, *J* = 13.8, 7.8, 1.4 Hz, 1H, Ar), 7.46 (tt, *J* = 7.5, 1.5 Hz, 1H, Ar), 7.34 (tt, *J* = 7.5, 1.6 Hz, 1H, Ar), 4.38 (t, *J* = 1.8 Hz, 2H, Cp), 4.33 (t, *J* = 1.8 Hz, 2H, Cp), 4.30 (s, 5H, C_5H_5), 2.26 - 0.95 (m, 22H, Cy_2), 0.99 - 0.82 (m, 3H, BH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.0 (Ar), 137.6 (d, *J* = 16.6 Hz, Ar), 134.3 (d, *J* = 5.7 Hz, Ar), 130.2 (d, *J* = 2.6 Hz, Ar), 127.7 (Ar), 127.3 (Ar), 127.0 (Cp), 126.9 (Cp), 92.7 (Cp), 71.4 (Cp), 69.6 (C_5H_5), 67.7 (Cp), 33.5 (d, *J* = 32.6 Hz, Cy), 28.8 (Cy), 27.86 (Cy), 26.9 (d, *J* = 12.0 Hz, Cy), 26.6 (d, *J* = 11.3 Hz, Cy), 25.7 (Cy); ^{31}P NMR (202 MHz, $CDCl_3$) δ 36.1 (d, *J* = 73.9 Hz), 24.1 (dd, *J* = 122.2, 50.0 Hz); ^{11}B NMR (160 MHz, $CDCl_3$) δ -43.

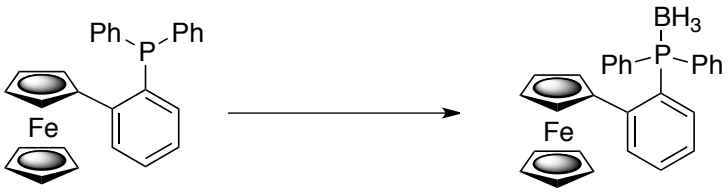
Synthesis of 2-((diisopropyl*l*)phosphineborane)-phenylferrocene



226 **432**

A solution of boron-dimethyl complex (3 drops) was added to 2-(diisopropylphosphino)phenylferrocene (50 mg 0.113 mmol) in degassed toluene (5 mL) and allowed to stir for 3 hours. The solvent was removed *in vacuo* and purified *via* flash chromatography to give the *title compound* as bright orange oil (53 mg, 99%). IR $\boldsymbol{\nu}_{max}/cm^{-1}$ (Film) 2848.72 (C-H), 1589.29 (C=C), 1423.08 (C-C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (ddd, *J* = 7.6, 2.8, 1.4 Hz, 1H, Ar), 8.04 (dd, *J* = 13.5, 8.1 Hz, 1H, Ar), 7.47 (tt, *J* = 7.4, 1.5 Hz, 1H, Ar), 7.34 (tt, *J* = 7.5, 1.6 Hz, 1H, Ar), 4.38 (q, *J* = 1.3, 0.8 Hz, 2H, Cp), 4.33 (t, *J* = 1.8 Hz, 2H, Cp), 4.29 (s, 5H, C_5H_5), 1.99 (dp, *J* = 14.2, 7.0 Hz, 2H, $CH(CH_3)_2$), 1.14 (dd, *J* = 15.3, 6.9 Hz, 6H, ^{i}Pr), 0.79 (dd, *J* = 15.7, 7.1 Hz, 6H, ^{i}Pr), 0.51 - 0.14 (m, 3H, BH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.0 (Ar), 137.7 (d, *J* = 16.2 Hz, Ar), 134.7 (d, *J* = 5.8 Hz, Ar), 130.4 (d, *J* = 2.0 Hz, Ar), 128.6 (Ar), 128.3 (Ar), 127.1 (Cp), 129.0 (Cp), 92.6 (Cp), 71.6 (Cp), 69.7 (C_5H_5), 67.7 (Cp), 23.9 (d, *J* = 33.1 Hz, $CH(CH_3)_2$), 19.2 (^{i}Pr), 18.8 (d, *J* = 2.3 Hz, ^{i}Pr); ^{31}P NMR (202 MHz, $CDCl_3$) δ 44.2 (d, *J* = 87.2 Hz); ^{11}B NMR (160 MHz, $CDCl_3$) δ -34 - -66 (m).

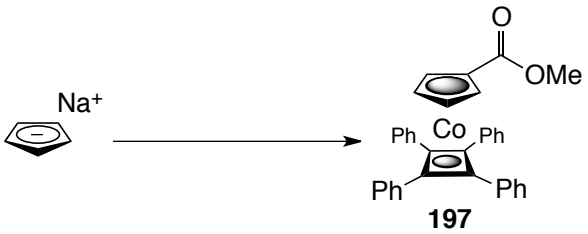
Synthesis of 2-((diphenyl)phosphineborane)-phenylferrocene



224 **433**

A solution of boron-dimethyl complex (3 drops) was added to 2-(diphenylphosphino)phenylferrocene (50 mg, 0.111 mmol) in degassed toluene (5 mL) and allowed to stir for 3 hours. The solvent was removed *in vacuo* and purified *via* flash chromatography to give the *title compound* as a bright orange oil (51 mg, 99%); $\boldsymbol{\nu}_{max}/cm^{-1}$ (Film) 1615.73 (C=C), 1437.34 (C-H), 1027.96 (P-Ar); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (ddd, *J* = 7.8, 4.2, 1.2 Hz, 1H, Ar), 7.67 (ddd, *J* = 10.5, 8.2, 1.5 Hz, 1H, Ar), 7.58 (d, *J* = 1.1 Hz, 1H, Ar), 7.56 (d, *J* = 1.5 Hz, 1H, Ar), 7.56 (d, *J* = 1.2 Hz, 1H, Ar), 7.54 (d, *J* = 1.4 Hz, 1H, Ar), 7.47 (ddt, *J* = 11.2, 5.1, 1.9 Hz, 1H, Ar), 7.41 (p, *J* = 1.5 Hz, 1H, Ar), 7.39 (d, *J* = 1.8 Hz, 1H, Ar), 7.38 (q, *J* = 1.4 Hz, 1H, Ar), 7.33 (d, *J* = 2.3 Hz, 1H, Ar), 7.32 (d, *J* = 2.3 Hz, 1H, Ar), 7.30 (d, *J* = 2.3 Hz, 1H, Ar), 7.21 (ddt, *J* = 8.8, 7.3, 1.6 Hz, 1H, Ar), 7.15 (ddd, *J* = 12.4, 7.9, 1.5 Hz, 1H, Ar), 4.24 (t, *J* = 1.9 Hz, 2H, Cp), 4.06 (s, 5H, C_5H_5), 3.89 (t, *J* = 1.9 Hz, 2H, Cp), 0.92 - 0.82 (m, 3H, BH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.3 (d, *J* = 8.3 Hz, Ar), 134.9 (d, *J* = 10.0 Hz, Ar), 134.2 (d, *J* = 8.0 Hz, Ar), 133.2 (d, *J* = 9.4 Hz, Ar), 132.7 (Ar), 132.2 (d, *J* = 8.7 Hz, Ar), 131.2 (d, *J* = 2.6 Hz, Ar), 130.8 (d, *J* = 2.4 Hz, Ar), 130.3 (d, *J* = 2.4 Hz, Ar), 128.9 (d, *J* = 9.7 Hz, Ar), 128.5 (d, *J* = 10.1 Hz, Ar), 126.3 (d, *J* = 10.0 Hz, Ar), 119.5 (Cp), 115.9 (Cp), 89.1 (Cp), 72.0 (Cp), 69.5 (C_5H_5), 67.8 (Cp); ^{31}P NMR (202 MHz, $CDCl_3$) δ 22.4 - 21.1 (m), 16.2 – 15.4 (m); ^{11}B NMR (160 MHz, $CDCl_3$) δ -33, -38 (m), -38 - -42 (m).

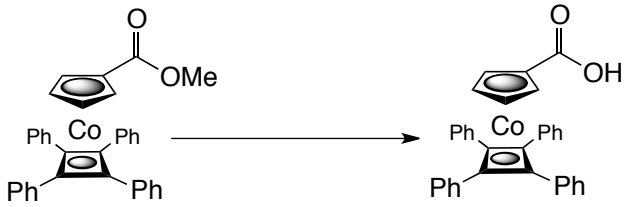
Synthesis of (η^5-carbomethoxycyclopentadienyl)-(η^4-tetraphenyl-cyclobutadiene)cobalt)



197

A flask is flushed with argon and charged with sodium cyclopentadiene (20 mL, 40 mmol), THF (20 mL) and dimethyl carbonate (10.2 mL, 120 mmol). The solution was heated to reflux and stirred for 4 hours. The flask was allowed to cool to room temperature and toluene (160 mL) was added followed by chlorotris(triphenylphosphine)cobalt(I)(30.8 g, 34.8 mmol) and diphenylacetylene (14.2 g, 80 mmol). The resulting mixture is heated to reflux for 16 h before allowing to cool and the solvent was removed *in vacuo* and suspended in hexane (300 mL). The solid is filtered and washed with hexane (3.5 L) and the resultant mustard coloured filter cake was dissolved in dichloromethane and collected into a different flask. The filtrate is concentrated and further purified with flash chromatography (90/10 hexane:ethyl acetate). This is combined with the dichloromethane extract to give the title compound as a mustard coloured solid (16.8 g, 90% yield) M.P. 225 ^{o}C; $\boldsymbol{\nu}_{max}$/cm^{-1} (Film) 1710.91 (C=O), 1573.85 (C=C), 1282.10 (C-O); ^{1}H NMR (500 MHz,$CDCl_3$) δ 7.43 (dd, *J* = 7.7, 1.8 Hz, 8H, Ph), 7.21 (d, *J* = 7.4 Hz, 12H, Ph), 5.23 (t, *J* = 2.2 Hz, 2H, Cp-α), 4.84 (t, *J* = 2.2 Hz, 2H, Cp-β), 2.05 (s, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.47, 135.34,

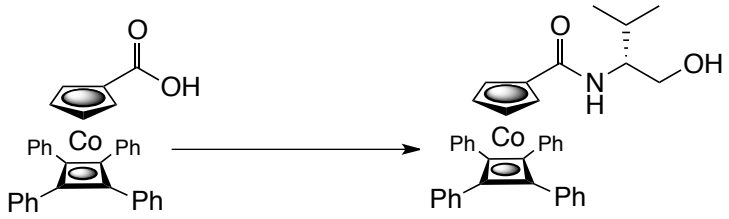
Synthesis of (η^5-Carboxycyclopentadienyl)(η^4-tetraphenylcyclobutadiene) Cobalt



197 **198**

(η^5-Carbomethoxycyclopentadienyl)-(η^4-tetraphenyl-cyclobutadiene)cobalt) (2.03 g, 3.74 mmol), LiI (1.01 g, 7.48 mmol, 2 equiv) and 2,4,6-collidine was added to a flask under inert atmosphere and refluxed for 16 hours. The solution is cooled to room temperature, diluted with dichloromethane (200 mL) and washed with 2 N aqueous hydrochloric acid (4 x 50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The compound was diluted in the minimum amount of dichloromethane and purified *via* flash chromatography (60/40 hexane:ethyl acetate) to provide title compound as an orange solid (1.5 g, 80% yield). 240-243 ^{o}C IR (neat): **ν**=3058, 2953, 1713, 1596, 1498, 1467, 1281, 1140 cm-1 ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (dd, *J* = 6.8, 2.1 Hz, 8H, Ph), 7.22 (d, *J* = 7.0 Hz, 12H, Ph), 6.78 (m, 1H, COO*H*), 5.23 (t, *J* = 2.2 Hz, 2H, Cp- α), 4.84 (t, *J* = 2.2 Hz, 2H, Cp-β); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5, 135.0, 131.6, 128.9, 128.2, 126.9, 126.7, 86.9, 85.6, 85.2, 77.7.

