Evaluation of Platinum Group Metal Lewis Acid Complexes of the Novel Biaryl-like R_2-CATPHOS Diphosphines in Catalysis

Declaration

All the work described in this thesis was conducted in Newcastle University laboratories under supervision of Dr S. Doherty and it is all original except where acknowledged by reference.

Acknowledgement

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Abstract

Recently, cationic 'coordinately unsaturated' square planar transition metal group Lewis acid complexes of the type $[M(Ligand)]^{2+}$ (M = Pt, Pd,) have been shown to exhibit a number of advantageous features, which include well defined coordination geometries and wide functional group tolerance. They have proven to be efficient catalysts for a host of important enantioselective transformations including Diels-Alder reactions and 1,3-dipolar cycloadditions, as well as cycloisomerisations and various cyclisations. The supporting ligands and the metal centre each assert significant effects on the reactivity of the catalyst where, in particular, those complexes based on biaryl diphosphines such as BINAP, BIPHEP, MeO-BIPHEP, and NUPHOS are established as highly efficient catalysts for various couplings and cyclisations. The Doherty group has recently synthesised the novel biaryl-like R_2-CATPHOS class of diphosphines and showed enantiopure (S)-Me_2-CATPHOS to be markedly efficient ligand for rhodium catalysed asymmetric hydrogenation of dehydroamino esters and (E)-β-aryl-β-(enamido)phosphonates. This thesis reports details of a systematic evaluation of the efficiency of Lewis acid platinum and palladium metal complexes of enantiopure (*S*)-Me_2-CATPHOS as catalysts for the asymmetric carbonyl-ene and Friedel-Crafts reaction and a comparison with their BINAP-based counterparts.

The performance of R_2-CATPHOS (R = H, Me, MeO) diphosphines as ligands for the palladium catalysed Suzuki-Miyaura cross-coupling, the Buchwald-Hartwig amination as well as a tandem carbopalladation-carbonylation sequence has also been investigated. Gold(I) complexes of R_2-CATPHOS have also been shown to form efficient Lewis acid catalysts for the cycloisomerisation of a range of propargylamides. A range of platinum, palladium, and gold(I) precatalysts have been prepared and spectroscopically characterised, and catalytic conditions optimised in order to establish the extent to which R_2-CATPHOS biaryl-like diphosphines are surrogates for their more conventional biaryl based counterparts such as BINAP and BIPHEP. The performance of catalysts based on R_2-CATPHOS has also been compared for selected reactions to establish the influence of R on catalyst efficiency.

This thesis evaluates the performance of R_2-CATPHOS-based Lewis acid catalysts in chiral and achiral transformations with not only palladium and platinum but also with relatively new bis-gold catalysts that have only recently emerged in catalysis and offer great research potentials due to the unique properties of gold.

Abbreviations

BINAP	2,2’-bis(diphenylphosphino)-1,1’-binaphthyl
xylylBINAP	2,2’-bis(di-3,5-dimethylphenyl-phosphino)-1,1’-binaphthyl
BINOL	1,1’-bi-2-naphthol
BIPHEP	2,2’-bis(diphenylphosphino)-1,1’-biphenyl
Ph_4-NUPHOS	1,4-bis(diphenylphosphino)-1,2,3,4-tetraphenyl-1,3-butadiene
KITPHOS	11-dicyclohexylphosphino-12-phenyl-9,10-ethenoanthracene
MOP	(2'-Methoxy-1,1'-binaphthalenyl-2-yl)-diphenyl-phosphane
CATPHOS	12,12’-bis(diphenylphosphino)-9,9’,10,10’-tetrahydro-11,11’-bi-9,10-ethenoanthracene
COD	1,5-cyclooctadiene
Cy	cyclohexyl
dba	dibenzylidene acetone
DBTA	di-*O*-benzoyl tartaric acid
DPEN	1,2-diphenylethylenediamine
DPPF	1,1’-bis(diphenylphosphino)ferrocene
DPPM	1,4’-bis(diphenylphosphino)methane
DPPE	1,2-Bis(diphenylphosphino)ethane
ee	enantiomeric excess
H_8-BINAP	2,2’-bis(diphenylphosphino)-5,5’,6,6’,7,7’,8,8’-octahydro-1,1’-binaphthyl
MeO-BIPHEP	2,2’-bis(diphenylphosphino)-6,6’-dimethoxy-1,1’-biphenyl
rac	racemic
SYNPHOS	[(5,6),(5’,6’)-bis(ethylenedioxy)biphenyl-2,2’-diyl]bis(diphenylphosphine)
THF	tetrahydrofuran
DMF	N,N-dimethylformamide
Tol-BINAP	2,2’-bis(di-*p*-tolylphosphino)-1,1’-binaphthyl
DUPHOS	1,2-Bis(2,5-dimethylphospholano)benzene

SEGPHOS	(4,4’-bi-1,3-benzodioxole)-5,5’-diylbis(diarylphosphine)
TUNAPHOS	[6,7,8,9-tetrahydro-dibenzo-1,6-dioxecin-1,14-diyl]-bis(diphenylphosphine)
Triflate	trifluoromethanesulfonic acid
Tosylate	toluenesulfonic acid
Mesylates	methanesulfonic acid
X-Phos	2-(dicyclohexylphosphino)-2’,4’,6’-triisopropylbiphenyl
tht	tetrahydrothiophene
MONOPHOS	3,4-(dinaphthalen-4-yl)dimethylamine
QUINAP	1-(2-diphenylphosphino-1-naphthyl)isoquinoline
DBTA	dibenzoyltartaric acid

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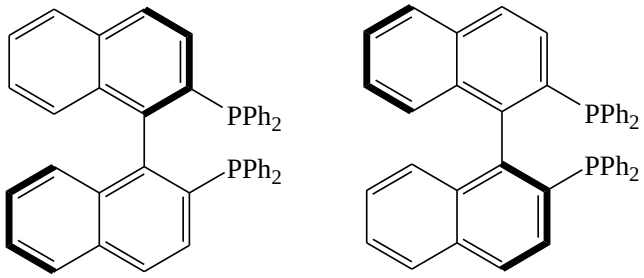
Chapter 1

Introduction

1.1 Emergence of Biaryl Diphosphines in Catalysis

Biaryl diphosphines have played an important role in both chiral and achiral catalysis since the synthesis of 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP).[1] It was the first class of diphosphine with axial chirality (Figure 1.1). Its discovery paved the way for the synthesis of various BINAP derivatives as well as other ligands with a characteristic biaryl motif over the past three decades, which have been used to catalyse a whole host of transformations such as carbon-carbon bond forming reactions[2-5] and asymmetric hydrogenation.[6] Biaryl diphosphines are now firmly established as, arguably, the most important class of ligand that is used in platinum group metal catalysts.

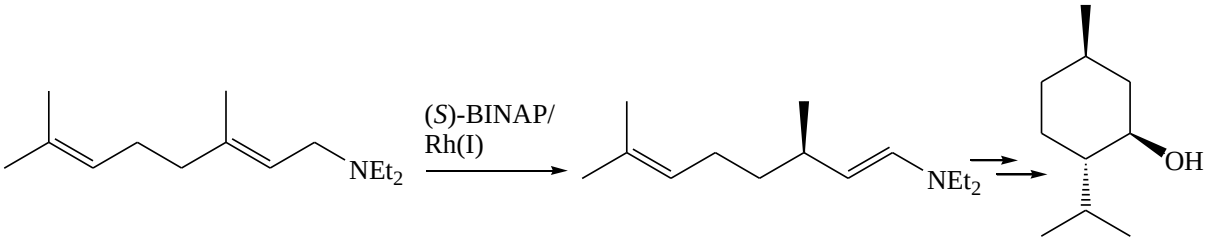


(*R*)-BINAP (*S*)-BINAP

Figure 1.1

Industry has placed increasing significance on the synthesis of chiral compounds as single enantiomers. Researchers such as Noyori, Knowles and Sharpless have recently shared the Nobel Prize in chemistry for their invaluable contributions to the field of asymmetric catalysis, further underscoring the importance attached to this field. High enantioselectivity is often attributed to chiral catalysts (bearing chiral ligands). In catalysis, it is widely believed that the supporting ligand of a catalyst conveys its chirality to the final product via the process of asymmetric induction where the reactants are in close proximity to the chiral environment of the catalyst complex during the reaction. Despite the widespread success of asymmetric catalysis in academia, its application in industry is still under-developed and only a handful of ligands have gone on to find large-scale application in industry, most notably BINAP and DUPHOS.[7] For instance, the industrial synthesis of *l*-menthol **1.1** involves a key asymmetric isomerisation which is catalysed by a Rh(I)/(*S*)-BINAP combination, as shown in Scheme 1.1. This highlights the viability of

biaryl diphosphines at the industrial level, hence the continued interest in the development of this class of ligand.



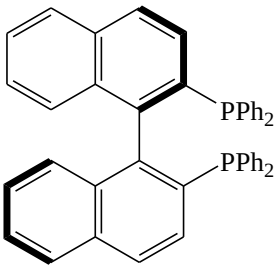
l-menthol (**1.1**)

Scheme 1.1

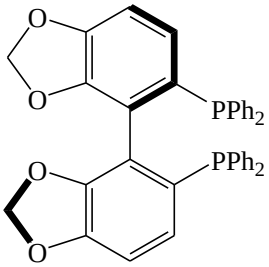
Prior to the emergence of chiral catalysis, chiral reagents were used as starting materials in asymmetric reactions to form the corresponding chiral products. However, this approach is very expensive and the associated costs render curiosity-based research unviable, especially at university-level hence the importance of chiral catalysts for grass-root development of new chemistry.

1.2 Biaryl diphosphines

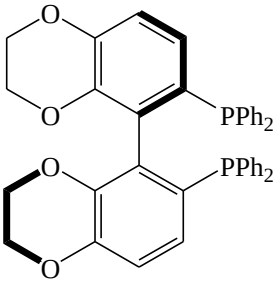
Biaryl diphosphines are a very important class of ligand in catalysis, especially in the field of platinum group metal catalysis and their respective catalysts are widely used in a vast number of reactions. Both chiral and achiral biaryl diphosphines have proven to be very important in catalysts mainly due to the unique features of the biaryl motif. Since its discovery in 1980, BINAP[1] has become indispensable to the field of catalysis and is now undoubtedly the most prominent biaryl diphosphine, so much so that a vast number of BINAP analogues have been synthesised over the years (Chart 1.1). The relatively short and more straightforward synthesis of BINAP compared to its predecessors[8] and the practical necessity to avoid using patented diphosphines, has contributed to the rising interest in BINAP analogues.



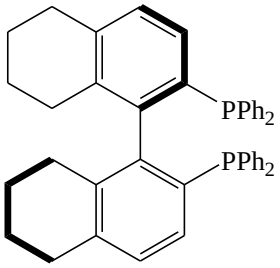
(*R*)-BINAP



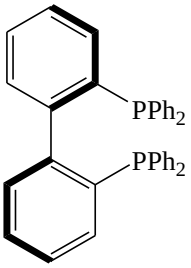
(*R*)-SEGPHOS



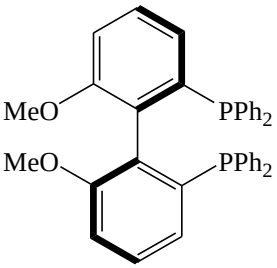
(*R*)-SYNPHOS



(*R*)-H_8-BINAP



(*R*)-BIPHEP



(*R*)-MeO-BIPHEP

Chart 1.1

1.2.1 Metal-Diphosphine Coordination and Stereo-chemical Model

Upon coordination of the diphosphine to a metal centre, a skewed seven-member chelate is formed with the four phenyl rings of the phosphorus atoms adopting an alternating edge-face arrangement, which means that on each phosphorus atom, one phenyl group adopts a *pseudo*-equatorial position while the other takes the *pseudo*-axial position. The *pseudo*-equatorial phenyl rings protrude away from the biaryl moieties while their respective *pseudo*-axial rings are aligned parallel to the biaryl backbone.[8]

This concept is better understood via the quadrant diagram (Figure 1.2) which depicts the alternating edge-face arrangement of the phosphorus-phenyl rings whereby the *pseudo*-equatorial rings from each phosphorus shield the upper right and lower left quadrants spaces and provide the necessary shielding, thus controlling the stereochemical outcome of the reaction. The *pseudo*-axial rings occupy the upper left and lower right quadrants spaces that are not in the path of the approaching substrate and, as such, these phenyl groups have considerably less effect on the shielding and stereochemical outcome of the reaction.

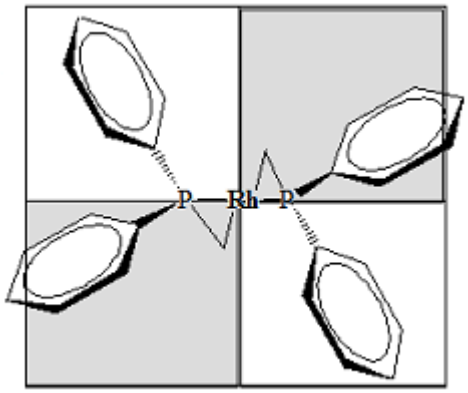


Figure 1.2

1.2.2 Electronic and Steric Properties

The electronic and steric properties of phosphine-based ligands have been extensively studied for a whole host of ligands and although there is no clear-cut universal rationale to account for the relationship between ligand structure and catalyst performance, some important general conclusions have been made. It is also noteworthy that not many phosphines conform to these general trends. The electronic properties of the ligands are commonly determined by measurement of the stretching frequency of the corresponding carbonyl-metal-phosphine complex. In theoretical terms, this measurement provided information about the π-acidity and σ-donation of the ligand in question, whereby the former is a measurement of the extent of back donation from the filled metal orbitals to the vacant phosphorus orbitals, whereas the latter is essentially a measurement of the electron donation of the phosphorus lone pair to the empty metal orbitals.

One prominent measure of the steric properties of phosphine ligands is the Tolman angle, θ, as shown in Figure 1.3. This parameter essentially encompasses the entire van der Waals surface of all the substituents thereby providing a very accurate indication of the entire bulk of the ligand in question.

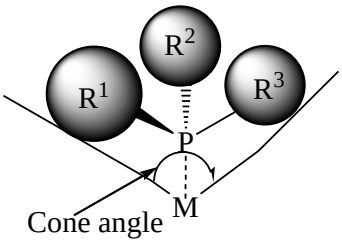


Figure 1.3

However in relation to biaryl diphosphines, the bite angle and dihedral angle of their metal complexes are more useful measurements (Figure 1.4).

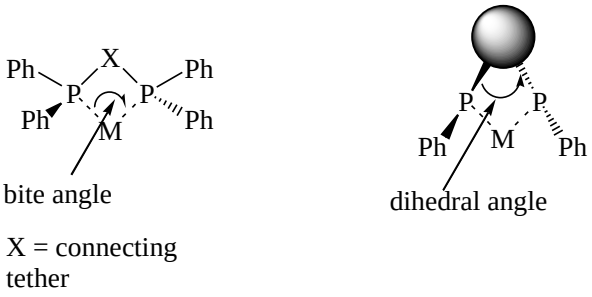


Figure 1.4

As illustrated in Figure 1.4, the bite angle is a measurement of the P-M-P angle which depends on the connecting tether and it is a reflection of both the steric bulk as well as the electronic properties of a complex.[9] For biaryl diphosphines, the dihedral angle is a measurement of the angle of the planes of the two aromatic moieties of the biaryl backbone of a phosphine-metal complex. Strong experimental evidence has led to the emergence of a prevailing hypothesis which draws a negative correlation between the dihedral angle and enantioselectivity levels; the narrowing of the dihedral angle leads to an increase in enantioselectivity. Herein it is suggested that the narrowing of the dihedral angle aligns the equatorial phosphorus-phenyl rings to project further inwards and, in essence, closer to the reactive metal site, creating even more steric hindrance for the approaching reactive substrate which, in turn, induces greater enantioselectivity.[10] Although BINAP is used industrially for the hydrogenation of 1-hydroxy-propan-2-one, it was found to be a poor ligand for the asymmetric hydrogenation of hydroxyacetone giving low ee levels, whereas BIPHEP and MeO-BIPHEP, both with narrower dihedral angles, give much higher enantioselectivities; > 99% for MeO-BIPHEP.[10]

1.2.3 Chirality

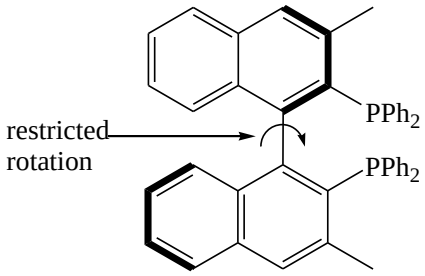
Chirality is a naturally occurring phenomenon prevalent all around us. It refers to the specific arrangement of atoms or groups in a molecule in such a way so as to give rise to two configurations (enantiomers) which are non-superimposable mirror images of each other. There are three types of chirality associated with phosphines. *P*-chirality' dictates that the phosphorus atom is the centre of chirality where, in most cases, three different groups are directly attached to the phosphorus atom with the lone pair of electrons on the phosphorus accounting for the fourth group thereby creating a tetrahedral chiral centre. On the other hand, central chirality refers to a molecule whose centre of chirality is not the phosphorus but at a different location within the molecule in question (Chart 1.2).

central chirality *P*-chirality

Chart 1.2

The third type is called 'axial chirality' which is a unique type of chirality where the molecule does not belong to the two aforementioned groups. Instead, the molecule in question has an axis, rotation about which leads to interconversion between enantiomeric conformations; chirality is caused by restricted rotation about the axis. This creates two distinct stable conformations (enantiomers) that are non-superimposable mirror images of each other, as illustrated in Figure 1.5. It is also noteworthy that there are two other types of chirality; planar chirality arises from substitution on a plane which breaks the plane of symmetry in a molecule. Helical chirality is where a linear molecule adopts a helical structure whereby the chirality is determined by the sense of screw of the helix.

Figure 1.5. Axial Chirality:(*R*)-Me-BINAP



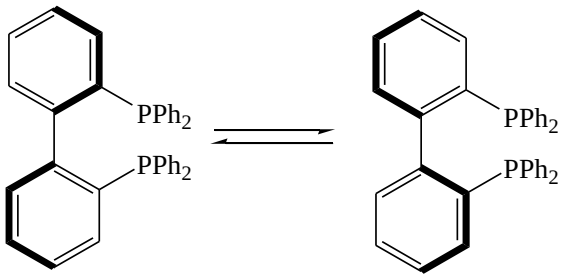
axial chirality

In the case of biaryl diphosphines the enantiomeric conformations resulting from rotation about the chiral axis are referred to as atropisomers, amongst which (*S*)/(*R*)-BINAP are perhaps the best known. They are defined as being separable species when they have a half life of at least 1000 s at ambient temperature.[11] The spatial group arrangement for each enantiomer is referred to as its absolute stereochemistry which gives each enantiomer its unique physical and biological properties. For instance, two enantiomers often have markedly different properties such as taste and smell (e.g. caraway and spearmint, enantiomers of carvone). Often they exhibit contrasting biological activity where one enantiomer is very useful for its therapeutic applications whereas the other is toxic or inactive.

In contrast, tropos molecules have an axis of rotation with a low energy barrier to rotation where the two conformations readily interconvert and are, as such, classed as achiral as the

two enantiomeric forms are equivalent. BIPHEP is a well know example of an achiral tropos molecule (Figure 1.6).

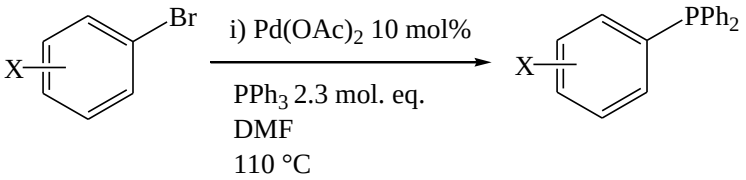
Figure 1.6. Two Interconverting Enantiomeric Conformations of BIPHEP.



(*R*)-BIPHEP (*S*)-BIPHEP

1.2.4 Synthesis

Amongst phosphine ligands, secondary and tertiary phosphines are predominately used as supporting ligands for catalysts. A relatively recent report by Kwong and Chan[12] outlined a versatile and straightforward route for the synthesis of tertiary phosphines **1.3a-d** (Equation 1). It follows a palladium-catalysed phosphination of substituted aryl bromides **1.2a-d** bearing nitrile, ester, aldehyde, ether and chloride functional groups, with triphenylphosphine employed as the phosphinating reagent. The reaction has also been successfully carried out with functionalised biaryl fragments as coupling partners as well.[12] This route has expanded the scope of the functional groups that can be incorporated into a ligand and is a straightforward one-step reaction.



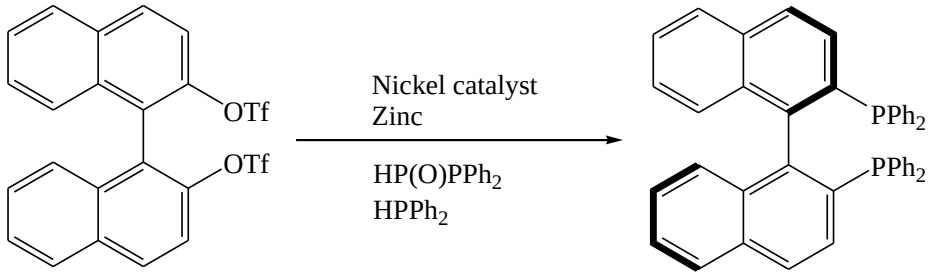
1.2a-d major **1.3a-d**

X = OMe (**1.2a**)
CN (**1.2b**)
Cl (**1.2c**)
^{t}Bu (**1.2d**)

Equation 1.1

There are two other routes that are commonly used for the synthesis of phosphines. They both have their limitations; the reaction of aryl Grignard or organolithium reagents with chlorophosphine is limited to compounds that are not base sensitive.[13] The second method is a nickel-catalysed phosphination of aryl triflates **1.4** which reacts with diphenyl

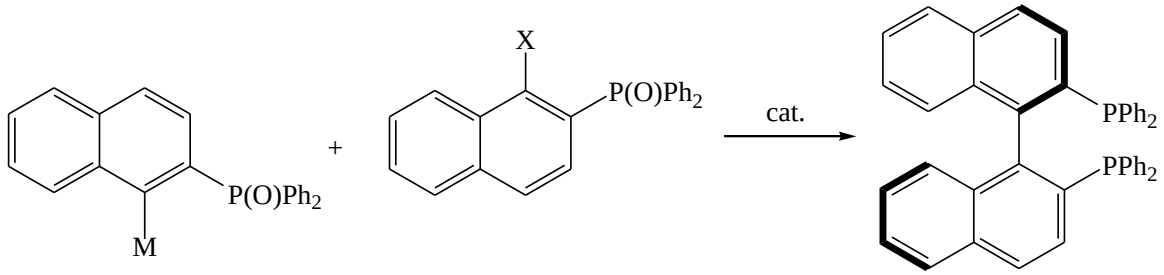
phosphine[14] to afford atropos BINAP **1.5**; both of the phosphinating reagents are air/moisture sensitive and the presence of zinc metal means that easily reducible functional groups are not well tolerated in this reaction (Equation 1.2).[15]



1.4 **1.5**

Equation 1.2

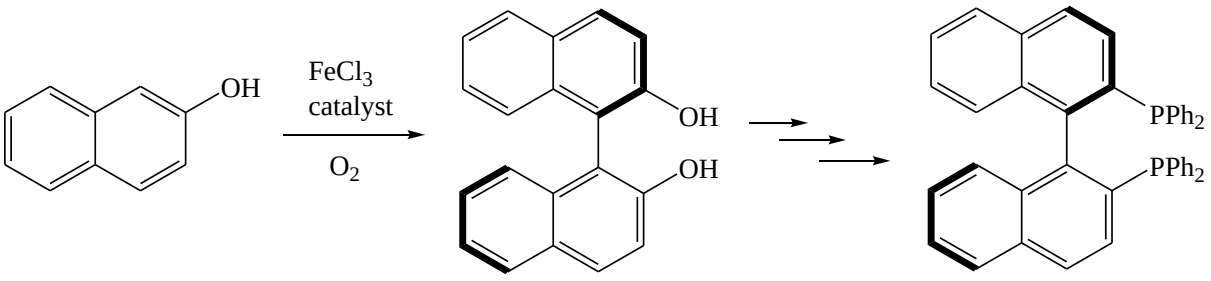
Alternative approaches to the synthesis of biaryl diphosphines involve construction of the biaryl unit via aryl-aryl couplings[16]. Equation 1.3 illustrates a well known transition metal catalysed cross coupling between ArX **1.7** (X = triflates, halides) and ArM **1.6** (M = Pd, boron) to afford the corresponding atropos biaryl diphosphines **1.8**. Buchwald has, and continues to, employ palladium-catalysed Suzuki coupling of biaryl mono-phosphines and phosphonates[17] and it has also been used in Kumada coupling for the synthesis of binaphthyl units.[18]



1.6 **1.7** **1.8**

Equation 1.3

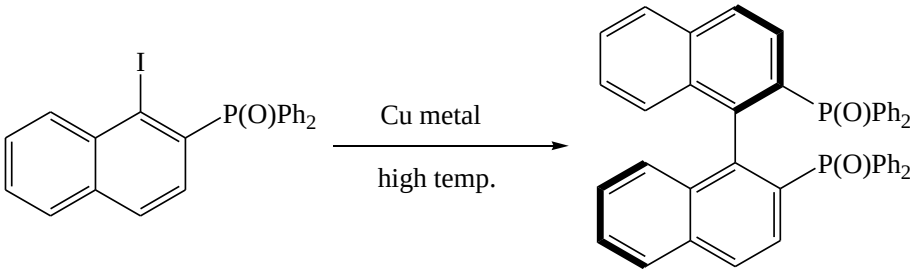
Another well known method involves the use of naphthols **1.9** where oxidative addition at the *ortho*-positions of electron-rich phenols is commonly catalysed by $FeCl_3$ in the presence of oxygen,[19] affording the corresponding atropos biaryl diol **1.10** with the characteristic C_4-tether bearing two hydroxyl groups at the two ends (Equation 1.4); **1.10** undergoes several subsequent steps to afford the corresponding final phosphine product **1.11**. This method has been used for the synthesis of diphosphines such as SEGPHOS[10] and SYNPHOS[20] but its real limitation is in the lack of diverse biaryl units with different functional groups.



1.9 **1.10** **1.11**

Equation 1.4

Perhaps the most widely used aryl-aryl coupling method is the Ullamnn coupling (Equation 1.5). The reaction involves o*rtho*-lithiation followed by iodination to afford two iodo-aryl fragments **1.12**, which are subsequently coupled together to afford the corresponding atropos biaryl diphosphine oxide **1.13** under high temperature in the presence of copper.[21] It is the method of choice for synthesis of SYNPHOS,[22] and MeO-BIPHEP.[23, 24] However the high temperature of this reaction results in the formation of significant amounts of by-products which lowers the yield of the desired biaryl product.



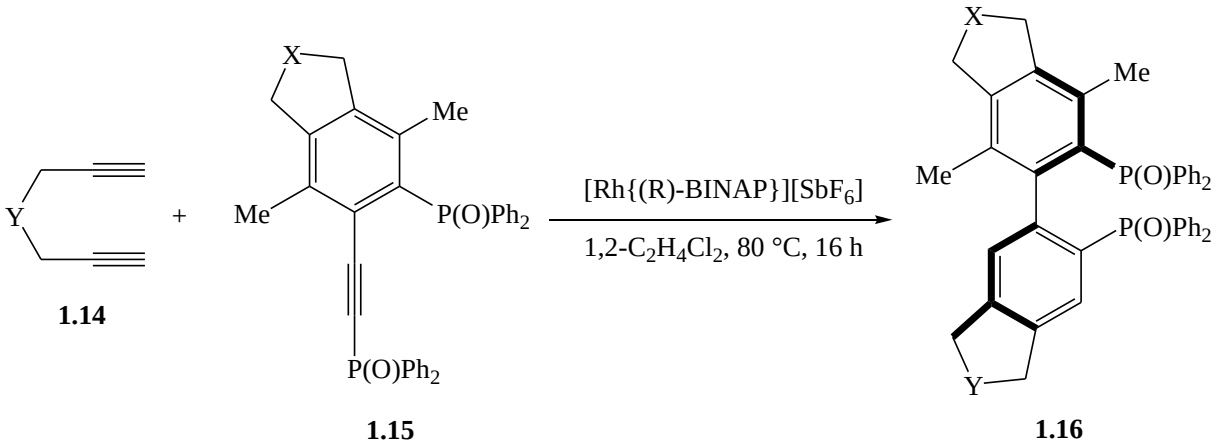
1.12 **1.13**

Equation 1.5

Finally a lesser-used nucleophilic aromatic substitution uses Grignard reagents to facilitate aryl-aryl coupling of electron-deficient aryl units.[25] However, it has not been widely adopted, despite affording yields > 90% with an ester functional group, due to practical difficulties of working with Grignard reagents and the limited functional group tolerance of this approach.

Transition-metal catalysed [2 + 2 + 2] cycloaddition is an extremely powerful tool often used for the synthesis of axially chiral biaryls, spirocycles, and helical polyaryls, with some of the recent advances attributed to research groups of Tanaka,[26, 27] and Shibata.[28, 29] The Doherty group has previously reported the first examples of the use of asymmetric rhodium-catalysed [2 + 2 + 2] cycloaddition; diphenylphosphine oxide fragment **1.15** and two equivalents of 1,6-diyne **1.14** react to afford the corresponding atropos diphosphine

oxides **1.16** in very high yields and with exceptionally high enantioselectivity >97% in all cases (Equation 1.6).[30]



X-Y = $C(CO_2Me)_2$ yield 79%
ee 97%

CH_2CH_2 yield: 84%
ee: 96%

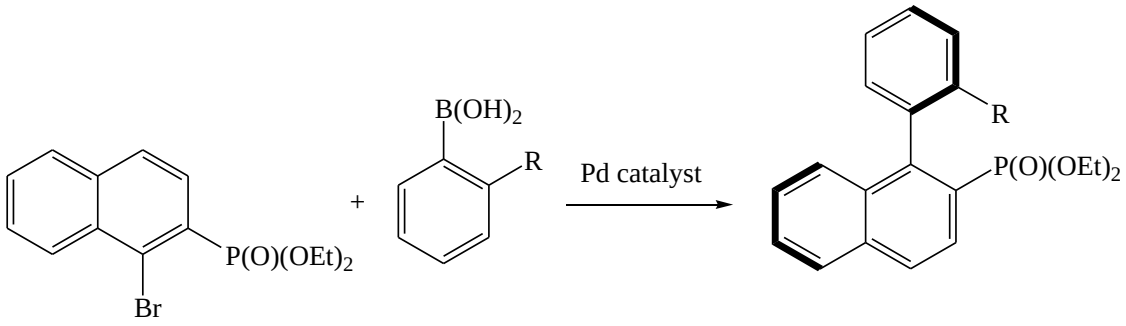
Equation 1.6

1.2.5 Resolution

Common methods employed for the separation of enantiomeric diphosphines from their respective racemic mixture involve the use of resolving reagents such as camphorsulfonic acid (CSA) or di-*O*-benzoyl tartaric acid (DBTA).[23, 31]On-metal resolution is also widely used as well, in which one enantiomer of a racemic mixture preferentially coordinates to a chiral metal complex to form the respective diastereoisomeric complexes which are subsequently separated by either fractional crystallisation or column chromatography. The real limitation of the latter route is the need to liberate the enantiomer from the respective chiral metal complex after separation which is not a very efficient process as it lowers the yield of pure enantiomer and the expensive precious metal is often not re-used.[32]

There has been considerable progress in developing alternative ways to obtain enantiopure ligands by avoiding the resolution procedures detailed above. One of the prominent approaches involves the palladium-catalysed Suzuki coupling in which a substituted boronic acid **1.18** is coupled to a bromo-aryl fragment bearing phosphorus-based functional groups **1.17** to afford the corresponding atropos biaryl diphosphine **1.19** (Equation 1.7). Buchwald has successfully demonstrated the efficacy of this reaction in some of his early research and synthesised chiral biaryl monophosphonates **1.19** with up to 92% ee.[17] One of the disadvantages is that hindered coupling partners are needed in order

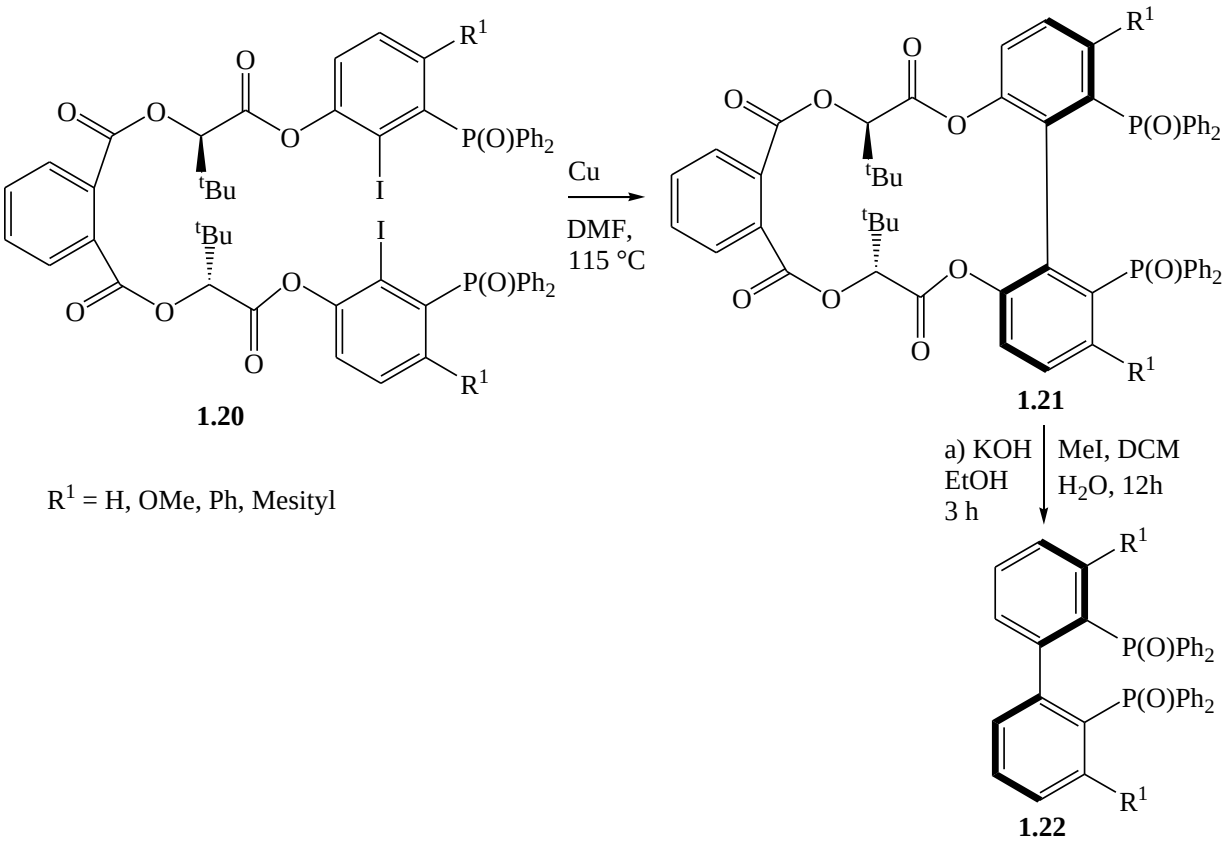
to form atropos chiral biaryl diphosphines (the existence of three *ortho*-substituents is the minimum requirement for the biaryl unit to be atropos). This severely hinders the reaction rate, in some cases preventing formation of desired product altogether. Also the need to prepare the boronic acids or bromo-aryl phosphonates with the desired functionalities can be time-consuming and expensive.



1.17 **1.18** **1.19**

Equation 1.7

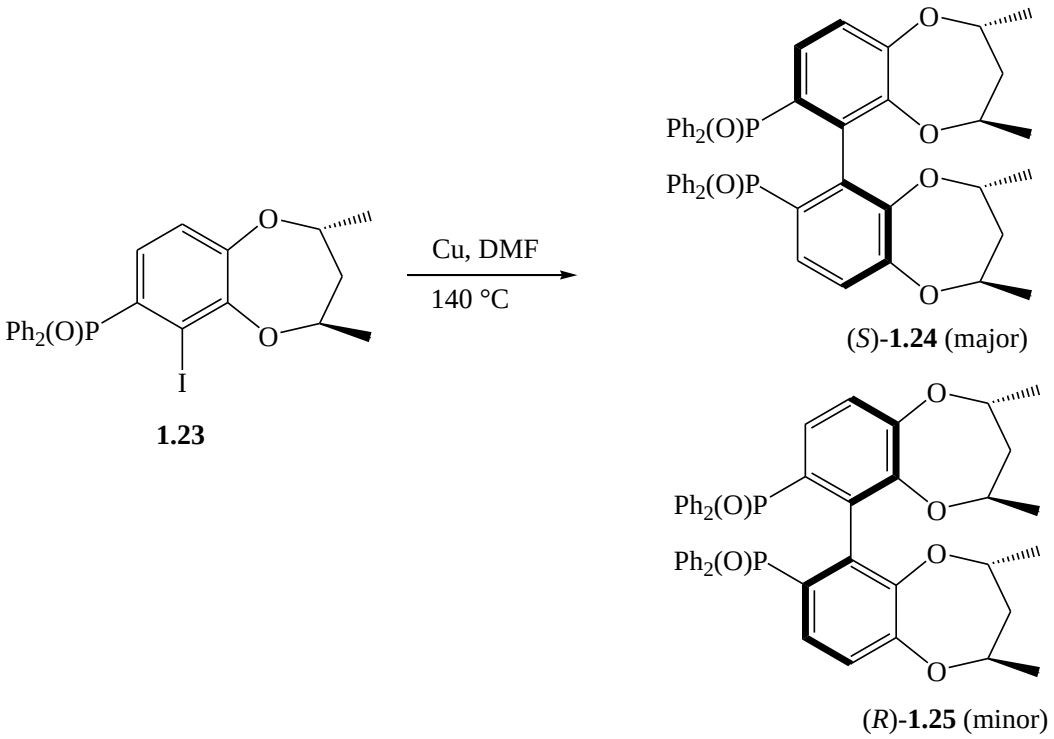
A recent development has seen the use of chiral tethers which link two aryl fragments together (Scheme 1.2). Such reactions are most commonly carried out via intramolecular Ullmann coupling. The advantage of this method is that it gives high enantioselectivity, in some cases up to >99% ee. In a recent example, Keay and colleagues successfully prepared a single diastereoisomer of several MeO-BIPHEP derivatives **1.21** by using a chiral tether which was later removed to afford the corresponding atropos MeO-BIPHEP **1.22** in >90% ee, as shown in Scheme 1.2 .[33] Other reports by Chan and colleagues[34] include synthesis of chiral TUNAPHOS-type derivatives via a similar approach and the [2 + 2 +2] cycloaddition.



R^1 = H, OMe, Ph, Mesityl

Scheme 1.2

Furthermore, asymmetric Ullmann coupling[35, 36] is also a common reaction which involves stereoselective aryl-aryl coupling.[36] This method has been employed by Chan and colleagues for the synthesis of two diastereoisomers of iodophosphine oxide (*S*)/(*R*)-**1.25**, as shown Equation 1.8.[37] This is a very effective reaction and it has been used for the synthesis of a number of diphosphines.[38, 39] However the lack of chiral starting materials and the cost associated with preparing those with the desired functional groups are significant disadvantages associated with this reaction



1.23

Equation 1.8

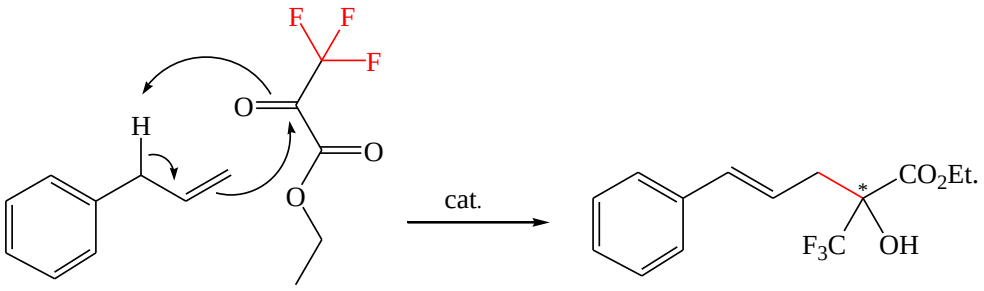
1.2.5.1 Resolution of Tropos Biaryl Diphosphines

It is well known that tropos biaryl diphosphines have two conformations (enantiomers) that readily interconvert at room temperature due to the low energy barrier to rotation. Gagné was the first to report that the coordination of tropos BIPHEP to a substitutionally inert metal complex slows atropinterconversion to such an extent that the atropos conformations can be resolved, separated and used in asymmetric catalysis.[40, 41] In this regard, Pt-(*S*)-BINOL metal complex was used to afford a diastereoisomeric mixture which, upon heating, afforded the thermodynamically favoured diastereoisomer of [((*S*)-BIPHEP)Pt{(*S*)-BINOL}] in high diastereopurity > 95%. The BINOL can be removed and the resulting Lewis acid can be used for asymmetric catalysis. It is noteworthy that the atropos/tropos nature of M-BIPHEP (M = Pd, Pt) is dependent on several factors: the nature of metal is important where Ru-BIPHEP complex has been shown to be tropos while its palladium counterpart forms an atropos complex.[42] Furthermore, the nature of the resolving agent is also very important where, in particular, amine-based DPEN exclusively forms atropos complex of high stereopurity whereas corresponding complex with DABN favours the tropos counterpart.[42]

1.3 Reactions Catalysed by Lewis Acids of Biaryl Diphosphines

1.3.1 The Carbonyl-Ene Reaction

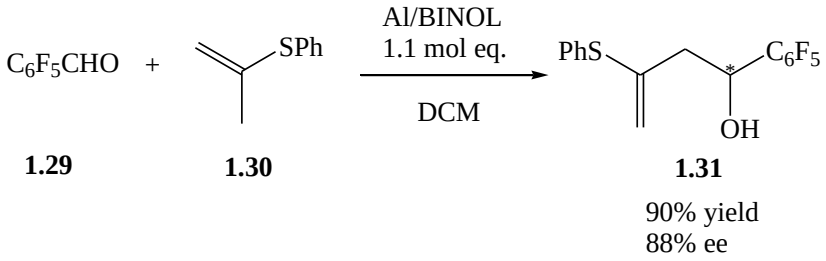
The carbonyl-ene reaction is a well-established, versatile and atom economical method for carbon-carbon bond formation that enables chemists to form biologically important and non-racemic unsaturated α-hydroxy esters (Equation 1.9).[43] The carbonyl-ene reaction involves alkene and a carbonyl-based coupling partner, reacting to form a homoallylic alcohol, as illustrated in Equation 1.9 in the reaction between allylbenzene **1.26** and ethyl trifluoropyruvate **1.27** to afford the corresponding α-hydroxy ester **1.28**.



1.26 **1.27** **1.28**

Equation 1.9

Maruoka and colleagues[3] were first to report a catalytic carbonyl-ene reaction in 1988 between isopropenylsulfanyl benzene **1.30** and 2,3,4,5,6-pentafluoro-benzaldehyde **1.29**, catalysed by chiral aluminium complex of enantiopure BINOL, to afford the corresponding α-hydroxy ester **1.31** in 90% yield and 88% ee (Equation 1.10). To highlight the significance of this paper, literature published prior to this report only afforded the enantiopure homoallylic alcohol products via reagent-based control of absolute stereochemistry where, for instance, expensive chiral starting materials such as glyoxylate were used in carbonyl-ene transformations in order to transfer the chirality across and afford the enantiopure final products.[44, 45] The key to success of asymmetric induction in this reaction was the presence of the bulky ligand 3,3-bis(triphenylsilyl)binaphthol as a chiral ligand in the Lewis acid metal complex. When the reaction was attempted with less bulky ligands such as 3,3-diphenylbinaphthol under the same reaction conditions, the racemic product was obtained in poor yield. This clearly demonstrates the crucial role of the ligand in influencing both the enantioselectivity and the final yield of the products. The scope of the carbonyl-ene reaction has been increased significantly over the years to include catalysts based on Co,[46] Cu[47] and other metals.[48, 49]

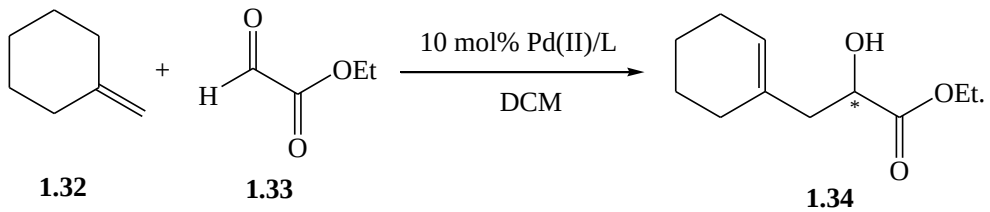


Equation 1.10

A wide variety of electron deficient enophiles such as alkyl and aryl glyoxylates or the less reactive *α*-ketoesters (e.g. ethyl trifluoropyruvate **1.27**) and 1,1-disubstituted or tri-substituted alkenes (e.g. allylbenzene **1.26**) have been used to form synthetically useful and versatile chiral α-hydroxy esters (Equation 1.10).[43, 50, 51] Recent examples include the asymmetric carbonyl-ene reaction between racemic silyloxyallenes and 2-bromobenzaldehyde to form substituted indanones with transfer of stereochemistry from the enantio-enriched carbinol to the C3 position of the corresponding product.[52] A whole host of efficient Lewis acids have been used in the carbonyl-ene reaction such as Ti-BINOL,[53] Cu-Sulfoximine,[54] Co-Salen,[46] Sc-PyBox[55] as well as Brønsted acid N,N-triflylphosphoramide-based organo-catalysts and Cu/Bisoxazoline.[56]

1.3.2 Lewis Acids of Biaryl Diphosphines

The choice of ligand has a significant effect on the reaction outcome and this was neatly highlighted in a report by Hao and colleagues[57] where BINAP and its analogues were found to be effective in the carbonyl-ene reaction. The reaction between methylenecyclohexane **1.32** and ethyl pyruvate **1.33** was catalysed by 10 mol% of Pd(II)/BINAP where (*S*)-*tol*-BINAP, in particular, gave the best results. The carbonyl-ene catalysis reaction gave the corresponding α-hydroxy ester **1.34** in 88% yield and 78% ee (Equation 1.11).



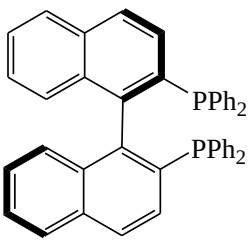
L = (*S*)-*tol*-BINAP, yield (88%), ee (78%)
(*S*)-BINAP, yield (82%), ee (61%)
(*S*)-Xylyl-BINAP, yield (87%), ee (42%)

Equation 1.11

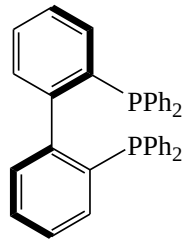
Furthermore, it was reported that (*S*)-*tol*-BINAP not only plays a crucial role in providing the necessary shielding to afford high ee values but it also imparts excellent control over the regioselectivity of the reaction, leading to homoallylic rather than allylic alcohols (formed when double bond in an allylic compound shifts to the next carbon atom). It was also shown that the same reactions carried out with less bulky (*S*)-BINAP gave slightly lower yields and ee's and the use of much bulkier (*S*)-Xylyl-BINAP gave comparable yields but much lower enantioselectivity levels for the respective product. These reactions clearly indicate that the right balance of steric factors can play a very important role in the outcome of the reaction. On some instances, improved yields were also obtained with moderate heating (25 °C to 60 °C) which was attributed to the breakdown of the coordination of the hydroxy group of the ene product to the active palladium centre after heating, which subsequently lead to improvement in results.

More recently our group has carried out an in-depth study of the electrophilic platinum group metal Lewis acid catalysts of the type $[M(BINAP)]^{2+}$ (M = Pd, Pt, Ni) for the competing reaction pathways between alkene dimerisation, intramolecular Friedel-Crafts alkylation and carbonyl-ene reactivity between α-methylstyrene derivatives and ethyl trifluoropyruvate.[58] The selectivity of the Lewis acids for either one of the aforementioned transformations was reported to be dependent on the metal centre. For instance the platinum-based Lewis acid is not selective for one reaction and catalyzes alkene dimerization, Friedel-Crafts alkylation and the carbonyl-ene reaction to give a mixture of products whereas its palladium counterpart is entirely selective for the ene reaction, with the corresponding nickel catalyst exhibiting platinum-like behaviour.

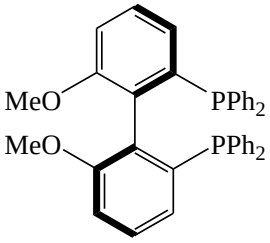
As part of an on-going programme to develop new, efficient and modular approaches to the synthesis of biaryl or biaryl-like diphosphine ligands (Chart 1.3), the Doherty group has previously developed a novel class of biaryl-like diphosphine R_2-CATPHOS (R = H, Me, OMe), the synthesis of which is outlined in Chapter 2. We aim to further evaluate the reactivity of α-methylstyrene derivatives with $[M(diphosphine)]^{2+}$ (M = Pd, Pt, Ni) Lewis acids employing (*S*)-Me_2-CATPHOS as the diphosphine supporting ligand in order to explore the affect of the supporting ligand, if any, on the selectivity for the ene-product, as previously discussed.[58]



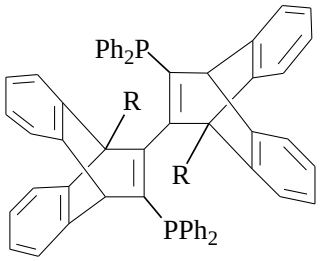
(*R*)-BINAP



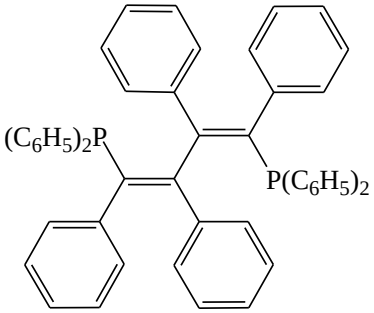
(*R*)-BIPHEP



(*R*)-MeO-BIPHEP



(*S*)/(*R*)-R_2-CATPHOS



Ph4-NUPHOS

Chart 1.3

1.3.3 Reaction Cycle

The carbonyl-ene reaction is catalysed by a Lewis acid and it is generally accepted that it proceeds via a concerted mechanism. An important feature of the reaction involves the binding of the Lewis acid to the carbonyl compound which is then activated towards reaction with the approaching nucleophilic terminal olefin. As illustrated in Figure 1.7, the first step of the reaction cycle involves coordination of the Pd(II) centre of the catalyst **1.35** to both carbonyl groups of ethyl trifluoropyruvate to form an activated pyruvate-catalyst adduct **1.36** (step A) which reacts with allylbenzene (step B) to afford the pyruvate-allylbenzene-catalyst transition state **1.37**. Subsequently, the two substrates react via carbon-carbon bond formation between the terminal carbon of the olefin and the carbonyl carbon atom (step C), during which a proton from the olefinic substrate is transferred to the reacting carbonyl oxygen in order to afford the allylic alcohol **1.38**. The final step involves the liberation of the product together with regeneration of the catalyst (step D). Overall the reaction between glyoxylates and α-olefins has proven to be a powerful tool for carbon-carbon bond formation,[49, 50, 59, 60] despite the obvious limitation of the lack of alternative enophiles to the glyoxylates.

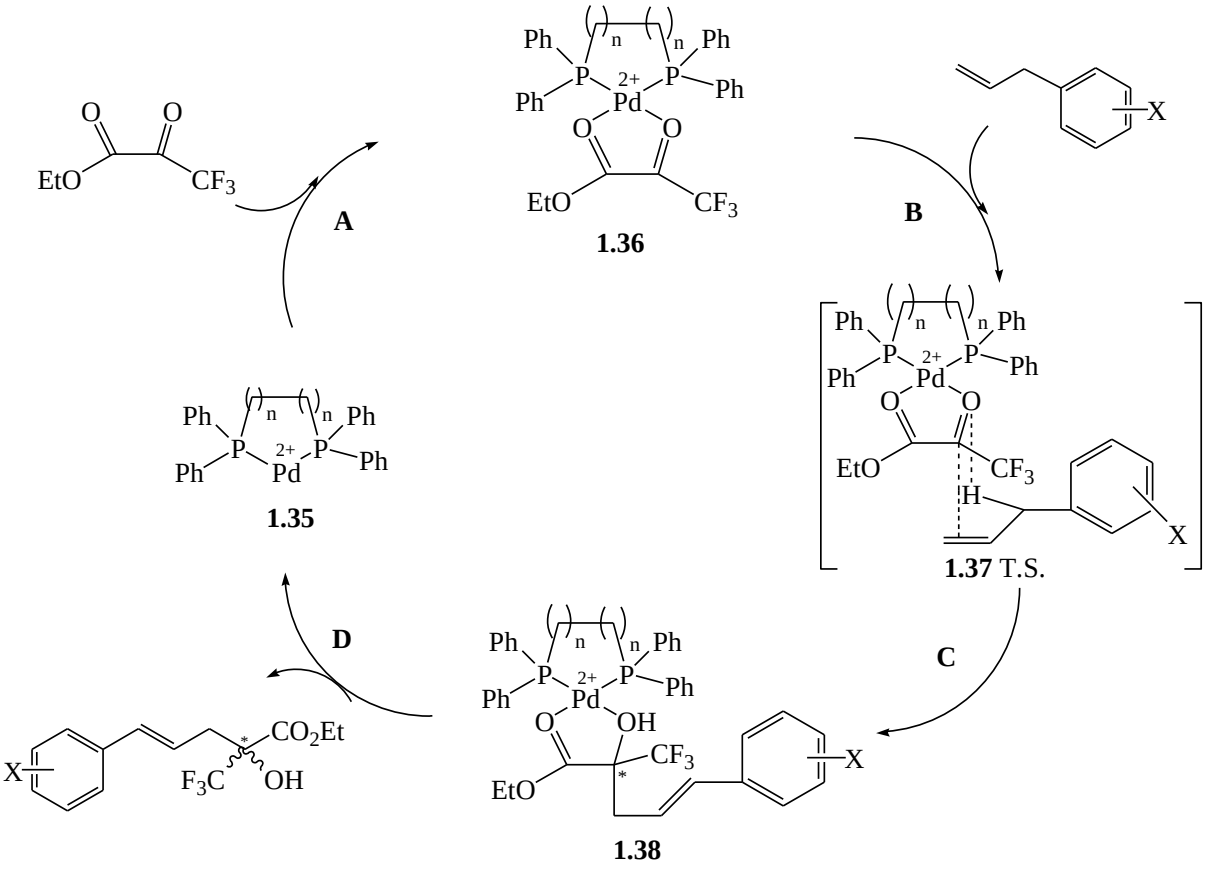


Figure 1.7

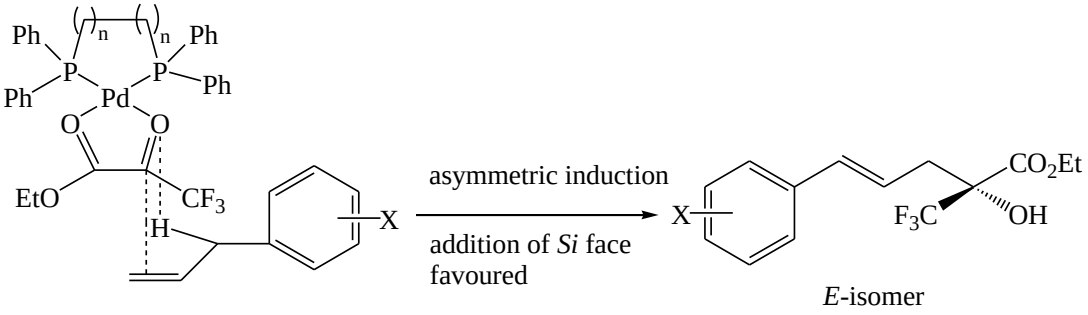
The recent development of 'coordinatively unsaturated' square planar platinum group metal complexes of the type $[M(diphosphine)]^{2+}$ (M = Pd, Pt, Ni)[61] has led to the development of a host of platinum group Lewis acids, which have proven to be efficient catalysts for asymmetric carbonyl-ene reactions. In a recent report by the Doherty group, reactions between *α*-methylstyrenes and ethyl trifluoropyruvate catalysed by [M{(*R*)-BINAP}][SbF_6]$_2$ (M = Pd, Pt, Ni) gave the expected α-hydroxy esters, as well as formation of unexpected alkene dimerization-carbonyl-ene adducts and carbonyl-ene-Friedel-Crafts alkylation adducts.[58] Herein, all the Lewis acids used proved to be active for the carbonyl-ene reaction but their respective selectivity for the desired carbonyl-ene product was dependant on the metal centres; the palladium-based catalysts favoured formation of the carbonyl-ene adduct as the major product whereas the platinum counterparts gave a mixture of the dimerisation and the Friedel-Craft alkylation adducts, in addition to the carbonyl-ene product. The reactivity of the platinum-based catalysts has been attributed to their relatively high carbophilicity. For instance, in the coupling of α-methylstyrene to ethyl trifluoropyruvate in dichloromethane at room temperature for 1 h, the palladium-based Lewis acid gave carbonyl-ene adduct in 89% yield and Friedel-Craft adduct in 11% yield with no trace of the dimerisation adduct. However, the same reaction with the

platinum counterpart gave the carbonyl-ene, Friedel-Craft and dimerisation adducts in 4%, 69% and 27% yields, respectively; the nickel counterpart exhibited platinum-like behaviour affording the same product mixture in a ratio of 23%, 64% and 13%, respectively. The lower carbophilicity of the palladium centre ensures it remains selective for the carbonyl-ene reaction by virtue of much lower rate of dimerisation and Friedel-Crafts alkylation.

1.3.4 Asymmetric Induction

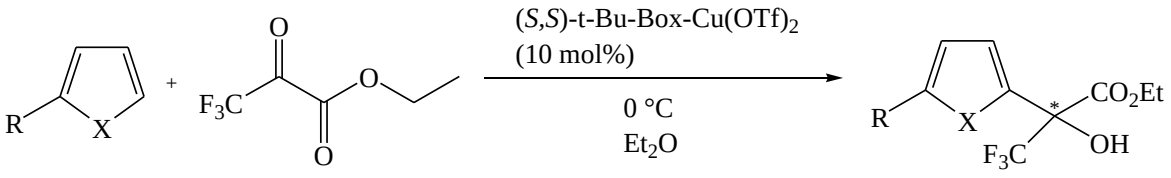
Achieving high levels of asymmetric induction is the key goal in the use of platinum group Lewis acid metal complexes in catalysis. In relation to the opening phase of our study, which involves reaction of α-methylstyrene derivatives with ethyl trifluoropyruvate, the coordinatively unsaturated Lewis acid $[M(diphosphine)]^{2+}$ (M = Pt, Pd, Ni) binds to the two carbonyl oxygen atoms of the pyruvate substrate to form the square-planar catalyst-pyruvate adduct, as shown in Figure 1.8. This model is similar to those proposed by Oi et al.[61] and Ghosh and Matsuda[62] for the [M{(S)-BINAP](X) (M = Pd, Pt)-catalysed Diels–Alder reaction between N-acryloyloxazolidinones and dienes and the [Cu{(*S*,*S*)-t-Bu-Box)][SbF_6]$_2$ catalysed Diels-Alder reaction of α-dicarbonyl substrates.[62] In both, the chiral ligand plays a crucial role in the stereochemistry of the catalyst-pyruvate adduct. According to this model, the palladium(II) and platinum(II) complexes of (*S*)-Me_2-CATPHOS have the same spatial arrangement of the P-Ph rings as their BINAP counterparts. The two equatorial phenyl rings occupy the upper right and lower left quadrant. This specific arrangement effectively shields the *Re*-face of the pyruvate via the non-bonded interaction between the phenyl rings and the approaching α-methylstyrene. Consequently, only the *Si*-face of the pyruvate reacts, leading to the observed (*R*)-enantioselectivity for the α-hydroxyester products.

Figure 1.8. Reaction Model Illustrating Preferential Reaction of Allylbenzene with *Si* face of the Catalyst-Pyruvate Adduct to Afford the Corresponding α-Hydroxyesters with (*R*)-Configurations.



1.4 Friedel-Crafts Alkylation

The addition of fluorine-containing carbonyl substrates to heteroaromatics via enantioselective Friedel-Crafts reactions forms high value products that are widely used in industry and in academia. A report by Jørgensen and colleagues[63] evaluated the electrophilic aromatic substitution reaction between various substituted heteroaromatics **1.39** and ethyl trifluoropyruvate **1.27**, an important fluorine-bearing substrate containing CF_3 group which exhibits unique physical and biological properties,[64] to afford a whole host of optically active α-hydroxy esters **1.40** with high levels of enantioselectivity (Equation 1.12). Furthermore, for a series of substituted indoles, the corresponding α-hydroxy ethyl esters are obtained in high yield and enantioselectivity. Reactions with furans and thiophenes also gave the desired product in high enantioselectivity but in poor yields. The poor yields obtained with the heterocycles was very surprising given that all the reactions were catalysed by 10 mol% of copper bis(oxazoline)-based complexes over 24-48 h. To our surprise, this reaction has not been further exploited with other catalysts such as Lewis acids of biaryl diphosphines in order to improve on final yields and use lower catalyst loading.



1.39 **1.27** **1.40**

X = S, R = Me, yield (16%), ee (79%)
X = O, R = Me, yield (65%), ee (93%)

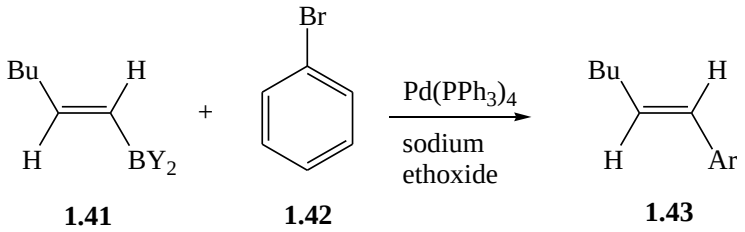
Equation 1.12

The mechanism for this reaction was postulated to follow the initial binding of the pyruvate dicarbonyl to the catalyst in a bidentate fashion to form the catalyst-pyruvate intermediate with a distorted square planar geometry,[65-67] as previously shown in Figure 1.8. This formation creates a so-called reactive quadrant site which renders the *re*-face of the dicarbonyl preferentially available for attack by the approaching heteroaromatic nucleophile. Herein, the efficacy of the catalyst was further evaluated with anilines as the nucleophilic coupling partner and it was found that the nitrogen centre unfavourably coordinates to the copper centre of the catalyst and reduces the efficacy of the copper-

bisoxazoline catalyst which lowers the enantioselectivity. Consequently, bulky protecting groups were introduced onto the nitrogen of the amine. Crystal structure determination of the corresponding intermediate showed that the nitrogen protecting groups are repelled by the *tert*-butyl substituents of the bis(oxazoline) ligand which prevents the unfavourable coordination between copper and the amine; this had the overall effect of increasing the enantioselectivity for the same reaction.

1.5 Suzuki-Miyaura Cross Coupling

The Suzuki-Miyaura reaction was first reported in 1979[68] in the cross coupling of alk-1-enyl-boranes **1.41** and aryl bromide **1.42** catalysed by $Pd(PPh_3)_4$ and a base such as sodium ethoxide, to give a range of arylated (*E*)-alkenes **1.43** (Equation 1.13). This was the first report of the application of a transition-metal catalyst for this reaction. Prior to this report, reactions were catalysed with other reagents based on organo-magnesium,[69] zinc,[70] and silicon.[71] The innocuous nature of boronic acids, which are generally non-toxic, air- and moisture stable, makes them the ideal coupling partners.

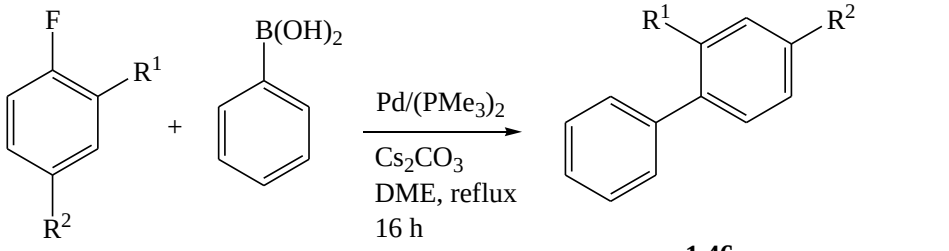


1.41 **1.42** **1.43**

Y = Bis(1,2-dimethylpropyl)

Equation 1.13

Diphosphine palladium complexes have proven to be highly efficient catalysts for Suzuki-Miyaura cross-couplings. In 2003, Widdowson and colleagues were first to report the successful coupling of highly unreactive fluoroarenes **1.44** to arylboronic acid **1.45** catalysed by $Pd/(PMe_3)_2$ combination (Equation 1.14) to afford the corresponding biaryls **1.46**.[72] The report also included successful reaction of aryl chlorides as coupling partners and interestingly, the absence of the catalyst lead to decomposition of the starting materials which established that the $Pd/(PMe_3)_2$ catalyst combination is involved in the reaction.



1.44 **1.45** **1.46**

$R^1 = R^2 = NO_2$, yield (85%)

$R^1 = CF_3$, $R^2 = NO_2$, yield (67%)

Equation 1.14

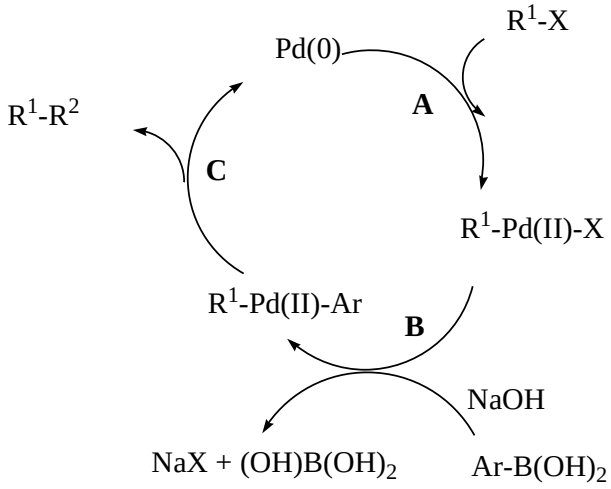
An early report by Herrmann and colleagues evaluated the performance of various palladium(II) complexes bearing NHC and triarylphosphines in the Suzuki-Miyaura cross coupling reaction between 4-chlorotoluene and phenylboronic acid in xylene at 130 °C. Although the optimal performance was with $Pd/(NHC)_2$ catalyst combination affording the corresponding biphenyl product in >99% conversion after 3 h, the bis-phosphine catalyst combination of $Pd/(PPh_3)_2$ also exhibited very high activity, giving the corresponding final product in 95% conversion after 3 h.[73] Herein, the steric bulk of the ligands is the decisive factor in governing the activity of the catalyst.[74]

There has only been a few reports on the use of catalysts bearing biaryl/biaryl-like diphosphines in Suzuki-Miyaura cross couplings and given the high activity of the aforementioned Pd/L (L = bis-phosphine) catalyst combinations, it is worthwhile to evaluate the efficacy of novel Pd/biaryl-diphosphines catalyst combinations in Suzuki-Miyaura cross couplings.

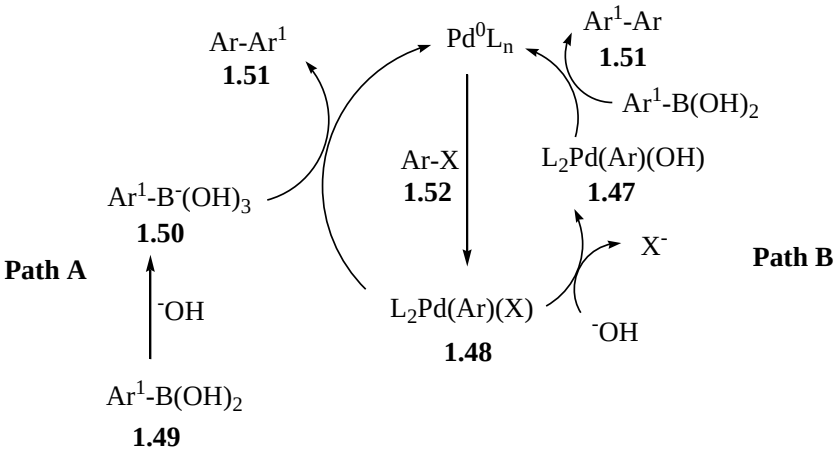
1.5.1 Reaction Cycle

The Suzuki-Miyaura cross coupling between ArX (X = Br, Cl, I, OTf) and a boronic acid[75, 76] has been greatly developed over the years and it continues to be a widely researched reaction due to its versatility and tolerance of a wide scope of functional groups. Factors such as the nature of the coupling partners, palladium catalyst and its supporting ligand, the strength of the base and the solvent all influence the overall efficiency of the reaction.[77-79] The fundamental mechanism of the reaction follows a 3-step catalytic cycle, as shown in Figure 1.9.[75] Oxidative addition (step A) of Pd(0) to aryl halide forms palladium-aryl-halide adduct which subsequently undergoes transmetalation (step B) with the arylboronic acid to form the aryl-palladium-aryl adduct. The final step is reductive elimination (step C) which liberates the desired biaryl product and regenerates the catalyst.

Figure 1.9. General Suzuki-Miyaura Catalytic Cycle with NaOH as Base.[80]



Although it has been established that this reaction occurs via an oxidative addition, transmetalation and reductive elimination sequence, the mechanism of the transmetalation step has been widely debated. It is a very important step as it is often proposed to be turnover limiting and dictates the choice of reaction conditions that can be used.[81] Suzuki-Miyaura couplings are often carried out in THF/H_2O with common base K_2CO_3 which leads to *in-situ* formation of $[OH]^-$ species. The two prevailing paths for the transmetalation step have been illustrated in Scheme 1.3. The first involves the attack of hydroxide on the Pd(II) centre to displace the halide and form the PdOH complex **1.47**, which is more active than the parent PdX complex **1.48** (X = Br, Cl, I) **(**Path B).[82] The second reaction path involves attack of the hydroxide ion on the arylboronic acid **1.49** to form the highly activated trihydroxyborate **1.50** which is believed to be more active towards transmetalation (Path A). It has been widely reported that Path A is the actual route of the transmetalation step, although data for path B have also been reported.[83-85]



Scheme 1.3

In 2011, the Hartwig group carried out various kinetic and thermodynamic studies which showed that Path B is, in fact, the most likely route for the transmetalation. Herein, they synthesised and isolated various aryl trihydroxyborate complexes **1.50** which subsequently reacted with ArPdX complexes **1.48** to afford corresponding biaryls **1.51**. Successful reactions were also carried out with isolated ArPdOH complexes **1.47** ligated to PPh_3/PCy_3 to form biaryl **1.51**.[81] The comparison of the two sets of results showed that the coupling of trihydroxyborate **1.50** is catalysed very slowly with [LPdArCl] complex **1.48** (< 10% conversion after 11 h with rate constant of 1.7×10^{-7} s^{-1}) whereas (Ar)PdOH **1.47** catalyses coupling of *p*-tolylboronic acid at significantly faster rate with a rate constant of 10^{-3} s^{-1}. Equilibrium data for interconversion of arylboronic acids **1.49** to trihydroxyborate **1.50**, as well as the equilibrium constant for interconversion of palladium halide **1.48** to its hydroxo counterpart **1.47** were also established whereby the concentration of arylboronic acid **1.49** and the corresponding trihydroxyborate **1.50** were found to be close to each other in organic solvents containing weak base and water, whereas a 25:1 mixture of THF and H_2O was found to be the optimal conditions favouring higher concentration of the palladium hydroxo species **1.47** compared to its halide counterpart **1.48**.

Thus, PdOH complex **1.47** was established to be both a kinetically and thermodynamically stable intermediate. Furthermore, the authors also established the same mode of reactivity with boronic esters, the second most common boron-containing species used in Suzuki-Miyaura cross coupling.

The oxidative addition is considered as the rate-limiting step of the cycle where the choice of the electrophile is important to the overall feasibility of the reaction. Since biaryl units are prevalent in many natural products, the Suzuki-Miyaura cross coupling reaction has been widely employed for synthesis of biaryl fragments from aryl coupling partners.[86] In terms of the effects of the electrophile on this step, aryl halides bearing electron-withdrawing substituents are more reactive than their electron-donating counterparts. The general order of reactivity for aryl halides is proposed to be as follows: I > Br > OTf > Cl.[87]

1.5.2 Coupling Partners

Aryl halides,[87] despite giving toxic credentials, are still widely used in C-C bond forming reactions such as in Suzuki-Miyaura cross couplings. They are commercially available with a wide variety of functional groups. Consequently, the emphasis of research is less on

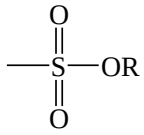
synthesis of the electrophilic coupling partner and more on finding straightforward and economical reaction conditions for their application.

Another important class of aromatic electrophile is based on phenols (Chart 1.4) with leaving groups such as triflates or mesylates on the oxygen. Herein, the inherently strong C-O bond is significantly weakened when a leaving group is bonded to the oxygen atom and, as such, the C-O bond is more easily cleaved via metal-catalysed reactions. The real attraction is the use of phenols as the feedstock, giving researchers access to a whole host of attractive functional groups and ring structures.[88] Substituted phenols are very useful as they are widely available and cost-effective with a wide range of functional groups.

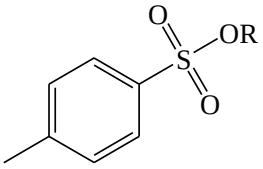
Triflate is a widely used leaving group in phenols and it has found numerous applications in a whole host of reactions but it has major limitations in that it is difficult to handle and has low stability.[87, 89, 90] Furthermore, at the time of its discovery, Suzuki and Miyaura found organic triflates very challenging to work with, especially the coupling of triflates to boronic acids in the presence of palladium-based catalysts, which often failed to work due to the decomposition of the catalysts by precipitation of palladium black at the early stages of the reaction. This is believed to occur due to the incompatibility of common ligands such as triphenylphosphine with triflates.[89]

Interestingly, phenols themselves have also been directly used in transition metal-catalysed reactions. For instance, in a recent study, Ackerman and colleagues used phenol as a pro-electrophile where the C-O bond was activated with a bulky ruthenium dichloride metal pre-catalyst at 120 °C and it was subsequently used in coupling reaction to form various biaryl complexes.[91] Unfortunately, such reactions continue to be challenging because of the inherent strength of the C-O bond.[92] Therefore, the emphasis continues to be on synthesising phenol-based electrophiles, a demand that is continually driving research towards finding alternatives to aryl halides and triflates with, preferably, better environmental credentials.

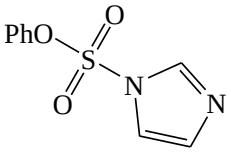
Imidazolylsulfonate is a relatively new class of leaving group and it has only very recently been used in palladium catalysed cross coupling reactions, as first reported by Albanese-Walker and colleagues[93] with a highly activated C-O bond.



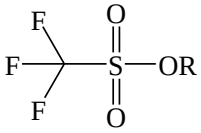
mesylate



tosylate



imidazolylsulfonate



triflate

Chart 1.4

1.5.3 Role of Water

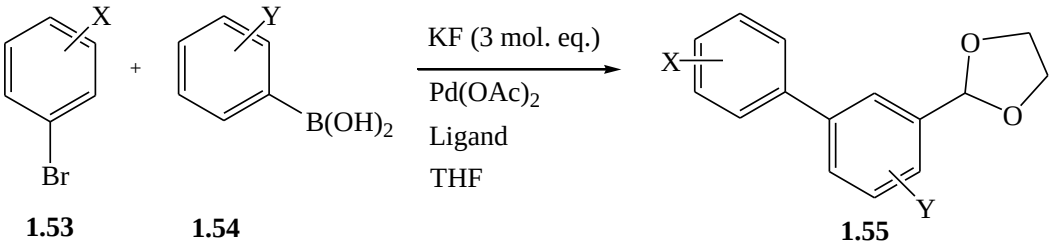
Hartwig and colleagues have recently reported important findings on the mechanistic aspects of Suzuki-Miyaura cross couplings in the presence of water. It now appears widely accepted that the addition of water is beneficial to the reaction. To this affect, Fu and colleagues reported important findings; evaluation of the reaction between 2-methyl-benzeneboronic acid and 1-bromo-3,5-methylbenzene in the presence of 0.5 mol% $Pd_2(dba)_3$ and 1.2 mol% $[HP(t\text{-}Bu)_3BF_4$[94] revealed that if the reaction is carried out with the arylboronic acid hydrate, as opposed to dry arylboronic acid, the yield increases from 14% to 96% at r/t. Subsequent studies have validated these findings and go further to show that the amount of water added is crucial to the final yield and the catalyst activation.[95] The addition of up to 4 equivalents of water to the dry reagents was shown to improve the yield of the final product but the addition of more water was detrimental and reduced the final yield.[94] In the same report, the so called 'wet' reaction conditions were applied to a host of other substrates including various alkyl- and arylboronic acids and substituted aryl bromides and the same trend was observed with higher yields obtained in the presence of 4 equivalents of water. Excess water is believed to cause catalyst deactivation[96] but the addition of the optimal quantity of water helps to greatly accelerate the generation of the required active species, namely boronates, which are involved in the reaction cycle[96] and help to increase the reaction rate.

1.5.4 Ligand Effects

Palladium-based catalysts are predominantly used in Suzuki-Miyaura cross coupling where the properties of the supporting ligand (i.e steric bulk and electronic properties) impart significant effect on the catalytic activity in both the oxidative addition and reductive elimination steps of the reaction cycle. Wolfe and colleagues reported the synthesis of biaryl diphosphines as supporting ligands, some of which were found to possess a fine balance between the steric and electronic properties which had the effect of accelerating the oxidative addition and also enhancing transmetalation and the reductive elimination step.[79] The electron-richness of the supporting ligands serves to enhance the rate of oxidative addition. It has been reported that highly electron-rich triarylphosphines often only enhance oxidative addition at the expense of decreasing the rate of reductive elimination.[97] The basic phosphine coordinates to the metal and promotes the oxidative addition, whereby there is a positive correlation between the electron-richness of the phosphine and the rate of oxidative addition. The metal-π interaction, which is consistent with what has been observed in other palladium complexes,[98, 99] adds further stability to the catalyst by the proposed stabilising interaction between the π system of the *ortho*-phenyl moiety and one of the metal d-orbitals. Furthermore, the steric bulk around the metal from the biaryl moiety of the ligand promotes reductive elimination. Interestingly, the steric bulk around the metal orientates the aryl groups of the reacting substrate to be perpendicular to the coordination plane of the catalyst,[79] a stereo-electronically favourable conformation for reductive elimination.

Although steric effects of the supporting ligand are important in influencing the efficacy of the catalyst,[100] the basicity of the phosphine is necessary to facilitate the oxidative addition,[101] especially for coupling involving relatively unreactive aryl chlorides. A case in point is a comparison of the catalytic activity of the bulky tris(2,4-di-*tert*-butylphenyl)phosphite ligand against less bulky but more electron-rich *o*-(di-*tert*-butylphosphino)biphenyl. The Suzuki-Miyaura coupling of 4-chlorotoluene to phenylboronic acid was catalysed by 1 mol% palladium acetate and 2 mol% tris(2,4-di-*tert*-butylphenyl)phosphite but no product was formed at room temperature; even at 100 °C, only 5% yield for the corresponding biaryl product was obtained. However, the same reaction with *o*-(di-*tert*-butylphosphino)biphenyl-based catalyst afforded the desired product in 95% yield after only 1 h at room temperature.[79]

Furthermore, the scope of the reaction was expanded to the Suzuki-Miyaura cross coupling between aryl bromides **1.53** and phenylboronic acids **1.54** catalysed by the Pd/*o*-(di-*tert*-butylphosphino)biphenyl combination which gave the corresponding biaryls **1.55** in high yields (of > 85%); those results were comparable to those obtained with the Pd/tris(2,4-di-*tert*-butylphenyl)phosphite[79] combination (Figure 1.15).



