Triaryl-like phosphines in gold and palladium catalysis

A dissertation for the degree of Doctor of Philosophy

by

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Declaration

All the work described within this dissertation was conducted in the chemistry laboratories of Newcastle University during the period of October 2010 – September 2013 and is original except where acknowledged by reference.

Acknowledgements

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Abbreviations

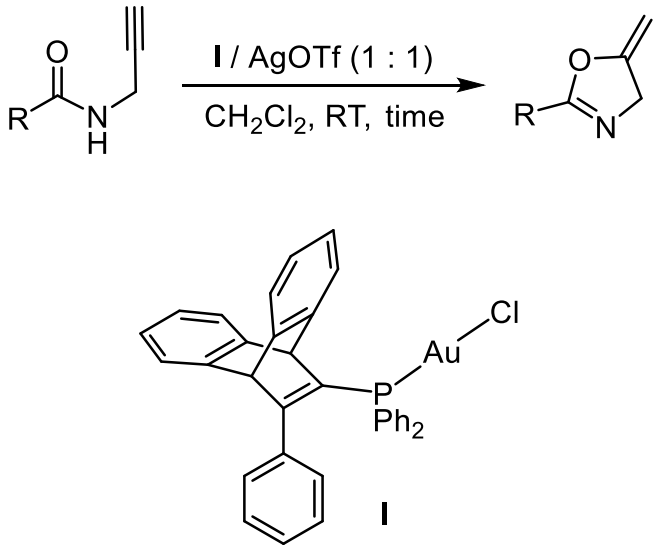
Ad	1-adamantyl
AgOAc	silver acetate
AgOTf	silver triflate (trifluoromethanesulphonate)
aq.	aqueous
Ar	aryl group
AuCl(tht)	gold (I) chloride tetrahydrothiophene
B_2pin_2	bis(pinacolato)diboron
BH_3. THF	borane tetrahydrofuran complex
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthalene
BINOL	1,1′-binaphthalene-2,2′-diol
BOX	2,2'-isopropylene bis[(4*S*)-4-*tert*-butyl-2-oxazoline]
BQ	1,4-benzoquinone
conc	concentrated
$Cu(OTf)_2$	copper(II) trifluoromethanesulfonate
Cy	cyclohexyl group (C_6H_{11})
CyMgCl	cyclohexylmagnesium chloride
Cyp	cyclopentene
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
decomp	decomposed
DIPA	*N*,*N*-diisopropylamine
DIPEA	*N*,*N*-diisopropylethylamine

DMAP	4-(dimethylamino)pyridine
dppp	1,3-bis(diphenylphosphino)propane
ee	enantiomeric excess
h	hour/s
IPr	*N*,*N*'-bis(2,6-diisopropylphenyl)imidazole-2-ylidene
in situ	in solution
IR	infrared spectroscopy
mes	mesityl group (2,4,6-trimethylbenzene)
MS	mass spectroscopy
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance spectroscopy
$Pd_2(dba)_3$	tris(dibenzylideneacetone)dipalladium(0)
Petrol	petroleum ether
PTSA	*para*-toluenesulphonic acid
py	pyridyl
pyr	pyrazole
RB	round bottomed flask
RT	room temperature
sat.	saturated aqueous solution
SM	Suzuki-Miyaura cross coupling
TAA	*tert*-amyl alcohol
THF	tetrahydrofuran

Abstract

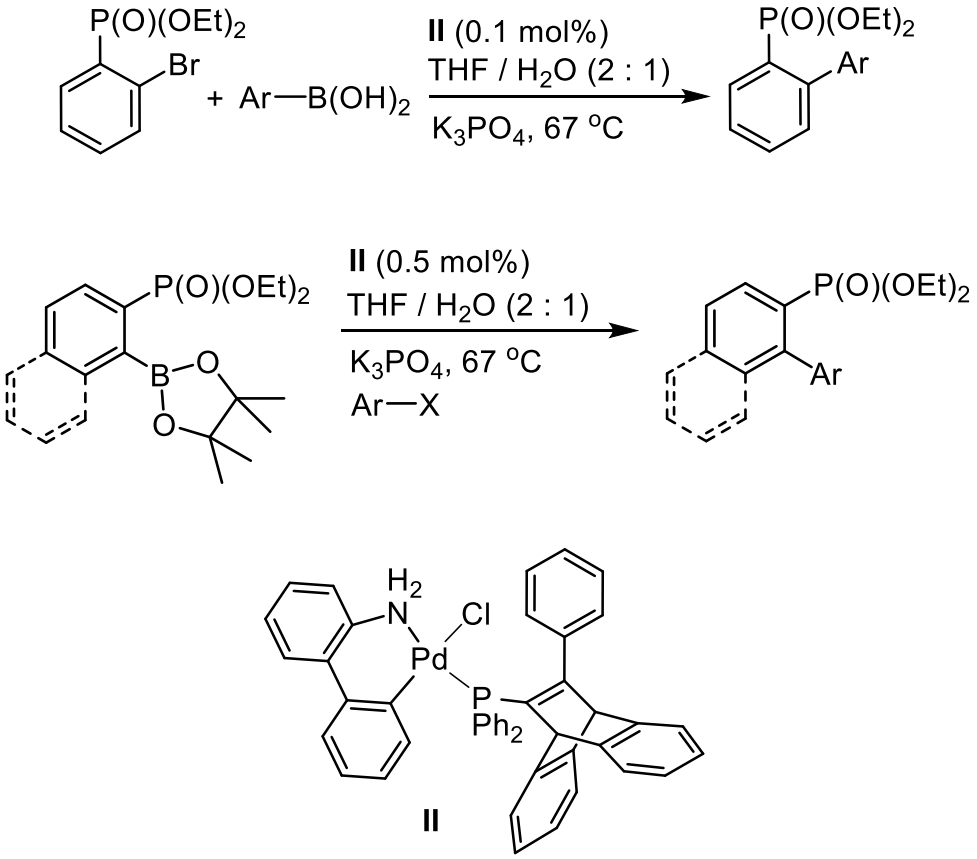
Bulky electron-rich phosphines have been extensively used for transition metal catalysis in organic synthesis to great success. In particular, cyclohexyl- and *tert*-butyl-substituted phosphines have been predominately used. Conversely, the use of less electron-rich phenyl-substituted phosphines has been largely overshadowed by their more electron-rich counterparts, with much of the current literature stipulating the need for electron-rich ligands. The Doherty-Knight group has recently demonstrated that complexes of phenyl-substituted KITPHOS phosphines outperform their more electron rich counterparts in gold-catalysed transformations. This project aimed to extend the range of available KITPHOS ligands and to elucidate the abilities of these triaryl-like phosphines in a range of catalytic processes.

In this thesis it has been demonstrated that these phosphines are highly efficient in the gold-catalysed cycloisomerisation of propargyl carboxamides to give methylene oxazolines (**scheme A**). Gold(I) complexes of these phosphines have also been shown to be highly effective in the cycloisomerisation of 2-[(2-alkynyl)phenyl]alcohols to isochromenes and capable of catalysing the formation of iminoisocoumarins exclusively from the relevant 2-(phenylethynyl)benzamides.



Scheme A. Gold-catalysed cycloisomerisation of propargyl carboxamides to give methylene oxazolines.

It has also been demonstrated that cyclopalladated pre-catalyst complexes bearing these KITPHOS phosphines are efficient in Suzuki-Miyaura cross coupling reactions involving a range of aryl- and heteroaryl bromides. These complexes are particularly effective in reactions involving either diethyl *o*-bromobenzenephosphonate or phenyl- and naphthylphosphonate-based boronic esters, giving excellent yields of the biaryl-phosphonate compounds using catalyst loadings of 0.1 – 2.0 mol% (**scheme B**).

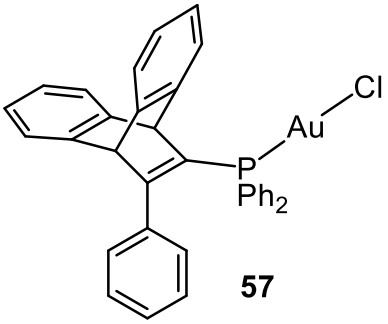


Scheme B. Suzuki-Miyaura cross coupling reactions involving arylphosphonates.

It has also been demonstrated that the phenyl-substituted KITPHOS phosphine complex **II** was remarkably more effective in the ethoxycarbonylation of styrene, than its cyclohexyl-substituted counterpart.

Summary of catalyst complexes

Gold(I) chloride complexes



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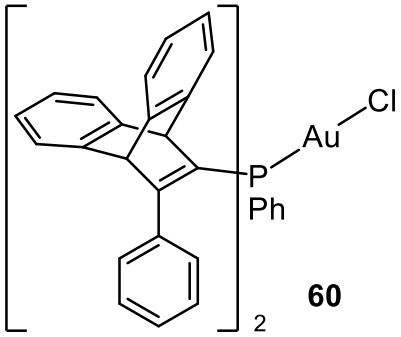

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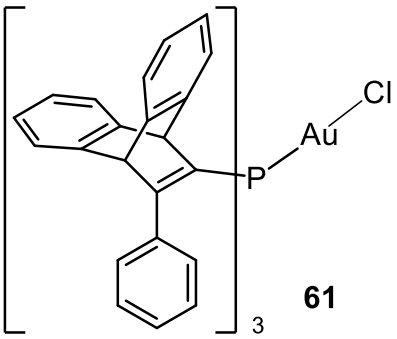

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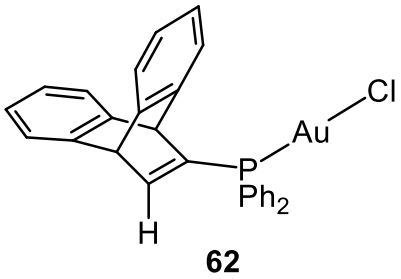

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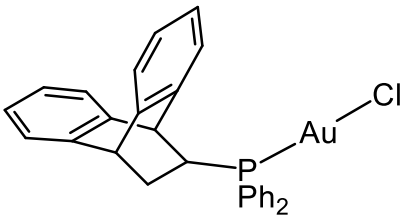

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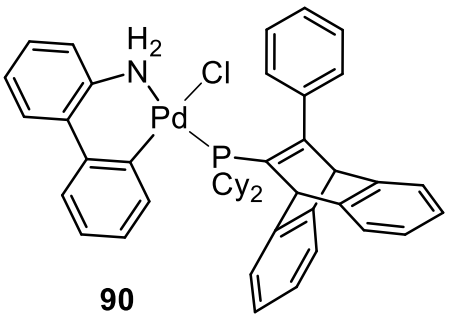
2-Phenylaniline-based palladium pre-catalysts



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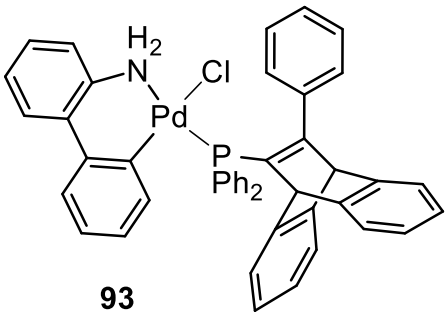

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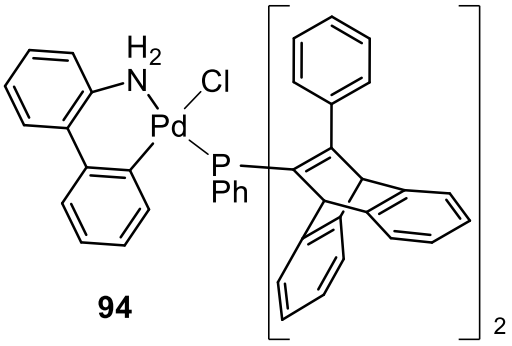

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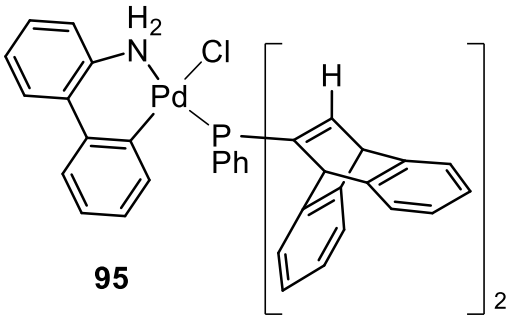

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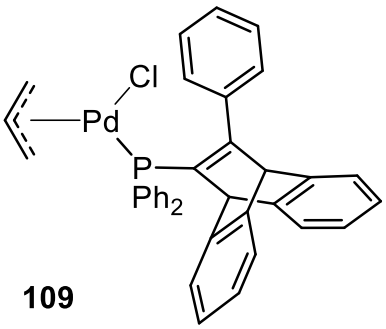
Allylpalladium-based pre-catalysts



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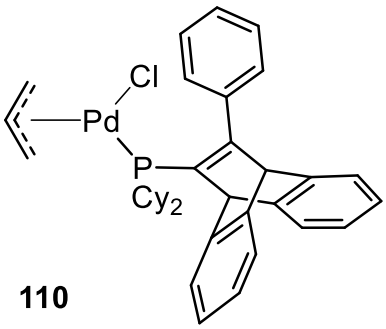

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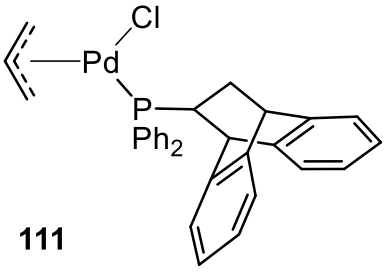

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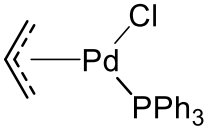

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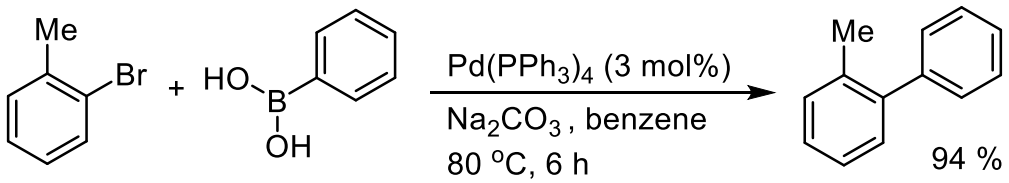
Chapter 1. Ligand development for catalysis reactions and the introduction of KITPHOS monophosphines

1.1 Advancements in ligand design

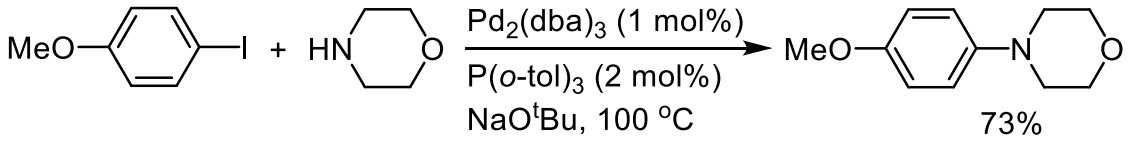
The success of organic synthesis today depends on the ability to form new C-C and C-heteroatom bonds. This success has been significantly enhanced by the use of a wide range of transition metal-catalysed bond-forming transformations. In particular, the use of phosphine-ligated transition metal complexes has proven instrumental, by increasing the efficiency of these reactions as well as opening up new transformations not accessible using simple metal salts. Advancements in the design of phosphines have allowed these transformations to be performed with greater yields, quicker reaction times and under milder conditions. One of the greatest impacts that phosphines have had is in palladium catalysis.[1]

To date there has been a huge number of different ligands used in palladium-catalysed reactions, displaying a wide range of success. The progression in ligand design for these reactions has typically followed the same general trend, starting with triarylphosphine-ligated catalysts such as $Pd(PPh_3)_4$ and $PdCl_2(PPh_3)_2$. One of the most influential discoveries was identified by Suzuki in 1981 who reported the palladium-catalysed cross coupling of an aryl halide with an aryl boronic acid to form biaryl compounds.[2] At the time, the palladium-catalysed synthesis of new C-C bonds was restricted to the use of either aryl magnesium or aryl zinc complexes.[3] These Suzuki-Miyaura cross coupling reactions used $Pd(PPh_3)_4$ to catalyse the coupling of, for example, 2-bromotoluene with benzeneboronic acid using the base Na_2CO_3 at 80 ^oC to give the biaryl product in 94% yield (**scheme 1**).



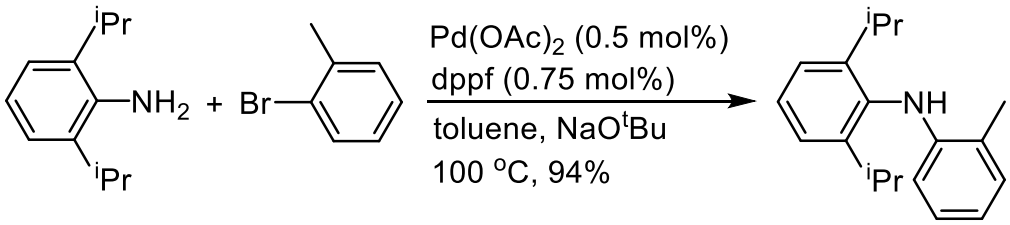
Scheme 1. Suzuki-Miyaura cross coupling reaction of 2-bromotoluene with benzeneboronic acid.

Buchwald then later demonstrated the first palladium-catalysed amination reactions, which coupled aryl bromides and iodides with aryl / alkyl amines in good yield using tri(*o*-tolyl)phosphine.[4] This negated the use of aminostannanes which were not only toxic, but also led to complications in the work-up and purification of the products from the crude reaction mixtures.[5] The emergence of this efficient C-N bond forming reaction has been of great significance in the synthesis of pharmaceuticals, natural products and biologically important molecules. **Scheme 2** shows the coupling of 4-iodoanisole with morpholine, which gave the product in 73% yield using $Pd_2(dba)_3$ (1 mol%), tri(*o*-tolyl)phosphine (2 mol%) and NaO^tBu at 100 °C.[6]

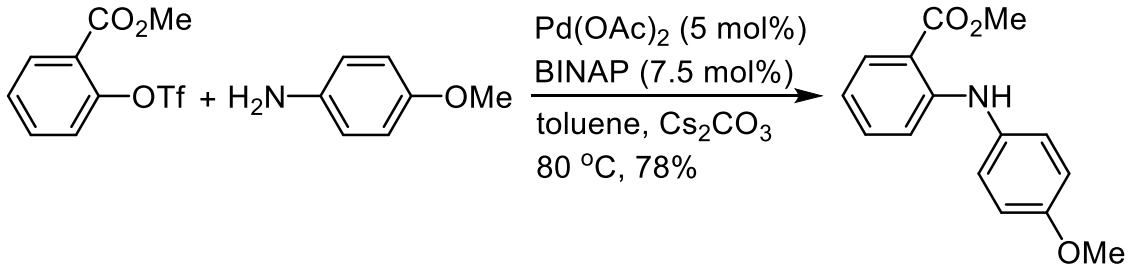


Scheme 2. The palladium-catalysed amination of 4-iodoanisole with morpholine.

It was then shown that diphosphines such as BINAP and dppf were more successful than these simple triarylphosphines, particularly for the coupling of more sterically hindered aryl bromides (**scheme 3**) as well as electronically less reactive aryl triflates (**scheme 4**).[7]

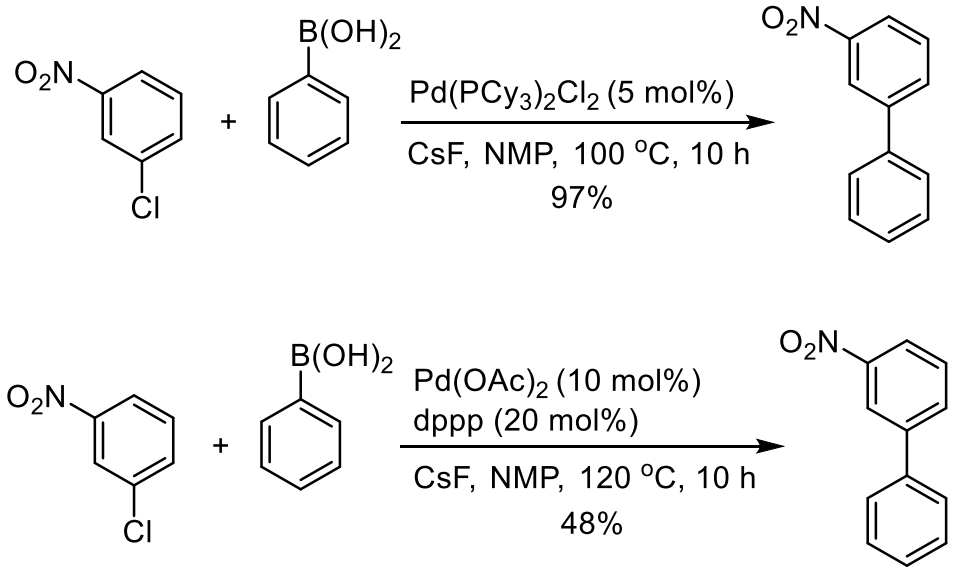


Scheme 3. Palladium-catalysed aminations of hindered aryl bromides can be achieved using diphosphines such as dppf.



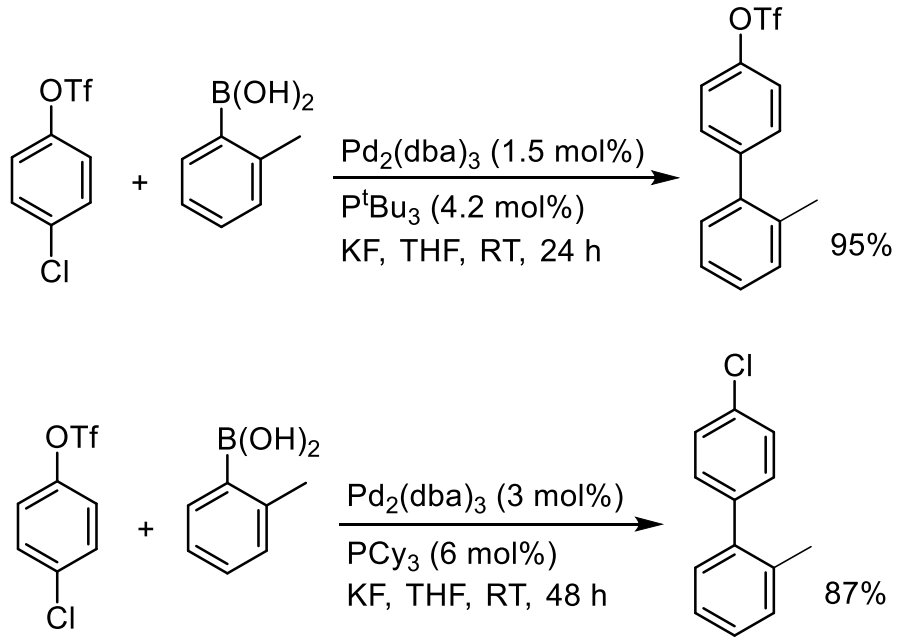
Scheme 4. Palladium-catalysed aminations of aryl triflates can be achieved using BINAP.

These catalysts were sufficient to couple aryl iodides, bromides and even some triflates, however aryl chlorides proved to be a tougher ask. Wang first demonstrated that the electron-rich trialkylphosphine PCy_3 outperformed a range of diphosphines such as dppf and dppp as well as the triarylphosphines PPh_3 and P(*o*-tol)$_3$ in Suzuki-Miyaura cross coupling reactions (SM reactions) of a range of aryl chlorides with phenylboronic acid.[8] $PdCl_2(PPh_3)_2$ was only sufficient when the aryl chloride possessed two strongly electron-withdrawing groups. Wang illustrated that $PdCl_2(PCy_3)_2$ catalysed the reaction with 1-chloro-3-nitrobenzene, using a catalyst loading of 5 mol% to give the product in 97% yield after 10 h at 100 ^oC (**scheme 5**). The diphosphine dppp on the other hand required a much higher catalyst loading of $Pd(OAc)_2$ (10 mol%) and dppp (20 mol%) as well as the higher temperature of 120 ^oC to afford the product in 48% yield.[8] This is one of many examples which demonstrate the advantage of using a trialkylphosphine-ligated catalyst over that of triaryl and diphosphines.



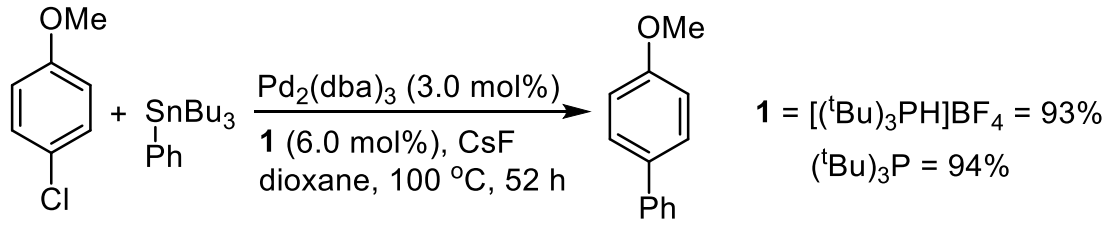
Scheme 5. Trialkylphosphines are significantly more active than both triarylphosphines and diphosphines in SM reactions involving aryl chlorides.

This discovery had a significant impact on ligand design for palladium catalysis due to the industrial need to use commercially available, relatively inexpensive aryl chlorides over the corresponding aryl bromides and iodides. This drive led to the pursuit and use of other electron-rich catalysts. More electron-rich phosphines were seen to increase the basicity at the metal centre, increasing the rate of oxidative addition and so enabling a more facile insertion of the metal centre into C-X bonds.[9] In particular, the electron-rich and sterically bulky P^tBu_3 has proven to be remarkably effective in catalysing both Suzuki-Miyaura cross coupling reactions and amination reactions involving unactivated aryl chlorides.[10] Interestingly however, for sterically hindered aryl chlorides PCy_3 proved to be significantly better, due to its decreased bulk yet electron-rich nature. This effect is echoed in the inability of P^tBu_3 to perform Suzuki-Miyaura cross coupling reactions with aryl triflates. Although aryl triflates are decidedly more reactive than the corresponding aryl chlorides, the bulk of the triflate group combined with the bulk of P^tBu_3 effectively inhibits insertion of the palladium catalyst into the C-O bond of the triflate. This difference in chemoselectivity was shown in the reaction between *o*-tolylboronic acid and 4-chlorophenyl trifluoromethanesulphonate. P^tBu_3 gave 4-trifluoromethanesulphonyloxy-2-methylbiphenyl in 95% yield whereas PCy_3 gave 4'-chloro-2-methylbiphenyl in 87% yield (**scheme 6**).[10a]



Scheme 6. The difference in chemoselectivity displayed in the SM reaction between *o*-tolylboronic acid with 4-chlorophenyl trifluoromethanesulphonate, using P^tBu_3 and PCy_3.

In addition to the Suzuki-Miyaura cross coupling reaction, trialkylphosphine catalysts have proven to be successful in many other C-C and C-N bond forming reactions such as Negishi,[11] Hiyama[12] and Sonogashira[13] cross coupling reactions. However they do possess drawbacks, the most significant being the innate sensitivity of these phosphines towards air and moisture. P^tBu_3 is an oil which is highly sensitive to air and moisture and so measuring out the minute quantities needed for a catalytic reaction is far from ideal, even through the use of serial dilutions. One solution to this was the generation of air stable phosphonium or phosphine salts of these trialkylphosphines. Fu demonstrated that trialkylphosphonium salts such as $[(^tBu)_3PH]BF_4$, **1** can act as direct replacements in a range of Suzuki-Miyaura and Stille cross coupling reactions as well as Heck reactions; giving similar yields to that of their phosphine counterparts (**scheme 7**).[14] These phosphonium salts can be easily synthesised in near quanititative yield and are stable with respect to long term storage; with no observed decomposition after four months and even after heating to 120 ^oC for 24 h in air. [14] This also allowed reactions to be performed in aqueous environments.[15]



Scheme 7. Stille coupling reaction using $[(^tBu)_3PH]BF_4$, **1**.

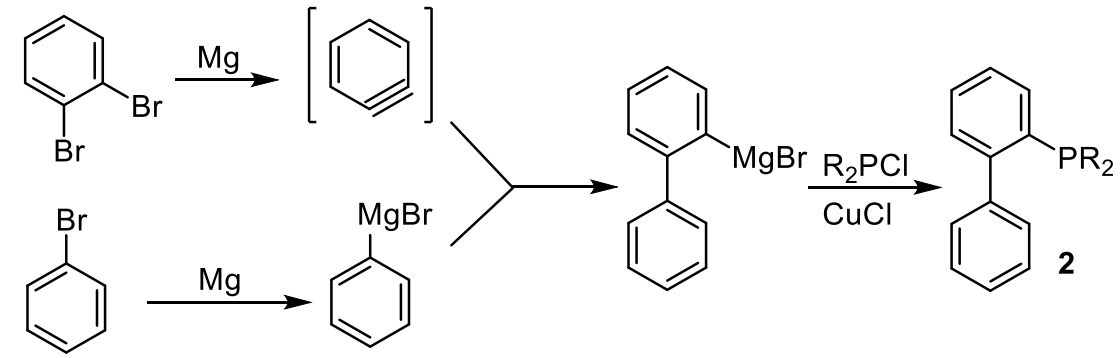
However it was the advent of dialkylbiarylphosphines which solved the oxidative instability issue due to the high stability towards air, moisture and heat demonstrated by these phosphines. Their design allows for huge variability and facile modification of the steric and electronic properties. This ability to systematically refine the properties of the phosphines allows for specific fine-tuning, giving rise to a number of highly efficient ligand architectures for a whole range of transformations. This versatility has led to dialkylbiarylphosphines being the most widespread ligands used in transition metal-catalysed cross coupling reactions.

1.1.1 Dialkylbiarylphosphines

Dialkylbiarylphosphines were first designed by Buchwald in 1997 and are still to this day the ligand of choice for many transition metal-catalysed transformations. They have proven to be efficient in the catalysis of many reactions, including Suzuki-Miyaura,[16] Negishi,[17] Kumada,[18] Sonogashira[19] and Hiyama[12] cross couplings as well as in aminations,[20] etherifications[21] and Heck[22] reactions. They have also been shown to have industrial uses and applications.[23]

Dialkylbiarylphosphines are not only extremely useful ligands in catalysis, particularly in palladium catalysis, but they are also simple to synthesise. A whole range of dialkylbiarylphosphines with various steric and electronic properties can be made in a one pot reaction through the addition of an aryl Grignard reagent to a benzyne intermediate generated *in situ*. This, in the presence of excess magnesium gives a

biphenyl Grignard species which is then trapped using a chlorodialkylphosphine and a catalytic amount of CuCl to give the desired dialkylbiarylphosphine (**2**) in good to excellent yield (**scheme 8**).[24]



Scheme 8. Synthesis of dialkylbiarylphosphines.

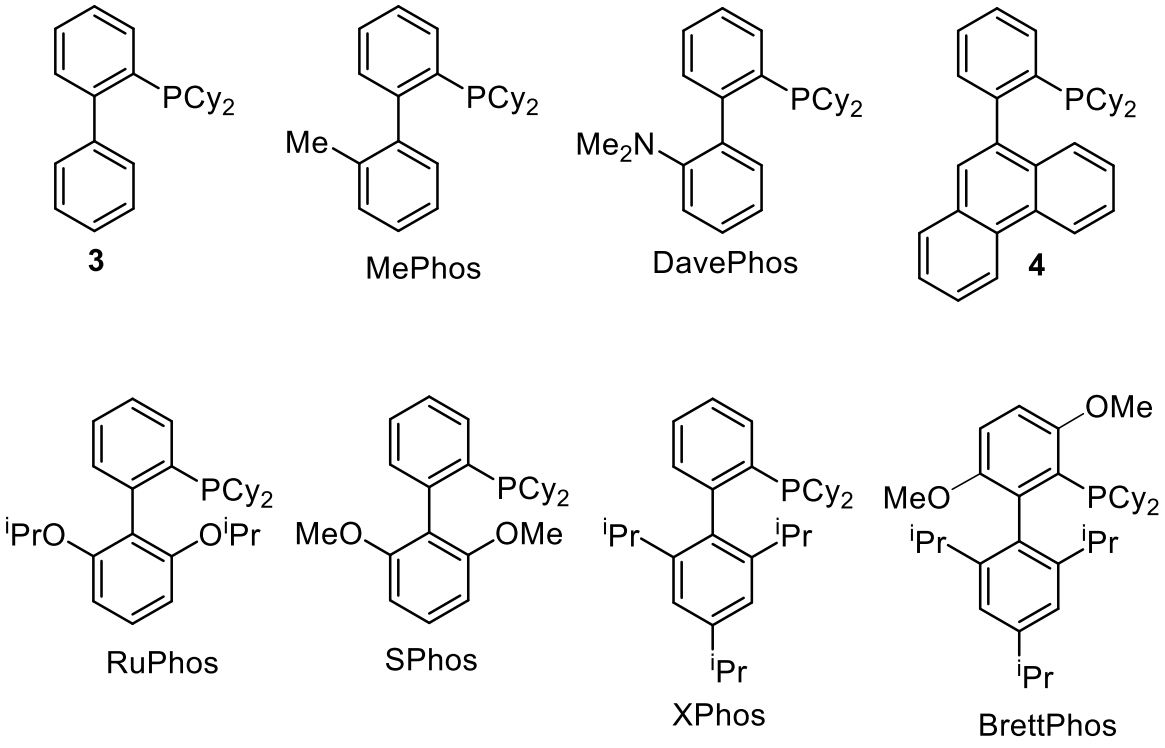
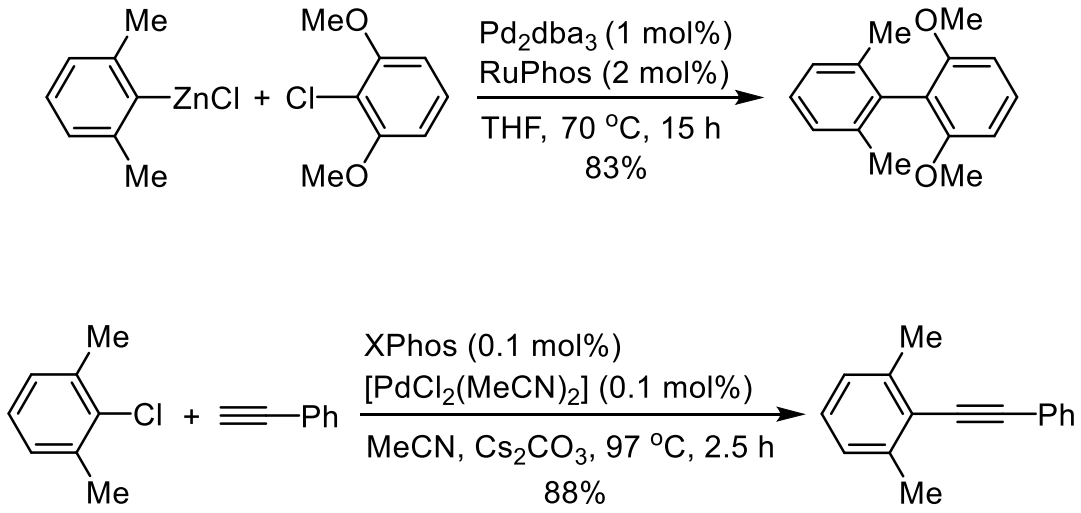


Figure 1. A collection of dialkylbiarylphosphines, successfully used in catalysis.

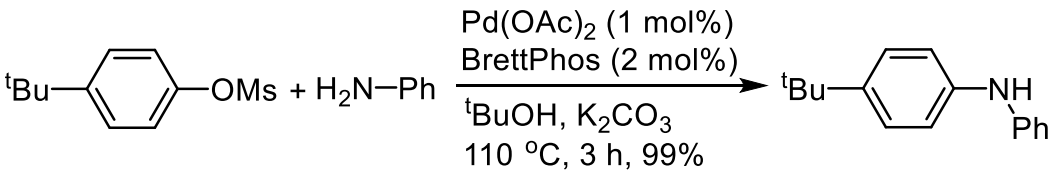
The structures of a number of dialkylbiarylphosphines are shown above, each exhibiting highly efficient catalysis (**figure 1**). These bulky, electron-rich phosphines favour the formation of the catalytically active mono-coordinate [L_nPd^0] species in solution, making them highly reactive. The high reactivity displayed by dialkylbiarylphosphines allows for reactions to take place under mild conditions, even for the most difficult substrates. For instance the Negishi reaction of the highly hindered combination of 2,6-dimethylphenylzinc chloride with 1-chloro-2,6-dimethoxybenzene gave the biaryl product in 83% yield using RuPhos (2 mol%).[17] Also the Sonogashira cross coupling reaction of 2-chloro-*m*-xylene with phenylacetylene required a catalyst loading of only 0.1 mol% to afford the product in 88% yield after stirring for 2.5 h at 97 °C (**scheme 9**).[19]



Scheme 9. Negishi and Sonogashira cross coupling reactions using dialkylbiarylphosphines.

Dialkylbiarylphosphines are also particularly efficient ligands for amination reactions, showing excellent yields for even the most hindered and deactivated substrate combinations. Buchwald has written a comprehensive review of dialkylbiarylphosphines in amination reactions, outlining either the choice ligand or at least one which is particularly efficient for each type of amination reaction.[20] One such example is the reaction of 4-*tert*-butylphenyl methanesulphonate with aniline

which produced the product in 99% yield after 3 h at 110 °C using BrettPhos (2 mol%) (**scheme 10**). This is a highly challenging transformation due to the inherent difficulty associated with coupling mesylates.[20]



Scheme 10. The reaction of 4-*tert*-butylphenyl methanesulphonate with aniline proceeds with relative ease on using BrettPhos.

1.1.2 Properties of dialkylbiarylphosphines

Since the initial discovery by Buchwald,[25] a number of investigations have been performed in an effort to subtly fine-tune the properties of these phosphines. **Figure 2** below shows the structure of a typical Buchwald dialkylbiarylphosphine with its relevant features highlighted in differing colours.

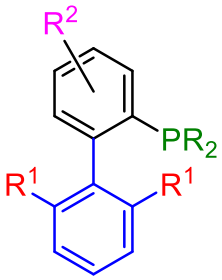


Figure 2. The structure of a dialkylbiarylphosphine designed by Buchwald.

The dialkyl part of the phosphine refers to the two alkyl groups (R) attached to the phosphorus centre, which are most commonly cyclohexyl (Cy) or *tert*-butyl (^{t}Bu)

groups. These groups, highlighted in green in **figure 2**, are electron-donating and so act to increase the electron-density at the phosphorus atom, favouring oxidative addition. The bulk of these groups is also reported to favour the formation of the catalytically active monoligated [LPd^0] species in palladium catalysis and so increase the rate of catalyst activation and reductive elimination.[26]

The presence of the lower aryl ring (blue in **figure 2**) enhances the stability of the resulting metal-coordinated phosphine species as well as the intermediate species in the catalytic cycle through the formation of η^n-interactions between the metal centre and the atoms of the lower aryl ring (usually *ipso* / *o*-C-atoms).[27] DFT studies have shown that these Pd-arene interactions, such as the one shown in **figure 3**, actually aid in both the oxidative addition and the reductive elimination steps of the catalytic cycle.[26, 28]

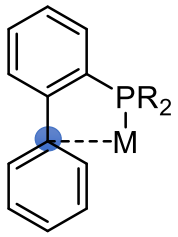


Figure 3. An example of η^1-interactions between a metal centre (M) and the *ipso*-C-atom of the lower aryl ring of a dialkylbiarylphosphine.

The presence of two groups (R^1) in the *ortho*-position of the lower aryl ring (red in **figure 2**) help to prevent cyclometalation and thus the formation of palladacycles, which are known to be responsible for catalyst deactivation.[29] Further, these groups enhance the stability of the overall catalyst complex if they contain a heteroatom such as OMe, through favourable interactions between the metal centre and the O-atoms of these groups.[30] Thus, the presence of these groups such as OMe leads to an increase in the activity and longevity of the catalyst.

Lastly, substituents (R^2) on the upper aryl ring of the biaryl architecture (pink in **figure 2**) have been shown to enhance the reductive elimination step of the catalytic cycle by fixing the conformation of the active catalyst species in solution.[21] The

properties of these dialkylbiarylphosphines have allowed excellent catalytic activity for various transformations to be exhibited over a broad range of substrates.

1.1.3 Other dialkylbiarylphosphines

The successes of these dialkylbiarylphosphines led to others to develop structurally similar motifs (**Figure 4**). Each example below possesses the biaryl structural unit indicative of Buchwald's ligands, with bulky electron-rich substituents on the phosphorus centre (Cy, ^{t}Bu or Ad).

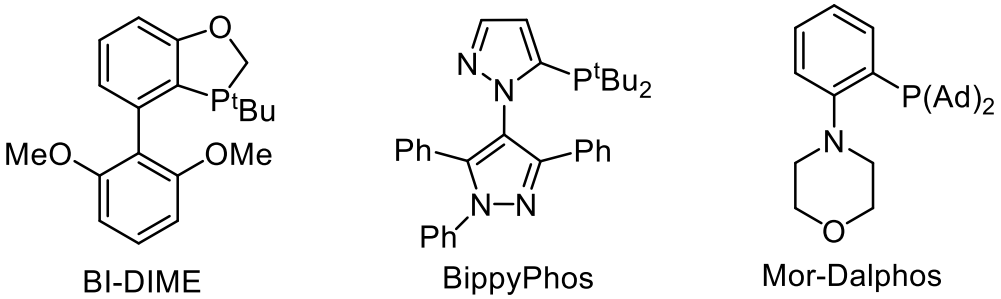


Figure 4. Phosphine ligands descended from Buchwald's dialkylbiarylphosphines.

Tang developed BI-DIME, an oxaphosphole ligand which has proven to be successful in Suzuki-Miyaura cross coupling reactions.[31] BippyPhos, designed by Singer, has proven to be efficient in Suzuki-Miyaura and ether cross coupling reactions as well as amination reactions.[32] Straddiato's Mor-Dalphos has shown success in aminations[33] as well as ammonia arylation reactions.[34] Arguably the most successful of these dialkylbiarylphosphines however, are the CataCXium family of phosphines, particularly PAP, as well as indolyl-based phosphines such as CM Phos, shown in **figure 5**.

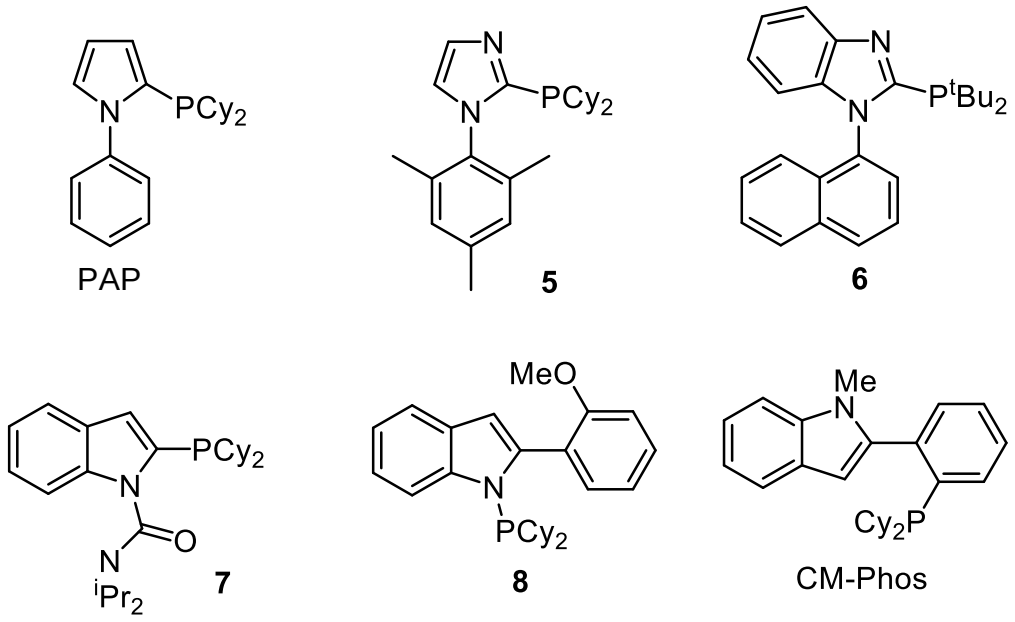
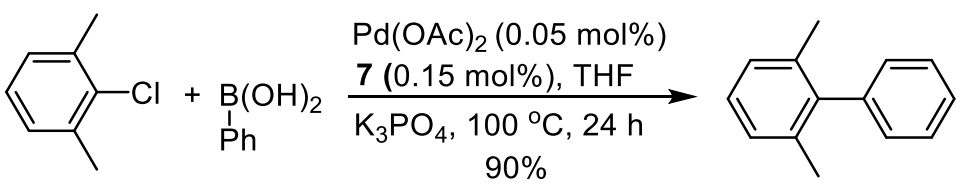


Figure 5. CataCXium and indolyl-based phosphine ligands.

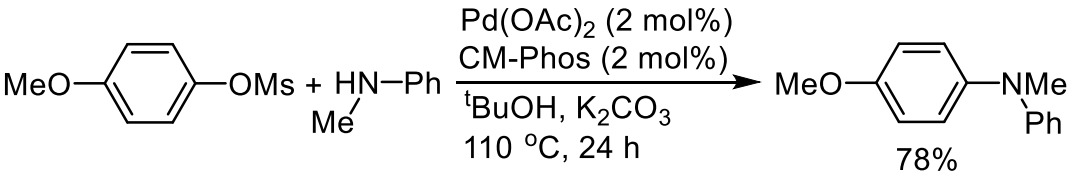
First developed by Beller, the phosphine-substituted *N*-aryl pyrrole ligand PAP took advantage of its dialkylbiarylphosphine architecture to exhibit excellent results with aryl chlorides in both amination reactions and Suzuki-Miyaura cross coupling reactions.[35] This group then explored the use of *N*-aryl-2-(dialkylphosphino)imidazole **5** and *N*-aryl-2-(dialkylphosphino)benzimidazoles **6** which also exhibited excellent catalytic activity.[36]

Kwong then recognised that further enhancement in the activity of these catalysts could be achieved through the incorporation of weakly coordinating O-atom of the methoxyl group in **8** [37] and the O-atom in the carbonyl of the urea functionality of **7**.[38] Kwong postulated that these hemilabile indolyl-based P,O ligands aid in the stabilisation of the metal and are particularly useful for transformations involving highly hindered substrates, such as that depicted in **scheme 11** using **7**.[38]

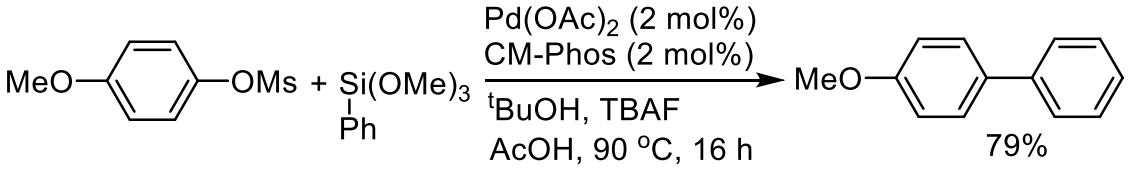


Scheme 11. SM reaction of 1-chloro-2,6-dimethylbenzene with benzeneboronic acid using **7**.

Kwong then developed CM-Phos, which is extremely efficient in Suzuki-Miyaura[39] and Hiyama cross coupling reactions[40] as well as amination reactions.[41] This ligand is responsible for the first reported palladium-catalysed transformation involving unactivated and sterically hindered mesylates. This discovery was of particular importance as mesylates are easily accessible from phenols and owing to their low molecular weight, are markedly more atom economical than the corresponding tosylates and triflates. However, mesylates are much less reactive than both tosylates and triflates and so the amination of 4-methoxyphenyl methanesulphonate with *N*-methylaniline to afford the product in 78% yield using CM-Phos (2 mol%) was an excellent result (**scheme 12**). CM-Phos has also been shown to be effective in Hiyama cross coupling reactions involving aryl mesylates, such as in the reaction between the unactivated 4-methoxyphenyl methanesulphonate and (trimethoxy)phenylsilane (**scheme 13**).[40]



Scheme 12. Palladium-catalysed amination of an aryl mesylate using CM-Phos.



Scheme 13. Palladium-catalysed Hiyama coupling of an aryl mesylate using CM-Phos.

1.1.4 N-Heterocyclic carbenes (NHC)

N-heterocyclic carbenes have proved to be highly efficient ligands in a vast array of transformations.[42] The most commonly used NHCs in catalysis possess a 5 membered ring azole unit with aryl substituents attached to each of the N-atoms. A whole range of NHCs with symmetrical and unsymmetrical substituent groups have been constructed, however the most prevalent in catalysis are the imidazolylidene-based **9**, **11** and **12** as well as the imidazolinylidene-based **10** (**figure 6**).[9, 43]

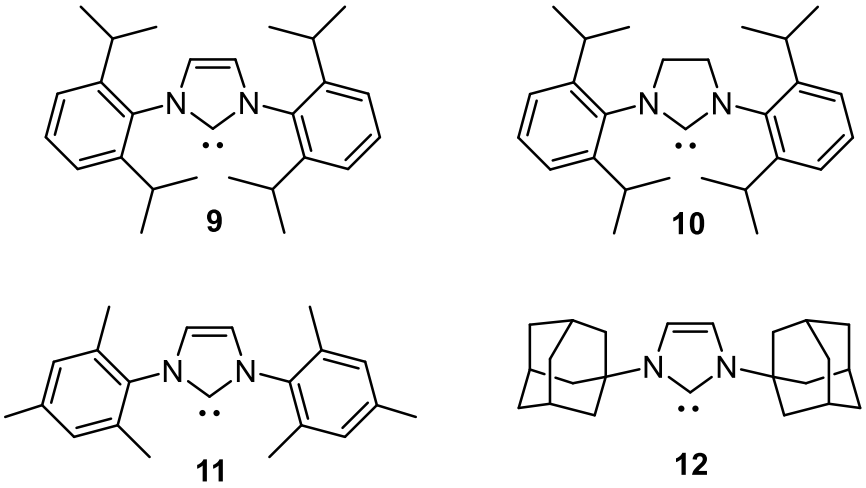


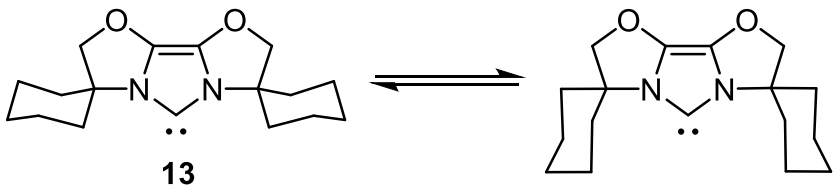
Figure 6. The structures of highly successful *N*-heterocyclic carbenes in the present literature.

NHCs are highly electron-rich ligands due to the lone pair of electrons positioned on the carbene carbon atom and as such are highly sensitive towards air and moisture. This means that their synthesis requires rigorously anhydrous conditions under nitrogen. This property has meant that NHCs are normally converted and stored in their azolium salt form and liberated through the simple treatment with a base.[44] NHCs are powerful neutral two electron donors which form particularly strong single bonds to a metal centre on coordination. In fact they are stronger σ-donors than phosphines and so form particularly stable catalysts, minimising degradation through ligand dissociation from the metal.[9] Thus NHCs can also be successfully stored for long periods of time on

complexation with a metal. This strong σ-donor ability enables palladium complexes of NHC to be highly accomplished in activating electron-deficient aryl and alkyl chlorides towards oxidative addition.[42]

In particular, bulky NHCs have been used to great effect in catalysis, as not only does this steric demand help stabilise the carbene, especially for the imidazolinylidene-based **10**, but it also provides a sterically controlled environment around a coordinated metal. This steric effect is significantly more pronounced in NHCs as their groups have been shown to encompass the metal centre as opposed to phosphine groups, which point away. This ensures the substituents on NHCs have a much greater impact on catalysis than those on phosphines.[42] The electronic properties of NHCs however, vary little in comparsion to those of phosphines with even NHCs bearing strongly electron-withdrawing groups still being electron-rich. Thus the main source of variability in NHCs is in their steric properties.

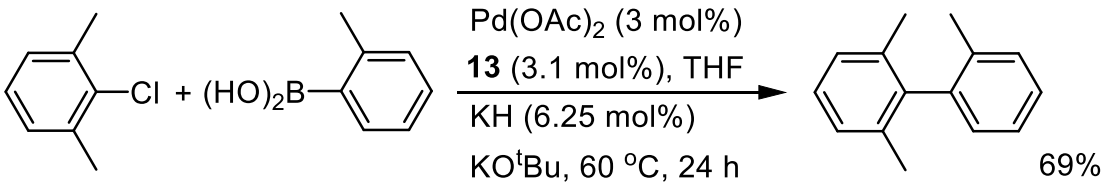
It was noticed by Glorius that despite the strongly electron-rich character of NHCs, the large steric bulk in their substituents which aids in reductive elimination, actually impedes the oxidative addition and transmetalation steps of the catalytic cycle, especially in reactions involving hindered substrates.[45] A solution to this was to construct the NHC **13** which possesses flexible steric bulk. Ring inversion of the cyclohexyl groups in **13** reduces the steric effect around the metal centre (**scheme 14**).[45]



13

Scheme 14. The interconversion between the conformers of the *N*-heterocyclic carbene **13**.

Ligand **13** is actually a weaker σ-donor than **12** due to the electron-withdrawing effect of the O-atoms. However, this flexible bulk allowed for the cross coupling of 1-chloro-2,6-dimethylbenzene with 2-methylphenylboronic acid to give the highly hindered biaryl product in 69% yield using **13** (3.1 mol%) (**scheme 15**).[45]



Scheme 15. *N*-heterocyclic carbenes with flexible bulk can couple highly hindered substrate combinations.

1.1.5 Ferrocenyl-based phosphine ligands

There has been a significant and ongoing interest in ferrocenyl-based phosphine ligands for palladium-catalysed transformations, with an evolution separate to that of other classes of phosphines but just as significant starting from the diphosphine dppf.[46] Some of the most successful of these are shown in **figure 7**.

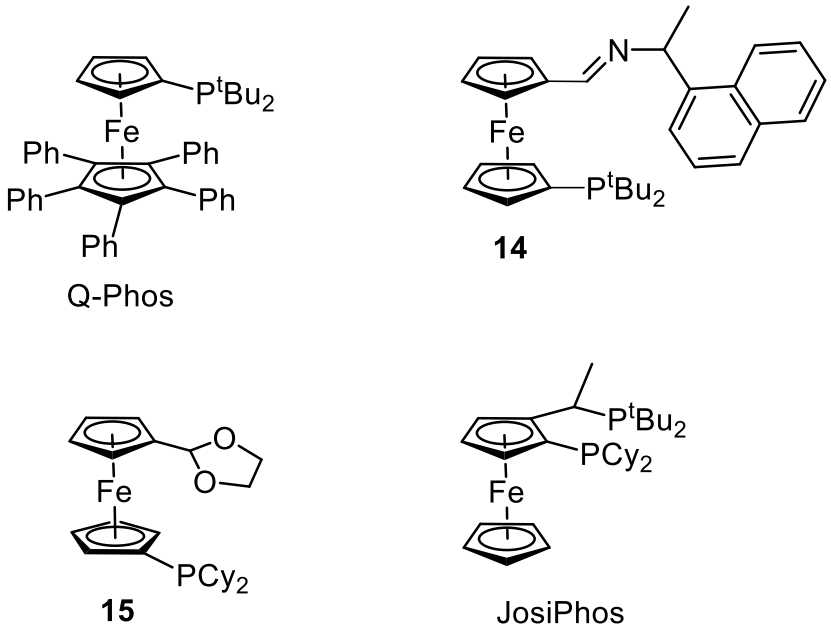
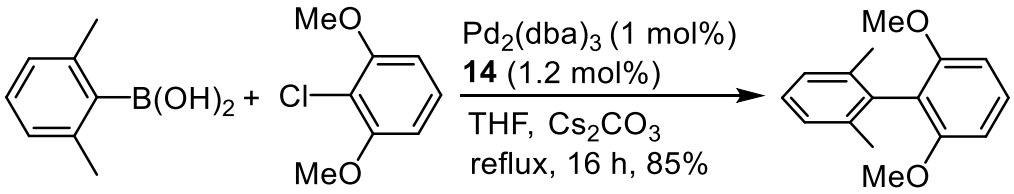


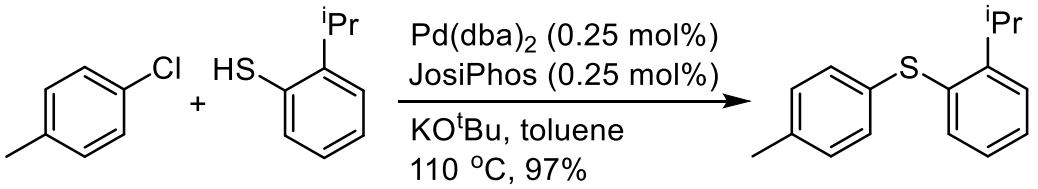
Figure 7. Ferrocenyl-based phosphines successfully used as ligands in palladium-catalysed coupling reactions.

Q-Phos has been used effectively in a vast array of transformations, giving good results in the coupling of hindered and unactivated aryl halides with alkylboronic acids.[14a, 47] Further enhancement has been achieved by synthesising ferrocenyl P,O and P,N ligands which incorporate both a strongly coordinating phosphine group as well as weakly coordinating heteroatom containing group, as previously seen in the indolyl-based phosphine ligands **7** and **8** (Chapter 1, section 1.1.3). In phosphine **14**, the N-atom of the imine group weakly coordinates to the metal giving a P,N ligand,[48] whilst in phosphine **15** either of the O-atoms weakly coordinates giving a P,O ligand.[49] The observed enhanced efficiency over monodentate ligands such as Q-Phos and chelating bidentate ligands such as dppf is due to the hemilability of this weakly coordinating group. It is proposed that this hemilability allows the phosphine to alternate its binding to the metal between the monodentate and chelated forms to maximise the stabilisation in the intermediates of the catalytic cycle.[48-49] This enhanced ligand design allows for highly efficient Suzuki-Miyaura cross coupling reactions between very hindered coupling partners (**scheme 16**).[48]



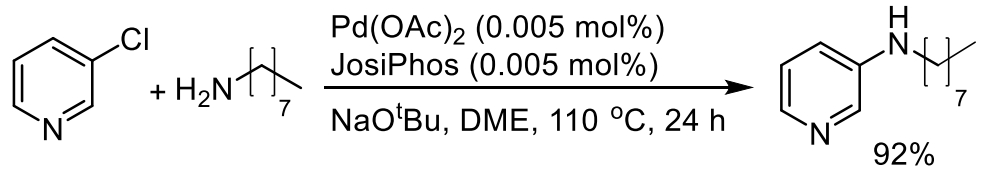
Scheme 16. Phosphine **14** has proven to be highly successful in palladium-catalysed Suzuki-Miyaura cross coupling reactions involving highly hindered substrates.

The P,P ligands of JosiPhos have also proven to be highly effective in catalysis, with excellent activities towards alkoxycarbonylations of aryl chlorides shown.[50] JosiePhos is also particularly active in C-S bond forming reactions of aryl chlorides with thiols, allowing high conversions even at very low catalyst loadings.[51] In the reaction of 4-chlorotoluene with 2-isopropylbenzenethiol, a catalyst loading of 0.25 mol% was sufficient to give the thiol ether product in 97% yield (**scheme 17**).



Scheme 17. The reaction of 4-chlorotoluene with 2-isopropylbenzenethiol using JosiPhos.

However the greatest impact of this catalyst is displayed in its ability to successfully perform a wide range of amination reactions at very low catalytic loadings. In a study by Hartwig, JosiPhos successfully performed the reaction of 3-chloropyridine with octylamine, using a catalyst loading of only 0.005 mol% to afford the product in 92% yield (**scheme 18**).[52]



Scheme 18. Amination reactions can be successfully performed at very low catalytic loadings using JosiPhos.

1.2 KITPHOS monophosphines

The Doherty-Knight research group have developed the KITPHOS monophosphine, which retains the biaryl-like architecture and the bulky electron-rich substituent groups characteristic of the dialkylbiarylphosphines. KITPHOS monophosphines have proven to be highly successful ligands in a range of palladium,

gold and ruthenium catalysed transformations. **Figure 8** shows a range of KITPHOS monophosphines successfully used in catalysis.

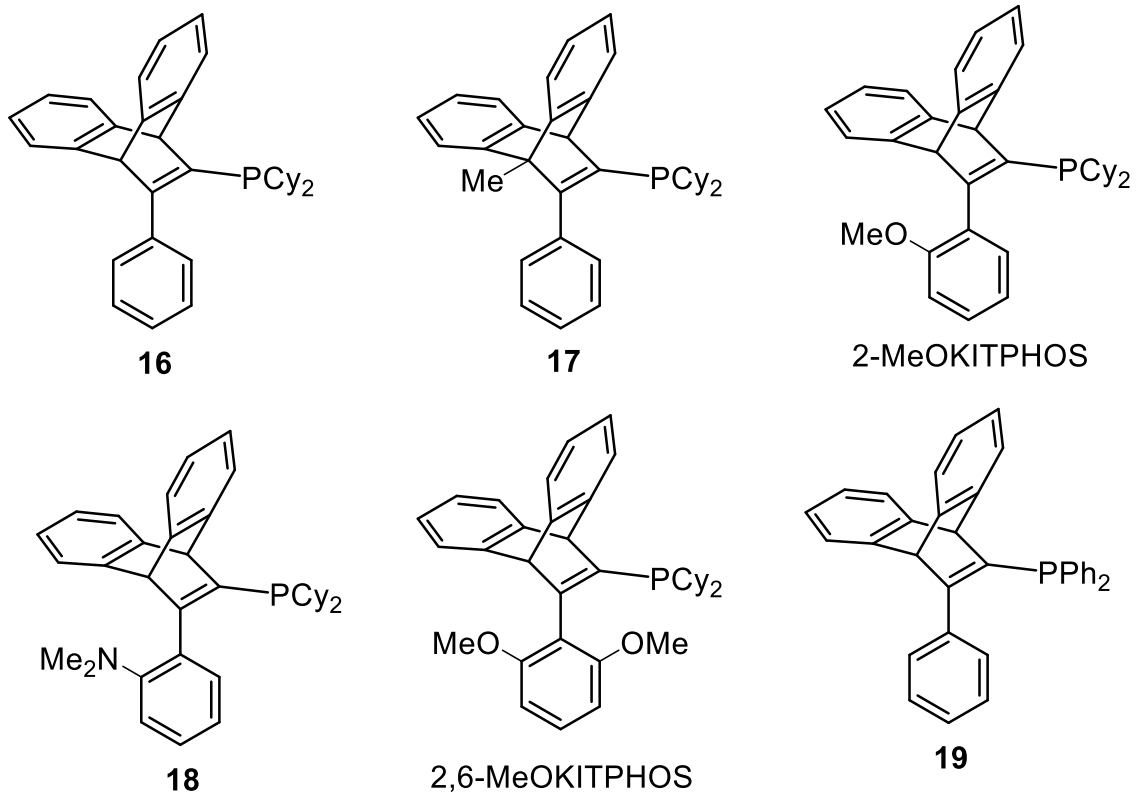
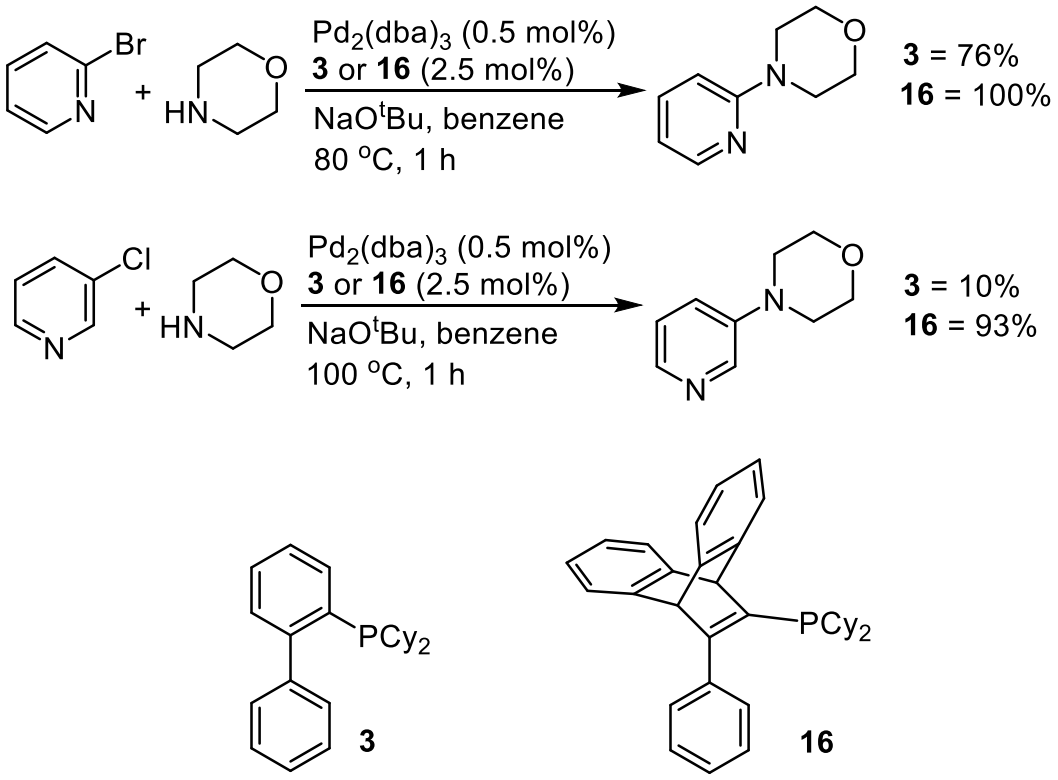


Figure 8. A range of KITPHOS monophosphines.

The characteristic structural framework associated with KITPHOS is the anthracenyl bridge which can further be modified to include a methyl group in the 9-position for added bulk, as shown in **17**.[53] The KITPHOS monophosphines, 2-MeOKITPHOS, **18** and 2,6-MeOKITPHOS bearing *ortho*-substituted lower phenyl rings have further enhanced the reactivity of these KITPHOS monophosphines for both amination reactions and Suzuki-Miyaura cross coupling reactions.[54]

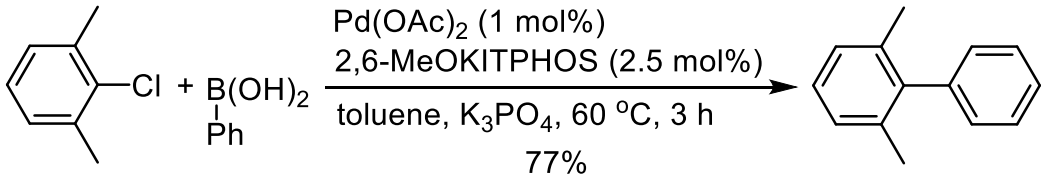
KITPHOS monophosphines are able to outperform the corresponding Buchwald dialkylbiarylphosphines in many instances, including the palladium-catalysed aminations shown in **scheme 19**.[54b] Here the amination reaction between 2-bromopyridine and morpholine required 2.5 mol % of the phosphine to give the product

in 100% yield for the KITPHOS ligand **16** after 1 h at 80 °C compared to 76% yield for the Buchwald ligand **3**. This enhancement in catalytic activity involving **16** was also demonstrated in the amination of 3-chloropyridine with morpholine which after 1 h at 100 °C gave the product in 93% yield for **16** compared to only 10% yield for **3**.



Scheme 19. Palladium-catalysed amination reactions using KITPHOS monophosphine **16** and the corresponding Buchwald dialkylbiarylphosphine **3**.

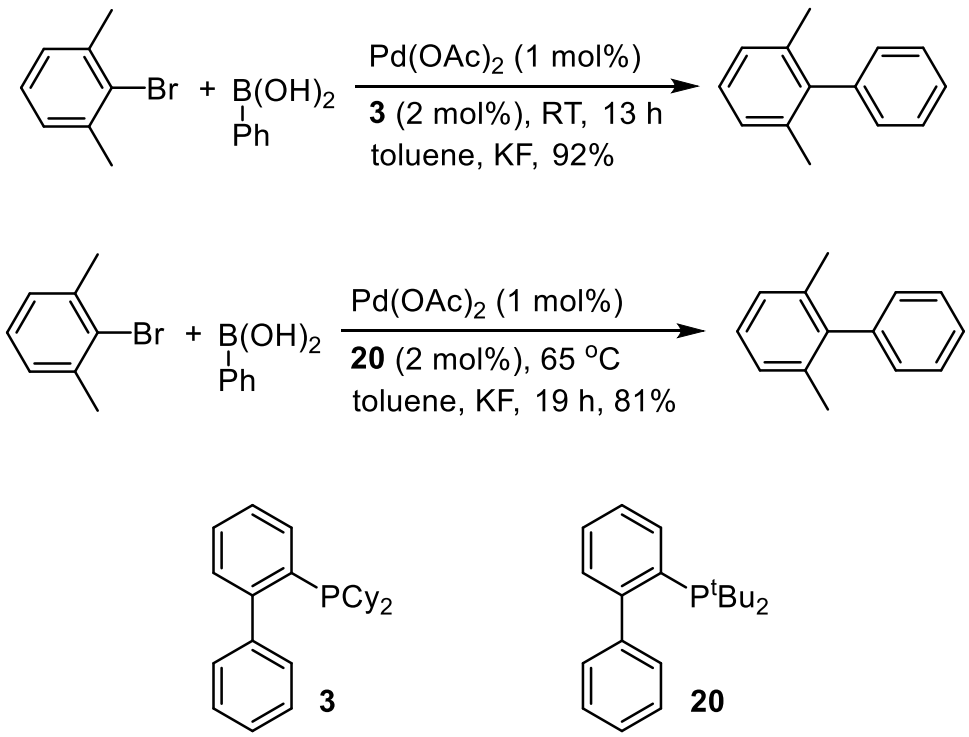
KITPHOS monophosphines are highly effective in Suzuki-Miyaura cross coupling reactions and are able to facilitate reactions with a range of electron-rich, electron deficient, unactivated and highly hindered aryl chlorides.[53,54] **Scheme 20** shows the successful coupling of the hindered aryl chloride, 1-chloro-2,6-dimethylbenzene using 2,6-MeOKITPHOS.[54a]



Scheme 20. The KITPHOS monophosphine 2,6-MeOKITPHOS is efficient in coupling even very hindered aryl chlorides.

1.2.1 Triaryl-like KITPHOS monophosphines

There is clear precedent in the literature for the need for bulky electron-rich groups on the phosphorus centre, particularly cyclohexyl or *tert*-butyl groups. It has been proposed that the bulk of these groups around the phosphorus aids in the reductive elimination step of the catalytic cycle. Interestingly however, **3** is more effective than the more bulky phosphine **20** when performing reactions at low catalyst loadings and when using sterically hindered substrates. For example, the coupling of 1-bromo-2,6-dimethylbenzene with phenylboronic acid can be performed at RT using **3** (2 mol%) to give the product in 92 % yield after 13 h, whereas on using the same catalyst loading but with **20**, the reaction requires 19 h at 65 °C to give the lower yield of 81% of the product (**scheme 21**).[55]



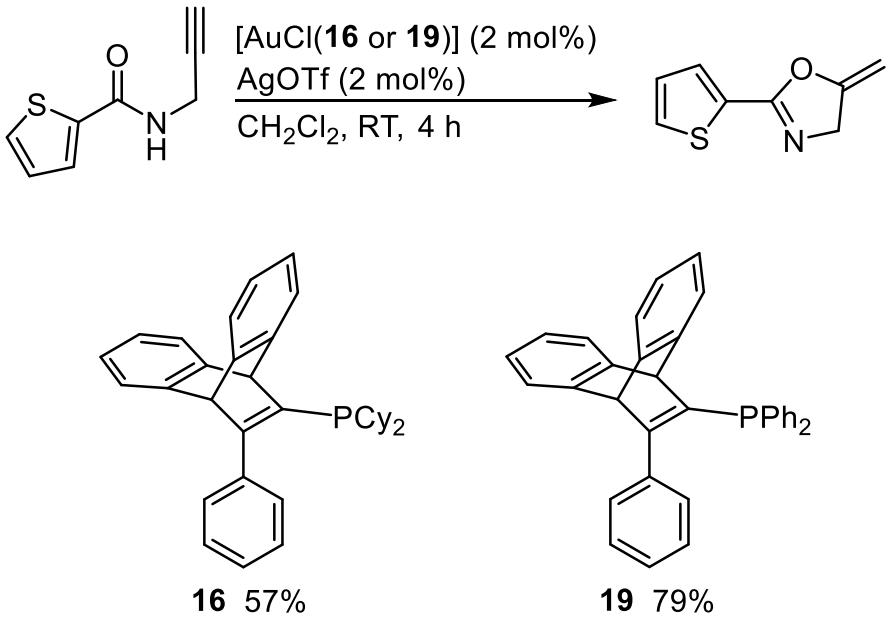
Scheme 21. The sterically less bulky cyclohexyl-substituted dialkylbiarylphosphines outperform their *tert*-butyl counterparts for sterically hindered coupling reactions.

The reason why phosphine **3** outperformed **20** in this transformation, was reported to be due to the reduced bulk of the cyclohexyl groups, which allows for a more facile transmetalation relative to that of the corresponding *tert*-butyl-substituted phosphine. This phenomenon has also been demonstrated on comparing reactions catalysed by PCy_3 and P^tBu_3.[10a]

Interestingly, there is only a relatively small difference in bulk between a cyclohexyl and a phenyl group, due to the former's free rotation about the P-C bond axis.[56] Therefore, it is surprising that there are not many examples in the literature of triarylphosphines incorporating a biaryl substituent being studied for such transformations.

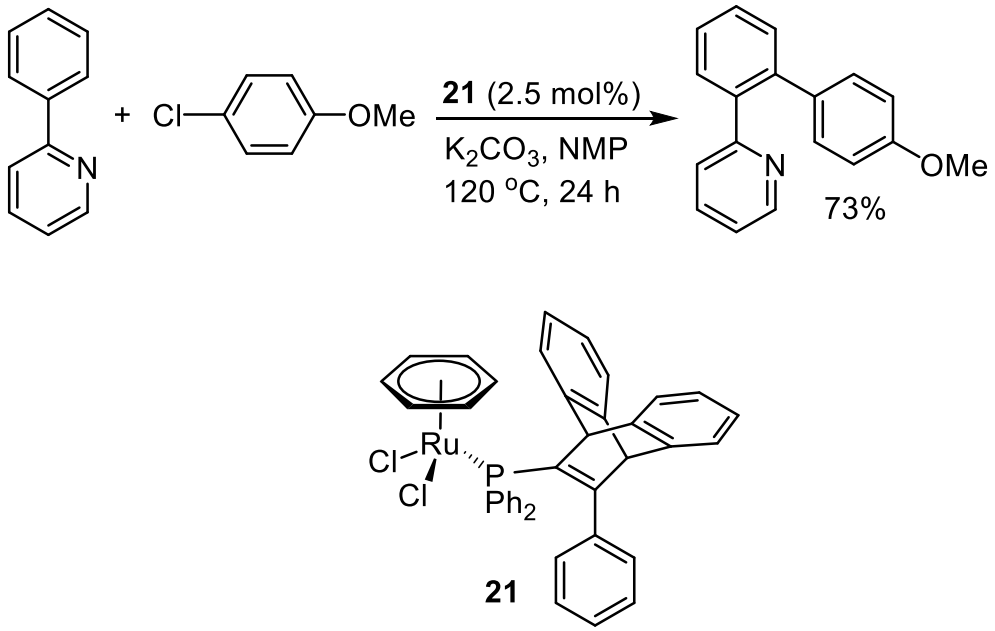
There is significant literature precedent for the need for electron-rich substituents to increase the favourability of the oxidative addition step of the catalytic cycle. However, this oxidative addition step is not always the rate determining step of the catalytic cycle. Also for some metal-catalysed transformations, such as for gold, this oxidative addition / reductive elimination catalytic cycle is not involved. For these

latter examples the use of electron-rich phosphines may not be essential for efficient catalysis. It has often been shown in gold catalysis that PPh_3 can outperform PCy_3 and can even give rise to different products.[57] In this regard the Doherty-Knight group chose to compare the catalytic ability of diphenyl-substituted KITPHOS monophosphines with their more electron-rich dicyclohexyl counterparts in the gold(I)-catalysed cycloisomerisation of propargyl carboxamides. Surprisingly, the diphenyl-substituted KITPHOS monophosphines substantially outperformed their dicyclohexyl counterparts. This can clearly be demonstrated in the cyclisation of *N*-prop-2-ynylthiophene 2-carboxamide, where the diphenylphosphine **19** gave the methylene oxazoline product in 79% conversion after 4 h, compared to 57% for the corresponding dicyclohexylphosphine **16** under the same reaction conditions (**scheme 22**).[58]



Scheme 22. Cyclisation of *N*-prop-2-ynylthiophene 2-carboxamide using **16** and **19**.

The diphenyl-substituted KITPHOS monophosphine **19** has also been shown to be effective in the ruthenium-catalysed directed *o*-arylations of 2-phenylpyridine and *N*-phenylpyrazole with a range of aryl chlorides (**scheme 23**).[59]



Scheme 23. The triaryl-like KITPHOS monophosphine **19** present in catalyst **21**, can be a highly successful ligand in ruthenium-catalysed directed *o*-arylation reactions.

1.3 Aims of the project

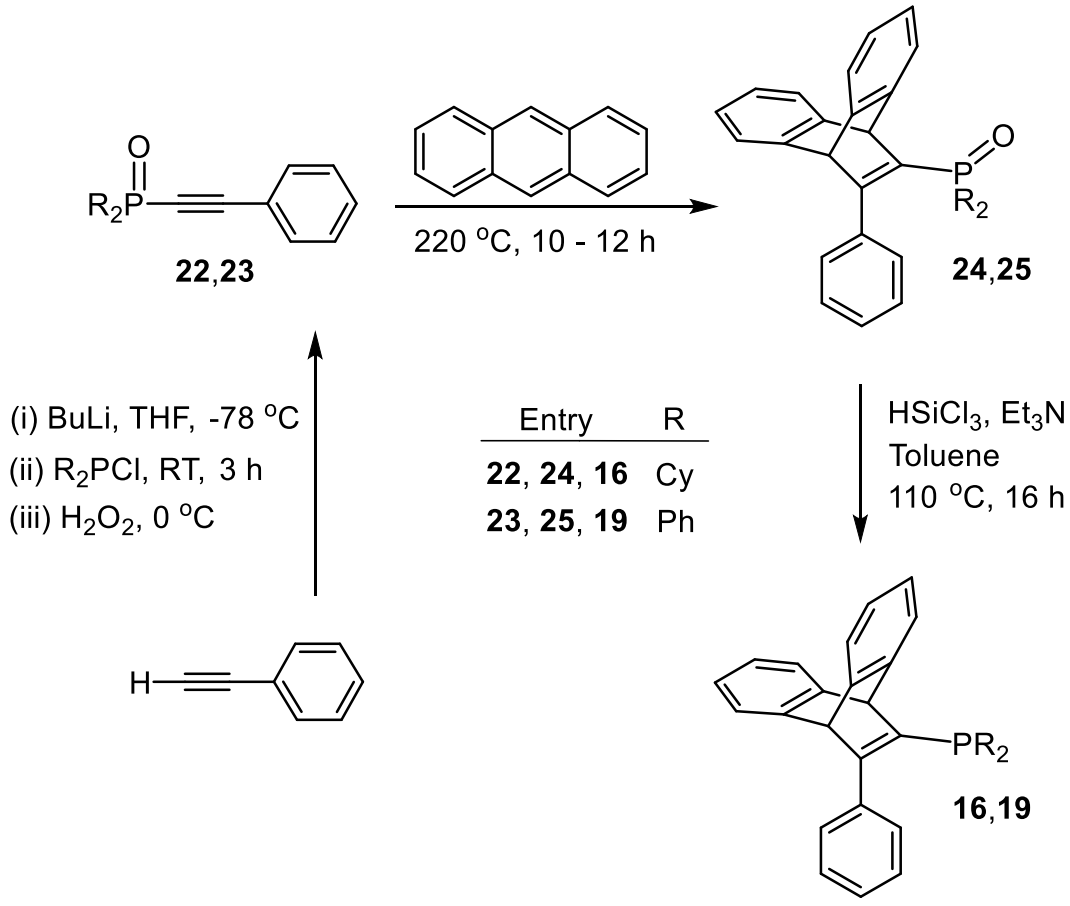
The success of **19**, which is essentially a triaryl-like phosphine, prompted further investigation into the capabilities and potential applications of these ligands in transition metal-catalysed transformations. This project aimed to:

- *Develop a range of triaryl-like KITPHOS monophosphines with differing steric and electronic properties*
- *Investigate the catalytic abilities of these phosphines in gold-catalysed reactions*
- *Explore the use of 2-phenylaniline- and allylpalladium-based pre-catalyst complexes of KITPHOS monophosphines in palladium-catalysed reactions*
- *Compare the relative efficiency of these triaryl-like KITPHOS monophosphines in palladium-catalysed reactions, against the more electron-rich dicyclohexyl-substituted KITPHOS monophosphine.*

Chapter 2. Synthesis of KITPHOS monophosphines

2.1 Synthesis of 11-(dicyclohexylphosphino)-12-phenyl-9,10-dihydro-9,10-ethenoanthracene and 11-(diphenylphosphino)-12-phenyl-9,10-dihydro-9,10-ethenoanthracene

In order to carry out this study a range of phenyl-substituted KITPHOS monophosphines bearing differing steric and electronic properties was required. Their synthesis is shown in this chapter. **Scheme 24** below shows the synthesis of the 12-phenyl-substituted KITPHOS monophosphine bearing either two phenyl groups (**19**) or two cyclohexyl groups (**16**) on the phosphorus. [53, 54b, 54c, 58, 59]

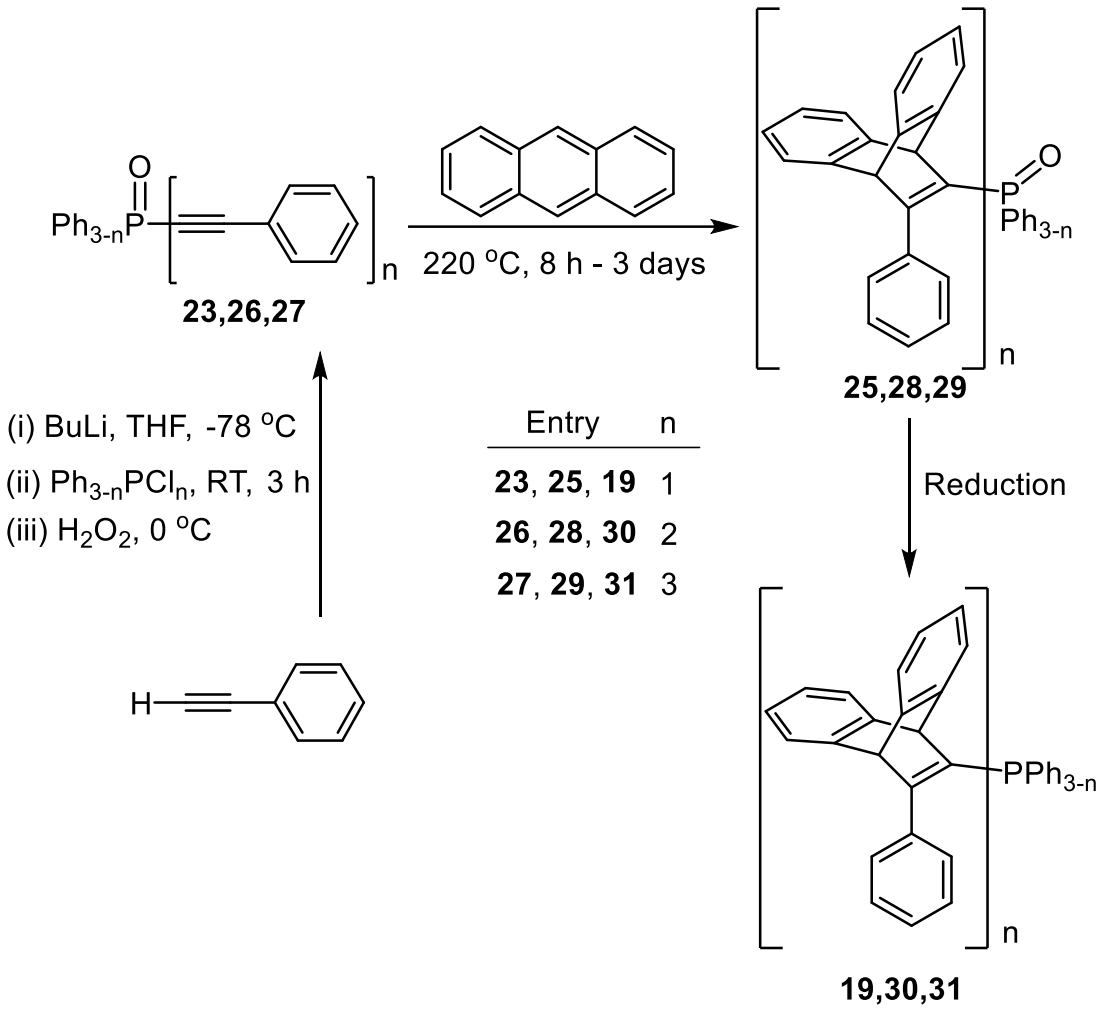


Scheme 24. Synthesis of KITPHOS monophosphines **16** and **19**.

The inexpensive commercially available phenylacetylene was deprotonated with ^{n}BuLi to form the corresponding lithiated alkynyl species *in situ*, to which was added either chlorodiphenylphosphine or chlorodicyclohexylphosphine followed by 35% aqueous solution of H_2O_2 to give the alkynylphosphine oxide **22** (R = Cy) in 76% and **23** (R = Ph) in 100% yield. The yield of **23** was assumed to be quantitative as the crude reaction mixture was sufficiently pure by ^{31}P and ^{1}H NMR to be used in the next step without further purification. The second step of this reaction sequence constructs the KITPHOS backbone on performing a Diels-Alder [4+2] cycloaddition of anthracene across the alkyne of the alkynylphosphine oxides **22** and **23**. This was performed on heating the phosphine oxide to 220 ^{o}C with 1.5 equivalents of anthracene for either 12 h to yield the KITPHOS phosphine oxide **24** (R = Cy) in 83% or 10 h to yield KITPHOS phosphine oxide **25** (R = Ph) in 67% yield. Reduction of the KITPHOS phosphine oxides by treatment with $HSiCl_3$ and Et_3N in toluene and heating to 110 ^{o}C for 16 h gave the phosphines **16** (75% yield) and **19** (71% yield). The overall yield after these three steps for the KITPHOS monophosphine **16** (R = Cy) was 43% and for **19** (R = Ph) was 48%. Thus the synthesis of **19** is not only more efficient but it is cheaper due to the cost of chlorodiphenylphosphine compared to chlorodicyclohexyphosphine and it is also slightly quicker as in the Diels-Alder step, **25** only requires 10 h compared to the 12 h required for **24**.

2.2 Synthesis of 11-[bis(12-phenyl-9,10-dihydro-9,10-etheno-anthracene)]phenylphosphine and 11-[tris(12-phenyl-9,10-dihydro-9,10-etheno-anthracen-11-yl)]phosphine

To explore the effect of increased steric bulk, the number of KITPHOS units were progressively increased around the phosphorus. **Scheme 25** shows the synthesis of the monoKITPHOS (**19**, n = 1), bisKITPHOS (**30**, n = 2) and trisKITPHOS (**31**, n = 3).



Scheme 25. The synthesis of KITPHOS monophosphines bearing one KITPHOS unit, **19**, two KITPHOS units, **30** (n = 2) and three KITPHOS units, **31** (n = 3).

30 and **31** were synthesised using the same methodology as for **16** and **19**. Firstly for the bisKITPHOS **30**, phenylacetylene was treated with ^{n}BuLi to form the lithiated alkynyl species *in situ*, to which was added dichlorophenylphosphine and following the addition of 35% aqueous solution of H_2O_2, the alkynylphosphine oxide **26** (n = 2) was obtained in 89% yield. The Diels-Alder cycloaddition was then performed using 2.5 equivalents of anthracene to give the KITPHOS phosphine oxide **28** (n = 2) in 82% yield after 8 h stirring at 220 °C. The reduction to afford **30** (n = 2) was accomplished by treatment of **28** with $HSiCl_3$ and Et_3N in toluene at 110 °C for 64 h to give **30** in 76% yield. The overall yield over the three steps was 55%, an improvement on that for **19** (n = 1) (48%).

For the trisKITPHOS **31**, lithiated phenylacetylene was reacted with trichlorophosphine and following the addition of 35% aqueous solution of H_2O_2, the alkynylphosphine oxide **27** (n = 3) was obtained in 94% yield. The Diels-Alder cycloaddition was then performed using 3.5 equivalents of anthracene to give the KITPHOS phosphine oxide **29** (n = 3) in only 35% yield after 3 days stirring at 220 ^oC. This much increased time needed and the low yield of the Diels-Alder reaction was attributed to the consequence of steric repulsion between the KITPHOS units on adding a third around the already congested phosphorus centre. The crystal structure of **29** is given below (**figure 9**).

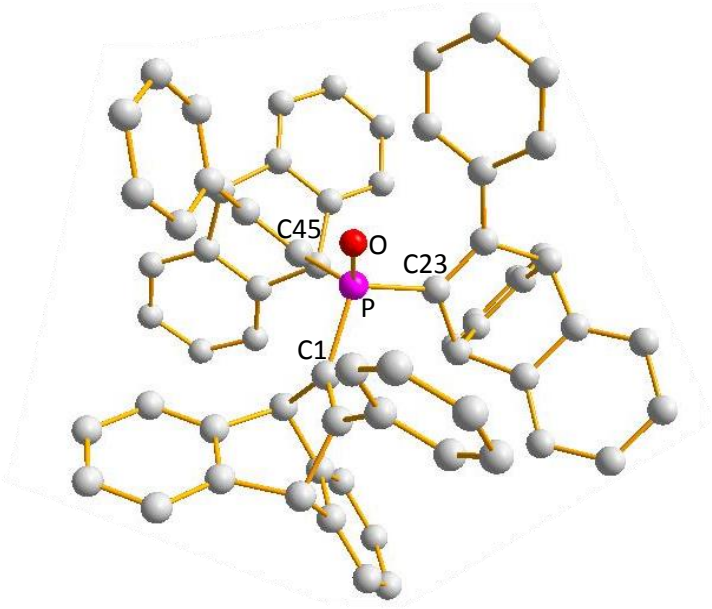


Figure 9. The crystal structure of 11-[tris(12-phenyl-9,10-dihydro-9,10-etheno-anthracene)]phosphine oxide (**29**). Hydrogen atoms and two solvent molecules (CH_2Cl_2) have been removed for clarity. Selected bond lengths (Å) / bond angles (^{o}): P-O = 1.4745(14), P-C1 = 1.808(2), P-C23 = 1.809(2), P-C45 = 1.812(2), O-P-C1 = 113.91(9), O-P-C23 = 113.72(9), O-P-C45 = 114.62(9), C1-P-C23 = 105.09(9), C1-P-C45 = 104.57(9), C23-P-C45 = 103.81(9).

Interestingly **29** exhibited broadening of its peaks in both ^1H and ^{13}C $\{^1H\}$ NMR at RT (Appendix, section B). A variable temperature NMR study, shown below in **figure 10**, demonstrates the gradual growth of these peaks in the ^1H NMR spectrum of **29**, on decreasing the temperature of the sample.

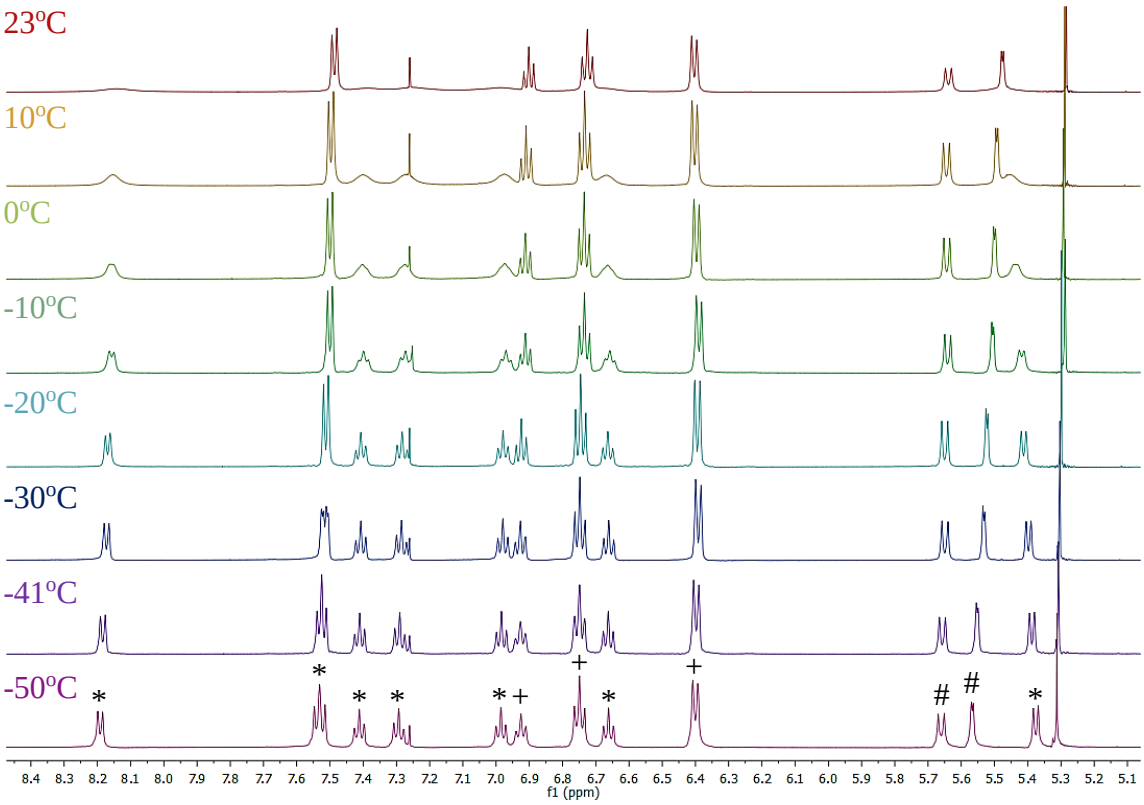


Figure 10. The gradual growth of peaks within the ^{1}H NMR spectrum of **29** on cooling the sample from 23 °C to -50 °C in $CDCl_3$. The resonance signals associated with the C_6H_4 groups are highlighted with an asterisk (*), whilst those associated with the C_6H_5 groups with a plus (+) and the bridgehead protons with a hash (#). The peak at δ 5.32 is CH_2Cl_2.