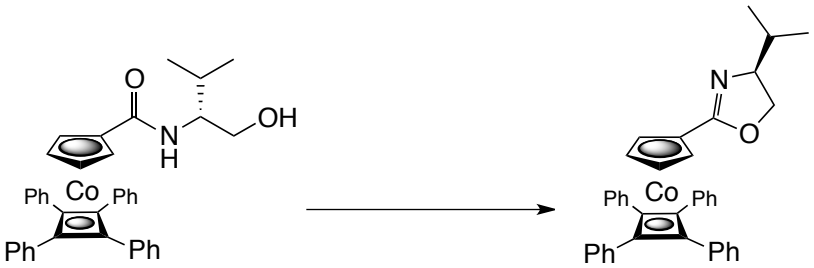
Synthesis of (η^5-(*S*)-*N*-2-(1-Hydroxy-3-methylbutyl)carboxamidecyclopentadienyl)(η^4-tetraphenylcyclobutadiene)cobalt.



198 **434**

To a solution of (η^5-carboxycyclopentadienyl)(η^4-tetraphenylcyclobutadiene) cobalt(I) (1.63 g, 3.1 mmol) in dichloromethane was added oxalyl chloride (0.12 mL, 1.4 mmol) and 3 drops of dimethylformamide. The resulting solution was allowed to stir until the effervescence stopped. The solvent and excess oxalyl chloride was removed *in vacuo*, this process was repeated 3 times. The crude acid chloride was dissolved n dichloromethane (10 mL) and added to a solution of (*S*)-valinol (0.086 g, 0.84 mmol) in triethylamine (0.2 mL) and dichloromethane (5 mL). The resulting solution was stirred for 6 hours, quenched with water and washed with brine. The aqueous layer was extracted with dichloromethane (3x20 mL), dried over $MgSO_4$, filtered and purified with flash chromatography (70/30 hexane:ethyl acetate) and afforded the title compound as yellow solid. (1.51 g, 80% yield); m.p. 216-218 ^oC; $\boldsymbol{\nu}_{max}/cm^{-1}$ (Film) 3434.15 (O-H), 3080.68 (N-H), 1614.96 (C=O), 1574.16 (C=C); ^1H NMR (500 MHz, $CDCl_3$) δ 7.46 (dt, *J* = 6.6, 1.6 Hz, 8H, Ph), 7.30 (m, 12H, Ph), 5.35 (d, *J* = 7.0 Hz, 1H, N*H*), 5.10 (dt, *J* = 3.0, 1.6 Hz, 1H, Cp-*H*), 4.96 (dt, *J* = 3.0, 1.6 Hz, 1H, Cp-*H*), 4.73 (td, *J* = 2.7, 1.5 Hz, 1H, Cp-*H*), 4.69 (td, *J* = 2.7, 1.5 Hz, 1H, Cp-*H*), 3.40 (dd, *J* = 10.6, 2.4 Hz, 1H, CH_2), 3.34 (td, *J* = 6.6, 2.0 Hz, 1H, NH-C*H*), 3.30 (dd, *J* = 10.7, 6.2 Hz, 1H, CH_2), 3.14 (s, 1H, CH_2OH), 1.62 (hept, *J* = 6.8 Hz, 1H, CH), 0.83 (d, *J* = 6.8 Hz, 3H, CH_3), 0.78 (d, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.4 (C=O), 135.2 (PhC), 128.8 (PhC), 128.2 (PhC), 126.9 (PhC), 90.1 (CpC), 87.0 (CpC), 86.7 (CpC), 82.1 (CpC), 82.1 (CpC), 76.3 (C_4Ph_4), 64.2 (-CH_2OH-), 58.6 (-$CHCH_2$-), 29.0, 29.4 (-$CH(CH_3)_2$), 19.2 (2 x – CH_3).

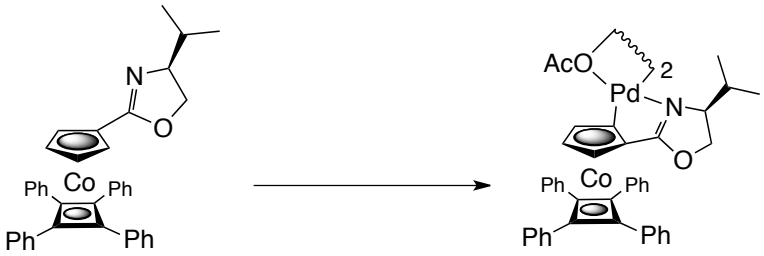
Synthesis of (η^5-(*S*)-2-(4-Methylethyl)oxazolinylcyclopentadienyl)-(η^4-tetraphenylcyclobutadiene)cobalt



434 **199**

To a solution of (η^5-(*S*)-*N*-2-(1-hydroxy-3-methylbutyl)carboxamidecyclopentadienyl)(η^4-tetraphenylcyclobutadiene)cobalt (5.00 g, 8.08 mmol) in dichloromethane (100 mL) was cooled to 0 ^{o}C. Methanesulfonyl chloride (1.58 mL. 2.5 equiv) was added in one portion and the resulting solution was warmed to room temperature. After 16 h, the solution was washed with sodium bicarbonate (50 mL) and brine (50 mL). The aqueous layer was extracted with dichloromethane (3 x 50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting dark yellow solid was dissolved in the minimum amount of dichloromethane and purified *via* flash chromatography (90/10 hexane:ethyl acetate). Evaporation of solvent afforded the title compound as a yellow solid (5.12 g, 81% yield). MP. 168-170 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 - 7.42 (m, 2H, Ph), 7.28 - 7.17 (m, 12H, Ph), 5.19 (s, 1H, Cp-H), 5.08 (s, 1H, Cp-H), 4.79 (s, 1H, Cp-H), 4.70 (s, 1H, Cp-H), 3.53 (t, *J* = 8.7 Hz, 1H, CH_2), 3.47 (d, *J* = 7.3 Hz, 1H, CH_2), 3.43 (dt, *J* = 9.7, 7.3 Hz, 1H, CH), 1.44 - 1.34 (m, 1H), 0.96 (d, *J* = 6.7 Hz, 3H, CH_3), 0.74 (d, *J* = 6.7 Hz, 3H, CH_3).^{13}C NMR (126 MHz, $CDCl_3$) δ 160.7 (Ph), 135.5 (Ph), 129.1 (Ph), 128.1 (Ph), 126.5 (Ph), 86.4 (Cp), 85.0 (Cp), 84.5 (Cp), 82.2 (Cp), 77.7 (Cp), 76.1 (Cp), 72.8 (C_4Ph_4), 69.6 ($CHCH_2$), 33.1 ($CH(CH_3)_2$), 19.7 (CH_3), 18.5 (CH_3).

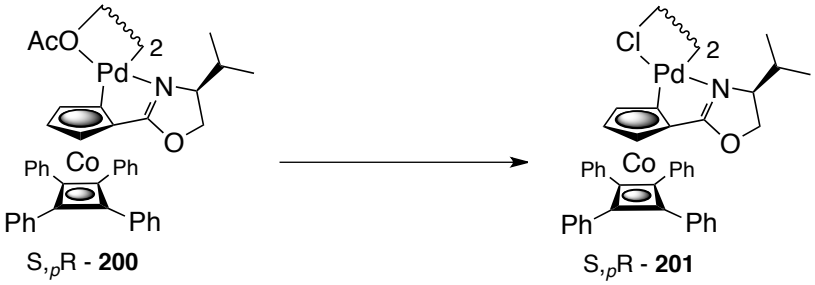
Synthesis of Di-μ-acetatobis[(η5-(*S*)-(*pR*)-2-(2'-(4'-methylethyl)oxazolinyl) cyclopentadienyl, 1-C, 3'-N)(η4-tetraphenylcyclobutadiene) cobalt]dipalladium.



199 S,*p*R - **200**

A solution of (η^5-(S)-2-(4-methylethyl)oxazolinylcyclopentadienyl)-(η^4-tetraphenylcyclobutadiene)cobalt (0.314 g, 0.53 mmol) and $Pd(OAc)_2$ (0.119 g, 0.53 mmol) in glacial acetic acid (1 mL) was heated for 1 hour at 95 ^oC. The resulting precipitate was filtered and washed with glacial acetic acid (10 mL) to afford the title compound as a dark yellow solid (0.29 g, 72% yield). MP 196-198 ^oC; $\boldsymbol{\nu}_{max}/cm^{-1}$ (Film) 1597.10 (C=C), 1397.12 (N=C), 1256.32 (C-O), 1178.32 (N-C); ^1H NMR (500 MHz, $CDCl_3$) δ 7.63 (dd, *J* = 8.1, 1.6 Hz, 16H, Ph), 7.21 (d, *J* = 7.4 Hz, 24H, Ph), 4.66 (dd, *J* = 2.7, 1.0 Hz, 2H, Cp-H), 4.60 (dd, *J* = 2.4, 1.0 Hz, 2H, Cp-H), 4.21 (t, *J* = 2.6 Hz, 2H, Cp-H), 4.06 (dd, *J* = 8.5, 4.0 Hz, 2H, CH_2), 3.34 (dd, *J* = 9.6, 8.5 Hz, 2H, CH_2), 2.97 (dt, *J* = 9.5, 3.5 Hz, 2H, CH), 1.94 (s, 3H, CO_2CH_3), 1.74 (td, *J* = 7.0, 2.7 Hz, 2H, CH), 0.44 (d, *J* = 7.2 Hz, 6H, CH_3), -0.03 (d, *J* = 6.7 Hz, 6H, CH_3);^{13}C NMR (126 MHz, $CDCl_3$) δ 180.7 (CO_2), 170.6 (C=N), 135.8 (PhC), 129.2 (PhC) , 127.9 (PhC), 126.0 (CpC), 86.5 (CpC), 85.2 (CpC), 84.7 (CpC), 79.2 (CpCCN), 76.0 (C_4Ph_4), 71.0 ($CHCH_2$), 64.8 ($CHCH_2$), 28.9 (CH_3CO_2), 23.9 ($CH(CH_3)_2$), 18.6 (CH_3), 13.1 (CH_3).

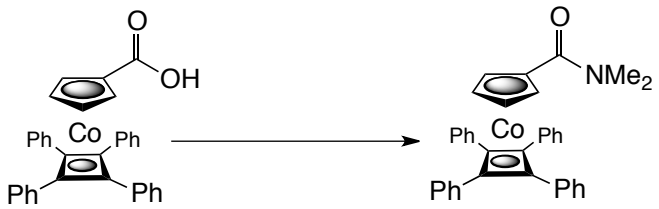
Synthesis of di-μ-chlorobis[(η5-(*S*)-(*pR*)-2-(2'-(4'-methylethyl)oxazolinyl)cyclopentadienyl, 1-C, 3'-N)(η4-tetraphenylcyclobutadiene) cobalt]dipalladium.[148]



S,*p*R - **200** S,*p*R - **201**

A solution of (η^5-(S)-2-(4-Methylethyl)oxazolinylcyclopentadienyl)-(η^4-tetraphenylcyclobutadiene)cobalt (0.89 g, 0.59 mmol) in dichloromethane (10 mL) was added brine (10 mL). The resulting mixture was allowed to stir at room temperature for 16 h. The mixture was washed with brine (10 mL), extracted into dichloromethane, dried over anhydrous $MgSO_4$, filtered and the solvent removed under reduced pressure. Giving the title compound as a dark mustard colored solid (0.82 g, 95% yield) 198-204 ºC. $\boldsymbol{\nu}_{max}/cm^{-1}$ (Film) 2927.00 (C=C), 1253.15 (C-O), 1183.22 C-N); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (dd, *J* = 7.6, 1.9 Hz, 8H, Ph), 7.60 (dd, *J* = 3.9, 2.6 Hz, 8H, Ph), 7.26 - 7.22 (m, 12H, Ph), 7.18 (qd, *J* = 3.9, 1.6 Hz, 12H, Ph), 4.99 (ddd, *J* = 6.0, 2.4, 1.0 Hz, 1H, Cp-H), 4.72 (ddd, *J* = 13.4, 2.8, 1.0 Hz, 1H, Cp-H), 4.39 (t, *J* = 2.6 Hz, 1H, Cp-H), 4.28 (t, *J* = 2.6 Hz, 1H, Cp-H), 4.19 (ddd, *J* = 8.2, 4.6, 2.9 Hz, 1H, CH_2), 3.49 (q, *J* = 7.0 Hz, 1H, CH_2), 3.44 (dd, *J* = 9.6, 8.4 Hz, 1H, CH_2), 3.35 (dd, *J* = 9.6, 8.4 Hz, 1H, CH2), 3.11 (ddd, *J* = 9.6, 4.5, 3.5 Hz, 1H, CH_2), 3.06 (ddd, *J* = 9.6, 4.7, 3.3 Hz, 2H, CH), 2.25 (dddq, *J* = 17.2, 10.3, 7.0, 3.4 Hz, 2H, CH), 0.78 (dd, *J* = 22.1, 7.0 Hz, 6H, CH_3), 0.73 (dd, *J* = 7.0, 3.8 Hz, 6H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.0 (C=N), 170.9 (C=N), 135.4 (PhC), 135.3 (PhC), 129.3 (PhC), 129.2 (PhC), 128.0 (PhC), 128.0 (PhC), 126.3 (CpC), 126.2 (CpC), 98.5 (CpC), 98.4 (CpC), 86.9 (CpC), 85.5 (CpC), 84.6 (CpC), 84.5 (CpC), 84.3 (CpC), 84.0 (CpC) (CpCCN), 80.7 (CpCCN), 80.3 (C_4Ph_4), 76.4 (C_4Ph_4), 71.3 (C-Cl), 71.2 (C-Cl), 65.8 (CH_2), 65.4 (CH_2), 29.0 ($CH(CH_3)_2$), 28.8 ($CH(CH_3)_2$), 18.8 (CH_3), 18.8 (CH_3), 14.3 (CH_3), 14.1 (CH_3).