1.53 **1.54** **1.55**

yield 86% (X = 3-(1,3-dioxolane), Y = 2-OMe)
yield 90% (X = 4-CHO, Y = 4-OEt)

Ligand = *o*-(di-*tert*-butylphosphino)biphenyl

Equation 1.15

Early Suzuki-Miyaura cross couplings were beset with many challenges such as limited scope of substrates that could be used and the issue of minimising competitive β-hydride elimination when alky halides and alkyl boron substrates are used.[102] The development of effective palladium/ligand catalysts and use of electron-rich and sterically bulky ligands has addressed many of the early challenges and, in some cases, has even facilitated the cross coupling of more challenging substrates at room temperature with low catalyst loading.[103] On a general note, Hartwig has argued that the effect of the ligand bulk on the oxidative addition is by way of increasing the energy of the ground state of the respective catalyst which subsequently provides a smaller energy difference between the ground state and that of the reactive catalyst intermediate which better facilitates the oxidative addition step.[100]

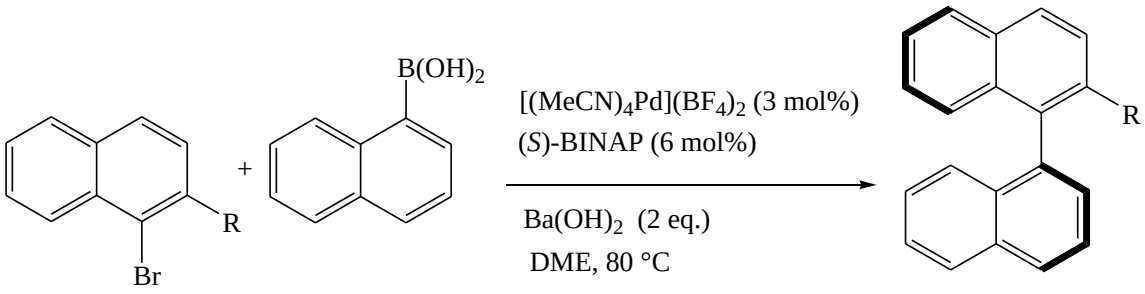
An early report by Fu and colleagues evaluated the coupling reaction between phenylboronic acids and aryl halides catalysed by Pd/P(*t*-Bu)$_3$. They made several important findings: the Pd/Ligand ratio is instrumental to the rate of product formation where a 1:1 ratio forms a very active catalyst giving a high rate of product formation whereas a 2:1 ratio leads to an extremely slow reaction.[87] However, the identity of the active catalyst was not established. Although phosphorus NMR analysis confirmed the presence of Pd(P(t-Bu)$_3$)$_2$ as the only phosphorus-containing constituent across a wide range of Pd:P(*t*-Bu)$_3$ ratios (also confirmed by Hartwig in a closely related study[104]), it

was argued that the presence of excess phosphorus-free $Pd_2(dba)_3$ (the source of palladium) leads to the formation of the active phosphine species. This assertion was confirmed when the reaction of 3-chloropyridine with *o*-tolylboronic acid in the presence of 3 mol% of Pd/P(*t*-Bu)$_3$ initially gave sluggish yields but on addition of free $Pd_2(dba)_3$, the rate of reaction and respective yields of products increased significantly.

Overall, for reactions with aryl halides, $Pd_2(dba)_3$ was the most active source of palladium with the $Pd_2(dba)_3$/P(*t*-Bu)$_3$ catalyst tolerating a wide range of functional groups; 2-bromotoluene was coupled successfully to electron-poor, neutral and electron-rich arylboronic acids to afford respective biaryl units in yields > 90% in vast majority of cases. However, $Pd_2(dba)_3$/P(*t*-Bu)$_3$ did not prove to be an efficient catalyst for coupling of aryl triflates to phenylboronic acid. Instead the $Pd(OAc)_2/PCy_3$ combination was found to be more active and it efficiently catalysed the coupling of a wide scope of aryl triflates to arylboronic acids, giving the corresponding biaryl in yields >90% in the majority of cases. Herein, the choice of the ligand was pivotal whereby the less bulky PCy_3 was found to be electron-rich enough to promote oxidative addition.[87]

1.5.4.1 Applications of Biaryl Diphosphines

Dicationic palladium complexes make for active and versatile catalysts for a variety of transformations.[105, 106] An important study by Mikami and colleagues[107] found that indeed the cationic complex $[(MeCN)_4Pd](BF_4)_2$ in the presence of BINAP and its derivatives was highly active for the synthesis of axially chiral biaryls (Eq. 1.16). For example, the coupling of various *ortho*-substituted arylbromides **1.56** to 1-naphthaleneboronic acid **1.57** catalysed by [(*S*)-BINAP]Pd^{2+} Lewis acids selectively gave the corresponding atropos binaphthyl fragment **1.58** in high yield. Furthermore, it was observed that the Suzuki-Miyaura cross coupling of arylbromide **1.56** (Eq. 1.16, R = OMe) to 1-naphthaleneboronic acid **1.57** catalysed by [(*S*)-Cy-BINAP]Pd^{2+} gave the corresponding product **1.58** in high enantioselectivity (70%), which was attributed to the sterically demanding nature of [(*S*)-Cy-BINAP]$PdCl_2$ which has not been previously seen with other Pd/BINAP catalyst combinations.[108] The ee was marginally increased to 84% when the same reaction was conducted at room temperature, though the yield was reduced to 17%. Similarly, the Pd/*tol*-BINAP combination was particularly active for the reaction involving OPr^i-substituted aryl bromide, affording the corresponding product in 86% yield.



R = OMe: yield (91%), ee (56%)

R = OPr^{i}: yield (99%), ee (50%)

R = OBn: yield (99%), ee (49%)

R = NMe_2: yield (61%), ee (58%)

Equation 1.16

Interestingly, Pd/BINAP was found to be highly effective for Suzuki-Miyaura cross coupling of challenging *ortho*-substituted aryl chloride **1.59** and aryl fluoride **1.62**; they were coupled to arylboronic acids **1.60** and **1.63**, respectively, to afford the corresponding biaryls **1.61** and **1.64** (Figure 1.10).[72] Even though the C-F bond is less reactive than the C-Cl bond, the corresponding product was afforded in 91% yield in only twice the time (4 h) it took to obtain the same yield with arylchlorides, as illustrated in Figure 1.10.

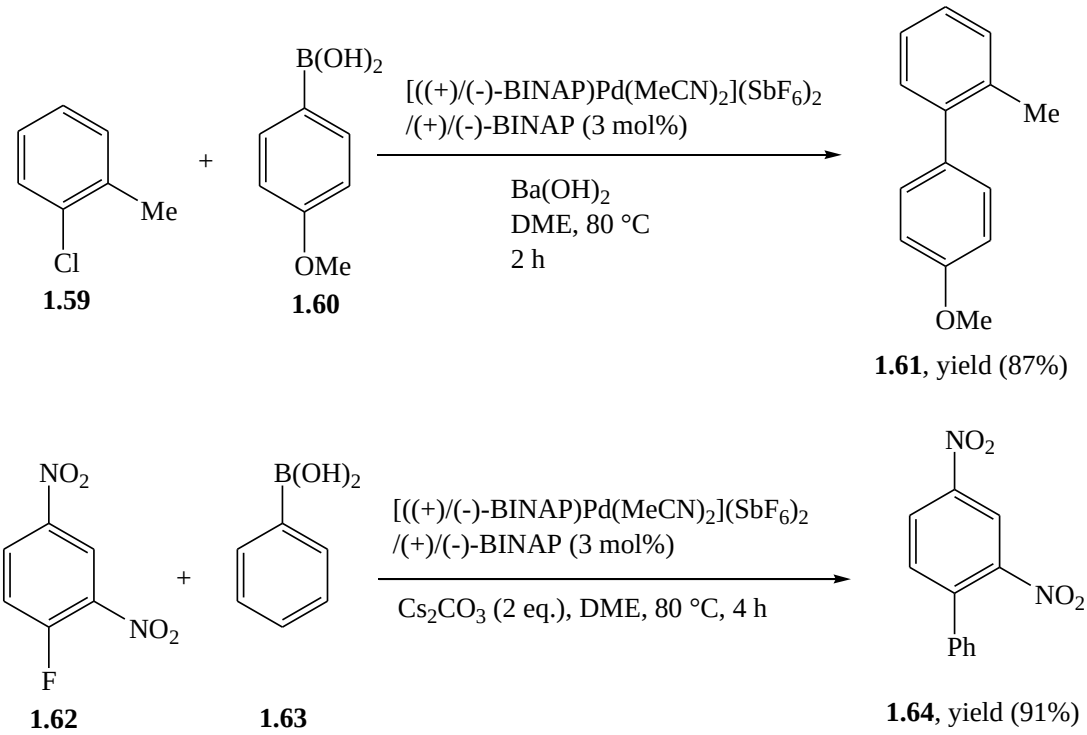
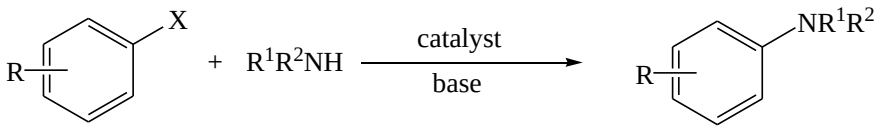


Figure 1.10

1.6 Buchwald-Hartwig Amination

Buchwald[109] and Hartwig[110] independently developed the palladium catalysed amination, a C-N bond forming reaction between an amine **1.66** and an aryl halide **1.65** (or triflate) carried out in the presence of a base and a catalyst (Eq. 1.17). This route presents a mild alternative to classical approaches to C-N bond formation, especially in the formation of arylamines which are inaccessible.[111]



1.65 **1.66** **1.67**

Equation 1.17

Palladium-based complexes of BINAP and other biaryl diphosphines, such as DPPF,[112] are widely used to catalyse aminations and have been subject to in-depth mechanistic studies. The Pd(0)/BINAP system is widely used in achiral aminations[113, 114] for a broad scope of substrates, such as anilines and alkylamines as nucleophilic coupling partners and arylhalides plus their triflate counterparts as electrophilic coupling partners, often at low catalyst loading.[114, 115] Interestingly, palladium-based Lewis acids of BINAP inhibit substrate racemisation in the arylation of α-chiral amines[116] and are potentially viable catalysts for chiral reactions as well.

1.6.1 Kinetic Studies

A recent report by Hartwig and colleagues evaluated the mechanism of the amination of aryl halides catalysed by Pd/BINAP (Figure 1.11).[117] Kinetic studies conducted for both isolated precatalysts and *in-situ* generated catalysts concluded that the rate of amination is independent of both the identity and the concentration of the amine. The major catalyst precursor was found to be [Pd(BINAP)$_2$]. The data suggests that the catalytic cycle is first order with respect to the bromoarene and inverse first order with respect to the ligand, which infers that the [Pd(BINAP)] complex **1.68**, generated from [Pd(BINAP)$_2$], binds to the bromoarene via the oxidative addition (step A) to form the [Pd(BINAP)(Ar)(Br)] complex **1.69** which subsequently reacts with the amine (step B) to afford the aryl-Pd(II)-amine intermediate **1.70** which subsequently reacts with base to form the aryl-palladium-amido complex **1.71** (step C). Finally reductive elimination (step D) regenerates the catalyst and liberates the arylamine as the product.

In the case of primary amines, the rate-limiting step is widely regarded to be the oxidative addition of the Pd(0) to the aryl halide (or triflate) but this is not always the case and is highly dependent on other factors such as the reaction conditions, the nature of the catalyst and the substrates. $Pd_2(dba)_3$ is the common source of palladium and the Pd(0)/BINAP catalytic cycle illustrated in Figure 1.11 closely resembles those of other cross coupling reactions.[117, 118]

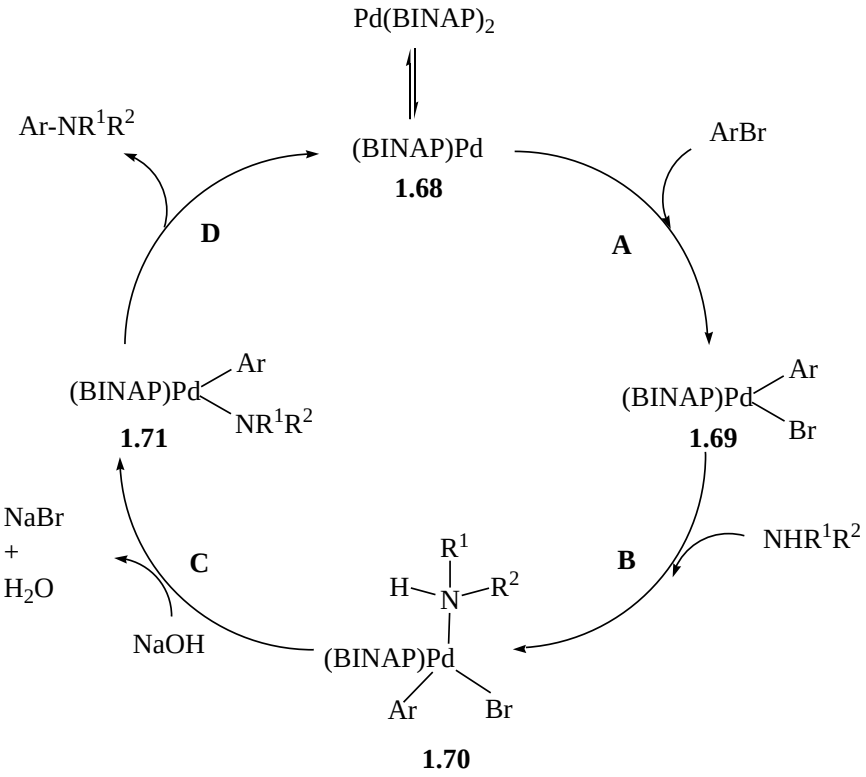


Figure 1.11

It is noteworthy that $Pd(OAc)_2$ is also used as a source of palladium where Pd(II) is initially reduced to Pd(0) *in-situ* with a mixture of base and amine. Herein, it is necessary to mix the $Pd(OAc)_2$ and the phosphine together prior to addition of the substrates in order to obtain high activity.

1.6.2 Applications of Diphosphines

It is worth mentioning that Pd(0) catalysts with other diphosphine ligands are not as efficient as Pd(0)/BINAP, the efficacy of which has been attributed to the specific structural features of BINAP. In other diphosphines, the dissociation of one arm of the respective chelating ligand from the metal is believed to facilitate β-hydride elimination. However, the rigid structure of BINAP, together with its relatively small bite angle,[108] creates a tight chelate and severely inhibits β-hydride elimination.[113] Pd(0)/BINAP catalyst is believed to inhibit formation of both catalytically inactive palladium bis-amine-

aryl halide complexes as well as bridging amido complexes, which do not readily undergo reductive elimination.[119, 120] The efficacy of Pd(0)/BINAP catalyst in amination was further evaluated by Buchwald and colleagues[113] where it was found that the catalyst performs particularly well in the presence of Cs_2CO_3 which, as a weak base, serves to broaden the scope of functional groups that can be used in the reaction. However this was not found to be the case with other weak bases. The favourable ionic character and better solubility of Cs_2CO_3 relative to other alkali metal carbonates are considered to be major factors for its superior performance.[121] NMR studies demonstrated that $Pd(OAc)_2$ is a better pre-catalyst than $Pd_2(dba)_3$, given that the rate of reaction decreases on addition of free dba to the reaction mixture. The rate of the reaction is also dependent on other reaction conditions such as the deprotonation step of the reaction. Moreover, the slower reaction rate obtained with bulky primary amines or secondary amines shows that the reaction is also substrate dependent.

1.6.3 Coupling Partners

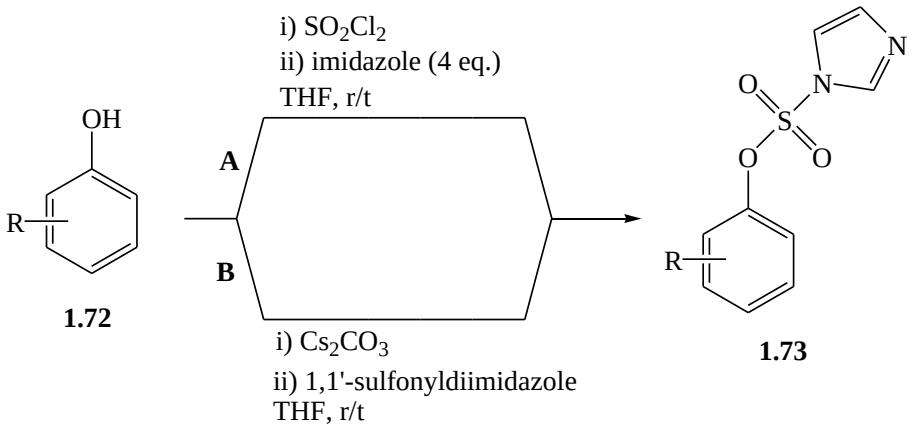
Aryl triflates[122] have often been used in aminations and provide an alternative to aryl halides. Given the problems associated with triflates, in terms of stability and expense of synthesis (trifluoromethanesulfonic anhydride and triflimide reagents), there is always great interest in using alternative leaving groups. Aryl tosylates and mesylates are alternatives to triflates for cross coupling reactions[123, 124] with better handling and stability properties but their reactivity is significantly diminished in the presence of palladium and the reactions exhibit marked dependence on solvent and substrate and the catalysts often only function in the presence of bulky electron-rich phosphines.[125]

The imidazolylsulfonate[93, 126, 127] moiety was first introduced by the Hanessian group[128, 129] as an excellent leaving group in sugar compounds.[129] The imidazolylsulfonate moiety has been used in the synthesis of a number of carbohydrate-containing natural products,[130, 131] cyclodextrin and substituted estradiol compounds.[132] The versatility of the imidazolylsulfonate prompted its application in cross coupling chemistry as well.[89] Aryl imidazolylsulfonates exhibit reactivity similar to their triflate counterpart but are much more stable, easier to handle and cheaper to prepare, especially on large scale.

1.6.4 Synthesis of Aryl Imidazolylsulfonates

There are two prevailing methods for synthesis of aryl imidazolylsulfonates, as shown in Scheme 1.4. A recent report by Albanese-Walker and colleagues evaluated the efficacy of these methods. [93] Method A involves the reaction of a substituted phenol **1.65** with

sulfuryl chloride followed by addition of large excess of imidazole to afford the corresponding aryl imidazolylsulfonate **1.66**. The yields of final product ranged from fair to moderate with this method over a narrow range of substituted phenols and one major drawback is the competitive chlorination, a side reaction which serves to reduce the yield of the final product. Method B requires addition of Cs_2CO_3 to substituted phenol **1.72** followed by addition of commercially available 1,1-sulfonyldiimidazole to form the corresponding aryl imidazolylsulfonate **1.73**. A wide range of substrates were used in this method, forming a host of aryl imidazolylsulfonates with electron-withdrawing and electron-donating groups and most of the reactions were completed within 16 h to afford the desired imidazolylsulfonate **1.73** in > 85% yield in all cases.[93]



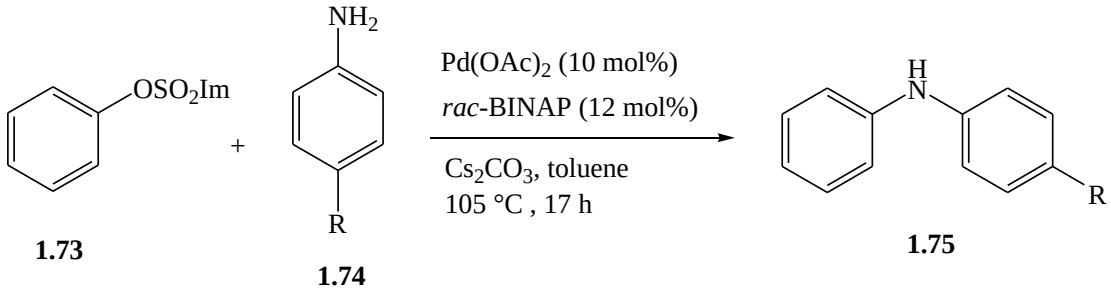
Scheme 1.4

1.6.4.1 Catalysis

In the last few years, aryl imidazolylsulfonates have been used as alternative electrophiles for C-C and C-N bond forming reactions. Early applications of aryl imidazolylsulfonates were in palladium-catalysed formation of aryl phosphonates[133] and the arylation of oxazoles.[134] Ackerman and colleagues were first to apply this class of electrophile in aminations where phenyl imidazolylsulfonate **1.73** was successfully coupled to a range of substituted anilines **1.74** catalysed by $Pd(OAc)_2$ (10 mol%), *rac*-BINAP (12 mol%) in toluene at 105 °C in the presence of Cs_2CO_3, giving the corresponding products **1.75** in yields > 80%, as illustrated in Equation 1.18.

The scope of the evaluation was further expanded by reaction of 4-methoxybenzene imidazolylsulfonate with 4-methylaniline to afford the desired diaryl amine in 92% yield. The palladium-catalysed reaction protocol tolerated various functional groups such as fluoro-, nitro-, cyano-substituents, as well as ester and ketone functionalities and the alkyl-substituted anilines were also successfully used as nucleophilic coupling partners.

Furthermore, the catalytic system exhibited good chemoselectivity with successful reaction of chloro-substituted aryl imidazolylsulfonate, results of which were complementary to those obtained with aryl tosylates[124] or mesylates.[135]



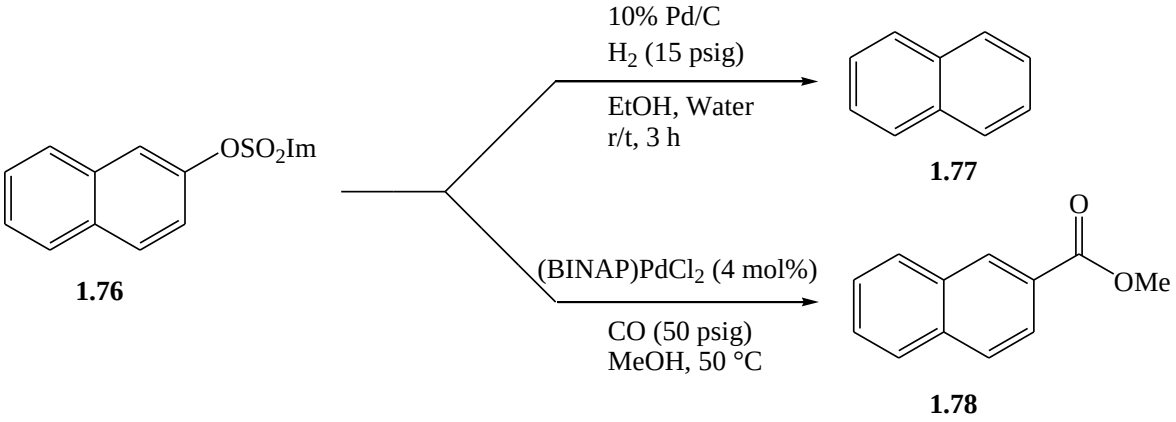
1.73 **1.74** **1.75**

R = OMe (87%)
R = Cl (70%)
R = CO_2Et (87%)
R = CF_3 (85%)

Equation 1.18

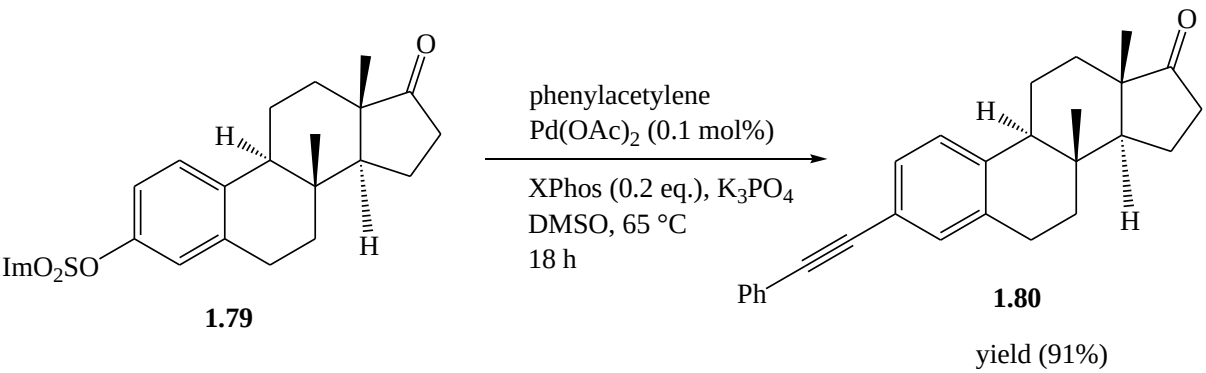
Albaneze-Walker and colleagues have also employed aryl imidazolylsulfonates in Suzuki-Miyaura and Negishi cross couplings. The reactions were carried out in different solvents and, in the case of Suzuki-Miyaura cross couplings, the presence of water was not detrimental to the reactivity of aryl imidazolylsulfonates. Moreover, these electrophiles exhibited a remarkably long shelf-life as the yields were not reduced by using aryl imidazolylsulfonates that had been stored at room temperature for 7 months.[93] Kinetic studies were conducted for the Suzuki-Miyaura cross coupling of 2-naphthyl triflate with 4-methylbenzeneboronic acid and the results were compared against its imidazolylsulfonate and tosylate counterparts: 2-naphthyl imidazolylsulfonate gave 98% conversion after 2.5 h compared to the same conversion in 30 mins with 2-naphthyl triflate. On the contrary, 2-naphthyl tosylate remained inert and did not react.

Interestingly, 2-naphthol imidazolylsulfonate **1.76** was also reduced under very mild conditions catalysed by Pd/C in ether to afford naphthalene **1.77**; **1.76** also underwent palladium-catalysed carbonylation to generate the corresponding ester **1.78** in excellent yield under exceedingly mild conditions,[93, 136] thus further underlying its versatility in different reactions (Scheme 1.5)



Scheme 1.5

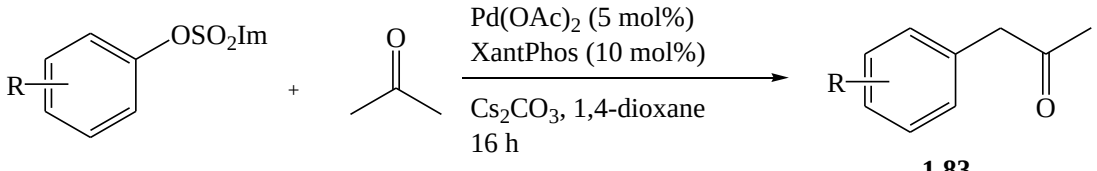
The versatility of aryl imidazolylsulfonates has also seen their successful application in Sonogashira cross coupling; 4-nitrobenzene imidazolylsulfonate was coupled with phenylacetylene catalysed by a mixture of $Pd(OAc)_2$ and PPh_3 in the presence of triethylamine to afford the corresponding diarylacetylene in 93% yield after 18 h at 65 °C. The scope of the reaction was expanded to include electron-rich, electron-poor, *ortho*-substituted and bicyclic imidazolylsulfonates, all of which reacted accordingly to afford the corresponding diarylacetylenes in good yields.[127] Shirban and colleagues carried out a test reaction with complex phenols, for which the corresponding halides are not available. The corresponding imidazolylsulfonate **1.79** was synthesised and successfully coupled to phenyl acetylene under the same optimised reaction conditions to afford the product **1.80** in excellent 91% yield (Eq. 1.19).



Equation 1.19

The Ackerman group has recently successfully employed aryl imidazolylsulfonate **1.81** as electrophiles in the palladium-catalysed mono-α-arylation of acetone **1.82**.[137] Mono-α-arylation of ketones has thus far remained elusive,[138, 139] in part due to the fact that the resulting mono-arylated acetone **1.83** is often more reactive than acetone **1.82** itself which leads to formation of unwanted polyarylated products. Herein, aryl imidazolylsulfonates

were employed as they are readily accessible and moreover, other fluorine-free phenol-derived electrophiles have been successfully utilised as directing groups in complex aromatic coupling strategies.[140, 141] Consequently, a whole range of aryl imidazolylsulfonates were successfully coupled with acetone to form the corresponding arylated acetones, some of which are shown in Equation 1.20. Palladium-based Lewis acid complexes of bis-phosphines such as XantPhos, DPPF and *rac*-BINAP efficiently catalysed mono-α-arylation of acetone with high chemoselectivity. It is noteworthy that the scope of the reaction was expanded to include a range of alkyl methyl ketones, all of which successfully reacted with aryl imidazolylsulfonates.

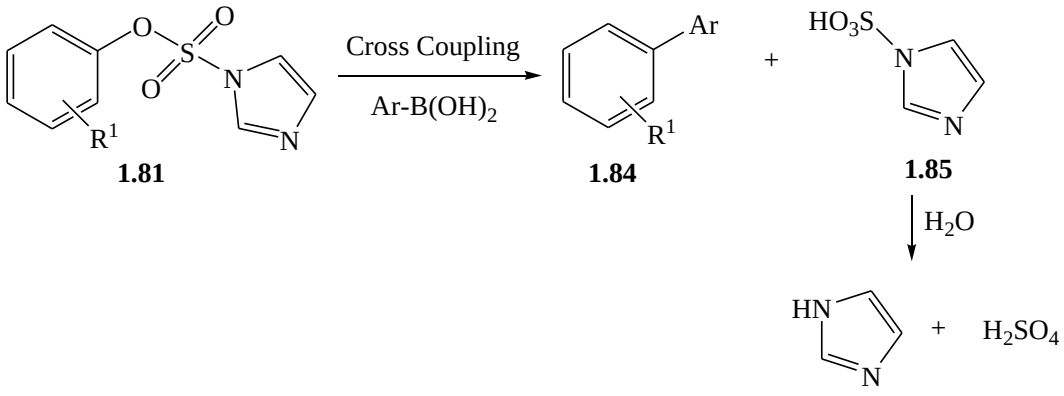


1.81 **1.82** **1.83**

R = 4-Me (82%)
R = 4-Et (73%)
R = 4-Cl (79%)
R = CF_3 (69%)
R = MeO (86%)

Equation 1.20

An important advantage of imidazolylsulfonates is their inherent ability to self-destruct into benign constituents. Safety considerations continue to assume greater importance, in part due to recently introduced regulations which focus on alkyl and aryl sulfonates as potential genotoxic impurities (PGIs). The by-product of aryl imidazolylsulfonates **1.81** coupling to phenylboronic acid is imidazolesulfonic acid **1.85** which, in the presence of water and a weak acid, hydrolyses to produce imidazole and sulfuric acidv (Scheme 1.6)/



1.81 **1.84** **1.85**

Scheme 1.6

1.7 Heck Reaction

The arylation and alkenylation of alkenes by palladium-based catalysts is a C-C bond forming reaction referred to as the Heck reaction and it has been widely exploited over the last few decades since its discovery in the 1960's.[142] Overall it is a substitution reaction, commonly involving reaction of an aryl/alkyl bromide with a terminal alkene. Different forms of the Heck reaction have been used for the synthesis of complex natural products such as the intramolecular Heck reaction which is used for the construction of quaternary centres[143] In a traditional Heck cycle (Figure 1.12), active Pd(0) catalyst **1.86** undergoes oxidative addition to the aryl halide (step A) to form organopalladium **1.87** which subsequently coordinates to the alkene substrate (step B) to form adduct **1.88**. Subsequently, the alkene substrate inserts itself into the palladium-carbon bond in a *syn*-addition step (step C) to form intermediate **1.89**, which is followed by β-hydride elimination (step D) to afford adduct **1.90**. The product is released (step E) to form **1.91** which undergoes reductive elimination (step F) to regenerate the active catalyst.

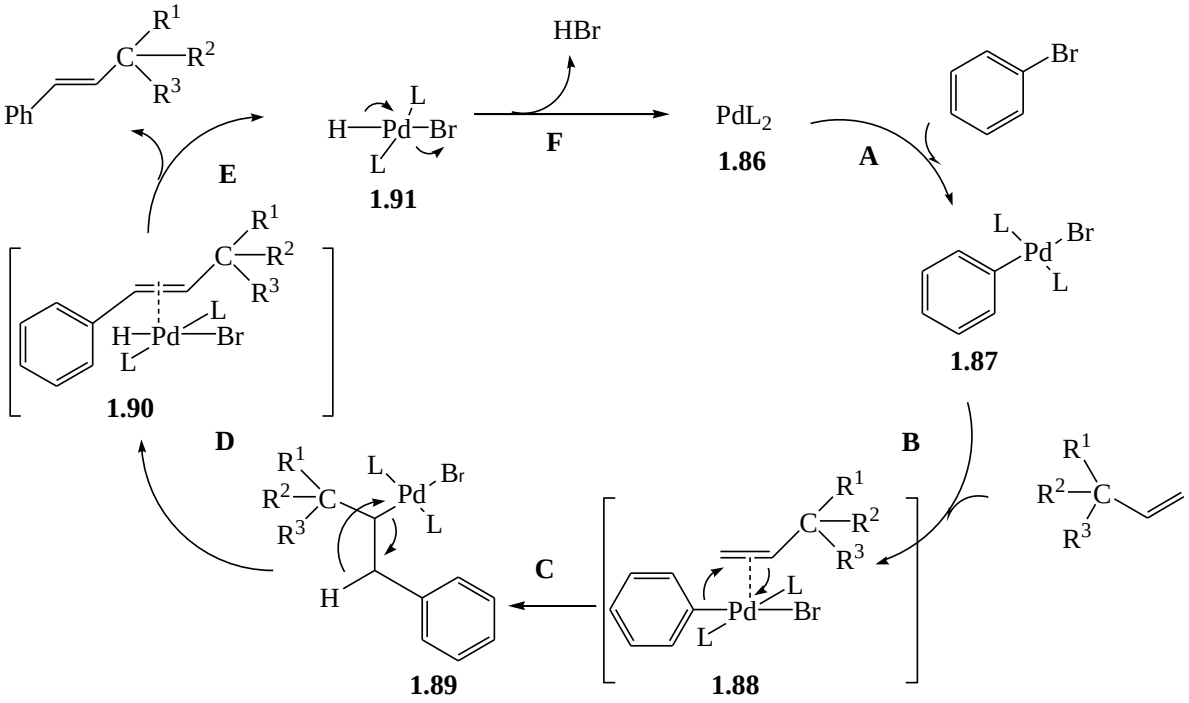


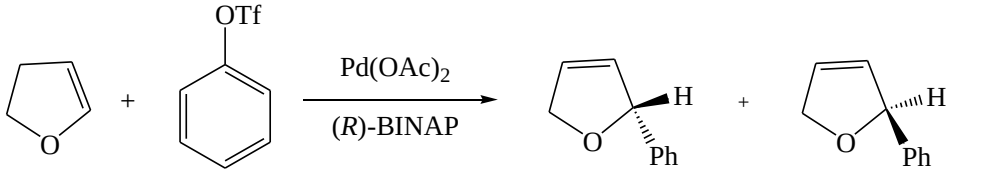
Figure 1.12

The oxidative addition step is widely regarded as the rate-determining step and as such, early evaluation of the Heck reaction focused on the nature of the active catalyst where it was proposed that the active species is the coordinately unsaturated 14 electron PdL_2, which is electron rich with a vacant site, and undergoes oxidative addition to the aryl halide to form the organopalladium intermediate. Less attention was paid to other reaction

parameters such as the nature of the supporting ligand, the electrophile, stoichiometric considerations and the reaction temperature. Since then, more detailed studies have been reported on the Heck catalytic cycle, where in a recent study[144] it was reported that a common catalytic combination of $Pd(OAc)_2$ and PPh_3 in polar solvents leads to the formation of the active $[Pd(PPh_3)_2(OAc)]^-$ which is coordinately unsaturated and nucleophilic, two important characteristics required for a rapid oxidative addition step. Furthermore, contrary to the general practice of adding excess ligand to assist with stabilisation of the Pd(0), it was found that addition of more than 3 equivalents of PPh_3 slows the rate of oxidative addition quite considerably.

Aryl iodides are highly reactive under relatively mild conditions but their bromide and even less reactive chloride counterparts often only react at elevated temperatures > 80 °C which, it was reported, can be at the expense of reducing the longevity of the catalyst.[144] A Further complication associated with high temperature is product contamination when PPh_3 is used with less reactive electrophiles[145] The use of bulkier P(*o*-tolyl)$_3$ with $Pd(OAc)_2$ addressed some of these challenges where, for instance, addition of a slight excess of P(*o*-tolyl)$_3$ resulted in the formation of a dimeric palladacycle which is thermally stable and shows no signs of decomposition even at temperatures of up to 250 °C.

Chelating phosphines, such as BINAP, are considered ideal in the Heck reaction of electron-rich alkenes with aryl or vinyl triflates[146] where the cationic Pd(II) intermediate binds strongly to an electron-rich alkene. The ability of chelating ligands, such as BINAP, to maintain the bidentate coordination of the Pd(0)-aryl intermediate **1.87** (Figure 1.12) is proposed to be essential in the successful reaction of electron-rich alkenes to give the final product in high regioselectivity and enantioselectivity; as illustrated in Equation 1.21;[144] enantioselective coupling of 2,3-dihydrofuran **1.92** to aryl triflate **1.93** affords the (*R*)-enantiomer of **1.94** as the major product. It is noteworthy that the choice of base used with the Pd/BINAP catalyst combination is also important because it facilitates the dissociation of the product from the Pd(II)-H species (Figure 1.12, step E); if this step is not sufficiently fast, it could lead to migration of the double bond in the final product.[146]



1.92 **1.93** (*R*)-**1.94** (major) (*S*)-**1.95** (minor)

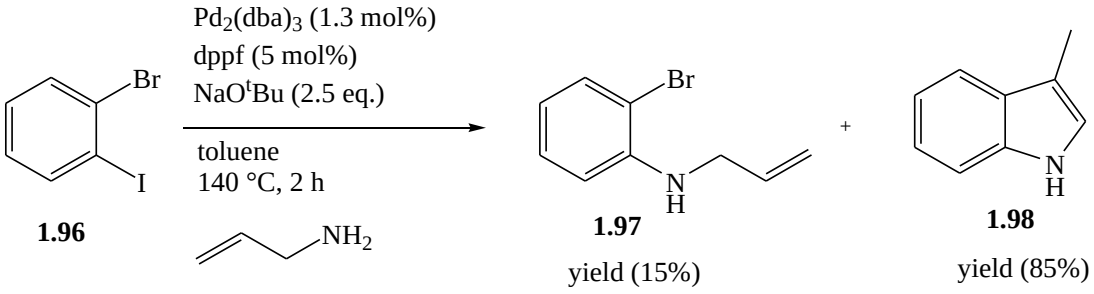
Equation 1.21

1.7.1 Domino Aryl Amination-Heck Cyclisation

Jørgensen and colleagues have recently reported the formation of substituted indoles bearing carbon substituents on the 3-position[147] via a domino aryl amination-Heck cyclisation sequence with aryl halides. Previously, there had only been a handful of reports employing aryl halides to this end. In 1980, Odle and colleagues[148] were first to report the Heck cyclisation of 2-halo-*N*-allylanilines using a palladium-based catalyst to form 3-methylindole. In 2002, Caddick and colleagues built on this and further exploited the intramolecular Heck cyclisation of 2-halo-*N*-allylanilines with palladium/imidazolium salt protocols at 140 °C to form corresponding substituted indoles.[149]

Such polycyclic units are of vital importance as they have biological applications in central nervous system drugs such as antipsychotics.[147] The domino sequence employed by Jørgensen and colleagues consisted of two distinct steps: intermolecular aryl amination and Heck cyclisation, a combination that has been previously reported Edmondson et al[150] and by Kondo and colleagues[151] in other transformations. It is noteworthy that aryl amination has already been used in indole chemistry, most famously in Fischer Indole synthesis to close the heterocyclic ring.[152] It was first reported by Kondratenko et al[153] and since has been developed by Hartwig, Buchwald and colleagues.[110]

The reaction evaluated by Jørgensen and colleagues involved amination of 1-bromo-2-iodobenzene **1.96** with allylamine followed by *in-situ* Heck cyclisation to form 3-methylindole **1.98** as the major product (85%) and *N*-allyl-2-bromoaniline **1.97** as minor product (15%) (Eq. 1.22). The reaction was evaluated with a whole host of catalyst combinations: Pd/BINAP and its XantPhos counterpart gave 3-methylindole **1.98** as the major product whereas Pd/XPhos and Pd/N-heterocyclic carbene combinations lead to a mixture of products, and PPh_3 and P(*o*-tolyl)$_3$ supporting ligands affording bromobenzene as the major product. The best yields for the desired product 3-methylindole **1.98** were obtained with Pd/DPPF and other palladium/phosphines combinations (i.e DavePhos and DpePhos). These disparate results clearly underline the importance of ligand on the outcome of the reaction. It is noteworthy this reaction was also successfully carried out on 10g scale to afford 3-methylindole **1.98** in 76% yield.



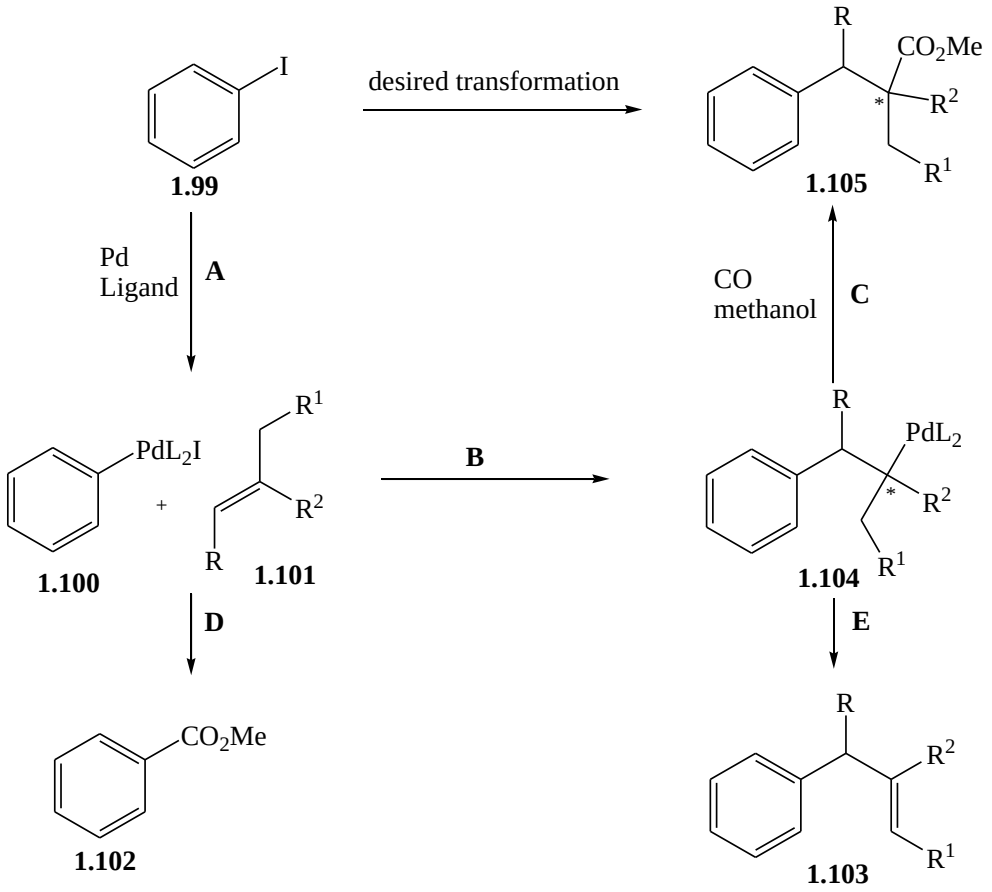
1.96 **1.97** yield (15%) **1.98** yield (85%)

Equation 1.22

The scope of the reaction was expanded to include both electron-withdrawing and electron-donating 1,2-dihalide substrates. The 3-methylindole was also further functionalised at the nitrogen by addition of aryl bromide or aryl halide to the reaction mixture after completion of the first two domino steps to afford the corresponding *N*-substituted 3-methylindoles. Surprisingly this straightforward and effective route for formation of 3-methylindole has not been further exploited given the important biological application of 3-methylindole, as aforementioned.

1.7.2 Domino Carbopalladation-Carbonylation

The continuous development of the Heck reaction has led to the synthesis of complex and congested architectures, of which asymmetric variants are available as well.[154] A recent expansion of the Heck method has led to 'tandem Heck reaction', where via molecular queuing a second reaction is introduced subsequent to carbopalladation and prior to β-hydride elimination. In a recent publication by Seashore-Ludlow and colleagues, complex natural architectures with vicinal stereocenters consisting of two carbon-carbon bonds were constructed in a concise and rapid fashion[155] via domino carbopalladation-carbonylation. As illustrated in Scheme 1.7, Pd(0) undergoes oxidative addition to the aryl iodide **1.99** (step A) to afford the corresponding organopalladium intermediate **1.100**. Depending on the rate of cyclisation, the organopalladium intermediate reacts with **1.101** (step B) to afford a palladium-alkyl intermediate **1.104** that is subsequently trapped by CO and nucleophilic abstraction by methanol (step C) then forms the desired ester **1.105**. Herein, reaction optimisation shows that the combination of DPPF and high CO pressure afford the highest yields for the desired product **1.105** and minimise the decomposition of the organopalladium intermediates **1.100** and **1.104** into undesired products **1.102** and **1.103**, respectively, via steps D and E.

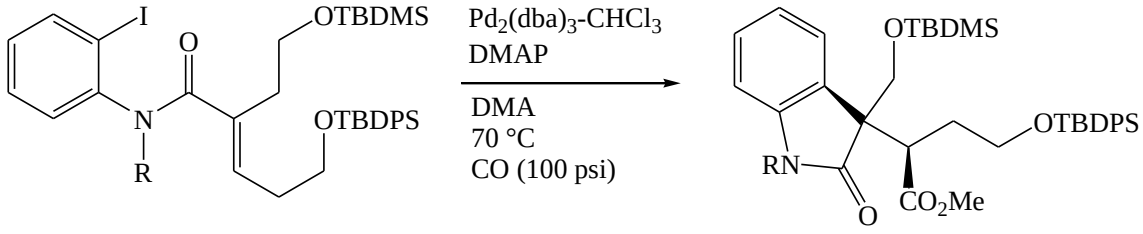


Scheme 1.7

The β-hydride elimination (Step E) is often minimised via use of substrates that are specifically designed not to undergo this step thus rendering them favourable for the CO insertion-nucleophilic attack sequence (step C). However, such an approach severely hinders the scope and applicability of this sequence (Scheme 1.7). It was recently demonstrated[155] that increasing CO pressure favours carbonylation (step C) over unwanted β-hydride elimination (step E); for instance at atmospheric CO pressure no desired product **1.103** was formed but by increasing CO pressure to 100 psi, the yield of the desired product **1.103** increased to 39%. This is an indication that reaction parameters can be manipulated to afford the desired product without the need to use specifically-designed starting materials.

The scope of the reaction was further expanded to include more complex amide starting materials. Herein, it was found that the performance of the reaction is also highly dependent on the *N*-protecting groups. As shown in the cyclisation of aryl iodide complex **1.106** which forms the corresponding complex **1.107** (Eq. 1.23), no product is formed where there is no protecting group on the nitrogen (R = H). However the yield of desired product **1.107** increases to 50% with methyl protecting groups and increases further to 69%

with *p*-CF_3-$C_6H_4CH_2$. Notably the same yield of 69% was obtained for **1.107** with *p*-MeO-$C_6H_4CH_2$ showing that the higher yields are as a result of purely steric effects and are not influenced by electronic properties of the protecting groups.



1.106 **1.107**

R = H, yield (0%)

R = Me, yield (50%)

R = *p*-CF_3-$C_6H_4CH_2$, yield (69%)

R = *p*-MeO-$C_6H_4CH_2$, yield (69%)

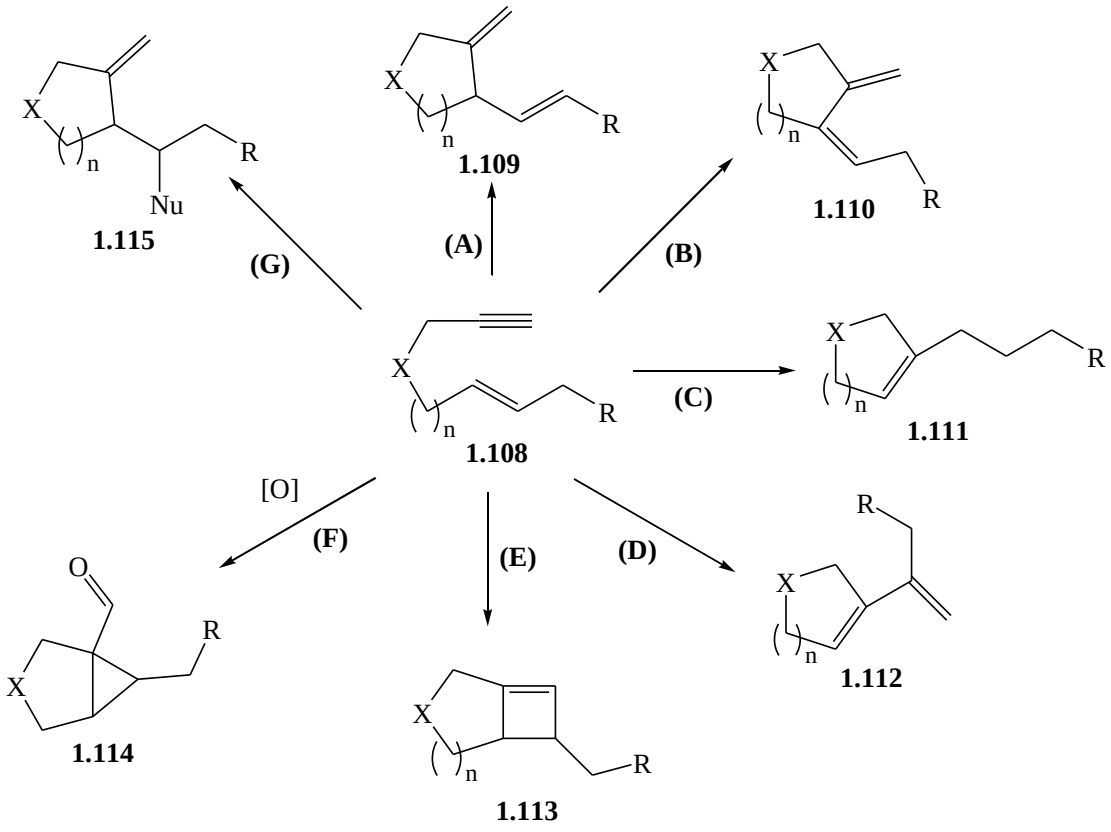
Equation 1.23

1.8 Cycloisomerisation with Substituted 1,*n*-Enynes

Transition metal catalysed cycloisomerisation is an atom efficient and versatile reaction that is often used in the synthesis of biologically important hetero- and carbocyclic compounds. The optimal catalysts often give the desired chemo- and regioselective products in high yields. This thesis will be concerned with cycloisomerisation of propargyl amides and 1,6-enyne substrates with both chiral and achiral gold-based catalyst, given their novelty, selectivity and efficacy in cyclisation reactions under relatively mild reaction conditions compared to other transition metal counterparts.[156, 157] Also importantly, it has been established that the efficacy of gold-based catalysts significantly influenced by the steric and electronic properties of the supporting ligand[158] and, as such, our evaluation will use the novel biaryl-like diphosphines R_2-CATPHOS (R = H, Me, OMe) as the supporting ligands of gold-based catalysts.

Following initial discovery of palladium-catalysed Alder-ene reaction by Trost and colleagues,[159] a whole host of palladium-based catalysts and enyne substrates have been employed in a wide array of cycloisomerisations.[160] Different products are formed via different reactions that are significantly dependent on the metal centre of the catalyst and the type of enyne and its respective substitution pattern. The electronic/steric properties of the supporting ligands are considered to have more effect on the efficacy of the catalyst as opposed to its selectivity.

Some prominent reactions of enynes **1.108** have been illustrated in Scheme 1.8. Path A shows the Alder-ene reaction which forms 1,4-diene **1.109** whilst pathway B forms the 1,3-diene cyclic **1.110**. Pathways C and D both follow skeletal rearrangements, affording **1.111** and **1.112**, respectively. Path E outlines formation of fused bicyclic structures **1.113** while path F shows oxidative cycloisomerisation in the presence of an oxidising reagent to form a cyclopropyl aldehyde **1.114**. In path G, initial cycloisomerisation is followed by a nucleophilic attack to form the corresponding products **1.115**. Some of the reactions, such as A and G, accommodate asymmetric catalysis and give products with a stereocenter. Many other transition metal-based catalysts have also been used in cycloisomerisation reactions where ruthenium, rhodium, iridium, and nickel catalysts have exhibited interesting activities and, by and large, have shown complementary selectivity to their palladium-based catalysts.



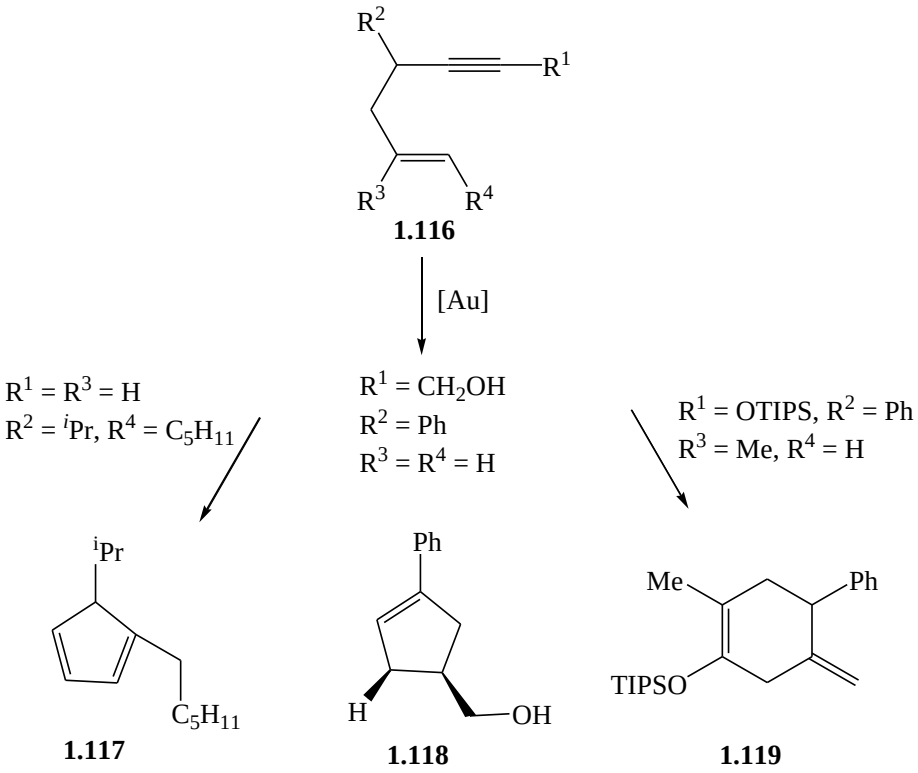
Scheme 1.8

Gold has only recently emerged as a useful metal in cycloisomerisations as it was previously considered inert and inactive towards catalysis. The early success in gold catalysis has spurred expansion of research on the synthesis of effective gold catalysts[161, 162] via novel methodologies.[163] Gold-catalysed enyne rearrangement is a significant area of research and it is being used as part of a wide program of research directed towards the discovery of novel and original reactions[164, 165] with pioneering work carried out by the

groups of Bond, Haruta, Hutchings, Ito and Hayashi.[166, 167] The relatively better selectivity of gold-based catalysts for cycloisomerisation of some enynes and the associated milder reaction conditions[168] are two of the real attractions for their rapid development in this area.

The reactivity of 1,5-enynes[160] is highly substrate-dependant and even the use of gold-based catalysts does not significantly affect their selectivity in most of the cases. For instance, Figure 1.13 shows cycloisomerisation of various 1,5-enyne substrates **1.116** catalysed by gold catalysts which afford different cyclic products (**1.117**, **1.118** and **1.119**) depending on the nature of the substituents and the substitution pattern.

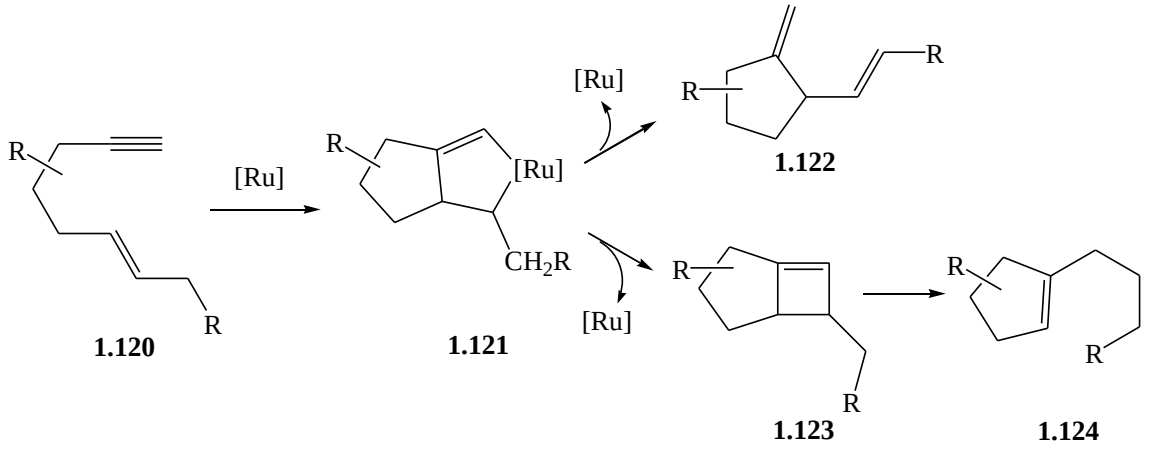
Figure 1.13. Au-catalysed Cycloisomerisation of 1,5-Enynes.



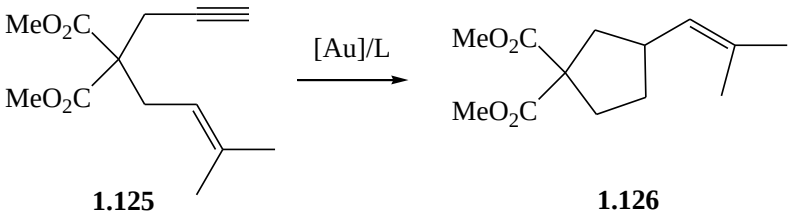
1.8.1 Cyclisation of 1,6-Enynes

Much better selectivity is obtained for cycloisomerisation of 1,6-enynes with gold-based catalysts compared to other transition-metal based systems. For instance, cycloisomerisation of 1,6-enyne **1.120** with ruthenium-based catalysts affords two different products (**1.122** and **1.124**) via two different reaction paths, as shown in Figure 1.14.

Figure 1.14. Key Intermediaries in Ruthenium-Catalysed Cycloisomerisation of 1,6-Enynes



However, cycloisomerisation of 1,6-enyne **1.125**[160] with gold-based catalysts exclusively affords **1.126** which was isolated with high yield in all cases (Figure 1.15). It was found that replacement of PPh_3 with bulkier and more electron rich phosphanes (Figure 1.15) leads to an increase in the activity of the respective gold catalysts.



Ligands:

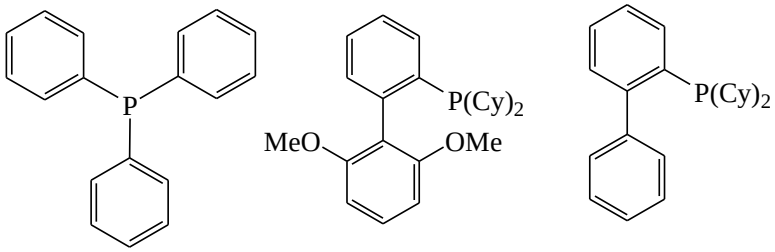
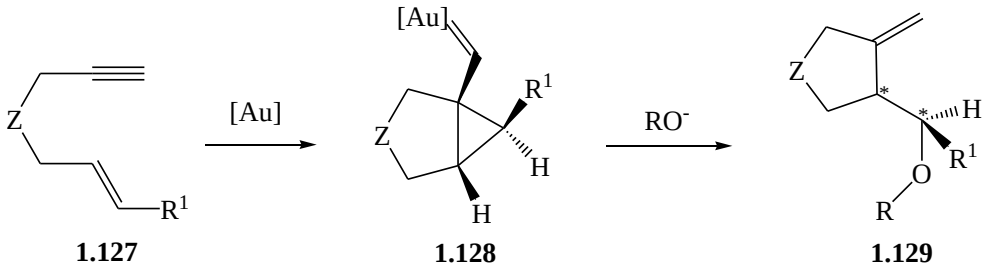


Figure 1.15

One common feature associated with the reactivity of 1,6-enynes catalysed by electrophilic transition-metal based catalysts is the formation cyclopropylcarbene intermediate **1.128** (Scheme 1.9) which can be trapped by either another alkene or by a sulfoxide. This intermediate reacts differently in the presence of nitrogen, oxygen or carbon nucleophiles. In particular, it has been established that the addition of an oxygen nucleophile in the presence of a gold-based catalyst proceeds with high efficiency and selectivity (Scheme 1.9). One main advantage of this reaction is the access to a wide variety of oxygen nucleophiles such as alcohols or ethers which can be used under extremely mild reaction

conditions to afford chiral final products and which can be catalysed by either gold(I)[168, 169] or gold(III) systems.[170, 171] In particular, Echavarren and colleagues found that the addition of a catalytic amount of methanolic trifluoroacetic acid (TFA) to [Au(PPh_3)Me] generates the very active [Au(PPh_3)(MeOH)]$^+$ [168, 172] and only 0.1 mol% of this is required to catalyse methoxycyclisation of 1,6-enyne **1.127** to give the corresponding chiral product **1.129** in excess of >75% yield at room temperature (Scheme 1.9).[169]



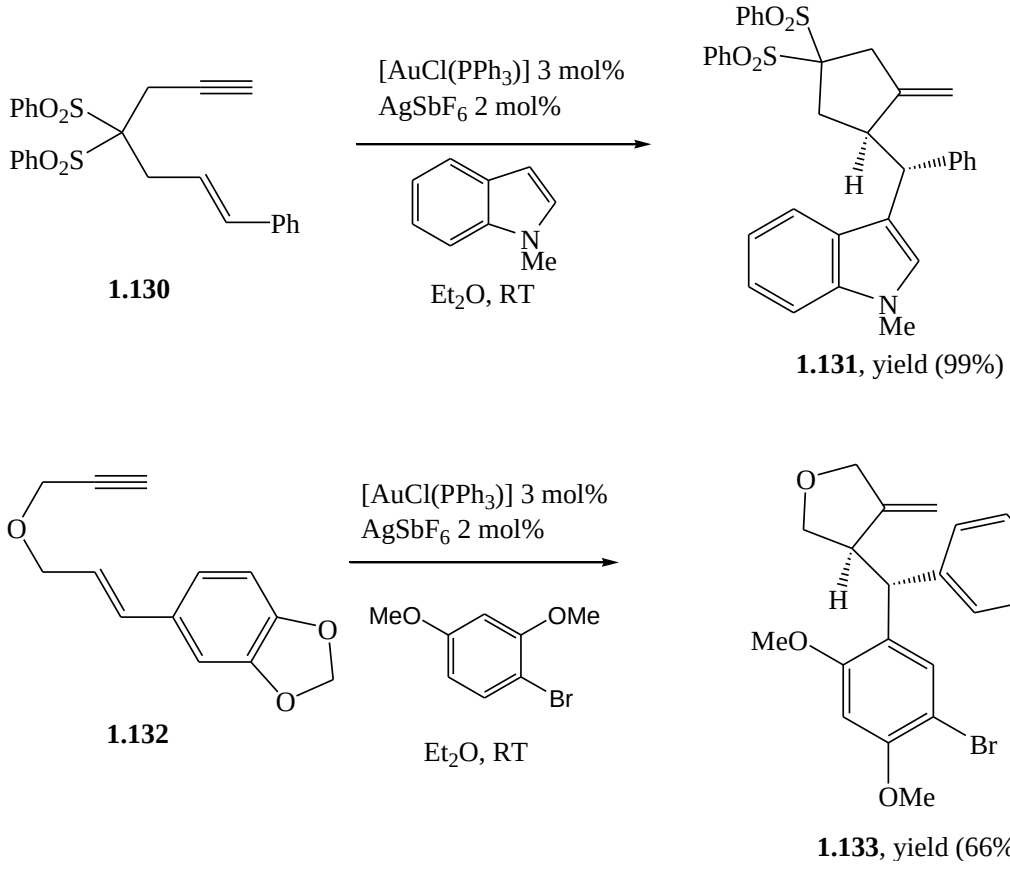
1.127 **1.128** **1.129**

Z = $C(CO_2Me)_2$, $C(SO_2Me)_2$

Scheme 1.9

As aforementioned, different nucleophiles can be used in this reaction and the respective research groups of Michelet and Génet evaluated the scope of the tandem Friedel-Crafts-type alkylation/cyclisation of 1,6-enyne reaction (catalysed by [(PPh_3)AuCl]/$AgSbF_6$ in diethyl ether at room temperature) with carbon nucleophiles as well (Figure 1.16).[173] Their evaluation covered a broad range of 1,6-enynes, bearing carbon, nitrogen or oxygen bridged tethers and their reactivity was measured in the presence of a range of electron-rich aromatic carbon-based nucleophiles such as indoles and pyrroles, and it was found that the vast majority of the reactions exclusively afford the desired product in good to excellent yield.[173] As illustrated in Figure 1.16, 1,6-enynes **1.130** and **1.132** were cyclised in the presence of *N*-methylindole and 2,4-dimethoxy-bromobenzene as nucleophiles to afford **1.131** and **1.133**, respectively. The research group of Echavarren also independently observed a similar reactivity pattern with various 1,6-enynes.[174]

Figure 1.16. Tandem Friedel-Craft-Type Alkylation/Cyclisation of Functionalised 1,6-Enynes.



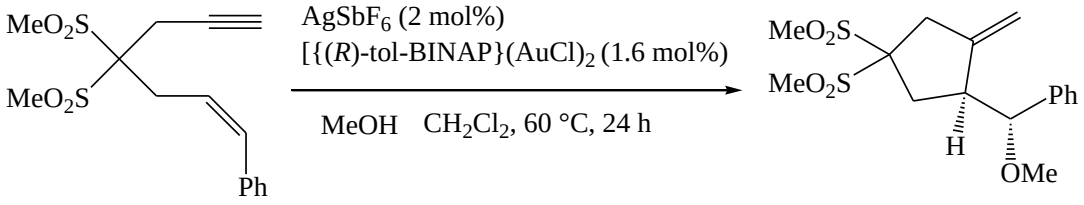
1.8.1.1 Lewis Acids of Bis-Gold/Biaryl Diphosphines

The cyclisation of enynes has been most commonly catalysed by transition metal catalysts, such as ruthenium and platinum, which to date have suffered from poor selectivity and often require harsh reaction conditions and overall the results have not been very promising.[5] The regiochemistry and enantioselectivity of the cyclisations are also highly dependent on the substitution pattern of the enyne, in particular the substituents on the terminal alkene and the carbon tether.[171, 175, 176] These factors have all contributed to hindering progress in this reaction.

Au/ phosphine systems have recently emerged as efficient catalysts in asymmetric enyne cyclisation reactions.[169, 177] One of the first examples of Au/phosphine catalysts in asymmetric catalysis was the successful application of chiral ferrocenylphosphine-Au(I) in the reaction of aldehydes with α-isocyanoacetate esters which gave the corresponding products in high enantioselectivity.[178, 179] This precedent led to the development of other ferrocenylphosphine-Au(I) catalysts and also saw emergence of bis-Au(I) diphosphine catalysts as well. In a recent report, Echavarren and colleagues reported the synthesis and application of various bis-Au(I) catalysts (Chart 1.5) in the asymmetric cyclisation of 1,6-

enynes. Their group also synthesised various other gold catalysts supported by mono- and bidentate phosphines for the enantioselective alkoxycyclisation of 1,6-enynes.[5]

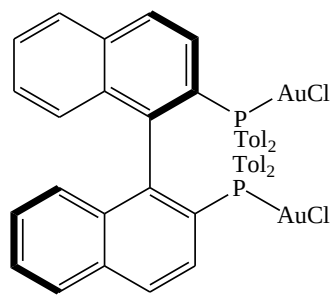
Equation 1.24. Selective Methoxycyclisation of 1,6-Enyne with Pt/L catalysts.



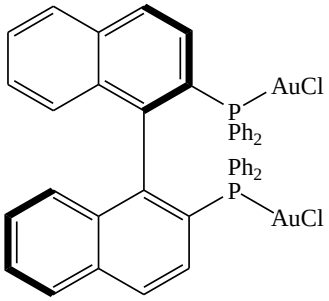
1.134 **1.135**

yield: > 99%
ee: 49%

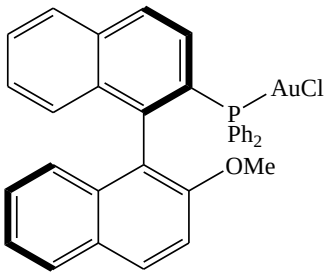
It is interesting to note that the supporting ligand has been shown to play a significant role and even 1,6-enynes were selectively cyclised with Pt/L (L = PPh_3, DPPF) catalysts to exclusively afford 6.5 in high yield and negligible quantity of unwanted product (Eq. 1.24).[5] In the absence of the bulky phosphine ligands, a mixture of products was formed.



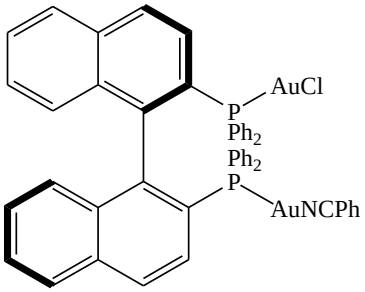
[{(*R*)-*tol*-BINAP}$(AuCl)_2$]



[{(*R*)-BINAP}$(AuCl)_2$]



[{(*R*)-MOP}$(AuCl)_2$]



[{(*R*)-BINAP}(AuCl)(AuNCPh)]

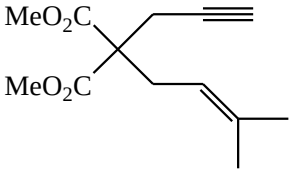
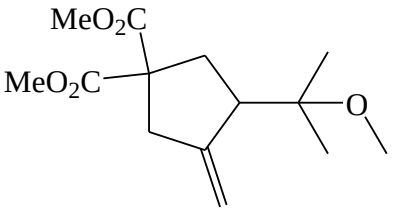
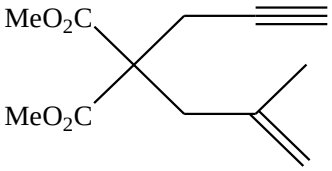
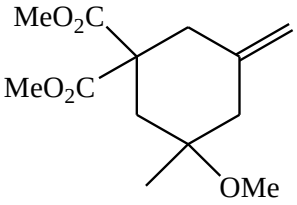
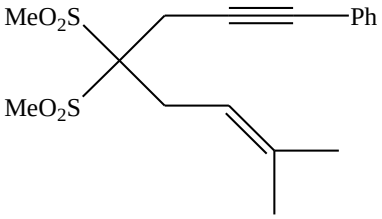
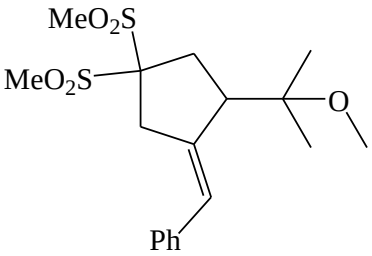
Chart 1.5

Reaction optimisation established that 1.6 mol% of bis-gold(I) catalyst and 2 mol% of silver salt were the optimal reaction conditions for the alkoxycyclisation of 1,6-enynes at room temperature. It was also shown that lowering the reaction temperature to -78 °C severely slows down the reaction and gives only a negligible quantity of alkoxycyclisation adduct 6.5 (Figure 6.3) and no conversion was observed in the absence of Au(I), even after long reaction time. The use of Au/(*R*)-MOP catalyst (Chart 1.5) gave good conversion but no enantioselectivity, whereas Au/(*R*)-BINAP affords the alkoxycyclisation adduct 6.5 in high conversion after short reaction with moderate enantioselectivity.[5] This case provides evidence that using bis-Au(I) catalysts can influence and increase enantioselectivity. Furthermore, in the absence of silver salts, the reaction proceeded at much slower rates and only gave the desired product in low enantioselectivity. It is noteworthy that Au/PPh_3 did not catalyse the methoxycyclisation in the presence of silver salts. This indicated that the corresponding *in-situ* prepared Lewis acid catalysts of [Au(PPh_3)(MeOH)]X (X = SbF_6, OTf) are either not stable or not reactive enough to catalyse this reaction. However, the use of bulky phosphines renders the corresponding cationic complex stable and reactive enough to catalyse the methoxycyclisation of various 1,6-enynes, underscoring the stabilising effects of the supporting bulky ligand.[5]

1.8.1.2 Effect of Substitution Pattern on Reactivity

Furthermore, the substitution pattern of the alkynes, especially on the alkene and the carbon tether, also have a significant influence on the enantioselectivity and reaction rate.[5] This was clearly demonstrated by Munoz and colleagues where a series of 1,6-enyne substrates were used in the methoxycyclisation of 1,6-enynes catalysed by [(*R*)-{*tol*-BINAP}$(AuCl)_2$], as shown in Table 1.1. The substitution pattern on the olefin terminus can affect the reaction and lead to formation of different regio-isomers. In entry 1, access to the terminal olefin of the enyne is severely hindered by the two methyl groups, as a direct result of which the cyclisation occurs via the internal olefin end affording the corresponding 5-membered ring. Conversely in entry 2, access to the internal olefin is restricted by the methyl group thereby directing the cyclisation to the terminal carbon atom to afford the corresponding 6-membered ring.

Table 1.1. Methoxycyclisation of 1,6-Enynes (entry 1-3) with [(*R*)-{*tol*-BINAP}$(AuCl)_2$].[5]

Entry	Enyne	Solvent	t (h)	Product (% yield)	% ee
1		methanol	7	 **(91%)**	0
2		methanol	72	 **(41%)**	30
3		methanol	168	 **(52%)**	94

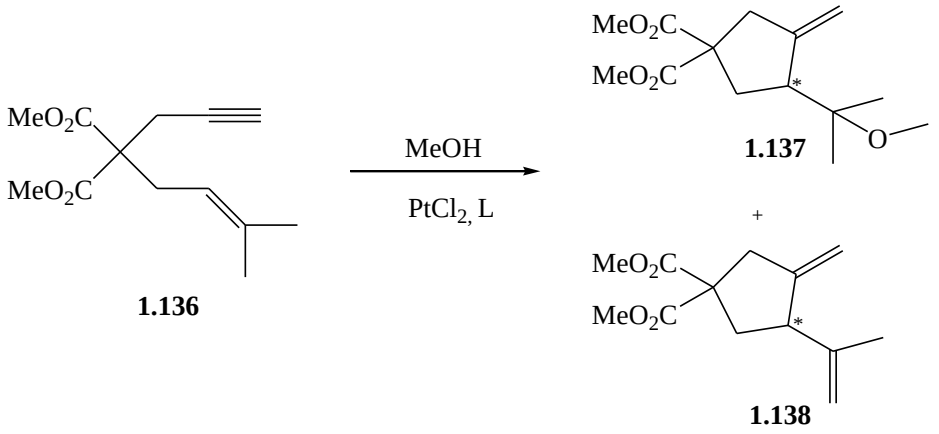
The 1,6-enyne substrate shown in entry 1 gives no enantioselectivity with [(*R*)-{*tol*-BINAP}$(AuCl)_2$]. However, altering the substitution pattern at the alkene increased the enantioselectivity to 30% (entry 2). Furthermore, a dramatic improvement in enantioselectivity was also observed with a bulky phenyl group at the terminal alkyne (entry 3, 94%). The major drawback in both the latter cases is the relatively long reaction and much lower yields obtained at the expense of higher enantioselectivity; entry 3 with 168 h reaction time affording only 52% yield but 94% ee. As such, our group is currently evaluating the efficacy of Au_2/(*S*)-Me_2-CATPHOS as a catalyst for the cycloisomerisation of different 1,6-enyne substrates.

1.8.1.3 Competing Reaction Pathways

Mechanistic studies with platinum-based catalysts clearly demonstrate that the use of both mono and bidentate phosphines as supporting ligands exclusively favours the reaction path leading to the formation of methoxycyclisation adduct **1.137**, as demonstrated by Munoz

and colleagues (Figure 1.17).[5] This is very interesting given that the presence of methanol does lead to formation of **1.138** as well.[180] However the presence of phosphine ligands inhibits this reaction pathway and exclusively favours the methoxycyclisation to form **1.137**. This is a somewhat surprising result given that the proposed reaction path for the formation of the unwanted **1.138** involves a formal 2-electron oxidation at the Pt(II) centre to form a Pt(IV) metallacycle[5] which, in turn, should be better stabilised by the stronger electron-donor diphosphine ligands and, as such, this reaction path for the formation of **1.138** might be expected to be favoured (Figure 1.17). This counter-intuitive preference for the formation of the methoxycyclisation product **1.137** is, perhaps, due to the phosphine inhibiting the reaction path leading to the formation of **1.138**.

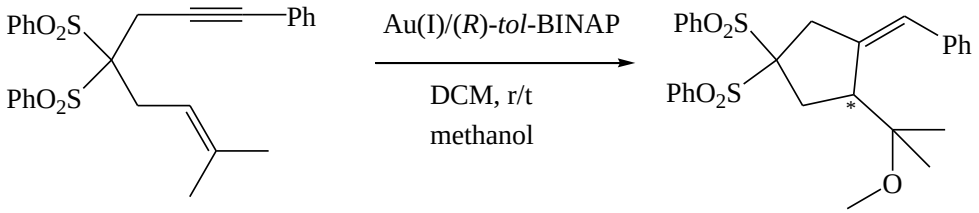
Figure 1.17. Methoxycyclisation of enyne 6.6.



L = PPh_3, **6.7**:**6.8** ratio: 99:1
DPPF, **6.7**:**6.8** ratio: 99:1.

1.8.1.4 Asymmetric Cyclisations with Au/BINAP

Bis-gold catalysts bearing biaryl diphosphines as supporting ligands have been found to be active catalysts. The alkoxycyclisation of 1,6-enyne **1.139** (Eq. 1.25) in presence of methanol was catalysed by [{(*S*)-*tol*-BINAP}$(AuCl)_2$] to afford the methoxycyclisation product **1.140** in 52% yield and 94% ee.[160] However, the scope of the reaction was limited to carbon-bridged enynes with two sulfone moieties and a substituted triple bond. The same reaction with a nitrogen tether and no methanol was also successfully catalysed with Au(I)/(*S*)-BINAP to afford the corresponding product in 95% yield but only 22% ee.[160] Other reports have also demonstrated the viability of bis-gold Lewis acids as catalysts for the cycloisomerisation of enynes.[181]

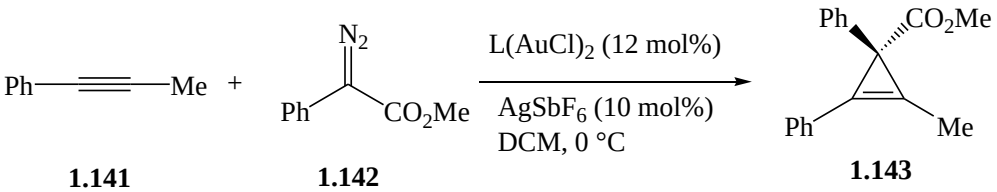


1.139 **1.140**

yield (54%), ee (94%)

Equation 1.25

Bis-gold catalysts with chiral biaryl diphosphines such as BINAP have enjoyed relatively good success in various other asymmetric transformations, with some pioneering publications by Toste and colleagues in enantioselective intramolecular hydroamination of allenes,[182] and intramolecular Au(I)-catalysed cyclopropanation.[183] Despite these strides, enantioselective Au(I)-catalysed cycloisomerisation reactions remain rare.[5] A recent publication by Davie and colleagues in 2012 reported the successful use of [{(*S*)-xylylBINAP(AuCl)$_2$}pre-catalyst to generate a very active Lewis acid for cyclopropenation of internal alkynes,[184] which gave the cyclopropenyl product in 81% yield and 93% enantioselectivity (Eq. 1.26). Although its BINAP and *tol*-BINAP counterparts gave **1.143** in lower yields of 26% and 74%, respectively, both afforded high enantioselectivity of 92%. The vital role of the supporting biaryl diphosphine was demonstrated when the same reaction was catalysed by the Lewis acid of [Diphosphine-(AuCl)] pre-catalyst which afforded **1.143** in 16% yield with no enantioselectivity. The temperature was not a significant parameter and reaction with [(*S*)-*tol*-BINAP(AuCl)$_2$] gave the final product **1.143** in 69% yield and 87% enantioselectivity at room temperature.



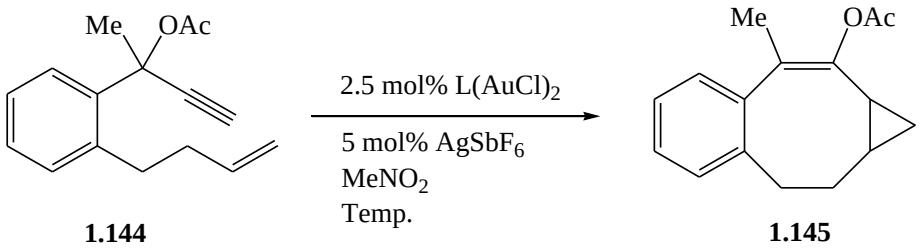
1.141 **1.142** **1.143**

L: (*S*)-BINAP, yield (62%), ee (92%)
(*S*)-*tol*-BINAP, yield (74%), ee (92%)
(*S*)-xylylBINAP, yield (81%), ee (93%)

Equation 1.26

A report by Toste and colleagues also found L(AuCl)$_2$ (L = BINAP and its analogues) to be efficient precursors for generation of highly active Lewis acids that were successfully used in the intramolecular bis-gold(I)-catalysed cyclopropanation of **1.144** to form **1.145** (Eq. 1.27). To date, the vast majority of enantioselective metal-catalysed

cycloisomerisations have been limited to the synthesis of 5- and 6-membered rings.[42, 185, 186] Herein the basic BINAP architecture proved to be the most efficient supporting ligand with gold(I) Lewis acids of (*S*)-xylylBINAP affording the highest enantioselectivity at room temperature. A SEGPHOS-based Lewis acid gave only 3% enantioselectivity despite its biaryl-like architecture. The enantioselectivity with (*S*)-xylylBINAP was increased to 92% at -25°C.