This broadening effect was proposed to be the result of an exchange process. On performing COSY, HSQC and HMBC experiments at -55 °C, it was found that aryl CH peaks from the KITPHOS backbone (C_6H_4 groups) were undergoing this exchange process. The COSY experiment is shown below in **figure 11**. This not only identified and enabled the assignment of C_6H_4 peaks of the KITPHOS unit, but also ruled out any exchange process involving the phenyl C_6H_5 fragments of the KITPHOS caused by restricted rotation about C16-C17 bond.

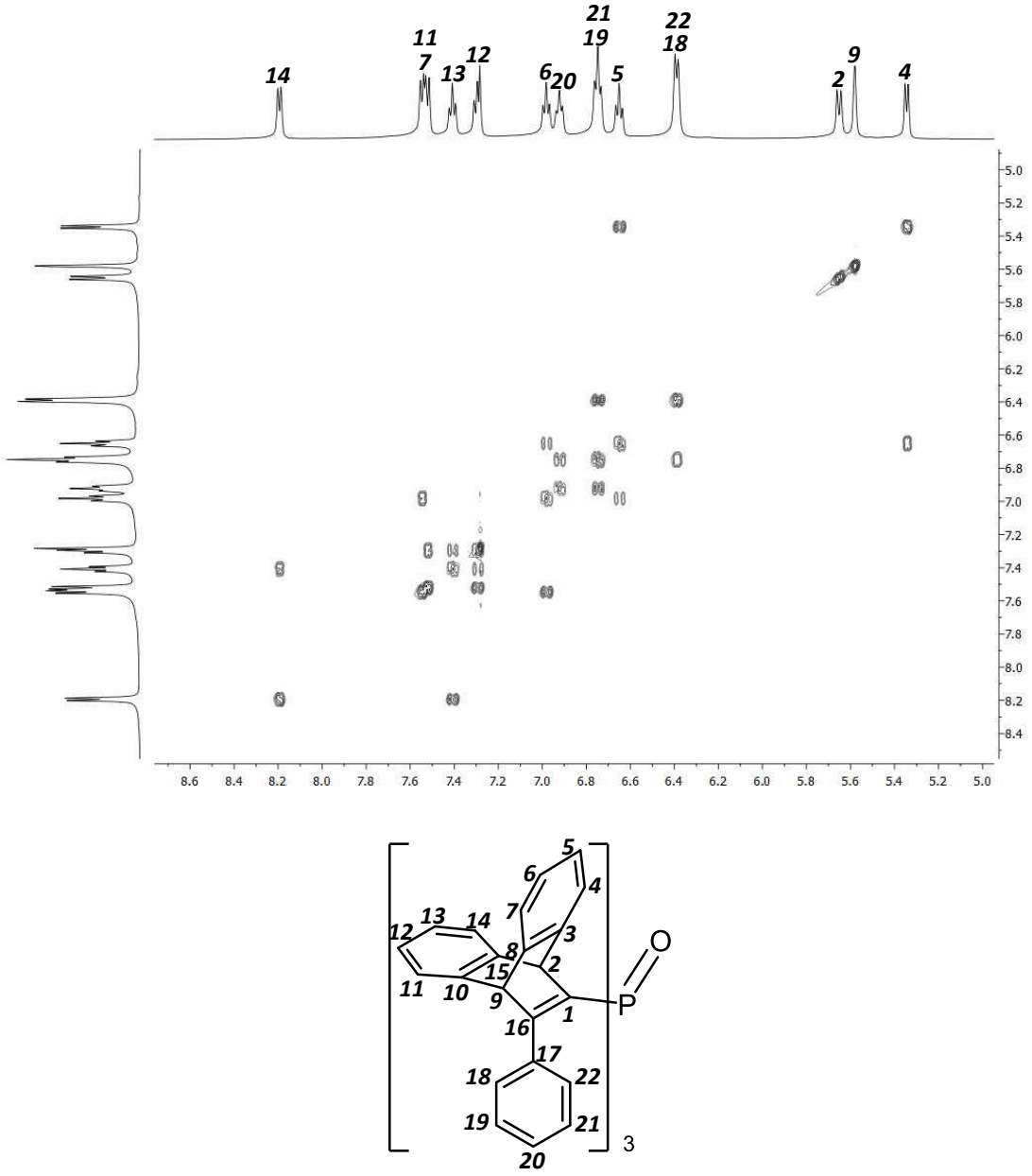


Figure 11. This shows the results from the COSY experiment of phosphine oxide **29** at -55 ^{o}C. The assignments made here are for each CH group positioned within each of the three identical KITPHOS units present in **29**.

An EXSY spectroscopic study at -30 ^{o}C was then performed on **29** (**figure 12**). This provided the correlation needed to confidently determine which protons were exchanging with each other. **Figure 12** shows that; the doublet resonance at δ 8.18 exchanges with the doublet at δ 5.37, the triplet resonance at δ 7.40 exchanges with the triplet at δ 6.65, and the triplet resonance at δ 7.29 exchanges with the doublet at δ 6.98. These results can be explained on the basis that throughout the exchange process each

KITPHOS unit around the P-atom remain equivalent to each other, and each has its effective symmetry lowered by concerted restricted rotation about the P-C bond. This is such that at lower temperatures the proton and carbon atoms of each C_6H_4 group within each particular KITPHOS substituent become inequivalent. The EXSY confirms this by showing three of the expected four pairs of cross-peaks mentioned above. The fourth of these, between the two overlapping peaks within the multiplet resonance at δ 7.54 – 7.51 (symbol §, **scheme 12**), is unobservable owing to the very small chemical shift difference.

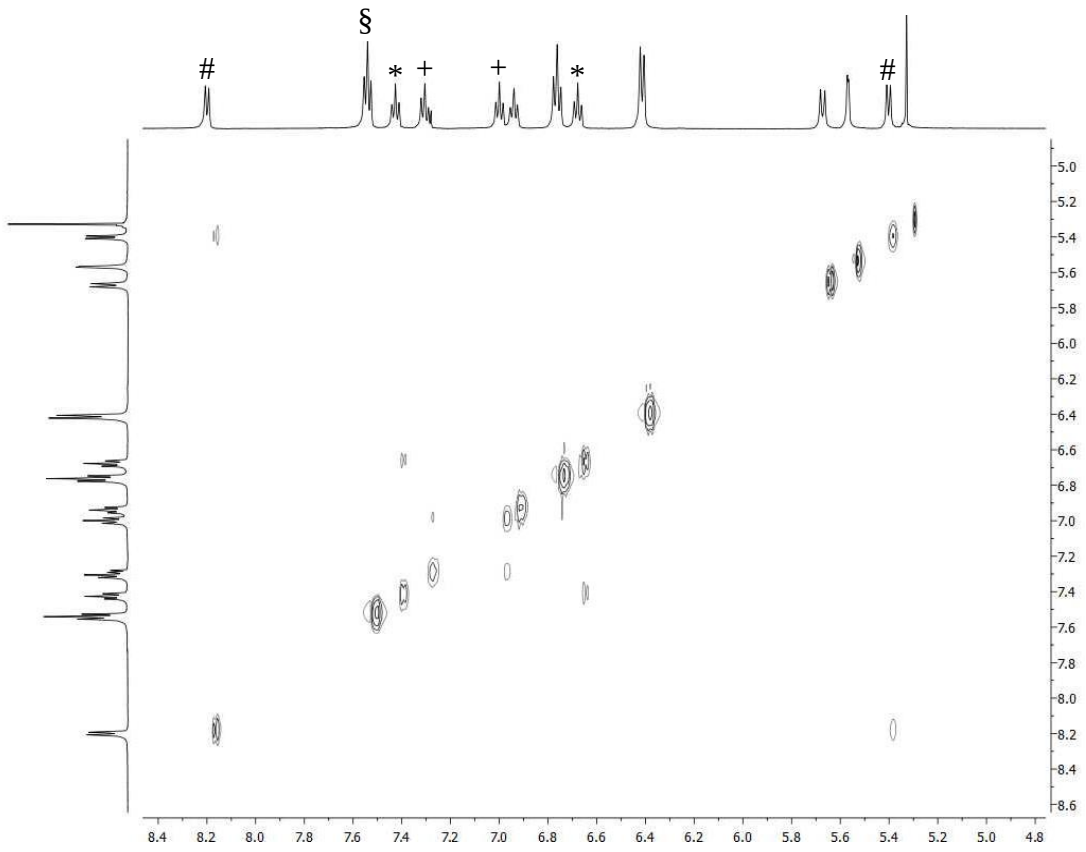
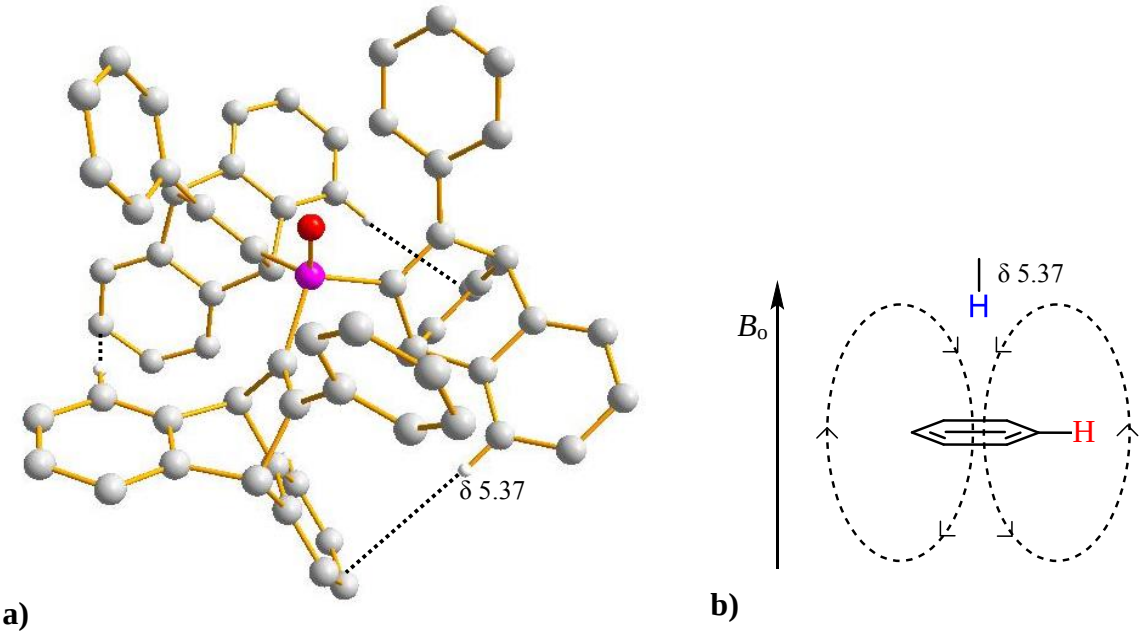


Figure 12. An EXSY experiment of 11-[tris(12-phenyl-9,10-dihydro-9,10-etheno-anthracen-11-yl)]phosphine oxide (**29**) at -30 ^{o}C. The symbols (*) (+) and (#) denote CH groups which exchange with one another. The symbol (§) denotes the resonant peak associated with other two CH groups within the C_6H_4 fragments. The peak at δ 5.32 is CH_2Cl_2.

The fact that the doublet resonance at δ 8.18 is shown to exchange with the doublet at δ 5.37 in **figure 12** is particularly surprising, as with a difference of nearly 3 ppm in the ^{1}H NMR of **29**, these two proton signals are shown to be in very different environments. The most probable reason for this is the proximity of the aryl protons at δ 5.37 relative to the aryl rings below them, as highlighted in **figure 13a**. When a magnetic field (B_o) is applied to an aryl group, as shown in **figure 13b**, the electrons in the aryl ring set up an anisotropic secondary magnetic field which opposes the applied magnetic field in the centre and supports it at the edge of the ring. Therefore, the protons on the edge of this ring, such as that highlighted in red, will require a lessened magnetic field applied to them in order to achieve resonance. They are thus deshielded. However, when another aryl proton is positioned perpendicular and above this aryl ring (blue in **figure 13b**), such as in the crystal structure of **29** below, this proton opposes the applied magnetic field and therefore exhibits shielding effects. This causes a high field shift in the chemical shift of this proton, which accounts for the low chemical shift value of δ 5.37, observed in ^{1}H NMR spectrum of **29**.



a) **b)**

Figure 13. a) This shows the proximity of the aryl proton at δ 5.37 to the aryl ring below it, as shown in the crystal structure and **b)** as demonstrated in a magnetic field diagram. This is the most likely reason for the relatively low chemical shift value observed in the ^{1}H NMR of **29** for this proton.

A NOESY experiment, which is given in the Appendix section C, confirms the assignment made in **figure 11**. An expansion of this NOESY, shown in **figure 14**, also supports the explanation for the low chemical shift value for the proton at δ 5.37 rationalised in **figure 13**. **Figure 14** below, shows a cross-peak between this proton in position 4 and those in positions 11, 12 and 13 on the other C_6H_4 group.

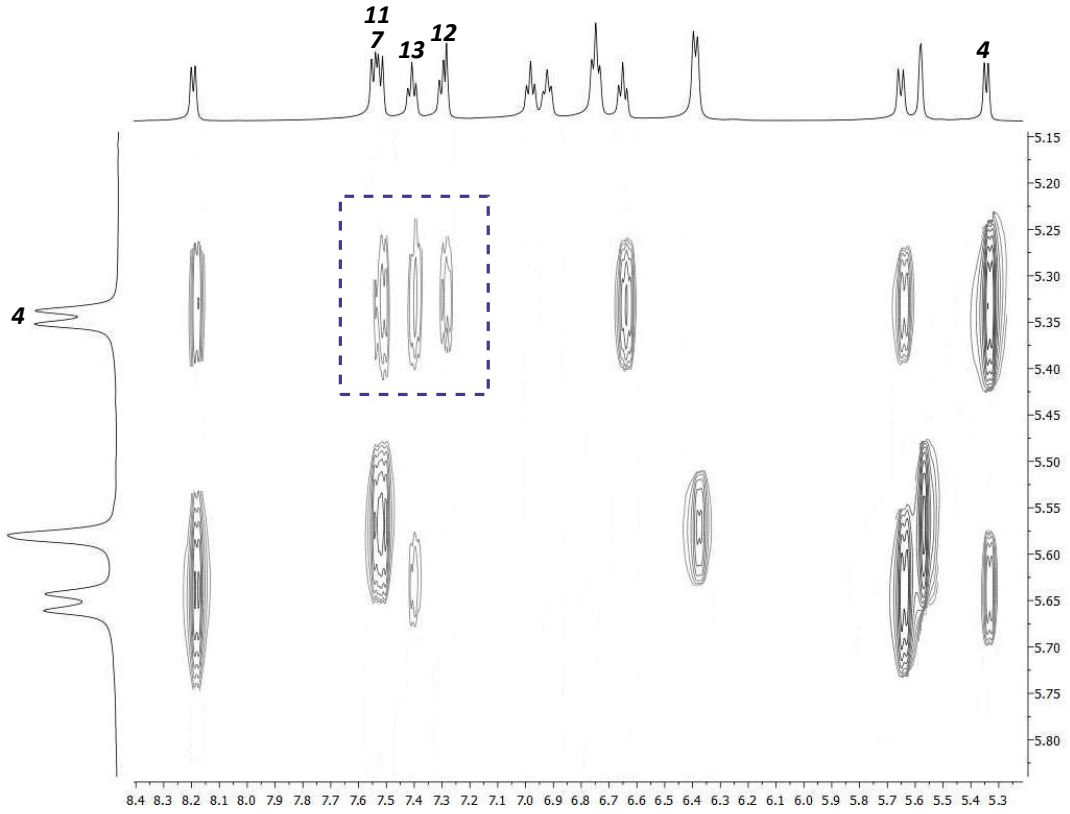
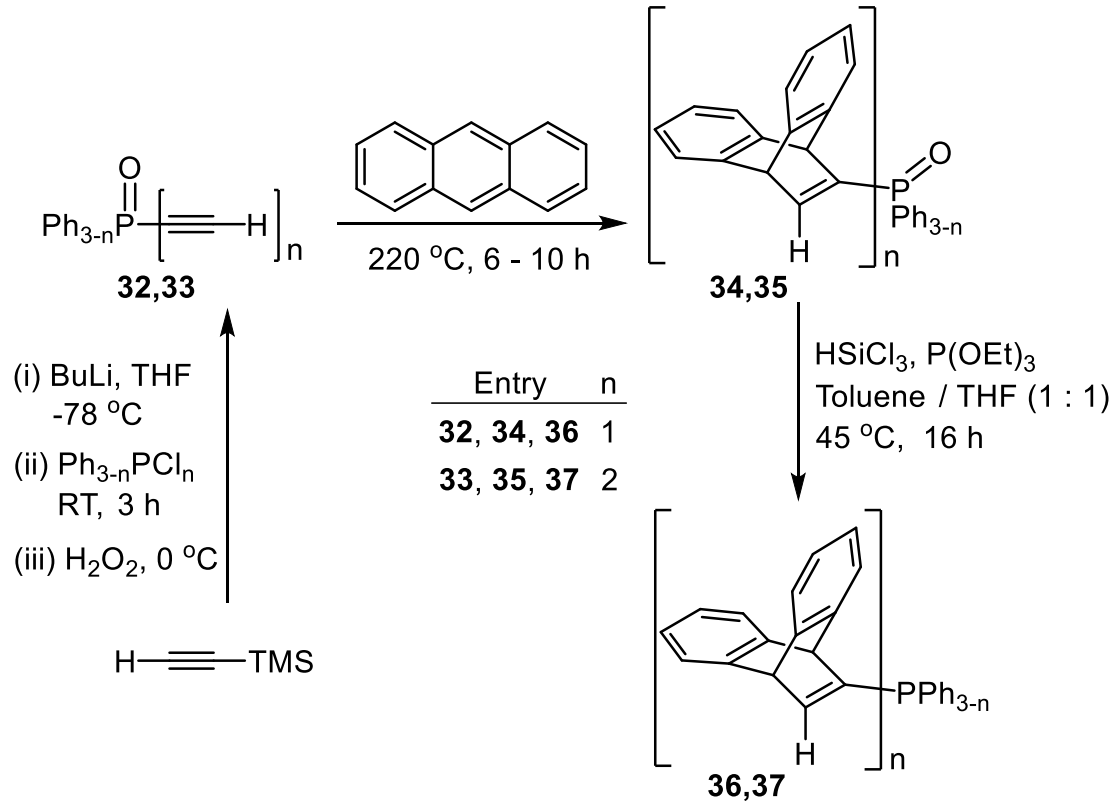


Figure 14. An expansion of the NOESY experiment on **29** at -55 ^{o}C.

Phosphine oxide **29** was then reduced using $HSiCl_3$ and tributylamine in xylenes at 130 ^{o}C for 96 h to give the phosphine **31** (n = 3) in 64% yield. Interestingly, the reduction reaction using $HSiCl_3$ and Et_3N in toluene was attempted with **29**, however, after heating at 110 ^{o}C for 64 h, none of phosphine **31** was afforded. The overall yield over the three steps in the synthesis of **31** was 21%. This low overall yield is the consequence of the poor yield of 33% for the Diels-Alder step of the reaction sequence and as such the overall yield of **31** was far below that of both **19** (48%) and **30** (55%).

2.3 Synthesis of 11-(diphenylphosphino)-9,10-dihydro-9,10-ethanoanthracene and 11-[bis(9,10-dihydro-9,10-etheno-anthracene)]phenylphosphine

The effect the aryl substituent in the 12-position of the KITPHOS unit has on its catalytic ability was then investigated. It has already been postulated that for dialkylbiarylphosphines, the presence of this lower aryl ring enhances the catalytic performance of the phosphine by increasing the stability of its derived catalysts against decay and thus prolongs the lifetime of the catalyst.[27] Therefore, KITPHOS monophosphines without the lower aryl rings were synthesised, in order to gain quantitative information on any resulting reduction in catalytic activity. The synthesis of these phosphines is shown in **scheme 26**.



Scheme 26. Synthesis of KITPHOS monophosphines without the lower aryl ring. **36** (n = 1) only possesses one KITPHOS unit whereas **37** (n = 2) has two.

Ligands **36** (n = 1)[59] and **37** (n = 2) were synthesised using the same methodology as for **19**. Firstly (trimethylsilyl)acetylene was treated with ^{n}BuLi to form the lithiated alkynyl species *in situ,* to which was added either chlorodiphenylphosphine or dichlorophenylphosphine. Oxidation with 35% aqueous solution of H_2O_2 occurred with concomitant desilylation to give the alkynylphosphine oxides **32** (n = 1, 81% yield) and **33** (n = 2, 73% yield). Next the Diels-Alder cycloaddition of **32** using 1.5 equivalents of anthracene at 220 ^{o}C for 6 h gave the KITPHOS phosphine oxide **34** (n = 1) in 81% yield. Similarly **35** (n = 2) was obtained using 2.5 equivalents of anthracene and stirring at 220 ^{o}C for 10 h to give the KITPHOS phosphine oxide in 54% yield. The reductions to form the KITPHOS monophosphines were performed by treatment of **34** and **35** with $HSiCl_3$ and $P(OEt)_3$ in a mixture of toluene / THF (1 : 1) at 45 ^{o}C for 16 h. **36** (n = 1) was obtained in 50% yield and **37** (n = 2) in 33% yield. The overall yield after the three consecutive steps for **36** was 33% and **37** was 13%. It must be noted that whilst **36** displays sensitivity towards oxidation on standing in solution, **37** must be always stored under nitrogen. In fact the inherent sensitivity of **37** towards oxidation is one reason for its low overall yield. This is clearly shown in the crystal structure of **37** which shows 15% occupancy of the oxide within its unit cell (**figure 15**). This oxygen must have come from a slight impurity of the nitrogen supply under which crystallisation was performed, as each solvent was degassed thoroughly and the phosphine itself showed no presence of the oxide by ^{31}P or ^{1}H NMR prior to crystallisation.

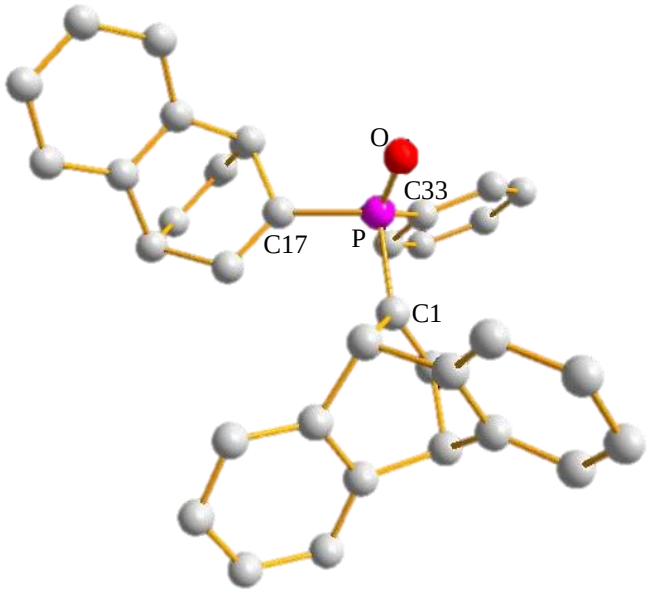
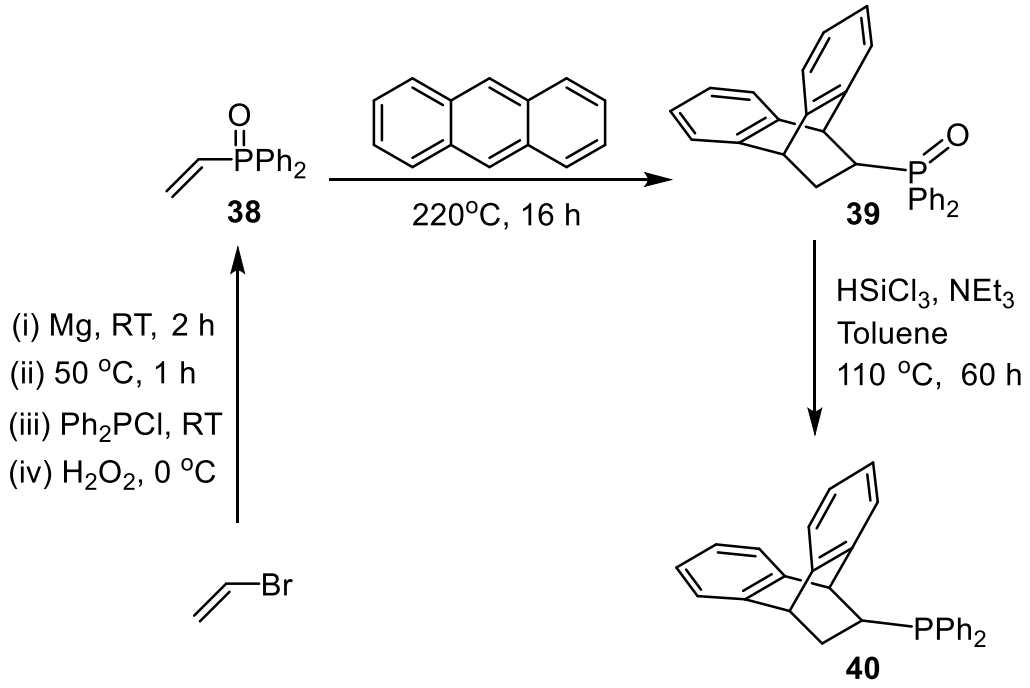


Figure 15. The crystal structure of 11-[bis(9,10-dihydro-9,10-etheno-anthracene)] phenylphosphine (**37**) displays 15% occupancy of the oxide in its unit cell. Hydrogen atoms and a solvent molecule ($CHCl_3$) have been removed for clarity. Selected bond lengths (Å) / bond angles (°): P-O = 1.329(9), P-C1 = 1.8080(18), P-C17 = 1.8076(17), P-C33 = 1.8255(18), O-P-C1 = 111.4(4), O-P-C17 = 116.2(4), O-P-C33 = 120.5(4), C1-P-C17 = 102.44(8), C1-P-C33 = 102.33(8), C17-P-C33 = 101.54(8).

2.4 Synthesis of 11-(diphenylphosphino)-9,10-dihydro-9,10-ethanoanthracene

The KITPHOS monophosphine **40** was then synthesised to investigate the effect of increased saturation within the KITPHOS unit combined with the absence of the lower aryl ring has on its catalysis. This synthesis is shown in **scheme 27**.

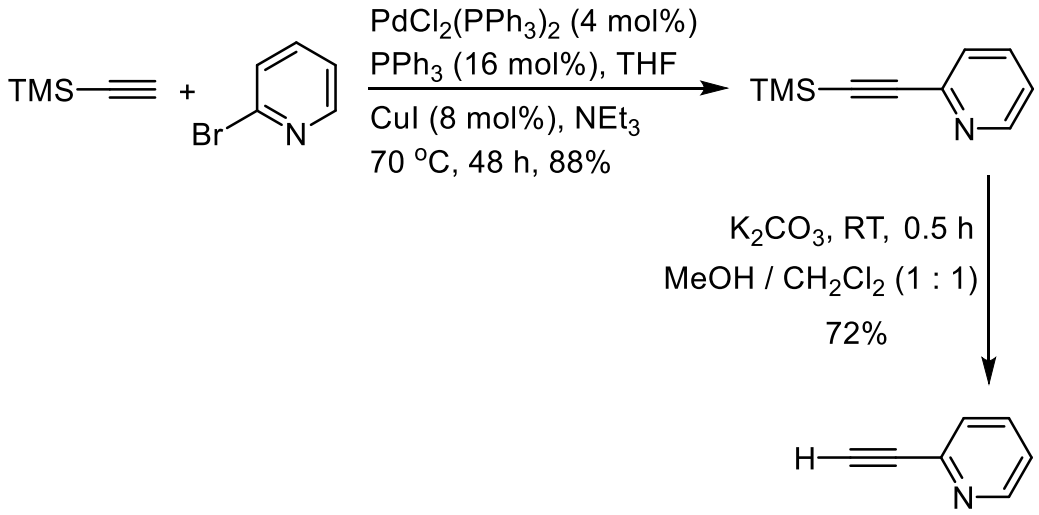


Scheme 27. The synthesis of KITPHOS monophosphine **40**.

Firstly vinyl bromide was treated with magnesium and heated to 50 °C to generate the vinyl Grignard reagent, to which was added chlorodiphenylphosphine and following the addition of 35% aqueous solution of H_2O_2, diphenyl(vinyl)phosphine oxide **38** was formed in 100% yield. Next the Diels-Alder cycloaddition was performed using 1.5 equivalents of anthracene to give the KITPHOS phosphine oxide **39** in 90% yield after 16 h stirring at 220 °C. The reduction of **39** was performed using $HSiCl_3$ and Et_3N in toluene at 110°C for 60 h to afford **40** in 74% yield. Thus **40** was produced in an overall yield of 67% from vinyl bromide. Compound **40** also exhibited sensitivity to oxidation, particularly when in solution. However this sensitivity is decidedly less than the corresponding cyclohexyl-substituted analogue of **40** which completely decomposes in any attempt to purify it through column chromatography.[53]

2.5 Synthesis of 11-(diphenylphosphino)-12-(2-pyridyl)-9,10-dihydro-9,10-ethenoanthracene

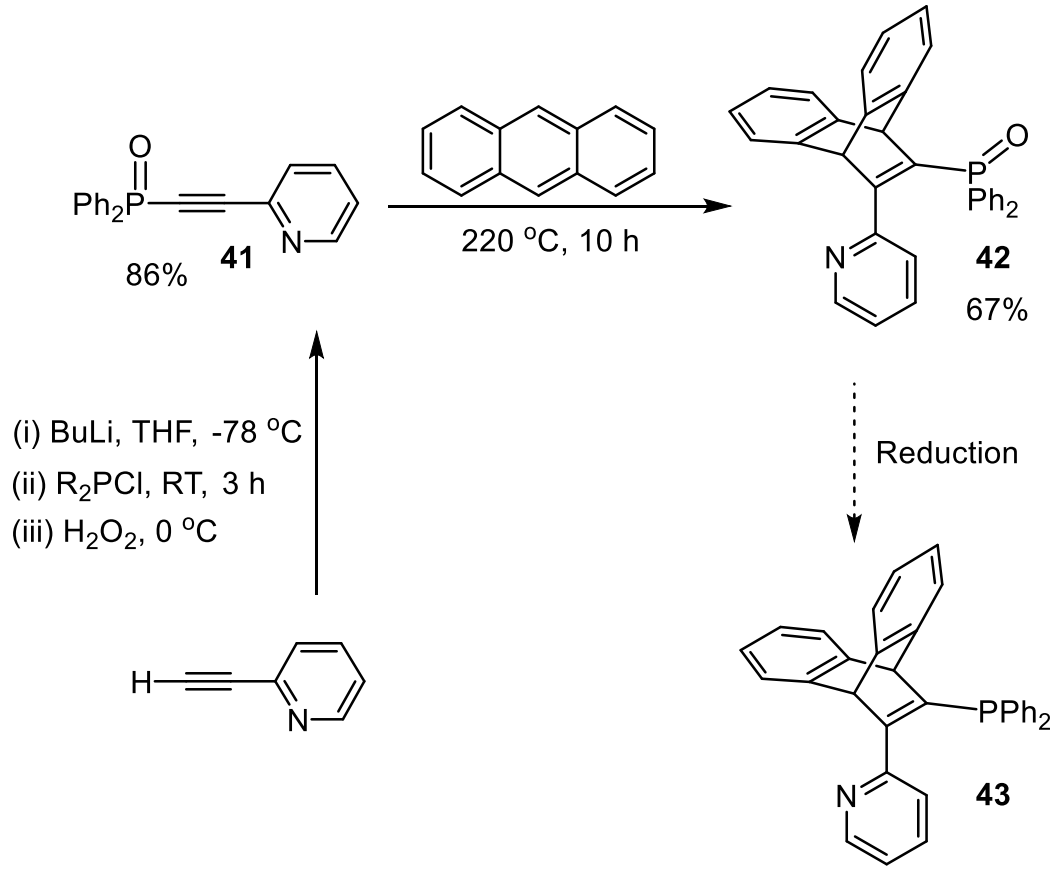
Due to the success of P,N ligands such as QUINAP[60] and diphenyl-2-pyridylphosphine,[61] the synthesis of a pyridyl analogue of KITPHOS was of great interest. The initial step in this synthesis was a Sonogashira cross coupling between 2-bromopyridine and trimethylsilyl acetylene. This was performed using $PdCl_2(PPh_3)_2$ (4 mol%), CuI (8 mol%), PPh_3 (16 mol%) and Et_3N and stirring the mixture in THF for 48 h at 70°C to give trimethylsilylethynylpyridine in 88% yield. This was then desilylated using excess K_2CO_3 in MeOH / CH_2Cl_2 (1 : 1) to give 2-ethynylpyridine in 72% yield (**scheme 28**).



Scheme 28. Synthesis of 2-ethynylpyridine from 2-bromopyridine.

Scheme 29 describes the rest of the attempted synthesis of this pyridyl analogue of a KITPHOS monophosphine. 2-Ethynylpyridine was then treated with ^nBuLi to form the lithiated alkynyl species *in situ*, to which was added chlorodiphenylphosphine and following the addition of 35% aqueous solution of H_2O_2, 2-(diphenylphosphinoylethynyl)pyridine **41** was obtained in 86% yield (**scheme 29**).

Next the Diels-Alder cycloaddition was performed using 1.5 equivalents of anthracene to give the KITPHOS phosphine oxide **42** in 67% yield after heating at 220 °C for 10 h. The crystal structure of **42** is given below (**figure 16**).



Scheme 29. Synthesis of pyridyl analogue of a KITPHOS monophosphine.

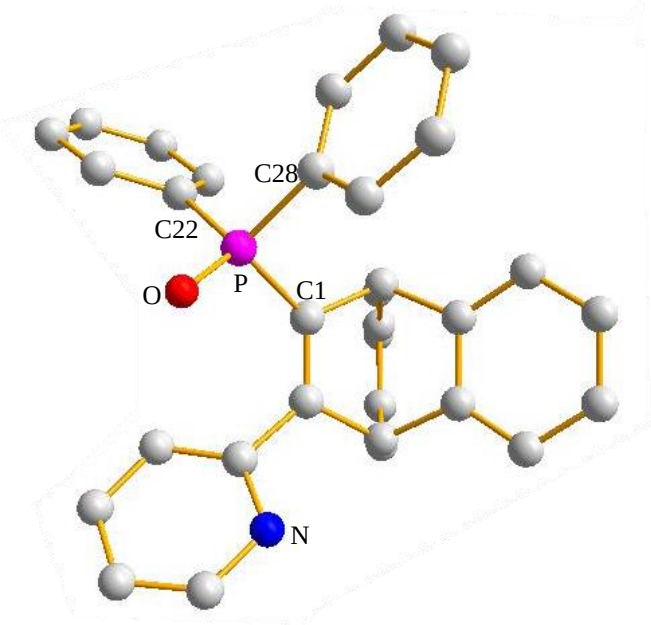
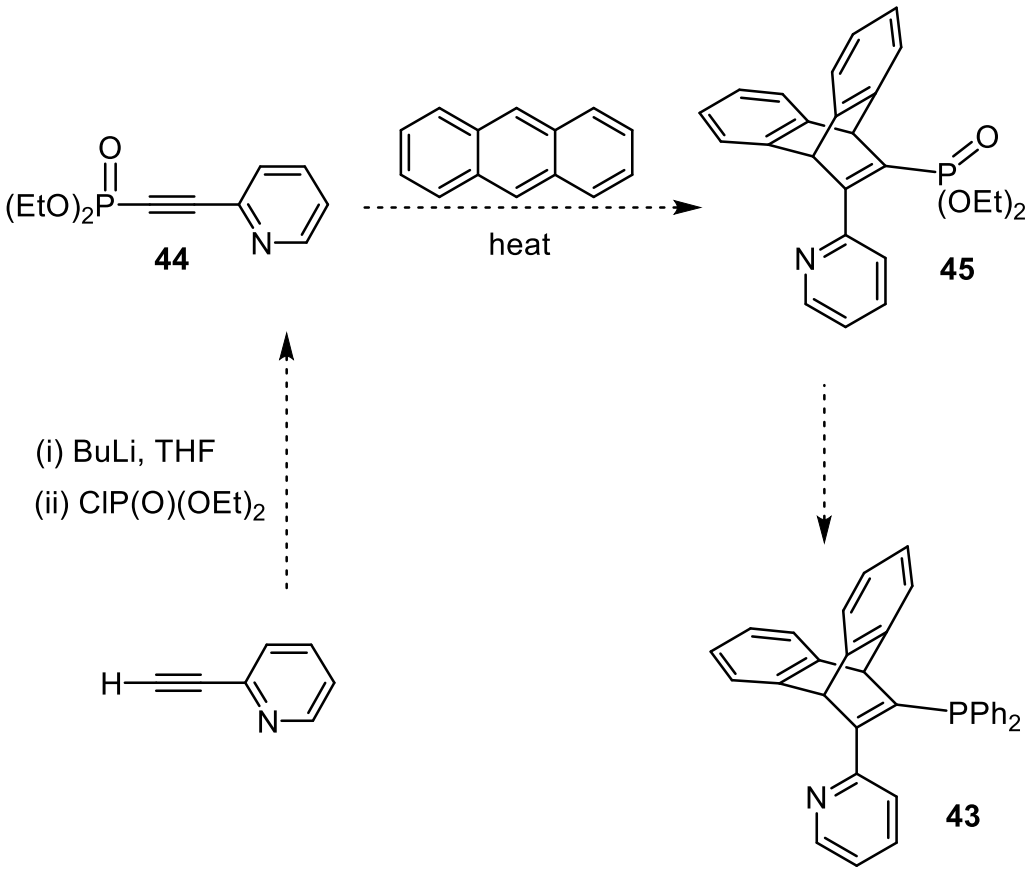


Figure 16. Crystal structure of 11-(diphenylphosphinoyl)-12-(2-pyridyl)-9,10-dihydro-9,10-ethenoanthracene **42**. Hydrogen atoms and a solvent molecule ($CHCl_3$) have been removed for clarity. Selected bond lengths (Å) / bond angles (°): P-O = 1.4781(12), P-C1 = 1.7948(17), P-C22 = 1.8012(17), P-C28 = 1.8019(17), O-P-C1 = 113.91(7), O-P-C22 = 112.50(8), O-P-C28 = 111.88(8), C1-P-C22 = 107.90(8), C1-P-C28 = 102.08(7), C22-P-C28 = 107.90(8).

However, the reduction step to yield the desired pyridyl analogue of KITPHOS monophosphine unfortunately gave no product. In fact the retro [4+2] Diels-Alder cycloaddition to yield anthracene and **41** occurred instead in near quantitative yield. Currently, the synthesis of this pyridyl-derived KITPHOS monophosphine is being investigated, through the modified synthetic route detailed in **scheme 30**.



Scheme 30. A proposed synthetic route to afford the pyridyl analogue of a KITPHOS monophosphine.

2-Ethynylpyridine will be deprotonated with ^{n}BuLi and subsequently quenched with diethyl chlorophosphate to give diethyl (pyridin-2-ylethynyl)phosphonate **44** (**scheme 30**). Next a Diels-Alder cycloaddition using anthracene will give the KITPHOS phosphonate **45**. This will then be reduced to the corresponding primary phosphine using $LiAlH_4$ and Me_3SiCl in THF.[62] From here either a coupling reaction using bromobenzene, $PdCl_2$(dppf) and a base will be performed on the primary phosphine or the primary phosphine will be converted to the dichlorophosphine KITPHOS adduct using PCl_5 to which the Grignard reagent phenylmagnesium bromide will be added to give **43**. This methodology is currently being attempted within the research group.

2.6 Properties of the KITPHOS monophosphines

The structures of all the KITPHOS monophosphines successfully constructed from section 1.2 are shown in **figure 17**. In order to attain quantitative data on the electronic properties of the phosphines, the J_{PSe} values were recorded after reacting each of these phosphines with two equivalents of KSeCN in MeOH at 50 ^{o}C for 20 h. The results of which are shown in **table 1**.

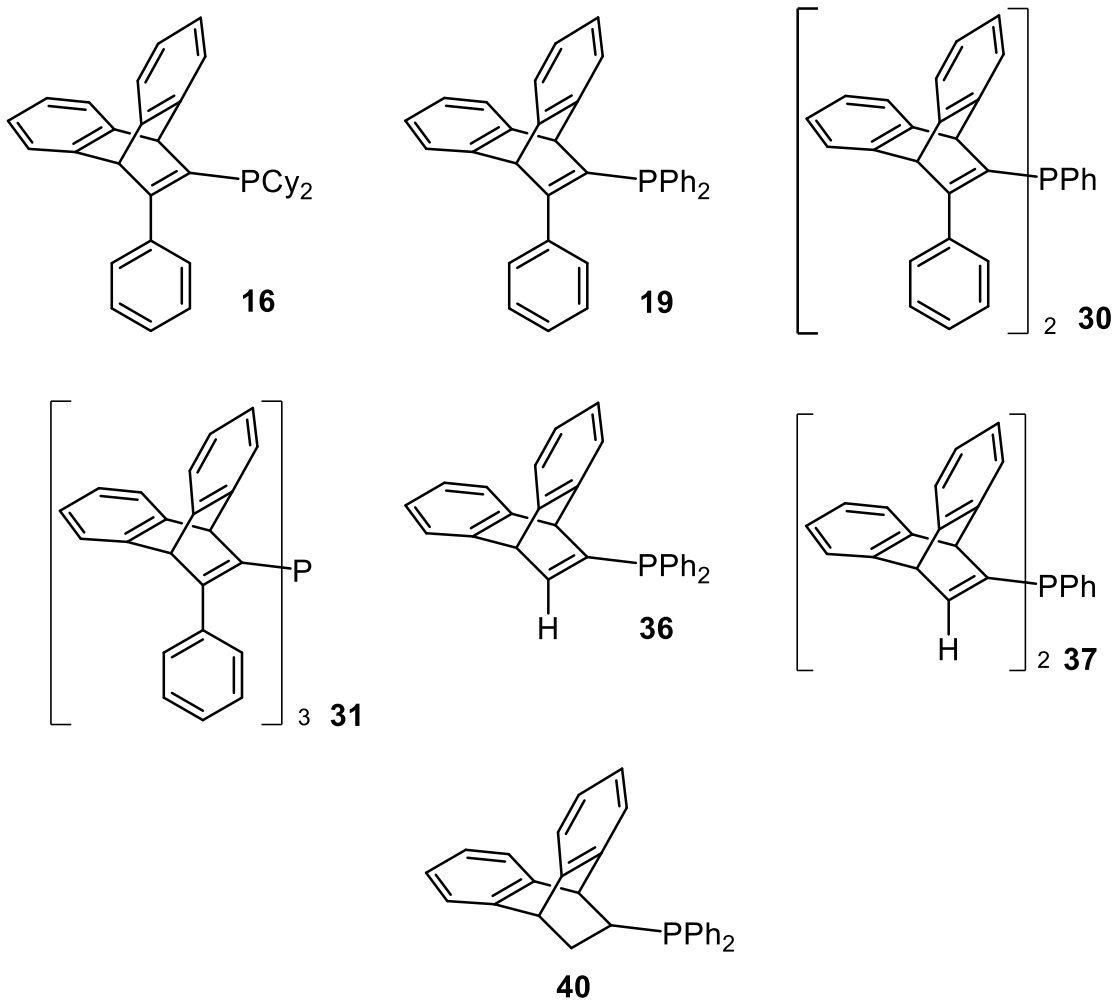
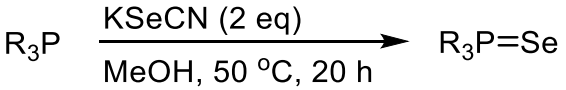


Figure 17. Structures of the KITPHOS monophosphines synthesised in section 1.2.

Table 1. J_{PSe} values for each of the KITPHOS monophosphine selenides synthesised in section 1.2.



Entry	**Phosphine**	**^{31}P / δ** [a]	**J_{PSe} / Hz**
1 [b]	**16**	60.5	702
2	**19**	32.8	723
3	**30**	27.8	701
4 [c]	**31**	-24.8	-
5	**36**	32.7	727
6	**37**	29.5	721
7	**40**	44.8	737
8	PPh_3	35.9	729

[a] ^{31}P {H} NMR (202.5 MHz, $CHCl_3$). [b] literature value.[53] [c] no reaction occurred using **31**. Only free phosphine was present in solution, thus no J_{PSe} value was available.

The magnitude of the ^{31}P-^{77}Se coupling constant, J_{PSe} is related to the basicity of the phosphine, with larger values of J_{PSe} in phosphine selenides corresponding to reduced basicity of the phosphine and an increase in the s character of the lone pair of electrons on the phosphorus atom.[56, 63] **Table 1** shows the J_{PSe} values for these KITPHOS monophosphines decrease in the order **40** > **36** > **19** > **16** > **30**. On comparing the phosphines bearing only one KITPHOS unit, as expected the cyclohexyl-substituted KITPHOS monophosphine **16** with a J_{PSe} value of 702 Hz (entry 1) is the most electron-rich followed by **19**, with a J_{PSe} value of 723 Hz (entry 2) and **36**, with a J_{PSe} value of 727 Hz (entry 5). Surprisingly however, **40**, possessing a saturated ethanoanthracene substituent, shows the largest J_{PSe} value of 737 Hz (entry 7). It is unlikely that this reflects the electronic influence of the phosphorus substituents, as an alkyl group might be expected to lead to a more electron-rich phosphine compared to that of the corresponding ethenoanthracene such as **19**. In fact, the s-character of the phosphorus lone pair can also be influenced by the size of the groups on the phosphorus. Larger groups on the phosphorus cause a widening of the intervalence angles at the

phosphorus atom. This widening decreases the s character of the lone pair on the phosphorus atom and results in a decrease in the J_{PSe} value. Thus the value of J_{PSe} is affected not only by the electron withdrawing / donating effect of the substituents on the phosphorus but also by steric factors.[63] This effect is observed in **30** and **37** which possess their corresponding two KITPHOS units. This additional bulk presumably causes **30** to have the lowest J_{PSe} value (701 Hz, entry 3) of all the phosphines measured due to the decreased s character of the phosphorus lone pair and **37** to have the decreased J_{PSe} value of 721 Hz (entry 6) compared to **19** (723 Hz, entry 2) and **36** (727 Hz, entry 5) bearing the corresponding mono KITPHOS units.

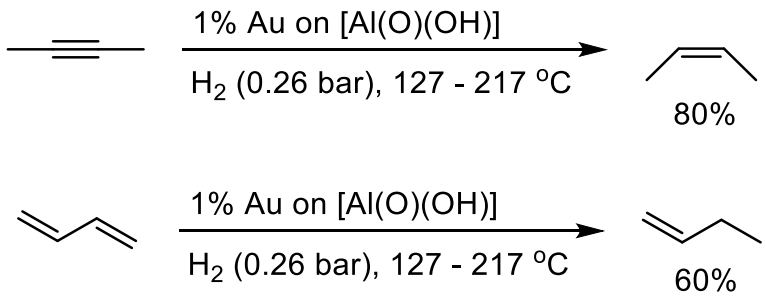
Ligand **31** did not react with KSeCN and so no J_{PSe} value could be obtained (entry 4). One would predict that the extra steric bulk associated with three KITPHOS units around the P-atom would result in a J_{PSe} value even lower than that of **30**. This will be discussed further in Chapter 3, section 3.2.1.

Chapter 3. Triaryl-like KITPHOS monophosphines in gold-catalysed transformations

3.1 Introduction to Gold Catalysis

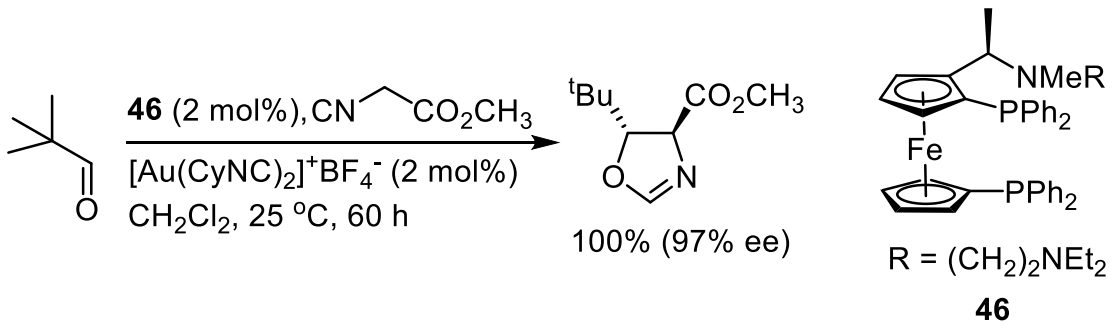
The use of gold catalysis has grown enormously in the past 15 years, with the vast majority of transformations involving the electrophilic activation of unsaturated bonds, such as alkynes and alkenes, followed by the subsequent attack of a nucleophile. Recent reviews on gold catalysis[64] have shown the versatility of these reactions in accommodating allenes, enynes, diynes and dienes as well as simple alkynes and alkenes into their transformations. A variety of nucleophiles have also been successfully employed, such as oxygen,[65] nitrogen,[66] sulphur[67] and carbon.[68] Typical transformations in gold catalysis include the hydration of alkynes,[69] hydroamination of alkenes[70] or alkynes[71] as well as many other notable cyclisations.[65a, 68d, 72] Gold catalysis has also successfully been employed to construct previously inaccessible new compounds and complex polycyclic aromatic systems[73] with applications into total synthesis.[74]

This element, once considered inert, was first reported as possessing catalytic behaviour by Bond, who demonstrated the selective hydrogenation of both 2-butyne into *cis*-2-butene and 1,3-butadiene into 1-butene using 1 % Au on [AlO(OH)] (boehmite) (**scheme 31**).[75]



Scheme 31. Gold catalysed selective hydrogenation of 2-butyne into *cis*-2-butene and 1,3-butadiene into 1-butene.

Gold has even been employed in asymmetric catalysis, with the first example being reported by Ito, Sawamura and Hayashi in 1986.[76] They reported an asymmetric aldol reaction between an aldehyde and an isocyanoacetate using a chiral ferrocenylphosphine-ligated gold(I) catalyst. This reaction successfully yielded the products, 5-alkyl / phenyl-2-oxazoline 4-carboxylates, in 100% conversion with an enantiomeric excess (ee) of 97%, under mild conditions (**scheme 32**).



Scheme 32. Gold-catalysed asymmetric aldol reaction.

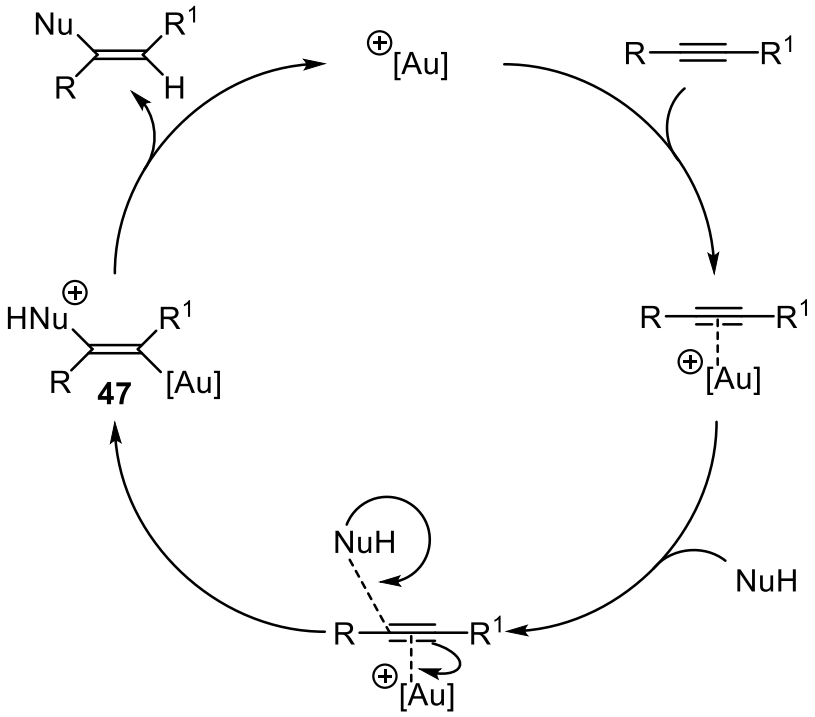
Many asymmetric reactions have subsequently been attempted with gold, however in the majority of cases these have resulted in poor ee values and/or very poor yields. It is only recently that other successful asymmetric gold-catalysed transformations have been accomplished with excellent stereoselectivities and yields.[77]

The distinct properties of gold bring with it many advantages over other types of catalysis, with its ability to perform transformations under very mild conditions whilst achieving excellent chemo- and regio-selectivities. The majority of gold catalytic reactions are performed using operationally straightforward procedures and importantly they are all able to increase the molecular complexity of the products relative to that of the reactants. However, with any type of catalysis there are disadvantages. For gold these include the need for long reaction times, with most gold reactions being performed over several hours and often the need for multistep synthetic procedures to afford the desired starting materials, which can be complex in design.[27e] The inability of gold to readily exchange between gold(I) and gold(III) redox states distinguishes itself from conventional transition metals such as palladium, by its inability to perform the classic oxidative addition / reductive elimination catalytic cycle.[78] This does however result in gold expressing high stability towards O_2 and H_2O, allowing many

gold-catalysed reactions to be successfully performed under aqueous conditions[79] in air.[68d, 72]

3.1.1 The gold catalytic cycle for nucleophilic addition to alkynes

The vast majority of gold transformations involve nucleophilic attack at a gold-coordinated alkyne, as shown in **scheme 33**. The catalytically active gold cationic species, [Au^+] first coordinates to the alkyne C≡C bond. The withdrawal of electron density away from the C≡C bond, due to this coordination, facilitates the nucleophilic attack of a nucleophile (NuH) to form a vinyl intermediate, **47**. Finally proto-deauration of this intermediate **47** regenerates the catalytically active gold species [Au^+] and most importantly, yields the product.



Scheme 33. The mechanism for the gold-catalysed nucleophilic addition to an alkyne.

Unsurprisingly it has been proven that electron-poor catalysts increase the electrophilic activation of the unsaturated bond and thus increase the rate of coordination to the alkyne. Toste[66b] and Xu[80] have shown that in hydroaminations, the barrier is lowered by these electron-poor catalysts due to enhanced coordination to alkenes. This step of the mechanism is in fact in equilibrium and often is considered to be rate determining, favouring coordination with more electron-deficient catalysts and favouring the formation of the starting material with more electron-rich ones, relative to Ph_3PAuCl.[66b] This supports a Lewis acid type explanation for gold catalysis in which an electron-deficient complex would withdraw more electron density from the C-C double or triple bond facilitating the subsequent nucleophilic attack more readily. With this hypothesis however, the proto-deauration step to liberate the product would favour a more electron-rich gold catalyst. As it has been proven that the catalytically active species is in fact a cationic gold complex [Au^+], more electron-rich and thus more basic ligands would result in the formation of a more stable [Au^+] species.[81] This more stable [Au^+] species would thus increase the favourability of this proto-deauration and increase the rate of this step in the catalytic cycle.

It has also been shown that the increased steric bulk associated with (2-$CH_3C_6H_4)_3P$ relative to (4-$CH_3C_6H_4)_3P$ also significantly increases the rate of electrophilic activation.[80] In fact, a study by Xu showed that the rate of electrophilic activation for (2-$CH_3C_6H_4)_3P$ was higher than that of $(C_6H_5)_3P$ even though the phosphine was more electron rich.[80] This shows that the steric bulk of the phosphine as well as the electronic properties significantly affect the performance of the catalyst in gold catalysis.

It is often assumed that proto-deauration is relatively fast and so is generally not considered the rate determining step, however this is not always the case. The properties of the ligands attached still affect the rate of this step, with electron-deficient / electron-withdrawing ligands on gold decreasing the rate of proto-deauration and electron-donating / electron rich ligands increasing the rate. This is however only a general rule as a single ligand can be both a σ-donor and a π-acceptor at the same time.[80] In the case of (2-$CH_3C_6H_4)_3P$ compared to (4-$CH_3C_6H_4)_3P$, the increased steric bulk of the phosphine actually caused a decrease in the rate of proto-deauration, however the use of *o*-biphenyl type ligands had the opposite effect and actually increased the rate. These *o*-biphenyl ligands such as Buchwald's

dialkylbiarylphosphines possess stabilising η^2-interactions between the gold centre and *ipso*-C-atom as well as *o*-C-atom of the lower aryl ring,[27b, 27c] as shown in **48** (**figure 18**) or even between the gold centre and *m*-C-atom as well as *ipso*-C.[27e] There is even an example of a Buchwald-type ligand possessing an η^6-interaction.[27d] Crystal structures of the architecturally similar KITPHOS ligands show the presence of these stabilising interactions, with **49** possessing an η^1-interaction between the gold centre and *ipso*-C-atom of the lower aryl ring, as depicted in **figure 18**.[58, 82]

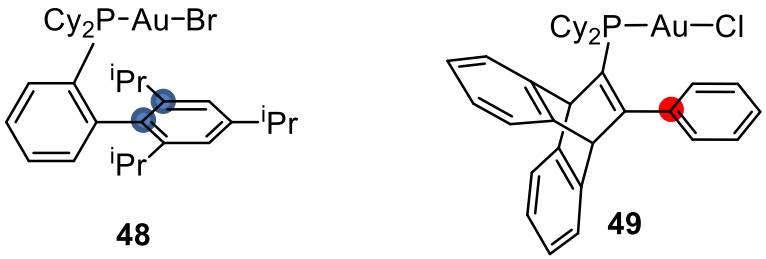
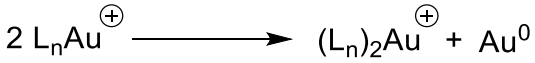


Figure 18. The Buchwald ligand **48** and the KITPHOS ligand **49** possess stabilising η-interactions between the gold centre and the highlighted atoms of the lower aryl ring.

This type of stabilising interaction is much more pronounced in palladium (II) complexes, where it greatly enhances the reactivity and lifetime of the catalysts. This interaction in gold however is only weak in comparison. Gray synthesised five of these gold (I) chloride compounds bound to differing dialkylbiarylphosphines which all possessed η^1/ η^2-interactions with bond lengths varying between 3.16 – 3.20 Å.[27c] Despite these bond lengths being significantly longer than that of a normal Au-C bond, theoretical studies of these interactions have shown that not only do they assist in stabilising the complex, but they also enhance the catalytic reactivity of the complex compared to the associated triaryl / trialkylphosphines.

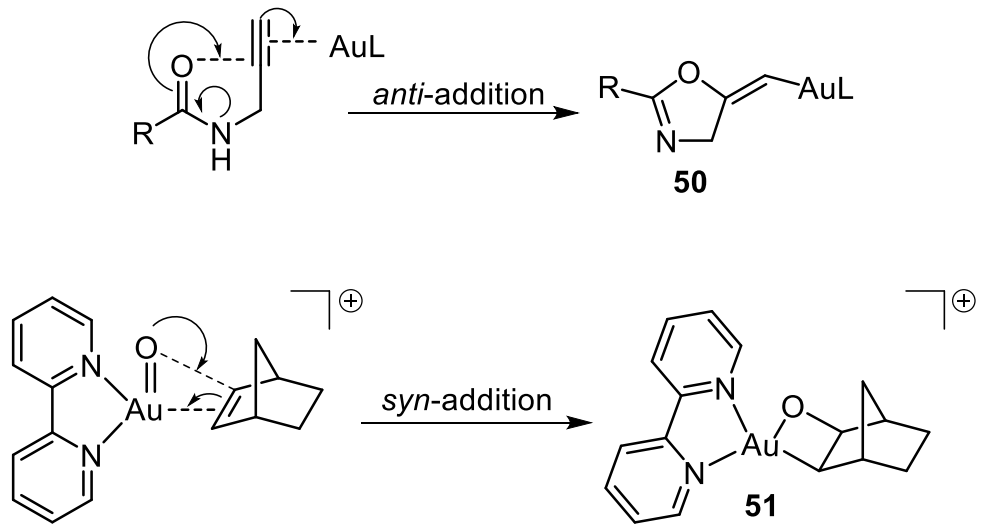
The decay of gold catalysts is also shown to be highly dependent on the properties of the ligand, with dialkylbiarylphosphines being significantly more resistant.[80] Interestingly this decay of the cationic gold complex to the neutral Au^0 species, shown in **scheme 34**, does not occur when the ligated gold(I) complex $[L_nAu^+]$ is alone in

solution, but only when it comes into contact with a substrate, such as a starting material, additive, product, or impurity.



Scheme 34. The decay of the catalytically active [L_nAu^+] to the neutral Au^0 species.

There are two possible modes of attack of the nucleophile in the mechanism of gold catalysis. In the majority of cases, such as in the cycliosomerisation of propargyl carboxamides, this attack has been proven to occur with an *anti*-conformational arrangement relative to the gold centre. This conformation was unambiguously demonstrated through *in situ* D-labelling NMR spectroscopy studies[83] as well as X-ray crystallography, through isolation of the vinyl-gold intermediate **50**.[84] There is one specific case, however, in which the nucleophilic attack on the gold-coordinated intermediate proceeds by *syn* addition. Cinellu reported this *syn* mode of addition to form the auraoxacyclobutane complex **51** in the gold-assisted synthesis of 2,3-epoxynorbornane (**scheme 35**).[85] The structure of this complex was confirmed by X-ray crystallography.



Scheme 35. Conformational modes of nucleophilic attack in gold reactions.

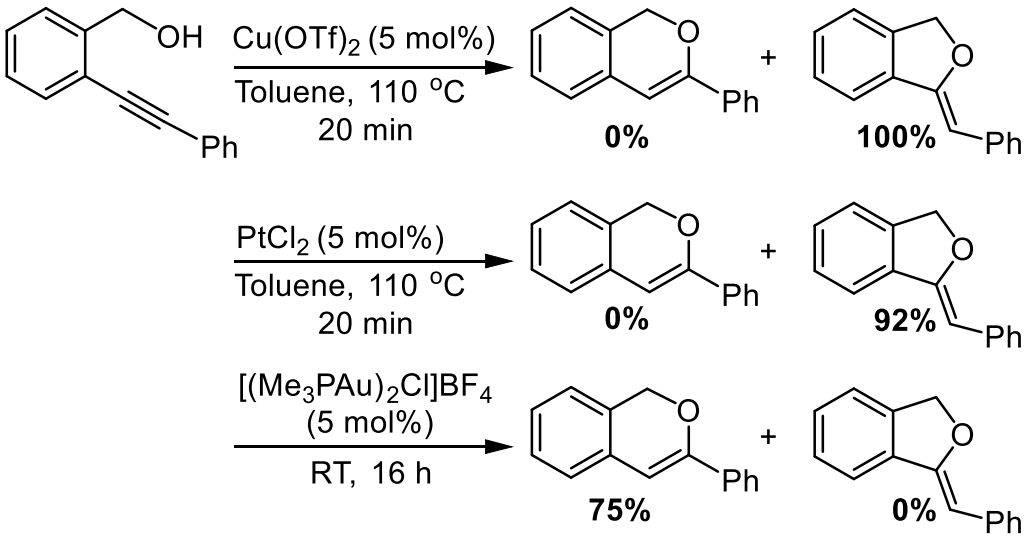
3.1.2 Relativistic effects of Gold

One of the keys to understanding the catalysis exhibited by gold, is an appreciation of the properties it possesses by being a third row transition metal in group 11 of the periodic table. Relativistic effects are significantly more pronounced in late transition metals where both the 5d and 4f orbitals are filled. Most notably the greatest of these effects is observed in gold.[86] These effects greatly determine the properties and ultimately the reactivity displayed by gold. Relativistic effects are due to the high velocities experienced by electrons orbiting around a late transition metal as they reach speeds close to that of the speed of light. As the velocity increases, the mass of the electron increases, causing an energetic stabilisation and a subsequent radial contraction in the area the electron is found. Electrons occupying s-orbitals display no orbital angular momentum and so lie closer to the nucleus of an atom. They therefore possess the highest velocities and so feel the greatest radial contraction. Those in p-orbitals also suffer a contraction, but to a lesser extent. The lowering of these s and p-orbitals then exhibits an increased shielding effect on both f- and d-electrons making them experience a lessened effective nuclear charge. This leads to a destabilisation of these orbitals and a subsequent radial expansion of d and f-orbitals. The ultimate result of this effect for gold is the contraction of its 6s and 6p orbitals and the subsequent expansion of the 5d orbital, which causes a reduction in the HOMO / LUMO energy difference (band gap). This effect is most pronounced in gold relative to the other late transition metals. This relativistic contraction of the 6s orbitals helps to explain gold's ability to form strong covalent bonds, as well as the high ionisation potential of its 6s-electron/s which accounts for its high stability to oxidation.[87] Relativistic effects are also seen to be responsible for the strong Lewis acidity shown by gold, due to its low-lying LUMO, which is more easily accessible to population.[88]

Silver which is in group 11 as well, also possesses these relativistic effects, although to a lesser extent and as a result can perform similar transformations to that of gold. Gold, with an electronegativity (EN) of 2.4 expresses stronger Lewis acidity than silver (EN = 1.9). This increased electron affinity expressed by gold is shown in the relative first ionisation potentials of these elements, with experimental values of 9.22 eV for gold and 7.58 eV for silver.[87] This difference is accounted for by the increased

contraction of gold's 6s orbital, which feels a greater effective nuclear charge and so is bound more strongly to the atom in comparison to silver's 5s.[89]

Platinum, with an electronegativity of 2.2, expresses strong relativistic effects and as such can also perform similar transformations to that of gold. The advantage gold has over platinum is in its ability to form strong covalent bonds to ligands such as phosphines, due to its greater electron density in the 6s orbital.[88] Platinum on the other hand can actually be inhibited by complexation or even addition of phosphine ligands.[68c] As a result most platinum-catalysed reactions are performed with simple salts. Gold's ability to form stable gold (I) complexes with ligands such as phosphines and *N*-heterocyclic[90] / acyclic[91] carbenes has opened up new avenues in catalysis. This is easily demonstrated in **scheme 36**, where the simple salts $PtCl_2$ and $Cu(OTf)_2$ both result in excellent conversion of [2-(2-phenylethynyl)phenyl]methanol into the 5-membered ring, dihydroisobenzofuran product. Catalysis by the phosphine-coordinated gold(I) dimer, on the other hand, produces solely the 6-membered ring, isochromene product.



Scheme 36. Difference in regioselectivity observed with salts of copper,[92] platinum[93] and phosphine-coordinated gold complexes.[94]

It must be mentioned that even though relativistic effects account for the largest contribution to the observed properties of gold, other factors, such as the lanthanide contraction do have an effect. The lanthanide contraction is the result of the f-electrons, 4f electrons in the case of gold, being poor shielders of nuclear charge and therefore as the atomic number increases across the lanthanides, a reduction in the atomic radii is observed. This increased effective nuclear charge exhibited on going from La to Lu, causes a contraction of the 5p, 5d and 6s orbitals, which as they fill up, causes the near equal radii of second and third row transition metals, such as Ag and Au.[87] However the lanthanide contraction predicts the contraction of the 5d orbital rather than the expansion predicted by relativistic effects and as a result is commonly ignored with respect to gold. Calculations have shown that ionisation energies and atomic radii are best described on the basis of relativistic effects. These give values significantly closer to that of experimental values.[87]

3.1.3 Gold-carbene- vs Gold-carbocation-stabilised intermediates

In many of its transformations, including the mechanism shown in **scheme 33**, gold could be considered merely to act as a rather expensive Lewis acid, however this is not the case. The fact that electrophiles can be trapped by vinyl-gold intermediates demonstrates that the mode of bonding in the gold species is more complex than a purely Lewis acid model can explain. Hammond[95] reported the first isolation of an intermediate gold(I) species in the gold-catalysed cyclisation of allenoates to γ-lactones. This subsequently led to other groups such as Gagné,[96] Hashmi[84, 97] and Shi[98] to isolate gold(I) intermediate species. Intermediates involving gold(III) were later published by Ahn,[99] who also reported the divinyl gold(III) intermediate species **52** (**figure 19**).

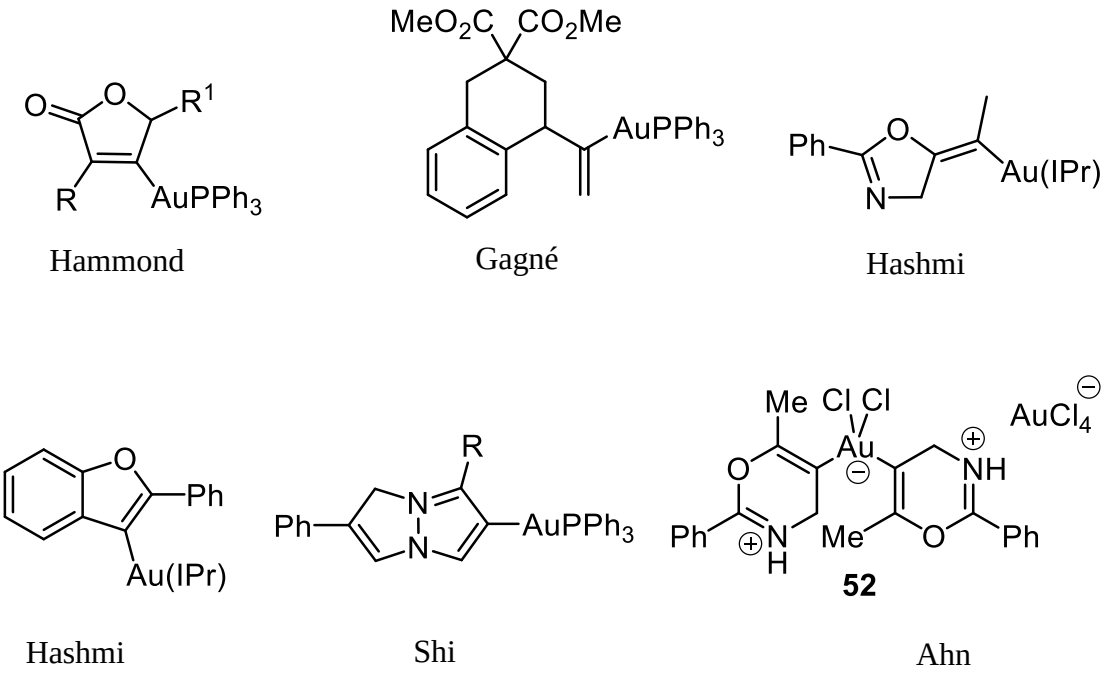
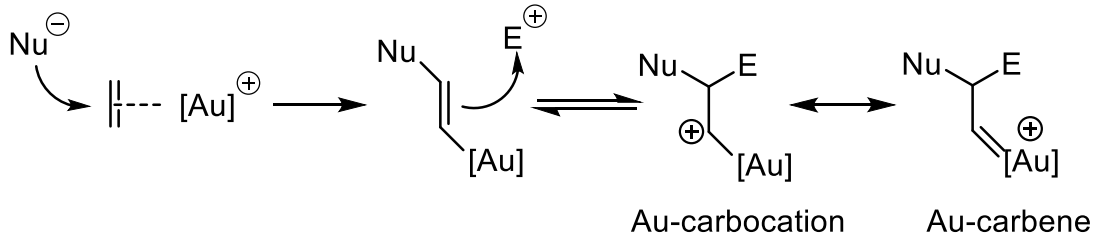


Figure 19. Examples of vinyl gold intermediates in the current literature which have been isolated and fully characterised.

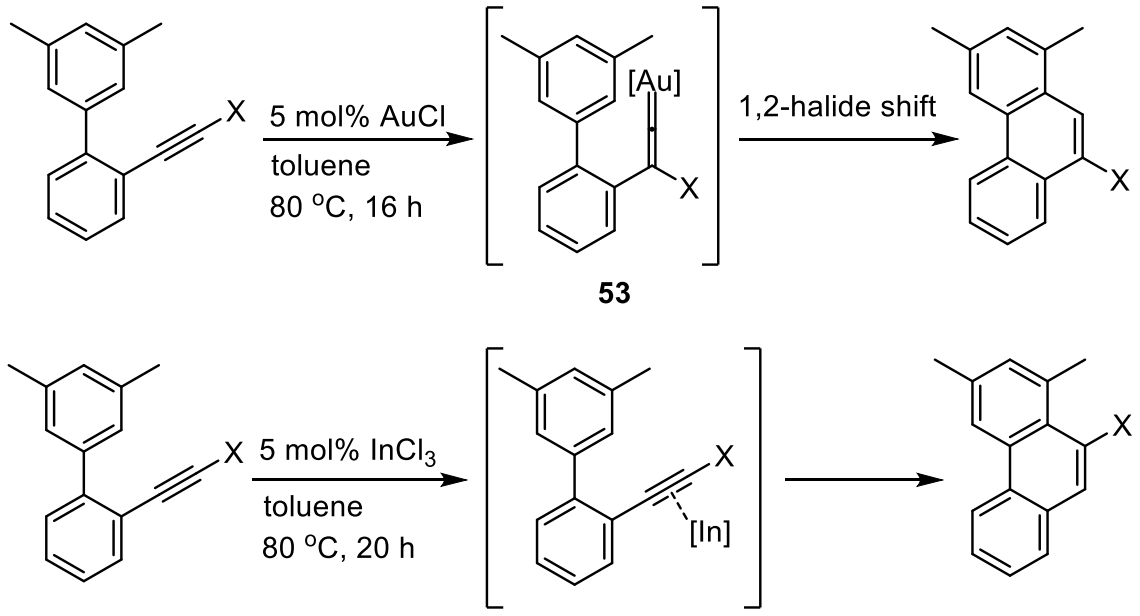
The discovery and isolation of these intermediates led to the proposal that donation of electron density from the relativistically expanded 5d orbitals of gold into empty p-orbitals of the vinyl substrate could be responsible for the apparent stability of vinyl-gold intermediates. In essence, "back bonding" could be responsible for this observed stabilisation, allowing isolation and full characterisation to be possible. This model of bonding is similar to the Dewar-Chatt Duncanson model[100] which involves back donation from metal d-orbitals into the π*-orbital of a substrate. However as π*-orbitals are too high in energy for meaningful overlap with gold's 5d-orbitals, it is proposed that this back donation is into lower energy empty p-orbitals instead.[101]

This then led to a debate over the exact bonding mode present in these intermediates and thus the mode of bonding present in the gold catalytic cycle. The vast majority of calculations and experimental evidence points towards the formation of intermediates with a mainly carbo-cationic gold character in the mechanistic cycle (**scheme 37**).[64f, 101-102] Conversion from the postulated carbocationic structure to the carbene stabilised resonance form would lead to a subsequent increase in Au-C π-bonding and a corresponding decrease in σ-bonding contributions.



Scheme 37. The possible resonance forms in vinyl-gold intermediates trapped by an electrophile.

It was not until reactions such as the cyclopropanation of enynes with alkenes,[103] intramolecular diyne cyclisations[73a, 104] and the synthesis of halophenathrenes[105] that evidence of the proposed gold-carbene bonding character present in gold intermediates became apparent. The products of these reactions were most easily explained through intermediates possessing this type of bonding mode. This is demonstrated clearly in **scheme 38**, showing the synthesis of halophenathrenes,[105] where $InCl_3$ gave the 10-haloanthrene product, exclusively, in a purely Lewis acid catalysed mechanism. The mechanism for AuCl however was proposed to proceed through a vinylidene Au-carbene bonded intermediate **53**, resulting from a 1,2-halide transfer to give the 9-haloanthrene in 100% yield when X = Br and 76% yield when X = I.

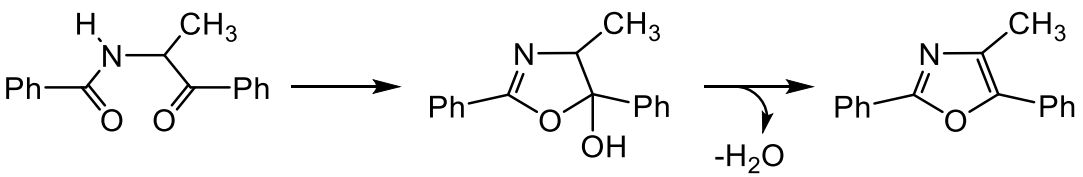


Scheme 38. Synthesis of haloanthrenes, using $InCl_3$ and AuCl.

The construction of metal carbenes is dependent upon the attached ligands on the gold catalyst, as well as the substrate. Phosphites, which are strongly π-acidic ligands withdraw electron density from the substrate, decreasing the back donation into the Au-C bond. This then causes a lengthening of the Au-C bond, leading to a more carbo-cationic bonding nature in the intermediate.[101] It must be noted though that the Au-C bond in these intermediates has a bond order ≈1. Therefore there is not a formal Au=C double bond present. Thus it has been proposed that the actual nature of this bonding exists on a continuum between the two extreme carbocation and carbene stabilised scenarios, possessing varying degrees of σ- and π-bonding. This is also supported by there being no crystallographic evidence of carbene-stabilised gold intermediates, as all the Au-C bond lengths have been far too long. This type of bonding is well established in ruthenium chemistry, for instance in the bonding of any of Grubb's catalysts, where a Ru=C carbene bond is seen as more useful in explaining their reactivity.[106]

3.2 Gold Catalysis in the synthesis of oxazoles / oxazolines

Oxazoles are present in many biologically active antitumour, antiviral, antibacterial, antifungal and antihistamine compounds, as well as many other natural products such as alkaloids.[107] The vast number of books and papers on the properties, uses and syntheses of oxazoles is testament to their usefulness. There are currently many methods for the synthesis of oxazoles without the need of catalysts, however they tend to require harsh conditions, such as high temperatures or strong acids. The most commonly used of these being the Robinson - Gabriel synthesis[107e, 108] in which an amido-ketone undergoes a cyclisation-dehydration reaction using a strong acid (**scheme 39**).

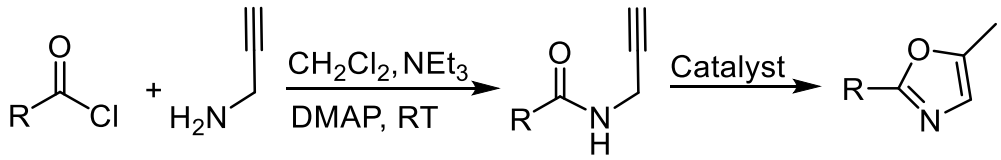


Scheme 39. Robinson – Gabriel synthesis of oxazoles. i) conc. H_2SO_4, RT, ii) H_2O.

However, this method invariably results in low yields, with only a few specific examples showing synthetically useful yields.[107, 108] This led to the pursuit for more efficient transition metal-catalysed syntheses.

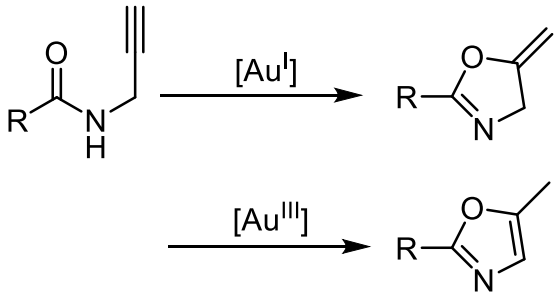
3.2.1 Cycloisomerisation of propargyl carboxamides

A very efficient route for the synthesis of oxazoles is the cycloisomerisation of propargyl carboxamides, which are easily synthesised in excellent yield through a single step condensation reaction between a propargyl amine and an acid chloride (**scheme 40**).



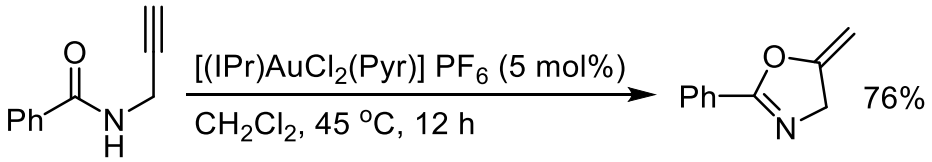
Scheme 40. Synthesis of oxazoles through propargyl carboxamides.

Palladium(II) catalysts have been used to achieve good yields of oxazoles from the corresponding propargyl carboxamides.[109] However these reactions tend to be performed at high temperatures and often give mixtures of several products. Many other catalysts have also been used.[110] Gold, with its ability to perform this transformation under mild conditions, including at RT, exhibits excellent functional group tolerance. However the product from the cyclisation of propargyl carboxamides depends on the oxidation state of the gold catalyst. Gold(III) catalysts[111] [Au^{III}] yield the corresponding oxazole product from these cyclisations, whereas gold(I) catalysts[83b, 83c, 112] [Au^{I}] actually give the oxazoline product, bearing an exocyclic methylene group (**scheme 41**).



Scheme 41. Gold(I) and gold(III) catalysts exhibit different product selectivity in the cycloisomerisation of propargl carboxamides.

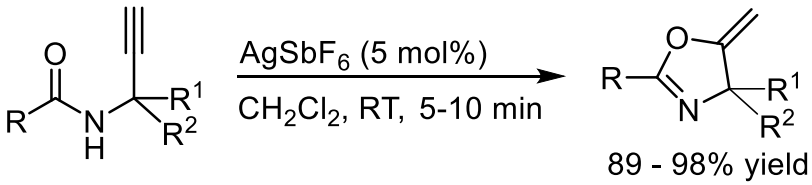
This difference in product selectivity between gold(I) and gold(III) has been observed in many other transformations.[113] Recently however, exceptions to this rule have been found. Blanc and Frémont[112b] used the gold(III) *N*-heterocyclic carbene catalyst [(IPr)$AuCl_2$(Pyr)] PF_6 to afford the 5-methylene-2-phenyl-4,5-dihydrooxazole (oxazoline) product from the associated *N*-prop-2-ynyl benzamide in 76% yield after stirring at 45 ^oC for 12 h (**scheme 42**). This yield of the product did however contain 7% of the 2-phenyl-5-methyloxazole by-product.



Scheme 42. Gold(III) catalyst, [(IPr)$AuCl_2$(Pyr)] PF_6 affords the oxazoline product in the cycloisomerisation of *N*-prop-2-ynyl benzamide.

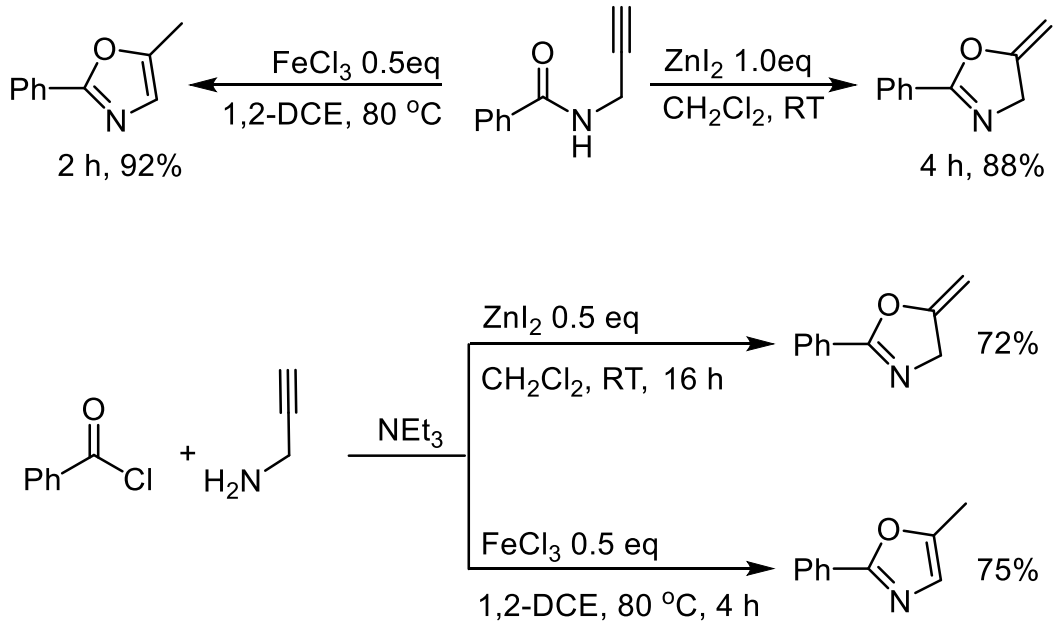
Oxazolines can also be made by replacing the propargyl methylene protons with aryl / alkyl groups (R^1, R^2) to prevent tautomerisation to the oxazole. This methodology has been successfully employed using copper(I) catalysts[109a, 114] which would otherwise promote cyclisation to give the oxazole; acheiving excellent yields but

requiring high temperatures. Harmata[115] has also used this philosophy to great effect on using $AgSbF_6$ (5 mol%) to give excellent yields of the oxazoline products with a range of substrates after only 5-10 min at RT, where R^1 and R^2 are alkyl groups (**scheme 43**).



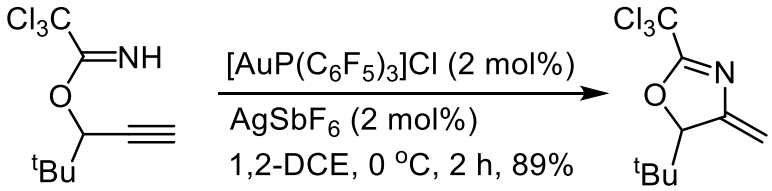
Scheme 43. Cycloisomerisation of propargyl carboxamides to yield 4,4-dialkyl-5-methylene oxazolines.

In an effort to increase the economic efficiency, Wang[116] demonstrated the use of inexpensive zinc and iron salts in affording the relative oxazoles / oxazolines selectively from a range of propargyl carboxamides in good to excellent yield. These catalysts were also shown to be able to perform these reactions directly from the corresponding acyl chlorides in good yield (**scheme 44**).



Scheme 44. Synthesis of oxazoles using $FeCl_3$ and oxazolines using ZnI_2 as the catalyst.

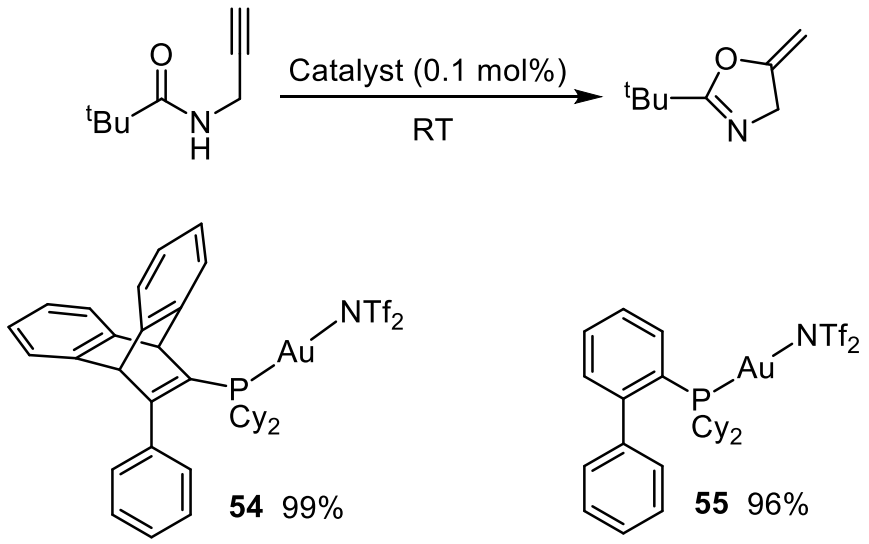
Gold[117] and silver[118] catalysts have also been used to give 4-alkylidene-2-(trichloromethyl)oxazolines by the cycloisomerisation of propargylic trichloroacetimidates (**scheme 45**). These work very well with both aromatic and aliphatic groups at the β-position to the alkyne (^{t}Bu group in **scheme 45**), however the need for the trichloro group limits the variety of substrates used. The added inability of purifying the starting reagents, the propargylic trichloroacetimidates, further disadvantages this synthetic procedure as this could impact the ease of isolation ability and thus the purity of the product after cyclisation. **Scheme 45** demonstrates the synthesis of 5-(*tert*-butyl)-4-methylene-2-(trichloromethyl)-4,5-dihydrooxazole in 89% yield using $[AuP(C_6F_5)_3]Cl$ (2 mol%) and $AgSbF_6$ (2 mol%) after stirring in 1,2-DCE at 0^{o}C for 2 h.[119]



Scheme 45. Synthesis of 4-methylene oxazolines from propargylic trichloroacetimidates.

3.2.2 KITPHOS phosphines in the gold(I)-catalysed cycloisomerisation of propargyl carboxamides

The Doherty-Knight group has previously reported the synthesis of methylene oxazolines from the corresponding propargyl carboxamides, using gold(I) complexes of KITPHOS monophosphine. These gold(I) complexes were not only shown to be highly efficient in this transformation, but also highly competitive with gold(I) complexes of Buchwald's dialkylbiarylphosphines (**scheme 46**).[54c]



Scheme 46. The cyclisation of 2,2-dimethyl-*N*-prop-2-ynylpropionamide to give the oxazoline product using gold(I) complexes of KITPHOS **54** and Buchwald phosphine **55.**

It is well known in gold catalysis that the properties of an attached ligand directly influence the properties of the resulting catalyst. This is due to the size and diffuse nature of the 5d orbitals on gold, which ensures that in gold-ligand complexes, the binding is dominated by orbital overlap rather than electrostatic charge. In this regard, the Doherty-Knight group then chose to investigate the effect of using a KITPHOS monophosphine bearing diphenyl groups in this reaction. It was found that KITPHOS ligands bearing the less electron-rich diphenylphosphino group **57** significantly outperformed those bearing the more electron-rich dicyclohexylphosphino group **56** in the gold-catalysed cyclisation of propargyl carboxamides (**figure 20**).[58]

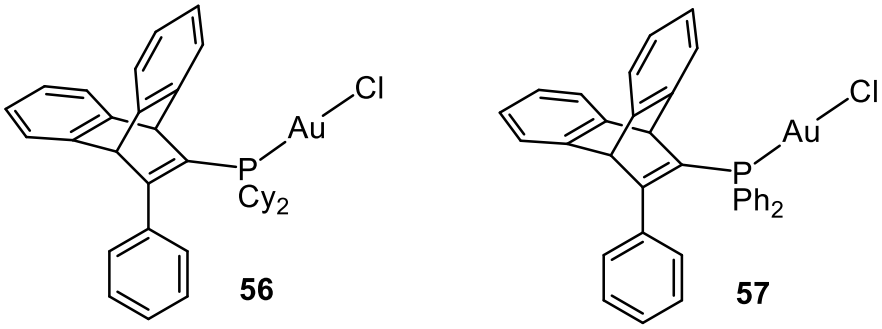
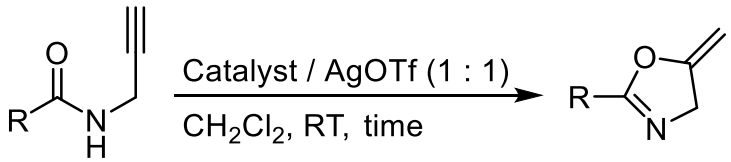
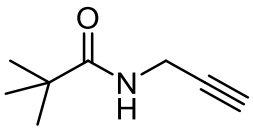
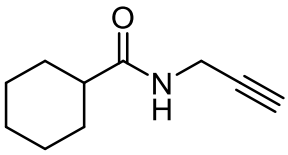
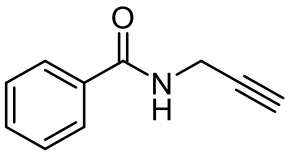
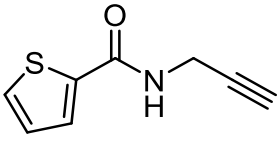
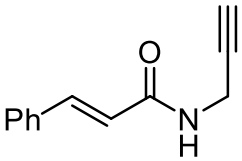


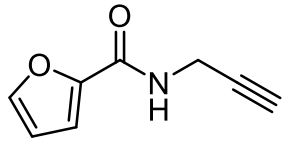
Figure 20. Gold(I) complexes of dicyclohexyl (**56**) and diphenyl (**57**) KITPHOS monophosphines.

Such differences in catalytic ability are demonstrated in the cyclisation of *N*-prop-2-ynylthiophene 2-carboxamide, which after 4 h stirring at RT gave conversions of 79% and 57% respectively (**table 2**, entries 7 and 8). This is echoed throughout **table 2**, with entries 3 and 4 showing the conversions of 84% for **57** and 63% for **56** to the 2-cyclohexyl-5-methylene-4,5-dihydrooxazole product. The results shown in **table 2** are a selection from this study.[58]

Table 2. Cycloisomerisation of propargyl carboxamides results using **57** and **56**, the gold(I) complexes of diphenyl / dicyclohexyl KITPHOS monophosphines.

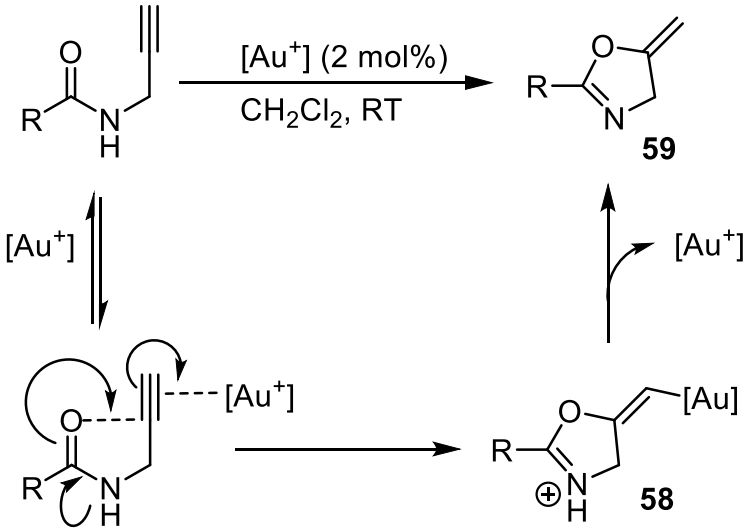


Entry [a]	Substrate	Catalyst	Time / h	Conversion / %
1		**57**	1	96
2		**56**	1	92
3		**57**	1.5	84
4		**56**	1.5	63
5		**57**	0.5	74
6		**56**	0.5	61
7		**57**	4	79
8		**56**	4	57
9 [b]		**57**	5	80
10 [b]		**56**	5	69

11		**57**	1.5	85
12		**56**	1.5	73

[a] i) 2 mol% ClAu[P], 2 mol% AgOTf, CH_2Cl_2 (2 ml), RT, 0.5 h, ii) propargyl carboxamide (0.5 mmol) added, RT, time. [b] reaction performed in 1,2-DCE, 50°C.