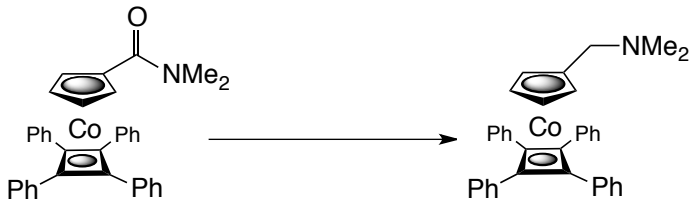
Synthesis of (η^5-(-*N*,*N*-dimethylcarboxamide)-cyclopentadienyl)-(η^4-tetraphenylcyclobutadiene)cobalt(I).[256]



198 **383**

A flask was charged with (η^5-carboxycyclopentadienyl)(η^4-tetraphenylcyclobutadiene)cobalt(I) (1.00 g, 1.91 mmol) and dissolved in dichloromethane (20 mL). Oxalyl chloride (0.33 mL, 3.81 mmol) and dimethylformaimde (3 drops) were added sequentially. After 30 minutes the solution was concentrated *in vacuo* to give the crude acid chloride as a red/brown solid. To a solution of dimethylamine hydrochloride (311 mg, 3.81 mmol) and triethylamine (2.30 mL, 16.4 mmol) in dichloromethane was added to a solution of the crude acid chloride in dichloromethane. The resulting solution was stirred for 16 hours, washed with water (50 mL), brine (50 mL) and extracted with dichloromethane (50 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was dissolved in the minimum amount of dichloromethane and purified *via* flash chromatography using 7:3 hexane/ethyl acetate. Evaporation of solvent gave the product as an orange solid (1.01 g, 1.83 mmol, 96% yield) M.p. 251 ^{o}C, IR (neat): n=3052, 2923, 1967, 1609, 1596, 1496, 1388, 1267, 1162, 1027 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, *J* = 1.2 Hz, 4H, Ph), 7.47 (d, *J* = 1.6 Hz, 4H, Ph), 7.28 - 7.26 (m, 3H, Ph), 7.26 - 7.24 (m, 8H, Ph), 7.21 (dd, *J* = 8.1, 6.4 Hz, 1H, Ph), 5.15 (t, *J* = 2.2 Hz, 1H, Cp-H), 4.74 (t, *J* = 2.1 Hz, 2H, Cp-H), 2.80 (s, 3H, CH_3), 2.64 (s, 3H, CH_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.0 (PhC), 135.6 (PhC), 129.0 (PhC), 128.1 (PhC), 126.6 (PhC), 91.7 (CpC), 85.4 (CpC), 84.9 (CpC), 76.2 (CpC), 60.5 (CpC), 38.7 (NMe), 36.9 (NMe).

Synthesis of *N,N*- Dimethylaminomethyl(η^5-cyclopentadienyl)-(η^4-tetraphenylcyclobutadiene)cobalt(I).[256]



383 **384**

(η^5-(-*N*,*N*-dimethylcarboxamide)-cyclopentadienyl)-(η^4-tetraphenylcyclobutadiene)cobalt(I) (986 mg, 1.78 mmol) was added to a flame dried flask and dissolved in THF under inert atmosphere. The solution was cooled to 0 ^{o}C and lithium aluminium hydride (241 mg, 5.34 mmol) was added in two portions. The reaction was left to stir for 16 hours and on completion, water (20 mL) was added. The aqueous layer was extracted with dichloromethane (3 x 20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the product as dark yellow solid (959 mg, 1.77 mmol, 99% yield). 189-192 ^{o}C

Method 2. [256]

380 **384**

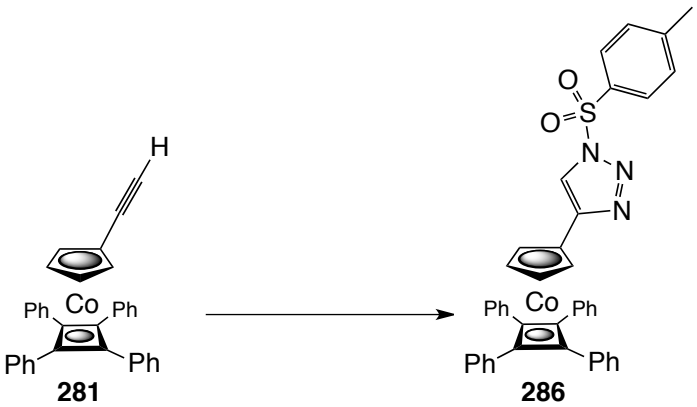
Phosphoric acid (2 mL, 0.01 mol) was added to a hot suspension of (η^5-cyclopentadienyl)-(η^4-tetraphenylcyclobutadiene)cobalt(I) (1.0 g, 2.08 mmol) in acetic acid (100 mL). *N,N,N',N'*-tetramethyldiaminomethane (5 mL, 0.07 mol) was added and the mixture was refluxed for 16 hours. On completion the mixture was cooled and poured into water (400 mL). The solution was washed with ethyl acetate (3 x 100 mL) and the organic extracts were collected and combined and then washed with $NaHCO_3$ (100 mL portions) until effervescence stopped. The organic phase was dried ($MgSO_4$) and filtered and the solvent was removed *in vacuo* to give the crude product. Purification was carried out using flash 70:25:5 Pet ether: EtOAc:NEt_3 giving the product (0.651 g, 58.2%) as a dark yellow solid. $\boldsymbol{\nu}_{max}$/cm^{-1} (Film) 1596.54 (C=C), 1243.98 (C-N); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 - 7.33 (m, 8H, Ar), 7.29 - 7.09 (m, 12H, Ar), 4.71 (t, *J* = 2.1 Hz, 1H, Cp-H), 4.61 - 4.59 (m, 2H, Cp-H), 2.67 (s, 2H, CH_2), 2.04 (s, 6H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.4 (Ar), 129.0 (Ar), 128.1 (Cp), 126.3 (Cp), 93.7, (Cp) 84.2 (Cp), 83.7 (Cp), 74.9 (CH_2NMe_2), 56.5 (CH_3), 44.9 (CH_3).

Synthesis of (η^5-cyclopentadienyl)-(η^4-tetraphenylcyclobutadiene)cobalt (I):

380

A solution of sodium cyclopentadienide in THF (2.8 mL of a 2M solution) was added to a suspension of *tris*(triphenylphosphine)cobalt (I) chloride (5.0 g, 5.7 mmol) and diphenylactylene (2.22 g, 0.01 mol) in dry toluene (50 mL). The mixture was refluxed for 16 hours and then cooled to 40 °C. The solvent was removed *in vacuo* and the residue was triturated with petroleum ether until copious amounts of precipitate were formed. The precipitate was washed with petroleum ether and dissolved in hot ethyl acetate and filtered. The filtrate was collected and solvent was removed *in vacuo* to give the product (1.56 g, 57.3 %) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.59 (s, 5H, Cp); 7.18 – 7.58 (m, 20H, Ar).

Synthesis of (η^5-cyclopentadienyl)-(η^4-tetraphenylcyclobutadiene)cobalt(I)-1-tosyl-1*H*-1,2,3-triazole.[265]



281 **286**

To a solution of (η^5-ethynylcyclopentadienyl)-(η^4-tetraphenylcyclobutadiene)cobalt(I) (100 mg, 0.19 mmol), 4-methylbenzenesulfonyl azide (39 mg, 0.19 mmol) and copper(II) acetate (6.9 mg, 20 Mol%) in dichloromethane was allowed to stir for 6 hours. The solvent removed *in vacuo* and crude product was purified *via* flash chromatography to give the title compound as a dark yellow oil (94 mg, 71% yield).

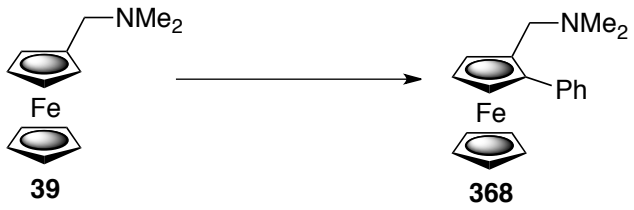
ν_{max}/cm^{-1} (Film) 1666.15 (N=N), 1596.28 (C=C), 1242.63 (C-N), 1048.10 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.4 Hz, 2H, Ar), 7.37 - 7.30 (m, 11H, Ar), 7.25 - 7.20 (m, 5H, Ar), 7.15 (t, *J* = 7.6 Hz, 8H, Ar), 5.07 (t, *J* = 2.1 Hz, 1H, Cp), 4.77 (t, *J* = 2.1 Hz, 1H, Cp), 2.43 (s, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.1 (Ar), 142.2 (Ar), 135.4 (Ar), 133.7 (Ar), 130.4 (Ar), 128.8 (Ar), 128.7 (Ar), 128.1 (Ar), 126.7 (CHN), 118.6 (CHN), 86.6 (Cp), 84.5 (Cp), 81.3 (Cp), 77.7 (Cp), 76.1 (Cp), 22.0 (CH_3).

Synthesis of rac-di-aceto-bis{[π-1-(dimethylaminomethyl)cyclopentadienyl-2C,N]tetraphenylcyclobutadiene cobalt(I)}-dipalladium(II).[256]

384 **426**

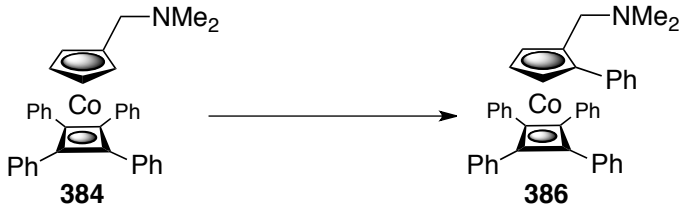
N,N-Dimethylaminomethyl(η^5-cyclopentadienyl)-(η^4-tetraphenylcyclobutadiene)cobalt(I) (100 mg, 0.18 mmol) and $Pd(OAc)_2$ (42 mg, 0.18 mmol) were added to toluene and heated to 80 ^oC for 2 hours. The solvent was removed *in vacuo* to afford the title compound as a yellow solid (124 mg, 95%); ^1H NMR (500 MHz, $CDCl_3$) δ 7.67 - 7.61 (m, 8H, Ph), 7.21 - 7.14 (m, 12H, Ph), 4.22 (dd, *J* = 2.5, 1.1 Hz, 1H, Cp), 4.06 (t, *J* = 2.4 Hz, 1H, Cp), 4.02 (dd, *J* = 2.4, 1.2 Hz, 1H, Cp), 3.05 (d, *J* = 13.9 Hz, 1H, CH_2), 2.76 (d, *J* = 13.9 Hz, 1H, CH_2), 2.30 (s, 3H, NMe), 2.15 (s, 3H, NMe), 1.72 (s, 3H, AcO); ^{13}C NMR (126 MHz, $CDCl_3$) δ 181.2 (C-O), 129.6 (Ph), 128.2 (Ph), 103.5 (Cp), 101.8 (Cp), 84.5 (Cp), 80.6 (Cp), 74.9 (Cp), 65.5 (CH_2), 54.4 (NMe), 52.2 (NMe), 24.5 (CH_3-AcO); IR (neat): n = 3055, 2920, 1577, 1498, 1412, 1261, 1176, 1023, 957, 740, 692, 617 cm^{-1}; Elemental analysis calcd. (%) for $C_{76}H_{68}Co_2N_2O_4Pd_2$: C 65.01, H 4.88, N 2.00; found C 65.18, H 4.96, N 2.04.