1.144 **1.145**

L = (*R*)-xylylBINAP, r/t, ee (70%)
(*R*)-BINAP, r/t, ee (53%)
(*R*)-DTBM-SEGPHOS, r/t, ee (3%)
(*R*)-xylylBINAP, -25 °C, ee (92%)

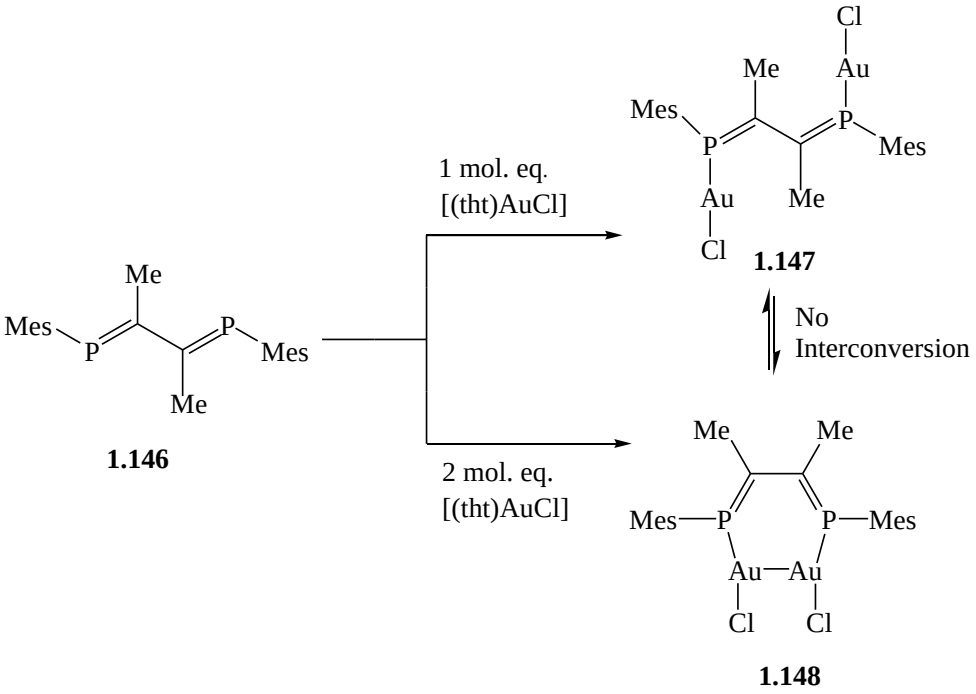
Equation 1.27

1.8.2 Aurophilic Au-Au Interaction

A unique feature of some bis-gold-phosphine catalysts is the presence of an aurophilic Au-Au interaction. Given the application of very few bis-gold diphosphine catalysts, there is no consensus about the effects of such an aurophilic interaction on the conformation of the catalyst structure and how that might affect its catalytic activity. In a recent report, a number of phospho-alkene-gold complexes were synthesised and their structure/catalytic activity relationship was studied. [181] In some cases it was established that the aurophilic Au-Au interaction in bis-gold complexes irreversibly distorts the framework of the supporting ligand. In the case of bis-gold complexes shown in Figure 1.18, 2,3-dimethyl-1,4-diphosphabuta-1,3-diene **1.146** reacts with [(tht)AuCl)] to form two distinct catalysts (**1.147** and **1.148**). Given that the two catalysts are not interconvertable even after heating, it was suggested that the presence of excess [(tht)AuCl] may facilitate different reaction paths for the formations of the two conformations. It was suggested, that the presence of excess [(tht)AuCl] may have formed Au_2-type intermediates which lead to **1.148** through a conformational change. Subsequently in catalysis applications, cycloisomerisation of 1,6-enyne was only found to be successful with the bis-gold catalyst that has Au-Au aurophilic interaction (**1.148**) with no product observed with **1.147** pre-catalyst isomer. This example

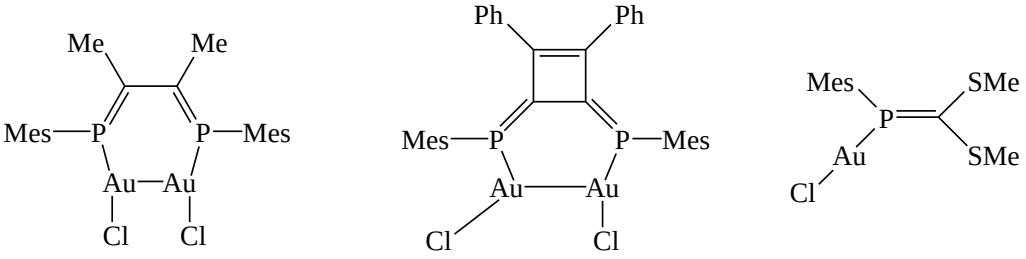
clearly demonstrates both that the aurophilic Au-Au interaction distorts the conformation of the catalyst and that the resulting species is active towards cycloisomerisation. It is noteworthy that the Lewis acids derived from pre-catalysts **1.149** and **1.150** (Figure 1.18) also showed good activity for cycloisomerisations, especially in the case of the latter that exhibits an aurophilic Au-Au interaction.

Scheme 1.10. Reaction of 2,3-Dimethyl-1,4-diphosphabuta-1,3-diene with [(tht)AuCl] Gold Pre-Catalyst Affording Two Distinct Bis-Gold Catalysts.



Although not conclusive, these findings certainly indicate that the aurophilic Au-Au interaction[187] is an important factor to be considered in the synthesis of gold catalysts as it may affect catalysis.[188] It is also noteworthy that for the particular classes of phosphor-alkene-gold catalysts, it was found that the LUMO of the phosphorus-carbon double bond effectively raises the Lewis acidity of the respective active catalyst thereby contributing to high catalyst activity as well.[181]

Figure 1.18. Phosphoalkene Gold Catalysts Showing Reactivity for Cycloisomerisation of 1,6-Enyne Substrates.



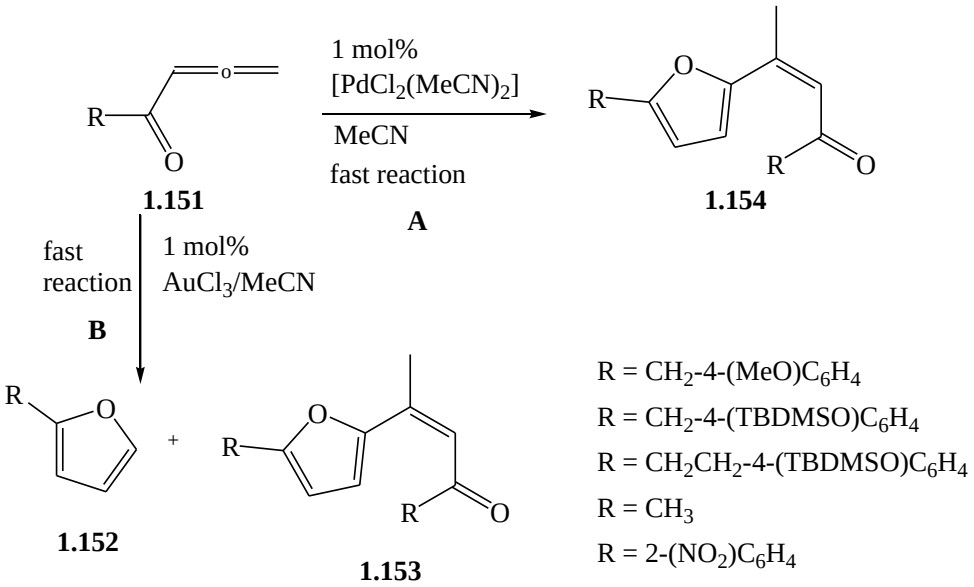
1.148 **1.149** **1.150**

1.9 Cycloisomerisation with Nucleophilic Carbonyl Oxygen

A report by Hashmi and colleagues in 2000 demonstrated gold-catalysed formation of furans by 5-*endo-trig* cyclisation of allenyl ketones which provided the first evidence that the carbonyl oxygen can act as a potent nucleophile in this rearrangement.[189] Herein, $AuCl_3$ catalyses the cycloisomerisation of allenyl ketones **1.151** to afford the corresponding furan **1.152** as the major product together with the unwanted dimerisation adduct **1.153** as a minor product (Scheme 1.11, step B). By contrast, $[PdCl_2(MeCN)_2]$ exclusively affords the dimerisation adduct **1.154** as the only product (step A). Allenes have received little attention due to problems associated with their enhanced reactivity in terms of regioselectivity[190], stereoselectivity and chemoselectivity where single or double addition can lead to formation of different products.[191]

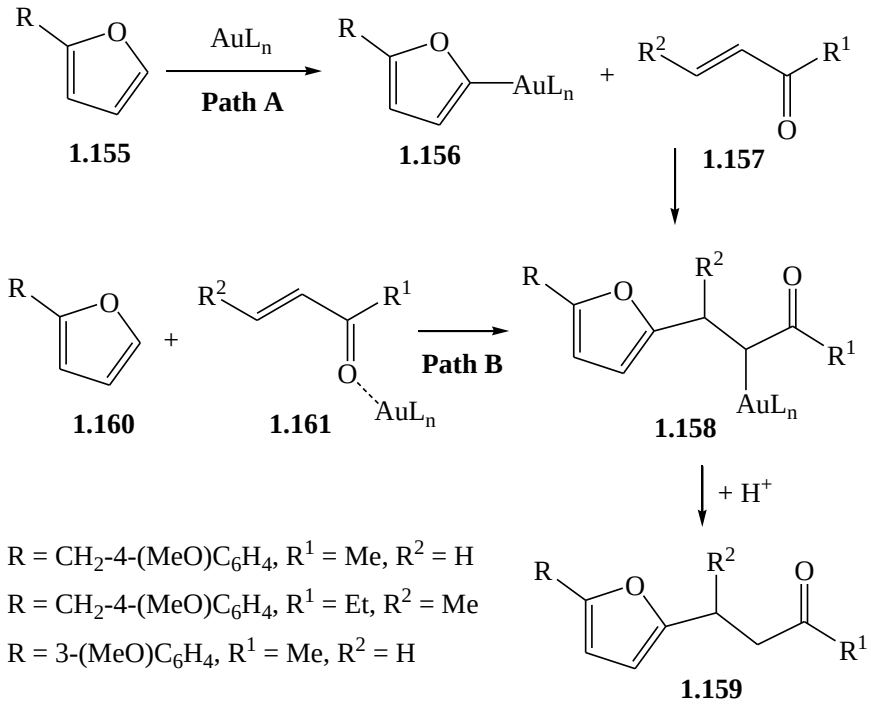
Interestingly Au(I)-based catalysts exhibited much better selectivity for C-O bond formation than their Pd(II) counterparts (which also catalyse C-C bond formation leading to side-product such as **1.154**). Furthermore, a Au(I)-based catalyst in the form of [AuCl(tetrahydrothiophene)] exclusively catalysed C-O bond formation to give the furan as the sole product. Interestingly Au(III)-based catalysts favour both C-O and C-C bond formation (Scheme 1.11); 1 mol% of gold(III)-based catalysts was used with copper to give the dimerisation adduct **1.153** (marginal major product) together with the substituted furan **1.152**.[189]

Scheme 1.11. Different Cycloisomerisation/Dimerisation Pathways of Terminal Allenyl ketones by Palladium(II)- or Gold(III)-based Catalysts.



It has also been suggested that the C-C bond formation with furan proceeds through the gold species shown in Scheme 1.12, where the gold catalyst either activates the enone to form activated intermediate **1.161** which subsequently reacts at the 5-position of the furan via electrophilic aromatic substitution to form the second gold intermediate **1.158** (path B). Alternatively the gold catalyst activates the 5-position of the furan **1.155** via direct electrophilic attack (auration)[192] to afford the first gold intermediate **1.156** (path A) which subsequently undergoes Michael addition with the enone to form a second gold intermediate **1.158**. The final step to form the product involves protonation instead of the more common β-hydride elimination observed in palladium-catalysed reactions to afford the desired product **1.159**.[193, 194] A review of the literature for these reactions shows that β-hydride elimination is in fact very rare for gold-catalysed reactions as it is a relatively slow process.[195]

Scheme 1.12. Proposed Mechanisms for C-C Gold-Catalysed Bond Formation.



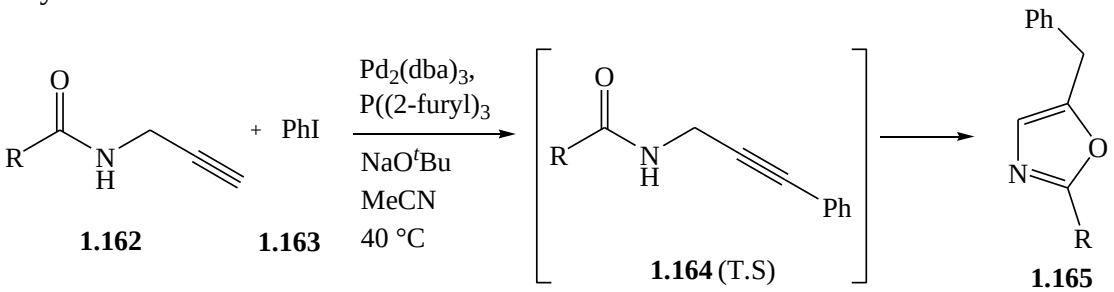
1.9.1 Activation of *N*-Propargyl Amides

The ability of Au(I)- and Au(III)-based catalysts to activate carbon-carbon triple bonds has played an influential role in the synthesis of various heterocycles. Activation of the triple bond is followed by intramolecular addition of a heteroatom nucleophile to afford the corresponding heterocycle. The first evidence for this reaction pattern was observed by

Utimoto and colleagues in 1987; intramolecular cyclisation of 5-alkynylamine catalysed by a gold(I) Lewis acid gave the 2,3,4,5-tetrahydropyridine.[196]

Initially, Hacksell[197] and colleagues also showed that propargylic amides could be cyclised to the corresponding oxazoles under basic reaction conditions, which has since proven to be a very popular method.[198-200] In a report in 2001, Arcadi and colleagues explored the possibility of synthesising disubstituted furans, a fundamental building block present in active drugs such as NCTC,[201] by palladium-catalysed cycloisomerisation of *N*-propargyl amides.[202] Their reaction consisted of a Pd(0)-catalysed coupling of *N*-propargyl amide **1.162** to phenyl iodide **1.163** followed by *in-situ* cyclisation to afford the corresponding disubstituted oxazoles **1.165** (Scheme 1.13). It is noteworthy that this reaction has also been widely used for the synthesis of other cyclic units such as indoles and pyrazoles as well.[203] Previous methods for formation of disubstituted furans included reactions using H_2SO_4 or $Hg(OAc)_2$ at high temperatures.[204]

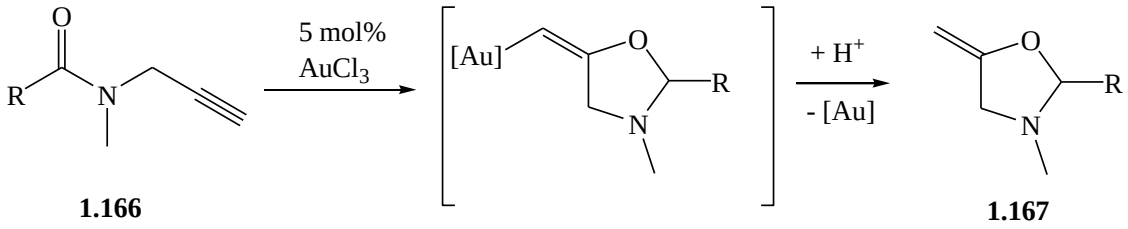
Scheme 1.13. Cycloisomerisation of *N*-Propargyl amides Catalysed by Pd(0)-based Catalysts.



R = Ph,
MeO-C_6H_4

In 2004, Hashmi and colleagues reported that gold(III)-based catalysts efficiently catalysed the formation of a range of disubstituted furans by cyclisation of *N*-propargyl amides.[205] The reactions were successfully carried out in dichloromethane at room temperature or in acetonitrile at 45 °C affording the corresponding product in high yields. The reaction tolerated a wide scope of functional groups. The conversion of the starting materials to the desired product can be affected by both coordinating and electronic factors where, for instance, steric hindrance at the terminal alkyne can prevent the formation of the desired products altogether. The relatively mild reaction conditions used for Au(III)-catalysed cycloisomerisation of *N*-propargyl amides allows observation of the methylene intermediate which has not been previously observed with substrates that do not possess the disubstitution that blocks isomerisation of the methylene intermediate to the aromatic

heterocycle. More recent reports have shown that this methylene intermediate (i.e. **1.167**) can be selectively formed with Au(I)-based catalysts (Eq. 1.28).[206]

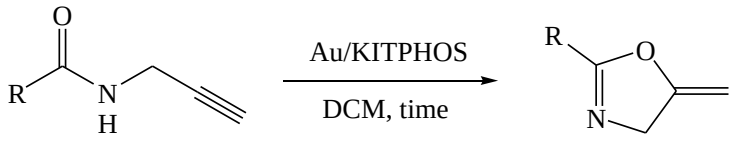


1.166 **1.167**

R = Ph
furyl

Equation 1.28

In a recent report, the Doherty group catalysed cycloisomerisation of a range of *N*-propargyl amides **1.168** with electrophilic gold complexes of KITPHOS monophosphines which gave the corresponding methylene products **1.169**.[207] A range of amides were successfully cyclised to the corresponding methylenes at room temperature (Eq. 1.29). It was found that the catalysts formed from diphenylphosphino-substituted KITPHOS monophosphines gave the optimal results which indicate that the biaryl/biaryl-like framework may be responsible for the high catalyst efficiency.



1.168 **1.169**

R = *tert*-butyl, (96%, 1 h)
R = cyclohexyl, (84%, 1.5 h)
R = phenyl, (74%, 0.5 h)
R = thiophene, (74 %, 4 h)

Equation 1.29

1.9.2 Synthesis of Oxazoles

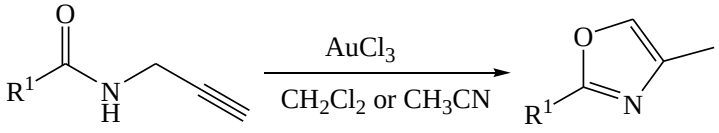
The synthesis of heterocycles via intra-molecular addition of a heteroatom to a carbon-carbon triple bond activated by gold catalysts has seen rapid development in recent years where it has proven to be a powerful tool for the synthesis of various functionalised heterocycles.[208] The synthesis of oxazole, in particular, has gained prominence as it is prevalent in a vast array of natural products, especially in substances of marine origin

which exhibit very interesting pharmaceutical properties and are widely used as anti-tumour and antifungal therapeutic agents.[209]

Prior to the emergence of gold-based catalysts, the classical routes for the synthesis of oxazoles involved various condensation pathways.[210, 211] However, most of these routes employ harsh reaction conditions and are not economically viable. The initial promising work with gold catalysts led to the emergence of many reports using gold catalysts bearing various types of supporting ligands,[212, 213] for the synthesis of various functionalised heterocycles.[214, 215] It is noteworthy that other transition metal catalysts have also been used to this end as well.[216, 217]

Hashmi and colleagues were first to report that the carbonyl oxygen can be used as a nucleophile in cyclisation involving allenyl ketones. Arcadi and colleagues later reported the synthesis of disubstituted oxazoles with *N*-propargylamides.[218] Hashmi and colleagues expanded the scope of this reaction by further evaluating the concept of the carbonyl oxygen acting as a nucleophile and carried out reactions with a whole host of substituted *N*-propargylamides **1.170** bearing different 'R' groups catalysed by $AuCl_3$,[205] as illustrated in Equation 1.30. These substrates are convenient to use as they are readily synthesised in a single step.[211, 216, 219] Herein, Hashmi and colleagues demonstrated that the R^1 group affects the reaction rate where, for instance, electron withdrawing groups have been shown to substantially reduce the nucleophilicity of the carbonyl oxygen and slow down the reaction rate.

Equation 1.30. Gold-Catalysed Cycloisomerisation of Propargylamides to Form the Corresponding Oxazoles.[220]



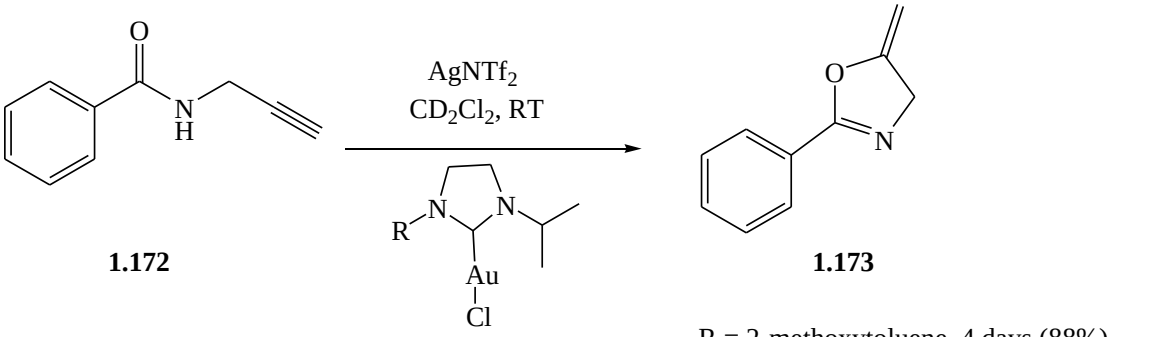
1.170 **1.171**

R^1 = Me, Ph, Furan, OEt, OMe.

It is noteworthy that, Au(III)-based catalyst afford the oxazole (Eq. 1.30) whereas Au(I)-based catalysts exclusively afford the methylene oxazoline, an intermediate with gold(III)-catalysts for this reaction, as the final product. The latter is also an important reaction and it highlights the selectivity of gold-based catalysts.

On a general note, the continuing importance of this reaction was highlighted in a recent report by Hashmi and colleagues (2012) showing the successful cyclisation of *N*-propargylamides[221] **1.172** catalysed by a range of Au(I) complexes of new NHC ligands to afford the oxazoline **1.173**, as shown in Equation 1.31. At very low catalyst loading (0.1 mol%), most of the catalysts required reaction times of 4 days to afford the methylene product **1.173** in yields > 80%. It is noteworthy that at 1 mol% of Au(I)/NHC (R = 2,6-dimethoxytoluene) catalyst, the methylene product was afforded in 97% yield after 9 h.

Equation 1.31. Cyclisation of Propargyl-amides with Substituted Au(I)-NHC Complexes.

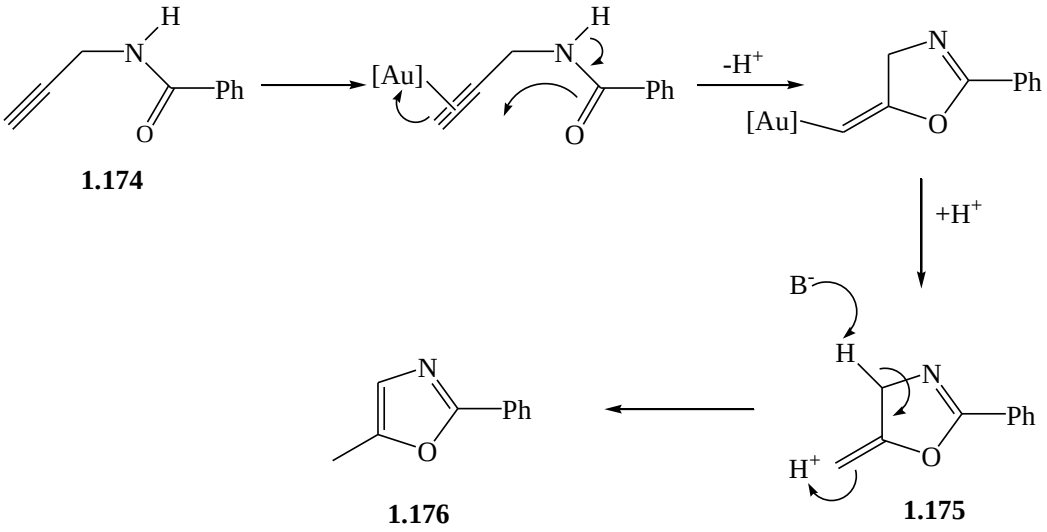


1.172 0.1 mol% **1.173**

R = 2-methoxytoluene, 4 days (88%)
2,6-dimethoxytoluene, 4 days (84%)
cyclohexyl, 4 days (86%)

1.9.2.1 Reaction Mechanism

The mechanism for cycloisomerisation of phenyl propargyl amide is outlined in scheme 1.14, as proposed by Hashmi at al.[220] It has been unequivocally established that the corresponding oxazole **1.176** forms via a methylene intermediate **1.175**. The specific formation of **1.175** strongly indicates that the alkyne activation and subsequent carbonyl oxygen attack is strictly stereospecific. As such, the carbonyl oxygen must attack the π-coordinated alkyne from the backside, initiating the stereospecific proto-demetalation of the gold-containing species to form the oxazole **1.176** and methylene oxazoline **1.175** using Au(III)- and Au(I)-based catalysts, respectively.[189, 222]



Scheme 1.14

There is a clear thermodynamic drive for this reaction route whereby the methylene intermediate **1.175** was measured to be -25.7 kcal/mol more stable than the corresponding *N*-propargyl amide starting material **1.174**. The subsequent aromatisation to form the oxazole ring **1.176** sets free an additional -16.8 kcal/mol in energy, rendering it more energetically stable than methylene intermediate **1.175**.[205]

As aforementioned, gold-catalysed cycloisomerisation reactions with *N*-propargyl amides have been studied in great depth with a broad array of R groups (Equation 1.30).[222] Hashmi and colleagues employed $AuCl_3$ as gold catalyst and most of their reactions gave successful conversions for the respective oxazole. However the vast majority of the reactions only give satisfactory conversion after reaction times of >11 h and, in some specific cases, as long as 21 h.[222] In a recent report in 2010, Doherty et al. successfully applied Au(I)/KITPHOS catalysts in this reaction where, most noticeably, the reaction times were reduced drastically; satisfactory conversions were obtained at room temperature in <1.5 h reactions in the vast majority of the cases.[207] Their study highlighted the important role of the biaryl monophosphine KITPHOS in the reactivity of the Au(I)/KITPHOS catalyst and it proved to be a markedly more efficient catalyst than Au/PPh_3 catalyst.[207]

1.10 Conclusions

Until recently, Lewis acid catalysis has traditionally involved hard transition metals such as Cu(II) and Zn(II). In recent years more attention has been focused on group 8-10 metals such as palladium and platinum and more recently with gold as well, in part spurred by the emergence of dicationic, square planar, 16 electron complexes of the type $[(\text{diphosphine})M]^{2+}$ (M = Pt, Pd, Ni,), which have proved to be efficient catalysts across a wide range of reactions. The supporting ligand of the catalyst is pivotal to its activity. Although an immense number of biaryl-based phosphines have already been developed, the substrate specificity of many reactions requires architectural modifications to be made which often proves to be time consuming and expensive and which involves non-trivial multi-step *de novo* synthesis. As such, there is a continuing interest in more efficient and straightforward synthesis and development of novel biaryl phosphines.

This thesis outlines a simple and straightforward novel 3-step synthesis for formation of R_2-CATPHOS ligands (R = H, Me, MeO). Their respective Lewis acid complexes have been applied in a host of transformations covering a wide scope of substrates and functional groups, with the final results compared against commercially available ligands such as BINAP. Extensive reaction optimisation across the range of reactions has demonstrated the efficacy and versatility of this ligand in various transformations.

1.11 References

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Chapter 2

R_2-CATPHOS: Synthesis and Resolution

2.1 Introduction

Atropos biaryl diphosphines continue to play an important role in a whole array of asymmetric transformations with the basic biaryl skeleton imparting significant influence on the efficacy of the catalyst. They now firmly belong to the privileged class of ligand/structure.[1] BINAP is undoubtedly one of the most well-known biaryl diphosphines that serves as an excellent ligand in a whole host of transition-metal catalysed reactions.[2-4] Although BINAP is widely used, it is not superior in all transformations and architectural modifications such as addition of substituents to the biaryl skeleton is often required to enhance the performance of the corresponding active catalyst. For instance, in the case of asymmetric hydrogenation of a dehydroamino acid[5, 6] the low ee of 15 % achieved with Rh/(*S*)-BINAP was increased dramatically to 99% when a 3,3'-disubstituted BINAP analogue was used as ligand. This is a clear example of the significant effect which the biaryl architecture can have on the performance of the active catalyst in asymmetric hydrogenation and it also applies to other platinum group metal catalysed transformations such as carbon-carbon coupling[7] and cycloisomerisation.[8]

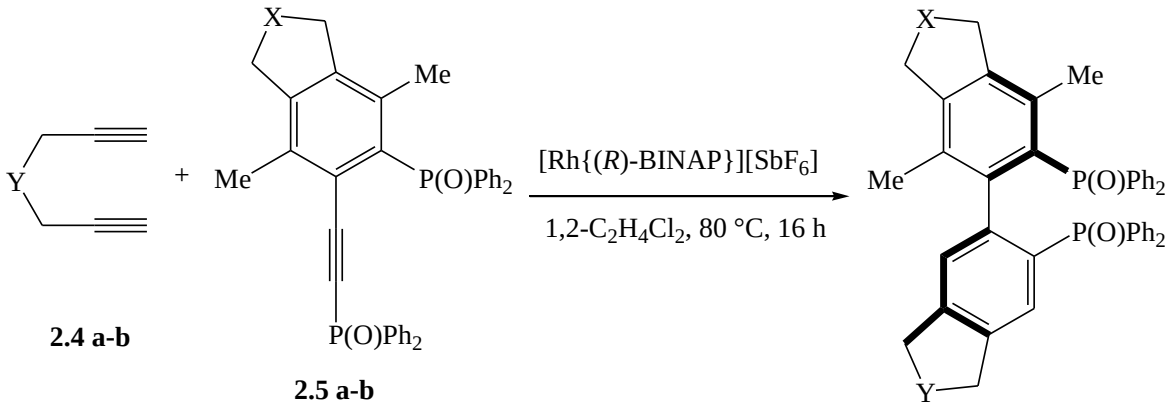
The basic biaryl (or biaryl-like) architecture has also found application in many transition metal catalysed achiral transformations, as discussed in Chapter 1.

However there is substantial cost associated with modifying the basic architecture of BINAP and, as such, there is continued interest in developing alternative biaryl structures through novel, effective, and cost-effective synthesis routes[9, 10] that would then enable straightforward modifications of the ligand structure.

2.1.1 Synthesis of Novel Biaryl Diphosphines

Given the difficulties associated with conventional methods used for synthesis of chiral biaryl diphosphines, the Doherty group has developed alternative methods for synthesis of biaryl diphosphines. Thus it was reasoned that chemoselective rhodium-catalysed double [2 + 2 + 2] cycloaddition of 1,4-bis-(diphenylphosphino)-1,3-butadiyne with an appropriate 1,n-diyne would provide a convenient one-pot route for the synthesis of BIPHEP oxides. Indeed, rhodium- and iridium-catalysed [2 + 2 + 2] cycloadditions have been used for the synthesis of spirocyclic structures and helical polyaryls and have recently emerged as a highly efficient strategy for synthesis of axially chiral compounds; the vast

majority of this is attributed to the research groups of Tanaka[11] and Shibata[12] and more recently Oshima and Yorimitsu.[13]. Consequently, the reaction of 1,7-octadiyne (2 equiv) **2.4a-c** with alkyne-phosphine oxide adducts **2.5a-b** in the presence of a cationic rhodium complex, generated from $[RhCl(COD)]_2$ and *rac*-BINAP, led to the formation of NU-BIPHEP oxides **2.6a-c**[14] in 95% yield, after purification by column chromatography (Eq. 2.1). The phosphine oxide was reduced in high yield by heating in THF/toluene in the presence of trichlorosilane, and triethylphosphite at 100 °C for 48 h to afford the corresponding NU-BIPHEP diphosphine. This methodology was successfully applied to the synthesis of a range of atropos NU-BIPHEP diphosphines with different tethered diynes **2.6a-b**, as outlined in Equation 2.1.[15] Interestingly, the versatility of this reaction strategy was further explored with more hindered internal diynes with partial success, underscoring the potential to use different types of diynes for the formation of different biaryl diphosphines altogether. The biaryl diphosphines of NU-BIPHEP-type have been resolved and the enantiopure Lewis acid has successfully been used in transition-metal catalysed Diels-Alder and carbonyl-ene reactions, giving excellent levels of enantioselectivity.[14]



2.6a X-Y: $C(CO_2Me)_2$, yield (79%), ee (97%)

2.6b X-Y: CH_2CH_2, yield (97%), ee (96%)

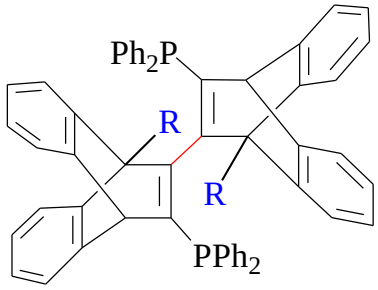
Equation 2.1.

This methodology clearly demonstrates that the 1,3-butadiyne unit is a viable building block for the synthesis of alternative 1,3-butadiene bridged diphosphines. Our group has been very active in the area of novel ligand synthesis, with commercialisation of a number of biaryl-based ligands over the last few years.[14, 16, 17]

One of the most recent developments involves synthesis of a biaryl-like CATPHOS architecture (Figure 2.1), of which both H_2-CATPHOS and Me_2-CATPHOS analogues

have been successfully synthesised and commercialised via an operationally straightforward and inexpensive 3-step reaction sequence.[16]

Figure 2.1. Illustrative structure of biaryl-like architecture CATPHOS; Me_2-CATPHOS (R = Me) and H_2-CATPHOS (R = H) previously synthesised and commercially available.[18]

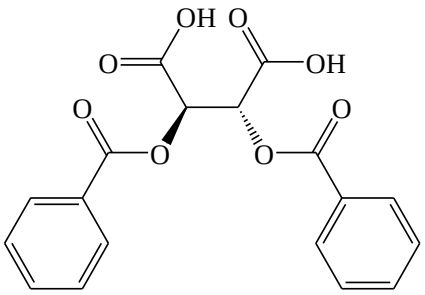


Given the close proximity of the bridgehead 'R' groups to the metal-phosphorus coordination site (Figure 2.1), we sought to expand this class of diphosphines by synthesising $(MeO)_2$-CATPHOS, bearing a bulky methoxy group at the 'R' position, resolving its enantiomers and exploring its efficacy in various Pd-catalysed transformations. Indeed, in the case of modified BINAP analogues, Lemaire and colleagues have demonstrated that adding substituents at the 3 and 3' positions could most influence, amongst other things, the steric environment around the catalytic site[5, 19].

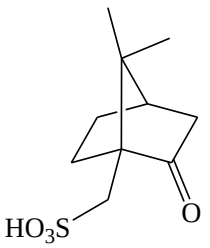
A comparison of the crystal structures of [{(*S*)-BINAP}$PdCl_2$} with its MeO-BINAP and O^{i}Pr counterparts shows that the P-Pd-P bite angle is reduced from 92.77° to 88.09° and 89.91°, respectively. Likewise, the torsion angle for the corresponding C_4 tether connecting the two biaryl moieties is also reduced as a direct result of structural modifications. These discrepancies place steric restrictions around the metal coordination site creating a smaller chiral pocket with one of the phenyl substituents on each of the phosphorus atoms undergoing π-stacking with the adjacent aromatic units of the biaryl moiety.[5] Given that the enantioselectivities for asymmetric hydrogenation of acetamidoacrylates increased from 21.2 % with BINAP to over 90% with MeO- and O^{i}Pr-counterparts,[5] where the only significant structural discrepancies were, in fact, the reduction of bite and torsion angles, it is reasonable to argue that the addition of those substituents significantly contributed to improving catalytic performance.

2.1.2 Common Resolution Methods

The enantiomers of atropos ligands are often resolved with chiral reagents such as di-*O*-benzoyl tartaric acid (DBTA) **2.7** or camphorsulfonic acid **2.8** (Chart 2.1).[20-22] The procedure follows co-crystallisation of one enantiomer of the racemic phosphine oxide with the enantiopure resolving reagent to form the corresponding diastereoisomeric complex, which is subsequently separated via fractional crystallisation, leaving a mother liquor enriched with the other diastereoisomer. Subsequently, the enantiopure phosphine oxide is liberated from the complex by treatment with a base. The same procedure is followed with the opposite enantiomer of the resolving reagent to obtain the other diastereoisomer. Despite the low yields associated with such resolution methods resulting from multiple fractional crystallizations, the benefits outweigh any disadvantages, especially in that it is a very practical and versatile method with the option of using various resolving reagents.



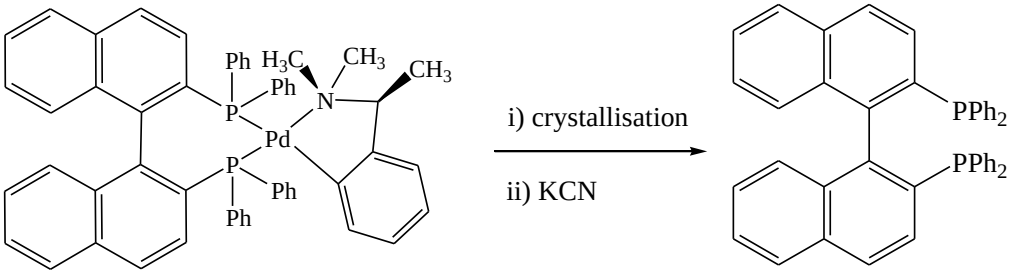
(-)-2,3-Di-*O*-benzoyl-*L*-tartaric acid (**2.7**)



(D-camphorsulfonic acid) (**2.8**)

Chart 2.1

Another resolution procedure less commonly used in research is ‘on-metal resolution’. Racemic BINAP **2.3** was initially separated into its enantiomers via coordination to a chiral metal entity to form the diastereoisomeric complex **2.9** (Eq. 2.2).[23] Fractional crystallisation was used to separate the diastereoisomers from each other and the pure ligand was liberated from the chiral metal complex by treatment with KCN to afford enantiopure BINAP **2.3** in 75% isolated yield.

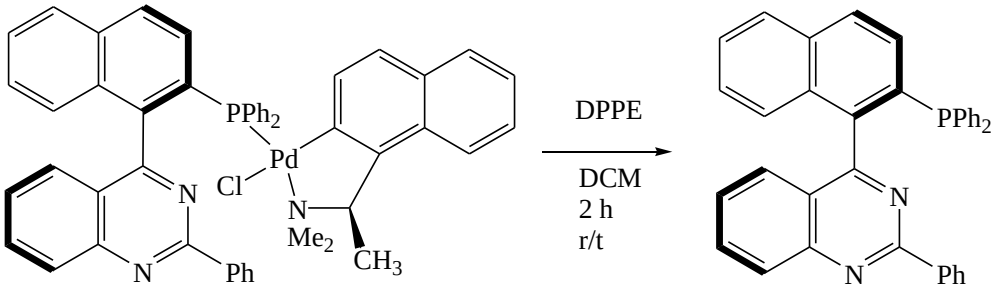


[{(*S*)/(*R*)-BINAP}-Pd-N(CH_3)$_2$C(CH_3)(C_6H_4)] (**2.9**)

(*S*)/(*R*) BINAP (**2.3**)

Equation 2.2

This method has been applied to resolve a variety of other ligands; for example, QUINAP has been resolved as diastereoisomeric palladium complexes of the (*R,R*)-Quinazolinap **2.10**, which was separated via fractional crystallisation and liberated from the chiral palladium complex by treatment with DPPE in dichloromethane at room temperature to afford enantiopure 2-phenyl-Quinazolinap **2.11**, as shown in Equation 2.3.[24]



(*S,R*)-**2.10**

(*R*)-**2.11**

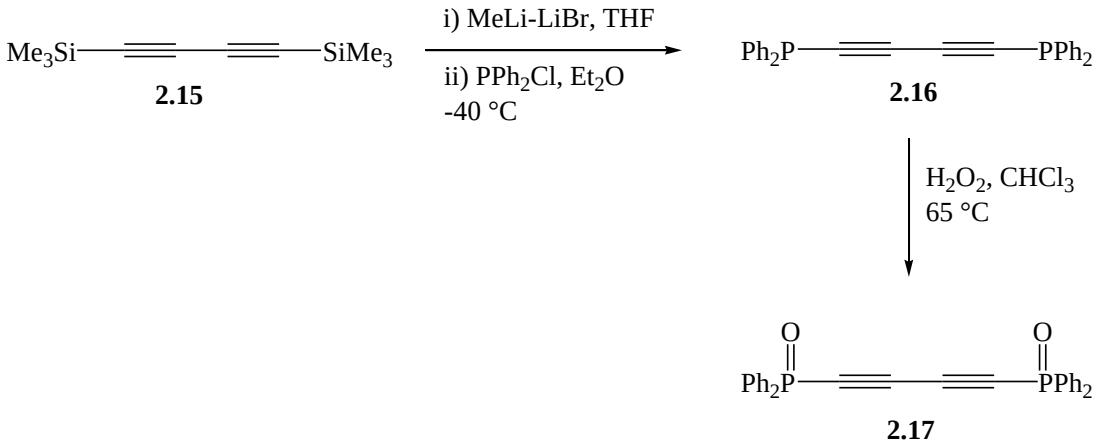
Equation 2.3

In some cases, the chloride diastereomeric mixtures cannot be separated from each other due to solubility issues. As such silver salts, such as $AgSbF_6$, are used to change the solubility of the complexes which can subsequently be separated via fractional crystallisation.

Results and Discussion

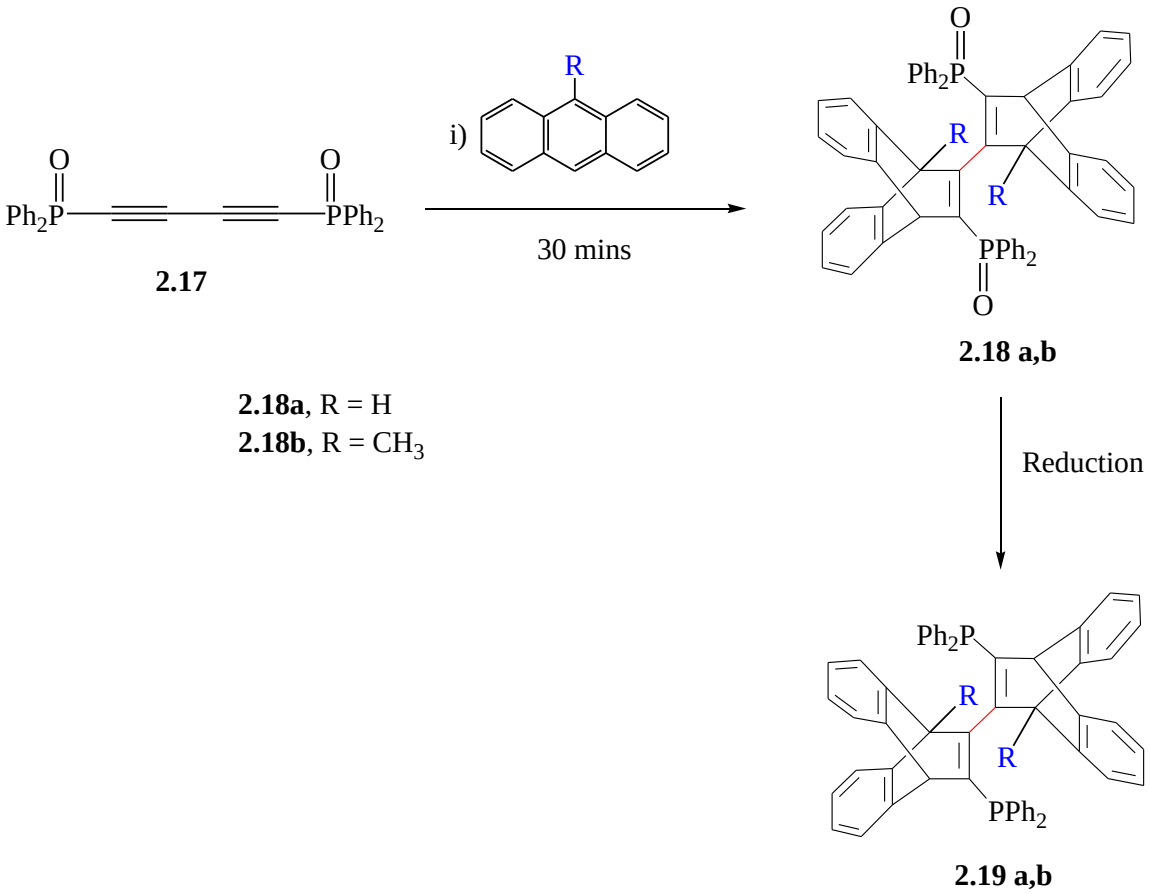
2.2 Synthesis of R_2-CATPHOS (R = H, Me)

Our group has successfully formulated an operationally straightforward and cost-effective 3-step synthesis of novel biaryl-like R_2-CATPHOS diphosphines: H_2-CATPHOS was successfully synthesised via Diels-Alder cycloaddition of anthracene with 1,4-bis(diphenylphosphinoyl)-1,3-butadiyne to afford the H_2-CATPHOS. The Doherty group has recently reported this novel synthesis procedure in a Nature Protocols publication.[25] In the first step, 1,4-bis(trimethylsilyl)-1,3-butadiyne **2.15** is lithiated with MeLi-LiBr (1 mol. eq.) in THF at room temperature under vigorous stirring overnight, after which chlorodiphenylphosphine is introduced at -40 °C to afford 1,4-bis(diphenylphosphine)-1,3-butadiyne adduct **2.16**. Subsequently, the diphosphine was oxidised in the presence of hydrogen peroxide in $CHCl_3$ under reflux at 65 °C for 30 min to afford the corresponding 1,4-bis(diphenylphosphinoyl)-1,3-butadiyne **2.17** (Scheme 2.1).[26]



Scheme 2.1

In the next step (scheme 2.2), 1,4-bis(diphenylphosphinoyl)-1,3-butadiyne **2.17** reacts with 9-methylanthracene via Diels-Alder cycloaddition at 200 °C to afford the atropos Me_2-CATPHOS oxide **2.18b**. The two biaryl moieties are connected through a C_4 tether which clearly fulfils the criteria for synthesis of an atropos biaryl diphosphine.[27] The tropos analogue H_2-CATPHOS oxide **2.18a** was also prepared by this route, by reaction of 1,4-bis(diphenylphosphinoyl)-1,3-butadiyne **2.17** with anthracene to afford **2.18a**. In both cases, the Diels-Alder cycloaddition proved to be rapid, reaching completion after 30 mins. The ^{31}P NMR spectrum for **2.18a** and **2.18b** shows a characteristic single peak at 26.2 and 24.2 ppm, respectively. The chiral HPLC chromatogram for **2.18b** clearly shows the presence of two peaks at 6.25 and 8.57 mins, confirming the atropos nature of *rac*–Me_2-CATPHOS.

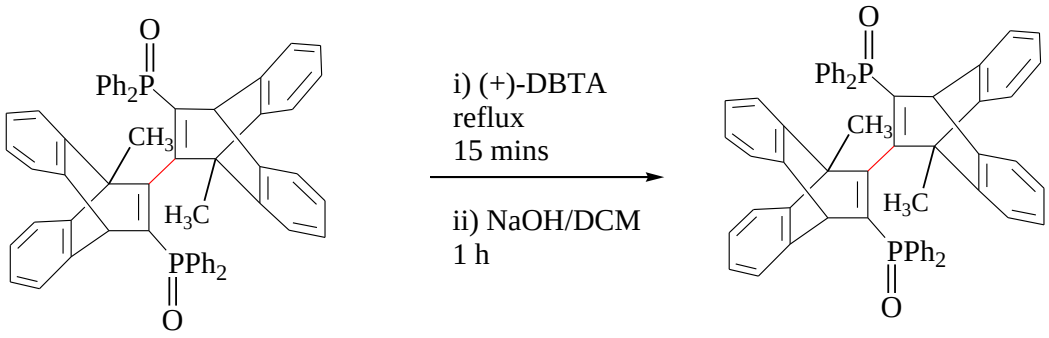


Scheme 2.2

Different reaction conditions were adopted for the reduction of **2.18a** and **2.18b**. As previously reported by the Doherty group, **2.18a** was reduced in a mixed solvent of toluene-THF in the presence of excess trichlorosilane and triethylphosphite at 40 °C to afford **2.19a** in near- quantitative yield as a pure white solid with a characteristic ^{31}P NMR signal at -15.3 ppm. However **2.18b** could only be reduced in xylene in the presence of both trichlorosilane and tri-*n*-butylamine after heating at 130 °C for 72 h, after which *rac*-Me_2-CATPHOS **2.19b** was obtained in 55% yield as a spectroscopically and analytically pure white solid, as previously reported;[28] The ^{31}P NMR spectrum shows a single characteristic peak at -13.9 ppm. The double Diels-Alder cycloaddition between 9-methylanthracene and **2.17** proceeds with high regioselectivity to afford **2.18b** as the major product of the three possible 80 egion-isomers, with the bulky methyl-substituted bridgehead carbon atoms attached to C(2) and C(3) of the butadiene tether where it would restrict rotation about the biaryl-like axis, such that it would be possible to resolve the axially chiral enantiomers, in much the same manner that 6,6'-substitution in 1,1'-bis(diphenylphosphino)biphenyl renders Me-BIPHEP atropos.

In line with previous work published by Doherty group, it has been unequivocally established that Me_2-CATPHOS belongs to the atropos class of diphosphine.[28] Quantum

chemical calculations using DFT reveal that for Me_2-CATPHOS, the energy barrier to atropinterconversion between the two axially chiral conformations is 130 kJ/mol^{-1}. The presence of the methyl group in the buta-1,3-diene bridgehead axis dramatically increases the barrier to atropinterconversion and, as such, the two conformations can be separated via fractional crystallisation. The corresponding energy barrier for H_2-CATPHOS is only 23 kJ/mol^{-1} which is easily overcome at ambient temperature, resulting in rapid interconversion between the two conformations and, as such, they cannot be resolved. Consequently *rac*-Me_2-CATPHOS oxide **2.18b** was resolved by fractional crystallisation of the diastereoisomeric complexes formed with (2*R*, 3*R*)-(-)-2,3-O-dibenzoyl-tartaric acid. As illustrated in Equation 2.4 by following the protocol developed by Noyori,[29] *rac*-Me_2-CATPHOS was dissolved in the minimum amount of hot chloroform and to this was added a solution of (+)-DBTA in ethyl acetate. The mixture was refluxed for 15 min and allowed to cool overnight, after which the corresponding ®-Me_2-CATPHOS.(+)-DBTA diastereoisomer precipitated out as a white solid.[28] The diastereoisomer was liberated from the corresponding (+)-DBTA to afford the enantiopure ®-Me_2-CATPHOS. Reoxidation of ®-Me_2-CATPHOS **2.19b** and analysis with chiral HPLC by comparison with racemic sample revealed that the stereochemical integrity of the 1,3-butadiyne C_4 tether remains intact after the reduction at high temperature for a prolonged period.



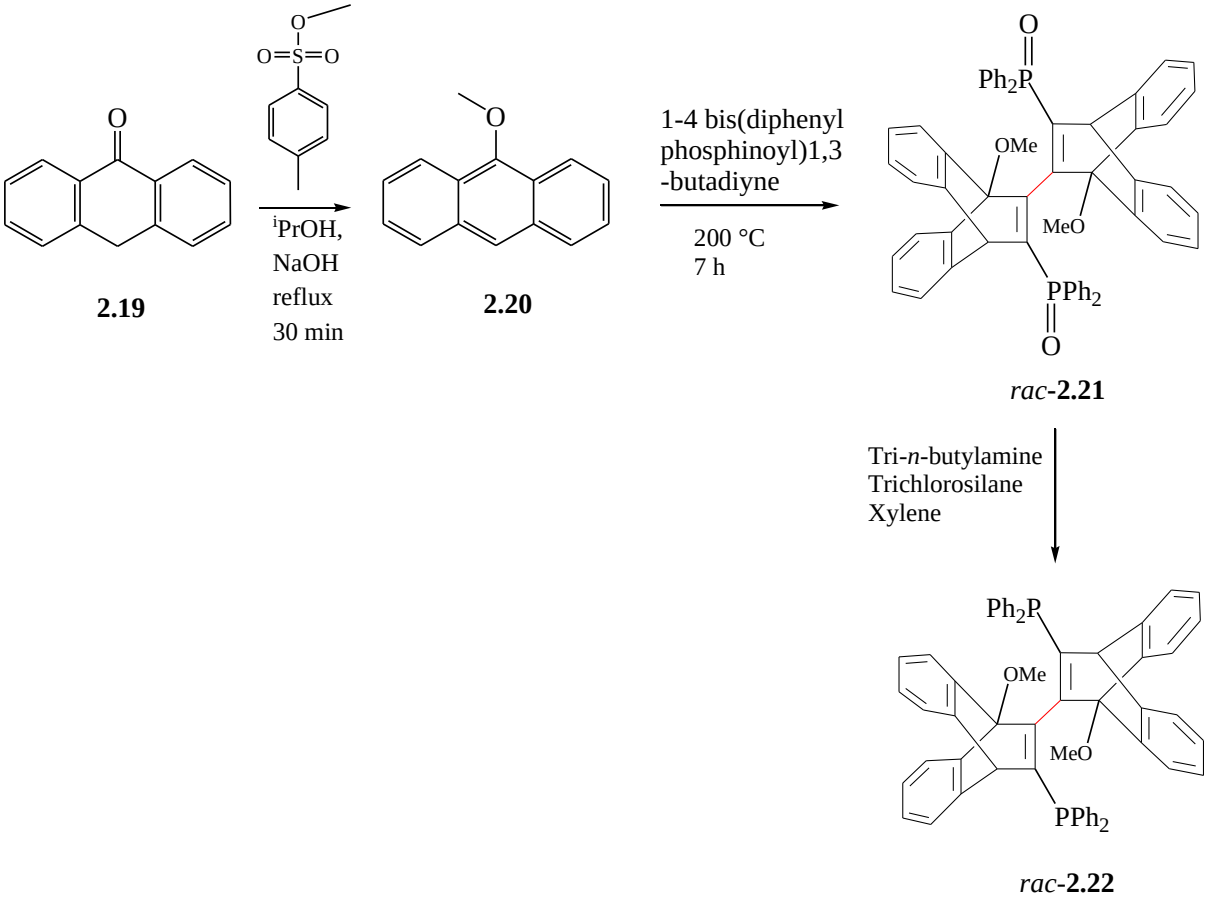
rac-**2.18b** (+)-**2.18b**

Equation 2.4

2.2.1 Synthesis of $(MeO)_2$-CATPHOS

The synthesis of *rac*-$(MeO)_2$-CATPHOS **2.22** is outlined in Scheme 2.3. It follows the same 3-step procedure that was previously used to prepare Me_2-CATPHOS (scheme 2.3). Initially 9-methoxyanthracene **2.20** was synthesised through reaction of anthrone **2.19** with methylating agent methyl-*p*-toluenesulfonate in the presence of isopropanol/sodium hydroxide solution under reflux for 30 mins where the reaction reached completion with near-quantitative yield. Subsequently **2.20** was mixed with 1,4-bis(diphenylphosphinoyl)-

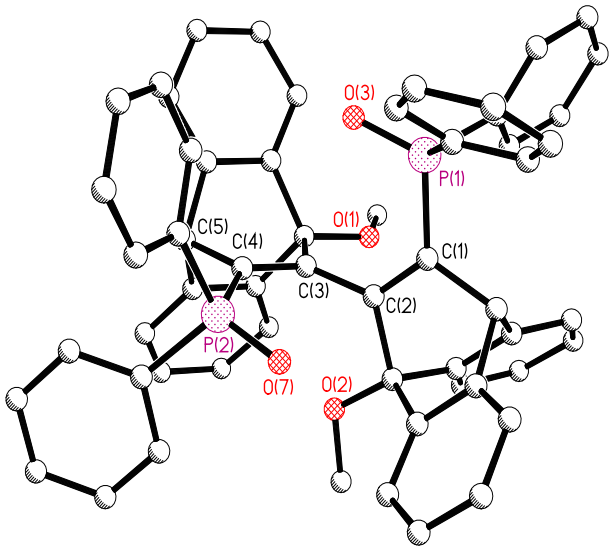
1,3-butadiyne and heated to 220 °C in a Woods metal bath and allowed to stir for 5 mins to form a golden-brown molten mixture, after which the temperature was reduced to 200 °C and stirring continued for 7 h to afford *rac*-$(MeO)_2$-CATPHOS oxide **2.21** as a golden-coloured powder in 55% yield; *rac*-$(MeO)_2$-CATPHOS oxide **2.21** was subsequently reduced in the same way as outlined with *rac*-Me_2-CATPHOS oxide (Scheme 2.3) by dissolving in xylene in the presence of both trichlorosilane and tri-*n*-butylamine and heating at 130 °C for 72 h to afford *rac*-$(MeO)_2$-CATPHOS **2.22** in 60% yield.



Scheme 2.3

The crystal structure of *rac*-$(MeO)_2$-CATPHOS oxide **2.21** is shown in Figure 2.2. The two biaryl moieties are connected by the 4-carbon tether. The two methoxy groups are depicted via O(1) and O(2) atoms with the corresponding P=O linkage denoted as P(2)-O(7) and P(1)-O(3), respectively. The C(2)-C(3) bond length, which binds the two biaryl-like moieties together, is 1.477(3) Å.

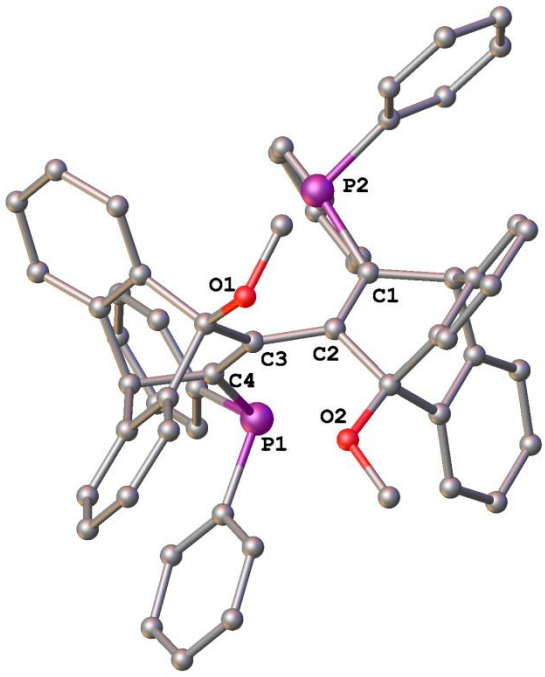
Figure 2.2. Crystallographically Independent Molecule of *rac*-$(MeO)_2$-CATPHOS Oxide (**2.21**).



The crystal structure of *rac*-$(MeO)_2$-CATPHOS is shown in Figure 2.3. The C(1)-C(2) and C(3)-C(4) bond lengths are 1.340(2) Å and 1.339(2), respectively, consistent with that of a double bond. Also they are same as the corresponding values for *rac*-$(MeO)_2$-CATPHOS oxide (Figure 2.2, 1.340(2) Å and 1.339(2) Å, respectively) and are comparable to the corresponding value for H_2-CATPHOS (1.354(5) Å). The C(2)-C(3) bond length of 1).476(2) Å, which connects the two biaryl moieties together, is the same as the respective bond length for *rac*-$(MeO)_2$-CATPHOS oxide (1.476(2) Å) and is also comparable to that of 1.460(4) Å for H_2-CATPHOS.[16] These values, together with the crystal structure of *rac*-$(MeO)_2$-CATPHOS, shows that the biaryl-like *rac*-$(MeO)_2$-CATPHOS has retained its structural integrity even after the harsh reduction conditions where the oxide counterpart was heated at 130 °C for 72 h, which demonstrates the viability of this straightforward 3-step synthesis method for formation of a range of CATPHOS analogues.

It is also noteworthy that the C(1)-P(2) and C(4)-P(1) bond length of 1.820(16) Å and 1.824(16) Å, respectively, for *rac*-$(MeO)_2$-CATPHOS are significantly longer than the respective bonds of 1.797(2) and 1.789(2) for *rac*-$(MeO)_2$-CATPHOS oxide (Figure 2.2).

Figure 2.3. Crystallographically Independent Molecule of *rac*-$(MeO)_2$-CATPHOS (**2.22**)



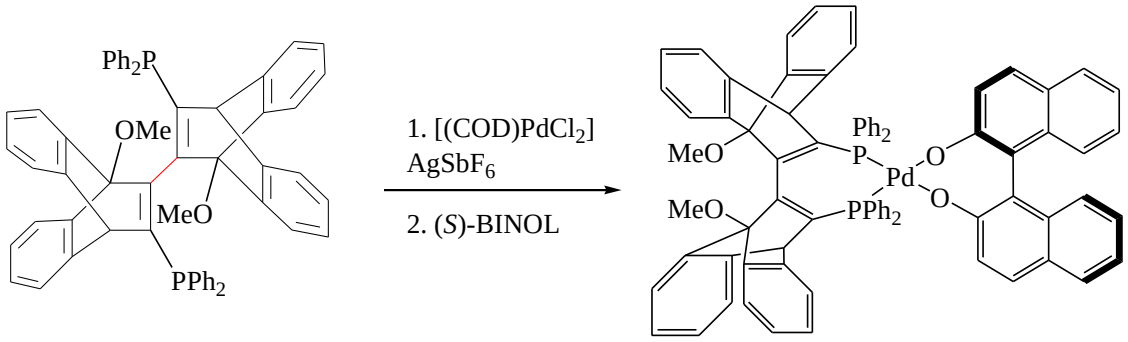
2.2.1.1 Attempted Resolution

The presence of a bridgehead methoxy group increases the energy barrier to atropinterconversion between the two conformation, as previously demonstrated with Me_2-CATPHOS,[16] thus rendering $(MeO)_2$-CATPHOS axially chiral. Initially we attempted to separate the enantiomers by co-crystallisation with (+)-DBTA, as previously carried out with Me_2-CATPHOS (Eq. 2.5).[29] NMR analysis shows the presence of two phosphorus signals, indicative of a diastereoisomeric mixture. However despite using various solvent systems, the two diastereoisomers could not be separated via fractional crystallization.

Subsequently, we attempted to separate the two enantiomers of *rac*-MeO-CATOHOS by coordination to chiral metal complexes. It has already been shown that conformationally flexible diphosphines that undergo rapid atropisomerism can infact be used in asymmetric transformations by on-metal resolution.[30] This was demonstrated by Michael Gagne and Doherty and colleagues with the conformationally flexible NUPHOS diphosphines.[31] Herein a metal centre, bearing a chiral entity such as (*S*)-BINOL, coordinates with *rac*-$(MeO)_2$-CATPHOS to form a mixture of two diastereoisomers which were separated via fractional crystallization. In the aforementioned publication, the diastereo-interconversion between the various chiral [(NUPHOS)Pt{(*S*)-BINOL}] complexes was thoroughly studied and, amongst other findings, it was demonstrated via kinetic studies that

substitution of (*S*)-BINOL with (*S*,*S*)-DPEN results in marked reduction in the energy barrier to atropinversion thus diastereoisomers were successfully separated by fractional crystallization. We sought to exploit the latter point in our attempts to separate *rac*-$(MeO)_2$-CATPHOS into its respective enantiomers.

Initially *rac*-$(MeO)_2$-CATPHOS was reacted with $[Pd(COD)Cl_2]$ in dichloromethane to afford [{(*rac*-$(MeO)_2$-CATPHOS)}$PdCl_2$]. Without extraction, it was treated with a solution of 50% (*S*)-BINOL and potassium-*tert*-butoxide resulting in a palladium complex [{(*S*)-**2.22**}-Pd-{(*S*)-BINOL}] and [{(*R*)-$(MeO)_2$-CATPHOS)}$PdCl_2$]; ^{31}P NMR showed the presence of two new peaks at δ 18.33 and δ 13.05, indicating the presence of diastereoisomers in the product mixture. Despite several attempts at fractional crystallization with various solvent systems, the chiral palladium complex could not be separated from the product mixture.

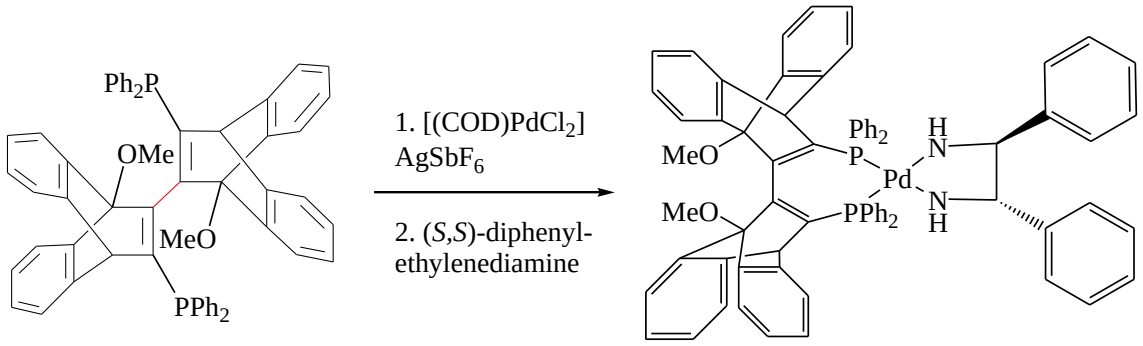


rac-**2.22**

[{(*S*)-**2.22**}-Pd-{(*S*)-BINOL}]

Equation 2.5

Given that the previous publication has shown the use of a different chiral entity can affect the energy barrier to atropisomerism as well as the solubility of the respective diastereoisomers,[31] we employed (1*S*,2*S*)-diphenylethylenediamine to form [{(*S*)-**2.22**}-Pd-{(1*S*, 2*S*)-diphenylethylenediamine}] (Equation 2.6). Initially *rac*-$(MeO)_2$-CATPHOS was reacted with $[(COD)PdCl_2]$ in DCM for 4 h. Given previous examples, we reasoned that[{*rac*-$(MeO)_2$-CATPHOS}$PdCl_2$] is formed after this step. Without isolation, $AgSbF_6$ was added (halogen abstraction) and the solution was reacted with (1*S*, *2S*)-diphenylethylenediamine afforded the [{(*S*)-$(MeO)_2$-CATPHOS}-Pd-{(1*S*, 2*S*)-diphenylethylenediamine}]. The ^{31}P NMR showed two diastereoisomers at 15.59 and 15.41 ppm to account for the two diastereoisomers. However, despite numerous attempts at fractional crystallisations with various solvent systems, the diastereoisomers could not be separated from each other.



rac-**2.22**

[{(*S*,*S*)-**2.22**}-Pd-{(1*S*,2*S*)-diphenylethylenediamine}]

Equation 2.6

2.3 Conclusions

A straightforward, cost-effective 3-step synthesis of a novel biaryl-like class of diphosphine, R_2-CATPHOS has been developed; H_2-CATPHOS is a tropos diphosphine and could not be resolved due to the low energy barrier to atropinterconversion between the two enantiomeric conformations. Addition of methyl groups (Me_2-CATPHOS) to the bridgehead carbon atoms increased the barrier to atropinterconversion and, as such, the chiral conformations of *rac*-Me_2-CATPHOS could be resolved. We have further demonstrated the viability of this methodology by synthesising *rac*-$(MeO)_2$-CATPHOS. Although our attempts to resolve *rac*-$(MeO)_2$-CATPHOS have not been successful to date, we have extended the viability of the 3-step synthesis with a bulkier bridgehead group. Given the proximity of the bridgehead group to the phosphorus-metal reaction site, we propose that different R_2-CATPHOS analogues will have different reactivity and, as such, we will evaluate the efficacy of R_2-CATPHOS ligands in various palladium-catalysed C-C and C-N bond forming transformations.

2.4 Experimental

General Comments. All manipulations involving air-sensitive materials were carried out using standard schlenk line techniques under an atmosphere of nitrogen or argon in oven-dried glassware. Dichloromethane was distilled from calcium hydride, diethyl ether from Na/K alloy, dioxane from sodium, THF from sodium/benzophenone and toluene from wired sodium. ^{1}H and ^{13}C NMR spectra were recorded on a JOEL ECS-400 instrument. Optical rotations were measured on an Optical Activity PolAAr 2001 digital polarimeter with a sodium lamp and are reported as follows: $[\alpha]_D^{20}$ (*c* g/100 mL, solvent). 1,4-Bis(trimethylsilyl)-1,3-butadiyne, anthracene, 9-methylanthracene, anthrone, (1*S*,2*S*)-diphenylethylenediamine, (*S*)-BINOL and trichlorosilane were purchased from commercial suppliers and used without further purification. Thin layer chromatography (TLC) was carried out on aluminium sheets pre-coated with silica gel 60F 254 and analytical high performance liquid chromatography (HPLC) was performed on an Agilent 110 Series HPLC equipped with a variable Wavelength detector using a Chiralpak AD-H column. The enantiomeric excess was calculated from the HPLC profile (Diacel Chiracel OJ, flow rate: 1 mL/min flow rate, hexane: 2-propanol = 90:10). Diels-Alder cycloaddition was carried out in Woods metal bath at 200 °C.

Synthesis of 1,4-bis(diphenylphosphine)-1,3-butadiyne (2.16). A solution of MeLi-LiBr (38.7 mL, 58.0 mmol) was added drop wise to a solution of bis(trimethylsilyl)-1,3-butadiyne (5.0 g, 25.8 mmol) in THF (29 mL) and allowed to stir at room temperature overnight. The resulting white precipitate was transferred drop wise to a solution of chlorodiphenyl phosphine (11.0 mL, 61.9 mmol) in ether (37 mL) at -40 °C and allowed to stir for 10 min. The reaction is warmed to room temperature and solution allowed to stir for a further 30 mins. At the end of this period, the dark brown solution was diluted with ether (15 mL), and washed with saturated aqueous NH_4Cl (5 x 60 mL). The aqueous phase was back extracted with ether, organic layers combined, dried over $MgSO_4$, filtered and solvent removed under reduced pressure to afford a dark brown solid. The solid was washed with methanol in a sinter funnel to remove soluble impurities and allowed to dry, affording a cream-coloured solid which was used without further purification (8.61 g, 80% yield). $^{31}P\{^{1}H\}$ NMR (400 MHz, $CDCl_3$, δ); -30.2 (s, PPh_2).

Synthesis 1,4-bis(diphenylphosphinoyl)1,3-butadiyne (2.17). 1,4-Bis(diphenylphosphine)-1,3-butadiyne (14.2 g, 34.0 mmol) was dissolved in $CHCl_3$ (170 mL) and H_2O_2 (8.4 mL, 85.1 mmol) was added in one portion. The solution was refluxed at 65 °C for 30 mins. At end of reaction period, the solution was allowed to cool to room

temperature and washed with water (5 x 30 mL). The aqueous layer was washed with $CHCl_3$ ((3 x 20 mL), organic layers separated, combined and dried over $MgSO_4$, filtered through celite and the solvent removed under reduced pressure to afford a pale brown solid. The crude solid was purified by column chromatography packed with silica (ethyl acetate/dichloromethane, 1:1 v/v) to afford the diphosphine oxide adduct in (7.95 g, 52%). ^{31}P {^1H} NMR (400 MHz, $CDCl_3$, δ); 9.89 (s, O=PPh_2); ^1H NMR (300 MHz, $CDCl_3$, δ); 7.78-7.61 (m, 8H, Ar-*H*), 7.57-7.47 (m, 4H, Ar-*H*), 7.46-7.32 (m, 8H, Ar-*H*); ^{13}C {^1H} NMR (300.0 MHz, $CDCl_3$, δ); 131.2 (C_6H_5), 131.1 (C_6H_5), 129.1 (C_6H_5), 129.0 (C_6H_5), 79.7 ($Ph_2PC{\equiv}C$), 77.2 ($Ph_2PC{\equiv}C$); LRMS (EI) $[M]^+$ *m/z* 282.

***Rac*-12,12'-Bis(diphenylphosphino)-9,9'-dimethyl-10,10'-dihydro-11,11'-bi-9,10-ethenoanthracene oxide (2.18b)**. This reaction was carried out without any solvent. 1,4-Bis(diphenylphosphinoyl)-1,3-butadiyne (5.0 g, 11.1 mmol) and 9-methylanthracene (4.7 g, 24.4 mmol) were mixed together. The solid mixture was gradually heated to 220 °C in a Woods metal bath and allowed to stir for 5 min. Subsequently, the temperature was lowered to 200 °C and stirring continued for a further 30 mins. The progress of the reaction was monitored by ^{31}P NMR analysis. At end of reaction period, the solid crude product was allowed to cool to room temperature and dissolved in minimum amount of dichloromethane. The crude product was purified by silica column chromatography. Initially the column was run with neat dichloromethane to remove excess 9-methylanthracene and the product was separated from impurities using dichloromethane/ethyl acetate mixture as eluant (3:1 v/v) to afford **2.18b** as white solid (6.02 g, 65%). ^{31}P {^1H} NMR (400 MHz, $CDCl_3$, δ); 24.3 (s, PPh_2). HPLC column conditions: chiral OJ (hexane/propanol, 9:1, 1 mL per min); t_R = 6.25, t_R = 8.57 min.

Rac-12,12'-Bis(diphenylphosphino)-9,9'-dimethyl-10,10'-dihydro-11,11'-bi-9,10-ethenoanthracene (*rac*-2.19b). A flame-dried schlenk was charged with *rac*-Me_2-CATPHOS oxide (1.9 g, 2.4 mmol), xylene (160 mL), and tri-*n*-butylamine (5.7 mL, 23.8 mmol). Trichlorosilane (12.9 g, 95.2 mmol) was added slowly to the reaction flask, after which the flask was tightly sealed and mixture was heated under reflux at 130 °C under vigorous stirring for 72 h. At the end of reaction period, a light yellow solution evolved. The reaction flask was cooled to 0 °C in an ice bath. The reaction flask was diluted with dichloromethane (120 mL) and transferred slowly via cannula to a 3-neck flask containing a solution of sodium hydroxide (180 mL) and ice (60 g), under vigorous stirring. Effervescence was observed with a white cloud forming over the reaction mixture. After addition was complete, the flask was sealed and the solution was stirred vigorously for 1 h

at room temperature. The organic layer was separated and the aqueous phase extracted with dichloromethane (3 x 120 mL), the organic fractions combined, washed with saturated $NaHCO_3$ (3 x 60 mL), water (3 x 60 mL), and brine (3 x 60 mL), dried over $MgSO_4$, filtered and solvent removed *in vacuo*. Xylene was removed on schlenk line via a distillation trap. The remaining yellow solid was triturated with hexane (3 x 50 mL) to remove the excess tri-*n*-butylamine to afford a white solid. The product was recrystallised by dissolving in the minimum amount of chloroform layered with a slight excess of methanol (1.0 g, 55%). ^{31}P {^{1}H} NMR (400 MHz, $CDCl_3$, δ); -13.9 (s, PPh_2); ^{1}H NMR (300 MHz, $CDCl_3$, δ); 7.40-7.37 (m, 2H, C_6H_5 *p*-H), 7.36 (t, *J* = 7.4 Hz, 4H, C_6H_5 *m*-H), 7.28 (t, *J* = 6.7 Hz, 4H, C_6H_5 *o*-H), 7.24 (d, *J* = 7.9 Hz, 2H, C_6H_4), 7.17-7.14 (m, 4H, C_6H_4, and C_6H_5 *p*-H), 7.12 (t, *J* = 7.5 Hz, 4H, C_6H_5 *m*-H), 7.01-6.97 (m, 4H, C_6H_4), 6.98-6.94 (m, 4H, C_6H_5, *o*-H), 6.81 (t, *J* = 7.0 Hz, 2H, C_6H_4), 6.75 (t, *J* = 7.4 Hz, 2H, C_6H_4), 6.54 (d, *J* = 7.0 Hz, 2H, C_6H_4), 6.45 (d, *J* = 7.4, 2H, C_6H_4), 4.98 (s, 2H, bridgehead C*H*), 1.34 (s, 6H, CH_3); ^{13}C {^{1}H} NMR (300 MHz, $CDCl_3$, δ); 164.0 (m, *C*=CP), 148.2 (C_6H_4), 146.7 (C_6H_4), 146.5 (C_6H_4), 146.4 (C_6H_4), 143.1 (C_6H_5), 138.2 (m, C_6H_5), 136.9 (m, C=*C*P), 134.4 (m, C_6H_5, *o*-C), 132.6 (m, C_6H_5 *o*-C), 128.6 (C_6H_5 *p*-C), 128.1 (m, C_6H_5 *m*-C), 127.9 (m, C_6H_5 *m*-C), 127.4 (C_6H_5, *p*-C), 124.4 (C_6H_4), 124.3 (C_6H_4), 123.9 (C_6H_4), 123.7 (C_6H_4), 123.0 (C_6H_4), 122.8 (C_6H_4), 121.4 (C_6H_4), 120.7 (C_6H_4), 55.0 (bridgehead), 54.9 (t, *J* = 4.0 Hz, bridgehead *C*H), 14.2 (*C*H_3). Anal Calcd for $C_{58}H_{44}P_2$: C, 86.76; H, 5.52. Found C, 86.94, H, 5.71; HRMS (EI) exact mass calculated for $C_{58}H_{44}P_2$ $[M]^+$ requires *m/z* 802.2918, found *m/z* 802.2938.

Resolution of *rac*-12,12'-Bis(diphenylphosphino)-9,9'-dimethyl-10,10'-dihydro-11,11'-bi-9,10-ethenoanthracene oxide ((*S*)-2.18b). *Rac*-Me_2-CATPHOS-oxide (0.9 g, 1.1 mmol) was dissolved in warm chloroform (45 mL). A solution of (-)-DBTA (0.5 g, 1.1 mmol) in ethyl acetate (10 mL) was added and the resulting solution was refluxed for 10 min. The solution was allowed to cool at room temperature overnight, after which a white solid had precipitated. The white solid was isolated and dried (filtrate, which contained (*R*)-enantiomer and (-)-DBTA diastereoisomer was retained); optical rotation of white solid +25.5 (*c* = 0.5 in acetone). The white solid was recrystallised overnight. The crystals were isolated, washed with hexane and thoroughly dried. A similar optical rotation value of +26.1 (*c* = 0.5 in acetone) was obtained. In order to liberate the (*S*)-enantiomer from the (-)-DBTA, the optically pure white solid was dissolved in dichloromethane and 20% aqueous NaOH with vigorous stirring at room temperature for 1 h. Then aqueous NaOH (40 mL) was added, the organic layer was removed and the resulting aqueous layer extracted with dichloromethane. The organic layers were combined, washed with aqueous

NaOH, water, brine and finally dried over $MgSO_4$. The solvent was removed *in vacuo* to afford optically pure (*S*)-Me_2-CATPHOS. The combined mother liquor was washed with aqueous NaOH, and the recrystallisation process was repeated with (+)-DBTA to afford the (*R*)-Me_2-CATPHOS as optically pure white solid. HPLC column conditions: chiral OJ (hexane/propanol, 9:1, 1 mL per min); (*S*)-enantiomer t_R = 8.40 min.

Reduction to form (*S*)-12,12'-Bis(diphenylphosphinoyl)-9,9'-dimethyl-10,10'-dihydro-11,11'-bi-9,10-ethenoanthracene ((*S*)-2.19b). A flame dried pressure flask was charged with (*S*)-Me_2-CATPHOS oxide (1.9 g, 2.3 mmol), xylenes (160 mL), and tri-*n*-butylamine (5.7 mL, 23.8 mmol). Trichlorosilane (12.9 g, 95.2 mmol) was added drop wise to the resulting solution, then flask was tightly sealed and reaction mixture heated at 130 °C for 72 h. At the end of reaction period, reaction flask was cooled to 0 °C, and the reaction mixture was diluted with dichloromethane, ice and 20% aqueous sodium hydroxide was added slowly under vigorous stirring. The reaction was allowed to stir at r/t for 1 h, organic layer was removed and the remaining aqueous layer was extracted with dichloromethane. All the organic fractions were combined, washed with $NaHCO_3$, water, brine, dried over $MgSO_4$, filtered and solvent removed *in vacuo*. Finally the product was washed with hexane to remove excess tri-*n*-butylamine. Finally the enantiopure (*S*)-Me_2-CATPHOS white solid was recrystallised by slow diffusion of a chloroform solution layered with methanol at room temperature (1.1 g, 60%). $[\alpha]_D$ = -97.5 (*S*)-enantiomer, +97.7 (*R*)-enantiomer (*c* = 1.0, CH_2Cl_2); ^{31}P {^1H} NMR (400 MHz, $CDCl_3$, δ); -13.9 (s, PPh_2); ^1H NMR (300 MHz, $CDCl_3$, δ); 7.40-7.38 (m, 2H, C_6H_5 *p*-H), 7.36 (t, *J* = 7.4 Hz, 4H, C_6H_5 *m*-H), 7.28 (t, *J* = 6.7 Hz, 4H, C_6H_5 *o*-H), 7.24 (d, *J* = 7.9 Hz, 2H, C_6H_4), 7.17-7.13 (m, 4H, C_6H_4, and C_6H_5 *p*-H), 7.12 (t, *J* = 7.5 Hz, 4H, C_6H_5 *m*-H), 7.01-6.97 (m, 4H, C_6H_4), 6.98-6.94 (m, 4H, C_6H_5, *o*-H), 6.81 (t, *J* = 7.0 Hz, 2H, C_6H_4), 6.75 (t, *J* = 7.4 Hz, 2H, C_6H_4),6.54 (d, *J* = 7.0 Hz, 2H, C_6H_4), 6.45 (d, *J* = 7.4, 2H, C_6H_4), 4.98 (s, 2H, bridgehead C*H*), 1.34 (s, 6H, CH_3); ^{13}C {^1H} NMR (300 MHz, $CDCl_3$, δ); 164.0 (m, *C*=CP), 148.2 (C_6H_4), 146.7 (C_6H_4), 146.5 (C_6H_4), 146.4 (C_6H_4), 143.1 (C_6H_5), 138.2 (m, C_6H_5), 136.9 (m, C=*C*P), 134.4 (m, C_6H_5, *o*-C), 132.6 (m, C_6H_5 *o*-C), 128.6 (C_6H_5 *p*-C), 128.1 (m, C_6H_5 *m*-C), 127.9 (m, C_6H_5 *m*-C), 127.4 (C_6H_5, *p*-C), 124.4 (C_6H_4), 124.3 (C_6H_4), 123.9 (C_6H_4), 123.7 (C_6H_4), 123.0 (C_6H_4), 122.8 (C_6H_4), 121.4 (C_6H_4), 120.7 (C_6H_4), 55.0 (bridgehead), 54.9 (t, *J* = 4.0 Hz, bridgehead *C*H), 14.2 (*C*H_3); Anal Calcd for $C_{58}H_{44}P_2$: C, 86.76; H, 5.52. Found C, 86.94, H, 5.71; HRMS (EI) exact mass calculated for $C_{58}H_{44}P_2$ $[M]^+$ requires *m/z* 802.2918, found *m/z* 802.2938.