The mechanism for the cycloisomerisation of propargyl carboxamides is shown in **scheme 47**. Firstly the gold complex [Au^+] coordinates to the alkyne C≡C bond. This initiates the attack of the amide carbonyl, from the concerted push of electron density through the lone pair of electrons on the N-atom, forming the vinyl-gold(I) intermediate **58**. Finally proto-deauration of intermediate **58** produces the methylene oxazoline **59** and regenerates the catalytically active species, [Au^+] and most importantly yields the oxazoline product.



Scheme 47. Mechanism for the gold(I) catalysed synthesis of oxazolines from propargyl carboxamides.

It has already been put forward that the rate determining step for this reaction is the proto-deauration step.[80] A dynamic equilibrium exists for coordination of the gold(I) catalysts to the alkyne. This equilibrium is expected to favour coordination more strongly for the less electron-rich diphenyl-substituted KITPHOS catalysts, due to their greater Lewis acidity. Proto-deauration on the other hand is favoured by more

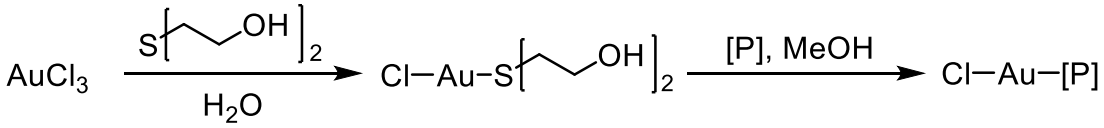
electron-rich catalysts. This is due to the increased stability of the cationic gold(I) species [L_nAu^+], which is regenerated in this step. As the rate determining step for this reaction is proto-deauration, the diphenyl catalysts might be expected to be less efficient in catalysis than their cyclohexyl counterparts, which is in contrast to the experimental results. It is possible that significantly more degradation takes place on the more reactive [L_nAu^+] active species of gold(I) complexes of dicyclohexyl KITPHOS monophosphines. This would lead to lower conversions to the products which would be exacerbated with increased reaction times.

In order to investigate this further, the effect of increasing the bulk of the KITPHOS monophosphine had on its catalytic ability was explored, through the progressive increase in the number of KITPHOS units around the phosphorus atom. Increased bulk around the gold centre has already been seen to enhance catalytic efficiency by stabilising the active gold(I) cationic species and thus increasing the rate of proto-deauration.[66b, 73b] The lower aryl ring of the KITPHOS moiety and Buchwald's dialkylbiarylphosphines has been presumed to enhance the stability of the overall gold catalyst, through weak interactions with the gold centre. To quantify this presumption, the catalytic ability of KITPHOS monophosphines without these lower aryls was investigated. The aim was to fine-tune the properties of the gold species, in order to gain a better understanding of the properties required for efficient gold catalysis.

3.2.3 Gold(I) complexes of KITPHOS monophosphines

To achieve this aim, firstly a range of differing phenyl-substituted KITPHOS monophosphines **19**, **30**, **31**, **36** and **40** were synthesised, as shown in Chapter 2. The associated gold(I) chloride complexes were then formed in good to excellent yield through the dropwise addition of 2,2'-thiodiethanol to an aqueous solution of gold(III) chloride at 0 ^oC, followed by addition of the phosphine [P] in methanol (**scheme 48**). All these gold catalysts were then purified by recrystallisation through the slow diffusion of methanol into a chloroform solution of the gold(I) chloride KITPHOS

complex and the crystal structures obtained (**figures 21** - **26**).



Scheme 48. Synthesis of gold(I) chloride complexes of KITPHOS monophosphines.

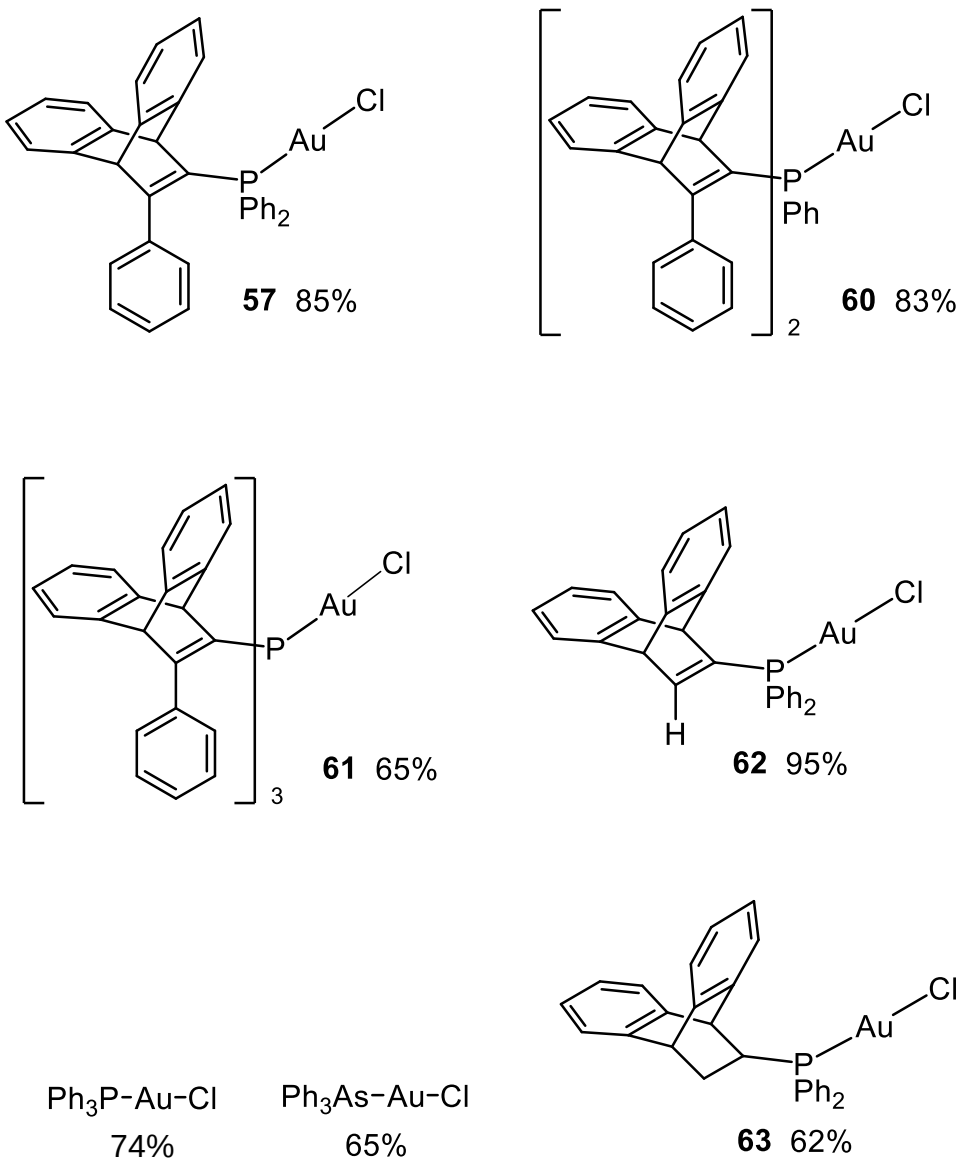


Figure 21. Structures and yields of gold(I) chloride complexes.

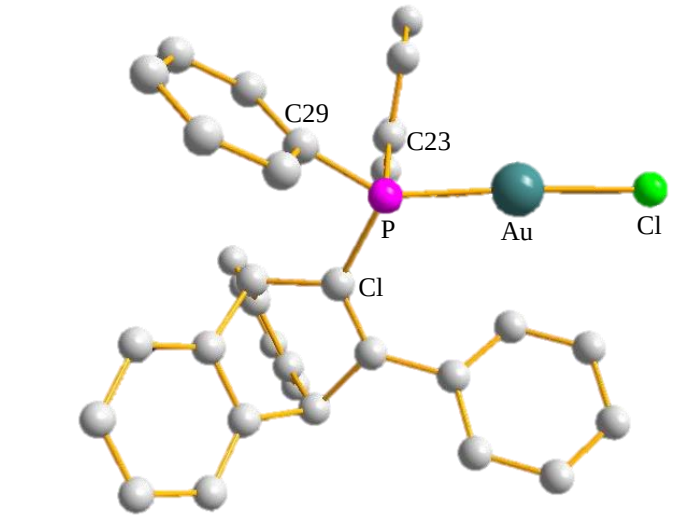


Figure 22. Crystal structure of [11-(diphenylphosphino)-12-phenyl-9,10-dihydro-9,10-ethenoanthracene]gold(I) chloride, **57**. Hydrogen atoms and a solvent molecule (CH_2Cl_2) have been removed for clarity. Selected bond lengths (Å) / bond angles (º): P-O = 1.4781(12), P-C1 = 1.7948(17), P-C22 = 1.8012(17), P-C28 = 1.8019(17), O-P-C1 = 113.91(7), O-P-C22 = 112.50(8), O-P-C28 = 111.88(8).

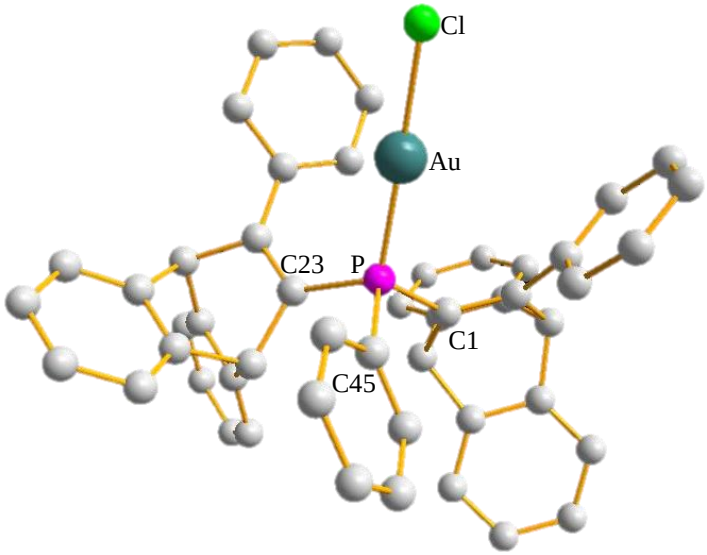


Figure 23. Crystal structure of [{bis(12-phenyl-9,10-dihydro-9,10-etheno-anthracen-11-yl)} phenylphosphine]gold(I) chloride, **60**. Hydrogen atoms and a solvent molecule ($CHCl_3$) have been removed for clarity. Selected bond lengths (Å) / bond angles (º): P-C1 = 1.805(3), P-C23 = 1.811(3), P-C45 = 1.815(3), Au-P-C1 = 115.30(10), Au-P-C23 = 114.49(10), Au-P-C45 = 112.20(11).

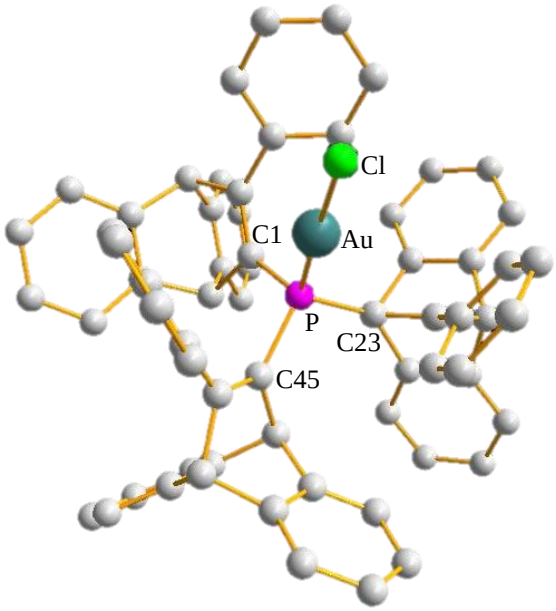


Figure 24. Crystal structure of [tris(12-phenyl-9,10-dihydro-9,10-etheno-anthracen-11-yl)]phenylphosphinegold(I) chloride, **61**. Hydrogen atoms have been removed for clarity. Selected bond lengths (Å) / bond angles (°): P-C1 = 1.801(3), P-C23 = 1.805(3), P-C45 = 1.806(3), Au-P-C1 = 113.06(9), Au-P-C23 = 113.28(9), Au-P-C45 = 114.94(10).

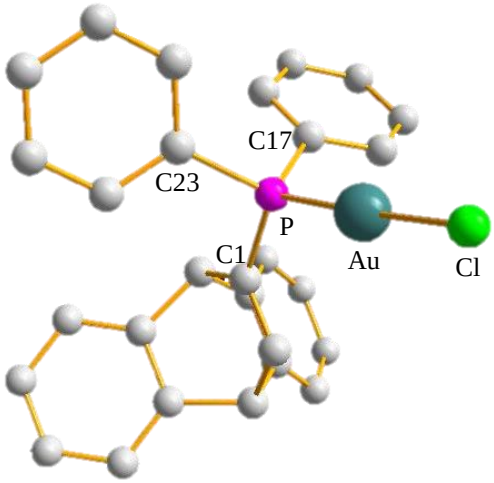


Figure 25. Crystal structure of [11-(diphenylphosphino)-2,12-dihydro-9,10-dihydro-9,10-ethenoanthracene]gold(I) chloride, **62**. Hydrogen atoms and a solvent molecule ($CHCl_3$) has been removed for clarity. Selected bond lengths (Å) / bond angles (°): P-C1 = 1.778(4), P-C17 = 1.804(5), P-C23 = 1.815(4), Au-P-C1 = 115.70(13), Au-P-C17 = 111.28(14), Au-P-C23 = 114.55(14).

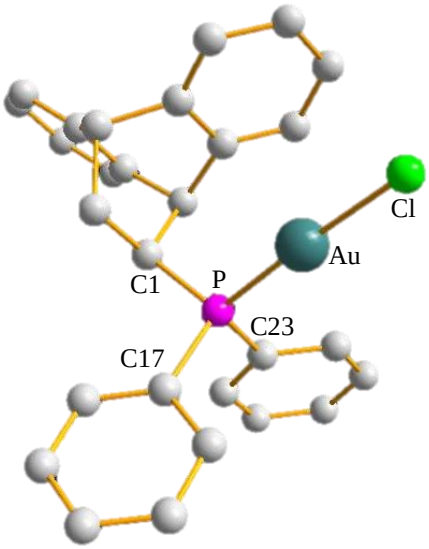


Figure 26. Crystal structure of [11-(diphenylphosphino)-2,12-dihydro-9,10-dihydro-9,10-ethanoanthracene]gold(I) chloride, **63**. Hydrogen atoms and two solvent molecules ($CHCl_3$) have been removed for clarity. Selected bond lengths (Å) / bond angles (°): P-C1 = 1.823(3), P-C17 = 1.820(3), P-C23 = 1.808(3), Au-P-C1 = 115.46(11), Au-P-C17 = 112.04(11), Au-P-C23 = 112.87(11).

Table 3. Key bond lengths / bond angles for gold(I) chloride complexes of KITPHOS monophosphines.

Gold complex	Au-Cl / Å	Au-P / Å	Cl-Au-P / (°)
57	2.2844(7), 2.2890(7)	2.2298(7), 2.2447(7)	176.34(20), 176.60(20)
60	2.2859(8)	2.2308(8)	177.88(3)
61	2.2921(9)	2.2299(7)	178.01(4)
62	2.3005(10)	2.2279(10)	175.61(4)
63	2.2900(8)	2.2236(8)	177.16(3)

The gold-ligand bond distances and angle from the crystal structures of the gold(I) complexes of KITPHOS monophosphines are shown in **table 3**. Gold complexes usually adopt a linear conformation, however our crystal structures show

degrees of deformation away from perfect linearity. The distortion from linearity presumably results from the difference in size between the phenyl rings on the phosphorus and the bulkier KITPHOS group. Surprisingly the presence of the lower aryl ring (the 12-phenyl group) does not seem to play a significant role in this distortion. In fact the presence of the lower aryl ring seems to aid in the adoption of a linear Cl-Au-P angle with **62** being 175.61^{o} and **57** being 176.34^{o} and 176.60^{o}. **57** possessed two independent molecules in the asymmetric unit and so two sets of values for each parameter are given. The symmetrically trisubstituted phosphorus in **61**, gave the greatest degree of linearity as expected (Cl-Au-P angle of 178.01^{o}).

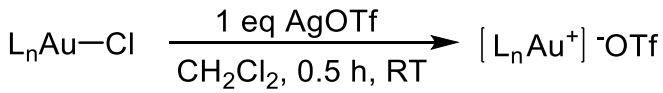
As explained in Chapter 1 section 1.3, larger values of J_{PSe} in phosphine selenides correspond to an increase in the s character of the lone pair of electrons on the phosphorus atom and subsequent shortening of any P-M bond.[56, 63] The J_{PSe} values for these KITPHOS monophosphines decrease in the order **40** > **36** > **19** > **30** (Chapter 2, section 2.6, **table 1**) and thus as expected, **table 3** shows the Au-P bond lengths increase in the reverse order **63** (**40**) < **62** (**36**) < **57** (**19**) < **60** (**30**). Steric factors also affect the J_{PSe} of a phosphine,[63] with the additional bulk in **30** causing the lowest J_{PSe} value (701 Hz) and the longest Au-P bond length (2.2308(8) Å) of all the phosphines measured. The KITPHOS monophosphine **31** did not react with KSeCN and so no J_{PSe} value could be obtained. One would predict that the extra steric bulk associated with three KITPHOS units around the phosphorus atom would result in a J_{PSe} value even lower than that of **30**. However the corresponding gold(I) chloride complex of this phosphine **61** possesses a Au-P bond length of 2.2299(7) Å, which is essentially the same as that in **60** (2.2308(8) Å). Thus, the J_{PSe} value of this phosphine in **61** would actually be expected to be almost identical to that of **30**. Interestingly, the dynamic behaviour observed in the NMR spectra of phosphine oxide **29** (Chapter 2, section 2.2) was not observed in **61**, despite **61** also displaying inequivalent C_6H_4 group resonance signals, within each particular KITPHOS substituent. This may be due to the larger Au-atom in **61** allowing less freedom of rotation compared to the O-atom in **29**.

As already mentioned in section 3.1.1 of this chapter, an essential property of this type of catalyst is the presence and strength of the stabilising interactions between the gold(I) centre and C-atoms in the lower aryl ring found in the KITPHOS unit.[120] These interactions in gold may only be weak, but they have been predicted to be vital for the longevity of the active catalyst. **57** shows the presence of two such interactions

(η^2-interactions) between the gold centre and the *ipso*-C-atom, 3.313(3), 3.329(3) Å as well as with one of the *o*-C-atoms, 3.253(3), 3.209(3) Å of the lower aryl ring. This leads to a non-planar arrangement between this lower aryl ring and the gold centre. The gold(I) chloride complex **60**, however, despite possessing two KITPHOS units only possesses one such interaction between the gold centre and *o*-C-atom of one of the two lower aryl rings with a bond length of 3.324(3) Å. This is a very weak η^1-interaction even for gold, with many of those of dialkylbiarylphosphines being between 3.16 – 3.20 Å.[27c] Ligand-ligand repulsions around the phosphorus atom are presumably responsible for the phosphine adopting a geometry in which these lower aryl rings are pushed further away from the gold centre in **60** relative to **57**. In this respect, it was of interest to see the effect that this increase in bulk, which was intended to increase the rate of the rate determining proto-deauration step, has on the cycloisomerisation of propargyl carboxamides. In particular the presence of these stabilising interactions was expected to favour the reaction of substrates which otherwise require long reaction times.

The gold(I) chloride complex **61** on the other hand possesses four such interactions, one between each *ipso*-C-atom and the gold centre (3 x η^1-interactions), with bond lengths of 3.192(3), 3.227(3) and 3.340(3) Å respectively as well as an η^1-interaction between an *o*-C-atom and the gold centre with a bond length of 3.193(3) Å. These three lower aryl rings are positioned around the phosphorus atom in a funnel shape, which extends out towards the gold and chlorine atoms. This, with the added bulk of having three KITPHOS units around the single phosphorus atom, leads to a particularly stable catalyst, which even after two years being left in air had undergone no visible degradation as judged by NMR spectroscopy. The gold(I) chloride complex **63** surprisingly does possess an η^1- interaction. As no lower aryl ring is present in **63**, this stabilising interaction is between the gold centre and one of the aromatic ring C-atoms (C11) in the anthracene backbone of the KITPHOS unit. This again is only weak, but at 3.309(3) Å it is shorter and thus stronger than the η^1- interaction of **60** (3.324(3) Å) and the interaction between the gold and the *ipso*-C-atom of **57** (3.313(3)/ 3.329(3) Å). However the interaction between the gold and the *o*-C-atom of **57** (3.253(3)/ 3.209(3) Å) is much stronger. The gold(I) chloride complex of **62** does not possess any lower aryl ring and nor does it possess any such stabilising interactions with the KITPHOS backbone.

Gold intrinsically favours formation of a two-coordinate species with a linear geometry when bonding, as represented above in the bonding of the KITPHOS monophosphine gold chloride complexes. Since the catalytically active gold species in solution requires a vacant coordination site, one of the ligands must dissociate. All the crystal structures of the gold(I) chloride complexes of KITPHOS monophosphines shown above possess Au-P bond lengths shorter than their corresponding Au-Cl bond lengths, which is a typical feature of gold(I) phosphine complexes.[64f] This means that abstraction of the chloride, which is more weakly bonded, is required for catalysis to occur. In our studies one equivalent of AgOTf was used (where OTf is a weakly coordinating anion) to abstract this chloride and generate the catalytically active cationic [L_nAu^+] species in solution, where L_n is a KITPHOS monophosphine (**scheme 49**).

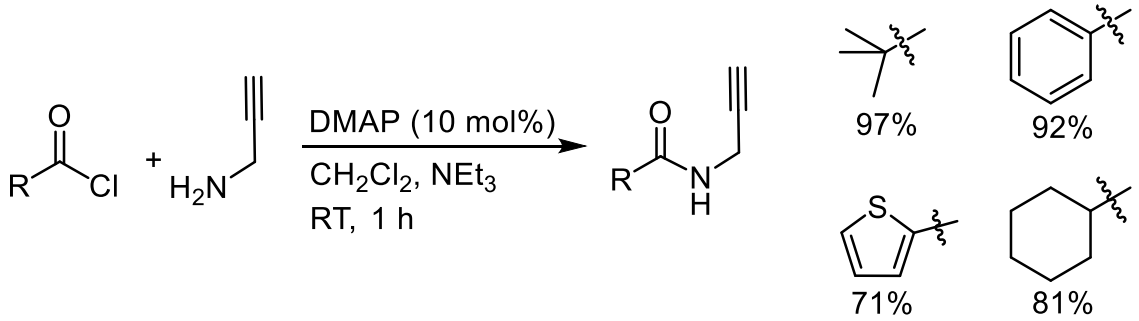


Scheme 49. Abstraction of the chloride to give the catalytically active [L_nAu^+] species.

Many groups have chosen to isolate this species for time efficiency and operational convenience, as this both removes the time needed to generate the *in situ* catalyst and minimises the error associated in accurately weighing very small quantities of hygroscopic silver salts. However, the Doherty-Knight group observed no difference in the catalytic performance of this isolated species relative to that on using the *in situ* approach, with respect to gold(I) KITPHOS complexes.[58] Scaling up the quantities of catalyst needed reduced the associated error and, as isolation of gold(I) triflate KITPHOS complexes could not be efficiently accomplished, the *in situ* approach was favoured.

3.2.4 Synthesis of propargyl carboxamides

A range of propargyl carboxamides was synthesised according to **scheme 50**. The acyl chlorides; 2,2-dimethylpropionyl chloride, cyclohexanoyl chloride, benzoyl chloride and thiophenylcarbonyl chloride were stirred at RT for 1 h, with a catalytic amount of DMAP and Et_3N to give the desired propargyl carboxamides in good to excellent yield. All were purified by column chromatography prior to use in catalysis.

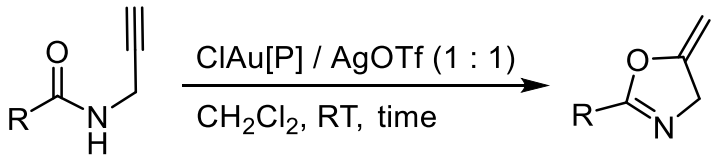


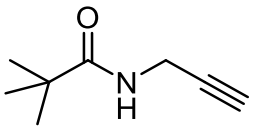
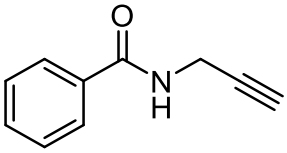
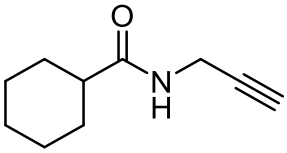
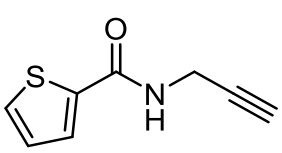
Scheme 50. Synthesis of a range of propargyl carboxamides.

3.2.3 Catalysis Results

The gold(I) chloride complexes of KITPHOS **57**, **60**, **61**, **62**, **63** (2 mol%) and silver triflate (2 mol%) were dissolved in CH_2Cl_2 and stirred at RT for 0.5 h to generate the active catalyst *in situ*. The propargyl carboxamide was then added and the reaction stirred for the specific time. The reaction mixture was then filtered through a silica plug, flushing with EtOAc and the solvent was removed under reduced pressure to give the desired oxazoline products. This procedure was repeated three times for each catalyst with each substrate and the average conversion recorded (**table 4**). A summary of the structures of the gold(I) complexes used in **table 4** is given on page xiii of this thesis.

Table 4. Results of the gold-catalysed cycloisomerisation of propargyl carboxamides.



Entry [a]	**Propargyl amide**	**Catalyst**	**Time/h**	**Conversion/%**
1		**57**	0.5	76
2		**60**	0.5	92
3		**61**	0.5	1
4		**62**	0.5	51
5		**63**	0.5	88
6		Ph_3PAuCl	0.5	50
7		**57**	0.5	71
8		**60**	0.5	>99
9		**61**	0.5	4
10		**62**	0.5	62
11		**63**	0.5	76
12		Ph_3PAuCl	0.5	41
13		**57**	1.5	88
14		**60**	1.5	98
15		**61**	1.5	4
16		**62**	1.5	69
17		**63**	1.5	80
18		Ph_3PAuCl	1.5	54
19		**57**	4	84
20		**60**	4	43
21		**61**	4	24
22		**62**	4	44
23		**63**	4	66
24		Ph_3PAuCl	4	42

[a] ClAu[P] (2 mol%), AgOTf (2 mol%), propargyl carboxamide (0.5 mmol), CH_2Cl_2 (2 ml), RT, time.

From **table 4** below one can clearly see that **57**, **60** and **63** are all highly efficient in the catalysis of propargyl carboxamides to methylene oxazolines. All the catalysts were compared against Ph_3PAuCl, the benchmark of gold catalysis. No tautomerisation to the corresponding oxazoles was evident in any of the cyclisations using Au(I) catalysts, which gave the desired methylene oxazolines exclusively.

The added steric bulk of **60** proved most advantageous in the reactions of 2,2-dimethyl-*N*-prop-2-ynylpropionamide (entry 2), *N*-prop-2-ynylbenzamide (entry 8) and *N*-prop-2-ynylcyclohexane carboxamide (entry 14) which required relatively short reaction times to give the desired oxazoline products in 92%, >99% and 98% respectively. **60** proved to be the best catalyst for the cyclisation of these first three substrates. Apart from the KITPHOS monophosphine **31** in the gold complex **61**, for which J_{PSe} could not be measured due to failure of the selenation, the KITPHOS monophosphine **30** (within the gold complex **60**) possesses the lowest J_{PSe} value of all these phosphines (701 Hz). The lower J_{PSe} for **30** indicates enhanced basicity as a result of the combination of electronic and steric effects and is expected to enhance the rate of proto-deauration. As proto-deauration is the rate determining step in these cycloisomerisations, **60** gave the greatest conversions for the first three substrates. However **60** gave a poor conversion of 43% for the cyclisation of *N*-prop-2-ynylthiophene 2-carboxamide (entry 20), which was essentially the same as the 42% observed on using Ph_3PAuCl (entry 24). This could be due to **60** possessing only a very weak stabilising η^1-interaction between the gold centre and one of the *ipso*-C-atoms of the lower aryl ring, according to its crystal structure. This interaction with a bond length of 3.324(3) Å is much weaker than those of **57**, **61** and **63** and ultimately might lead to reduced stability of the catalyst. This reduced stability would become significant when performing reactions which require longer reaction times due to decay of the active catalytic species.

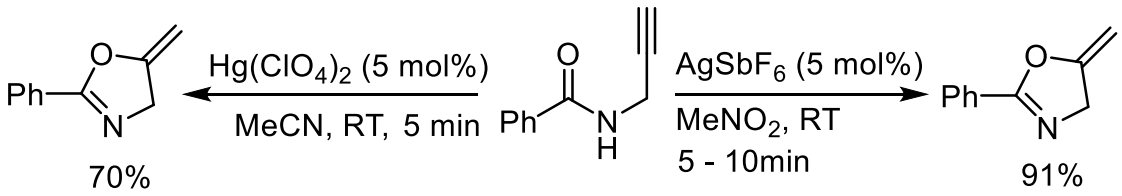
57 gave excellent results for each of the four substrates tested here, significantly better than that of Ph_3PAuCl in all cases. This was especially evident in the cyclisations which required longer reaction times, like *N*-prop-2-ynylcyclohexane carboxamide, but particularly for *N*-prop-2-ynyl-thiophene-2-carboxamide, where **57** gave significantly the best result of 84% conversion after 4 h (entry 19).

The benefit of possessing the lower aryl ring of the KITPHOS moiety is easily seen on comparing the results of **57** against those of **62**. **57** outperforms **62** with respect to each of the four substrates. This is best emphasised in the reaction of *N*-prop-2-ynylthiophene 2-carboxamide, where **57** gave a conversion of 84% (entry 19) compared to 44% using **62** (entry 22). This clearly demonstrates the benefit of the gold η^2-interaction with the *ipso*- and *o*-C-atom of the lower aryl ring in **57** along with the extra bulk of this group. In fact **62** gave results essentially equal to those of Ph_3PAuCl for both 2,2-dimethyl-*N*-prop-2-ynylpropionamide (entries 4 and 6) and *N*-prop-2-ynylthiophene 2-carboxamide (entries 22 and 24), with advantages only displayed in the other two substrates. Thus **62** could be considered to act as a slightly bulkier version of Ph_3PAuCl.

63 obtained excellent results for each of the four substrates tested. The KITPHOS ligand **40**, within the gold complex **63** is the least basic, as shown in Chapter 2 section 2.6 (J_{PSe} = 737 Hz), and so would be expected to possess the greatest rate of coordination and activation of the alkyne. However **40** would also give the slowest rate of proto-deauration. Interestingly, for substrates requiring short reaction times (0.5 h), **63** actually outperformed **57** giving 88% conversion compared to 76% for 2,2-dimethyl-*N*-prop-2-ynylpropionamide (entries 5 and 1) and 76% compared to 71% for *N*-prop-2-ynylbenzamide (entries 11 and 7). The added stabilisation due to the η^1-interaction present in **63** appears to aid its catalytic performance with respect to all the substrates. However the increased stability of **57** which possesses an η^2-interaction compared to the η^1-interaction displayed in **63** impacts on the catalysis of *N*-prop-2-ynylcyclohexane carboxamide and *N*-prop-2-ynylthiophene 2-carboxamide. These two substrates require longer reaction times and so catalyst stability and associated decay have a greater impact. This is seen in the 88% and 84% conversions displayed in **57** (entries 13 and 19) compared to 80% and 66% for **63** (entries 17 and 23).

The huge bulk and dramatic structure of **61**, as shown in its crystal structure (**figure 24**) clearly gives it great stability. It is likely that the low catalytic activity of **61** reflects this stability and the steric inaccessibility of the metal, as shown in entries 3, 9 and 15. The best result using **61** was interestingly in the cyclisation of *N*-prop-2-ynylthiophene 2-carboxamide, the most difficult substrate, which gave a conversion of 24% after 4 h (entry 21). Even so this was still the worst conversion of the six catalysts tested.

Harmata successfully used $AgSbF_6$ to catalyse the cycloisomerisation of propargyl carboxamides to oxazolines.[115] Excellent results were obtained when the two methylene protons of the propargyl carboxamides were replaced by two methyl groups. The reaction with *N*-prop-2-ynylbenzamide could also be performed successfully using $AgSbF_6$ (5 mol%) to give the oxazoline in 91% yield after 5 – 10 min at RT (**scheme 51**). Interestingly they found that there was no conversion on using CH_2Cl_2 as the solvent. In our studies AgOTf (5 mol%) didn't show any catalytic activity with any of the substrates in CH_2Cl_2 or even in a test reaction in $MeNO_2$ using *N*-prop-2-ynylbenzamide. Thus this confirms that all the conversions shown in **table 4** are due to the gold(I) catalysts.

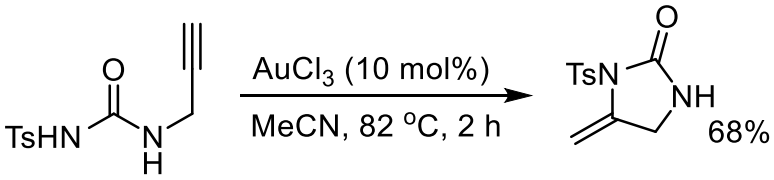


Scheme 51. Syntheses of 5-methylene-2-phenyl-4,5-dihydrooxazole.

Qian reported that $Hg(ClO_4)_2$ (5 mol%) in MeCN afforded the 5-methylene-2-phenyl-4,5-dihydrooxazole product from *N*-prop-2-ynylbenzamide in 70% conversion, after only 5 min stirring at RT (**scheme 51**).[110b] The toxicity of mercury along with the need to use stoichiometric equivalents in the vast majority of its transformations makes its use rather unattractive. These two catalytic systems have been demonstrated to effect cycloisomerisation in a very restricted range of substrates. Gold on the other hand has been shown to access these oxazoline products with a wide range of different groups at the 2-position, without the need for alkyl groups at the 4-position to aid the cyclisation.

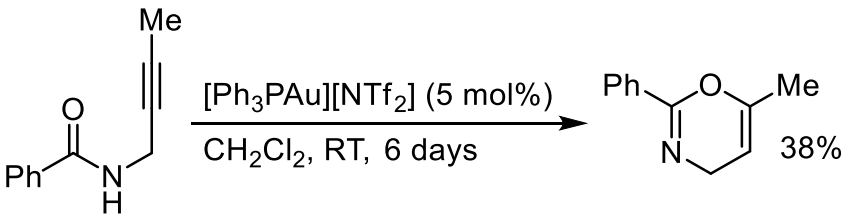
Admittedly however, there are limitations to the gold(I) catalysed cyclisation of the propargyl carboxamides. Longer reaction times and lower yields are often result from employing substrates with electron withdrawing groups in the 2- position, in addition *N*-propargylureas fail to cyclise to the corresponding oxazoline. Padwa reported that *N*-tosyl-*N*-propargylureas cyclise through the tosyl-protected N-atom to

give the imidazolidinone product rather than through the carbonyl O-atom to give the oxazoline.[66a] In fact this cyclisation only occurs on using $AuCl_3$ and only on using a tosyl-protected urea, as shown in **scheme 52**.



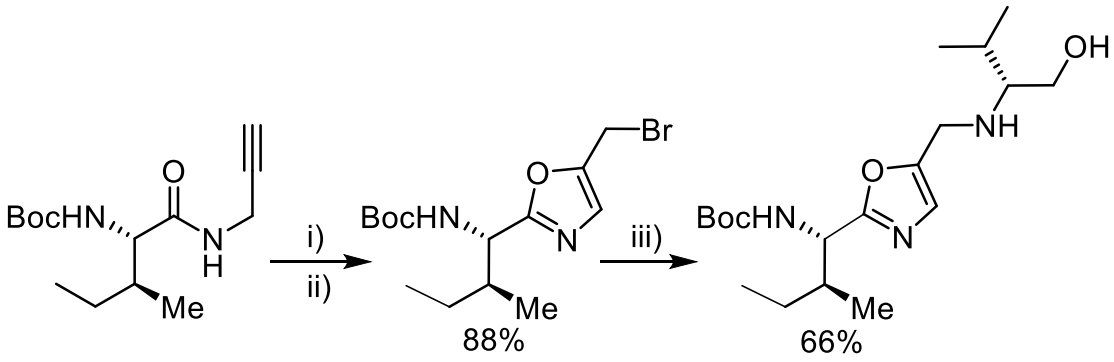
Scheme 52. Gold-catalysed cyclisation of *N*-propargylureas.

A further limitation of this transformation is the need to use a terminal alkyne to generate the desired oxazoline product in good yield. Hashmi even showed that when $R^1 \neq H$ the 6-*endo-dig* cyclisation can often be favoured on using very long reaction times (**scheme 53**, R^1= Me).[84]



Scheme 53. Long reaction times can favour the 6-*endo-dig* cyclisation of a propargyl carboxamide bearing an internal alkyne.

One method that has been used to overcome this limitation is the cyclisation and subsequent bromination of terminal propargyl carboxamides to give the corresponding 5-bromomethyloxazoles, to which a nucleophilic substitution reaction can be performed. De Brabander used these sequential three step two pot reactions to prepare oxazoles with chiral groups attached such as the example shown in **scheme 54**, using the amino alcohol D-valinol as the nucleophile.[111b] However most examples gave only moderate yields for each of the two steps.



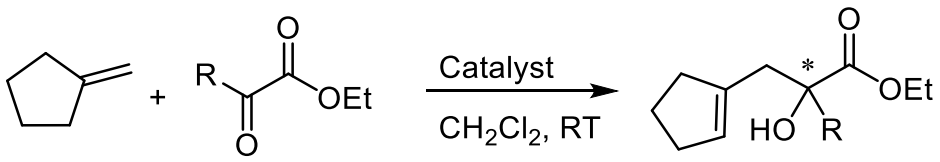
Scheme 54. Synthesis of chiral oxazoles from propargyl carboxamides.[111b] i) $AuCl_3$ (5 mol%), $CHCl_3$, RT. ii) 2,6-lutidine, Br_2, $CHCl_3$, 0 °C - RT, 88%. iii) *D*-valinol, RT, 16 h, 66%.

Our aim to extend this chemistry was to use the potentially reactive exocyclic methylene group of oxazolines generated from the gold(I) catalysed cycloisomerisation of propargyl carboxamides in a subsequent asymmetric reaction. The ability to perform this in one pot would then be investigated in order to gain access to a range of new enantiopure compounds in a single step.

3.2.4 Carbonyl-ene reaction

Methylene oxazolines, produced by the cycloisomerisation of propargyl carboxamides, are potentially reactive synthetic intermediates. Therefore, their use in asymmetric carbonyl-ene reactions was investigated. The Doherty-Knight group has previous experience in successfully performing asymmetric carbonyl-ene reactions, with $PdCl_2$(BINAP) being the benchmark for reactions on terminal alkenes such as methylene cyclopentane.[121] Therefore a brief investigation of the choice co-catalyst was performed (**table 5**). $PdCl_2$(*S*-BINAP) (5 mol%) and AgX (5 mol%) were stirred for 0.5 h in CH_2Cl_2 at RT. The methylene cyclopentane was then added followed by the pyruvate and the reaction was stirred at RT for the specified time. The results are shown in **table 5**.

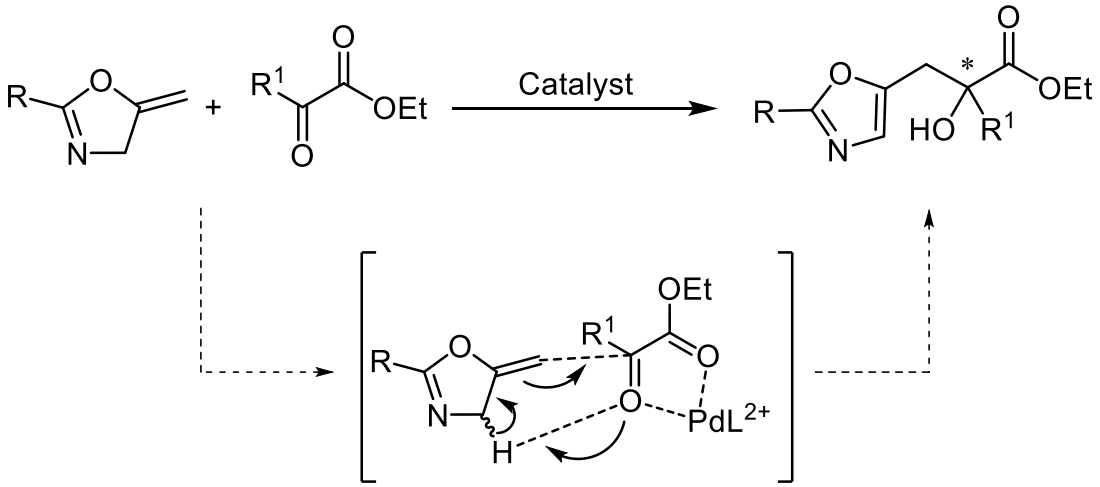
Table 5. Optimisation of the silver counterion in the asymmetric carbonyl-ene reaction of methylene cyclopentane with pyruvate.



R [a]	Catalyst	Loading/mol%	Time/h	Conversion/%	ee/%
CF_3	$PdCl_2$(*S*-BINAP)/ AgOTf (1 : 1)	5	16	0	-
CF_3	$PdCl_2$(*S*-BINAP)/ $AgSbF_6$ (1 : 1)	5	0.5	100	>95
CH_3	$PdCl_2$(*S*-BINAP)/ $AgSbF_6$ (1 : 1)	5	0.5	100	>95

[a] oxazoline (0.4 mmol), pyruvate (0.6 mmol), CH_2Cl_2 (3ml), time, RT.

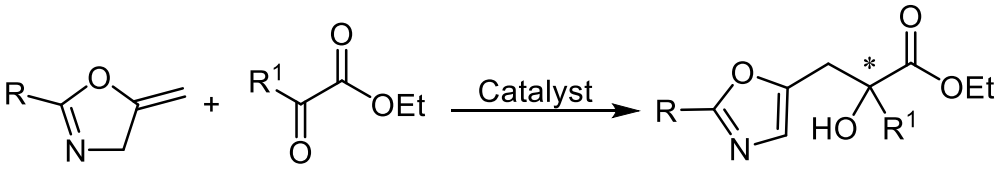
Surprisingly the use of AgOTf as a co-catalyst gave no yield of the product. However by simply changing it to $AgSbF_6$, the product was formed in 100% conversion and >95% ee. The mechanism of this transformation is thought to involve the coordination of the transition metal catalyst between the two carbonyl oxygen atoms of the pyruvate, which constrains the conformation of this molecule. This allows transfer of the chirality of the catalyst onto the substrate, controlling the preferential attack on one face of the coordinated carbonyl, as depicted in **scheme 55**.



Scheme 55. Proposed mechanism for the asymmetric carbonyl-ene reaction between a methylene oxazoline and pyruvate.

This catalyst system was then used to investigate the carbonyl-ene reaction on methylene oxazolines. For this $PdCl_2$(*S*-BINAP) (5 mol%) and $AgSbF_6$ (5 mol%) were stirred for 0.5 h in CH_2Cl_2 at RT. The methylene oxazoline was then added, followed by the pyruvate and the reaction was stirred at RT for the specified time. The reaction was worked up and the results are shown in **table 6**.

Table 6. Results of carbonyl-ene reaction of pyruvates with methylene oxazolines.

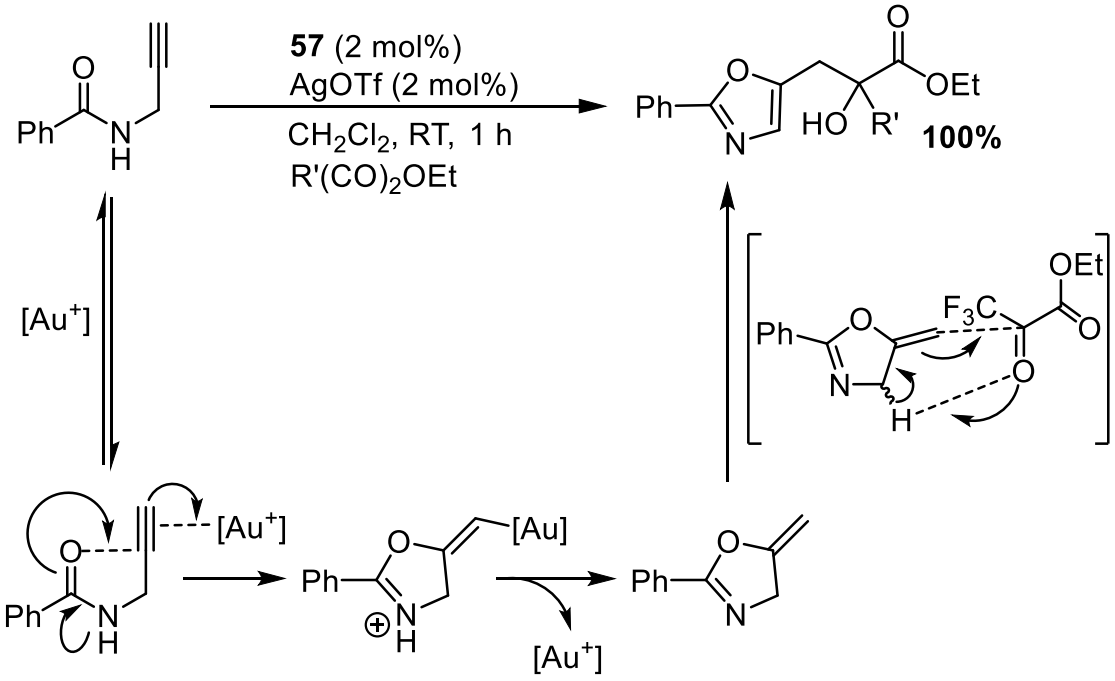


Entry [a]	R	R^1	Catalyst	Time / min	Conv. / % [b]	ee/% [c]
1	^{t}Bu	CF_3	$PdCl_2$(*S*-BINAP)/ $AgSbF_6$	8	100	0
2	Ph	CF_3	$PdCl_2$(*S*-BINAP)/ $AgSbF_6$	10	100	0
3	Cy	CF_3	$PdCl_2$(*S*-BINAP)/ $AgSbF_6$	10	100	0
4 [d,e]	S	CF_3	$PdCl_2$(*S*-BINAP)/ $AgSbF_6$	30	100[b]	0
5 [f]	^{t}Bu	CF_3	$Cu(OTf)_2$/ BOX	20	100	0
6 [f]	Ph	CF_3	$Cu(OTf)_2$/ BOX	20	100	0
7	^{t}Bu	CH_3	$PdCl_2$(*S*-BINAP)/ $AgSbF_6$	16 h	0	-
8	Ph	CH_3	$PdCl_2$(*S*-BINAP)/ $AgSbF_6$	16 h	0	-
9	^{t}Bu	CF_3	none	30	20	0
10	Ph	CF_3	none	10	100	0

[a] $PdCl_2$(*S*-BINAP) (5 mol%), $AgSbF_6$ (5 mol%), oxazoline (0.4 mmol), pyruvate (0.6 mmol), CH_2Cl_2 (3ml), time, RT. [b] conversion measured by ^{1}H NMR, [c] ee measured by chiral GC, [d] S = thiophenyl. [e] reaction time not optimised, [f] $Cu(OTf)_2$ (10 mol%), BOX (2,2'-isopropylidene bis[(4*S*)-4-*tert*-butyl-2-oxazoline]) (10 mol%), oxazoline (0.4 mmol), pyruvate (0.6 mmol), CH_2Cl_2 (3ml), time, RT.

The carbonyl-ene reaction between ethyl trifluoropyruvate and all the methylene oxazolines proceeded with quantitative conversions after only 8 – 30 min, however with 0% ee (entries 1 - 4). On changing the catalyst to $Cu(OTf)_2$/ BOX, the racemic product was again obtained (entries 5 and 6). In an attempt to slow down the reaction rate methyl pyruvate was used instead of the much more reactive ethyl trifluoropyruvate, however no product was obtained even after 16 h at 61 ^oC in $CHCl_3$ as well as at RT (entries 7 and 8). Both the oxazoline and the pyruvate were recovered from the reaction mixture. The uncatalysed reaction with ethyl trifluoropyruvate was then investigated. On employing 2-*tert*-butyl-5-methylene-4,5-dihydrooxazole, 20% conversion to the carbonyl-ene product was observed after 30 min (entry 9). However for 2-phenyl-5-methylene-4,5-dihydrooxazole, 100% conversion to the product was observed after only 10 min (entry 10), which is the same result as shown in the "catalysed" reaction (entry 2). This clearly shows that the uncatalysed mechanistic pathway competes with the catalysed route, negating any possible asymmetric induction from the chiral catalyst. Even on employing $Cu(OTf)_2$ with BOX, which is a well-established catalyst system used in carbonyl-ene reactions, no ee was obtained for any of the substrates.

As the reaction with 2-phenyl-5-methylene-4,5-dihydrooxazole and ethyl trifluoropyruvate proceeded to completion after only 10 min, a one pot synthesis from the propargyl carboxamide was established. This tandem gold(I) catalysed cycloisomerisation / carbonyl-ene reaction was successfully performed in one pot with 100% conversion and 99% yield after only 1 h (**scheme 56**).



Scheme 56. The tandem cycloisomerisation / carbonyl-ene reaction of *N*-prop-2-ynylbenzamide with ethyl trifluoropyruvate.

3.2.5 Conclusions to the gold-catalysed cyclisation of propargyl carboxamides

Gold(I) complexes of KITPHOS monophosphines have proven highly efficient in the cycloisomerisation of propargyl carboxamides to give methylene oxazolines exclusively. Optimisation of these KITPHOS monophosphines has shown that those bearing less electron-rich phenyl substituents rather than cyclohexyl, dramatically increases the catalytic efficiency for these transformations. The presence of stabilising η^n interactions, where n = 1 or 2 in these catalysts, may be responsible for the improvement in catalytic efficiency by increasing the lifetime of the catalyst. Increasing the bulk around the P-atom, as shown in **60**, can enhance catalytic performance, except for substrates which require longer reaction times. However addition of too much bulk has been shown to inhibit catalysis (**61**).

A carbonyl-ene reaction was successfully performed between the exocyclic methylene of a range of oxazolines and ethyl trifluoropyruvate, giving quantitative conversions after 8 – 30 minutes. From these results a tandem one pot cycloisomerisation / carbonyl-ene reaction from *N*-prop-2-ynylbenzamide to give the ethyl 3-[5'-(2-phenyloxazole)]-2-(trifluoromethyl)-2-hydroxypropanoate product in quantitative yield after only one hour, has been achieved. Unfortunately, the use of chiral catalysts did not lead to asymmetric induction in the carbonyl-ene reaction.

3.3 Gold-catalysed synthesis of isochromenes

Isochromenes are synthetically useful compounds present in many biologically active products and natural products such as the antibacterials Obionin B and anhydrofusurabin lactone (**figure 27**).

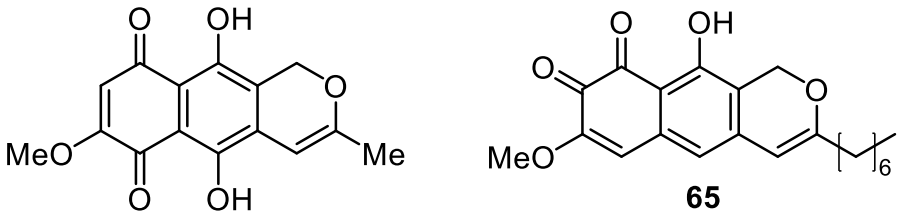
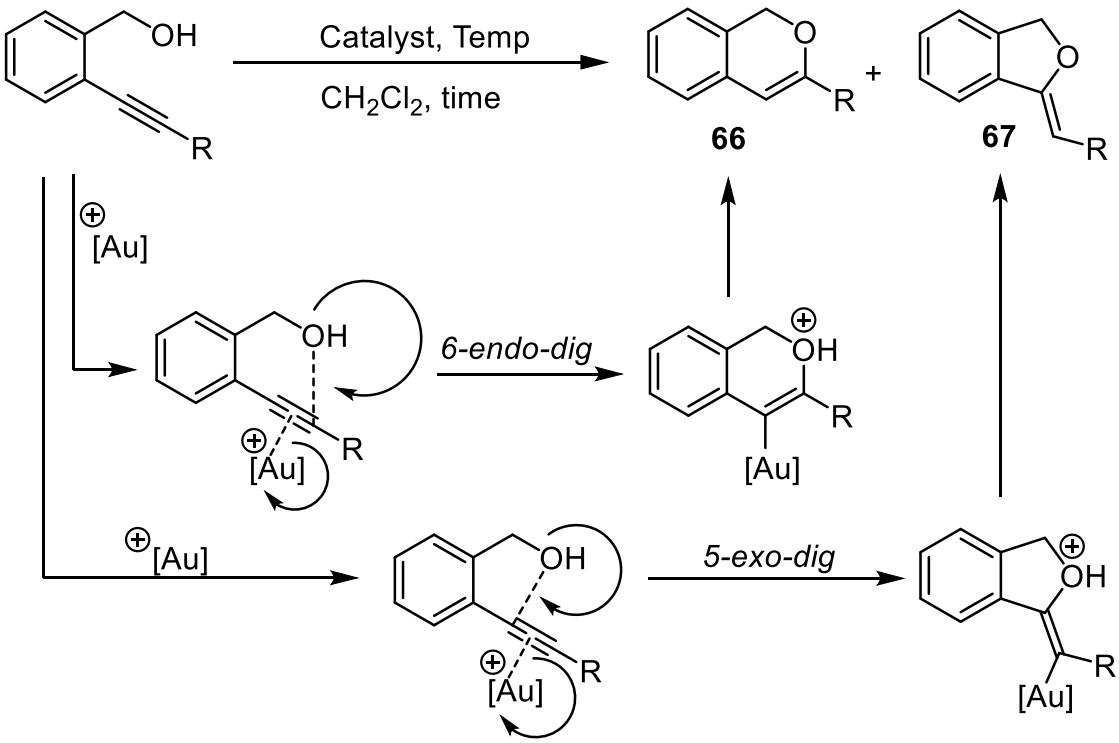


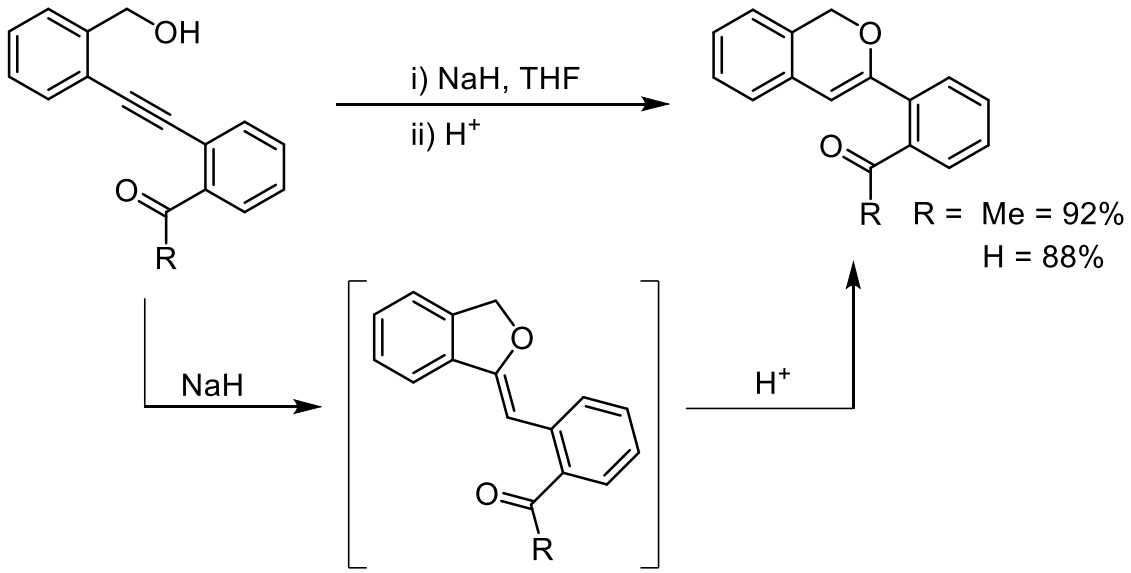
Figure 27. Structures of Obionin B (**64**) and anhydrofusurabin lactone (**65**).



Scheme 57. The possible mechanistic pathways for the gold-catalysed cyclisation of 2-[(2-alkynyl)phenyl]methanols.

Although the most common method of synthesis of these compounds is from the cycloisomerisation of 2-[(2-alkynyl)phenyl]methanols, none of the reported procedures have been shown to tolerate a wide range of differing substituents and functional groups. In this cyclisation there are two possible products, resulting from the 6-*endo-dig* cyclisation to give the 6-membered ring isochromene product **66** and the 5-*exo-dig* cyclisation to give the 5-membered ring dihydroisobenzofuran product **67** (**scheme 57**).

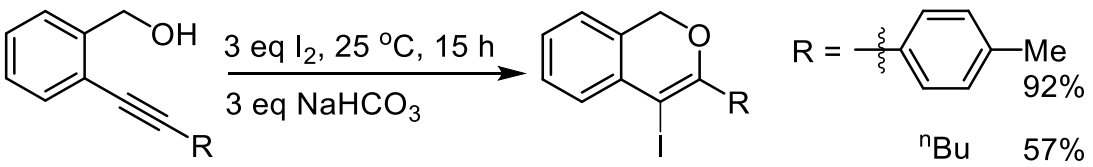
Padwa and Weingarten showed that 2-[(2-alkynyl)phenyl]methanols possessing phenyl substituents bearing an *ortho*-carbonyl group attached to the end of the alkyne, can be cyclised to the isochromene product in excellent yield though treatment with a base, followed by an acid work-up.[122] It was shown that this reaction proceeded initially through a base-mediated 5-*exo-dig* cyclisation to produce the dihydroisobenzofuran product, which following an acid work-up underwent a rapid acid-catalysed rearrangement to yield the isochromene (**scheme 58**).[122] In this case NaH was used as the base, although KOH has also been used to the same effect.[123]



Scheme 58. The synthesis of isochromenes from 2-[(2-alkynyl)phenyl]methanols.

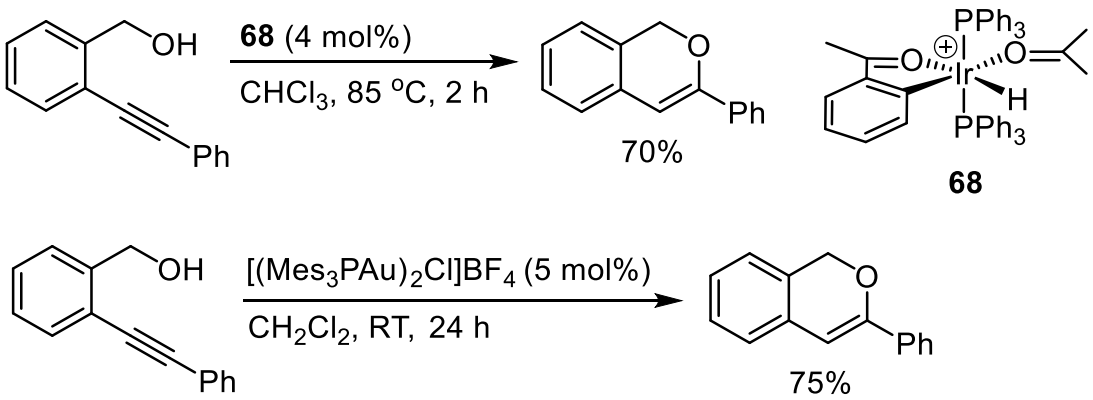
Iodine has successfully been used in the synthesis of these 6-membered ring products, giving 3-iodo-1*H*-isochromenes in good to excellent yield when the alkyne substituent was an aromatic ring.[124] However a dramatic reduction in yield was

recorded on employing an alkyl group instead (**scheme 59**).



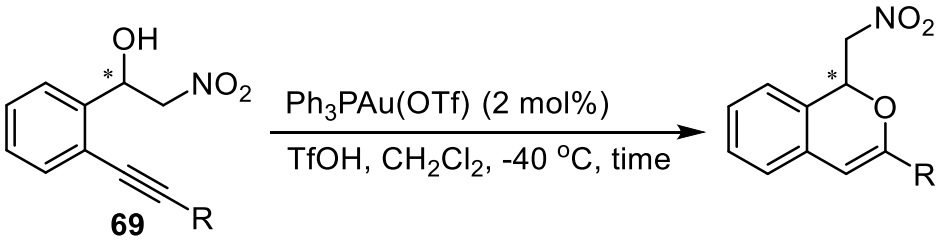
Scheme 59. Iodine mediated synthesis of 3-iodo-1*H*-isochromenes from 2-[(2-alkynyl)phenyl]methanols.

Palladium-based catalysts[125] have also been employed in an effort to yield the desired isochromenes. However the most efficient of these, the PdI_2/KI catalyst either gave a resulting poor yield or required high temperatures. The ruthenium catalyst $CpRuCl(PPh_3)_2$ has also been used, however it is limited to use on terminal alkynes and requires a catalyst loading of 10 mol% as well as temperatures of 90 °C to achieve effective catalysis.[126] Crabtree has reported the use of the iridium-based catalyst **68** which affords the isochromene products exclusively in good to excellent yield (**scheme 60**).[127] However it was then discovered that gold could perform the same cyclisation but at RT instead, albeit using a slightly higher catalyst loading. Hashmi used the gold dimer, $[(Mes_3PAu)_2Cl]BF_4$ to give the desired 3-phenylisochromene in 75% yield after stirring for 24 h at RT, as demonstrated in **scheme 60**.[94] However, respectable yields were limited to only two substrates, including that shown in **scheme 60**.



Scheme 60. The comparison between the iridium and gold-catalysed synthesis of 3-phenylisochromene from [2-(2-phenylethynyl)phenyl]methanol.

The reactivity of 2-[(2-alkynyl)phenyl]methanols towards cyclisation can be increased by replacing the primary alcohol group with a secondary or tertiary alcohol. This rate enhancement is probably a result of ground-state destabilisation due to increased steric interactions which reduces the energy penalty required to reach the reactive conformation.[125a] This cyclisation can also be successfully performed by replacing the alcohol group with an aldehyde.[117, 125b, 128] In an elegant extension of this, isochromenes were produced with excellent enantioselectivities from a copper(II) catalysed asymmetric Henry reaction of *o*-alkynylbenzaldehydes to yield **69**, from which the gold(I) catalysed cycloisomerisation liberates the isochromene product (**scheme 61**).[77d]



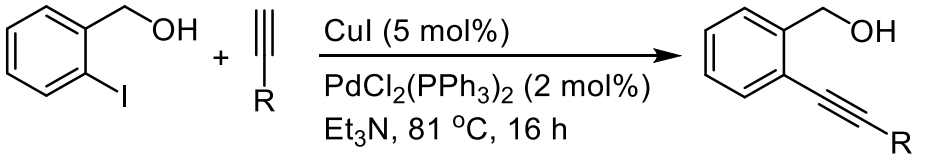
Scheme 61. Gold-catalysed synthesis of isochromenes with excellent enantioselectivities.

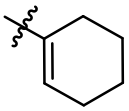
Following these reports on the use of gold catalysts in the cycloisomerisation of 2-[(2-alkynyl)phenyl]alcohols, the performance of our gold(I) complexes of KITPHOS monophosphine in this reaction was investigated.

3.3.1 Synthesis of 2-[(2-alkynyl)phenyl] alcohols

The synthesis of 2-[(2-alkynyl)phenyl]alcohols starts from the commercially available 2-iodobenzyl alcohol, which via Sonogashira reactions involving $PdCl_2(PPh_3)_2$

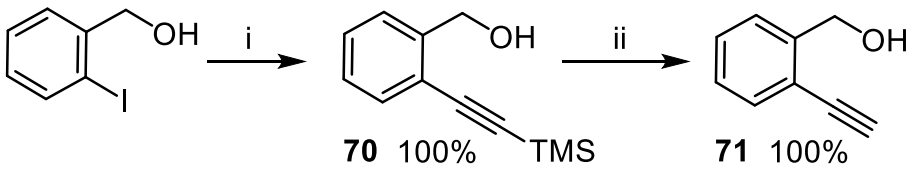
(2 mol%), CuI (5 mol%) and a terminal alkyne in triethylamine liberates the products in excellent yield after 16 h at 81 °C. **Scheme 62**, shows this synthesis and the corresponding yields of the relevant 2-[(2-alkynyl)phenyl]alcohols.



R = Ph = 100%, ^{n}Pr = 100%, ^{n}Bu = 100%, 4-MeC$_6$H$_5$ = 75%  = 99%

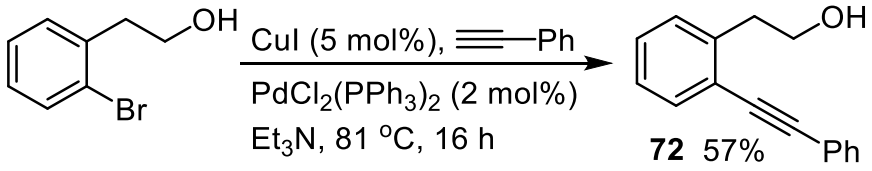
Scheme 62. The synthesis of 2-[(2-alkynyl)phenyl]alcohols from 2-iodobenzyl alcohol.

The terminal alkyne, 2-hydroxymethylphenylacetylene **71** was synthesised in 100% yield through a two-step procedure. The first step was a Sonogashira reaction between 2-iodobenzyl alcohol and trimethylsilyl acetylene using $PdCl_2(PPh_3)_2$ (2 mol%) and CuI (5 mol%) in triethylamine, which after heating for 16 h at 81 °C gave the product, [2-(2-trimethylsilylethyn-1-yl)phenyl]methanol **70** in 100% yield. **70** was then desilylated using excess K_2CO_3 dissolved in CH_2Cl_2 / MeOH (1 : 2) and after 4 h stirring at RT, **71** was afforded in quantitative yield (**scheme 63**).



Scheme 63. The synthesis of 2-hydroxymethylphenylacetylene. i) $PdCl_2(PPh_3)_2$, CuI, NEt_3, trimethylsilyl acetylene, 81 °C, 16 h, 100%. ii) K_2CO_3, CH_2Cl_2 / MeOH (1 : 2), RT, 4 h, 100%.

2-[(2-Phenylethynyl)phenyl]-1-ethanol **72** was also synthesised. This was produced in 57% yield from the Sonogashira reaction between 2-(2-bromophenyl)ethanol and phenylacetylene using $PdCl_2(PPh_3)_2$ (2 mol%) and CuI (5 mol%) in triethylamine after heating for 16 h at 81 ^oC (**scheme 64**).



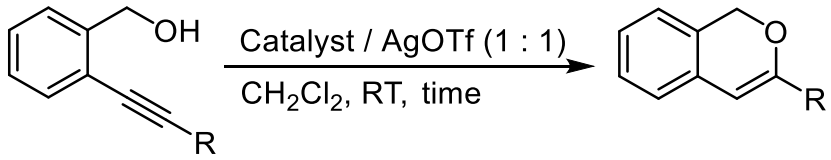
Scheme 64. The synthesis of 2-[(2-phenylethynyl)phenyl]-1-ethanol

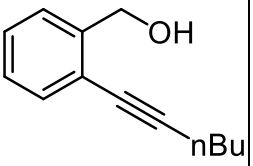
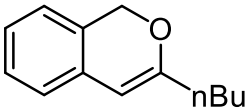
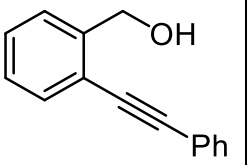
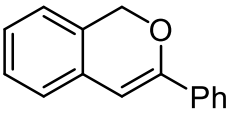
2-(2-Phenylethynyl)benzoic acid was also used as a substrate in the gold (I) catalysed transformations mentioned in section 3.3.2 below. The synthesis of this compound is highlighted in section 3.4.1 of this chapter. All compounds were purified by column chromatography before use in catalysis.

3.3.2 Catalysis results for cycloisomerisation of 2-[(2-alkynyl)phenyl] alcohols

Firstly the aim was to establish which of the gold catalysts achieved the best yields of the isochromene products. To do this a preliminary study was performed to investigate the catalytic abilities of gold(I) complexes **57**, **60**, **61**, **62**, **63**, $ClAuPPh_3$, $ClAuAsPh_3$ and $AuCl_3$ in the cyclisomerisation of 2-hex-1-ynylbenzyl alcohol and [2-(2-phenylethynyl)phenyl]methanol into the corresponding isochromene products. The gold(I) chloride complexes (2 mol %) and silver triflate (2 mol %) were dissolved in CH_2Cl_2 and stirred at RT for 0.5 h. The 2-[(2-alkynyl)phenyl] alcohol was then added and the reaction stirred for the specific time. This procedure was repeated three times for each catalyst with each substrate and the average conversion recorded (**table 7**). A summary of the structures of the gold(I) complexes used in **table 7** is given on page xiii of this thesis.

Table 7. Preliminary results of gold-catalysed cycloisomerisation of 2-[(2-alkynyl)phenyl]alcohols.



Entry[a]	Substrate	Catalyst	Time[b]	Product	Conv/%[c]([d])
1		**57**	1		100 (99)
2		**60**	1		- (40)
3		**61**	1		19 (-)
4		**62**	1		- (37)
5		**63**	1		- (81)
6		Ph_3PAuCl	1		- (27)
7		$Ph_3AsAuCl$	1		- (32)
8		$AuCl_3$	1		5 (-)
9[e]		**57**	16		100 (85)
10[e]		$Ph_3AsAuCl$	16		7 (-)
11[e]		$AuCl_3$	16		29 (-)
12[e,f]		[Au]	24		100 (75)

[a] catalyst (0.5 mol%), AgOTf (0.5 mol%), (*o*-alkynylphenyl)alcohol (0.4 mmol), CH_2Cl_2, RT, time. [b] time / h, [c] conversion measured by ^{1}H NMR. [d] isolated yield. [e] catalyst (2.0 mol%), AgOTf (2.0 mol%), [f] [Au] = $[(Mes_3PAu)_2Cl]BF_4$ (5.0 mol%) from literature.[94]

Firstly there was no evidence for the formation of the 5-*exo*-*dig* dihydroisobenzofuran product in any of the cyclisations above. With the 2-hex-1-ynylbenzyl alcohol substrate, the gold complex **57** was clearly the best, affording the product in 99% isolated yield (entry 1). A very good yield of 81% for this same substrate was obtained by **63** (entry 5). Gabriele has reported the use of PdI_2 / KI (2 mol%) for the cyclisation of 2-hex-1-ynylbenzyl alcohol which afforded the isochromene product in 63% yield, after 2.5 h at 80 °C.[125a] As can be seen in **table 7**, **57** and **63** gave higher yields at a quarter of the catalyst loading, at RT instead of 80 °C

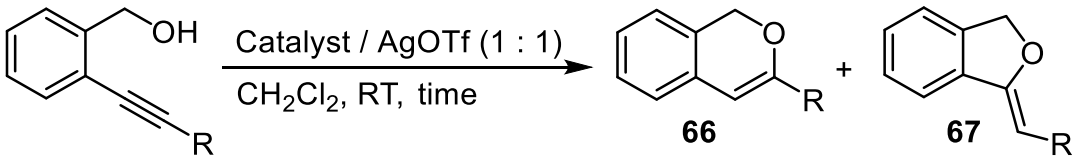
and after 1 h instead of 2.5 h. This enhanced catalytic performance might be the result of the stabilising η^2-interaction in **57** and the η^1-interaction in **63**. **60** with a yield of 40% (entry 2) showed no enhancement in reactivity over **57** despite the increased bulk of the phosphine and the presence, although very weak, of its η^1-interaction between the gold centre and one of its lower aryl rings. In fact **60** actually gave almost the same result as **62**, which gave the product in 37% yield (entry 4). **61** once again displayed the lowest catalytic ability of the gold(I) complexes of KITPHOS monophosphines, giving 19% conversion to the isochromene (entry 3).

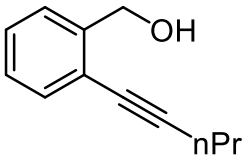
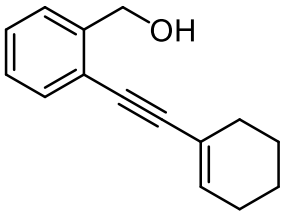
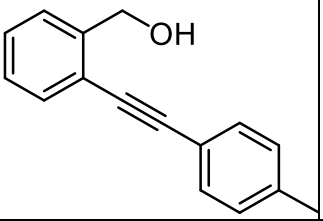
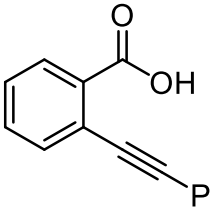
Triphenylphosphine has proven to be a particularly useful ligand in many gold(I) catalysed transformations and so bearing this in mind it was decided to also investigate the ability of triphenylarsine as a ligand in these transformations. It was interesting to see whether the larger, softer nature of the As-atom in triphenylarsine had any effect on catalysis compared to triphenylphosphine in the gold(I) catalysed cyclisation of 2-hex-1-ynylbenzyl alcohol. This effect was actually very small, as $Ph_3AsAuCl$ only marginally outperformed PPh_3AuCl in this cyclisation, with respective yields of 32% and 27% (entries 7 and 6). These yields were significantly less than those attained by both **57** and **63**.

On performing the reaction with [2-(2-phenylethynyl)phenyl]methanol, once again **57** gave an excellent yield, affording the product in 85% isolated yield (entry 9). This clearly outperformed the $[(Mes_3PAu)_2Cl]BF_4$ catalyst used by Hashmi[94] which is reported to give the product in 75% yield after 24 h using a catalyst loading of 5 mol% (entry 12), compared to 2 mol% used for **57** and 16 h reaction time. **57** also outperformed the iridium catalyst **68** which is reported to give 70% yield of the product, using a catalyst loading of 3 mol% after 2 h at 85 ^oC.[127] $AuCl_3$ was ineffective at catalysing the cyclisation of both 2-hex-1-ynylbenzyl alcohol and [2-(2-phenylethynyl)phenyl]methanol, as no isochromene product was isolated after purification by column chromatography (entries 8 and 11).

The success of the gold(I) complex **57** in this preliminary work led to further investigation, for which an extended table of results is shown below (**table 8**).

Table 8. Results of the gold-catalysed cyclisation of 2-[(2-alkynyl)phenyl] alcohols.



Entry [a]	Substrate	Cat.	Time/ h	Conv. 66 / % [b] ([c])	Conv. 67 / % [b] ([c])
1		**57**	1	98 (50)	0
2		AgOTf	1	7	0
3		[Au] [d, e]	24	- (31)	0
4		**57**	1	- (90)	0
5		AgOTf [f]	1	8	0
6		**57**	1	29	71 (40)
7		**57** [e]	16	40	60
8		AgOTf [f]	16	24	22
9		**57**	0.25	100 (100)	0
10		AgOTf	1	100 (100)	0

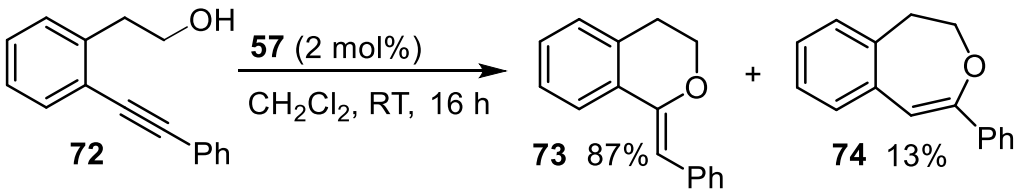
[a] catalyst (0.5 mol%), AgOTf (0.5 mol%), (*o*-alkynylphenyl)alcohol (0.4 mmol), CH_2Cl_2, RT, time, [b] conversion measured by ^{1}H NMR, [c] isolated yield, [d] [Au] = $[(Mes_3PAu)_2Cl]BF_4$ (2.5 mol%) from literature.[94] [e] catalyst (2.0 mol%), AgOTf (2.0 mol%). [f] AgOTf (2.0 mol%).

Once again **57** proved to be an efficient catalyst for the cyclisation of 2-[(2-alkynyl)phenyl]alcohols by giving a 98% conversion in the cyclisation of 2-pent-1-ynylbenzyl alcohol (entry 1) after 1 h using only 0.5 mol% catalyst. However only 50% isolated yield was obtained after purification by column chromatography. This loss may have been due to degradation of the product on the column, although this problem

was not reported by Crabtree who used the iridium catalyst **68** (4 mol%) to obtain the product in 77% yield after 2 h at 80 °C.[127] **57** did manage to outperform $[(Mes_3PAu)_2Cl]BF_4$ (2.5 mol%) which only gave 31% yield after 24 h (entry 3). **57** also achieved a 90% yield in the cyclisation of 2-(cyclohex-1-enylethynylphenyl)methanol (entry 4) and a 100% yield for cyclisation of 2-(2'-phenylethynyl)benzoic acid (entry 9) to the corresponding isochromene / isocoumarin products. Interestingly AgOTf also catalysed the formation of 2-(2'-phenylethynyl)benzoic acid in 100% isolated yield after 1 h (entry 10). However AgOTf proved to be a poor catalyst for the cyclisation of the alcohols (entries 2, 5, 8). In fact it has been reported that the reaction with 2-(2'-phenylethynyl)benzoic acid can be performed in near quantitative yield by simply using a strong acid, such as triflic acid.[129]

The cyclisation of [2-(2-{4-methylphenyl}ethynyl)phenyl]methanol (entry 6) occurred with unexpected regioselectivity. The use of **57** gave the 5-membered ring product, 1-(4-methyl-benzylidene)-1,3-dihydroisobenzofuran in 71% conversion, 40% isolated yield, with 29% conversion to the isochromene indicated by NMR, but none isolated on attempted purification by column chromatography. On using a higher catalyst loading of **57** (2 mol%) and stirring for 16 h, a slightly higher conversion of the isochromene product (40%) was afforded (entry 7). Thus, as [2-(2-phenylethynyl)phenyl]methanol required a reaction time of 16 h and **57** (2 mol%) to afford the isochromene product in 85% yield (**table 7**, entry 9), it could be that with extended time even more of the isochromene product could be afforded from the 5-membered product. Also no conversion to the isochromene products was achieved using any of the gold(I) complexes of KITPHOS monophosphines with the terminal alkyne **71** (R = H) or **70** (R = TMS). This is in agreement with results reported using other gold catalysts.[94]

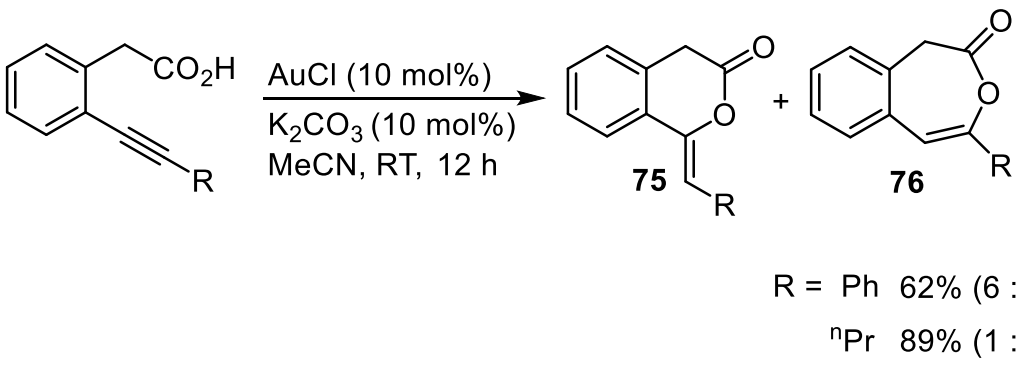
Both Hashmi[94] and Crabtree[127] reported the failure of the attempted cyclisation using (2-{2-ethynylphenyl}phenyl)-1-ethanol **72**. Satisfyingly, **57** facilitated the cyclisation of this substrate to give both the 6 and 7-membered ring products. Even though the conditions for this reaction have not yet been optimised, **57** (2 mol%) produced 1-benzylideneisochromane **73** in 87% yield and 4-phenyl-1,2-dihydrobenzo[*d*]oxepine **74** in 13% yield after 16 h stirring at RT (**scheme 65**). The successful cyclisation of this substrate has not been previously reported.



Scheme 65. The gold-catalysed cyclisation of 2-[(2-ethynylphenyl)phenyl]ethan-1-ol.

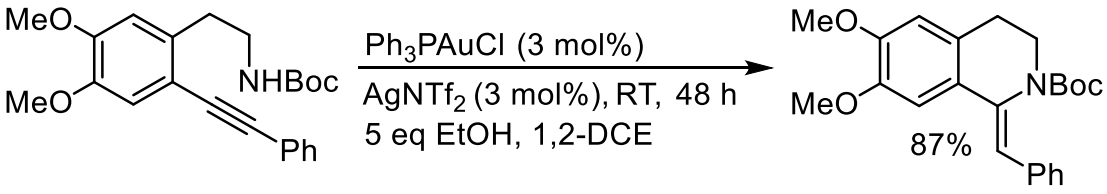
The products **73** and **74** exhibit similar ^{1}H and ^{13}C NMR spectra, therefore a two-dimensional INADEQUATE experiment was performed to identify direct ^{13}C-^{13}C connections within the molecules. This experiment unambiguously identified **73** through the direct connectivity of the *ipso*-carbon atom of the phenyl-substituent at δc = 136.6 to the vinylidene (C=<u>C</u>H) carbon atom at δc = 103.4. This INADEQUATE experiment is shown in the Appendix, section D. The 7-membered ring product **74** doesn't possess this connectivity and thus was identified accordingly.

In fact 6-*exo*-*dig* cyclisations are not common.[117, 130] Uriac has successfully performed gold-catalysed cycloisomerisations to afford a range of benzylidene isochromanones (**75**) and benzo[*d*]oxepinones (**76**) (**scheme 66**).[131] These required 10 mol% AuCl, and 12 h stirring at RT to attain good yields of the products. Interestingly the product selectivity was highly dependent on the R group, with the 6-membered ring product being favoured when R = Ph and the 7-membered ring product being preferred when R = ^{n}Pr.



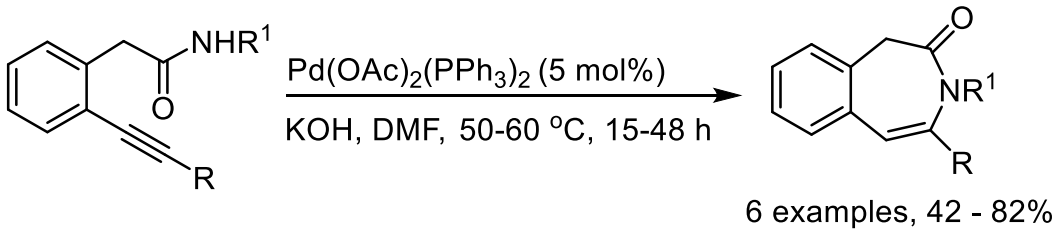
Scheme 66. Gold-catalysed cycloisomerisations of 2-[(2-alkynyl)phenyl]acetic acids.

Takemoto reported the gold(I) catalysed 6-exo-dig cyclisation to afford 1-alkylidenyl-1,2,3,4-tetrahydroisoquinolines.[132] Five examples were given with yields ranging from 75 – 87 %, using 3 mol% catalyst loading at RT with reaction times of 5 – 15 h. An example is given below in **scheme 67**.



Scheme 67. Gold-catalysed synthesis of tetrahydroisoquinolines through a 6-*exo-dig* cyclisation.

Mitchell reported the synthesis of 4-alkyl-2*H*-3-benzazepin-2-ones from palladium-catalysed 7-*endo-dig* cyclisations of *o*-alkynylbenzeneacetamides (**scheme 68**).[133] Lower yields were obtained when R^1 = Ph / H due to the weaker nucleophilicity of the amide. In one specific case they observed the 6-*exo-dig* reaction (R = Ph, R^1 = Me) to yield the isoquinolinone product. This however was unstable when left standing at RT and subsequently decomposed to give a mixture of products.



Scheme 68. Palladium-catalysed cyclisation of *o*-alkynylbenzeneacetamides.

It must be noted that the 6-*exo-dig* and 7-*endo-dig* cyclisation performed by **57** on 2-[(2-ethynylphenyl)phenyl]ethan-1-ol (**scheme 65**) has not yet been optimised.

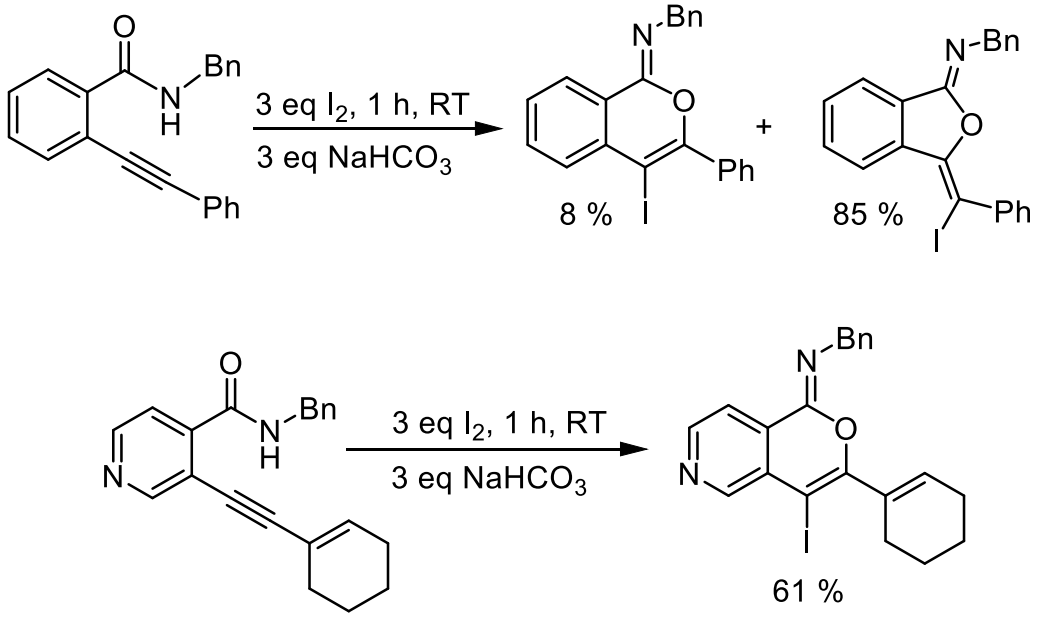
Further work is currently being undertaken on developing this cyclisation with (*o*-alkynylphenyl)ethanols bearing a variety of electron-withdrawing and electron-donating groups.

3.3.3 Conclusions from the cycloisomerisation of 2-[(2-alkynyl)phenyl] alcohols

Gold(I) complexes of KITPHOS monophosphines have been shown to catalyse the cycloisomerisation of 2-[(2-alkynyl)phenyl]alcohols to isochromenes. In particular the gold(I) complex **57** was shown to be remarkably effective in these transformations. The use of **57** gave greater yields whilst using shorter reaction times and lower catalyst loadings when compared to other catalyst systems. The gold(I) complex of KITPHOS monophosphine **57** was also effective in catalysing the synthesis of a benzylidene-isochromane and a dihydrobenzo[*d*]oxepine from 2-[(2-ethynylphenyl)phenyl]ethan-1-ol, through a 6-*exo*-*dig* and a 7-*endo*-*dig* cyclisation pathway respectively, a previously unreported cyclisation.

3.4 Gold-catalysed synthesis of iminoisocoumarins

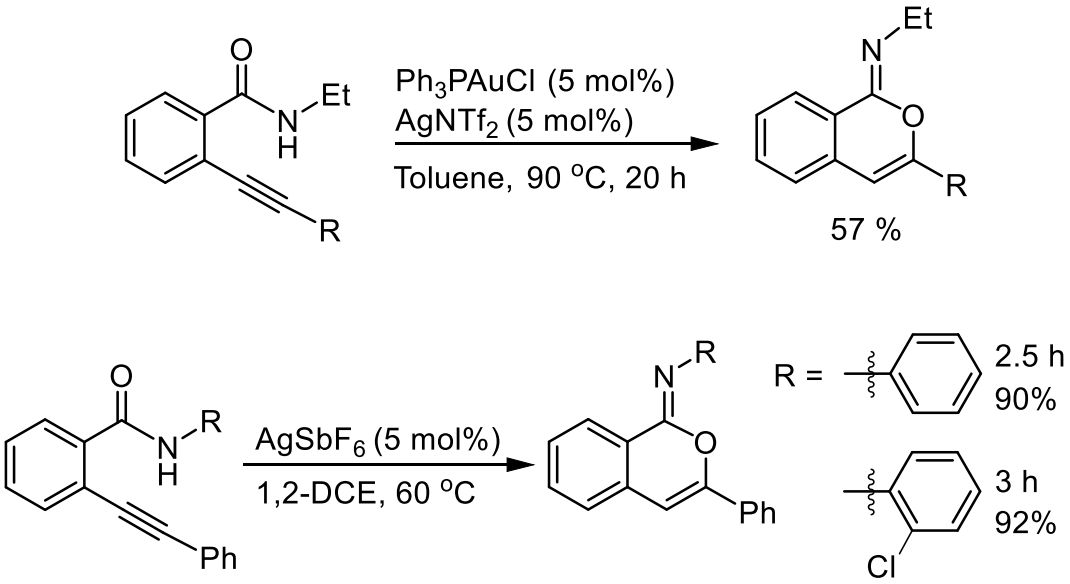
Whilst assessing the ability of gold to catalyse the cyclisation of 2-[(2-alkynyl)phenyl]alcohols to isochromenes, investigations were also being performed on the related cyclisation of 2-(phenylethynyl)benzamides to give iminoisocoumarins. Previously, classical Lewis acids such as I_2 and ICl were thought to induce cyclisation through the N-atom to give either the isoindolin-1-one, 5-membered ring product or isoquinolin-1-one, 6-membered ring product.[134] However it has recently come to light that I_2 and ICl actually induce cyclisation through the O-atom instead.[135] The products from the 5-*exo-dig* cyclisation of 2-(phenylethynyl)benzamides dominate, with a mixture of regioisomers present in all but one reaction reported (**scheme 69**). In this one example the 6-*endo-dig* cyclisation occurred to give the pyridin-1-ylidene aniline in 61% yield using 3 equivalents of I_2 after 0.5 h at RT (**scheme 69**).[135a]



Scheme 69. Reported regioselectivities obtained in the iodine-mediated cyclisation of 2-(phenylethynyl)benzamides.

Palladium has also been used in these transformations. However a mixture of regioisomers is most often the result.[136] Gold on the other hand yields exclusively the isochromen-1-ylidene product through the 6-*endo-dig* cyclisation through the O-atom

(**scheme 70**).[137] This same selectivity has also been well demonstrated using silver salts such as $AgSbF_6$.[138] These reactions were shown to give excellent yields using 5 mol% catalyst, after 0.5 – 3 h stirring at 60 °C (**scheme 70**).



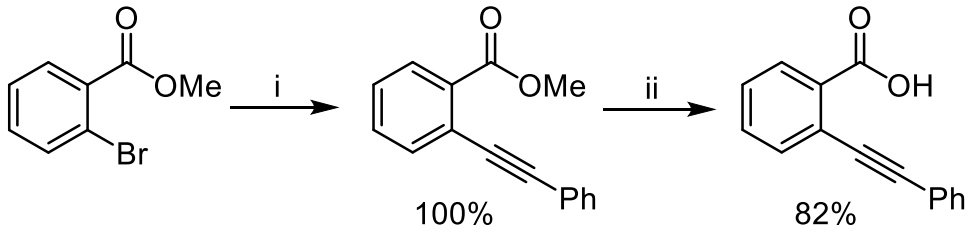
Scheme 70. Gold and silver-catalysed cyclisations of 2-(phenylethynyl)benzamides.

Gold's ability to often perform such reactions at RT rather than elevated temperatures, as already demonstrated for 2-[(2-alkynyl)phenyl]alcohols, led us to investigate the feasibility of using gold(I) complexes of KITPHOS monophosphines for these cyclisations.

3.4.1 Synthesis of 2-(phenylethynyl)benzamides

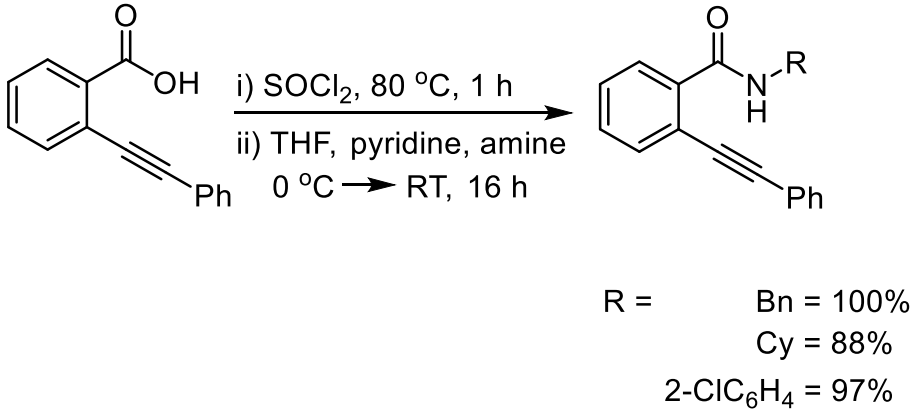
A number of 2-(phenylethynyl)benzamides were synthesised in a linear four-step reaction sequence starting from the commercially available methyl 2-bromobenzoate. The first step was a Sonogashira reaction between methyl 2-bromobenzoate and phenylacetylene using $PdCl_2(PPh_3)_2$ (2 mol%) and CuI (5 mol%) in triethylamine, which after heating for 16 h at 81 °C gave methyl 2-(phenylethynyl)benzoate in 100%

yield. This was then hydrolysed by stirring with excess K_2CO_3 in CH_2Cl_2 / MeOH (1 : 2) for 24 h at RT and following an acidic work-up, 2-(2-phenylethynyl)benzoic acid was afforded in 82% yield (**scheme 71**).



Scheme 71. The synthesis of 2-(2-phenylethynyl)benzoic acid.[125a, 127] i) $PdCl_2(PPh_3)_2$, CuI, NEt_3, phenylacetylene, 81 °C, 16 h, 100%. ii) K_2CO_3, CH_2Cl_2 / MeOH (1 : 2), RT, 24 h, 82%.