Synthesis of 1-dimethylaminomethyl-2-phenylferrocene.[236]



N,*N*-Dimethylaminomethylferrocene (300 mg, 1.23 mmol), K_2CO_3 (169 mg, 1.23 mmol), *N*-acetyl-phenyl-*D*-alanine (51 mg, 20 mol%), palladium acetate (28 mg, 10 mol%) and *tetra*-N-butylammonium bromide (149 mg, 1.23 mmol) was added to a schlenk tube along with DMF (10 mL). The solution was heated to 60 ^{o}C for 16 h in air. The resulting solution was washed with distilled water (20 mL), extracted with diethyl ether (3 x 15 mL), dried over $MgSO_4$, filtered and purified *via* flash chromatography (5/10/85; triethylamine:hexane:ethyl acetate) to afford title compound as a dark yellow oil (164 mg, 42% yield). $\boldsymbol{\nu}_{max}/cm^{-1}$ (Film) 2851.28 (C-H), 1601.73 (C=C), 1258.82 (N-C) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (t, *J* = 1.7 Hz, 1H, Ar-H), 7.70 (t, *J* = 1.1 Hz, 1H, Ar-H), 7.35 - 7.28 (m, 2H, Ar-H), 7.23 (ddt, *J* = 8.1, 6.6, 1.3 Hz, 1H, Ar-H), 4.50 - 4.41 (m, 1H, Cp-H), 4.31 (dd, *J* = 2.5, 1.5 Hz, 1H, Cp-H), 4.24 (t, *J* = 2.5 Hz, 1H, Cp-H), 4.05 (s, 5H, C_6H_5), 3.65 (d, *J* = 12.9 Hz, 1H, CH_2), 3.18 (d, *J* = 12.8 Hz, 1H, CH_2), 2.17 (s, 6H, NMe_2). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.0(Ar), 129.5 (Ar), 128.1 (Ar), 126.2 (Ar), 88.4 (Cp), 82.2 (Cp), 71.7 (Cp), 70.2 (C_5H_5), 70.0 (Cp), 67.3 (Cp), 58.0 (CH_2), 45.1 (NMe_2).

Synthesis of 1-dimethylaminomethyl-2-phenyl-(η^5-cyclopentadienyl)-(η^4-tetraphenylcyclobutadiene)cobalt (I).[236]



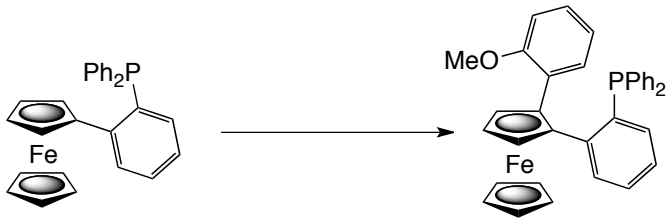
N,N-Dimethylaminomethyl-(η^5-cyclopentadienyl)-(η^4-tetraphenylcyclobutadiene)cobalt(I (200 mg, 0.537 mmol), K_2CO_3 (51.4 mg, 0.537 mmol), Boc-D-Valine (20 mg, 20 mol%), palladium acetate (8 mg, 10 mol%), phenylboronic acid (130.95, 1.074 mmol) and *tetra*-N-butylammonium bromide (147 mg, 0.537 mmol) was added to a Schlenk tube along with DMF (10 mL). The solution was heated to 80 ^oC for 16 h in air. The resulting solution was washed with distilled water (20 mL), extracted with diethyl ether (3 x 15 mL), dried over $MgSO_4$, filtered and purified *via* flash chromatography (5/20/75; triethylamine:hexane:ethyl acetate) to afford *title compound* as a dark yellow solid (164 mg, 42% yield). MP 75-78 ^oC; IR ν_{max}/cm^{-1} (Film) 3026.70 (C-H), 1669.75 (C=C), 1252.11 (C-N)^1H NMR (500 MHz, $CDCl_3$) δ 7.47 - 7.41 (m, 1H, Ar), 7.32 - 7.26 (m, 8H, Ar), 7.24 (d, *J* = 1.7 Hz, 1H, Ar), 7.23 (t, *J* = 1.3 Hz, 1H, Ar), 7.21 (d, *J* = 2.1 Hz, 1H, Ar), 7.20 (t, *J* = 1.4 Hz, 1H, Ar), 7.14 (dd, *J* = 8.1, 6.8 Hz, 8H, Ar), 7.09 (dt, *J* = 8.7, 2.0 Hz, 2H, Ar), 7.00 (dd, *J* = 8.3, 7.0 Hz, 2H, Ar), 4.89 (dd, *J* = 2.7, 1.8 Hz, 1H, Cp), 4.71 (t, *J* = 2.2 Hz, 1H, Cp), 4.62 (t, *J* = 2.7 Hz, 1H, Cp), 3.03 (d, *J* = 13.2 Hz, 1H, CH_2), 2.67 (d, *J* = 13.1 Hz, 1H, CH_2), 2.04 (s, 6H, NMe_2). ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.1 (Ar), 135.2 (Ar), 135.0 (Ar), 129.0 - 128.6 (m) (Ar), 128.3 (Ar), 128.0 (Ar), 128.0 (Ar), 127.2 (Ar), 126.3 (Ar), 126.0 (Ar), 98.7 (Cp), 88.9 (Cp), 86.5 (Cp), 84.0 (Cp), 83.4 (Cp), 75.0 (C_5H_5), 55.5 (CH_2), 45.1 (NMe), 29.9 (NMe); HRMS (FTMS + p NSI Full ms) M^+H $C_{42}H_{37}CoN$ requires 614.2253 found 614.2246; The enantiomeric excess was determined by ChiralPak® IA (25 cm), Hexanes / IPA = 96.9 / 3.1, 0.3 mL/min, λ = 254 nm, t (minor) = 12.44 min, t (major) = 26.06 min.

Synthesis of 2-phenyl-2-(diphenylphosphino)phenylferrocene

224 **408**

2-(Diphenylphosphino)phenylferrocene (300 mg, 0.67 mmol), K_2CO_3 (92.6 mg, 0.67 mmol), *N*-acetyl-phenyl-*D*-alanine (27 mg, 20 Mol%), palladium acetate (15 mg, 10 Mol%) and *tetra*-N-butylammonium bromide (245 mg, 0.67 mmol) was added to a Schlenk tube along with DMF (10 mL). The solution was heated to 60 ^{o}C for 16 h in air. The resulting solution was washed with distilled water (20 mL), extracted with diethyl ether (3 x 15 mL), dried over $MgSO_4$, filtered and purified *via* flash chromatography (99.9/0.1 hexane:ethyl acetate) to afford *title compound* as a dark yellow oil (1.64 mg, 3% yield). $\boldsymbol{\nu}_{max}/cm^{-1}$ (Film) 2926.04 (C-H), 1598.00 (C=C), 1124.91 (P-Ar). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (ddd, *J* = 7.7, 4.4, 1.4 Hz, 0H), 7.33 (td, *J* = 7.5, 1.4 Hz, 0H), 7.30 - 7.27 (m, 1H), 7.22 - 7.10 (m, 1H), 7.10 (tt, *J* = 4.7, 2.4 Hz, 1H), 6.92 (ddd, *J* = 7.7, 3.7, 1.3 Hz, 0H), 6.86 (ddd, *J* = 8.6, 7.2, 1.5 Hz, 0H), 4.59 (dd, *J* = 2.5, 1.5 Hz, 1H, Cp), 4.27 (t, *J* = 2.5 Hz, 1H, Cp), 4.22 (dt, *J* = 2.7, 1.5 Hz, 1H, Cp), 4.16 (s, 5H, C_5H_5). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.1 (Ar), 142.9 (Ar), 138.6 (Ar), 138.5 (Ar), 138.4 (Ar), 137.8 (d, *J* = 3.7 Hz, Ar), 137.7 (d, *J* = 2.8 Hz, Ar), 133.8 (d, *J* = 1.2 Hz, Ar), 133.7 (d, *J* = 2.3 Hz, Ar), 133.6 (d, *J* = 5.2 Hz, Ar), 133.5 (d, *J* = 2.9 Hz, Ar), 129.0 (Ar), 128.3 (Ar), 128.2 (Ar), 128.2 (Ar), 128.1 (Ar), 128.1 (Ar), 127.6 (Ar), 127.0 (Ar), 125.7 (Ar), 89.3 (d, *J* = 10.1 Hz, Cp), 88.0 (d, *J* = 2.0 Hz, Cp), 72.8 (d, *J* = 7.7 Hz, Cp), 70.5 (C_5H_5), 68.8 (Cp), 66.6 (Cp). ^{31}P NMR (202 MHz, $CDCl_3$) δ -13.7 (*P*Ph_2).

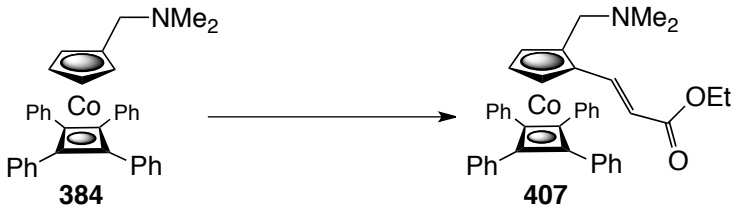
Synthesis of 2-(2-methoxyphenyl)-2-(diphenylphosphino)phenylferrocene



224 **411**

2-(Diphenylphosphino)phenylferrocene (300 mg, 0.67 mmol), K_2CO_3 (92.6 mg, 0.67 mmol), *N*-acetyl-phenyl-*D*-alanine (27 mg, 20 mol%), palladium acetate (15 mg, 10 mol%) and *tetra*-N-butylammonium bromide (245 mg, 0.67 mmol) was added to a Schlenk tube along with DMF (10 mL). The solution was heated to 60 ^{o}C for 16 h in air. The resulting solution was washed with distilled water (20 mL), extracted with diethyl ether (3 x 15 mL), dried over $MgSO_4$, filtered and purified *via* flash chromatography (99.9/0.1 hexane:ethyl acetate) to afford title compound as a dark yellow oil (263 mg, 64% yield). $\boldsymbol{\nu}_{max}$/cm^{-1} (Film) 1876.87 (C-H), 1678.98 (C=C) 1145.36 (C-O) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (ddd, *J* = 7.7, 4.4, 1.4 Hz, 0H), 7.44 (dd, *J* = 7.6, 1.8 Hz, 4H, Ar), 7.19 (tddd, *J* = 9.1, 5.6, 4.3, 2.1 Hz, 5H, Ar), 7.11 (tt, *J* = 7.5, 1.4 Hz, 2H, Ar), 6.94 (dt, *J* = 6.6, 1.4 Hz, 1H, Ar), 6.92 (dt, *J* = 5.1, 1.6 Hz, 2H, Ar), 6.78 (td, *J* = 7.5, 1.2 Hz, 1H, Ar), 6.66 (dd, *J* = 8.2, 1.1 Hz, 1H, Ar), 4.68 (dd, *J* = 2.5, 1.5 Hz, 1H, Cp), 4.29 (t, *J* = 2.5 Hz, 1H, Cp), 4.25 (td, *J* = 2.3, 1.5 Hz, 1H, Cp), 4.15 (s, 5H, C_5H_5), 3.45 (s, 3H, OMe); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.3, 144.9, 144.7, 139.0 (d, *J* = 12.9 Hz), 138.7 (d, *J* = 14.6 Hz), 136.7 (d, *J* = 15.1 Hz), 134.3 (d, *J* = 1.4 Hz), 134.1, 134.0, 133.9 (d, *J* = 5.6 Hz), 133.7 (d, *J* = 8.1 Hz), 133.5, 132.9, 128.4, 128.3, 128.2, 128.2, 128.2, 128.0, 128.0, 127.5, 126.7, 126.5, 119.9, 111.0, 89.9 (d, *J* = 9.5 Hz), 86.0, 71.6 (d, *J* = 9.1 Hz), 71.3, 70.7, 66.6, 55.2 ^{31}P NMR (202 MHz, $CDCl_3$) δ -14.3; HRMS (FTMS + p APCI) M^+H $C_{35}H_{30}FeOP$ requires 553.1378 found 553.1385