12,12'-Bis(diphenylphosphino)-9,9',10,10'-dihydro-11,11'-bi-9,10-ethenoanthracene oxide (2.18a). 1,4-Bis(diphenylphosphenoyl)-1,3-butadiyne (4.7 g, 10.4 mmol) and anthracene (5.5 g, 31.1 mmol) were charged in a flask, mixed together and heated gradually to 220 °C using a Woods metal bath. The molten mixture was stirred for 5 mins before temperature was lowered to 200 °C and stirring continued for a further 30 mins. The progress of reaction was monitored with ^{31}P NMR analysis. The product was purified on column chromatography eluting with chloroform/acetone (1:0 then 6:1) to afford a white solid (6.53 g, 78%). ^{31}P {^{1}H} NMR (400 MHz, $CDCl_3$, δ): 26.2 (PPh_2)

Synthesis of 9,9',10,10'-tetrahydro-9,10,9',10'-biethenobianthracene-11,11'-bis-(diphenylphosphanyl)-12,12'diyl (2.19a). A flame-dried schlenk was charged with H_2-CATPHOS oxide (6.4 g, 7.9 mmol), THF (100 mL), toluene (100 mL), and triethylphosphite (13.5 mL, 78.8 mmol). Trichlorosilane (24 mL, 0.236 mmol) was added slowly and the mixture heated at 40 °C for 16 h. The reaction mixture was diluted with diethyl ether (100 mL) and added slowly to a mixture of ice (80.0 mg) and 20% aqueous NaOH (280 mL). After stirring vigorously at room temperature for 1 h, the mixture was filtered through celite, the organic layer removed and the aqueous phase extracted with diethyl ether (3 x 30 mL). The organic fractions were combined, dried over $MgSO_4$, filtered and finally the solvent removed *in vacuo* to afford H_2-CATPHOS as a spectroscopically pure white powder. The white solid was recrystallised by slow diffusion of a chloroform solution layered with methanol at room temperature (5.26 g, 85%). ^{31}P {^{1}H} NMR (400 MHz, $CDCl_3$, δ): -15.9 (s, PPh_2); ^{1}H NMR (300 MHz , $CDCl_3$, δ); 7.24-7.19 (m, 4H, C_6H_5) *p*-H), 7.20 (t, *J* = 7.4 Hz, 8H, C_6H_5 *m*-H), 7.15 (br s, 4H, C_6H_4), 7.07-7.02 (m, 8H, C_6H_5 *o*-H), 6.93 (t, *J* = 7.2 Hz, 4H, C_6H_4), 6.90 (t, *J* = 7.2 Hz, 4H, C_6H_4), 6.83 (d, *J* = 7.1 Hz, 4H, C_6H_4), 5.03 (s, 2H, bridgehead C*H*), 4.94 (s, 2H, bridgehead C*H*); ^{13}C {^{1}H} NMR (300 MHz, $CDCl_3$, δ), 161.0 (m, *C*=CP), 145.8 (C_6H_4), 144.4 (C_6H_4), 141.7 (m, C=*C*P), 136.9 (m, C_6H_5), 133.2 (m, C_6H_5 o-C), 127.8 (t, *J* = 3.0 Hz, C_6H_5, m-C), 127.9 (C_6H_5 p-C), 124.5 (C_6H_4), 124.3 (C_6H_4), 123.0 (C_6H_4), 122.9 (C_6H_4), 56.5 (t, *J* = 3.9 Hz, bridgehead *C*H), 54.7 (t, *J* = 3.2 Hz, bridgehead *C*H), Anal Calc for $C_{56}H_{40}P_2$: C, 86.80; H, 5.20. Found: C, 87.01; H, 5.56; HRMS (EI) exact mass calculated for $C_{56}H_{41}P_2$ $[M+H]^+$ requires *m/z* 775.2684, found *m/z* 775.2679.

Synthesis of 9-methoxyanthracene (2.20). To a solution of anthrone (2.6 g, 13.4 mmol), isopropanol (80 mL) and aqueous NaOH (120 mL) was added methyl-toluene sulfonate (12.4 g, 66.8 mmol) in small portions. The resulting solution was heated under reflux for 30 mins. The reaction mixture was diluted with distilled water (150 mL) and the resulting

gold-coloured precipitate was allowed to cool to room temperature. The precipitate was separated, and recrystallized with hot methanol to afford high purity 9-methoxyanthracene (2.51 g, 90%).[32] ^{1}H NMR (300 MHz, $CDCl_3$, δ); 8.23-8.17 (m, 2H, C_6H_4), 8.10 (s, 1H, Ar-*H*), 7.85 (d, *J* = 8.31 Hz, 2H, C_6H_4), 7.43-7.31 (m, 4H, C_6H_4), 4.02 (s, 3H, OCH_3); ^{13}C {^{1}H} NMR (300.0 MHz, $CDCl_3$, δ); 152.2 (C_6H_1), 134.0 (C_6H_1), 132.4 (C_6H_4), 128.4 (C_6H_4), 127.2 (C_6H_4), 125.8 (C_6H_4), 124.7 (C_6H_4), 122.2 (C_6H_1), 63.1 (OCH_3); LRMS (EI) $[M]^+$ *m/z* 208.

Rac-12,12'-Bis(diphenylphosphino)-9,9'-dimethoxy-10,10'-dihydro-11,11'-bi-9,10-ethenoanthracene oxide (*rac*-2.21). This Diels-Alder reaction was carried out without solvent. 1,4-Bis(diphenylphosphino)-1,3-butadiyne (0.5 g, 1.2 mmol) and 9-methylanthracene (0.5 g, 2.5 mmol) were mixed together. The solid mixture was gradually heated to 220 °C in a Woods metal bath and allowed to stir for 5 min. Subsequently the temperature was lowered to 200 °C and stirring continued for 7 h. The progress of the reaction was monitored by ^{31}P NMR spectroscopy. At end of reaction period, the solid crude product was allowed to cool to room temperature and dissolved in minimum amount of dichloromethane. The crude product was purified by column chromatography. Initially the column was eluted with neat dichloromethane in order to remove the excess 9-methoxyanthracene then product separated using dichloromethane/ethyl acetate (2:1 v/v) as eluant to afford product as a light yellow powder (0.58 g, 60%). ^{31}P {^{1}H} NMR (400 MHz, $CDCl_3$, δ); 25.7 (s, PPh_2).

Rac-12,12'-Bis(diphenylphosphino)-9,9'-dimethoxy-10,10'-dihydro-11,11'-bi-9,10-ethenoanthracene (*rac*-2.22). A flame-dried Schlenk was charged with *rac*-$(MeO)_2$-CATPHOS oxide (1.1 g, 1.2 mmol), xylene (90 mL), and tri-*n*-butylamine (2.9 mL, 12.4 mmol). Trichlorosilane (5.0 mL, 49.6 mmol) was added slowly to the flask which was then sealed and heated at 130 °C with vigorous stirring for 72 h. At the end of reaction, a light yellow solution evolved. Subsequently the reaction flask was cooled to 0 °C in an ice bath. The reaction flask was diluted with dichloromethane (90 mL) and transferred slowly via cannulae to a 3-neck flask containing a solution of aqueous NaOH (95 mL) and ice (35 g) under vigorous stirring. Heavy effervescence was observed with a white cloud forming over the reaction mixture. The solution was stirred vigorously for 1 h at room temperature. The organic layer was separated and aqueous phase extracted with dichloromethane (3 x 90 mL), organic fractions combined, washed with saturated $NaHCO_3$ (3 x 60 mL), water (3 x 60 mL), and brine (3 x 60 mL), dried over $MgSO_4$, filtered and solvent removed *in vacuo*. Xylene was removed on schlenk line via a distillation trap. Subsequently the yellow solid

was triturated with hexane (3 x 50 mL) to remove the excess ^{n}butylamine to afford a white solid. The product was recrystallized by dissolving in minimum amount of chloroform and layered with slight excess of methanol (0.58 g, 55%). ^{31}P {^{1}H} NMR (400 MHz, $CDCl_3$, δ); -13.7 (s, PPh_2); ^{1}H NMR (300 MHz, $CDCl_3$, δ); 7.58 (d, J = 7.4 Hz, 2H, C_6H_5 *p*-H), 7.36-7.28 (m, 8H, C_6H_5 *m*-H/ *o*-H), 7.24-7.14 (m, 6H, C_6H_4/C_6H_5 *p*-H), 7.12-6.97 (m, 8H, C_6H_4/C_6H_5 *m*-H), 6.98-6.94 (m, 4H, C_6H_5, *o*-H), 6.81-6.75 (m, 4H, C_6H_4**),** 6.90-6.78 (m, 4H, C_6H_4), 6.54-6.45 (m, 4H, C_6H_4), 4.72 (s, 2H, bridgehead C*H*), 3.35 (s, 6H, OCH_3); ^{13}C {^{1}H} NMR (300 MHz, $CDCl_3$, δ); 164.0 (m, *C*=CP), 148.2 (C_6H_4), 146.7 (C_6H_4), 146.5 (C_6H_4), 146.4 (C_6H_4), 143.1 (C_6H_5), 138.2 (m, C_6H_5), 136.9 (m, C=*C*P), 134.4 (m, C_6H_5, *o*-C), 132.6 (m, C_6H_5 *o*-C), 128.6 (C_6H_5 *p*-C), 128.1 (m, C_6H_5 *m*-C), 127.9 (m, C_6H_5 *m*-C), 127.4 (C_6H_5, *p*-C), 124.4 (C_6H_4), 124.3 (C_6H_4), 123.9 (C_6H_4), 123.7 (C_6H_4), 123.0 (C_6H_4), 122.8 (C_6H_4), 121.6 (C_6H_4), 121.2 (C_6H_4), 55.0 (bridgehead), 54.9 (t, J = 4.0 Hz, bridgehead *C*H), 93.3 (O*C*H_3); Anal Calcd for $C_{58}H_{44}P_2O_2$: C, 83.44; H, 5.31. Found C, 83.94, H, 5.71; HRMS (EI) exact mass calculated for $C_{58}H_{44}P_2O_2$ $[M+H]^+$ requires *m/z* 835.2885, found *m/z* 835.2894.

[Pd{(*S*)-2.22}(*S*)-BINOL].[31] A flame-dried schlenk was charged with [$PdCl_2$(Cycloocta-1,5-diene)] (40.8 mg, 0.14 mmol) and dissolved in dichloromethane (4 mL). To this solution was added a solution of *rac*-$(MeO)_2$-CATPHOS (120 mg, 0.14 mmol) in dichloromethane (4 mL). The reaction mixture was stirred rapidly for 4 h at room temperature. After 30 min, a dark brown solution evolved. The reaction mixture was dried *in vacuo*, dissolved in toluene (3 mL) and set to stir at room temperature. A flame-dried schlenk was charged with (*S*)-BINOL (20.6 mg, 0.07 mmol) and THF (4 mL). The solution was transferred slowly to a rapidly stirring solution of freshly sublimed sodium *tert*-butoxide (27.6 mg, 0.29 mmol) in THF (4 mL). The reaction was stirred for 15 min at room temperature. The resulting solution was transferred to the previously prepared solution of [Pd(*rac*-$(MeO)_2$-CATPHOS)Cl_2] in toluene and allowed to stir for 90 min at room temperature. At end of reaction period, the solvent was removed *in vacuo* to afford a dark red solid. The product was extracted with chloroform and filtered to remove sodium chloride. The solvent was removed *in vacuo* and triturated with hexane. The ^{31}P NMR spectra contained two peaks at 18.33 and 13.05 ppm and confirmed the presence of two diastereoisomers in the mixture.[31] Solvent used for attempted fractional crystallisations; DCM/hexane, chloroform/hexane, DCM/methanol, chloroform/methanol, methanol/ethyl acetate, ethyl acetate/petrol, DCM/ethyl acetate, methanol/chloroform. ^{31}P {^{1}H} NMR (400 MHz, $CDCl_3$, δ); 18.33 (s, PPh_2, Pd-(*S*)-BINOL), 13.05 (s, PPh_2, $PdCl_2$). HRMS (EI)

exact mass calculated for $C_{78}H_{58}P_2O_4Pd$ $[M+4H]^+$ requires *m/z* 1231.5690, found *m/z* 1231.5702.

[Pd{(*S*)-2.22}{(1*S*,2*S*)-diphenylethylenediamine}]. A flame-dried Schlenk was charged with [(*rac*-$(MeO)_2$-CATPHOS)$PdCl_2$] (50.0 mg, 49.5 mmol) and dichloromethane (5 mL). To this was added $AgSbF_6$ (34.0 mg, 98.9 mmol) and solution allowed to stir at room temperature for 30 min. Subsequently (1*S*,2*S*)-diphenylethylenediamine (10.52 mg, 24.8 mmol) was added to solution in one portion and solution stirred for 2 h at room temperature. A brown solution evolved. Solvent used for attempted fractional crystallisations: DCM/hexane, DCM/methanol, chloroform/hexane, chloroform/methanol, DCM/ethyl acetate, ethyl acetate/petrol, methanol/chloroform, methanol/ethyl acetate, DCM/acetic nitrile. ^{31}P $\{^1H\}$ NMR (400 MHz, $CDCl_3$, δ); 15.59 (s, PPh_2, Pd-(1*S*, 2*S*)-diphenylethylenediamine), 15.41 (s, PPh_2, $PdCl_2$). HRMS (EI) exact mass calculated for $C_{72}H_{60}P_2O_2N_2Pd$ $[M-H]^+$ requires *m/z* 1151.3106, found *m/z* 1151.3104.

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Chapter 3

Asymmetric Carbonyl-Ene and Friedel–Crafts Reactions

3.1 Introduction

Stereoselective C-C bond forming reactions catalysed by chiral, electrophilic transition-metal Lewis acid complexes have evolved and have now become an essential tool for the synthesis of enantiopure organic molecules.[1] Traditionally, plenty of emphasis has been placed on Lewis acids of the early metals and Cu(II)/Zn(II)-based catalysts [2] rather than examination of group 8-10 metals in Lewis acid catalysis. Lewis acid complexes, such as halides of trivalent boron or aluminium and tetravalent titanium or tin, have been widely used in asymmetric transformations.[3] The focus is now shifting, with more and more research being carried out on group 8-10 metals. In particular, the Group 10 dicationic square planar Lewis acid complexes of palladium(II) and platinum(II) have emerged as very useful catalysts and have featured prominently in asymmetric catalysis over the last decade.[4, 5] In particular, cationic and coordinatively unsaturated square planar platinum group metal complexes of the type $[M(diphosphine)]^{2+}$ (M = Pt, Pd, Ni) have become prominent in asymmetric catalysis and, as such, they have been successfully applied in very common asymmetric transformations such as in Diels-Alder reaction of α, β-unsaturated carbonyl compounds with dienes,[6] ene-type reaction between aldehydes and 1,3-dienes,[7] as well as cycloisomerisations and cyclisations.[8, 9]

Recent research has revealed that transition metals, such as palladium(II) and platinum(II), exhibit Lewis acid character and, as such, have been used in Lewis acid complexes. In general, palladium(II) and platinum(II) Lewis acids hold many advantages over the more traditional Lewis acid complexes in that they are much less sensitive to air and moisture, have much higher functional group tolerance, higher turnover numbers, well defined coordination geometry enabling control of stereochemical environment, high carbophilicity, slow rate of ligand exchange and tunable electronic properties.[3] Furthermore, in a key milestone report, palladium(II) Lewis acid complexes with an atropos diphosphine, such as BINAP, have been found to give excellent yield and enantioselectivity for reaction of N-acryloyloxazolidinone with either cyclopentadiene or cyclohexadiene.[3]

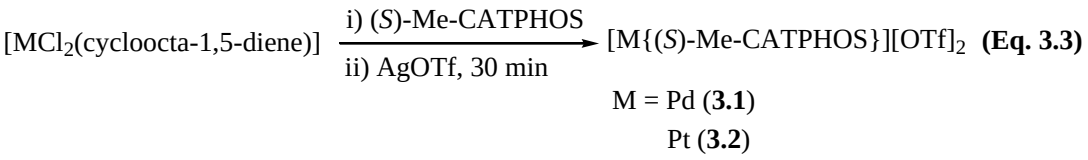
The stereoelectronic properties of palladium(II) and platinum(II) are very different from the early transition metals and first row late metals such as Cu(II) and Zn(II). Consequently, they can affect selectivity and reactivity and can subsequently lead to favourable results such as affording the corresponding products in high enantioselectivity, lowering of reaction temperature and so forth. Furthermore, owing to the softness of the Pd(II) and Pt(II) metal centres, their corresponding Lewis acid complexes have relatively higher carbophilicity and much lower ligand exchange rate (via associative mechanisms) which makes them very favourable catalysts. High carbophilicity, in particular, is a very important feature of Lewis acids and its significance has been clearly demonstrated by Sodeoka and by Jujimura[10-12] in an in-depth report of the reaction mechanisms of $[P_2Pd]^{2+}[A]^-_2$ Lewis acids in the transformations of imine and aldehyde alkylation by Mukaiyama-type nucleophiles. In a mechanistic study for one reaction, it was proposed that the reaction proceeds via an active palladium-enolate intermediate which, after further optimisation, affords a series of ester products in high yields in excess of 75%, with ee values > 80%. Interestingly, it was demonstrated that traces of water in the reaction mixture were necessary for the function of the active catalyst.[10]

Since platinum group metal Lewis acid complexes based on BINAP[5, 13], BIPHEP[14] , MeO-BIPHEP[15] and NUPHOS[16] have proven to be efficient catalysts for the carbonyl-ene transformation, we considered this to be an ideal reaction for a comparative study to evaluate the performance of the platinum group metal complexes of (*S*)-Me_2-CATPHOS against its BINAP counterpart. In this regard, previous studies by the Doherty group have already firmly established that rhodium complexes of enantiopure (*S*)-Me_2-CATPHOS are highly efficient catalysts for the asymmetric hydrogenation of (*E*)-β-aryl-β-(enamido)phosphonates where ee's in excess of 99% have been obtained; the highest reported values for this class of substrates.[17, 18]

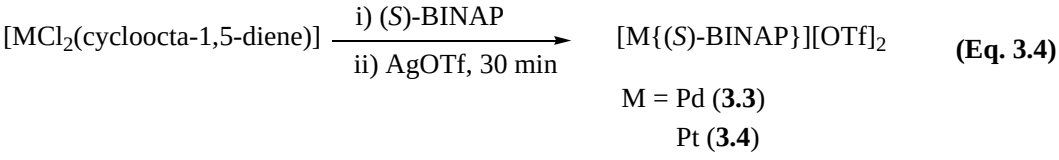
Our in-depth study will employ a host of aromatic and heteroaromatic substrates in conjunction with ethyl trifluoropyruvate as the coupling partner. These reactions will be catalysed by enantiopure platinum(II) and palladium(II) Lewis acid metal complexes. Traditionally speaking, organofluorine compounds play an important role in several science disciplines where the synthesis of fluorine-containing compounds is, on its own, an important field in chemistry.[19] Ethyl trifluoropyruvate is an important source of fluorine and it is been found to have very interesting and diverse physical and biological properties as well as being highly electrophilic, which enhances its carbonyl-ene reactivity.[20] As such we will use the latter as the enophile in our studies.

3.2 Styrene Derivatives

Our study began with the comparison of the performance of Pd/(*S*)-Me_2-CATPHOS, Pd/(*S*)-BINAP and their platinum counterparts. The active catalysts are prepared *in-situ* by the reaction of [MCl_2(cycloocta-1,5-diene)] (M = Pd, Pt) with either (*S*)-Me_2-CATPHOS or (*S*)-BINAP in dichloromethane to generate [MCl_2(diphosphine)] (M = Pd, Pt). Subsequently, the corresponding Lewis acid complexes [M(diphosphine)][OTf]$_2$ (**3.1**-**3.4**) are generated by addition of two equivalents of silver trifluoromethanesulfonate to a dichloromethane solution of [MCl_2(diphosphine)] and stirring for 30 min at room temperature (Eqs. 3.3 and 3.4). Silver hexafluoroantimonate was also used to generate the active Lewis acid [M(diphosphine)][SbF_6]$_2$ (M = Pd, Pt) in the same way. We also found that the isolation of the [MCl_2(diphosphine)] pre-catalyst and its subsequent application to form the active catalyst gives the same final results for the catalysis reactions as well. Subsequently, the alkene and dienophile were added and the progress of the reaction monitored by GC. The reactions were carried out in dichloromethane as the solvent of choice which, according to previous reports and our initial studies, consistently gives the highest ee values compared to other solvents such as THF, toluene, chloroform and 1,2-dichloroethane.



(Eq. 3.3)

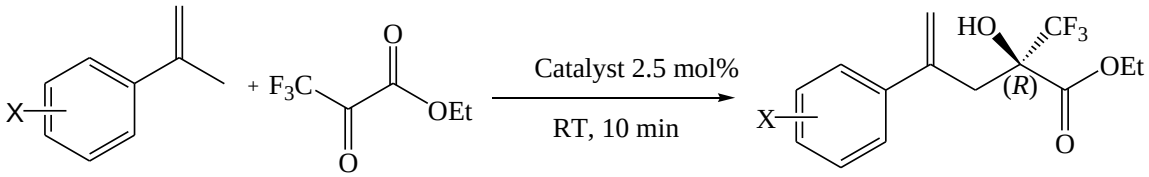


(Eq. 3.4)

Palladium(II) and platinum(II) complexes of C_4-bridged chiral diphosphines, such as BINAP, have been previously applied in carbonyl-ene reaction between styrene derivatives and glyoxylates.[5] The Doherty group has previously demonstrated that both Pd/(*S*)-BINAP and its platinum counterpart successfully form the α-hydroxyesters **3.6a-b** in very high yields and with enantioselectivity in excess of 90%. We sought to evaluate the performance of both Pd/(*S*)-Me_2-CATPHOS and its platinum counterpart with α-methylstyrene derivatives, the results of which are shown in Table 3.1. Initially the ene

reaction between α-methylstyrene and its derivatives and ethyl trifluoropyruvate was catalysed by (*S*)-**3.1** and (*S*)-**3.2** and the performance compared to their respective BINAP counterparts. The corresponding α-hydroxyester **3.6a-c** were all obtained in near-quantitative yields and the absolute configuration was assigned as (*R*) by analogy with the corresponding product obtained from the reaction between methylenecyclohexane and ethyl trifluoropyruvate.[21]

Table 3.1. Asymmetric Carbonyl-ene Reaction between Styrene Derivatives **3.5a-c** and Ethyl Trifluoropyruvate to Form the Corresponding α-Hydroxyesters **3.6a-c**[a].



3.5a-c **3.6a-c**

Entry	X	3.5a-c	Catalyst	% Yield [b,d]	% ee [b,c]
1	H	**3.5a**	(*S*)-**3.1**	93	65
2	H	**3.5a**	(*S*)-**3.2**	97	55
3	H	**3.5a**	(*S*)-**3.3**	98	79
4	H	**3.5a**	(*S*)-**3.4**	93	36
5	4-Cl	**3.5b**	(*S*)-**3.1**	97	38
6	4-Cl	**3.5b**	(*S*)-**3.2**	98	43
7	4-Cl	**3.5b**	(*S*)-**3.3**	91	88
8	4-Cl	**3.5b**	(*S*)-**3.4**	94	58
9	2-Me	**3.5c**	(*S*)-**3.1**	94	50
10	2-Me	**3.5c**	(*S*)-**3.2**	90	20
11	2-Me	**3.5c**	(*S*)-**3.3**	97	82
12	2-Me	**3.5c**	(*S*)-**3.4**	96	31

[a] Reaction conditions: [M(cycloocta-1,5-diene)] (2.5 mol%), (*S*)-Me_2-CATPHOS or (*S*)-BINAP (2.5 mol%), CH_2Cl_2, AgOTf (5 mol%), ethyl trifluoropyruvate (1.5 mol. eq.) and allylbenzene at r/t. [b]Average of three runs. [c] Enantioselectivity calculated by chiral GC using SUPELCO BETA DEX column. [d] Isolated yield

All the reactions shown in Table 3.1 (entries 1-12) gave the products **3.6a-c** in near-quantitative yields with fair to moderate ee's. In all but one of the reactions, the palladium(II) Lewis acids outperform their platinum counterparts with higher ee values. For instance, in the reaction of **3.5c** with ethyl trifluoropyruvate, the corresponding α-hydroxyester product **3.6c** was obtained in 50% ee when catalysed by Pd/(*S*)-Me_2-CATPHOS which compares well against the markedly lower ee of 20% obtained with Pt/(*S*)-Me_2-CATPHOS (entry 9 vs 10). Similarly for the same reaction, Pd/(*S*)-BINAP affords product **3.6c** in 82% ee compared to 31% with Pt/(*S*)-BINAP (entry 11 vs 12).

3.3 Allylbenzene Derivatives

The carbonyl-ene reaction involving allylbenzene and its derivatives is a very straightforward and atom-economic pathway to formation of enantiopure homo-allylic alcohols and, as such, there continues to be huge interest in finding effective reaction protocols for this transformation with, in particular, identification of suitable ligands for chiral Lewis acid metal complexes. However, an in-depth study of this area has not been carried out.

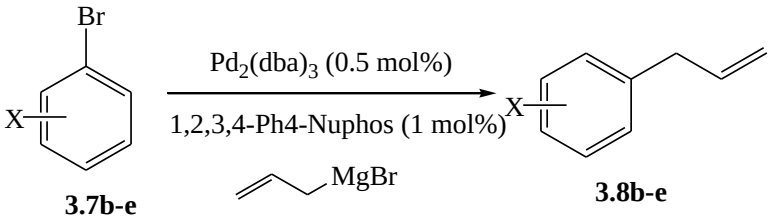
A previous study by the Doherty group has already shown that Pd/(*S*)-BINAP and Pt/(*S*)-BINAP are effective catalysts for the reaction of allylbenzene with ethyl trifluoropyruvate, affording corresponding chiral hydroxyl esters in near quantitative yields with 97% and 99% ee's respectively.[21] Also a 2004 publication has clearly demonstrated that the Lewis acid complex generated from SEGPHOS-$PdCl_2$ also affords the chiral hydroxyl ester in near quantitative yield with 96% ee after only 15 min at room temperature.[22] It is interesting to note that this paper states that the enantioselectivity with methylenecyclohexane is inversely correlated with the dihedral angle of the diphosphine-metal complex where the narrower dihedral angle of the metal complexes induce more effective shielding[44] with the diphenyl groups which, in turn, contributes to give high ee values.

In other reports, ligands such as NU-BIPHEP and BIPHEP have also been successfully used in this reaction to give the corresponding α-hydroxyesters in high yields and high enantioselectivity.[23, 24] However there are drawbacks in these reaction protocols; NU-BIPHEP based reactions were carried out over a relatively long time and BIPHEP based reactions only afford the α-hydroxyester in reasonably high enantioselectivity at low temperature. Consequently, given the general need for an in-depth study of functionalised allylbenzene derivatives with a versatile and effective Lewis acid metal complex at room temperature and the disparate, substrate specific and metal-phosphine dependent performance of styrene derivatives in the carbonyl-ene reaction, we sought further

evaluation of this reaction protocol with the carbonyl-ene reaction, employing a range of allylbenzene derivatives.

Initially a set of allylbenzene derivatives were synthesised, as shown in Table 3.2. Herein, substituted bromobenzene derivatives **3.7b-e** react with allylbromide in the presence of a catalytic amount of 1,2,3,4-Ph4-NUPHOS and $Pd_2(dba)_3$ to form the corresponding allylbenzene derivatives **3.8b-e**.

Table 3.2. Substituted Arylbromides **3.7b-e** React with Allylmagnesium Bromide to Form the Corresponding Substituted Arylbromides **3.8b-e**.[a]



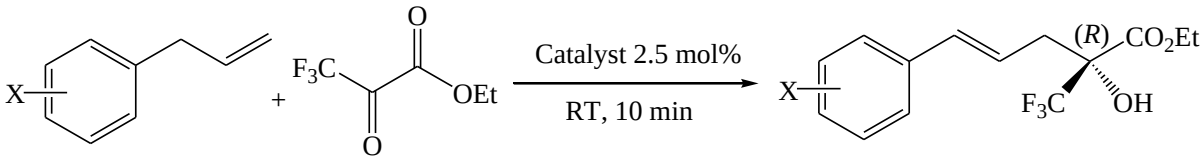
3.7b-e **3.8b-e**

Entry	**1**	X	% Yield **3.8b-e** [b]
1	**b**	4-Me	90
2	**c**	2-Me	78
3	**d**	3,5-Me_2	80
4	**e**	4-Cl	75

[a] Reaction conditions: i) $Pd_2(dba)_3$ (0.5 mol%), 1,2,3,4-Ph_4-Nuphos (1 mol%), dioxane, 10 min, r/t ii) aryl bromide then dropwise addition of allylmagnesium bromide (1.1 mol. eq.) iii) heat 80 °C for 16 h. [b] Isolated yield

The allylbenzene derivatives **3.8a-e** were employed in the carbonyl-ene reaction with a slight excess of ethyl trifluoropyruvate, full details of which are shown in Table 3.3. The absolute configuration of α-hydroxyesters **3.9a-e** were determined to be (*R*) by comparison of the GC retention times and the specific rotations with those already reported in the literature.[30] Furthermore, the sense of asymmetric induction was entirely consistent with the stereochemical model shown in Figure 3.1 which was used to rationalise the stereochemical outcome of the ene reaction between styrene and ethyl trifluoropyruvate.

Table 3.3. Asymmetric Carbonyl-ene Reaction Between Allylbenzene and its Derivatives **3.8a-e** and Ethyl Trifluoropyruvate to Form the Corresponding α-Hydroxyesters **3.9a-e.**[a]



3.8a-e **3.9a-e**

Entry	X	**3.8**	Catalyst	% Yield **3.9a-e**[b,d]	% ee **3.9a-e**[b,c]
1	H	**3.8a**	(*S*)-**3.1**	98	72
2	H	**3.8a**	(*S*)-**3.2**	97	93
3	H	**3.8a**	(*S*)-**3.3**	98	99
4	H	**3.8a**	(*S*)-**3.4**	95	99
5	4-Me	**3.8b**	(*S*)-**3.1**	92	70
6	4-Me	**3.8b**	(*S*)-**3.2**	90	55
7	4-Me	**3.8b**	(*S*)-**3.3**	93	97
8	4-Me	**3.8b**	(*S*)-**3.4**	91	93
9	2-Me	**3.8c**	(*S*)-**3.1**	95	60
10	2-Me	**3.8c**	(*S*)-**3.2**	89	67
11	2-Me	**3.8c**	(*S*)-**3.3**	94	90
12	2-Me	**3.8c**	(*S*)-**3.4**	93	96
13	3,5-Me_2	**3.8d**	(*S*)-**3.1**	92	78
14	3,5-Me_2	**3.8d**	(*S*)-**3.2**	96	94
15	3,5-Me_2	**3.8d**	(*S*)-**3.3**	90	99
16	3,5-Me_2	**3.8d**	(*S*)-**3.4**	94	99
17	4-Cl	**3.8e**	(*S*)-**3.1**	95	72
18	4-Cl	**3.8e**	(*S*)-**3.2**	97	>99
19	4-Cl	**3.8e**	(*S*)-**3.3**	94	93
20	4-Cl	**3.8e**	(*S*)-**3.4**	98	99

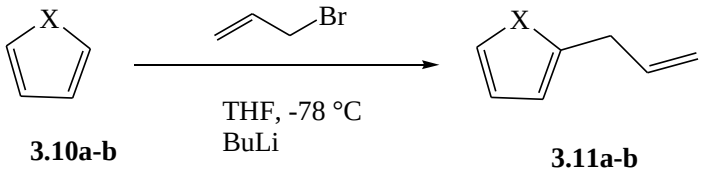
[a] Reaction conditions: [M(cycloocta-1,5-diene)] (2.5 mol%), (*S*)-Me_2-CATPHOS or (*S*)-BINAP (2.5 mol%), CH_2Cl_2, AgOTf (5 mol%), ethyl trifluoropyruvate (1.5 mol. eq.) and α-methylstyrene at r/t. . [b]Average of three runs. [c] Enantioselectivity calculated by chiral GC using SUPELCO BETA DEX column. [d] Isolated yield.

Initial results indicate that unlike the styrene derivatives, the platinum(II) Lewis acids outperform their palladium counterparts in the vast majority of the cases reported in Table 3.3. Furthermore, the difference in the corresponding enantioselectivities between systems based on (*S*)-BINAP and (*S*)-Me_2-CATPHOS is not as pronounced as with the α-methylstyrene derivatives (Table 3.1 vs Table 3.3). The Pt/(*S*)-BINAP combination consistently gave the highest ee's ranging from 93% to 99%. More encouragingly, the Pt/(*S*)-Me_2-CATPHOS Lewis acid complex also gave comparably high ee's; allylbenzene, 1-allyl-3,5-dimethylbenzene and 1-allyl-4-chlorobenzene substrates afford the α-hydroxyesters **3.9a**, **3.9d** and **3.9e** in 93%, 94% and > 99% ee's, respectively, which all compare favourably with literature values; For instance, Mikami has recently resolved a platinum(II) complex of 1,1'-bis(diphenylphosphino)biphenyl and subsequently applied it in the carbonyl-ene reaction between allylbenzene and ethyl trifluoropyruvate to give the corresponding ester in 85% ee and with complete *E*-selectivity.[24]

3.4 Allyl-Substituted Heterocycles

Subsequently the study was expanded to include substituted heterocycles, namely 2-allylfuran and 2-allylthiophene under the same reaction conditions. These substrates were synthesised following known literature procedures (Figure 3.2). The heterocycles **3.10a-b** each react with allylbromide in presence of excess ^{n}BuLi to afford the corresponding 2-allyl substituted derivatives **3.11a-b.**

Figure 3.1. Synthesis of 2-Allylfuran **3.11a** and 2-Allylthiophene **3.11b**.[a]



3.10a-b **3.11a-b**

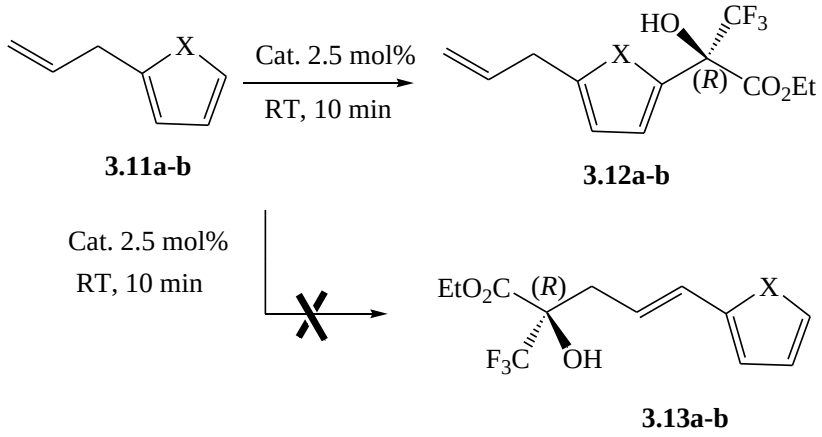
3.10a (X = O)
3.10b (X = S)

[a] Reaction conditions: **3.11a** i) Furan, THF, ^{n}BuLi(1.1 mol. eq.) at -78 °C, stir for 3 h at 0 °C ii) allyl bromide (1.1 mol. eq.), -78 °C, stir 1 h at 0 °C. **3.11b**: i) Thiophene, ether ^{n}BuLi (1.1 mol. eq.) at 0 °C, stir 1 h at r/t ii) allyl bromide (1.4 mol. eq.), -20 °C iii) heat under reflux, 18 h.

The results for the corresponding catalysis reactions are shown in Table 3.4, where the reactions of 2-allylfuran and 2-allylthiophene with ethyl trifluoropyruvate both selectively favour the formation of the Friedel-Crafts adducts **3.12a** and **3.12b** with no trace of the

expected carbonyl-ene adducts **3.13a-b**. The identity of **3.12a-b** as the sole products of the Friedel-Crafts type alkylation at the 4-position of the heterocycle was unequivocally established through a combination of ^{1}H and $^{`13}C$ NMR spectroscopy, high resolution mass spectroscopy and elemental analysis after purification through column chromatography.

Table 3.4. Asymmetric Friedel-Crafts Reaction between 3-Allylfuran/3-Allylthiophene **3.11a-b** and Ethyl Trifluoropyruvate to Form the Corresponding α-Hydroxyesters **3.12a-b**.[a]



3.11a-b **3.12a-b**

3.13a-b

Entry	X	**3.11a-b**	Catalyst	% Yield **3.12a-b** [b,d]	% ee **3.12a-b** [b,c]
1	O	**3.11a**	(*S*)-**3.1**	87	50
2	O	**3.11a**	(*S*)-**3.2**	98	67
3	O	**3.11a**	(*S*)-**3.3**	97	43
4	O	**3.11a**	(*S*)-**3.4**	95	12
5	S	**3.11b**	(*S*)-**3.1**	99	31
6	S	**3.11b**	(*S*)-**3.2**	92	43
7	S	**3.11b**	(*S*)-**3.3**	93	60
8	S	**3.11b**	(*S*)-**3.4**	95	63

[a]Reaction conditions: [M(cycloocta-1,5-diene)] (2.5 mol%), (*S*)-Me_2-CATPHOS or (*S*)-BINAP (2.5 mol%), CH_2Cl_2, AgOTf (5 mol%), ethyl trifluoropyruvate (1.5 mol. eq.) and 2-allyl substituted heterocycle at r/t. . [b]Average of three runs. [c] Enantioselectivity calculated by chiral GC using SUPELCO BETA DEX column. [d] Isolated yield

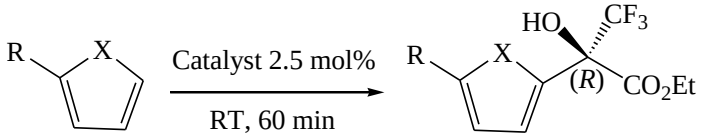
As far as the enantioselectivity is concerned, our results with the 2-allyl-substituted heterocycles proved to be variable and substrate specific with the ee's of the final products dependant on the architecture of the ligand and, to a lesser extent, the metal center. For

instance, in the case of 2-allylfuran, both (*S*)-Me_2-CATPHOS-based Lewis acid catalysts outperformed their BINAP counterparts (Table 3.4, entries 1-4). In particular, the poor performance of Pt/(*S*)-BINAP (12% ee) falls well short of the ee of 67% obtained with its Me_2-CATPHOS counterpart. On the contrary, in the case of 2-allylthiophene, both (*S*)-BINAP-based catalysts outperformed their Me_2-CATPHOS counterparts (Table 3.4, entries 5-8).

Given the preference of 2-allylfuran **3.11a** and 2-allylthiophene **3.11b** to selectively undergo Friedel-Crafts alkylation, the reaction was expanded to include Friedel-Crafts alkylation with furan, thiophene and their 2-methyl substituted derivatives, the results of which are shown in Table 3.5. A review of the literature reveals only a handful of papers that report on the Friedel-Crafts alkylation with furan, thiophene and their 2-Me-substituted derivatives, the most prominent of which was published by Jørgenson in 2001.[25] Given the lack of research in this area and the prominence of heterocycles in natural products, we sought to further evaluate this particular transformation with our reaction protocol and ligand system.

Substrates **3.14a-d** each reacts with ethyl trifluoropyruvate to afford the corresponding α-hydroxyesters **3.15a-d** in near quantitative yield, as shown in Table 3.5. The absolute configuration was confirmed by comparing the signs of the specific rotation with those reported by Jørgenson for the bis(oxazoline)-copper(II) catalysed Friedel-Crafts reaction of furan, thiophene and their 2-Me-substituted derivatives with ethyl trifluoropyruvate, which affords the corresponding α-hydroxyester in low yield but good enantioselectivity.[25, 26] For example, Jørgenson and colleagues synthesised α-hydroxyesters **3.15a**, **3.15c** and **3.15d** in good ee's but yields of only 15%, 65% and 16%, respectively, at 0°C over long reaction times.[25] On the other hand, our study clearly demonstrates that Pd/(*S*)-Me_2-CATPHOS, Pt/(*S*)-Me_2-CATPHOS and their BINAP counterparts all afford the α-hydroxyesters **3.15a-d** in near-quantitative yields after only 10 min. Furthermore, most of our ee's are moderately high and some in excess of 80% (Table 3.5, entries 8, 9, 13, and 16). Considering that our reactions were conducted at room temperature, there is definitely room for improving the ee values by optimising the reaction protocol in future research and perhaps lowering reaction temperature.

Table 3.5. Asymmetric Friedel-Crafts Reaction between Heterocycle Derivatives **3.14a-d** and Ethyl Trifluoropyruvate to Form the Corresponding α-Hydroxyesters **3.15a-d**.[a]



3.14a-d **3.15a-d**

Entry	R	X	**3.14a-d**	Catalyst	Yield (%) **3.15a-d** [b,d]	% ee [b,c]
1	H	O	**3.14a**	(*S*)-**3.1**	96	67
2	H	O	**3.14a**	(*S*)-**3.2**	93	57
3	H	O	**3.14a**	(*S*)-**3.3**	98	52
4	H	O	**3.14a**	(*S*)-**3.4**	92	45
5	H	S	**3.14b**	(*S*)-**3.1**	90	30
6	H	S	**3.14b**	(*S*)-**3.2**	97	80
7	H	S	**3.14b**	(*S*)-**3.3**	98	32
8	H	S	**3.14b**	(*S*)-**3.4**	90	83
9	Me	O	**3.14c**	(*S*)-**3.1**	98	80
10	Me	O	**3.14c**	(*S*)-**3.2**	90	17
11	Me	O	**3.14c**	(*S*)-**3.3**	96	62
12	Me	O	**3.14c**	(*S*)-**3.4**	94	40
13	Me	S	**3.14d**	(*S*)-**3.1**	95	76
14	Me	S	**3.14d**	(*S*)-**3.2**	99	60
15	Me	S	**3.14d**	(*S*)-**3.3**	95	57
16	Me	S	**3.14d**	(*S*)-**3.4**	90	84

[a]Reaction conditions: [M(cycloocta-1,5-diene)] (2.5 mol%), (*S*)-Me_2-CATPHOS or (*S*)-BINAP (2.5 mol%), CH_2Cl_2, AgOTf (5 mol%), ethyl trifluoropyruvate (1.5 mol. eq.) and heterocycle at r/t. [b]Average of three runs. [c] Enantioselectivity calculated by chiral GC using SUPELCO BETA DEX column. [d] Isolated yield.

The general trend in the case of furan and 2-methylfuran derivatives is that both Pd/(*S*)-BINAP and Pd/(*S*)-Me_2-CATPHOS outperform their platinum counterparts (Table 3.5, entries 1-4 and 9-12). In contrast, in the case of thiophene and its 2-methyl derivative, both the Pt/(*S*)-BINAP and Pt/(*S*)-Me_2-CATPHOS systems outperform their palladium counterparts in all but one of the reactions (Table 3.5).

3.4.1 Thiophene vs 2-Methythiophene

The reaction of thiophene with ethyl trifluoropyruvate catalysed by Pt/(*S*)-Me_2-CATPHOS and Pt/(*S*)-BINAP gave Friedel-Crafts adduct **3.15b** in 80% ee and 83% ee, respectively, in near quantitative yield in both cases as well. The same two reactions were carried out with 2-methylthiophene and the corresponding Friedel-Crafts adduct **3.15d** was formed successfully in both the cases. In this case, the ee with Pt/(*S*)-BINAP is essentially identical 84% (vs 83% for **3.15b**) whereas its Me_2-CATPHOS counterpart gave **3.15d** in only 60% ee (vs 80% for **3.15b**). So it appears that, at least for Pt/(*S*)-Me_2-CATPHOS the performance is substrate dependent.

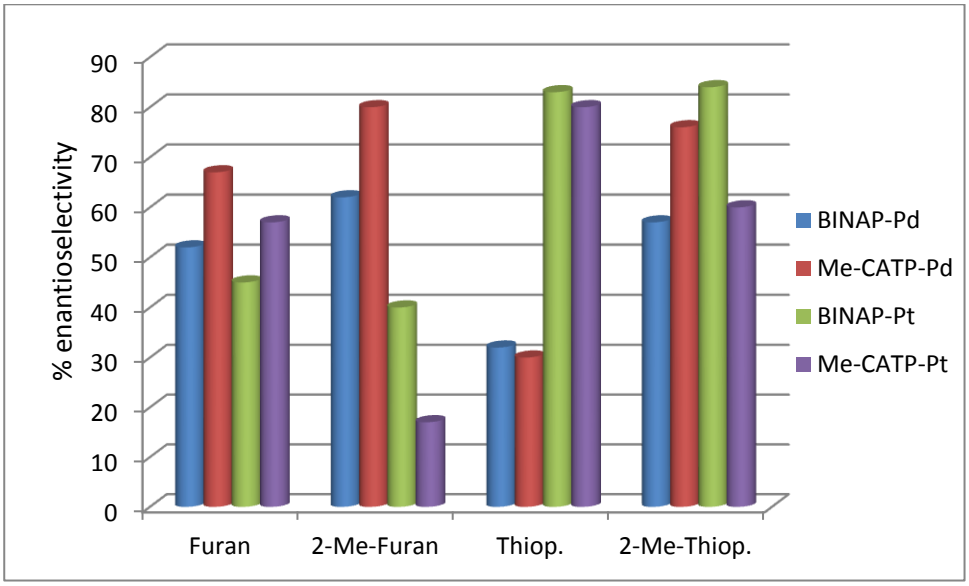
However, the palladium-based Lewis acids react more favourably in the presence of the methyl group where its presence significantly increases ee's. For the non-methylated substrates, Pd/(*S*)-Me_2-CATPHOS and its BINAP counterpart gave adduct **3.15b** in 30% and 32% ee respectively. For comparison, 2-methylthiophene adduct **3.15d** was obtained in 76% and 57% ee with Pd/(S)-Me_2-CATPHOS and its Pd/(*S*)-BINAP, respectively. In this case, the addition of only a methyl group appears to lead to an increase in enantioselectivity with palladium(II)-based Lewis acids.

3.4.2 Furan vs 2-Methyfuran

In these set of reactions, both the platinum(II) and the palladium(II) Lewis acids successfully catalyse the formation of the furan and 2-methylfuran Friedel-Crafts adducts **3.15a** and **3.15c**, respectively, with the palladium(II) Lewis acids giving the highest enantioselectivity. Table 3.5 shows that both the palladium-based catalysts gave 2-methylfuran adduct **3.15c** in higher ee's than furan adducts **3.14c** (entries 1-4 and 9-12). It is worth highlighting that the same trend was observed with thiophene and 2-methylthiophene where both palladium-based Lewis acids again gave significantly higher ee's for the methyl-substituted heterocycle. Even more encouragingly, Pd/(*S*)-Me_2-CATPHOS affords the 2-methylfuran adduct **3.15c** in 80% ee (entry 9) compared to only 62% for its BINAP counterpart. In the absence of the methyl group, Pd/(*S*)-Me_2-CATPHOS and its BINAP counterpart both followed the overall trend and gave the corresponding furan adduct **3.15a** with lower ee's of 67% and 52%, respectively. Yet again, the absence of methyl substituent results in lower enantioselectivity with the palladium(II) Lewis acids.

Pt/(*S*)-Me_2-CATPHOS and Pt/(*S*)-BINAP systems both successfully catalyse the formation of adducts **3.15a** and **3.15c** as well. In a trend that was previously observed with their thiophene counterparts, both Pt/(*S*)-Me_2-CATPHOS and its BINAP counterpart gave the 2-methyl substituted adduct in lower ee than its unsubstituted counterpart. For instance, Pt/(*S*)-Me_2-CATPHOS gave adduct **3.15a** in 57% ee compared to an ee of only 17% for the 2-methylfuran adduct **3.15c** (entries 2 vs 10). The results are summarised in Figure 3.3 clearly illustrating the substrate and metal dependent reactivity of the Lewis acids.

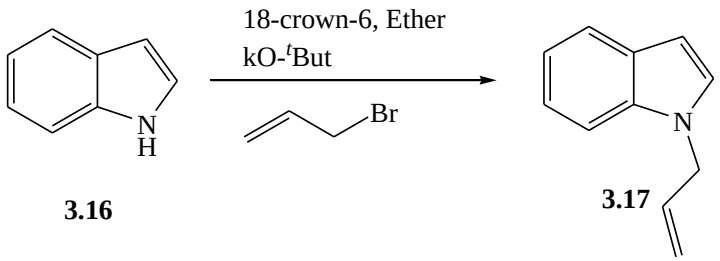
Figure 3.2. Comparative performance of M/(*S*)-Me_2-CATPHOS (M = Pd, Pt) and its BINAP counterparts in Friedel-Crafts alkylation of Furan, Thiophene and their respective 2-Me derivatives.



3.5 Indole and *N*-allylindole Derivatives

The Friedel-Crafts alkylation was expanded to include indole and N-allylindole **3.17**. The latter was synthesised by reaction of indole **3.16** with slight excess of allylbromide in presence of potassium *tert*-butoxide and catalyst 18-crown-6 (Figure 3.4).[42]

Figure 3.3. Reaction of indole **3.16a** with allyl bromide to form *N*-allylindole **3.17.**[a]



3.16 **3.17**

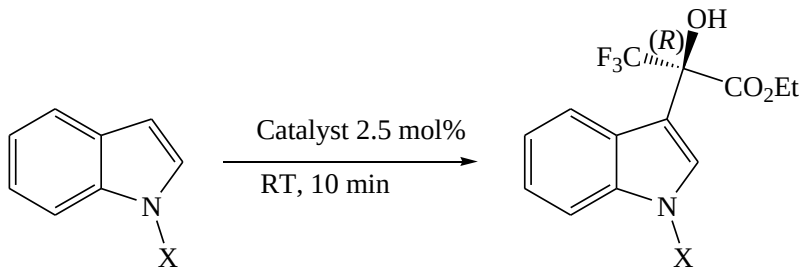
[a] Reaction conditions: i) 18-crown-6 (8 mol%), KO^{t}Bu (1.1 mol. eq.), in ether then indole and stir at r/t for 15 min ii) allyl bromide (1.1 mol. eq.) at 0 °C; dropwise iii) 1 h at r/t.

Both *N*-allylindole **3.17** and indole **3.16** underwent Friedel-Crafts alkylation with ethyl trifluoropyruvate, catalysed by M/(*S*)-Me$_2$-CATPHOS or M/(*S*)-BINAP (M = Pt, Pd), the results of which are shown in Table 3.6. The identity of **3.18a-b** as the products of the Friedel-Crafts alkylation at the 3-position of the heterocyclic derivatives was unequivocally established by a combination of ^{1}H and ^{13}C NMR spectroscopy and high resolution mass spectrometry and comparison with literature precedents.[27] The absolute configurations of **3.18a-b** were assigned as (*R*) which was determined by the sign of the optical rotation and analogy with literature[28] and the enantiomeric excess was determined by HPLC.[29, 30]

Each of the Lewis acid complexes catalyze the Friedel-Crafts reaction between indole **3.16** and ethyl trifluoropyruvate at room temperature to give **3.18a** as a racemic mixture (entries 1-4). The yields are near quantitative after only 10 min. No product was observed when the reaction was carried out with no catalyst. A review of the literature reveals that many precedents for this transformation give **3.18a** in near-quantitative yields with no enantioselectivity in the final product.[31, 32] Significant enantioselectivity is only obtained at very low temperatures. For example, **3.18a** was obtained in 95% yield and 95% ee at -78 °C catalysed by 10 mol% of various chiral imidazoline/Cu(OTf)$_2$ Lewis acids.[33] Other reactions involve chiral catalysts based on Zn(ClO$_4$)$_2$.6H$_2$O at 0 °C and Zn(OTf)$_2$ at -20 °C,

which give the corresponding products in 24% and 66% ee, respectively, with near quantitative yields in both cases.[27]

Table 3.6. Asymmetric Friedel-Crafts Reaction between Indole **3.16**/*N*-Allylindole **3.17** and Ethyl Trifluoropyruvate to form the Corresponding α-Hydroxyesters **3.18a-b**.[a]



3.16-3.17 **3.18a-b**

Entry	X	**3.16/3.17**	Catalyst	% Yield **3.18a-b** [b,d]	% ee [b,c]
1	H	**3.16**	(*S*)-**3.1**	98	racemic
2	H	**3.16**	(*S*)-**3.2**	97	racemic
3	H	**3.16**	(*S*)-**3.3**	92	racemic
4	H	**3.16**	(*S*)-**3.4**	96	racemic
5	Allyl	**3.17**	(*S*)-**3.1**	>99	30
6	Allyl	**3.17**	(*S*)-**3.2**	95	racemic
7	Allyl	**3.17**	(*S*)-**3.3**	92	25
8	Allyl	**3.17**	(*S*)-**3.4**	93	racemic

[a]Reaction conditions: [M(cycloocta-1,5-diene)] (2.5 mol%), (*S*)-Me_2-CATPHOS or (*S*)-BINAP (2.5 mol%), CH_2Cl_2, AgOTf (5 mol%), ethyl trifluoropyruvate (1.5 mol. eq.) and indole derivatives at r/t. . [b]Average of three runs. [c] Enantioselectivity calculated by chiral GC using SUPELCO BETA DEX column. [d] Isolated yield

However, in the separate reactions of *N*-allylindole **3.17** and ethyl trifluoropyruvate with either Pd/(*S*)-Me_2-CATPHOS or its BINAP counterpart, the corresponding α-hydroxyester **3.18b** is obtained in near quantitative yields and 30% and 25% ee's, respectively (entries 1, 7). However the platinum(II)-based Lewis acids gave **3.18b** in near-quantitative yield but as a racemic mixture.

Although the ee's obtained for **3.18b** with the palladium(II)-based Lewis acids are poor, they do provide some encouragement. First and foremost, they have been obtained at room temperature and given the dependence of enantioselectivity on very low temperatures for vast majority of the reported literature, it would be worthwhile repeating these reactions at

different temperatures. These findings are a platform for further reaction optimisation in order to obtain higher ee's at room temperature.

3.6 Conclusions

We have successfully demonstrated that $[M((S)\text{-}Me_2\text{-}CATPHOS)]^{2+}$ (M = Pd, Pt) can catalyse both the carbonyl-ene and Friedel-Crafts reactions with a range of aromatic and heterocyclic substrates via an operationally straightforward one-pot reaction protocol, all at room temperature. All the reactions afford their corresponding α-hydroxyesters in near quantitative yields after only 10 min with complete *E*-selectivity for the corresponding α-hydroxyesters and with negligible formation of side-products. Throughout this study, the M/(*S*)-Me_2-CATPHOS (M = Pd, Pt) combinations gave some encouragingly high ee's that are either comparable to or higher than those obtained with their BINAP counterparts.

While both M/(*S*)-Me_2-CATPHOS (M = Pd, Pt) catalysts successfully catalyse reaction of α-methylstyrenes and ethyl trifluoropyruvate to afford the corresponding α-hydroxyesters in very high yields and moderate enantioselectivity, the palladium(II) Lewis acid was much more active and consistently outperformed its platinum counterpart. In terms of the effects of the chiral ligand on the enantioselectivity, M/(*S*)-BINAP (M = Pd, Pt) consistently outperformed their Me_2-CATPHOS counterparts for the majority of the substrate combination. However M/(*S*)-Me_2-CATPHOS (M = Pd, Pt) also gave moderately high ee's for selected substrates.

In the case of allylbenzene and its derivatives, the platinum(II) Lewis acids outperformed their palladium counterparts in the vast majority of cases. In particular the performance of M/(*S*)-Me_2-CATPHOS (M = Pd, Pt) is very encouraging with Pt/(*S*)-Me_2-CATPHOS giving ee's as high as 99%. These values are not only comparable with their BINAP counterparts but also outperform the vast majority of the reported literature precedents for this reaction carried out at room temperature.

Our study also revealed that 2-allylfuran and 2-allylthiophene preferentially undergo Friedel-Crafts alkylation at the 4-position rather than ene-type reactivity. Encouragingly, M/(*S*)-Me_2-CATPHOS (M = Pd, Pt) both outperform their BINAP counterparts in the Friedel-Crafts reaction with 2-allylfuran. While these results are surprising, they do highlight the substrate specific and metal-phosphine dependant performance of our Lewis acid catalysts. Furthermore, they consistently demonstrate that Me_2-CATPHOS is indeed a potential viable alternative to BINAP. Similarly, *N*-allylindole also undergoes preferential

Friedel-Crafts reaction but the corresponding α-hydroxyester **3.10b** is obtained in poor ee with the palladium Lewis acids while their platinum counterparts give racemic products.

Our study was extended to include furan, thiophene and their 2-methyl derivatives in order to further evaluate the efficacy of this class of Lewis acids in classical Friedel-Crafts transformations. In general, the palladium(II) Lewis acids outperformed their platinum counterparts in the formation of the furan and 2-methylfuran adducts. In contrast, the platinum(II) Lewis acids are more effective than their palladium counterparts for the reaction involving thiophene and its 2-Me derivative.

3.7 Experimental

General Comments. All manipulations involving air-sensitive materials were carried out using standard Schlenk line techniques under an atmosphere of nitrogen or argon in oven-dried glassware. Dichloromethane was distilled from calcium hydride, diethyl ether from Na/K alloy, dioxane from sodium and THF from sodium/benzophenone. Ethyl trifluoropyruvate, allylmagnesium bromide, aryl bromides, allyl benzene, indole and styrenes were purchased from commercial suppliers and used without further purification. (*S*)-Me_2-CATPHOS, 1,2,3,4-Ph_4-NUPHOS, allylbenzene derivatives,[34] 2-allylfuran,[35] 2-allylthiophene[36] and *N*-allylindole[37] were all prepared as previously described. ^{1}H and ^{13}C NMR spectra were recorded on a JOEL ECS-400 instrument. Optical rotations were measured on an Optical Activity PolAAr 2001 digital polarimeter with a sodium lamp and are reported as follows: $[\alpha]_D^{20}$ (*c* g/100 mL, solvent). Thin layer chromatography (TLC) was carried out on aluminium sheets pre-coated with silica gel $60F_{254}$ and column chromatography was performed using Merck Kieselgel 60. Gas chromatography was performed on a Shimadzu 2010 series gas chromatograph equipped with a split-mode capillary injection system and flame ionisation detection using SUPELCO BETA DEX column (Inj. Temp. 170 °C; column conditions 140 °C for 45 min ramp to 180 °C at 3 °C/min, pressure 21 psi, hold for 40 min) and enantiomeric excesses were calculated from the GC profile.

2-Allylfuran (3.11a). A solution of furan (1.00 g, 14.7 mmol) in THF (5 mL) was cooled to -78 °C in ice/acetone bath and treated with BuLi (6 mL, 2.5 M solution in ether, 15 mmol) in a dropwise manner. The solution was warmed to 0 °C and stirred for 3 h. Initially a white creamy solution evolved which changed to a light brown solution. Subsequently the reaction mixture was cooled to -78 °C and a solution of allylbromide (1.6 mL, 18.4 mmol) in THF (2 mL) was added dropwise via cannula. The reaction mixture was warmed to 0 °C and stirred for a further 1 h after which it was quenched with brine (20 mL), diluted with water (15 mL) and the organic phase extracted with diethyl ether (15 mL). The combined organic layers were washed with water (2 x 20 mL), brine (2 x 20 mL), dried over $MgSO_4$, filtered and solvent removed under reduced pressure. Purification by column chromatography eluting with petrol/ethyl acetate gave the allylfuran (1.03g, 65%) as a colourless oil.[35] ^{1}H NMR (300.0 MHz, $CDCl_3$, δ): 7.28-7.25 (m, 1H, C_4H_3O), 6.25 (t, *J* = 2.5 Hz, 1H, C_4H_3O), 5.86 (d, *J* = 3.2 Hz, 1H, C_4H_3O), 5.84-5.81 (m, 1H, =C*H*), 5.12-5.01 (m, 2H, =CH_2), 3.37-3.30 (d, *J* = 6.6 Hz, 2H, =CHCH_2); ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$, δ): 154.0 (C_4H_3O), 141.2 (C_4H_3O), 134.0 (=*C*HCH_2), 116.8 (=*C*H_2), 110.3 (C_4H_3O), 115.6 (C_4H_3O), 32.5 (*C*H_2); LRMS (EI) *m/z* 109 $[M+H]^+$.

2-Allylthiophene (3.11b). A flame-dried Schlenk flask was charged with thiophene (1.4 mL, 17.9 mmol), and dry ether (2 mL) and this solution was added dropwise to an ice-cold solution of BuLi (7.2 mL, 2.5 M BuLi in ether, 18.0 mmol). Subsequently the solution was warmed to room temperature and allowed to stir at room temperature for 1 h. The reaction mixture was cooled to -20 °C and treated with a solution of allylbromide (2.2 mL, 15.0 mmol) in ether (5 mL) in a dropwise manner. Subsequently the mixture was warmed and heated under reflux for 18 h. At the end of the reaction period, the mixture was cooled and poured onto crushed ice. The organic layer was extracted with ether (10 mL x 3). The combined organic layers were washed with water (10 mL x 3), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The product was purified by column chromatography[3] (DCM/hexane, 1:4) to give allylthiophene (1.63g, 75%) as a colourless oil.[36] ^{1}H NMR (300.0 MHz, $CDCl_3$, δ): 7.30-7.25 (d, J = 5.2 Hz, 1H, C_4H_3S), 7.10-7.05 (m, 1H, C_4H_3S), 6.99-6.91 (m, 1H, C_4H_3S), 6.21-6.05 (m, 1H, =C*H*), 5.37-5.20 (m, 2H, =CH_2), 3.75-3.69 (d, J = 6.5 Hz, 2H, CH_2); ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$, δ): 143.0 (S*C*C=C), 136.5 (*C*H=C), 126.4 (C_4H_3S), 124.3 (C_4H_3S), 123.6 (C_4H_3S), 116.0 (*C*H_2=C), 34.3 (*C*H_2C=C); LRMS (EI) *m/z* 124 $[M]^+$.

***N*-Allylindole (3.17).** To a solution of 18-crown-6 (226 mg, 0.8 mmol) in ether (15 mL) was added potassium *tert*-butoxide (1.10 g, 10.0 mmol) under rapid stirring. Indole (1.00 g, 9.0 mmol) was added to the reaction mixture in a single portion. The solution was allowed to stir at room temperature for 15 minutes. Subsequently the solution was cooled in an ice bath and to it was added a solution of allylbromide (1.20 g, 10.0 mmol) in ether (7 mL) in a dropwise manner after which mixture was warmed to room temperature and allowed to stir for 1 hour. The reaction was quenched with water (6 mL), and extracted with ether (2 x 10 ml). The combined organic layers were washed with saturated $NaCl_{(aq)}$ (30 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The product was purified by column chromatography (DCM/hexane, 1:9) to give allylindole (0.81g, 60%) as a colourless oil.[37]

^{1}H NMR (300.0 MHz, $CDCl_3$, δ): 7.60-7.50 (d, J = 7.66 Hz, 1H, Ar-*H*), 7.30-7.00 (m, 4H, Ar-*H*), 6.50-6.40 (d, J = 3.04 Hz, 1H, =C*H*), 6.10-5.80 (m, 1H, =C*H*), 5.16-5.08 (d, J = 10.14 Hz, 1H, =C$H_a$$H_b$), 5.1-4.92 (d, J = 17.2 Hz, 1H, =C$H_a$$H_b$), 4.70-4.55 (d, J = 5.37 Hz, 2H, NCH_2); ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$, δ): 132.5 (*C*=CH_2), 123.5 (C_6H_4), 122.9 (C_6H_4), 122.4 (C_6H_4), 120.5 (=*C*HN), 120 (C_6H_4), 118.1 (C=*C*H_2), 108.5 (C_6H_4), 100.1 (NCH=*C*H), 77.0 (*C*=CN), 47.1 (*C*H_2N); LRMS (EI) *m/z* 158 $[M + H]^+$.

General Procedure for Synthesis of Allylbenzene Derivatives. A flame-dried Schlenk flask was charged with $Pd_2(dba)_3$ (24.0 mg, 0.025 mmol), 1,2,3,4-Ph_4 NUPHOS (38.1 mg, 0.050 mmol) and dioxane (10 mL). The mixture was allowed to stir at room temperature for 30 minutes. Arylbromide (5.2 mmol) was added followed by allylmagnesium bromide (6 mL, 5.7 mmol) in a drop wise manner. The solution was heated at 80 °C for 16 h. On addition of allylmagnesium bromide, a light brown solution evolved. The reaction mixture was quenched by slow addition of 10% aqueous HCl (20 mL) and the product was extracted with ether (3 x 10 mL). The organic phases were combined, dried over $MgSO_4$ and the solvent was removed under reduced pressure to leave a yellow brown crude product. Purification by column chromatography (100% hexane) afforded the pure product as a colourless oil.[34]

1-Allyl-4-methylbenzene (3.7b). A sample was prepared according to the general procedure described above and isolated as a colourless oil after purification by column chromatography with 90% yield. ^{1}H NMR (300.0 MHz, $CDCl_3$, δ): 7.4-7.23 (m, 4H, C_6H_4), 6.30-6.10 (m, 1H, =C*H*), 5.39-5.21 (m, 2H, =CH_2), 3.65-3.50 (d, J = 6.25 Hz, 2H, CH_2), 2.67 (s, 3H, CH_3); ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$, δ): 137.1 (C_6H_4), 136.5 (C_6H_4), 134.9 (C_6H_4), 128.5 (=*C*H_2), 123.1 (C_6H_4), 114.8 (*C*H=CH_2), 39.6 (*C*H_2), 20.0 (C_6H_4*C*H_3); LRMS (EI) *m/z* 132 $[M]^+$.

1-Allyl-2-methylbenzene (3.7c). A Sample was prepared according to the general procedure described above and isolated as a colourless oil after purification by column chromatography with 78% yield. ^{1}H NMR (300.0 MHz, $CDCl_3$, δ): 7.12-7.01 (m, 4H, Ar-*H*), 6.0-5.8 (m, 1H, =C*H*), 5.02-4.89 (m, 2H, =CH_2), 3.32-3.29 (d, J = 6.30 Hz, 2H, C_6H_4CH_2), 2.22 (s, 3H, CH_3); ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$, δ): 137.1 (C_6H_4), 136.5 (C_6H_4), 134.9 (C_6H_4), 134.6 (C_6H_4), 128.5 (=*C*H_2), 124.6 (C_6H_4), 123.1 (C_6H_4), 114.8 (=*C*H), 39.6 (*C*H_2), 22.1 (*C*H_3); LRMS (EI) *m/z* 132 $[M]^+$.

1-Allyl-3,5-dimethylbenzene (3.7d). A sample was prepared according to the general experimental procedure outlined above and isolated as a colourless oil after purification by column chromatography with 80% yield. ^{1}H NMR (300.0 MHz, $CDCl_3$, δ): 6.78 (br s, 1H, Ar-*H*), 6.72 (br s, 2H, Ar-*H*), 5.95-5.80 (m, 1H, =C*H*), 5.1-5.0 (m, 2H, =CH_2), 3.29-3.21 (d, J = 6.82 Hz, 2H, CH_2), 2.21 (s, 6H, C_6H_3(CH_3)$_2$); ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$, δ): 140.4 (C_6H_3), 138.3 (C_6H_3), 129.6 (=*C*H_2), 127.5 (C_6H_3), 124.4 (C_6H_3), 117.1 (=*C*H), 41.0 (*C*H_2), 21.8 (C_6H_3(*C*H_3)$_2$). LRMS (EI) *m/z* 146 $[M]^+$.

1-Allyl-4-chlorobenzene (3.7e). A sample was prepared according to the general experimental outlined above and was isolated as a colourless oil after purification by column chromatography with 75% yield. ^{1}H NMR (300.0 MHz, $CDCl_3$, δ): 7.40-7.30 (m, 2H, Ar-*H*), 7.30-7.15 (m, 2H, Ar-*H*), 6.11-5.95 (m, 1H, =C*H*CH_2), 5.28-5.15 (m, 2H, C*H*$_2$), 3.50-3.40 (d, J = 6.7 Hz, 2H, C*H*$_2$=CH); ^{13}C {^{1}H} NMR 75.5 MHz, $CDCl_3$, δ): 137.5 (C_6H_4), 135.2 (C_6H_4), 131.4 (C_6H_4), 127.5 (C_6H_4), 125.0 (CH_2=*C*), 115.0 (HC=*C*H_2), 38.8 (*C*H_2); LRMS (EI) *m/z* 153 $[M]^+$.

General Procedure for Carbonyl-Ene and Friedel-Crafts Reactions between Aromatic Derivatives and Ethyl Trifluoropyruvate. A flame-dried schlenk flask was charged with [MCl_2(cycloocta-1,5-diene)] (0.013 mmol,), (*S*)-Me_2CATPHOS (0.010 g, 0.013 mmol) and CH_2Cl_2 (2 mL) and solution was stirred at room temperature for 1 h. After this time, $AgSbF_6$ (0.009 g, 0.025 mmol) was added and the reaction was stirred at room temperature for 30 min to form the active Lewis acid. Ethyl trifluoropyruvate (0.099 mL, 0.75 mmol) was added followed by the aromatic nucleophile (0.057 mL, 0.5 mmol) and the resulting mixture was stirred for a further 10 min at room temperature. The solution was flushed through a short plug of silica with dichloromethane, the solvent was removed under reduced pressure and the resulting residue was purified by column chromatography (hexane/DCM, 7:3).

Ethyl-3,3,3-trifluoro-2-hydroxy-2-(1H-indol-3-yl)-propanoate (3.18a). A sample was prepared according to the general procedure described above and isolated as a colourless oil after purification by column chromatography. $[\alpha]_D$ = 0 (*c* 1.0, $CHCl_3$, racemic); ^{1}H NMR (300.0 MHz, $CDCl_3$, δ): 8.25-8.15 (br s, 1H, N*H*), 7.85 (d, J = 7.9 Hz, 1H, C*H*N), 7.37-7.35 (d, J = 2.9 Hz, 1H, Ar-*H*), 7.25 (d, J = 7.7 Hz, 1H, Ar-*H*), 7.2-7.00 (m, 2H, Ar-*H*), 4.40-4.20 (m, 3H, OC*H*$_2$, O*H*), 1.30-1.20 (t, J = 7.0 Hz, 3H, OCH_2C*H*$_3$); ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$, δ): 170.0 (*C*=O), 136.4 (C_6H_4), 125.0 (C_6H_4), 124.5 (C_6H_4), 123.0 (C_6H_4), 122.0 (q, $J_{C\text{-}F}$ = 286 Hz, *C*F_3), 121.0 (C_6H_4), 120.3 (=*C*HN), 112.0 (C_6H_4), 108.7 (=*C*CN), 77.0 (q, $J_{C\text{-}F}$ = 32 Hz, *C*CF_3), 64.3 (O*C*H_2), 14.1 (OCH_2*C*H_3); LRMS (EI) *m/z* 288 $[M+H]^+$. The enantiomeric excess was calculated from the HPLC profile (Diacel Chiracel OD-H, flow rate: 0.5 mL/min, hexane: 2-propanol = 90:10). Retention times: (*R*)-enantiomer t_r = 27.6 min, (*S*)-enantiomer t_r = 31.3 min. Absolute stereochemistry assigned by analogy.

Ethyl 2-(1-allyl-1H-indol-3-yl)-3,3,3-trifluoro-2-hydroxypropanoate (3.18b). Sample prepared according to the general procedure described above and isolated as a dark yellow oil after purification by column chromatography. $[\alpha]_D$ = -5.7 (*c* 1.0, $CHCl_3$, 30% ee); ^{1}H

NMR (300.0 MHz, $CDCl_3$, δ): 7.85 (d, J = 8.0 Hz, 1H, =*CH*N), 7.30 (s, 1H, Ar-*H*), 7.25 (d, J = 8.0 Hz, 1H, Ar-*H*), 7.20-7.10 (t, J = 7.5 Hz, 1H, Ar-*H*), 7.10-7.05 (t, J = 7.5 Hz, 1H, Ar-*H*), 6.00-5.85 (m, 1H, =*CH*CH_2), 5.20-5.12 (d, J = 10.1 Hz, 1H, =CH_aH_b), 5.10- 5.00 (d, J = 17.0 Hz, 1H, =CH_aH_b), 4.70-4.60 (d, J = 5.5 Hz, 2H, *CH*$_2$CH), 4.42-4.20 (m, 2H, O*CH*$_2$), 1.30-1.20 (t, J = 7.1 Hz, 3H, O*C*H_2C*H*$_3$); $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$, δ): 169.5 (*C*=O), 137.3 (C_6H_4), 133.0 (*C*=CH_2), 128.0 (C_6H_4), 126.0 (C_6H_4), 122.1 (q, $J_{C\text{-}F}$ = 286 Hz, *C*F_3), 121.3 (=*C*HN), 120.1 (C_6H_4), 119.8 (C_6H_4), 118.3 (C=*C*H_2), 110.0 (C_6H_4), 107.3 (=*C*CCF_3), 77.3 (q, $J_{C\text{-}F}$ = 32 Hz, *C*CF_3), 64.1 (O*C*H_2), 49.1 (=C*C*H_2), 14.2 (OCH_2*C*H_3); LRMS (EI) *m/z* 328 $[M+H]^+$; HRMS (EI) exact mass calculated for $C_{16}H_{16}NO_3F_3$ $[M+H]^+$ requires *m/z* 328.1155, found *m/z* 328.1159. Enantiomeric excess was calculated from the HPLC profile (Diacel Chiracel OD-H, flow rate: 0.5 ml/min, hexane: 2-propanol = 90:10). Retention times: major (*R*)-enantiomer t_r = 14.43 min, minor (*R*)-enantiomer t_r = 30.1 min; 30% ee. Absolute stereochemistry assigned by analogy.

Ethyl-(2-hydroxy-4-phenyl-2-trifluoromethyl)-pent-4-enoate (3.6a). Sample prepared according to the general procedure outlined above and isolated as colourless oil after purification by column chromatography. $[\alpha]_D$ = +26.1 (*c* 1.0, CH_2Cl_2, 65% ee); ^1H NMR (300.0 MHz, $CDCl_3$, δ): 7.26-7.17 (m, 5H, Ar-*H*), 5.30 (s, 1H, =CH_aH_b), 5.20 (s, 1H, =CH_aH_b), 3.99-3.89 (m, 1H, OCH_aH_b), 3.78 (s br, 1H, O*H*), 3.60-3.50 (m, 1H, OCH_aH_b), 3.24 (d, J = 14.0 Hz, 1H, =CCH_aH_b), 3.0 (d, J = 13.9 Hz, 1H, =CCH_aH_b), 1.01 (t, J = 7.2 Hz, 3H, OCH_2*CH*$_3$); $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$, δ): 169.8 (*C*=O), 141.6 (C_6H_5), 141.4 (*C*=CH_2), 128.2 (C_6H_5), 127.7 (C_6H_5), 126.8 (C_6H_5), 122.1 (q, $J_{C\text{-}F}$ = 286.1 Hz, *C*F_3), 119.0 (C=*C*H_2), 78.1 (q, $J_{C\text{-}F}$ = 29.1 Hz, *C*CF_3), 64.1 (O*C*H_2CH$_3$), 38.1 (=C*C*H_2), 13.4 (OCH_2*C*H_3); LRMS (EI) *m/z* 289 $[M+H]^+$. Retention times: major (2*R*)-enantiomer t_r = 51.3 min, minor (2*S*)-enantiomer t_r = 52.1 min; 65% ee. Absolute stereochemistry assigned by analogy.

Ethyl 4-(4-chlorophenyl)-2-hydroxy-2-(trifluoromethyl)pent-4-enoate (3.6b). Sample prepared according to the general procedure outlined above and isolated as a colourless oil after purification by column chromatography. $[\alpha]_D$ = +14.7 (*c* 1.0, CH_2Cl_2, 38% ee); ^1H NMR (300.0 MHz, $CDCl_3$, δ): 7.25-7.10 (m, 4H, Ar-*H)*, 5.29 (s, 1H, =CH_aH_b), 5.19 (s, 1H, =CH_aH_b), 4.19-3.95 (m, 1H, OCH_aH_b), 3.76-3.61 (m, 1H, OCH_aH_b), 3.79 (s, 1H, O*H*), 3.20 (d, J = 14.1 Hz, 1H, =CCH_aH_b) , 3.01 (d, J = 14.1 Hz, 1H, =CCH_aH_b), 1.11 (t, J = 7.2 Hz, 3H, CH_2CH_3); $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$, δ): 170.0 (*C*=O), 141.0 (C_6H_4), 140.1 (*C*=CH_2), 134.2 (C_6H_4), 128.3 (C_6H_4), 128.1 (C_6H_4), 122.1 (q, $J_{C\text{-}F}$ = 286.2 Hz, *C*F_3), 120.0 (C=*C*H_2), 78.1 (q, $J_{C\text{-}F}$ = 29 Hz, *C*CF_3), 64.5 (O*C*H_2), 38.2 (=C*C*H_2), 14.8

OCH_2CH_3); LRMS (EI) *m/z* 323 $[M+H]^+$. Retention times major (2*R*)-enantiomer t_r = 63.9 min; (2*S*)-enantiomer t_r = 63.7 min; 38% ee. Absolute stereochemistry assigned by analogy.

Ethyl 2-hydroxy-4-(o-tolyl)-2-(trifluoromethyl)pent-4-enoate (3.6c). Sample was prepared according to the general procedure outlined above and isolated as a colourless oil after purification by column chromatography. $[\alpha]_D$ = +43.0 (*c* 1.0, CH_2Cl_2, 82% ee); ^{1}H NMR (300.0 MHz, $CDCl_3$, δ): 7.15-6.95 (m, 4H, Ar-*H*), 5.35 (s, 1H, =CH_aH$_b$), 5.1 (s, 1H, =CH$_a$$H_b$), 3.95-3.82 (m, 1H, OC$H_aH_b$), 3.75 (s, 1H, O*H*), 3.50-3.38 (m, 1H, OCH$_a$$H_b$), 3.2-3.1 (d, *J* = 14.6 Hz, 1H, =CCH_aH$_b$), 2.95-2.85 (d, *J* = 13.7 Hz, 1H, =CCH$_a$$H_b$), 2.25 (s, 3H, C$H_3$), 1.10-1.03 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3); ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$, δ): 169.5 (*C*=O), 141 (C_6H_4), 140.7 (C_6H_4), 135.2 (*C*=CH_2), 130.4 (C_6H_4), 129.2 (C_6H_4), 127.7 (C_6H_4), 125.7 (C_6H_4), 122.1 (q, J_{C-F} = 286 Hz, *C*F_3), 121.7 (C=*C*H_2), 78.1 (q, J_{C-F} = 29 Hz, *C*CF_3), 63.8 (O*C*H_2), 38.9 (=C*C*H_2), 20.2 (*C*H_3), 13.7 (CH_2CH_3); LRMS (EI) *m/z* 302 $[M]^+$, HRMS (EI): exact mass calculated for $C_{15}H_{17}O_3F_3$ $[M]^+$ requires *m/z* 302.1489, found *m/z* 302.1474. Retention times: major (2*R*)-enantiomer t_r = 51.4 min; (2*S*)-enantiomer t_r = 51.8 min; 82% ee. Absolute stereochemistry assigned by analogy.

(E)-Ethyl 2-hydroxy-4-phenyl-2-(trifluoromethyl) but-3-enoate (3.9a). Sample was prepared according to the general procedure described above and isolated as a colourless oil after purification by column chromatography. $[\alpha]_D$ = +44.6 (*c* 1.0, CH_2Cl_2, 93% ee); ^{1}H NMR (300.0 MHz, $CDCl_3$, δ): 7.35-7.11 (m, 5H, C_6H_5), 6.50-6.41 (d, *J* = 15.9 Hz, 1H, =C*H*), 6.10-5.95 (m, 1H, =C*H*), 4.38-4.21 (m, 2H, OCH_2), 3.90-3.81 (br s, 1H, O*H*), 2.89-2.71 (m, 2H, CH_2), 1.30-1.19 (t, *J* = 7.1 Hz, 3H, CH_3); ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$, δ): 170.0 (*C*=O), 137.4 (C_6H_5), 136.0 (C_6H_5*C*H), 132.5 (C_6H_5), 124.6 (C_6H_5), 123.1 (C_6H_5), 121.4 (q, J_{C-F} = 286.4 Hz, *C*F_3), 120.8 (=*C*HCH_2), 77.8 (q, J_{C-F} = 29.3 Hz, *C*CF_3), 64.6 (O*C*H_2CH_3), 50.0 (CH*C*H_2), 14.7 (OCH_2CH_3); LRMS (EI) *m/z* 270 $[M-OH]^+$. Enantiomeric excess determined by GC using SUPELCO BETA DEX column (injection temp 140 °C; column conditions 140 °C for 45 min, ramp to 180 at 3°C/min, hold for 20 min): major (*R*)-enantiomer t_r = 35.7 min, minor (*S*)-enantiomer t_r = 33.6 min; 93% ee. Absolute stereochemistry assigned by analogy.