Then to afford the 2-(phenylethynyl)benzamide products, 2-(2-phenylethynyl) benzoic acid was dissolved in excess $SOCl_2$ and refluxed at 80 °C for 1 h. The excess $SOCl_2$ was then removed under reduced pressure and THF, pyridine and the amine were then added at 0 °C. The reaction was stirred for 16 h at RT and, following a work-up and purification by column chromatography, the desired 2-(phenylethynyl)benzamides were produced in excellent yield (**scheme 72**).

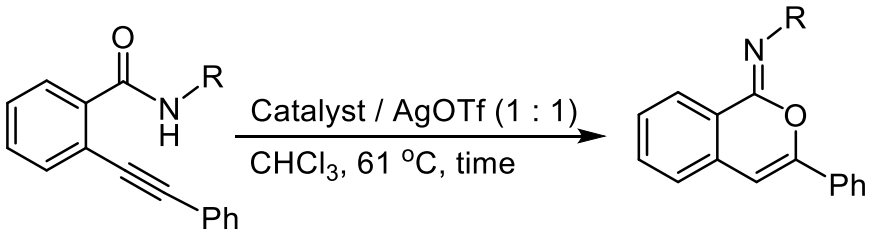


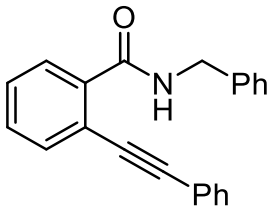
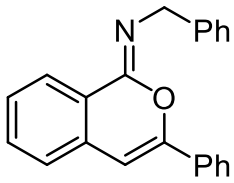
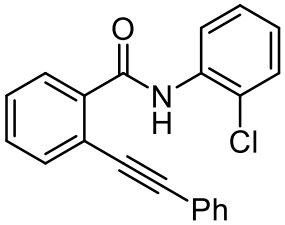
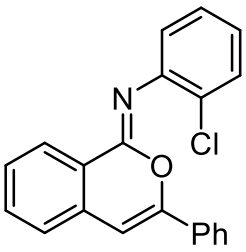
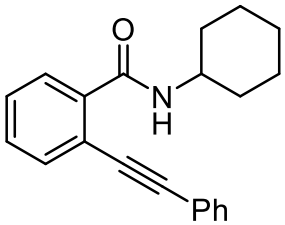
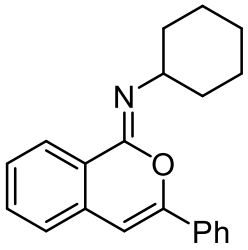
Scheme 72. Synthesis of 2-(phenylethynyl)benzamides.

3.4.2 Catalysis results for cycloisomerisation of 2-(phenylethynyl)benzamides

The gold(I) chloride complex of KITPHOS monophosphine **57** (2 mol%) and AgOTf (2 mol%) were dissolved in CH_2Cl_2 and stirred at RT for 0.5 h. The 2-(phenylethynyl)benzamide was then added and the reaction stirred for the specific time. This procedure was repeated three times for each catalyst with each substrate and the average conversion recorded (**table 9**).

Table 9. Results from the cycloisomerisation of 2-(phenylethynyl) benzamides.



Entry	Substrate	Catalyst	Time/h	Product	Yield/%
1 [a] *2* [b] *3* [c]		**57** **57** AgOTf	3.5 16 2		71 5 90
4 [a] *5* [a] *6* [c]		**57** **57** AgOTf	2 16 2		37 100 66
7 [d] *8* [d] *9* [e]		**57** **57** AgOTf	2 4 2		60 100 53

[a] 2-(phenylethynyl)benzamide (0.4 mmol), catalyst (2.0 mol%), AgOTf (2.0 mol%), $CHCl_3$, 61 °C, time. [b] CH_2Cl_2, RT. [c] 2-(phenylethynyl)benzamide (0.4 mmol), AgOTf (2.0 mol%), $CHCl_3$, 61 °C, time. [d] catalyst (5.0 mol%), AgOTf (5.0 mol%). [e] AgOTf (5.0 mol%).

For each of the three 2-(phenylethynyl)benzamides, **57** catalysed the reaction with complete regioselectivity for the 6-*endo-dig* cyclisation to the relevant iminoisocoumarin products. Unfortunately AgOTf managed to outperform **57** in the cyclisation of *N*-benzyl-2-(phenylethynyl)benzamide by giving 90% of the product after 2 h (entry 3) compared to 71% after 3.5 h using **57** (entry 1). This was actually slightly better than that reported for $AgSbF_6$, which obtained the same yield but after 2.5 h cyclisation.[138a] AgOTf also outperformed **57** in the cyclisation of 1-*N*-2-chlorophenyl-2-(phenylethynyl)benzamide, producing 66% of the product after 2 h (entry 6) compared to 37% after the same time using **57** (entry 4). Interestingly in the cyclisation of 2-[(2-alkynyl)phenyl]alcohols, AgOTf showed almost no conversion to the relevant isochromene products in contrast to gold(I) complex **57** which was an effective catalyst. **57** did manage to outperform AgOTf in the cyclisation of *N*-cyclohexyl-2-(phenylethynyl)benzamide. This more difficult substrate required a catalyst loading of 5 mol% instead of 2 mol% for the others and cyclised to give the iminoisocoumarin product in 60% yield after 2 h using **57** (entry 7) compared to 53% using AgOTf (entry 9).

All these transformations required an elevated temperature of 61 ^{o}C to obtain reasonable yields, which is consistent with previous literature for these transformations using $AgSbF_6$ as the catalyst.[138] Attempts to perform these reactions at RT using gold(I) catalysts proved unsuccessful. One such reaction is shown in **table 9** above for *N*-benzyl-2-(phenylethynyl)benzamide, which gave the product in 5% yield using **57** (2 mol%) after 16 h (entry 3).

3.3.4 Conclusions from the gold-catalysed synthesis of iminoisocoumarins

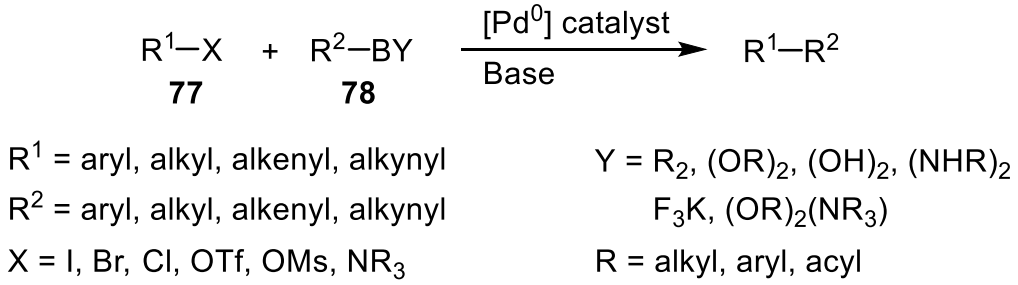
The gold(I) complex **57** was able to catalyse the cyclisation of 2-(phenylethynyl) benzamides with complete regiocontrol to the relevant iminoisocoumarin products, in moderate yield. The simple silver salt AgOTf proved to be a more effective catalyst for these cyclisations, giving greater yields for all but one substrate. On considering the relative costs between **57** and AgOTf, in addition to the fact that one equivalent of

AgOTf is used together with the gold complex **57** in each reaction, this one result in favour of **57** would be overlooked from a commercial point of view in favour of an increased catalyst loading of AgOTf.

Chapter 4. Triaryl-like KITPHOS monophosphines in palladium-catalysed Suzuki-Miyaura and esterification reactions

4.1 Suzuki-Miyaura cross coupling reaction

The palladium-catalysed Suzuki-Miyaura cross coupling reaction (SM reaction) is one of the most useful C-C bond forming reactions in organometallic catalysis today.[16a, 139] This reaction involves the coupling of an organoboron compound **78** with an electrophile **77**. It has many advantages over other C-C bond forming reactions such as the Stille (organostannane), Kumada (organomagnesium) and Negishi (organozinc) due to its ability to perform reactions under mild conditions, which allows for high tolerance of sensitive functional groups. The by-products from SM reactions are non-toxic and easily separable by an aqueous workup or through column chromatography. The commercial availability and stability of its reagents towards heat, air and moisture allows for reactions to be performed without the need of a glove box. This transformation accommodates a vast range of differing substrates with great success (**scheme 73**).



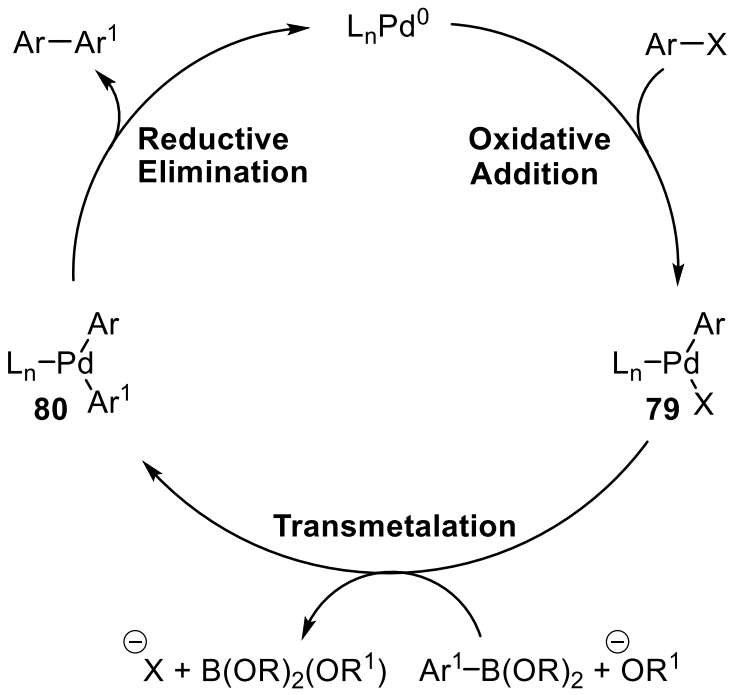
Scheme 73. The Suzuki-Miyaura cross coupling reaction.

The SM reaction was initially used to construct biaryl compounds through the coupling of an aryl halide, ArX, where X = I, Br or Cl with an aryl boronic acid [$ArB(OH)_2$] using a palladium catalyst and a base. It has expanded away from the first initial report by Suzuki[2] in 1981 and now is able to accommodate a whole range of

differing alkyl, alkenyl and alkynyl coupling partners as well as the classical aryl. This expansion now allows for triflate, mesylate and halide compounds to be coupled with various boron species including boronic acids, boronate esters, cyclic triolborates and organotrifluoroborates.[9, 140] SM reactions have been performed in entirely aqueous environments using water soluble catalytic species,[141] in ionic liquids[142] and using polymer supported catalysts.[143] Also the SM reaction has been shown to be successful on an industrial scale[144] as well as in total synthesis.[145]

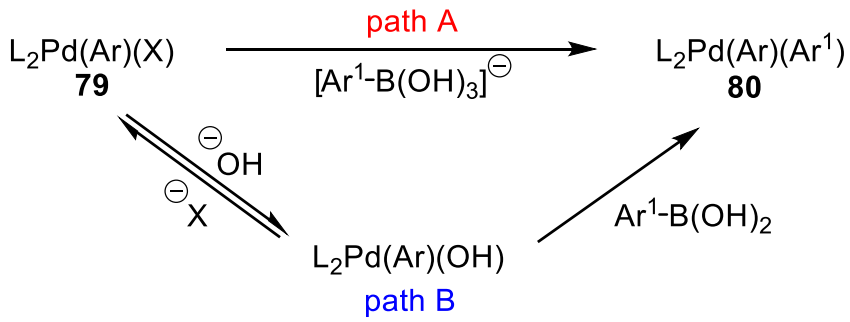
As is the case in most transition metal-catalysed reactions, the major improvements to date have been driven by ligand optimisation. Dramatic enhancements in catalytic activity have been achieved through modification of the properties of the ligands and so great effort has been put into optimising the design of these ligands.

4.1.1 Mechanism for Suzuki-Miyaura reactions



Scheme 74. The general mechanism for the Suzuki-Miyaura cross coupling reaction.

The mechanism for the palladium-catalysed SM reaction is given in **scheme 74**. The main features of this mechanism are; the activation of the catalyst to generate the [L_nPd^0] species, oxidative addition, transmetalation and reductive elimination. The catalytically active species in SM reactions is the [L_nPd^0] species, with palladium in the zero oxidation state. Therefore before entering the catalytic cycle most catalysts will require activation to generate this species in solution. This activation can either be through ligand dissociation if the palladium source is already in the zero oxidation state, such as $Pd_2(dba)_3$ or through a reduction step if the palladium source is in the 2+ oxidation state, such as $Pd(OAc)_2$. Once this [L_nPd^0] species is generated, oxidative addition occurs, which involves the insertion of the palladium species into the C-X bond of the electrophile. Electron withdrawing groups on the aryl group of intermediate **79** help to facilitate this step of the cycle by removing electron density from the C-X bond, making it easier to cleave. Oxidative addition is often the rate determining step of the catalytic cycle. Next is the transmetalation step of the cycle. This is the base-mediated exchange of the R group on the boron species with the X group on intermediate **79**.[146] The mechanism of this step is given below (**scheme 75**).



Scheme 75. Transmetalation has been proposed to proceed through either of two pathways.[147, 148]

It was previously thought that the base binds to the organoboron derivative to form a more reactive tetra-coordinate boronate species, which then displaces the X^- species and transfers the organic group to the palladium to form intermediate **80** (path A, **scheme 75**).[9, 147] However, more recent kinetic studies have provided strong evidence that in the presence of a weak base transmetalation preferentially occurs

between a base-coordinated palladium species and the tri-coordinated $Ar^1B(OH)_2$ species (path B, **scheme 75**).[148] In fact these studies show that both pathways are available to facilitate transmetalation, although the rate of path B is considerably faster under these conditions.[148]

Reductive elimination then occurs to liberate the product and regenerate $[L_nPd^0]$, the active catalytic species which then re-enters the catalytic cycle. The rate of this step is also increased when electron-withdrawing groups are present on the aryl groups in **scheme 74**. These remove electron density away from the metal, aiding in the favourability of this step. However the steric bulk of the ligands has a greater influence on the rate of this step, with bulky groups strongly favouring this step through the relief of steric congestion around the palladium centre.[149] It has also been proposed that the base can aid in the propagation of this step, through coordination to intermediate **80** which would also lead to increased steric congestion around the palladium centre.[148b]

4.1.2 Bulky electron-rich ligands in Suzuki-Miyaura reactions

The influence of ligand structure is by far the most investigated factor in the development of improved catalysis for the SM reaction. To date there have been a huge number of catalysts with different ligands used for SM reactions showing a wide variation of success. The progression in ligand design has also followed the trend shown in Chapter 1 section 1.1, with catalysts such as $Pd(PPh_3)_4$ and $PdCl_2(PPh_3)_2$ initially being used followed by diphosphines such as BINAP and dppf.[2, 150] The trialkylphosphines PCy_3 and P^tBu_3 have had a significant impact and are still highly efficient ligands, however their instability towards air and moisture has led to other air stable catalysts being used instead.[8, 10a, 151]

Arguably the greatest successes in SM reactions have been through the use of bulky electron-rich ligands. The electron-rich nature of the resulting catalysts enables facile insertion of the palladium species into C-X bonds, allowing these reactions to accommodate halides, tosylates, mesylates and triflates with great success.[9] The reductive elimination step of the catalytic cycle is more favoured with bulky ligands due

to the extra steric relief resulting from this step.[16a] The more facile dissociation of bulky ligands relative to less bulky ones enhances the formation of the monoligated catalytically active [L_1Pd^0] species in solution.[149] As oxidative addition and transmetalation are faster in L_1Pd species than the corresponding L_2Pd species, this increases the turnover frequency of the reaction.

N-Heterocyclic carbenes have been used to great effect in a vast array of transformations including SM reactions.[9, 43, 45] However phosphines have been more thoroughly explored. The most effective of these are highlighted below in sections 4.1.2.1 to 4.1.2.5 of this chapter.

4.1.2.1 Ferrocenyl-based phosphines

Ferrocenyl-based phosphine ligands, such as QPhos[47] have proven to be highly effective in SM reactions. The high catalytic activity demonstrated by these ligands was then further enhanced on construction of the P,N and P,O ligands **14** and **15** due to the hemilability of the weakly coordinating imine group in **14** and the dioxolane group in **15** (**figure 28**).[48-49] These hemilabile groups act to further enhance the stabilisation of the transition states and intermediates in the catalytic cycle, through the ability to form monoligated and chelated transition metal species in solution.

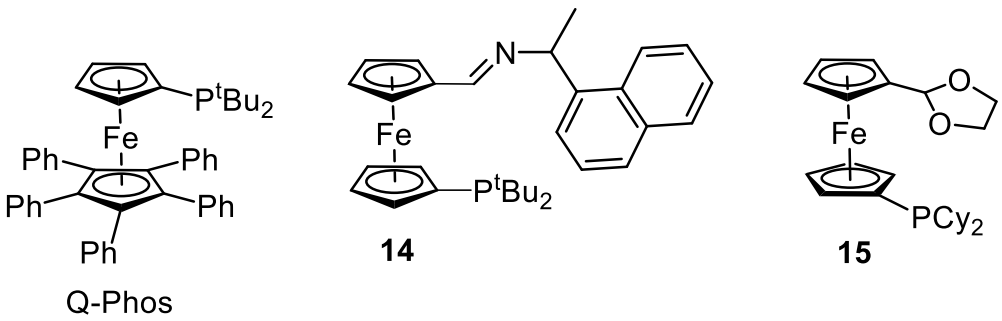
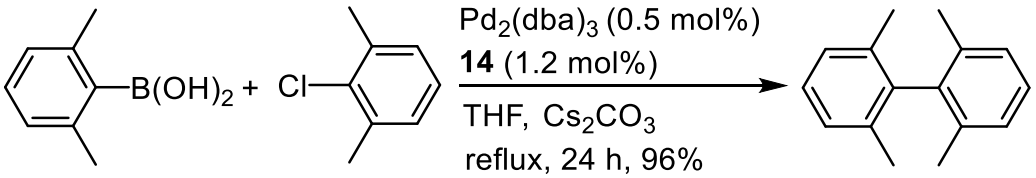


Figure 28. Ferrocenyl-based phosphines successfully used in SM reactions.

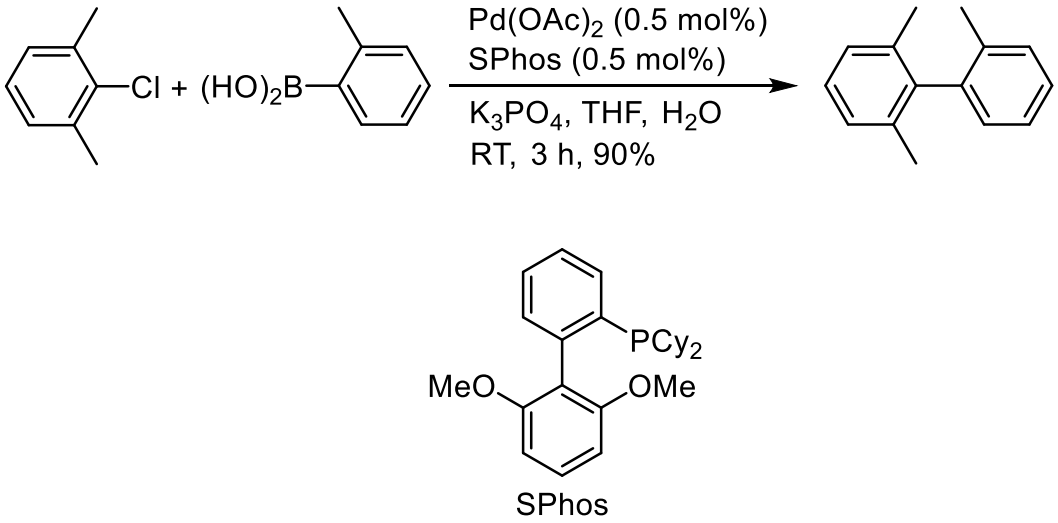
In particular, **14** expresses exceptional activity even with highly hindered substrate combinations. In the SM reaction between 1-chloro-2,6-dimethylbenzene and 2,6-dimethylphenylboronic acid, the biaryl product was formed in 96% yield after refluxing in THF for 24 h using $Pd_2(dba)_3$ (0.5 mol%),and **14** (1.2 mol%) (**scheme 76**).[48]



Scheme 76. Ligand **14** is highly efficient in SM reactions involving highly hindered substrates.

4.1.2.2 Dialkylbiarylphosphines

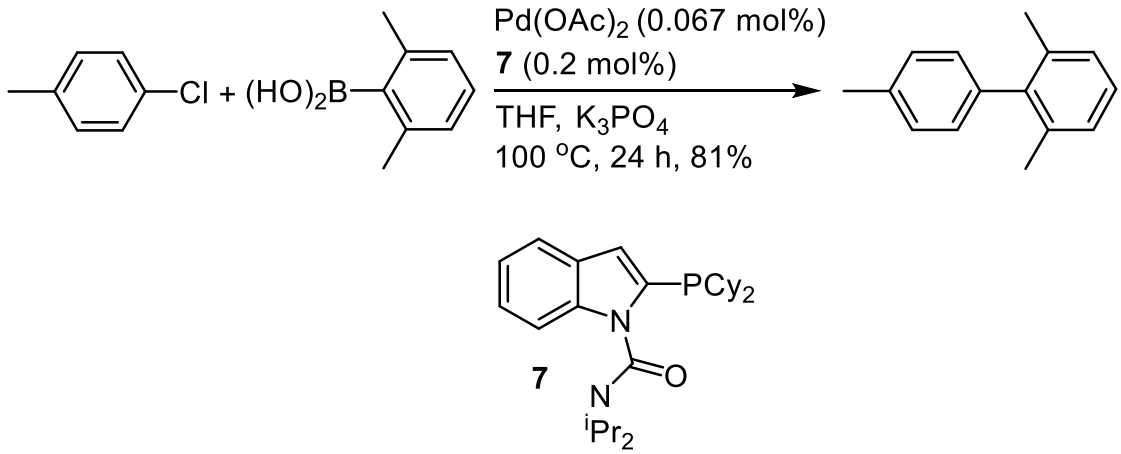
One of the most successful ligand designs has been Buchwald's dialkylbiarylphosphines due to their exceptional catalytic activity for a broad range of transformations and the facile modification of their steric and electronic properties. The presence of Pd-arene interactions in dialkylbiarylphosphines further enhances the propagation of both the oxidative addition and reductive elimination steps of the catalytic cycle, due to the increased stabilisation of the corresponding intermediate species.[26] These enhancements allow for reactions to be performed at lower catalyst loadings, lower temperatures and milder conditions. These mild conditions allow the accommodation of sensitive functional groups and unstable substrates, such as strongly electron deficient organoboranes which are readily proto-deboronated.[9] The bulky, electron-rich properties of these phosphines favour the formation of the catalytically active mono-coordinate $[L_1Pd^0]$ species in solution, making them highly reactive and thus able to couple even very hindered substrate combinations (**scheme 77**).[30]



Scheme 77. The dialkylbiarylphosphine SPHOS is a particularly successful ligand for SM reactions.

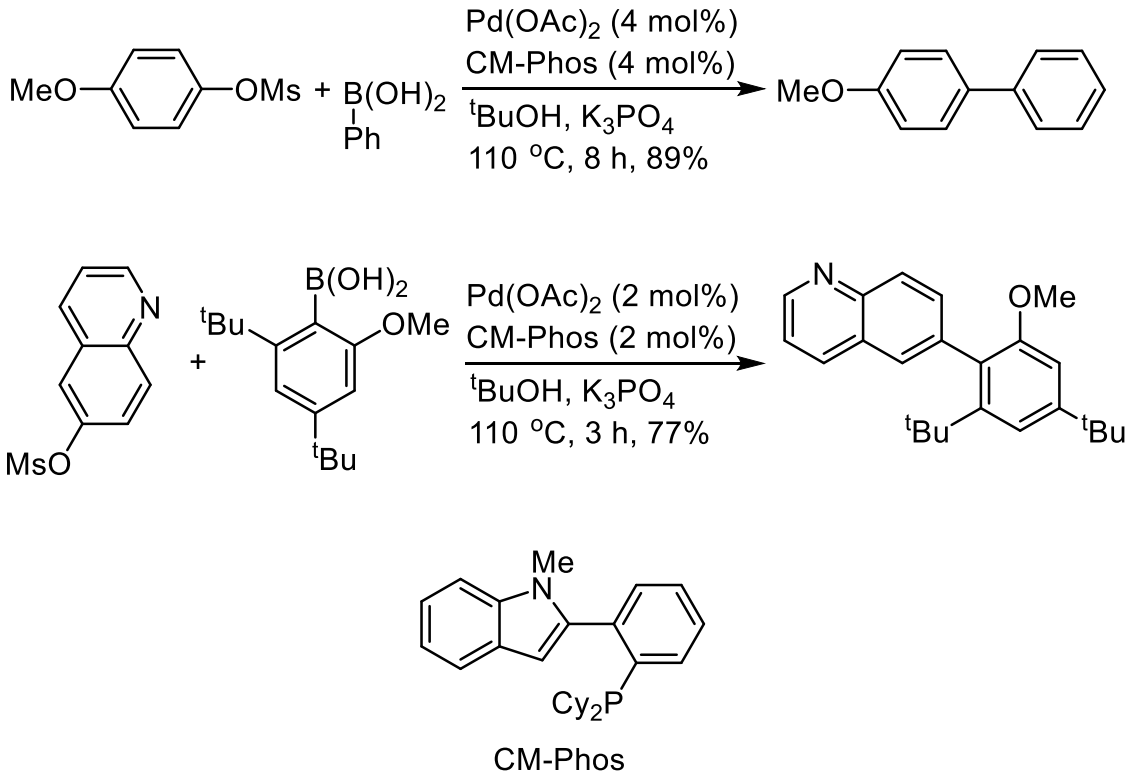
4.1.2.3 Indolyl-based phosphines

Kwong's indolyl phosphine ligands have also shown remarkable ability in SM reactions.[37-38] The coupling of the unactivated 4-chlorotoluene with the sterically hindered 2,6-dimethylphenylboronic acid to give the product in 90% yield after 24 h at 100 °C using **7** (0.2 mol%) is testament to this (**scheme 78**).[38]



Scheme 78. The indolyl phosphine **7** is highly efficient in SM reactions

These indolyl-based phosphine ligands are particularly effective in SM reactions involving aryl chlorides. The most effective of these is CM-Phos, which possesses a dialkylbiaryl-type architecture. This architecture further enhances the catalytic activity of CM-Phos relative to the other indolyl-based ligands. Evidence for this enhancement is demonstrated in the ability to access a range of aryl mesylates, including unactivated and heteroaryl mesylates (**scheme 79**).[39b]

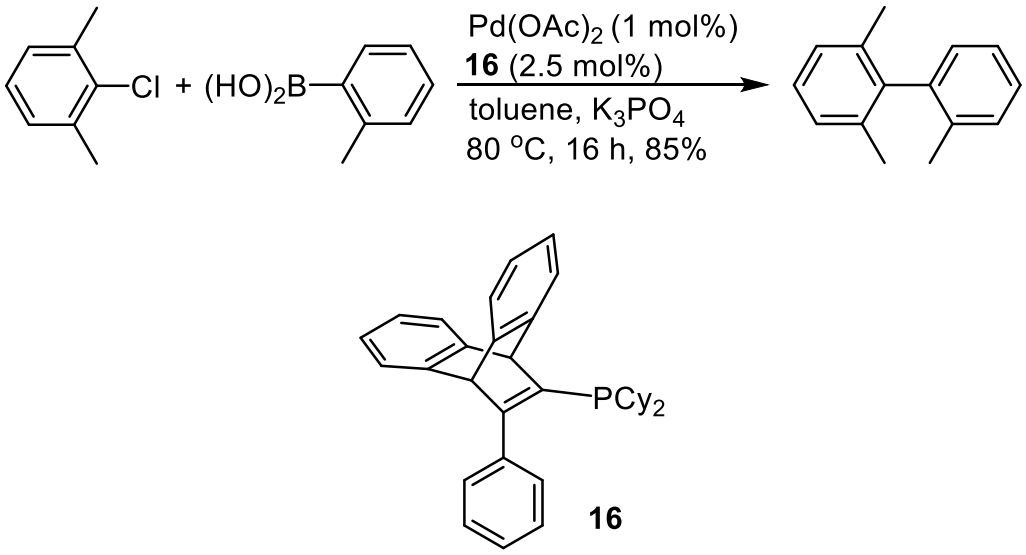


Scheme 79. CM-Phos can successfully couple heteroaryl and unactivated aryl mesylates.

4.1.2.4 KITPHOS monophosphines

KITPHOS monophosphines have also taken advantage of their dialkylbiaryl-phosphine architecture by exhibiting high catalytic activity for a range of transformations including SM reactions. In the SM reaction involving 2-methylphenyl-

boronic acid with 1-chloro-2,6-dimethylbenzene, $Pd(OAc)_2$ (1 mol%) and **16** (2.5 mol%) were used to produce the biaryl product in 85% yield after 16 h at 80 ^oC (**scheme 80**).[54b]



Scheme 80. KITPHOS monophosphines express high catalytic activity in SM reactions.

Modification of this KITPHOS moiety with methoxy or amine groups has been shown to further enhance catalytic performance due to the extra stability associated with P,O- and P,N-type ligands. This is shown in 2-MeOKITPHOS, **18** and 2,6-MeOKITPHOS (chapter 1, section 1.1.6).

4.1.2.5 Triarylphosphines

It has long been acknowledged that sterically bulky electron-rich ligands, particularly phosphines and NHCs, are required for coupling reactions involving aryl chlorides. It is thought that the electron-rich nature of these ligated catalysts is essential in order to activate the C-Cl bond towards oxidative addition. However, recently it has

been shown that triaryl-like phosphines, which are significantly less electron-rich, are also able to perform these reactions and in some cases actually outperform their more electron-rich alkyl counterparts. The structures of four of these triarylphosphines are shown below, with all being highly successful in SM reactions (**figure 29**).

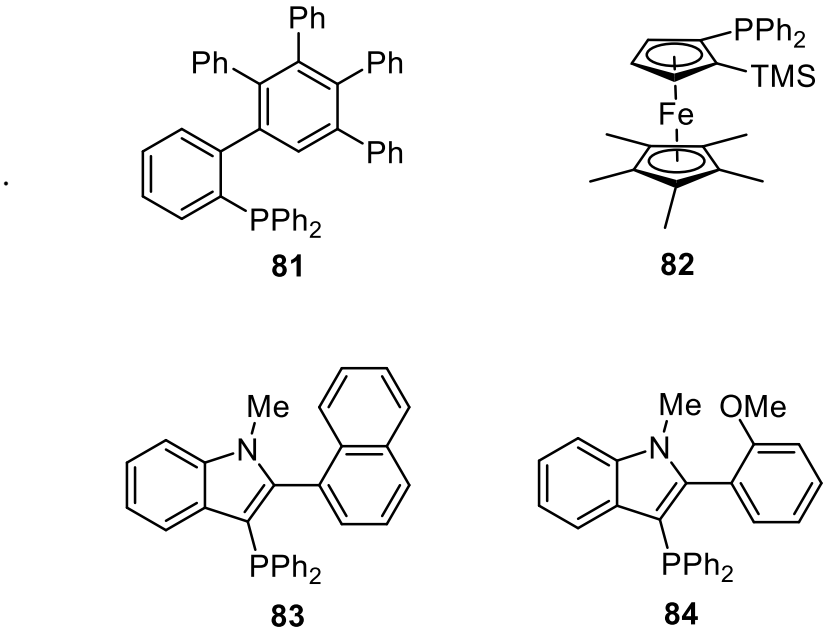
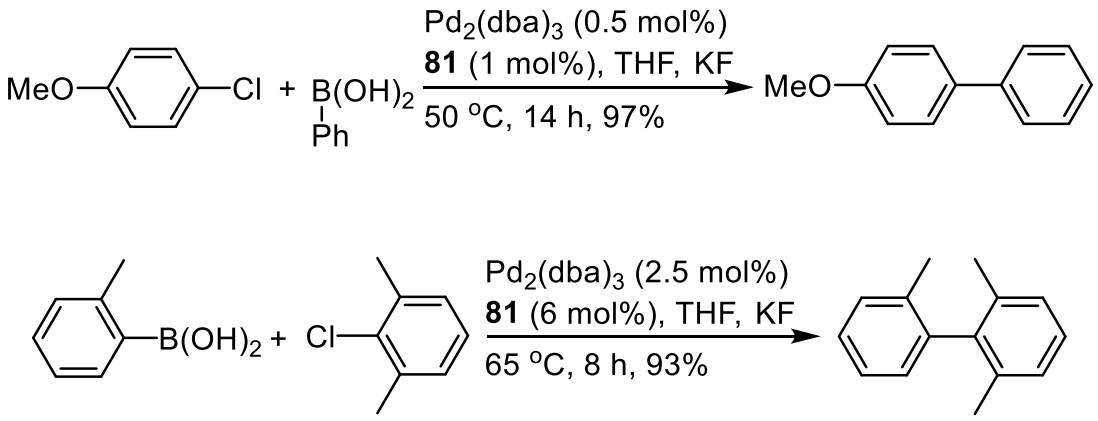


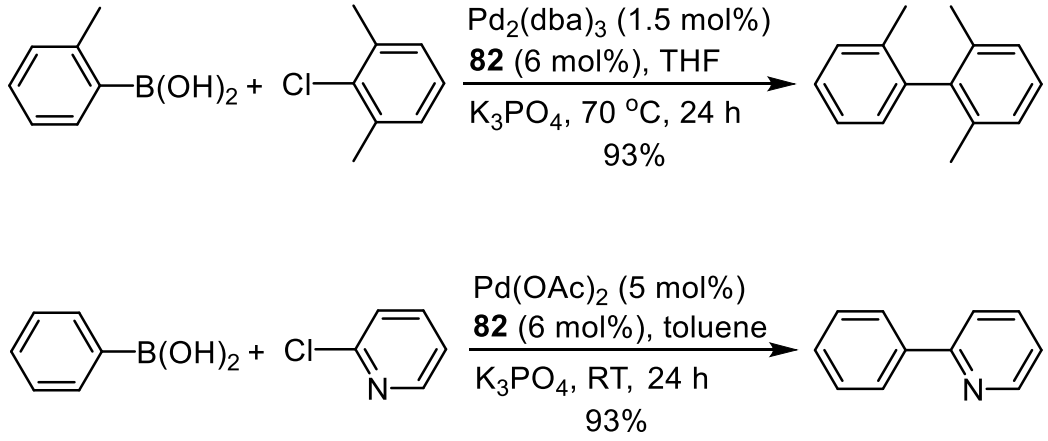
Figure 29. The structures of triarylphosphines which are highly efficient in Suzuki-Miyaura cross coupling reactions.

The 2,3,4,5-tetraphenylphenyl-type ligand **81** has shown high efficacy in Mizoroki-Heck and SM reactions as well as palladium-catalysed silylations.[152] Despite being a triarylphosphine, **81** can effectively couple unactivated chlorides using low catalyst loadings and can even accommodate very hindered substrate combinations (**scheme 81**).[152] Although long reactions times were required in both of the examples shown in **scheme 81**, these reactions were performed under relatively mild reaction conditions, such as temperatures of 50 ^{o}C and 65 ^{o}C.



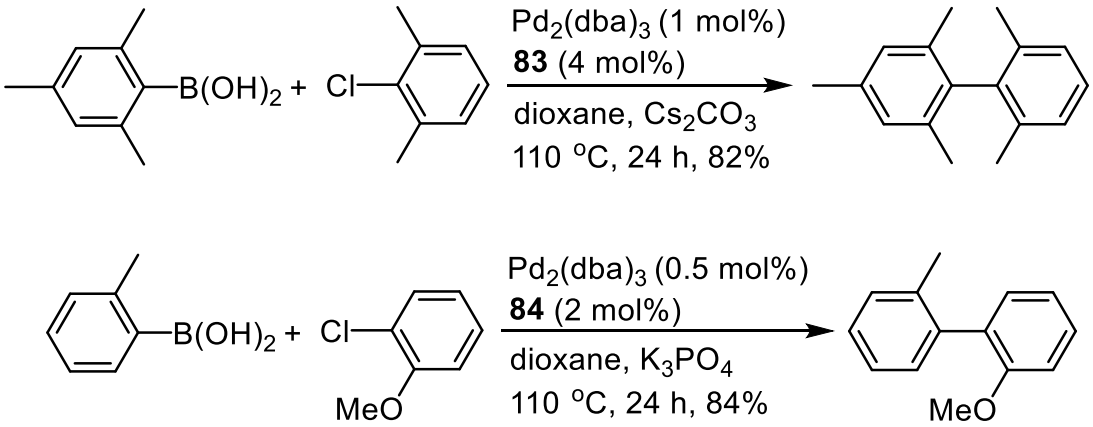
Scheme 81. The 2,3,4,5-tetraphenylphenyl-type ligand **81** can perform SM reactions involving unactivated and highly hindered aryl chlorides.

Fu also reported that the ferrocenyl-type triarylphosphine **82** displayed remarkable activity towards difficult SM reactions using aryl chlorides.[153] Although using a relatively high catalyst loading of **82** (6 mol%), this ligand could facilitate the coupling of hindered aryl chlorides and was also capable of coupling activated heteroaryl chlorides at RT (**scheme 82**).



Scheme 82. The ferrocenyl-type triarylphosphine **82** is capable of successfully coupling hindered aryl chlorides and even heteroaryl chlorides at RT.

Kwong demonstrated that the indolyl-based triarylphosphine **83** actually outperformed its dicyclohexyl counterpart in SM reactions.[154] The coupling of 1-chloro-2,6-dimethylbenzene with 2-mesitylboronic acid was achieved using $Pd_2(dba)_3$ (1 mol%), **83** (4 mol%) and Cs_2CO_3 at 110 ^oC in dioxane for 24 h, to give the biaryl product in 82% yield (**scheme 83**). On using the cyclohexyl equivalent of **83**, the biaryl product was obtained in only 10% yield. The indolyl-based phosphine **84** was also shown to be highly effective in coupling aryl chlorides (**scheme 83**).



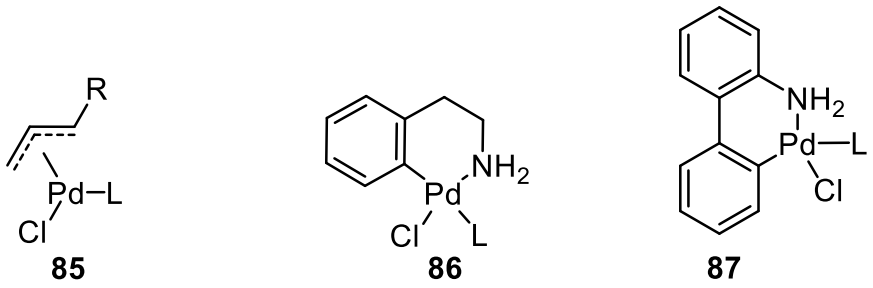
Scheme 83. The indolyl-based triarylphosphines **83** and **84**, are highly efficient in Suzuki-Miyaura cross coupling reactions involving aryl chlorides.

4.1.2.6 Pre-Catalysts

In SM reactions, the ability of the catalyst is not simply dependent on the nature of the ligand but also on the source of palladium used to generate the active catalytic species.[149] The catalytically active species in SM reactions is a $[L_nPd^0]$ species, where the palladium is in the zero oxidation state. This species can be generated in solution through the activation of a palladium source initially in the zero or 2+ oxidation state, as mentioned previously in section 4.1.1 of this chapter. The performance of the catalyst system strongly depends on the efficiency of this activation step. The palladium

sources $Pd_2(dba)_3$ and $Pd(OAc)_2$ are commonly used in transition metal-catalysed transformations, however they possess inherent disadvantages. The palladium(0) complex $Pd_2(dba)_3$ is found to contain varying amounts of palladium nanoparticles and free dibenzylideneacetone (dba), which have been shown to interfere with the progression of the reaction.[155] The palladium(II) complex $Pd(OAc)_2$ is free from these problems but needs to be reduced in solution to give the active catalytic species.[155] Thus, the efficiency of this reduction directly governs the ability of the catalyst system and so if this reduction is inadequate, this will have a detrimental effect on the progression of the ensuing reaction.

It has often been postulated that a ratio of Pd / L ≈ 1 : 1, where L is the ligand, is best to promote the highest possible concentration of the active $[LPd^0]$ species in solution. This has already been demonstrated within this chapter in **schemes 76**, **77**, **79** and **81** for dialkylbiarylphosphines, *N*-heterocyclic carbenes, ferrocenyl-based phosphines and for the indolyl-based phosphine CM-Phos. However in small scale reactions, it is very difficult to accurately measure the tiny amounts of catalyst and ligand required to achieve this 1 : 1 ratio. This led to investigations into the synthesis of pre-catalysts already possessing the ratio Pd / L (1 : 1), which can efficiently generate the $[L_nPd^0]$ species in solution, thereby negating the deficiencies associated with $Pd_2(dba)_3$ and $Pd(OAc)_2$. The use of pre-catalysts[156] not only provides strict control of the Pd / L ratio but also prevents the unnecessary use of excess amounts of often expensive ligands. The most commonly used pre-catalysts are the η^3-allyl-type **85** where R is often either a proton, methyl or phenyl group and the cyclopalladated phenethylamine-type (**86**) and 2-phenylaniline-type (**87**) pre-catalysts (**figure 30**).

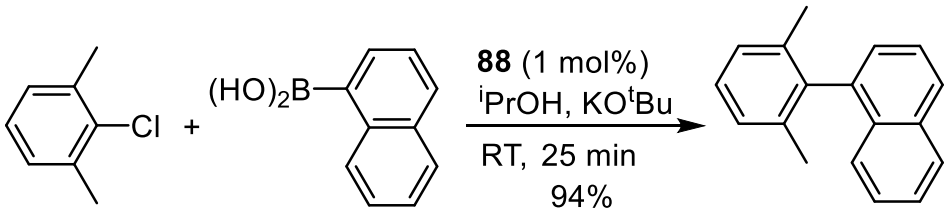


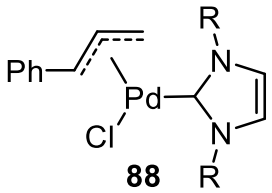
85 **86** **87**

Figure 30. Pre-catalysts used successfully in palladium-catalysed reactions.

All of the above palladium pre-catalysts are in the 2+ oxidation state and are air and moisture stable. 2-Phenylaniline-type pre-catalysts **87**, for example, are readily synthesised in excellent yield using wet solvents in air. For SM reactions, these pre-catalysts are activated on treatment with a base, which is already present in the reaction mixture and so does not require the addition of any additives.

The η^3-allyl-type pre-catalysts **85** have been successfully used in a range of transformations such as amination[157] and hydroesterification[157c] reactions as well as arylations.[158] The activation of allyl-type pre-catalysts requires the use of a strong base, such as KO^{t}Bu, with activation in amination reactions only initiated in solution on heating to 70 ^{o}C.[157a] This need for strongly basic conditions impacts on the compatibility of this type of pre-catalyst for reactions involving substrates bearing sensitive functionalities. Despite this, allyl-type pre-catalysts such as [Pd(**9**)(cinnamyl)] complex **88** have proven remarkably efficient in SM reactions involving hindered aryl chlorides. This aptitude is clearly demonstrated in the coupling of 1-chloro-2,6-dimethylbenzene with naphthylboronic acid, which gave the biaryl product in 94% yield using **88** (1 mol%) after only 25 min at RT (**scheme 84**).[157a]





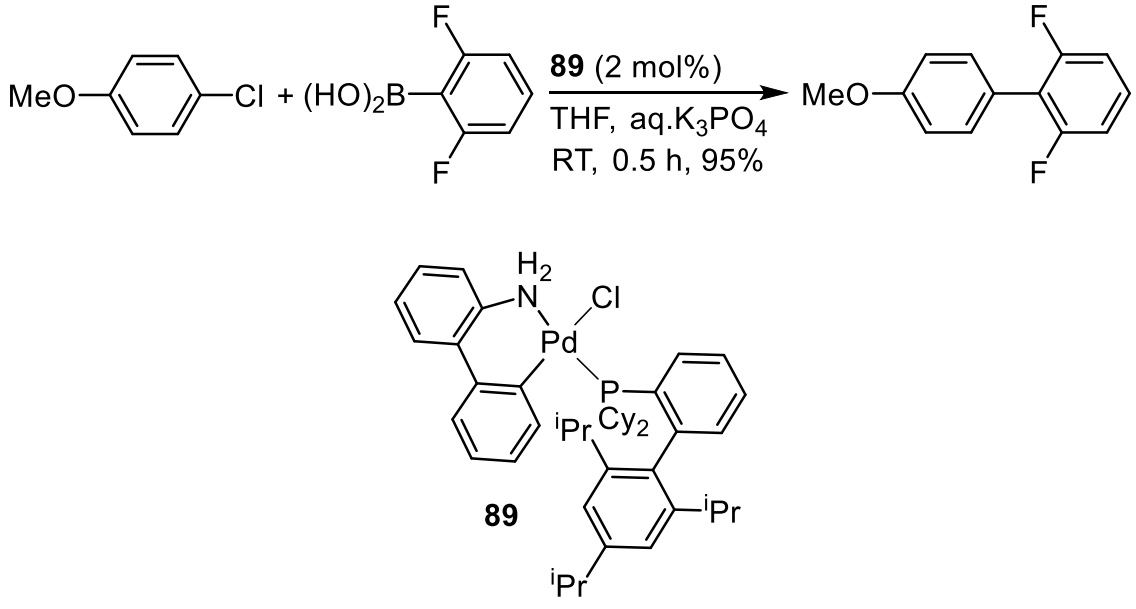
88

Scheme 84. [Pd(NHC)(cinnamyl)] complexes, such as **88**, have proven extremely efficient in SM reactions involving hindered aryl chlorides (R = 2,6-^{i}Pr$_2$C$_6$H$_4$).

The phenethylamine-type pre-catalyst **86** is an excellent source of the catalytically active [LPd^0] species and has been widely used to great effect, particularly in amination

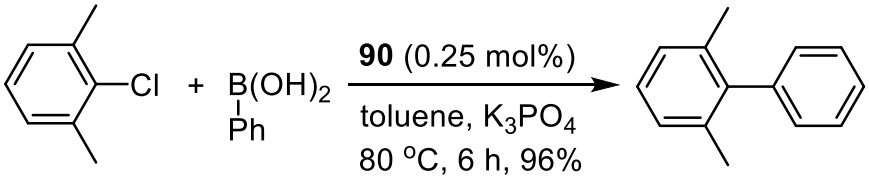
reactions.[159] These pre-catalysts are synthesised in a two-step one pot reaction, in good to excellent yield and are activated through deprotonation with a base. This deprotonation is rapid on treatment with a strong base like NaO^tBu, which when L is RuPhos is complete after only 3 min.[159b] However this activation is slow on using a weak base, even at elevated temperatures and in fact doesn't occur at all using aqueous K_3PO_4.

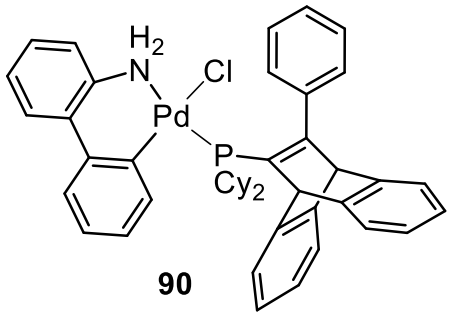
The 2-phenylaniline-type pre-catalyst **87** on the other hand benefits from the higher acidity of palladium-coordinated aromatic amine compared to the aliphatic amine of the phenethylamine pre-catalyst **86**. This allows for instant activation to occur even in the presence of a weak base at RT to give the 9*H*-carbazole and the desired catalytically active [L_nPd^0] species quantitatively in solution.[160] These complexes are air and moisture stable and are synthesised in a single step one pot procedure in excellent yield. This rapid activation under mild conditions is synthetically significant as it minimises the impact of deboronation. Thus these 2-phenylaniline-type pre-catalysts are particularly good in SM reactions involving unstable boronic acids such as polyfluorophenylboronic acids, which are particularly susceptible to protodeboronation. The ability of the 2-phenylaniline-type pre-catalyst **89** to couple 4-chloroanisole with 2,6-difluorophenylboronic acid using **89** (2 mol%) to give the biaryl product in 95% yield after only 0.5 h at RT was an excellent result (**scheme 85**).[160]



Scheme 85. The rapid activation of 2-phenylaniline-type pre-catalysts under mild conditions allows for efficient coupling of highly sensitive boronic acids.

Knowing this, the Doherty Knight group conducted a study on the catalytic ability of cyclopalladated 2-phenylaniline-type complexes of KITPHOS monophosphine for SM reactions. This investigation demonstrated that complex **90** was a highly efficient source of the active [LPd^0] species and as a result exhibited excellent catalytic activity. One such example is in the coupling of 1-chloro-2,6-dimethylbenzene with phenylboronic acid, which on using **90** (0.25 mol%), the biaryl product was produced in 96% yield after 6 h at 80 °C (**scheme 86**).[53]





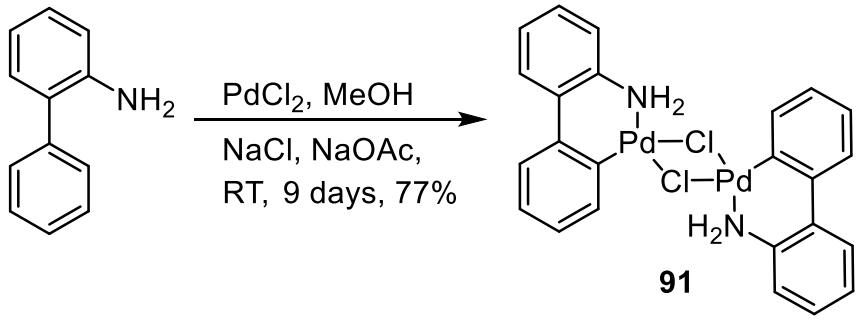
90

Scheme 86. The KITPHOS-ligated pre-catalyst **90** is proficient in SM reactions, achieving excellent yields using low catalyst loadings.[53]

Triaryl equivalents of highly efficient electron-rich catalysts, such as CM-Phos, have already been shown to display remarkable activity towards SM reactions in section 4.1.2.5 of this chapter. Thus, the aim was to investigate the catalytic ability of 2-phenylaniline-type pre-catalysts of less electron-rich phenyl-substituted KITPHOS monophosphines in a range of SM reactions. These pre-catalysts were then compared against the more electron-rich cyclohexyl-substituted KITPHOS monophosphine-ligated pre-catalyst **60**, which has already been shown to highly efficient in catalysing SM reactions.[53]

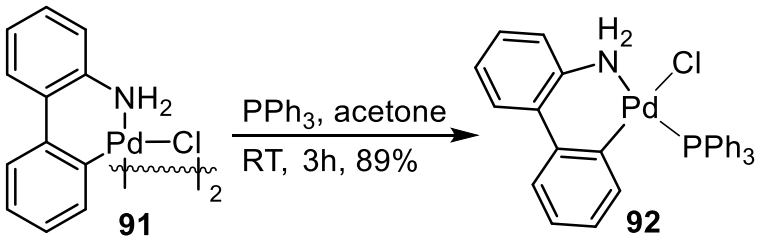
4.1.3 Synthesis of 2-phenylaniline-based cyclopalladated pre-catalysts

The synthesis of these pre-catalysts is through a linear two step procedure, starting from the inexpensive commercially available 2-phenylaniline. The first step of this sequence involves the formation of the cyclopalladated dimer complex **91**, by stirring a mixture of $PdCl_2$, NaCl, NaOAc and biphenyl-2-ylamine in MeOH at RT for 9 days, to give the product **91** in 77 % yield (**scheme 87**).[161]



Scheme 87. Synthesis of the cyclopalladated dimer **91** from 2-phenylaniline.[161]

Then to construct the pre-catalysts of KITPHOS monophosphines, the cyclopalladated dimer **91** was simply stirred in acetone with the phosphine at RT for 3 h and then recrystallised to liberate the products. **Scheme 88** highlights the synthesis of the triphenylphosphine-ligated pre-catalyst **92**. The structures of the pre-catalysts of KITPHOS monophosphines are given below with their corresponding yield. All compounds **93**, **94**, **95**, and **96** were synthesised using this same procedure, with their structures and yields given in **figure 31**.



Scheme 88. The synthesis of [{triphenylphosphine}-2-(2'-amino-1,1'-biphenyl)] palladium(II) chloride] **92**.[161]

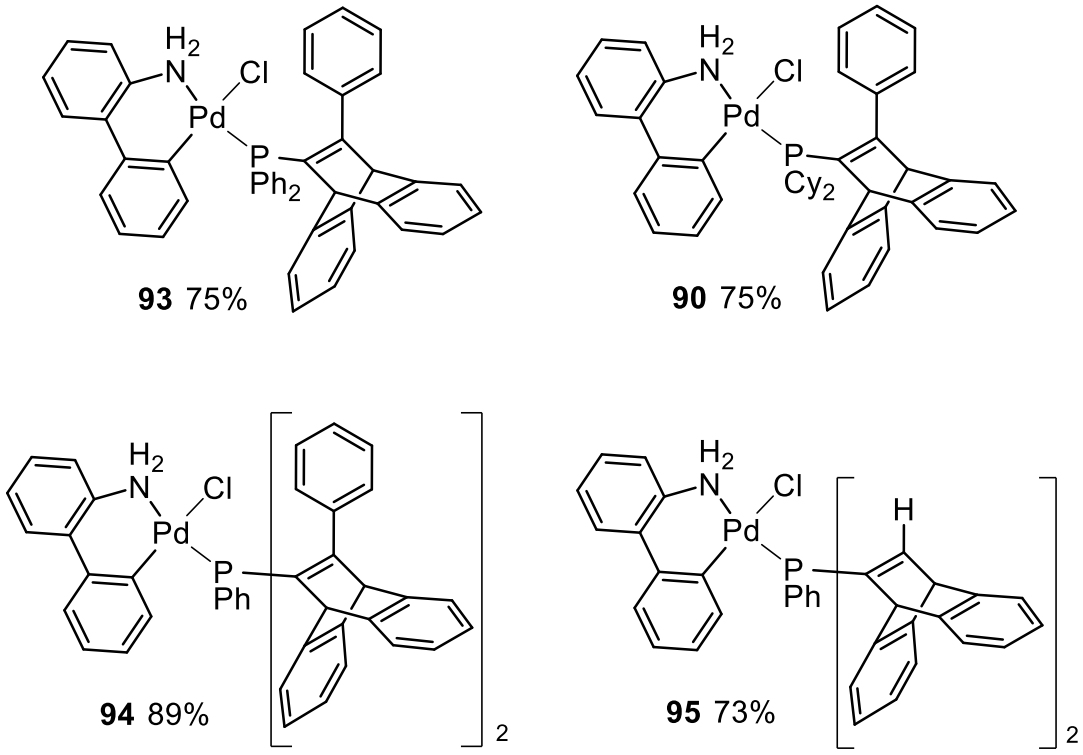


Figure 31. The structures of the pre-catalysts of KITPHOS monophosphines **90**, **93**, **94**, **95** with their yields.

These pre-catalysts all exhibited characteristic broadening of the NH_2 resonances in ^{1}H NMR spectra. They also displayed a broadening in their ^{31}P NMR resonances. **93**, **90**, **95** and **92** showed single peaks in the ^{31}P NMR at δ 30.9, δ 48.3, δ 30.1 and δ 36.5 respectively whilst **94** showed two peaks, one at δ 35.8 and the other at δ 25.7. These properties are consistent with other 2-phenylaniline-type complexes of both

KITPHOS monophosphines and other dialkylbiarylphosphines.[53] The line broadening displayed in these NMR spectra is postulated to be due to the presence of rotamers, through the restricted rotation about the Pd-P bond.[53]

All these palladium pre-catalysts were purified by recrystallisation through the slow diffusion of MeOH into a $CHCl_3$ solution of the complexes. The crystal structures of **92** and **90** are already known. No crystals suitable for X-ray crystallography could be grown for **95** and so its structure was not obtained. Gratifyingly, suitable crystals of **93** and **94** were produced, with their crystal structures shown in **figures 32** and **33**. **Table 10** highlights some key bond lengths and angles present in these crystal structures.

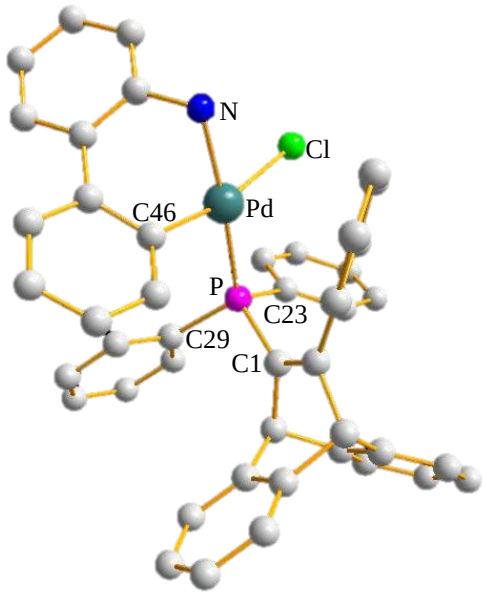


Figure 32. Crystal structure of [{11-(diphenylphosphino)-12-phenyl-9,10-dihydro-9,10-ethenoanthracene}-2-(2'-amino-1,1'-biphenyl)]palladium(II) chloride] **93**. Hydrogen atoms and a solvent molecule ($CHCl_3$) have been removed for clarity. Selected bond angles (°): Pd-P-C1 = 117.38(11), 116.24(11), 115.56(11); Pd-P-C23 = 111.77(11), 110.89(11), 111.26(8); Pd-P-C29 = 118.08(12), 120.93(11), 119.88(8).

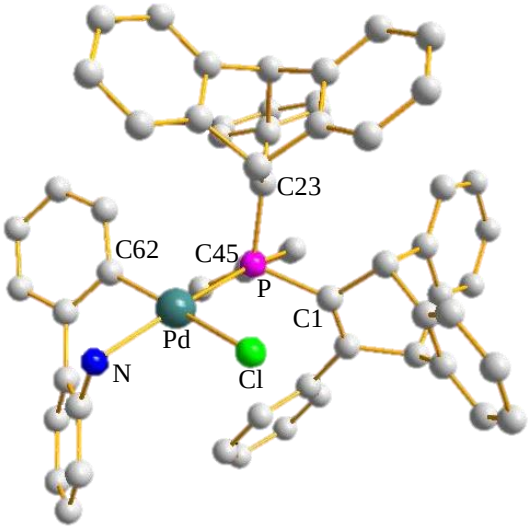


Figure 33. Crystal structure of [{11-[bis(12-phenyl-9,10-dihydro-9,10-etheno-anthracene)]phenylphosphine}-2-(2'-amino-1,1'-biphenyl)]palladium(II) chloride] **94**. Hydrogen atoms and a solvent molecule ($CHCl_3$) have been removed for clarity. Selected bond angles (°): Pd-P-C1 = 114.41(7) Pd-P-C23 = 107.69(7), Pd-P-C45 = 120.34(7).

Table 10. Selected bond lengths and angles from the crystal structures **93**, **94** and **90**.

Property	**93** [a]	**94**	**90** [b]
Pd-P / Å	2.2652(9), 2.2620(9), 2.2685(9)	2.2443(5)	2.2699(7)
Pd-C / Å[c]	2.009(4), 2.020(4), 2.001(4)	2.004(2)	2.005(3)
Pd-N / Å	2.108(2), 2.103(2), 2.113(2)	2.1244(9)	-
Pd-Cl / Å	2.4233(10), 2.4226(10), 2.4364(10)	2.3997(6)	-
Cl-Pd-P / °	96.96(3), 100.59(3), 96.62(3)	93.38(2)	96.99(2)
C-Pd-P / °	94.22(9), 90.82(9), 94.92(9)	93.65(6)	-
N-Pd-P / °	175.52(9), 173.98(9), 178.01(9)	172.35(6)	-

[a] Three independent molecules are present in the asymmetric unit of **93**, therefore three sets of values are present for each bond length and angle. [b] literature values.[53] [c] Pd-C46 bond length in **93** and **90**, Pd-C62 bond length in **94**.

These two crystal structures shown in **figures 32** and **33** exhibit a distorted square planar conformation, with the angle between each of the four groups around the palladium centre distorted away from the ideal 90°. In both of these complexes, the phosphine is *trans* to the amine group in the square planar conformation. This is consistent with other complexes reported in the literature.[53, 161] The aromatic carbon atom in the square planar arrangement around the palladium centre exerts the highest *trans* influence of the four groups due to its strongly σ-donating ability and so occupies the position opposite to the chloride group, which possesses the weakest *trans* influence. Thus the Pd-C bond lengths in both **93** and **94** are the shortest of the four Pd-L bonds and the Pd-Cl bond lengths are the longest (**table 10**). This effect causes the phosphine to be positioned opposite to the amine as shown in the crystal structures of both **93** and **94** (**figures 32** and **33**).[162]

The *trans* influence is the extent to which a ligand weakens the M-X bond *trans* to itself in its ground state, where X is any other ligand.[162b] As the *trans* influence of a phosphine is largely independent of its bulk and typically depends on its electronic properties, assumptions can be made about the σ-donor strength of the ligand in question. Thus, as the Pd-P bond length present in **94**, 2.2443(5) Å is shorter than that in **93**, 2.2652(9), 2.2620(9), 2.2685(9) Å and the Pd-N bond length in **94** (2.1244(9) Å) is longer than that in **93** [2.108(2), 2.103(2), 2.113(2) Å], **94** exhibits a greater *trans* influence than **93**. This greater trans influence implies that **94** is in fact a stronger σ-donor than **93**.[162b]

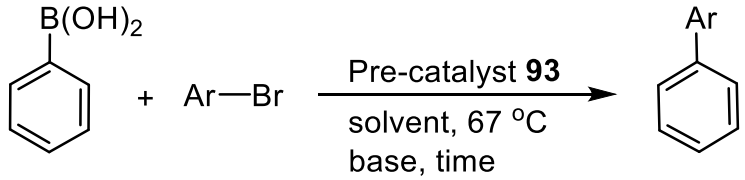
The properties of the crystal structures of **93** and **90** are very similar and in fact are also consistent with 2-phenylaniline pre-catalyst complex of XPHOS (**89**).[163] The Cl-Pd-P bond angles of 96.96(3), 100.59(3), 96.62(3)° for **93** and 93.38(2)° for **94** along with the Cl-Pd-P bond angles of 94.22(9), 90.82(9), 94.92(9)° for **93** and 93.65(6)° for **94**, demonstrate the distortion present in these cyclopalladated complexes away from the ideal value of 90° for a square planar conformation. These values combined with the N-Pd-P bond angles of 175.52(9), 173.98(9), 178.01(9)° for **93** and 172.35(6)° for **94**, illustrate the greater planarity present in **93** with its distortion displayed mainly within the interpartitional angles of the square planar conformation. **94** on the other hand retains bond angles more similar to that of the ideal, however as it possesses a significantly larger phosphine in **30**, a deformation in planarity results in order to best accommodate this extra steric bulk of the phosphine. These distortions allow **93** to

adopt a conformation which possesses a favourable stabilising η^1-interaction between the palladium centre and the *ortho*-C-atom of the lower aryl ring of KITPHOS unit, with bond lengths of 2.959(3), 2.922(3) and 2.926(3) Å in its three independent molecules within the asymmetric unit. **94** cannot access these favourable Pd-arene stabilising interactions, therefore the phosphine distorts the planarity of the palladium complex in order to adopt a conformation in which both lower aryl rings of the two KITPHOS moieties form weakly stabilising π-π stacking interactions with the phenyl ring directly attached to the phosphorus atom. In total there are six of these present in the crystal structure, with five of these being between the *ipso/ortho*-C-atoms of one of the KITPHOS units with the *ipso/ortho*-C-atom of the phenyl ring and the other being between the *ipso*-C-atom of the other KITPHOS unit with the *ipso*-C-atom of the phenyl ring. These bond lengths are 3.012(3), 3.212(3), 3.200(3), 3.243(3), 3.343(3), 3.101(3) Å and are each less than the sum of the van der Waals radii of two C-atoms (<3.40 Å).[164]

4.1.4 Suzuki-Miyaura reaction results using the 2-phenylaniline-based pre-catalysts

In order to investigate the effectiveness of these 2-phenylaniline-based pre-catalysts, a range of SM reactions were performed using the pre-catalysts **92**, **93**, **94** and **95**. The results from these reactions were then compared against the *in situ* generated active catalyst derived from $Pd(OAc)_2$ and PPh_3. Firstly, the reaction conditions were optimised using the pre-catalyst **93** for the coupling of either 4-bromoacetophenone or 5-bromopyrimidine with phenylboronic acid (**table 11**). A summary of the structures of the pre-catalyst complexes used in **tables 11 - 16** is given on page xiv of this thesis.

Table 11. Optimisation procedure for SM reactions using the pre-catalyst **93**.



Entry [a]	Solvent	93 / mol%	Base	Time / min	Conv. / % [b]
1	THF	2.0	K_3PO_4	120	59
2	THF / H_2O [c]	2.0	K_3PO_4	20	94
3	Dioxane	2.0	K_3PO_4	20	15
4	Dioxane / H_2O [c]	2.0	K_3PO_4	20	56
5	Toluene	2.0	K_3PO_4	20	25
6	Toluene / H_2O [c]	2.0	K_3PO_4	20	65
7	THF / H_2O [c]	2.0	Cs_2CO_3	20	73
8	THF / H_2O [c]	0.5	K_3PO_4	30	71
9	THF / H_2O [c]	0.5	KF	30	22
10 [d]	THF / H_2O [c]	0.5	K_3PO_4	30	80
11 [d]	THF / H_2O [e]	0.5	K_3PO_4	20	98
12 [d]	THF / H_2O [f]	0.5	K_3PO_4	15	100

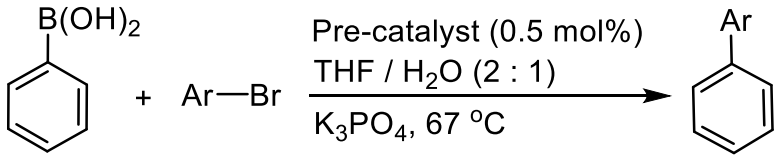
[a] 4-bromoacetophenone (0.4 mmol), phenylboronic acid (0.6 mmol), base (0.8 mmol), **93**, total solvent volume (3 ml), 67 °C, time. [b] conversion measured by ^{1}H NMR (average of three runs). [c] H_2O added (0.2 ml). [d] 5-bromopyrimidine (0.4 mmol). [e] H_2O added (0.6 ml). [f] H_2O added (1.0 ml).

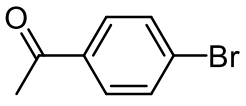
Initially THF was chosen as the solvent for the coupling of 4-bromoacetophenone with phenylboronic acid, using **93** (2 mol%), K_3PO_4 as the base and after 120 min at 67 °C, the product was formed in 59% conversion (entry 1). The addition of H_2O substantially increased the rate of reaction using **93**, giving a conversion of 94% after only 20 min (entry 2). The addition of water aids in the solvation of both the base and the boronic acid.[165] This then increases the favourability for the formation of the reactive tetra-coordinate boronate species which facilitates transmetalation. On varying the solvent to incorporate dioxane and toluene including addition of water (entries 3, 4, 5, 6) it was concluded that THF / H_2O with a conversion of 94% after 20 min (entry 2)

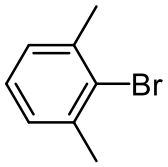
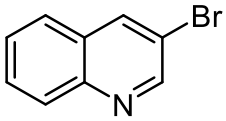
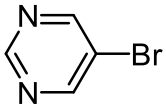
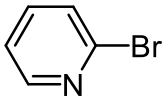
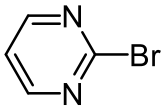
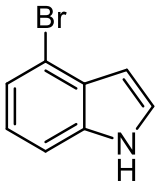
was the best combination. Then on examining the effect of changing the base to Cs_2CO_3 (entry 7) a decrease in activity was observed, with a conversion of 73% compared to the 94% on using K_3PO_4 (entry 2). Likewise on employing KF (entry 9), a decrease in conversion was also observed on comparing against K_3PO_4 (entry 8). It was then shown that a reduced catalyst loading of **93** (0.5 mol%) could be employed and still lead to an efficient conversion of 71% to the product after 30 min (entry 8). Then in the reaction with 5-bromopyrimidine it was shown that using the solvent system THF / H_2O (2 : 1) using 1 ml of H_2O, resulted in the best conversion to the product, with 100% conversion after 15 min (entry 12) compared with 98% after 20 min using 0.6 ml (entry 11) and 80% after 30 min using 0.2 ml (entry 10).

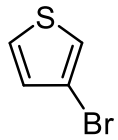
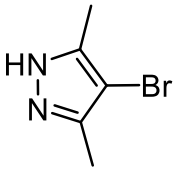
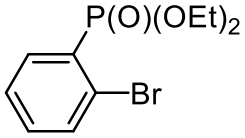
Thus, the optimised set of conditions for SM reactions using the pre-catalyst **93** were THF / H_2O (2 : 1), 0.5 mol% catalyst loading, 67 ^oC and using K_3PO_4 as the base. These conditions were applied in order to compare the catalytic performances of the pre-catalysts **92**, **93**, **94**, **95** and the *in situ* catalyst generated from $Pd(OAc)_2$ (0.5 mol%) and PPh_3 (1.0 mol%) for SM reactions involving a range of aryl bromides and either phenylboronic acid or 2-methylphenylboronic acid. **Table 12** shows the results from the reactions using phenylboronic acid.

Table 12. Suzuki-Miyaura cross coupling reactions using phenylboronic acid.



Entry [a]	Aryl Bromide	Pre-catalyst	Time / min	Conv. / % [b]
1 [c]		**93**	15	71
2		**94**	15	99
3		**95**	15	83
4 [c]		**92**	15	98
5 [c,d]		$Pd(OAc)_2$ / PPh_3	15	71
6 [e]		**92**	2 h	93

7		**93**	15	92
8		**94**	15	95
9		**95**	15	83
10		**92**	15	83
11 [d]		$Pd(OAc)_2$ / PPh_3	15	73
12		**93**	15	81
13		**94**	15	71
14		**95**	15	81
15		**92**	15	97
16 [d]		$Pd(OAc)_2$ / PPh_3	15	94
17		**93**	15	85
18		**94**	15	55
19		**95**	15	88
20 [c]		**92**	15	100
21 [c,d]		$Pd(OAc)_2$ / PPh_3	15	91
22		**93**	15	66
23		**94**	15	65
24		**95**	15	20
25		**92**	15	56
26 [d]		$Pd(OAc)_2$ / PPh_3	15	43
27		**93**	8 h	37
28		**94**	8 h	33
29		**95**	8 h	13
30		**92**	8 h	47
31 [d]		$Pd(OAc)_2$ / PPh_3	8 h	70
32		**93**	15	86
33		**94**	15	100
34		**95**	15	60
35		**92**	15	88
36 [d]		$Pd(OAc)_2$ / PPh_3	15	79

37 [f]		**93**	15	86
38 [f]		**94**	15	>99
39 [f]		**95**	15	64
40 [f]		**92**	15	100
41 [d,f]		$Pd(OAc)_2$ / PPh_3	15	88
42 [g]		**93**	48 h	62 (23) [h,i]
43 [g]		**94**	48 h	97 (3) [h,i]
44 [g]		**95**	48 h	26 (14) [h,i]
45 [g]		**92**	48 h	36 (21) [h,i]
46 [d,g]		$Pd(OAc)_2$ / PPh_3	48 h	34 (19) [h,i]
47		**93**	15	100
48		**94**	15	100
49		**95**	15	41
50		**92**	15	33
51 [d]		$Pd(OAc)_2$ / PPh_3	15	9
52 [d]		$Pd(OAc)_2$ / PPh_3	16 h	52

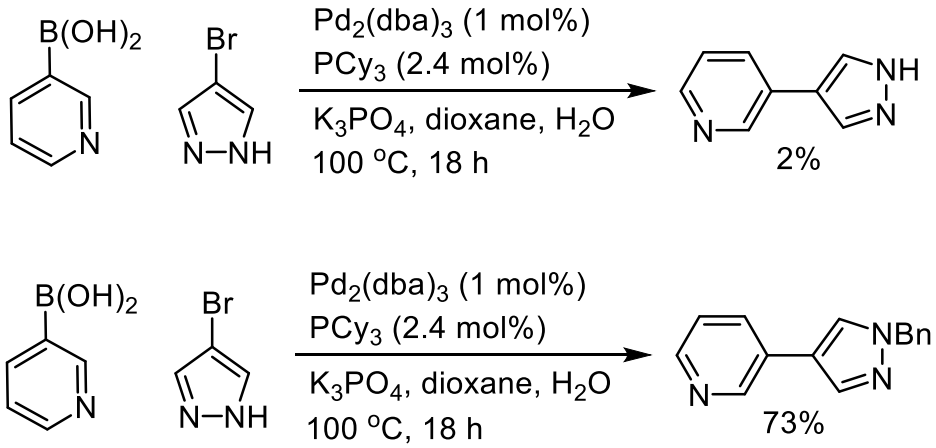
[a] Aryl bromide (0.4 mmol), phenylboronic acid (0.6 mmol), base (0.8 mmol), pre-catalyst (0.5 mol%), THF / H_2O (2 : 1) (3 ml), 67 °C, time. [b] conversion measured by ^1H NMR (average of three runs). [c] pre-catalyst (0.1 mol%). [d] *in situ* $Pd(OAc)_2$ (0.5 mol%) / PPh_3 (1.0 mol%). [e] RT. [f] conversion measured by GC. [g] toluene / H_2O (2 : 1) as solvent, 100 °C. [h] yield of product given. [i] yield of de-brominated 3,5-dimethylpyrazole by-product, in brackets.

Firstly, this table of results shows that highly efficient reaction conditions have been identified for the coupling of a broad range of aryl bromides with phenylboronic acid. On comparing the *in situ* generated catalyst system ($Pd(OAc)_2$ / PPh_3) with that of the cyclopalladated pre-catalyst **92**, it is clear to see that for the vast majority of transformations, the cyclopalladated species gave significantly better conversions. The only anomaly to this conclusion was seen in the reaction with 2-bromopyrimidine, where after 8 h, 70% conversion of the product was observed for the *in situ* generated $Pd(OAc)_2$ / PPh_3 catalyst (entry 31) compared to the 47% for **92** (entry 30). Interestingly on addition of one extra equivalent of PPh_3 to the pre-catalyst **92**, the conversion for the reaction involving 2-bromopyrimidine increased to 67%, an almost identical conversion to that resulting from the *in situ* catalyst. Thus, on the whole the use of this type of cyclopalladated pre-catalyst results in a more efficient activation of the catalyst to yield the $[(PPh_3)Pd^0]$ species in solution and therefore the use of pre-

catalysts provides a more efficient source of the true catalyst.

In nearly all of these coupling reactions, the pre-catalyst **95** displayed the lowest activity for each of the aryl bromides, with the exception of entry 19, for 5-bromopyrimidine where a conversion of 88% after 15 min was observed. However **92** obtained the best result for this substrate, giving the product in 100% conversion after 15 min using a catalyst loading of only 0.1 mol% (entry 20). A general trend is observed in **table 12**. The pre-catalyst **92** proved to be the catalyst of choice for substrates governed by electronics as it possessed the greatest catalytic activity for 4-bromoacetophenone (entry 4), 3-bromoquinoline (entry 15), 5-bromopyrimidine (entry 20), and 3-bromothiophene (entry 40). It must be mentioned though that **94** gained essentially the same conversion for 3-bromothiophene, giving the product in >99% yield after 15 min (entry 38) compared to the 100% conversion obtained by **92** (entry 40).

However for more sterically hindered substrates the pre-catalysts **93** and **94** produced the best conversions, for example 1-bromo-2,6-dimethylbenzene gave 92% conversion after 15 min for **93** (entry 7) and 95% for **94** (entry 8). This was also demonstrated for the highly hindered 4-bromo-3,5-dimethyl-1*H*-pyrazole, which after 48 h gave the product in 97% conversion for **94** (entry 43) and 62% for **93** (entry 42). The pre-catalyst **92** in comparison gave the product in a conversion of only 36% (entry 45), with the *in situ* generation converting 34% to the product (entry 46) and **95** giving 26% (entry 44). These reactions with 4-bromo-3,5-dimethyl-1*H*-pyrazole did require the use of toluene as the solvent and the elevated temperature of 100 ^{o}C to obtain these conversions. It has previously been demonstrated on a number of occasions that the pyrazole NH must be protected in order to facilitate coupling reactions successfully. Fu demonstrated this well in the cross coupling of 3-pyridine boronic acid with both 4-bromo-1*H*-pyrazole and 4-bromo-1-benzylpyrazole (**scheme 89**). Both reactions used $Pd_2(dba)_3$ (1 mol%), PCy_3 (2.4 mol%) and K_3PO_4 in dioxane / H_2O, which on heating at 100 ^{o}C for 18 h gave the product in <2% yield when 4-bromo-1*H*-pyrazole was used but 73% yield for the benzyl-protected pyrazole.[151]



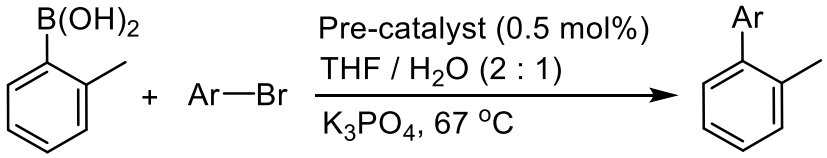
Scheme 89. Unprotected pyrazoles are much less accessible towards SM reactions than their benzyl-protected counterparts.

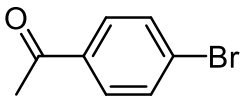
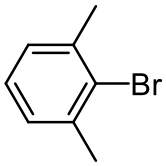
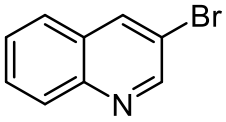
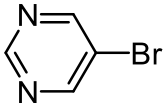
Thus the pre-catalysts **93** and **94** displayed excellent activity towards the SM reaction involving phenylboronic acid and 4-bromo-3,5-dimethyl-1*H*-pyrazole. In fact entry 14 in **table 12** shows the best result to date for a SM reaction involving the substitution at the 4-position of an unprotected pyrazole. Surprisingly though, SM reactions with unprotected indoles proceed relatively easily, with **94** greatly outperforming the others to give the product in 100% conversion after only 15 min (entry 33). The efficacy in SM reactions using unprotected indoles is widespread in the literature.[151]

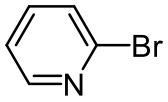
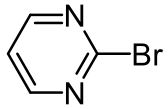
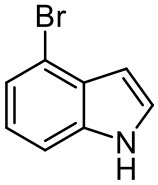
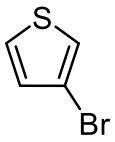
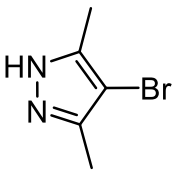
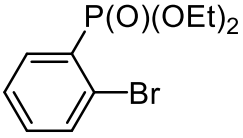
The most dramatic result in favour of the use of pre-catalyst complexes of KITPHOS monophosphines was shown in the reactions involving diethyl *o*-bromobenzenephosphonate. On performing the reactions at 67 °C in THF / H_2O (2 : 1) using K_3PO_4 and a catalyst loading of 0.5 mol%, the product was formed in a conversion of 100% for both **93** and **94**, 41% for **95**, 33% for **92** and only 9% using the *in situ* catalyst after 15 min (entries 47 - 51). In fact on using the $Pd(OAc)_2$ (0.5 mol%) / PPh_3 (1.0 mol%) catalyst generated *in situ*, the conversion to the product was only 52% after 16 h (entry 52). This demonstrates a remarkable enhancement in activity on using both **93** and **94** to catalyse the reaction with phenylboronic acid.

In order to investigate the ability of these pre-catalysts further, the more sterically demanding 2-methylphenylboronic acid was coupled with the same aryl bromides as used previously with phenylboronic acid. The results are given in **table 13**.

Table 13. Suzuki-Miyaura cross coupling reactions using 2-methylphenylboronic acid.



Entry [a]	Aryl Bromide	Pre-catalyst	Time / min	Conv. / % [b]
1		**93**	15	90
2		**94**	15	99
3		**95**	15	76
4		**92**	15	100
5 [c]		$Pd(OAc)_2$ / PPh_3	15	99
6		**93**	30	99
7		**94**	30	93
8		**95**	30	65
9		**92**	15	81
10 [c]		$Pd(OAc)_2$ / PPh_3	30	74
11		**93**	15	97
12		**94**	15	95
13		**95**	15	96
14		**92**	15	100
15 [c]		$Pd(OAc)_2$ / PPh_3	15	99
16		**93**	15	70
17		**94**	15	71
18		**95**	15	65
19		**92**	15	96
20 [c]		$Pd(OAc)_2$ / PPh_3	15	99

21		**93**	30	90
22		**94**	30	85
23		**95**	30	60
24		**92**	30	90
25 [c]		$Pd(OAc)_2$ / PPh_3	30	83
26		**93**	8 h	57
27		**94**	8 h	45
28		**95**	8 h	25
29		**92**	8 h	76
30 [c]		$Pd(OAc)_2$ / PPh_3	8 h	88
31		**93**	15	97
32		**94**	15	98
33		**95**	15	66
34		**92**	15	77
35 [c]		$Pd(OAc)_2$ / PPh_3	15	49
36 [d]		**93**	15	87
37 [d]		**94**	15	>99
38 [d]		**95**	15	68
39 [d]		**92**	15	80
40 [c,d]		$Pd(OAc)_2$ / PPh_3	15	76
41 [e]		**93**	48 h	10 (15) [f,g]
42 [e]		**94**	48 h	16 (0.6) [f,g]
43 [e]		**95**	48 h	3 (10) [f,g]
44 [e]		**92**	48 h	2 (36) [f,g]
45 [c,e]		$Pd(OAc)_2$ / PPh_3	48 h	1 (23) [f,g]
46		**93**	3 h	78
47		**94**	3 h	20
48		**95**	3 h	<1
49		**92**	3 h	0
50 [c]		$Pd(OAc)_2$ / PPh_3	3 h	<1
51 [c]		$Pd(OAc)_2$ / PPh_3	16 h	6

[a] Aryl bromide (1 eq), 2-methylphenylboronic acid (1.5 eq), base (2 eq), pre-catalyst (0.5 mol%), THF / H_2O (2 : 1), 67 °C, time. [b] conversion measured by ^1H NMR (average of three runs). [c] *in situ* $Pd(OAc)_2$ (0.5 mol%) / PPh_3 (1.0 mol%). [d] conversion measured by GC. [e] toluene / H_2O (2 : 1) as solvent, 100 °C. [f] yield of product given. [g] yield of de-brominated 3,5-dimethylpyrazole by-product, in brackets.

In the majority of cases, the coupling reactions using 2-methylphenylboronic acid are significantly more difficult than those using phenylboronic acid, due to steric hindrance associated with the *ortho*-methyl group. Also for the majority of aryl bromides, the pre-catalysts of KITPHOS monophosphines **93** and **94** greatly outperform those of **95** and **92** as well as the *in situ* generated catalyst. This advantage can easily be seen in the reactions using 4-bromo-1*H*-indole, where the conversion after only 15 min for **93** was 97% and **94** was 98% compared to 66% for **95**, 77% for **92** and 49% for the *in situ* catalyst (entries 31 - 35). **94** greatly outperformed the other pre-catalysts in the reaction of 3-bromothiophene, which after 15 min gave the product in >99% conversion (entry 37).

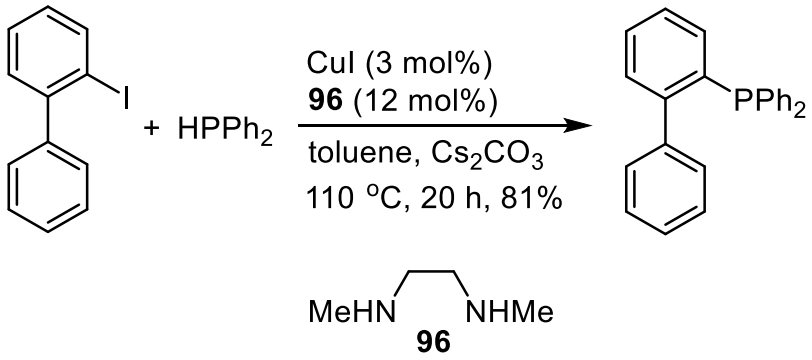
However the pre-catalyst **92** did outperform both **94** and **93** in the reactions of 5-bromopyrimidine and 2-bromopyrimidine, with **92** gaining the products in 96% yield after 15 min (entry 19) and 76% after 8 h (entry 29) respectively, compared to the 70% (entry 16) and 57 % (entry 26) for **93**. Once again the advantage of using the 2-phenylaniline pre-catalyst **92** over the simple *in situ* approach using $Pd(OAc)_2$ / PPh_3 can be easily seen in the reaction involving 1-bromo-2,6-dimethylbenzene, with **92** affording the product in 81% after only 15 min compared to 74% after 30 min using the *in situ* approach (entries 9 and 10).

The coupling reactions involving 4-bromo-3,5-dimethyl-1*H*-pyrazole with 2-methylphenylboronic acid proved much more difficult than the corresponding couplings with phenylboronic acid. As a result, exceedingly low yields were obtained using all the catalysts (entries 41 - 45). These results invoke the possible need to protect the pyrazole NH on using a more sterically hindered boronic acid. **94** gained the best result for this transformation yielding the product in 16% yield with <1% of the de-brominated 3,5-dimethylpyrazole by-product liberated (entry 42). The other catalysts produced much larger amounts of the de-brominated by-product, with diminished conversions to the product.

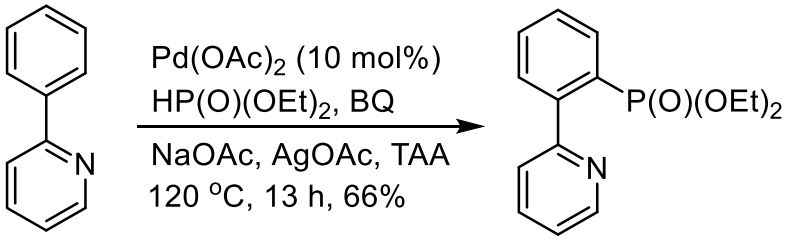
Interestingly in the reaction involving diethyl *o*-bromobenzenephosphonate, **93** afforded the product in 78% conversion after 3 h (entry 46). This coupling appears to be particularly difficult, with **94** only giving 20% conversion and **92** giving no conversion, whereas **95** and the *in situ* catalyst gave only 1% of the product (entries 47 - 50). In fact after 16 h using the $Pd(OAc)_2$ / PPh_3 catalyst generated *in situ*, the product

was formed in only 6% conversion (entry 51). This demonstrates a clear enhancement in activity on using the pre-catalyst **93** for the reactions involving diethyl *o*-bromobenzenephosphonate with both phenyl- and 2-methylphenylboronic acid, which gave excellent yields under mild conditions.

Currently the main alternative transition metal catalysed syntheses of these biaryl-phosphine derivatives involve P-C coupling reactions[166] and directed phosphorylations.[60, 167] Buchwald highlighted two such C-P coupling reactions, both involving 1-phenyl-2-iodobenzene. One such reaction involves the coupling of the 1-phenyl-2-iodobenzene with diphenylphosphine using CuI (3 mol%) and *N*,*N*''-dimethyl-1,2-diaminoethane, **96** (12 mol%) which liberated the product in 81% yield (**scheme 90**).[166a] Alternatively, the directed phosphorylation of 2-phenylpyridine with $HP(O)(OEt)_2$ can be achieved using $Pd(OAc)_2$ (10 mol%) to give the product in 66% yield (**scheme 91**).[167]



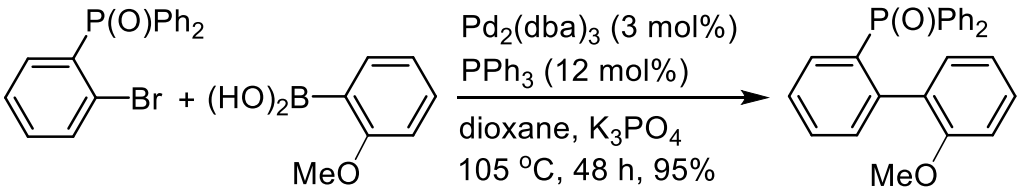
Scheme 90. The synthesis of biarylphosphines / phosphonates can be achieved through C-P coupling reactions.



Scheme 91. Biarylphosphines / phosphonates can be synthesised through the directed phosphorylation of 2-phenylpyridine.

However for success in these reactions, the use of high temperatures, long reaction times and relatively high catalyst loadings are needed. Also the need for the substrate to bear either an iodide or a directing group for success in these syntheses limits the diversity and the number of differing substrate combinations which can be used in these transformations.[166a, 167] SM reactions are more advantageous due to the commerical availability of the starting materials such as boronic acids and aryl halides as well as the relatively mild reaction conditions used.

Xiao has previously demonstrated successful SM reactions involving (2-bromophenyl)diphenylphosphine oxide with a number of boronic acids, including 2-methoxyphenylboronic acid, which produced the product in 95% yield using $Pd_2(dba)_3$ (3 mol%) and PPh_3 (12 mol%) after heating at 105 ^oC for 48 h (**scheme 92**).[168]



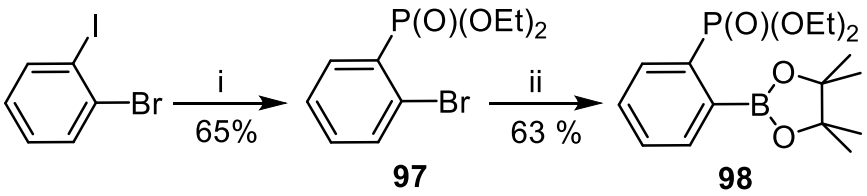
Scheme 92. The SM reaction between (2-bromophenyl)diphenylphosphine oxide and 2-methylphenylboronic acid can be achieved using PPh_3.

Interestingly, on performing this reaction under the same conditions but with $P(^tBu)_3$ instead of PPh_3, a lower yield of 71% was afforded.[168] Knowing this, an investigation to compare the efficacy of these 2-phenylaniline-based pre-catalysts of phenyl-substituted KITPHOS monophosphines, against the more-electron rich pre-catalyst complex **90**, was warranted. Due to the success of the SM reactions using diethyl *o*-bromobenzenephosphonate with both phenyl- and 2-methylphenylboronic acid, shown in **tables 12** and **13**, the aim was to extend this study to include a series of differing boronic acids. Ideally the SM reactions involving these pre-catalysts of KITPHOS monophosphines would negate the need for the relatively high catalyst loadings, high temperatures and very long reaction times shown in **schemes 90** and **91**.

The possibility of performing the complementary reactions using a range of aryl halides with the corresponding phenylphosphonate boronate ester was then investigated. These types of coupling reactions have great potential in the synthesis of novel phosphine architectures. In the drive towards efficient and readily modified catalyst designs, the facile procedure and mild conditions associated with SM reactions could potentially be highly valued.

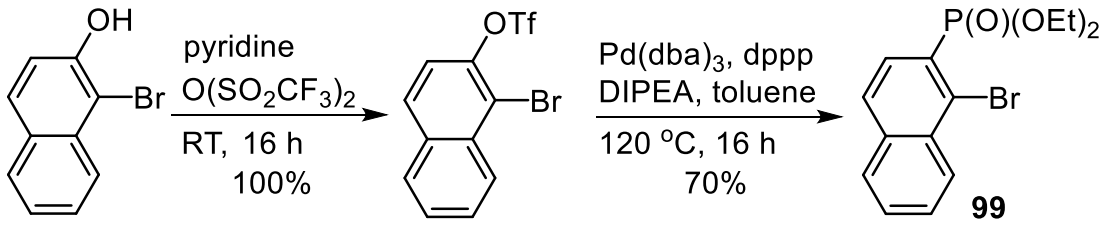
4.1.5 Synthesis of substrates for Suzuki-Miyaura reactions involving phosphonates

Firstly, diethyl *o*-bromobenzenephosphonate **97** was synthesised by chemoselective phosphonation of 1-bromo-2-iodobenzene using $Pd(OAc)_2$ (2 mol%), PPh_3 (20 mol%), $HP(OEt)_2$ and *N*,*N*-diisopropylethylamine (DIPEA) whilst heating the mixture under reflux in EtOH for 48 h to afford the product in 65% yield (**scheme 93**).[169] The corresponding pinacolboronate adduct was then prepared by reacting diethyl *o*-bromobenzene-phosphonate with $Pd(dppf)Cl_2$ (5 mol%), KOAc and bis(pinacolato)diboron in dioxane and heating the reaction at 90 ^oC for 84 h to give diethyl [2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]phosphonate, **98** in 63% yield (**scheme 93**).



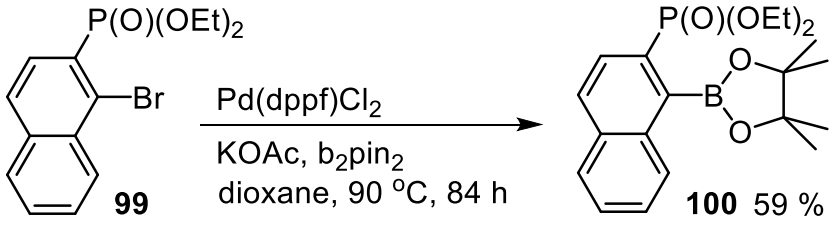
Scheme 93. The preparation of diethyl *o*-bromobenzenephosphonate, **97** and its boronate adduct, **98**. i) $Pd(OAc)_2$, PPh_3, $HP(OEt)_2$, DIPEA, EtOH, reflux, 48 h, 65%; ii) KOAc, $Pd(dppf)Cl_2$, B_2pin_2, dioxane, 90 ^oC, 84 h, 63%.