Synthesis of (*E*)-ethyl-3-(2-((dimethylamino)methyl)-(η^5-cyclopentadienyl)-(η^4-tetraphenylcyclobutadiene)cobalt (I) acrylate. [239]



N,N-Dimethylaminomethyl-(η^5-cyclopentadienyl)-(η^4-tetraphenylcyclobutadiene)cobalt(I (200 mg, 0.537 mmol), K_2CO_3 (51.4 mg, 0.537 mmol), boc-*L*-phenylalanine (21.71 mg, 20 mol%), palladium acetate (9.18 mg, 10 mol%) and *tetra*-N-butylammonium bromide (147 mg, 0.537 mmol) was added to a Schlenk tube along with DMF (10 mL). The solution was heated to 60 ^oC for 16 hours in air. The resulting solution was washed with distilled water (20 mL), extracted with diethyl ether (3 x 15 mL), dried over $MgSO_4$, filtered and purified *via* flash chromatography (5/90/5; triethylamine:hexane:ethyl acetate) to afford title compound as a dark yellow oil (169 mg, 49% yield). $\boldsymbol{\nu}_{max}/cm^{-1}$ (Film) 3102.98 (C-H), 1671.45 (C=C), 1777.98 (C-O), 1256.23 (C-N); ^1H NMR (500 MHz, $CDCl_3$) δ 7.52 - 7.49 (m, 1H, Ph), 7.46 - 7.43 (m, 7H, Ph), 7.32 - 7.27 (m, 12H, Ph), 7.14 (d, *J* = 15.8 Hz, 1H CH_2), 5.74 (d, *J* = 15.7 Hz, 1H, CH_2), 4.90 (dd, *J* = 2.9, 1.6 Hz, 1H, Cp), 4.87 (t, *J* = 2.0 Hz, 1H, Cp), 4.78 (t, *J* = 2.8 Hz, 1H, Cp), 4.20 (q, *J* = 7.1 Hz, 1H, CH_2CH_3), 2.91 (d, *J* = 13.3 Hz, 1H, CH_2), 2.80 (d, *J* = 13.4 Hz, 1H, CH_2), 2.11 (s, 6H, NMe_2), 1.36 (t, *J* = 7.1 Hz, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.8 (C=O), 135.2 (C=C), 128.8 (Ph), 128.2 (Ph), 126.6 (Ph), 116.5 (C=C), 89.8 (Cp), 88.0 (Cp), 85.8 (Cp), 80.4 (Cp), 75.9 (Cp), 60.0 (CH_2NMe_2), 53.8 (NMe), 50.1 (NMe), 46.3 (CH_2), 32.1 (CH_3); HRMS (FTMS + p NSI Full ms) M^+H $C_{41}H_{39}CoNO_2$ requires 636.2307 found 636.2295; The enantiomeric excess was determined ChiralPak® IA (25 cm), Hexanes / IPA = 97.5 / 2.5, 0.3 mL/min, λ = 254 nm, t (major) = 22.46 min, t (minor) = 23.95 min.

References

[1] Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**,107, 5318–5365. Muzart, J. *J. Mol. Catal. A: Chem*. **2007**, 276, 62–72. Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, 106, 4644–4680. Buchwald, S. L.;, Mauger C.; Mignani, G.; Scholz, U. *Adv. Synth. Catal.* **2006**, 348, 23–39. Cacchi, S.;Fabrizi, G. *Chem. Rev.* **2005**, 105, 2873–2920. Zeni, G.; Larock, R. C. *Chem. Rev*. **2004**, 104, 2285–2309. Muzart, J. *Tetrahedron*, **2005**, 61, 5955–6008. Muzart, J. *Tetrahedron*, **2005**, 61, 9423–9463. Stahl, S. S. *Angew. Chem. Int. Ed*. **2004**, 43, 3400–3420. Sigman, M. S.; Schultz, M. *J. Org. Biomol. Chem.* **2004**, 2, 2551–2554. Stoltz, B. M. Chem. Lett. 2004, 33, 362–367. Tietze, L. F.; Ila, H.; Bell, H. P. *Chem. Rev.* **2004**, 104, 3453–3516. Nishimura, T.; Uemura, S. *Synlett* **2004**, 201–216. Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, 103, 2945–2963. Agrofoglio, L. A.; Gillaizeau, I.; Saito, Y. *Chem. Rev*. **2003**, 103, 1875-1916. Negishi, E.-I.; Anastasia, L. *Chem. Rev*. **2003**, 103, 1979–2017. Kiss, G. *Chem. Rev.* **2001**, 101, 3435–3456. Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, 100, 3009-3066. Zimmer, R.; Dinesh, C. U.; Nandanan, E.; Khan, F. A. *Chem. Rev*. **2000**, 100, 3067-3125. Amatore, C.; Jutand, A. *Acc. Chem. Res*. **2000**, 33, 314–321. Miyaura, N.; Suzuki, A. *Chem. Rev*. **1995**, 95, 2457–2483. Tsuji, J. *Synthesis*, **1990**, 739–749.

[2] Allan. B, Canty, J. *Acc. Chem. Res*. **1992**, 25 (2), p 83-90

[3] Poli. G, Giambastiani. G, Heumann. A, *Tetrahedron,* **2000**, 56, 5959–5989.

[4] (a) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: New York, **2002**. (b) Tsuji, J. *Palladium Reagents and Catalysts*: *Innovations in Organic Synthesis*; Wiley and Sons: New York, **1995**. (c) Tsuji, J. *Palladium Reagents and Catalysts: New Perspectives for the 21st Century*; Wiley and Sons: New York, **2003**. (d) *Palladium in Organic Synthesis*; Tsuji, J., Ed.; Springer: Berlin, **2005**. (e) Heck, R. F. *Palladium Reagents in Organic Synthesis; Academic Press*: New York, **1985**. (f) Li, J. J.; Gribble, G. W. *Palladium in Heterocyclic Chemistry*; Pergamon: New York, **2000**. (g) Heumann, A.; Jens, K.- J.; Reglier, M. *Progress in Inorganic Chemistry*; Karlin, K. D., Ed.; Wiley and Sons: New York, *1994*; Vol. 42, pp. 483–576.

[5] R. Martin and Stephen L. Buchwald. *Accounts of Modern Chemical Research*, Vol 41, No 11, **2008**, 1461-1473

[6] Bosnich. *J. Am. Chem. Soc*., **1985**, 107, 2033-2046

[7] E.P. Kundig, C. M. Saudan, F. Viton, *Adv. Synth. Cat*., **2001**, 343, 51-56

[8] D.W. Allen, Organophosphorus Chemistry 2006, 35, 1-91

[9] E.G. Hope, A. M. Stuart, *Multiphase Homogenous Catalysis* **2005**, 1, 354-361

[10] R. Engel, J. I Rizzo, *Curr. Org. Chem*. **2006**, 10, 2393, 2405

[11] Tsuji, J.; Yamada, T.; Minami, I; Yuhara, M.; Nisar, M.; Shimizu, I. *J. Org. Chem.* **1987**, 52. 2988

[12] Trost, B. M.; Lautens, M. *Tetrahedron*. **1987**, 43, 4871.

[13] Trost, B. M.; Lautens, M. *J. Am. Chem. Soc.* **1987**, 109, 1469.

[14] Trost, B. M; Toste, F. D. *J. Am. Chem. Soc*. **1999**, 121, 4545.

[15] Casey, C. P.; Whiteker, G. T. *Isr, J. Chem*. **1990**, 30, 299.

[16] Casey, C. P.; Whiteker, G. T.; Melville, M. G; Petrovich, L M.; Gavney, J. A., Jr.; Powell, D. R. *J. Am. Chem. Soc*. **1992**, 114, 5535.

[17] Pearson. R. G, *J. Am. Chem. Soc.* **1963**, 85, 3533.

[18] Pearson, R. G, *J. Chem. Educ*. **1968**, 45, 643.

[19] Kataoka. N, Shelby. Q, Stambuli. J. P, Hartwig, J. F. *J. Org. Chem.* **2002**, 67, 5553

[20] Wolfe. J. P, Tomori. H, Sadighi. J. P, Yin. J. J. Buchwald. S. L, *J. Org. Chem*. **2000**, 65, 1158.

[21] Mislow. K, *Trans*. *New York. Acad. Sci.* **1973**, 35, 227

[22] Baechler. R. D, Mislow. K, *J. Am. Chem. Soc*. **1970**, 92, 3090.

[23] Knowles. W. S, *Angew. Chem., Int. Ed. Engl*. **2002**, 41, 1999.

[24] Juge. S, Stephan. M, Laffitte. J. A, Genet. J. P, *Tetrahedron Lett*. **1990**, 31, 6357.

[25] Werner. H, *Angew. Chem., Int. Ed. Engl*. **2004**, 43, 938

[26] Marynick. D. S. *J. Am. Chem. Soc.* **1984**, 106, 4046.

[27] Giordan. J. C, Moore. J. H, Tossell. J. A, *Acc. Chem. Res.* **1986**, 19, 281.

[28] Xiao. S. X, Trogler. W. C, Ellis. D. E, Berkovitchyellin. Z, *J. Am. Chem. Soc*., **1983**, 105, 7033-7037

[29] Marynick. D. S, *J. Am. Chem. Soc*, **1984**, 106, 4064-4065

[30] Pacchioni. G, Bagus. P. S, *Inorg. Chem.*, **1992**, 31, 4391-4398

[31] Dunne. B. J, Morris. R. B, Orpen. A. G, *J. Chem. Soc, Dalton Trans.* **1991**, 653.

[32] Orpen. A. G, Connelly. N. G, *Organometallics* **1990**, 9, 1206

[33] Leyssens. T, Peeters. D, Orpen. A. G, Harvey. J. N, *Organometallics* **2007**, 26, 2637

[34] Tolman. C. A, *Chem. Rev.* **1977**, 77, 313

[35] Tolman. C. A, *J. Am. Chem. Soc.* **1970**, 92, 2956.

[36] Pauson. P. L, Kealy. T. J, *Nature*, **1951**, *168*, 1039.

[37] Miller. S. A, Tebboth. T. A, Tremaine. J. F, *J. Chem. Soc.*, **1952**, 632.

[38] Wilkinson. G, Rosenblum. M, Whiting. M. C, Woodward. R. B., *J. Am. Chem. Soc.*, **1952**, 74, 2125.

[39] Schlègl. K, Fried. M, *Monatsh. Chem.*, **1964**, *95*, 558.

[40] Carter. O. L, McPhail. A. T, Sim. G. A, *J. Chem. Soc*., **1967**, 365.

[41] Schlègl. K, Fried. M, *Top. Stereochem.*, **1967**, *1*, 39.

[42] Schlögl, K. In *Topics in Stereochemistry*; Allinger, N. L., Eliel, E. L., Eds.; Wiley: Hoboken, NJ, **1967**; Chapter Stereochemistry of Metallocenes, pp 39**–**91.

[43] *Ferrocenes. Homogeneous Catalysis. Organic Synthesis, Materials Science*; Togni. A, Hayashi. T, Eds.; VCH: Weinheim, Germany, **1995**.

[44] Breuer. M, Ditrich. K, Habicher. T, Hauer. B, Kebeler. M, StTrmer. R, Zelinski. T, *Angew. Chem.* **2004**, 116, 806 – 843; *Angew. Chem. Int. Ed*. **2004**, 43, 788 – 824.

[45] Sanders. R and Muller-Westerhoff. U.T, *J. Organomet. Chem*., 512. **1996**. 219-224

[46] Gan. K. S, Horin. T. S. A, *Ferrocenes. Homogeneous Catalysis, Organic Synthesis, Materials Science* (Eds.: Togni A, Hayashi. T.), VCH, Weinheim, **1995**, pp. 3 – 104; Colacot. T. J, *Platinum Met. Rev.* **2001**, 45, 22 – 30; Siemeling. U, Auch. T.-C, *Chem. Soc. Rev*. **2005**, 34, 584 – 594.

[47] Bulter. I. R, Cullen. W. R, Kim. T. J, Rettig. S. J, Trotter. J, *Organometallics* **1985**, 4, 972.