(E)-Ethyl 2-hydroxy-5-(p-tolyl)-2-(trifluoromethyl)pent-4-enoate (3.9b). Sample was prepared according to the general procedure described above and isolated as a colourless oil after purification by column chromatography. $[\alpha]_D$ = +34.2 (*c* = 1.0, CH_2Cl_2, 70% ee); ^{1}H NMR (300.0 MHz, $CDCl_3$, δ): 7.15-7.05 (m, 4H, C_6H_4), 6.74-6.65 (d, *J* = 15.9 Hz, C_6H_4C*H*=), 5.97-5.84 (m, 1H, =*C*HCH_2), 4.35-4.23 (m, 2H, OCH_2), 3.85 (s, 1H, O*H*), 2.88-2.76 (m, 2H, CH_2CH=), 2.24 (s, 3H, C_6H_4CH_3), 1.33-1.27 (t, *J* = 7.3 Hz, 3H,

OCH_2CH_3); $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$, δ): 170.0 (*C*=O), 137.3 (C_6H_4CH=), 135.9 (C_6H_4), 130.5 (C_6H_4), 128.2 (C_6H_4), 127.1 (C_6H_4), 123.5 (q, J_{C-F} = 286 Hz, CF_3), 122.4 (=$CHCH_2$), 77.1 (q, J_{C-F} = 29.3 Hz, CCF_3), 64.4 (OCH_2), 37.1 (=$CHCH_2$), 20.9 ($C_6H_4CH_3$), 15.2 (OCH_2CH_3); LRMS (EI) *m/z* 301 $[M-H]^+$. Enantiomeric excess determined by GC using SUPELCO BETA DEX column (injection temp 140 °C; column conditions 140 °C for 45 min, ramp to 180 at 3°C/min, hold for 20 min): major (*R*)-enantiomer t_r = 52.2 min, minor (*S*) -enantiomer t_r = 50.9 min; 70% ee. Absolute stereochemistry assigned by analogy.

(E)-Ethyl 2-hydroxy-5-(o-tolyl)-2-(trifluoromethyl)pent-4-enoate (3.9c). Sample was prepared according to the general procedure outlined above and isolated as a colourless oil after purification by column chromatography. $[\alpha]_D$ = +21.4 (*c* 1.0, CH_2Cl_2, 67% ee); ^1H NMR (300.0 MHz, $CDCl_3$, δ): 7.15-7.1 (m, 4H, C_6H_4), 6.74-6.65 (d, *J* = 15.9 Hz, C_6H_4CH=), 5.97-5.84 (m, 1H, =$CHCH_2$), 4.35-4.23 (m, 2H, OCH_2), 3.85 (s, 1H, O*H*), 2.88-2.76 (m, 2H, =$CHCH_2$), 2.24 (s, 3H, $C_6H_4CH_3$), 1.33-1.27 (t, *J* = 7.3 Hz, 3H, OCH_2CH_3); $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$, δ): 170.04 (*C*=O), 137.3 (C_6H_4CH=), 135.9 (C_6H_4), 135.4 (C_6H_4), 130.5 (C_6H_4), 128.2 (C_6H_4), 127.8 (C_6H_4), 127.1 (C_6H_4), 123.5 (q, J_{C-F} = 286 Hz, CF_3), 122.4 (=$CHCH_2$), 77.1 (q, J_{C-F} = 29.1 Hz, CCF_3), 64.4 (OCH_2), 37.1 (=$CHCH_2$), 20.9 ($C_6H_4CH_3$), 15.2 (OCH_2CH_3); LRMS (EI) *m/z* 301 $[M-H]^+$. Enantiomeric excess determined by GC using SUPELCO BETA DEX column (injection temp 110 °C; column conditions 110 °C for 35 min, ramp to 180 at 3°C/min, hold for 20 min): major (*R*)-enantiomer t_r = 49.8 min, minor (*S*)-enantiomer t_r = 50.2 min; 67% ee. Absolute stereochemistry assigned by analogy.

(E)-Ethyl 5-(3,5-dimethylphenyl)-2-hydroxy-2-(trifluoromethyl)pent-4-enoate (3.9d). Sample was prepared according to the general experimental procedure outlined above and isolated as a colourless oil after purification by column chromatography. $[\alpha]_D$ = +43.0 (*c* 1.0, CH_2Cl_2, 94% ee); ^1H NMR (300.0 MHz, $CDCl_3$, δ): 6.90-6.80 (m, 3H, Ar-*H*), 6.45 (d, *J* = 16.0 Hz, 1H, C_6H_3CH=), 6.04-5.91 (m, 1H, =$CHCH_2$), 4.33-4.23 (m, 2H, OCH_2), 3.82 (s, 1H, O*H*), 2.81-2.73 (m, 2H, =$CHCH_2$), 2.30-2.20 (s, 6H, $(CH_3)_2C_6H_4$), 1.31 (t, *J* = 7.2 Hz, 3H, CH_2CH_3); $^{13}C\{^1H\}$ NMR 75.5 MHz, $CDCl_3$, δ): 169.1 (*C*=O), 137.2 (C_6H_3), 136.2 (Ar*C*H=), 135.6 (C_6H_3), 128.8 (C_6H_3), 125.0 (C_6H_3), 123.5 (q, J_{C-F} = 286 Hz, CF_3), 119.5 (=$CHCH_2$), 77.3 (q, J_{C-F} = 29.1 Hz, CCF_3), 63.1 (OCH_2), 35.2 (=$CHCH_2$), 20.1 ($C_6H_3(CH_3)_2$), 13.1 (OCH_2CH_3); LRMS (EI) *m/z* 315 $[M-H]^+$. Enantiomeric excess determined by GC using SUPELCO BETA DEX column (injection temp 140 °C; column conditions 140 °C for 45 min, ramp to 180 at 3°C/min, hold for 20 min): major (*R*)-

enantiomer t_r = 57.42 min; minor (*S*)-enantiomer t_r = 56.80 min; 94% ee. Absolute stereochemistry assigned by analogy.

Ethyl *E*-5-(4-chlorophenyl)-2-hydroxy-2-(trifluoromethyl)pent-4-enoate (3.9e). Sample was prepared according to the general experimental procedure outlined above and isolated as colourless oil after purification by column chromatography. $[\alpha]_D$ = +33.5 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (300.0 MHz, $CDCl_3$, δ): 7.30-7.19 (m, 4H, Ar-*H*), 6.49-6.39 (d, *J* = 15.7 Hz, 1H, ArC*H*=), 6.10-5.95 (m, 1H, =C*H*CH_2), 4.38-4.24 (m, 2H, OC*H*$_2$$CH_3$), 3.82 (br s, 1H, O*H*), 2.82-2.74 (m, 2H, =CHC*H*$_2$), 1.30 (t, *J* = 7.1 Hz, 3H, C*H*$_3$); ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$, δ): 170.0 (*C*=O), 135.1 (C_6H_4), 134.8 (C_6H_4), 134.1 (C_6H_4*C*H=), 133.6 (C_6H_4), 130.0 (C_6H_4), 123.2 (q, $J_{C\text{-}F}$ = 286 Hz, *C*F_3), 121.0 (=*C*HCH_2), 77.8 (q, $J_{C\text{-}F}$ = 29.1 Hz, *C*CF_3), 64.6 (O*C*H$_2$$CH_3$), 35.8 (=CH*C*H$_2$), 14.2 (OCH$_2$*C*H$_3$); LRMS (EI) *m/z* 321 [M-H]$^+$. Enantiomeric excess determined by GC using SUPELCO BETA DEX column (injection temp 140 °C; column conditions 140 °C for 45 min, ramp to 180 at 3°C/min, hold for 20 min): major (*R*)-enantiomer t_r = 60.3 min; minor (*S*)-enantiomer t_r = 59.6 min; >99% ee. Absolute stereochemistry assigned by analogy.

Ethyl 2-(5-allylthiophen-2-yl)-3,3,3-trifluoro-2-hydroxypropanoate (3.12b). Sample was prepared according to the general procedure outlined above and isolated as a colourless oil after purification by column chromatography. $[\alpha]_D$ = -16.0 (*c* 1.0, $CHCl_3$, 60% ee); ^{1}H NMR (300.0 MHz, $CDCl_3$, δ): 7.14-7.10 (d, *J* = 3.6 Hz, 1H, C_4*H*$_2$S), 6.70 (d, *J* = 3.6 Hz, 1H, C_4*H*$_2$S), 5.96-5.81 (m, 1H, =C*H*C_4H_2S), 5.11-4.99 (m, 2H, =C*H*), 4.49 (s, 1H, O*H*), 4.42 (q, *J* = 7.1 Hz, 2H, OC*H*$_2$), 3.49 (d, *J* = 6.7 Hz, 2H, C*H*$_2$), 1.35 (t, *J* = 7.1 Hz, 3H, C*H*$_3$); ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$, δ): 168.2 (*C*=O), 145.0 (C_4H_2S), 135.9 (C_4H_2S), 133.5 (H*C*=CH_2), 127.6 (C_4H_2S), 125.0 (C_4H_2S), 121.1 (q, *J* = 283.2 Hz, *C*F_3), 116.9 (HC=*C*H_2), 77.0 (q, *J* = 27.1 Hz, *C*CF_3), 65.1 (O*C*H_2), 34.2 (=C*C*H_2), 14.0 (OCH$_2$*C*H$_3$); LRMS [M]$^+$ *m/z* 294; HRMS (ESI): exact mass calculated for $C_{12}H_{13}O_3F_3S$ [M]$^+$ requires *m/z* 294.0534, found *m/z* 294.0547. Enantiomeric excess determined by GC using SUPELCO BETA DEX column (injection temp 140 °C; column conditions 140 °C for 45 min, ramp to 180 at 3°C/min, hold for 20 min): major (*R*)-enantiomer t_R = 25.5 min, minor (*S*)-enantiomer t_R = 25.1 min; 60% ee. Absolute stereochemistry assigned by analogy.

Ethyl 3,3,3-trifluoro-2-hydroxy-2-(thiophen-2-yl)propanoate (3.15b). Sample was prepared according to the general procedure outlined above and isolated as a colourless oil after purification by column chromatography. $[\alpha]_D$ = -13.7 (*c* 1.0, $CHCl_3$, 80% ee); ^{1}H NMR (300.0 MHz, $CDCl_3$, δ): 7.35-7.29 (d, *J* = 5.1 Hz, 2H, C_4*H*$_3$S), 6.99 (dd, *J* = 3.9 Hz,

1.2 Hz, 1H, C_4H_3S), 4.58 (br s, 1H, O*H*), 4.46-4.32 (m, 2H, OCH_2), 1.35 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3); $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$, *δ*): 167.0 (*C*=O), 137.2 (C_4H_3S), 135.6 (C_4H_3S), 127.1 (C_4H_3S), 127.0 (C_4H_3S), 119.8 (q, J_{C-F} = 282.9 Hz, CF_3), 76.8 (q, J_{C-F} = 27.8 Hz, CCF_3), 64.2 (OCH_2), 12.5 (OCH_2CH_3); LRMS (EI) *m/z* 253 $[M-H]^+$. Enantiomeric excess determined by GC using SUPELCO BETA DEX column (injection temp 120 °C; column conditions 120 °C for 60 min, ramp to 180 at 3°C/min, hold for 20 min): major (*R*)-enantiomer t_R = 16.5 min, minor (*S*)-enantiomer t_R = 16.8 min; 80% ee. Absolute stereochemistry assigned by analogy.

Ethyl 3,3,3-trifluoro-2-hydroxy-2-(5-methylthiophen-2-yl)-propanoate (3.15d). Sample was prepared according to the general procedure outlined above and isolated as a colourless oil after purification by column chromatography. $[\alpha]_D$ = -6.1 (*c* 1.0, $CHCl_3$, 67% ee); ^1H NMR (300.0 MHz, $CDCl_3$, *δ*): 7.08 (d, *J* = 3.7 Hz, 1H, C_4H_2S), 6.62 (d, *J* = 3.7 Hz, 1H, C_4H_2S), 4.55 (br s, 1H, O*H*) 4.39-4.25 (m, 2H, OCH_2), 2.36 (s, 3H, CH_3), 1.32 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3); $^{13}C\{^1H\}$ NMR 75.5 MHz, $CDCl_3$, *δ*): 167.1 (*C*=O), 140.8 (C_4H_2S), 132.2 (C_4H_2S), 126.4 (C_4H_2S), 124.5 (C_4H_2S), 120.0 (q, J_{C-F} = 283.0 Hz, CF_3), 76.9 (q, J_{C-F} = 26.8 Hz, CCF_3), 63.9 (OCH_2), 14.9 (OCH_2CH_3), 13.8 (CH_3); LRMS (EI) *m/z* 268 $[M-H]^+$. Enantiomeric excess determined by GC using SUPELCO BETA DEX column (injection temp 110 °C; column conditions 110 °C for 60 min, ramp to 180 at 3°C/min, hold for 20 min): major (*R*)-enantiomer t_R = 43.1 min, minor (*S*)-enantiomer t_R = 43.7 min; 67% ee. Absolute stereochemistry assigned by analogy.

Ethyl 2-(5-allylfuran-2-yl)-3,3,3-trifluoro-2-hydroxypropanoate (3.12a). Sample was prepared according to the general procedure described above and isolated as a colourless oil after purification by column chromatography. $[\alpha]_D$ = -16.1 (*c* 1.0, $CHCl_3$, 50% ee); ^1H NMR (300.0 MHz, $CDCl_3$, *δ*): 6.48-6.45 (d, *J* = 3.3 Hz, 1H, C_4H_2O), 6.00 (d, *J* = 3.2 Hz, 1H, C_4H_2O), 5.92-5.78 (m, 1H, =C*H*CH_2), 5.13-5.05 (m, 2H, CH_2=CH=), 4.40 (q, *J* = 7.1 Hz, 2H,OCH_2), 4.30 (br s, 1H, O*H*), 3.50-3.40 (m, 2H, CH_2=CH=), 1.32 (t, *J* = 7.6 Hz, 3H, CH_3); $^{13}C\{^1H\}$ NMR 75.5 MHz, $CDCl_3$, *δ*): 167.0 (*C*=O), 152.6 (O*C*C=), 143.1 (O*C*CH_2), 134.0 (*C*H=CH_2), 120.0 (q, J_{C-F} = 288.3 Hz, CF_3), 116.8 (*C*H_2=CH), 110.1 (C=*C*HC), 115.8 (C=*C*HC), 76.9 (q, J_{C-F} = 29.2 Hz, CCF_3), 63.9 (OCH_2), 32.5 (=CH*C*H_2), 14.0 (OCH_2CH_3); LRMS (ESI) $[M]^+$ *m/z* 278; HRMS (ESI) exact mass calculated for $C_{12}H_{13}O_4F_3$ $[M]^+$ requires *m/z* 278.0760, found *m/z* 278.0747. Enantiomeric excess determined by GC using SUPELCO BETA DEX column (injection temp 120 °C; column conditions 120 °C for 25 min, ramp to 180 at 3°C/min, hold for 20 min): major (*R*)-

enantiomer t_R = 22.3 min, minor (*S*)-enantiomer t_R = 22.8 min; 50% ee. Absolute stereochemistry assigned by analogy.

Ethyl 3,3,3-trifluoro-2-(furan-2-yl)-2-hydroxypropanoate (3.15a). Sample was prepared according to the general procedure described above and isolated as a colourless oil after purification by column chromatography. $[\alpha]_D$ = -15.1 (*c* 1.0, $CHCl_3$, 67% ee); ^{1}H NMR (300.0 MHz, $CDCl_3$, δ): 7.40 (s, 1H, C_4H_3O), 6.56 (s, 1H, C_4H_3O), 6.36 (s, 1H, C_4H_3O), 4.56 (br s, 1H, O*H*), 4.45-4.30 (m, 2H, OCH_2), 1.28 (t, *J* = 7.6 Hz, 3H, OCH_2CH_3); $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$, δ): 167.0 (*C*=O), 152.6 (O*C*C=), 143.1 (O*C*CH), 120.0 (q, J_{C-F} = 283.5 Hz, CF_3), 115.8 (C=*C*HC), 110.1 (C=*C*HC), 76.9 (q, J_{C-F} = 27.4 Hz, CCF_3), 63.9 (OCH_2CH_3), 14.0 (OCH_2CH_3); LRMS (EI) *m/z* 236 $[M-H]^+$. Enantiomeric excess determined by GC using SUPELCO BETA DEX column (injection temp 110 °C; column conditions 110 °C for 60 min, ramp to 180 at 3°C/min, hold for 20 min): major (*R*)-enantiomer t_R = 10.3 min, (*S*)-enantiomer t_R = 10.9 min; 67% ee. Absolute stereochemistry assigned by analogy.

Ethyl 3,3,3-trifluoro-2-hydroxy-2-(5-methylfuran-2-yl)propanoate (3.15c). Sample was prepared according to the general procedure described above and isolated as a colourless oil after purification by column chromatography. $[\alpha]_D$ = -11.8 (*c* 1.0, $CHCl_3$, 80% ee); ^{1}H NMR (300.0 MHz, $CDCl_3$, δ): 6.41 (d, *J* = 3.3 Hz, 1H, C_4H_2O), 5.92 (d, J = 3.3 Hz, 1H, C_4H_2O), 4.43-4.32 (m, 2H, OCH_2), 2.22 (s, 3H, CH_3), 1.32 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3); $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$, δ): 167.0 (*C*=O), 152.6 (O*C*C=), 143.1 (O*C*CH), 120.0 (q, J_{C-F} = 283.0 Hz, CF_3), 115.8 (C=*C*HC), 110.1 (C=*C*HC), 76.9 (q, J_{C-F} = 26.8 Hz, CCF_3), 63.9 (OCH_2), 14.0 (OCH_2CH_3), 10.1 (CH_3); LRMS (EI) *m/z* 251 $[M-H]^+$. Enantiomeric excess determined by GC using SUPELCO BETA DEX column (injection temp 110 °C; column conditions 110 °C for 60 min, ramp to 180 at 3°C/min, hold for 20 min): major (*R*)-enantiomer t_R = 15.5 min, minor (*S*)-enantiomer t_R = 15.9 min; 80% ee. Absolute stereochemistry assigned by analogy.

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Chapter 4

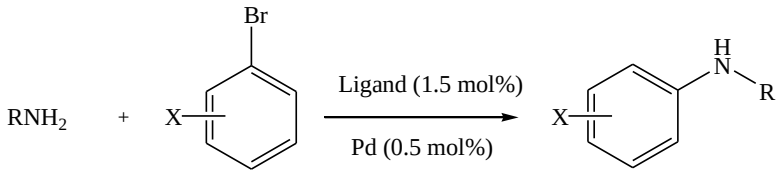
Buchwald-Hartwig Amination

4.1 Introduction

Catalytic amination of aryl halides represents a mild alternative to the classical C-N bond formation reactions and provides a route to aniline derivatives that are otherwise inaccessible.[1, 2] In this light the biaryl architecture has found extensive application in palladium-catalysed inter- and intra-molecular amination of aryl halides.[3-5]

Catalytic amination (Eq. 4.1) was developed independently by both Buchwald [6] and Hartwig.[7] The reaction has been widely studied to better understand its synthetic and mechanistic aspects.[8] It is a very useful reaction used so form substituted anilines and the set of reaction conditions pioneered by Buchwald and Hartwig tolerate a wide scope of substrates[4] and are commonly used in aminations. The metal of choice employed in amination is Pd(0) with either $Pd_2(dba)_3$ or $Pd(OAc)_2$ commonly used as sources of palladium; the former providing Pd(0) and latter Pd(II). In the case of Pd(II), it initially needs to be reduced to Pd(0), which is thought to occur *in situ* with a mixture of amine and base. BINAP is widely employed in a host of aminations due to its relatively broad functional group tolerance compared to other biaryl diphosphine ligands.

Equation 4.1. An Illustrative Reaction Scheme for Palladium-Catalysed Amination between Primary Amine and Substituted Arylbromide Substrates.



X = Me, Cl, CN, NO_2
R = Ph, Allyl, Propargyl

Substituted aryl halides are the most widely used electrophilic coupling partners in these transformations. One part of our research is focused on application of aryl bromides since their chloride counterparts are not activated by BINAP/Pd(0) and, as such, cannot be used for comparative catalysis.

Furthermore, phenol-based electrophiles are also used as coupling partners. Hydroxy groups are frequently converted into sulfonates because the RSO_3^- is an excellent leaving group. For instance, amongst the perfluoroalkanesulfonates, the triflate group is the most popular[9] and has been widely applied in cross coupling reactions, primarily because the

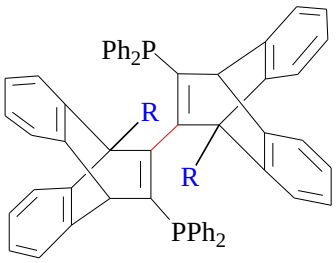
strong electron withdrawing effect of the perfluoroalkyl chain greatly weakens the C-O bond enabling easy cleavage via smooth transition-metal insertion into the carbon-oxygen bond. We also evaluated the efficacy of imidazolylsulfonates in amination (see Chapter 1). Over the last few years, they have emerged as an alternative leaving group to the more traditional triflate-based electrophiles for weakening C-O bond.[9, 10] There have only been a few publications on the application of imidazolylsulfonates in both amination and other cross coupling reactions.[11-13] These early studies have demonstrated their advantages over triflates, namely in handling, preparation and the ease with which the imidazolyl leaving group can be broken down into harmless components, which highlights their superior green credentials over halogen and triflate-based electrophiles. However, there is plenty of scope for improvement in reaction conditions but also in evaluating the efficacy of different supporting ligands with these electrophiles.

4.1.1 Application of Biaryl/Biaryl-like Diphosphines

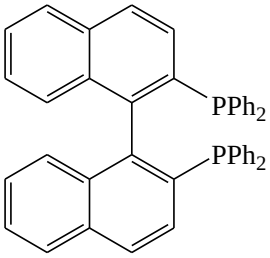
Over the years, biaryl (and biaryl-like) diphosphines have found useful applications in a host of achiral C-N bond forming reactions. Previous work by the Doherty group has already established that catalysts based on Pd(0)/H_2-CATPHOS can compete effectively with its BINAP counterpart.[14] Therefore, this reaction was considered ideal for undertaking a comparison of the efficiency of *rac*-Me_2-CATPHOS and *rac*-$(MeO)_2$ -CATPHOS.

Even though BINAP is an excellent ligand for a host of palladium-catalysed aminations, it is not superior in all transformations and is often substrate specific where substitutions on the biaryl architecture of the ligand have dramatic affect on catalyst performance (Chapter 1, Chapter 2).[15, 16] As such, there is considerable interest in developing alternative bicyclic diphosphines that are easy to prepare, effective over a wide range of reactions and wide scope of functional groups and modular in nature.

Figure 4.1. Back-bone Structures of *rac*-R_2-CATPHOS and *rac*-BINAP



rac-CATPHOS
R = H (**2.5a**)
Me (**2.5b**)
OMe (**2.5c**)



rac-BINAP

Through synthesis of CATPHOS analogues, the Doherty group has demonstrated the versatility and viability of the inexpensive and straightforward three-step ligand synthesis method. We have used BINAP as the benchmark catalyst for our comparative study as it continues to be the most widely used bidentate ligand for the coupling of aryl bromides with amines[3] despite the emergence of a range of other bulky and electron-rich diphosphine or monophosphine ligands.[17-19] We have compared the performance of three CATPHOS analogues against BINAP in order to reveal any relevant differences in activity with the aim of guiding future phosphine synthesis to identify an optimal catalyst. It is worth noting that Hartwig has demonstrated that, under some conditions, DPPF (1,1'-bis(diphenylphosphino)ferrocene) is highly effective for certain classes of substrates.[20]

4.2 Aryl Bromides

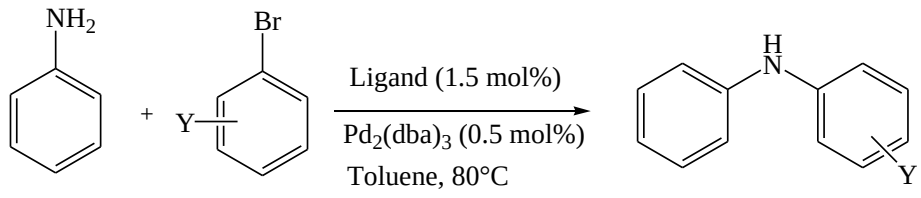
4.2.1 Coupling to Aniline

Our initial study in this area focused on the amination of a range of aryl bromides with aniline using *rac*-Me_2-CATPHOS and *rac*-BINAP. The efficacy of H_2-CATPHOS and *rac*-$(MeO)_2$-CATPHOS were also investigated in some of these aminations in order to evaluate the effect of the ligand structure on catalyst efficiency. All the reactions were carried out with Pd(0)/ligand (0.5 mol% Pd/1.5 mol% ligand) in toluene at 80 °C with strong base NaO-*t*-Bu, full details of which are given in Table 4.1. Following well-established reaction protocols, only a slight excess of the amine is used (1.1 mol. eq.) in order to minimise formation of unwanted side products, especially triarylamine.[14]

Under these conditions, we found that all but one of the conversions was complete within 12 h. Our results with *rac*-BINAP and H_2-CATPHOS were comparable to the previous work in the Doherty group.[14] Initially a range of aminations between aniline **4.1a** and various substituted aryl bromides **4.2a-e** were carried out. The initial results were very promising, in particular in the reaction involving the challenging 1-bromo-3,5-dimethylbenzene **4.2c**: Pd(0)/*rac*-Me_2-CATPHOS gave **4.3c** with 98% conversion after 2 h compared to only 60% with its BINAP counterpart (entries 7-9). Promisingly, Pd(0)/H_2-CATPHOS catalyst also gave a conversion of 95% in the same time. Similarly, the reaction involving 1-bromo-4-chlorobenzene **4.2a** catalysed by Pd(0)/*rac*-Me_2-CATPHOS gave **4.3a** with 84% conversion after 2 h compared to 70% with its *rac*-BINAP counterpart (entries 1 and 4).

The Pd(0)/*rac*-Me_2-CATPHOS system showed promising performance in the reaction involving the electron deficient 1-bromo-4-chlorobenzene **4.2a** (entries 1-4). Here, it is worth noting that the highest conversion for the corresponding product **4.3a** was obtained with Pd(0)/H_2-CATPHOS (98%) amongst the CATPHOS-based catalysts which was markedly better than that of 70% obtained with Pd(0)/*rac*-BINAP. Furthermore, reaction with challenging disubstituted 1-bromo-3,5-dimethylbenzene **4.2c** also gave **4.3c** in high conversions in shorter time (entries 7-9) with *rac*-Me_2-CATPHOS (98% after 2 h) compared to *rac*-BINAP (60% after 2 h). These results demonstrate that both the electronic and the steric hindrance factors contribute to the reaction outcome.

Table 4.1. Palladium Catalysed Amination between Aniline **4.1a** and Aryl Bromides **4.2a-e** Catalysed by Pd/*rac*-Me_2-CATPHOS and its *rac*-$(MeO)_2$-CATPHOS and H_2-CATPHOS Counterparts; a Comparison with Pd/*rac*-BINAP.[a]



4.1a **4.2a-e** **4.3a-e**

Ent.	Y	Ligand	Time (h)	% Conversion **4.3a-e**[b, c]	% Yield
1	4-Cl	Me_2-CATPHOS	2	84 (**4.3a**)	75
2	4-Cl	$(MeO)_2$-CATPHOS	2	67 (**4.3a**)	63
3	4-Cl	H_2-CATPHOS	2	98 (**4.3a**)	95
4	4-Cl	BINAP	2	70 (**4.3a**)	60
5	4-Me	Me_2-CATPHOS	6	61 (**4.3b**)	60
6	4-Me	BINAP	6	69 (**4.3b**)	58
7	3,5-Me_2	Me_2-CATPHOS	2	98 (**4.3c**)	96
8	3,5-Me_2	H_2-CATPHOS	2	95 (**4.3c**)	85
9	3,5-Me_2	BINAP	2	60 (**4.3c**)	55
10	2-Me	Me_2-CATPHOS	4.5	65 (**4.3d**)	61
11	2-Me	$(MeO)_2$-CATPHOS	4.5	84 (**4.3d**)	80
12	2-Me	H_2-CATPHOS	4.5	95 (**4.3d**)	90
13	2-Me	BINAP	4.5	80 (**4.3d**)	78
14	H	Me_2-CATPHOS	2	60 (**4.3e**)	56
15	H	BINAP	2	85 (**4.3e**)	72

[a]Reaction conditions: $Pd_2(dba)_3$ (0.5 mol %), ligand (1.5 mol%), NaO-*t*-Bu (1.3 mol. eq.) and 12 mL of toluene, then aryl bromide and aniline (1.1 mol. eq.) at 80 °C for allocated time. [b]GCMS conversion with internal standard. [c]Average of three runs.

Furthermore, 1-bromo-4-methylbenzene **4.2b** also proved to be an effective coupling partner with aniline **4.1a**, affording **4.3b** in 61% conversion catalysed by Pd(0)/*rac*-Me_2-CATPHOS, which is comparable to that of 69% obtained for **4.3b** with its BINAP counterpart after 6 h. The reaction time required to achieve acceptable conversions for the amination with the methyl-substituted aryl bromide **4.2b** (6 h) was much longer than that needed for 1-bromo-4-chlorobenzene **4.2a** (2 h) because it is electron rich.[21]

In a closely related reaction involving the more sterically hindered 1-bromo-2-methylbenzene **4.2d**, the same pattern was maintained and **4.3d** was obtained in 65% and 80% conversions with Pd(0)/*rac*-Me_2-CATPHOS and Pd(0)/*rac*-BINAP, respectively. Here Pd(0)/*rac*-$(MeO)_2$-CATPHOS and Pd(0)/H_2-CATPHOS gave **4.3d** in 95% and 84% conversions, respectively, outperforming their *rac*-Me_2-CATPHOS and *rac*-BINAP counterparts (entries 10-13).

It is noteworthy that the conversions with 1-bromo-2-methylbenzene **4.2d** were obtained after only 4.5 h (compared to 6 h with 1-bromo-4-methylbenzene) even though it is a sterically challenging substrate. Indeed there is clear precedent in the literature for this phenomenon,[4] where in a recent report the reaction of 4-bromoanisole with *n*-hexylamine using 0.5 mol % catalyst afforded 26% conversion to the desired product whereas the same reaction with the more sterically hindered and more electron rich 4-bromo-3-methylanisole proceeded to near-completion in the same time and reaction conditions. Also, the reaction with the more sterically hindered 1-bromo-2-methylbenzene **4.2d** showed formation of negligible amounts of triarylated amine side-product which is a problem commonly associated with ortho-substituted or highly active electron deficient aryl bromides. Formation of the undesired triarylated amine arises by subsequent arylation of the desired product and hence reduces the final yield of the diarylamine.

4.2.2 Coupling to Substituted Anilines

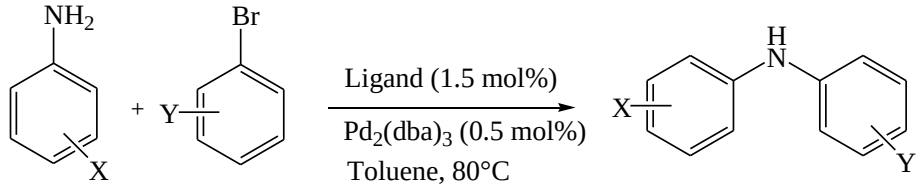
Buoyed by the initial results, we proceeded to expand the reaction series by including substituted anilines **4.1b-c** as coupling partners with substituted aryl bromides **4.2a-e** in order to further evaluate the functional group tolerance of our CATPHOS-based catalysts, full details of which are shown in Table 4.2

In the initial reactions with 4-methoxyaniline **4.1b**, we obtained very encouraging results with both bromobenzene **4.2a** and 1-bromo-4-chlorobenzene **4.2b** compared to precedents in the literature where, for example, a recent report for reaction of 4-methoxyaniline and

bromobenzene catalysed by CuI/*L*-Proline catalyst combination was carried out at 90 °C for 40 h to give the corresponding biaryl product in 90% yield.[22] However, entries 1 and 2 show that catalysts based on *rac*-Me_2-CATPHOS and *rac*-BINAP gave **4.3f** in 71% and 88% conversions, respectively, after only 8 h at 80 °C.

Other literature precedent for reaction of 4-methoxyaniline with 1-bromo-4-chlorobenzene catalysed by Cu/2-carboxylic acid pyrrole gives conversion of 76% for the final product after 24 h at 100 °C, with unacceptably high 20 mol% 2-carboxylic acid loading and 10 mol% copper-iodide.[23] With our reaction protocol, *rac*-Me_2-CATPHOS gave **4.3g** in 40% conversion after 8 h (72% with *rac*-BINAP) with only 1.5 mol% catalyst (Table 4.2, entries 3-4,). For the coupling of 4-bromotoluene to 4-methoxyaniline, Hartwig and colleagues have recently found a reaction system which uses 0.05 mol% loading of [(CyPF-^{t}Bu)$PdCl_2$] pre-catalyst to give the corresponding product in 98% conversion after 48 h at 110°C.[24] We obtained **4.3e** in 45% conversion for this reaction after 48 h with *rac*-Me_2-CATPHOS based catalyst compared to 67% with *rac*-BINAP (entries 5-6), both with 0.5 mol% catalyst. Literature precedents show that reactions with the electron-rich 4-methoxyaniline are problematic and often require high reaction temperatures and long reaction times.[22, 23] We have successfully demonstrated that Pd(0)/*rac*-Me_2-CATPHOS can catalyse a range of aminations with the electron-rich 4-methoxyaniline **4.1b**, giving conversions that compare favourably with those obtained with *rac*-BINAP, and certainly much superior to recent literature precedents in all but one of the conversions. We expanded the range of the substrates to include the electron poor 4-chloroaniline **4.1c** as the nucleophilic coupling partner and with this amine the reaction with bromobenzene **4.2a** afforded the product **4.3i** in high conversion with both *rac*-$(MeO)_2$-CATPHOS (85%) and H_2-CATPHOS (89%) but a very low conversion with *rac*-Me_2-CATPHOS (15%), under the same reaction conditions (entries 7-10). In the reaction of 4-chloroaniline **4.1c** with 1-bromo-4-chlorobenzene **4.2b**, good conversions were achieved for **4.3j** with *rac*-Me_2-CATPHOS (70%) and H_2-CATPHOS (56%) but a very low conversion for *rac*-$(MeO)_2$-CATPHOS (13%). These results (entries 11-14) clearly show that modifications of the CATPHOS architecture can greatly affect the reaction outcome.

Table 4.2. Amination of Aryl bromides with Substituted Anilines Catalysed by Pd/*rac*-Me_2-CATPHOS and its *rac*-$(MeO)_2$-CATPHOS and H_2-CATPHOS Counterparts, a Comparison with *rac*-BINAP.



4.1b-c **4.2a-b,e** **4.3f-k**

Ent.	X	Y	Ligand	Time (h)	% Conversion (**4.3f-k**)	% Yield
1	4-OMe	H	Me_2-CATPHOS	8	71 (**4.3f**)	65
2	4-OMe	H	BINAP	8	88 (**4.3f**)	78
3	4-OMe	4-Cl	Me_2-CATPHOS	8	40 (**4.3g**)	35
4	4-OMe	4-Cl	BINAP	8	72 (**4.3g**)	68
5	4-OMe	4-Me	Me_2-CATPHOS	48	45 (**4.3h**)	40
6	4-OMe	4-Me	BINAP	48	67 (**4.3h**)	60
7	4-Cl	H	Me_2-CATPHOS	4	15 (**4.3i**)	8
8	4-Cl	H	$(MeO)_2$-CATPHOS	4	85 (**4.3i**)	82
9	4-Cl	H	H_2-CATPHOS	4	89 (**4.3i**)	80
10	4-Cl	H	BINAP	4	95 (**4.3i**)	90
11	4-Cl	4-Cl	Me_2-CATPHOS	3.5	70 (**4.3j**)	60
12	4-Cl	4-Cl	$(MeO)_2$-CATPHOS	3.5	13 (**4.3j**)	10
13	4-Cl	4-Cl	H_2-CATPHOS	3.5	56 (**4.3j**)	52
14	4-Cl	4-Cl	BINAP	3.5	83 (**4.3j**)	80
15	4-Cl	4-Me	Me_2-CATPHOS	4	85 (**4.3k**)	82
16	4-Cl	4-Me	BINAP	4	98 (**4.3k**)	90

[a]Reaction Conditions: $Pd_2(dba)_3$ (0.5 mol %), ligand (1.5 mol%), NaO-*t*-Bu (1.3 mol. eq.) and 12 mL of toluene followed by aryl bromide and aniline (1.1 mol. eq.) at 80 °C for allocated time, followed by addition of internal standard. [b]Conversion obtained by GC. [c]Average of three runs.

4.2.3 Coupling to Functionalised Primary Amines

In the final part of this section, non-aryl amines were used as coupling partners (Table 4.3). Overall the catalysts based on CATPHOS diphosphine gave higher conversions than their *rac*-BINAP counterparts in all these reactions, with moderate to very high conversions achieved in reasonable reaction times. Initially, the reaction of 2-aminopyridine **4.5a** with 1-bromo-2-methylbenzene **4.4a** gave the product **4.6a** in very high conversions with both

rac-Me_2-CATPHOS (87%) and *rac*-$(MeO)_2$-CATPHOS (86%) whereas *rac*-BINAP and H_2-CATPHOS afforded much lower conversions of 32% and 30% respectively (entries 1-4).

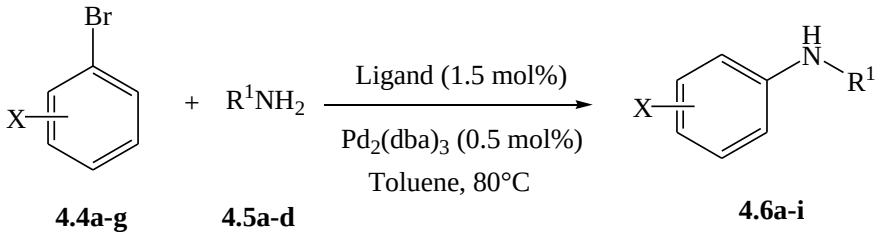
In the reactions of *n*-hexylamine **4.5b** with 1-bromo-4-chlorobenzene **4.4b**, *rac*-BINAP based catalyst gave a conversion of only 14% after 2 h compared to 98% with Pd(0)/*rac*-$(MeO)_2$-CATPHOS and 65% for Pd(0)/*rac*-Me_2-CATPHOS after the same time (entries 5-8).

In the amination of 1-bromo-4-methylbenzene **4.4e** (entries 15-16) with *n*-hexylamine **4.5b**, Pd(0)/*rac*-Me_2-CATPHOS and Pd(0)/*rac*-BINAP catalysed the reaction to give **4.6e** in 95% and 65% conversions, respectively, whereas reaction with the more sterically hindered 1-bromo-2-methylbenzene **4.4a** gave the corresponding product **4.6a** in 96% conversion with Pd(0)/*rac*-Me_2-CATPHOS after only 2.5 h at the same temperature (entries 11-14). A prominent literature example for this exact reaction uses 2 mol% of $Pd(OAc)_2$ and a ferrocene-based ligand to give > 99% conversion after 16 h at 110 °C. [25] Reaction of *n*-hexylamine **4.5b** with the more challenging 1-bromo-3,5-dimethylbenzene **4.4c** also afforded **4.6c** in higher conversion for *rac*-Me_2-CATPHOS (84%) than *rac*-BINAP (72%).

The promising performance of CATPHOS analogues is further demonstrated in a separate reaction between 4-bromobenzonitrile **4.4e** and propargyl amine **4.5c** where a mere 14% conversion was obtained for **4.6g** with *rac*-BINAP in comparison with conversions of 99% and 78% obtained with *rac*-Me_2-CATPHOS and H_2-CATPHOS, respectively (entries 20-22). This is a useful reaction as the final disubstituted amine could undergo reactions at both the alkyne, and the nitrile group which is attached to the benzene ring.

Similarly, in two conversions involving allyl amine **4.5d** reacting with each of bromobenzene **4.4e** and 1-bromo-2-iodobenzene **4.4g**, very high conversions were obtained for the corresponding products **4.6h** and **4.6i** with CATPHOS ligands compared to their BINAP counterpart (entries 23-28). The difference in their performance was most evident in the case of aniline **4.4f** where *rac*-BINAP afforded **4.6h** in 10% conversion after 1 h compared to a conversion of 80% with H_2-CATPHOS.

Table 4.3. Palladium Catalysed Amination of Aryl bromides with Aliphatic Amines and 2-Amino Pyridine.[a]



4.4a-g **4.5a-d** **4.6a-i**

Ent.	X	Ligand	Amine	Time(h)	% Conv. **4.6a-i**	% Yield
1	2-Me	Me_2-CATPHOS	2-$PyNH_2$	4	87 (**4.6a**)	82
2		$(MeO)_2$-CATPHOS		4	86 (**4.6a**)	80
3		H_2-CATPHOS		4	30 (**4.6a**)	20
4		BINAP		4	32 (**4.6a**)	20
5	4-Cl	Me_2-CATPHOS	*n*-Hex-NH_2	1	65 (**4.6b**)	60
6		$(MeO)_2$-CATPHOS		1	98 (**4.6b**)	90
7		H_2-CATPHOS		1	33 (**4.6b**)	24
8		BINAP		1	14 (**4.6b**)	10
9	3,5-Me_2	Me_2-CATPHOS	*n*-Hex-NH_2	5	84 (**4.6c**)	75
10		BINAP		5	72 (**4.6c**)	64
11	2-Me	Me_2-CATPHOS	*n*-Hex-NH_2	2.5	96 (**4.6d**)	88
12		$(MeO)_2$-CATPHOS		2.5	97 (**4.6d**)	90
13		H_2-CATPHOS		2.5	98 (**4.6d**)	91
14		BINAP		2.5	78 (**4.6d**)	69
15	4-Me	Me_2-CATPHOS	*n*-Hex-NH_2	1	95 (**4.6e**)	85
16		BINAP		1	65 (**4.6e**)	60
17	H	Me_2-CATPHOS	*n*-Hex-NH_2	1	84 (**4.6f**)	80
18		$(MeO)_2$-CATPHOS		1	98 (**4.6f**)	90
19		BINAP		1	95 (**4.6f**)	92
20	4-CN	Me_2-CATPHOS	HC≡C-	6	>99 (**4.6g**)	95
21		H_2-CATPHOS	CH_2-NH_2	6	78 (**4.6g**)	72
22		BINAP		6	14 (**4.6g**)	10
23	H	Me_2-CATPHOS	Allyl-NH_2	1	67 (**4.6h**)	61
24		H_2-CATPHOS		1	80 (**4.6h**)	72
25		BINAP		1	10 (**4.6h**)	5
26	2-I	Me_2-CATPHOS	Allyl-NH_2	6	80 (**4.6i**)	72
27		H_2-CATPHOS		6	77 (**4.6i**)	70
28		BINAP		6	51 (**4.6i**)	45

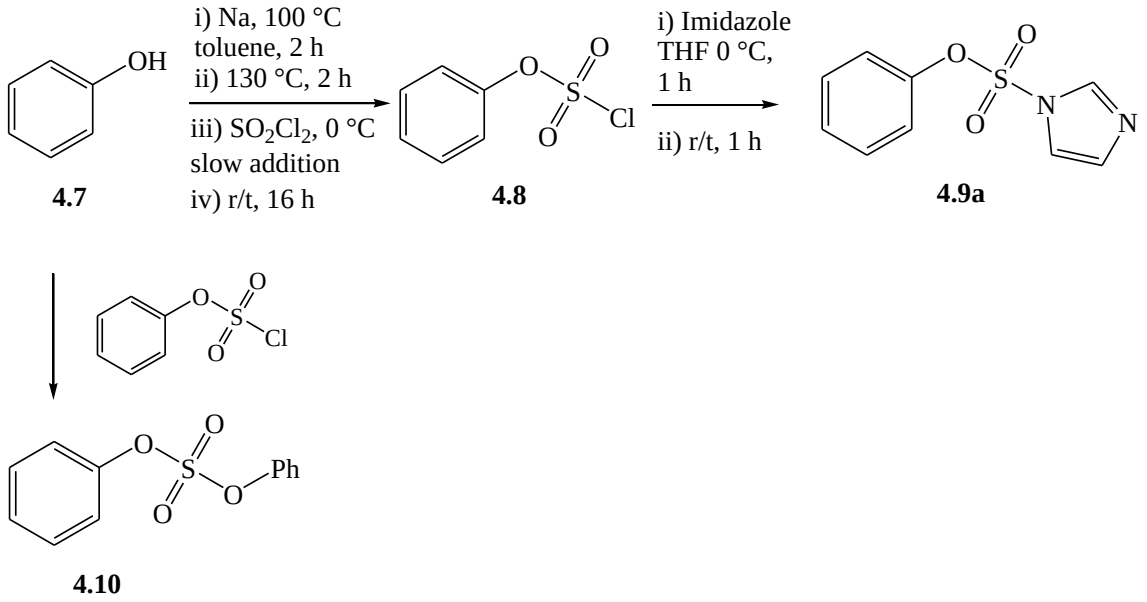
[a]Reaction Conditions: $Pd_2(dba)_3$ (0.5 mol %), ligand (1.5 mol%), NaO-t-Bu (1.3 mol. eq.) and 12 mL of toluene followed by aryl bromide and aniline (1.1 mol. eq.) at 80 °C for allocated time. [b]Conversion obtained by GC in comparison with internal standard. [c]Average of three runs.

The reactions with a variety of primary amines demonstrated the broad substrate scope of CATPHOS-based catalysts which in all cases outperformed their BINAP counterpart. Some of these reactions are novel and could pave the way for the synthesis of useful multifunctional intermediates.

4.3 Aryl Imidazolylsulfonates

4.3.1 Synthesis

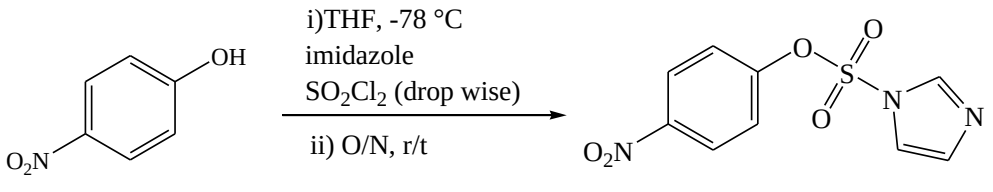
Our interest in imidazolylsulfonates was raised because of their ease of handling, higher stability and reactivity and also relative novelty in chemistry compared to the commonly used triflates which are less stable and very expensive to prepare due to the high cost of the starting reagents. On the contrary, imidazolylsulfonates are environmentally friendly[11] and, as such, there is likely to be increasing interest in their use as electrophiles for cross coupling. Thus, we carried out a comparative amination study and the choice of metal was palladium given the well established application of Pd/BINAP in the catalytic amination of aryl triflates. [26, 27] Initially two aryl imidazolylsulfonates were prepared and because of their different electronic properties, two different routes were employed (Scheme 4.1, Figure 4.2). Phenyl imidazolylsulfonate **4.9a** was prepared via a two step synthesis from the corresponding phenol, as illustrated in Scheme 4.1. The intermediate phenyl chlorosulphate **4.8** was prepared and purified by column chromatography with a moderate 70% yield.[28] Equimolar amounts of phenol **4.7** and sulphuryl chloride were used in this first step of the reaction in order to minimise reaction of the phenol with the product **4.8** to form undesired sulphuric acid diphenyl ester **4.10** via the less favoured reaction pathway (Scheme 4.1). In the second step, phenyl chlorosulphate **4.8** was reacted with large excess of imidazole to form phenyl imidazolylsulfonate **4.9a** in 85% conversion after 2 h.[29]



4.7 **4.8** **4.9a** **4.10**

Scheme 4.1. Synthesis of **4.8**: i) Na, 100 °C, 2 h, Toluene; ii) 130 °C, 2 h; iii) SO_2Cl_2, 0 °C, slow addition; iv) r/t, 16 h. Synthesis of **4.9a**: i) Imidazole (4 mol. eq.), 0 °C, 1 h, r/t, THF; ii) r/t, 1 h**.**

In contrast, the electron-withdrawing 4-nitrophenyl imidazolylsulfonate **4.9b** was prepared via a one step reaction between 4-nitrophenol **4.11** and an excess of imidazole (6 mol. eq.) in THF at -78 °C with drop wise addition of sulphuryl chloride (Figure 4.2); the reaction was subsequently allowed to warm to room temperature and stirred overnight.[11]

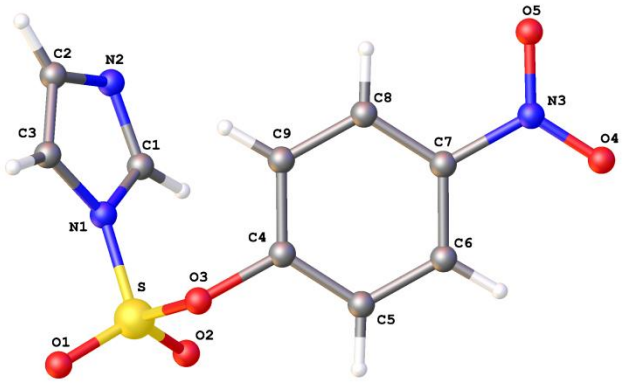


4.11 **4.9b**

Figure 4.2. Synthesis of compound **4.9b**: i) Imidazole (6 mol. eq.), -78 °C, THF, SO_2Cl_2 (slow addition); ii) r/t, 16 h.

The crystal structure of 4-nitrophenyl imidazolylsulfonate **4.9b** is shown in Figure 4.3, with a sulphur-nitrogen bond length of 1.649 (17) Å. The O(3)-C(4) bond length is 1.421 (3) Å

Figure 4.3. Molecular structure of 4-Nitrobenzene Imidazolylsulfonate.

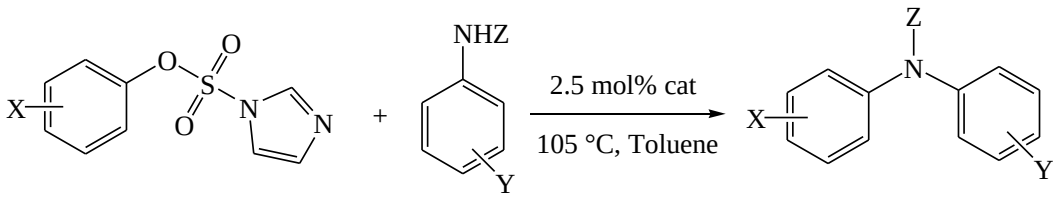


4.3.2 Coupling to Aniline and its Derivatives

Having successfully synthesised two aryl imidazolylsulfonates, their effectiveness as electrophiles in the Buchwald-Hartwig amination was investigated using catalyst based on H_2-CATPHOS and *rac*-BINAP and initially employing the same conditions previously reported by Ackermann and colleagues.[12]

Given the relative novelty of application of this electrophile in amination, we set about to improve the existing reaction conditions outlined in the literature especially in reaction times and catalyst loading, before carrying out exhaustive catalyst testing. Initial amination studies with exact literature conditions showed that high conversions were achieved within a matter of a few hours compared to the 17 h reported in the literature.[12] Further optimisation studies were carried out which showed that the catalyst loading could be reduced from 10 mol% to 2.5 mol% without significantly affecting conversions or reaction times. These optimised reaction conditions were thereafter employed in a comparative study to test the efficacy of H_2-CATPHOS against *rac*-BINAP and the scope of amination of imidazolylsulfonates. Initially the aryl imidazolylsulfonates were reacted with anilines bearing useful functional groups such as nitro, chloro, trifluoromethane and methoxy, full details are outlined in Table 4.4.

Table 4.4. Amination between Imidazylates **4.9a-b** and Anilines **4.12a-f**.[a]



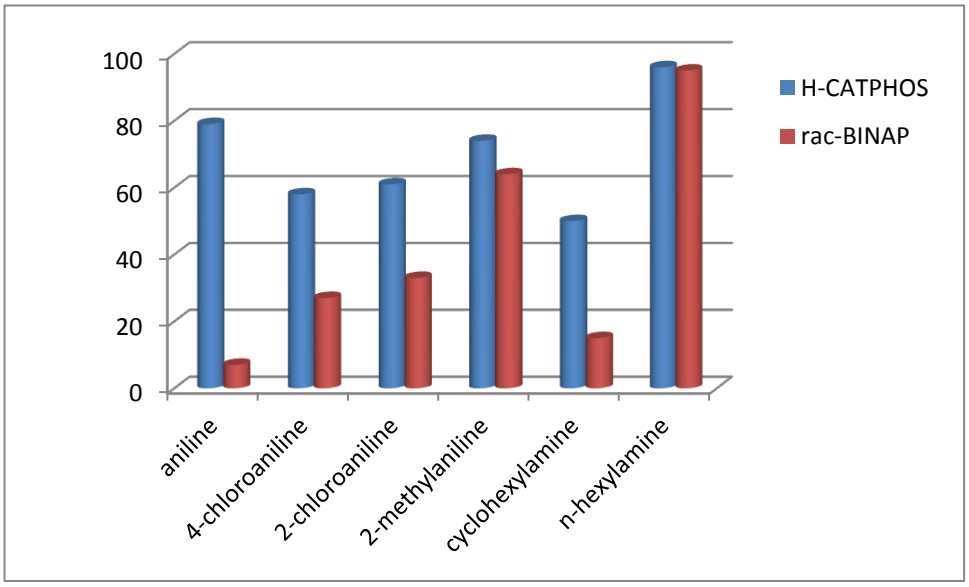
4.9a-b **4.1a-g** **4.13a-k**

Ent.	X	Y	Z	Ligand	Time(h)	% Conv.[b,c]	% Yield
1	H	H	H	H_2-CATPHOS	3	79 (**4.13a**)	72
2	H	H	H	BINAP	3	7 (**4.13a**)	6
3	H	4-Cl	H	H_2-CATPHOS	3	97 (**4.13b**)	92
4	H	4-Cl	H	BINAP	3	42 (**4.13b**)	38
5	H	4-CF_3	H	H_2-CATPHOS	3	97 (**4.13c**)	90
6	H	4-CF_3	H	BINAP	3	24 (**4.13c**)	21
7	H	4-OMe	H	H_2-CATPHOS	2	24 (**4.13d**)	20
8	H	4-OMe	H	H_2-CATPHOS	6	73 (**4.13d**)	70
9	4-NO_2	H	H	H_2-CATPHOS	1	98 (**4.13e**)	93
10	4-NO_2	H	H	X-Phos	1	10 (**4.13e**)	8
11	4-NO_2	4-Cl	H	H_2-CATPHOS	1	58 (**4.13f**)	52
12	4-NO_2	4-Cl	H	BINAP	1	27 (**4.13f**)	23
13	4-NO_2	4-Cl	H	X-Phos	1	0 (**4.13f**)	0
14	4-NO_2	2-Cl	H	H_2-CATPHOS	3	61 (**4.13g**)	58
15	4-NO_2	2-Cl	H	BINAP	3	33 (**4.13g**)	29
16	4-NO_2	4-OMe	H	H_2-CATPHOS	4	97 (**4.13h**)	93
17	4-NO_2	4-CF_3	H	H_2-CATPHOS	1/2	98 (**4.13i**)	85
18	4-NO_2	4-CF_3	H	H_2-CATPHOS	1/6	21 (**4.13i**)	15
19	4-NO_2	H	CH_3	H_2-CATPHOS	1	70 (**4.13j**)	65
20	4-NO_2	H	CH_3	BINAP	1	30 (**4.13j**)	23
21	4-NO_2	2-Me	H	H_2-CATPHOS	4	74 (**4.13k**)	70
22	4-NO_2	2-Me	H	BINAP	4	64 (**4.13k**)	55
23	4-NO_2	H	H	*rac*-Me_2-CATPHOS	6	0 (**4.13e**)	0
24	4-NO_2	H	H	*rac*-$(MeO)_2$-CATPHOS	6	0 (**4.13e**)	0

[a] Reaction conditions: 2.5 mol % ligand loading, $Pd(OAc)_2$ (2.5 mol %) imidazylates, aniline and Cs_2CO_3 2 mL of toluene at 105 °C for allocated time. [b]Conversion by GC with internal standard. [c] Average of three runs.

One clear pattern that has emerged from this preliminary study is that in all the reactions shown above, the catalyst based on H_2-CATPHOS outperformed its *rac*-BINAP counterpart by moderate to significant margins, for all the substrates examined. For instance, entries 1 and 2 show conversions of 79% and 7% for **4.12a** catalysed by H_2-CATPHOS and *rac*-BINAP respectively, for the reaction between phenyl imidazolylsulfonate **4.9a** and aniline **4.1a**. Conversions in favour of H_2-CATPHOS were consistently observed across a range of substrate combinations (entries 5, 6, 17 and 18), as depicted in Figure 4.4 for a selection of the results.

Figure 4.4. Amination between Imidazolylsulfonates and Aniline and its Derivatives Catalysed by Pd/ H_2-CATPHOS and its *rac*-BINAP Counterpart.



Interestingly, aminations carried out with the electron poor 4-(trifluoromethyl)-aniline **4.1c** coupling partner gave higher conversions in shorter times compared to those with the electron rich 4-methoxy aniline **4.1d**. This can be seen by directly comparing the conversions in entries 5 and 8. Furthermore, much shorter reaction times were required for the corresponding aminations of the electron-withdrawing 4-nitrophenyl imidazolylsulfonate **4.9b** compared with phenyl imidazolylsulfonate **4.9a**. For instance, by comparing entries 5 and 17, it can be seen that reaction of phenyl imidazolylsulfonate **4.9a** with 4-(trifluoromethyl)-aniline **4.1c** gave **4.13c** in a conversion of 97% after 3 h compared to a 98% conversion for **4.13i** after only 30 minutes with the more electron withdrawing 4-nitrophenyl imidazolylsulfonate **4.9b**. Although these results are by no means exhaustive, they do highlight the role of the electronic factors where higher conversion rates were obtained with electron poor substrates, compared to more electron rich substrates for the same reaction period.

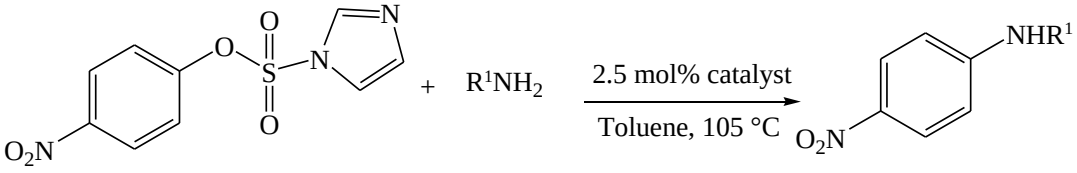
In the reactions involving 2-chloroaniline **4.1e** and 4-chloroaniline **4.1b** (entries 11-15), the results show that in the reactions catalysed by Pd/H_2-CATPHOS, 2-chloroaniline **4.1e** requires 3 h to give **4.13g** in 61% conversion whereas 4-chloroaniline **4.1b** achieved 58% conversion for **4.13f** in only 1 h under the same reaction conditions. A similar pattern also emerged with reaction of 4-chloroaniline **4.1b** and 4-nitrophenyl imidazolylsulfonate **4.9b** catalysed by Pd/*rac*-BINAP where **4.13f** was obtained in 27% conversion after 1 h, compared to the same reaction with 2-chloroaniline **4.1e** which gave corresponding product **4.13g** in 33% conversion after 3 h. These results are an indication of the significant roles played by the substituents on the aromatic ring of the aniline derivative. These results indicate that substituents on the phenyl rings that are in close proximity to the nitrogen reaction site provide significant steric hindrance and slow down the reaction.

Furthermore, where 2-chloroaniline **4.1e** was replaced with 2-methylaniline **4.1g**, a conversion of 74% conversion was obtained for **4.13k** after 4 h, which is comparable to that of 61% obtained with 2-chloroaniline after 3 h (entries 14 and 21), despite the different electronic properties of *ortho*-methyl and chlorine substituents that are in close proximity to the reaction site. This result is further evidence that for the substrates tested in our study, steric factors are more significant in influencing the rate of the reaction than electronic factors. No product **4.13e** was obtained in the coupling of 4-nitrobenzene imidazolylsulfonate to aniline catalysed by Pd/*rac*-Me_2-CATPHOS and its $(MeO)_2$-CATPHOS counterpart, highlighting the significant role of bridgehead substituent of the ligand on the efficacy of the catalyst in this reaction (Table 4.4, entries 23-24).

4.3.3 Coupling to Non-aromatic Amines

We further evaluated the scope of these aminations by conducting further experiments (Table 4.5) with secondary amines.

Table 4.5. Aminations between Imidazylate **4.9b** and Aniline Substrates **4.13g-i** Catalysed by H_2-CATPHOS and *rac*-BINAP in Toluene.[a]



4.9b **4.13l-n**

Ent.	Ligand	Time (h)	Amine (R^1)	% Conv. (**4.13l-n**) [b, c]	% Yield
1	H_2-CATPHOS	2	cyclohex-NH_2	50 (**4.13l**)	45
2	BINAP	2	cyclohex-NH_2	15 (**4.13l**)	9
3	H_2-CATPHOS	8	*n*-hex-NH_2	96 (**4.13m**)	95
4	BINAP	8	*n*-hex-NH_2	95 (**4.13m**)	93
5	H_2-CATPHOS	8	piperidine	71 (**4.13n**)	60
6	BINAP	8	piperidine	65 (**4.13n**)	58

[a] Reaction conditions: ligand (2.5 mol%), $Pd(OAc)_2$ (2.5 mol %) imidazylates, aniline (1.1 mol. eq.) and Cs_2CO_3 (2 mol. eq.) toluene (2 mL) at 105 °C for allocated time. [b] Conversion calculated by GC against internal standard. [c] Average of three runs.

In the above reaction of 4-nitrophenyl imidazolylsulfonate **4.9b** with cyclohexylamine (Table 4.5), a moderate 50% conversion was obtained for **4.13l** with Pd/H_2-CATPHOS after 2 h compared to the 98% conversion in the same reaction with aniline after 1 h (Table 4.4, entry 9). Similarly the same reaction was carried out with *n*-hexylamine which gave 96% conversion for **4.13m** after 8 h reaction time (Table 4.5, entry 3). It is experimentally evident that the reaction with aromatic amine gives higher conversion after shorter reaction times. Although the reaction with cyclohexylamine gives poor conversion compared to the aniline, it far outperforms the conversion obtained with the *n*-hexylamine. In comparison to Pd/BINAP catalysts, the H_2-CATPHOS system gives markedly higher conversions with cyclohexylamine (50% vs 15%) whereas it rivals the BINAP system with *n*-hexylamine (entries 3-4).

Although this short study focused on amination catalysis with primary amines, reactions were also conducted with challenging secondary amines such as *N*-methylaniline (Table 4.4) and piperidine (Table 4.5) under the same reaction conditions. The latter is a particularly challenging substrate because the reaction site is within the cyclic ring making it even more difficult to reach. It has been reported that the steric bulk of the ligand structure makes the nucleophilic attack by a secondary amine on a three-coordinated palladium complex difficult.[30] As such any system which successfully facilitates amination with secondary amines is desirable. Under our conditions, Pd/H_2-CATPHOS gave good conversions for both of the aforementioned secondary amines. In the case of the reaction of *N*-methylaniline with 4-nitrophenyl imidazolylsulfonate **4.9b**, 70% conversion was obtained for **4.13j** with Pd/H_2-CATPHOS compared to only 30% with its *rac*-BINAP counterpart after 1 h (Table 4.4, entries 17-18).

Encouragingly, Pd/H_2-CATPHOS also gave 71% in the reaction with piperidine, marginally outperforming its BINAP counterpart (65%). Although these reactions were for exploratory purposes and comparative catalyst evaluation between H_2-CATPHOS and BINAP, they have shown that aryl imidazolylsulfonates are effective electrophiles for Buchwald-Hartwig aminations.

4.4 Conclusions

This amination study has demonstrated the efficacy of H_2-CATPHOS and its architectural analogues *rac*-Me_2-CATPHOS and *rac*-$(MeO)_2$-CATPHOS under different reaction protocols across a wide range of substrates. In our initial study with the amination of substituted aryl bromides to aniline, Pd/CATPHOS-based diphosphines gave encouraging conversions, outperforming their BINAP counterpart in the amination of 1-bromo-3,5-dimethylbenzene and 1-bromo-4-chlorobenzene. Moreover, some of the subsequent reactions with substituted anilines resulted in great improvements in the final conversions compared to the literature.[23]

More promisingly, catalyst based on CATPHOS diphosphines outperformed their BINAP counterpart for amination involving primary amines bearing useful functional groups such as allyl and propargyl; these catalysts could therefore find use in the synthesis of multifunctional intermediates.

Our evaluation of imidazolylsulfonates also gave very promising results which is particularly useful given its recent emergence as new class of electrophile for cross coupling. We successfully optimised the reaction conditions used by Ackermann and colleagues by lowering reaction times and, more importantly, catalyst loading. In all the conversions with aniline derivatives, H_2-CATPHOS outperformed its *rac*-BINAP counterpart by moderate to significant margins. Encouragingly, superior conversions were also obtained with H_2-CATPHOS in reactions with cyclohexylamine, piperidine and *N*-methylaniline as shown in Table 4.4. However no conversion was obtained with both *rac*-Me_2-CATPHOS and *rac*-$(MeO)_2$-CATPHOS based catalysts despite repeated attempts.

In summary, catalysts based on CATPHOS either rivalled or outperformed their BINAP counterpart for the majority of the substrates combinations listed. Further work should involve the synthesis of electron-rich dicyclohexyl phosphine-based CATPHOS diphosphines with the aim of developing efficient catalysts for the cross coupling of chloride-based electrophiles.

4.5 Experimental

General Comments. All manipulations involving air-sensitive materials were carried out using standard Schlenk line techniques under an atmosphere of nitrogen or argon in oven-dried glassware. Dichloromethane was distilled from calcium hydride, diethyl ether from Na/K alloy, dioxane from sodium, THF from sodium/benzophenone, toluene from sodium and methyl *tert*-butyl ether. Aniline derivatives and palladium(II) acetate were purchased from commercial suppliers and used without further purification. H_2-CATPHOS[31], *rac*-Me_2-CATPHOS[31], *rac*-$(MeO)_2$-CATPHOS (Chapter 2) and imidazolylsulfonates[11, 28, 29] were all prepared as previously described. ^{1}H and ^{13}C {^{1}H} NMR spectra were recorded on a JOEL ECS-400 instrument. Thin layer chromatography (TLC) was carried out on aluminium sheets pre-coated with silica gel 60F $_{254}$. Gas chromatography mass spectrometry was performed on a Varian GCMS Saturn 2200 equipped with a CP-3800 Gas chromatograph and conversions were calculated from GCMS profile.

General Procedure for Amination between Aryl Bromide and Aniline Derivatives. $Pd_2(dba)_3$ (0.002 g, 0.003 mmol), *rac*-BINAP (0.005 g, 0.009 mmol), sodium *tert*-butoxide (0.08 g, 0.82 mmol) and toluene (12 mL) were mixed together to give a solution to which was added aryl bromide (0.58 mmol) followed by aniline (0.058 mL, 0.64 mmol). The reaction mixture was heated at 80 °C for the allocated time. The solution was allowed to cool to room temperature, diluted with diethyl ether (15 mL) and passed through a short plug of celite. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (DCM/hexane).

4-Chloro-*N*-phenylaniline (4.3a). A sample was prepared by following the method outlined above and purified by column chromatography. ^{1}H NMR (300.0 MHz, $CDCl_3$, δ): 7.23-7.16 (t, J = 8.1 Hz, 3H, Ar-*H*), 7.14-7.11 (d, J = 9.0 Hz, 2H, Ar-*H*), 6.97-6.94 (d, J = 8.04 Hz, 2H, Ar-*H*), 6.92 – 6.89 (d, J = 8.9 Hz, 2H, Ar-*H*), 5.62 (br s, 1H, N*H*), ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$, δ): 142.6 (C_6H_4), 141.8 (C_6H_4), 129.4 (C_6H_4), 129.2 (C_6H_4), 125.4 (C_6H_5), 121.5 (C_6H_5), 118.8 (C_6H_5), 118.1 (C_6H_5); LRMS (EI) $[M]^+$ *m/z* 203; HRMS (EI) exact mass calculated for $C_{12}H_{10}NCl$ $[M]^+$ requires *m/z* 204.0575, found *m/z* 204.0570.

***N*-(*o*-Tolyl)pyridin-2-amine (4.6a).** A sample was prepared by following the method outlined above and purified by column chromatography**.** ^{1}H NMR (300.0 MHz, $CDCl_3$, δ): 8.12 (d, J = 4.7 Hz, 1H, Ar-*H*), 7.42-7.34 (m, 2H, Ar-*H*), 7.20-7.12 (m, 2H, Ar-*H*), 7.02 (t, J = 7.5 Hz, 1H, Ar-*H*), 6.67-6.57 (m, 2H, Ar-*H*), 6.24 (br s, 1H, N*H*), 2.22 (s, 3H, CH_3); ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$, δ): 155.9 (N=*C*NH), 147.7 (N=*C*CH), 137.6 (C_6H_4),

136.6 (C_5H_4N), 130.6 (C_5H_4N), 129.8 (C_5H_4N), 125.9 (C_6H_4), 123.5 (C_6H_4), 122.1 (C_6H_4), 113.5 (C_6H_4), 106.7 (C_6H_4), 16.7 (CH_3); LRMS (EI) $[M]^+$ *m/z* 185.

2-Methyl-*N*-phenylaniline (4.3d). A sample was prepared by following the method outlined above and purified by column chromatography. ^{1}H NMR (300.0 MHz, $CDCl_3$, δ): 7.20-7.00 (m, 4H, Ar-*H*), 6.9-6.76 (m, 4H, Ar-*H*), 5.31 (br s, 1H, N*H*), 2.18 (s, 3H, CH_3); $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$, δ): 143.8.1 (C_6H_5), 141.2 (C_6H_4), 137.6 (C_6H_4), 130.9 (C_6H_5), 130.8 (C_6H_5), 129.3 (C_6H_5), 128.0 (C_6H_5), 126.6 (C_6H_5), 121.9 (C_6H_4), 118.6 (C_6H_4), 22.9 (CH_3); LRMS (EI) $[M+H]^+$ *m/z* 184; HRMS (EI) exact mass calculated for $C_{13}H_{13}N$ $[M]^+$ requires *m/z* 184.1121, found *m/z* 184.1116.

***N*-Hexyl-2-methylaniline (4.6d).** A sample was prepared by following the method outlined above and purified by column chromatography**.** ^{1}H NMR (300.0 MHz, $CDCl_3$, δ): 7.08-6.94 (m, 2H, Ar-*H*), 6.6-6.5 (q, *J* = 7.2 Hz, 2H, CH_2CH$_3$), 3.38 (br s, 1H, N*H*), 3.1 (t, *J* = 7.17 Hz, 2H, Ar-*H*), 2.06-2.03 (s, 3H, CH_3), 1.64-1.52 (m, 2H, HNCH_2), 1.41-1.20 (m, 6H, CH_2CH_2CH_2), 0.85-0.81 (t, *J* = 6.82 Hz, 3H, CH_3CH$_2$); $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$, δ): 145.5 (C_6H_4), 129.2 (C_6H_4), 126.1 (C_6H_4), 120.9 (C_6H_4), 115.7 (C_6H_4), 108.9 (C_6H_4), 43.0 (NCH_2), 30.8 (CH_2), 28.7 (CH_2), 26.1 (CH_2), 21.6 (CH_2), 16.4 (Ar-CH_3), 12.7 (CH_3CH_2); LRMS (EI) $[M+H]^+$ *m/z* 192; HRMS (EI) exact mass calculated for $C_{13}H_{21}N$ $[M]^+$ requires *m/z* 192.1747, found *m/z* 192.1742.

4-Chloro-*N*-hexylaniline (4.6b). A sample was prepared by following the method outlined above and purified by column chromatography. ^{1}H NMR (300.0 MHz, $CDCl_3$, δ): 7.08-6.99 (d, *J* = 8.8 Hz, 2H, C_6H_4), 6.47-6.38 (d, *J* = 8.9 Hz, 2H, C_6H_4), 3.69 (br s, 1H, N*H*), 3.04 (t, *J* = 7.1 Hz, 2H, CH_2), 1.57-1.46 (pent, *J* = 6.95 Hz, 2H, hexyl), 1.30-1.13 (m, 6H, hexyl), 0.87 (t, *J* = 6.7 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$, δ): 147.5 (q, =*C*CN), 129 (C_6H_4), 121.7 (C_6H_4), 113.3 (C_6H_4), 44.1 (CH_2), 31.9 (CH_2), 29.3 (CH_2), 27.0 (CH_2), 23.1 (CH_2), 14.1 (CH_3); LRMS (EI) $[M]^+$ *m/z* 212; HRMS (EI) exact mass calculated for $C_{12}H_{18}NCl$ $[M]^+$ requires *m/z* 212.1210, found *m/z* 212.1206.

4-Chloro-*N*-(prop-2-yn-1-yl)aniline. A sample was prepared by following the method outlined above and purified by column chromatography. ^{1}H NMR (300.0 MHz, $CDCl_3$, δ): 7.26-7.1 (m, 3H, C_6H_4), 6.61 (d, *J* = 8.9 Hz, 1H, C_6H_4), 4.1 (br s, 1H, N*H*), 3.84 (s, 2H, CH_2), 1.56 (s, 1H, C≡C*H*), $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$, δ): 145.6 (C_6H_4), 132.9 (C_6H_4), 129.0 ((C_6H_4), 128.6 (C_6H_4), 114.4 (NC*C*≡C), 86.7 (NCC≡*C*), 34.4 (N*C*C≡C); LRMS (EI) $[M]^+$ *m/z* 166.

***N*-Allylaniline (4.6h).** A sample was prepared by following the method outlined above and purified by column chromatography. ^{1}H NMR (300.0 MHz, $CDCl_3$, δ): 7.2-7.11 (m, 4H, C_6H_5), 6.59-6.52 (m, 2H, C_6H_5 + N*H*), 5.94-5.84 (m, 1H, =C*H*), 5.19-5.25 (d, *J* = 17.2 Hz, 1H, =CH_aH$_b$), 5.08-5.13 (d, *J* = 10.3 Hz, 1H, =CH$_a$$H_b$), 3.77 (t, *J* = 5.6 Hz, 2H, CH_2); ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$, δ): 148.0 (C_6H_5), 135.4 (H*C*=CH_2), 129.1 (C_6H_5), 117.8 (C=*C*H_2), 116.4 (C_6H_5), 112.9 (C_6H_5), 46.6 (*C*H_2); LRMS (EI) $[M]^+$ *m/z* 133.

***N*-Allyl-2-bromoaniline (4.6i).** A sample was prepared by following the method outlined above and purified by column chromatography. ^{1}H NMR (300.0 MHz, $CDCl_3$, δ): 7.38 (d, *J* = 7.8 Hz, 1H, C_6H_4), 7.13 (t, *J* = 7.9 Hz, 1H, C_6H_4), 6.60-6.45 (m, 2H, C_6H_4), 5.95-5.79 (m, 1H, =C*H*), 5.27-5.17 (d, *J* = 17.4 Hz, 1H, C=CH_aH$_b$), 5.16-5.1 (d, *J* = 10.2 Hz, 1H, C=CH$_a$$H_b$), 4.49 (br s, 1H, N*H*), 3.81 (t, *J* = 5.4 Hz, 2H, CH_2); ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$, δ): 145.4 (C_6H_4), 135.0 (=*C*H), 132.9 (C_6H_4), 128.8 (C_6H_4), 118.2 (=*C*H_2), 116.8 (C_6H_4), 112.1 (C_6H_4), 110.1 (C_6H_4), 46.6 (*C*H_2); LRMS (EI) $[M+H]^+$ *m/z* 213.

4-(Prop-2-yn-1-ylamino)-benzonitrile (4.6g). A sample was prepared by following the method outlined above and purified by column chromatography. ^{1}H NMR (300.0 MHz, $CDCl_3$, δ): 7.42-7.39 (d, J = 8.75 Hz, 2H, Ar-*H*), 6.61-6.58 (d, *J* = 8.79 Hz, 2H, Ar*H*), 4.45-4.31 (br s, 1H, N*H*), 3.96-3.86 (s, 2H, CH_2), 2.22-2.18 (s, 1H, C*H*); ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$, δ): 150.7 (C_6H_4), 133.7 (C_6H_4), 120.3 (C_6H_4), 113.3 (C_6H_4), 101.3 (*C*≡N), 79.8 (*C*≡CH), 72.2 (C≡*C*H), 33.4 (*C*H_2); LRMS (EI) $[M]^+$ *m/z* 157; HRMS (EI) exact mass calculated for $C_{10}H_8N_2$ requires *m/z* 157.0774, found *m/z* 157.0766.

***N*-Hexyl-4-methylaniline (4.6e).** A sample was prepared following the the method outlined above and purified by column chromatography. ^{1}H NMR (300.0 MHz, $CDCl_3$, δ): 6.94 (d, *J* = 8.2 Hz, 2H, C_6H_4), 6.53 (d, *J* = 7.1 Hz, 2H, C_6H_4), 3.1 (br s, 1H, N*H*), 2.21 (s, 3H, Ar-CH_3), 1.59-1.44 (pent, *J* = 7.04 Hz, 2H, CH_2), 1.37-1.15 (m, 7H, (CH_2)$_3$CH_aH$_b$), 0.89 (s, 3H, CH$_2$CH_3); ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$, δ): 146.9 (C_6H_4), 128.9 (C_6H_4), 119.1 (C_6H_4), 113.1 (C_6H_4), 44.7 (*C*H_2), 31.9 (*C*H_2), 29.9 (*C*H_2), 23.6 (*C*H_2), 23.5 (Ar-*C*H_3), 21.7 (*C*H_2), 14.0 (*C*H_3); LRMS (EI) $[M+H]^+$ *m/z* 192.

Diphenylamine (4.3e). A sample was prepared by following the method outlined above and purified by column chromatography. ^{1}H NMR (300.0 MHz, $CDCl_3$, δ): 7.23-7.16 (m, 4H, C_6H_5), 7.04 (d, *J* = 8.5 Hz, 4H, C_6H_4), 6.89 (t, *J* = 7.33 Hz, 2H, C_6H_5), 5.70 (br s, 1H, N*H*); ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$, δ): 142.2 (C_6H_5), 128.4 (C_6H_5), 120.0 (C_6H_5), 116.9 (C_6H_5); LRMS (EI) $[M]^+$ *m/z* 169.

***N*-Hexylaniline (4.6f).** A sample was prepared by following the method outlined above and purified by column chromatography. ^{1}H NMR (300.0 MHz, $CDCl_3$, δ): 7.14-7.05 (m, 2H, C_6H_5), 6.66-6.49 (m, 3H, C_6H_5), 3.76 (br s, 1H, N*H*), 1.62-1.47 (pent, J = 6.83 Hz, 2H, CH_2), 1.41-0.93 (m, 8H, $(CH_2)_4$), 0.87 (t, J = 6.8 Hz, 3H, CH_3); ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$, δ): 148.3 (C_6H_5), 128.9 (C_6H_5), 117.1 (C_6H_5), 112.7 (C_6H_5), 43.8 (NCH_2), 31.4 (CH_2), 29.3 (CH_2), 26.5 (CH_2), 22.4 (CH_2), 13.8 (CH_3); LRMS (EI) $[M]^+$ *m/z* 177.

***N*-Hexyl-3,5-dimethylaniline (4.6c).** A sample was prepared by following the method outlined above and purified by column chromatography. ^{1}H NMR (300.0 MHz, $CDCl_3$, δ): 6.30 (s, 1H, Ar*H*), 6.2 (s, 2H, C_6H_3), 3.05 (t, J = 7.2 Hz, 2H, CH_2), 2.20 (s, 6H, $(CH_3)_2$), 1.60-1.43 (pent, J = 6.7 Hz, 2H, CH_2), 1.40-1.15 (m, 7H, $(Ar\text{-}CH_3)_2$ + N*H*), 0.88 (t, J = 6.7 Hz, 3H, CH_2CH_3); ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$, δ): 148.5 (C_6H_3), 138.7 (C_6H_3), 119.4 (C_6H_3), 110.6 (C_6H_3), 44.0 (CH_2), 31.4 (CH_2), 29.4 (CH_2), 26.7 (CH_2), 22.4 ($Ar\text{-}CH_3$), 21.1 (CH_2), 13.9 (CH_2CH_3); LRMS (EI) $[M]^+$ *m/z* 205.

4-Methyl-(*N*-phenyl)-aniline (4.3b). A sample was prepared by following the method outlined above and purified by column chromatography. ^{1}H NMR (300.0 MHz, $CDCl_3$, δ): 7.20-7.0 (m, 4H, Ar*H*), 6.9-6.76 (m, 4H, Ar*H*), 5.31 (br s, 1H, N*H*), 2.18 (s, 3H, CH_3); ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$, δ): 143.8.1 (C_6H_5), 141.2 (C_6H_4), 137.6 (C_6H_4), 130.9 (C_6H_5), 129.3 (C_6H_5), 126.6 (C_6H_5), 121.9 (C_6H_4),120.3 (C_6H_4), 118.6 (C_6H_4), 117.8 (C_6H_4), 22.9 (CH_3); LRMS (EI) $[M+H]^+$ *m/z* 184.

4-Chloro-(*N*-phenyl)-aniline (4.3a). A sample was prepared by following the method outlined above and purified by column chromatography. ^{1}H NMR (300.0 MHz, $CDCl_3$, δ): 7.28-7.06 (m, 4H, C_6H_4), 7.01-6.84 (m, 5H, C_6H_5), 5.71 (br s, 1H, N*H*); ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$, δ): 142.9 (C_6H_4), 142.2 (C_6H_4), 129.4 (C_6H_4), 129.2 (C_6H_4), 125.7 (C_6H_4), 121.6 (C_6H_5), 118.9 (C_6H_5), 118.3 (C_6H_5); LRMS (EI) $[M]^+$ *m/z* 203; HRMS (EI) exact mass calculated for $C_{12}H_{10}NCl$ $[M]^+$ requires *m/z* 203.0493, found *m/z* 203.0499.