With a view to ultimately preparing atropisomeric biaryl-phosphonate derivatives, naphthyl equivalents of both the diethyl *o*-bromobenzenephosphonate and its corresponding pinacolboronate adduct were synthesised. The synthesis of these compounds is highlighted in **scheme 94**. Firstly 1-bromo-2-naphthol dissolved in pyridine was treated with triflic anhydride and the mixture was stirred at RT for 16 h to give 1-bromo-2-naphthyl triflate in 100% yield.[170] This was then treated with $Pd_2(dba)_3$ (5 mol%), dppp (5 mol%), DIPEA and $HP(OEt)_2$ and was heated in toluene at 120 ^oC for 16 h to afford diethyl 1-bromo-2-naphthylphosphonate, **99** in 70% yield.[171]



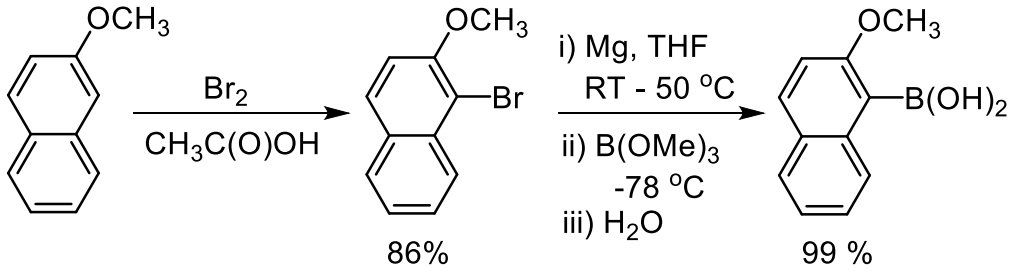
Scheme 94. The synthesis of diethyl 1-bromo-2-naphthylphosphonate **99**.

The corresponding pinacolboronate adduct **100** was then synthesised in 59% yield through a Miyaura Borylation reaction of diethyl 1-bromo-2-naphthylphosphonate using $Pd(dppf)Cl_2$ (5 mol%), KOAc and bis(pinacolato)diboron in dioxane at 90 ^oC for 16 h (**scheme 95**).[172]



Scheme 95. The synthesis of diethyl 1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-ylphosphonate **100**.

The coupling of diethyl 1-bromo-2-naphthylphosphonate **99** and the boronate adduct **100** with a range of boronic acids and aryl halides was then to be investigated. The majority of these aryl halides and boronic acids were commercially available, however it was necessary to synthesise 2-methoxy-1-naphthylboronic acid. This was afforded through a two-step procedure. Firstly the commercially available 2-methoxynaphthalene was reacted with bromine in acetic acid to give 1-bromo-2-methoxynaphthalene in 86% yield.[173] This was then converted to the corresponding Grignard reagent and quenched with trimethylborate at -78 ^{o}C to give 2-methoxy-1-naphthylboronic acid in 99% yield (**scheme 96**).[174]

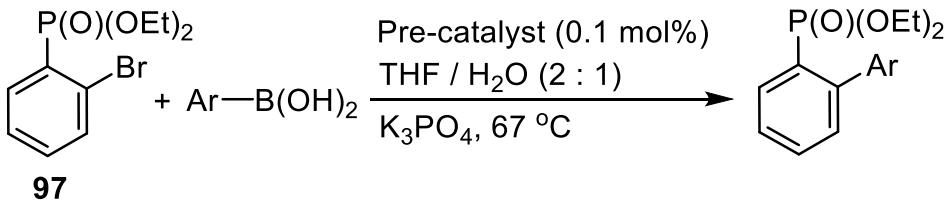


Scheme 96. The synthesis of 2-methoxy-1-naphthylboronic acid.

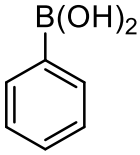
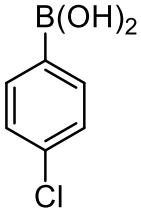
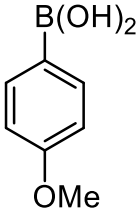
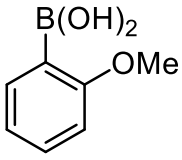
4.1.6 Suzuki-Miyaura reaction results for the synthesis of biarylphosphonate compounds

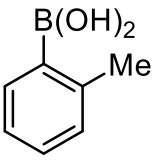
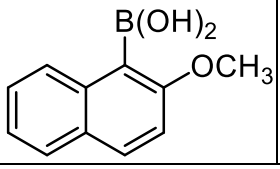
An array of SM reactions were then performed using the bromophosphonate **97** as well as the pinacolboronates **98** and **100**. The results from the reactions involving diethyl *o*-bromobenzenephosphonate (**97**) using the pre-catalysts **90**, **92**, **93** and **94** as well as the *in situ* generated catalyst from $Pd(OAc)_2$ and PPh_3 are shown in **table 14**.

Table 14. Suzuki-Miyaura reactions using diethyl *o*-bromobenzenephosphonate **97**.



97

Entry [a]	**Boronic acid**	**Pre-catalyst**	**Time / min**	**Yield / %** [b]
1		**93**	15	83
2		**94**	15	23
3 [c]		**94**	15	100
4 [c]		**92**	15	33
5 [d]		$Pd(OAc)_2$ / PPh_3	16 h	52
6		**90**	15	68
7		**93**	15	99
8		**94**	15	25
9 [c]		**92**	15	8
10 [d]		$Pd(OAc)_2$ / PPh_3	15	28
11		**90**	15	68
12		**93**	15	100
13		**94**	15	50
14		**92**	15	17
15 [d]		$Pd(OAc)_2$ / PPh_3	15	58
16		**90**	15	70
17 [c]		**93**	15	69
18 [c]		**94**	15	13
19 [c]		**92**	15	1
20 [d]		$Pd(OAc)_2$ / PPh_3	15	4
21 [c]		**90**	15	100
22		**90**	1 h	93

23 [c]		**93**	3 h	78
24 [c]		**94**	3 h	20
25 [c]		**92**	3 h	0
26 [d]		$Pd(OAc)_2$ / PPh_3	16 h	6
27 [c]		**90**	1 h	99
28 [c]		**90**	16 h	2
29 [c,e]		**90**	16 h	4
30 [e,f]		**90**	16 h	8

[a] Diethyl *o*-bromobenzenephosphonate (0.4 mmol), 2-methylphenylboronic acid (0.6 mmol), base (0.8 mmol), pre-catalyst (0.1 mol%), THF (2 ml), H_2O (1 ml), 67 °C, time. [b] isolated yield (average of three runs). [c] pre-catalyst (0.5 mol%). [d] *in situ* $Pd(OAc)_2$ (0.5 mol%) / PPh_3 (1.0 mol%). [e] toluene (2 ml), H_2O (1 ml) as solvent, 100 °C. [f] pre-catalyst (2.0 mol%).

From **table 14** it is clear that both **93** and **90** are highly efficient at catalysing SM reactions of diethyl *o*-bromobenzenephosphonate with a range of boronic acids, using catalyst loadings of only 0.1 mol% in the vast majority of cases. In the reaction with phenylboronic acid, **93** (0.1 mol%) obtained the product in 83% yield after only 15 min stirring at 67 °C in THF / H_2O (2 : 1) (entry 1). At this level of catalyst loading (0.1 mol%) this was in fact the best result of all the catalysts, even outperforming the more electron-rich pre-catalyst **90**, which gave the product in 68% yield under the same reaction conditions (entry 6). Both these values were markedly better than those obtained by **92** (0.5 mol%) and $Pd(OAc)_2$ (0.5 mol%) / PPh_3 (1.0 mol%), which yielded the products in 33% after 15 min and 52 % after 16 h respectively (entries 4 and 5).

In fact **93** actually outperformed **90** in the reaction involving 4-chlorophenyl-boronic acid by giving the product in 99% conversion (entry 7) compared to 68% (entry 11) and for the reaction with 4-methoxyphenylboronic acid, which afforded the product in 100% yield after 15 min (entry 12) compared to 70% (entry 16).

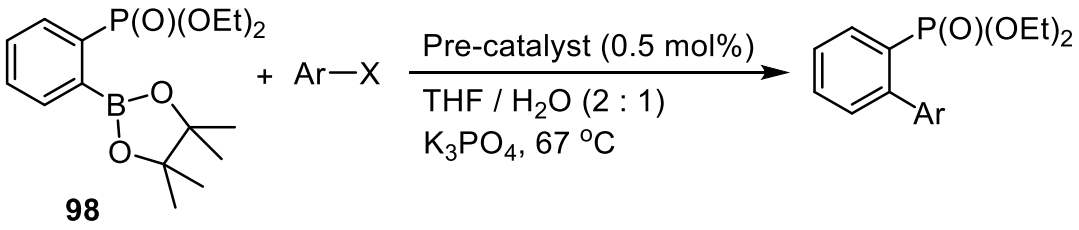
The extra bulk associated with **94**, which proved successful in the SM reactions in **table 12**, proved disadvantageous in reactions involving diethyl *o*-bromobenzene-phosphonate. **94** still produced yields of 100% for 4-chlorophenylboronic acid, 4-methoxyphenylboronic acid and 4-methoxyphenylboronic acid after 15 min, however required a higher catalyst loading of 0.5 mol%. The decreased capacity of **94** is likely to be due to the extra steric hindrance of the phosphine with the *ortho*-substituted

bromide, which disfavours the oxidative addition step of the catalytic mechanism relative to both **93** and **90**. Thus, in the reaction with phenylboronic acid **94** gave the product in 23% yield relative to 83% and 68% on using **93** and **90** respectively (entries 1, 2 and 6).

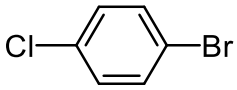
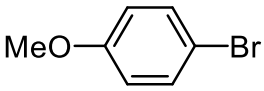
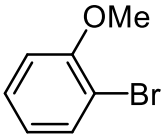
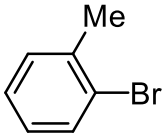
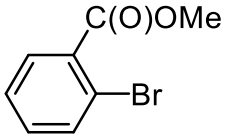
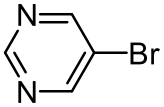
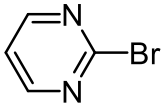
However for more sterically congested boronic acids, such as 2-methoxyphenyl-boronic acid and 2-methylphenylboronic acid, **90** outcompeted the less electron-rich pre-catalyst **93**. In the reaction with 2-methoxyphenylboronic acid, **93** (0.5 mol%) gave the product in 69% yield after 15 min (entry 17) which is considerably better than the 13% obtained by **94** (entry 18) and the 1% obtained by **92** (entry 19). However **90** gave the product in 100% yield under the same conditions and on employing a catalyst loading of 0.1 mol%, the product was formed in 93% yield after only 1 h (entry 22). This enhanced activity of **90** with more sterically demanding boronic acids was again evident in the reaction involving 2-methylphenylboronic acid, where **93** gave the product in 78% yield after 3 h (entry 23) whilst **90** gave the product in 99% yield after only 1 h (entry 27). Unfortunately this efficacy of **90** for SM reactions involving diethyl *o*-bromobenzenephosphonate was not evident in the reaction with 2-methoxy-1-naphthylboronic acid. Despite employing a catalyst loading of 2 mol% and heating the reaction at the elevated temperature of 100 ^{o}C in toluene / H_2O (2 : 1) for 16 h, a yield of only 8% of the product resulted (entry 30).

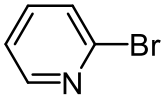
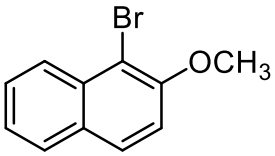
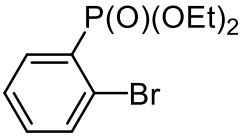
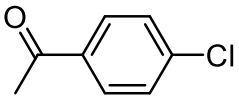
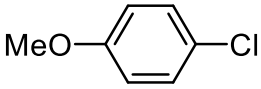
On establishing the ability of pre-catalysts **93** and **90** for SM reactions between a range of boronic acids and diethyl *o*-bromobenzenephosphonate, the complementary reactions between the boronate adduct, diethyl [2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]phosphonate (**98**) and a range of aryl halides was then investigated. The results of which are shown in **table 15**.

Table 15. Suzuki-Miyaura cross coupling reactions involving diethyl [2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]phosphonate.



98

Entry [a]	**Boronic acid**	**Pre-catalyst**	**Time / h**	**Yield / %** [b]
1		**93**	1	70
2		**90**	1	90
3		**93**	1	60
4		**90**	1	66
5		**90**	2	100
6		**93**	4	30
7		**90**	4	60
8		**90**	8	100
9		**93**	2	61
10		**90**	2	91
11		**93**	8	0
12		**90**	4	40
13		**90**	16	40
14		**93**	2	30
15		**90**	2	50
16		**93**	8	30
17		**90**	8	63
18		**93**	8	24
19		**90**	4	57
20		**90**	8	91

21 *22*		**93** **90**	4 4	62 91
23 *24*		**93** **90**	16 16	0 46
25 [c] *26* [c]		**93** **90**	16 16	0 0
27 *28* *29* [d]		**93** **90** **90**	16 16 16	16 39 41
30 *31*		**93** **90**	16 16	0 4

[a] Aryl halide (0.2 mmol), diethyl [2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]phosphonate (0.3 mml), base (0.4 mmol), pre-catalyst (0.5 mol%), THF (2 ml), H_2O (1 ml), 67 °C, time. [b] isolated yield (average of three runs). [c] pre-catalyst (2.0 mol%). [d] pre-catalyst (1.0 mol%).

The results from **table 15** show that **90** formed a highly efficient catalyst for coupling unactivated, sterically hindered and heteroaryl bromides with diethyl [2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]phosphonate, **98**. SM reactions involving the boronate ester **98** were clearly more difficult than the associated SM reactions involving diethyl *o*-bromobenzenephosphonate, with both higher catalyst loadings (0.5 mol%) and longer reaction times required for effective catalysis.

90 was clearly a much more effective pre-catalyst than **93** in all of these SM reactions. For instance in the reaction involving 2-bromopyridine, **93** with a catalyst loading of 0.5 mol% gave the product in 24% yield after 8 h (entry 18), whilst **90** gave the product in 57% yield after only 4 h and 91% after 8 h under the same reaction conditions (entries 19 and 20).

Notably while these pre-catalysts were efficient in reactions involving aryl bromides, aryl chlorides were markedly more challenging. In the reaction with 4-chloroacetophenone **93** gave the product in 16% yield and **90** in 39% yield after 16 h

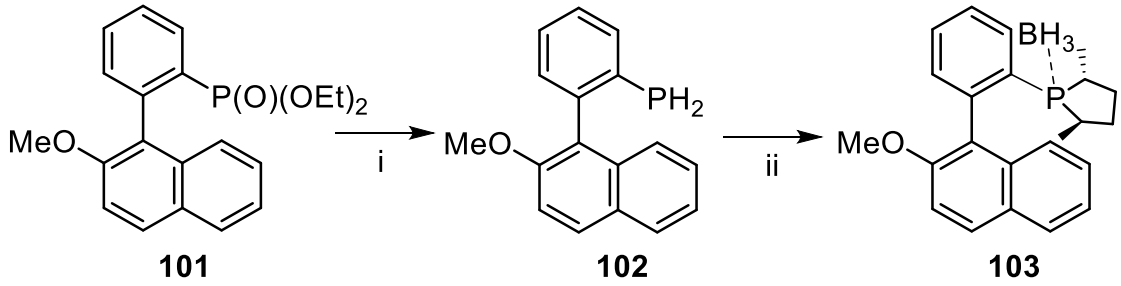
using a catalyst loading of 0.5 mol% (entries 27 and 28). Even on increasing this catalyst loading to 1.0 mol%, **90** only afforded the product in 41% yield after 16 h (entry 29). Thus significant deactivation of the catalyst must have occurred on using aryl chlorides, as no increase in turnover was observed even on increasing the catalyst loading. This was reiterated in the coupling of 4-chloroanisole which gave no product on using **93** and only 4% yield using **90** after 16 h (entries 30 and 31). However, this relative inability to couple aryl chlorides does allow for efficient chemoselectivity to be shown in the reaction using 1-bromo-4-chlorobenzene. As these pre-catalysts can only facilitate the coupling with the bromide group, the diethyl 2-(4-chlorophenyl)phenylphosphonate product formed exclusively in 70% yield for **93** and 90% yield for **90** after only 1 h (entries 1 and 2).

Unfortunately no reaction was observed between diethyl *o*-bromobenzene-phosphonate **97** and the boronate ester **98** on employing either of these pre-catalysts (entries 25 and 26). This was most likely due to the large steric encumbrance between the two diethyl phosphonate groups prohibiting the approach of substrates during the transmetalation step of the catalytic cycle.

Gratifyingly, the reaction with the hindered 1-bromo-2-methoxynaphthylene proceeded in 46% yield using 0.5 mol% **90** after 16 h (entry 24). This was unexpected as the reactions involving the boronate ester **98** have proven more difficult than those using diethyl *o*-bromobenzenephosphonate, whereas in this reaction with 2-methoxy-1-naphthylboronic acid only 8% of the product was obtained using **90** (2.0 mol%) in toluene / H_2O (2 : 1) on heating at 100 ^oC for 16 h (**table 14**, entry 30).

In order to demonstrate the feasibility and potential application of these phosphonates towards the synthesis of phosphines, 2-methoxy-1-(2'-diethoxyphosphorylphenyl)naphthalene **101**, the product from the SM reaction involving 1-bromo-2-methoxynaphthylene and the boronate ester **98** was converted into its corresponding phospholane borane compound **103** (**scheme 97**). The synthesis of a phospholane was chosen due to the many uses and applications of these compounds in asymmetric transition-metal-catalysed transformations.[166c, 169, 175] Firstly **101** was synthesised in 46% yield from the SM reaction of 1-bromo-2-methoxynaphthylene with the boronate ester **98**. This phosphonate was then reduced to the primary phosphine **102** using a suspension of Me_3SiCl (1 eq) and $LiAlH_4$ (1 eq) in THF to give the product in

98% yield. Phosphine **102** was then lithiated with ^{n}BuLi and (2*S*,5*S*)-2,5-hexanediol cyclic sulphate was added. Then following the repeated addition of further amounts of ^{n}BuLi, BH_3.THF solution was added to yield the phospholane borane adduct **103** in 32% yield, as an a*R*,*R*,*R* and a*S*,*R*,*R* (1 : 1) mixture of diastereomers.



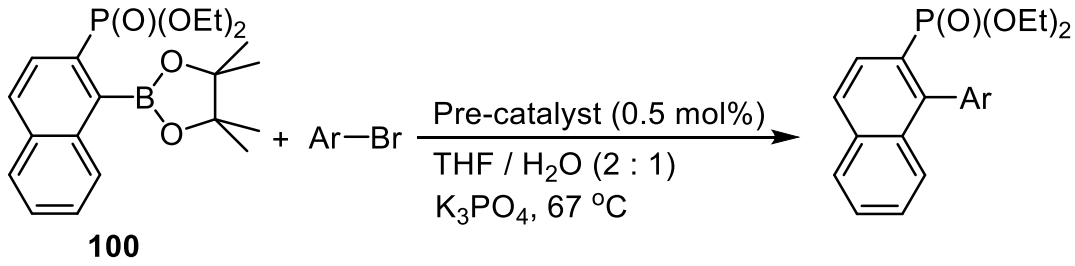
101 **102** **103**

Scheme 97. The synthesis of phospholane adduct **103**. i) Me_3SiCl, $LiAlH_4$, THF, 98%; ii) ^{n}BuLi, (2*S*,5*S*)-2,5-hexanediol cyclic sulphate, ^{n}BuLi, then BH_3.THF, 32%.

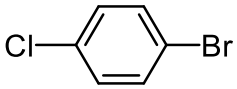
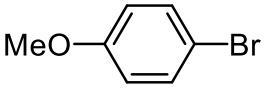
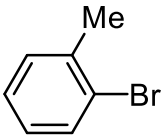
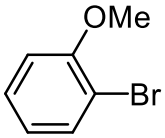
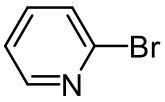
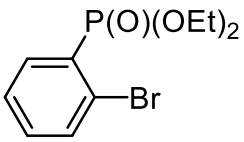
The results shown in **table 15** on using the boronate ester **98** demonstrate the first examples of successful Suzuki-Miyaura cross coupling reactions using phosphonates as the nucleophilic partner. These results complement those in **table 14** where diethyl *o*-bromobenzenephosphonate is successfully coupled with a range of boronic acids. There are already examples in the literature of the use of bromophosphonates and phosphites in SM reactions, however this use of the phenylphosphonate-based boronate ester **98** provides a means which can avoid the use of unstable boronic acids, such as pyridin-2-ylboronic acid.

In order to gain access to a wider range of biaryl phosphonate compounds, the ability of performing SM reactions involving a naphthylphosphonate-based boronate ester with a range of aryl bromides was then investigated. In the SM reactions involving diethyl [2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl] phosphonate **98** (**table** 15), **90** proved to be markedly more active than **93**. Therefore SM reactions between diethyl 1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-naphthalen-2-ylphosphonate, **100** and a range of aryl bromides were performed using pre-catalyst **90**. The results of these SM reactions are shown in **table 16**.

Table 16. Suzuki-Miyaura cross coupling reactions involving diethyl 1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-naphthalen-2-ylphosphonate, **100**.



100

Entry [a]	Boronic acid	Pre-catalyst	Time / h	Yield / % [b]
1		**90**	2	86
2		**90**	2	62
3 [c]		**90**	2	94
4 [c]		**90**	2	92
5		**90**	20	76
6 [c]		**90**	16	0

[a] Aryl halide (0.2 mmol), diethyl 1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-naphthalen-2-ylphosphonate (0.3 mmol), base (0.4 mmol), pre-catalyst (0.5 mol%), THF (2 ml), H_2O (1 ml), 67 °C, time. [b] isolated yield (average of three runs). [c] pre-catalyst (2.0 mol%).

This limited but valuable study demonstrates the synthetic viability of these SM reactions for the facile construction of naphthylphosphonate-based biaryl compounds. The pre-catalyst **90** was able to effectively couple 1-bromo-4-chlorobenzene, 4-bromoanisole and 2-bromopyridine with the boronate ester **100** using a catalyst loading of only 0.5 mol%. The products from the reactions with 1-bromo-4-chlorobenzene and 4-bromoanisole were formed in 86% conversion (entry 1) and 62% conversion (entry 2) respectively, after only 2 h. Once again the reaction involving 1-bromo-4-chlorobenzene is highly chemoselective, with the diethyl (1-(4'-chlorophenyl)-2-naphthyl)phosphonate being the sole product. The reaction with 2-bromopyridine gave the product in 76% conversion after 20 h (entry 5). The SM reactions involving 2-bromotoluene and 2-bromoanisole required a catalyst loading of 2 mol% to obtain the products in 94% and 92% yield respectively, after 2 h (entries 3 and 4). Unfortunately, the reaction with diethyl *o*-bromobenzenephosphonate did not yield any product, despite using a catalyst loading of 2.0 mol% (entry 6).

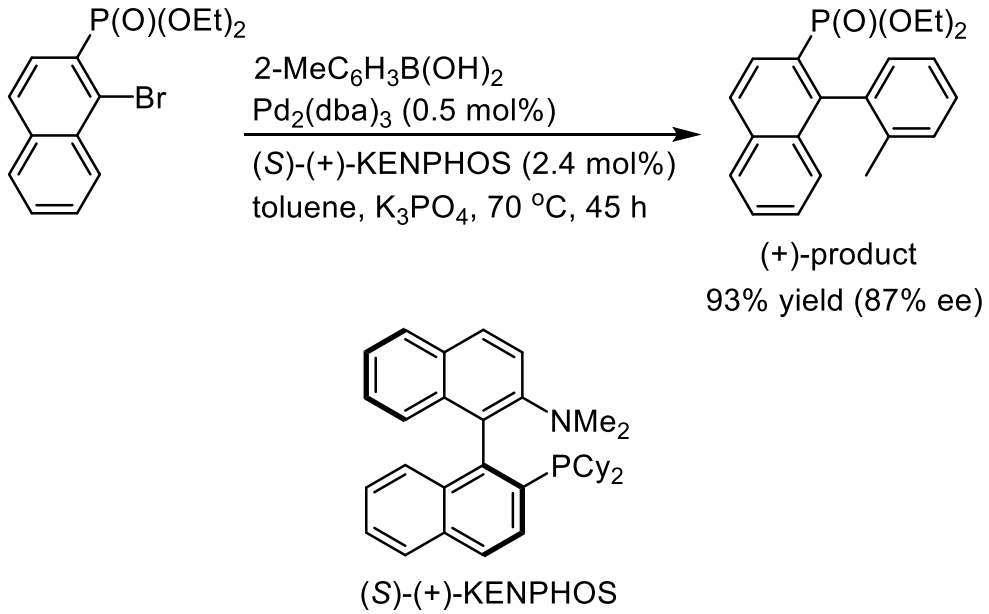
4.1.7 Conclusions from Suzuki-Miyaura cross coupling reactions

A series of 2-phenylaniline-type cyclopalladated pre-catalysts of KITPHOS monophosphines and triphenylphosphine were synthesised in good to excellent yield. These pre-catalysts were all able to catalyse SM reactions involving a range of aryl bromides with both phenyl- and 2-methylphenylboronic acid. These pre-catalysts displayed enhanced catalytic activity over the $Pd(OAc)_2$ / PPh_3 catalyst generated *in situ* due to their highly efficient activation. In particular the KITPHOS-ligated pre-catalysts **93** and **90** showed extraordinary catalytic activity towards SM reactions involving diethyl *o*-bromobenzenephosphonate as well as the phenyl- and naphthylphosphonate-based boronic esters **98** and **100**. The phosphonate-substituted biaryl products from these SM reactions were obtained in good to excellent yield using 0.1 - 2.0 mol% of the pre-catalyst. The use of the boronate esters **98** and **100** are the first examples of Suzuki-Miyaura cross coupling reactions where the phosphonate species is the nucleophilic partner in the transformation. The complementary use of these phosphonates as the

nucleophilic as well as the electrophilic partner in SM reactions provides a convenient and easy synthetic route for a range of phosphonate-substituted biaryl compounds with potential applications in ligand synthesis, under mild reaction conditions. This synthetic route uses lower catalyst loadings, lower temperatures and relatively short reaction times in comparison to alternative means of synthesis for these types of compound.

4.1.8 Future work

There are several reports in the literature of the asymmetric synthesis of axially chiral biarylphosphonates, mainly binaphthylphosphonates using SM reactions.[176] In general, ligands bearing dicyclohexyl groups have significantly outperformed those of diphenyl groups, as highlighted in our results.[177] The best results so far have been performed by Buchwald, using the P,N ligand KENPHOS.[171] These include the reaction of 1-bromo-2-naphthylphosphonate with 2-methylphenylboronic acid which on using $Pd_2(dba)_3$ (0.5 mol%), (*S*)-(+)-KENPHOS (2.4 mol%), K_3PO_4 in toluene and heating to 70 ^oC for 45 h, gave the product in 93% yield, 87% ee (**scheme 98**).

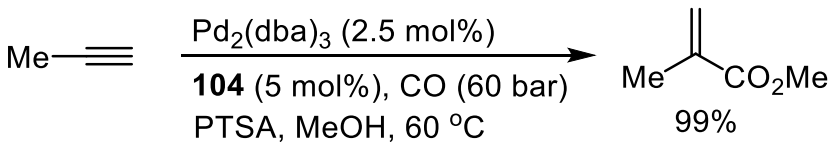


Scheme 98. Enantioselective synthesis of axially chiral phosphonate-substituted biaryls.[171]

It is our intention to use the methodology developed in the synthesis of achiral biarylphosphonates to develop a chiral pre-catalyst system for use in enantioselective SM reactions involving both 1-bromo-arylphosphonates as well as arylphosphonate-based boronate esters. The aim will be to provide access to a range of architecturally important axially chiral biaryl and heterobiaryls for ligand synthesis.

4.2 Hydroesterification reactions

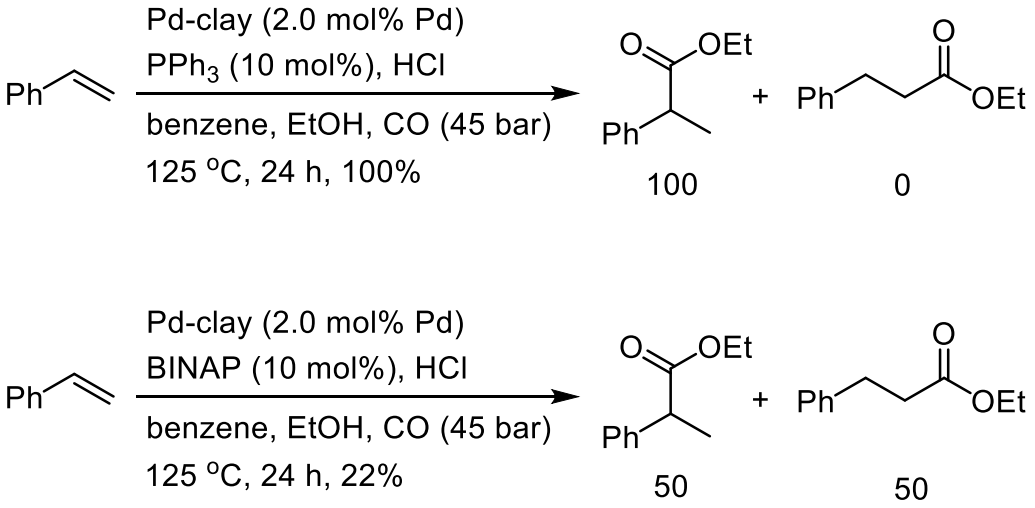
Hydroesterification reactions of alkynes and alkenes are very useful tranformations in the synthesis of α,β-unsaturated carboxylic esters. The most important of these reactions is the methoxycarbonylation of propyne to give methyl methacrylate, which is produced on an industrial scale due to its importance as an intermediate in polymer synthesis. There has therefore been considerable interest in the development of an efficient synthesis of methyl methacrylate, using a range of different palladium catalysts. It has emerged that the properties of the ligands are of particular importance as they are not only responsible for activating and stabilising the catalyst, but they also dramatically affect both the performance and selectivity of the reaction.[178] Although many different ligands have been used successfully, 2-pyridylphosphines have arguably had the most success, with diphenyl-2-pyridylphosphine **104** currently being employed industrially by Shell for this purpose.[61] Methyl methacrylate can be obtained in >99% selectivity on reacting propyne in MeOH using $Pd_2(dba)_3$ (2.5 mol%), diphenyl-2-pyridylphosphine **104** (5 mol%), CO (60 bar) and para-toluenesulphonic acid (PTSA) whilst heating at 60 °C (**scheme 99**).



Scheme 99. The methoxycarbonylation of propyne using diphenyl-2-pyridylphosphine.

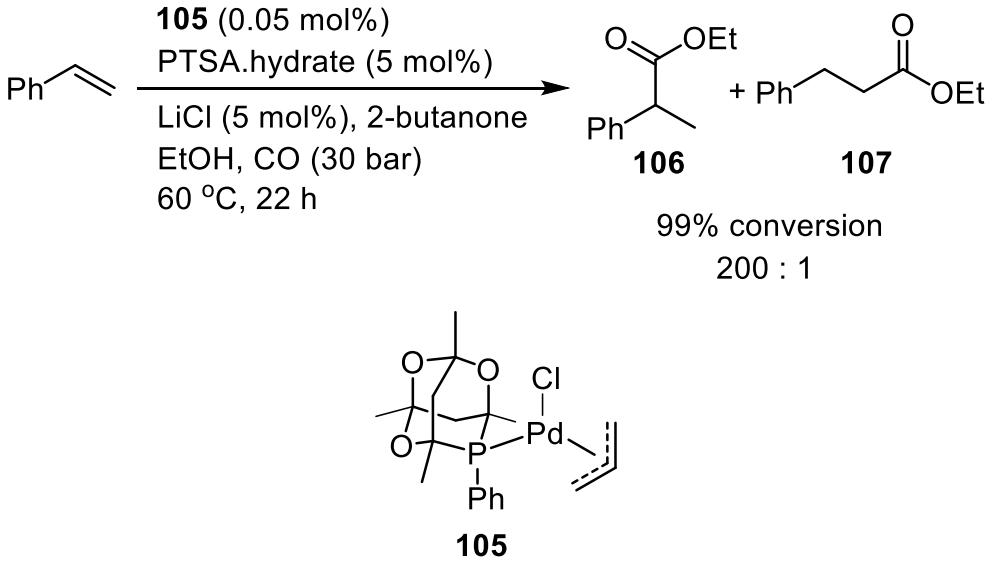
Due to the commercial application of methyl methacrylate, the methoxycarbonylation of propyne has been extensively studied, however the use of other alcohols such as ethanol and *tert*-butanol has proven less successful. In the drive for fine chemicals and pharmaceuticals, there has lately been a resurgence in interest in the hydroesterification of alkenes.[178] The methoxycarbonylation of styrene and other alkenes has been well studied, however, there are very few accounts of using EtOH as

the nucleophile instead. Similar to the methoxycarbonylation reactions, in ethoxycarbonylations, catalysts bearing bidentate phosphines largely favour the formation of the linear product whilst those possessing monodentate phosphines favour the formation of the branched product.[179] It has previously been shown that, using Pd-clay (2.0 mol% Pd) and PPh_3 (10 mol%), styrene can be converted to the branched ethyl 2-phenylpropanoate product in 100% conversion and 100% selectivity after 24 h at 125 ^oC (**scheme 100**).[180] However, on using BINAP (10 mol%) instead, a conversion to the products of only 22% resulted with a branched / linear selectivity of 1 : 1, under the same reactions.[180]



Scheme 100. Difference in conversion and product selectivity between PPh_3 and BINAP in the ethoxycarbonylation of styrene.[180]

Interestingly, it has been shown in hydroesterification reactions that catalysts derived from triarylphosphines outperform those derived from trialkylphosphines.[178, 179c] Clarke recently published a paper highlighting the efficient hydroesterification of styrene using an allylpalladium pre-catalyst bearing trioxo-adamantyl caged phosphines.[157c] These bulky electron-poor phosphines exhibited extraordinary activity, giving the product in 99% conversion with a branched / linear product selectivity of >200 : 1. Ethyl 2-phenylpropanoate (**106**) was liberated in 83% isolated yield on using the pre-catalyst **105** (0.05 mol%), as shown in **scheme 101**.



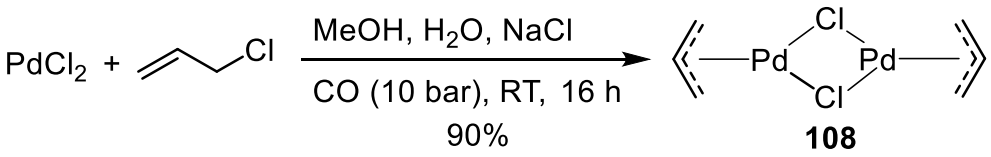
Scheme 101. The pre-catalyst **105** has proven to be highly efficient in hydroesterification reactions.

In fact these phosphines were proven to be remarkable ligands on using benzyl alcohol, iPrOH and tBuOH as well as EtOH in the hydroesterification reactions of styrene, greatly favouring the synthesis of the branched ester products.

The fact that often triarylphosphines outperform trialkylphosphines coupled with the success of pre-catalysts in this field led us to investigate the application of pre-catalysts of KITPHOS monophosphines in hydroesterification reactions. The aim was to compare the effectiveness of 2-phenylaniline and allylpalladium pre-catalysts of KITPHOS monophosphines against the allylpalladium pre-catalyst **105**, with respect to the ethoxycarbonylation of styrene. The intention then was to explore the ability of these catalysts towards using other nucleophilic sources in these hydroesterification reactions and to later apply this methodology to reactions involving phenylacetylene.

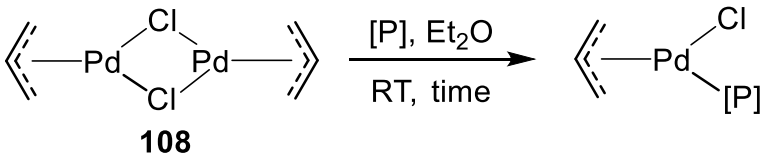
4.2.1 Allylpalladium pre-catalyst synthesis

To synthesise the allylpalladium pre-catalysts of KITPHOS monophosphines **16**, **19** and **40** as well as the PPh_3 equivalent, the [bis(η^3-allyl)di-μ-chlorodipalladium] precursor, **108** was first prepared. This was synthesised on stirring a solution of $PdCl_2$ and NaCl in H_2O with allyl chloride dissolved in MeOH under CO (10 bar) at RT for 16 h (**scheme 102**). The product was purified by recrystallisation from a $CHCl_3$ solution layered with MeOH to give yellow/green crystals of **108** in 90% yield.[181]



Scheme 102. The synthesis of [bis(η^3-allyl)di-μ-chlorodipalladium] precursor **108**.

Then, to generate the phosphine-ligated allylpalladium pre-catalysts, the relevant phosphine was added to a solution of **108** dissolved in Et_2O and stirred at RT for the relevant time (**scheme 103**). The structures and yields of the desired pre-catalyst complexes are shown in **figure 34**.



Scheme 103. The synthesis of the phosphine-ligated allylpalladium pre-catalysts.

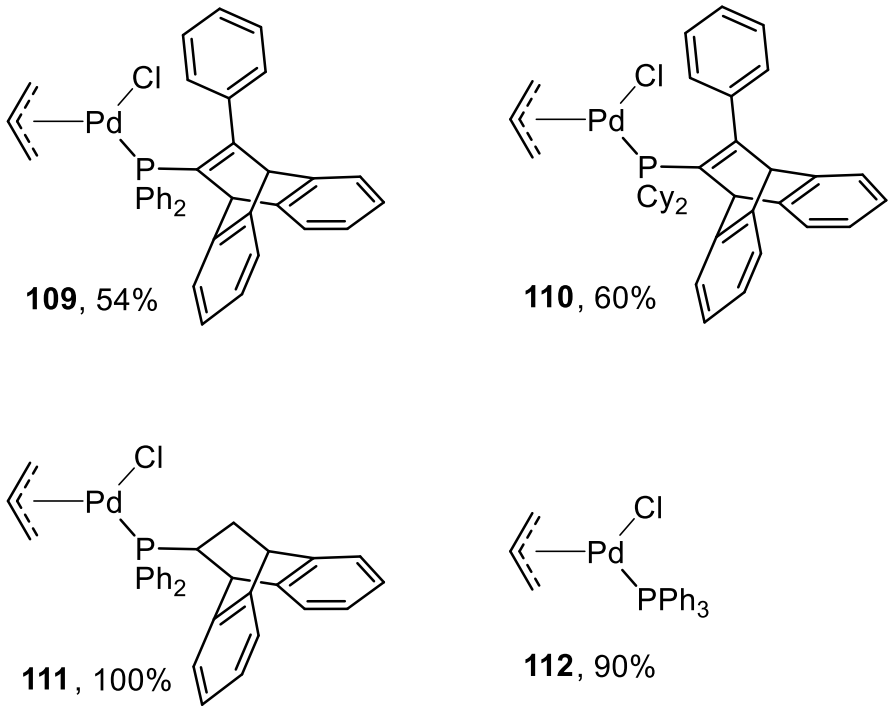


Figure 34. The structures and associated yields of the allylpalladium pre-catalyst complexes synthesised.

The allylpalladium pre-catalyst **109** was obtained in 54% yield on stirring for 2 h, whilst **112** was formed in 90% yield after only 1 h. As triphenylphosphine-ligated palladium complexes have often proven to be successful in catalysing hydroesterification reactions, the efficiency of the allylpalladium pre-catalyst **112** was compared against those of KITPHOS monophosphines. The pre-catalyst **110** was obtained after 2 h stirring and then purified by recrystallisation from a $CHCl_3$ solution layered with MeOH to give colourless crystals of **110** in 60% yield. The KITPHOS monophosphine **16** present in **110**, possessing the electron-rich cyclohexyl groups, provides an effective comparison of the relative abilities of triaryl-like (**19**) and dialkylbiarylphosphines in hydroesterification reactions. Interestingly **111** was obtained in quantitative yield on increasing the reaction time to 16 h. Thus significantly better yields for both **109** and **110**, can possibly be achieved by simply extending the reaction time. The KITPHOS monophosphine **40** present in **109** was chosen for this study due to it being the weakest σ-donor of the KITPHOS monophosphines synthesised, as demonstrated in Chapter 2, section 2.6, complementing the comparison with **110**.

5.2.2 Ethoxycarbonylation of styrene

Initially the conditions employed by Clarke were adopted firstly as a basis, due to the high success demonstrated on using his bulky trioxo adamantyl-based pre-catalysts.[157c] This involved the use of an allylpalladium catalyst (0.1 mol%), PTSA.hydrate (5 mol%), LiCl (5 mol%) and CO (30 bar) in EtOH whilst heating at 80 ^{o}C for 16 h. The preliminary results of this reaction using the allylpalladium pre-catalyst **109** are shown in **table 17**.

Table 17. Preliminary results for the ethoxycarbonylation of styrene.

Entry [a]	**Conv. / %** [b]	**Ratio 106 / 107** [c]
1	24	100 : 0
2 [d]	8	-
3 [e]	12	40 : 1
4 [f,e]	24	10 : 1

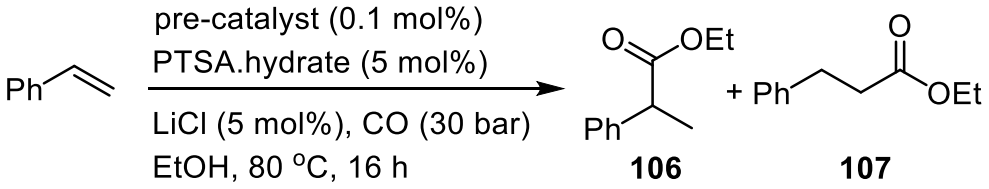
[a] styrene (2 mmol), **109** (0.1 mol%), PTSA.hydrate (5 mol%), LiCl (5 mol%), CO (30 bar), EtOH (3 ml), 80 ^{o}C, 16 h. [b] conversion measured by ^{1}H NMR. [c] measured by ^{1}H NMR. [d] No LiCl added. [e] 2-butanone as solvent, EtOH (2 eq). [f] **109** (0.5 mol%).

Interestingly no enhancement in conversion was obtained on increasing the catalyst loading of **109** in the ethoxycarbonylation of styrene. On using **109** (0.1 mol%), 24 % conversion to the product was recorded (entry 1). This was identical to that obtained on using **109** (0.5 mol%) instead (entry 4). However this increased catalyst loading actually significantly reduced the selectivity towards the desired branched product **106** from 100 : 0 (entry 1) to 10 : 1 (entry 4). Clarke reported that

increased conversion to the product can be achieved by using 2-butanone as the solvent with 2 equivalents of EtOH added. The results in **table 17** however, showed that on doing this a lower conversion of 12% was obtained, as well as a significant loss in selectivity (entry 3). Many transition metal-catalysed reactions can be strongly influenced by addition of a halide source.[182] The resultant halide effects have been shown to alter the rate, the selectivity and enantioselectivity of reactions. Halide effects have also be shown to allow for milder conditions to be used for reactions. This was well demonstrated in **table 17**, where the omission of LiCl resulted in a threefold decrease in conversion and the product was formed in only 8% conversion (entry 2).

It was then chosen to investigate the compatibility and catalytic efficiency of both the allylpalladium pre-catalysts **109**, **110**, **111, 112** and the 2-phenylaniline-based pre-catalysts **92**, **93**, **90** on the ethoxycarbonylation of styrene (**table 18**). The structures of the pre-catalyst complexes used in **table 18** are given on page xiv of this thesis.

Table 18. Ethoxycarbonylation of styrene results.



Entry [a]	Pre-catalyst	Conv. / % [b]	Ratio 107 / 108	Yield 107 / %
1	**112**	-	20 : 1	25
2	**109**	24	100 : 0	-
3 [c]	**110**	13	9 : 1	-
4	**111**	10	55 : 1	-
5	**92**	17	150 : 1	-
6	**93**	36	70 : 1	-
7 [d]	**93**	100	100 : 1	88
8 [c]	**90**	11	190 : 1	-

[a] styrene (2 mmol), pre-catalyst (0.1 mol%), PTSA.hydrate (5 mol%), LiCl (5 mol%), CO (30 bar), EtOH (3 ml), 80 °C, 16 h. [b] conversion measured by ^{1}H NMR. [c] 20 h reaction time. [d] pre-catalyst (0.5 mol%).

On employing the reaction conditions highlighted in **table 18**, pre-catalyst **112** gave the branched product **106** in 25% isolated yield. This was consistent with results available in the literature.[157c] Pre-catalyst **109** produced a conversion of 24% with a selectivity of 100 : 0 in favour of **106** (entry 2). This result is similar to that obtained for **112**. The other allylpalladium pre-catalysts **110** and **111** were significantly less effective, with conversions of 13% and 10% obtained respectively (entries 3 and 4). The abilities of the corresponding 2-phenylaniline-based pre-catalysts **92**, **93** and **90** from section 4.1.4 of this chapter, were then investigated. **92** gave a lower conversion of 17% in comparison to its allyl-based partner **112**, but an increased selectivity of 150 : 1 in favour of the branched product (entry 5). Contrary to this, **93** exhibited an increase in conversion from 24 % to 36%, but a diminished selectivity of 70 : 1 to the branched product (entry 6). Interestingly the same loss in conversion was demonstrated on omitting LiCl from the reaction mixture with **93** as displayed in the preliminary results using **109** (**table 17**). However in contrast to the allylpalladium pre-catalyst **109**, on increasing the catalyst loading of **93** to 0.5 mol%, 100% conversion and a branched / linear selectivity of 100 : 1 was observed (entry 7). The ethyl 2-phenylpropanoate product **106** was isolated in 88% yield after purification by column chromatography. **90**, with a conversion of only 11% was only marginally lower than the 13% demonstrated by its allyl equivalent **110**, however the increase in selectivity from 9 : 1 to 190 : 1 was significant (entries 8 and 3).

In fact with all of these pre-catalysts, the conversions obtained using a catalyst loading of 0.1 mol% were poor. The excellent conversion and yield obtained on using **93** (0.5 mol%) was itself a good result. However this result was significantly less efficient than that reported by Clarke (**scheme 101**), where pre-catalyst **105** gave ethyl 2-phenylpropanoate in 83% yield whilst conducting the reaction at 60 ^{o}C instead of 80 ^{o}C and using a catalyst loading of only 0.05mol%.[157c]

Despite being only a limited study, the results in **table 18** have shown that the diphenyl-substituted KITPHOS monophosphine **19** outperformed its more electron-rich cyclohexyl counterpart **16** in the ethoxycarbonylation of styrene. This enhancement in reactivity was evident in both the allylpalladium and the 2-phenylaniline-based cyclopalladated pre-catalyst systems. In particular, the 2-phenylaniline pre-catalyst **91** exhibited the greatest activity of the catalysts tested in **table 18**, however it was still far less efficient than the trioxo-adamantyl phosphine pre-catalyst **105** reported by Clarke.

4.2.3 Conclusions from ethoxycarbonylation of styrene

The effectiveness of the ethoxycarbonylation of styrene has been shown to depend on the electronic properties of the phosphine as well as the pre-catalyst type. It has also been shown that the pre-catalysts of KITPHOS monophosphines derived from chlorodiphenylphosphine are significantly more effective in the ethoxycarbonylation of styrene than those derived from chlorodicyclohexylphosphine. Thus, the more electron-rich catalysts have proven to be decidedly less efficient than their less electron-rich counterparts in this transformation. The 2-phenylaniline pre-catalyst **93** was shown to give the ethyl 2-phenylpropanoate product in 88% isolated yield, using a catalyst loading of only 0.5 mol%.

Chapter 5. Conclusions to the use of triaryl-like phosphines in gold and palladium catalysis

5.1 Conclusions from the gold-catalysed transformations

Gold(I) complexes of KITPHOS monophosphines have proved to be highly efficient in the cycloisomerisation of propargyl carboxamides to give methylene oxazoline exclusively. It has been shown within this thesis, that less electron-rich phenyl-substituted KITPHOS monophosphines outperform their more electron-rich cyclohexyl-substituted counterparts in these reactions. A number of phenyl-substituted KITPHOS monophosphines bearing differing electronic and steric properties were synthesised. It was found that the additional bulk present in **60**, which possessed two KITPHOS units around the P-atom, enhanced the catalytic efficiency in the cycloisomerisation of propargyl amides, except for substrates which required longer reaction times. However, the addition of a third KITPHOS unit around the same P-atom (**61**) was shown to inhibit catalysis. It was found that KITPHOS monophosphines possessing the 12-phenyl lower aryl ring, displayed improved catalytic activity in gold-catalysed transformations. This has been postulated to be due to the presence of stabilising η^1- / η^2-interactions between the gold atoms and *ipso*/*o*-carbon atoms of the lower aryl rings, as seen in the crystal structures of their gold(I) chloride complexes. These η^n-interactions increase the stability and thus lifetime of the catalyst complexes.

A carbonyl-ene reaction was successfully performed between a range of methylene oxazolines and ethyl trifluoropyruvate, with quantitative conversions reported after 8 – 30 minutes. However, no asymmetric induction was observed in any of these reactions using either $PdCl_2$(*S*-BINAP) / $AgSbF_6$ or $Cu(OTf)_2$ / BOX catalyst systems. Also no reaction was observed on replacement of ethyl trifluoropyruvate with the less reactive methyl pyruvate. Despite this, a tandem one pot cycloisomerisation / carbonyl-ene reaction was successfully performed from *N*-prop-2-ynylbenzamide to give the ethyl 3-[5'-(2-phenyloxazole)]-2-(trifluoromethyl)-2-hydroxypropanoate product in quantitative yield after only one hour.

Gold(I) complexes of phenyl-substituted KITPHOS monophosphines have been shown to catalyse the cycloisomerisation of 2-[(2-alkynyl)phenyl]alcohols to isochromenes. In particular, the gold(I) complex **57** which possessed a single KITPHOS unit around the P-atom, was shown to be remarkably effective in these transformations. **57** gave greater yields after shorter reaction times whilst using lower catalyst loadings when compared to other catalysts in the literature as well as the other gold(I) complexes tested. In this thesis, **57** was also shown to catalyse the cyclisation of 2-[(2-ethynylphenyl)phenyl]ethan-1-ol, which afforded the 1-benzylideneisochromane in 87% yield through the 6-*exo*-*dig* reaction pathway, a previously unreported cyclisation.

The gold(I) complex **57** catalysed the cyclisation of 2-(phenylethynyl) benzamides to the relevant iminoisocoumarin products, in moderate yield. However, the simple silver salt AgOTf proved to be more efficient in these cyclisations.

5.2 Conclusions from the palladium-catalysed transformations

A series of 2-phenylaniline-type cyclopalladated pre-catalysts of KITPHOS monophosphines and triphenylphosphine were synthesised in good to excellent yield. These pre-catalysts were all able to catalyse Suzuki-Miyaura cross coupling reactions involving a range of aryl bromides with both phenyl- and 2-methylphenylboronic acid. The highly efficient activation of this pre-catalyst system was evident on comparing the triphenylphosphine-ligated pre-catalyst complex with the $Pd(OAc)_2$ / PPh_3 catalyst generated *in situ*, the former displayed enhanced catalytic activity in these SM reactions. It was shown that pre-catalyst **94**, which possessed the phosphine with two KITPHOS units around its P-atom, was remarkedly effective in the coupling of the 4-bromo-3,5-dimethyl-1H-pyrazole with phenylboronic acid to give the product in 97% yield. This is the best result to date for a SM reaction involving substitution at the 4-position of an unprotected pyrazole, as most require protection of the pyrazole NH to facilitate the coupling reaction.

The initial pre-catalyst screening of a range of aryl bromides with phenyl- and 2-methylphenylboronic acid, highlighted the remarkable efficacy of pre-catalyst **93** in the coupling of diethyl *o*-bromobenzenephosphonate. Further investigations showed that the KITPHOS-ligated pre-catalysts **93** and **90** possessed extraordinary catalytic activity towards SM reactions involving diethyl *o*-bromobenzenephosphonate with a range of boronic acids. The phosphonate-substituted biaryl products from these reactions were obtained in good to excellent yield using 0.1 - 2.0 mol% of the pre-catalysts. These two pre-catalysts easily outcompeted pre-catalysts **94**, **92** and the *in situ* generated $Pd(OAc)_2$ / PPh_3 catalyst in these SM reactions. Satisfyingly, pre-catalyst **93** which possessed the diphenyl-substituted KITPHOS phosphine **19** outcompeted its more electron-rich dicyclohexyl-substituted counterpart (**90**) in a number of these reactions. However, greater efficacy was demonstrated by pre-catalyst **90** in SM reactions involving phenylphosphonate-based boronic ester **98**. Pre-catalyst **93** also proved highly efficient in SM reactions involving the naphthylphosphonate-based boronic ester **100** with a range of aryl bromides, giving excellent yields using 0.5 – 2.0 mol% catalyst loading.

Despite these successes, both pre-catalyst **90** and **93** proved ineffective in coupling aryl chlorides with boronic ester **98**. The coupling of diethyl *o*-bromobenzenephosphonate with boronate esters **98** and **100** also proved unsuccessful using both pre-catalyst **93** and **90**.

The use of the boronate esters **98** and **100** are the first examples of Suzuki-Miyaura cross coupling reactions where the phosphonate species is the nucleophilic partner in the transformation. The complementary use of these phosphonates as the nucleophilic as well as the electrophilic partner in SM reactions, provides a convenient and easy synthetic route for a range of phosphonate-substituted biaryl compounds. This synthetic route uses lower catalyst loadings, lower temperatures and relatively short reaction times in comparison to alternative means of synthesis for these types of compound. Interestingly, these compounds have numerous potential applications, particularly in ligand synthesis, such as the reported synthesis of phospholane borane adduct **103**, via the primary phosphine in an operationally simple approach.

In order to further demonstrate the potential application and uses of these less electron-rich phosphines in palladium catalysis, the ethoxycarbonylation of styrene was performed using 2-phenylaniline-based and allylpalladium pre-catalyst complexes of KITPHOS monophosphines **16**, **19**, **40** and triphenylphosphine. It had previously been shown by other research groups, that catalysts based on triarylphosphines often outperform their trialkylphosphine counterparts in these reactions. This was also evident in KITPHOS monophosphines, as pre-catalysts **109** and **93**, based on the diphenyl-substituted phosphine **19** proved more efficient in this transformation than pre-catalysts **110** and **90** based on the dicyclohexyl-substituted phosphine **16**. The 2-phenylaniline pre-catalyst **93** proved the most effective of those tested in the ethoxycarbonylation of styrene. **93** gave the ethyl 2-phenylpropanoate product in 88% isolated yield, using a catalyst loading of only 0.5 mol%.

5.3 Concluding remarks

In conclusion, even though electron-rich phosphines are justifiably highly regarded in organometallic chemistry due to their high catalytic abilities for a wide variety of transformations, the application of these triaryl-like phosphines to transition metal catalysis should not be ignored. These triaryl-like phosphines are not only significantly cheaper and more resistant to degradation, but they are still the ligands of choice for a number of transition metal catalysed transformations.

Chapter 6. Experimental section

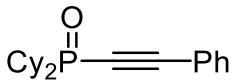
6.1 General comments

All manipulations involving air-sensitive materials were carried out using standard Schlenk line techniques under an atmosphere of nitrogen in flame-dried glassware. All solvents were distilled under an atmosphere of nitrogen with; $CHCl_3$, CH_2Cl_2 and NEt_3 from CaH_2; MeOH and EtOH from magnesium; 1,4-dioxane, Et_2O and THF from Na / benzophenone; toluene from sodium; CH_3CN from K_2CO_3. Pyridine and DIPEA were distilled immediately prior to use. All other chemicals were bought from commercial suppliers and used without further purification. $Pd(dppf)Cl_2$[181] and propargyl ammonium chloride[182] were prepared as described in the literature references. ^1H and $^{13}C\{^1H\}$ NMR spectra were recorded on either a JEOL LAMBDA 500, JEOL ECS 400 or a Bruker Avance 300 instrument. All ^1H / ^{13}C NMR were referenced relative to $CDCl_3$ (δ_H = 7.26, δ_C = 77.16) or d_6-DMSO (δ_H = 2.50, δ_C = 39.52). All ^{31}P NMR spectra were referenced relative to phosphoric acid and ^{11}B NMR spectra to trimethyl borate. Gas chromatography was performed using a Shimadzu 2010 series gas chromatograph with a Supelco Beta DEX column. Mass spectra were recorded on a Micromass LCT Premier Mass Spectrometer. Thin layered chromatography was carried out on aluminium sheets pre-coated with silica gel 60F 254 and column chromatography was performed using Merck Kieselgel 60. All new compounds were fully characterised. Full characterisation for known compounds can be found from the literature references.

6.2 Experimental from chapter 2

6.2.1 Synthesis of KITPHOS monophosphines

(Dicyclohexylphosphinoylethynyl)benzene (**22**).



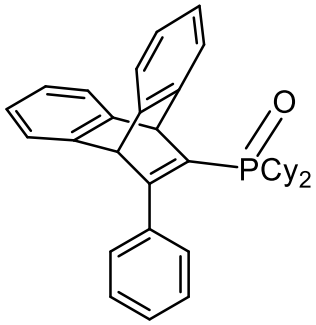
A flame-dried Schlenk flask was charged with PCl_3 (1.57 ml, 18.0 mmol) and Et_2O (50 ml). This was then cooled to -78 ^oC and CyMgCl (36 ml, 1 M in THF, 36 mmol) was added over 1.5 h. After addition, the suspension was allowed to warm to RT and was stirred for a further 30 min to generate Cy_2PCl *in situ*.

Meanwhile another flame-dried Schlenk flask was charged with phenyl acetylene (2.04 ml, 18.5 mmol) and THF (60 ml). This was then cooled to -78 ^oC and ^{n}BuLi (7.42 ml, 2.5 M in toluene, 18.5 mmol) was added dropwise. The reaction mixture was allowed to warm to RT and then was transferred via cannula into the Cy_2PCl solution at RT, which was then stirred for 1 h. The solution was then cooled to 0 ^oC, H_2O_2 (35 % aq solution, 3.0 ml, 30 mmol) added and then left to stir at RT for 16 h. H_2O (150 ml) was added and the aqueous phase extracted with Et_2O (3 x 150 ml). The combined organic extracts were washed with brine (100 ml), dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The crude product was purified by column chromatography, eluting with EtOAc/petrol (4 : 1) to give the phosphine oxide **22**, as a white solid (4.28 g, 76 %).

^{31}P {H} NMR (161.8 MHz, CH_2Cl_2): δ = 36.3; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.56 – 7.54 (m, 2 H, C_6H_5 *o-H*), 7.45 – 7.41 (m, 1 H, C_6H_5 *p-H*), 7.39 – 7.35 (m, 2 H, C_6H_5 *m-H*), 2.08 – 2.05 (m, 2 H, Cy-*H*), 2.00 – 1.95 (m, 2 H, Cy-*H*), 1.92 – 1.84 (m, 6 H, Cy-*H*), 1.75 – 1.73 (m, 2 H, Cy-*H*), 1.61 – 1.50 (m, 4 H, Cy-*H*), 1.27 – 1.24 (m, 6 H, Cy-*H*); **^{13}C {H} NMR** (400 MHz, $CDCl_3$) δ = 132.5, 130.3, 128.6, 120.5 (d, *J* = 2.9

Hz), 103.3 (d, *J* = 22 Hz), 81.4 (d, *J* = 136 Hz), 36.9 (d, *J* = 79 Hz), 26.4 (d, *J* = 10.0 Hz), 26.3 (d, *J* = 9.5 Hz), 26.0, 25.6 (d, *J* = 2.8 Hz), 24.8 (d, *J* = 2.8 Hz). This is consistent with data reported in the literature.[54b]

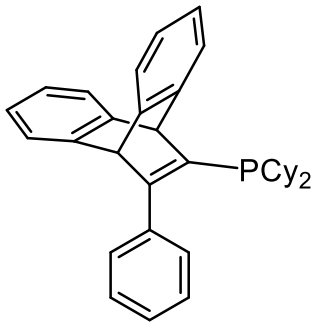
11-(Dicyclohexylphosphinoyl)-12-phenyl-9,10-dihydro-9,10-ethenoanthracene (**24**).



(Dicyclohexylphosphinoylethynyl) benzene (4.00 g, 16.5 mmol), **22**, was mixed with anthracene (4.41 g, 24.8 mmol), heated to 220 ^{o}C and stirred at this temperature for 12 h. The resultant crude product was then purified by column chromatography eluting first with CH_2Cl_2 to remove excess anthracene and then with CH_2Cl_2 / MeOH (95 : 5) to give the phosphine oxide **24**, as an off - white solid (6.79 g, 83 %).

^{31}P {H} NMR (161.8 MHz, CH_2Cl_2): δ = 48.1; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.41 – 7.39 (m, 2 H, Ar-*H*), 7.33 – 7.31 (m, 5 H, Ar-*H*), 7.08 – 7.05 (m, 2 H, Ar-*H*), 7.04 – 7.01 (m, 4 H, Ar–*H*), 5.61 (d, *J* = 6.8 Hz, 1 H, bridgehead *H*), 5.23 (d, *J* = 2.9 Hz, 1 H, bridgehead *H*), 1.83 – 1.80 (m, 2 H, Cy-*H*), 1.72 – 1.70 (m, 2 H, Cy-*H*), 1.58 – 1.48 (m, 6 H, Cy-*H*), 1.35 – 1.22 (m, 4 H, Cy-*H*), 1.20 – 1.15 (m, 3 H, Cy-*H*), 1.11 – 1.05 (m, 3 H, Cy-*H*), 1.00 – 0.94 (m, 2 H, Cy-*H*); **^{13}C {^{1}H} NMR** (400 MHz, $CDCl_3$) δ = 164.0 (d, *J* = 5.0 Hz), 144.7, 144.4, 139.3 (d, *J* = 3.3 Hz), 136.5 (d, *J* = 80 Hz), 128.1, 128.0, 126.9, 125.2, 125.1, 123.7, 123.3, 61.6 (d, *J* = 8.9 Hz), 52.7 (d, *J* = 8.4 Hz), 37.1 (d, *J* = 67.9 Hz), 26.6, 26.5, 25.8, 25.8, 25.5. This is consistent with data reported in the literature.[54b]

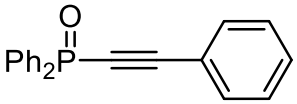
11-(Dicyclohexylphosphino)-12-phenyl-9,10-dihydro-9,10-ethenoanthracene (**16**).



A flame dried Schlenk flask was charged with the 11-(dicyclohexylphosphinoyl)-12-phenyl-9,10-dihydro-9,10-ethenoanthracene, **24** (2.55 g, 5.55 mmol), toluene (100 ml) and NEt_3 (29 ml, 222 mmol). Trichlorosilane (5.60 ml, 55.5 mmol) was then added and the reaction mixture was heated at 110 ^oC for 64 h. The reaction mixture was then cooled to RT, diluted with Et_2O (150 ml), ice (50 g) and 20 % aq NaOH (100 ml) and was stirred for 30 min at this temperature. The resulting emulsion was filtered through celite, washing with Et_2O (3 x 50 ml). The organic layer was then separated, dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The crude product was purified by column chromatography, eluting with petrol to remove the NEt_3, then petrol / EtOAc (10 : 1) and the product recrystallised from a $CHCl_3$ solution layered with MeOH to give the phosphine **16**, as white crystals (1.99 g, 75 % yield).

^{31}P {^{1}H} NMR (161.8 MHz, $CDCl_3$): δ = -12.9; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.35 - 7.24 (m, 6 H, Ar-*H*), 7.20 – 7.17 (m, 3 H, Ar-*H*), 7.01 - 6.98 (m, 4 H, Ar-*H*), 5.54 (s, 1 H, bridgehead *H*), 5.31 (s, 1 H, bridgehead *H*), 1.99 (t, *J* = 10.6 Hz, 2 H, Cy-*H*), 1.76-1.69 (m, 4 H, Cy-*H*), 1.63 – 1.53 (m, 4 H, Cy-*H*), 1.31 – 0.95 (m, 12 H, Cy-*H*); **^{13}C {^{1}H} NMR** (125.8 MHz, $CDCl_3$) δ = 163.1 (d, *J* = 26 Hz), 145.9, 145.1, 141.5 (d, *J* = 29 Hz), 140.1, 128.3 (d, *J* = 3.3 Hz), 127.9, 127.3, 124.8, 124.7, 123.1, 122.9, 59.8 (d, *J* = 6.1 Hz), 54.4 (d, *J* = 6.3 Hz), 34.6 (d, *J* = 11.9 Hz), 30.8 (d, *J* = 16.6 Hz), 30.4 (d, *J* = 9.4 Hz), 27.4 (d, *J* = 11.6 Hz), 27.2 (d, *J* = 8.3 Hz), 26.5. This is consistent with data reported in the literature.[54b]

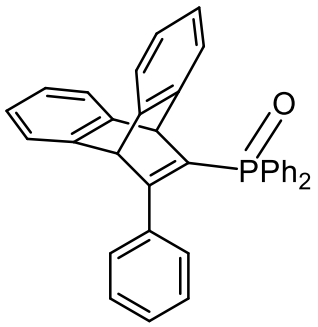
(Diphenylphosphinoylethynyl)benzene (**23**).



A solution of phenylacetylene (12.0 ml, 109 mmol) in THF (120 ml) was cooled to -78 ^{o}C and ^{n}BuLi (43.7 ml, 2.5 M in hexanes, 109 mmol) was added. The resulting mixture was then stirred at this temperature for 30 min. This was allowed to warm to 0 ^{o}C and stirred at this temperature for a further 30 min. The solution was then cooled to -78 ^{o}C and chlorodiphenylphosphine (20.1 ml, 109 mmol) added dropwise. The solution was allowed to warm to RT and stirred for 2.5 h at this temperature. This was then cooled to 0 ^{o}C and H_2O_2 (35 % aq solution, 40.0 ml, 143 mmol) added dropwise. The solution was allowed to warm to RT and was stirred for a further 30 min. H_2O (150 ml) was then added and the product was extracted with Et_2O (3 x 150 ml). The combined organic extracts were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The pale yellow crude product (33.0 g) was sufficiently pure by NMR to be used without further purification and as a result no accurate yield was attained.

^{31}P {H} NMR (202.5 MHz, CH_2Cl_2): δ = 9.0; **^{1}H NMR** (400 MHz, $CDCl_3$) δ =7.85 – 7.79 (m, 4 H, 4 x C_6H_5 *o-H*), 7.45 – 7.43 (m, 2 H, 4 x C_6H_5 *p-H*), 7.40 – 7.32 (m, 6 H, 4 x C_6H_5 *m-H*, 2 x C_6H_5 *o-H*), 7.29 – 7.25 (m, 1 H, C_6H_5 *p-H*), 7.22 – 7.18 (m, 2 H, 2 x C_6H_5 *m-H*); **^{13}C {H} NMR** (100.5 MHz, $CDCl_3$) δ = 132.5 (d, *J* = 122 Hz, C_6H_5 *C*P), 132.1 (d, *J* = 1.2 Hz, C_6H_5 *p-C*), 132.0 (d, *J* = 2.5 Hz, C_6H_5 *p-C*), 130.6 (d, *J* = 11.4 Hz, C_6H_5 *o-C*), 130.5 (C_6H_5 *o-C*), 128.4 (d, *J* = 13.6 Hz, C_6H_5 *m-C*), 128.3 (C_6H_5 *m-C*), 119.3 (d, *J* = 3.9 Hz, C_6H_5 *Q*), 105.3 (d, *J* = 30.2 Hz, PC≡*C*), 82.5 (d, *J* = 170 Hz, P*C*≡C); **mp** = 96 – 98 ^{o}C; **IR** (neat, cm^{-1}) 2174, 1440, 1195, 1119, 843, 754, 721, 687, 639, 541; **HRMS** (ESI^{+}) exact mass calculated for $C_{20}H_{16}PO$ $[M+H]^{+}$ *m/z* = 303.0939, found *m/z* = 303.0930. This is consistent with data reported in the literature.[185]

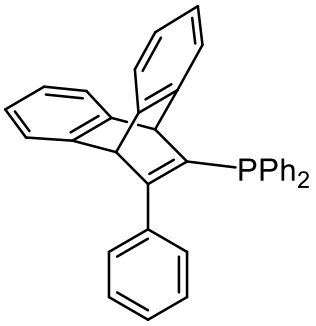
11-(Diphenylphosphinoyl)-12-phenyl-9,10-dihydro-9,10-ethenoanthracene (**25**).



(Diphenylphosphinoylethynyl)benzene, **23** (6.28 g, 20.8 mmol) was mixed with anthracene (5.55 g, 31.1 mmol), heated to 220 ^{o}C and stirred for 10 h. The resultant crude product was then purified by column chromatography eluting first with CH_2Cl_2 to remove excess anthracene and then CH_2Cl_2 / MeOH (98 : 2) to yield the phosphine oxide (**25**), a light yellow solid (6.69 g, 67 % yield).

^{31}P {H} NMR (202.5 MHz, CH_2Cl_2): δ = 25.0; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.42 – 7.34 (m, 8 H, Ar-*H*), 7.27 – 7.22 (m, 4 H, Ar-*H*), 7.09 – 6.97 (m, 11 H, Ar-*H*), 5.40 (d, *J* = 3.7 Hz, 1 H, bridgehead *H*), 5.23 (d, *J* = 9.2 Hz, 1H, bridgehead *H*); **^{13}C {H} NMR** (100.5 MHz, $CDCl_3$) δ = 165.6 (d, *J* = 7.7 Hz, *C*CP), 144.8 (d, *J* = 1.4 Hz, C_6H_4 *Q*), 144.8 (d, *J* = 2.6 Hz, C_6H_4 *Q*), 144.5 (2 x C_6H_4 *Q*), 137.8 (d, *J* = 4.0 Hz, C_6H_5 *Q*), 136.5 (d, *J* = 102 Hz, *C*P), 133.3 (d, *J* = 109 Hz, C_6H_5 *Q*), 131.6 (d, *J* = 10.6 Hz, C_6H_5 *o*-*C*), 131.5 (C_6H_5 *p*-*C*), 128.3 (d, *J* = 12.6 Hz, C_6H_5 *m*-*C*), 128.0 (C_6H_5 *p*-*C*), 127.7 (C_6H_5 *o*-*C*), 127.6 (C_6H_5 *m*-*C*), 125.4 (C_6H_4), 125.3 (C_6H_4), 125.2 (C_6H_4), 125.1 (C_6H_4), 123.8 (C_6H_4), 123.7 (C_6H_4), 123.5 (C_6H_4), 123.5 (C_6H_4), 61.3 (d, *J* = 9.7 Hz, bridgehead *C*H), 54.0 (d, *J* = 11.4 Hz, bridgehead *C*H); **IR** (neat, cm^{-1}) 2980, 1437, 1120, 777, 749, 724, 634, 631, 572, 537; **HRMS** (ESI^{+}) exact mass calculated for $C_{34}H_{26}PO$ $[M+H]^+$ *m/z* = 481.1721, found *m/z* = 481.1704. This is consistent with data reported in the literature.[54b]

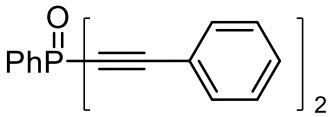
11-(Diphenylphosphino)-12-phenyl-9,10-dihydro-9,10-ethenoanthracene (**19**).



A flame dried Schlenk flask was charged with the 11-(diphenylphosphinoyl)-12-phenyl-9,10-dihydro-9,10-ethenoanthracene, **25**, (6.63 g, 13.8 mmol), toluene (120 ml) and NEt_3 (70 ml). Trichlorosilane (14.0 ml, 138 mmol) was then added and the flask heated at 110 ^oC for 22 h. The reaction mixture was cooled to 0 ^oC and diluted with Et_2O (150 ml). Ice (60 g) and 20 % aq NaOH (150 ml) were both added very slowly and the resulting mixture was then stirred for 30 min, the organic layer removed, and the aqueous phase was extracted with EtOAc (3 x 150 ml). The combined organic extracts were then washed with sat. $NaHCO_3$ (2 x 150 ml), H_2O (2 x 150 ml), brine (2 x 150 ml), dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The crude product was purified by column chromatography, eluting with petrol / EtOAc (9 : 1) and then recrystallised from a $CHCl_3$ solution layered with MeOH to give the phosphine (**19**) as white crystals (4.55 g, 71 % yield).

^{31}P {H} NMR (161.8 MHz, CH_2Cl_2): δ = -12.8; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.38 – 7.26 (m, 13 H, C_6H_5, C_6H_4), 7.22 – 7.18 (t, *J* = 7.4 Hz, 4 H, C_6H_5), 6.97 (t, *J* = 7.4 Hz, 2 H, C_6H_4), 6.89 (t, *J* = 7.4 Hz, 2 H, C_6H_4), 6.78 (d, *J* = 7.2 Hz, 2 H, C_6H_4), 5.52 (d, *J* = 2.8 Hz, 1 H, bridgehead *H*), 5.04 (s, 1 H, bridgehead *H*); **^{13}C {H} NMR** (400 MHz, $CDCl_3$): δ = 163.7 (d, *J* = 29.0 Hz, *C*CP), 145.8 (C_6H_4 *Q*), 145.3 (C_6H_4 *Q*), 139.3 (d, *J* = 23.4 Hz, *C*P), 138.7 (d, *J* = 6.0 Hz, C_6H_5 *Q*), 137.0 (d, *J* = 11.5 Hz, C_6H_5 *Q*), 133.4 (d, *J* = 18.4 Hz, C_6H_5 *o-C*), 128.6 (C_6H_5 *p-C*), 128.5 (d, *J* = 6.7 Hz, C_6H_5 *m-C*), 128.2 (C_6H_5 *p-C*), 128.1 (C_6H_5 *o-C*), 128.0 (C_6H_5 *m-C*), 124.8 (C_6H_4), 124.7 (C_6H_4), 123.2 (C_6H_4), 122.9 (C_6H_4), 59.5 (d, *J* = 6.5 Hz, bridgehead *C*H), 55.2 (d, *J* = 5.7 Hz, bridgehead *C*H); **IR** (neat, cm^{-1}) 1456, 1434, 768, 742, 696, 629, 610, 520; **HRMS** (ESI^+) exact mass calculated for $C_{34}H_{26}P$ $[M+H]^+$ *m/z* = 465.1772, found *m/z* = 465.1750. This is consistent with data reported in the literature.[54b]

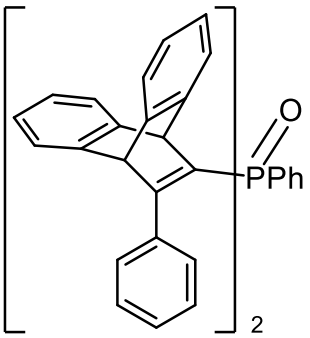
Bis(phenylacetylene)phenyl phosphine oxide (**26**).



A solution of phenylacetylene (0.97 ml, 8.8 mmol) in THF (20 ml) was cooled to -78 ^{o}C, ^{n}BuLi (3.0 ml, 1.6 M in hexane, 4.8 mmol) was added and the mixture was then stirred for 30 min at this temperature. This was allowed to warm to 0 ^{o}C and stirred for a further 20 min at this temperature. The solution was then cooled to -78 ^{o}C and dichlorophenylphosphine (0.54 ml, 4.0 mmol) added dropwise. The solution was allowed to warm to RT and stirred for 2.5 h at this temperature. This was then cooled to 0 ^{o}C and H_2O_2 (35 % aq solution, 1.8 ml, 6.4 mmol) added dropwise. The solution was allowed to warm to RT and was stirred for a further 30 min. H_2O (20 ml) was then added and the product was extracted with Et_2O (3 x 20 ml). The combined organic extracts were dried ($MgSO_4$) and solvent removed under reduced pressure. Purification by column chromatography, eluting with petrol / EtOAc (3 : 1) gave the phosphine oxide **26** as a yellow crystalline solid (1.15 g, 89 % yield).

^{31}P {H} NMR (202.5 MHz, CH_2Cl_2): δ = -18.7; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.10 – 8.04 (m, 2H, C_6H_5 *o-H*), 7.59 – 7.51 (m, 7 H, Ar-*H*), 7.43 – 7.39 (m, 2 H, C_6H_5 *p-H*), 7.35 – 7.31 (m, 4 H, C_6H_5 *m-H*); **^{13}C {H} NMR** (125.8 MHz, $CDCl_3$) δ = 132.8 (d, *J* = 2.8 Hz, C_6H_5 *p-C*), 132.7 (d, *J* = 142.6 Hz, C_6H_5 *Q*), 132.6 (d, *J* = 1.4 Hz, C_6H_5 *o-C*), 130.9 (C_6H_5 *p-C*), 130.4 (d, *J* = 12.6 Hz, C_6H_5 *o-C*), 128.8 (d, *J* = 15.0 Hz, C_6H_5 *m-C*), 128.6 (C_6H_5 *m-C*), 119.6 (d, *J* = 4.6 Hz, C_6H_5 *Q*), 103.8 (d, *J* = 37.9 Hz, *C*≡C), 83.1 (d, *J* = 37.9 Hz, C≡*C*); **IR** (neat, cm^{-1}) 2173, 1206, 855, 756, 686, 662, 632; **HRMS** (ESI^{+}) exact mass calculated for $C_{22}H_{16}PO$ $[M+H]^{+}$ *m/z* = 327.0939, found *m/z* = 327.0942. This is consistent with data reported in the literature.[186]

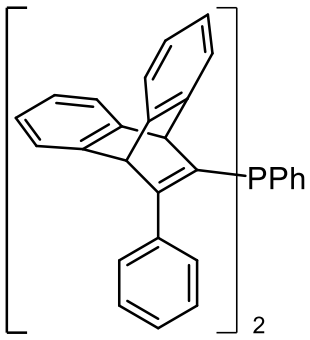
11-[Bis(12-phenyl-9,10-dihydro-9,10-etheno-anthracene)]phenylphosphine oxide (**28**).



(Diethynylbenzene)phenylphosphine oxide, **26**, (2.27 g, 7.51 mmol) was mixed with anthracene (2.01 g, 11.3 mmol), heated to 220 ^{o}C and stirred for 8 h. The resultant crude product was then purified by column chromatography eluting first with CH_2Cl_2 to remove excess anthracene and then CH_2Cl_2 / MeOH (20 : 1) to yield the phosphine oxide, **28** as a light yellow solid (4.20 g, 82 % yield).

^{31}P {H} NMR (161.8 MHz, CH_2Cl_2): δ = 25.0; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.41 – 7.35 (m, 5 H, C_6H_4), 7.19 (td, *J* = 7.7, 2.8 Hz, 2 H, Ar-*H*), 7.13 – 7.02 (m, 12 H, Ar-*H*), 7.97 – 6.91 (m, 6 H, Ar-*H*), 6.76 (d, *J* = 7.2 Hz, 4 H, Ar-*H*), 6.71 (d, *J* = 7.2 Hz, 2 H, C_6H_4), 5.33 (d, *J* = 3.4 Hz, 2 H, bridgehead *H*), 5.26 (d, *J* = 9.2 Hz, 2 H, bridgehead *H*); **^{13}C {H} NMR** (125.8 MHz, $CDCl_3$) δ = 165.8 (d, *J* = 7.6 Hz, *C*CP), 144.8 (d, *J* = 1.4 Hz, C_6H_4 *Q*), 144.8 (d, *J* = 2.6 Hz, C_6H_4 *Q*), 144.5 (2 x C_6H_4 *Q*), 137.8 (d, *J* = 4.0 Hz, C_6H_5 *Q*), 136.5 (d, *J* = 102 Hz, *C*P), 133.3 (d, *J* = 109 Hz, C_6H_5 *Q*), 131.6 (d, *J* = 10.8 Hz, C_6H_5 *o-C*), 131.3 (C_6H_5 *p-C*), 128.2 (d, *J* = 12.5 Hz, C_6H_5 *m-C*), 127.9 (C_6H_5 *p-C*), 127.7 (C_6H_5 *o-C*), 127.6 (C_6H_5 *m-C*), 125.4 (C_6H_4), 125.3 (C_6H_4), 125.2 (C_6H_4), 125.1 (C_6H_4), 123.8 (C_6H_4), 123.7 (C_6H_4), 123.5 (C_6H_4), 123.5 (C_6H_4), 61.3 (d, *J* = 9.7 Hz, bridgehead *C*H), 54.0 (d, *J* = 11.4 Hz, bridgehead *C*H); **mp** = 169 ^{o}C; **IR** (neat, cm^{-1}) 765, 746, 694, 629, 571, 519; **HRMS** (ESI^{+}) exact mass calculated for $C_{50}H_{36}PO$ $[M+H]^{+}$ *m/z* = 683.2504, found *m/z* = 683.2507 gmol^{-1}.

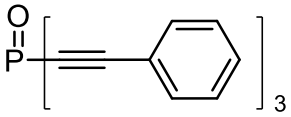
11-[Bis(12-phenyl-9,10-dihydro-9,10-etheno-anthracene)]phenylphosphine (**30**).



A flame dried Schlenk flask was charged with 11-[bis(12-phenyl-9,10-dihydro-9,10-etheno-anthracene)]phenylphosphine oxide, **28**, (4.00 g, 5.86 mmol), toluene (100 ml) and NEt_3 (35 ml). Trichlorosilane (7.00 ml, 69.0 mmol) was then added and the flask heated at 110 ^oC for 18 h. The reaction mixture was cooled to 0 ^oC and then diluted with Et_2O (110 ml). Ice (50 g) and 20 % aq NaOH (110 ml) were added very slowly and the resulting mixture was then stirred for 30 min, the organic layer removed and the aqueous phase extracted with Et_2O (3 x 120 ml). The combined organic layers were washed with sat. $NaHCO_3$ (2 x 150 ml), H_2O (2 x 150 ml), brine (2 x 110 ml), dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The crude product was purified by recrystallisation from a $CHCl_3$ solution layered with MeOH to give the phosphine, **30**, as white crystals (2.93 g, 75 % yield).

^{31}P {H} NMR (161.8 MHz, CH_2Cl_2): δ = -18.7; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.45 – 7.35 (m, 7 H, Ar-*H*), 7.29 – 7.27 (m, 2 H, Ar-*H*), 7.12 – 6.99 (m, 14 H, Ar-*H*), 6.85 (t, *J* = 7.4 Hz, 2 H, C_6H_4), 6.79 – 6.77 (m, 4 H, C_6H_5), 6.37 (d, *J* = 7.3 Hz, 2 H, C_6H_4), 5.50 (d, *J* = 3.2 Hz, 2 H, bridgehead *H*), 5.24 (d, *J* = 1.9 Hz, 2 H, bridgehead *H*); **^{13}C {H} NMR** (125.8 MHz, $CDCl_3$) δ = 162.2 (d, *J* = 29.6 Hz, *C*CP), 146.1 (C_6H_4 *Q*), 145.6 (C_6H_4 *Q*) 145.4 (C_6H_4 *Q*), 145.2 (C_6H_4 *Q*), 139.9 (d, *J* = 25.6 Hz, *C*P), 138.6 (d, *J* = 6.1 Hz, C_6H_5 *Q*), 138.4 (d, *J* = 10.1 Hz, C_6H_5 *Q*), 133.1 (d, *J* = 17.6 Hz, C_6H_5 *o*-*C*), 128.6 (d, *J* = 5.0 Hz, C_6H_5 *m*-*C*), 128.1 (C_6H_5 *p*-*C*), 127.7 (C_6H_5 *o*-*C*), 127.7 (C_6H_5 *m*-*C*), 127.4 (C_6H_4), 127.3 (C_6H_4), 125.1 (C_6H_4), 124.9 (C_6H_4), 124.8 (C_6H_4), 123.6 (C_6H_4), 123.4 (C_6H_4), 123.1 (C_6H_4), 59.4 (d, *J* = 6.3 Hz, bridgehead *C*H), 56.8 (d, *J* = 5.9 Hz, bridgehead *C*H); **mp** = 256 ^oC; **IR** (neat, cm^{-1}) 1465, 1156, 763, 743, 694, 631, 607; **HRMS** (ESI^+) exact mass calculated for $C_{50}H_{36}P$ $[M+H]^+$ *m/z* = 667.2555, found *m/z* = 667.2569.

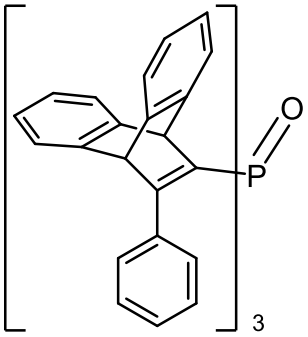
Tris(phenylacetylene) phosphine oxide (**27**).



A solution of phenylacetylene (4.79 ml, 43.6 mmol) in THF (60 ml) was cooled to -78 ^{o}C and ^{n}BuLi (21.8 ml, 1.6 M in hexane, 34.9 mmol) was added. The resulting mixture was then stirred at this temperature for 30 min. This was allowed to warm to 0 ^{o}C and stirred for a further 30 min at this temperature. The solution was then cooled to -78 ^{o}C and PCl_3 (0.95 ml, 10.9 mmol) was added dropwise. The solution was allowed to warm to RT and stirred for 2.5 h at this temperature. This was then cooled to 0 ^{o}C and H_2O_2 (35 % aq solution, 5.0 ml, 17.9 mmol) added dropwise. The solution was allowed to warm to RT and was stirred for a further 30 min. H_2O (100 ml) was then added and the product was extracted with Et_2O (3 x 100 ml). The combined organic layers dried ($MgSO_4$) and solvent removed under reduced pressure. The yellow crude product (3.58 g, 94% yield) was sufficiently pure by NMR to be used without further purification.

^{31}P {H} NMR (202.5 MHz, CH_2Cl_2): δ = -50.7; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.65 – 7.63 (m, 6 H, C_6H_5 *o-H*), 7.50 – 7.46 (m, 3 H, C_6H_5 *p-H*), 7.41 – 7.38 (m, 6 H, C_6H_5 *m-H*); **^{13}C {H} NMR** (125.8 MHz, $CDCl_3$): δ = 132.9 (d, *J* = 2.0 Hz, C_6H_5 *o-C*), 131.2 (C_6H_5 *p-C*), 128.7 (C_6H_5 *m-C*), 119.5 (d, *J* = 5.1 Hz, C_6H_5 *Q*), 102.6 (d, *J* = 47.0 Hz, *C*≡CP), 83.2 (d, *J* = 241 Hz, C≡*C*P); **mp** = 122 – 123 ^{o}C; **IR** (neat, cm^{-1}) 2172, 1488, 1443, 1208, 856, 754, 687, 663; **HRMS** (ESI^{+}) exact mass calculated for $C_{24}H_{16}PO$ $[M+H]^{+}$ *m/z* = 351.0939 [1], found *m/z* = 351.0943. This is consistent with data reported in the literature.[185]

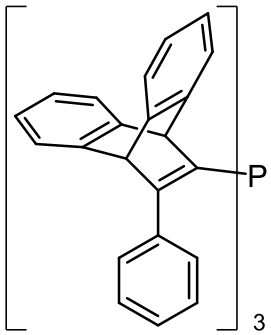
11-[Tris(12-phenyl-9,10-dihydro-9,10-etheno-anthracene)]phosphine oxide (**29**).



Tris(ethynylbenzene) phenylphosphine oxide, **27**, (3.04 g, 8.67 mmol) was mixed with anthracene (2.32 g, 13.0 mmol), heated to 220 ^{o}C and stirred for 32 h. The resultant crude product was then purified by column chromatography eluting first with petrol to remove excess anthracene and then with EtOAc. The product was then recrystallised from a CH_2Cl_2 solution layered with MeOH to give the phosphine oxide **29** as colourless crystals (2.72 g, 35 % yield).

^{31}P {H} NMR (161.8 MHz, CH_2Cl_2): δ = 18.6; **^{1}H NMR** (500 MHz, $CDCl_3$, -50 ^{o}C) δ = 8.19 (d, *J* = 7.1 Hz, 3 H, C_6H_4), 7.54 – 7.51 (m, 6 H, C_6H_4), 7.41 (t, *J* = 7.4 Hz, 3 H, C_6H_4), 7.29 (t, *J* = 7.4 Hz, 3 H, C_6H_4), 6.99 (t, *J* = 7.4 Hz, 3 H, C_6H_4), 6.93 (t, *J* = 7.4 Hz, 3 H, C_6H_5 *p-H*), 6.75 (t, *J* = 7.8 Hz, 6 H, C_6H_5 *m-H*), 6.66 (t, *J* = 7.4 Hz, 3 H, C_6H_4), 6.40 (d, *J* = 7.3 Hz, 6 H, C_6H_5 *o-H*), 5.66 (d, *J* = 9.1 Hz, bridgehead *H*, 3 H), 5.57 (d, *J* = 2.9 Hz, bridgehead *H*, 3 H), 5.38 (d, *J* = 7.3 Hz, 3 H, C_6H_4); **^{13}C {H} NMR** (126 MHz, $CDCl_3$, -41 ^{o}C) δ = 165.6 (d, *J* = 7.1 Hz, *C*CP), 145.7 (C_6H_4 *Q*), 144.4 (C_6H_4 *Q*), 144.3 (d, *J* = 4.2 Hz, C_6H_4 *Q*), 144.0 (C_6H_4 *Q*), 137.1 (d, *J* = 3.8 Hz, C_6H_5 *Q*), 137.0 (d, *J* = 102.8 Hz, *C*P), 128.3 (C_6H_5 *p-C*), 127.5 (C_6H_5 *o-C*), 127.4 (C_6H_5 *m-C*), 125.9 (C_6H_4), 125.8 (C_6H_4), 125.4 (C_6H_4), 125.2 (C_6H_4), 124.6 (C_6H_4), 124.3 (C_6H_4), 123.3 (C_6H_4), 123.1 (C_6H_4), 60.4 (d, *J* = 9.2 Hz, bridgehead *C*H), 53.8 (d, *J* = 11.6 Hz, bridgehead *C*H); **mp** = 349 ^{o}C (decomposition); **IR** (neat, cm^{-1}) 1456, 1207, 1157, 978, 761, 748, 692, 630; **HRMS** (ESI^{+}) exact mass calculated for $C_{66}H_{46}PO$ $[M+H]^{+}$ *m/z* = 885.3286, found *m/z* = 885.3287.

11-[Tris(12-phenyl-9,10-dihydro-9,10-etheno-anthracen-11-yl)]phosphine (**31**).

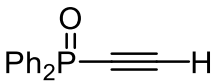


A flame dried Schlenk flask was charged with 11-[tris(12-phenyl-9,10-dihydro-9,10-etheno-anthracene)]phosphine oxide, **29**, (1.03 g, 1.17 mmol), degassed xylenes (75 ml), degassed tributylamine (4.33 ml, 23.4 mmol). Trichlorosilane (6.34 ml, 46.8 mmol) was added and the resulting mixture was heated at 130 ^{o}C for 96 hrs. The reaction mixture was then transferred to a RB flask under nitrogen and cooled to 0 ^{o}C. This was then diluted with CH_2Cl_2 (80 ml), ice (40 g) and 20 % aq NaOH (80 ml) and stirred vigorously for 1 hr. The organic layer was removed and the aqueous phase extracted with CH_2Cl_2 (3 x 80 ml). The combined organic extracts were washed with sat. $NaHCO_3$ (2 x 80 ml), H_2O (2 x 80 ml), brine (2 x 80 ml), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Tributylamine was then removed by dissolving the crude product in CH_2Cl_2 (30 ml) and washing it with 10% aq HCl solution (3 x 20 ml). The aqueous phase was extracted with EtOAc (2 x 30 ml). The combined organic extracts were then dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The crude product was then purified by column chromatography, eluting with petrol to remove any residual tributylamine and then petrol / EtOAc (1 : 1) to yield the phosphine **31** as an off-white solid (0.65g, 64 % yield).

^{31}P {H} NMR (161.8 MHz, CH_2Cl_2): δ = -24.8; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.18 (d, *J* = 7.1 Hz, 3 H, C_6H_4), 7.46 – 7.44 (m, 6 H, C_6H_4), 7.37 (t, *J* = 7.2 Hz, 3 H, C_6H_4), 7.23 (t, *J* = 7.4 Hz, 3 H, C_6H_4), 6.91 (t, *J* = 7.4 Hz, 3 H, C_6H_4), 6.85 (t, *J* = 7.4 Hz, 3 H, C_6H_5 *p-H*), 6.70 (t, *J* = 7.7 Hz, 6 H, C_6H_5 *m-H*), 6.60 (t, *J* = 7.4 Hz, 3 H, C_6H_4), 6.31 (d, *J* = 7.8 Hz, 6 H, C_6H_5 *o-H*), 5.73 (s, 3 H, C_6H_4), 5.50 – 5.48 (m, 6 H, bridgehead *H*); **^{13}C {H} NMR** (100.5 MHz, $CDCl_3$) δ = 161.6 (d, *J* = 31.5 Hz, *C*CP), 146.0 (C_6H_4 *Q*), 146.0 (C_6H_4 *Q*), 145.7 (C_6H_4 *Q*), 144.0 (C_6H_4 *Q*), 142.3 (d, *J* = 25.9 Hz, *C*P), 138.4 (d, *J* = 6.7 Hz, C_6H_5 *Q*), 127.7 (C_6H_5 *p-C*), 127.5 (C_6H_5), 127.2 (d, *J* =

4.9 Hz, C_6H_5), 125.6 (C_6H_4), 125.5 (C_6H_4), 125.2 (C_6H_4), 124.8 (C_6H_4), 124.2 (C_6H_4), 124.2 (C_6H_4), 123.3 (C_6H_4), 122.5 (C_6H_4), 59.3 (d, *J* = 6.2 Hz, bridgehead *C*H), 58.6 (d, *J* = 6.0 Hz, bridgehead *C*H); **IR** (neat, cm^{-1}) = 1457, 761, 748, 694, 628, 606, 523; **HRMS** (ESI^+) exact mass calculated for $C_{66}H_{46}P$ $[M+H]^+$ *m/z* = 869.3337, found *m/z* = 869.3343.

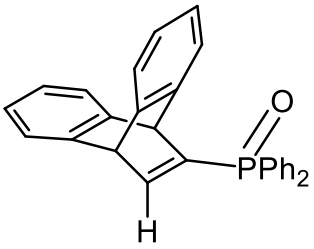
Diphenyl(ethynyl)phosphine oxide (**32**).



A solution of trimethylsilylacetylene (2.82 ml, 20.4 mmol) in THF (20 ml) was cooled to -78 ^oC and ^nBuLi (12.7 ml, 1.6 M, 20.4 mmol) added. The resulting mixture was stirred for 20 min at this temperature, allowed to warm to 0 ^oC and then stirred for a further 20 min at this temperature. The solution was then cooled to -78 ^oC and chlorodiphenylphosphine (3.76 ml, 20.4 mmol) added dropwise. This solution was allowed to warm to RT and stirred for 2 h at this temperature. This was then cooled to 0 ^oC and H_2O_2 (35 % aq solution, 6.2 ml, 26.5 mmol) added dropwise. The solution was allowed to warm to RT and was stirred for a further 30 min. H_2O (100 ml) was then added and the product extracted with Et_2O (2 x 100 ml). The combined organic extracts were dried ($MgSO_4$) and solvent removed under reduced pressure. This was then purified by column chromatography, eluting with CH_2Cl_2 / EtOAc (8 : 1) to give the phosphine oxide **32**, as a yellow solid (3.71g, 81 % yield).