[48] Bishop. J. J, Davision. A, Katcher. M. L, Lichtenberger. D. W, Merrill. E, Smart. J. C. *J. Organomet. Chem*. **1971**, 27, 241

[49] Bulter. I. R, Cullen. W. R, Ni. J, Rettig. S. R, *Organometallics* **1985** 4, 2196-2201

[50] Togni. A, Breutel. C, Schnyder. A, Spindler. F, Landert. H, Tijani. A, *J. Am. Chem. Soc*., 116, **1994**, p. 4062–4066.

[51] Farrell. A, Goddard. R, Guiry. P. J, *J. Org. Chem.* **2002**, 67, 4209-4217

[52] Nishibayashi. Y, Arikawa. Y, Ohe. K, Uemura. S, *J. Org. Chem*. **1996**, 61, 1172.

[53] Ganter. C, Wagner. T, *Chem. Ber*. **1995**, 128, 1157.

[54] Richards. C. J, Locke. A. J, *Tetrahedron: Asymmetry*, 9, **1998**, p. 2377–2407.

[55] T. Hayashi. T, T. Mise. T, M. Fukushima. M, M. Kagotani. M, N. Nagashima. N, Y. Hamada. Y, Matsumoto. A, Kawakami. S, Knoishi. M, Yammoto. K, Kumada. M, *Bull. Chem. Soc. Jpn*., 53, **1980**, p. 1138–1151.

[56] Abbenhuis. H. C. L, Burkhardt. U, Gramlich. V, Köllner. C, Salzmann. R, Pregosin. S, Togni. A, *Organometallics*, 14, **1995**, p. 759–766.

[57] Abbenhuis. H. C. L, Burkhardt. U, Gramlich. V, Köllner. C, Salzmann. R, Pregosin. S, Togni. A, *Organometallics*, 14, **1995**, p. 759–766.

[58] Nishibayashi. Y, Segawa. K, Ohe. K, Uemura. S, *Organometallics* **1995**, 14, 5486.

[59] Nishibayashi. Y, Uemura. S, *Synlett*, **1995**, 79.

[60] Ahn. K. H, Cho. C.-W, Baek. H.-H, Park. J, Lee. S, *J. Org. Chem*. **1996**, 61, 4937.

[61] Richards. C. J, Damalidis. T, Hibbs. D. E, Hursthouse. M. B, *Synlett* **1995**, 74. Richards. C. J, lvaney. A. W, *Tetrahedron: Asymmetry* **1996**, 7, 1419.

[62] Özçubukçu. S, Schmidt. F, Bolm. C, *Org. Lett*. **2005**, 7, 1407 – 1409.

[63] García-Mancheńo. O, Priego. J, Cabrera. S, Gömez-Arrays. R, Llamas. T, Carretero. J. C, *J. Org. Chem.* **2003**, 68, 3679 – 3686.

[64] Lotz. M, Polborn. K, Knochel. P, *Angew. Chem*. **2002**, 114, 4902 – 4905; *Angew. Chem. Int. Ed*. **2002**, 41, 4708 – 4711.

[65] Tsukazaki. M, Tinkl. M, Roglans. A, Chapell. B. J, Taylor. N. J, Snieckus. V, *J. Am. Chem. Soc.* **1996**, 118, 685 – 686.

[66] Nishibayashi. Y, Arikawa. Y, Ohe. K, Uemura. S, *J. Org. Chem.* **1996**, 61, 1172 – 1174.

[67] Price. D, Simpkins. N. S., *Tetrahedron Lett.* **1995**, 36, 6135 – 6136.

[68] Bolm. C, MuPiz. K, Seger. A, Raabe. G, Guenther. K, *J. Org. Chem*. **1998**, 63, 7860 – 7867

[69] Butler. I. R, Cullen. W. R , Kim. T.-J, Rettig. S. J, Trotter. J, *Organometallics*, **1985**, 4, 972.

[70] Adeleke. J. A, Chen. Y.-W, Liu. L.-K, *Organometallics*, **1992**, 11, 2543.

[71] Lai. L.-L. Dong. T.-Y, *J. Chem. Soc., Chem. Commun*., **1994**, 2347.

[72] Bulter. I. R, Cullen. W. R, Kim. T. J, Rettig. S. J, Trotter. J, *Organometallics* **1985**, 4, 972.

[73] Bulter. I. R, Cullen, W. R, Kim. T.-J, *Synth. React. Inorg. Met.- Org. Chem.,* **1985**, 15, 109.

[74] Dai. L.-X, Tu. T., You. S.-L, Deng. W.-P, Hou. X.-L, *Acc. Chem. Res*., **2003**, 36, 659.

[75] Boyes. A. L, Butler. I. R, Quayle. S. C, *Tetrahedron Lett*., **1998**, 39, 7763.

[76] Dong. T.-Y, Ho. P.-H, Chang. C.-K, *J. Chin. Chem. Soc.,* **2000**, 47, 421.

[77] Laly. M, Broussier. R, Gautheron. B, *Tetrahedron Lett.*, **2000**, 41, 1183

[78] Brunner. H, Janura. M*, Synthesis*, **1998**, 45.

[79] Nettekoven. U, Kamer. P. C. J, Widhalm. M, Van Leeuwen. P. W. N. M*, Organometallics*, **2000**, 19, 4596.

[80] Atkinson. R. C. J., Gibson V. C., Long N. J.; *Chem. Soc. Rev*., **2004**, 33, 313– 328

[81] Nettekoven, U.; Kamer, P. C. J.; van Leeuwen. P. W. N. M.; Widhalm, M.; Spek, A. L.; Lutz, M. *J. Org. Chem*. **1999**, 64, 3996.

[82] Nettekoven, U.; Kamer, P. C. J.; van Leeuwen*, Organometallics* **2000**, 19, 4596-4607

[83] Chen. W, Mbafor. W, Roberts S. M, Whittall. J, *J. Am. Chem. Soc.* **2006**, 128, 3922-3923

[84] Bueno. A, Moreno. R. M, Moyano. A, *Tetrahedron: Asymmetry* **2005**, 16, 1763 – 1778.

[85] Jin. M.-J, Takale. V. B, Sarkar. M. S, Kim. Y.-M, *Chem. Commun*. **2006**, 663 – 664

[86] Danjo. H, Higuchi. M, Yada. M, Imamoto. T, *Tetrahedron Lett.* **2004**, 45, 603 – 606.

[87] García-Mancheño. O, J. Priego. J, Cabrera. S, Gómez-Arrayás. R, Llamas. T, Carretero. J. C, *J. Org. Chem.* **2003**, 68, 3679 – 3686.

[88] Hu. X, Chen. H, Dai. H, Zheng. Z, *Tetrahedron: Asymmetry* **2003**, 14, 3415 – 3421; Hu. X, Chen. H, Dai. H, Zheng. Z, *J. Mol. Catal. A* **2004**, 218, 107 – 112.

[89] Geisler. F. M, Helmchen. G, *J. Org. Chem*. **2006**, 71, 2486 – 2492.

[90] Dai. L.-X, Tu. T, You. S.-L, Deng. W.-P, Hou. X.-L., *Acc. Chem. Res*. **2003**, 36, 659 – 667.

[91] Zheng. W.-H, Sun. N, Hou. X.-L*, Org. Lett.* **2005**, 7, 5151 – 5154.

[92] A. Leitner. A, Larsen. J, Steffens. C, Hartwig. C. J, *J. Org. Chem*. **2004**, 69, 7552 – 7557.

[93] Shibasaki. M, Vogl. E. M, Ohshima. T, *Adv. Synth. Catal*. **2004**, 346, 1533 – 1552.

[94] Deng. W.-P, Hou. X.-L, Dai. L.-X, Dong. X.-W, *Chem. Commun*. **2000**, 1483 – 1484.

[95] Kilroy. T. G, Hennessy. A. J, Connolly. D. J, Malone. Y. M, Farrell. A, Guiry. P. J, *J. Mol. Catal*. *A* **2003**, 196, 65 – 81.

[96] Kiely. D, Guiry. P. J, *Tetrahedron Lett*. **2003**, 44, 7377 – 7380

[97] Loiseleur. O, Meier. P, Pfaltz. A, *Angew. Chem*. **1996**, 108, 218 –220; *Angew. Chem. Int. Ed. Engl*. **1996**, 35, 200 – 202.

[98] Bringmann. G, Mortimer. A. J. P, Keller. P. A, Gresser. M. J, Garner. J, Breuning. M, *Angew. Chem*. **2005**, 117, 5518 -5563; *Angew. Chem. Int. Ed*. **2005**, 44, 5384 – 5427.

[99] Zhou. Y, Wang. S, Wu. W, Li. Q, He. Y, *Org. Lett*, **2013**, Vol. 15, No. 21,

[100] Baudoin. O, *Eur. J. Org. Chem*. **2005**, 4223 – 4229.

[101] Cammidge. A. N, Crépy. K. V. L, *Chem. Commun.* **2000**, 1723 –1724.

[102] Cammidge. A. N, Crépy. K. V. L, *Tetrahedron* **2004**, 60, 4377 – 4386.

[103] Bringmann. G, Hamm. A, Schraut. M, *Org. Lett*. **2003**, 5, 2805 – 2808.

[104] Davies. D. L, Donald. S. M. A, Macgregor. S. A, *J. Am. Chem. Soc,* **2005**, 127 , 13754.

[105] Albrecht. M, Spek. A. L, Van Koten. G, *J. Am. Chem. Soc*, **2001**, 123 , 7233

[106] Shaw. B. L, Truelock. M. M, *J. Organomet. Chem,* **1975**, 102, 517.

[107] Schwarz. J, Herdtweck. E, Herrmann. W.A, *Organometallics*, **2000**,19, 3154.

[108] Cope, A. C, Friedrich, E. C. *J. Am. Chem. Soc.* **1968**, 90, 909.

[109] Arlen. C, Pfeffer. M, Bars. O, Grandjean. D, *J. Chem Soc., Dalton Trans*. **1983**, 1535

[110] Dehand. J, Pfeffer. M, Zinsius. M*, Inorg. Chim. Acta* **1975**, 13, 229.

[111] Dehand. J, Jordanov. J, Pfeffer. M, Zinsius. M. C. R, *Hebd. Seances Acad. Sci., Ser. C* **1975**, 281, 651.

[112] Braunstein. P, Dehand. J. Pfeffer. M, *Inorg. Nucl. Chem. Lett.* **1974,** 10, 581.

[113] Lenarda. M, Ros. R, Graziani. M, Belluco. U. *J, Organomet. Chem*. **1974**, 65, 407-416.

[114] Holton. R. A, Kjonaas. R. A*, J. Am. Chem. Soc*. **1977**, 99, 4177. Holton. R. A, Zoeller. J.R, *J. Am. Chem. Soc*. **1985**, 107, 2124.

[115] Dupont. J, Halfen. R. A. P, Schenato. R, Berger. A, Horner. A, Bortoluzzi. A, Maichle-Mössmer. C, *Polyhedron* **1996**, 15, 3465.

[116] Trofimenko, S. *Inorg. Chem*. **1973**, 12, 1215.

[117] Goel. A. B, Pfeffer. M, *Inorg. Synth*. **1989**, 26, 211.

[118] Yao. Q, Kinney. E. P, Zheng. C, *Org. Lett*. **2004**, 6, 2997.

[119] Dupont. J, Beydoun. N, Pfeffer. M, *J. Chem. Soc., Dalton Trans*. **1989**, 1715.

[120] Meijer. M. D, Mulder. B, Van Klink. G. P. M, Van Koten. G, *Inorg. Chim. Acta.* **2003**, 352, 247.

[121] Granell. J, Sainz. D, Sales. J, Solans. X, Fontaltaba. M, *J. Chem. Soc., Dalton Trans.* **1986**, 1785.

[122] Holli. T. K, Overman. L. E, *J. Organomet. Chem.* **1999**, 576, 290.

[123] Dunina. V. V, Gorunova. O. N, Livantsov. M. V, Grishin. Y. K, Kuz'mina. L. G, Kataeva. N. A, Churakov. A. V, *Tetrahedron: Asymmetry* **2000**, 11, 3967.

[124] Wu. Y. J, Cui. X. L, Du. C. X, Wang. W. L, Guo. R. Y, Chen. R. F, *J. Chem. Soc., Dalton Trans*. **1998**, 3727.

[125] Sokolov. V. I. *J. Organomet. Chem*. **1995**, 500, 299.

[126] Zhao. G, Wang. Q. G, Mak. T. C. W, *Tetrahedron: Asymmetry* **1998**, 9, 1557

[127] Benito. M, Lopez. C, Solans. X, Font-Bardia, M. *Tetrahedron: Asymmetry* **1998**, 9, 4219.