4-Methoxy-(*N*-phenyl)-aniline (4.3f). A sample was prepared by following the method outlined above and purified by column chromatography. ^{1}H NMR (300.0 MHz, $CDCl_3$, δ): 7.20-7.10 (m, 3H, C_6H_4), 7.03-6.97 (m, 2H, C_6H_5), 6.85-6.73 (m, 4H, C_6H_5), 5.47 (br s, 1H, N*H*), 3.73 (s, 3H, OCH_3); ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$, δ): 145.1 (C_6H_4), 140.2 (C_6H_5), 132.5 (C_6H_5), 128.3 (C_6H_4), 121.4 (C_6H_4), 118.8 (C_6H_4), 115.1 (C_6H_5), 113.9 (C_6H_5), 54.6 (OCH_3); HRMS (EI) exact mass calculated for $C_{13}H_{13}NO$ $[M]^+$ requires *m/z* 199.0994, found *m/z* 199.0996.

4-Chloro-*N*-(4-methoxyphenyl)-aniline (4.3g). A sample was prepared by following the method outlined above and purified by column chromatography. ^{1}H NMR (300.0 MHz, $CDCl_3$, δ): 7.11-7.04 (m, 2H, C_6H_4), 7.01-6.94 (m, 2H, C_6H_4), 6.83-6.71 (m, 4H, C_6H_4), 5.40 (br s, 1H, N*H*), 3.73 (s, 3H, OCH_3); ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$, δ): 155.8 (C_6H_4), 144.1 (C_6H_4), 135.4 (C_6H_4), 129.2 (C_6H_4), 124.2 (C_6H_4), 122.5 (C_6H_4), 116.8 (C_6H_4), 114.9 (C_6H_4), 55.8 (O*C*H_3); LRMS (EI) $[M\text{-}H]^+$ *m/z* 233.

4-Methoxy-*N*-(p-tolyl)-aniline (4.3h). A sample was prepared by following the method outlined above and purified by column chromatography. ^{1}H NMR (300.0 MHz, $CDCl_3$, δ): 7.00-6.91 (m, 4H, C_6H_4), 6.82-6.73 (m, 4H, C_6H_4), 5.33 (br s, 1H, N*H*), 3.72 (s, 3H, OCH_3), 2.20 (s, 3H, CH_3); ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$, δ): 155.4 (C_6H_4), 142.6 (C_6H_4), 137.1 (C_6H_4), 129.7 (C_6H_4), 129.4 (C_6H_4), 121.2 (C_6H_4), 116.8 (C_6H_4), 114.8 (C_6H_4), 55.8 (O*C*H_3), 20.6 (*C*H_3); LRMS (EI) $[M]^+$ *m/z* 213.

4-Chloro-*N*-(p-tolyl)-aniline (4.3k). A sample was prepared by following the method outlined above and purified by column chromatography. ^{1}H NMR (300.0 MHz, $CDCl_3$, δ): 7.11 (d, J = 8.8 Hz, 2H, C_6H_4), 7.03 (d, J = 8.2 Hz, 2H, C_6H_4), 6.97-6.79 (m, 4H, C_6H_4), 5.80 (br s, 1H, N*H*), 2.24 (s, 3H, CH_3); ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$, δ): 143.1 (C_6H_4), 140.2 (C_6H_4), 130.0 (C_6H_4), 129.2 (C_6H_4), 129.6 (C_6H_4), 125.1 (C_6H_4), 119.7 (C_6H_4), 118.3 (C_6H_4), 20.8 (*C*H_3); LRMS (EI) $[M]^+$ *m/z* 217.

Bis-(4-chlorophenyl)-amine (4.3j). A sample was prepared by following the method outlined above and purified by column chromatography. ^{1}H NMR (300.0 MHz, $CDCl_3$, δ): 7.16-7.10 (m, 4H, C_6H_4), 6.91-6.84 (m, 4H, C_6H_4), 5.61 (br s, 1H, N*H*); ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$, δ): 140.7 (C_6H_4), 128.6 (C_6H_4), 125.5 (C_6H_4), 118.6 (C_6H_4); LRMS (EI) $[M\text{-}H]^+$ *m/z* 237.

General Procedure for Synthesis of Phenyl Chlorsulphate (4.8).[29] A solution of phenol (2.5 g, 26.6 mmol) in dry toluene (55 mL) was stirred with small pieces of sodium (0.06 g, 26.6 mmol) at 100 °C for 2 h. The temperature was increased to 130 °C and the reaction was stirred for a further 2 h. Subsequently the solution was cooled to 0 °C and was added drop wise to a 0 °C cooled solution of sulphuryl chloride (2.15 mL, 26.6 mmol) in dry toluene (30 mL). The reaction mixture was allowed to warm to room temperature and subsequently stirred for 16 h. At end of reaction, crude product was washed with water (3 x 20 mL), dried over $MgSO_4$ and solvent was removed under reduced pressure affording light brown oil. The crude was columned (hexane) to afford product phenyl chlorosulphate (3.8 g, 70%) as a colourless oil. ^{1}H NMR (300.0 MHz, $CDCl_3$, δ): 7.48-7.21 (m, 5H, C_6H_5); ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$, δ): 149.7 (C_6H_5), 129.3 (C_6H_5), 127.8 (C_6H_5), 122.1

(C_6H_5), 120.7 (C_6H_5); $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$, δ): 149.5 (C_6H_5), 129.5 (C_6H_5), 129.3 (C_6H_5), 127.8 (C_6H_5), 122.1 (C_6H_5), 120.7 (C_6H_5); LRMS (EI) *m/z* 192 $[M\text{-}H]^+$.

Experimental Procedure for the Synthesis of Phenyl Imidazolylsulfonate (4.9a). A solution of imidazole (1.4 g, 20.6 mmol) in dry THF (10 mL) was cooled to 0 °C. To this mixture was added a solution of phenyl chlorosulphate (1.31 g, 6.8 mmol) in THF (8 mL) in a drop wise manner. The Solution was stirred at 0 °C for 1 h, warmed to room temperature and stirred for a further 1 h. At end of reaction period, crude reaction mixture was filtered through silica plug to remove insoluble impurities and the solvent was removed under reduced pressure. The crude product was columned (EtOAc-hexane, 1:2 v/v) and product was isolated as a colourless oil (0.92g, 60%). ^1H NMR (300.0 MHz, $CDCl_3$, δ): 7.62 (s, 1H, C*H*=CH), 7.34-7.24 (m, 3H, C_6H_5), 7.23-7.19 (m, 1H, C_6H_5), 7.09 (dd, J = 1.6, 0.7 Hz, 1H, C_6H_5), 6.89-6.80 (m, 2H, CH=C*H*); $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$, δ): 148.4 (C_6H_5), 136.5 (*C*=N), 130.4 (C_6H_5), 129.3 (C_6H_5), 127.6 (N*C*=C), 120.4 (C_6H_5), 117.4 (C_6H_5); LRMS (EI) *m/z* 225 $[M+H]^+$; HRMS (EI) exact mass calculated for $C_9H_8SO_3N_2$ $[M+H]^+$ requires *m/z* 225.0334, found *m/z* 225.0337.[12]

Experimental Procedure for the Synthesis of 4-Nitrophenyl Imidazolylsulfonate (4.9b). A Schlenk was charged with 4-nitrophenol (0.5 g, 3.6 mmol), imidazole (1.5 g, 22.03 mmol) and dry THF (20 mL). The solution was cooled to -70 °C and set to stir rapidly for 5 mins. Subsequently neat sulphuryl chloride (0.5 mL, 6.12 mmol) was added drop wise to the reaction mixture over a period of 10 mins. The reaction was allowed to warm to room temperature and stirred overnight. At end of reaction period, reaction mixture was diluted with EtOAc (20 mL), washed with water (4 x 10 mL) and brine (4 x 10 mL). The organic phases were separated, combine and dried over $MgSO_4$. The solvent was removed under reduced pressure. The crude product was columned (EtOAc-petrol) and crystallised (EtOAc-petrol) to afford a white powder (0.62 g, 65%). ^1H NMR (300.0 MHz, $CDCl_3$, δ): 8.24-8.18 (m, 2H, (N*H*C=C)$_2$), 7.72 (s, 1H, *H*C=N), 7.26 (t, J = 1.5 Hz, 1H, Ar*H*), 7.15 (dd, J = 1.1, 0.7 Hz, 1H, Ar*H*), 7.12-7.06 (m, 2H, C_6H_4), ^{13}C $\{^1H\}$ NMR (75.5 MHz, $CDCl_3$, δ) 152.7 (C_6H_4), 147.4 (C_6H_4), 137.3 (*C*=N), 131.7 (C_6H_4), 125.9 (N*C*), 122.5 (C_6H_4), 118.2 (C_6H_4), 115.5 (C_6H_4); LRMS (EI) *m/z* 270 $[M+H]^+$; HRMS (EI) exact mass calculated for $C_9H_7N_3O_5S$ $[M+H]^+$ requires *m/z* 270.0179, found *m/z* 270.0184.[13]

General Procedure for Amination between Aniline Derivatives and Imidazolylsulfonate Substrates. Aniline (0.024 mL, 0.27 mmol), $Pd(OAc)_2$ (0.001 g, 0.006 mmol), *Rac*-BINAP (0.003 g, 0.006 mmol) and Cs_2CO_3 (0.094 g, 0.29 mmol) were suspended in toluene (2 mL) and mixture was set to stir at room temperature for 10 mins.

Subsequently, aryl imidazolylsulfonate (0.2 mmol) was added and mixture was set to stir at 105 °C for the allocated time period. At end of reaction period, reaction mixture was cooled to room temperature and saturated with $NaHCO_3$ (10 mL). The organic layers was extracted with ^{t}BuOMe (3 x 10 mL) and dried over $MgSO_4$. Solvent concentrated under reduced pressure and purified by column chromatography (hexane-EtOAc).[12]

Diphenyl amine (4.13a). Reaction carried out following above method and sample was isolated as yellow oil after purification by column chromatography. ^{1}H NMR (300.0 MHz, $CDCl_3$, δ): 7.25-7.12 (m, 4H, C_6H_5), 7.03-6.97 (m, 4H, C_6H_4), 6.89-6.81 (m, 2H, C_6H_4), 5.65 (br s, 1H, N*H*); ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$, δ): 142.5 (C_6H_5), 128.4 (C_6H_5), 120.1 (C_6H_5), 117.1 (C_6H_5); LRMS (EI) *m/z* 169 $[M]^+$; HRMS (EI) exact mass calculated for $C_{12}H_{11}N$ $[M+H]^+$ requires *m/z* 170.0965, found *m/z* 170.0963.

4-Chloro-(*N*-phenyl)-aniline (4.13b). Reaction carried out following above method and sample was isolated as yellow oil after purification by column chromatography. ^{1}H NMR (300.0 MHz, $CDCl_3$, δ): 7.28-7.06 (m, 4H, C_6H_4), 7.01-6.84 (m, 5H, C_6H_5), 5.71 (br s, 1H, N*H*); ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$, δ): 142.9 (C_6H_4), 142.2 (C_6H_4), 129.4 (C_6H_4), 129.2 (C_6H_4), 125.7 (C_6H_4), 121.6 (C_6H_5), 118.9 (C_6H_5), 118.3 (C_6H_5); LRMS (EI) *m/z* 203 $[M]^+$; HRMS (EI) exact mass calculated for $C_{12}H_{10}NCl$ $[M]^+$ requires *m/z* 203.0493, found *m/z* 203.0499.

4-(Trifluoromethyl)-*N*-phenyl aniline (4.13c). Reaction carried out following above method and sample was isolated as yellow oil after purification by column chromatography.^{1}H NMR (300.0 MHz, $CDCl_3$, δ): 7.39 (d, J = 8.5 Hz, 2H, C_6H_4), 7.26 (t, J = 7.8 Hz, 2H, C_6H_4), 7.07 (d, J = 7.8 Hz, 2H, C_6H_5), 6.98 (t, J = 7.8 Hz, 3H, C_6H_5), 5.94 (br s, 1H, N*H*); ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$, δ): 146.8 (C_6H_4), 141.2 (C_6H_4), 129.6 (C_6H_5), 127.5 (q, $J_{C\text{-}F}$ = 3.7 Hz, CF_3), 126.8 (C_6H_5), 122.9 (C_6H_5), 120.0 (C_6H_4), 117.8 (C_6H_4), 115.3 (C_6H_5); ^{19}F NMR (400 MHz, $CDCl_3$, δ): -61.3 (s, F, C*F*$_3$); LRMS (EI) *m/z* 237 $[M]^+$; HRMS (EI) exact mass calculated for $C_{13}H_{10}NF_3$ $[M]^+$ requires *m/z* 237.0759, found *m/z* 237.0766.

4-Methoxy-(*N*-phenyl)-aniline (4.13d). Reaction carried out following above method and sample was isolated as yellow oil after purification by column chromatography.^{1}H NMR (300.0 MHz, $CDCl_3$, δ): 7.20-7.10 (m, 3H, C_6H_4), 7.03-6.97 (m, 2H, C_6H_5), 6.85-6.73 (m, 4H, C_6H_5), 5.47 (br s, 1H, N*H*), 3.73 (s, 3H, OC*H*$_3$); ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$, δ): 142.2 (C_6H_4), 139.5 (C_6H_5), 129.2 (C_6H_5), 128.3 (C_6H_4), 121.4 (C_6H_4), 118.8 (C_6H_4), 115.1 (C_6H_5), 113.9 (C_6H_5), 54.6 (O*C*H$_3$); LRMS (EI) *m/z* 199 $[M]^+$; HRMS (EI) exact mass calculated for $C_{13}H_{13}NO$ $[M]^+$ requires *m/z* 199.0994, found *m/z* 199.0996.

4-Nitro-(*N*-phenyl)-aniline (4.13e). Reaction carried out following above method and sample was isolated as yellow oil after purification by column chromatography.[1]H NMR (300.0 MHz, $CDCl_3$, δ): 8.09-8.01 (m, 2H, C_6H_4), 7.36-7.27 (m, 2H, C_6H_4), 7.17-7.06 (m, 3H, C_6H_5), 6.90-6.83 (m, 2H, C_6H_5), 6.28 (br s, 1H, N*H*), $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$, δ): 149.3 (C_6H_4), 139.3 (C_6H_4), 138.8 (C_6H_4), 128.8 (C_6H_4), 125.1 (C_6H_4), 123.9 (C_6H_5), 121.1 (C_6H_5), 112.9 (C_6H_5); LRMS (EI) *m/z* 214 $[M]^+$; HRMS (EI) exact mass calculated for $C_{12}H_{10}N_2O_2$ $[M]^+$ requires *m/z* 214.0736, found *m/z* 214.0745.

***N*-Methyl-4-nitro-(N-phenyl)-aniline (4.13j).** Reaction carried out following above method and sample was isolated as yellow oil after purification by column chromatography. ^1H NMR (300.0 MHz, $CDCl_3$, δ): 8.02-7.94 (m, 2H, C_6H_4), 7.42-7.33 (m, 2H, C_6H_4), 7.29-7.09 (m, 3H, C_6H_5), 6.63-6.54 (m, 2H, C_6H_5), 3.35 (s, 3H, NCH_3); $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$, δ): 153.9 (C_6H_4), 146.6 (C_6H_4), 138.6 (C_6H_4), 130.2 (C_6H_4), 126.7 (C_6H_5), 126.6 (C_6H_5), 125.6 (C_6H_5), 112.6 (C_6H_5), 40.4 (CH_3); LRMS (EI) *m/z* 228 $[M]^+$; HRMS (EI) exact mass calculated for $C_{13}H_{12}N_2O_2$ $[M]^+$ requires *m/z* 228.0894, found *m/z* 228.0887.

4-Chloro-N-(4-nitrophenyl)-aniline (4.13f). Reaction carried out following above method and sample was isolated as yellow oil after purification by column chromatography.[1]H NMR (300.0 MHz, $CDCl_3$, δ): 8.12-8.02 (m, 2H, C_6H_4), 7.31-7.23 (m, 2H, C_6H_4), 7.11-7.03 (m, 2H, C_6H_4), 6.89-6.81 (m, 2H, C_6H_4), 6.23 (br s, 1H, N*H*); $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$, δ): 150.3 (C_6H_4), 149.6 (C_6H_4), 138.4 (C_6H_4), 129.8 (C_6H_4), 126.1 (C_6H_4), 123.2 (C_6H_4), 114.0 (C_6H_4), 30.4 (C_6H_4); LRMS (EI) *m/z* 248 $[M-H]^+$; HRMS (EI) exact mass calculated for $C_{12}H_9N_2O_2Cl$ $[M]^+$ requires *m/z* 249.0425, found *m/z* 249.0421.

4-Nitro-(*N*-hexyl)-aniline (4.13m). Reaction carried out following above method and sample was isolated as yellow oil after purification by column chromatography.[1]H NMR (300.0 MHz, $CDCl_3$, δ): 8.04-7.95 (m, 2H, C_6H_4), 6.48-6.39 (m, 2H, C_6H_4), 4.52 (br s, 1H, N*H*), 3.13 (td, J = 7.1, 5.6 Hz, 2H, $NHCH_2$), 1.62-1.44 (m, 2H, CH_2), 1.35-1.14 (m, 4H, $(CH_2)_2$), 0.84 (dd, J = 8.9, 4.7 Hz, 2H, CH_2), 0.03 (s, 3H, CH_3); $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$, δ): 152.4 (C_6H_4), 137.3 (C_6H_4), 125.4 (C_6H_4), 110.1 (C_6H_4), 42.5 (CH_2), 30.6 (CH_2), 28.3 (CH_2), 25.6 (CH_2), 21.5 (CH_2), 12.8 (CH_3); LRMS (EI) *m/z* 223 $[M+H]^+$.

4-Methoxy-*N*-(4-nitrophenyl)-aniline (4.13h). Reaction carried out following above method and sample was isolated as yellow oil after purification by column chromatography. ^1H NMR (300.0 MHz, $CDCl_3$, δ): 8.05-7.96 (m, 2H, C_6H_4), 7.13-7.04 (m, 2H, C_6H_4), 6.90-6.82 (m, 2H, C_6H_4), 6.73-6.65 (m, 2H, C_6H_4), 6.10 (br s, 1H, N*H*), 3.77 (s,

3H, OC*H*$_3$); ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$, δ): 157.6 (C_6H_4), 151.6 (C_6H_4), 139.4 (C_6H_4), 132.2 (C_6H_4), 126.1 (C_6H_4), 125.5 (C_6H_4), 115.1 (C_6H_4), 112.7 (C_6H_4), 55.5 (O*C*H$_3$); LRMS (EI) *m/z* 245 $[M+H]^+$.

4-Nitro-*N*-(4-(trifluoromethyl)phenyl)-aniline (4.13i). Reaction carried out following above method and sample was isolated as yellow oil after purification by column chromatography. ^{1}H NMR (300.0 MHz, $CDCl_3$, δ): 8.15-8.05 (m, 2H, C_6H_4), 7.55 (d, J = 8.5 Hz, 2H, C_6H_4), 7.22-7.19 (m, 2H, C_6H_4), 7.05-6.98 (m, 2H, C_6H_4), 6.38 (br s, 1H, N*H*); ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$, δ): 148.2 (C_6H_4), 143.3 (C_6H_4), 135.1 (C_6H_4), 127.91 (q, $J_{C\text{-}F}$ = 3.7 Hz, *C*F$_3$), 125.8 (C_6H_4), 125.92 (C_6H_4), 119.7 (C_6H_4), 119.4 (C_6H_4), 115.4 (C_6H_4). LRMS (EI) *m/z* 282 $[M]^+$; HRMS (EI) exact mass calculated for $C_{13}H_9N_2O_2F_3$ $[M]^+$ requires *m/z* 282.0613, found *m/z* 282.0621.

1-(4-Nitro-phenyl)-piperidine (4.13n). Reaction carried out following above method and sample was isolated as yellow oil after purification by column chromatography. ^{1}H NMR (300.0 MHz, $CDCl_3$, δ): 8.06-7.99 (m, 2H, C_6H_4), 6.78-6.88 (m, 2H, C_6H_4), 3.41 (br s, 4H, C*H*$_2$NC*H*$_2$), 1.66-1.57 (m, 5H, $C_5H_{10}N$), 1.51 (s, 1H, $C_5H_{10}N$); ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$, δ): 159.1 (NC_6H_4), 137.0 (C_6H_4), 125.0 (C_6H_4), 111.4 (C_6H_4), 47.6 (N-*C*H$_2$), 24.3 (*C*H$_2$), 23.3 (*C*H$_2$); LRMS (EI) *m/z* 205 $[M-H]^+$.

***N*-Cyclohexyl-4-nitroaniline (4.13l).** Reaction carried out following above method and sample was isolated as yellow oil after purification by column chromatography. ^{1}H NMR (300.0 MHz, $CDCl_3$, δ): 8.03-7.94 (m, 2H, C_6H_4), 6.46-6.38 (m, 2H, C_6H_4), 4.42 (br s, 1H, N*H*), 2.04-1.92 (m, 2H, Cy-*H*), 1.79-1.57 (m, 3H, Cy-*H*), 1.37-1.06 (m, 5H, Cy-*H*); ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$, δ): 151.5 (C_6H_4), 125.5 (C_6H_4), 125.0 (C_6H_4), 110.3 (C_6H_4), 50.6 (C_6H_{11}), 31.9 (C_6H_{11}), 24.8 (C_6H_{11}), 23.4 (C_6H_{11}); LRMS (EI) *m/z* 221 $[M+H]^+$; HRMS (EI) exact mass calculated for $C_{12}H_{16}N_2O_2$ $[M]^+$ requires *m/z* 221.1285, found *m/z* 221.1279.

2-Chloro-*N*-(4-nitrophenyl)-aniline (4.13g). Reaction carried out following above method and sample was isolated as yellow oil after purification by column chromatography. ^{1}H NMR (300.0 MHz, $CDCl_3$, δ): 8.09-8.01 (m, 2H, C_6H_4), 7.31-7.24 (m, 2H, C_6H_4), 7.11-7.04 (m, 2H, C_6H_4), 6.89-6.82 (m, 2H, C_6H_4), 6.23 (br s, 1H, N*H*); ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$, δ): 150.3 (C_6H_4), 149.6 (C_6H_4), 138.4 (C_6H_4), 130.4 (C_6H_4), 129.8 (C_6H_4), 129.5 (C_6H_4), 126.1 (C_6H_4), 123.2 (C_6H_4), 123.0 (C_6H_4), 114.0 (C_6H_4),; HRMS (EI) exact mass calculated for $C_{12}H_9N_2O_2Cl$ $[M]^+$ requires *m/z* 249.0425, found *m/z* 249.0423.

2-Methyl-*N*-(4-nitrophenyl)-aniline (4.13k). Reaction carried out following above method and sample was isolated as yellow oil after purification by column chromatography. ^{1}H NMR (300.0 MHz, $CDCl_3$, δ): 8.07-7.98 (m, 2H, C_6H_4), 7.26-7.06 (m, 4H, C_6H_4), 6.69-6.59 (m, 2H, C_6H_4), 5.95 (br s, 1H, N*H*), 2.19 (s, 3H, CH_3); $^{13}C\{^{1}H\}$ NMR (75.5 MHz, $CDCl_3$, δ): 150.1 (C_6H_4), 149.7 (C_6H_4), 136.7 (C_6H_4), 132.4 (C_6H_4), 130.5 (C_6H_4), 126.3 (C_6H_4), 125.3 (C_6H_4), 125.2 (C_6H_4), 123.9 (C_6H_4), 112.2 (C_6H_4), 16.7 (CH_3); LRMS (EI) *m/z* 228 $[M]^+$; HRMS (EI) exact mass calculated for $C_{13}H_{12}N_2O_2$ $[M]^+$ requires *m/z* 229.0972, found *m/z* 229.0967.

4.6 References

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Chapter 5

Palladium-Catalysed Carbon-Carbon Bond Formations to form Cyclic Compounds

5.1 Introduction

5.1.1 Suzuki-Miyaura Cross Coupling

Suzuki-Miyaura cross coupling is one of the most important and a widely used cross-coupling reaction for many carbon-carbon bond formation, particularly in the synthesis of natural products and bioactive compounds.[1, 2] It is a versatile reaction that can be used for the synthesis of important biaryl architectures which are broadly used in agrochemicals, pharmaceuticals and the materials field.[3] Consequently, there is continuing interest in finding economical and environmentally friendly reaction conditions that can accommodate a wide scope of substrates and functional groups. As such, we aim to evaluate the usefulness of our Pd/R_2-CATPHOS catalysts in Suzuki-Miyaura cross coupling reactions.

An evaluation with functionalised aryl coupling partners has been conducted and is outlined in this chapter. They tolerate a variety of functional groups in the presence of various metals such as palladium, nickel and copper and they are highly selective and undergo simple and selective oxidative addition. The latter point assumes great importance because extensive studies with known palladium- or nickel catalysts in cross coupling reactions suggest that the oxidative addition of the electrophile is a problematic step and often leads to formation of unwanted side-products for many reactions.[4-6]

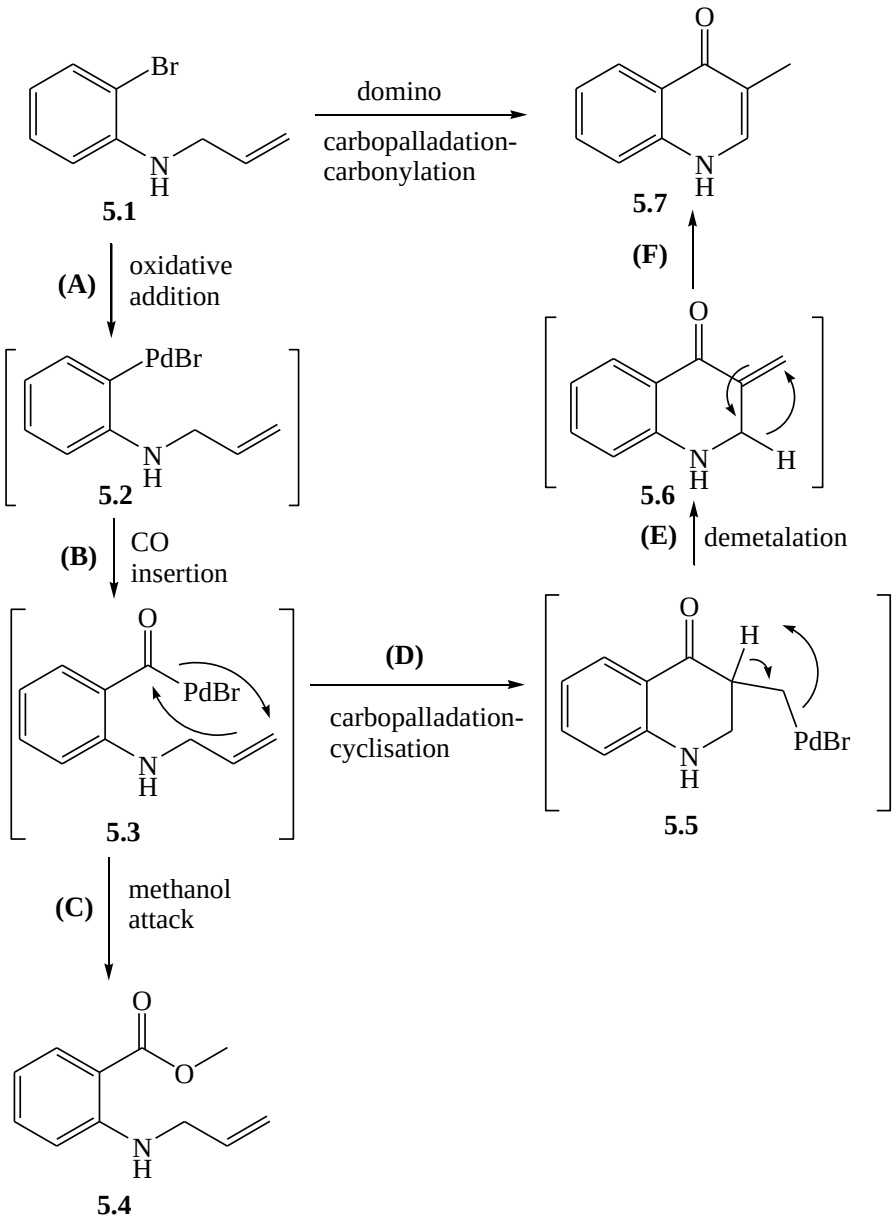
We will investigate the efficacy of Pd/R_2-CATPHOS catalysts with arylbromides as electrophilic coupling partners as they continue to be widely used in Suzuki-Miyaura cross coupling.[7, 8] Furthermore, we will also expand our investigation to aryl imidazolylsulfonates, a recently developed class of electrophile that has only recently been reported in Suzuki-Miyaura cross couplings.[9] Imidazolylsulfonates offer many advantages over triflates in handling and reactivity and are environmentally friendly.[9] They have also been widely applied in palladium-catalysed formation of various aryl phosphonates[10] and in the arylation of oxazoles.[11]

5.1.2 Domino Carbopalladation-Carbonylation

In our research programme, we explored the utility of a relatively new Heck-type reaction that is used to construct naturally occurring and biologically important polycyclic units, a

challenging task with current mainstream technologies.[15] The domino carbopalladation-carbonylation sequence (Chapter 1) was born from an expansion of the traditional Heck cycle where a second reaction step ensues after the transmetallation and prior to the β-hydride elimination step.[16-20] A recent publication by Ludlow and colleagues[21] shows that the CO insertion is a key step in this reaction sequence and it has been demonstrated that the CO pressure has a significant influence on the final product distribution.

In our study, we aim to employ this reaction sequence to form the functionalised bicyclic structure **5.7**, as proposed in Scheme 5.1. We will use palladium as the metal of choice for our transformation because it has very favourable properties such as two stable oxidation states, i.e., 0 and +2, that can be readily inter-converted, as well as availability of palladium precursors that have one or more empty and filled non-bonding orbitals and, moreover, its ability to take part in processes such as migratory insertion and carbometalation makes it particularly relevant to the domino carbopalladation-carbonylation synthesis.[22]



Scheme 5.1

A reaction scheme for the proposed domino carbopalladation-carbonylation reaction sequence with *N*-methyl-2-bromoaniline **5.1** as the starting material is outlined above in Scheme 5.1. We propose that initially the oxidative addition of Pd(0) to *N*-allyl-2-bromoaniline **5.1** (step A) forms the organopalladium **5.2** which subsequently undergoes CO insertion (step B) to form **5.3**. We reasoned that **5.3** would preferentially undergo ring carbopalladation-cyclisation (step D) to form **5.5** instead of undergoing early nucleophilic attack by methanol to form **5.4** (step C). Indeed recent literature reports show that Heck cyclisation is the favoured step subsequent to oxidative addition,[21] especially at high CO pressure. Finally, demetalation of **5.5** (step E) forms **5.6** which rapidly undergoes isomerisation (step F) to form the more stable and conjugated product 3-methylquinolin-4-one **5.7**.

The absolute key to viability of the carbopalladation-carbonylation reaction sequence is to ensure the designated substrate undergoes successful CO insertion (step B) and to either completely avoid or severely limit the competitive nucleophilic methanol attack (step C). Indeed recent advances in alkyl cross couplings have provided us with novel ways to do this, the most prominent of which is by simply increasing the CO pressure to favour the carbonylation step. Alternatively starting materials are often specifically synthesised to avoid competitive steps (such as β-hydride elimination) which, in turn, not only limits the scope of the application but also renders the whole process more expensive and time intensive. In our proposed mechanism (Scheme 5.1), we have decided to simplify our procedure by using *N*-allyl-2-bromobenzene so as to completely avoid early β-hydride elimination and concentrate on making the sequence viable for the synthesis of **5.7**.

5.2 Suzuki-Miyaura Cross Coupling

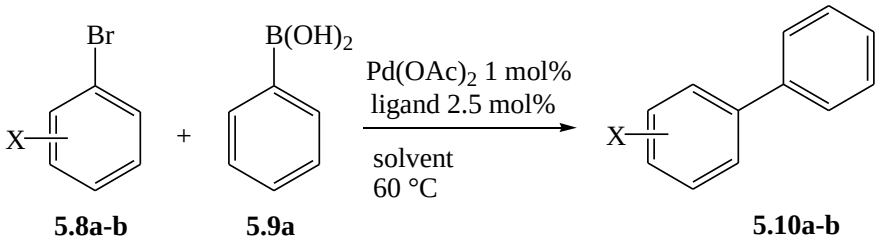
5.2.1 Aryl Bromides

We initially sought to test the efficacy of our Pd/R_2-CATPHOS catalysts against their *rac*-BINAP counterpart in a Suzuki-Miyaura cross coupling comparative study. The reaction conditions initially employed were the same as those previously used by the Doherty group[23] with the coupling between phenylboronic acid **5.9a** and bromobenzene **5.8a** in the presence of 1 mol% $Pd(OAc)_2$, 2.5 mol% ligand and K_3PO_4 (Table 5.1). It has been well-documented that the addition of a strong base will greatly accelerate the transmetallation step.[7] However, the strength of the base is inversely proportional to its functional group tolerance and, as such, we decided to use K_3PO_4 in our study in order to broaden the scope of the substrate range.

We initially carried out the reaction in different solvents; the cross coupling of phenylboronic acid **5.9a** to bromobenzene **5.8a** catalysed by Pd/*rac*-Me_2-CATPHOS in DMF afforded 1,1-biphenyl **5.10a** in 26% conversion. The same reaction carried out in toluene or THF gave **5.10a** in 24% and 44% conversions, respectively (entries 3 and 7). The reactions catalysed by the corresponding Pd/BINAP combination gave **5.10a** in high conversions where, for instance, the cross coupling of phenylboronic acid **5.9a** to bromobenzene **5.8a** in toluene gave **5.10a** in 96% conversion, compared to only 24% with the Pd/*rac*-Me_2-CATPHOS combination.

Given recent reports about the beneficial role of water in some Suzuki-Miyaura cross couplings between phenylboronic acid and arylbromides[24] (Chapter 1:section 1.3.3.1), our reactions were carried out in THF/H_2O using 4 equivalents of water. It is noteworthy that initial optimisation studies showed that the addition of more water was detrimental and reduced the conversions. Our initial result with THF/H_2O were very promising; conversions to 1,1-biphenyl **5.10a** increased by two fold from initial 44% in THF to 80% in THF/H_2O with both of the reactions catalysed by Pd/*rac*-Me_2-CATPHOS (entries 6 and 9). Pd/*rac*-$(MeO)_2$-CATPHOS catalyst in THF/H_2O gave **5.10a** in 50% conversion compared to 30% in THF only (entries 7-8). The improvement in conversions obtained in THF/H_2O compared to THF was most pronounced in the coupling of 1-bromo-4-methylbenzene **5.8b** to phenylboronic acid **5.9a** (entries 13-15) where the corresponding product 4-methyl biphenyl **5.10b** was obtained in 13% conversion in THF and 13% in toluene after 4 h, compared to 48% conversion in THF/H_2O after same time.

Table 5.1 Suzuki-Miyaura Cross-Coupling between Arylbromides **5.8a-b** and Phenylboronic acid **5.9a** to Afford the Corresponding Biphenyls **5.10a-b**.[a]



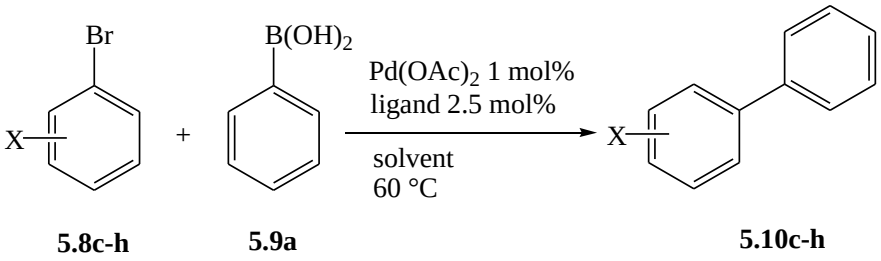
5.8a-b **5.9a** **5.10a-b**

Ent.	X	**5.10a-b**	Ligand	Solvent	Time (h)	% Conv. **5.10a-b**[b,c]	% Yield
1	H	**5.10a**	Me_2-CATPHOS	DMF	6	26	19
2	H	**5.10a**	BINAP	DMF	6	32	25
3	H	**5.10a**	Me_2-CATPHOS	Toluene	6	24	20
4	H	**5.10a**	BINAP	Toluene	6	96	90
5	H	**5.10a**	H_2-CATPHOS	Toluene	6	11	7
6	H	**5.10a**	Me_2-CATPHOS	THF/H_2O	6	80	70
7	H	**5.10a**	$(MeO)_2$-CATPHOS	THF/H_2O	6	50	45
8	H	**5.10a**	$(MeO)_2$-CATPHOS	THF	6	30	23
9	H	**5.10a**	Me_2-CATPHOS	THF	6	44	35
10	H	**5.10a**	BINAP	THF/H_2O	6	98	90
11	H	**5.10a**	BINAP	THF	6	68	60
12	H	**5.10a**	H_2-CATPHOS	THF/H_2O	6	2	0
13	4-Me	**5.10b**	Me_2-CATPHOS	THF	6	13	8
14	4-Me	**5.10b**	Me_2-CATPHOS	THF/H_2O	6	48	42
15	4-Me	**5.10b**	Me_2-CATPHOS	Toluene	6	13	10

[a]Reaction conditions: $Pd(OAc)_2$ (1 mol%), diphosphine ligand (2.5 mol%), K_3PO_4 (2 mol. eq.), phenylboronic acid (1.5 mol. eq.), THF (3mL) and H_2O (4 eq.) then bromobenzene. [b]Average of three runs. [c]Conversion calculated from the GC profile with internal standard.

Given these promising improvements in conversions, the scope of the reaction was expanded to include substituted aryl bromides, the results of which are shown in Table 5.2.

Table 5.2 Suzuki-Miyaura Cross-Coupling between Arylbromides **5.8c-h** and Phenylboronic acid **5.9a** to Afford **5.10c-h.**



5.8c-h **5.9a** **5.10c-h**

Ent.	X	**5.8c-h**	Ligand	Solvent	Time (h)	% Conv. **5.10 c-h**[b,c]	% Yield
1	4-OMe	**5.8c**	Me_2-CATPHOS	THF	10	85 (**5.10c**)	79
2	4-OMe	**5.8c**	Me_2-CATPHOS	THF/H_2O	10	65 (**5.10c**)	58
3	4-NO_2	**5.8d**	Me_2-CATPHOS	THF	10	38 (**5.10d**)	32
4	4-NO_2	**5.8d**	Me_2-CATPHOS	THF/H_2O	10	87 (**5.10d**)	80
5	4-NO_2	**5.8d**	$(MeO)_2$-CATPHOS	THF/H_2O	10	98 (**5.10d**)	92
6	4-NO_2	**5.8d**	H_2-CATPHOS	THF/H_2O	10	0 (**5.10d**)	0
7	4-CN	**5.8e**	Me_2-CATPHOS	THF/H_2O	6	45 (**5.10e**)	40
8	4-Cl	**5.8f**	Me_2-CATPHOS	THF	6	17 (**5.10f**)	15
9	4-Cl	**5.8f**	Me_2-CATPHOS	THF/H_2O	6	47 (**5.10f**)	42
1	4-^{t}butyl	**5.8g**	Me_2-CATPHOS	THF/H_2O	10	51 (**5.10g**)	45
11	4-^{t}butyl	**5.8g**	$(MeO)_2$-CATPHOS	THF/H_2O	10	13 (**5.10g**)	9
12	4-^{t}butyl	**5.8g**	H_2-CATPHOS	THF/H_2O	10	9 (**5.10g**)	7
13	3,5-Me_2	**5.8h**	Me_2-CATPHOS	THF/H_2O	19	91 (**5.10h**)	85
14	3,5-Me_2	**5.8h**	Me_2-CATPHOS	THF	19	51 (**5.10h**)	45
15	3,5-Me_2	**5.8h**	$(MeO)_2$-CATPHOS	THF/H_2O	19	61 (**5.10h**)	58
16	3,5-Me_2	**5.8h**	H_2-CATPHOS	THF/H_2O	19	16 (**5.10h**)	13
17	3,5-Me_2	**5.8h**	$(MeO)_2$-CATPHOS	THF	19	40 (**5.10h**)	39

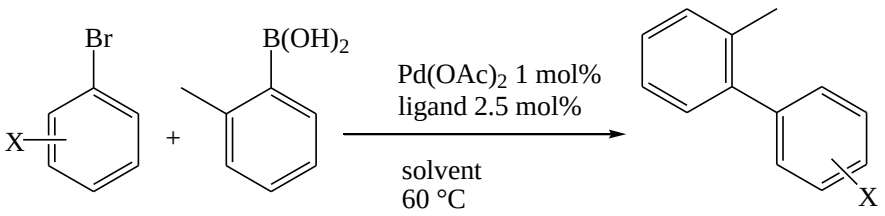
[a]Reaction conditions: $Pd(OAc)_2$ (1 mol%), diphosphine ligand (2.5 mol%), K_3PO_4 (2 mol. eq.), phenylboronic acid (1.5 mol. eq.), THF (3mL) and H_2O (4 eq.) then bromobenzene. [b]Average of three runs. [c]Conversion calculated from the GC profile with internal standard.

In the reaction of 1-bromo-4-methoxybenzene **5.8c** with phenylboronic acid **5.9a**, the corresponding product 4-methoxy biphenyl **5.10c** was obtained in 85% conversion with Pd/*rac*-Me_2-CATPHOS in THF compared to only 65% conversion in THF/H_2O (entries 1-2). The cross coupling with 1-bromo-4-nitrobenzene **5.8d** followed the prevailing trend and gave 4-nitro-biphenyl **5.10d** in higher conversion in THF/H_2O than THF (entries 3-6). Similarly, 1-bromo-4-chlorobenzene **5.8f** coupled selectively at the bromo- position to phenylboronic acid **5.9a** to afford 4-chloro-biphenyl **5.10f**; the conversion increased from 17% in THF to 47% in THF/H_2O after 6 h (entries 8-9).

Similarly, coupling reactions of 1-bromo-4-*tert*-butylbenzene **5.8g** and 1-bromo-3,5-dimethylbenzene **5.8h** with phenylboronic acid catalysed by Pd/*rac*-Me_2-CATPHOS gave the corresponding products **5.10g** and **5.10h**, respectively, in higher conversions in THF/H_2O compared to THF (entries 10-16). In particular, the coupling of 1-bromo-3,5-dimethylbenzene **5.8h** with phenylboronic acid **5.9a** catalysed by Pd/*rac*-Me_2-CATPHOS gave 1,3-dimethyl biphenyl **5.10h** in 51% conversion in THF compared to 91% in THF/H_2O; **5.10h** was obtained in 61% and 16% conversions with Pd/*rac*-$(MeO)_2$-CATPHOS and its H_2-CATPHOS counterpart, respectively, in THF/H_2O compared to only 40% conversion in THF with Pd/*rac*-$(MeO)_2$-CATPHOS (entry 17).

The reaction scope was further expanded to include 2-methylbenzeneboronic acid with the vast majority of the reactions carried out in THF/H_2O, the results of which are shown in Table 5.3.

Table 5.3. Suzuki-Miyaura Cross-Coupling between Arylbromides **5.8a-d** and 2-Methylbenzeneboronic acid **5.9b** to Afford Biaryls **5.10i-k**.



5.8a-c **5.9b** **5.10i-k**

Ent.	X	**5.8a-d**	Ligand	Solvent	Time (h)	% Conv. **5.10i-k**[b,c]	% Yield
1	H	**5.8a**	Me_2-CATPHOS	THF/H_2O	6	98 (**5.10i**)	95
2	H	**5.8a**	$(MeO)_2$-CATPHOS	THF/H_2O	6	73 (**5.10i**)	68
3	H	**5.8a**	H_2-CATPHOS	THF/H_2O	6	13 (**5.10i**)	10
4	4-OMe	**5.8c**	Me_2-CATPHOS	THF/H_2O	10	85 (**5.10j**)	78
5	4-OMe	**5.8c**	Me_2-CATPHOS	THF	10	64 (**5.10j**)	58
6	4-OMe	**5.8c**	$(MeO)_2$-CATPHOS	THF/H_2O	10	68 (**5.10j**)	60
7	4-NO_2	**5.8d**	Me_2-CATPHOS	THF/H_2O	10	70 (**5.10k**)	60
8	4-NO_2	**5.8d**	$(MeO)_2$-CATPHOS	THF/H_2O	10	99 (**5.10k**)	95

[a]Reaction conditions: $Pd(OAc)_2$ (1 mol%), diphosphine ligand (2.5 mol%), K_3PO_4 (2 mol. eq.), 2-methylbenzeneboronic acid (1.5 mol. eq.), THF (3 mL) and H_2O (4 eq.) then bromobenzene. [b]Average of three runs. [c]Conversion calculated from the GC profile against internal standard.

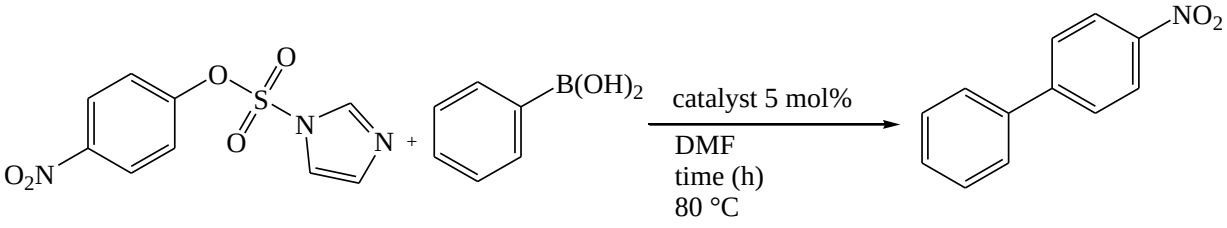
The reaction of 2-methylphenylboronic acid **5.9b** with bromobenzene **5.8a** catalysed by Pd/*rac*-Me-CATPHOS gave 2-methyl-biphenyl **5.10ia** in 98% conversion after 6 h. This was a very high conversion and is significantly better than the previous coupling between phenylboronic acid **5.9a** and bromobenzene **5.8a** which gave the corresponding product **5.10a** in 80% conversion (Table 5.1, entry 6). Furthermore, the reaction of 2-methylphenylboronic acid **5.9b** with 1-bromo-4-methoxybenzene **5.8c** gave the corresponding 4-methoxy-2-methyl-biphenyl **5.10j** in 85% conversion compared to only 65% conversion with phenylboronic acid **5.9a** (Table 5.1). These results demonstrate that the more hindered 2-methylphenylboronic acid **5.9b** appears to couple more efficiently than phenylboronic acid. However, the same trend was not observed in the coupling of 2-methylphenylboronic acid **5.9b** to 1-bromo-4-nitrobenzene **5.8d** which gave **5.10k** in 70%

conversion, which is markedly lower than the 87% conversion for **5.10d** with phenylboronic acid (Table 5.2, entry 4).

5.2.2. 4-Nitrobenzene Imidazolylsulfonate

Given the precedent set by Ackermann and colleagues in using aryl imidazolylsulfonates in Suzuki-Miyaura cross couplings with single component pre-catalysts,[11] we decided to initially apply the same reaction protocol in the novel reaction between 4-nitrobenzene imidazolylsulfonate **5.11** and phenylboronic acid **5.9a**, the results of which are shown in Table 5.4.

Table 5.4. Suzuki-Miyaura Cross Coupling between 4-Nitrobenzene Imidazolylsulfonate **5.11** and Phenylboronic acid **5.9a** to Afford 4-Nitrobiphenyl **5.10d**.



5.11 **5.9a** **5.10d**

Entry	Pre-Catalyst	Time (h)	Base	X	% Conv. **5.10d**[b,c]	% Yield
1	[H-CATPHOS]$PdCl_2$	17	K_2CO_3	H	10	5
2	[BINAP]$PdCl_2$	17	K_2CO_3	H	14	8
3	[Me-CATPHOS]$PdCl_2$	17	K_2CO_3	H	0	0
4	[H-CATPHOS]$PdCl_2$	17	K_3PO_4	H	6	0
5	[H-CATPHOS]$PdCl_2$	17	KF	H	0	0
6	[H-CATPHOS]$PdCl_2$	17	NEt_3	H	20	13

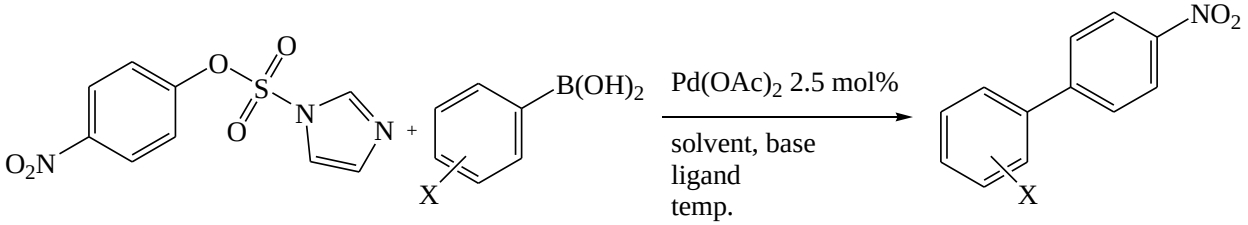
[a]Reaction conditions: $Pd(OAc)_2$ (1 mol%), diphosphine ligand (2.5 mol%), K_3PO_4 (2 mol. eq.), phenylboronic acid (1.5 mol. eq.), THF and H_2O (4 eq.) then imidazylate **5.11**. [b]Average of three runs. [c]Conversion calculated from the GC profile against internal standard.

Initially we synthesised the dichloride pre-catalysts with different ligands and in our initial evaluation, the corresponding product 4-nitro-biphenyl **5.10d** was obtained in only 10%

and 14% conversion with the catalyst derived from [{H_2-CATPHOS}$PdCl_2$] pre-catalyst and its *rac*-BINAP counterpart, respectively, and no product was obtained with [{*rac*-Me_2-CATPHOS}$PdCl_2$] (entries 1-3). Subsequently, we used different bases and although improvement in conversion was observed with triethylamine (entry 6, 20%), we reasoned that overall this reaction protocol was not giving high-enough conversions to warrant further optimisation.

In a more recent publication, Ackermann and colleagues reported a reaction protocol for the arylation of various substituted oxazoles with substituted aryl imidazolylsulfonates[11] using $Pd(OAc)_2$ (5 mol%) and DPPE (7.5 mol%) at 100 °C. We reasoned that given the versatility of imidazolylsulfonates and their successful application in various reactions under very different reaction protocols[9-11], the aforementioned reaction protocol should be tested in our Suzuki-Miyaura reaction. A clear advantage with this reaction protocol is that it does not require the synthesis and purification of the dichloride pre-catalyst and is therefore operationally much more straightforward. Consequently, we carried out optimisation studies on the coupling between 4-nitrobenzene imidazolylsulfonate **5.11** and phenylboronic acids **5.9a-c**, the results of which are shown in Table 5.5.

Table 5.5. Suzuki-Miyaura Cross Coupling between 4-Nitrobenzene Imidazolylsulfonate **5.11** and Phenylboronic Acids **5.9a-c** to Afford the Corresponding Biphenyls **5.10d-l.**.



5.11 **5.9a-c** **5.10d,k,l**

Entry	X	**5.9a-c**	Ligand	Base	Solvent	Temp. (°C)	%Conv. **5.10d,k,l**[b,c]
1	H	**5.9a**	H_2-CATPHOS	K_3PO_4	Toluene	80	24 (**5.10d**)
2	H	**5.9a**	H_2-CATPHOS	NEt_3	Toluene	80	23 (**5.10d**)
3	H	**5.9a**	H_2-CATPHOS	NEt_3	Toluene	80	0 (**5.10d**)
4	H	**5.9a**	H_2-CATPHOS	KF	THF	60	23 (**5.10d**)
5	H	**5.9a**	H_2-CATPHOS	K_3PO_4	THF	60	40 (**5.10d**)
6	H	**5.9a**	H_2-CATPHOS	K_3PO_4	THF/water	60	44 (**5.10d**)
7	H	**5.9a**	BINAP	K_3PO_4	THF	60	36 (**5.10d**)
8	2-Me	**5.9b**	H_2-CATPHOS	K_3PO_4	THF	60	0 (**5.10k**)
9	H	**5.9a**	H_2-CATPHOS	K_2CO_3	THF	60	28 (**5.10d**)
10	H	**5.9a**	H_2-CATPHOS	NEt_3	THF	60	33 (**5.10d**)
11	H	**5.9a**	H_2-CATPHOS	NEt_3	DMF	80	31 (**5.10d**)
12	H	**5.9a**	H_2-CATPHOS	K_2CO_3	DMF	80	98 (**5.10d**)
13	H	**5.9a**	BINAP	K_2CO_3	DMF	80	97 (**5.10d**)
14	H	**5.9a**	Me_2-CATPHOS	K_2CO_3	DMF	80	99 (**5.10d**)
15	H	**5.9a**	$(MeO)_2$-CATPHOS	K_2CO_3	DMF	80	99 (**5.10d**)
16	2-Me	**5.9b**	H_2-CATPHOS	K_2CO_3	DMF	80	57 (**5.10k**)
17	2-Me	**5.9b**	Me_2-CATPHOS	K_2CO_3	DMF	80	>99 (**5.10k**)
18	2,6-Me_2	**5.9c**	H_2-CATPHOS	K_2CO_3	DMF	80	0 (**5.10l**)
19	2,6-Me_2	**5.9c**	Me_2-CATPHOS	K_2CO_3	DMF	80	0 (**5.10l**)
20	2,6-Me_2	**5.9c**	$(MeO)_2$-CATPHOS	K_2CO_3	DMF	80	0 (**5.10l**)

[a]Reaction conditions: $Pd(OAc)_2$ (1 mol%), diphosphine ligand (2.5 mol%), K_2CO_3 (2 mol. eq.), arylboronic acid (1.5 mol. eq.) and DMF (8 mL) then aryl imidazolylsulfonate. [b]Average of three runs. [c]Conversion calculated from the GC profile against internal standard.

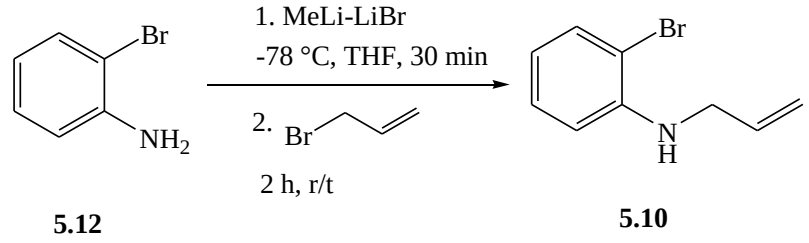
The literature protocol used NMP and toluene as the solvents of choice but given the toxic properties of NMP (identified as a reproductive toxicant by European Commission in 2003), we initially only used toluene in our evaluation. The initial reactions between 4-nitrobenzene-imidazolylsulfonate **5.11** and phenylboronic acid **5.9a** was carried out in toluene with triethylamine and potassium phosphate which gave **5.10d** in only 23% and 24% conversions, respectively (entries 1-2). By changing solvent from the reported toluene to THF, 4-nitro-biphenyl **5.10d** was obtained in only slightly improved conversions, even with different bases (entries 4-9). For instance, entry 5 shows that the reaction with potassium phosphate at 60 °C in THF gave 4-nitro biphenyl **5.10d** in 40% conversion which was only a slight improvement over the 23% conversion obtained in toluene 80 °C. The reaction in THF/water afforded **5.10d** in slightly higher conversion of 44% (entry 6)

We decided to further optimise our protocol and incorporate some of the conditions from one of our previous reactions.[9] Interestingly, 4-nitro-1,1-biphenyl **5.10d** was obtained in > 99% conversion with Pd/H_2-CATPHOS catalyst combination in DMF and K_2CO_3 as base at 80 °C, a result which is closely comparable with that obtained with its *rac*-BINAP counterpart (Table 5.5, entries 12, 13). Similarly, 99% conversion was obtained with both Pd/*rac*-Me_2-CATPHOS catalyst and its $(MeO)_2$-CATPHOS counterpart (entry 14-15). The same reaction with the more sterically hindered 2-methylbenzeneboronic acid gave **5.10k** in 57 % conversion catalysed by Pd/H_2-CATPHOS catalyst and, promisingly, 99% conversion with its *rac*-Me_2-CATPHOS counterpart (entries 16-17). However no conversion was observed with 2,6-dimethylbenzeneboronic acid (entries 18-20).

It is also noteworthy that the imidazolylsulfonate moiety has been used in other reactions such as Negishi cross coupling, hydrogenolysis, carbonylation[9] and the Buchwald-Hartwig amination.[25]

5.3 Domino Carbopalladation-Carbonylation

The starting material *N*-allyl-2-bromoaniline **5.10** was synthesised according to Figure 5.1. Initially 2-bromoaniline was lithiated in THF at – 78 °C followed by dropwise addition of a slight excess of allylbromide before warming to room temperature and allowed to stir for 2 h to afford *N*-allyl-2-bromoaniline in 65% isolated yield.



5.12 **5.10**

Figure 5.1. Reaction Conditions: i) 2-bromoaniline, THF at -78 °C then MeLi-LiBr (1.2 mol. eq.) drop wise, 30 min stir, ii) allyl bromide (1.2 mol. eq.) at -78 °C for 10 min, iii) 2 h at r/t.

Recent reports have shown that increasing the CO pressure from 1 atm to 100 psi favours the carbonylation (Scheme 5.1, step B). In a recent report, the yield of the desired product was increased from 0% at atmospheric pressure to 39% by increasing CO pressure to 100 psi.[26] Therefore, we can deduce that an increase in CO pressure is likely to increase the rate of carbonylation. As such, we reasoned that increasing the CO pressure would favour formation of desired product **5.7**.

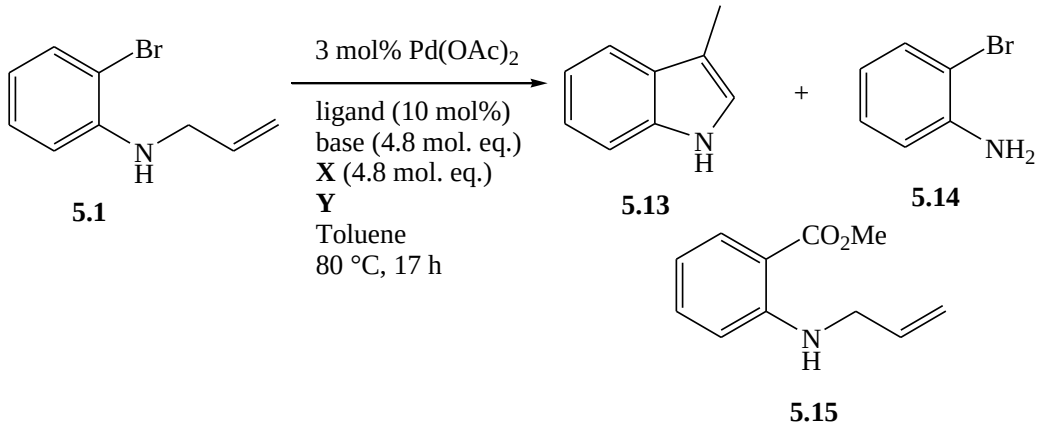
Recent reports also showed that the choice of ligand has a significant impact on the product distribution as well. Biaryl diphosphines, such as DPPF, favour high conversions to the desired functionalised polycyclic units.[21] Consequently, we started our evaluation by carrying out reactions with Pd/*rac*-BINAP as well as its DPPF, H_2-CATPHOS and X-Phos counterparts, at 1 atm CO and in methanol, the results of which are shown in Table 5.6.

The reactions catalysed by the Pd/*rac*-BINAP combination did not go to completion and the starting material was recovered as the major component, with 3-methylindole **5.13** and 2-bromoaniline **5.14** as two minor components in the crude product mixture. The same reaction was carried out in the absence of atmospheric CO which gave improved conversions for 2-bromoaniline **5.14** and 3-methylindole **5.13** (entry 2) but the starting material *N*-allyl-2-bromoaniline **5.1** was still the major component in the crude mixture (entries 1-2). Surprisingly, both of these reactions catalysed by the Pd/BINAP catalyst gave the unexpected de-allylated product 2-bromoaniline **5.14** in 15% and 24% conversions, respectively, (entries 1-2) and small quantities of 3-methylindole **5.13**.

The two reactions with the Pd/H_2-CATPHOS catalyst combination went to near-completion under the same reaction conditions and gave the de-allylated product 2-bromoaniline **5.14** as the major product and 3-methylindole **5.13** as minor product (entries 3-4). Closer inspection of these two reactions shows that with no CO, conversion to 3-methylindole **5.13** was increased from 16% to 40% while, on the other hand, conversions to 2-bromoaniline **5.14** decreased from 83% to 60%. This indicated to us that the presence

of CO severely hinders the formation of 3-methylindole **5.13** and favours de-allylation to afford 2-bromoaniline **5.14**.

Table 5.6. Intra-molecular Heck-type Cyclisation with *N*-Allyl-2-bromoaniline **5.1** Catalysed by Pd(II)/Ligand Combination (Ligand = H-CATPHOS, BINAP, X-Phos, DPPF).[a]



Entry	Ligand	Base	X	Y (bar)	% Conv. **5.13**[b,c]	% Conv. **5.14**[b,c]	% Conv. **5.15**[b,c]
1	BINAP	NEt_3	methanol	CO (1)	15	10	0
2	BINAP	NEt_3	methanol		24	14	0
3	H_2-CATPHOS	NEt_3	methanol	CO (1)	16	83	0
4	H_2-CATPHOS	NEt_3	methanol		39	60	0
5	DPPF	NEt_3	methanol	CO(1)	30	69	0
6	X-Phos	NEt_3	methanol	CO(1)	78	8	13
7	X-Phos	NEt_3	methanol	CO(50)	74	9	11
8	X-Phos	NEt_3		CO(50)	0	0	0
9	X-Phos	NEt_3			47	0	0
10	X-Phos	NEt_3	methanol		84	0	0
11	X-Phos	NEt_3		CO(1)	0	0	0
12	S-Phos	NEt_3	methanol	CO(1)	62	0	0

[a]Reaction conditions: Aryl amine, $Pd(OAc)_2$ (3 mol%), diphosphine ligand (10 mol%), NEt_3 (4.8 mol. eq.), toluene (3 mL), methanol (4.8 mol. eq.) and CO at the stated pressure. [b]Average of three runs. [c]Conversion calculated from the GC profile against internal standard.

In further evaluation to form **5.7** (Scheme 5.1), Pd/X-Phos was used under the same reaction conditions (entry 6). In the presence of both methanol and atmospheric CO, 3-methylindole **5.13** was formed as the major product (78% conversion) with **5.14** and **5.15** afforded in 8% and 13% conversions, respectively.

As previously mentioned, a positive correlation between CO pressure and the formation of the desired product **5.7** has been reported. As such, the reaction was conducted at 50 bar of CO pressure (entry 7). However, this gave 3-methylindole **5.13** as the sole product with no trace of the desired product **5.7**. Herein, the conversion for 3-methylindole **5.13** only changed slightly, from 78% with atmospheric CO to 74% with high CO pressure, which indicated to us that in our reaction, high CO pressure has a very minor influence on the product distribution with no evidence for the formation of **5.7** (Scheme 5.1).

It is noteworthy that the reaction catalysed by Pd/X-Phos did give 3-methyindole **5.13** in high 78% conversion (entry 6). A literature search for formation of 3-methyindole **5.13** from *N*-allyl-2-bromoaniline **5.1** revealed only two reports, to date, for this reaction, both of which were carried out at much higher temperatures and catalysed by palladium/tris(2-tolyl)phosphine (110 °C) and palladium/imidazolium (140 °C) catalyst combinations to afford 3-methylindole **5.13** in 80% and 77% yields, respectively.[27, 28] Furthermore, in a recent publication in 2008, a tandem two step synthesis was reported with the coupling of 1-bromo-2-iodobenzene to allylamine in the presence of 2.5 mol% $Pd_2(dba)_3$ and 5 mol% DPPF in toluene,[29] which gave 3-methylindole **5.13** in 85% conversion. This reaction, although successful, required very precise handling; the yield of 3-methylindole **5.13** only increased from 59% to 85% by initiating the reaction at room temperature, then gradually heating to 140 °C over 30 min and finally maintaining heating at 140 °C for a further 2 h. Even a slight deviation from this procedure led to a high yield of the unwanted *N*-allyl-2-bromoaniline as the major product. Given these findings and our serendipitous reaction protocol for formation of 3-methylindole **5.13** under milder and more straightforward reaction conditions, namely as low as 80 °C, we decided to further optimise our reaction conditions for the formation of 3-methylindole.

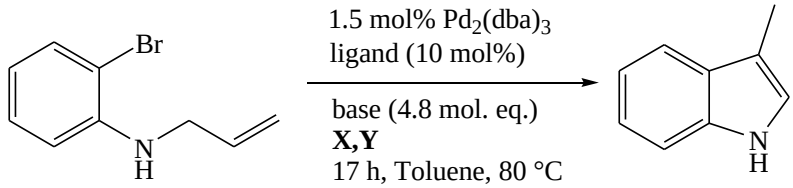
Initially it was important to investigate this effect of CO and methanol on the formation of 3-methylindole **5.13**. Consequently, we carried out a series of reactions with the Pd/X-Phos system; in the absence of both methanol and atmospheric CO; 3-methylindole **5.13** was obtained in significantly lower 47% conversion compared to the previous 78% conversion for the reaction with atmospheric pressure CO and methanol (Table 5.6, entries 6). The reaction in the presence of methanol and absence of CO gave 3-methylindole **5.13** in very high 84% conversion (entry 10). However in the two reactions with CO (atmospheric and at 50 bar) and no methanol (entry 8, 11), no evidence for formation of 3-methylindole **5.13** was obtained from the reaction and only starting material *N*-allyl-2-bromoaniline **5.1** was recovered. These results unequivocally establish the beneficial role

of methanol in the formation of 3-methylindole **5.13** and the detrimental influence of CO in blocking this reaction path.

5.3.1 Reaction Optimisation

A recent literature report for the synthesis of 3-methylindole **5.13** used $Pd_2(dba)_3$[29] where Pd(0) is readily oxidised in the first oxidative step of the reaction cycle whereas with $Pd(OAc)_2$, Pd(II) requires initial reduction *in situ* to Pd(0) before undergoing oxidative addition to form Pd(II), rendering $Pd_2(dba)_3$ more efficient to use. As such, we evaluated the use of $Pd_2(dba)_3$ in our reaction for the synthesis of 3-methylindole **5.13**, the results of which are shown in Table 5.7.

Table 5.7. Intra-molecular Heck Cyclisation of *N*-Allyl-2-bromoaniline to Form 3-Methyl-indole.



5.1 **5.13**

Entry	Ligand	Base	X	Y (bar)	% Yield **5.13**[b,c]
1	X-Phos	NEt_3	methanol	CO (1)	95
2	X-Phos	NaO-*t*-Bu	methanol	CO (1)	94
3	X-Phos	K_2CO_3	methanol	CO (1)	61
4	X-Phos	NEt_3	methanol		>99
5	X-Phos	NEt_3			60
6	X-Phos	K_2CO_3	methanol		72

[a]Reaction conditons: Aryl amine, $Pd_2(dba)_3$ (1.5 mol%), X-Phos (10 mol%), NEt_3 (4.8 mol. eq.), and toluene (3 mL) then methanol (4.8 mol. eq.). [b]Average of three runs. [c]Conversion calculated from the GC profile against internal standard.

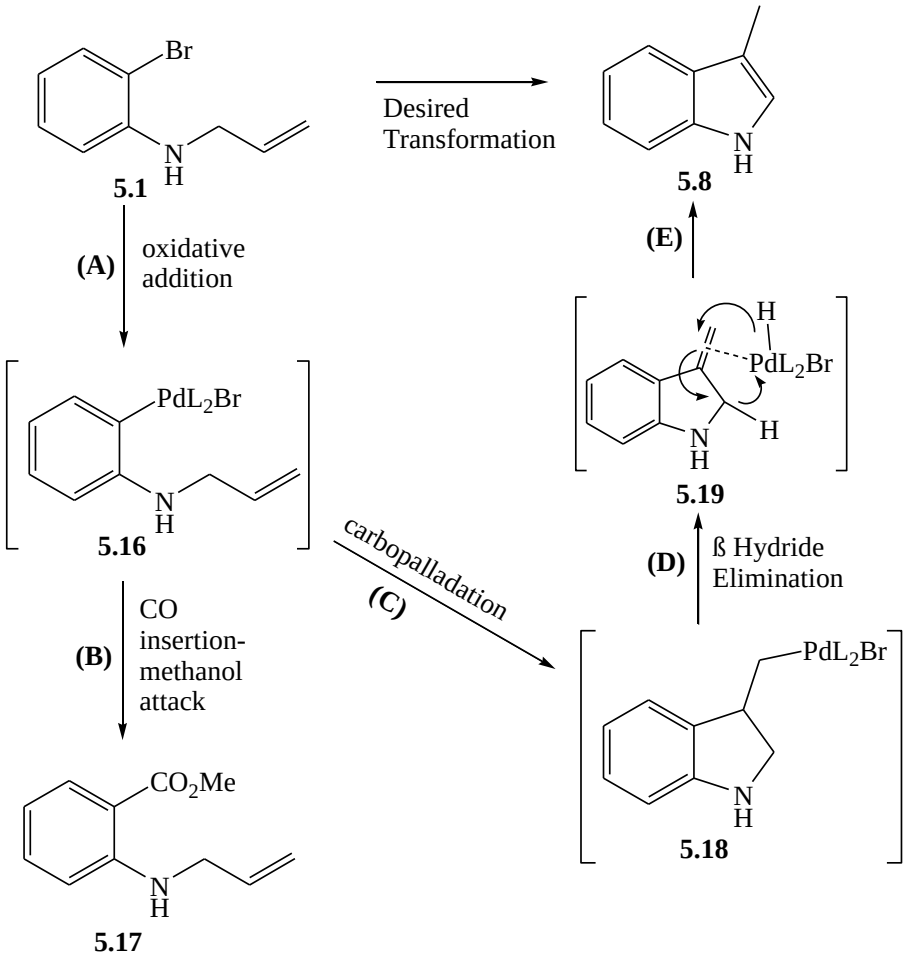
As previously observed with $Pd(OAc)_2$, the highest conversion was obtained in the presence of methanol and absence of CO, affording 3-methylindole **5.13** in > 99% conversion (entry 4). This finding, on its own, is a significant improvement on the same reaction with $Pd(OAc)_2$, which gave 3-methylindole **5.13** in 78% conversion (Table 5.6). The use of different bases also had a significant effect on the conversion, where NaO-*t*-Bu gave 3-methylindole **5.13** in 94% conversion whereas K_2CO_3 afforded 3-methylindole

5.13 in only 61% conversion (entries: 2 vs 3) but overall triethylamine was found to be the optimal base for this reaction (entries 1, 4).

5.3.2 Proposed Reaction Mechanism

Given that our reaction protocol favours formation of 3-methylindole **5.13**, we have revised our initial reaction cycle (Scheme 5.1) and propose that the conversion of *N*-allyl-2-bromoaniline **5.1** to 3-methylindole **5.13** follows the reaction cycle shown below in Scheme 5.2. The Pd(0)/X-Phos catalyst combination undergoes oxidative addition to *N*-allyl-2-bromoaniline **5.1** (step A) to afford **5.16**, which subsequently undergoes carbopalladation-cyclisation (step C) to afford **5.18**. The latter undergoes β-hydride elimination (step D) to afford **5.19** which subsequently isomerises and undergoes demetalation (step E) to afford 3-methylindole **5.8** as the final product (i.e. the simple Heck reaction).

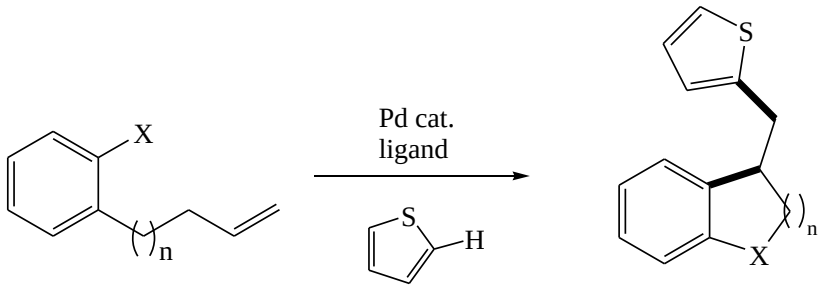
It is also noteworthy that **5.16** undergoes CO insertion-methanol attack (step B) to afford 2-allylamino-benzoic acid methyl ester **5.17** as minor side-product (Table 5.6, entry 6-7). Given that this was a minor product, even at high 50 bar CO pressure, the step for formation of **5.17** is evidently not favoured in our reaction.



Scheme 5.2

5.3.3 Addition of Thiophene

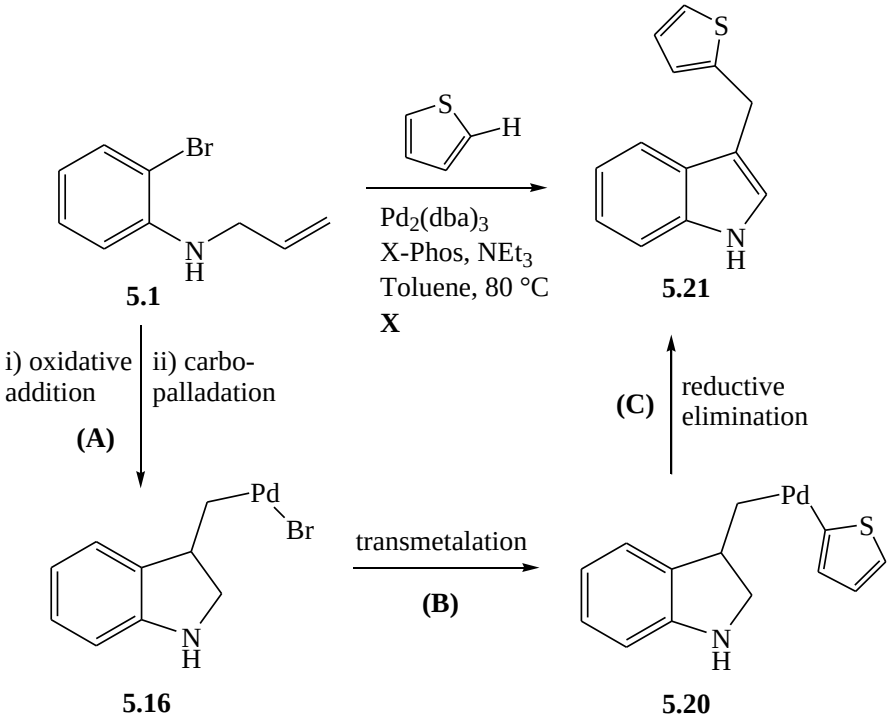
A recent report has outlined a domino Heck cyclisation-direct arylation synthesis in which an initial intramolecular Heck cyclisation is followed by an inter-molecular direct arylation with sulphur-based heterocycles, such as thiophenes, used as direct arylation coupling partners (Eq. 5.1).[16] More details on this report and mechanistic aspects of the reaction are highlighted in Chapter 1 (section 1.7.2).



Equation 5.1

Consequently, we added thiophene to our reaction protocol as the coupling partner and propose that the reaction will follow the synthesis outlined in Scheme 5.3. The initial

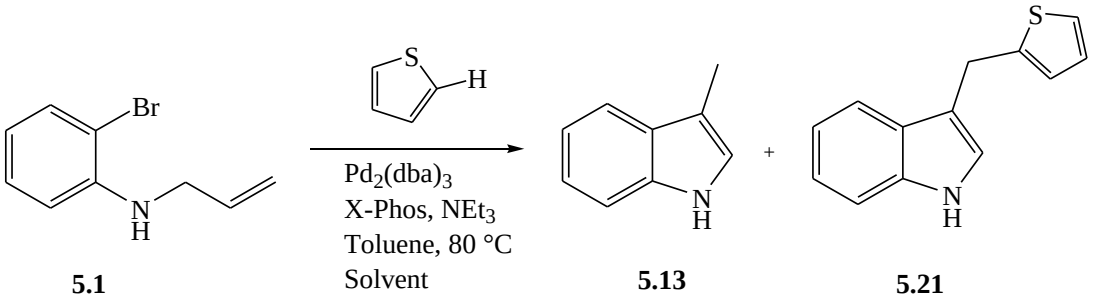
oxidative addition and carbopalladation (step A) affords **5.16**, as previously outlined in scheme 5.2 (steps A + C) which subsequently undergoes transmetalation of thiophene to the palladium(II) centre (step B) to afford **5.20**. Subsequently the latter undergoes demetalation to afford **5.21**.



Scheme 5.3

Given the previously established vital role of methanol in accelerating the formation of 3-methylindole **5.13**, as previously discussed, the modified reaction was carried out both in the presence as well as in the absence of methanol, the results of which are shown in Table 5.8 (entries 1-2). Our results only showed the formation of 3-methylindole **5.13** with no evidence for the proposed product **5.21**. The conversion for formation of 3-methylindole **5.13** was much higher in the presence of methanol (85%) compared to reaction with no methanol (48%), as previously observed.

Table 5.8. Attempted Domino Palladium Catalysed Heck Intra-molecular Direct Arylation.



5.1 **5.13** **5.21**

Entry	Solvent	% Conversion **5.13**[a]	% Conversion **5.21**[b,c]
1	methanol	85	0
2		48	0

[a]Reaction conditions: Aryl amine, $Pd_2(dba)_3$ (1.5 mol%), X-Phos (10 mol%), NEt_3 (4.8 mol. eq.), and toluene (3 mL) then methanol (4.8 mol. eq.) [b]Average of three runs. [c]Conversion calculated from the GC profile against internal standard.

Given limited time, we did not carry out further evaluation with other coupling partners but given previous reports of domino Heck cyclisations, we believe that incorporation of a coupling partner into our synthetic route (Scheme 5.3) is feasible and is worthy of further investigation. Indeed a Heck cyclisation-direct arylation reaction sequence[30] has recently been reported where the initial Heck cyclisation of 2-halo-*N*-allylanilines is followed by direct arylation using sulphur-containing heterocycles such as thiophene and benzothiophenes as coupling partners (Chapter 1: section 1.3.5.2) to form the corresponding functionalised heterocycles.

5.4 Conclusions

In conclusion our evaluation of the CATPHOS-based diphosphines in Suzuki-Miyaura cross coupling catalysed by Pd/*rac*-Me_2-CATPHOS in THF/H_2O gave very high conversions compared to other solvents for the vast majority of reactions between arylboronic acids and substituted aryl-bromides; furthermore the results with Pd/*rac*-Me_2-CATPHOS catalyst are comparable with Pd/BINAP for a significant number of reactions. Our results clearly demonstrate the successful reactivity of Pd/R_2-CATPHOS catalysts in the presence of water which shows that this class of diphosphine can maintain high reactivity over long time periods even in the presence of water thus expanding its scope of application beyond the anhydrous reaction conditions. Furthermore, Pd/*rac*-Me_2-CATPHOS catalyst gave higher conversions with substituted 2-methylbenzeneboronic acid compared to phenylboronic acid for the vast majority of the reactions which is especially encouraging given that reports by Suzuki and Miyaura shows slower reactivity of coupling reactions with more hindered arylboronic acids due to steric hindrance.[7] Although these results are not exhaustive, they do provide a platform for further evaluation.

We also successfully used 4-nitrobenzene imidazolylsulfonate in Suzuki-Miyaura cross coupling reactions with arylboronic acids and we successfully formulated an optimal reaction protocol with $Pd(OAc)_2$ (1 mol%) and R_2-CATPHOS 2.5 mol% (R = H, Me, OMe) in DMF with K_2CO_3 as mild base to give conversions in excess of 99%, results of which are comparable with their *rac*-BINAP counterpart. Encouragingly, Pd/R_2-CATPHOS catalysts gave good conversions with the hindered 2-methylbenzeneboronic acid as well. Overall, these results are particularly encouraging given the novelty of aryl imidazolylsulfonates as electrophilic coupling partners and that our initial conversions were all less than 30% with previous reaction protocols.

Furthermore, we have formulated a straightforward and relatively mild reaction protocol for the synthesis of biologically important 3-methylindole. Our results show that reactions with Lewis acid complexes of biaryl-based diphosphines like *rac*-Me_2-CATPHOS and *rac*-BINAP favour de-allylation of *N*-allyl-2-bromoaniline to afford 2-bromoaniline as major product. The original objective of the project to form the functionalised polycycle **5.7** via CO insertion was not achieved. Instead our methodology exclusively favours formation of the Heck product 3-methylindole.[22]

Our reaction methodology gave 3-methylindole under straightforward and mild reaction conditions which are much better than current literature precedents that include much harsher reaction conditions.[27] We have also established that the presence of methanol increases the conversion for 3-methylindole and there is no reason to suggest this reaction protocol cannot be used with other substrates as well.