^{31}P {H} NMR (161.8 MHz, CH_2Cl_2): δ = 9.2; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.88 – 7.81 (m, 4 H, C_6H_5 *o-H*), 7.60 – 7.54 (m, 2 H, C_6H_5 *p-H*), 7.53 – 7.47 (m, 4 H, C_6H_5 *m-H*), 3.34 (dd, *J* = 9.9, 1.7 Hz, 1 H, C≡C*H*); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ = 132.1 (d, *J* = 2.6 Hz), 131.5 (d, *J* = 120.5 Hz), 130.4 (d, *J* = 11.3 Hz), 128.3 (d, *J* = 13.6 Hz), 95.3 (d, *J* = 28.0 Hz), 77.9 (d, *J* = 161.7 Hz). This is consistent with data reported in the literature.[187]

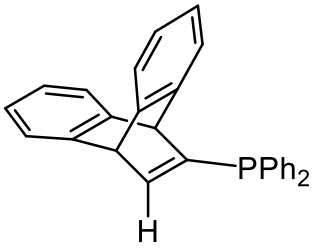
11-(Diphenylphosphinoyl)-9,10-dihydro-9,10-ethenoanthracene (**34**).



Diphenyl(ethynyl)phosphine oxide **32** (1.56 g, 6.90 mmol) was mixed with anthracene (1.84g, 10.3 mmol), heated to 220 °C and stirred at this temperature for 6 h. The resultant crude product was then purified by column chromatography eluting first with petrol to remove excess anthracene and then with petrol / EtOAc (1 : 1) the phosphine oxide **34**, as a pale yellow solid (2.27 g, 81 % yield).

^{31}P {H} NMR (161.8 MHz, CH_2Cl_2): δ = 26.4; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.51 – 7.46 (m, 6 H, Ar-*H*), 7.40 – 7.35 (m, 5 H, Ar-*H*), 7.28 (d, *J* = 6.8 Hz, 2 H, Ar-*H*), 7.13 (d, *J* = 6.8 Hz, 2 H, Ar-*H*), 6.99 – 6.92 (m, 4 H, Ar-*H*, *H*C=CP), 5.36 (d, *J* = 8.1 Hz, 1 H, bridgehead *H*), 5.28 (dd, *J* = 5.9, 2.7 Hz, 1 H, bridgehead *H*); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ = 154.3 (d, *J* = 10.3 Hz, H*C*=CP), 145.4 (d, *J* = 105 Hz, *C*P), 144.8 (d, *J* = 2.6 Hz, C_6H_4 *Q*), 144.5 (d, *J* = 1.8 Hz, C_6H_4 *Q*), 132.1 (d, *J* = 2.7 Hz, C_6H_5 *p-C*), 132.0 (d, *J* = 10.4 Hz, C_6H_5 *o-C*), 131.3 (d, *J* = 106 Hz, C_6H_5 *Q*), 128.5 (d, *J* = 12.3 Hz, C_6H_5 *m-C*), 125.03 (C_6H_4), 125.02 (C_6H_4), 123.7 (C_6H_4), 123.4 (C_6H_4), 52.4 (d, *J* = 11.1 Hz, bridgehead *C*H), 52.0 (d, *J* = 9.6 Hz, bridgehead *C*H); **mp** = 87 – 89 °C; **IR** (neat, cm^{-1}) 1458, 1437, 1182, 1119, 746, 722, 693, 641; **HRMS** (ESI^+) exact mass calculated for $C_{28}H_{22}PO$ $[M+H]^+$ *m/z* = 405.1408, found *m/z* = 405.1405. This is consistent with data reported in the literature.[59]

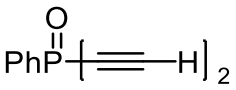
11-(Diphenylphosphino)-9,10-dihydro-9,10-ethanoanthracene. (**36**)



A flame dried Schlenk flask was charged with 11-(diphenylphosphinoyl)-9,10-dihydro-9,10-ethenoanthracene, **34** (1.28 g, 3.16 mmol), toluene (20 ml), THF (20 ml), and $P(OEt)_3$ (2.71 ml, 15.8 mmol). Trichlorosilane (4.79 ml, 47.4 mmol) was then added and the flask was heated at 45 ^oC for 16 h. The reaction mixture was cooled to 0 ^oC and then diluted with Et_2O (60 ml), ice (50 g) and 20 % aq NaOH (60 ml) and then stirred for 1 h. The resulting emulsion was filtered through celite, washing with diethyl ether (3 x 50 ml). The organic layer was then washed with sat. $NaHCO_3$ (2 x 50 ml), water (2 x 50ml), brine (2 x 50 ml), dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude product was purified by column chromatography eluting with petrol / EtOAc (97 : 3) to give the phosphine **36**, as a white solid (0.61 g, 50% yield).

^{31}P {H} NMR (161.8 MHz, CH_2Cl_2): δ = -7.8; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.36 - 7.19 (m, 12 H Ar-*H*), 7.08 - 7.06 (m, 2 H, Ar-*H*), 6.99 - 6.91 (m, 4 H, Ar-*H*), 6.82 (td, *J* = 6.1, 1.7 Hz, 1 H, *H*C=CP), 5.16 (d, *J* = 5.9 Hz, 1 H, bridgehead *H*), 5.01 (dd, *J* = 6.1, 1.5 Hz, 1 H, bridgehead *H*); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ = 148.9 (d, *J* = 18.0 Hz, *C*P), 146.8 (d, *J* = 16.7 Hz, *C*=CP), 145.8 (C_6H_4 *Q*), 145.7 (C_6H_4 *Q*), 135.4 (d, *J* = 9.9 Hz, C_6H_5 *Q*), 134.2 (d, *J* = 19.4 Hz, C_6H_5 *o*-*C*), 129.0 (C_6H_5 *p*-*C*), 128.5 (d, *J* = 7.3 Hz, C_6H_5 *m*-*C*), 124.7 (C_6H_4), 124.5 (C_6H_4), 123.4 (C_6H_4), 122.8 (C_6H_4), 55.1 (d, *J* = 15.2 Hz, bridgehead *C*H), 52.5 (d, *J* = 5.4 Hz, bridgehead *C*H); **IR** (neat, cm^{-1}) 1458, 1436, 1099, 1022, 745, 964, 641, 530; **HRMS** (ESI^+) exact mass calculated for $C_{28}H_{22}P$ $[M+H]^+$ *m/z* = 389.1459, found *m/z* = 389.1463. This is consistent with data reported in the literature.[59]

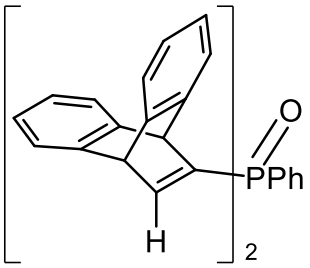
Bis(ethynyl)phenylphosphine oxide (**33**).



A solution of trimethylsilyl acetylene (6.76 ml, 48.9 mmol) in THF (60 ml) was cooled to -78 ^{o}C, ^{n}BuLi (26.9 ml, 1.6 M, 43.0 mmol) added and the resulting mixture was stirred at this temperature for 30 min. This was allowed to warm to 0 ^{o}C and then was stirred at this temperature for a further 20 min. The solution was cooled to -78 ^{o}C and dichlorophenylphosphine (2.65 ml, 19.6 mmol) added dropwise. This was then allowed to warm to RT and was stirred at this temperature for a further 2.5 h. The solution was then cooled to 0 ^{o}C and H_2O_2 (35 % aq solution, 7.3 ml, 31.3 mmol) added dropwise. The solution was allowed to warm to RT and was stirred for a further 30 min. H_2O (100 ml) was then added and the product was extracted with Et_2O (3 x 80 ml). The combined organic extracts were dried ($MgSO_4$) and solvent removed under reduced pressure. This was then purified by column chromatography, eluting with CH_2Cl_2 / EtOAc (8 : 1) to give the phosphine oxide **33**, as a white solid (2.49 g, 73% yield).

^{31}P {H} NMR (161.8 MHz, CH_2Cl_2): δ = -20.0; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.97 – 7.90 (m, 2 H, C_6H_5 *o-H*), 7.63 – 7.59 (m, 1 H, C_6H_5 *p-H*), 7.55 – 7.50 (m, 2 H, C_6H_5 *m-H*), 3.33 (d, *J* = 11.0 Hz, 2 H, C≡C*H*); **^{13}C {^{1}H} NMR** (125.8 MHz, $CDCl_3$) δ = 133.4 (d, *J* = 2.9 Hz, C_6H_5 *p-C*), 130.9 (d, *J* = 143 Hz, C_6H_5 *Q*), 130.4 (d, *J* = 13.0 Hz, C_6H_5 *o-C*), 129.0 (d, *J* = 15.3 Hz, C_6H_5 *m-C*), 93.1 (d, *J* = 35.9 Hz, H*C*≡CP), 78.4 (d, *J* = 194 Hz, HC≡*C*P); **mp** = 83 – 84 ^{o}C; **IR** (neat, cm^{-1}) 3158, 2050, 1436, 1193, 1113, 714, 688, 642; **HRMS** (ESI^{+}) exact mass calculated for $C_{10}H_8PO$ $[M+H]^{+}$ *m/z* = 175.0313, found *m/z* = 175.0315. This is consistent with data reported in the literature.[188]

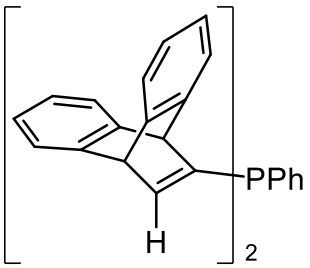
11-[Bis(9,10-dihydro-9,10-etheno-anthracene)]phenylphosphine oxide (**35**).



Bis(ethynyl)phenylphosphine oxide, **33**, (2.77 g, 15.9 mmol) was mixed with anthracene (4.26g, 23.9 mmol), heated to 220 °C and then stirred at this temperature for 10 h. The resultant crude product was then purified by column chromatography eluting first with petrol to remove excess anthracene and then with petrol / EtOAc (1 : 2) to give the phosphine oxide **35**, as a light brown solid (4.55g, 54 % yield).

^{31}P {H} NMR (161.8 MHz, CH_2Cl_2): δ = 27.2; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.50 – 7.47 (m, 1 H, C_6H_5), 7.32 – 7.22 (m, 8 H, Ar-*H*), 7.17 (dd, *J* = 12.9, 5.9 Hz, 2 H, *H*C=CP), 7.07 – 6.92 (m, 12 H, C_6H_4), 5.25 (d, *J* = 8.1 Hz, 2 H, bridgehead *H*), 5.20 – 5.18 (m, 2 H, bridgehead *H*); **^{13}C {^{1}H} NMR** (125.8 MHz, $CDCl_3$) δ = 153.8 (d, *J* = 10.7 Hz, H*C*=CP), 144.8 (C_6H_4 Q) 144.5 (C_6H_4 Q), 144.3 (d, *J* = 105 Hz, *C*P), 132.1 (C_6H_5 *p-C*), 131.9 (d, *J* = 10.7 Hz, C_6H_5 *o-C*), 130.3 (d, *J* = 108 Hz, C_6H_5 *Q*), 128.5 (d, *J* = 12.4 Hz, C_6H_5 *m-C*), 125.13 (C_6H_4), 125.11 (C_6H_4), 125.03 (C_6H_4), 124.97 (C_6H_4), 123.8 (C_6H_4), 123.7 (C_6H_4), 123.5 (2 x C_6H_4), 54.7 (d, *J* = 15.1 Hz, bridgehead *C*H), 52.4 (d, *J* = 5.9 Hz, bridgehead *C*H); **mp** = 87 – 89 °C; **IR** (neat, cm^{-1}) 2981, 1189, 1124, 728, 543; **HRMS** (ESI^+) exact mass calculated for $C_{38}H_{28}PO$ $[M+H]^+$ *m/z* = 531.1878, found *m/z* = 531.1879.

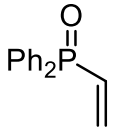
11-[Bis(9,10-dihydro-9,10-etheno-anthracene)]phenylphosphine (**37**).



A flame dried Schlenk flask was charged with 11-[bis(9,10-dihydro-9,10-etheno-anthracene)]phenylphosphine oxide **35** (2.50 g, 4.71 mmol), toluene (40 ml), THF (40 ml) and $P(OEt)_3$ (4.04 ml, 23.6 mmol). Trichlorosilane (7.14 ml, 70.7 mmol) was then added and the flask heated at 45 ^oC for 16 h. The reaction mixture was then cooled to 0 ^oC and was diluted with Et_2O (100 ml), ice (60 g) and 20 % aq NaOH (100 ml). The reaction mixture was stirred for 1 h at this temperature. The resulting immulsion was filtered through celite, washing with Et_2O. The organic layer was then washed with brine (2 x 100 ml), dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The crude product was purified by column chromatography eluting with petrol / EtOAc (9 : 1) and then the product was recrystallised from a $CHCl_3$ solution layered with MeOH to give the phosphine **37**, as colourless crystals (0.80 g, 33 % yield).

^{31}P {H} NMR (161.8 MHz, CH_2Cl_2): δ = -11.1; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.31 (t, *J* = 7.4 Hz, 1 H, Ar-*H*), 7.24 - 7.16 (m, 6 H, Ar-*H*, *H*C=CP), 7.06 - 6.84 (m, 14 H, Ar-*H*), 6.78 – 6.74 (t, *J* = 5.8 Hz, 2 H, Ar-*H*), 5.07 (d, *J* = 5.8 Hz, 2 H, bridgehead *H*), 4.94 (d, *J* = 5.9 Hz, 2 H, bridgehead *H*); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ = 147.3 (d, *J* = 18.3 Hz, C=*C*P), 147.2 (d, *J* = 16.7 Hz, *C*=CP), 145.8 (C_6H_4 *Q*), 145.7 (C_6H_4 *Q*), 145.6 (C_6H_4 *Q*), 145.5 (C_6H_4 *Q*), 134.6 (d, *J* = 19.7 Hz, C_6H_5 *o*-*C*), 133.4 (d, *J* = 8.4 Hz, C_6H_5 *Q*), 129.2 (C_6H_5 *p*-*C*), 128.4 (d, *J* = 7.3 Hz, C_6H_5 *m*-*C*), 124.7 (C_6H_4), 124.6 (C_6H_4), 124.6 (C_6H_4), 124.5 (C_6H_4), 123.5 (C_6H_4), 123.2 (C_6H_4), 122.9 (C_6H_4), 122.9 (C_6H_4), 54.7 (d, *J* = 15.1 Hz, bridgehead *C*H), 52.4 (d, *J* = 5.9 Hz, bridgehead *C*H); **IR** (neat, cm^{-1}); **HRMS** (ESI^+) exact mass calculated for $C_{38}H_{27}P$ $[M+Na]^+$ requires *m/z* = 537.1748 $gmol^{-1}$, found *m/z* = 537.1747 $gmol^{-1}$.

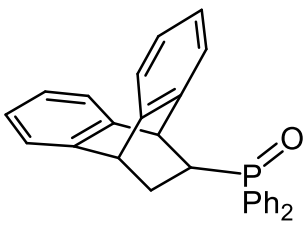
Diphenyl(vinyl)phosphine oxide (**38**).



A solution of chlorodiphenylphosphine (0.81 ml, 4.53 mmol), in THF (30 ml) was cooled to -78 ^{o}C and then vinyl magnesium bromide (4.76 ml, 1.0 M in THF, 4.76 mmol) was added dropwise. The reaction mixture was then allowed to warm to RT and stirred for 2 h. Sat. NH_4Cl (30 ml) was then added and the product extracted with $CHCl_3$ (3 x 30 ml). The combined organic extracts were dried ($MgSO_4$), filtered and half of the solvent was removed under reduced pressure. H_2O_2 (5.6 ml, 35 % aqueous, 181.2 mmol) was then added and the reaction was stirred at RT for 14 h. Sat. NH_4Cl (30 ml) was then added and the product extracted with $CHCl_3$ (3 x 20 ml). The combined organic extracts were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure, to give the phosphine oxide **38**, as a white solid (1.03 g, 100 % yield).

^{31}P {H} NMR (161.8 MHz, CH_2Cl_2): δ = 24.5; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.65 – 7.60 (m, 4 H, C_6H_5 *o-H*), 7.46 – 7.42 (m, 2 H, C_6H_5 *p-H*), 7.40 – 7.35 (m, 4 H, C_6H_5 *m-H*), 6.67 – 6.53 (m, 1 H, PC*H*=CH_2), 6.30 – 6.14 (m, 2 H, PC=C*H*$_2$); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ = 134.7, 132.1 (d, *J* = 105 Hz), 131.9 (d, *J* = 2.6 Hz), 131.2 (d, *J* = 10.0 Hz), 131.0 (d, *J* = 98.2 Hz), 128.5 (d, *J* = 12.0 Hz). This is consistent with data reported in the literature.[189]

11-Diphenylphosphinoyl-9,10-dihydro-9,10-ethanoanthracene (**39**).

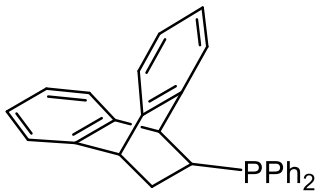


Diphenyl(vinyl)phosphine oxide (0.68 g, 2.98 mmol), **38**, was mixed with

anthracene (0.80 g, 4.47 mmol), heated to 220 ^{o}C and stirred at this temperature for 16 h. The resultant crude product was then purified by column chromatography eluting first with CH_2Cl_2 to remove excess anthracene and then with CH_2Cl_2 / MeOH (97.5 : 2.5) to give the phosphine oxide **39**, as an off – white solid (1.09 g, 90 % yield).

^{31}P {H} NMR (161.8 MHz, CH_2Cl_2): δ = 31.8; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.78 – 7.73 (m, 2 H, Ar-*H*), 7.58 – 7.43 (m, 5 H, Ar-*H*), 7.36 (td, *J* = 7.4, 1.3 Hz, 1 H, Ar-*H*), 7.29 – 7.21 (m, 4 H, Ar-*H*), 7.18 – 7.00 (m, 6 H, Ar-*H*), 4.58 (d, *J* = 5.5, 1.5 Hz, 1 H, bridgehead *H*), 4.35 (br, 1 H, bridgehead *H*), 3.85 (m, 1 H, P-C*H*), 2.14 – 1.98 (m, 2 H, PCC*H*$_2$); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ = 144.6 (C_6H_4 *Q*), 144.5 (C_6H_4 *Q*), 143.6 (d, *J* = 5.1 Hz, C_6H_4 *Q*), 139.9 (C_6H_4 *Q*), 133.4 (d, *J* = 96.4 Hz, C_6H_5 *Q*), 132.2 (d, *J* = 95.9 Hz, C_6H_5 *Q*), 131.8 (d, *J* = 2.5 Hz, C_6H_5 *p-C*), 131.4 (C_6H_5 *p-C*), 131.3 (d, *J* = 8.6 Hz, C_6H_5 *o-C*), 131.1 (d, *J* = 8.9 Hz, C_6H_5 *o-C*), 128.8 (d, *J* = 11.4 Hz, C_6H_5 *m-C*), 128.3 (d, *J* = 11.2 Hz, C_6H_5 *m-C*), 126.3 (C_6H_4), 126.2 (C_6H_4), 126.0 (2 x C_6H_4), 125.6 (C_6H_4), 124.0 (C_6H_4), 123.0 (C_6H_4), 122.9 (C_6H_4), 44.1 (d, *J* = 4.2 Hz, bridgehead *C*H), 43.7 (s, bridgehead *C*H), 39.2 (d, *J* = 71.2 Hz, P*C*HCH$_2$), 29.4 (PCH*C*H$_2$); **mp** = 107 – 109 ^{o}C; **IR** (neat, cm^{-1}) 1208, 858, 754, 688, 662, 537; **HRMS** (ESI^{+}) exact mass calculated for $C_{28}H_{24}PO$ $[M+H]^{+}$ *m/z* = 407.1565, found *m/z* = 407.1565.

11-(Diphenylphosphino)-9,10-dihydro-9,10-ethanoanthracene (**40**).

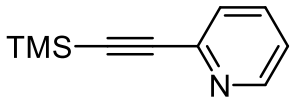


A flame dried Schlenk flask was charged with 11-Diphenylphosphinoyl-9,10-dihydro-9,10-ethanoanthracene, **39** (1.00 g, 2.46 mmol), toluene (60 ml) and NEt_3 (14 ml). Trichlorosilane (24.6 ml, 2.49 mmol) was then added and the flask heated at 110 ^{o}C for 60 h. The reaction mixture was cooled to 0 ^{o}C and diluted with Et_2O (40 ml). Ice (20 g) and 20 % aq NaOH (40 ml) were then added slowly and the resulting mixture

then stirred for 30 min. The organic layer was removed and the aqueous phase extracted with Et_2O (3 x 60 ml). The combined organic extracts were washed with sat. $NaHCO_3$ (2 x 50 ml), H_2O (2 x 50 ml), brine (2 x 50 ml), dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The crude product was then purified by column chromatography, eluting with petrol / EtOAc (40 : 1) and then by recrystallisation from a $CHCl_3$ solution layered with MeOH to give phosphine **40**, as white crystals (0.711g, 74 % yield).

^{31}P {H} NMR (161.8 MHz, CH_2Cl_2): δ = - 7.2; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.62 – 7.57 (m, 2 H, Ar-*H*), 7.45 – 7.42 (m, 3 H, Ar-*H*), 7.38 – 7.34 (m, 2 H, Ar-*H*), 7.29 – 7.08 (m, 11 H, Ar-*H*), 4.33 (br s, 1 H, bridgehead C*H*), 4.05 (dd, *J* = 4.1, 1.9 Hz, 1 H, bridgehead C*H*), 2.76 – 2.70 (m, 1 H, PC*H*CH_2), 2.07 – 1.99 (m, 1 H, PCHC*H*$_2$), 1.59 – 1.50 (m, 1 H, PCHC*H*$_2$); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ = 144.3 (d, *J* = 7.6 Hz, C_6H_4 *Q*), 143.5 (C_6H_4 *Q*), 143.4 (C_6H_4 *Q*), 141.0 (d, *J* = 4.2 Hz, C_6H_5 *Q*), 138.2 (d, *J* = 16.4 Hz, C_6H_5 *Q*), 137.1 (d, *J* = 14.5 Hz, C_6H_5 *Q*), 133.9 (d, *J* = 20.2 Hz, C_6H_5 *o-C*), 133.3 (d, *J* = 19.1 Hz, C_6H_5 *o-C*), 129.4 (C_6H_5 *p-C*), 128.7 (d, *J* = 7.3 Hz, C_6H_5 *m-C*), 128.6 (C_6H_5 *p-C*), 128.3 (d, *J* = 6.8 Hz, C_6H_5 *m-C*), 126.4 (C_6H_4), 126.0 (C_6H_4), 125.9 (C_6H_4), 125.7 (C_6H_4), 125.5 (d, *J* = 1.2 Hz, C_6H_4), 123.8 (C_6H_4), 123.4 (C_6H_4), 123.0 (C_6H_4), 45.8 (d, *J* = 16.4 Hz, bridgehead *C*H), 44.4 (d, *J* = 1.5 Hz, bridgehead *C*H), 37.0 (d, *J* = 9.2 Hz, P*C*HCH_2), 32.8 (d, *J* = 18.5 Hz, PCH*C*H_2); **mp** = 132 – 133 ^{o}C; **IR** (neat, cm^{-1}) 1465, 1431, 744, 698, 559; **HRMS** (ESI^+) exact mass calculated for $C_{28}H_{24}P$ $[M+H]^+$ *m/z* = 391.1616, found *m/z* = 391.1629.

2-Trimethylsilylethynylpyridine.

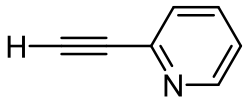


A flame dried Schlenk flask was charged with $PdCl_2(PPh_3)_2$ (1.05 g, 1.50 mmol), CuI (0.57 g, 3.00 mmol), PPh_3 (1.57 g, 6.00 mmol), THF (60 ml), 2-bromopyridine (2.93 ml, 30.0 mmol) and triethylamine (16.7 ml, 120 mmol). Trimethylsilylacetylene

(6.22 ml, 45.0 mmol) was then added and the mixture stirred at 70 ºC, for 48 h. H_2O (60 ml) and sat. NH_4Cl (60 ml) were then added and the mixture was diluted with Et_2O (100 ml). The organic layer was separated and washed with sat. NH_4Cl (3 x 50 ml). The aqueous washings were combined and extracted with Et_2O (3 x 100 ml). The combined organic extracts were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The crude product was purified by column chromatography, eluting with CH_2Cl_2 / petrol (3: 1) to give the alkyne, as a yellow oil (4.65 g, 88 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.56 – 8.54 (m, 1 H, Ar-*H*), 7.61 (t, J = 12 Hz, 1 H, Ar-*H*), 7.42 (d, *J* = 12 Hz, 1 H, Ar-*H*), 7.24 - 7.17 (m, 1 H, Ar-*H*), 0.25 (s, 9 H, Si(C*H*$_3$)$_3$); **^{13}C {H} NMR** (100.5 MHz, $CDCl_3$) δ = 150.1, 143.1, 136.0, 127.5, 123.0, 103.7, 94.9, -0.3. This is consistent with data reported in the literature.[190]

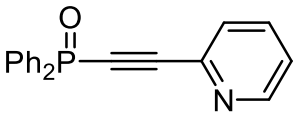
2-Ethynylpyridine.



K_2CO_3 (18.1 g, 131 mmol) was added to a solution of 2-trimethylsilylethynyl-pyridine, (2.70 g, 15.3 mmol), dissolved in CH_2Cl_2 (50 ml). MeOH (50 ml) was then added and the reaction was stirred at RT until completion, monitoring by TLC (30 min). The reaction was then quenched with water (100 ml) and the product extracted with Et_2O (3 x 50 ml). The organics were then combined, washed with brine (3 x 50 ml), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product was then purified by column chromatography, eluting with petrol/ EtOAc (4 : 1) to give the alkyne, as a light yellow oil (1.13 g, 72 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.56 - 8.54 (m, 1 H, Ar-*H*), 7.62 (t, *J* = 7.8 Hz, 1 H, Ar-*H*), 7.45 (d, *J* = 7.8 Hz, 1 H, Ar-*H*), 7.24 - 7.18 (m, 1 H, Ar-*H*), 3.13 (s, 1 H, C≡C*H*); **^{13}C {H} NMR** (100.5 MHz, $CDCl_3$) δ = 150.2, 142.5, 136.2, 127.7, 123.5, 82.9, 77.6. This is consistent with data reported in the literature.[190]

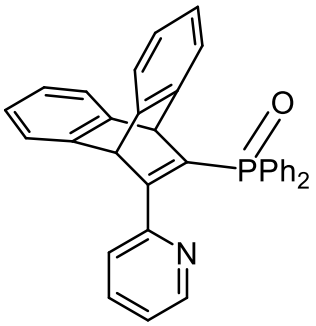
2-(Diphenylphosphinoylethynyl)pyridine (**41**).



A solution of 2-ethynylpyridine (1.83 g, 17.8 mmol) in THF (30 ml) was cooled to -78 ^{o}C and ^{n}BuLi (11.1 ml, 1.6 M, 17.8 mmol) was added. The resulting solution was stirred for 30 min at this temperature. This was then allowed to warm to 0 ^{o}C and was stirred for a further 20 min at this temperature. The solution was then cooled to -78 ^{o}C and chlorodiphenylphosphine (3.28 ml, 17.8 mmol) added dropwise. The solution was allowed to warm to RT and stirred for 2.5 h at this temperature. This was then cooled to 0 ^{o}C and H_2O_2 (35 % aq solution, 8.10 ml, 28.5 mmol) added dropwise. The solution was allowed to warm to RT and was stirred for a further 30 min. H_2O (40 ml) was added and the product was extracted with Et_2O (3 x 30 ml). The combined organic extracts were dried ($MgSO_4$), filtered and solvent removed under reduced pressure. This was then purified by column chromatography, eluting with CH_2Cl_2/ methanol (92:8) to give the phosphine oxide **41**, as an off - white solid (4.17g, 86% yield).

^{31}P {H} NMR (202.5 MHz, CH_2Cl_2): δ = 9.4; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.59 (d, *J* = 4.8 Hz, 1 H, C_5H_4N), 7.90 - 7.84 (m, 4 H, C_6H_5 *o-H*), 7.66 (t, *J* = 7.7 Hz, 1H, C_5H_4N), 7.56 (d, *J* = 7.8 Hz, 1 H, C_5H_4N), 7.52 - 7.41 (m, 6 H, C_6H_5 m-*H*, C_6H_5 *p-H*), 7.31 - 7.28 (m, 1 H, C_5H_4N); **^{13}C {H} NMR** (100.5 MHz, $CDCl_3$) δ = 150.6 (C_5H_4N), 140.9 (d, *J* = 4.0 Hz, C_5H_4N *Q*), 136.5 (C_5H_4N), 132.6 (C_6H_5 *p-C*), 132.5 (d, *J* = 122 Hz, C_6H_5 *Q*), 131.2 (d, *J* = 11.2 Hz, C_6H_5 *o-C*), 128.9 (d, *J* = 13.5 Hz, C_6H_5 *m-C*), 128.8 (C_5H_4N), 124.9 (C_5H_4N), 103.0 (d, *J* = 28.1 Hz, *C*≡CP), 82.4 (d, *J* = 163 Hz, C≡*C*P); **mp** = 129 ^{o}C; **IR** (neat, cm^{-1}) 2187, 1193, 1121, 863, 725, 705, 690; **HRMS** (ESI^{+}) exact mass calculated for $C_{19}H_{15}NOP$ $[M+H]^{+}$ *m/z* = 304.0891, found *m/z* = 304.0887.

11-(Diphenylphosphinoyl)-12-(2-pyridyl)-9,10-dihydro-9,10-ethenoanthracene (**42**).



2-(Diphenylphosphinoylethynyl)pyridine, **41**, (6.28 g, 20.8 mmol) was mixed with anthracene (5.55 g, 31.1 mmol), heated to 220 ^{o}C and stirred at this temperature for 10 h. The resultant crude product was purified by column chromatography eluting first with CH_2Cl_2 to remove excess anthracene and then with CH_2Cl_2 / MeOH (98 : 2). The product was then recrystallised from a $CHCl_3$ solution layered with MeOH give the phosphine oxide **42**, as colourless crystals (6.70 g, 67 % yield).

^{31}P {H} NMR (202.5 MHz, CH_2Cl_2): δ = 26.7; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.45 – 8.44 (m, 1 H, C_5H_4N), 7.47 – 7.40 (m, 6 H, Ar-*H*), 7.38 (td, *J* = 7.4, 1.4 Hz, 2 H, Ar-*H*), 7.28 – 7.23 (m, 5H, Ar-*H*), 7.18 (td, *J* = 7.6, 1.8 Hz, 1 H, C_5H_4N), 7.05-6.95 (m, 6 H, Ar-*H*), 6.91 (ddd, *J* = 7.4, 4.9, 1.3 Hz, 1 H, C_5H_4N), 5.81 (d, *J* = 3.6 Hz, 1H, bridgehead *H*), 5.21 (d, *J* = 9.3 Hz, 1H, bridgehead *H*); **^{13}C {H} NMR** (100.5 MHz, $CDCl_3$) δ = 165.0 (d, *J* = 7.3 Hz, *C*=CP), 154.8 (d, *J* = 4.7 Hz, C_5H_4N *Q*), 144.9 (C_5H_4N), 144.7 (d, *J* = 1.9 Hz, C_6H_4 *Q*), 144.6 (d, *J* = 2.9 Hz, C_6H_4 *Q*), 138.8 (d, *J* = 100 Hz, C=*C*P), 135.2 (C_5H_4N), 132.5 (d, *J* = 106 Hz, C_6H_5 *Q*), 131.7 (d, *J* = 9.9 Hz, C_6H_5 *o*-*C*), 131.6 (d, *J* = 2.6 Hz, C_6H_5 *p*-*C*), 128.4 (d, *J* = 12.1 Hz, C_6H_5 *m*-*C*), 125.3 (C_5H_4N), 125.3 (C_6H_4), 125.1 (C_6H_4), 123.7 (C_6H_4), 123.7 (C_6H_4), 122.9 (C_5H_4N), 58.2 (d, *J* = 9.3 Hz, bridgehead *C*H), 54.2 (d, *J* = 10.9 Hz, bridgehead *C*H); **mp** = 222 – 223 ^{o}C (decomp); **IR** (neat, cm^{-1}) 1198, 753, 695, 631, 530; **HRMS** (ESI^{+}) exact mass calculated for $C_{33}H_{25}NOP$ $[M+H]^{+}$ *m/z* = 482.1674, found *m/z* = 482.1678.

6.2.2 General Procedure for reactions of KITPHOS monophosphines with potassium selenocyanate

A flame-dried Schlenk flask was charged with the phosphine and KSeCN (2 eq). These were then suspended in MeOH (2 ml) and heated at 50 ^{o}C for 20 h, unless otherwise stated.* The solvent was removed under reduced pressure to give white solids.

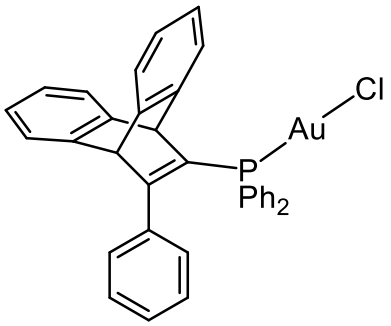
^{31}P {H} NMR (202.5 MHz, CH_2Cl_2): δ = **19**(Se), 32.8 (J_{PSe} = 723 Hz); **30**(Se), 27.8 (J_{PSe} = 701 Hz); **36**(Se), 32.7 (J_{PSe} = 727 Hz); **37**(Se), 29.5 (J_{PSe} = 721 Hz); **40**(Se), 44.8 (J_{PSe} = 737 Hz); **Ph_3P**(Se), 35.9 (J_{PSe} = 729.3 Hz). No reaction was observed with **31**.

** **30** was heated in diglyme at 162 ^{o}C for 20 h. **37** was stirred in MeOH at RT for 30 min.*

6.3 Experimental for chapter 3

6.3.1 Formation of gold(I) complexes of KITPHOS monophosphines

11-(Diphenylphosphino)-12-phenyl-9,10-dihydro-9,10-ethenoanthracene gold(I) chloride (**57**).

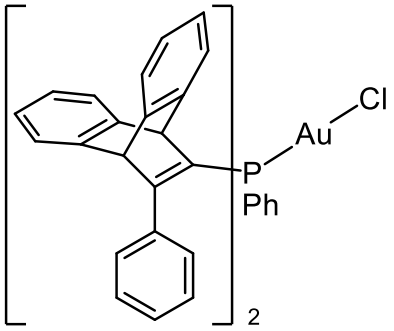


A solution of $AuCl_3$. $3H_2O$ (0.393 g, 1.00 mmol) in H_2O (3 ml) under nitrogen was cooled to 0 ^oC and 2,2'-thiodiethanol (0.300 ml, 3.00 mmol) was added over 45 min. 11-(Diphenylphosphino)-12-phenyl-9,10-dihydro-9,10-ethenoanthracene, **19** (0.465 g, 1.00 mmol) and EtOH (15 ml) were then added and the solution was stirred at RT for 3 h. The resulting precipitate was filtered and washed with MeOH (2 x 10 ml). The solid was then dissolved in CH_2Cl_2 (10 ml) filtered through fluted filter paper and the solvent removed under reduced pressure. The crude product was purified by recrystallisation from a $CHCl_3$ solution layered with MeOH to give the gold(I) chloride complex **57**, as white crystals (0.530 g, 85 %).

^{31}P {H} NMR (161.8 MHz, $CDCl_3$): δ = 23.3; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.55 (td, *J* = 7.2, 1.6 Hz, 2 H, C_6H_5), 7.45 – 7.31 (m, 13 H, Ar-*H*), 7.07 – 7.03 (m, 4 H, Ar-*H*), 6.99 (td, *J* = 7.5, 1.1 Hz, 2 H, C_6H_4), 6.88 (d, *J* = 7.2 Hz, 2 H, C_6H_4), 5.50 (d, *J* = 4.0 Hz, 1 H, bridgehead *H*), 4.95 (d, *J* = 7.9 Hz, 1H, bridgehead *H*); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ = 169.1 (d, *J* = 13.8 Hz, *C*CP), 144.3 (d, *J* = 1.3 Hz, C_6H_4 *Q*), 144.2 (d, *J* = 1.7 Hz, C_6H_4 *Q*), 137.4 (d, *J* = 7.2 Hz, C_6H_5 *Q*), 133.9 (d, *J* = 13.7 Hz, C_6H_5 *o-C*), 132.1 (d, *J* = 59.8 Hz, *C*P), 131.8 (C_6H_5 *p-C*), 129.8 (C_6H_5 *p-C*), 129.5 (d, *J* = 63.0 Hz C_6H_5 *Q*), 129.3 (d, *J* = 11.7 Hz C_6H_5 *m-C*), 128.8 (C_6H_5 *o-C*), 127.8 (C_6H_5 *m-C*), 125.6 (C_6H_4), 125.4 (C_6H_4), 123.6 (C_6H_4), 123.3 (C_6H_4), 60.9 (d, *J* = 8.3 Hz,

bridgehead *C*H), 54.8 (d, *J* = 5.1 Hz, bridgehead *C*H); **mp** = >350 ºC; **IR** (neat, cm^{-1}) 1436, 1105, 750, 741, 698, 687, 536; **HRMS** (ESI^+) exact mass calculated for $C_{34}H_{25}PClAuNa$ $[M+Na]^+$ *m/z* = 719.0946, found *m/z* = 719.0981. This is consistent with data reported in the literature.[58]

11-[Bis(12-phenyl-9,10-dihydro-9,10-etheno-anthracene)]phenylphosphine gold(I) chloride (**60**).

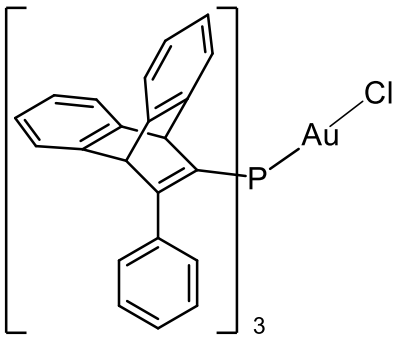


A solution of $AuCl_3$. $3H_2O$ (0.295 g, 0.75 mmol) in H_2O (3 ml) under nitrogen was cooled to 0 ºC and 2,2'-thiodiethanol (0.225 ml, 2.25 mmol) was added over 45 min. 11-[Bis(12-phenyl-9,10-dihydro-9,10-etheno-anthracene)]phenylphosphine, **30** (0.500 g, 0.75 mmol) and EtOH (15 ml) were then added and the solution stirred at RT for 3 h. The resulting precipitate was filtered and washed with MeOH (2 x 10 ml). The solid was then dissolved in CH_2Cl_2 (10 ml), filtered through fluted filter paper and the solvent removed under reduced pressure. The crude product was purified by recrystallisation from a $CHCl_3$ solution layered with MeOH to give the gold(I) chloride complex **60**, as colourless crystals (0.557 g, 83 %).

^{31}P {H} NMR (161.8 MHz, $CDCl_3$): δ = 12.4; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.64 (t, *J* = 7.0 Hz, 1 H, Ar-*H*), 7.52 – 7.41 (m, 6 H, Ar-*H*), 7.29 – 7.07 (m, 17 H, Ar-*H*), 6.90 (t, *J* = 7.3 Hz, 2 H, C_6H_4), 6.61 (br d, *J* = 7.0 Hz, 4 H, Ar-*H*), 6.39 (br s, 1 H, Ar-*H*), 5.50 (d, *J* = 4.1 Hz, 2 H, bridgehead *H*), 5.14 (d, *J* = 7.1 Hz, 2 H, bridgehead *H*); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ = 168.1 (d, *J* = 16.0 Hz, *C*CP), 144.6 (d, *J* = 1.5 Hz, C_6H_4 *Q*), 144.6 (C_6H_4 *Q*), 144.4 (d, *J* = 1.2 Hz, C_6H_4 *Q*), 144.4 (d, *J* = 1.1 Hz, C_6H_4*Q*), 137.4 (d, *J* = 7.6 Hz, C_6H_5 *Q*), 133.6 (d, *J* = 44.2 Hz, *C*P), 133.3 (d, *J* = 13.6

Hz, C_6H_5 *o-C*), 131.5 (d, *J* = 1.5 Hz, C_6H_5 *p-C*), 131.4 (d, *J* = 64.2 Hz, C_6H_5 *Q*), 129.6 (C_6H_5 *p-C*), 129.5 (d, *J* = 11.5 Hz, C_6H_5 *m-C*), 128.5 (C_6H_5 *o-C*), 127.3 (C_6H_5 *m-C*), 125.7 (C_6H_4), 125.6 (2 x C_6H_4), 125.5 (C_6H_4), 123.8 (C_6H_4), 123.8 (C_6H_4), 123.7 (C_6H_4), 123.4 (C_6H_4), 60.6 (d, *J* = 8.4 Hz, bridgehead *C*H), 55.4 (d, *J* = 2.6 Hz, bridgehead *C*H); **mp** = >350 ºC; **IR** (neat, cm^{-1}) 1457, 1438, 1157, 747, 698, 629; **HRMS** (ESI^+) exact mass calculated for $C_{50}H_{35}PClAuNa$ $[M+Na]^+$ *m/z* = 921.1648, found *m/z* = 921.1723.

11-[Tris(12-phenyl-9,10-dihydro-9,10-etheno-anthracene)]phenylphosphine gold(I) chloride (**61**).

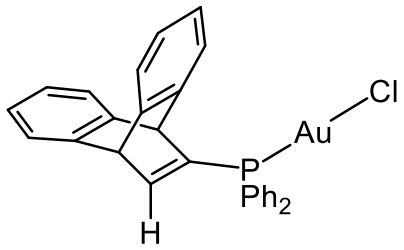


A solution of $AuCl_3$. $3H_2O$ (0.125 g, 345 µmol in H_2O (2 ml) under nitrogen was cooled to 0 ºC and 2,2'-thiodiethanol (0.104 ml, 345 µmol) was added over 45 min. 11-[Tris(12-phenyl-9,10-dihydro-9,10-etheno-anthracen-11-yl)]phosphine **31** (0.300 g, 345 µmol) and EtOH (6 ml) were then added and the solution was stirred at RT for 3 h. The resulting precipitate was filtered and washed with MeOH (2 x 10 ml). The solid was then dissolved in CH_2Cl_2 (10 ml) filtered through fluted filter paper and the solvent removed under reduced pressure. The crude product was purified by recrystallisation from a $CHCl_3$ solution layered with MeOH to give the gold(I) chloride complex **61**, as colourless crystals (0.246 g, 65 %).

^{31}P {H} NMR (161.8 MHz, $CDCl_3$): δ = 5.6; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.17 (d, *J* = 7.1 Hz, 3 H, C_6H_4), 7.50 (dd, *J* = 7.0, 4.4 Hz, 6 H, C_6H_4), 7.41 (td, *J* = 7.5, 0.9 Hz, 3 H, C_6H_4), 7.28 (t, *J* = 7.6 Hz, 3 H, C_6H_4), 7.06 (t, *J* = 7.5 Hz, 3 H, C_6H_5 *p-H*), 6.99 (td, *J* = 8.4, 7.4, 0.9 Hz, 3 H, C_6H_4), 6.80 (t, *J* = 7.8 Hz, 6 H, C_6H_5 *m-H*), 6.66 (d, *J*

= 7.5 Hz, 3 H, C_6H_4), 6.16 (br d, *J* = 7.1 Hz, 6 H, C_6H_5 *o-H*), 5.75 (d, *J* = 6.6 Hz, 3 H, bridgehead *H*), 5.50 (d, *J* = 4.2 Hz, 3 H, bridgehead *H*), 5.44 (d, *J* = 7.2 Hz, 3 H, C_6H_4); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ = 167.0 (d, *J* = 17.4 Hz, *C*CP), 145.3 (d, *J* = 1.6 Hz, C_6H_4 *Q*), 144.8 (d, *J* = 2.4 Hz, C_6H_4 *Q*), 144.5 (C_6H_4 *Q*), 144.0 (C_6H_4 *Q*), 137.0 (d, *J* = 7.9 Hz, *C*P), 135.3 (d, *J* = 59.4 Hz, C_6H_5 *Q*), 129.5 (C_6H_5 *p-C*), 128.1 (C_6H_5 *o-C*), 127.3 (C_6H_5 *m-C*), 126.0 (C_6H_4), 125.9 (C_6H_4), 125.5 (C_6H_4), 125.5 (C_6H_4), 124.6 (C_6H_4), 124.1 (C_6H_4), 123.2 (C_6H_4), 123.0 (C_6H_4), 60.6 (d, *J* = 8.5 Hz, bridgehead *C*H), 56.5 (s, bridgehead *C*H); **mp** = >350 °C (decomposition); **IR** (neat, cm^{-1}) 1457, 762, 747, 694, 630, 607, 527; **HRMS** (ESI^+) exact mass calculated for $C_{66}H_{45}PClAuNa$ $[M+Na]^+$ *m/z* = 1123.2511, found *m/z* = 1123.2505.

[11-(Diphenylphosphino)-9,10-dihydro-9,10-ethenoanthracene] gold(I) chloride (**62**).

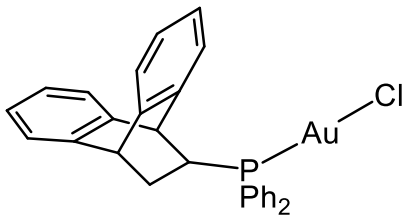


A solution of $AuCl_3$. $3H_2O$ (0.394 g, 1.00 mmol) in H_2O (3 ml) under nitrogen was cooled to 0 °C and 2,2'-thiodiethanol (0.300 ml, 1.00 µmol) was added over 45 min. 11-(Diphenylphosphino)-9,10-dihydro-9,10-ethenoanthracene **36** (0.390 g, 1.00 µmol) and EtOH (20 ml) were then added and the solution was stirred at RT for 3 h. The resulting precipitate was filtered and washed with MeOH (2 x 10 ml). The solid was then dissolved in CH_2Cl_2 (10 ml), filtered through fluted filter paper and the solvent removed under reduced pressure. The crude product was purified by recrystallisation from a $CHCl_3$ solution layered with MeOH to give the gold(I) chloride complex **62**, as white crystals (0.384 g, 62 %).

^{31}P {H} NMR (202.5 MHz, $CDCl_3$): δ = 29.5; **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.54 – 7.49 (m, 2 H, C_6H_5 *p-H*), 7.40 – 7.37 (m, 8 H, C_6H_5 *o-H*, *m-H*), 7.30 – 7.28 (m, 2

H, C_6H_4), 7.17 – 7.11 (m, 3 H, 2 x C_6H_4, PCC*H*), 7.03 – 6.96 (m, 4 H, C_6H_4), 5.27 (dd, *J* = 6.0, 2.4 Hz, 1 H, bridgehead *H*), 5.17 (dd, *J* = 10.0, 1.7 Hz, 1 H, bridgehead *H*); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ = 154.7 (d, *J* = 9.7 Hz, PC*C*H), 144.4 (C_6H_4 *Q*), 144.3 (C_6H_4 *Q*), 141.7 (d, *J* = 59.6 Hz, *C*P), 134.3 (d, *J* = 14.1 Hz, C_6H_5 *o*-*C*), 132.3 (d, *J* = 1.8 Hz, C_6H_5 *p*-*C*), 129.3 (d, *J* = 12.2 Hz, C_6H_5 *m*-*C*), 127.2 (d, *J* = 64.1 Hz, C_6H_5 *Q*), 125.4 (C_6H_4), 125.4 (C_6H_4), 123.8 (C_6H_4), 123.5 (C_6H_4), 54.3 (d, *J* = 13.3 Hz, bridgehead *C*H), 52.7 (d, *J* = 10.2 Hz, bridgehead *C*H); **mp** = 221 – 222 °C; **IR** (neat, cm^{-1}) 1458, 1434, 1101, 1018, 745, 691, 637; **HRMS** (ESI^+) exact mass calculated for $C_{28}H_{22}PClAuNa$ $[M+H]^+$ *m/z* = 621.0813, found *m/z* = 621.0794.

[11-(Diphenylphosphino)-2,12-dihydro-9,10-dihydro-9,10-ethanoanthracene] gold(I) chloride (**63**).



A solution of $AuCl_3$. $3H_2O$ (0.393 g, 1.00 mmol) in H_2O (3 ml) under nitrogen was cooled to 0 °C and 2,2'-thiodiethanol (0.300 ml, 1.00 µmol) was added over 45 min. 11-(Diphenylphosphino)-9,10-dihydro-9,10-ethanoanthracene **40** (0.392 g, 1.00 µmol) and EtOH (20 ml) were then added and the solution was stirred at RT for 3 h. The resulting precipitate was filtered and washed with MeOH (2 x 10 ml). The solid was then dissolved in CH_2Cl_2 (10 ml), filtered through fluted filter paper and the solvent removed under reduced pressure. The crude product was purified by recrystallisation from a $CHCl_3$ solution layered with MeOH to give the gold(I) chloride complex **63**, as white crystals (0.595 g, 95 %).

^{31}P {H} NMR (202.5 MHz, $CDCl_3$): δ = 42.2; **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.88 – 7.83 (m, 2 H, C_6H_5), 7.65 – 7.57 (m, 5 H, C_6H_5), 7.44 – 7.40 (m, 1 H, C_6H_5), 7.37 – 7.25 (m, 6 H, C_6H_5, C_6H_4), 7.20 – 7.09 (m, 4 H, C_6H_4), 4.40 (br t, *J* = 2.4 Hz, 1 H,

bridgehead *H*), 4.09 (dd, *J* = 5.5, 1.2 Hz, 1 H, bridgehead *H*), 3.14 – 3.07 (m, 1 H, PC*H*CH_2), 2.08 (dtd, *J* = 12.5, 9.8, 2.8 Hz, 1 H, PCHC*H*$_2$), 1.92 (dddd, *J* = 24.2, 12.7, 5.6, 2.4 Hz, 1 H, PCHC*H*$_2$); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ = 143.3 (C_6H_4 *Q*), 143.2 (d, *J* = 39.3 Hz, C_6H_5 *Q*), 143.2 (C_6H_4 *Q*), 138.9 (C_6H_4 *Q*), 138.9 (C_6H_4 *Q*), 134.2 (d, *J* = 13.5 Hz, C_6H_5 *o-C*), 133.8 (d, *J* = 13.0 Hz, C_6H_5 *o-C*), 132.4 (d, *J* = 1.8 Hz, C_6H_5 *p*-C), 131.9 (d, *J* = 1.8 Hz, C_6H_5 *p*-C), 129.6 (d, *J* = 11.5 Hz, C_6H_5 *m-C*), 129.1 (d, *J* = 11.2 Hz, C_6H_5 *m-C*), 127.5 (C_6H_4), 127.2 (C_6H_4), 126.7 (C_6H_4), 126.2 (C_6H_4), 126.0 (C_6H_4), 124.1 (C_6H_4), 124.1 (C_6H_4), 123.2 (C_6H_4), 44.5 (d, *J* = 4.0 Hz, bridgehead *C*H), 43.8 (d, *J* = 3.5 Hz, bridgehead *C*H), 36.9 (d, *J* = 39.4 Hz, P*C*HCH_2), 32.4 (d, *J* = 7.2 Hz, PCH*C*H_2); **mp** = 275 ^{o}C; **IR** (neat, cm^{-1}) 1458, 1435, 1100, 749, 690, 564, 527; **HRMS** (ESI^+) exact mass calculated for $C_{28}H_{23}PClAuNa$ $[M+Na]^+$ *m/z* = 645.0789, found *m/z* = 645.0791.

6.3.2 Other catalysts

Triphenylphosphinegold(I) chloride.

A solution of PPh_3 (0.3378, 1.29 mmol) in EtOAc (10 ml) was added dropwise to a solution of $AuCl_3$. $3H_2O$ (0.233g, 0.64 mmol) in EtOAc (30 ml) at 0 ^{o}C and the resulting mixture was stirred for 3 h at this temperature. The mixture was allowed to warm to RT and then filtered, washing with EtOAc (3 x 15 ml). The crude product was purified by recrystallisation from a $CHCl_3$ solution layered with n - hexane to give **Ph_3PAuCl**, as colourless crystals (0.236 g, 74 %).

^{31}P {H} NMR (161.8 MHz, $CDCl_3$): δ = 33.8; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.55-7.47 (m, 15 H, Ar-*H*); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$): δ = 134.2 (d, *J* = 15.2 Hz), 132.1, 129.3 (d, *J* = 11.9 Hz), 128.7 (d, *J* = 62.6 Hz); **IR** (neat, cm^{-1}) 1433, 1102, 747, 712, 690, 543; **HRMS** (ESI^+) exact mass calculated for $C_{18}H_{15}PClAuNa$ $[M+Na]^+$ *m/z* = 517.0163, found *m/z* = 517.0151. This is consistent with data reported in the literature.[191]

Triphenylarsinegold(I) chloride.

A solution of $AuCl_3$. $3H_2O$ (0.200 g, 589 µmol) in H_2O (3 ml) under nitrogen was cooled to 0 ^oC and 2,2'-thiodiethanol (0.177 ml, 1.77 µmol) was added over 45 min. A solution of $AsPh_3$ (0.180 g, 589 µmol) in EtOH (5 ml) was then added and the solution was stirred at RT for 3 h. The resulting precipitate was filtered and washed with MeOH (2 x 10 ml). The solid was then dissolved in CH_2Cl_2, filtered through fluted filter paper and the solvent removed. The crude product was purified by recrystallisation from a $CHCl_3$ solution layered with MeOH to give $Ph_3AsAuCl$, as colourless needle - like crystals (0.206 g, 65 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.55 – 7.46 (m, 15 H, Ar-*H*); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ = 133.4, 131.7, 131.0, 129.8; **IR** (neat, cm^{-1}) 1481, 1435, 1080, 1024, 999, 738, 689; **mp** = 209 – 210 ^oC; **HRMS** (ESI^+) exact mass calculated for $C_{18}H_{15}ClAsAu$ $[M+Na]^+$ requires *m/z* = 560.9642 $gmol^{-1}$, found *m/z* = 560.9630 $gmol^{-1}$. This is consistent with data reported in the literature.[192]

Synthesis of [(rac-BINAP)PdCl$_2$].

$PdCl_2$ (0.182 g, 1.03 mmol) was dissolved by warming in conc. HCl (5 ml). This solution was then cooled to RT and diluted with EtOH (15 ml), filtered and washed with EtOH (2 x 10 ml). 1,5-Cyclooctadiene (0.111 ml, 1.03 mmol) was then added to the filtrate and solution was stirred at RT for 10 min. The suspension was filtered and the yellow precipitate washed with Et_2O (3 x 10 ml). This precipitate was then dissolved in CH_2Cl_2 (20 ml), *rac*-BINAP* (0.641 g, 1.03 mmol) added and the solution was stirred at RT for 10 min. Petrol (10 ml) was then added and the suspension was filtered, washing with Et_2O (2 x 10 ml). The crude product was then purified by recrystallisation from a $CHCl_3$ solution layered with n-hexane to give the BINAP complex, as yellow crystals (0.72 g, 87 % yield).

^{31}P {H} NMR (161.8 MHz, $CDCl_3$): δ = 29.2; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.86 – 7.81 (m, 4 H, Ar-*H*), 7.72 – 7.62 (br s, 4 H, Ar-*H*), 7.58 (d, *J* = 8.1 Hz, 2H, Ar-*H*), 7.51 (dd, *J* = 9.0, 1.4 Hz, 2H, Ar-*H*), 7.48 – 7.39 (m, 8 H, Ar-*H*), 7.31 (dd, *J* = 9.8, 8.9 Hz, 2H, Ar-*H*), 7.14 (ddd, *J* = 8.3, 6.8, 1.2 Hz, 2H, Ar-*H*), 6.90 – 6.85 (d, *J* = 8.6 Hz, 2H, Ar-*H*), 6.77 (d, *J* = 8.6 Hz, Ar-*H*), 6.72 – 6.67 (m, 4H, Ar-*H*). This is consistent with data reported in the literature.[183a, 193]

***** *The synthesis of [$PdCl_2$(S-BINAP)] was identical to that of [$PdCl_2$(rac-BINAP)] except S-BINAP was used instead of rac-BINAP.*

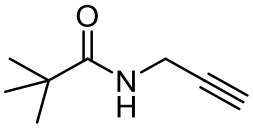
Synthesis of $PdCl_2(PPh_3)_2$.

$PdCl_2$ (0.364 g, 2.06 mmol) was dissolved by warming in conc. HCl (10 ml). This solution was then cooled to RT and diluted with EtOH (30 ml), filtered and washed with EtOH (2 x 20 ml). 1,5-Cyclooctadiene (0.252 ml, 2.06 mmol) was then added to the filtrate and solution was stirred at RT for 10 min. The suspension was filtered and the yellow precipitate washed with Et_2O (3 x 10 ml). This precipitate was then dissolved in CH_2Cl_2 (20 ml), PPh_3 (1.08 g, 4.12 mmol) added and the solution was stirred at RT for 10 min. Petrol (10 ml) was then added and the suspension was filtered, washing with Et_2O (2 x 20 ml). The crude product was then recrystallized from hot $CHCl_3$, the resulting golden yellow crystals were filtered and washed with Et_2O (2 x 10 ml) to give the phosphine complex (1.39 g, 96 % yield).

^{31}P {H} NMR (161.8 MHz, $CDCl_3$): δ = 23.9; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.73 – 7.68 (m, 12 H, C_6H_5 *o-H*), 7.46 – 7.42 (m, 6 H, C_6H_5 *p-H*), 7.40 – 7.36 (m, 12 H, C_6H_5 *m-H*); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$): δ = 135.2 (t, *J* = 6.2 Hz), 130.7, 129.7 (t, *J* = 24.8 Hz), 128.2 (t, *J* = 5.2 Hz). This is consistent with data reported in the literature.[183a, 193]

6.3.3 Syntheses of propargyl amides

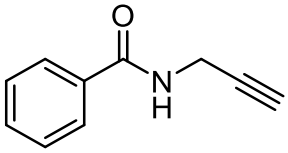
2,2-Dimethyl-N-prop-2-ynylpropionamide.



A flask was charged with propargyl ammonium chloride (1.01 g, 11.0 mmol), DMAP (0.140 g, 1.10 mmol), CH_2Cl_2 (60 ml) and cooled to 0 °C. NEt_3 (4.25 ml, 30.5 mmol) and 2,2-dimethylpropionyl chloride (1.34 g, 10.9 mmol) were then added and the reaction was stirred at RT for 1.5 h. HCl (1.0 M, 100 ml, 0.10 mol) was then added slowly and the solution was extracted with $CHCl_3$ (2 x 50 ml). The combined organic extracts were combined, washed with brine (100 ml), dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The crude product was purified by column chromatography, eluting with petrol / EtOAc (3 : 1) to give the amide, as a white solid (1.47 g, 97 % yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.83 (br s, 1 H, N*H*), 4.03 (dd , *J* = 5.1, 2.4 Hz, 2 H, CH_2), 2.22 (t, *J* = 2.7 Hz, 1 H, C≡C*H*), 1.20 (s, 9 H, CH_3); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ = 178.2, 79.9, 71.9, 38.8, 29.5, 27.6. This is consistent with data reported in the literature.[194]

N-prop-2-ynylbenzamide.

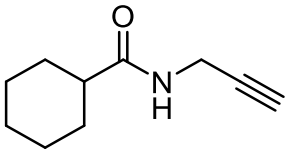


A flask was charged with propargyl ammonium chloride (1.02 g, 11.1 mmol), DMAP (0.140 g, 1.10 mmol), CH_2Cl_2 (60 ml) and cooled to 0 °C. NEt_3 (4.33 ml, 31.1 mmol) and benzoyl chloride (1.29 g, 11.1 mmol) were then added and the reaction was

stirred at RT for 1.5 h. HCl (1.0 M, 100 ml, 0.10 mol) was then added slowly and the solution was extracted with $CHCl_3$ (2 x 50 ml). The combined organic extracts were combined, washed with brine (100 ml), dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The crude product was purified by column chromatography, eluting with petrol / EtOAc (3 : 1) to give the amide, as a white solid (1.62 g, 92 % yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.80 – 7.77 (m, 2 H, C_6H_5 *o-C*), 7.52 – 7.49 (m, 1 H, C_6H_5 *p-C*), 7.44 – 7.41 (m, 2 H, C_6H_5 *m-C*), 6.50 (br s, N*H*), 4.25 (dd, *J* = 5.2, 2.6 Hz, 2 H, CH_2), 2.27 (t, *J* = 2.6 Hz, 1 H, C≡C*H*); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ = 167.2, 133.8, 131.9, 128.7, 127.2, 79.6, 72.0, 29.9. This is consistent with data reported in the literature.[194]

N-prop-2-ynylcyclohexane carboxamide.

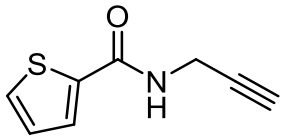


A flask was charged with propargyl ammonium chloride (1.00 g, 10.9 mmol), DMAP (0.140 g, 1.10 mmol), CH_2Cl_2 (60 ml) and cooled to 0 ^{o}C. NEt_3 (4.25 ml, 30.5mmol) and cyclohexane carbonyl chloride (2.23 g, 16.7 mmol) were then added and the reaction was stirred at RT for 1.5 h. HCl (1.0 M, 100 ml, 0.10 mol) was then added slowly and the solution was extracted with $CHCl_3$ (2 x 50 ml). The combined organic extracts were combined, washed with brine (100 ml), dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The crude product was purified by column chromatography, eluting with petrol / EtOAc (3 : 1) to give the amide, as a white solid (2.12 g, 81 % yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.75 (br s, 1 H, N*H*), 4.03 (dd , *J* = 5.2, 2.5 Hz, 2 H, CH_2), 2.21 (t, *J* = 2.5 Hz, 1 H, C≡C*H*), 2.09 (tt, *J* = 11.8, 3.5 Hz, 1 H, Cy-*H*), 1.87 – 1.76 (m, 4 H, Cy-*H*), 1.67 – 1.64 (m, 1 H, Cy-*H*), 1.47 – 1.37 (m, 2 H, Cy-*H*), 1.31 – 1.17 (m, 3 H, Cy-*H*); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ = 175.8, 79.9, 71.9, 45.3,

29.6, 29.2, 25.8. This is consistent with data reported in the literature.[58]

N-prop-2-ynylthiophene 2-carboxamide.



A flask was charged with propargyl ammonium chloride (1.00 g, 10.9 mmol), DMAP (0.140 g, 1.10 mmol), CH_2Cl_2 (60 ml) and cooled to 0 ^oC. NEt_3 (4.25 ml, 30.5 mmol) and thiophenylcarbonyl chloride (1.20 g, 11.2 mmol) were then added and the reaction was stirred at RT for 1.5 h. HCl (1.0 M, 100 ml, 0.10 mol) was then added slowly and the solution was extracted with $CHCl_3$ (2 x 50 ml). The combined organic extracts were combined, washed with brine (100 ml), dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The crude product was purified by column chromatography, eluting with petrol / EtOAc (3 : 1) to give the amide, as a white solid (1.27 g, 71 % yield).

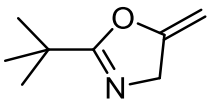
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.59 (dd, *J* = 3.7, 1.1 Hz, 1 H, C_4H_3S), 7.48 (dd, *J* = 5.0, 1.0 Hz, 1 H, C_4H_3S), 7.06 (dd, *J* = 4.9, 3.8 Hz, 1 H, C_4H_3S), 6.67 (br s, 1 H, N*H*), 4.22 (dd, *J* = 5.3, 2.6 Hz, 2 H, CH_2), 2.26 (t, *J* = 2.5 Hz, 1 H, C≡C*H*); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ = 161.8, 138.2, 130.6, 128.7, 127.8, 79.5, 71.9, 29.7. This is consistent with data reported in the literature.[109a]

6.3.4 General procedure for Gold-catalysed reaction to form methylene oxazolines.

A flame dried Schlenk flask was charged with the gold(I) chloride phosphine complex (10 μmol; **57** (7.0 mg), **60** (9.0 mg), **61** (11.0 mg), **62** (6.2 mg), **63** (6.2 mg), **(Ph_3P)AuCl** (4.9 mg)) and AgOTf (2.6 mg, 10 μmol). CH_2Cl_2 (2 ml) was then added

and the solution was stirred for 0.5 h to generate the active catalyst *in situ*. The propargyl amide (500 μmol) was then added and the reaction was stirred at RT for the specified amount of time. 1,3-dinitrobenzene (84 mg, 500 μmol) was then added as an internal standard and the resulting mixture was passed through a short silica plug, flushing with EtOAc. The solvent was then removed under reduced pressure and the conversion measured by ^{1}H NMR spectroscopy, through the integration of the methylene protons of the product and those of the starting material.

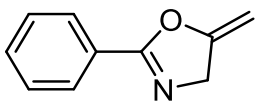
2-tert-Butyl-5-methylene-4,5-dihydrooxazole.



Following the procedure above, this reaction was performed using 2,2-dimethyl-*N*-prop-2-ynylpropionamide (70.0 mg, 500 μmol). The product was a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.59 (q, *J* = 2.9 Hz, 1 H, C=C*H*$_2$), 4.35 (t, *J* = 2.8 Hz, 2 H, NC*H*$_2$), 4.18 (q, *J* = 2.6 Hz, 1 H, C=C*H*$_2$), 1.20 (s, 9 H, C*H*$_3$); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ = 173.8, 159.5, 82.8, 57.3, 33.4, 27.4; **LRMS** (EI^+) m/z 140 $[M+H]^+$. This is consistent with data reported in the literature.[58]

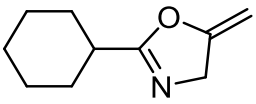
5-Methylene-2-phenyl-4,5-dihydrooxazole.



Following the procedure above, this reaction was performed using *N*-prop-2-ynylbenzamide (79.6 mg, 500 μmol). The product was a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.98 – 7.96 (m, 2 H, C_6H_5 *o-C*), 7.62 – 7.48 (m, 1 H, C_6H_5 *p-C*), 7.44 – 7.40 (m, 2 H, C_6H_5 *m-C*), 4.81 (q, *J* = 2.9 Hz, 1 H, C=CH_2), 4.64 (t, *J* = 2.8 Hz, 2 H, NCH_2), 4.35 (q, *J* = 2.7 Hz, 1 H, C=CH_2); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ = 163.8, 158.9, 131.9, 128.6, 128.1, 126.8, 83.9, 57.8; **LRMS** (EI^+) m/z 160 $[M+H]^+$. This is consistent with data reported in the literature.[58]

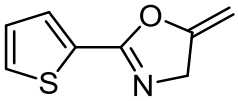
2-Cyclohexyl-5-methylene-4,5-dihydrooxazole.



Following the procedure above, this reaction was performed using *N*-prop-2-ynyl-cyclohexane carboxamide (82.1 mg, 500 μmol). The product was a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.60 (q, *J* = 2.9 Hz, 1 H, C=CH_2), 4.37 – 4.35 (m, 2 H, NCH_2), 4.20 (q, *J* = 2.6 Hz, 1 H, C=CH_2), 2.36 – 2.28 (m, 1 H, Cy-*H*), 1.95 – 1.91 (m, 2 H, Cy-*H*), 1.78 – 1.74 (m, 2 H, Cy-*H*), 1.64 – 1.61 (m, 1 H, Cy-*H*), 1.47 – 1.37 (m, 2 H, Cy-*H*), 1.32 – 1.18 (m, 3 H, Cy-*H*); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ = 170.7, 159.2, 82.8, 57.2, 37.4, 29.4, 25.8, 25.6; **LRMS** (EI^+) m/z 165 $[M]^+$. This is consistent with data reported in the literature.[58]

5-Methylene-2-(thiophen-2-yl)-4,5-dihydrooxazole.



Following the procedure above, this reaction was performed using *N*-prop-2-ynyl-thiophene 2-carboxamide (83.0 mg, 500 μmol). The product was a yellow oil.

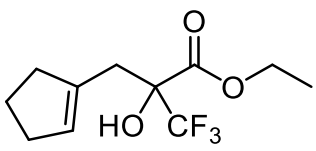
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.64 (dd, *J* = 3.8, 1.1 Hz, 1 H, C_4H_3S), 7.48 (dd, *J* = 5.0, 1.2 Hz, 1 H, C_4H_3S), 7.08 (dd, *J* = 5.0, 3.7 Hz, 1 H, C_4H_3S), 4.79 (q, *J* = 2.9 Hz, 1 H, C=CH_2), 4.59 (t, *J* = 2.8 Hz, 2 H, N-CH_2), 4.34 (q, *J* = 2.7 Hz, 1 H, C=CH_2); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ = 159.7, 158.5, 147.3, 130.9, 130.6, 127.8, 84.2, 57.6; **LRMS** (EI^+) m/z = 165 $[M]^+$. This is consistent with data reported in the literature.[58]

6.3.5 General procedure for the carbonyl-ene reaction on the methylene cyclopentane

A flame dried Schlenk flask was charged with $PdCl_2$(BINAP) (20 mg, 25 μmol) and $AgSbF_6$ (13.7 mg, 50 μmol).* CH_2Cl_2 (2 ml) was added and the solution was stirred for 0.5 h to generate the active catalyst *in situ*. Methylene cyclopentane (53 μL, 500 μmol) was added, followed by the pyruvate (750 μmol) and the reaction was then stirred at RT for the specified time. Decane (97 μL, 500 μmol) was then added as an internal standard and the reaction passed through a short silica plug, flushing with EtOAc. The solvent was then removed under reduced pressure. The conversion and enantioselectivity were measured by GC.

* *$Cu(OTf)_2$ (18 mg, 50 μmol) with BOX (2,2'-isopropylene bis[(4S)-4-tert-butyl-2-oxazoline]) (15 mg, 50 μmol) was also used.*

Ethyl 3-(cyclopenten-1'-yl)-2-(trifluoromethyl)-2-hydroxypropanoate

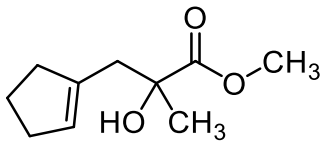


Following the carbonyl-ene procedure described above, this reaction was

performed using ethyl 3,3,3-trifluoropyruvate (99 μL, 750 μmol) as the pyruvate. The product was a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.53 (br s, 1 H, Cyp C*H*), 4.37 – 4.29 (m, 2 H, OCH_2), 3.81 (s, 1 H, O*H*), 2.86 (d, *J* = 14.3 Hz, 1 H, CH_2), 2.67 (d, *J* = 14.3 Hz, 1 H, CH_2), 2.37 – 2.16 (m, 4 H, Cyp CH_2), 1.82 (p, *J* = 7.6 Hz, 2 H, Cyp CH_2), 1.33 (t, *J* = 7.1 Hz, 3 H, CH_3); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ = 169.8, 136.6, 130.2, 123.5 (q, *J* = 287 Hz), 77.9 (d, *J* = 28.6 Hz), 63.8, 36.1, 33.2, 32.6, 23.7, 14.1. Supelco Beta DEX column (injection temp 135 °C; column conditions 100 °C for 45 min ramp to 170 °C at 5°C / min; hold 10 min, pressure 21 psi) major (2*S*)-enantiomer *t*R) 26.8 min, (2*R*)-minor enantiomer *t*R) 24.6 min. This is consistent with data reported in the literature.[121a]

Ethyl 3-(cyclopenten-1'-yl)-2-(trifluoromethyl)-2-hydroxypropanoate.



Following the carbonyl-ene procedure described above, this reaction was performed using methyl pyruvate (77 μL, 750 μmol) as the pyruvate. The product was a yellow oil.

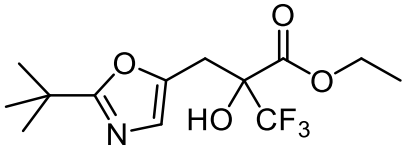
^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.46 (s, 1 H, Cyp C*H*), 3.11 (br s, 1 H, O*H*), 3.74 (s, 3 H, OCH_3), 2.59 (d, *J* = 13.9 Hz, 1 H, CH_2), 2.46 (d, *J* = 13.9 Hz, 1 H, CH_2), 2.29 – 2.17 (m, 4 H, Cyp CH_2), 1.84 – 1.79 (m, 2 H, Cyp CH_2), 1.41 (s, 3 H, CH_3); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ = 177.5, 140.2, 128.9, 74.8, 53.0, 42.1, 36.1, 32.8, 26.5, 24.0. This is consistent with data reported in the literature.[195]

6.3.6 General procedure for the tandom carbonyl-ene reaction on the methylene oxazolines

A flame dried Schlenk flask was charged with the gold(I) chloride KITPHOS complex (7.0 mg, 10 μmol) and silver triflate (2.6 mg, 10 μmol). CH_2Cl_2 (2 ml) was added and the solution was stirred for 0.5 h to generate the active catalyst *in situ*. The propargyl amide (500 μmol) was then added and the reaction was stirred at RT for the specified time. The resulting mixture was passed through a short silica plug, flushing with EtOAc. The solvent was then removed under reduced pressure to obtain the corresponding methylene oxazoline. Meanwhile another flame dried Schlenk flask was charged with $PdCl_2$(BINAP) (20 mg, 25 μmol) and $AgSbF_6$ (13.7 mg, 50 μmol).* CH_2Cl_2 (2 ml) was added and the solution was stirred for 0.5 h to generate the active catalyst *in situ*. The methylene oxazoline was then added, followed by ethyl 3,3,3-trifluoropyruvate (99 μL, 750 μmol), and the reaction was stirred at RT for the specified time. Decane (97 μL, 500 μmol) was added as an internal standard, the reaction passed through a short silica plug, flushing with EtOAc, and the solvent was removed under reduced pressure. The conversion was measured by GC (ratio of P / SM). The selectivity (ee) of the reaction was also measured by GC.

* *$Cu(OTf)_2$ (18 mg, 50 μmol) with BOX (2,2'-isopropylene bis[(4S)-4-tert-butyl-2-oxazoline]) (15 mg, 50 μmol) was also used.*

Ethyl 3-{2-tert-butyloxazol-5-yl}-2-(trifluoromethyl)-2-hydroxypropanoate.

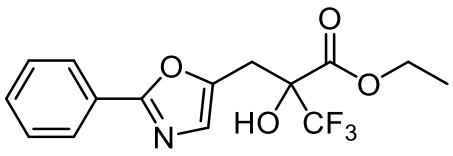


Following the procedure above, this reaction was performed using 2,2-dimethyl-*N*-prop-2-ynylpropionamide (70.0 mg, 500 μmol). The product was an off-white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.78 (s, 1 H, C_3HNO-*H*), 4.45 – 4.30 (m, 2 H,

OC*H*$_2$CH$_3$), 3.93 (br s, 1 H, O*H*), 3.42 (d, *J* = 15.2 Hz, 1 H, C*H*$_2$) , 3.23 (d, *J* = 15.6 Hz, 1 H, C*H*$_2$), 1.36 (t, *J* = 7.2 Hz, 3 H, OCH$_2$C*H*$_3$), 1.33 (s, 9 H, C(C*H*$_3$)$_3$); **^{13}C {^{1}H} NMR** (100.5 MHz, CDCl$_3$) δ = 168.5 (*C*O), 167.2 (C$_3$HNO *Q*), 145.3 (C$_3$HNO *Q*), 125.8 (C$_3$HNO), 121.4 (q, *J* = 287 Hz, *C*F$_3$), 76.5 (q, *J* = 29.8 Hz, *C*CF$_3$), 64.5 (O*C*H$_2$CH$_3$), 33.8 (*C*(CH$_3$)$_3$ *Q*), 28.9 (*C*H$_2$), 28.6 (C(*C*H$_3$)$_3$), 13.9 (OCH$_2$*C*H$_3$); **mp** = 72 – 73 ^{o}C; **IR** (neat, cm^{-1}) 3210, 1744, 1315, 1168, 1112, 991, 714, 520; **HRMS** (ESI$^+$) exact mass calculated for C$_{13}$H$_{19}$NO$_4$F$_3$ [M+H]$^+$ *m/z* = 310.1266, found *m/z* = 310.1263. Supelco Beta DEX column (injection temp 135 °C; column conditions 100 °C for 45 min ramp to 170 °C at 5°C / min; hold 10 min, pressure 21 psi) one enantiomer *t*R) 39.9 min, other enantiomer *t*R) 41.9 min.

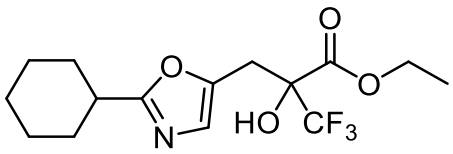
Ethyl 3-{2-phenyl oxazol-5-yl}-2-(trifluoromethyl)-2-hydroxypropanoate.



Following the procedure above, this reaction was performed using *N*-prop-2-ynylbenzamide (79.6 mg, 500 μmol). The product was a white solid.

^{1}H NMR (400 MHz, CDCl$_3$) δ = 7.96 – 7.94 (m, 2 H, C$_6$H$_5$ *o-H*), 7.43 – 7.41 (m, 3 H, C$_6$H$_5$ *m-H, p-H*), 7.01 (s, 1 H, C$_3$HNO-*H*), 4.40 – 4.32 (m, 2 H, OC*H*$_2$CH$_3$), 4.08 (br s, 1 H, O*H*), 3.52 (d, *J* = 15.2 Hz, 1 H, C*H*$_2$), 3.34 (d, *J* = 15.2 Hz, 1 H, C*H*$_2$), 1.31 (t, *J* = 7.2 Hz, 3 H, OCH$_2$C*H*$_3$); **^{13}C {^{1}H} NMR** (100.5 MHz, CDCl$_3$) δ = 168.5 (*C*O), 161.5 (C$_3$HNO *Q*), 145.2 (C$_3$HNO *Q*), 130.8 (C$_6$H$_5$ *p-C*), 129.0 (m, C$_6$H$_5$ *o-C*), 127.5 (C$_3$HNO), 127.2 (C$_6$H$_5$ *Q*), 126.3 (C$_6$H$_5$ *m-C*), 123.2 (q, *J* = 287 Hz, *C*F$_3$), 76.8 (q, *J* = 29.1 Hz, *C*CF$_3$), 64.2 (O*C*H$_2$CH$_3$), 29.1 (*C*H$_2$), 14.0 (OCH$_2$*C*H$_3$); **mp** = 92 – 93 ^{o}C; **IR** (neat, cm^{-1}) 3233, 1743, 1315, 1167, 1111, 991, 713, 514; **HRMS** (ESI$^+$) exact mass calculated for C$_{15}$H$_{15}$NO$_4$F$_3$ [M+H]$^+$ *m/z* = 330.0953, found *m/z* = 330.0959. Supelco Beta DEX column (injection temp 135 °C; column conditions 100 °C for 90 min ramp to 170 °C at 5°C / min; hold 10 min, pressure 21 psi) one enantiomer *t*R) 74.0 min, other enantiomer *t*R) 74.4 min.

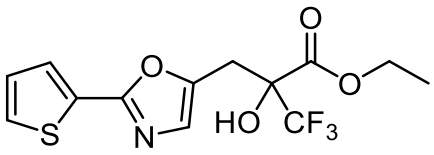
Ethyl 3-{2-cyclohexyl oxazol-5-yl}-2-(trifluoromethyl)-2-hydroxypropanoate.



Following the procedure above, this reaction was performed using *N*-prop-2-ynyl-cyclohexane carboxamide (82.1 mg, 500 μmol). The product was a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.75 (s, 1 H, C_3HNO-*H*), 5.07 (br s, 1 H, O*H*), 4.35 - 4.27 (m, 2 H, OC*H*$_2$$CH_3$), 3.37 (d, *J* = 15.2 Hz, 1 H, C*H*$_2$) , 3.18 (d, *J* = 15.2 Hz, 1 H, C*H*$_2$), 2.69 (tt, *J* = 11.4, 3.6 Hz, 1 H, Cy-*H*), 1.95 – 1.92 (m, 2 H, Cy-*H*), 1.76 – 1.72 (m, 2 H, Cy-*H*), 1.66 – 1.63 (m, 1 H, Cy-*H*), 1.50 – 1.41 (m, 2 H, Cy-*H*), 1.35 – 1.17 (m, 3 H, Cy-*H*), 1.29 (t, *J* = 7.1 Hz, 3 H, OCH_2C*H*$_3$); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ = 168.5 (*C*O), 167.2 (C_3HNO *Q*), 144.1 (C_3HNO *Q*), 125.3 (C_3HNO), 123.1 (q, *J* = 287 Hz, *C*F_3), 76.6 (q, *J* = 29.8 Hz, *C*CF_3), 64.1 (O*C*H_2CH_3), 37.4 (Cy-*H*), 30.4 (Cy-*H*), 30.3 (Cy-*H*), 29.0 (O*C*H_2CH_3), 25.7 (Cy-*H*), 25.5 (Cy-*H*), 13.9 (OCH_2*C*H_3); **IR** (neat, cm^{-1}) = 1746, 1178, 1130; **HRMS** (ESI^+) exact mass calculated for $C_{15}H_{21}NO_4F_3$ $[M+H]^+$ *m/z* = 336.1423, found *m/z* = 336.1428. Supelco Beta DEX column (injection temp 135 °C; column conditions 100 °C for 45 min ramp to 170 °C at 5°C / min; hold 10 min, pressure 21 psi) one enantiomer *t*R) 33.1 min, other enantiomer *t*R) 34.0 min.

Ethyl 3-{2-(thiophen-2-yl)oxazol-5-yl}-2-(trifluoromethyl)-2-hydroxypropanoate.



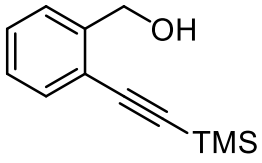
Following the procedure above, this reaction was performed using *N*-prop-2-ynyl-thiophene 2-carboxamide (83.0 mg, 500 μmol). The product was a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.64 (dd, *J* = 3.8, 1.1 Hz, 1 H, C_4H_3S), 7.42 (dd, *J* = 5.0, 1.2 Hz, 1 H, C_4H_3S), 7.11 (dd, *J* = 5.0, 3.9 Hz, 1 H, C_4H_3S), 7.01 (s, 1 H,

C_3HNO-*H*), 4.54 (br s, 1 H, O*H*), 4.45 – 4.37 (m, 2 H, OC*H*$_2$CH$_3$), 3.52 (d, *J* = 15.3 Hz, 1 H, C*H*$_2$) , 3.33 (d, *J* = 15.3 Hz, 1 H, C*H*$_2$), 1.37 (t, *J* = 7.1 Hz, 3 H, OCH$_2$C*H*$_3$); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ = 168.5 (*C*O), 167.1 (C_3HNO *Q*), 158.3 (C_4H_3S *Q*), 144.8 (C_3HNO *Q*), 128.9 (C_4H_3S), 128.4 (C_4H_3S), 128.3 (C_4H_3S), 127.4 (C_3HNO), 121.4 (q, *J* = 287 Hz, *C*F$_3$), 76.5 (q, *J* = 29.7 Hz, *C*CF$_3$), 64.6 (O*C*H$_2$CH$_3$), 29.1 (C*H*$_2$), 14.1 (OCH$_2$*C*H$_3$); **IR** (neat, cm^{-1}) = 1747, 1177, 1143, 1126, 724, 654; **HRMS** (ESI$^+$) exact mass calculated for $C_{13}H_{12}NO_4F_3S$ $[M+H]^+$ requires *m/z* = 336.0517 gmol^{-1}, found *m/z* = 336.0515 gmol^{-1}. Supelco Beta DEX column (injection temp 135 °C; column conditions 100 °C for 45 min ramp to 170 °C at 5°C / min; hold 10 min, pressure 21 psi) one enantiomer *t*R) min, other enantiomer *t*R) min.

6.3.7 Synthesis of (alkynylphenyl) alcohols/amides

[2-(2-Trimethylsilylethyn-1-yl)phenyl]methanol (**70**).

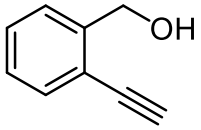


A round bottomed (RB) flask was charged with $PdCl_2(PPh_3)_2$ (90 mg, 128 μmol), CuI (61 mg, 321 μmol), 2-iodobenzyl alcohol (1.50 g, 6.41 mmol), NEt_3 (20 ml) and trimethylsilyl acetylene (1.36 ml, 9.61 mmol) and the mixture was heated at 81 ºC for 16 h. This was then cooled to RT and H_2O (40 ml), sat. NH_4Cl (50 ml) and Et_2O (100 ml) were added. The organic phase was separated and washed with sat. NH_4Cl (3 x 50 ml). The aqueous phase was then extracted with Et_2O and the combined organic extracts were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The crude product was then purified by column chromatography eluting with petrol / EtOAc (4 : 1) to give the alkyne **70** as a brown oil (1.31 g, 100 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 (dd, *J* = 7.6, 1.2, 1 H, Ar-*H*), 7.42 – 7.40 (m, 1 H, Ar-*H*), 7.32 (td, *J* = 7.6, 1.4 Hz, 1 H, Ar-*H*), 7.22 (td, *J* = 7.6, 1.3 Hz, 1 H, Ar-

H), 4.81 (s, 2 H, OC*H*$_2$), 2.56 (br s, 1 H, O*H*), 0.27 (s, 9 H, C*H*$_3$); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$): δ = 143.3, 132.4, 129.0, 127.3, 127.1, 121.1, 102.7, 99.6, 63.9, 0.04. This is consistent with data reported in the literature.[196]

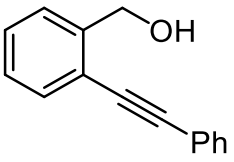
2-Hydroxymethylphenylacetylene (**71**).



[2-(2-Trimethylsilylethyn-1-yl)phenyl]methanol **70** (1.18 g, 5.77 mmol) was dissolved in CH_2Cl_2 (10 ml) and K_2CO_3 (3.99 g, 28.9 mmol) in MeOH (20 ml) was added. The resulting mixture was stirred at RT for 4 h. H_2O (30 ml) was added and the product was extracted with CH_2Cl_2 (3x 30 ml). The combined organic extracts, washed with brine (50 ml), dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The crude product was then purified by column chromatography eluting with petrol / EtOAc (5 : 1) to give the alkyne **71** as a white solid (0.76 g, 100 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51 (dd, *J* = 7.6, 1 H, Ar-*H*), 7.45 (ddd, *J* = 7.5 Hz, 1 H, Ar-*H*), 7.37 (t, *J* = 7.5 Hz, 1 H, Ar-*H*), 7.26 (t, *J* = 7.5 Hz, 1 H, Ar-*H*), 4.83 (s, 2 H, OC*H*$_2$), 3.35 (s, 1 H, C≡C*H*), 1.87 (br s, 1 H, O*H*); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$): δ = 143.3, 132.9, 129.3, 127.5, 127.3, 120.2, 82.1, 81.3, 63.7. This is consistent with data reported in the literature.[196]

[2-(2-Phenylethynyl)phenyl]methanol.

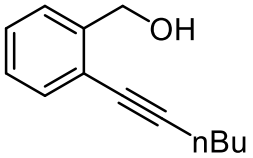


A round bottomed flask was charged with $PdCl_2(PPh_3)_2$ (48 mg, 68.4 μmol), CuI

(33 mg, 171 μmol), 2-iodobenzyl alcohol (0.800 g, 3.42 mmol), NEt_3 (20 ml) and phenylacetylene (0.56 ml, 5.13 mmol) and the mixture was heated at 81 °C for 16 h. This was then cooled to RT and H_2O (40 ml), sat. NH_4Cl (50 ml) and Et_2O (100 ml) were added. The organic phase was separated and washed with sat. NH_4Cl (3 x 50 ml). The aqueous phase was then extracted with Et_2O and the combined organic extracts were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The crude product was then purified by column chromatography eluting with petrol / EtOAc (4 : 1) to give the alkyne as an orange solid (0.78 g, 100 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56 – 7.53 (m, 3 H, Ar-*H*), 7.50 – 7.48 (m, 1 H, Ar-*H*), 7.39 – 7.35 (m, 4 H, Ar-*H*), 7.30 (td, *J* = 7.5, 1.3 Hz, 1 H, Ar-*H*), 4.93 (s, 2 H, OC*H*$_2$), 1.96 (br s, 1 H, O*H*); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$): δ = 142.7, 132.3, 131.7, 128.9, 128.7, 128.6, 127.7, 127.4, 123.0, 121.5, 94.3, 86.8, 64.2. This is consistent with data reported in the literature.[124]

2-(Hex-1-ynyl)benzyl alcohol.

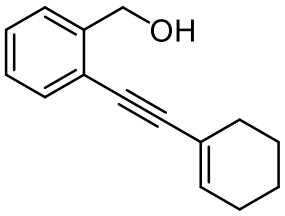


A round bottomed flask was charged with $PdCl_2(PPh_3)_2$ (48 mg, 68.4 μmol), CuI (33 mg, 171 μmol), 2-iodobenzyl alcohol (0.800 g, 3.42 mmol), NEt_3 (20 ml), and 1-hexyne (0.61 ml, 5.13 mmol) and the mixture was heated at 81 °C for 16 h. This was then cooled to RT and H_2O (40 ml), sat. NH_4Cl (50 ml) and Et_2O (100 ml) were added. The organic phase was separated and washed with sat. NH_4Cl (3 x 50 ml). The aqueous phase was then extracted with Et_2O and the combined organic extracts were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The crude product was then purified by column chromatography eluting with petrol / EtOAc (4 : 1) to give the alkyne as a brown oil (1.20 g, 100 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42 – 7.38 (m, 2 H, Ar-*H*), 7.29 (td, *J* = 7.5, 1.5 Hz, 1 H, Ar-*H*), 7.22 (td, *J* = 7.5, 1.4 Hz, 1 H, Ar-*H*), 4.80 (s, 2 H, OC*H*$_2$), 2.44 (t, *J*

= 7.0 Hz, 2 H, C*H*$_2$), 1.65 – 1.58 (m, 2 H, C*H*$_2$), 1.54 – 1.45 (m, 2 H, C*H*$_2$), 0.96 (t, *J* = 7.3 Hz, 3 H, C*H*$_3$); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$): δ = 142.5, 132.4, 128.1, 127.6, 127.4, 122.3, 95.7, 78.2, 64.5, 31.0, 22.2, 19.4, 13.8. This is consistent with data reported in the literature.[124]

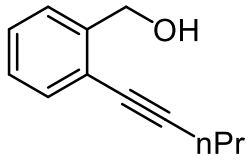
2-(Cyclohex-1-enylethynyl)phenylmethanol.



A round bottomed flask was charged with $PdCl_2(PPh_3)_2$ (48 mg, 68.4 μmol), CuI (33 mg, 171 μmol), 2-iodobenzyl alcohol (0.800 g, 3.42 mmol), NEt_3 (20 ml) and ethynylcyclohexene (0.60 ml, 5.13 mmol) and the mixture was heated at 81 ^{o}C for 16 h. This was then cooled to RT and H_2O (40 ml), sat. NH_4Cl (50 ml) and Et_2O (100 ml) were added. The organic phase was separated and washed with sat. NH_4Cl (3 x 50 ml). The aqueous phase was then extracted with Et_2O and the combined organic extracts were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The crude product was then purified by column chromatography eluting with petrol / EtOAc (9 : 1) to give the alkyne as a brown oil (0.72 g, 99 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 – 7.40 (m, 2 H, Ar-*H*), 7.30 (td, *J* = 7.5, 1.5 Hz, 1 H, Ar-*H*), 7.24 (td, *J* = 7.6, 1.5 Hz, 1 H, Ar-*H*), 6.24 – 6.22 (m, 1 H, =C*H*CH_2), 4.81 (d, *J* = 5.7 Hz, 2 H, OC*H*$_2$), 2.52 (br s, 1 H, O*H*), 2.26 – 2.21 (m, 2 H, C*H*$_2$), 2.18 – 2.14 (m, 2 H, C*H*$_2$), 1.72 – 1.60 (m, 4 H, 2 x C*H*$_2$); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$): δ = 142.4, 135.8, 132.2, 128.4, 127.5, 127.4, 122.0, 120.6, 96.4, 84.2, 64.4, 29.3, 25.9, 22.4, 21.6. This is consistent with data reported in the literature.[124]

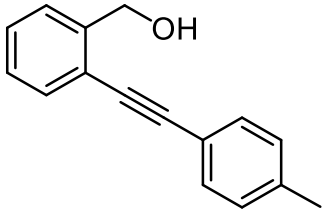
2-Pent-1-ynylbenzyl alcohol.



A round bottomed flask was charged with $PdCl_2(PPh_3)_2$ (48 mg, 68.4 μmol), CuI (33 mg, 171 μmol), 2-iodobenzyl alcohol (0.800 g, 3.42 mmol), NEt_3 (20 ml) and 1-pentyne (0.51 ml, 5.13 mmol) and the mixture was heated at 81 ^oC for 16 h. This was then cooled to RT and H_2O (40 ml), sat. NH_4Cl (50 ml) and Et_2O (100 ml) were added. The organic phase was separated and washed with sat. NH_4Cl (3 x 50 ml). The aqueous phase was then extracted with Et_2O and the combined organic were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The crude product was then purified by column chromatography eluting with petrol / EtOAc (9 : 1) to give the alkyne as a brown oil (0.60 g, 100 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42 – 7.38 (m, 2 H, Ar-*H*), 7.28 (td, *J* = 7.5, 1.5 Hz, 1 H, Ar-*H*), 7.22 (td, *J* = 7.5, 1.4 Hz, 1 H, Ar-*H*), 4.80 (s, 2 H, OCH_2), 2.43 (t, *J* = 7.0 Hz, 2 H, CH_2), 2.26 (br s, 1 H, O*H*), 1.65 (sextet, *J* = 7.2 Hz, 2 H, CH_2), 1.06 (t, *J* = 7.4 Hz, 3 H, CH_3); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$): δ = 142.5, 132.3, 128.1, 127.5, 127.3, 122.3, 95.5, 78.4, 64.4, 22.4, 21.7, 13.7. This is consistent with data reported in the literature.[127]

{2-[2-(4-Methylphenyl)ethynyl]phenyl}methanol.