[128] Komatau. T, Nonoyama M, Fujita. *J, Bull. Chem. Soc. Jp*. **1981**. 54, 186-139. Sokolov. K. S. Nechaeva. V. J, Reutov. O. A, *J. Organomet Chem.* **1983**, 253, C55-C58.

[129] Dunlna. V. V, Gorunova. O. N, Llvantsov. M. V, Grishin. Y. K, Kuz'mlma. L. G, Kataeva. N. A, A. Churakov. V, *Tetrahedron: Asymmetry*, **2000**. 11. 3967-3984.

[130] Sokolov. V. I, Troltskaya. L. L, Reutov. O. A, *J. Organomet. Chem.* **1977**, 133, C2B-C30

[131] C. López. C, Bosque. R, Solans. X, Font-Bardie. M, *Tetrahedron: Asymmetry*, **1996**. 7, 2527-2530.

[132] Holla. T. K, Overman. L. E, *Tetrahedron Lett.* **1997** *38,* 8837-8840.

[133] Sokolov. V. I, Troltskaya. L. L, *Chimia,* **1978,** *32,* 122-123. Sokolov. V. I, Troltskaya. L. L, Reutov. O. A, *J. Organomet. Chem.* **1979**, 162, 537-546.

[134] Miyaura. N, Sugiome. H, Suzuki. A, *Tetrahedron Lett*. **1979**, 36, 3437

[135] Beller. M, Fischer. H, Herrmann. W.A, *Angew. Chem, Int. Ed.* **1995**, 34, 1848.

[136] Lin. S, Danishefsky. S. J, *Angew. Chem., Int. Ed. Engl.* **2002**, 41, 512-515

[137] Kotha. S, Lahiri. K, Kashinath. D, *Tetrahedron*, **2002**, 58, 9633.

[138] Miyaura. N, *Top. Curr. Chem.*, **2002**, *219*, 11

[139] Wolfe. J. P, Tomori. H, Sadighi. P, Yin. J, Buchwald. S. L, *J. Org. Chem*., **2000**, 65, 1158. Barder. T. E, Buchwald. S. L, *Org. Lett.*, **2004**, *6*, 2649.

[140] Kirchhoff. J. H, Netherton. M. R, Hills. I. D, Fu. G. C, *J. Am. Chem. Soc.*, **2002**, *124*, 13662. Zhou. J, Fu. G. C, *J. Am. Chem. Soc.*, **2004**, 126, 1340

[141] Navarro. O, Kelly. R. A, Nolan. S. P, *J. Am. Chem. Soc*., **2003**, *125*, 16194.

[142] Bedford. R. B, Hazelwood. S. L, Limmert. M. E, Albisson. D. A, Draper. S. M, Scully. P. N, Coles. S. J, Hursthouse. M. B, *Chem. Eur. J*., **2003**, 9, 3216.

[143] Belle. M, Fischer. H, *Angew. Chem. Int. Ed*, **1995**, 34, 1848.

[144] Mehmandoust. M, Petit. Y, Larcheveque. M, *Tetrahedron. Lett*. **1992**, 33, 4313-4316.

[145] Calter. M, Hollis. K. T, Overman. L. E, *J. Org. Chem.* **1997**, 62, 1449-1456.

[146] Hollis. T. K, Overman. L. E, *Tetrahedron Lett*. **1997**, 38, 8837-8840

[147] Hollis. T. K, Overman. L. E, *J. Organomet. Chem.* **1999**, 576, 290-299.

[148] Stevens. A. M, Richards. C. J, *Organometallics,* **1999**, 18, 1346-1348.

[149] Anderson. C. E, Overman. L. E, *J. Am. Chem. Soc.* **2003**, 125, 12412-12413

[150] Jautze. S, Peters. R, *Angew. Chem., Int. Ed*. **2008**, 47, 9284.

[151] Henry. P. M. *Handbook of Organopalladium Chemistry for Organic Synthesis*; Wiley-Interscience: New York, **2002**; Vol. 2, p 2119. (b) Fanning. K. N, Jamieson. A. G, Sutherland. A, Curr. *J.Org. Chem*. **2006**, 10, 1007.

[152] Fürstner. A, Davies. P. W, *Angew. Chem., Int. Ed*. **2007**, 46, 3410. Chianese. A. R, Lee. S. J, Gagné. M. R, *Angew. Chem., Int. Ed*. **2007**, 46, 4042.

[153] Molander. G, Dehmel. F, *J. Am. Chem. Soc*., ***2004***, 126 (33), p 10131-10318

[154] Heck. R. F, Nolley. J. P, *J. Org. Chem.*, **1972**, *37* (14), pp 2320–2322

[155] Miyaura. N, Suzuki. A., *J. Chem. Soc., Chem. Commun*., **1979**, 866-867

[156] Stille, J. K. *Angew. Chem. Int. Ed. Engl*. **1986**, 25, 508–524

[157] Herrmann. W. A., C. Brossmer, K. Öfele, Reisinger. C. P, Priermeier. T, Beller. T, Fischer. H, *Angew. Chem. Int. Ed.,* **1995**, 34, (17), 1844

[158] Old. D. W, Wolfe. J. P, Buchwald. S. L, *J. Am. Chem. Soc*., **1998**, *120*, 9722.

[159] Roy. A. H, Hartwig. J. F, *J. Am. Chem. Soc*., **2001**, *123*, 1232.

[160] Grushin. V. V, Alpe. H, *Chem. Rev*., **1994**, *94*, 1047.

[161] Allenmark. S. *Tetrahedron Lett*., **1974**, 371.

[162] Wolfe, J. P, Tomori. H, Sadighi. J. P., Yin. J., Buchwald. S. L., *J. Org. Chem*., **2000**, *65*, 1158.

[163] Kočovsky. P, Vyskočil. S, Lloyd-Jones. G. C, Stephen. S. C, *J. Am. Chem. Soc*., **1999**, *121*, 7714.

[164] *Comprehensive Organometallic Chemistry*; G. Wilkinson, F. G. A. Stone, E. W. Abel, Ed.; Pergamon: Oxford, **1982**, *8*, 1013.

[165] Gómez. M, Granell. J, Martinez. M, *Eur. J. Inorg. Chem*., **2000**, 217.

[166] Roca. F. X, Richards. C. J, *Chem. Commun*., **2003**, 3002-3003

[167] Rebiere. F, Samuel. O, Kagan. H. B, *Tetrahedron Lett.*, **1990**, *31*, 3121.

[168] Arnold. R, Matchett. S. A, Rosenblum. M, *Organometallics*, **1988**, *7*, 2261.

[169] Thesis of Francesc Xavier Roca, *Synthesis and Application of Novel Planar Chrial Ferrocene Ligands and Phosphapalladacycles*. **2006** page 53-54

[170] Sanders. A. P, *J. Am. Chem. Soc*., **1964**, *86*, 1376.

[171] Roca. F. X, Motevalli. M, and Richards. C. J, *J. Am. Chem. Soc*. **2005**, 127, 2388-2389

[172] Alyea. E. C, Song. S, *Comments Inorg. Chem*. **1996,** 18, 189-221; White. D, Coville. N. *J. Adv. Organomet. Chem*. **1994**, 77, 95-158.

[173] Tolman, C. A. *Chem. Rev*. **1977**, 77, 313-348

[174] Song. S, Alyea, E, C. *Comments. Inorg. Chem*., **1996**, 18, 145-164

[175] Allman. T, Geol. R. G, *Can. J. Chem*, **1982**, 60, 716-722; Derencsenyi. T. T, *Inorg. Chem*. **1981**, 20, 665-670

[176] Cammidge. A. N, Crepy. K. V. L, *Chem. Commun*., **2000**, 1723.

[177] Cammidge. A. N, Crepy. K. V. L, *Tetrahedron*, **2004**, 4377.

[178] Buchwald. S. L, Yin. J, *J. Am. Chem. Soc.*, **2000**, *122*, 12051.

[179] Pickett. T, Richards. C, *Tetrahedron. Lett*., 42, **2001**, 3767-3769

[180] Sammakia. T, Latham. H. A, *J. Org. Chem*. **1995**, 60, 6002.

[181] Thesis of Francesc Xavier Roca, *Synthesis and Application of Novel Planar Chrial Ferrocene Ligands and Phosphapalladacycles*. **2006**, page 57-58.

[182] Nozaki. K, Takaya. H, *J. Am. Chem. Soc.*, **1997**, *119* (19), pp 4413–4423

[183] Kaye. S, Fox. J. M, Hicks. F. A, Buchwald. S. L, *Adv. Synth. Catal.* **2001**, 343, 789-794

[184] HPLC condtions for **KetPhos** Conc. = 0.6 mg/ml, Column = Chiralpak IA-3, Sample dissolved in 10% IPA in Hexane, Major peak @ 11.034 mins.

[185] Chen. W, Roberts. S. M, Whittall. J, *J. Am. Chem. Soc*. **2006**, 128, 3922-3923

[186] Allen. D. V, Venkataraman. D, *J . Org. Chem* . **2003**, 68, 4590-4593

[187] Gelman. D, Jiang. L, Buchwald. S. L, *Org. Lett.* Vol. 5, No. 13, **2003**, 2315-2318

[188] Cai. D. W, Payack. J. F, Bender. D. R, Hughes D. L, Verhoeven. T. R, Reider. P. J, *J. Org. Chem*., **1994**, 59, 7180.

[189] Imamoto. T, Oshiki. T, Onozawa. T, Matsuo. M, Hikosaka. T, Yanagawa. M, *Heteroatom Chem*., **1992**, 3, 799.

[190] Korff. C, Helmchen. G, *Chem. Commun*., **2004**, 530-531.

[191] Gaumont. A. C, Hursthouse. M. B, Coles. S. J, Brown. J. M, *Chem. Commun.* **1999**, 63-64.

[192] Gillie. A, Stille. K. J, *J. Am. Chem. Soc.* **1980**, 102, 4933-4941.

[193] Åkerman. B, Ljunqvist. A, *J. Organomet. Chem*. **1979**, 182, 59-75.

[194] Austeri. M, Enders. M, Nieger. M, Bräse. S, *Chem. Eur. J*., Vol. 2013, 9, **2013**, 1667-1670

[195] Cope. A. C, Siekman. R W, *J. Am. Chem. Soc*. **1965**, 87, 3272-3273.

[196] Herrman. W. A, Brossmer. C, Ofele. K, Reisinger. C. P, *Angew. Chem*. **1995**, 34, 1844-1848

[197] Wolfe. J. P, Ahman. J, Sadighi. J. P, Singer. R. A, Buchwald. S. L, *Tetrahedron Lett*. **1997**, 38, 6367-6370

[198] Santra. P. K, Saha. C. R, *J. Mol. Catal.* **1987**, 39, 279

[199] Louie. J, Hartwig. J. F, *Angew. Chem., Int. Ed*., **1996**, *35*, 2359.

[200] Shaw. B. L, *New. J. Chem*., **1998**, 77.

[201] Striter. E. R, Buchwald. S. L, *Angew. Chem., Int. Ed. Engl.,* **2006**, *45*, 925.

[202] Fairlamb. I. J. S, Kapdi. A. R, Lee. A. F, Sánchez. G, López. G, *Dalton Trans*., **2004**, *23*, 3970.

[203] Echavarren. A. M, Gómez-Lorr. B, Gonzalez. J. J, De Frutos. O, *Synlett*, **2003**, 585.

[204] (a) Cheney. A. J, Shaw. B. L, *J. Chem. Soc., Dalton Trans*. (**1972**) 860. (b) Herrmann. W. A, Brossmer. C, Reisinger. C.-P, Riermeier. T. H, Öfele. K, Beller. M, *Chem. Eur. J*. 3 (**1997**) 1357. (c) Shaw. B. L, Perera. S. D, Staley. E. A, *Chem. Commun*. (**1998**) 1361.

[205] Nakamoto. K, *Infrared and Raman Spectra of Inorganic and Coordination Compounds*, third ed., Wiley-Interscience, New York, **1978**.

[206] Zhao. G, Yang. Q.-C, Mak. T. C. W, *Organometallics.* 18 (**1999**) 3623. Mercier. A, Wagschal. S, Guénée. L, Besnard. C, Kündig. E. P, *Organometallics.* 32 (**2013**) 3932

[207] Sokolov. V. I, Troitskaya. L, Reutov. O. A, *J. Organomet. Chem*. **1979**, 182, 537

[208] Garcia-Cuadrado. D, de Mendoza. P, Braga. A. A. C, *J. Am. Chem. Soc.* **2007**, 129, 6880.