Given time restrictions, we only briefly touched upon the domino direct arylation reaction as an alternative way of introducing more functionality onto 3-methylindole. Herein, only thiophene was used as the coupling partner and although no desired product was obtained, this route does require further evaluation with other coupling partners, given that the domino Heck cyclisation-direct arylation has only recently emerged in chemistry and it employs favourable mild reaction conditions.[16]

5.5 Experimental

General Comments. All manipulations involving air-sensitive materials were carried out using standard schlenk line techniques under an atmosphere of nitrogen or argon in oven-dried glassware. Dichloromethane was distilled from calcium hydride, diethyl ether from Na/K alloy, dioxane from sodium, THF from sodium/benzophenone, toluene from sodium and methyl *tert*-butyl ether. Tris(dibenzylideneacetone)palladium(0), palladium(0) acetate, *rac*-BINAP and X-Phos, were purchased from Strem Chemicals Co. Aniline derivatives and phenylboronic acids were purchased from commercial suppliers and used without further purification. H-CATPHOS (Chapter 2), *rac*-Me-CATPHOS (Chapter 2) and 4-nitrobenzene imidazolylsulfonate[9] were all prepared as previously described. ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra were recorded on a JOEL ECS-400 instrument. Thin layer chromatography (TLC) was carried out on aluminium sheets pre-coated with silica gel 60F 254. Gas chromatography mass spectrometry was performed on a Varian GCMS Saturn 2200 equipped with a CP-3800 Gas Chromatograph and yields were calculated from the GC profile. High pressure carbonylation was conducted in high pressure metal cyclinder.

Synthesis of {(12,12'-bis(diphenylphosphino)-9,9',10,10'-tetrahydro-11,11'-bi-9,10-ethenoanthracene)$PdCl_2$}. A solution of [(cycloocta-1,5-diene)$PdCl_2$] (0.073 g, 0.26 mmol) in dichloromethane (3 mL) was added to a solution of H-CATPHOS (0.2 g, 0.26 mmol) in dichloromethane (5 mL) and the mixture was stirred at r/t for 8 h. The resulting solution was filtered to remove insoluble impurities and solvent removed *in vacuo* to leave a pale yellow solid. The solid was triturated with hexane (3 x 5 mL) and crystallised by slow diffusion of a slight excess of hexane over the dichloromethane solution layer at room temperature. $^{31}P\{^{1}H\}$ NMR (300 MHz, $CDCl_3$, δ): 22.4 (s, PPh_2); ^{1}H NMR (300 MHz, $CDCl_3$, δ); 7.63 (d, J = 7.1 Hz, 2H, C_6H_4), 7.51 (dt, J = 7.2, 2.0 Hz, 2H, C_6H_5 *p*-H), 7.44-7.34 (m, 8H, C_6H_5 *m*-H), 7.17-7.12 (m, 4H, C_6H_5 *p*-H, C_6H_4), 7.07-7.01 (m, 6H, C_6H_5 *o*-H, C_6H_4), 6.94 (dt, J = 7.8 Hz, 1.0 Hz, 2H, C_6H_4), 6.91 (dt, J = 7.3 Hz, 1.3 Hz, 2H, C_6H_4), 6.88-6.82 (m, 6H, C_6H_5 *m*-H, C_6H_4), 6.78 (d, J = 7.0 Hz, 2H, C_6H_4), 6.68 (d, J = 7.4 Hz, 2H, C_6H_4), 5.23 (d, J = 3.8 Hz, 2H, bridgehead C*H*), 4.76 (d, J = 7.1 Hz, 2H, bridgehead C*H*); $^{13}C\{^{1}H\}$ NMR (300 MHz, $CDCl_3$, δ); 157.5 (m, *C*=CP), 144.2 (C_6H_4), 143.5 (C_6H_4), 142.7 (C_6H_4), 141.6 (C_6H_4), 140.2 (dd, J = 44.0, 1.8 Hz, C=*C*P), 133.5 (d, J = 13.0 Hz, C_6H_5 *o*-C), 131.3 (d, J = 3.0 Hz, C_6H_5 *p*-C), 130.9 (d, J = 3.0 Hz, C_6H_5 *p*-C), 129.9 (d, J = 63.0 Hz, C_6H_5), 128.7 (d, J = 12.0 Hz, C_6H_5 *m*-C), 128.3 (d, J = 11.8 Hz, C_6H_5 *m*-C), 126.8 (dd, J = 53.0, 2.0 Hz, C_6H_5), 125.9 (C_6H_4), 125.6 (C_6H_4), 126.5 (C_6H_4), 125.3 (C_6H_4), 123.9 (C_6H_4), 123.2 (C_6H_4), 122.9 (C_6H_4), 55.5 (d, J = 7.5 Hz, bridgehead

*C*H), 54.8 (d, *J* = 4.7 Hz, bridgehead *C*H). Anal Calculated for $C_{56}H_{40}Cl_2P_2Pd$: C, 70.64; H, 4.23. Found C, 70.78; H, 4.67.

General method for Suzuki-Miyaura Cross Coupling Reaction between Aryl Bromides and Substituted Arylboronic Acids. A flame-dried Schlenk was charged with $Pd(OAc)_2$ (0.002 g, 0.01 mmol), K_3PO_4 (0.405 g, 1.91 mmol), *rac*-BINAP (0.015 g, 0.024 mmol), benzeneboronic acid (0.175 g, 1.431 mmol) and THF (9 mL). The solution was stirred at room temperature for 5 minutes before addition of bromobenzene (0.15 g, 0.954 mmol). The reaction mixture was stirred at 60 °C for the allocated time. At the end of reaction, the mixture was allowed to cool to room temperature, distilled water (2 mL) and diethyl ether (2 mL) were added, the organic layers separated and combined, and ran through a short celite plug. The GC profile was recorded with an internal standard and the crude product was purified by column chromatography (petrol/EtOAc).

1, 1'-Biphenyl (5.10a). A sample was prepared by following the method outlined above and the product isolated as a colourless oil. ^{1}H NMR (300.0 MHz, $CDCl_3$, δ): 7.52 (dt, *J* = 8.2, 1.8 Hz, 4H, C_6H_5), 7.40-7.31 (m, 4H, C_6H_5), 7.30-7.21 (m, 2H, C_6H_5); $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$, δ): 140.4 (C_6H_5), 127.7 (C_6H_5), 126.3 (C_6H_5), 126.2 (C_6H_5); LRMS (EI) $[M]^+$ *m/z* 154.

4-Methyl-1, 1'-biphenyl (5.10b). A sample was prepared by following the method outlined above and the product was isolated as a colourless oil. ^{1}H NMR (300.0 MHz, $CDCl_3$, δ): 7.53-7.47 (m, 2H, C_6H_4), 7.45-7.39 (m, 2H, C_6H_5), 7.38-7.31 (m, 2H, C_6H_5), 7.28-7.21 (m, 1H, C_6H_5), 7.17 (dd, *J* = 5.4, 2.9 Hz, 2H, C_6H_4), 2.38 (s, 3H, CH_3); $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$, δ): 140.4 (C_6H_5), 137.5 (C_6H_5), 136.0 (C_6H_5), 135.9 (C_6H_5), 128.5 (C_6H_4), 127.7 (C_6H_4), 126.0 (C_6H_4), 125.9 (C_6H_4), 20.0 (CH_3); LRMS (EI) $[M]^+$ *m/z* 168.

4-Methoxy-1, 1'-biphenyl (5.10c). A sample was prepared by following the method outlined above and the product was isolated as a colourless oil. ^{1}H NMR (300.0 MHz, $CDCl_3$, δ): 7.50-7.42 (m, 4H, C_6H_4), 7.38-7.30 (m, 2H, C_6H_5), 7.26-7.16 (m, 1H, C_6H_5), 6.94-6.87 (m, 2H, C_6H_5), 3.77 (s, 3H, OCH_3); $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$, δ): 158.4 (C_6H_4), 140.1 (C_6H_5), 133.0 (C_6H_4), 127.7 (C_6H_4), 127.2 (C_6H_4), 125.8 (C_6H_5), 125.6 (C_6H_5), 113.4 (C_6H_4), 54.4 (OCH_3); LRMS (EI) $[M]^+$ *m/z* 184.

4-Nitro-1, 1'-biphenyl (5.10d). A sample was prepared by following the method outlined above and the product was isolated as a colourless oil. ^{1}H NMR (300.0 MHz, $CDCl_3$, δ): 8.26-8.18 (m, 2H, C_6H_4), 7.70-7.62 (m, 2H, C_6H_4), 7.59-7.50 (m, 2H, C_6H_5), 7.48-7.33 (m,

3H, C_6H_5); ^{13}C {^1H} NMR (75.5 MHz, $CDCl_3$, δ): 146.7 (C_6H_4), 146.4 (C_6H_4), 137.9 (C_6H_5), 128.2 (C_6H_5), 127.9 (C_6H_5), 126.8 (C_6H_5), 126.4 (C_6H_4), 123.1 (C_6H_4); LRMS (EI) $[M]^+$ *m/z* 199.

1, 1'-Biphenyl-4-carbonitrile (5.10e). A sample was prepared by following the method outlined above and the product was isolated as a colourless oil. ^1H NMR (300.0 MHz, $CDCl_3$, δ): 7.67-7.55 (m, 4H, C_6H_4), 7.54-7.46 (m, 2H, C_6H_5), 7.44-7.30 (m, 3H, C_6H_5); $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$, δ): 145.7 (C_6H_4), 139.2 (C_6H_5), 132.5 ((C_6H_4), 129.0 (C_6H_4), 128.6 ((C_6H_5), 127.7 (C_6H_5), 127.1 (C_6H_5), 118.6 (C_6H_4), 111.2 ($C\equiv N$); LRMS (EI) $[M]^+$ *m/z* 179.

4-Chloro-1,1'-biphenyl (5.10f). A sample was prepared by following the method outlined above and the product was isolated as a colourless oil. ^1H NMR (300.0 MHz, $CDCl_3$, δ): 7.55-7.40 (m, 4H, C_6H_4), 7.38-7.20 (m, 5H, C_6H_5); $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$, δ): 141.4 (C_6H_5), 140.0 (C_6H_4), 139.7 (C_6H_4), 133.4 (C_6H_4), 129.0 (C_6H_4), 128.3 (C_6H_5), 127.5 (C_6H_5), 127.0 (C_6H_5); LRMS (EI) $[M]^+$ *m/z* 188.

4-(^{t}Butyl)-1,1'-biphenyl (5.10g). A sample was prepared by following the method outlined above and the product was isolated as a colourless oil. ^1H NMR (300.0 MHz, $CDCl_3$, δ): 7.54-7.42 (m, 4H, C_6H_4), 7.41-7.30 (m, 4H, C_6H_5), 7.27-7.20 (m, 1H, C_6H_5); 1.28 (br s, 9H, (CH_3)$_3$); $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$, δ): 150.2 (C_6H_5), 141.1 (C_6H_4), 138.4 (C_6H_5), 128.6 (C_6H_5), 127.0 (C_6H_5), 126.8 (C_6H_4), 125.6 (C_6H_4), 125.4 (C_6H_4), 34.5 ($C(CH_3)_3$), 31.3 (CH_3); LRMS (EI) $[M]^+$ *m/z* 210.

3,5-Dimethyl-1,1'-biphenyl (5.10h). A sample was prepared by following the method outlined above and the product was isolated as a colourless oil. ^1H NMR (300.0 MHz, $CDCl_3$, δ): 7.51-7.45 (m, 2H, C_6H_5), 7.36-7.29 (m, 2H, C_6H_5), 7.27-7.20 (m, 1H, C_6H_5), 7.13 (br s, 2H, C_6H_3), 6.91 (br s, 1H, C_6H_3), 2.30 (s, 6H, (CH_3)$_2$); $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$, δ): 141.6 (C_6H_5), 141.3 (C_6H_3), 138.1 (C_6H_3), 128.8 (C_6H_3), 128.5 (C_6H_3), 127.2 (C_6H_5), 127.0 (C_6H_5), 125.1 (C_6H_5), 21.3 (CH_3); LRMS (EI) $[M]^+$ 182.

2-Methyl-1, 1'-biphenyl (5.10i). A sample was prepared by following the method outlined above and the product was isolated as a colourless oil. ^1H NMR (300.0 MHz, $CDCl_3$, δ): 7.37-7.30 (m, 2H, C_6H_5), 7.29-7.21 (m, 3H, C_6H_5), 7.20-7.13 (m, 4H, C_6H_4), 2.20 (s, 3H, CH_3); ^{13}C {^1H} NMR (75.5 MHz, $CDCl_3$, δ): 142.1 (C_6H_5) , 135.3 (C_6H_4), 130.2 (C_6H_4) , 129.3 (C_6H_4), 129.1 (C_6H_5), 127.9 (C_6H_5), 127.2 (C_6H_5), 126.9 (C_6H_4), 126.7 (C_6H_4), 125.6 (C_6H_4), 20.3 (CH_3); LRMS (EI) *m/z* 168 $[M]^+$.

4'-Methoxy-2-methyl-1,1'-biphenyl (5.10j). A sample was prepared by following the method outlined above and the product was isolated as a colourless oil. ^{1}H NMR (300.0 MHz, $CDCl_3$, δ): 7.21-7.11 (m, 6H, Ar-*H*), 6.91-6.83 (m, 2H, C_6H_5), 3.76 (br s, 3H, OCH_3), 2.26 (br s, 3H, CH_3); $^{13}C\{^{1}H\}$ NMR (75.5 MHz, $CDCl_3$, δ): 158.6 (C_6H_4), 141.7 (C_6H_4), 135.4 (C_6H_4) , 134.5 (C_6H_4), 132.2 (C_6H_4), 130.2 (C_6H_4), 129.8 (C_6H_4), 129.2 (C_6H_4), 126.8 (C_6H_4), 125.6 (C_6H_4), 115.8 (C_6H_4), 113.6 (C_6H_4), 55.2 (OCH_3), 20.2 (CH_3); LRMS (EI) $[M]^+$ *m/z* 198.

2-Methyl-4'-nitro-1,1'-biphenyl (5.10k). A sample was prepared by following the method outlined above and the product was isolated as a colourless oil. ^{1}H NMR (300.0 MHz, $CDCl_3$, δ): 8.23-8.16 (m, 2H, C_6H_4), 7.44-7.38 (m, 2H, C_6H_4), 7.28-7.10 (m, 4H, C_6H_5), 2.20 (br s, 3H, CH_3); $^{13}C\{^{1}H\}$ NMR (75.5 MHz, $CDCl_3$, δ): 148.8 (C_6H_4), 147.0 (C_6H_4), 139.7 (C_6H_4), 139.5 (C_6H_4), 134.9 (C_6H_4), 130.7 (C_6H_4), 130.0 (C_6H_4), 129.3 (C_6H_4), 128.4 (C_6H_4), 126.0 (C_6H_4), 128.8 (C_6H_4), 123.3 (C_6H_4) 19.8 (CH_3); LRMS (EI) $[M]^+$ *m/z* 213.

***N*-Allyl-2-bromoaniline (5.1).** A solution of 2-bromoaniline (1 g, 5.81 mmol) in THF (15 mL) was cooled to -78 °C under vigorous stirring. To this was added MeLi-LiBr solution (5 mL, 1.5 M) in a drop wise manner and the solution was allowed to stir at -78 °C for 30 min. On addition of MeLi-LiBr, a light green solution evolved. Allyl bromide (554 μL, 0.7 g) was added drop wise at -78 °C and solution allowed to stir for 10 min then reaction warmed to r/t and allowed to stir for 2 h. At end of reaction period, $NaHCO_3$ was added and mixture was extracted with ethyl acetate (3 x 30 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated under *in vacuo*. The crude mixture was purified by column chromatography (petrol/ethyl acetate, 98:2) and product isolated (0.8 g, 65%). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.32 (d, *J* = 7.9 Hz, 1H, Ar-*H*), 7.19-7.01 (m, 1H, Ar-*H*), 6.57-6.42 (m, 2H, C_6H_4), 5.93-5.77 (m, 1H, =C*H*), 5.25-4.99 (m, 2H, $=CH_2$), 4.38 (br s, 1H, N*H*), 3.73 (t, *J* = 5.5 Hz, 2H, CH_2); $^{13}C\{^{1}H\}$ NMR (75.5 MHz, $CDCl_3$, δ): 145.2 (C_6H_4), 135.2 (=*C*H), 132.9 (C_6H_4), 128.8 (C_6H_4), 118.3 ($=CH_2$), 116.7 (C_6H_4), 112.2 (C_6H_4), 110.2 (C_6H_4), 46.8 (CH_2); LRMS (EI) $[M]^+$ *m/z* 213.[31]

Synthesis of 2-Bromo-*N*-(prop-2-yn-1-yl)-aniline. A solution of 2-bromoaniline (2 g, 11.63 mmol), propargyl bromide (2.67 mL, 23.25 mmol), and potassium carbonate (3.21 g, 23.25 mmol) in dry THF (15 mL) was heated under reflux for 8 hours. At the end of the reaction period, mixture was cooled, washed with water, brine, dried over magnesium sulphate and purified on column chromatography (petrol:ethyl acetate 95:5). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.37 (dd, *J* = 7.9, 1.5 Hz, 1H, Ar-*H*), 7.19-7.09 (m, 1H, Ar-*H*), 6.68 (dd,

J = 8.2, 1.4 Hz, 1H, Ar-*H*), 6.60-6.53 (m, 1H, Ar-*H*), 4.48 (br s, 1H, N*H*), 3.91 (dd, *J* = 6.1, 2.4 Hz, 2H, CH_2), 2.16 (t, *J* = 2.4 Hz, 1H, ≡C*H*); $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$, *δ*): 144.7 (C_6H_4), 133.3 (C_6H_4), 129.2 (C_6H_4), 119.5 (C_6H_4), 112.6 (C_6H_4), 110.8 (C_6H_4), 80.8 (≡*C*CH_2), 71.8 (≡*C*H), 33.9 (*C*H_2); LRMS (EI) $[M+H]^+$ *m/z* 211.

General Procedure for Carbopalladation-Carbonylation: To a flame dried schlenk was added aryl amine (0.1 g, 0.472 mmol) $Pd(OAc)_2$ (3.18 mg, 0.014 mmol), X-Phos (22.48 mg, 0.047 mmol), NEt_3 (0.315 mL, 2.26 mmol) followed by toluene (6 mL). Solution was set to stir and methanol (1.8 mL) was added. Subsequently the reaction vessel was pressurised with CO and reaction allowed to stir overnight at 80 °C. At end of reaction period, crude reaction mixture was allowed to cool to room temperature and very slowly de-pressurised. The reaction was diluted with ethyl acetate and water. The aqueous layer was extracted with ethyl acetate, dried over $MgSO_4$, filtered through a short silica plug and concentrated *in vacuo*.[21, 32]

3-Methyl-1H-indole (5.13). A sample was prepared following general procedure outlined above. ^1H NMR (300 MHz, $CDCl_3$, *δ*): 7.91 (br s, 1H, N*H*), 7.54-7.49 (m, 1H, Ar-*H*), 7.30-7.24 (m, 1H, Ar-*H*), 7.15-7.01 (m, 2H, Ar-*H*), 6.91-6.88 (m, 1H, =C*H*), 2.30-2.24 (s, 3H, CH_3); $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$, *δ*): 135.8 (C_6H_4), 127.7 (C_6H_4), 127.5 (C_6H_4), 120.9 (C_4H_1N), 120.4 (C_6H_4), 118.3 (C_6H_4), 117.8 (C_6H_4), 110.9 (C_4H_1N), 13.2 (*C*H_3); LRMS (EI) $[M]^+$ *m/z* 130.

Methyl 2-(allylamino)-benzoate (5.15). A sample was prepared following general procedure outlined above. ^1H NMR (300 MHz, $CDCl_3$, *δ*): 7.84 (dd, *J* = 8.0, 1.7 Hz, 2H, C_6H_4), 7.31-7.24 (m, 1H, Ar-*H*), 6.62-6.48 (m, 2H, Ar-*H*, N*H*), 5.95-5.81 (m, 1H, =C*H*), 5.27-5.22 (m, 1H, =CH_aH_b), 5.14-5.08 (m, 1H, =CH_aH_b), 3.84-3.77 (m, 5H, OCH_3, CH_2); $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$, *δ*): 169.5 (*C*=O), 151.2 (C_6H_4), 135.1(=*C*H), 132.1 (C_6H_4), 134.8 (C_6H_4), 116.6 (=*C*H_2), 115.2 (C_6H_4), 111.7 (C_6H_4), 110.5 (C_6H_4), 51.9 (*C*H_3), 45.8 (*C*H_2); LRMS (EI) $[M+H]^+$ *m/z* 191.

2-Bromoaniline (5.14). A sample was prepared following general procedure outlined above. ^1H NMR (300 MHz, $CDCl_3$, *δ*): 7.43 (dt, *J* = 8.9, 2.7 Hz, 1H, Ar-*H*), 7.17-7.09 (m, 1H, Ar-*H*), 6.82-6.75 (m, 1H, Ar-*H*), 6.69-6.62 (m, 1H, Ar-*H*), 4.05 (br s, 2H, NH_2); $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$, *δ*): 143.9 (C_6H_4), 132.6 (C_6H_4), 128.4 (C_6H_4), 119.5 (C_6H_4), 115.7 (C_6H_4), 109.5 (C_6H_4); LRMS (EI) $[M+H]^+$ *m/z* 174.

Modified Procedure for Suzuki-Miyaura Cross Coupling with 4-Nitrophenyl Imidazolylsulfonate and Substituted Phenylboronic Acids: A flame- dried schlenk was

charged with $Pd(OAc)_2$ (1.7 mg, 0.007 mmol), *rac*-Me-CATPHOS (14.91 mg, 0.019 mmol), K_3CO_3 (0.205 g, 1.49 mmol), benzeneboronic acid (0.136 g, 1.12 mmol), and toluene (8 mL). To this solution was added 4-nitrobenzene imidazolylsulfonate (0.2 g, 0.743 mmol) and the reaction mixture was stirred at 80 °C for the allocated time period. At the end of the reaction period, crude reaction mixture was allowed to cool to r/t, diethyl ether (8 mL) and distilled water added (8 mL). Organic layer was extracted with diethyl ether, run through short silica plug and solvent removed *in vacuo*. The conversion was recorded from GC profile with an internal standard. The crude product was purified by column chromatography (petrol/ethyl acetate, 8:2 v/v).

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Chapter 6

Cyclisations with Bis-Gold Catalysts based on R_2-CATPHOS

6.1 Introduction

The catalytic activation of carbon-carbon π-bonds by carbophilic Au(I) and Au(III)-based catalysts is evolving into a very versatile and powerful approach for the synthesis of complex heterocyclic architectures that are prevalent in natural products.[1-4] In the vast majority of the transformations, the gold catalyst activates an alkyne towards nucleophilic addition whereby the activated alkyne undergoes a subsequent inter- or intra-molecular cyclisation.[5-8] The efficacy of gold-catalysed reactions, to a great extent, depends on the steric bulk and electronic properties of the supporting ligand.[9] Similarly, in palladium catalysed C-C and C-N bond reactions, it is now widely accepted that electron-richness and steric bulk of the supporting ligand has a positive correlation with efficient catalysis.[10]

Fukuda and Utimoto were first to report on the activation of alkynes towards nucleophilic attack by water/methanol catalysed by tetrachloroaurate.[11] Subsequently, Tele reported the intermolecular addition of alcohol to internal and terminal alkynes catalysed by cationic Au(I)/phosphine catalysts.[12] This was indeed pioneering work where Tele also made important in-roads in finding ways to generate cationic Au(I) catalysts by halide extraction using silver salts. These early fundamental studies also demonstrated that the Lewis basic character of the supporting ligand inversely correlates with catalyst activity which is befitting of the prevailing hypothesis that higher carbophilicity of the active gold centre of the Lewis acid, in turn, confers greater reactivity.

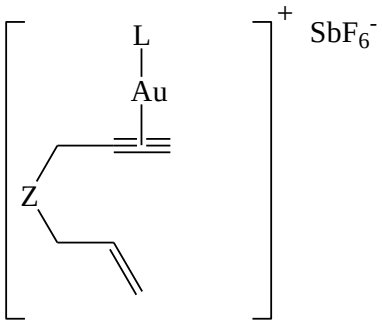
We aim to add to this exciting area of research by evaluating the Lewis acidic Au(I)/R_2-CATPHOS catalysts (R = H, Me, OMe) for the cycloisomerisation of a range of propargyl amides. The initial aim of our evaluation is to establish the efficacy of Au(I)/*rac*-R_2-CATPHOS catalysts (R = H, Me, OMe) in cycloisomerisation reactions before expansion to evaluate its effectiveness in the synthesis of biologically important chiral entities.

We also aim to employ Au(I)/(*S*)-Me_2-CATPHOS in the asymmetric methoxycyclisation of 1,6-enyne. This is a widely reported reaction in asymmetric Au(I)-based catalysis and, in general, exemplifies the emerging role of alkynes in enantioselective gold catalysis. Although both Au(I) and Au(III) have shown similar reactivity patterns, especially asymmetric transformations, they make for inherently different catalysts. Au(III)-based catalysts have, in essence, four binding sites and most often adopt a square-planar

geometry but there has been no reported example of alkyne or alkene asymmetric activation with Au(III)-based catalysts.[13] This is somewhat surprising given the presence of four binding sites would, in theory, enable building of a favourable chiral environment for asymmetric catalysis.

On the other hand, Au(I)-based catalysts have readily found application in asymmetric activation of alkynes and alkenes. It is widely, though not unequivocally, accepted that they have two binding sites with either a linear or near-linear geometry for the P-Au(I)-Cl linkage. The latter point assumes great significance given that any supporting chiral ligand of the catalyst is positioned on the opposite side of the Au(I) reaction site, as illustrated in Figure 6.1. This is one of the reasons that renders asymmetric catalysis with Au(I)-based Lewis acids extremely challenging.

Figure 6.1. Proposed Structure of Au(I)-Enyne where Z = $(CO_2Me)_2$ and L = (*R*)-BINAP[14]

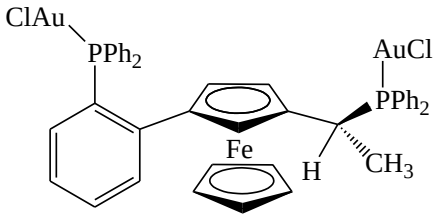


6.2 Coordination Studies

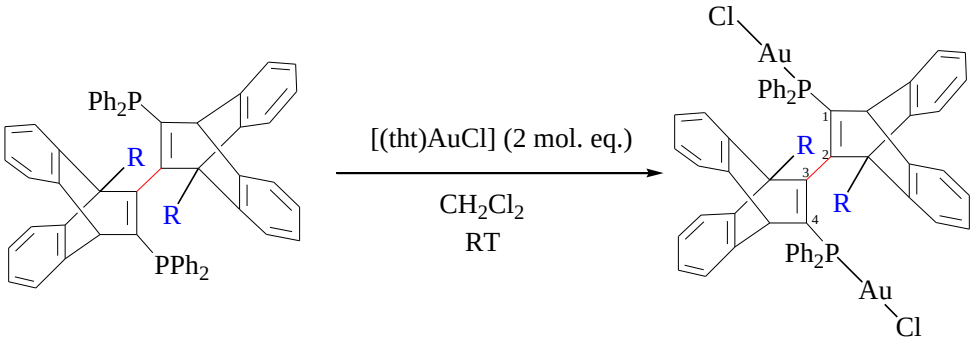
6.2.1 Gold Complexes of R_2-CATPHOS-Diphosphines

In a study by Echavarren and colleagues, a whole host of gold catalysts were synthesised, isolated and characterised. Very interestingly, these studies revealed the predisposition of Au(I) to coordinate exclusively to the phosphorus,[15] unlike Pd(II) and Cu(I) which coordinate to phosphorus and sulphur indiscriminately.[16, 17] The analysis of a ferrocene-based Au(I)-catalyst bearing a diphosphine supporting ligand shows two singlet signals in the ^{31}P NMR spectrum providing evidence that the two phosphorus atoms are coordinated to two separate Au(I) atom (Figure 6.2).[14] This observation paved the way for the successful synthesis, isolation and characterisation of various bis-Au(I) catalysts with BINAP and *tol*-BINAP. In fact, numerous attempts to synthesise diphosphine-based catalysts with both the phosphorus atoms coordinated to the same Au(I) atom have been unsuccessful to date.[18]

Figure 6.2. Ferrocene-based Bis-gold Pre-Catalyst.



With the intention of undertaking comparative catalyst testing with Au(I)/R_2-CATPHOS (R = H, Me, OMe) catalysts, we prepared each of the [R_2-CATPHOS(AuCl)$_2$] pre-catalysts by reaction of 2 molar equivalents of [(tht)AuCl][19] with the corresponding biaryl-like diphosphine R_2-CATPHOS (R = H, Me, OMe) in dichloromethane at room temperature, as shown in Equation 6.1. In each case, the [R_2-CATPHOS (AuCl)$_2$] (R = H, Me, OMe) complex was isolated and characterised by a combination of NMR spectroscopy, high resolution mass spectroscopy and elemental analysis and a single-crystal X-ray structure determination. Very few [{diphosphine}(AuCl)$_2$] structures have been crystallographically characterised and the analysis of these structures will be very informative.



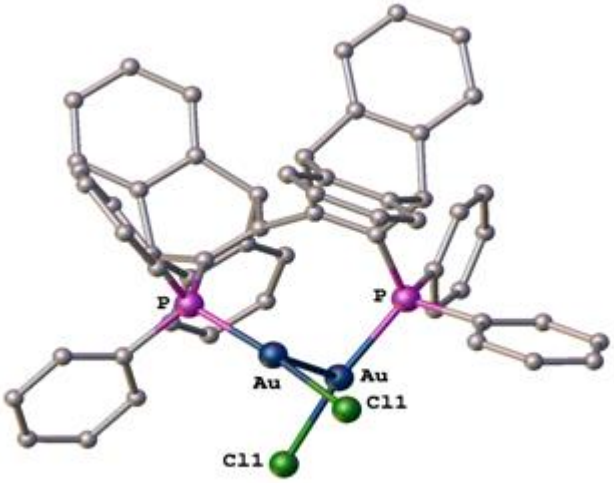
R = H (**6.1**)
Me (**6.2**)
MeO (**6.3**)

Equation 6.1. Synthesis of [R_2-CATPHOS$(AuCl)_2$] (R = H, Me, OMe) with the corresponding R_2-CATPHOS and 2 molar equivalent of [(tht)AuCl) in dichloromethane at room temperature.

6.2.2 $(AuCl)_2$-Crystal Structures of [R_2-CATPHOS]

In our study, we initially set about evaluating the structural features of **6.1** (Equation 6.1), the X-ray crystal structure of which is shown in Figure 6.3. The crystal structure shows the spatial arrangement of the P-Ph rings and the relative position of the two biaryl-like moieties which are inter-connected to each other via the C_1-C_2-C_3-C_4 tether (Equation 6.1). Each of the phosphorus atoms is bonded to one Au(I) atom. The P-Au-Cl linkage adopts a near-linear geometry with an angle of 169.52(4)° which is comparable with the P(1)-Au(1)-Cl(1) value of 172.69(4)° for [(*R*)-{BINAP}$(AuCl)_2$].[14] The spatial arrangement of P-Ph rings also closely resembles that in [(*R*)-{BINAP}$(AuCl)_2$] as well, where the two equatorial phenyl rings (P-Ph) project into the P-Au-Cl in-plane coordination site with the two corresponding axial rings orientated away from the coordination site. Consequently an asymmetric environment is created by the alternating edge-face arrangement of the two sets of P-Ph rings. The ^{1}H NMR spectrum contains two signals at δ 5.28 and δ 4.85 (2H for each) for the bridgehead C-H protons which are characteristic of the CATPHOS architecture. Similarly, the two corresponding bridgehead carbon atoms appear at δ 54.08 and δ 59.01 in the ^{13}C spectrum.

Figure 6.3. Molecular Structure of **6.1**. Hydrogen atoms Omitted for Clarity.

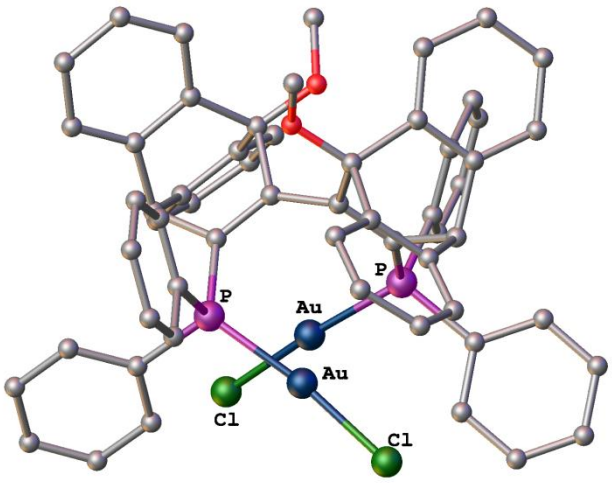


It is also noteworthy that the crystal structure of **6.1** depicts a rigid biaryl-like structure where there is strong π-π stacking interaction between the aromatic groups of the H_2-CATPHOS backbone moieties. Generally speaking, this is believed to determine the chiral environment of such bis-Au(I) diphosphine catalysts in the solid state.[13] However, whether these interactions continue to exist in solution is still unclear.

A unique feature of the **6.1** crystal structure is the aurophilic Au(I)-Au(I) interaction (Figure 6.3) with the Au-Au-Cl (1) natural bite angle of 98.62(4)° and an Au-Au distance of 3.2433(6)Å. The aurophilic Au-Au interaction in gold complexes is dependent on the rigidity of the supporting ligand and has a typical length of about 3.0Å.[20] The aurophilic Au(I)-Au(I) interaction is a rare structural feature that can be observed in bis-Au(I) catalysts. Munoz and co-workers have successfully obtained crystal structures of a few bis-Au(I) BINAP-based dichloride complexes, all of which have a nearly-linear P-Au-Cl bond angle (175°).[14] More interestingly, the steric bulk and rigidity of the biaryl moieties of the respective supporting ligands of these bis-Au(I) catalysts is believed to create a sizeable distance between the two Au(I) where no aurophilic Au-Au interaction is observed; the bis-gold complexes [(*R*)-{*tol*-BINAP}$(AuCl)_2$], [(*R*)-{BINAP}$(AuCl)_2$], [(*R*)-{BINAP}(AuCl)(AuNCPh)] and [(*R*)-{BINAP}$(AuMe)_2$] did not exhibit aurophilic Au-Au interaction given the rigid structure of the BINAP backbone. However, the geometry of H_2-CATPHOS is such that we clearly observe aurophilic Au(I)-Au(I) interaction in its corresponding dichloride pre-catalyst (**6.1**).

With a view of conducting a comparative study, the methoxy substituted bis-Au dichloride catalyst *rac*-**6.3** was prepared following the same procedure as for **6.1**; a molecular structure is shown in Figure 6.4.

Figure 6.4. Molecular Structure of *rac*-**6.3**. The Oxygen atom is Shown in Red. Hydrogen Atoms Omitted for Clarity.

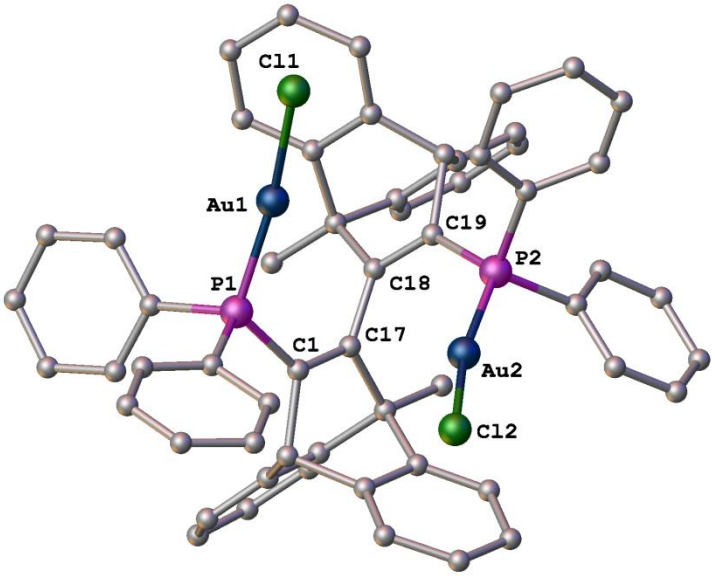


The crystal structure of *rac*-**6.3** closely resembles that of **6.1**, shown in Figure 6.3. The P-Au-Cl angle is 171.19(3)° which is comparable with P-Au-Cl angle of 169.52(4)° in its H_2-CATPHOS counterpart and also with 172.69(4)° of [{(*R*)-BINAP}$(AuCl)_2$].[14] The ^{13}C NMR provides further structural confirmation, with a characteristic signal at δ 68.3 for the O*C*H_3 group. Interestingly, no aurophilic Au(I)-Au(I) interaction is observed in the crystal structure. This indicates that the bridgehead methoxy group of the *rac*-**6.3** catalyst does, in fact, impart some steric hindrance in the P-Au-Cl plane so as to prevent the characteristic aurophilic Au(I)-Au(I) interaction, given that all other factors between the two crystal structures remain similar. Furthermore, the P-Au and Au-Cl bond lengths for *rac*-**6.3** are 2.2219(8)Å and 2.2741(8)Å, respectively; compared to the corresponding values of 2.2205(11)Å and 2.2859(13)Å for its H_2-CATPHOS counterpart, with a sizeable discrepancy in Au-Cl bond lengths of the two complexes observed.

The presence of MeO groups increase the barrier to rotation around the central C(2)-C(3) bond, which gives rise to atropisomerism and enables separation of the two conformations. This restriction in rotation is what presumably restricts the conformational freedom and prevents the aurophilic interaction from being formed.

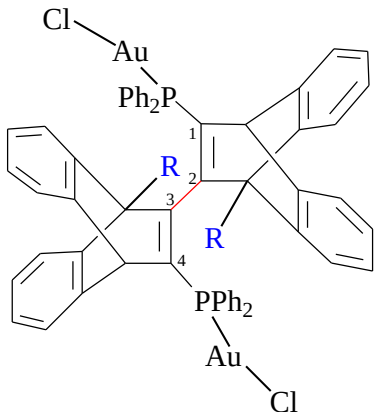
With a view to conducting asymmetric catalysis, the chiral methyl-substituted (*S*)-**6.2** pre-catalyst was synthesised and characterised as before; the single X-ray crystal structure shown is Figure 6.5.

Figure 6.5. Independent Structure of (*S*)-**6.2**, Illustrating the Absolute Stereochemistry about the Biaryl-like Axis C(17)-C(18). Hydrogen Atoms Omitted for Clarity.



The structure shows that each phosphorus atom is attached to Au(I) and clearly shows the absolute configuration of the biaryl fragment. The P(1)-Au(1)-Cl(1) and P(2)-Au(2)-Cl(2) angles are 168.62(6)° and 167.62(7)°, respectively, which are comparable to 172.69(4)° for [{(*R*)-BINAP}$(AuCl)_2$] and those for H_2-CATPHOS and *rac*-$(MeO)_2$-CATPHOS counterparts (Figure 6.3 and Figure 6.4). Some of the structural measurements of all three [{R_2-CATPHOS}$(AuCl)_2$] complexes have been tabulated in Table 6.1. It is clear that all three complexes have a very rigid backbone. As expected all three structures exhibit a near-linear P-Au-Cl linkage with very similar dihedral angles about the two biaryl fragments.

Table 6.1. Coordination Studies of [{R_2-CATPHOS}$(AuCl)_2$] Pre-catalyst Complexes.



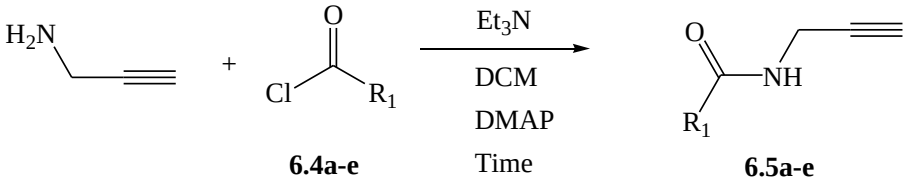
R	Au-Cl (Å)	Au-P (Å)	Au-Au (Å)	P-Au-Cl (°)	P-C_1 –C_2 (°)	Au-P-C_1(°)	Dihedral (°)
H	2.2859(13)	2.2205(11)	3.2433(6)	169.52(4)	124.9(3)	111.03(14)	127.2(4)
Me	2.2926(17)	2.2255(16)		168.62(6)	119.4(5)	106.8(2)	127.6(6)
MeO	2.2741(8)	2.2219(8)		171.19(3)	124.5(2)	109.31(10)	127.1(3)

6.3 Catalysis with Propargyl Amides

6.3.1 Synthesis

Initially we sought to evaluate the efficacy of Au(I)/R_2-CATPHOS (R = H, Me, MeO) for the cyclisation of various *N*-propargyl amides (Figure 6.4). They have been selected as the substrate of choice for the primary study as they are readily accessible in a single step.[21-25] The oxazoline is an important intermediate and its isomeric oxazole counterpart is a recurring substructure in a number of natural products and bioactive compounds.[26] The propargyl amides are prepared in a single step reaction between propargylamine and substituted acyl chlorides **6.4a-e** in dichloromethane in the presence of excess triethylamine to afford the corresponding *N*-propargyl amides **6.5a-e** in moderate to high yields (Figure 6.6).

Figure 6.6. Synthesis of Propargyl Amides **6.5a-e.**



6.4a-e **6.5a-e**

Entry	R_1	% yield **6.5a-e** [a]	Time (h)
1	^{t}Bu	65	1
2	Cy	80	1
3	Ph	72	1
4	Furan	69	3
5	Thiophene	83	4

[a] Isolated yield

All of the catalytic reactions were carried out in dichloromethane at room temperature. The reaction protocol involves the initial reaction of [R_2-CATPHOS ($AuCl_2$)] (R = H, Me, OMe) with two equivalents of silver salt $AgSbF_6$ in dichloromethane for 30 min in order to generate the corresponding Lewis acid (Eq. 6.2). Subsequently, the amide **6.5a-e** was added to the reaction mixture which was allowed to stir at room temperature for the allocated time.

$$[R_2\text{-CATPHOS (AuCl)}_2] + AgSbF_6\ (2\ \text{mol. eq.}) \xrightarrow[\text{r/t}]{30\ \text{min}} [Au_2\{R_2\text{-CATPHOS}\}][SbF_6]_2 \quad \textbf{(6.2)}$$

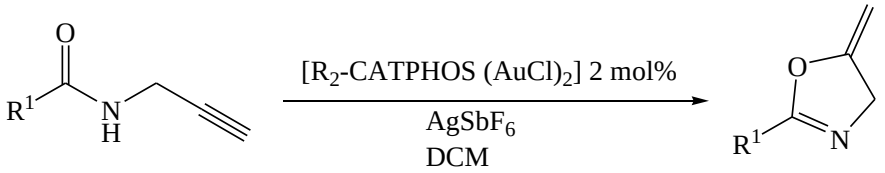
R = H
Me
OMe

6.3.2 Cycloisomerisation

Each Au_2/R_2-CATPHOS system (Eq. 6.2) successfully catalysed the cyclisation of propargyl amides **6.5a-e** to afford the corresponding methyleneoxazoline **6.6a-e**, as shown in Table 6.2. The formation of methyleneoxazoline unit is entirely consistent with previous work in our group and indeed other studies that have firmly established Au(I)-based catalyst are entirely selective for the synthesis of methyleneoxazoline derivative while their Au(III) counterparts are selective for the formation of the oxazole.[27, 28] The conversion for each reaction was calculated from the ^{1}H NMR spectrum against the 3H signal of bromomesitylene, which was added as an internal standard.

Our evaluation began with application of Au_2/*rac*-Me_2-CATPHOS catalyst where the corresponding active Lewis acid was generated using 2 mol% of [{Me_2-CATPHOS}$(AuCl)_2$] with 4 mol% of silver hexafluoroantimonate (eq. 6.2) in dichloromethane. Initially the cyclisation of the *tert*-butyl-based propargyl amide **6.5a** was catalysed by Au_2/*rac*-Me_2-CATPHOS to give the corresponding methyleneoxazoline **6.6a** in 75% conversion after 2 h. The reactions with cyclohexyl- (**6.5b**) and phenyl- (**6.5c)** substituted propargyl amides also gave the corresponding methyleneoxazolines **6.6b** and **6.6c** in 93% and 98% conversion, respectively, after 2 h. Given these encouraging results, the substrate scope was expanded to include furan and thiophene- substituted propargyl amides **6.5d** and **6.5e**; Au_2/*rac*-Me_2-CATPHOS catalyst gave the corresponding products **6.6d** and **6.6e** in 33% and 80% conversions, respectively (Table 6.2, entries 4-5). Although the furan-substituted adduct **6.6d** is formed in only 33% conversion after 2 h, this is still a very encouraging result given that **6.5d** has proven to be a very challenging substrate to work with; in a previous report by the Doherty group, no conversion was reported for furan-substituted propargyl amide at room temperature. In that report, **6.5d** only successfully reacted to give **6.6d** in dichloroethane at elevated temperature of 50 °C.[29]

Table 6.2. Methoxycyclisation of Propargyl Amides **6.5a-e** Catalysed by Au_2/R_2-CATPHOS Catalysts (R = H, Me, OMe) to form the Alkylidene Oxazolines **6.6a-e**.[a]



6.5a-e **6.6a-e**

Entry	R^1	Amide **6.5**	Catalyst	Time (h)	% Conversion **6.6a-e** [b-c]
1	^{t}butyl	**6.5a**	*rac*-**6.2**	2	75
2	Cy	**6.5b**	*rac*-**6.2**	2	93
3	Ph	**6.5c**	*rac*-**6.2**	2	98
4	furyl	**6.5d**	*rac*-**6.2**	2	33
5	thiop.	**6.5e**	*rac*-**6.2**	2	80
6	^{t}butyl	**6.5a**	*rac*-**6.3**	4	86
7	Cy	**6.5b**	*rac*-**6.3**	4	60
8	Ph	**6.5c**	*rac*-**6.3**	4	68
9	furyl	**6.5d**	*rac*-**6.3**	4	30
10	thiop.	**6.5e**	*rac*-**6.3**	4	38
11	^{t}butyl	**6.5a**	**6.1**	2	84
12	Cy	**6.5b**	**6.1**	6	67
13	Ph	**6.5c**	**6.1**	2	73
14	furyl	**6.5d**	**6.1**	2	0
15	thiop.	**6.5e**	**6.1**	4	67

[a] i) 2 mol% of [{R_2-CATPHOS}$(AuCl)_2$], 4 mol% $AgSbF_6$ in dichloromethane for 30 min ii) addition of propargyl amides and allowed to stir for allocated time period iii) 1 mol. eq. of an internal standard (bromomesitylene) added and crude filtered through a short silica plug.[b] % conversion calculated from ^{1}H NMR against unreacted bromomesitylene as the internal standard.[c] Average of 2 runs.

The evaluation was extended to include Au_2/*rac*-$(MeO)_2$-CATPHOS catalyst with the bulky $(MeO)_2$-CATPHOS supporting ligand. General literature reports for Au(I)/phosphine catalysts show that bulky supporting ligands are an integral part of the

respective gold catalyst which have been used in various C-C and C-O bond formations with an initial activation of the alkyne bond.[9, 30]

The subsequent reactions of Au_2/*rac*-$(MeO)_2$-CATPHOS catalyst with the same set of propargyl amides **6.5a-e** successfully gave all the corresponding methyleneoxazoline products **6.6a-e** in moderate to high conversion after 4 h. The *tert*-butyl adduct **6.6a** was obtained in 86% conversion after 4 h (vs 75% with Au_2/*rac*-Me_2-CATPHOS after only 2 h) and **6.6b-c** adducts were only afforded in conversions comparable to their Me_2-CATPHOS counterpart after 4 h (Table 6.2, entries: 2-3 vs 7-8). The most drastic drop in the conversion was obtained in the formation of the thiophene adduct **6.6e**, which was afforded in only 38% conversion, even after 4 h, compared to 80% with Au_2/*rac*-Me_2-CATPHOS catalyst in only 2 h (Table 6.2, entry: 5 vs 10). The reaction with the furan adduct **6.5d** gave **6.6d** in only 30% conversion after 4 h, compared to 33% with the Au_2 /*rac*-Me_2-CATPHOS catalyst after 2 h.

The scope of the evaluation was expanded to include catalysis with Au_2/H_2-CATPHOS catalyst. Our preliminary results show that in the majority of the reactions, Au_2/H_2-CATPHOS catalyst outperforms its $(MeO)_2$-CATPHOS counterpart but proves to be less efficient than the Au_2/*rac*-Me_2-CATPHOS combination. The methyleneoxazoline **6.6a** is afforded in 84% conversion after 2 h, which is comparable to the conversion of 86% obtained with Au_2/*rac*-$(MeO)_2$-CATPHOS and is marginally better than that of 75% obtained with its *rac*-Me_2-CATPHOS counterpart. Furthermore, Au_2/H_2-CATPHOS outperforms its $(MeO)_2$-CATPHOS counterpart with both phenyl and thiophene-based substrates; the corresponding products **6.6c** and **6.6e** are obtained in 73% and 67%, respectively (Table 6.2, entries 13, 15). Surprisingly, no conversion was obtained with the furan-based substrate **6.5d**.

Herein, the 'R' group affect is the most pronounced with the Au_2/H_2-CATPHOS catalyst which gives no conversion at all with furan-based amide **6.5d** (entry 14), compared to the Au_2/*rac*-Me_2-CATPHOS and Au_2/*rac*-$(MeO)_2$-CATPHOS catalysts which both catalysed the cyclisation of **6.5d** to give **6.6d** in 33% and 30% conversion, respectively (entries: 4, 9, 14). As mentioned above, given the difficult nature of furan-based propargyl amide, which usually requires elevated reaction temperatures, these results are encouraging and do demonstrate that the 'R' bridgehead group of the CATPHOS-type architecture does influence the efficacy of the Lewis acid catalyst derived from {{R_2-CATPHOS}$(AuCl)_2$].

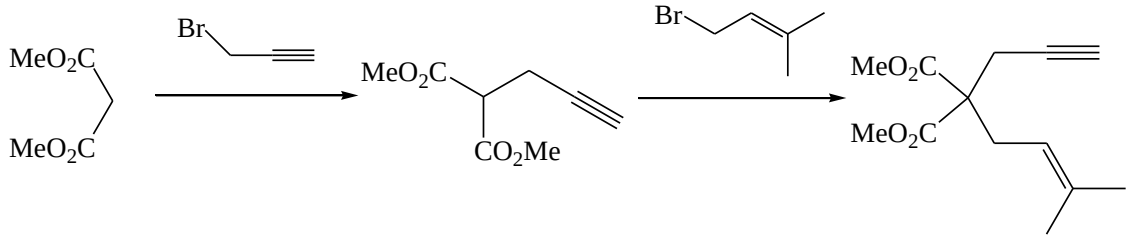
6.4 Catalysis with 1,6-Enyne

6.4.1 Synthesis of Propargyl Malonate

Having established the efficacy of the Lewis acid combination Au/R_2-CATPHOS in the cycloisomerisation of propargyl amides (Table 6.2), we carried out a brief evaluation with the cyclisation of 1,6-enyne **6.8**, the synthesis of which is outlined in scheme 6.1. In the initial step, a solution of dimethyl malonate in THF was added slowly to a solution of sodium hydride in THF and allowed to stir for 1 h at room temperature. Subsequently, neat propargyl bromide was added and the solution was allowed to stir at room temperature overnight to afford dimethyl propargyl malonate **6.7** in 75% crude yield, which was used without further purification. In the next step, the crude intermediate **6.7** and caesium carbonate (1.5 mol. eq.) were dissolved in acetone and to this solution was added 3,3-dimethylallyl bromide (2 mol. eq.) and the resulting mixture heated under reflux for 16 h to afford 1,6-enyne **6.8** in 90% isolated yield.

Given that the enyne **6.8** has been previously cyclised by [(*R*)-{*tol*-BINAP}$(AuCl)_2$], [14] we chose this substrate for the initial phase of the catalyst testing in order to test the efficacy of Au_2/(*S*)-Me_2-CATPHOS in a chiral methoxycyclisation reaction.[31-33]

Scheme 6.1. Two-step Synthesis of Dimethyl-2-propargyl,2-dimethylallyl Malonate **6.8**.[34, 35]

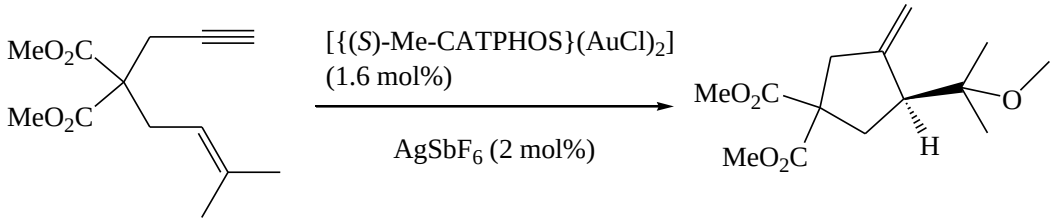


6.7 **6.8**

6.4.2 Methoxycyclisation

Literature reports have demonstrated that the optimal reaction conditions for the methoxycyclisation of the 1,6-enyne **6.8** is 1.6:2 molar ratio of [Ligand$(AuCl)_2$] and silver salt which subsequently forms a highly active monocationic gold catalyst.[13] As such, we employed the same reaction conditions with Au_2/(*S*)-Me_2-CATPHOS. The reaction was carried out in dichloromethane with excess methanol and allowed to stir for 7 h at room temperature, the results of which are shown in Figure 6.7.

Figure 6.7. Methoxycyclisation of 1,6-enyne **6.8** Catalysed Au(I)/(*S*)-Me_2-CATPHOS.



6.8

6.9
racemic

The reaction afforded the methoxycyclisation adduct **6.9** in 98% conversion. Encouragingly, Au_2/(*S*)-Me_2-CATPHOS catalyst is entirely selective for the synthesis of the desired product **6.9**, with no trace of the unwanted diene side-product in the crude mixture (Figure 6.4). Despite repeated attempts of the reaction, **6.9** was only obtained as a racemic mixture with two peaks corresponding to the racemic methoxycyclisation **6.9** appearing at 11.53 and 12.36 mins on the chiral HPLC chromatogram. The same reaction catalysed by 1.6 mol% of [(*S*)-{*tol*-BINAP}$(AuCl)_2$] is reported to afford **6.9** in 91% yield after 7 h at room temperature with no enantioselectivity as well.[14] Achieving high levels of enantioselectivity with this class of substrates is very challenging given that the active catalyst is coordinated to the alkyne and is pointing away from the attacking alkene. This is further compounded by the fact that the near-linear Au-ligand geometry places the chiral ligand even further away from the Au(I) reaction site. However the enantioselectivity levels with 1,6-enynes appear to be more dependent on substitution pattern, as previously mentioned in Table 6.1.

6.5 Conclusions

We have successfully synthesised and characterised three crystal structures of the type [{R_2-CATPHOS}$(AuCl)_2$] (R = H, Me, OMe) and, given the rapid emergence of gold catalysis especially in the area of alkyne activation, there is on-going interest in the development and evaluation of such novel gold catalysts. The disparate performance of the [{R_2-CATPHOS}$(AuCl)_2$] suggests that the R groups of the CATPHOS-type supporting ligands can influence the catalyst reactivity.

Our initial evaluation involved the cycloisomerisation of propargyl amides where the vast majority of the reactions afforded the corresponding oxazoline adduct in moderate to high conversions at room temperature. The Au_2/*rac*-Me_2-CATPHOS catalyst consistently outperformed its H_2-CATPHOS and $(MeO)_2$-CATPHOS counterparts. Promisingly, cyclisation of the challenging furyl-substituted propargyl amide was catalysed by Au_2/*rac*-Me_2-CATPHOS and its $(MeO)_2$-CATPHOS counterpart at room temperature which had previously only reacted at 50 °C in dichloroethane.[29]

Given time restrictions, methoxycyclisation of a 1,6-enyne derived from dimethyl malonate was investigated only briefly. The Au_2/(*S*)-Me_2-CATPHOS system exclusively afforded the methoxycyclisation adduct **6.9** in high yield at room temperature with no trace of the unwanted diene adduct which is commonly obtained with platinum-based catalyst systems at reaction temperatures 60-80 °C.[14]

6.6 Experimental

General Comments. All manipulations involving air-sensitive materials were carried out using standard schlenk line techniques under an atmosphere of nitrogen or argon in oven-dried glassware. Dichloromethane was distilled from calcium hydride, diethyl ether from Na/K alloy, dioxane from sodium, THF from sodium/benzophenone, toluene from sodium and methyl *tert*-butyl ether. Propargyl amide derivatives were prepared, as previously described. ^{1}H and ^{13}C {^{1}H} NMR spectra were recorded on a JOEL ECS-400 instrument. Thin layer chromatography (TLC) was carried out on aluminium sheets pre-coated with silica gel 60F 254. Conversion rates were calculated from crude ^{1}H NMR studies. The enantiomeric excess was calculated from the HPLC profile (Diacel Chiracel OJ, flow rate: 1 mL/min flow rate, hexane: 2-propanol = 90:10).

***N*-(Prop-2-yn-1-yl)-benzamide.** To a solution of propargylamine (1.0 g, 18.2 mmol) in dichloromethane (40 mL) was added benzoyl chloride (2.6 g, 18.3 mmol) and Et_3N (3.0 mL, 22.0 mmol) at 0 °C. Subsequently the reaction mixture was warmed to r/t and stirred for 1 h. The resulting crude product mixture was poured into 1.0 M HCl (100 mL) and extracted with $CHCl_3$ (2 x 50 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$ and solvent removed *in vacuo* to afford the product as a white solid (0.72 g, 72%).[21] ^{1}H NMR (300.0 MHz, $CDCl_3$, δ): 7.86 (m, 2H, C_6H_5), 7.59-7.40 (m, 3H, C_6H_5), 6.35 (br s, 1H, N*H*), 4.28 (dd, *J* = 5.2, 2.6 Hz, 2H, CH_2), 2.31 (t, J = 2.6 Hz, 1H, ≡C*H*); ^{13}C{^{1}H} NMR 75.5 MHz, $CDCl_3$, δ): 166.6 (*C*=O), 134.0 (C_6H_5), 131.6 (C_6H_5), 128.5 (C_6H_5), 127.0 (C_6H_5), 79.5 (*C*≡CH), 71.8 (C≡*C*H), 29.7 (*C*H_2); LRMS (EI) $[M-H]^+$ *m/z* 158.

***N*-(Prop-2-yn-1-yl)-pivalamide**. The product was synthesised and purified according to the procedure above, as outlined in the literature, to afford the product as white powder (65%).[21] ^{1}H NMR (300.0 MHz, $CDCl_3$, δ): 5.80 (br s, 1H, N*H*), 3.98 (dd, *J* = 5.1, 2.6 Hz, 2H, CH_2), 2.27 (t, *J* = 2.6 Hz, 1H, ≡C*H*), 1.25 (s, 9H, (CH_3)$_3$); ^{13}C{^{1}H} NMR 75.5 MHz, $CDCl_3$, δ): 177.6 (*C*=O), 79.8 (*C*≡CH), 71.1 (*C*≡CH), 38.6 (*C*$(CH_3)_3$), 29.3 (*C*H_2), 27.2 (*C*H_3); LRMS (EI) $[M+H]^+$ *m/z* 140.

***N*-(Prop-2-yn-1-yl)-thiophene-2-carboxamide.** The product was synthesised and purified according to the procedure above, as outlined in the literature, to afford the product as white powder (83%).[23] ^{1}H NMR (300.0 MHz, $CDCl_3$, δ): 7.45 (ddd, *J* = 6.1, 4.4, 1.1 Hz, 2H, C_4H_3S), 7.02 (dd, J = 5.0, 3.7 Hz, 1H, C_4H_3S), 6.13 (br s, 1H, N*H*), 4.21-4.11 (dd, *J* = 5.3, 2.6 Hz, 2H, CH_2), 2.22 (t, J = 2.6 Hz, 1H, ≡C*H*); ^{13}C{^{1}H} NMR 75.5 MHz, $CDCl_3$,

δ): 161.4 (*C*=O), 138.1 (C_4H_3S), 130.2 (C_4H_3S), 128.5 (C_4H_3S), 127.5 (C_4H_3S), 79.3 (*C*≡CH), 71.8 (C≡*C*H), 29.7 (*C*H_2); LRMS (EI) $[M]^+$ *m/z* 165.

***N*-(Prop-2-yn-1-yl)-furan-2-carboxamide.** The product was synthesised and purified according to the procedure above, as outlined in the literature, to afford the product as white powder (69%).[23] ^{1}H NMR (300.0 MHz, $CDCl_3$, δ): 7.5 (dd, *J* = 1.7, 0.8 Hz, 1H, C_4H_3O), 7.17 (dd, *J* = 3.5, 0.7 Hz, 1H, C_4H_3O), 6.64-6.41 (m, 2H, N*H* + C_4H_3O), 4.25 (dd, *J* = 5.4, 2.6 Hz, CH_2), 2.30 (t, J = 2.4 Hz, 1H, ≡C*H*); ^{13}C{^{1}H} NMR 75.5 MHz, $CDCl_3$, δ): 157.6 (*C*=O), 147.5 (C_4H_3O), 144.1 (C_4H_3O), 114.4 (C_4H_3O), 111.9 (C_4H_3O), 79.5 (*C*≡CH), 71.5 (*C*≡CH), 28.6 (*C*H_2); LRMS (EI) $[M+H]^+$ *m/z* 150.

***N*-(Prop-2-yn-1-yl)-cyclohexanecarboxamide.** The product was synthesised and purified according to the procedure above, as outlined in the literature, to afford the product as white powder (80%).[23] ^{1}H NMR (300.0 MHz, $CDCl_3$, δ): 5.63 (br s, 1H, N*H*), 4.1 (dd, *J* = 5.1, 2.6 Hz, 2H, CH_2), 2.24 (t , *J* = 2.6 Hz, 1H, ≡C*H*), 2.11 (tt, *J* = 11.7, 3.5 Hz, 1H, C_6H_{11}), 1.94-1.58 (m, 6H, C_6H_{11}), 1.45 (dd, *J* = 23.8, 12.0 Hz, 2H, C_6H_{11}),1.36-1.17 (m, 2H, C_6H_{11}), 1.51-1.15 (m, 4H, C_6H_{11}); ^{13}C{^{1}H} NMR 75.5 MHz, $CDCl_3$, δ): 175.3 (*C*=O), 79.8 (*C*≡CH), 71.1 (C≡*C*H), 45.0 (C_6H_{11}), 29.5 (*C*H_2), 29.1 (C_6H_{11}), 25.7 (C_6H_{11}), 25.6 (C_6H_{11}); LRMS (EI) $[M+H]^+$ *m/z* 166.

***N*-(Prop-2-yn-1-yl)-morpholine-4-carboxamide**. The product was synthesised and purified according to the procedure above, as outlined in the literature, to afford the product as white powder.[23] ^{1}H NMR (300.0 MHz, $CDCl_3$, δ): 4.85 (br s, 1H, N*H*), 4.11-3.96 (m, 2H, CH_2), 3.73-3.66 (m, 4H, (OCH_2)$_2$) , 3.41 (dd, *J* = 6.4, 3.5 Hz, 4H, (NCH_2)$_2$) , 3.31-3.21 (m, 1H, ≡C*H*); ^{13}C{^{1}H} NMR 75.5 MHz, $CDCl_3$, δ): 156.9 (*C*=O), 80.6 (*C*≡CH), 71.1 (*C*≡CH), 66.4 (O*C*H_2), 44.2 (*N*CH_2), 30.6 (≡CCH_2); LRMS (EI) $[M+H]^+$ *m/z* 169.

General Procedure for the Synthesis of [{R_2-CATPHOS}(AuCl)$_2$] (R = H, Me, OMe). A flame-dried schlenk was charged with [(tht)AuCl] (0.4 g, 1.3 mmol) and dissolved in dry dichloromethane (10 mL). The flask was charged with H_2-CATPHOS (0.5 g, 0.6 mmol) and solution was allowed to stir at r/t for 1 h. At end of reaction, solvent was removed *in vacuo* and product was recrystallised with dichloromethane/chloroform and hexane.[19]

[{9,9',10,10'-Tetrahydro-9,10,9',10'-biethenobianthracene-11,11'-bis-(diphenylphosphanyl)-12,12'diyl}(AuCl)$_2$]. ^{31}P {^{1}H} NMR (300 MHz, $CDCl_3$, δ): 22.26 (s, PPh_2); ^{1}H NMR (300.0 MHz, $CDCl_3$, δ): 7.78-7.68 (m, 6H, C_6H_4), 7.64-7.58 (m, 2H, C_6H_5 *p*-H), 7.59-7.40 (m, 8H, C_6H_5 *m*-H), 7.3-7.1 (m, 10H, C_6H_5, C_6H_4), 6.92-6.87 (t, *J* =

5.2 Hz, 2H, C_6H_4), 6.81-6.73 (t, *J* = 5.8 Hz, 2H, C_6H_4), 6.53-6.48 (m, 6H, C_6H_5, *m*-H, C_6H_4),5.28-5.21 (d, *J* = 4.8 Hz, 2H, bridgehead C*H*), 4.85-4.80 (d, *J* = 6.8 Hz, 2H, bridgehead C*H*); ^{13}C {^{1}H} NMR (300 MHz, $CDCl_3$, *δ*); 164.8 (d, *J* = 16.02 Hz, *C*=CP), 145.13 (C_6H_4), 144.7 (C_6H_4 q), 142.8 (C_6H_4 q), 140.3 (C_6H_4 q), 135.7 (d, *J* = 50.8 Hz, C=*C*P), 134.9 (d, J = 13.7 Hz,C_6H_5 *o*-C), 134.4 (d, *J* = 14.3 Hz, C_6H_5 *p*-C), 131.9 (d, *J* = 14.3 Hz, C_6H_5 *p*-C), 130.9 (C_6H_5 q), 130.4 (C_6H_4), 129.6 (dd, J = 12.4, 34.4 Hz, C_6H_4), 128.7 (C_6H_4), 125.9 (t, J = 20.1 Hz, C_6H_5 *m*-C), 125.0 (C_6H_4), 124.4 (d, *J* = 8.7 Hz, C_6H_5 *p*-C), 123.6 (d, *J* = 14.5 Hz, C_6H_4), 59.01 (bridgehead C*H*), 54.8 (bridgehead C*H*). Isotope profile patterns calculated for $C_{56}H_{40}P_2Au_2Cl_2$ $[M\text{-}Cl]^+$ shows species at 1204.3, 1205.3, 1206.3, 1207.3, 1209.2, found species at 1206.2, 1207.2, 1208.2, 1210.2, 1212.2. Single X-ray crystal structure (Figure 6.5). Analytical calcd for $C_{56}H_{40}P_2Au_2Cl_2$: C, 54.23, H, 3.25. Found C, 54. 49, H, 3.42.

[{(*S*)-9,9'-Dimethyl-9,9',10,10'-tetrahydro-9,10,9',10'-biethenobianthracene-11,11'-bis-(diphenylphosphanyl)-12,12'diyl}(AuCl)$_2$]. ^{31}P {^{1}H} NMR (400.0 MHz, $CDCl_3$, *δ*): 24.27 (*P*-Au-Cl); ^{1}H NMR (300.0 MHz, $CDCl_3$, *δ*): 7.72-7.60 (m, 6H, C_6H_5), 7.59-7.50 (m, 4H, C_6H_5), 7.49-7.38 (m, 8H, C_6H_5), 7.35-7.23 (m, 2H, C_6H_5), 7.21-7.05 (m, 6H, C_6H_4), 7.04-6.93 (m, 2H, C_6H_4), 6.88-6.72 (m, 4H, C_6H_4), 6.11-5.92 (m, 2H, C_6H_4), 5.19-5.07 (m, 2H, C_6H_4), 1.52-1.45 (m, 2H, bridgehead C*H*), 1.10-0.82 (s, 6H, (CH_3)$_2$); ^{13}C {^{1}H} NMR (300 MHz, $CDCl_3$, *δ*); 165.7 (m, *C*=CP), 147.9 (C_6H_4 q), 144.9 (C_6H_4 q), 144.6 (C_6H_4 q), 143.8 (C_6H_4 q), 137.4 (d, *J* = 53.15 Hz, C=*C*P), 136.2 (d, *J* = 14.41 Hz, C_6H_5 *o*-C), 134.4 (d, *J* = 13.7 Hz, C_6H_5 *p*-C), 132.6 (C_6H_5 *p*-C), 131.4 (C_6H_5 q), 130.2 (C_6H_4), 129.7 (C_6H_4), 129.5 (C_6H_4), 129.1 (m, C_6H_5 *m*-C), 126 (C_6H_4), 125.3 (d, *J* = 7.2 Hz, C_6H_5 *p*-C), 124.4 (d, *J* = 28.3 Hz, C_6H_4), 123.8 (C_6H_4), 122.1 (d, *J* = 28.3 Hz, C_6H_4), 54.3 (d, J = 7.9 Hz, C=*C*P) 13.9 (*C*H_3); isotope profile pattern calculated for $C_{58}H_{44}P_2Au_2Cl_2$ $[M\text{-}Cl]^+$ shows species at 1231.2, 1232.2, 1233.2, 1234.2, 1235.2, found species at 1231.2, 1232.2, 1233.2 1234.2, 1235.2. Analytical calcd for $C_{58}H_{44}P_2Au_2Cl_2$: C, 54.94, H, 3.50. Found C, 55.25, H, 3.81.

[*Rac*-{9,9'-Dimethoxy-9,9',10,10'-tetrahydro-9,10,9',10'-biethenobianthracene-11,11'-bis-(diphenylphosphanyl)-12,12'diyl}(AuCl)$_2$]. ^{31}P {^{1}H} NMR (400.0 MHz, $CDCl_3$, *δ*): 22.22 (*P*-Au-Cl); ^{1}H NMR (300.0 MHz, $CDCl_3$, *δ*): 7.71-7.67 (d, *J* = 7.3 Hz, 2H, C_6H_4), 7.67-7.58 (m, 4H, C_6H_5 *p*-H), 7.57-7.46 (m, 8H, C_6H_5, *m*-H), 7.38-7.32 (t, *J* = 8.3 Hz, 4H, C_6H_5 *p*-H), 7.31-7.25 (t, *J* = 6.7 Hz, 4H, C_6H_5 *o*-H), 7.22-7.17 (t, *J* = 5.62 Hz, 4H, C_6H_4), 7.04-6.97 (q, *J* = 7.2 Hz, 4H, C_6H_4), 6.93-6.87 (t, *J* = 7.4 Hz, 2H, C_6H_4), 6.82-6.75 (d, *J* = 7.2 Hz, 2H, C_6H_4), 6.53-6.47 (t, *J* = 7.6 Hz, 2H, C_6H_4), 4.68-4.67 (d, *J* = 7.51 Hz, 2H, bridgehead C*H*), 3.30 (s, 6H, (OCH_3)$_2$); ^{13}C {^{1}H} NMR (300 MHz, $CDCl_3$, *δ*);

167.2 (d, *J* = 17.4 Hz, *C*=CP), 147.9 (C_6H_4 q), 144.4 (C_6H_4 q), 143.8 (C_6H_4 q), 142.9 (C_6H_4 q), 137.4 (dd, *J* = 15.3 Hz, C=*C*P), 133.3 (d, *J* = 12.3 Hz, C_6H_5 *o*-C), 132.8 (C_6H_5 *p*-C), 132.0 (C_6H_5 *p*-C), 131.6 (C_6H_5 *p*-C), 130.4 (d, *J* = 12.4 Hz), 127.5, 127.0, 126.5 (C_6H_5 q), 126.0 (m, C_6H_5 *m*-C), 124.4 (C_6H_4), 96.2 (d, *J* = 11.4 Hz, C_6H_4), 68.3 (OCH_3), 57.3 (bridgehead *C*H); isotope profile pattern calculated for $C_{58}H_{44}P_2O_2Au_2Cl_2$ [M-Cl]+ shows species at 1263.2, 1264.2, 1265.2, 1266.2, 1267.2, found species at 1263.2, 1264.2, 1265.2, 1266.2, 1267.4. Single X-ray Crystal structure. Analytical calcd for $C_{58}H_{44}P_2O_2Au_2Cl_2$: C, 53.59, H, 3.42. Found C, 53. 95, H, 3.78

General Procedure for Gold-Catalysed Cycloisomerisation using Propargyl Amide Precursors. A flame-dried schlenk was charged with [{(*S*)-Me_2-CATPHOS}$(AuCl)_2$] (5.0 mg, 0.004 mmol), $AgSbF_6$ (2.8 mg, 0.008 mmol), and dichloromethane (1 mL) and stirred at r/t for 30 min, after which phenylpropargyl amide (0.2 g, 1.2 mmol) was added and the resulting mixture was stirred for the allocated time at r/t. At the end of reaction, the mixture was diluted with diethyl ether, internal standard bromo mesitylene added and the resulting mixture passed through a short silica plug. The solvent was removed *in vacuo* and the residue analysed by ^{1}H NMR spectroscopy in order to determine % conversions before the product was purified by column chromatography. The known purified products were characterised by a combination of ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry.[29]

2-(^{t}Butyl)-5-methylene-4,5-dihydrooxazole. The product was synthesised and purified according to the procedure above. ^{1}H NMR (300.0 MHz, $CDCl_3$, δ): 4.56 (dd, *J* = 5.7, 3.0 Hz, 1H, =CH_aH$_b$), 4.32 (td, *J* = 2.9, 1.4 Hz, 2H, CH_2), 4.16 (q, *J* = 2.6 Hz, 1H, =CH$_a$$H_b$), 1.22 (s, 9H, (C$H_3$)$_3$; ^{13}C{^{1}H} NMR 75.5 MHz, $CDCl_3$, δ): 178.3 (*C*=N), 158.3 (*C*=CH_2), 83.6 (=*C*H_2), 57.3 (*C*C=CH_2), 33.1 (*C*$(CH_3)_3$), 27.4 (*C*H_3); LRMS (EI) $[M]^+$ *m/z* 140.

5-Methylene-2-phenyl-4,5-dihydrooxazole. The product was synthesised and purified according to the procedure above. ^{1}H NMR (300.0 MHz, $CDCl_3$, δ): 7.95 (d, *J* = 8.4 Hz, 2H, C_6H_5), 7.49-7.26 (m, 3H, C_6H_5), 4.81 (br s, 1H, =CH_aH$_b$), 4.63 (t, *J* = 2.8 Hz, 2H, CH_2), 4.38 (br s, 1H, =CH$_a$$H_b$); ^{13}C{^{1}H} NMR 75.5 MHz, $CDCl_3$, δ): 164.1 (*C*=N), 158.6 (*C*=CH_2), 131.7 (C_6H_5), 128.4 (C_6H_5), 127.9 (C_6H_5), 126.7 (C_6H_5), 83.9 (C=*C*H_2), 57.7 (*C*H_2); LRMS (EI) $[M]^+$ *m/z* 160.

5-Methylene-2-(thiophen-2-yl)-4,5-dihydrooxazole. The product was synthesised and purified according to the procedure above. ^{1}H NMR (300.0 MHz, $CDCl_3$, δ): 7.64 (d, *J* = 3.4 Hz, 1H, C_4H_3S), 7.44 (d, *J* = 4.7 Hz, 1H, C_4H_3S), 7.07-7.02 (m, 1H, C_4H_3S), 4.75 (q, *J* = 2.9 Hz, 1H, =CH_aH$_b$), 4.56 (t, *J* = 2.7 Hz, 2H, CH_2), 4.30 (dd, *J* = 5.3, 2.6 Hz, 1H,

=CH_aH_b); $^{13}C\{^1H\}$ NMR 75.5 MHz, $CDCl_3$, δ): 159.5 (*C*=CH_2), 158.7 (*C*=N), 130.5 (C_4H_3S), 130.2 (C_4H_3S), 129.3 (C_4H_3S), 127.6 (C_4H_3S), 83.8 (C=*C*H_2), 57.6 (*C*H_2); LRMS (EI) $[M+H]^+$ *m/z* 166.

2-(Furan-2-yl)-5-methylene-4,5-dihydrooxazole. The product was synthesised and purified according to the procedure above. ^1H NMR (300.0 MHz, $CDCl_3$, δ): 7.50 (s, 1H, furyl-*H*), 6.98 (d, *J* = 3.4 Hz, 1H, furyl-*H*), 6.46 (dd, *J* = 3.4, 1.7 Hz, 1H, furyl-*H*), 4.76 (q, J = 3.0 Hz, 1H, C*H*$_a$H$_b$), 4.60 (t, *J* = 2.6 Hz, 2H, C*H*$_2$), 4.33 (q, J = 2.7 Hz, 1H, CH$_a$*H*$_b$); $^{13}C\{^1H\}$ NMR 75.5 MHz, $CDCl_3$, δ): 156.9 (*C*=N), 155.7 (*C*=CH_2), 144.9 (C_4H_3O), 141.1 (C_4H_3O), 114.6 (C_4H_3O), 110.7 (C_4H_3O), 83.7 (=*C*H_2), 56.8 (*C*H_2); LRMS (EI) *m/z* 149.

2-Cyclohexyl-5-methylene-4,5-dihydrooxazole. The product was synthesised and purified according to the procedure above. ^1H NMR (300.0 MHz, $CDCl_3$, δ): 4.65 (q, *J* = 3.0 Hz, 1H, C*H*$_a$H$_b$), 4.40 (td, *J* = 2.9, 1.2 Hz, 2H, C*H*$_2$), 4.27 (dd, *J* = 5.5, 2.7 Hz, 1H, CH$_a$*H*$_b$), 2.42-2.28 (m, 1H, Cy-*H*), 1.96-1.85 (m, 2H, Cy-*H*), 1.79-1.68 (m, 2H, Cy-*H*), 1.66-1.57 (m, 1H, Cy-*H*), 1.40 (dd, *J* = 23.9, 12.0 Hz, 2H, Cy-*H*), 1.31-1.13 (m, 3H, Cy-*H*); $^{13}C\{^1H\}$ NMR 75.5 MHz, $CDCl_3$, δ): 172.7 (*C*=N), 158.5 (*C*=CH_2), 84.7 (=*C*H_2), 56.3 (*C*H_2), 38.0 (Cy), 29.4 (Cy), 25.6 (Cy), 25.3 (Cy); LRMS (EI) *m/z* 165.

Synthesis of Dimethyl 2-(prop-2-yn-1-yl)-malonate. A flame dried schlenk was charged with sodium hydride (0.48 g, 0.02 mmol) and THF (15 mL). To this suspension was added a solution of dimethylmalonate (2.6 g, 0.02 mmol) in THF (20 mL) in a drop wise manner. The suspension was stirred at room temperature for 1 h. On addition of dimethyl malonate (3.0 g, 0.02 mmol) solution, a clear solution evolved. Neat propargyl bromide (2.4 g, 0.02 mmol) was added and reaction was stirred at room temperature overnight. At the end, crude product mixture was quenched with $NH_4Cl_{(aq.)}$ (35 mL) and extracted with diethyl ether (3 x 25 mL), dried over $MgSO_4$ and dried *in vacuo* to afford dimethylpropargyl malonate in 75% crude yield. The crude product was used without further purification. ^1H NMR (300.0 MHz, $CDCl_3$, δ): 3.79-3.73 (s, 6H, (C*H*$_3$)$_2$), 3.65-3.50 (m, 1H, ≡C*H*), 2.82-2.76 (m, 2H, C*H*$_2$), 2.05-1.95 (t, *J* = 2.75 Hz, C*H*).

Dimethyl 2-(3-methylbut-2-en-1-yl)-2-(prop-2-yn-1-yl)-malonate. Dimethyl 2-(prop-2-yn-1-yl)-malonate. Dimethylpropargyl malonate (0.2 g, 1.2 mmol) and caesium carbonate (0.489 g, 1.5 mmol) were added a round bottomed flask and dissolved in acetone (10 mL). Under rapid stirring, neat 3,3-dimethylallyl bromide (276.0 µL, 2.35 mmol) was added and the mixture was heated under reflux for 16 h. At end of reaction period, crude mixture was filtered through short silica plug, solvent removed *in vacuo* and product was isolated on column chromatography (petrol:diethyl ether, 6:1). ^1H NMR (300.0 MHz, $CDCl_3$, δ): 4.83

(t, *J* = 7.7 Hz, 1H, =C*H*), 3.72 (s, 6H, (OC*H*$_3$)$_2$), 2.75-2.65 (m, 4H, (C*H*$_2$)$_2$), 1.94 (t, *J* = 2.6 Hz, 1H, ≡C*H*), 1.61 (d, *J* = 14.1 Hz, =C(C*H*$_3$)$_2$); ^{13}C {^{1}H} NMR (75.5 MHz, $CDCl_3$, *δ*); 170.3 (*C*=O), 136.9 (=*C*(CH$_3$)$_2$), 117.1 (=*C*H), 79.5 (HC≡*C*), 70.8 (H*C*≡C), 56.9 (O*C*H$_3$), 52.1 (*C*(CO$_2$Me)), 30.7 (=C*C*H$_2$), 25.9 (=C*C*H$_{3a}$CH$_{3b}$), 22.4 (≡ C*C*H$_2$), 17.6 (=C*C*H$_{3a}$*C*H$_{3b}$); LRMS (EI) [M+H]$^+$ *m/z* 239.