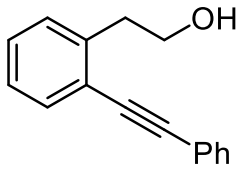


A round bottomed flask was charged with $PdCl_2(PPh_3)_2$ (44 mg, 63.2 μmol), CuI (30 mg, 158 μmol), 2-iodobenzyl alcohol (0.880 g, 3.76 mmol), NEt_3 (20 ml) and (4-

methylphenyl)acetylene (0.72 ml, 5.64 mmol) and the mixture was heated at 81 ºC for 16 h. This was then cooled to RT and H_2O (40 ml), sat. NH_4Cl (50 ml) and Et_2O (100 ml) were added. The organic phase was separated and washed with sat. NH_4Cl (3 x 50 ml). The aqueous phase was then extracted with Et_2O and the combined organic extracts were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The crude product was then purified by column chromatography eluting with petrol / EtOAc (10 : 1) to give the alkyne as an off-white solid (0.63 g, 75 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53 (dd, *J* = 7.5, 1.3 Hz, 1 H, Ar-*H*), 7.47 (d, *J* = 7.7 Hz, 1 H, Ar-*H*), 7.43 (d, *J* = 8.1 Hz, 2 H, Ar-*H*), 7.35 (td, *J* = 7.5, 1.4 Hz, 1 H, Ar-*H*), 7.28 (td, *J* = 7.6, 1.4 Hz, 1 H, Ar-*H*), 7.17 (d, *J* = 8.0 Hz, 2 H, Ar-*H*), 4.91 (d, *J* = 3.4 Hz, 2 H, C*H*$_2$), 2.38 (s, 3 H, C*H*$_3$), 2.19 (br s, 1 H, O*H*); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$): δ = 142.6, 138.9, 132.2, 131.6, 129.3, 128.7, 127.6, 127.4, 121.6, 119.9, 94.6, 86.2, 64.2, 21.7. This is consistent with data reported in the literature.[124]

2-[(2-phenylethynyl)phenyl]-1-ethanol (**72**).

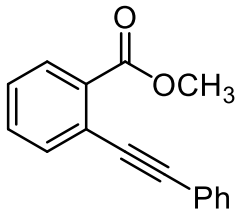


A round bottomed flask was charged with $PdCl_2(PPh_3)_2$ (105 mg, 150 μmol), CuI (71 mg, 375 μmol), NEt_3 (20 ml), 2-(2-bromophenyl)ethanol (1.50 g, 7.46 mmol) and phenylacetylene (1.23 ml, 11.2 mmol) and the mixture was heated at 81 ºC for 16 h. This was then cooled to RT and H_2O (40 ml), sat. NH_4Cl (50 ml) and Et_2O (100 ml) were added. The organic phase was separated and washed with sat. NH_4Cl (3 x 50 ml). The aqueous phase was then extracted with Et_2O and the combined organic extracts were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The crude product was then purified by column chromatography eluting with CH_2Cl_2 / MeOH (95 : 5) to give the alkyne **72** as a colourless oil (0.95 g, 57 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57 – 7.53 (m, 3 H, Ar-*H*), 7.39 – 7.34 (m, 3 H, Ar-*H*), 7.30 – 7.22 (m, 3 H, Ar-*H*), 3.97 (t, *J* = 6.7 Hz, 2 H, OC*H*$_2$CH$_2$), 3.15 (t, *J* = 6.7

Hz, 2 H, $OCH_2C\underline{H_2}$) O*H* not detected; **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$): δ = 140.5, 132.5, 131.6, 129.8, 128.6, 128.5, 128.5, 126.6, 123.6, 123.1, 93.3, 87.9, 62.9, 38.2. This is consistent with data reported in the literature.[197]

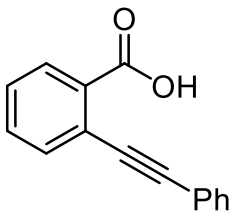
Methyl 2-(phenylethynyl)benzoate.



A Schlenk flask was charged with $PdCl_2(PPh_3)_2$ (0.199 g, 284 µmol), CuI (0.135 g, 710 µmol), NEt_3 (20 ml), methyl 2-bromobenzoate (3.06 g, 14.2 mmol) and phenyl acetylene (2.35 ml, 21.4 mmol) and the flask was heated at 81 °C for 16 h. This was then cooled to RT and H_2O (40 ml), sat. NH_4Cl (50 ml) and Et_2O (100 ml) were added. The organic phase was separated and washed with sat. NH_4Cl (3 x 50 ml). The aqueous phase was then extracted with Et_2O and the combined organic extracts were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The crude product was then purified by column chromatography eluting with petrol / EtOAc (20 : 1) to give the ester as an orange/brown oil (3.64 g, 100 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 – 7.97 (m, 1 H, Ar-*H*), 7.65 (d, *J* = 7.8, 1 H, Ar-*H*), 7.59 – 7.57 (m, 2 H, Ar-*H*), 7.50 (td, *J* = 7.6, 1.3 Hz, 1 H, Ar-*H*), 7.41 – 7.35 (m, 4 H, Ar-*H*), 3.97 (s, 3 H, OCH_3); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$): δ = 166.9, 134.1, 132.0, 131.9, 131.9, 130.6, 128.7, 128.5, 128.0, 123.8, 123.4, 94.5, 88.3, 52.4. This is consistent with data reported in the literature.[125a]

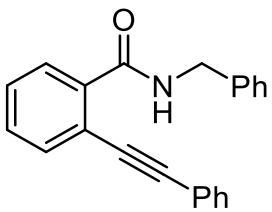
2-(2-Phenylethynyl)benzoic acid.



Methyl 2-(phenylethynyl)benzoate (0.710 g, 3.28 mmol) was added to a solution of K_2CO_3 (4.53 g, 32.8 mmol) in MeOH (30 ml) and the mixture was stirred at RT for 24 h. The solvent was then removed under reduced pressure and the residue was diluted with H_2O (20 ml). This was then washed with Et_2O (2 x 50 ml) to remove any unreacted methyl 2-(phenylethynyl)benzoate and the aqueous layer was cooled to 0 ^oC, acidified to pH 2 with 1.0 M HCl and then extracted with CH_2Cl_2 (3 x 50 ml). The combined organic extracts were dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. The crude product was then purified by column chromatography eluting with CH_2Cl_2 / MeOH (95 : 5) to give the carboxylic acid as a white solid (0.54 g, 82 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (dd, *J* = 7.8, 1.2 Hz, 1 H, Ar-*H*), 7.69 (dd, *J* = 7.7, 1.1 Hz, 1 H, Ar-*H*), 7.59 – 7.54 (m, 3 H, Ar-*H*), 7.43 (td, *J* = 7.6, 1.3 Hz, 1 H, Ar-*H*), 7.33 – 7.28 (m, 3 H, Ar-*H*), COO*H* not detected; **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$): δ = 171.3, 134.3, 132.7, 131.9, 131.5, 130.7, 128.8, 128.5, 128.1, 124.5, 123.2, 95.5, 88.2. This is consistent with data reported in the literature.[127]

N-benzyl 2-(phenylethynyl)benzamide.

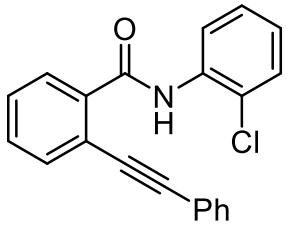


2-(2-Phenylethynyl)benzoic acid (1.51 g, 6.84 mmol) was dissolved in $SOCl_2$ (4.0

ml, 54.7 mmol) and the mixture was refluxed at 80 °C for 1 h. This was then cooled to RT and the excess $SOCl_2$ was removed under reduced pressure. THF (30 ml) and pyridine (1.66 ml, 20.5 mmol) were then added and the solution was cooled to 0 °C. Benzylamine (0.75 ml, 6.84 mmol) was added dropwise and the solution was stirred at this temperature for 30 min. The reaction was allowed to warm to RT and then was stirred for a further 16 h at this temperature. The reaction mixture was then diluted with $CHCl_3$ (100 ml). This was then washed with 2 M HCl (50 ml) and sat. aq. $NaHCO_3$ (50 ml) and the combined organic extracts were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The crude product was then purified through column chromatography by eluting with petrol / EtOAc (4 : 1), to give the amide as a white solid (2.00 g, 94 % yield)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.17 – 8.14 (m, 1 H, Ar-*H*), 7.80 (br s, 1 H, N*H*), 7.61 – 7.58 (m, 1 H, Ar-*H*), 7.47 – 7.45 (m, 2 H, Ar-*H*), 7.39 – 7.32 (m, 3 H, Ar-*H*), 7.27 – 7.24 (m, 5 H, Ar-*H*), 7.14 – 7.11 (m, 2 H, Ar-*H*), 4.71 (d, *J* = 5.4 Hz, 2 H, C*H*$_2$); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$): δ = 166.2, 138.0, 135.1, 133.7, 131.5, 130.8, 130.4, 129.1, 129.0, 128.9, 128.6, 128.3, 127.7, 122.0, 119.7, 95.9, 87.6, 44.7. This is consistent with data reported in the literature.[138a]

N-2-chlorophenyl 2-(phenylethynyl)benzamide.

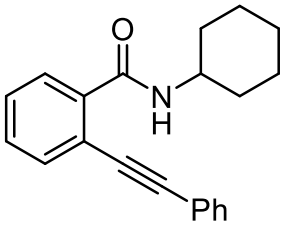


2-(2-phenylethynyl)benzoic acid (1.00 g, 4.50 mmol) was dissolved in $SOCl_2$ (2.61 ml, 36.0 mmol) and the mixture was refluxed at 80 °C for 1 h. This was then cooled to RT and the excess $SOCl_2$ was removed under reduced pressure. THF (30 ml) and pyridine (1.09 ml, 13.5 mmol) were then added and the solution was cooled to 0 °C. 2-Chloroaniline (0.47 ml, 4.50 mmol) was added dropwise and the solution was stirred at this temperature for 30 min. The reaction was allowed to warm to RT and then was

stirred for a further 16 h at this temperature. The reaction mixture was then diluted with $CHCl_3$ (100 ml). This was then washed with 2 M HCl (50 ml) and sat. aq. $NaHCO_3$ (50 ml) and the combined organic extracts were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The crude product was then purified through column chromatography by eluting with petrol / EtOAc (10 : 1), to give the amide as a white solid (1.45 g, 97 % yield)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.32 (br s, 1H, N*H*), 8.62 (d, *J* = 8.1 Hz, 1 H, Ar-*H*), 8.07 – 8.05 (m, 1 H, Ar-*H*), 7.70 – 7.67 (m, 1 H, Ar-*H*), 7.54 – 7.44 (m, 4 H, Ar-*H*), 7.38 – 7.29 (m, 5 H, Ar-*H*), 7.08 (td, *J* = 7.8, 1.5 Hz, 1 H, Ar-*H*); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$): δ = 165.1, 136.3, 135.0, 133.9, 131.9, 131.2, 130.2, 129.3, 129.1, 129.0, 128.5, 127.9, 125.0, 123.3, 122.4, 122.3, 120.2, 96.7, 86.9. This is consistent with data reported in the literature.[138a]

N-cyclohexyl 2-(phenylethynyl)benzamide.



2-(2'-phenylethynyl)benzoic acid (1.00 g, 4.50 mmol) was dissolved in $SOCl_2$ (2.61 ml, 36.0 mmol) and the mixture was refluxed at 80 ^{o}C for 1 h. This was then cooled to RT and the excess $SOCl_2$ was removed under reduced pressure. THF (30 ml) and pyridine (1.09 ml, 13.5 mmol) were then added and the solution was cooled to 0 ^{o}C. Cyclohexylamine (0.51 ml, 4.50 mmol) was added dropwise and the solution was stirred at this temperature for 30 min. The reaction was allowed to warm to RT and then was stirred for a further 16 h at this temperature. The reaction mixture was diluted with $CHCl_3$ (100 ml). This was then washed with 2 M HCl (50 ml) and sat. aq. $NaHCO_3$ (50 ml) and the combined organic extracts were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The crude product was then purified through column chromatography by eluting with petrol / EtOAc (10 : 1), to give the

amide as a white solid (1.20 g, 88 % yield).

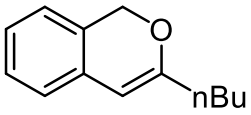
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 – 8.01 (m, 1 H, C_6H_4), 7.60 – 7.56 (m, 1 H, C_6H_4), 7.54 – 7.51 (m, 2 H, C_6H_5 *o-C*), 7.44 – 7.37 (m, 5 H, C_6H_5 *m-C*, *p-C*, 2 x C_6H_4), 7.24 (br d, *J* = 6.7 Hz, 1 H, N*H*), 4.08 – 3.99 (m, 1 H, Cy-*H*), 2.05 – 2.01 (m, 2 H, Cy-*H*), 1.72 – 1.66 (m, 2 H, Cy-*H*), 1.61 – 1.56 (m, 1 H, Cy-*H*), 1.44 – 1.33 (m, 2 H, Cy-*H*), 1.27 – 1.06 (m, 3 H, Cy-*H*); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$): δ = 165.4 (*C*O), 136.1 (C_6H_4 *Q*), 133.3 (ArCH), 131.3 (C_6H_5 *o-C*), 130.0 (ArCH), 129.6 (ArCH), 128.9 (ArCH), 128.6 (ArCH), 128.4 (C_6H_5 *m-C*), 122.1 (C_6H_5 Q), 119.4 (C_6H_4 Q), 95.1 (*C*≡C), 87.5 (C≡*C*), 48.7 (Cy *C*H), 32.9 (Cy *C*H_2), 25.5 (Cy *C*H_2), 24.6 (Cy *C*H_2); **mp** = 131 ^{o}C; **IR** (neat, cm^{-1}) 3276, 2935, 2852, 1635, 1536, 751, 684; **HRMS** (ESI^{+}) exact mass calculated for $C_{21}H_{22}NO$ $[M+H]^{+}$ *m/z* = 304.1701, found *m/z* = 304.1703.

6.3.8 General procedure for Gold catalysed synthesis of isochromenes

A flame dried Schlenk flask was charged with the gold(I) chloride phosphine complex and AgOTf (1 : 1) and CH_2Cl_2 (2 ml) was added. The solution was stirred for 30 min to generate the active catalyst *in situ*, after which the alkynylphenylmethanol substrate was added and the reaction was stirred at RT for the specified amount of time.* The reaction mixture was then filtered through a silica plug, flushing with EtOAc and the solvent removed under reduced pressure. The conversion was measured by ^{1}H NMR and products were then purified through column chromatography to obtain an isolated yield, eluting with petrol / EtOAc (95 : 5).

* *For reactions with only AgOTf or only $AuCl_3$. The solution was still stirred for 30 min before substrate was added.*

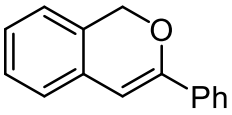
3-Butyl-1H-isochromene.



Following the general procedure above the gold(I) chloride phosphine complex (**57** (1.4 mg), **60** (1.8 mg), **61** (2.2 mg), **62** (1.2 mg), **63** (1.2 mg), **(Ph$_3$P)AuCl** (1.0 mg), (Ph$_3$As)AuCl (1.1 mg), all 2.0 µmol), AgOTf (500 µg, 2.0 µmol) and 2-hex-1-ynylbenzyl alcohol (75 mg, 400 µmol), reaction time 1 h, gave the isochromene as an off-white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21 – 7.16 (m, 1 H, Ar-*H*), 7.09 (td, *J* = 7.4, 1.3 Hz, 1 H, Ar-*H*), 7.00 – 6.98 (m, 1 H, Ar-*H*), 6.92 (d, *J* = 7.4 Hz, 1 H, Ar-*H*), 5.65 (s, 1 H, =C*H*), 5.04 (s, 2 H, OCH_2), 2.20 (t, *J* = 7.4 Hz, 2 H, CH_2), 1.60 – 1.52 (m, 2 H, CH_2), 1.43 – 1.34 (m, 2 H, CH_2), 0.94 (t, *J* = 7.3 Hz, 3 H, CH_3); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$): δ = 159.1, 132.2, 128.2, 127.3, 125.7, 123.8, 122.4, 101.0, 68.9, 33.5, 29.3, 22.5, 14.1. This is consistent with data reported in the literature.[125a]

3-Phenyl-1H-isochromene.

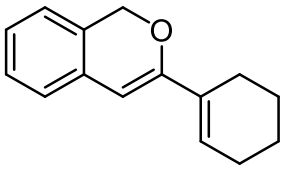


Following the general procedure above, the gold(I) chloride phosphine complex (**57** (5.6 mg), (Ph$_3$As)AuCl (1.1 mg), both 8.0 µmol), AgOTf (2.1 mg, 8.0 µmol) and [2-(2-phenylethynyl)phenyl]methanol (75 mg, 400 µmol), reaction time 16 h, gave the isochromene as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 8.0 Hz, 2 H, Ar-*H*), 7.29 – 7.22 (m, 3 H, Ar-*H*), 7.15 – 7.12 (m, 1 H, Ar-*H*), 7.05 (t, *J* = 7.4 Hz, 1 H, Ar-*H*), 6.99 – 6.95 (m, 2 H, Ar-*H*), 6.35 (s, 1 H, =C*H*), 5.11 (s, 2 H, CH_2); **^{13}C {^{1}H} NMR** (100.5 MHz,

$CDCl_3$): δ = 154.3, 134.4, 132.1, 129.0, 128.5, 128.4, 128.2, 126.6, 125.2, 123.9, 101.3, 69.1. This is consistent with data reported in the literature.[127]

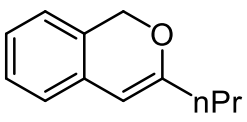
3-(Cyclohex-1-enyl)-1H-isochromene.



Following the general procedure above, the gold(I) chloride phosphine complex **57** (700 µg, 1.0 µmol), AgOTf (260 µg, 1.0 µmol) and 2-(cyclohex-1-enylethynylphenyl)methanol (43 mg, 200 µmol), reaction time 1 h gave the isochromene as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22 – 7.18 (m, 1 H, Ar-*H*), 7.11 (td, *J* = 7.4, 1.1 Hz, 1 H, Ar-*H*), 7.03 – 7.00 (m, 2 H, Ar-*H*), 6.47 – 6.44 (m, 1 H, =C*H*CH_2), 5.92 (s, 1 H, C*H*=CO), 5.04 (s, 2 H, OCH_2), 2.27 – 2.17 (m, 4 H, 2 x CH_2), 1.75 – 1.69 (m, 2 H, CH_2), 1.65 – 1.59 (m, 2 H, CH_2); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$): δ = 155.0 (*C*O *Q*), 132.4 (C_6H_4 *Q*), 130.5 (C_6H_9 *Q*), 128.6 (C_6H_4 *Q*), 128.1 (C_6H_4), 127.0 (=*C*HCH_2), 126.1 (C_6H_4), 123.8 (C_6H_4), 123.5 (C_6H_4), 100.3 (*C*HCO), 68.7 (OCH_2), 25.8 (CH_2), 24.5 (CH_2), 22.7 (CH_2), 22.3 (CH_2); **mp** = 71 – 72 °C; **IR** (neat, cm^{-1}) 1018, 952, 759; **HRMS** (ESI^+) exact mass calculated for $C_{15}H_{17}O$ $[M+H]^+$ *m/z* = 213.1279, found *m/z* = 213.1269.

3-Propyl-1H-isochromene.

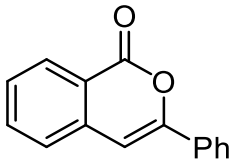


Following the general procedure above, the gold(I) chloride phosphine complex

57 (700 µg, 1.0 µmol), AgOTf (260 µg, 1.0 µmol) and 2-pent-1-ynylbenzyl alcohol (35 mg, 200 µmol), reaction time 1 h gave the isochromene as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (td, *J* = 7.5, 1.4 Hz, 1 H, Ar-*H*), 7.18 (t, *J* = 7.6 Hz, 1 H, Ar-*H*), 7.09 (td, *J* = 7.5, 1.1 Hz, 1 H, Ar-*H*), 6.99 (d, *J* = 7.4 Hz, 1 H, Ar-*H*), 5.65 (s, 1 H, =C*H*), 5.04 (s, 2 H, OCH_2), 2.33 (t, *J* = 7.4 Hz, 2 H, CH_2), 1.67 (sextet, *J* = 7.1 Hz, 2 H, CH_2), 1.26 (t, *J* = 7.1 Hz, 3 H, CH_3); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$): δ = 158.8, 132.1, 128.1, 127.3, 125.7, 123.7, 122.4, 101.1, 68.8, 35.7, 20.4, 13.8. This is consistent with data reported in the literature.[121a]

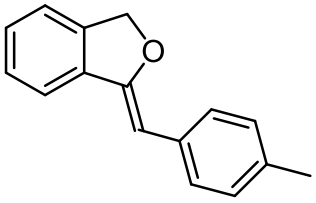
3-Phenylisocoumarin.



Following the general procedure above, the gold(I) chloride phosphine complex **57** (700 µg, 1.0 µmol), AgOTf (260 µg, 1.0 µmol) and 2-(2'-phenylethynyl)benzoic acid (44 mg, 200 µmol), reaction time 1 h gave the isocoumarin as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.23 – 8.21 (m, 1 H, Ar-*H*), 7.81 – 7.77 (m, 2 H, Ar-*H*), 7.66 – 7.61 (m, 1 H, Ar-*H*), 7.43 – 7.36 (m, 5 H, Ar-*H*), 6.86 (s, 1 H, =C*H*); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$): δ = 162.2, 153.4, 137.4, 134.8, 131.8, 129.9, 129.5, 128.7, 128.1, 126.0, 125.1, 120.4, 101.7. This is consistent with data reported in the literature.[191]

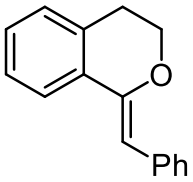
1-(4-Methylbenzylidene)-1,3-dihydroisobenzofuran.



Following the general procedure above, the gold(I) chloride phosphine complex **57** (700 µg, 1.0 µmol), AgOTf (260 µg, 1.0 µmol) and [2-(2-{4-methylphenyl}ethynyl)phenyl]methanol (44 mg, 200 µmol), reaction time 1 h gave the dihydroisobenzofuran as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 8.3 Hz, 2 H, Ar-*H*), 7.26 – 7.22 (m, 1 H, Ar-*H*), 7.19 (d, *J* = 7.7 Hz, 2 H, Ar-*H*), 7.17 – 7.13 (m, 1 H, Ar-*H*), 7.09 – 7.06 (m, 2 H, Ar-*H*), 6.42 (s, 1 H, =C*H*), 5.21 (s, 2 H, OCH_2), 2.38 (s, 3 H, CH_3); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$): δ = 154.3, 139.1, 132.3, 131.6, 129.2, 128.3, 128.1, 127.2, 125.2, 123.9, 123.4, 100.6, 69.1, 21.5. This is consistent with data reported in the literature.[92]

(Z)-1-Benzylideneisochromane (**73**).

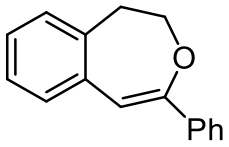


Following the general procedure above, the gold(I) chloride phosphine complex **57** (5.6 mg, 1.0 µmol), AgOTf (210 µg, 8.0 µmol) and [2-(2-ethynylphenyl)phenyl]-1-ethanol (89 mg, 400 µmol), reaction time 16 h. For full characterisation, the product was purified by column chromatography eluting with petrol / EtOAc (95 : 5), to give the isochromane **73** as a colourless oil (R_f = 0.7).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81 (d, *J* = 7.8 Hz, 2 H, C_6H_5 *o-H*), 7.77 – 7.74 (m, 1 H, C_6H_4), 7.38 (t, *J* = 7.7 Hz, 2 H, C_6H_5 *m-H*), 7.33 – 7.26 (m, 2 H, C_6H_4), 7.23 – 7.18 (m, 2 H, C_6H_5 *p-H*, C_6H_4), 6.19 (s, 1 H, =C*H*), 4.32 (t, *J* = 5.5 Hz, 2 H, OCH_2CH_2), 2.99 (t, *J* = 5.5 Hz, 2 H, OCH_2CH_2); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$): δ = 150.2

(*C*O *Q*), 136.6 (C_6H_5 *Q*), 134.1 (C_6H_4 *Q*), 130.8 (C_6H_4 *Q*), 128.7 (C_6H_5 *o-C*), 128.3 (C_6H_5 *m-H*), 128.2 (C_6H_4), 127.9 (C_6H_4), 127.0 (C_6H_4), 125.8 (C_6H_5 *p-C*), 124.3 (C_6H_4), 103.4 (=*C*H), 64.9 (O*C*H_2CH_2), 29.7 (OCH_2*C*H_2); **IR** (neat, cm^{-1}) 1628, 1492, 1123, 1089, 762, 693; **HRMS** (ESI^+) exact mass calculated for $C_{16}H_{14}O$ $[M+H]^+$ *m/z* = 223.1123, found *m/z* = 223.1121.

4-Phenyl-1,2-dihydrobenzo[d]oxepine (**74**).



By-product from the reaction above using [2-(2-ethynylphenyl)phenyl]-1-ethanol. The oxepine product **74** was a colourless oil with an R_f = 0.8, on elution in petrol / EtOAc (95 : 5).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73 – 7.71 (m, 2 H, C_6H_5 *o-H*), 7.41 – 7.32 (m, 3 H, C_6H_5 *m-H, p-H*), 7.27 – 7.25 (m, 1 H, C_6H_4), 7.22 – 7.18 (m, 1 H, C_6H_4), 7.13 – 7.07 (m, 2 H, C_6H_4), 6.16 (s, 1 H, =C*H*), 4.53 – 4.49 (m, 2 H, OCH_2CH_2), 3.25 – 3.22 (m, 2 H, OCH_2CH_2); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$): δ = 154.4 (*C*O *Q*), 138.7 (C_6H_5 *Q*), 138.1 (C_6H_4 *Q*), 135.2 (C_6H_4 *Q*), 130.4 (C_6H_4), 128.9 (C_6H_4), 128.5 (C_6H_5 *p-C*), 128.3 (C_6H_5 *m-H*), 126.6 (C_6H_4), 126.1 (C_6H_5 *o-C*), 125.3 (C_6H_4), 103.6 (=*C*H), 69.9 (O*C*H_2CH_2), 39.0 (OCH_2*C*H_2); **IR** (neat, cm^{-1}) 1625, 1493, 1122, 1093, 764, 751, 691; **HRMS** (ESI^+) exact mass calculated for $C_{16}H_{14}O$ $[M+H]^+$ *m/z* = 223.1123, found *m/z* = 223.1125.

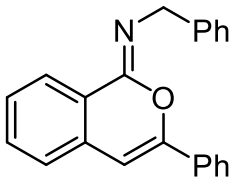
6.3.9 General procedure for Gold catalysed synthesis of iminoisocoumarins

A flame dried Schlenk flask was charged with the gold(I) chloride KITPHOS complex and AgOTf (1 : 1) and $CHCl_3$ (3 ml) was added. The solution was stirred for

30 min to generate the active catalyst *in situ*, after which the alkynylbenzamide (200 µmol) was added and the reaction was stirred at 61 ºC for the specified amount of time.* The reaction mixture was then filtered through a silica plug, flushing with EtOAc and the solvent removed under reduced pressure. The conversion was measured by ^{1}H NMR and products were then purified through column chromatography to obtain an isolated yield, eluting with petrol / EtOAc (95 : 5).

* *For reactions with only AgOTf. The solution was still stirred for 30 min before substrate was added.*

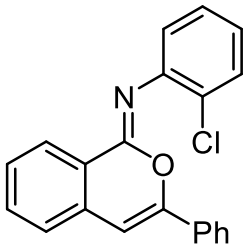
1-Phenyl-N-(3-phenyl-1H-isochromen-1-ylidene)methanamine.



Following the general procedure above, the gold(I) chloride phosphine complex **57** (2.8 mg, 4.0 µmol), AgOTf (260 µg, 4.0 µmol) and *N*-benzyl 2-(phenylethynyl)benzamide (62 mg, 200 µmol), reaction time 3.5 h gave the iminoisocoumarin as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.34 (d, *J* = 7.8 Hz, 1 H, Ar-*H*), 7.81 – 7.79 (m, 2 H, Ar-*H*), 7.55 (d, *J* = 7.3 Hz, 2 H, Ar-*H*), 7.51 – 7.26 (m, 9 H, Ar-*H*), 6.67 (s, 1 H, =C*H*), 4.90 (s, 2 H, NCH_2); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$): δ = 151.8, 150.8, 141.1, 133.2, 133.1, 131.9, 129.5, 128.9, 128.5, 128.1, 127.8, 127.0, 126.6, 125.6, 124.8, 124.1, 101.0, 50.2. This is consistent with data reported in the literature.[138a]

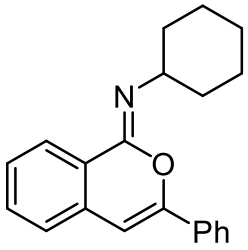
2-Chloro-N-(3-phenyl-1H-isochromen-1-ylidene)aniline.



Following the general procedure above, the gold(I) chloride phosphine complex **57** (7.0 mg, 10 µmol), AgOTf (260 µg, 1.0 µmol) and 1-*N*-2-chlorophenyl 2-(phenylethynyl)benzamide (66 mg, 200 µmol), reaction time 2 h gave the iminoisocoumarin as a pale yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.46 (d, *J* = 7.9 Hz, 1 H, Ar-*H*), 7.60 (dd, *J* = 7.5, 1.2 Hz, 1 H, Ar-*H*), 7.52 – 7.49 (m, 3 H, Ar-*H*), 7.47 – 7.43 (m, 1 H, Ar-*H*), 7.37 (d, *J* = 7.6 Hz, 1 H, Ar-*H*), 7.34 – 7.28 (m, 4 H, Ar-*H*), 7.22 (dd, *J* = 7.9, 1.7 Hz, 1 H, Ar-*H*), 7.11 – 7.07 (m, 1 H, Ar-*H*), 6.75 (s, 1 H, =C*H*); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$): δ = 151.8, 151.4, 144.9, 134.2, 133.0, 132.3, 129.8, 129.6, 128.8, 128.4, 127.9, 127.3, 126.5, 125.8, 124.7, 124.4, 123.2, 123.0, 101.2. This is consistent with data reported in the literature.[138a]

N-(3-phenyl-1H-isochromen-1-ylidene)cyclohexylamine.



Following the general procedure above, the gold(I) chloride phosphine complex **57** (7.0 mg, 10 µmol), AgOTf (260 µg, 1.0 µmol) and *N*-cyclohexyl 2-(phenylethynyl)benzamide (61 mg, 200 µmol), reaction time 2 h, gave the iminoisocoumarin as a white solid.

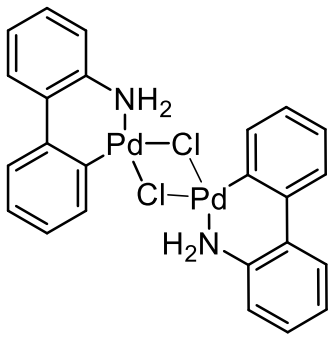
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.22 (d, *J* = 8.2 Hz, 1 H, C_6H_4), 7.80 – 7.77 (m,

2 H, C_6H_5 *o-C*), 7.49 – 7.39 (m, 4 H, C_6H_4, C_6H_5 *p-C m-C*), 7.32 (td, *J* = 7.7, 1.2 Hz, 1 H, C_6H_4), 7.25 (d, *J* = 7.5 Hz, 1 H, C_6H_4), 6.61 (s, 1 H, =C*H*), 4.04 – 3.98 (m, 1 H, Cy-*H*), 1.97 – 1.85 (m, 4 H, Cy-*H*), 1.73 – 1.69 (m, 1 H, Cy-*H*), 1.58 – 1.42 (m, 4 H, Cy-*H*), 1.38 – 1.31 (m, 1 H, Cy-*H*); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$): δ = 151.7 (N*C*O *Q*), 148.6 (*C*O *Q*), 133.3 (C_6H_5 *Q*), 133.2 (C_6H_4 *Q*), 131.5 (C_6H_5 *p-C*), 129.4 (C_6H_4), 128.9 (C_6H_5 *o-C*), 127.9 (C_6H_4), 126.9 (C_6H_4), 125.5 (C_6H_4), 124.7 (C_6H_5 *m-C*), 124.5 (C_6H_4 *Q*), 100.5 (=*C*H), 54.9 (Cy-*C*H), 33.8 (Cy-*C*H_2), 26.2 (Cy-*C*H_2), 25.3 (Cy-*C*H_2); **mp** = 89 – 91 ^{o}C; **IR** (neat, cm^{-1}) 2923, 1659, 1060, 822, 764, 687, 670; **HRMS** (ESI^+) exact mass calculated for $C_{21}H_{22}NO$ $[M+H]^+$ *m/z* = 304.1701, found *m/z* = 304.1702.

6.4 Experimental from chapter 4

6.4.1 Synthesis of 2-phenylaniline pre-catalysts

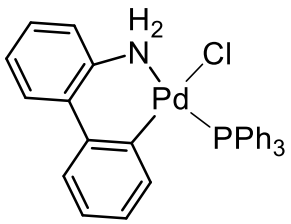
Bis[2-(2'-amino-1,1'-biphenyl)]dipalladium-μ-dichloride (**91**).



A flame-dried Schlenk flask was charged with $PdCl_2$ (1.91 g, 11.3 mmol), NaCl (1.32 g, 22.6 mmol), NaOAc (0.898 g, 10.9 mmol) and 2-phenylaniline (1.91 g, 11.3 mmol), MeOH (70 ml) was added and the resulting mixture was stirred at RT for 9 days. The resulting precipitate was filtered, washed with H_2O (3 x 20 ml), Et_2O (3 x 20 ml), $CHCl_3$ (3 x 20 ml) and dried under vacuum to leave **91** as a grey solid (2.69 g, 77 % yield).

^{1}H NMR (400 MHz, d_6-DMSO): δ = 7.57 – 7.20 (br m, 18 H, C_6H_4, 2 x N*H*$_2$), 6.41 (br s, 2 H, N*H*$_2$); **^{13}C {^{1}H} NMR** (100.5 MHz, d_6-DMSO) δ = 148.0 (C_6H_4 *Q*), 139.0 (C_6H_4 *Q*), 137.5 (C_6H_4 *Q*), 136.1 (C_6H_4 *Q*), 135.5 (C_6H_4), 127.5 (br, 3 C, C_6H_4), 125.7 (C_6H_4), 125.2 (C_6H_4), 124.9 (C_6H_4), 120.9 (C_6H_4); **mp** = 221 °C (decomp); **IR** (neat, cm^{-1}) 3287, 3230, 1567, 1492, 1415, 1107, 1088, 1027, 750, 734. This is consistent with data reported in the literature.[161]

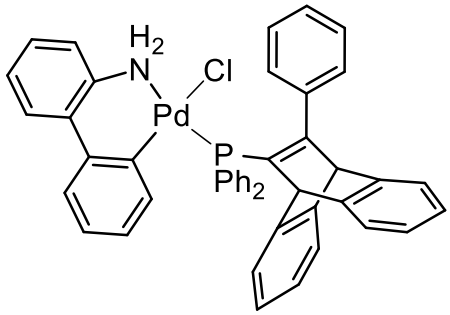
[{Triphenylphosphine}-2-(2'-amino-1,1'-biphenyl)]palladium(II) chloride] (**92**).



Bis[2-(2'-amino-1,1'-biphenyl)]dipalladium-μ-dichloride **91** (90.0 g, 0.145 mmol), was dissolved in acetone (20 ml) and PPh_3 (76 mg, 0.289 mmol) added. This was then left to stir at RT for 3 h. The solvent was removed under reduced pressure and the solid was then dissolved in $CHCl_3$, filtered and the solvent removed under reduced pressure. The crude product was purified by recrystallisation from a $CHCl_3$ solution layered with MeOH to give the phosphine complex **92**, as white crystals (0.251 g, 89 % yield).

^{31}P {^{1}H} NMR (161.8 MHz, $CDCl_3$) δ = 36.5; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.54 – 7.49 (m, 1 H, Ar-*H*), 7.37 – 6.33 (m, 3 H, Ar-*H*), 7.28 – 7.22 (m, 15 H, Ar-*H*), 6.89 (td, *J* = 7.5, 0.9 Hz, 1 H, C_6H_4), 6.55 – 6.52 (m, 2 H, C_6H_4), 6.47 (dd, *J* = 7.3, 1.2 Hz, 1 H, C_6H_4), 4.98 (br s, 2 H, N*H*$_2$); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ = 139.9 (C_6H_4 *Q*), 138.6 (C_6H_4 *Q*), 138.2 (C_6H_4 *Q*), 135.2 (C_6H_4 *Q*), 134.9 (d, *J* = 11.7 Hz, C_6H_5 *m-C*), 130.8 (d, *J* = 49.9 Hz, C_6H_5 *Q*), 130.4 (C_6H_5 *p-C*), 128.2 (d, *J* = 10.8 Hz, C_6H_5 *o-C*), 128.1 (C_6H_4), 127.8 (C_6H_4), 127.3 (C_6H_4), 127.3 (C_6H_4), 125.7 (C_6H_4), 125.6 (C_6H_4), 124.9 (C_6H_4), 120.6 (C_6H_4); **mp** = 209 ºC (decomp); **IR** (neat, cm^{-1}) 1573, 1099, 1052, 747, 738, 690, 530, 514; **HRMS** (ESI$^+$) exact mass calculated $C_{30}H_{25}NPClPd$ $[M]^+$ *m/z* = 571.0448, found *m/z* = 571.0436. This is consistent with data reported in the literature.[161]

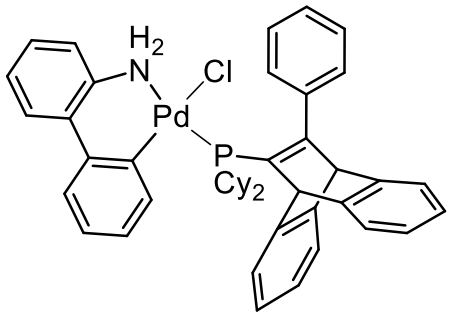
[{11-(Diphenylphosphino)-12-phenyl-9,10-dihydro-9,10-ethenoanthracene}-2-(2'-amino-1,1'-biphenyl)]palladium(II) chloride] (**93**).



Bis[2-(2'-amino-1,1'-biphenyl)]dipalladium-μ-dichloride **91** (90.0 mg, 0.145 mmol), was dissolved in acetone (20 ml) and 11-(diphenylphosphino)-12-phenyl-9,10-dihydro-9,10-ethenoanthracene, **19** (0.134 g, 0.289 mmol) added. This was then left to stir at RT for 3 h. The solvent was removed under reduced pressure and the solid was then dissolved in $CHCl_3$, filtered and the solvent removed under reduced pressure. The crude product was purified by recrystallisation from a $CHCl_3$ solution layered with MeOH to give the phosphine complex **93**, as colourless crystals (0.169 g, 75 % yield).

^{31}P {H} NMR (161.8 MHz, CH_2Cl_2): δ = 30.9; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.43 – 6.83 (m, 29 H, Ar-*H*), 6.25 (t, *J* = 6.7 Hz, 1 H, Ar-*H*), 6.18 (t, *J* = 7.2 Hz, 1 H, Ar-*H*), 5.34 (d, *J* = 3.4 Hz, 1 H, bridgehead *H*), 5.21 (d, *J* = 7.6 Hz, 1 H, bridgehead *H*), 4.77 (br s, 2 H, N*H*$_2$); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ = 162.3 (d, *J* = 7.7 Hz, *C*CP), 148.1 (C_6H_4 *Q*), 144.8 (2 x C_6H_4 *Q*), 144.4 (2 x C_6H_4 *Q*), 139.9 (C_6H_4 *Q*), 138.5 (C_6H_5 *Q*), 138.4 (C_6H_4 *Q*), 138.4 (C_6H_4 *Q*), 137.4 (C_6H_5), 137.3 (C_6H_5), 135.3 (br, *C*P), 135.3 (C_6H_5), 135.2 (C_6H_5), 130.2 (C_6H_5), 129.7 (br, C_6H_5 *Q*), 127.9 – 127.6 (br m, 6 C, 2 x C_6H_5, 4 x C_6H_4), 127.1 (C_6H_4), 127.1 (C_6H_4), 126.0 (C_6H_4), 125.4 (C_6H_4), 125.1 (C_6H_4), 125.0 (C_6H_4), 125.0 (C_6H_4), 123.9 (br, 2 x C_6H_4), 123.1 (2 x C_6H_4), 120.3 (C_6H_4), 60.9 (d, *J* = 7.7 Hz, bridgehead *C*H), 55.4 (d, *J* = 5.5 Hz, bridgehead *C*H), observed complexity due to presence of rotamers; **mp** = 185 ^{o}C (decomp); **IR** (neat, cm^{-1}) 2981, 1488, 1459, 1158, 1022, 968, 746, 694, 630; **HRMS** (ESI^+) exact mass calculated for $C_{46}H_{35}NPClPd$ $[M]^+$ *m/z* = 773.1230, found *m/z* = 773.1208.

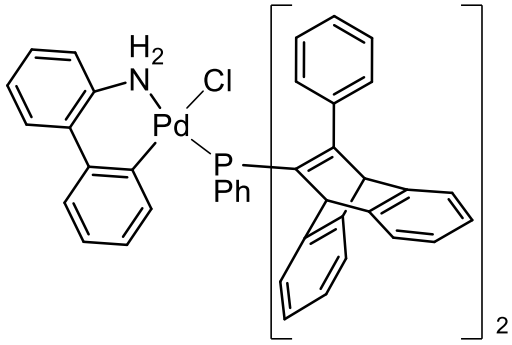
[{11-(Dicyclohexylphosphino)-12-phenyl-9,10-dihydro-9,10-ethenoanthracene}-2-(2'-amino-1,1'-biphenyl)]palladium(II) chloride] (**90**).



Bis[2-(2'-amino-1,1'-biphenyl)]dipalladium-μ-dichloride **91** (64.5 g, 0.104 mmol), was dissolved in acetone (20 ml) and 11-(dicyclohexylphosphino)-12-phenyl-9,10-dihydro-9,10-ethenoanthracene **16** monophosphine (0.100 g, 0.208 mmol) added. This was then left to stir at RT for 3 h. The solvent was removed under reduced pressure and the solid was then dissolved in $CHCl_3$, filtered and the solvent removed under reduced pressure. The crude product was purified by recrystallisation from a $CHCl_3$ solution layered with MeOH to give the phosphine complex **90**, as colourless crystals (0.122 g, 75 % yield).

^{31}P {H} NMR (161.8 MHz, $CDCl_3$): δ = 48.3; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.81 (br s, 1 H, Ar-*H*), 7.45 (br s, 1 H, Ar-*H*), 7.38 (br s, 1 H, Ar-*H*), 7.33 (d, *J* = 7.1 Hz, Ar-*H*), 7.34 – 7.14 (m, 11 H, Ar-*H*), 7.04 (m, 4 H, Ar-*H*), 6.98 (t, *J* = 7.0 Hz, 1 H, Ar-*H*), 6.15 – 6.08 (m, 2 H, Ar-*H*, bridgehead *H*), 5.21 (d, *J* = 2.3 Hz, 1 H, bridgehead *H*), 4.88 (br s, 1 H, N*H*), 4.58 (br s, 1 H, N*H*), 2.82 (br s, 1 H, Cy-*H*), 2.20 (br s, 1 H, Cy-*H*), 1.63 (br s, 3 H, Cy-*H*), 1.41 – 1.16 (m, 5 H, Cy-*H*), 1.09 – 0.89 (br m, 8 H, Cy-*H*), 0.78 – 0.67 (br m, 2 H, Cy-*H*), 0.22 (br s, 1 H, Cy-*H*), 0.04 (br s, 1 H, Cy-*H*); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ = 159.4 (d, *J* = 22.9 Hz), 148.3, 145.1, 144.7, 144.4, 143.8, 140.4 (d, *J* = 2.3 Hz), 140.0, 139.2, 135.7 (d, *J* = 8.2 Hz), 135.5, 134.9 (d, *J* = 29.5 Hz), 128.7, 128.2, 127.7, 127.6, 126.9, 126.8, 125.2, 125.2, 125.0, 124.6, 123.9, 123.0, 122.7, 120.4, 62.3 (d, *J* = 6.7 Hz), 56.5 (d, *J* = 15.4 Hz), 37.3 (d, *J* = 25.6 Hz), 36.6 (d, *J* = 23.9 Hz), 32.5, 30.9, 30.2, 29.8, 28.0, 27.6, 27.5, 27.3, 26.3, 25.9; **mp** = 188 ^{o}C (decomp); **IR** (neat, cm^{-1}) 2929, 2851, 1457, 1019, 1002, 747, 702, 632; **HRMS** (ESI^{+}) exact mass calculated for $C_{46}H_{47}NPClPd$ $[M]^{+}$ *m/z* = 785.2169, found *m/z* = 785.2186. This is consistent with data reported in the literature.[53]

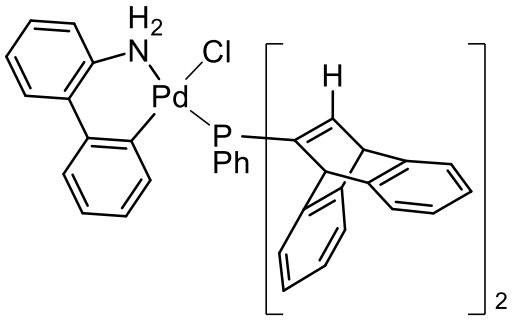
[{11-[Bis(12-phenyl-9,10-dihydro-9,10-etheno-anthracene)]phenylphosphine}-2-(2'-amino-1,1'-biphenyl)]palladium(II) chloride] (**94**).



Bis[2-(2'-amino-1,1'-biphenyl)]dipalladium-μ-dichloride **91** (90.0 mg, 0.145 mmol), was dissolved in acetone (20 ml) and 11-[bis(12-phenyl-9,10-dihydro-9,10-etheno-anthracene)]phenylphosphine, **30** (0.193 g, 0.289 mmol) added. This was then left to stir at RT for 3 h. The solvent was removed under reduced pressure and the resulting solid was then dissolved in $CHCl_3$, filtered and the solvent removed under reduced pressure. The crude product was purified by recrystallisation from a $CHCl_3$ solution layered with MeOH to give the phosphine complex **94**, as yellow crystals (0.251 g, 89 % yield). No ^{1}H or $^{13}C\{^{1}H\}$ NMR data is available due to presence of rotamers which give very broad complicated spectra.

^{31}P {H} NMR (161.8 MHz, CH_2Cl_2): δ = 35.8, 25.7 (br); **mp** = 210 °C (decomp); **IR** (neat, cm^{-1}) 1558, 1490, 1456, 1261, 1089, 1021, 745, 691, 628; **HRMS** (ESI^+) exact mass calculated for $C_{62}H_{45}NPClPd$ $[M]^+$ *m/z* = 975.2013, found *m/z* = 975.2001.

[{11-[Bis(9,10-dihydro-9,10-etheno-anthracene)]phenylphosphine}-2-(2'-amino-1,1'-biphenyl)]palladium(II) chloride] (**95**).

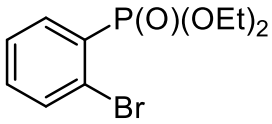


Bis[2-(2'-amino-1,1'-biphenyl)]dipalladium-μ-dichloride **91** (90.0 mg, 0.145 mmol), was dissolved in acetone (20 ml) and 11-[bis(9,10-dihydro-9,10-etheno-anthracene)]phenylphosphine **37** (0.193 g, 0.289 mmol) added. This was then left to stir at RT for 3 h. The solvent was removed under reduced pressure and the solid was then dissolved in $CHCl_3$, filtered and the solvent removed under reduced pressure, to give the phosphine complex **95**, as an off-white solid (0.173 g, 73 % yield). No ^{13}C {^1H} NMR data is available due to presence of rotamers to give a very broad complicated spectrum.

^{31}P {^1H} NMR (161.8 MHz, $CDCl_3$) δ = 30.1; **^1H NMR** (400 MHz, $CDCl_3$) δ = 7.54 (d, *J* = 7.0 Hz, 1 H, Ar-*H*), 7.41 – 6.79 (m, 24 H, Ar-*H*, *H*C=CP), 6.63 (br s, 2 H, Ar-*H*), 6.30 (br s, 1 H, Ar-*H*), 6.25 (td, *J* = 7.4, 1.2 Hz, 1 H, Ar-*H*), 5.81 (br t, *J* = 6.4 Hz, 1 H, Ar-*H*), 5.64 (br s, 1 H, Ar-*H*), 5.25 – 5.23 (m, 2 H, bridgehead *H*), 5.05 (br, 1 H, N*H*$_2$), 4.90 (br, 2 H, bridgehead *H*), 4.71 (br, 1 H, N*H*$_2$); **mp** = 183 ºC (decomp); **IR** (neat, cm^{-1}) 1572, 1458, 1021, 746, 696, 641; **HRMS** (ESI^+) exact mass calculated for $C_{50}H_{37}NPClPd$ $[M]^+$ *m/z* = 823.1387, found *m/z* = 823.1389.

6.4.2 Synthesis of substrates for Suzuki Miyaura cross couplings

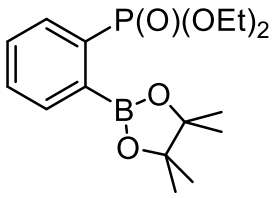
Diethyl o-bromobenzenephosphonate (**97**).



A flame dried Schlenk flask was charged with $Pd(OAc)_2$ (0.210 g, 0.934 mmol), PPh_3 (2.45 g, 9.34 mmol), EtOH (180 ml), 1-bromo-2-iodobenzene (6.0 ml, 46.7 mmol), $HP(OEt)_2$ (30 ml, 234 mmol) and DIPEA (51 ml, 292 mmol) and the mixture was heated under reflux for 48 h. The solution was then diluted with Et_2O (200 ml) and washed with 1 M HCl (200 ml). The aqueous phase was extracted with Et_2O (3 x 100 ml). The combined organic extracts were then washed with 2.5 M NaOH solution (50 ml), brine (50 ml), dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The crude product was then purified by column chromatography eluting with EtOAc to give the phosphonate **97** as a light yellow oil (8.90 g, 65 %).

^{31}P {H} NMR (161.8 MHz, $CDCl_3$): δ = 15.4; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.02 – 7.96 (m, 1 H, Ar-*H*), 7.66 – 7.62 (m, 1 H, Ar-*H*), 7.40 – 7.32 (m, 2 H, Ar-*H*), 4.22 – 4.05 (m, 4 H, OCH_2), 1.33 (t, *J* = 7.1 Hz, 6 H, CH_3); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$): δ = 136.4 (d, *J* = 8.4 Hz), 134.4 (d, *J* = 11.3 Hz), 133.7 (d, *J* = 2.6 Hz), 129.5 (d, *J* = 192 Hz), 127.0 (d, *J* = 13.6 Hz), 125.3 (d, *J* = 3.8 Hz), 62.7 (d, *J* = 5.4 Hz), 16.4 (d, *J* = 6.6 Hz). This is consistent with data reported in the literature.[169]

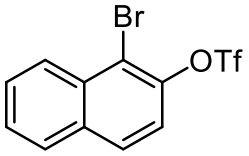
Diethyl [2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]phosphonate (**98**).



A flame dried Schlenk flask was charged with Pd(dppf)Cl_2 (25 mg, 0.034 mmol), KOAc (0.201 g, 2.05 mmol), bis(pinacolato)diboron (0.260 g, 1.02 mmol), dioxane (4 ml) and diethyl *o*-bromobenzenephosphonate **97** (0.200 g, 0.68 mmol) and the reaction was heated at 90 ^oC for 84 h. The solvent was removed under reduced pressure and the crude product was purified by column chromatography eluting with petrol / EtOAc (1 : 2) to give the boronate **98** as a colourless oil (147 mg, 63 %).

^{31}P {H} NMR (161.8 MHz, $CDCl_3$): δ = 20.5; **^{11}B NMR** (400 MHz, $CDCl_3$): δ = 30.4; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.82 (dd, *J* = 13.1, 7.2 Hz, 1 H, Ar-*H*), 7.62 – 7.58 (m, 1 H, Ar-*H*), 7.49 (tt, *J* = 7.4, 1.6 Hz, 1 H, Ar-*H*), 7.44 (tdd, *J* = 7.4, 3.9, 1.3 Hz, 1 H, Ar-*H*), 4.21 – 4.02 (m, 4 H, OCH_2), 1.40 (s, 12 H, 4 x CH_3), 1.32 (t, *J* = 7.1 Hz, 6 H, CH_2CH_3); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$): δ = 133.5 (d, *J* = 17.3 Hz, C_6H_4P), 132.3 (d, *J* = 11.0 Hz, C_6H_4P), 131.7 (d, *J* = 187 Hz, C_6H_4P *C*P), 131.4 (d, *J* = 2.9 Hz, C_6H_4P), 129.2 (d, *J* = 14.6 Hz, C_6H_4P), 84.4 (BO*C* *Q*), 62.1 (d, *J* = 5.1 Hz, CH_2), 25.0 (4 x CH_3), 16.5 (d, *J* = 6.6 Hz, CH_2CH_3) *C*B not detected; **IR** (neat, cm^{-1}) 1347, 1143, 1019, 962, 761, 564; **HRMS** (ESI^+) exact mass calculated for $C_{16}H_{26}O_5BP$ $[M+H]^+$ *m/z* = 341.1689, found *m/z* = 341.1678.

1-Bromo-2-naphthyl triflate.

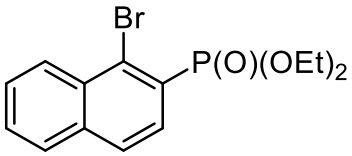


1-bromo-2-naphthol (5.0 g, 21.1 mmol) was dissolved in pyridine (40 ml), cooled

to 0 °C and triflic anhydride (7.10 ml, 42.4 mmol) added. The resulting mixture was stirred at this temperature for 30 min and was then allowed to warm to RT and was stirred for 16 h. Et_2O (100 ml) and 3 M HCl (100 ml) were then added and the layers were separated. The aqueous layer was further extracted with Et_2O (3 x 50 ml). The combined organic extracts were then washed with 3 M HCl (2 x 100 ml), sat. $NaHCO_3$ (100 ml), brine (50 ml), dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. The crude product was purified by column chromatography eluting with petrol / EtOAc (10 : 1), to give the triflate as a white solid (7.47 g, 100 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.33 (d, *J* = 9.3 Hz, 1 H, Ar-*H*), 7.91 – 7.89 (m, 2 H, Ar-*H*), 7.70 (ddd, *J* = 8.5, 6.9, 1.3 Hz, 1 H, Ar-*H*), 7.62 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1 H, Ar-*H*), 7.44 (d, *J* = 9.0 Hz, 1 H, Ar-*H*); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$): δ = 145.0, 133.0, 132.6, 129.8, 128.8, 128.3, 127.8, 127.6, 119.8, 118.8 (q, *J* = 320 Hz), 116.2. This is consistent with data reported in the literature.[170]

Diethyl 1-bromo-2-naphthylphosphonate (**99**).

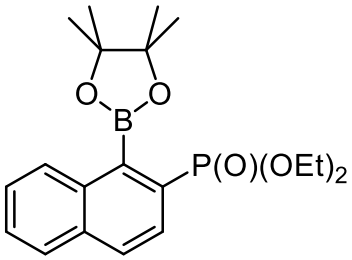


A flame-dried Schlenk flask was charged with 1-bromo-2-naphthyl triflate (7.44 g, 21 mmol), $Pd_2(dba)_3$ (604 mg, 1.05 mmol), dppp (433 mg, 1.05 mmol), toluene (60 ml), DIPEA (5.49 ml, 31.5 mmol) and $HP(OEt)_2$ (3.25 ml, 25.2 mmol) and the mixture was heated to 120 °C for 16 h. The flask was then cooled to RT and the solvent was removed under reduced pressure. The crude product was then purified by column chromatography eluting with petrol / EtOAc starting with (8 : 2) then increasing to (1 : 1) and then by crystallisation from hot *n*-hexane to give the phosphonate **99** as a white crystalline solid (5.00 g, 70 % yield).

^{31}P {H} NMR (161.8 MHz, $CDCl_3$): δ = 16.1; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.47 – 8.45 (m, 1 H, Ar-*H*), 8.03 (dd, *J* = 12.2, 8.5 Hz, 1 H, Ar-*H*), 7.88 – 7.82 (m, 2 H, Ar-*H*), 7.66 – 7.58 (m, 2 H, Ar-*H*), 4.28 – 4.11 (m, 4 H, C*H*$_2$), 1.36 (t, *J* = 7.1, 6 H,

C*H*$_3$); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$): δ = 136.1 (d, *J* = 2.4 Hz, $C_{10}H_6$ *Q*), 132.6 (d, *J* = 13.0 Hz, $C_{10}H_6$ *Q*), 130.3 (d, *J* = 8.2 Hz, $C_{10}H_6$), 128.8 ($C_{10}H_6$), 128.6 ($C_{10}H_6$), 128.3 ($C_{10}H_6$), 128.3 (d, *J* = 4.3 Hz, $C_{10}H_6$ *Q*), 128.2 ($C_{10}H_6$), 127.8 (d, *J* = 191 Hz, $C_{10}H_6$ *C*P), 127.6 (d, *J* = 13.5 Hz, $C_{10}H_6$), 62.7 (d, *J* = 5.4 Hz, *C*H_2), 16.4 (d, *J* = 6.6 Hz, *C*H_3); **mp** = 66 °C; **IR** (neat, cm^{-1}) 2980, 1240, 1047, 1018, 966, 740, 670, 622; **HRMS** (ESI^+) exact mass calculated for $C_{14}H_{17}O_3PBr$ $[M+H]^+$ *m/z* = 343.0099, found *m/z* = 343.0092. This is consistent with data reported in the literature.[171]

Diethyl 1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-ylphosphonate (**100**).

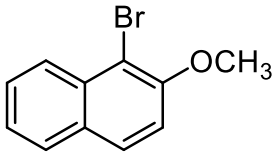


A flame dried Schlenk flask was charged with diethyl 1-bromo-2-naphthylphosphonate **99** (1.50 g, 4.37 mmol), Pd(dppf)Cl_2 (157 mg, 215 µmol), KOAc (1.30 g, 13.1 mmol), bis(pinacolato)diboron (1.67 g, 6.65 mmol) and dioxane (20 ml) and the mixture was heated to 90 °C for 16 h. The solvent was then removed and the crude product was purified by column chromatography eluting with petrol / EtOAc (1 : 2) and then by crystallisation from hot *n*-hexane to give the boronate **100** as a white crystalline solid (1.00 g, 59 % yield).

^{31}P {H} NMR (161.8 MHz, $CDCl_3$): δ = 21.4; **^{11}B NMR** (400 MHz, $CDCl_3$): δ = 30.1; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.09 – 8.07 (m, 1 H, Ar-*H*), 7.86 (dd, *J* = 8.4, 4.0 Hz, 1 H, Ar-*H*), 7.83 – 7.81 (m, 1 H, Ar-*H*), 7.72 (dd, *J* = 11.1, 8.4 Hz, 1 H, Ar-*H*), 7.54 – 7.52 (m, 2 H, Ar-*H*), 4.23 – 4.00 (m, 4 H, C*H*$_2$), 1.54 (s, 12 H, 4 x C*H*$_3$), 1.30 (t, *J* = 7.1 Hz, 6 H, $CH_2C\underline{H_3}$); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$): δ = 139.2 (br m, C_6H_{10} *C*B), 135.3 (d, *J* = 19.9 Hz, $C_{10}H_6$ *Q*), 134.3 (d, *J* = 2.6 Hz, $C_{10}H_6$ *Q*), 129.4 (d, *J* = 185 Hz, $C_{10}H_6$ *C*P), 129.0 (d, *J* = 14.1 Hz, $C_{10}H_6$), 128.6 ($C_{10}H_6$), 128.4 ($C_{10}H_6$), 127.8 ($C_{10}H_6$), 126.7 ($C_{10}H_6$), 126.6 (d, *J* = 10.7 Hz, $C_{10}H_6$), 84.7 (BO*C* *Q*), 62.1 (d, *J* = 4.6

Hz, *C*H_2), 25.8 (4 x *C*H_3), 16.4 (d, *J* = 6.4 Hz, $CH_2\underline{C}H_3$); **mp** = 86 ºC; **IR** (neat, cm^{-1}) 2978, 1370, 1288, 1124, 1048, 1019, 960, 940, 749, 663, 539; **HRMS** (ESI^+) exact mass calculated for $C_{20}H_{29}O_5BP$ $[M+H]^+$ *m/z* = 391.1846, found *m/z* = 391.1842. This is consistent with data reported in the literature.[172]

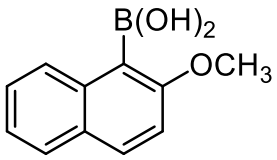
1-Bromo-2-methoxynaphthalene.



A solution of bromine (3.24 ml, 63.2 mmol) in acetic acid (100 ml) was added dropwise to a solution of 2-methoxynaphthalene (10.0 g, 63.2 mmol) in acetic acid (200 ml) using a pressure – equalising dropping funnel. Any remnants of bromine were quenched using 20% aq. sodium metabisulphite, although sodium thiosulphate can also be used. The solution was stirred at RT for 16 h, after which the bromine colour had disappeared to leave a light yellow solution. H_2O was then added until the solution had neutralised and the white precipitate formed was filtered, washing with H_2O (2 x 20 ml) and dried under reduced pressure. The crude product was then purified by column chromatography eluting with petrol / EtOAc (4 : 1) to give the bromide as a white solid (12.91 g, 86 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.23 (d, *J* = 8.4 Hz, 1 H, Ar-*H*), 7.83 (d, *J* = 9.0 Hz, 1 H, Ar-*H*), 7.79 (d, *J* = 8.3 Hz, 1 H, Ar-*H*), 7.57 (ddd, *J* = 8.3, 6.8, 1.2 Hz, 1 H, Ar-*H*), 7.40 (ddd, *J* = 8.1, 6.9, 1.0 Hz, 1 H, Ar-*H*), 7.28 (d, *J* = 9.0 Hz, 1 H, Ar-*H*), 4.04 (s, 3 H, O*CH*$_3$); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$): δ = 153.9, 133.2, 129.9, 129.1, 128.2, 127.9, 126.3, 124.5, 113.7, 108.8, 57.2. This is consistent with data reported in the literature.[173]

2-Methoxy-1-naphthylboronic acid.



A flame dried Schlenk flask was charged with magnesium turnings (0.513 g, 21.1 mmol) and stirred for 16 h under nitrogen. THF (40 ml) and 1-bromo-2-methoxynapthalene (4.0 g, 16.9 mmol) were then added, the mixture was stirred at RT for 2 h and then at 50 ^{o}C for 1 h. The solution was then cooled to -78^{o}C and trimethyl borate (6.12 ml, 55.0 mmol) was added. The solution was stirred at -78^{o}C for 2 h and then allowed to warm to RT overnight. H_2O (50 ml) was added and the THF was removed under reduced pressure. The reaction mixture was then extracted with CH_2Cl_2 (3 x 100 ml) and the combined organic extracts were dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. The crude product was then purified by recrystallisation from CH_2Cl_2 to give the boronic acid as a white solid (4.20 g, 99 % yield).

^{11}B NMR (400 MHz, $CDCl_3$): δ = 29.2; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.84 (d, *J* = 8.7 Hz, 1 H, Ar-*H*), 7.95 (d, *J* = 9.0 Hz, 1 H, Ar-*H*), 7.78 (d, *J* = 8.2 Hz, 1 H, Ar-*H*), 7.51 (t, *J* = 7.7 Hz, 1 H, Ar-*H*), 7.37 (t, *J* = 7.4 Hz, 1 H, Ar-*H*), 7.29 (d, *J* = 9.1 Hz, 1 H, Ar-*H*), 6.13 (s, 2 H, O*H*), 4.03 (s, 3 H, OCH_3); **^{13}C {^{1}H} NMR** (100.5 MHz, d_6-DMSO): δ = 158.6, 135.8, 129.4, 128.5, 128.0, 127.4, 125.9, 123.1, 121.9, 113.7, 56.2. This is consistent with data reported in the literature.[174]

6.4.3 General procedure for Suzuki Miyaura cross-couplings

A flame-dried Schlenk flask was charged with pre-catalyst [2.0 μmol; **92** (1.0mg), **93** (1.6mg), **94** (2.0mg), **95** (1.6mg) or $Pd(OAc)_2$ (0.4mg, 2.0 μmol) with PPh_3 (1.3mg, 5.0 μmol)], K_3PO_4 (0.170 g, 800 μmol) and aryl bromide (400 μmol). Solvent (2 ml) was then added,[a,b] followed by the boronic acid (600 μmol) and H_2O (1 ml) and the Schlenk flask was then lowered into a pre-heated oil bath and stirred at the

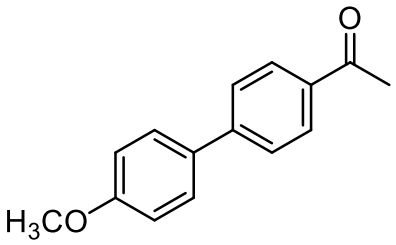
corresponding temperature for the allotted time. The reaction mixture was filtered through a silica plug, flushing with CH_2Cl_2 / MeOH (9 :1) and the solvent was removed under reduced pressure.[c] The conversion was then monitored by ^{1}H NMR or by GC.

[a] *For aryl bromides which were liquids; the solvent was added first, and then the bromide.*

[b] *Decane (78 µl, 400 µmol) was added after the solvent, when the aryl bromide was 3-Bromothiophene.*

[c] *For analysis using the GC, the work up was altered. After filtering through a silica plug, the organic layer was separated using CH_2Cl_2, dried using $MgSO_4$ and then the solvent removed.*

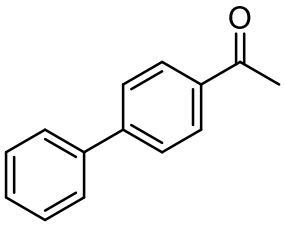
4-(4-Methoxyphenyl)acetophenone.



Following the Suzuki Miyaura cross-coupling procedure described above, this reaction was performed using 4-methoxyphenylboronic acid (91 mg) and 4-bromoacetophenone (80 mg). The product was a white solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 8.4 Hz, 2 H, Ar-*H*), 7.64 (d, *J* = 8.4 Hz, 2 H, Ar-*H*), 7.58 (d, *J* = 8.9 Hz, 2 H, Ar-*H*), 7.00 (d, *J* = 8.8 Hz, 2 H, Ar-*H*), 3.86 (s, 3 H, OC*H*$_3$), 2.63 (s, 3 H, C*H*$_3$); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ = 197.9, 160.0, 145.5, 135.4, 132.3, 129.1, 128.5, 126.7, 114.5, 55.5, 26.8. This is consistent with data reported in the literature.[198]

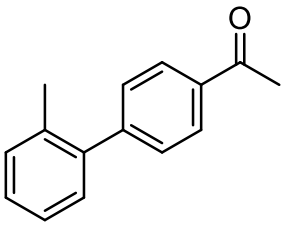
4-Phenylacetophenone.



Following the Suzuki Miyaura cross-coupling procedure described above, this reaction was performed using phenylboronic acid (73 mg) and 4-bromoacetophenone (80 mg). The product was a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (d, *J* = 8.3 Hz, 2 H, Ar-*H*), 7.69 (d, *J* = 8.3 Hz, 2 H, Ar-*H*), 7.63 (d, *J* = 7.3 Hz, 2 H, Ar-*H*), 7.48 (d, *J* = 7.4 Hz, 2 H, Ar-*H*), 7.41 (d, *J* = 7.3 Hz, 2 H, Ar-*H*), 2.64 (s, 3 H, C*H*$_3$); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ = 197.9, 145.8, 139.9, 135.9, 129.1, 129.0, 128.3, 127.4, 127.3, 26.8. This is consistent with data reported in the literature.[54a]

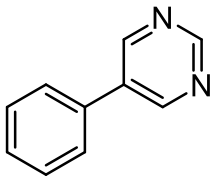
4-(2-Methylphenyl)acetophenone.



Following the Suzuki Miyaura cross-coupling procedure described above, this reaction was performed using (2-methylphenyl)boronic acid (82 mg) and 4-bromoacetophenone (80 mg). The product was a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 8.3 Hz, 2 H, Ar-*H*), 7.44 (d, *J* = 8.3 Hz, 2 H, Ar-*H*), 7.32 – 7.22 (m, 4 H, Ar-*H*), 2.66 (s, 3 H, C*H*$_3$), 2.29 (s, 3 H, C*H*$_3$); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ = 197.9, 147.0, 140.8, 135.6, 135.2, 130.6, 129.6, 129.5, 128.3, 128.0, 126.0, 26.7, 20.5. This is consistent with data reported in the literature.[54a]

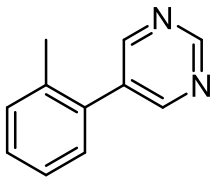
5-Phenylpyrimidine.



Following the Suzuki Miyaura cross-coupling procedure described above, this reaction was performed using phenylboronic acid (73 mg) and 5-bromopyrimidine (64 mg). The product was a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.23 (s, 1 H, Ar-*H*), 8.96 (s, 2 H, Ar-*H*), 7.57 – 7.43 (m, 5 H, Ar-*H*); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ = 157.0, 154.8, 134.5, 133.8, 129.5, 129.2, 127.0. This is consistent with data reported in the literature.[199]

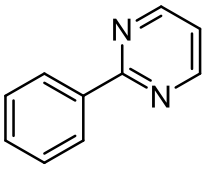
5-(2-Methylphenyl)pyrimidine.



Following the Suzuki Miyaura cross-coupling procedure described above, this reaction was performed using (2-methylphenyl)boronic acid (82 mg) and 5-bromopyrimidine (64 mg). The product was a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.21 (s, 1 H, Ar-*H*), 8.74 (s, 2 H, Ar-*H*), 7.38 – 7.29 (m, 3 H, Ar-*H*), 7.21 (d, *J* = 7.4 Hz, 1 H, Ar-*H*), 2.30 (s, 3 H, CH_3); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ = 157.2, 156.7, 135.8, 135.5, 134.3, 131.0, 130.0, 129.1, 126.6, 20.4. This is consistent with data reported in the literature.[199]

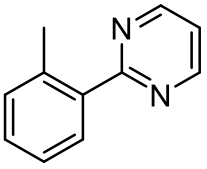
2-Phenylpyrimidine.



Following the Suzuki Miyaura cross-coupling procedure described above, this reaction was performed using phenylboronic acid (73 mg) and 2-bromopyrimidine (64 mg). The product was a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.81 (d, *J* = 4.8 Hz, 2 H, Ar-*H*), 8.45 - 8.43 (m, 2 H, Ar-*H*), 7.51 – 7.49 (m, 3 H, Ar-*H*), 7.18 (t, *J* = 4.8 Hz, 1 H, Ar-*H*); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ = 164.9, 157.4, 137.6, 130.9, 128.7, 128.3, 119.2. This is consistent with data reported in the literature.[199]

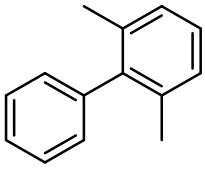
2-(2-Methylphenyl)pyrimidine.



Following the Suzuki Miyaura cross-coupling procedure described above, this reaction was performed using (2-methylphenyl)boronic acid (82 mg) and 2-bromopyrimidine (64 mg). The product was a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.84 (d, *J* = 4.8 Hz, 2 H, Ar-*H*), 7.80 – 7.78 (m, 1 H, Ar-*H*), 7.37 – 7.28 (m, 3 H, Ar-*H*), 7.21 (t, *J* = 4.9 Hz, 1 H, Ar-*H*), 2.54 (s, 3 H, C*H*$_3$); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ = 167.9, 157.0, 138.2, 137.3, 131.4, 130.5, 129.5, 126.0, 118.6, 21.1. This is consistent with data reported in the literature.[199]

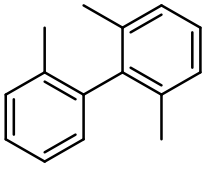
2,6-Dimethyl-1-phenylbenzene.



Following the Suzuki Miyaura cross-coupling procedure described above, this reaction was performed using phenylboronic acid (73 mg) and 2-bromo-*m*-xylene (47 μl). The product was a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43 (t, *J* = 7.4 Hz, 2 H, Ar-*H*), 7.35 (t, *J* = 7.4 Hz, 1 H, Ar-*H*), 7.20 – 7.08 (m, 5 H, Ar-*H*), 2.04 (s, 6 H, CH_3); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ = 142.0, 141.2, 136.2, 129.1, 128.5, 127.4, 127.1, 126.7, 21.0. This is consistent with data reported in the literature.[54a]

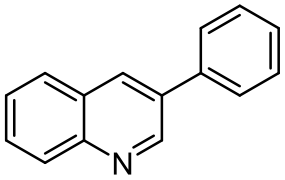
2,6-Dimethyl-2'-methyl-1,1'-biphenyl.



Following the Suzuki Miyaura cross-coupling procedure described above, this reaction was performed using (2-methylphenyl)boronic acid (82 mg) and 2-bromo-*m*-xylene (47 μl). The product was a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 – 7.27 (m, 3 H, Ar-*H*), 7.23 – 7.20 (m, 1 H, Ar-*H*), 7.17 – 7.15 (m, 2 H, Ar-*H*), 7.08 – 7.05 (m, 1 H, Ar-*H*), 2.02 (s, 3 H, CH_3), 2.00 (s, 6 H, CH_3); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ = 141.2, 140.7, 136.0, 135.7, 130.1, 129.0, 127.3, 127.1, 127.0, 126.2, 20.5, 21.0. This is consistent with data reported in the literature.[54a]

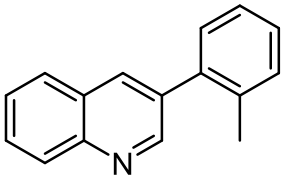
3-Phenylquinilone.



Following the Suzuki Miyaura cross-coupling procedure described above, this reaction was performed using phenylboronic acid (73 mg) and 3-bromoquinoline (54 μl). The product was a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.19 (d, *J* = 2.3 Hz, 1 H, Ar-*H*), 8.28 (d, *J* = 2.2 Hz, 1 H, Ar-*H*), 8.16 (d, *J* = 8.8 Hz, 1 H, Ar-*H*), 7.85 (d, *J* = 8.1 Hz, 1 H, Ar-*H*), 7.73 – 7.69 (m, 3 H, Ar-*H*), 7.56 (t, *J* = 7.5 Hz, 1 H, Ar-*H*), 7.51 (t, *J* = 7.6 Hz, 2 H, Ar-*H*), 7.43 (t, J = 7.4 Hz, 1 H, Ar-*H*); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ = 149.9, 147.3, 137.9, 136.1, 133.9, 133.3, 129.5, 129.2, 128.2, 128.1, 127.9, 127.5, 127.1. This is consistent with data reported in the literature.[199]

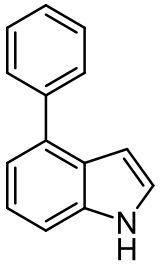
3-(2-Methylphenyl)quinilone.



Following the Suzuki Miyaura cross-coupling procedure described above, this reaction was performed using (2-methylphenyl)boronic acid (82 mg) and 3-bromoquinoline (54 μl). The product was a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.94 (d, *J* = 2.2 Hz, 1 H, Ar-*H*), 8.17 (d, *J* = 8.5 Hz, 1 H, Ar-*H*), 8.10 (d, *J* = 2.0 Hz, 1 H, Ar-*H*), 7.86 (d, *J* = 8.2 Hz, 1 H, Ar-*H*), 7.75 (ddd, *J* = 8.5, 6.9, 1.4 Hz, 1 H, Ar-*H*), 7.61 – 7.57 (m, 1 H, Ar-*H*), 7.36 – 7.32 (m, 4 H, Ar-*H*), 2.34 (s, 3 H, C*H*$_3$); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ = 151.6, 147.1, 138.2, 136.0, 135.5, 134.9, 130.8, 130.3, 129.5, 129.4, 128.3, 128.0, 127.9, 127.0, 126.3, 20.6. This is consistent with data reported in the literature.[199]

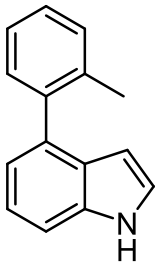
4-Phenyl-1H-indole.



Following the Suzuki Miyaura cross-coupling procedure described above, this reaction was performed using pheny boronic acid (73 mg) and 4-bromo-1*H*-indole (50 µl). The product was a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.12 (br s, 1 H, N*H*), 7.84 – 7.82 (m, 2 H, Ar-*H*), 7.60 – 7.56 (m, 2 H, Ar-*H*), 7.49 – 7.31 (m, 4 H, Ar-*H*), 7.23 (t, *J* = 2.8 Hz, 1 H, Ar-*H*), 6.82 (m, 1 H, Ar-*H*); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ = 141.3, 136.3, 134.5, 128.9, 128.6, 127.1, 126.2, 124.6, 122.4, 119.8, 110.4, 102.1. This is consistent with data reported in the literature.[200]

4-(2-Methylphenyl)-1H-indole.

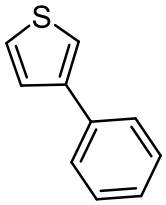


Following the Suzuki Miyaura cross-coupling procedure described above, this reaction was performed using (2-methylphenyl)boronic acid (82 mg) and 4-bromo-1*H*-indole (50 µl). The product was an off-white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (br s, 1 H, N*H*), 7.46 – 7.32 (m, 6 H, 4 x C_6H_4, 2 x C_8H_5NH), 7.18 (br t, *J* = 2.4 Hz, 1 H, C_8H_5NH), 7.12 (d, *J* = 7.1 Hz, 1 H, C_8H_5NH), 6.36 (m, 1 H, C_8H_5NH), 2.30 (s, 3 H, C*H*$_3$); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ = 140.9 (C_6H_4 *Q*), 136.3 (C_6H_4 *Q*), 135.7 (C_8H_5NH *Q*), 134.6 (C_8H_5NH *Q*), 130.2 (C_6H_4), 130.2 (C_6H_4), 127.3 (C_6H_4), 127.2 (C_8H_5NH *Q*), 125.6 (C_6H_4), 124.3

(C_8H_5NH), 121.9 (C_8H_5NH), 120.6 (C_8H_5NH), 110.0 (C_8H_5NH), 102.5 (C_8H_5NH), 20.4 (CH_3); **mp** = 145 - 146 ^oC; **IR** (neat, cm^{-1}) 3407, 753, 726; **HRMS** (ESI^+) exact mass calculated for $C_{15}H_{13}N$ $[M+H]^+$ *m/z* = 208.1126, found *m/z* = 208.1135.

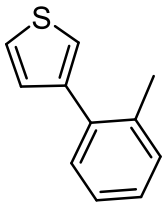
3-Phenylthiophene.



Following the Suzuki Miyaura cross-coupling procedure described above, this reaction was performed using phenylboronic acid (73 mg) and 3-bromothiophene (37 µl). The product was a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63 – 7.60 (m, 2 H, Ar-*H*), 7.46 (dd, *J* = 2.6, 1.8 Hz, 1 H, Ar-*H*), 7.43 – 7.39 (m, 4 H, Ar-*H*), 7.32 – 7.29 (m, 1 H, Ar-*H*); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ = 142.5, 136.0, 128.9, 127.3, 126.6, 126.5, 126.3, 120.4. Supelco Beta DEX column (injection temp 135 °C; column conditions 100 °C for 50 min ramp to 170 °C at 5°C / min; hold 10 min, pressure 21 psi) product 45.8 min. This is consistent with data reported in the literature.[199]

3-(2-Methylphenyl)thiophene.

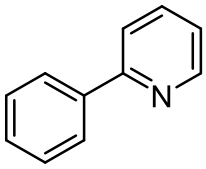


Following the Suzuki Miyaura cross-coupling procedure described above, this

reaction was performed using (2-methylphenyl)boronic acid (82 mg) and 3-bromothiophene (37 μl). The product was a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 (dd, *J* = 4.9, 2.9 Hz, 1 H, Ar-*H*), 7.35 – 7.33 (m, 1 H, Ar-*H*), 7.29 – 7.23 (m, 4 H, Ar-*H*), 7.18 (dd, *J* = 4.9, 1.2 Hz, 1 H, Ar-*H*), 2.37 (s, 3 H, C*H*$_3$); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ = 142.3, 136.7, 135.8, 130.6, 129.9, 129.1, 127.4, 125.9, 125.0, 122.7, 20.9. Supelco Beta DEX column (injection temp 135 °C; column conditions 100 °C for 50 min ramp to 170 °C at 5°C / min; hold 10 min, pressure 21 psi) product 45.1 min. This is consistent with data reported in the literature.[199]

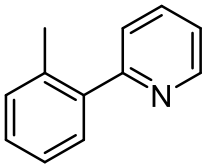
2-Phenylpyridine.



Following the Suzuki Miyaura cross-coupling procedure described above, this reaction was performed using phenylboronic acid (73 mg) and 2-bromopyridine (38 μl). The product was a golden yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.71 – 8.69 (m, 1 H, Ar-*H*), 8.01 – 7.98 (m, 2 H, Ar-*H*), 7.77 – 7.71 (m, 2 H, Ar-*H*), 7.50 – 7.40 (m, 3 H, Ar-*H*), 7.24 – 7.21 (m, 1 H, Ar-*H*); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ = 157.6, 149.8, 139.5, 136.2, 129.1, 128.9, 127.0, 122.2, 120.7. This is consistent with data reported in the literature.[199]

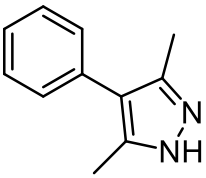
2-(2-Methylphenyl)pyridine.



Following the Suzuki Miyaura cross-coupling procedure described above, this reaction was performed using (2-methylphenyl)boronic acid (82 mg) and 2-bromopyridine (38 μl). The product was a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.69 (d, *J* = 4.7 Hz, 1 H, Ar-*H*), 7.73 (td, *J* = 7.7, 1.8 Hz, 1 H, Ar-*H*), 7.41 – 7.38 (m, 2 H, Ar-*H*), 7.30 – 7.26 (m, 3 H, Ar-*H*), 7.24 – 7.21 (m, 1 H, Ar-*H*), 2.37 (s, 3 H, C*H*$_3$); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ = 160.1, 149.2, 140.5, 136.2, 135.8, 130.8, 129.7, 128.3, 125.9, 124.1, 121.7, 20.3. This is consistent with data reported in the literature.[199]

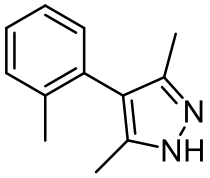
3,5-Dimethyl-4-phenyl-1H-pyrazole.



Following the Suzuki Miyaura cross-coupling procedure described above, this reaction was performed using phenylboronic acid (73 mg) and 4-bromo-3,5-dimethyl-1*H*-pyrazole (70 mg). The product was a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.51 (br s, 1H, N*H*), 7.44 (d, *J* = 7.6 Hz, 2 H, C_6H_5 *o*-*H*), 7.33 – 7.29 (m, 3 H, C_6H_5 *p*-H, *m*-*C*), 2.38 (s, 6 H, C*H*$_3$); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$): δ = 141.8 (pyr *C5/C3 Q*), 134.0 (C_6H_5 *Q*), 129.4 (C_6H_5 *o*-*C*), 128.5 (C_6H_5 *m*-*C*), 126.2 (C_6H_5 *p*-*C*), 118.3 (pyr *C4 Q*), 11.6 (*C*H$_3$); **mp** = 132 °C; **IR** (neat, cm^{-1}) 2925, 780, 754, 701, 541; **HRMS** (ESI^{+}) exact mass calculated for $C_{11}H_{12}N_2$ $[M+H]^+$ *m/z* = 173.1079, found *m/z* = 173.1077.

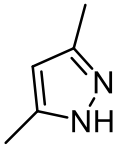
3,5-Dimethyl-4-(2-methylphenyl)-1H-pyrazole.



Following the Suzuki Miyaura cross-coupling procedure described above, this reaction was performed using (2-methylphenyl)boronic acid (82 mg) and 4-bromo-3,5-dimethyl-1*H*-pyrazole (70 mg). The product was a white crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.25 (br s, 1 H, N*H*), 7.30 – 7.20 (m, 3 H, C_6H_4), 7.11 (d, *J* = 7.2 Hz, 1 H, C_6H_4), 2.14 (s, 3 H, C*H*$_3$), 2.14 (s, 6 H, 2 x C*H*$_3$); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$): δ = 142.3 (pyr *C5/C3 Q*), 137.9 (C_6H_5 *Q*), 133.1 (C_6H_5 *Q*), 131.3 (C_6H_5), 130.1 (C_6H_5), 127.4 (C_6H_5), 125.7 (C_6H_5), 118.3 (pyr *C4 Q*), 20.0 (*C*H$_3$), 11.4 (2 x *C*H$_3$); **mp** = 115 – 116 ^{o}C; **IR** (neat, cm^{-1}) 2926, 2853, 1010, 750, 521; **HRMS** (ESI^{+}) exact mass calculated for $C_{12}H_{15}N_2$ $[M+H]^+$ *m/z* = 341.1689, found *m/z* = 341.1678.

3,5-Dimethyl-1H-pyrazole.



Following the Suzuki Miyaura cross-coupling procedure described above, this is the major de-brominated by-product of the reactions using 4-bromo-3,5-dimethyl-1*H*-pyrazole. This was a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.80 – 11.25 (br s, N*H*, 1H), 5.87 (s, 1H), 2.38 (6 H, C*H*$_3$), 2.34 (s, 6 H, C*H*$_3$); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$): δ = 144.4, 104.1, 12.3. This is consistent with data reported in the literature.[201]

6.4.4 Suzuki Miyaura cross coupling procedures with either diethyl o-bromobenzenephosphonate or diethyl [2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl] phosphonate

Procedure A

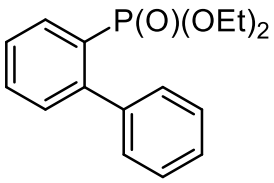
A flame-dried Schlenk flask was charged with the pre-catalyst [2.0 μmol; **92** (1.0mg), **93** (1.6mg), **90** (1.6mg), **94** (2.0mg), **95** (1.6mg) or $Pd(OAc)_2$ (0.4mg, 2.0 μmol) with PPh_3 (1.3mg, 5.0 μmol)], K_3PO_4 (170 mg, 800 μmol), the boronic acid (600 μmol) and THF (2 ml). Diethyl *o*-bromobenzenephosphonate (117 mg, 400 μmol) and H_2O (1 ml) were then added, the Schlenk flask lowered into a pre-heated oil bath and the reaction was stirred at the corresponding temperature for the allotted time. The reaction suspension was then filtered through a silica plug flushing with CH_2Cl_2 / MeOH (9 :1) and the solvent removed under reduced pressure. The product was purified by column chromatography eluting with EtOAc / petrol (2 : 1) to obtain the yield and was fully characterised.

Procedure B

A flame-dried Schlenk flask was charged with the pre-catalyst [1.0 μmol; **93** (0.8mg), **90** (0.8mg)], K_3PO_4 (85 mg, 400 μmol), aryl bromide (200 μmol) and THF (2 ml).[a] Diethyl [2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl] phosphonate (102 mg, 300 μmol) and H_2O (1 ml) were then added. The Schlenk flask was lowered into a pre-heated oil bath and the reaction stirred at the corresponding temperature for the allotted time. The reaction suspension was then filtered through a silica plug flushing with CH_2Cl_2 / MeOH (9 :1) and the solvent removed under reduced pressure. The product was purified by column chromatography eluting with EtOAc / petrol (2 : 1) to obtain the yield and was fully characterised.

[a] *For aryl bromides which were liquids; the solvent was added first, and then the bromide*

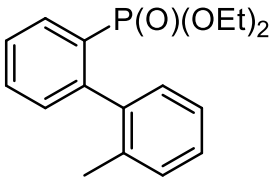
Diethyl 1,1'-biphenyl-2-ylphosphonate.



Following procedure A described above, this reaction was performed using phenylboronic acid (73 mg). The product was a colourless oil.

^{31}P {H} NMR (161.8 MHz, $CDCl_3$): δ = 18.7; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.98 (ddd, *J* = 14.3, 7.7, 1.3 Hz, 1 H, C_6H_4P), 7.46 (tt, 7.5, 1.4 Hz, 1 H, C_6H_4P), 7.38 – 7.28 (m, 6 H, C_6H_5, C_6H_4P), 7.24 (ddd, *J* = 7.2, 5.6, 1.1 Hz, 1 H, C_6H_5), 3.90 – 3.71 (m, 4 H, C*H*$_2$), 1.05 (t, *J* = 7.1 Hz, 6 H, C*H*$_3$); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ = 145.8 (d, *J* = 9.8 Hz, C_6H_4P *Q*), 141.2 (d, *J* = 4.3 Hz, C_6H_5 *Q*) , 133.6 (d, *J* = 9.7 Hz, C_6H_4P), 131.8 (d, *J* = 2.7 Hz, C_6H_4P), 131.2 (d, *J* = 14.0 Hz, C_6H_4P), 129.1 (2 x C_6H_5 *m*-*C*), 127.3 (2 x C_6H_5 *o*-*C*), 126.7 (C_6H_5 *p*-*C*), 126.7 (d, *J* = 14.0 Hz, C_6H_4P), 126.7 (d, *J* = 187 Hz, C_6H_4P *C*P), 61.6 (d, *J* = 6.1 Hz, *C*H_2), 15.9 (d, *J* = 6.8 Hz, *C*H_3); **IR** (neat, cm^{-1}) 1239, 1054, 1018, 958, 754, 700; **HRMS** (ESI^+) exact mass calculated for $C_{16}H_{20}PO_3$ $[M+H]^+$ *m/z* = 291.1150, found *m/z* = 291.1139. This is consistent with data reported in the literature.[169]

Diethyl 2-(2-methylphenyl)phenylphosphonate.

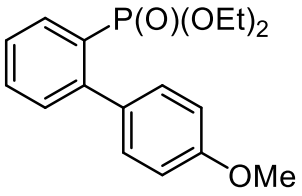


Following procedure A described above, this reaction was performed using (2-methylphenyl)boronic acid (82 mg). Following procedure B described above, the reaction was performed with 2-bromotoluene (24 µL, 200 µmol). The product was a

colourless oil.

^{31}P {H} NMR (161.8 MHz, $CDCl_3$): δ = 18.3; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.04 (ddd, *J* = 14.2, 7.8, 1.3 Hz, 1 H, C_6H_4P), 7.54 (tt, *J* = 7.6, 1.4 Hz, 1 H, C_6H_4P), 7.43 (tdd, *J* = 7.5, 3.7, 1.2 Hz, 1 H, C_6H_4P), 7.25 – 7.17 (m, 5 H, $C_6H_4CH_3$, C_6H_4P), 3.95 – 3.69 (m, 4 H, CH_2), 2.05 (s, 3 H, CH_3), 1.16 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3), 1.12 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ = 145.4 (d, *J* = 9.8 Hz, C_6H_4P *Q*), 140.7 (d, *J* = 3.9 Hz, $C_6H_4CH_3$ *Q*), 136.3 ($C_6H_4CH_3$ *Q*), 133.6 (d, *J* = 10.3 Hz, C_6H_4P), 131.9 (d, *J* = 2.7 Hz, C_6H_4P), 131.1 (d, *J* = 14.4 Hz, C_6H_4P), 130.0 ($C_6H_4CH_3$), 129.5 ($C_6H_4CH_3$), 127.7 ($C_6H_4CH_3$), 127.6 (d, *J* = 190 Hz, C_6H_4P $\underline{C}P$), 126.9 (d, *J* = 14.9 Hz, C_6H_4P), 124.6 ($C_6H_4CH_3$), 61.8 (t, *J* = 6.2 Hz, CH_2), 20.4 (CH_3), 16.3 (d, *J* = 6.6 Hz, $CH_2\underline{C}H_3$), 16.2 (d, *J* = 6.7 Hz, $CH_2\underline{C}H_3$); **IR** (neat, cm^{-1}) 1240, 1048, 1020, 958, 759, 554; **HRMS** (ESI^+) exact mass calculated for $C_{17}H_{21}O_3P$ $[M+H]^+$ *m/z* = 305.1307, found *m/z* = 305.1304.

Diethyl 2-(4-methoxyphenyl)phenylphosphonate.

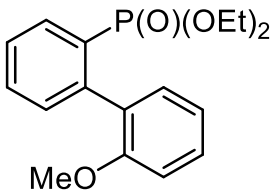


Following procedure A described above, this reaction was performed using (4-methoxyphenyl)boronic acid (91 mg). Following procedure B described above, the reaction was performed with 4-bromoanisole (25 µL, 200 µmol). For full characterisation this product was purified by column chromatography eluting with EtOAc / petrol (1 : 1). The product was a white solid.

^{31}P {H} NMR (161.8 MHz, $CDCl_3$): δ = 19.0; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.98 (dd, *J* = 14.1, 7.8 Hz, 1 H, C_6H_4P), 7.48 (t, 7.5 Hz, 1 H, C_6H_4P), 7.38 – 7.33 (m, 3 H, 2 x $C_6H_4OCH_3$, C_6H_4P), 7.27 – 7.24 (m, 1 H, C_6H_4P), 6.89 (d, *J* = 8.7 Hz, 2 H, $C_6H_4OCH_3$), 3.95 – 3.75 (m, 4 H, CH_2), 3.78 (s, 3 H, OCH_3), 1.11 (t, *J* = 7.1 Hz, 6 H, CH_2CH_3); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ = 159.0 ($C_6H_4OCH_3$ *Q*), 145.7 (d, *J* =

10.0 Hz, C_6H_4P *Q*), 133.7 (d, *J* = 9.4 Hz, C_6H_4P), 133.7 ($C_6H_4OCH_3$ *Q*), 131.9 (d, *J* = 2.7 Hz, C_6H_4P), 131.5 (d, *J* = 14.2 Hz, C_6H_4P), 130.4 (2 x $C_6H_4OCH_3$), 126.8 (d, *J* = 187 Hz, C_6H_4P *C*P), 126.5 (d, *J* = 14.2 Hz, C_6H_4P), 112.8 (2 x $C_6H_4OCH_3$), 61.7 (d, *J* = 6.0 Hz, *C*H_2), 55.2 (O*C*H_3), 16.1 (d, *J* = 6.8 Hz, CH_2*C*H_3); **mp** = 63 – 64 °C; **IR** (neat, cm^{-1}) 1242, 1022, 956, 763, 552; **HRMS** (ESI^+) exact mass calculated for $C_{17}H_{21}O_4P$ $[M+H]^+$ *m/z* = 321.1256, found *m/z* = 321.1265.

Diethyl 2-(2-methoxyphenyl)phenylphosphonate.