[209] (a) Campeau. L.-C, Parisien. M, Leblanc. M, Fagnou. K, *J. Am. Chem. Soc*. **2004**, 126, 9186. (b) Hennessy. E. J, Buchwald. S. L, *J. Am. Chem. Soc*. **2003**, 125, 12084.

[210] Dunina. V. V, Razmyslova. E. D, Gorunova. O. N, Livantsov. M. V, Grishin. Y. K, *Tetrahedron: Asymmetry*, **2003**, *14*, 2331.

[211] Panchal. K, Amin. J, Roca. F. X, Motevalli. M, Richards. C. J, **2014**, *manuscript in preparation*.

[212] Thesis of Francesc Xavier Roca, *Synthesis and Application of Novel Planar Chrial Ferrocene Ligands and Phosphapalladacycles*. **2006** page 138

[213] Roca. F. X, Motevalli. M, Richards. C. J, *J. Am. Chem. Soc.* **2005**, 127, 2388

[214] Burg. A. B, Wagner. R. I, *J. Am. Chem. Soc.* **1953**, 75, 3872

[215] Bernoud. E, Veillard. R, Alayrac. C, Gaumont. A. C, *Molecules*. **2012**, 17, 14573-14587

[216] Naumann. K, Zon. G, Mislow. K, *J. Am. Chem. Soc*., **1969**, 91, 7012-7023

[217] Krenske. E, *J. Org. Chem*., **2012**, 77, 1-4

[218] Horner. L, Balzer. W. D, *Tet. Lett.* **1965**, 6, 1157-1162

[219] Zon. G, DeBruin. K. E, Naumann. K, Mislow. K, *J. Am. Chem. Soc*. **1969**, 91, 7023-7027

[220] Thesis of Francesc Xavier Roca, *Synthesis and Application of Novel Planar Chrial Ferrocene Ligands and Phosphapalladacycles*. **2006** page 138

[221] Günay. M. E, Richards. C. J, *Tetrahedron. Asymmetry*., 21, **2010**, 2782-2787

[222] Günay. E. M, Ilyashenko G, Richards. C. J, *Tetrahedron: Asymmetry* 21 (**2010**) 1782-2787

[223] Jacobsen. E. N, Larrow. J. F, Keith. J. M, *Adv. Synth. Catal*., **2001**, 343, 5

[224] Willis. M. C, *J. Am. Chem. Soc. Perkins. Trans*., **1999**.

[225] Roca. F. X, Richards. C. J, *Chem. Commun*., **2003**, 3002-3003

[226] Watts. W. E, in *Comprehensive Organometallic Chemistry*, Eds. G. *Wilkinson, F. G. A. Stone and E. W. Abel, Pergamon: Oxford*, **1982**; Vol. 8, pp. 1013**–**1024.

[227] a) Miyaura. N, Suzuki. A, *Chem. Rev*. **1995**, 95, 2457; b) Miyaura. N, *J. Organomet. Chem.* **2002**, 653, 54; c) Miyaura. N, *Top. Curr. Chem*. **2002**, 219, 11; d) Suzuki. A, *J. Organomet. Chem. 1999*, 576, 147; e) Miyaura. N, Ishiyama. T, Ishikawa. M, Suzuki. A, *Tetrahedron Lett.* **1986**, 27, 6369; f) Chemler. S. R, Trauner. D, Danishefsky. S. J, *Angew. Chem*. **2001**, 113, 4676; *Angew. Chem. Int. Ed*. **2001**, 40, 4544; g) Nicolaou. K. C, Carenzi. G. E. A, Jeso. V, *Angew. Chem*. **2005**, 117, 3963; *Angew. Chem. Int. Ed*. **2005**, 44, 4442.

[228] a) Littke. A. F,. Fu. G. C, *Angew. Chem*. **2002**, 114, 4350; *Angew. Chem. Int. Ed*. **2002**, 41, 4176; b) Old. D. W, Wolfe. J. P, Buchwald. S. L, *J. Am. Chem. Soc*. **1998**, 120, 9722 – 9723; c) Littke. A. F, Dai. C, Fu. G. C, *J. Am. Chem. Soc*. **2000**, 122, 4020; d) Wolfe. J. P, Singer. R. A, Yang. B. H, Buchwald. S. L, *J. Am. Chem. Soc*. **1999**, 121, 9550; e) Hu. Q.-S, Lu. Y, Tang. Z.-Y, Yu. H.-B, *J. Am. Chem. Soc*. **2003**, 125, 2856.

[229] a) Dyker. G, *Handbook of C-H Transformations. Applications in Organic*

Synthesis,Wiley-VCH,Weinheim, **2005**; b) Murai. S, *Activation of Unreactive Bonds and Organic Synthesis*. Springer, Berlin, **1999**, pp. 48 – 78;

[230] Alberico. D, Scott. M. E, Lautens. M, *Chem. Rev*. **2007**, 107, 174;

[231] Jia. C, Piao. D, Oyamada. J, Lu. W, Kitamura. T, Fujiwara. Y, *Science* **2000**, 287, 1992; b) Chen. X, Li. J.-J, Hao. X.-S, Goodhue. C. E, Yu. J.-Q, *J. Am. Chem. Soc*. **2006**, 128, 78; c) Campo. M. A, Huang. Q, Yao. T, Tian. Q, Larock. R. C, *J. Am. Chem. Soc*. **2003**, 125, 11 506; d) Bressy. C, Alberico. D, Lautens. M, *J. Am. Chem. Soc*. **2005**, 127, 13148; e) Hennessy. E. J, Buchwald. S. L, *J. Am. Chem. Soc*. **2003**, 125, 12 084; f) Wang. X, Lane. B. S, Sames. D, *J. Am. Chem. Soc*. **2005**, 127, 4996; g) Kalyani. D, Deprez. N. R, Desai. L. V, Sanford. M. S, *J. Am. Chem. Soc*. **2005**, 127, 7330;

[232] a) Chen. X, Goodhue. C. E, Yu. J.-Q, *J. Am. Chem. Soc*. **2006**, 128, 12634; b) Giri. R, Maugel. N, Li. J.-J, Wang. D.-H, Breazzano. S. P, L. B. Saunders, Yu. J.-Q, *J. Am. Chem. Soc.* **2007**, 129, 3510.

[233] Pastine. S. J, Gribkov. D. V, Sames. D, *J. Am. Chem. Soc*. **2006**, 128, 14220.

[234] (a) Hayashi, T., Togni, A., Eds. *Ferrocenes; VCH: Weinheim*, 1995. (b) Richards. C. J, Locke. A. J, *Tetrahedron: Asymmetry* **1998**, 9, 2377. (c) Dai. L.-X, Tu. T, You. S.-L, Deng. W.-P. Hou. X.-L, *Acc. Chem. Res*. **2003**, 36, 659. (d) Colacot, T. J. *Chem. Rev*. **2003**, 103, 3101. (e) Arraya´s. R. G, Adrio. J, Carretero. J. C, *Angew. Chem., Int. Ed*. **2006**, 45, 7674.

[235] Battelle. L. F, Bau. R, Gokel. G. W, Oyakawa. R. T, Ugi. I. K, *J. Am. Chem. Soc*. **1973**, 95, 482. (b) Gokel. G. W, Marquarding. D, Ugi. I. K, *J. Org. Chem*. **1972**, 37, 3052.

[236] Goa. D. W, Shi. Y. C, You., Shu-Li, *J. Am. Chem. Soc*. **2013**, 135, 86-89

[237] Ogasawara. M, Watanabe. S, Fan. L, Nakajima. K, Takahashi. T, *Organometallics* **2006**, 25, 5201.

[238] *Modern Arylation Methods*; Ackermann, L., Ed.; Wiley-VCH: Weinheim, Germany, 2009. (b) Alberico. D, Scott. M. E, Lautens. M, *Chem. Rev*. **2007**, 107, 174. (c) Ackermann. L, Vicente. R, Kapdi. A. R, *Angew. Chem., Int. Ed*. **2009**, 48, 9792. (d) Chen. X, Goodhue. C. E, Yu. J.-Q, *J. Am. Chem. Soc*. **2006**, 128,12634.

[239] Pi. C, Li. Y, Cui. X, Wu. Y, *Chem. Sci*., **2013**, 4, 2675-2679

[240] Zaitsev. V. G, Daugulis. O, *J. Am. Chem. Soc*., **2005**, 127, 4156

[241] Wu. J. L, Cui. X. L, Chen. L. M, Jiang. G. J, Wu. Y. J, *J. Am. Chem. Soc*., **2009**, 131, 13888; (b) Patureau. F, Glorius. F, *Angew. Chem., Int. Ed*., **2011**, 50, 1977.

[242] Ng. K. H, Chan. A. S. C, Yu. W. Y, *J. Am. Chem. Soc*., **2010**, 132, 12862.

[243] Tan. Y, Hartwig. J. F, *J. Am. Chem. Soc*., **2010**, 132, 3676.

[244] Guimond. N, Gouliara. C, Fagnou. K, *J. Am. Chem. Soc*., **2010**, 132, 6908.

[245] Zhang. H, Cui. X. L, Yao. X. N, Wang. H, Zhang. J. Y, Wu. Y. J, *Org. Lett*., **2012**, 14, 3012.

[246] Nomura. H, Richards. C. J, *Chem. Asian J*. **2010**, 5, 1726-1740

[247] Rausch. M. D, Genetti. R. A, *J. Org. Chem.,* Vol. 35, 11, **1970**, p 3888-3897

[248] Woodward. R. B, Rosenblum. M, Whiting. M. C, *J. Amer. Chem*. 74, 3458 **1952**

[249] Nesmeyanov. A. N, Kochetkova. N. S, *Dokl. Akad. Nauk. SSSR*, 109, 543, **1956**.

[250] Vogel. M, Rausch. M. D, Rosenberg. H, *J. Org. Chem.*, 22, 1016, **1957**.

[251] Schlögl. K, *Monatsh. Chem*., 88, 601, **1957**

[252] Rausoh. M. D, Vogel. M, Rosenberg. H, *J. Org. Chem*., 29, 900 **1957**.

[253] A. Nakamura and N. Hagihara, *Bull. Chem. Soc. Jap*., 84, 452, **1961**

[254] J. L. Boston, D. W. Sharpe, and G. Wilkinson, *J . Chem. Soc*., 3488, **1962**.

[255] A. J. Kresge, M, Dubeck, and H. C. Brown. *J . Org. Chem.,* 32, 745, 752, 756, **1967**.

[256] Cassar. D. J, Richards. C. J, *Chem. Eur. J*. **2013**, 19, 17951 - 17962

[257] Rausch. M. D, Genetti. R. A, *J. Org. Chem.,* Vol. 35, 11, **1970**, p 3888-3897

[258] Izumi. T, Maemura. M, Endoth. K, Oikawa. T, Zakozi. S, Kasahara. A, *Bull. Chem. Soc. Jpn*. **1981**, 54, 836.

[259] *The Pd-C Building Block of Palladacycles: A Cornerstone for Stoichiometric C-C and C-X Bond Assemblage*. in: Dupont. J, Pfeffer. M (Eds.), Palladacycles. Synthesis, characterisation and applications Wiley-VCH Verlag GmbH, Weinheim, **2008**, pp. 87-108.

[260] Dupont. J, Consorti. C.S, Spencer. J, *Chem. Rev.* 105 (**2005**) 2527-2571.

[261] Sokolov. V. I, Troitskay. L. L, Reutov. O. A, *J. Organomet. Chem*. 202 (**1980**) 58 - 60.

[262] L.L. Troitskaya, Z.A. Starikova, T.V. Demeshchik, V.I. Sokolov, *Russ. Chem. Bull*. 48 (**1999**) 1738-1743.

[263] Bolm. C, Wenz. K, Raabe. G, *J. Organomet. Chem*. 662 (**2002**) 23-33

[264] Stepanova. V. A, Dunina. V. V, Smoliakova. I. P, *Organometallics*. 28. (**2009**) 6546-6558.

[265] Liu. Y, Wang. X, Xu. J, Zhang. Q, Zhao. Y, Hu. Y, *Tetrahedron* 67 (**2011**) 6294 – 6299