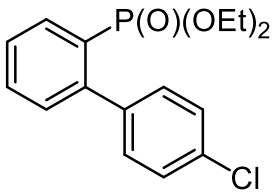


Following procedure A described above, this reaction was performed using (2-methoxyphenyl)boronic acid (91 mg). Following procedure B described above, the reaction was performed with 2-bromoanisole (25 µL, 200 µmol). For full characterisation this product was purified by column chromatography eluting with EtOAc / petrol (1 : 1). The product was a colourless oil.

^{31}P {H} NMR (161.8 MHz, $CDCl_3$): δ = 18.7; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.03 (ddd, *J* = 14.2, 7.7, 1.3 Hz, 1 H, C_6H_4P), 7.50 (tt, 7.5, 1.5 Hz, 1 H, C_6H_4P), 7.39 (tdd, *J* = 7.5, 3.6, 1.2 Hz, 1 H, C_6H_4P), 7.32 (td, *J* = 8.1, 1.7 Hz, 1 H, $C_6H_4OCH_3$), 7.28 – 7.24 (m, 1 H, C_6H_4P), 7.21 (dd, *J* = 7.4, 1.7 Hz, 1 H, $C_6H_4OCH_3$), 6.95 (dt, *J* = 7.4, 0.8 Hz, 1 H, $C_6H_4OCH_3$), 6.91 (d, *J* = 8.3 Hz, 1 H, $C_6H_4OCH_3$), 3.93 – 3.75 (m, 4 H, C*H*$_2$), 3.69 (s, 3 H, OC*H*$_3$), 1.12 (t, *J* = 7.0 Hz, 3 H, CH_2C*H*$_3$), 1.11 (t, *J* = 7.0 Hz, 3 H, CH_2C*H*$_3$); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ = 156.6 ($C_6H_4OCH_3$ *Q*), 142.3 (d, *J* = 9.4 Hz, C_6H_4P *Q*), 133.7 (d, *J* = 10.0 Hz, C_6H_4P) , 131.8 (d, *J* = 14.1 Hz, C_6H_4P), 131.5 (d, *J* = 2.5 Hz, C_6H_4P), 131.4 ($C_6H_4OCH_3$), 129.9 (d, *J* = 3.9 Hz, $C_6H_4OCH_3$ *Q*), 129.0 ($C_6H_4OCH_3$), 127.6 (d, *J* = 187 Hz, C_6H_4P *C*P), 126.8 (d, *J* = 14.9 Hz, C_6H_4P), 119.5 ($C_6H_4OCH_3$), 110.2 ($C_6H_4OCH_3$), 61.6 (t, *J* = 6.1 Hz, *C*H_2), 55.3 (O*C*H_3), 16.1 (t, *J* = 6.7 Hz, CH_2*C*H_3); **IR** (neat, cm^{-1}) 1230, 1050, 1019, 959, 748, 554; **HRMS** (ESI^+) exact

mass calculated for $C_{17}H_{21}O_4P$ $[M+H]^+$ *m/z* = 321.1256, found *m/z* = 321.1270.

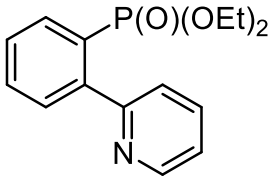
Diethyl 2-(4-chlorophenyl)phenylphosphonate.



Following procedure A described above, this reaction was performed using (4-chlorophenyl)boronic acid (94 mg). Following procedure B described above, the reaction was performed with 1-bromo-4-chlorobenzene (38 mg, 200 µmol). The product was a colourless oil.

^{31}P {H} NMR (161.8 MHz, $CDCl_3$): δ = 18.4; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.97 (ddd, *J* = 14.5, 7.6, 1.2 Hz, 1 H, C_6H_4P), 7.49 (tt, *J* = 7.4, 1.3 Hz, 1 H, C_6H_4P), 7.38 (tdd, *J* = 7.5, 3.5, 1.1 Hz, 1 H, C_6H_4P), 7.30 (s, 4 H, C_6H_4Cl), 7.23 – 7.20 (m, 1 H, C_6H_4P), 3.94 – 3.77 (m, 4 H, CH_2), 1.09 (t, *J* = 7.1 Hz, 6 H, CH_3); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ = 144.9 (d, *J* = 9.6 Hz, C_6H_4P *Q*), 140.0 (d, *J* = 4.0 Hz, C_6H_4Cl *Q*), 134.0 (d, *J* = 9.6 Hz, C_6H_4P), 133.8 (C_6H_4Cl Q), 132.3 (d, *J* = 2.7 Hz, C_6H_4P), 131.4 (d, *J* = 13.9 Hz, C_6H_4P), 130.8 (2 x C_6H_4Cl), 127.8 (2 x C_6H_4Cl), 127.4 (d, *J* = 14.7 Hz, C_6H_4P), 127.1 (d, *J* = 188 Hz, C_6H_4P *C*P), 62.1 (d, *J* = 5.9 Hz, CH_2), 16.2 (d, *J* = 6.7 Hz, CH_3); **IR** (neat, cm^{-1}) 1232, 1052, 1017, 959, 764, 569; **HRMS** (ESI^+) exact mass calculated for $C_{16}H_{19}PO_3Cl$ $[M+H]^+$ *m/z* = 325.0760, found *m/z* = 325.0748.

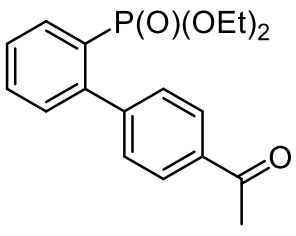
Diethyl 2-(pyridin-2-yl)phenylphosphonate.



Following procedure B described above, the reaction was performed with 2-bromopyridine (19 µL, 200 µmol). The product was a yellow solid**.**

^{31}P {H} NMR (161.8 MHz, $CDCl_3$): δ = 18.4; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.62 (d, *J* = 4.9 Hz, 1 H, C_5H_4N), 7.98 (dd, *J* = 14.2, 7.7 Hz, 1 H, C_6H_4P), 7.69 (t, 7.6 Hz, 1 H, C_5H_4N), 7.60 (d, *J* = 8.2 Hz, 1 H, C_5H_4N), 7.56 (d, *J* = 7.5 Hz, 1 H, C_6H_4P), 7.49 – 7.44 (m, 2 H, C_6H_4P), 7.26 – 7.23 (m, 1 H, C_5H_4N), 3.96 – 3.83 (m, 4 H, C*H*$_2$), 1.10 (t, *J* = 7.0 Hz, 6 H, C*H*$_3$); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ = 158.9 (d, *J* = 4.5 Hz, C_5H_4N *Q*), 148.8 (C_5H_4N), 144.7 (d, *J* = 9.9 Hz, C_6H_4P *Q*), 135.6 (C_5H_4N), 133.8 (d, *J* = 9.3 Hz, C_6H_4P), 132.2 (d, *J* = 2.5 Hz, C_6H_4P), 130.9 (d, *J* = 13.6 Hz, C_6H_4P), 127.9 (d, *J* = 14.3 Hz, C_6H_4P), 126.5 (d, *J* = 186 Hz, C_6H_4P *C*P), 124.7 (C_6H_4N), 122.4 (C_6H_4N), 62.0 (t, *J* = 5.8 Hz, *C*H_2), 16.1 (d, *J* = 7.0 Hz, *C*H_3); **mp** = 74 – 76 °C; **IR** (neat, cm^{-1}) 1259, 1083, 1011, 794, 753; **HRMS** (ESI^+) exact mass calculated for $C_{15}H_{18}O_3NP$ $[M+H]^+$ m/z = 292.1103, found m/z = 292.1097. This is consistent with data reported in the literature.[167]

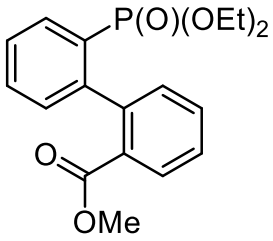
1-(2-Diethoxyphosphorylphenyl)-4-acetophenone.



Following procedure B described above, the reaction was performed with 4-chloroacetophenone (26 µl, 200 µmol). The product was a white solid.

^{31}P {H} NMR (161.8 MHz, $CDCl_3$): δ = 18.2; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.02 (ddd, *J* = 15.1, 8.1, 1.3 Hz, 1 H, C_6H_4P), 7.97 (d, *J* = 8.3 Hz, 2 H, $C_6H_4COCH_3$), 7.56 (tt, *J* = 7.6, 1.2 Hz, 1 H, C_6H_4P), 7.52 (d, *J* = 8.3 Hz, 2 H, $C_6H_4COCH_3$), 7.45 (tdd, *J* = 7.6, 3.5, 1.2 Hz, 1 H, C_6H_4P), 7.30 – 7.27 (m, 1 H, C_6H_4P), 3.97 – 3.80 (m, 4 H, CH_2), 2.62 (s, 3 H, CH_3), 1.11 (t, *J* = 7.1 Hz, 6 H, $CH_2C\underline{H_3}$); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ = 198.0 (*C*O), 146.4 (d, *J* = 4.1 Hz, $C_6H_4COCH_3$ *Q*), 144.8 (d, *J* = 9.6 Hz, C_6H_4P *Q*), 136.1 ($C_6H_4COCH_3$ *Q*), 133.9 (d, *J* = 9.4 Hz, C_6H_4P), 132.2 (d, *J* = 2.6 Hz, C_6H_4P), 131.0 (d, *J* = 14.0 Hz, C_6H_4P), 129.7 (2 x $C_6H_4COCH_3$), 127.6 (2 x $C_6H_4COCH_3$), 127.6 (d, *J* = 14.6 Hz, C_6H_4P), 126.9 (d, *J* = 187 Hz, C_6H_4P $\underline{C}P$), 62.0 (t, *J* = 6.0 Hz, $\underline{C}H_2$), 26.8 (CH_3), 16.2 (d, *J* = 6.6 Hz, $CH_2\underline{C}H_3$); **mp** = 78 – 79 °C; **IR** (neat, cm^{-1}) 1680, 1230, 1046, 1019, 960, 767, 569; **HRMS** (ESI^+) exact mass calculated for $C_{18}H_{22}O_4P$ $[M+H]^+$ *m/z* = 333.1256, found *m/z* = 333.1268.

Methyl (2'-diethoxyphosphorylphenyl[1,1'-biphenyl])-2-benzoat.e

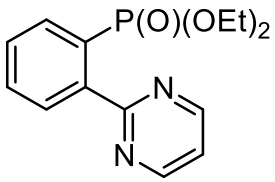


Following procedure B described above, the reaction was performed with methyl-2-bromobenzoate (28 µl, 200 µmol). The product was a colourless oil.

^{31}P {H} NMR (161.8 MHz, $CDCl_3$): δ = 18.8; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.04 (dd, *J* = 7.8, 1.4 Hz, 1 H, $C_6H_4CO_2CH_3$), 8.01 (ddd, *J* = 14.3, 7.7, 1.3 Hz, 1 H, C_6H_4P), 7.56 – 7.52 (m, 1 H, C_6H_4P), 7.50 (dd, *J* = 7.5, 1.4 Hz, 1 H, $C_6H_4CO_2CH_3$), 7.45 (dd, *J* = 7.7, 1.3 Hz, 1 H, $C_6H_4CO_2CH_3$), 7.45 – 7.41 (m, 1 H, C_6H_4P), 7.30 (dd, *J* = 7.6 Hz, 1.3 Hz, 1 H, $C_6H_4CO_2CH_3$), 7.23 – 7.20 (m, 1 H, C_6H_4P), 3.94 – 3.71 (m, 4 H, CH_2), 3.57 (s, 3 H, OCH_3), 1.10 (q, *J* = 6.9 Hz, 6 H, $CH_2C\underline{H_3}$); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ = 167.2 (*C*O), 145.7 (d, *J* = 8.9 Hz, C_6H_4P *Q*), 142.4 (d, *J* = 4.0 Hz, $C_6H_4CO_2CH_3$ *Q*), 133.3 (d, *J* = 9.9 Hz, C_6H_4P), 131.6 (d, *J* = 2.7 Hz, C_6H_4P), 131.5 ($C_6H_4CO_2CH_3$), 131.0 ($C_6H_4CO_2CH_3$), 130.2 (d, *J* = 14.2 Hz, C_6H_4P), 130.0

($C_6H_4CO_2CH_3$), 130.0 ($C_6H_4CO_2CH_3$ *Q*), 127.8 ($C_6H_4CO_2CH_3$), 126.8 (d, *J* =14.9 Hz, C_6H_4P), 126.3 (d, *J* = 187 Hz, C_6H_4P *C*P), 61.9 (d, *J* = 6.1 Hz, *C*H_2), 61.6 (d, *J* = 5.8 Hz, *C*H_2), 51.8 (O*C*H_3), 16.2 – 16.1 (m, CH_2*C*H_3); **IR** (neat, cm^{-1}) 1721, 1239, 1025, 957, 777, 765, 551; **HRMS** (ESI^+) exact mass calculated for $C_{18}H_{22}O_5P$ $[M+H]^+$ *m/z* = 349.1205, found *m/z* = 349.1217.

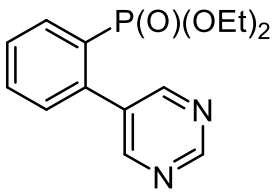
Diethyl 2-(pyrimid-2-yl)phenylphosphonate.



Following procedure B described above, the reaction was performed with 2-bromopyrimidine (32 mg, 200 µmol). The product was a golden yellow oil.

^{31}P {H} NMR (161.8 MHz, $CDCl_3$): δ = 18.0; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.82 (d, *J* = 5.0 Hz, 2 H, 2 x $C_4H_3N_2$), 7.99 (dd, *J* = 14.3, 7.3 Hz, 1 H, C_6H_4P), 7.75 – 7.72 (m, 1 H, C_6H_4P), 7.62 (t, *J* = 7.6 Hz, 1 H, C_6H_4P), 7.53 (tdd, *J* = 7.7, 3.6, 1.2 Hz, 1 H, C_6H_4P), 7.28 (t, *J* = 4.8 Hz, 1 H, $C_4H_3N_2$), 4.11 – 3.95 (m, 4 H, C*H*$_2$), 1.22 (t, *J* = 7.1 Hz, 6 H, C*H*$_3$); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ = 167.1 (d, *J* = 4.8 Hz, $C_4H_3N_2$ *Q*), 156.7 (2 x $C_4H_3N_2$), 143.5 (d, *J* = 9.4 Hz, C_6H_4P *Q*), 133.9 (d, *J* = 8.5 Hz, C_6H_4P), 132.2 (d, *J* = 2.7 Hz, C_6H_4P), 130.6 (d, *J* = 13.1 Hz, C_6H_4P), 128.9 (d, *J* = 14.0 Hz, C_6H_4P), 127.3 (d, *J* = 187 Hz, C_6H_4P *C*P), 119.5 ($C_4H_3N_2$), 62.2 (d, *J* = 5.7 Hz, *C*H_2), 16.3 (t, *J* = 6.7 Hz, *C*H_3); **IR** (neat, cm^{-1}) 1557, 1413, 1233, 1018, 958, 759, 566; **HRMS** (ESI^+) exact mass calculated for $C_{14}H_{18}O_3N_2P$ $[M+H]^+$ *m/z* = 293.1055, found *m/z* = 293.1066.

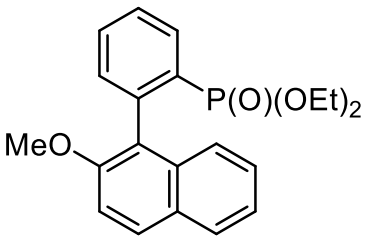
Diethyl 2-(pyrimid-5-yl)phenylphosphonate.



Following procedure B described above, the reaction was performed with 5-bromopyrimidine (32 mg, 200 µmol). The product was a golden yellow oil.

^{31}P {H} NMR (161.8 MHz, $CDCl_3$): δ = 17.6; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.22 (s, 1 H, $C_4H_3N_2$), 8.76 (s, 2 H, $C_4H_3N_2$), 8.11 (dd, *J* = 14.5, 7.6 Hz, 1 H, C_6H_4P), 7.64 (t, 7.6 Hz, 1 H, C_6H_4P), 7.55 (td, *J* = 7.7, 3.6 Hz, 1 H, C_6H_4P), 7.32 – 7.29 (m, 1 H, C_6H_4P), 4.00 – 3.89 (m, 4 H, C*H*$_2$), 1.16 (t, *J* = 7.1 Hz, 6 H, C*H*$_3$); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ = 157.7 ($C_4H_3N_2$), 156.5 (2 x $C_4H_3N_2$), 138.3 (d, *J* = 8.7 Hz, C_6H_4P *Q*), 135.2 (d, *J* = 4.1 Hz, $C_4H_3N_2$ *Q*), 134.3 (d, *J* = 9.6 Hz, C_6H_4P), 132.6 (d, *J* = 2.5 Hz, C_6H_4P), 131.3 (d, *J* = 13.5 Hz, C_6H_4P), 128.7 (d, *J* = 14.5 Hz, C_6H_4P), 128.1 (d, *J* = 187.2 Hz, C_6H_4P *C*P), 62.3 (d, *J* = 6.1 Hz, *C*H_2), 16.3 (d, *J* = 6.4 Hz, *C*H_3); **IR** (neat, cm^{-1}) 1408, 1238, 1046, 1015, 963, 764, 728, 573; **HRMS** (ESI^+) exact mass calculated for $C_{14}H_{18}O_3N_2P$ $[M+H]^+$ *m/z* = 293.1055, found *m/z* = 293.1068.

2-Methoxy-1-(2'-diethoxyphosphorylphenyl)naphthalene (**101**).

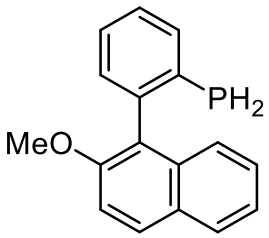


Following procedure B described above, the reaction was performed with 2-methoxy-1-naphthylboronic acid (61 mg, 200 µmol). The product was a white crystalline solid.

^{31}P {H} NMR (161.8 MHz, $CDCl_3$): δ = 18.3; **^{1}H NMR** (400 MHz, $CDCl_3$): δ =

8.19 (dd, *J* = 14.2, 7.7 Hz, 1 H, C_6H_4P), 7.88 (d, *J* = 9.1 Hz, 1 H, $C_{10}H_6OCH_3$), 7.79 – 7.77 (m, 1 H, $C_{10}H_6OCH_3$), 7.63 (tt, *J* = 7.4, 1.3 Hz, 1 H, C_6H_4P), 7.54 – 7.49 (m, 1 H, C_6H_4P), 7.34 (d, *J* = 9.1 Hz, 1 H, $C_{10}H_6OCH_3$), 7.30 – 7.24 (m, 3 H, 2 x $C_{10}H_6OCH_3$, C_6H_4P), 7.12 – 7.10 (m, 1 H, $C_{10}H_6OCH_3$), 3.83 (s, 3 H, O*C*H_3), 3.80 – 3.49 (m, 4 H, C$\underline{H_2}$$CH_3$), 0.96 (t, *J* = 7.1 Hz, 3 H $CH_2C\underline{H_3}$), 0.71 (t, *J* = 7.1 Hz, 3 H, $CH_2C\underline{H_3}$); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ = 154.1 ($C_{10}H_6OCH_3$ *Q*), 140.6 (d, *J* = 8.9 Hz, C_6H_4P *Q*), 134.3 (d, *J* = 10.0 Hz, C_6H_4P), 134.1 ($C_{10}H_6OCH_3$ *Q*), 132.2 (C_6H_4P), 132.2 (d, *J* = 11.2 Hz, C_6H_4P), 129.5 ($C_{10}H_6OCH_3$), 129.3 (d, *J* = 189 Hz, C_6H_4P $\underline{C}P$), 128.4 ($C_{10}H_6OCH_3$ *Q*), 127.6 ($C_{10}H_6OCH_3$), 127.1 (d, *J* = 14.7 Hz, C_6H_4P), 125.9 ($C_{10}H_6OCH_3$), 125.6 ($C_{10}H_6OCH_3$), 123.7 (d, *J* = 3.8 Hz, $C_{10}H_6OCH_3$ *Q*), 123.2 ($C_{10}H_6OCH_3$), 112.9 ($C_{10}H_6OCH_3$), 61.6 (d, *J* = 5.7 Hz, $\underline{C}H_2CH_3$), 61.4 (d, *J* = 6.0 Hz, $\underline{C}H_2CH_3$), 56.2 (O*C*H_3), 16.0 (d, *J* = 6.6 Hz, $CH_2\underline{C}H_3$), 15.5 (d, *J* = 7.0 Hz, $CH_2\underline{C}H_3$); **mp** = 128 – 129 °C; **IR** (neat, cm^{-1}) 1234, 1070, 1048, 1020, 966, 771, 750, 559; **HRMS** (ESI$^+$) exact mass calculated for $C_{21}H_{23}PO_4$ $[M+Na]^+$ *m/z* = 393.1232, found *m/z* = 393.1234.

2-(2'-Methoxy-1'-naphthyl)phenylphosphine (**102**).

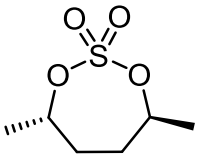


A suspension of $LiAlH_4$ (41 mg, 1.08 mmol) in THF (4 ml) was cooled to -78 °C and chlorotrimethylsilane (0.14 ml, 1.08 mmol) added. This was then allowed to warm to RT over 30 min, then cooled again to -78 °C and 2-methoxy-1-(2'-diethoxyphosphorylphenyl)naphthalene **101** (0.133 g, 35.9 µmol) in THF (4 ml) was added. The mixture was allowed to warm to RT and stirred at this temperature for 16 h. The reaction was quenched with degassed H_2O (10 ml) and the product was extracted with degassed Et_2O (2 x 15 ml). The combined organic extracts were then washed with H_2O (10 ml), dried ($MgSO_4$), filtered and the solvent removed under reduced pressure

to give the primary phosphine **102**, as a white solid (93 mg, 98 %).

^{31}P NMR (161.8 MHz, $CDCl_3$): δ = -127.8 (t, $^3J_{P-H}$ = 204 Hz); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 9.0 Hz, 1 H, $C_{10}H_6OCH_3$), 7.87 – 7.85 (m, 1 H, C_6H_4P), 7.73 (t, *J* = 7.1 Hz, 1 H, C_6H_4P), 7.44 (t, *J* = 7.5 Hz, 1 H, C_6H_4P), 7.39 (d, *J* = 9.1 Hz, 1 H, $C_{10}H_6OCH_3$), 7.38 – 7.34 (m, 3 H, $C_{10}H_6OCH_3$), 7.27 – 7.23 (m, 2 H, $C_{10}H_6OCH_3$, C_6H_4P), 3.89 (s, 3 H, O*C*H_3), 3.59 (dd, $^3J_{P-H}$ = 204 Hz, $^1J_{H-H}$ = 12.3 Hz, 1 H, P*H*), 3.54 (dd, $^3J_{P-H}$ = 204 Hz, $^1J_{H-H}$ = 12.3 Hz, 1 H, P*H*); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ = 153.8 ($C_{10}H_6OCH_3$ *Q*), 141.1 (d, *J* = 14.0 Hz, C_6H_4P *Q*), 135.2 (d, *J* = 11.3 Hz, C_6H_4P *Q*), 133.3 ($C_{10}H_6OCH_3$ *Q*), 131.2 ($C_{10}H_6OCH_3$ *Q*), 131.1 (d, *J* = 2.7 Hz, C_6H_4P), 130.1 (d, *J* = 212 Hz, $C_{10}H_6OCH_3$ *C*P), 129.8 ($C_{10}H_6OCH_3$), 128.4 (C_6H_4P), 128.1 ($C_{10}H_6OCH_3$), 127.5 (d, *J* = 4.0 Hz, C_6H_4P), 126.8 ($C_{10}H_6OCH_3$), 124.9 ($C_{10}H_6OCH_3$), 124.6 (d, *J* = 3.2 Hz, $C_{10}H_6OCH_3$ *Q*), 123.8 ($C_{10}H_6OCH_3$), 113.5 ($C_{10}H_6OCH_3$), 56.7 (O*C*H_3); **IR** (neat, cm^{-1}) 2360, 1258, 1069, 1010, 783; **HRMS** (ESI^+) exact mass calculated for $C_{17}H_{15}OP$ $[M+H]^+$ *m/z* = 266.0861, found *m/z* = 266.0863.

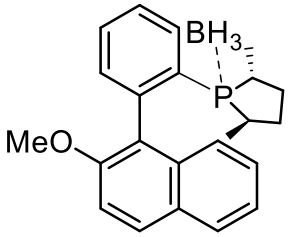
(2S,5S)-2,5-hexanediol cyclic sulphate.



(2*S*,5*S*)-2,5-hexanediol (0.5 g, 4.23 mmol) was dissolved in CCl_4 (2 ml), $SOCl_2$ (0.38 ml, 5.29 mmol) was added and the solution was heated at 80 ^oC for 1.5 h. The solvent was then removed under reduced pressure and CCl_4 (2 ml), CH_3CN (2 ml), H_2O (3 ml) added. The reaction mixture was cooled to 0 ^oC and $RuCl_3$ (6.0 mg, 29 μmol), $NaIO_4$ (1.81 g, 8.46 mmol) were added. The mixture was stirred at RT for 1 h. H_2O (10 ml) was then added and the product was extracted with Et_2O (2 x 10 ml). The combined organic extracts were washed with brine (10 ml), dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. The crude product was purified by recrystallisation from Et_2O / hexane to give the sulphate as a white solid (0.48 g, 63 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.85 – 4.77 (m, 2 H, OC*H*), 2.00 – 1.87 (m, 4 H, CH_2), 1.42 (d, *J* = 6.4 Hz, 6 H, CH_3); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ = 81.6 (*C*H), 34.6 (*C*H_2), 21.7 (*C*H_3). This is consistent with data reported in the literature.[175b]

1-[2-(2'-Methoxy-1'-naphthyl)phenyl]-2,5-dimethylphospholanium-1-yl](trihydrido) borate (**103**).



2-(2'-methoxy-1'-naphthyl)phenylphosphine **102** (93 mg, 349 µmol) dissolved in degassed THF (20 ml) was cooled to -78 °C and ^{n}BuLi (2.5 M in hexanes, 0.15 ml, 384 µmol) was added dropwise. The solution was then allowed to warm to RT and stirred at this temperature for 1 h. A solution of (2*S*,5*S*)-2,5-hexanediol cyclic sulphate (69 mg, 384 µmol) in THF (10 ml) was then added at RT and the resulting solution was stirred until the dark red solution decolourised to pale yellow (2 h). The solution was cooled to -78 °C and a second portion of ^{n}BuLi (2.5 M in hexanes, 0.15 ml, 384 µmol) was added dropwise. The solution was allowed to warm to RT and was stirred again until the dark red solution decolourised to pale yellow (20 h). The solution was cooled again to -78 °C and a third portion of ^{n}BuLi (2.5 M in hexanes, 0.15 ml, 384 µmol) was added dropwise. The solution was allowed to warm to RT and then stirred at this temperature for 36 h. BH_3.THF solution (1.0 M in THF, 0.70 ml, 700 µmol) was then added at 0 °C and the solution was stirred at RT for 16 h. H_2O (10 ml) was then added and the solvent was removed under reduced pressure. The residue was extracted with Et_2O (3 x 15 ml) and the combined organic extracts were washed with H_2O (10 ml), dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The crude product was purified by column chromatography eluting with petrol / EtOAc (5 : 1) to give the phosphine borane **103** as a white solid (33 mg, 26 %).

^{11}B NMR (400 MHz, $CDCl_3$): δ = -39.6 (d, $J_{P\text{-}B}$ = 49 Hz); **^{31}P {H} NMR** (161.8 MHz, $CDCl_3$): δ = 40.7 (br m); **^{1}H NMR** (400 MHz, $CDCl_3$): mixture of diasterioisomers (1 : 1): δ = 8.11 – 7.90 (m, 4 H, 2 x $C_{10}H_6OCH_3$, 2 x C_6H_4P), 7.84 – 7.81 (m, 2 H, $C_{10}H_6OCH_3$), 7.58 – 7.50 (m, 4 H, C_6H_4P), 7.34 – 7.30 (m, 6 H, $C_{10}H_6OCH_3$), 7.23 – 7.18 (m, 2 H, C_6H_4P), 7.15 – 7.08 (m, 2 H, $C_{10}H_6OCH_3$), 3.844 (s, 3 H, OC*H*$_3$), 3.839 (s, 3 H, OC*H*$_3$), 2.22 – 2.11 (m, 2 H, 2 x PC*H*), 1.94 – 1.81 (m, 2 H, 2 x PC*H*), 1.63 – 1.50 (m, 4 H, 2 x C*H*$_2$), 1.31 – 1.12 (m, 4 H, 2 x C*H*$_2$), 1.00 – 0.88 (m, 6 H, 2 x C*H*$_3$), 0.49 (d, *J* = 6.6 Hz, 3H, C*H*$_3$) , 0.47 (d, *J* = 6.7 Hz, 3H, C*H*$_3$); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$): δ = 154.4 ($C_{10}H_6$ *Q*), 153.7 ($C_{10}H_6$ Q), 141.8 (d, *J* = 6.0 Hz, *Q*), 141.4 (d, *J* = 2.7 Hz, *Q*), 136.1, 135.0, 135.4, 135.3, 134.6 (*Q*), 134.4 (*Q*), 133.1 (d, *J* = 7.5 Hz), 132.8 (d, *J* = 6.8 Hz), 130.8 (d, *J* = 2.3 Hz), 130.7 (d, *J* = 2.0 Hz), 128.6 (d, *J* = 38.1 Hz, C_6H_4P *C*P), 128.6 (*Q*), 128.6 (*Q*), 128.2, 128.0 (d, *J* = 37.0 Hz, C_6H_4P *C*P), 128.0, 127.5 (d, *J* = 10.7 Hz), 127.2 (d, *J* = 9.5 Hz), 127.0, 126.6, 125.3, 125.1, 123.7, 123.6 (d, *J* = 1.7 Hz, *Q*), 123.5, 123.2 (d, *J* = 2.4 Hz, *Q*), 112.7, 112.5, 55.8 (O*C*H$_3$) 36.8 (d, *J* = 37.2 Hz, *C*HCH$_3$), 36.6 (d, *J* = 37.6 Hz, *C*HCH$_3$), 35.0 (2 x *C*H$_2$), 34.2 (d, *J* = 5.8 Hz, *C*H$_2$), 34.0 (d, *J* = 5.4 Hz, *C*H$_2$), 32.8 (d, *J* = 34.5 Hz, *C*HCH$_3$), 31.5 (d, *J* = 34.0 Hz, *C*HCH$_3$), 15.6 (d, *J* = 2.9 Hz, CH*C*H$_3$) 15.2 (d, *J* = 2.6 Hz, CH*C*H$_3$), 14.4 (d, *J* = 4.7 Hz, CH*C*H$_3$), 13.7 (d, *J* = 4.6 Hz, CH*C*H$_3$) mixture (1 : 1) of diastereomers; **IR** (neat, cm^{-1}) 2929, 2370, 1265, 1065, 807, 730, 677; **HRMS** (ESI$^+$) exact mass calculated for $C_{23}H_{28}BOP$ $[M+Na]^+$ *m/z* = 385.1869, found *m/z* = 385.1857.

6.4.5 Suzuki Miyaura cross coupling procedure with diethyl 1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-ylphosphonate.

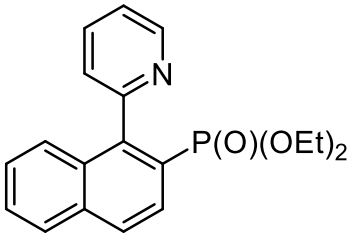
A flame-dried Schlenk flask was charged with pre-catalyst **90**, K_3PO_4 (85 mg, 400 μmol), aryl bromide (200 μmol) and diethyl 1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-naphthalen-2-ylphosphonate **100** (78 mg, 300 μmol). Solvent[ab] was then added, the Schlenk flask then lowered into the oil bath and the reaction was stirred at the corresponding temperature for the allotted time. The reaction suspension was then filtered through a silica plug flushing with CH_2Cl_2 / MeOH (9 : 1) and the solvent was

removed under reduced pressure. The product was purified by column chromatography eluting with EtOAc / petrol (2 : 1) to obtain the yield and was fully characterised.

[a] *For aryl bromides which were liquids; the solvent was added first, and then the bromide.*

[b] *Solvent was either THF (2 ml) with H_2O (1 ml) or toluene (3 ml).*

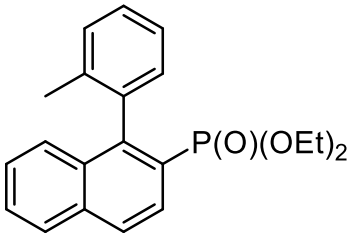
Diethyl (1-(2'-pyridyl)-2-naphthyl)phosphonate.



Following the Suzuki Miyaura cross-coupling procedure described above, this reaction was performed using **90** (0.8 mg, 1.0 μmol) and 2-bromopyridine (19 μL). The product was a yellow solid.

^{31}P {H} NMR (161.8 MHz, $CDCl_3$): δ = 18.5; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.77 (d, *J* = 4.9 Hz, 1 H, C_5H_4N), 8.06 (dd, *J* = 11.8, 8.5 Hz, 1 H, $C_{10}H_6P$), 7.98 (dd, *J* = 8.6, 3.8 Hz, 1 H, $C_{10}H_6P$), 7.91 (d, *J* = 8.2 Hz, 1 H, $C_{10}H_6P$), 7.84 (td, *J* = 7.7, 1.8 Hz, 1 H, C_5H_4N), 7.58 – 7.53 (m, 2 H, $C_{10}H_6P$, C_6H_4N), 7.43 – 7.39 (m, 2 H, $C_{10}H_6P$, C_6H_4N), 7.33 (d, *J* = 8.5 Hz, 1 H, $C_{10}H_6P$), 4.06 – 3.91 (br m, 4 H, CH_2), 1.19 (t, *J* = 6.9 Hz, 6 H, CH_3); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ = 157.6 (d, *J* = 5.9 Hz, C_5H_4N *Q*), 148.9 (C_5H_4N), 143.8 (d, *J* = 10.1 Hz, $C_{10}H_6P$ *Q*), 135.9 (C_5H_4N), 135.3 (d, *J* = 2.5 Hz, $C_{10}H_6P$ *Q*), 132.5 (d, *J* = 15.9 Hz, $C_{10}H_6P$ *Q*), 128.3 (d, *J* = 23.8 Hz, $C_{10}H_6P$), 128.3 (C_5H_4N), 128.1 (C_5H_4N), 128.1, 127.1, 127.1, 126.4 ($C_{10}H_6P$), 124.4 (d, *J* = 186 Hz, $C_{10}H_6P$ *C*P), 122.8 ($C_{10}H_6P$), 62.0 (d, *J* = 5.6 Hz, CH_2), 16.3 (d, *J* = 4.4 Hz, CH_3); **mp** = 97 – 99 °C; **IR** (neat, cm^{-1}) = 1239, 1047, 1017, 960, 782, 747, 656, 565; **HRMS** (ESI^+) exact mass calculated for $C_{19}H_{21}O_3NP$ $[M+H]^+$ *m/z* = 342.1259, found *m/z* = 342.1257.

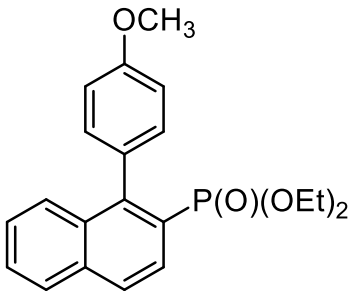
Diethyl (1-(2'-methylphenyl)-2-naphthyl)phosphonate.



Following the Suzuki Miyaura cross-coupling procedure described above, this reaction was performed using **90** (3.1 mg, 4.0 μmol) and 2-bromotoluene (24 μL). The product was a golden yellow oil.

^{31}P {H} NMR (161.8 MHz, $CDCl_3$): δ = 18.6; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.09 (dd, *J* = 12.1, 8.6 Hz, 1 H, $C_{10}H_6P$), 7.94 – 7.92 (m, 1 H, $C_{10}H_6P$), 7.90 (d, *J* = 8.6 Hz, 1 H, $C_{10}H_6P$), 7.55 (t, *J* = 7.44 Hz, 1 H, $C_{10}H_6P$), 7.39 – 7.28 (m, 5 H, 2 x $C_{10}H_6P$, 3 x $C_6H_4CH_3$), 7.21 (d, *J* = 6.8 Hz, 1 H, $C_6H_4CH_3$), 3.99 – 3.73 (m, 4 H, CH_2), 1.92 (s, 3 H, CH_3), 1.19 (t, *J* = 7.1 Hz, 3 H, CH_3), 1.17 (t, *J* = 7.1 Hz, 3 H, CH_3); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ = 145.0 (d, *J* = 10.0 Hz, $C_{10}H_6P$ *Q*), 137.9 (d, *J* = 5.2 Hz, $C_6H_4CH_3$ *Q*), 137.7 ($C_6H_4CH_3$ *Q*), 135.10 (s, $C_{10}H_6P$ *Q*), 135.07 (s, $C_{10}H_6P$ *Q*), 132.5 (d, *J* = 16.3 Hz, $C_{10}H_6P$ *Q*), 130.8 ($C_6H_4CH_3$), 129.4 (2 x $C_6H_4CH_3$), 128.4 (d, *J* = 10.3 Hz, $C_{10}H_6P$), 128.1 ($C_{10}H_6P$), 127.9 ($C_{10}H_6P$), 127.4 (d, *J* = 14.5 Hz, $C_{10}H_6P$), 127.2 ($C_{10}H_6P$), 126.9 ($C_{10}H_6P$), 125.0 ($C_6H_4CH_3$), 125.0 (d, *J* = 190 Hz, $C_{10}H_6P$ $\underline{C}P$), 62.0 (d, *J* = 6.5 Hz, $\underline{C}H_2CH_3$), 61.9 (d, *J* = 6.0 Hz, $\underline{C}H_2CH_3$), 20.1 (CH_3), 16.4 (d, *J* = 6.6 Hz, $CH_2\underline{C}H_3$), 16.2 (d, *J* = 6.8 Hz, $CH_2\underline{C}H_3$); **IR** (neat, cm^{-1}) = 1241, 1049, 1020, 955, 753, 649, 570, 533; **HRMS** (ESI^+) exact mass calculated for $C_{21}H_{24}O_3P$ $[M+H]^+$ *m/z* = 355.1463, found *m/z* = 343.1452. This is consistent with data reported in the literature.[176c]

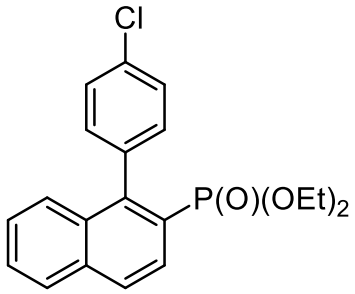
Diethyl (1-(4'-methoxyphenyl)-2-naphthyl)phosphonate.



Following the Suzuki Miyaura cross-coupling procedure described above, this reaction was performed using **90** (0.8 mg, 1.0 μmol) and 4-bromoanisole (25 μL). The product was a white solid.

^{31}P {H} NMR (161.8 MHz, $CDCl_3$): δ = 19.0; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.07 (dd, *J* = 12.1, 8.6 Hz, 1 H, $C_{10}H_6P$), 7.93 – 7.90 (m, 1 H, $C_{10}H_6P$), 7.88 (d, *J* = 8.5 Hz, 1 H, $C_{10}H_6P$), 7.54 (t, *J* = 7.4 Hz, 1 H, $C_{10}H_6P$), 7.50 (d, *J* = 8.5 Hz, 1 H, $C_{10}H_6P$), 7.41 – 7.37 (m, 1 H, $C_{10}H_6P$), 7.29 (d, *J* = 8.6 Hz, 2 H, $C_6H_4OCH_3$), 7.01 (d, *J* = 8.6 Hz, 2 H, $C_6H_4OCH_3$), 4.00 – 3.82 (m, 4 H, $C\underline{H_2}CH_3$), 3.90 (s, 3 H, OCH_3), 1.20 (t, *J* = 7.1 Hz, 6 H, $CH_2C\underline{H_3}$); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ = 159.3 ($C_6H_4OCH_3$ *Q*), 145.4 (d, *J* = 10.4 Hz, $C_{10}H_6P$ *Q*), 135.2 (d, *J* = 2.5 Hz, $C_{10}H_6P$ *Q*), 133.5 (d, *J* = 16.1 Hz, $C_{10}H_6P$ *Q*), 131.8 (2 x $C_6H_4OCH_3$), 130.5 (d, *J* = 5.7 Hz, $C_6H_4OCH_3$ *Q*), 128.4 (d, *J* = 10.1 Hz, $C_{10}H_6P$), 127.9 ($C_{10}H_6P$), 127.8 ($C_{10}H_6P$), 127.8 ($C_{10}H_6P$), 127.3 (d, *J* = 14.4 Hz, $C_{10}H_6P$), 126.6 ($C_{10}H_6P$), 125.1 (d, *J* = 188 Hz, $C_{10}H_6P$ $\underline{C}P$), 113.0 (2 x $C_6H_4OCH_3$), 61.8 (d, *J* = 6.0 Hz, $C\underline{H_2}CH_3$), 55.4 (OCH_3), 16.3 (d, *J* = 6.7 Hz, $CH_2\underline{C}H_3$); **mp** = 105 °C; **IR** (neat, cm^{-1}) = 1237, 1021, 972, 956, 760; **HRMS** (ESI^+) exact mass calculated for $C_{21}H_{24}O_4P$ $[M+H]^+$ *m/z* = 371.1412, found *m/z* = 371.1397.

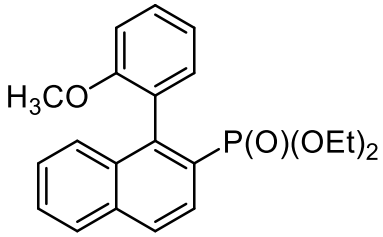
Diethyl (1-(4'-chlorophenyl)-2-naphthyl)phosphonate.



Following the Suzuki Miyaura cross-coupling procedure described above, this reaction was performed using **90** (0.8 mg, 1.0 μmol) and 1-bromo-4-chlorobenzene (38 mg). The product was a white solid.

^{31}P {H} NMR (161.8 MHz, $CDCl_3$): δ = 18.6; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.07 (dd, *J* = 12.1, 8.6 Hz, 1 H, $C_{10}H_6P$), 7.95 (dd, *J* = 8.6, 3.7 Hz, 1 H, $C_{10}H_6P$), 7.90 (d, *J* = 8.2 Hz, 1 H, $C_{10}H_6P$), 7.57 (ddd, *J* = 8.1, 5.0, 2.9 Hz, 1 H, $C_{10}H_6P$), 7.46 (d, *J* = 8.3 Hz, 2 H, C_6H_4Cl), 7.42 – 7.41 (m, 2 H, $C_{10}H_6P$), 7.31 (d, *J* = 8.3 Hz, 2 H, C_6H_4Cl), 4.02 – 3.84 (m, 4 H, C*H*$_2$), 1.20 (t, *J* = 7.1 Hz, 6 H, C*H*$_3$); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ = 144.0 (d, *J* = 9.9 Hz, $C_{10}H_6P$ *Q*), 136.9 (d, *J* = 5.2 Hz, C_6H_4Cl *Q*), 135.1 (d, *J* = 2.4 Hz, $C_{10}H_6P$ *Q*), 133.9 (C_6H_4Cl *Q*), 132.9 (d, *J* = 15.7 Hz, $C_{10}H_6P$ *Q*), 132.1 (2 x C_6H_4Cl), 128.3 (d, *J* = 9.7 Hz, $C_{10}H_6P$), 128.1 ($C_{10}H_6P$), 128.0 ($C_{10}H_6P$), 127.8 (d, *J* = 14.0 Hz, $C_{10}H_6P$), 127.8 (2 x C_6H_4Cl), 127.5 ($C_{10}H_6P$), 126.9 ($C_{10}H_6P$), 125.1 (d, *J* = 188 Hz, $C_{10}H_6P$ *C*P), 62.0 (d, *J* = 5.9 Hz, *C*H_2), 16.3 (d, *J* = 6.7 Hz, *C*H_3); **mp** = 60 – 61 ^{o}C; **IR** (neat, cm^{-1}) = 1241, 1049, 1016, 955, 818, 749, 666, 566; **HRMS** (ESI^{+}) exact mass calculated for $C_{20}H_{21}O_3P$ $[M+H]^+$ *m/z* = 375.0917, found *m/z* = 375.0908.

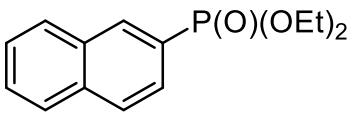
Diethyl (1-(2'-methoxyphenyl)-2-naphthyl)phosphonate.



Following the Suzuki Miyaura cross-coupling procedure described above, this reaction was performed using **90** (3.1 mg, 4.0 μmol) and 2-bromoanisole (25 ml). The product was a white solid.

^{31}P {H} NMR (161.8 MHz, $CDCl_3$): δ = 19.0; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.11 (dd, *J* = 12.0, 8.6 Hz, 1 H, $C_{10}H_6P$), 7.92 (dd, *J* = 8.6, 3.7 Hz, 1 H, $C_{10}H_6P$), 7.88 (d, *J* = 8.2 Hz, 1 H, $C_{10}H_6P$), 7.53 (ddd, *J* = 8.1, 6.0, 1.9 Hz, 1 H, $C_{10}H_6P$), 7.47 – 7.43 (m, 1 H, $C_6H_4OCH_3$), 7.41 – 7.35 (m, 2 H, $C_{10}H_6P$), 7.23 (dd, *J* = 7.4, 1.7 Hz, 1 H, $C_6H_4OCH_3$), 7.07 (td, *J* = 7.5, 1.0 Hz, 1 H, $C_6H_4OCH_3$), 7.01 (d, *J* = 8.3 Hz, 1 H, $C_6H_4OCH_3$), 4.00 – 3.78 (m, 4 H, $C\underline{H_2}CH_3$), 3.64 (s, 3 H, OCH_3), 1.18 (t, *J* = 7.0 Hz, 3 H, $CH_2C\underline{H_3}$), 1.18 (t, *J* = 7.0 Hz, 3 H, $CH_2C\underline{H_3}$); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$) δ = 157.6 ($C_6H_4OCH_3$ *Q*), 142.6 (d, *J* = 9.6 Hz, $C_{10}H_6P$ *Q*), 135.0 (d, *J* = 2.2 Hz, $C_{10}H_6P$ *Q*), 132.9 (d, *J* = 15.9 Hz, $C_{10}H_6P$ *Q*), 132.3 ($C_6H_4OCH_3$), 129.6 ($C_6H_4OCH_3$), 128.7 (d, *J* = 10.2 Hz, $C_{10}H_6P$), 128.0 ($C_{10}H_6P$), 127.8 ($C_{10}H_6P$), 127.4 (d, *J* = 14.4 Hz, $C_{10}H_6P$), 127.4 ($C_{10}H_6P$), 127.2 (d, *J* = 5.2 Hz, $C_6H_4OCH_3$ *Q*), 126.5 ($C_{10}H_6P$), 125.1 (d, *J* = 188 Hz, $C_{10}H_6P$ $\underline{C}P$), 120.0 ($C_6H_4OCH_3$), 110.2 ($C_6H_4OCH_3$), 61.9 (d, *J* = 5.5 Hz, $O\underline{C}H_2CH_3$), 61.7 (d, *J* = 5.9 Hz, $\underline{C}H_2CH_3$), 55.4 (OCH_3), 16.3 (t, *J* = 6.7 Hz, $CH_2\underline{C}H_3$); **mp** = 60 – 61 °C; **IR** (neat, cm^{-1}) 1226, 1212, 1047, 1021, 974, 754, 648; **HRMS** (ESI^+) exact mass calculated for $C_{21}H_{23}O_4P$ $[M+H]^+$ *m/z* = 371.1412, found *m/z* = 371.1412. This is consistent with data reported in the literature.[176d]

Diethyl 2-naphthylphosphonate.

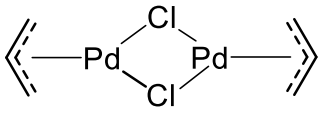


Following the Suzuki Miyaura cross-coupling procedure described above, this was the major impurity, when any was present. This phosphonate was a white solid.

^{31}P {H} NMR (161.8 MHz, $CDCl_3$): δ = 19.7; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.43 (d, *J* = 15.6 Hz, 1 H, Ar-*H*), 7.94 – 7.89 (m, 2 H, Ar-*H*), 7.86 (d, *J* = 8.0 Hz, 1 H, Ar-*H*), 7.78 – 7.72 (m, 1 H, Ar-*H*), 7.61 – 7.53 (m, 2 H, Ar-*H*), 4.23 – 4.04 (m, 4 H, C*H*$_2$), 1.32 (t, *J* = 7.1, 6 H, C*H*$_3$); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$): δ = 135.1 (d, *J* = 2.5 Hz), 134.2 (d, *J* = 10.3 Hz), 132.4 (d, *J* = 16.7 Hz), 129.0, 128.5 (d, *J* = 14.5 Hz), 128.4, 127.9, 127.0, 126.5 (d, *J* = 10.0 Hz), 125.4 (d, *J* = 188 Hz), 62.3 (d, *J* = 5.4 Hz), 16.5 (d, *J* = 6.3 Hz). This is consistent with data reported in the literature.[202]

6.4.6 Synthesis of allylpalladium pre-catalysts

[Bis(η^3-allyl)di-μ-chlorodipalladium] (**108**).

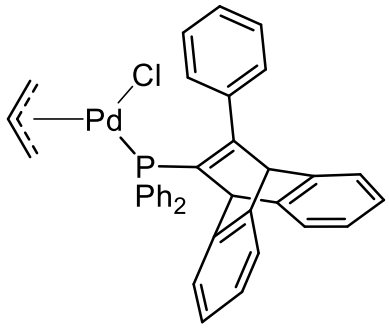


A solution of $PdCl_2$ (5.00 g, 28.2 mmol) and NaCl (3.30 g, 56.4 mmol) in hot H_2O (20 ml), was added to a solution of allyl chloride (6.21 ml, 76.1 mmol) in MeOH (30 ml) and the flask placed in an autoclave. This was then purged with a constant flow of nitrogen for 5 min and filled and evacuated with CO (10 bar) three times before pressurising with CO (10 bar). The mixture was then stirred at RT for 16 h. The CO was released slowly and the solution was extracted with $CHCl_3$ (3 x 50 ml), dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The crude product

was then purified by recrystallisation from a $CHCl_3$ solution layered with MeOH to give the allyl palladium chloride complex **108** as yellow/green crystals (4.68g, 90 % yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.46 (tt, *J* = 12.1, 6.7 Hz, 1 H, C*H*), 4.11 (d, *J* = 6.7 Hz, 2 H, CH_2), 3.04 (d, *J* = 12.1 Hz, 2 H, CH_2); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$): δ = 111.3, 63.1. This is consistent with data reported in the literature.[181]

[11-(Diphenylphosphino)-12-phenyl-9,10-dihydro-9,10-ethenoanthracene] allylpalladium(II) chloride (**109**).

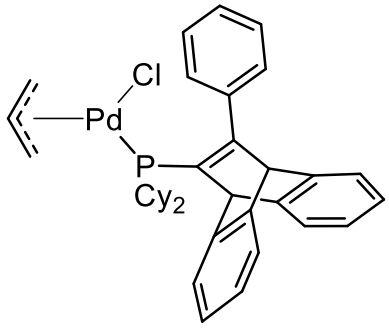


[Bis(η^3-allyl)di-μ-chlorodipalladium] **108** (40 μg, 108 μmol) was dissolved in Et_2O (10 ml) and 11-(diphenylphosphino)-12-phenyl-9,10-dihydro-9,10-ethenoanthracene, **19** (0.100 g, 216 μmol) was added. The reaction mixture was stirred at RT for 2 h and then Et_2O (5 ml) was added. The resulting suspension was filtered to give the phosphine complex **109**, as an off-white solid (75 μg, 54 %).

^{31}P {H} NMR (161.8 MHz, $CDCl_3$): δ = 15.3; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.48 – 7.27 (m, 17 H, Ar-*H*), 7.02 (t, *J* = 7.3 Hz, 2 H, C_6H_4), 6.95 (td, *J* = 7.3, 3.6 Hz, 2 H, C_6H_4), 6.81 (d, *J* = 7.0 Hz, 2 H, C_6H_4), 5.51 (d, *J* = 3.8 Hz, 1 H, bridgehead *H*), 4.96 (d, *J* = 6.2 Hz, 1 H, bridgehead *H*), 4.64 (tt, *J* = 13.6, 7.4 Hz, 1 H, allyl-C*H*), 4.25 (t, *J* = 7.2 Hz, 1 H, allyl-CH_2), 2.84 (dd, *J* = 13.5, 9.9 Hz, 1 H, allyl-CH_2), 2.55 (d, *J* = 6.3 Hz, 1 H, allyl-CH_2), 1.61 (d, *J* = 11.9 Hz, 1 H, allyl-CH_2); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$): δ = 165.3 (d, *J* = 16.5 Hz, *C*CP), 144.7 (C_6H_4 *Q*), 144.6 (2 x C_6H_4 *Q*), 144.5 (C_6H_4 *Q*), 138.2 (d, *J* = 5.7 Hz, C_6H_5 *Q*), 136.4 (d, *J* = 33.2 Hz, *C*P), 134.0 (m, 4 x C_6H_5 *o*-*C*), 131.5 (d, *J* = 41.0 Hz, C_6H_5 *Q*), 130.9 (d, *J* = 41.4 Hz, C_6H_5 *Q*), 130.3 (2 x C_6H_5 *p*-*C*), 129.0 (C_6H_5 *o*-*C*), 128.5 (d, *J* = 9.9 Hz, 2 x C_6H_5 *m*-*C*), 128.3 (C_6H_5 *p*-*C*),

127.8 (C_6H_5 *m-C*), 125.2 (2 x C_6H_4), 125.1 (C_6H_4), 125.1 (C_6H_4), 123.5 (C_6H_4), 123.4 (C_6H_4), 123.2 (C_6H_4), 123.2 (C_6H_4), 116.3 (d, *J* = 5.0 Hz, allyl-*C*H), 78.4 (d, *J* = 30.7 Hz, allyl-*C*H_2), 60.5 (allyl-*C*H_2), 60.4 (d, *J* = 8.1 Hz, bridgehead *C*H), 55.1 (bridgehead *C*H); **mp** = 190 ^oC (decomp); **IR** (neat, cm^{-1}) 2981, 1457, 1435, 744, 693; **HRMS** (ESI^+) exact mass calculated for $C_{37}H_{31}PClPd$ $[M]^+$ *m/z* = 647.0887, found *m/z* = 647.0916.

[11-(Dicyclohexylphosphino)-12-phenyl-9,10-dihydro-9,10-ethenoanthracene] allylpalladium(II) chloride (**110**).

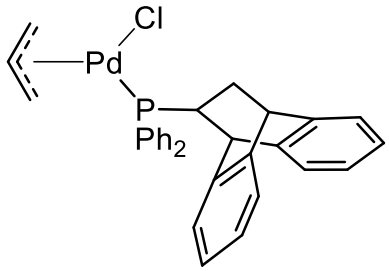


[Bis(η^3-allyl)di-μ-chlorodipalladium] **108** (38 μg, 104 μmol) was dissolved in Et_2O (10 ml) and 11-(dicyclohexylphosphino)-12-phenyl-9,10-dihydro-9,10-ethenoanthracene **16** (0.100 g, 208 μmol) was added. The reaction mixture was stirred at RT for 2 h and then Et_2O (5 ml) was added. The resulting suspension was filtered to yield an off-white solid. The product was then recrystallised through slow diffusion of a $CHCl_3$ solution layered with MeOH to give the phosphine complex **110**, as colourless crystals (40 μg, 60 %).

^{31}P {H} NMR (161.8 MHz, $CDCl_3$): δ = 20.7; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.41 – 7.28 (m, 9 H, Ar-*H*), 7.06 – 7.00 (m, 4 H, Ar-*H*), 5.57 (d, *J* = 4.1 Hz, 1 H, bridgehead *H*), 5.30 (d, *J* = 3.1 Hz, 1 H, bridgehead *H*), 4.34 (br s, 1 H, allyl-C*H*), 4.23 (td, *J* = 7.2, 1.7 Hz, 1 H, allyl-CH_2), 2.99 (dd, *J* = 13.3, 9.5 Hz, 1 H, allyl-CH_2), 2.85 (d, *J* = 5.7 Hz, 1 H, allyl-CH_2), 2.67 – 2.47 (br m, 2 H, Cy-*H*), 2.08 – 1.96 (br m, 2 H, Cy-*H*), 1.77 – 1.63 (br m, 6 H, 5 x Cy-*H*, allyl C-*H*), 1.51 – 1.05 (m, 13 H, Cy-*H*); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$): δ = 165.0 (d, *J* = 13.1 Hz, *C*CP), 144.7 (2 x C_6H_4 *Q*), 144.6 (C_6H_4 *Q*), 144.5 (C_6H_4 *Q*), 139.2 (d, *J* = 5.2 Hz, C_6H_5 *Q*), 136.3 (d, *J* = 20.7 Hz, *C*P),

128.8 (C_6H_5 *o*-*C*), 127.9 (C_6H_5 *p*-*C*), 127.7 (C_6H_5 *m*-*C*), 125.3 (2 x C_6H_4), 125.1 (2 x C_6H_4), 123.6 (C_6H_4), 123.5 (C_6H_4), 123.3 (2 x C_6H_4), 114.8 (d, *J* = 4.8 Hz, allyl-*C*H), 78.9 (d, *J* = 29.3 Hz, allyl-*C*H_2), 63.1 (allyl-*C*H_2), 61.7 (d, *J* = 7.4 Hz, bridgehead *C*H), 55.0 (bridgehead *C*H), 54.1 (allyl-*C*H_2), 35.5 (d, *J* = 17.1 Hz, Cy-*C*H), 35.3 (d, *J* = 17.6 Hz, Cy-*C*H), 29.9 – 29.8 (m, 2 x Cy-*C*H_2), 29.3 (Cy-*C*H_2), 29.0 (Cy-*C*H_2), 27.3 (Cy-*C*H_2), 27.2 (Cy-*C*H_2), 27.1 (d, *J* = 4.5 Hz, Cy-*C*H_2), 27.0 (d, *J* = 3.6 Hz, Cy-*C*H_2), 26.2 (2 x Cy-*C*H_2); **mp** = 167 ^oC; **IR** (neat, cm^{-1}) 1319, 1146, 1118, 995, 559, 548, 539; **HRMS** (ESI^+) exact mass calculated for $C_{37}H_{42}PClPd$ $[M]^+$ *m/z* = 658.1747, found *m/z* = 658.1772.

[11-(Diphenylphosphino)-9,10-dihydro-9,10-ethanoanthracene] allylpalladium(II) chloride (**111**).

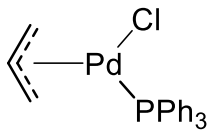


[Bis(η^3-allyl)di-μ-chlorodipalladium] **108** (47 μg, 178 μmol) was dissolved in Et_2O (10 ml) and 11-(diphenylphosphino)-9,10-dihydro-9,10-ethanoanthracene **40** (0.100 g, 256 μmol) was added. The reaction was stirred at RT for 16 h and then Et_2O (5 ml) was added. The resulting suspension was filtered to give the phosphine complex **111**, as an off-white solid (147 μg, 100 %).

^{31}P {H} NMR (161.8 MHz, $CDCl_3$): δ = 30.8; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.70 – 7.52 (m, 3 H, Ar-*H*), 7.39 – 7.08 (m, 14 H, Ar-*H*), 7.02 (t, *J* = 7.0 Hz, 1 H, Ar-*H*), 5.48 – 5.39 (m, 1 H, allyl-C*H*), 4.94 (d, *J* = 5.9 Hz, 1 H, bridgehead *H*), 4.62 (t, *J* = 7.2 Hz, 1 H, allyl-CH_2), 4.31 (s, 1 H, bridgehead *H*), 3.31 – 2.20 (m, 2 H, PCHC$\underline{H_2}$), 3.13 (s, 1 H, allyl-CH_2), 2.16 – 2.08 (m, 1 H, allyl-CH_2), 1.60 – 1.50 (m, 1 H, PC$\underline{H}$$CH_2$), 1.36 (d, *J* = 12.4 Hz, 1 H, allyl-CH_2); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$): δ = 144.9 (C_6H_4 *Q*), 144.8 (C_6H_4 *Q*), 142.5 (C_6H_4 *Q*), 140.0 (C_6H_4 *Q*), 134.4 – 134.1 (br m, C_6H_5 *Q*), 133.8 (d, *J* = 12.9 Hz, C_6H_5 *o*-*C*), 133.2 – 132.9 (br m, C_6H_5 *Q*), 132.7 (d, *J*

= 10.7 Hz, C_6H_5 *o-C*), 130.5 (C_6H_5 *p-C*), 130.0 (d, *J* = 1.4 Hz, C_6H_5 *p-C*), 128.6 – 128.3 (m, C_6H_5 *m-C*), 126.3 (2 x C_6H_4), 126.1 (C_6H_4), 126.0 (2 x C_6H_4), 124.1 (C_6H_4), 123.0 (C_6H_4), 122.9 (C_6H_4), 116.1 (br, allyl-*C*H), 80.9 (d, *J* = 29.5 Hz, allyl-*C*H_2), 57.0 (allyl-*C*H_2), 45.5 (d, *J* = 8.5 Hz, bridgehead *C*H), 44.1 (bridgehead *C*H), 38.4 (d, *J* = 21.9 Hz, P*C*HCH_2), 31.4 (PCH*C*H_2); **mp** = 204 ºC (decomp); **IR** (neat, cm^{-1}) 1434, 1094, 903, 764, 734, 724, 689, 560; **HRMS** (ESI^+) exact mass calculated for $C_{31}H_{28}PClPd$ $[M]^+$ *m/z* = 572.0652, found *m/z* = 572.0660.

Triphenylphosphine allylpalladium(II) chloride (**112**).



PPh_3 (0.147g, 560 μmol) was added to a solution of [bis(η^3-allyl)di-μ-chlorodipalladium] **108** (0.103 g, 280 μmol) in THF (8 ml) and Et_2O (8 ml). The mixture was stirred at RT for 1 h and then Et_2O (5ml) was added. The resulting suspension was filtered to give the phosphine complex **112**, as an off white solid (0.225g, 90%).

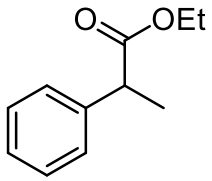
^{31}P {H} NMR (161.8 MHz, $CDCl_3$): δ = 23.3; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.61 – 7.56 (m, 6 H, C_6H_5 *o-H*), 7.46 – 7.38 (m, 9 H, C_6H_5 *m-H*, *p-C*), 5.61 (ddd, *J* = 20.3, 13.9, 7.3 Hz, 1 H, allyl-C*H*), 4.76 (td, *J* = 7.3, 2.0 Hz, 1 H, allyl-CH_2), 3.77 (dd, *J* = 13.7, 9.8 Hz, 1 H, allyl-CH_2), 3.11 (d, *J* = 6.7 Hz, 1 H, allyl-CH_2), 2.83 (d, *J* = 12.2 Hz, 1 H, allyl-CH_2); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$): δ = 134.1 (d, *J* = 12.8 Hz), 132.4 (d, *J* = 42.0 Hz), 130.6 (d, *J* = 1.5 Hz), 128.7 (d, *J* = 10.3 Hz), 118.2 (d, *J* = 4.9 Hz), 80.2 (d, *J* = 30.9 Hz), 61.2 (d, *J* = 1.4 Hz). This is consistent with data reported in the literature.[157c]

6.4.7 General procedure for alkoxycarbonylations

A round bottomed flask was charged with the pre-catalyst (2.0 μmol),[a] lithium chloride (4.2 mg, 100 μmol), *para*-toluenesulphonic acid (19.0 mg, 100 μmol), EtOH (3 ml) and substrate (2.0 mmol). This flask was then placed inside an autoclave and was purged with a constant flow of nitrogen for 5 mins and filled and evacuated with CO (30 bar) three times before pressurising with CO (30 bar). This was then stirred at 80 ^{o}C for 16 h. The autoclave was then removed from the heat and allowed to cool. The CO was then released slowly by bubbling through H_2O, and the solvent was removed under reduced pressure. The crude material was then dissolved in $CHCl_3$, filtered and the solvent removed under reduced pressure. Conversion was measured using ^{1}H NMR. The products were purified by column chromatography eluting with 5% EtOAc/petrol.

[a] *Allylpalladium pre-catalysts **109** (1.3 mg), **110** (1.3 mg), **111** (1.1 mg), **112** (0.9 mg) or 2-phenylaniline-based pre-catalysts **92** (1.1 mg), **93** (1.6 mg), **90** (1.5 mg).*

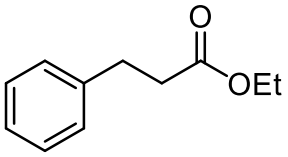
Ethyl 2-phenylpropanoate (**106**).



Following the alkoxycarbonylations procedure described above, this reaction was performed using styrene (0.229 ml) as the substrate.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30 – 7.18 (m, 5 H, Ar-*H*), 4.14 – 4.00 (m, 2 H, C*H*$_2$), 3.66 (q, *J* = 7.2 Hz, 1 H, C*H*CH_3), 1.45 (d, *J* = 7.2 Hz, 3 H, CHC*H*$_3$), 1.16 (t, *J* = 7.1 Hz, 3 H, CH_2C*H*$_3$); **^{13}C {^{1}H} NMR** (100.5 MHz, $CDCl_3$): δ = 174.7, 140.8, 128.7, 127.6, 127.2, 60.8, 45.7, 18.7, 14.2. This is consistent with data reported in the literature.[157c]

Ethyl 3-phenyl-propanoate (**107**).



Following the alkoxycarbonylations procedure described above, this reaction was performed using styrene (0.229 ml) as the substrate. This product could not be isolated and so was only identified by ^{1}H NMR (300 MHz, $CDCl_3$) in the crude reaction mixture, as the small quantities produced in the reactions were not significant enough to allow for full characterisation. The signals which were attributed to the product were: δ = 2.94 (2 H, CH_2), 2.61 (2 H, CH_2). As such full characterisation can be found in the supplementary information of this reference.[203]

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Appendix

A. Crystal Structure Data

Table 19. Crystal data and structure refinement for phosphine oxide 29.

Chemical formula (moiety)	$C_{68}H_{49}Cl_4OP$	
Chemical formula (total)	$C_{68}H_{49}Cl_4OP$	
Formula weight	1054.84	
Temperature	150(2) K	
Radiation, wavelength	MoKα, 0.71073 Å	
Crystal system, space group	monoclinic, $P12_1/n1$	
Unit cell parameters	a = 13.1207(11) Å	α = 90°
	b = 21.9524(17) Å	β = 94.508(9)°
	c = 18.5508(15) Å	γ = 90°
Cell volume	5326.7(7) $Å^3$	
Z	4	
Calculated density	1.315 g/cm^3	
Absorption coefficient μ	0.298 mm^{-1}	
F(000)	2192	
Crystal colour and size	colourless, 0.40 × 0.40 × 0.30 mm^3	
Reflections for cell refinement	10764 (θ range 3.0 to 28.6°)	
Data collection method	Xcalibur, Atlas, Gemini ultra thick-slice ω scans	
θ range for data collection	3.0 to 28.6°	
Index ranges	h –17 to 17, k –28 to 29, l –19 to 24	
Completeness to θ = 26.0°	99.2 %	
Reflections collected	57429	
Independent reflections	12068 (R_{int} = 0.0469)	
Reflections with $F^2>2\sigma$	9286	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.8901 and 0.9159	
Structure solution	direct methods	
Refinement method	Full-matrix least-squares on F^2	
Weighting parameters a, b	0.0620, 5.3146	
Data / restraints / parameters	12068 / 0 / 667	
Final R indices [$F^2>2\sigma$]	R1 = 0.0557, wR2 = 0.1344	
R indices (all data)	R1 = 0.0771, wR2 = 0.1517	
Goodness-of-fit on F^2	1.041	
Largest and mean shift/su	0.000 and 0.000	
Largest diff. peak and hole	0.87 and –0.99 e $Å^{-3}$	

Table 20. Crystal data and structure refinement for phosphine oxide 37.

Chemical formula (moiety)	$C_{38}H_{27}PO_{0.15}\cdot 0.5CH_2Cl_2$	
Chemical formula (total)	$C_{38.50}H_{28}ClO_{0.15}P$	
Formula weight	559.43	
Temperature	150(2) K	
Radiation, wavelength	MoKα, 0.71073 Å	
Crystal system, space group	monoclinic, $P12_1/c1$	
Unit cell parameters	a = 9.5705(5) Å	α = 90°
	b = 9.4460(6) Å	β = 91.466(5)°
	c = 30.8918(17) Å	γ = 90°
Cell volume	2791.8(3) $Å^3$	
Z	4	
Calculated density	1.331 g/cm^3	
Absorption coefficient μ	0.223 mm^{-1}	
F(000)	1169	
Crystal colour and size	colourless, 0.40 x 0.30 x 0.30 mm^3	
Reflections for cell refinement	6245 (θ range 2.9 to 28.7°)	
Data collection method	Xcalibur, Atlas, Gemini ultra thick-slice ω scans	
θ range for data collection	2.9 to 28.8°	
Index ranges	h -12 to 12, k -12 to 12, l -40 to 40	
Completeness to θ = 25.0°	99.8 %	
Reflections collected	18061	
Independent reflections	6020 (R_{int} = 0.0383)	
Reflections with $F^2>2\sigma$	4903	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.9163 and 0.9362	
Structure solution	direct methods	
Refinement method	Full-matrix least-squares on F^2	
Weighting parameters a, b	0.0680, 0.8543	
Data / restraints / parameters	6020 / 0 / 363	
Final R indices [$F^2>2\sigma$]	R1 = 0.0483, wR2 = 0.1264	
R indices (all data)	R1 = 0.0597, wR2 = 0.1342	
Goodness-of-fit on F^2	1.084	
Extinction coefficient	0.0023(8)	
Largest and mean shift/su	0.000 and 0.000	
Largest diff. peak and hole	0.62 and -0.29 e $Å^{-3}$	

Table 21. Crystal data and structure refinement for phosphine oxide 42.

Chemical formula (moiety)	$C_{33}H_{24}NOP$	
Chemical formula (total)	$C_{33}H_{24}NOP$	
Formula weight	481.50	
Temperature	150(2) K	
Radiation, wavelength	MoKα, 0.71073 Å	
Crystal system, space group	orthorhombic, Pbca	
Unit cell parameters	a = 17.4356(5) Å	α = 90°
	b = 15.3250(5) Å	β = 90°
	c = 18.1978(6) Å	γ = 90°
Cell volume	4862.5(3) $Å^3$	
Z	8	
Calculated density	1.315 g/cm^3	
Absorption coefficient μ	0.141 mm^{-1}	
F(000)	2016	
Crystal colour and size	colourless, 0.50 x 0.40 x 0.40 mm^3	
Reflections for cell refinement	6533 (θ range 2.8 to 28.6°)	
Data collection method	Xcalibur, Atlas, Gemini ultra thick-slice ω scans	
θ range for data collection	2.8 to 28.7°	
Index ranges	h -18 to 22, k -19 to 20, l -24 to 21	
Completeness to θ = 25.0°	99.8 %	
Reflections collected	19897	
Independent reflections	5477 (R_{int} = 0.0515)	
Reflections with $F^2>2\sigma$	4296	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.9329 and 0.9458	
Structure solution	direct methods	
Refinement method	Full-matrix least-squares on F^2	
Weighting parameters a, b	0.0417, 2.9979	
Data / restraints / parameters	5477 / 0 / 325	

Table 22. Crystal data and structure refinement for gold(I) complex 60.

Chemical formula (moiety)	$C_{51}H_{36}AuCl_4P$	
Chemical formula (total)	$C_{51}H_{36}AuCl_4P$	
Formula weight	1018.53	
Temperature	150(2) K	
Radiation, wavelength	MoKα, 0.71073 Å	
Crystal system, space group	monoclinic, $P12_1/n1$	
Unit cell parameters	a = 13.6875(3) Å	α = 90°
	b = 18.8693(3) Å	β = 105.083(2)°
	c = 17.1115(4) Å	γ = 90°
Cell volume	4267.20(15) $Å^3$	
Z	4	
Calculated density	1.585 g/cm^3	
Absorption coefficient μ	3.771 mm^{-1}	
F(000)	2016	
Crystal colour and size	colourless, 0.42 × 0.40 × 0.40 mm^3	
Reflections for cell refinement	15172 (θ range 3.0 to 28.5°)	
Data collection method	Oxford Diffraction Gemini A Ultra diffractometer thick-slice ω scans	
θ range for data collection	3.1 to 28.6°	
Index ranges	h −18 to 14, k −24 to 23, l −22 to 21	
Completeness to θ = 26.0°	98.2 %	
Reflections collected	26635	
Independent reflections	9187 (R_{int} = 0.0300)	
Reflections with $F^2>2\sigma$	7047	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.3003 and 0.3138	
Structure solution	direct methods	
Refinement method	Full-matrix least-squares on F^2	
Weighting parameters a, b	0.0388, 0.0000	
Data / restraints / parameters	9187 / 0 / 478	
Final R indices [$F^2>2\sigma$]	R1 = 0.0239, wR2 = 0.0647	
R indices (all data)	R1 = 0.0353, wR2 = 0.0665	
Goodness-of-fit on F^2	0.960	
Largest and mean shift/su	0.003 and 0.000	
Largest diff. peak and hole	0.60 and −0.59 e $Å^{-3}$	

Table 23. Crystal data and structure refinement for gold(I) complex 61.

Chemical formula (moiety)	$C_{66}H_{45}PAuCl \cdot 0.5CH_2Cl_2 \cdot 3CH_4O$	
Chemical formula (total)	$C_{69.50}H_{58}AuCl_2O_3P$	
Formula weight	1240.00	
Temperature	150(2) K	
Radiation, wavelength	MoKα, 0.71073 Å	
Crystal system, space group	triclinic, $P\bar{1}$	
Unit cell parameters	a = 11.9837(3) Å	α = 90.812(2)°
	b = 13.0538(4) Å	β = 97.792(2)°
	c = 19.8023(6) Å	γ = 114.377(3)°
Cell volume	2787.06(14) $Å^3$	
Z	2	
Calculated density	1.478 g/cm^3	
Absorption coefficient μ	2.813 mm^{-1}	
F(000)	1254	
Reflections for cell refinement	18848 (θ range 2.8 to 29.0°)	
Data collection method	Xcalibur, Atlas, Gemini ultra thick-slice ω scans	
θ range for data collection	2.8 to 29.0°	
Index ranges	h –15 to 15, k –17 to 17, l –25 to 26	
Completeness to θ = 25.0°	99.8 %	
Reflections collected	41645	
Independent reflections	12527 (R_{int} = 0.0365)	
Reflections with $F^2>2\sigma$	11234	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.91986 and 1.00000	
Structure solution	direct methods	
Refinement method	Full-matrix least-squares on F^2	
Weighting parameters a, b	0.0431, 1.2459	
Data / restraints / parameters	12527 / 0 / 622	
Final R indices [$F^2>2\sigma$]	R1 = 0.0312, wR2 = 0.0809	
R indices (all data)	R1 = 0.0363, wR2 = 0.0837	
Goodness-of-fit on F^2	1.101	
Largest and mean shift/su	0.001 and 0.000	
Largest diff. peak and hole	0.89 and –1.09 e $Å^{-3}$	

Table 24. Crystal data and structure refinement for gold(I) complex 62.

Chemical formula (moiety)	$C_{29}H_{22}AuCl_4P$	
Chemical formula (total)	$C_{29}H_{22}AuCl_4P$	
Formula weight	740.20	
Temperature	150(2) K	
Radiation, wavelength	MoKα, 0.71073 Å	
Crystal system, space group	monoclinic, $P12_1/c1$	
Unit cell parameters	a = 11.5325(6) Å	α = 90°
	b = 10.1282(4) Å	β = 101.746(5)°
	c = 23.9101(11) Å	γ = 90°
Cell volume	2734.3(2) $Å^3$	
Z	4	
Calculated density	1.798 g/cm^3	
Absorption coefficient μ	5.847 mm^{-1}	
F(000)	1432	
Crystal colour and size	colourless, 0.40 × 0.05 × 0.05 mm^3	
Reflections for cell refinement	4788 (θ range 2.9 to 28.5°)	
Data collection method	Oxford Diffraction Gemini A Ultra diffractometer	
	thick-slice ω scans	
θ range for data collection	3.0 to 28.5°	
Index ranges	h −13 to 15, k −11 to 13, l −22 to 32	
Completeness to θ = 25.0°	99.8 %	
Reflections collected	16326	
Independent reflections	5899 (R_{int} = 0.0330)	
Reflections with $F^2>2\sigma$	4741	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.2032 and 0.7587	
Structure solution	direct methods	
Refinement method	Full-matrix least-squares on F^2	
Weighting parameters a, b	0.0191, 6.4397	
Data / restraints / parameters	5899 / 0 / 320	
Final R indices [$F^2>2\sigma$]	R1 = 0.0291, wR2 = 0.0577	
R indices (all data)	R1 = 0.0429, wR2 = 0.0630	
Goodness-of-fit on F^2	1.030	
Largest and mean shift/su	0.001 and 0.000	
Largest diff. peak and hole	1.55 and −1.67 e $Å^{-3}$	

Table 25. Crystal data and structure refinement for gold(I) complex 63.

Chemical formula (moiety)	$C_{30}H_{25}AuCl_7P$	
Chemical formula (total)	$C_{30}H_{25}AuCl_7P$	
Formula weight	861.59	
Temperature	150(2) K	
Radiation, wavelength	MoKα, 0.71073 Å	
Crystal system, space group	monoclinic, C2/c	
Unit cell parameters	a = 20.9184(9) Å	α = 90°
	b = 10.0861(4) Å	β = 95.662(4)°
	c = 29.9559(18) Å	γ = 90°
Cell volume	6289.4(5) $Å^3$	
Z	8	
Calculated density	1.820 g/cm^3	
Absorption coefficient μ	5.344 mm^{-1}	
F(000)	3344	
Crystal colour and size	colourless, 0.24 × 0.20 × 0.20 mm^3	
Reflections for cell refinement	12438 (θ range 3.0 to 28.4°)	
Data collection method	Xcalibur, Atlas, Gemini ultra thick-slice ω scans	
θ range for data collection	3.1 to 28.5°	
Index ranges	h –25 to 27, k –12 to 13, l –37 to 38	
Completeness to θ = 25.0°	99.8 %	
Reflections collected	33126	
Independent reflections	7064 (R_{int} = 0.0516)	
Reflections with $F^2>2\sigma$	6225	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.3603 and 0.4145	
Structure solution	direct methods	
Refinement method	Full-matrix least-squares on F^2	
Weighting parameters a, b	0.0174, 10.7256	
Data / restraints / parameters	7064 / 0 / 352	
Final R indices [$F^2>2\sigma$]	R1 = 0.0282, wR2 = 0.0543	
R indices (all data)	R1 = 0.0358, wR2 = 0.0573	
Goodness-of-fit on F^2	1.082	
Largest and mean shift/su	0.002 and 0.000	
Largest diff. peak and hole	0.93 and –0.97 e $Å^{-3}$	

Table 26. Crystal data and structure refinement for 2-phenylaniline-based pre-catalyst 93.

Chemical formula (total)	$C_{46}H_{35}NPClPd$	
Formula weight	1096.18	
Temperature	120(2) K	
Radiation, wavelength	MoKσ, 0.71073 Å	
Crystal system, space group	triclinic, $P12_1/c1$	
Unit cell parameters	a = 13.5306(7) Å	α = 73.9259(16)°
	b = 18.3786(10) Å	β = 73.7859(17)°
	c = 22.8721(12) Å	γ = 77.1431(17)°
Cell volume	5182.5(5) $Å^3$	
Z	6	
Calculated density	1.489 g/cm^3	
Absorption coefficient μ	0.697 mm^{-1}	
F(000)	2376.0	
Crystal colour and size	colourless, 0.185 x 0.129 x 0.074 mm^3	
Reflections for cell refinement	13681 (θ range 2.8 to 28.5°)	
Data collection method	Xcalibur, Atlas, Gemini ultra thick-slice ω scans	
θ range for data collection	2.8 to 28.6°	
Index ranges	h -17 to 17, k -23 to 23, l -29 to 29	
Completeness to θ = 25.0°	99.8 %	
Reflections collected	76010	
Independent reflections	23902 (R_{int} = 0.0683, R_{sigma} = 0.0929)	
Reflections with $F^2>2\sigma$	9112	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.8296 and 0.8815	
Structure solution	direct methods	
Refinement method	Full-matrix least-squares on F^2	
Weighting parameters a, b	0.0438, 2.3865	
Data / restraints / parameters	23902/0/1327	
Final R indices [$F^2>2\sigma$]	R1 = 0.0485, wR2 = 0.0870	
R indices (all data)	R1 = 0.1082, wR2 = 0.1037	
Goodness-of-fit on F^2	0.961	
Largest and mean shift/su	0.000 and 0.000	
Largest diff. peak and hole	1.27 and -0.53 e $Å^{-3}$	

Table 27. Crystal data and structure refinement for 2-phenylaniline-based pre-catalyst 94.

Chemical formula (moiety)	$C_{62}H_{45}ClNPPd \cdot CHCl_3$	
Chemical formula (total)	$C_{63}H_{46}Cl_4NPPd$	
Formula weight	1096.18	
Temperature	150(2) K	
Radiation, wavelength	MoKσ, 0.71073 Å	
Crystal system, space group	monoclinic, $P12_1/c1$	
Unit cell parameters	a = 12.0435(2) Å	α = 90°
	b = 19.6260(4) Å	β = 102.562(2)°
	c = 22.1316(5) Å	γ = 90°
Cell volume	5105.92(18) $Å^3$	
Z	4	
Calculated density	1.426 g/cm^3	
Absorption coefficient μ	0.647 mm^{-1}	
F(000)	2240	
Crystal colour and size	colourless, 0.30 x 0.30 x 0.20 mm^3	
Reflections for cell refinement	13681 (θ range 2.8 to 28.5°)	
Data collection method	Xcalibur, Atlas, Gemini ultra thick-slice ω scans	
θ range for data collection	2.8 to 28.6°	
Index ranges	h -16 to 16, k -26 to 24, l -29 to 25	
Completeness to θ = 25.0°	99.8 %	
Reflections collected	31929	
Independent reflections	10915 (R_{int} = 0.0296)	
Reflections with $F^2>2\sigma$	9112	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.8296 and 0.8815	
Structure solution	direct methods	
Refinement method	Full-matrix least-squares on F^2	
Weighting parameters a, b	0.0438, 2.3865	
Data / restraints / parameters	10915 / 0 / 603	
Final R indices [$F^2>2\sigma$]	R1 = 0.0338, wR2 = 0.0860	
R indices (all data)	R1 = 0.0443, wR2 = 0.0916	
Goodness-of-fit on F^2	1.062	
Largest and mean shift/su	0.000 and 0.000	
Largest diff. peak and hole	0.40 and -0.48 e $Å^{-3}$	

B. ^{1}H and ^{13}C {^{1}H} NMR spectra of 11-[tris(12-phenyl-9,10-dihydro-9,10-etheno-anthracen-11-yl)]phosphine oxide.

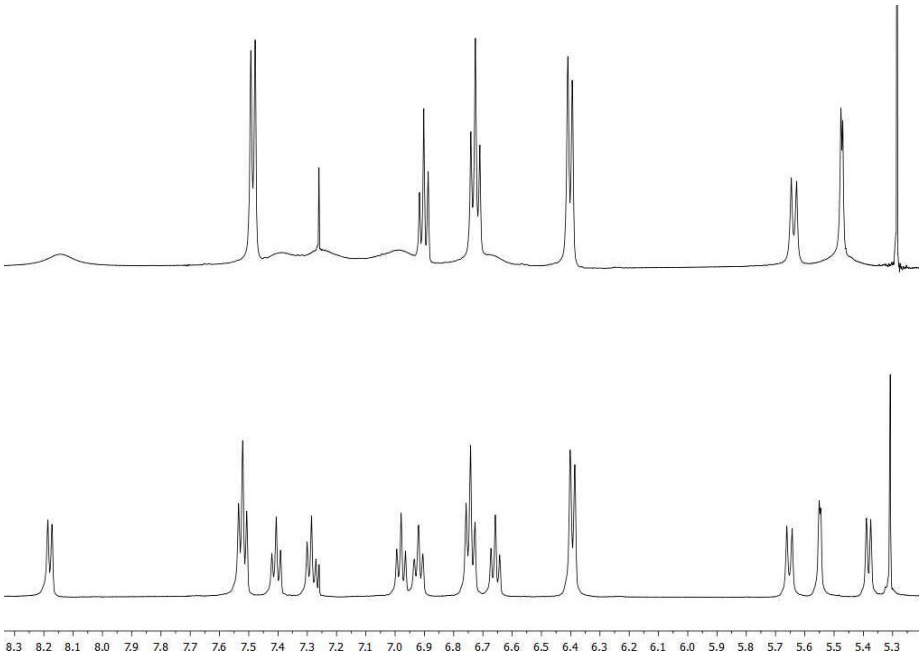

Figure 36. The ^{1}H NMR spectra of **29** at 24 ^{o}C (top) and -41 ^{o}C (bottom) in $CDCl_3$ using the JEOL ECS 400 NMR instrument. The peak at δ 5.32 is CH_2Cl_2.

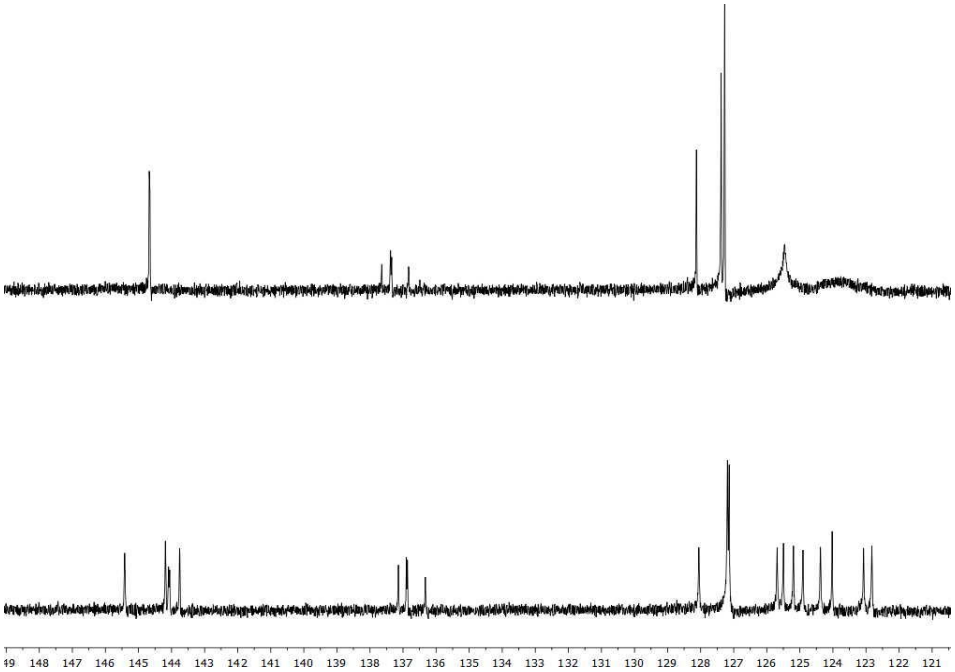

Figure 37. The ^{13}C {^{1}H} NMR spectra of **29** at 24 ^{o}C (top) and -41 ^{o}C (bottom) in $CDCl_3$ using the JEOL ECS 400 NMR instrument. The two bridgehead carbon resonance signals at δ 60.4 and δ 53.8, and the doublet peak δ 165.6 have been omitted for clarity, as no broadening was observed. This experiment was performed.

C. NOESY experiment of 11-[tris(12-phenyl-9,10-dihydro-9,10-etheno-anthracen-11-yl)]phosphine oxide.

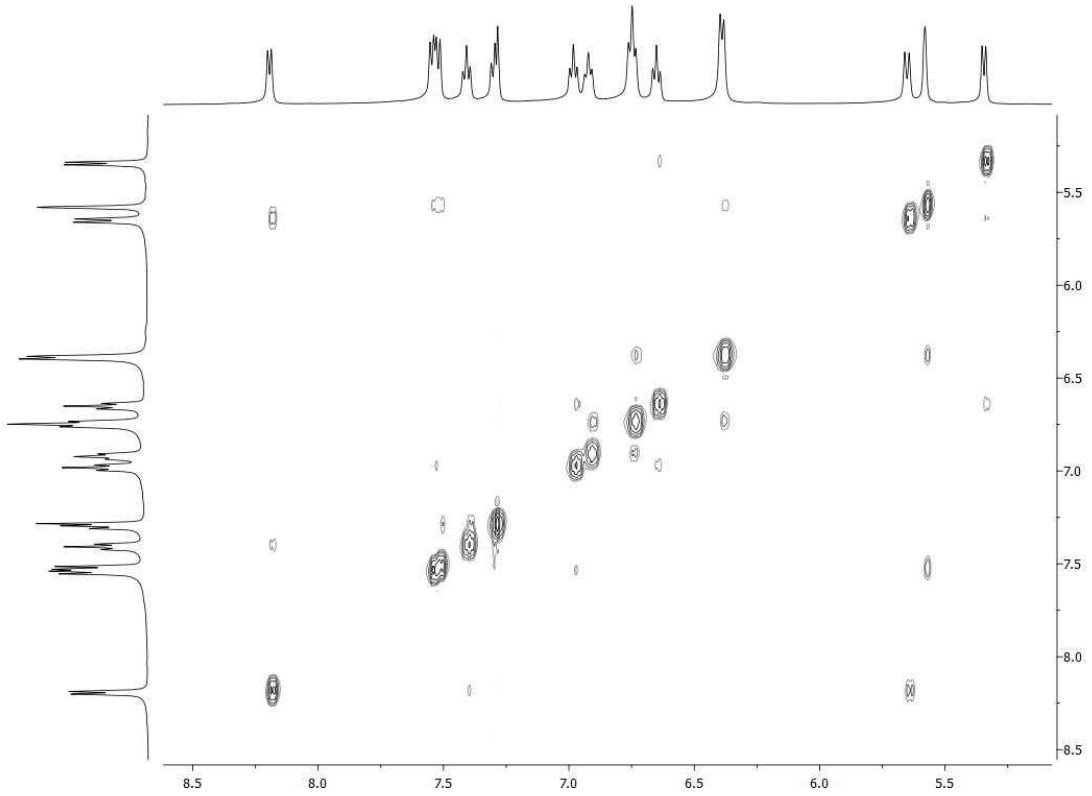

Figure 38. The NOESY experiment on **29**. This experiment was performed in $CDCl_3$ at -55 ^oC using the JEOL ECS 400 NMR instrument.

D. INADEQUATE experiment for (*Z*)-1-benzylideneisochromane.

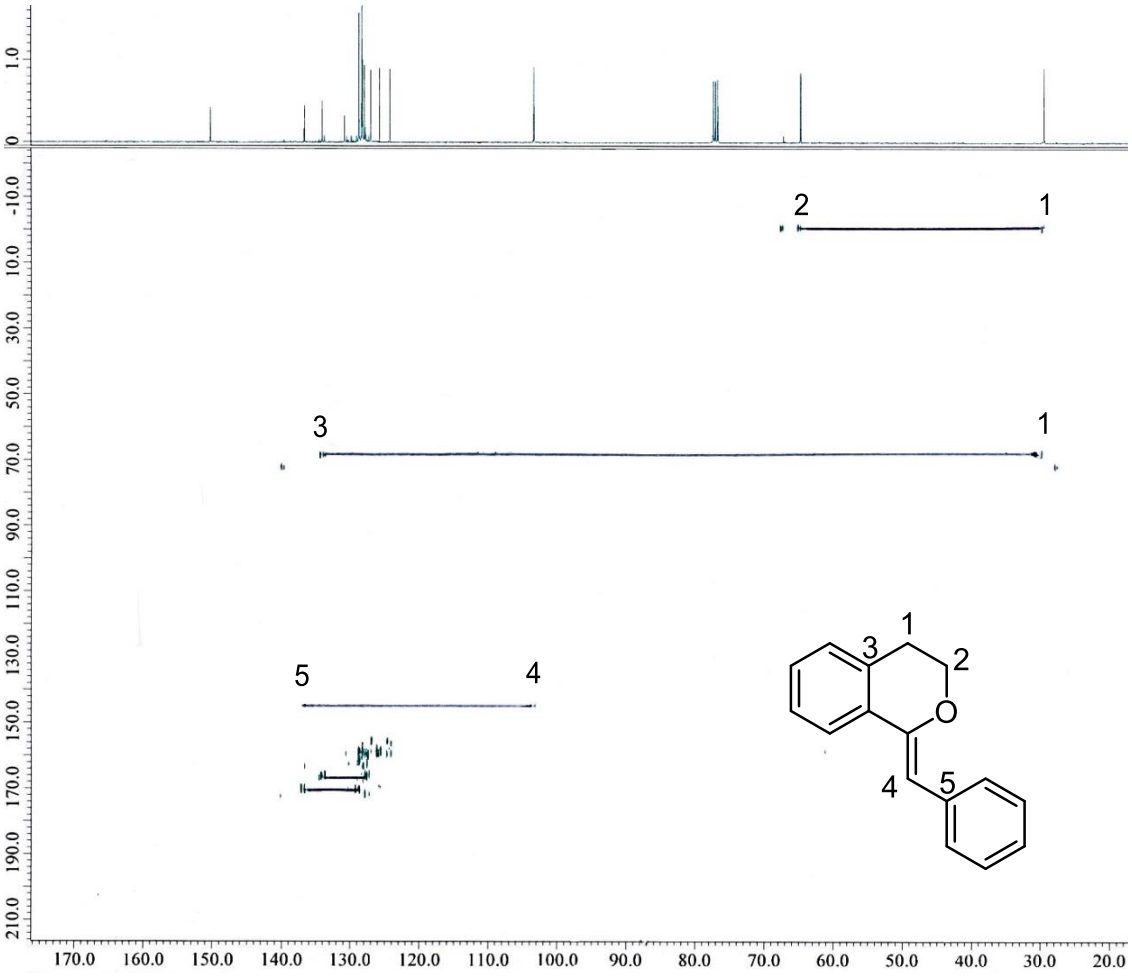

Figure 39. The INADEQUATE experiment used to determine the structure of (*Z*)-1-benzylideneisochromane **74**. This experiment was performed using the JEOL ECS 400 NMR instrument.