Dimethyl 3-(2-methoxypropan-2-yl)-4-methylenecyclopentane-1,1-dicarboxylate. A flame-dried schlenk was charged with [(*S*)-Me$_2$-CATPHOS (AuCl)$_2$] (4.0 mg, 0.0032 mmol) and $AgSbF_6$ (1.40 mg, 0.004 mmol) in methanol (2 mL) and was stirred at room temperature for 5 min. Subsequently, the dimethyl-1,1-propargyldimethylallyl malonate (0.2 g, 0.843 mmol) in methanol (12 mL) was added to the reaction and reaction stirred at room temperature for 12 h. At end of reaction, the crude mixture was filtered through short plug of celite and solvent removed *in vacuo* and purified by column chromatography (hexane-EtOAc). HPLC column conditions: chiral OJ (hexane/propanol, 9:1, 1 mL per min); t_R 22.9 and 29.9 min. ^{1}H NMR (300.0 MHz, $CDCl_3$, *δ*): 4.94 (d, *J* = 19.9 Hz, 2H, =C*H*$_2$), 3.69-3.63 (s, 6H, (OC*H*$_3$)$_2$), 3.16 (s, 3H, OC*H*$_3$), 2.88-2.69 (m, 3H, C$_5$*H*$_5$), 2.56-2.40 (m, 1H, C*H*), 1.94 (dd, *J* = 13.4, 9.3 Hz, 1H, C$_5$*H*$_5$), 1.08 (d, *J* = 18.2 Hz, (C*H*$_3$)$_2$); ^{13}C {^{1}H} NMR (75.5 MHz, $CDCl_3$, *δ*); 171.9 (*C*=O), 171.8 (*C*=O), 148.3 (*C*=CH$_2$), 110.3 (C=*C*H$_2$), 76.7 (*C*(CH$_3$)$_2$CH), 58.6 (*C*H), 52.4 (*C*(C=O)$_2$), 49.5 (O*C*H$_3$), 48.8 (*C*H$_2$), 43.4 (O*C*H$_3$), 36.0 (*C*H$_2$), 22.6 (*C*H$_3$), 22.1 (*C*H$_3$); LRMS (EI) [M-OCH$_3$]$^+$ *m/z* 239. The enantiomeric excess was calculated from the HPLC profile (Diacel Chiracel OJ, flow rate: 1 mL/min flow rate, hexane: 2-propanol = 90:10). Retention times: major (*S*)-enantiomer t_r = 11.53 min, minor (*R*)-enantiomer t_r = 12.36 min; 7% ee. Absolute stereochemistry assigned by analogy.

6.7 References

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Crystal Structure Data

7.1 [(Me-CATPHOS)$(AuCl)_2$]

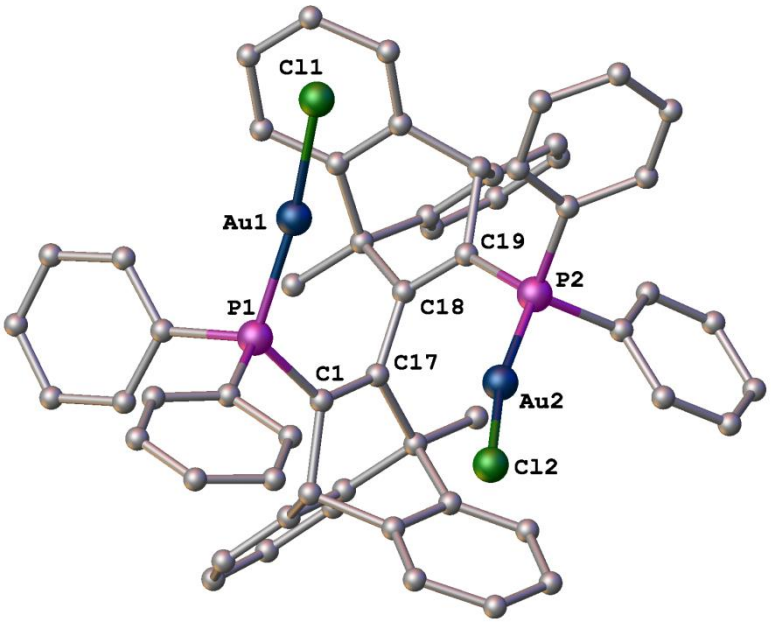

Table 1. Crystal data and structure refinement for sd310.

Identification code	sd310	
Chemical formula (moiety)	$C_{31}H_{24}AuCl_7P$	
Chemical formula (total)	$C_{31}H_{24}AuCl_7P$	
Formula weight	872.59	
Temperature	150(2) K	
Radiation, wavelength	MoKα, 0.71073 Å	
Crystal system, space group	monoclinic, $P12_11$	
Unit cell parameters	a = 10.6536(5) Å	α = 90°
	b = 20.1228(10) Å	β = 94.898(4)°
	c = 14.9090(7) Å	γ = 90°
Cell volume	3184.5(3) Å^3	
Z	4	
Calculated density	1.820 g/cm^3	
Absorption coefficient μ	5.279 mm^{-1}	
F(000)	1692	
Reflections for cell refinement	12141 (θ range 2.9 to 28.6°)	
Data collection method	Oxford Diffraction Gemini A Ultra diffractometer thick-slice ω scans	
θ range for data collection	2.9 to 26.0°	
Index ranges	h –13 to 13, k –24 to 24, l –18 to 18	
Completeness to θ = 26.0°	99.1 %	
Reflections collected	29525	
Independent reflections	12218 (R_{int} = 0.0370)	
Reflections with $F^2>2\sigma$	11211	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.44478 and 1.00000	
Structure solution	direct methods	
Refinement method	Full-matrix least-squares on F^2	
Weighting parameters a, b	0.0445, 5.6257	
Data / restraints / parameters	12218 / 1 / 721	
Final R indices [$F^2>2\sigma$]	R1 = 0.0367, wR2 = 0.0853	
R indices (all data)	R1 = 0.0428, wR2 = 0.0897	
Goodness-of-fit on F^2	1.032	
Absolute structure parameter	–0.010(5)	
Largest and mean shift/su	0.001 and 0.000	
Largest diff. peak and hole	1.47 and –0.98 e Å^{-3}	

Table 2. Atomic coordinates and equivalent isotropic displacement parameters ($Å^2$) for sd310. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
Au(1)	–0.57046(2)	0.119678(11)	0.004661(17)	0.02296(8)
Au(2)	–0.43744(2)	–0.088903(11)	0.001420(18)	0.02308(8)
P(1)	–0.38316(15)	0.11751(9)	0.08311(11)	0.0208(3)
P(2)	–0.60303(15)	–0.08620(9)	0.08343(11)	0.0198(3)
Cl(1)	–0.74271(17)	0.13320(10)	–0.09680(12)	0.0355(4)
Cl(2)	–0.29120(17)	–0.10965(10)	–0.09922(13)	0.0330(4)
C(1)	–0.3394(6)	0.0505(3)	0.1616(4)	0.0192(15)
C(2)	–0.1974(5)	0.0328(3)	0.1829(5)	0.0196(14)
C(3)	–0.1898(6)	–0.0424(4)	0.1729(5)	0.0224(14)
C(4)	–0.1149(6)	–0.0764(4)	0.1165(5)	0.0317(17)
C(5)	–0.1191(8)	–0.1464(4)	0.1190(6)	0.039(2)
C(6)	–0.1949(7)	–0.1803(4)	0.1736(6)	0.0377(19)
C(7)	–0.2702(7)	–0.1447(4)	0.2291(5)	0.0324(17)
C(8)	–0.2685(6)	–0.0768(4)	0.2279(5)	0.0263(16)
C(9)	–0.3473(6)	–0.0304(3)	0.2819(5)	0.0225(15)
C(10)	–0.2479(6)	0.0133(4)	0.3353(5)	0.0258(15)
C(11)	–0.2333(7)	0.0203(4)	0.4274(5)	0.0340(18)
C(12)	–0.1378(8)	0.0602(4)	0.4669(6)	0.042(2)
C(13)	–0.0563(7)	0.0913(4)	0.4137(6)	0.040(2)
C(14)	–0.0721(6)	0.0851(4)	0.3207(5)	0.0270(16)
C(15)	–0.1681(6)	0.0461(4)	0.2827(5)	0.0244(15)
C(16)	–0.4317(7)	–0.0675(4)	0.3425(5)	0.0296(17)
C(17)	–0.4172(6)	0.0167(3)	0.2111(5)	0.0197(14)
C(18)	–0.5561(6)	0.0207(3)	0.2064(5)	0.0181(14)
C(19)	–0.6381(6)	–0.0186(3)	0.1588(5)	0.0194(15)
C(20)	–0.7771(6)	–0.0025(3)	0.1729(4)	0.0194(13)
C(21)	–0.7917(6)	–0.0106(3)	0.2718(5)	0.0212(14)
C(22)	–0.8790(6)	–0.0495(4)	0.3115(5)	0.0261(16)
C(23)	–0.8784(8)	–0.0515(5)	0.4040(6)	0.042(2)
C(24)	–0.7921(8)	–0.0135(5)	0.4566(6)	0.041(2)
C(25)	–0.7046(7)	0.0259(4)	0.4183(5)	0.0350(18)
C(26)	–0.7030(6)	0.0290(4)	0.3247(5)	0.0266(16)
C(27)	–0.6186(6)	0.0703(4)	0.2700(5)	0.0205(14)
C(28)	–0.7114(6)	0.1102(3)	0.2073(4)	0.0205(14)
C(29)	–0.7202(7)	0.1788(4)	0.2038(5)	0.0300(17)
C(30)	–0.8132(7)	0.2085(4)	0.1456(6)	0.0369(18)
C(31)	–0.8955(8)	0.1696(4)	0.0939(6)	0.037(2)
C(32)	–0.8879(6)	0.0997(4)	0.0968(5)	0.0263(16)
C(33)	–0.7962(6)	0.0711(4)	0.1541(5)	0.0211(14)
C(34)	–0.5260(6)	0.1131(4)	0.3262(5)	0.0315(17)
C(35)	–0.2682(6)	0.1180(5)	0.0037(4)	0.0258(16)
C(36)	–0.2172(8)	0.1741(4)	–0.0293(6)	0.0349(19)
C(37)	–0.1352(9)	0.1720(5)	–0.0956(6)	0.045(2)
C(38)	–0.0998(7)	0.1137(5)	–0.1323(5)	0.0393(19)
C(39)	–0.1489(8)	0.0540(4)	–0.1024(5)	0.038(2)
C(40)	–0.2335(7)	0.0564(4)	–0.0349(6)	0.0349(19)
C(41)	–0.3530(7)	0.1938(3)	0.1443(5)	0.0269(16)
C(42)	–0.4397(7)	0.2450(3)	0.1426(5)	0.0292(17)
C(43)	–0.4118(8)	0.3042(4)	0.1878(6)	0.040(2)

C(44)	–0.2965(9)	0.3124(4)	0.2349(6)	0.040(2)
C(45)	–0.2076(7)	0.2636(6)	0.2387(5)	0.0418(18)
C(47)	–0.7384(6)	–0.0889(4)	0.0034(4)	0.0171(14)
C(46)	–0.2335(7)	0.2042(4)	0.1926(5)	0.0339(18)
C(48)	–0.7569(8)	–0.0416(4)	–0.0597(6)	0.039(2)
C(49)	–0.8583(8)	–0.0418(5)	–0.1256(6)	0.043(2)
C(50)	–0.9424(7)	–0.0943(5)	–0.1270(5)	0.0366(18)
C(51)	–0.9274(7)	–0.1429(4)	–0.0656(6)	0.039(2)
C(52)	–0.8262(7)	–0.1412(4)	0.0003(5)	0.0259(16)
C(53)	–0.6093(7)	–0.1614(4)	0.1500(5)	0.0259(15)
C(54)	–0.6904(8)	–0.1684(4)	0.2164(6)	0.0386(19)
C(55)	–0.6916(8)	–0.2259(5)	0.2665(5)	0.043(2)
C(56)	–0.6111(10)	–0.2779(4)	0.2501(6)	0.048(2)
C(57)	–0.5342(8)	–0.2715(4)	0.1846(6)	0.038(2)
C(58)	–0.5286(7)	–0.2143(4)	0.1341(6)	0.0332(18)
Cl(14)	0.6954(4)	0.3352(2)	–0.5044(3)	0.1020(14)
Cl(13)	0.6815(5)	0.1930(2)	–0.5076(4)	0.157(3)
Cl(12)	0.4612(3)	0.2679(3)	–0.5152(4)	0.1305(16)
Cl(11)	0.1093(3)	0.06976(16)	–0.3365(2)	0.0759(8)
Cl(8)	0.4789(3)	0.04175(17)	–0.2182(2)	0.0737(8)
Cl(5)	0.0081(4)	–0.0934(2)	–0.3754(2)	0.1091(14)
Cl(7)	0.4891(4)	–0.0548(2)	–0.3603(2)	0.1012(12)
Cl(10)	0.0218(4)	0.2037(2)	–0.3482(3)	0.0981(11)
Cl(6)	0.6884(4)	0.04012(18)	–0.3286(2)	0.0867(11)
Cl(4)	–0.1404(5)	–0.1699(3)	–0.5050(3)	0.1347(19)
Cl(9)	0.2741(4)	0.1738(3)	–0.3885(3)	0.1192(15)
Cl(3)	–0.1970(5)	–0.1626(5)	–0.3172(3)	0.210(4)
C(62)	0.6085(11)	0.2660(8)	–0.5459(6)	0.084(4)
C(61)	0.1531(12)	0.1542(6)	–0.3228(7)	0.068(3)
C(60)	0.5773(10)	–0.0094(5)	–0.2790(6)	0.052(2)
C(59)	–0.1385(13)	–0.1244(8)	–0.4060(8)	0.090(5)

Table 3. Bond lengths [Å] and angles [°] for sd310.

Au(1)–P(1)	2.2255(16)	Au(1)–Cl(1)	2.2926(17)
Au(2)–P(2)	2.2312(16)	Au(2)–Cl(2)	2.2918(18)
P(1)–C(1)	1.820(7)	P(1)–C(35)	1.775(7)
P(1)–C(41)	1.800(7)	P(2)–C(19)	1.822(7)
P(2)–C(47)	1.793(7)	P(2)–C(53)	1.815(7)
C(1)–C(2)	1.560(8)	C(1)–C(17)	1.340(10)
C(2)–H(2A)	1.000	C(2)–C(3)	1.524(9)
C(2)–C(15)	1.518(10)	C(3)–C(4)	1.388(10)
C(3)–C(8)	1.403(10)	C(4)–H(4A)	0.950
C(4)–C(5)	1.410(11)	C(5)–H(5A)	0.950
C(5)–C(6)	1.375(12)	C(6)–H(6A)	0.950
C(6)–C(7)	1.397(11)	C(7)–H(7A)	0.950
C(7)–C(8)	1.368(11)	C(8)–C(9)	1.530(10)
C(9)–C(10)	1.543(10)	C(9)–C(16)	1.523(10)
C(9)–C(17)	1.560(9)	C(10)–C(11)	1.376(11)
C(10)–C(15)	1.374(10)	C(11)–H(11A)	0.950
C(11)–C(12)	1.387(11)	C(12)–H(12A)	0.950
C(12)–C(13)	1.376(13)	C(13)–H(13A)	0.950
C(13)–C(14)	1.389(11)	C(14)–H(14A)	0.950
C(14)–C(15)	1.372(10)	C(16)–H(16A)	0.980
C(16)–H(16B)	0.980	C(16)–H(16C)	0.980
C(17)–C(18)	1.478(9)	C(18)–C(19)	1.337(9)
C(18)–C(27)	1.564(9)	C(19)–C(20)	1.548(9)
C(20)–H(20A)	1.000	C(20)–C(21)	1.506(9)
C(20)–C(33)	1.519(9)	C(21)–C(22)	1.386(10)
C(21)–C(26)	1.421(10)	C(22)–H(22A)	0.950
C(22)–C(23)	1.379(11)	C(23)–H(23A)	0.950
C(23)–C(24)	1.386(13)	C(24)–H(24A)	0.950
C(24)–C(25)	1.384(12)	C(25)–H(25A)	0.950
C(25)–C(26)	1.398(10)	C(26)–C(27)	1.513(10)
C(27)–C(28)	1.530(9)	C(27)–C(34)	1.509(10)
C(28)–C(29)	1.384(10)	C(28)–C(33)	1.393(10)
C(29)–H(29A)	0.950	C(29)–C(30)	1.395(11)
C(30)–H(30A)	0.950	C(30)–C(31)	1.363(12)
C(31)–H(31A)	0.950	C(31)–C(32)	1.411(11)
C(32)–H(32A)	0.950	C(32)–C(33)	1.368(10)
C(34)–H(34A)	0.980	C(34)–H(34B)	0.980
C(34)–H(34C)	0.980	C(35)–C(36)	1.363(12)
C(35)–C(40)	1.429(13)	C(36)–H(36A)	0.950
C(36)–C(37)	1.375(12)	C(37)–H(37A)	0.950
C(37)–C(38)	1.362(13)	C(38)–H(38A)	0.950
C(38)–C(39)	1.398(12)	C(39)–H(39A)	0.950
C(39)–C(40)	1.409(11)	C(40)–H(40A)	0.950
C(41)–C(42)	1.384(10)	C(41)–C(46)	1.423(10)
C(42)–H(42A)	0.950	C(42)–C(43)	1.387(11)
C(43)–H(43A)	0.950	C(43)–C(44)	1.372(12)
C(44)–H(44A)	0.950	C(44)–C(45)	1.363(13)
C(45)–H(45A)	0.950	C(45)–C(46)	1.395(13)
C(47)–C(48)	1.341(12)	C(47)–C(52)	1.405(11)
C(46)–H(46A)	0.950	C(48)–H(48A)	0.950
C(48)–C(49)	1.397(11)	C(49)–H(49A)	0.950
C(49)–C(50)	1.384(12)	C(50)–H(50A)	0.950
C(50)–C(51)	1.340(12)	C(51)–H(51A)	0.950
C(51)–C(52)	1.395(11)	C(52)–H(52A)	0.950
C(53)–C(54)	1.375(10)	C(53)–C(58)	1.401(10)
C(54)–H(54A)	0.950	C(54)–C(55)	1.379(12)

C(55)–H(55A)	0.950	C(55)–C(56)	1.387(12)
C(56)–H(56A)	0.950	C(56)–C(57)	1.334(13)
C(57)–H(57A)	0.950	C(57)–C(58)	1.379(11)
C(58)–H(58A)	0.950	Cl(14)–C(62)	1.755(12)
Cl(13)–C(62)	1.734(17)	Cl(12)–C(62)	1.672(12)
Cl(11)–C(61)	1.769(13)	Cl(8)–C(60)	1.772(10)
Cl(5)–C(59)	1.708(16)	Cl(7)–C(60)	1.729(10)
Cl(10)–C(61)	1.734(13)	Cl(6)–C(60)	1.759(10)
Cl(4)–C(59)	1.735(14)	Cl(9)–C(61)	1.730(12)
Cl(3)–C(59)	1.696(13)	C(62)–H(62A)	1.000
C(61)–H(61A)	1.000	C(60)–H(60A)	1.000
C(59)–H(59A)	1.000		

P(1)–Au(1)–Cl(1)	168.62(6)	P(2)–Au(2)–Cl(2)	167.62(7)
Au(1)–P(1)–C(1)	121.4(2)	Au(1)–P(1)–C(35)	106.8(2)
Au(1)–P(1)–C(41)	111.3(3)	C(1)–P(1)–C(35)	106.2(4)
C(1)–P(1)–C(41)	106.3(3)	C(35)–P(1)–C(41)	103.3(4)
Au(2)–P(2)–C(19)	124.7(2)	Au(2)–P(2)–C(47)	105.2(2)
Au(2)–P(2)–C(53)	110.3(2)	C(19)–P(2)–C(47)	103.8(3)
C(19)–P(2)–C(53)	105.5(3)	C(47)–P(2)–C(53)	105.9(4)
P(1)–C(1)–C(2)	119.4(5)	P(1)–C(1)–C(17)	126.4(5)
C(2)–C(1)–C(17)	114.0(6)	C(1)–C(2)–H(2A)	113.2
C(1)–C(2)–C(3)	105.4(5)	C(1)–C(2)–C(15)	105.9(5)
H(2A)–C(2)–C(3)	113.2	H(2A)–C(2)–C(15)	113.2
C(3)–C(2)–C(15)	105.2(6)	C(2)–C(3)–C(4)	125.9(7)
C(2)–C(3)–C(8)	113.1(6)	C(4)–C(3)–C(8)	121.0(7)
C(3)–C(4)–H(4A)	121.5	C(3)–C(4)–C(5)	117.1(7)
H(4A)–C(4)–C(5)	121.5	C(4)–C(5)–H(5A)	118.9
C(4)–C(5)–C(6)	122.1(7)	H(5A)–C(5)–C(6)	118.9
C(5)–C(6)–H(6A)	120.2	C(5)–C(6)–C(7)	119.5(7)
H(6A)–C(6)–C(7)	120.2	C(6)–C(7)–H(7A)	120.2
C(6)–C(7)–C(8)	119.6(8)	H(7A)–C(7)–C(8)	120.2
C(3)–C(8)–C(7)	120.6(7)	C(3)–C(8)–C(9)	112.9(6)
C(7)–C(8)–C(9)	126.5(7)	C(8)–C(9)–C(10)	103.7(5)
C(8)–C(9)–C(16)	113.0(6)	C(8)–C(9)–C(17)	105.4(5)
C(10)–C(9)–C(16)	112.8(6)	C(10)–C(9)–C(17)	105.7(5)
C(16)–C(9)–C(17)	115.3(6)	C(9)–C(10)–C(11)	126.0(7)
C(9)–C(10)–C(15)	114.2(6)	C(11)–C(10)–C(15)	119.8(7)
C(10)–C(11)–H(11A)	120.0	C(10)–C(11)–C(12)	120.0(8)
H(11A)–C(11)–C(12)	120.0	C(11)–C(12)–H(12A)	120.2
C(11)–C(12)–C(13)	119.6(8)	H(12A)–C(12)–C(13)	120.2
C(12)–C(13)–H(13A)	119.8	C(12)–C(13)–C(14)	120.4(8)
H(13A)–C(13)–C(14)	119.8	C(13)–C(14)–H(14A)	120.5
C(13)–C(14)–C(15)	119.1(7)	H(14A)–C(14)–C(15)	120.5
C(2)–C(15)–C(10)	112.9(6)	C(2)–C(15)–C(14)	126.1(7)
C(10)–C(15)–C(14)	121.0(7)	C(9)–C(16)–H(16A)	109.5
C(9)–C(16)–H(16B)	109.5	C(9)–C(16)–H(16C)	109.5
H(16A)–C(16)–H(16B)	109.5	H(16A)–C(16)–H(16C)	109.5
H(16B)–C(16)–H(16C)	109.5	C(1)–C(17)–C(9)	113.5(6)
C(1)–C(17)–C(18)	127.6(6)	C(9)–C(17)–C(18)	118.9(6)
C(17)–C(18)–C(19)	126.7(6)	C(17)–C(18)–C(27)	118.9(6)
C(19)–C(18)–C(27)	114.0(6)	P(2)–C(19)–C(18)	127.6(5)
P(2)–C(19)–C(20)	119.2(5)	C(18)–C(19)–C(20)	113.1(6)
C(19)–C(20)–H(20A)	112.4	C(19)–C(20)–C(21)	106.9(5)
C(19)–C(20)–C(33)	107.1(5)	H(20A)–C(20)–C(21)	112.4
H(20A)–C(20)–C(33)	112.4	C(21)–C(20)–C(33)	105.2(5)
C(20)–C(21)–C(22)	127.5(6)	C(20)–C(21)–C(26)	111.3(6)
C(22)–C(21)–C(26)	121.2(7)	C(21)–C(22)–H(22A)	120.1

C(21)–C(22)–C(23)	119.9(7)	H(22A)–C(22)–C(23)	120.1
C(22)–C(23)–H(23A)	120.2	C(22)–C(23)–C(24)	119.7(8)
H(23A)–C(23)–C(24)	120.2	C(23)–C(24)–H(24A)	119.3
C(23)–C(24)–C(25)	121.4(8)	H(24A)–C(24)–C(25)	119.3
C(24)–C(25)–H(25A)	119.9	C(24)–C(25)–C(26)	120.2(8)
H(25A)–C(25)–C(26)	119.9	C(21)–C(26)–C(25)	117.7(7)
C(21)–C(26)–C(27)	114.0(6)	C(25)–C(26)–C(27)	128.3(7)
C(18)–C(27)–C(26)	106.2(5)	C(18)–C(27)–C(28)	104.5(5)
C(18)–C(27)–C(34)	114.2(6)	C(26)–C(27)–C(28)	103.6(5)
C(26)–C(27)–C(34)	113.9(6)	C(28)–C(27)–C(34)	113.4(6)
C(27)–C(28)–C(29)	125.7(6)	C(27)–C(28)–C(33)	113.9(6)
C(29)–C(28)–C(33)	120.2(6)	C(28)–C(29)–H(29A)	120.3
C(28)–C(29)–C(30)	119.5(7)	H(29A)–C(29)–C(30)	120.3
C(29)–C(30)–H(30A)	120.2	C(29)–C(30)–C(31)	119.7(7)
H(30A)–C(30)–C(31)	120.2	C(30)–C(31)–H(31A)	119.3
C(30)–C(31)–C(32)	121.5(7)	H(31A)–C(31)–C(32)	119.3
C(31)–C(32)–H(32A)	120.8	C(31)–C(32)–C(33)	118.3(7)
H(32A)–C(32)–C(33)	120.8	C(20)–C(33)–C(28)	112.1(6)
C(20)–C(33)–C(32)	127.0(6)	C(28)–C(33)–C(32)	120.8(7)
C(27)–C(34)–H(34A)	109.5	C(27)–C(34)–H(34B)	109.5
C(27)–C(34)–H(34C)	109.5	H(34A)–C(34)–H(34B)	109.5
H(34A)–C(34)–H(34C)	109.5	H(34B)–C(34)–H(34C)	109.5
P(1)–C(35)–C(36)	124.4(8)	P(1)–C(35)–C(40)	118.7(7)
C(36)–C(35)–C(40)	116.7(7)	C(35)–C(36)–H(36A)	118.9
C(35)–C(36)–C(37)	122.2(8)	H(36A)–C(36)–C(37)	118.9
C(36)–C(37)–H(37A)	119.0	C(36)–C(37)–C(38)	122.0(8)
H(37A)–C(37)–C(38)	119.0	C(37)–C(38)–H(38A)	120.4
C(37)–C(38)–C(39)	119.3(7)	H(38A)–C(38)–C(39)	120.4
C(38)–C(39)–H(39A)	120.7	C(38)–C(39)–C(40)	118.5(8)
H(39A)–C(39)–C(40)	120.7	C(35)–C(40)–C(39)	121.4(7)
C(35)–C(40)–H(40A)	119.3	C(39)–C(40)–H(40A)	119.3
P(1)–C(41)–C(42)	122.4(6)	P(1)–C(41)–C(46)	119.7(6)
C(42)–C(41)–C(46)	117.8(7)	C(41)–C(42)–H(42A)	119.5
C(41)–C(42)–C(43)	121.1(7)	H(42A)–C(42)–C(43)	119.5
C(42)–C(43)–H(43A)	120.1	C(42)–C(43)–C(44)	119.8(8)
H(43A)–C(43)–C(44)	120.1	C(43)–C(44)–H(44A)	119.2
C(43)–C(44)–C(45)	121.6(8)	H(44A)–C(44)–C(45)	119.2
C(44)–C(45)–H(45A)	120.3	C(44)–C(45)–C(46)	119.3(7)
H(45A)–C(45)–C(46)	120.3	P(2)–C(47)–C(48)	120.5(6)
P(2)–C(47)–C(52)	122.7(6)	C(48)–C(47)–C(52)	116.8(7)
C(41)–C(46)–C(45)	120.4(7)	C(41)–C(46)–H(46A)	119.8
C(45)–C(46)–H(46A)	119.8	C(47)–C(48)–H(48A)	118.3
C(47)–C(48)–C(49)	123.4(8)	H(48A)–C(48)–C(49)	118.3
C(48)–C(49)–H(49A)	120.9	C(48)–C(49)–C(50)	118.2(8)
H(49A)–C(49)–C(50)	120.9	C(49)–C(50)–H(50A)	119.8
C(49)–C(50)–C(51)	120.5(7)	H(50A)–C(50)–C(51)	119.8
C(50)–C(51)–H(51A)	119.9	C(50)–C(51)–C(52)	120.2(8)
H(51A)–C(51)–C(52)	119.9	C(47)–C(52)–C(51)	120.9(7)
C(47)–C(52)–H(52A)	119.6	C(51)–C(52)–H(52A)	119.6
P(2)–C(53)–C(54)	122.2(6)	P(2)–C(53)–C(58)	119.3(5)
C(54)–C(53)–C(58)	118.5(7)	C(53)–C(54)–H(54A)	119.6
C(53)–C(54)–C(55)	120.7(7)	H(54A)–C(54)–C(55)	119.6
C(54)–C(55)–H(55A)	119.9	C(54)–C(55)–C(56)	120.2(8)
H(55A)–C(55)–C(56)	119.9	C(55)–C(56)–H(56A)	120.5
C(55)–C(56)–C(57)	119.0(8)	H(56A)–C(56)–C(57)	120.5
C(56)–C(57)–H(57A)	118.7	C(56)–C(57)–C(58)	122.5(8)
H(57A)–C(57)–C(58)	118.7	C(53)–C(58)–C(57)	119.1(8)
C(53)–C(58)–H(58A)	120.5	C(57)–C(58)–H(58A)	120.5

Cl(14)–C(62)–Cl(13)	110.3(7)	Cl(14)–C(62)–Cl(12)	111.4(8)
Cl(14)–C(62)–H(62A)	108.5	Cl(13)–C(62)–Cl(12)	109.6(7)
Cl(13)–C(62)–H(62A)	108.5	Cl(12)–C(62)–H(62A)	108.5
Cl(11)–C(61)–Cl(10)	109.1(7)	Cl(11)–C(61)–Cl(9)	110.8(7)
Cl(11)–C(61)–H(61A)	108.4	Cl(10)–C(61)–Cl(9)	111.8(6)
Cl(10)–C(61)–H(61A)	108.4	Cl(9)–C(61)–H(61A)	108.4
Cl(8)–C(60)–Cl(7)	110.8(6)	Cl(8)–C(60)–Cl(6)	109.5(6)
Cl(8)–C(60)–H(60A)	108.7	Cl(7)–C(60)–Cl(6)	110.4(5)
Cl(7)–C(60)–H(60A)	108.7	Cl(6)–C(60)–H(60A)	108.7
Cl(5)–C(59)–Cl(4)	111.4(7)	Cl(5)–C(59)–Cl(3)	110.2(7)
Cl(5)–C(59)–H(59A)	106.0	Cl(4)–C(59)–Cl(3)	116.6(10)
Cl(4)–C(59)–H(59A)	106.0	Cl(3)–C(59)–H(59A)	106.0

Table 4. Anisotropic displacement parameters ($Å^2$) for sd310. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ...+ 2hka^*b^*U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Au(1)	0.01796(14)	0.02525(17)	0.02523(15)	0.00303(14)	–0.00068(11)	–0.00044(13)
Au(2)	0.01886(14)	0.02398(17)	0.02702(16)	–0.00349(14)	0.00551(11)	–0.00012(13)
P(1)	0.0166(8)	0.0196(8)	0.0261(8)	0.0016(8)	0.0009(6)	–0.0002(7)
P(2)	0.0180(8)	0.0170(8)	0.0246(8)	–0.0001(8)	0.0032(6)	0.0001(7)
Cl(1)	0.0261(9)	0.0457(12)	0.0329(10)	0.0080(9)	–0.0070(7)	–0.0011(8)
Cl(2)	0.0280(9)	0.0349(10)	0.0377(10)	–0.0060(8)	0.0120(8)	0.0006(7)
C(1)	0.012(3)	0.027(4)	0.018(3)	–0.006(3)	–0.008(3)	0.006(3)
C(2)	0.008(3)	0.022(4)	0.028(4)	0.000(3)	0.001(2)	0.002(2)
C(3)	0.018(3)	0.021(3)	0.027(4)	–0.002(3)	–0.004(3)	0.008(3)
C(4)	0.017(3)	0.033(5)	0.044(4)	–0.003(4)	0.001(3)	0.000(3)
C(5)	0.030(4)	0.035(5)	0.051(5)	–0.008(4)	0.003(4)	0.017(3)
C(6)	0.041(5)	0.021(4)	0.049(5)	0.001(4)	–0.004(4)	0.009(3)
C(7)	0.032(4)	0.025(4)	0.039(5)	0.002(3)	–0.003(3)	0.006(3)
C(8)	0.023(3)	0.028(4)	0.026(4)	0.001(3)	–0.011(3)	0.007(3)
C(9)	0.021(4)	0.023(4)	0.023(4)	0.004(3)	–0.003(3)	0.003(3)
C(10)	0.018(3)	0.024(4)	0.035(4)	0.003(3)	–0.001(3)	0.004(3)
C(11)	0.034(4)	0.033(4)	0.034(4)	0.002(3)	–0.005(3)	0.006(3)
C(12)	0.038(5)	0.056(6)	0.029(4)	–0.010(4)	–0.011(4)	0.010(4)
C(13)	0.027(4)	0.045(5)	0.045(5)	–0.017(4)	–0.012(4)	0.010(4)
C(14)	0.019(4)	0.023(4)	0.038(4)	–0.002(3)	–0.003(3)	–0.001(3)
C(15)	0.020(3)	0.024(4)	0.028(4)	–0.001(3)	–0.004(3)	0.006(3)
C(16)	0.029(4)	0.031(4)	0.028(4)	0.005(3)	–0.002(3)	0.007(3)
C(17)	0.018(3)	0.018(3)	0.023(4)	0.004(3)	0.002(3)	0.000(3)
C(18)	0.017(3)	0.009(3)	0.028(4)	0.004(3)	0.004(3)	0.002(2)
C(19)	0.020(4)	0.018(3)	0.020(4)	0.005(3)	–0.001(3)	0.002(3)
C(20)	0.018(3)	0.019(3)	0.021(3)	0.004(3)	0.001(3)	–0.001(3)
C(21)	0.017(3)	0.023(3)	0.023(4)	–0.001(3)	–0.001(3)	0.005(3)
C(22)	0.021(3)	0.019(4)	0.039(4)	0.000(3)	0.012(3)	0.004(3)
C(23)	0.034(4)	0.054(6)	0.040(5)	0.012(4)	0.015(4)	0.013(4)
C(24)	0.041(5)	0.052(5)	0.034(5)	0.013(4)	0.018(4)	0.012(4)
C(25)	0.034(4)	0.041(5)	0.030(4)	–0.003(4)	0.001(3)	0.013(4)
C(26)	0.023(4)	0.026(4)	0.030(4)	–0.006(3)	0.003(3)	0.008(3)
C(27)	0.018(3)	0.022(4)	0.021(4)	–0.003(3)	0.001(3)	0.004(3)
C(28)	0.022(3)	0.022(4)	0.018(3)	–0.002(3)	0.006(2)	0.008(3)
C(29)	0.027(4)	0.025(4)	0.038(4)	–0.003(3)	–0.002(3)	0.004(3)
C(30)	0.042(5)	0.022(4)	0.048(5)	0.003(4)	0.007(4)	0.011(4)
C(31)	0.031(4)	0.039(5)	0.042(5)	0.012(4)	0.004(4)	0.013(4)
C(32)	0.017(3)	0.036(4)	0.026(4)	0.003(3)	0.004(3)	0.004(3)
C(33)	0.016(3)	0.026(4)	0.022(4)	0.002(3)	0.009(3)	0.000(3)
C(34)	0.026(4)	0.031(4)	0.037(4)	–0.009(4)	–0.006(3)	0.002(3)
C(35)	0.030(4)	0.031(4)	0.016(3)	0.007(4)	–0.005(3)	–0.007(4)
C(36)	0.040(5)	0.036(5)	0.029(4)	–0.001(4)	0.002(4)	–0.001(4)
C(37)	0.049(5)	0.042(5)	0.046(5)	0.011(4)	0.015(4)	–0.016(4)
C(38)	0.035(4)	0.057(6)	0.028(4)	–0.001(4)	0.011(3)	0.001(4)
C(39)	0.040(5)	0.045(5)	0.031(5)	–0.007(4)	0.008(4)	0.000(4)
C(40)	0.025(4)	0.038(5)	0.042(5)	0.001(4)	0.008(3)	–0.008(3)
C(41)	0.048(5)	0.015(3)	0.017(3)	–0.001(3)	0.002(3)	0.002(3)
C(42)	0.028(4)	0.024(4)	0.035(4)	0.005(3)	–0.003(3)	0.003(3)

C(43)	0.045(5)	0.022(4)	0.053(6)	0.000(4)	0.000(4)	0.004(4)
C(44)	0.057(6)	0.025(4)	0.037(5)	–0.004(4)	0.006(4)	–0.003(4)
C(45)	0.043(4)	0.034(4)	0.045(4)	–0.003(5)	–0.008(3)	–0.011(5)
C(47)	0.024(3)	0.012(3)	0.016(3)	–0.008(4)	0.007(3)	0.006(4)
C(46)	0.028(4)	0.026(4)	0.047(5)	–0.001(4)	–0.006(3)	–0.003(3)
C(48)	0.038(5)	0.037(5)	0.041(5)	0.000(4)	–0.008(4)	–0.018(4)
C(49)	0.053(5)	0.039(5)	0.035(5)	0.010(4)	–0.013(4)	–0.001(4)
C(50)	0.027(4)	0.052(5)	0.030(4)	–0.007(4)	–0.003(3)	0.001(4)
C(51)	0.025(4)	0.045(5)	0.046(5)	–0.020(4)	0.003(4)	–0.011(3)
C(52)	0.024(4)	0.017(3)	0.036(4)	0.001(3)	–0.001(3)	–0.006(3)
C(53)	0.029(4)	0.021(4)	0.027(4)	0.000(3)	0.004(3)	–0.001(3)
C(54)	0.048(5)	0.023(4)	0.047(5)	0.003(4)	0.020(4)	0.007(4)
C(55)	0.058(5)	0.032(5)	0.041(4)	0.007(4)	0.025(4)	0.009(4)
C(56)	0.069(6)	0.025(5)	0.052(6)	0.008(4)	0.012(5)	0.004(4)
C(57)	0.047(5)	0.027(4)	0.040(5)	–0.001(4)	0.005(4)	0.010(4)
C(58)	0.035(4)	0.024(4)	0.040(5)	0.001(3)	0.003(3)	0.008(3)
Cl(14)	0.114(3)	0.100(3)	0.087(2)	0.012(2)	–0.018(2)	–0.057(3)
Cl(13)	0.160(4)	0.082(3)	0.206(5)	–0.085(3)	–0.117(4)	0.062(3)
Cl(12)	0.072(2)	0.102(3)	0.220(5)	–0.057(4)	0.023(2)	0.002(3)
Cl(11)	0.109(2)	0.0619(17)	0.0549(17)	–0.0085(14)	–0.0020(16)	–0.0060(16)
Cl(8)	0.085(2)	0.0671(18)	0.0730(19)	–0.0019(16)	0.0300(16)	0.0083(17)
Cl(5)	0.143(3)	0.131(3)	0.0543(17)	0.001(2)	0.0174(19)	–0.062(3)
Cl(7)	0.134(3)	0.083(2)	0.083(2)	–0.025(2)	–0.009(2)	–0.037(2)
Cl(10)	0.108(3)	0.087(2)	0.101(3)	0.019(2)	0.020(2)	0.016(2)
Cl(6)	0.120(3)	0.074(2)	0.073(2)	–0.0211(17)	0.0507(19)	–0.033(2)
Cl(4)	0.121(3)	0.157(4)	0.133(4)	–0.076(3)	0.046(3)	–0.055(3)
Cl(9)	0.088(3)	0.140(4)	0.132(3)	0.054(3)	0.022(2)	–0.006(2)
Cl(3)	0.156(5)	0.387(11)	0.084(3)	0.061(5)	–0.007(3)	–0.155(6)
C(62)	0.106(9)	0.103(9)	0.046(5)	–0.011(7)	0.020(5)	–0.070(9)
C(61)	0.083(8)	0.083(8)	0.035(5)	0.009(5)	–0.008(5)	–0.012(6)
C(60)	0.063(7)	0.052(6)	0.040(5)	–0.001(5)	0.007(5)	–0.002(5)
C(59)	0.093(10)	0.119(12)	0.061(8)	0.030(8)	0.017(7)	0.044(9)

Table 5. Hydrogen coordinates and isotropic displacement parameters ($Å^2$) for sd310.

	x	y	z	U
H(2A)	–0.1407	0.0573	0.1443	0.023
H(4A)	–0.0631	–0.0535	0.0780	0.038
H(5A)	–0.0679	–0.1710	0.0817	0.046
H(6A)	–0.1961	–0.2275	0.1735	0.045
H(7A)	–0.3223	–0.1677	0.2675	0.039
H(11A)	–0.2886	–0.0022	0.4640	0.041
H(12A)	–0.1287	0.0660	0.5304	0.050
H(13A)	0.0111	0.1173	0.4408	0.048
H(14A)	–0.0171	0.1074	0.2838	0.032
H(16A)	–0.3798	–0.0961	0.3840	0.044
H(16B)	–0.4919	–0.0949	0.3054	0.044
H(16C)	–0.4775	–0.0355	0.3769	0.044
H(20A)	–0.8375	–0.0308	0.1347	0.023
H(22A)	–0.9391	–0.0747	0.2751	0.031
H(23A)	–0.9370	–0.0788	0.4316	0.051
H(24A)	–0.7930	–0.0146	0.5202	0.050
H(25A)	–0.6456	0.0510	0.4557	0.042
H(29A)	–0.6632	0.2054	0.2408	0.036
H(30A)	–0.8191	0.2555	0.1419	0.044
H(31A)	–0.9594	0.1902	0.0551	0.045
H(32A)	–0.9451	0.0730	0.0600	0.032
H(34A)	–0.5718	0.1427	0.3643	0.047
H(34B)	–0.4771	0.1398	0.2866	0.047
H(34C)	–0.4689	0.0848	0.3644	0.047
H(36A)	–0.2390	0.2160	–0.0057	0.042
H(37A)	–0.1022	0.2125	–0.1165	0.054
H(38A)	–0.0423	0.1136	–0.1776	0.047
H(39A)	–0.1257	0.0127	–0.1272	0.046
H(40A)	–0.2682	0.0162	–0.0145	0.042
H(42A)	–0.5196	0.2396	0.1100	0.035
H(43A)	–0.4724	0.3389	0.1862	0.048
H(44A)	–0.2782	0.3531	0.2656	0.048
H(45A)	–0.1288	0.2699	0.2725	0.050
H(46A)	–0.1710	0.1704	0.1934	0.041
H(48A)	–0.6981	–0.0062	–0.0596	0.047
H(49A)	–0.8693	–0.0069	–0.1684	0.052
H(50A)	–1.0113	–0.0959	–0.1718	0.044
H(51A)	–0.9858	–0.1786	–0.0669	0.047
H(52A)	–0.8165	–0.1758	0.0436	0.031
H(54A)	–0.7463	–0.1332	0.2278	0.046
H(55A)	–0.7477	–0.2300	0.3124	0.051
H(56A)	–0.6107	–0.3174	0.2850	0.058
H(57A)	–0.4813	–0.3078	0.1722	0.045
H(58A)	–0.4708	–0.2108	0.0892	0.040
H(62A)	0.6049	0.2665	–0.6131	0.101
H(61A)	0.1836	0.1616	–0.2582	0.082
H(60A)	0.6231	–0.0410	–0.2360	0.062
H(59A)	–0.1938	–0.0850	–0.4202	0.108

Table 6. Torsion angles [°] for sd310.

Cl(1)–Au(1)–P(1)–C(1)	−151.3(4)	Cl(1)–Au(1)–P(1)–C(35)	−29.6(6)
Cl(1)–Au(1)–P(1)–C(41)	82.4(4)	Cl(2)–Au(2)–P(2)–C(19)	−164.6(4)
Cl(2)–Au(2)–P(2)–C(47)	−45.4(5)	Cl(2)–Au(2)–P(2)–C(53)	68.4(4)
Au(1)–P(1)–C(1)–C(2)	153.6(4)	Au(1)–P(1)–C(1)–C(17)	−32.6(7)
C(35)–P(1)–C(1)–C(2)	31.6(6)	C(35)–P(1)–C(1)–C(17)	−154.6(6)
C(41)–P(1)–C(1)–C(2)	−77.9(6)	C(41)–P(1)–C(1)–C(17)	95.9(7)
P(1)–C(1)–C(2)–C(3)	−131.4(5)	P(1)–C(1)–C(2)–C(15)	117.3(5)
C(17)–C(1)–C(2)–C(3)	54.0(7)	C(17)–C(1)–C(2)–C(15)	−57.2(8)
C(1)–C(2)–C(3)–C(4)	123.5(7)	C(1)–C(2)–C(3)–C(8)	−56.4(7)
C(15)–C(2)–C(3)–C(4)	−124.8(7)	C(15)–C(2)–C(3)–C(8)	55.3(7)
C(2)–C(3)–C(4)–C(5)	178.4(6)	C(8)–C(3)–C(4)–C(5)	−1.7(10)
C(3)–C(4)–C(5)–C(6)	0.9(12)	C(4)–C(5)–C(6)–C(7)	−0.4(12)
C(5)–C(6)–C(7)–C(8)	0.6(12)	C(6)–C(7)–C(8)–C(3)	−1.4(11)
C(6)–C(7)–C(8)–C(9)	178.1(7)	C(2)–C(3)–C(8)–C(7)	−178.0(6)
C(2)–C(3)–C(8)–C(9)	2.3(8)	C(4)–C(3)–C(8)–C(7)	2.0(10)
C(4)–C(3)–C(8)–C(9)	−177.6(6)	C(3)–C(8)–C(9)–C(10)	−56.9(7)
C(3)–C(8)–C(9)–C(16)	−179.3(6)	C(3)–C(8)–C(9)–C(17)	53.9(7)
C(7)–C(8)–C(9)–C(10)	123.5(7)	C(7)–C(8)–C(9)–C(16)	1.1(10)
C(7)–C(8)–C(9)–C(17)	−125.7(7)	C(8)–C(9)–C(10)–C(11)	−123.1(7)
C(8)–C(9)–C(10)–C(15)	55.8(7)	C(16)–C(9)–C(10)–C(11)	−0.5(10)
C(16)–C(9)–C(10)–C(15)	178.4(6)	C(17)–C(9)–C(10)–C(11)	126.3(7)
C(17)–C(9)–C(10)–C(15)	−54.8(7)	C(9)–C(10)–C(11)–C(12)	178.5(7)
C(15)–C(10)–C(11)–C(12)	−0.3(11)	C(10)–C(11)–C(12)–C(13)	−1.5(12)
C(11)–C(12)–C(13)–C(14)	2.4(12)	C(12)–C(13)–C(14)–C(15)	−1.6(11)
C(13)–C(14)–C(15)–C(2)	−178.8(7)	C(13)–C(14)–C(15)–C(10)	−0.3(11)
C(9)–C(10)–C(15)–C(2)	1.0(8)	C(9)–C(10)–C(15)–C(14)	−177.8(6)
C(11)–C(10)–C(15)–C(2)	179.9(6)	C(11)–C(10)–C(15)–C(14)	1.2(10)
C(1)–C(2)–C(15)–C(10)	54.3(7)	C(1)–C(2)–C(15)–C(14)	−127.1(7)
C(3)–C(2)–C(15)–C(10)	−57.1(7)	C(3)–C(2)–C(15)–C(14)	121.6(7)
P(1)–C(1)–C(17)–C(9)	−171.4(5)	P(1)–C(1)–C(17)–C(18)	7.2(11)
C(2)–C(1)–C(17)–C(9)	2.6(8)	C(2)–C(1)–C(17)–C(18)	−178.8(6)
C(8)–C(9)–C(17)–C(1)	−57.2(8)	C(8)–C(9)–C(17)–C(18)	124.1(7)
C(10)–C(9)–C(17)–C(1)	52.2(8)	C(10)–C(9)–C(17)–C(18)	−126.6(6)
C(16)–C(9)–C(17)–C(1)	177.4(6)	C(16)–C(9)–C(17)–C(18)	−1.3(9)
C(1)–C(17)–C(18)–C(19)	94.5(9)	C(1)–C(17)–C(18)–C(27)	−92.6(9)
C(9)–C(17)–C(18)–C(19)	−86.9(9)	C(9)–C(17)–C(18)–C(27)	85.9(7)
C(17)–C(18)–C(19)–P(2)	−2.3(11)	C(17)–C(18)–C(19)–C(20)	177.2(6)
C(27)–C(18)–C(19)–P(2)	−175.5(5)	C(27)–C(18)–C(19)–C(20)	4.1(8)
Au(2)–P(2)–C(19)–C(18)	−31.9(7)	Au(2)–P(2)–C(19)–C(20)	148.5(4)
C(47)–P(2)–C(19)–C(18)	−151.8(6)	C(47)–P(2)–C(19)–C(20)	28.6(6)
C(53)–P(2)–C(19)–C(18)	97.1(7)	C(53)–P(2)–C(19)–C(20)	−82.5(5)
P(2)–C(19)–C(20)–C(21)	120.6(5)	P(2)–C(19)–C(20)–C(33)	−127.0(5)
C(18)–C(19)–C(20)–C(21)	−59.0(7)	C(18)–C(19)–C(20)–C(33)	53.4(7)
C(19)–C(20)–C(21)–C(22)	−126.1(7)	C(19)–C(20)–C(21)–C(26)	55.0(7)
C(33)–C(20)–C(21)–C(22)	120.2(7)	C(33)–C(20)–C(21)–C(26)	−58.6(7)
C(20)–C(21)–C(22)–C(23)	179.5(7)	C(26)–C(21)–C(22)–C(23)	−1.7(10)
C(21)–C(22)–C(23)–C(24)	1.3(11)	C(22)–C(23)–C(24)–C(25)	−0.9(12)
C(23)–C(24)–C(25)–C(26)	1.0(12)	C(24)–C(25)–C(26)–C(21)	−1.3(11)
C(24)–C(25)–C(26)–C(27)	177.9(7)	C(20)–C(21)–C(26)–C(25)	−179.3(6)
C(20)–C(21)–C(26)–C(27)	1.3(8)	C(22)–C(21)–C(26)–C(25)	1.7(10)
C(22)–C(21)–C(26)–C(27)	−177.6(6)	C(21)–C(26)–C(27)–C(18)	−54.4(7)
C(21)–C(26)–C(27)–C(28)	55.4(7)	C(21)–C(26)–C(27)–C(34)	179.0(6)
C(25)–C(26)–C(27)–C(18)	126.4(7)	C(25)–C(26)–C(27)–C(28)	−123.9(7)

C(25)–C(26)–C(27)–C(34)	−0.2(10)	C(17)–C(18)–C(27)–C(26)	−122.2(6)
C(17)–C(18)–C(27)–C(28)	128.7(6)	C(17)–C(18)–C(27)–C(34)	4.2(9)
C(19)–C(18)–C(27)–C(26)	51.6(8)	C(19)–C(18)–C(27)–C(28)	−57.6(7)
C(19)–C(18)–C(27)–C(34)	178.0(6)	C(18)–C(27)–C(28)–C(29)	−129.3(7)
C(18)–C(27)–C(28)–C(33)	54.2(7)	C(26)–C(27)–C(28)–C(29)	119.6(7)
C(26)–C(27)–C(28)–C(33)	−56.9(7)	C(34)–C(27)–C(28)–C(29)	−4.4(10)
C(34)–C(27)–C(28)–C(33)	179.1(6)	C(27)–C(28)–C(29)–C(30)	−177.3(7)
C(33)–C(28)–C(29)–C(30)	−1.1(11)	C(28)–C(29)–C(30)–C(31)	1.1(12)
C(29)–C(30)–C(31)–C(32)	−1.0(13)	C(30)–C(31)–C(32)–C(33)	0.8(12)
C(31)–C(32)–C(33)–C(20)	175.2(7)	C(31)–C(32)–C(33)–C(28)	−0.8(10)
C(27)–C(28)–C(33)–C(20)	1.1(8)	C(27)–C(28)–C(33)–C(32)	177.6(6)
C(29)–C(28)–C(33)–C(20)	−175.6(6)	C(29)–C(28)–C(33)–C(32)	0.9(10)
C(19)–C(20)–C(33)–C(28)	−55.9(7)	C(19)–C(20)–C(33)–C(32)	127.8(7)
C(21)–C(20)–C(33)–C(28)	57.6(7)	C(21)–C(20)–C(33)–C(32)	−118.7(7)
Au(1)–P(1)–C(35)–C(36)	89.9(7)	Au(1)–P(1)–C(35)–C(40)	−84.4(6)
C(1)–P(1)–C(35)–C(36)	−139.2(7)	C(1)–P(1)–C(35)–C(40)	46.5(6)
C(41)–P(1)–C(35)–C(36)	−27.5(7)	C(41)–P(1)–C(35)–C(40)	158.2(6)
P(1)–C(35)–C(36)–C(37)	−175.2(7)	C(40)–C(35)–C(36)–C(37)	−0.8(12)
C(35)–C(36)–C(37)–C(38)	−0.1(14)	C(36)–C(37)–C(38)–C(39)	0.6(14)
C(37)–C(38)–C(39)–C(40)	−0.2(12)	C(38)–C(39)–C(40)–C(35)	−0.7(12)
P(1)–C(35)–C(40)–C(39)	175.9(6)	C(36)–C(35)–C(40)–C(39)	1.1(11)
Au(1)–P(1)–C(41)–C(42)	1.7(7)	Au(1)–P(1)–C(41)–C(46)	−174.8(5)
C(1)–P(1)–C(41)–C(42)	−132.5(6)	C(1)–P(1)–C(41)–C(46)	51.1(7)
C(35)–P(1)–C(41)–C(42)	115.8(7)	C(35)–P(1)–C(41)–C(46)	−60.6(7)
P(1)–C(41)–C(42)–C(43)	−177.6(6)	C(46)–C(41)–C(42)–C(43)	−1.1(11)
C(41)–C(42)–C(43)–C(44)	0.2(13)	C(42)–C(43)–C(44)–C(45)	−0.1(14)
C(43)–C(44)–C(45)–C(46)	1.0(13)	Au(2)–P(2)–C(47)–C(48)	−59.3(7)
Au(2)–P(2)–C(47)–C(52)	117.7(5)	C(19)–P(2)–C(47)–C(48)	73.1(7)
C(19)–P(2)–C(47)–C(52)	−110.0(6)	C(53)–P(2)–C(47)–C(48)	−176.1(6)
C(53)–P(2)–C(47)–C(52)	0.8(7)	C(44)–C(45)–C(46)–C(41)	−2.0(13)
P(1)–C(41)–C(46)–C(45)	178.6(6)	C(42)–C(41)–C(46)–C(45)	2.0(12)
P(2)–C(47)–C(48)–C(49)	178.1(7)	C(52)–C(47)–C(48)–C(49)	1.0(12)
C(47)–C(48)–C(49)–C(50)	−1.4(14)	C(48)–C(49)–C(50)–C(51)	1.1(13)
C(49)–C(50)–C(51)–C(52)	−0.3(13)	C(50)–C(51)–C(52)–C(47)	−0.2(12)
P(2)–C(47)–C(52)–C(51)	−177.2(6)	C(48)–C(47)–C(52)–C(51)	−0.2(11)
Au(2)–P(2)–C(53)–C(54)	170.0(6)	Au(2)–P(2)–C(53)–C(58)	−9.5(7)
C(19)–P(2)–C(53)–C(54)	33.0(7)	C(19)–P(2)–C(53)–C(58)	−146.6(6)
C(47)–P(2)–C(53)–C(54)	−76.6(7)	C(47)–P(2)–C(53)–C(58)	103.9(6)
P(2)–C(53)–C(54)–C(55)	−179.1(7)	C(58)–C(53)–C(54)–C(55)	0.4(12)
C(53)–C(54)–C(55)–C(56)	−0.4(14)	C(54)–C(55)–C(56)–C(57)	−0.9(15)
C(55)–C(56)–C(57)–C(58)	2.1(15)	C(56)–C(57)–C(58)–C(53)	−2.1(13)
P(2)–C(53)–C(58)–C(57)	−179.7(6)	C(54)–C(53)–C(58)–C(57)	0.8(12)

7.2 [(H-CATPHOS)$(AuCl)_2$]

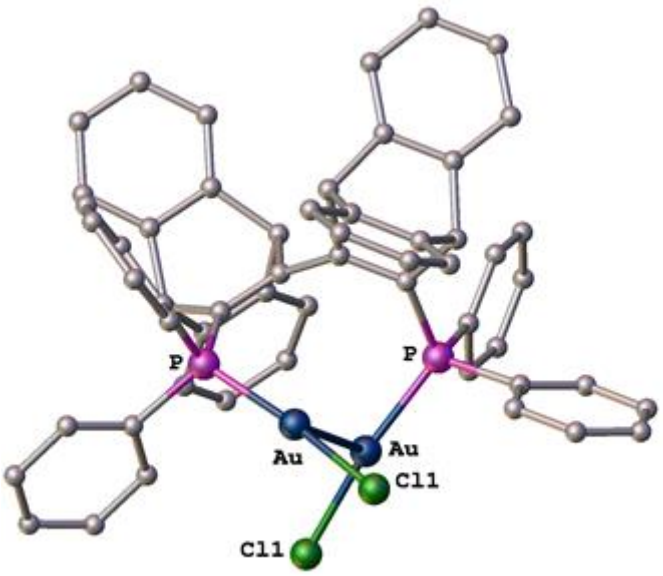

Table 1. Crystal data and structure refinement for sd313.

Identification code	sd313	
Chemical formula (moiety)	$C_{58}H_{44}Au_2Cl_6P_2$	
Chemical formula (total)	$C_{58}H_{44}Au_2Cl_6P_2$	
Formula weight	1409.51	
Temperature	150(2) K	
Radiation, wavelength	MoKα, 0.71073 Å	
Crystal system, space group	monoclinic, C12/c1	
Unit cell parameters	a = 23.816(3) Å	α = 90°
	b = 11.7622(19) Å	β = 95.630(11)°
	c = 18.378(3) Å	γ = 90°
Cell volume	5123.3(13) $Å^3$	
Z	4	
Calculated density	1.827 g/cm^3	
Absorption coefficient μ	6.135 mm^{-1}	
F(000)	2728	
Reflections for cell refinement	3892 (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 28.7°	
Index ranges	h −28 to 23, k −14 to 15, l −21 to 22	
Completeness to θ = 25.0°	99.9 %	
Reflections collected	15981	
Independent reflections	5516 (R_{int} = 0.0543)	
Reflections with $F^2>2\sigma$	4754	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.77582 and 1.00000	
Structure solution	direct methods	
Refinement method	Full-matrix least-squares on F^2	
Weighting parameters a, b	0.0318, 7.8196	
Data / restraints / parameters	5516 / 0 / 326	
Final R indices [$F^2>2\sigma$]	R1 = 0.0334, wR2 = 0.0750	
R indices (all data)	R1 = 0.0421, wR2 = 0.0821	
Goodness-of-fit on F^2	1.079	
Largest and mean shift/su	0.002 and 0.000	
Largest diff. peak and hole	1.07 and −1.50 e $Å^{-3}$	

Table 2. Atomic coordinates and equivalent isotropic displacement parameters ($Å^2$) for sd313. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
Au	0.476715(7)	0.020173(16)	0.164066(9)	0.02501(8)
Cl(1)	0.40892(7)	–0.11681(14)	0.16727(8)	0.0606(5)
Cl(2)	0.76585(7)	0.23896(19)	0.13392(11)	0.0813(6)
Cl(3)	0.8253(2)	0.0763(4)	0.0485(6)	0.056(2)
Cl(3A)	0.81234(19)	0.1162(8)	0.0132(3)	0.056(2)
P	0.54163(4)	0.14611(9)	0.13927(5)	0.0157(2)
C(1)	0.56470(16)	0.2516(4)	0.20798(19)	0.0149(8)
C(2)	0.53105(15)	0.3039(3)	0.25166(19)	0.0131(8)
C(3)	0.56287(16)	0.3897(4)	0.30487(19)	0.0162(8)
C(4)	0.61009(16)	0.3229(4)	0.3477(2)	0.0184(9)
C(5)	0.62084(18)	0.3143(4)	0.4234(2)	0.0237(9)
C(6)	0.66670(19)	0.2511(4)	0.4530(2)	0.0304(11)
C(7)	0.70120(17)	0.1955(4)	0.4082(2)	0.0286(11)
C(8)	0.69024(17)	0.2047(4)	0.3323(2)	0.0259(10)
C(9)	0.64497(16)	0.2674(4)	0.3026(2)	0.0172(8)
C(10)	0.62714(16)	0.2892(4)	0.2217(2)	0.0179(8)
C(11)	0.62708(16)	0.4181(4)	0.2128(2)	0.0176(9)
C(12)	0.65900(19)	0.4815(4)	0.1685(2)	0.0256(10)
C(13)	0.65583(19)	0.5995(4)	0.1708(2)	0.0292(11)
C(14)	0.62110(19)	0.6542(4)	0.2152(2)	0.0283(10)
C(15)	0.58892(18)	0.5905(4)	0.2594(2)	0.0226(9)
C(16)	0.59219(18)	0.4734(4)	0.2576(2)	0.0187(9)
C(17)	0.51989(17)	0.2227(4)	0.0554(2)	0.0190(9)
C(18)	0.48083(18)	0.1709(4)	0.0031(2)	0.0242(9)
C(19)	0.4665(2)	0.2239(5)	–0.0638(2)	0.0314(11)
C(20)	0.49043(19)	0.3270(5)	–0.0788(2)	0.0334(12)
C(21)	0.52875(19)	0.3780(5)	–0.0269(2)	0.0339(12)
C(22)	0.54374(19)	0.3266(4)	0.0394(2)	0.0278(10)
C(23)	0.60600(17)	0.0732(4)	0.1209(2)	0.0196(9)
C(24)	0.62487(18)	0.0725(4)	0.0522(2)	0.0251(10)
C(25)	0.6736(2)	0.0128(4)	0.0404(3)	0.0365(13)
C(26)	0.7030(2)	–0.0451(4)	0.0979(3)	0.0366(12)
C(27)	0.6847(2)	–0.0461(4)	0.1663(3)	0.0358(12)
C(28)	0.6355(2)	0.0136(4)	0.1781(3)	0.0256(10)
C(29)	0.8109(5)	0.2173(12)	0.0688(7)	0.047(4)
C(29A)	0.8164(5)	0.1601(13)	0.1045(7)	0.046(4)

Table 3. Bond lengths [Å] and angles [°] for sd313.

Au–AuA	3.2433(6)	Au–Cl(1)	2.2859(13)
Au–P	2.2205(11)	Cl(2)–C(29)	1.703(13)
Cl(2)–C(29A)	1.652(12)	Cl(3)–C(29)	1.742(15)
Cl(3A)–C(29A)	1.749(14)	P–C(1)	1.816(4)
P–C(17)	1.816(4)	P–C(23)	1.816(4)
C(1)–C(2)	1.338(5)	C(1)–C(10)	1.548(5)
C(2)–C(2A)	1.474(7)	C(2)–C(3)	1.551(5)
C(3)–H(3A)	1.000	C(3)–C(4)	1.526(6)
C(3)–C(16)	1.526(6)	C(4)–C(5)	1.392(5)
C(4)–C(9)	1.393(6)	C(5)–H(5A)	0.950
C(5)–C(6)	1.388(6)	C(6)–H(6A)	0.950
C(6)–C(7)	1.384(7)	C(7)–H(7A)	0.950
C(7)–C(8)	1.397(6)	C(8)–H(8A)	0.950
C(8)–C(9)	1.374(6)	C(9)–C(10)	1.527(5)
C(10)–H(10A)	1.000	C(10)–C(11)	1.525(6)
C(11)–C(12)	1.385(6)	C(11)–C(16)	1.388(6)
C(12)–H(12A)	0.950	C(12)–C(13)	1.391(7)
C(13)–H(13A)	0.950	C(13)–C(14)	1.376(7)
C(14)–H(14A)	0.950	C(14)–C(15)	1.390(6)
C(15)–H(15A)	0.950	C(15)–C(16)	1.381(6)
C(17)–C(18)	1.409(6)	C(17)–C(22)	1.391(6)
C(18)–H(18A)	0.950	C(18)–C(19)	1.390(6)
C(19)–H(19A)	0.950	C(19)–C(20)	1.380(7)
C(20)–H(20A)	0.950	C(20)–C(21)	1.390(7)
C(21)–H(21A)	0.950	C(21)–C(22)	1.375(6)
C(22)–H(22A)	0.950	C(23)–C(24)	1.382(6)
C(23)–C(28)	1.395(6)	C(24)–H(24A)	0.950
C(24)–C(25)	1.392(6)	C(25)–H(25A)	0.950
C(25)–C(26)	1.387(8)	C(26)–H(26A)	0.950
C(26)–C(27)	1.370(7)	C(27)–H(27A)	0.950
C(27)–C(28)	1.400(7)	C(28)–H(28A)	0.950
C(29)–H(29A)	0.990	C(29)–H(29B)	0.990
C(29A)–H(29C)	0.990	C(29A)–H(29D)	0.990

AuA–Au–Cl(1)	98.62(4)	AuA–Au–P	91.23(3)
Cl(1)–Au–P	169.52(4)	C(29)–Cl(2)–C(29A)	32.5(5)
Au–P–C(1)	118.82(12)	Au–P–C(17)	111.03(14)
Au–P–C(23)	109.90(15)	C(1)–P–C(17)	107.03(19)
C(1)–P–C(23)	104.37(18)	C(17)–P–C(23)	104.60(18)
P–C(1)–C(2)	124.9(3)	P–C(1)–C(10)	121.9(3)
C(2)–C(1)–C(10)	113.1(3)	C(1)–C(2)–C(2A)	129.2(4)
C(1)–C(2)–C(3)	113.1(3)	C(2A)–C(2)–C(3)	116.9(3)
C(2)–C(3)–H(3A)	112.6	C(2)–C(3)–C(4)	106.3(3)
C(2)–C(3)–C(16)	106.5(3)	H(3A)–C(3)–C(4)	112.6
H(3A)–C(3)–C(16)	112.6	C(4)–C(3)–C(16)	105.7(3)
C(3)–C(4)–C(5)	127.4(4)	C(3)–C(4)–C(9)	112.7(3)
C(5)–C(4)–C(9)	119.9(4)	C(4)–C(5)–H(5A)	120.3
C(4)–C(5)–C(6)	119.5(4)	H(5A)–C(5)–C(6)	120.3
C(5)–C(6)–H(6A)	119.7	C(5)–C(6)–C(7)	120.6(4)
H(6A)–C(6)–C(7)	119.7	C(6)–C(7)–H(7A)	120.2
C(6)–C(7)–C(8)	119.6(4)	H(7A)–C(7)–C(8)	120.2
C(7)–C(8)–H(8A)	120.0	C(7)–C(8)–C(9)	120.0(4)
H(8A)–C(8)–C(9)	120.0	C(4)–C(9)–C(8)	120.4(4)
C(4)–C(9)–C(10)	112.1(3)	C(8)–C(9)–C(10)	127.5(4)
C(1)–C(10)–C(9)	106.4(3)	C(1)–C(10)–H(10A)	112.8
C(1)–C(10)–C(11)	106.0(3)	C(9)–C(10)–H(10A)	112.8

C(9)–C(10)–C(11)	105.6(3)	H(10A)–C(10)–C(11)	112.8
C(10)–C(11)–C(12)	127.2(4)	C(10)–C(11)–C(16)	113.3(3)
C(12)–C(11)–C(16)	119.4(4)	C(11)–C(12)–H(12A)	120.5
C(11)–C(12)–C(13)	119.0(4)	H(12A)–C(12)–C(13)	120.5
C(12)–C(13)–H(13A)	119.3	C(12)–C(13)–C(14)	121.5(4)
H(13A)–C(13)–C(14)	119.3	C(13)–C(14)–H(14A)	120.3
C(13)–C(14)–C(15)	119.5(5)	H(14A)–C(14)–C(15)	120.3
C(14)–C(15)–H(15A)	120.4	C(14)–C(15)–C(16)	119.3(4)
H(15A)–C(15)–C(16)	120.4	C(3)–C(16)–C(11)	111.7(4)
C(3)–C(16)–C(15)	126.9(4)	C(11)–C(16)–C(15)	121.3(4)
P–C(17)–C(18)	118.6(3)	P–C(17)–C(22)	121.8(3)
C(18)–C(17)–C(22)	119.4(4)	C(17)–C(18)–H(18A)	120.1
C(17)–C(18)–C(19)	119.9(4)	H(18A)–C(18)–C(19)	120.1
C(18)–C(19)–H(19A)	120.0	C(18)–C(19)–C(20)	120.0(4)
H(19A)–C(19)–C(20)	120.0	C(19)–C(20)–H(20A)	120.0
C(19)–C(20)–C(21)	119.9(4)	H(20A)–C(20)–C(21)	120.0
C(20)–C(21)–H(21A)	119.5	C(20)–C(21)–C(22)	120.9(5)
H(21A)–C(21)–C(22)	119.5	C(17)–C(22)–C(21)	119.9(4)
C(17)–C(22)–H(22A)	120.1	C(21)–C(22)–H(22A)	120.1
P–C(23)–C(24)	121.9(3)	P–C(23)–C(28)	118.0(3)
C(24)–C(23)–C(28)	120.0(4)	C(23)–C(24)–H(24A)	120.1
C(23)–C(24)–C(25)	119.7(4)	H(24A)–C(24)–C(25)	120.1
C(24)–C(25)–H(25A)	120.1	C(24)–C(25)–C(26)	119.7(5)
H(25A)–C(25)–C(26)	120.1	C(25)–C(26)–H(26A)	119.3
C(25)–C(26)–C(27)	121.4(5)	H(26A)–C(26)–C(27)	119.3
C(26)–C(27)–H(27A)	120.5	C(26)–C(27)–C(28)	119.0(5)
H(27A)–C(27)–C(28)	120.5	C(23)–C(28)–C(27)	120.1(4)
C(23)–C(28)–H(28A)	119.9	C(27)–C(28)–H(28A)	119.9
Cl(2)–C(29)–Cl(3)	116.3(9)	Cl(2)–C(29)–H(29A)	108.2
Cl(2)–C(29)–H(29B)	108.2	Cl(3)–C(29)–H(29A)	108.2
Cl(3)–C(29)–H(29B)	108.2	H(29A)–C(29)–H(29B)	107.4
Cl(2)–C(29A)–Cl(3A)	120.4(9)	Cl(2)–C(29A)–H(29C)	107.2
Cl(2)–C(29A)–H(29D)	107.2	Cl(3A)–C(29A)–H(29C)	107.2
Cl(3A)–C(29A)–H(29D)	107.2	H(29C)–C(29A)–H(29D)	106.9

Symmetry operations for equivalent atoms
A –x+1,y,–z+1/2

Table 4. Anisotropic displacement parameters ($Å^2$) for sd313. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ...+ 2hka^*b^*U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Au	0.02812(12)	0.01992(12)	0.02897(12)	–0.00620(6)	0.01279(7)	–0.00994(7)
Cl(1)	0.0740(10)	0.0475(9)	0.0674(9)	–0.0242(7)	0.0422(8)	–0.0435(8)
Cl(2)	0.0477(10)	0.0887(15)	0.1106(14)	–0.0442(12)	0.0237(9)	–0.0114(9)
Cl(3)	0.0333(19)	0.051(2)	0.085(5)	0.003(2)	0.019(2)	0.0066(16)
Cl(3A)	0.0310(18)	0.097(5)	0.041(3)	–0.009(3)	0.0048(15)	–0.005(2)
P	0.0149(5)	0.0144(5)	0.0185(5)	–0.0019(4)	0.0047(4)	–0.0012(4)
C(1)	0.0143(19)	0.014(2)	0.0171(19)	0.0016(15)	0.0042(14)	–0.0007(16)
C(2)	0.0136(19)	0.011(2)	0.0145(19)	0.0016(15)	0.0009(14)	–0.0032(15)
C(3)	0.018(2)	0.019(2)	0.0128(18)	–0.0026(16)	0.0032(14)	–0.0030(17)
C(4)	0.018(2)	0.018(2)	0.019(2)	0.0033(16)	0.0007(15)	–0.0051(17)
C(5)	0.025(2)	0.025(3)	0.021(2)	–0.0005(18)	0.0020(16)	–0.0072(19)
C(6)	0.028(3)	0.037(3)	0.024(2)	0.007(2)	–0.0060(18)	–0.009(2)
C(7)	0.012(2)	0.033(3)	0.038(3)	0.014(2)	–0.0068(17)	–0.0017(19)
C(8)	0.015(2)	0.028(3)	0.035(2)	0.002(2)	0.0020(17)	–0.0042(19)
C(9)	0.0146(19)	0.017(2)	0.020(2)	–0.0009(16)	0.0011(15)	–0.0072(16)
C(10)	0.0139(19)	0.019(2)	0.022(2)	0.0001(17)	0.0058(15)	–0.0041(17)
C(11)	0.0120(19)	0.024(2)	0.0161(19)	0.0021(16)	–0.0019(14)	–0.0046(17)
C(12)	0.020(2)	0.035(3)	0.022(2)	0.0007(19)	0.0013(17)	–0.0107(19)
C(13)	0.027(2)	0.031(3)	0.029(2)	0.010(2)	0.0006(18)	–0.015(2)
C(14)	0.033(3)	0.020(3)	0.029(2)	0.0020(19)	–0.0083(19)	–0.009(2)
C(15)	0.023(2)	0.021(2)	0.022(2)	–0.0013(17)	–0.0020(16)	–0.0066(19)
C(16)	0.018(2)	0.022(2)	0.017(2)	–0.0017(16)	0.0010(15)	–0.0060(17)
C(17)	0.016(2)	0.023(2)	0.018(2)	–0.0045(17)	0.0047(15)	0.0015(17)
C(18)	0.024(2)	0.025(3)	0.023(2)	–0.0030(18)	0.0022(16)	–0.0023(19)
C(19)	0.034(3)	0.040(3)	0.020(2)	–0.004(2)	0.0005(18)	0.002(2)
C(20)	0.028(3)	0.049(3)	0.023(2)	0.009(2)	0.0017(18)	0.003(2)
C(21)	0.029(3)	0.036(3)	0.036(3)	0.018(2)	0.0001(19)	–0.008(2)
C(22)	0.025(2)	0.029(3)	0.030(2)	0.0021(19)	0.0020(18)	–0.006(2)
C(23)	0.020(2)	0.015(2)	0.025(2)	–0.0066(17)	0.0039(16)	0.0015(17)
C(24)	0.025(2)	0.022(3)	0.030(2)	–0.0052(19)	0.0103(17)	–0.0010(19)
C(25)	0.030(3)	0.032(3)	0.051(3)	–0.012(2)	0.023(2)	0.002(2)
C(26)	0.025(3)	0.023(3)	0.063(3)	–0.009(2)	0.011(2)	0.005(2)
C(27)	0.029(3)	0.023(3)	0.055(3)	0.002(2)	0.000(2)	0.006(2)
C(28)	0.025(2)	0.020(3)	0.033(3)	0.0021(18)	0.0086(19)	0.0034(19)
C(29)	0.041(7)	0.047(9)	0.051(8)	0.015(6)	–0.011(5)	–0.007(6)
C(29A)	0.038(6)	0.052(9)	0.045(8)	–0.003(7)	–0.011(5)	–0.001(6)

Table 5. Hydrogen coordinates and isotropic displacement parameters ($Å^2$) for sd313.

	x	y	z	U
H(3A)	0.5374	0.4283	0.3373	0.019
H(5A)	0.5970	0.3514	0.4544	0.028
H(6A)	0.6745	0.2459	0.5046	0.036
H(7A)	0.7322	0.1514	0.4288	0.034
H(8A)	0.7141	0.1676	0.3012	0.031
H(10A)	0.6520	0.2501	0.1888	0.022
H(12A)	0.6827	0.4450	0.1370	0.031
H(13A)	0.6781	0.6433	0.1411	0.035
H(14A)	0.6191	0.7349	0.2155	0.034
H(15A)	0.5649	0.6272	0.2904	0.027
H(18A)	0.4643	0.0999	0.0134	0.029
H(19A)	0.4402	0.1891	–0.0991	0.038
H(20A)	0.4807	0.3631	–0.1245	0.040
H(21A)	0.5448	0.4494	–0.0373	0.041
H(22A)	0.5703	0.3620	0.0742	0.033
H(24A)	0.6046	0.1125	0.0131	0.030
H(25A)	0.6868	0.0118	–0.0067	0.044
H(26A)	0.7365	–0.0849	0.0897	0.044
H(27A)	0.7050	–0.0867	0.2051	0.043
H(28A)	0.6223	0.0135	0.2252	0.031
H(29A)	0.8471	0.2556	0.0848	0.057
H(29B)	0.7950	0.2550	0.0232	0.057
H(29C)	0.8197	0.0907	0.1351	0.055
H(29D)	0.8522	0.2025	0.1147	0.055

Table 6. Torsion angles [°] for sd313.

AuA–Au–P–C(1)	−32.52(15)	AuA–Au–P–C(17)	−157.25(14)
AuA–Au–P–C(23)	87.51(14)	Cl(1)–Au–P–C(1)	167.5(3)
Cl(1)–Au–P–C(17)	42.8(4)	Cl(1)–Au–P–C(23)	−72.5(3)
Au–P–C(1)–C(2)	−38.4(4)	Au–P–C(1)–C(10)	141.2(3)
C(17)–P–C(1)–C(2)	88.2(4)	C(17)–P–C(1)–C(10)	−92.2(3)
C(23)–P–C(1)–C(2)	−161.2(4)	C(23)–P–C(1)–C(10)	18.3(4)
P–C(1)–C(2)–C(2A)	−10.2(6)	P–C(1)–C(2)–C(3)	180.0(3)
C(10)–C(1)–C(2)–C(2A)	170.2(3)	C(10)–C(1)–C(2)–C(3)	0.4(5)
C(1)–C(2)–C(3)–C(4)	−56.2(4)	C(1)–C(2)–C(3)–C(16)	56.2(4)
C(2A)–C(2)–C(3)–C(4)	132.7(3)	C(2A)–C(2)–C(3)–C(16)	−115.0(4)
C(2)–C(3)–C(4)–C(5)	−125.5(4)	C(2)–C(3)–C(4)–C(9)	55.1(4)
C(16)–C(3)–C(4)–C(5)	121.6(4)	C(16)–C(3)–C(4)–C(9)	−57.8(4)
C(3)–C(4)–C(5)–C(6)	−178.7(4)	C(9)–C(4)–C(5)–C(6)	0.6(6)
C(4)–C(5)–C(6)–C(7)	−0.9(7)	C(5)–C(6)–C(7)–C(8)	1.0(7)
C(6)–C(7)–C(8)–C(9)	−0.9(7)	C(7)–C(8)–C(9)–C(4)	0.6(6)
C(7)–C(8)–C(9)–C(10)	178.6(4)	C(3)–C(4)–C(9)–C(8)	179.0(4)
C(3)–C(4)–C(9)–C(10)	0.7(5)	C(5)–C(4)–C(9)–C(8)	−0.5(6)
C(5)–C(4)–C(9)–C(10)	−178.7(4)	C(4)–C(9)–C(10)–C(1)	−56.2(4)
C(4)–C(9)–C(10)–C(11)	56.1(4)	C(8)–C(9)–C(10)–C(1)	125.7(4)
C(8)–C(9)–C(10)–C(11)	−122.0(4)	P–C(1)–C(10)–C(9)	−123.5(3)
P–C(1)–C(10)–C(11)	124.4(3)	C(2)–C(1)–C(10)–C(9)	56.1(4)
C(2)–C(1)–C(10)–C(11)	−55.9(4)	C(1)–C(10)–C(11)–C(12)	−127.4(4)
C(1)–C(10)–C(11)–C(16)	55.5(4)	C(9)–C(10)–C(11)–C(12)	120.0(4)
C(9)–C(10)–C(11)–C(16)	−57.1(4)	C(10)–C(11)–C(12)–C(13)	−176.1(4)
C(16)–C(11)–C(12)–C(13)	0.8(6)	C(11)–C(12)–C(13)–C(14)	−1.0(6)
C(12)–C(13)–C(14)–C(15)	0.8(6)	C(13)–C(14)–C(15)–C(16)	−0.3(6)
C(14)–C(15)–C(16)–C(3)	176.4(4)	C(14)–C(15)–C(16)–C(11)	0.2(6)
C(10)–C(11)–C(16)–C(3)	0.2(5)	C(10)–C(11)–C(16)–C(15)	176.9(3)
C(12)–C(11)–C(16)–C(3)	−177.1(3)	C(12)–C(11)–C(16)–C(15)	−0.4(6)
C(2)–C(3)–C(16)–C(11)	−55.8(4)	C(2)–C(3)–C(16)–C(15)	127.7(4)
C(4)–C(3)–C(16)–C(11)	56.9(4)	C(4)–C(3)–C(16)–C(15)	−119.6(4)
Au–P–C(17)–C(18)	−24.4(4)	Au–P–C(17)–C(22)	160.4(3)
C(1)–P–C(17)–C(18)	−155.5(3)	C(1)–P–C(17)–C(22)	29.2(4)
C(23)–P–C(17)–C(18)	94.1(3)	C(23)–P–C(17)–C(22)	−81.1(4)
P–C(17)–C(18)–C(19)	−175.4(4)	C(22)–C(17)–C(18)–C(19)	−0.1(6)
C(17)–C(18)–C(19)–C(20)	−0.1(7)	C(18)–C(19)–C(20)–C(21)	−0.2(7)
C(19)–C(20)–C(21)–C(22)	0.6(8)	C(20)–C(21)–C(22)–C(17)	−0.7(7)
P–C(17)–C(22)–C(21)	175.7(4)	C(18)–C(17)–C(22)–C(21)	0.5(7)
Au–P–C(23)–C(24)	112.0(4)	Au–P–C(23)–C(28)	−65.8(4)
C(1)–P–C(23)–C(24)	−119.5(4)	C(1)–P–C(23)–C(28)	62.7(4)
C(17)–P–C(23)–C(24)	−7.3(4)	C(17)–P–C(23)–C(28)	175.0(3)
P–C(23)–C(24)–C(25)	−178.3(4)	C(28)–C(23)–C(24)–C(25)	−0.5(7)
C(23)–C(24)–C(25)–C(26)	−0.2(7)	C(24)–C(25)–C(26)–C(27)	0.7(8)
C(25)–C(26)–C(27)–C(28)	−0.5(8)	P–C(23)–C(28)–C(27)	178.5(4)
C(24)–C(23)–C(28)–C(27)	0.7(7)	C(26)–C(27)–C(28)–C(23)	−0.2(7)
C(29A)–Cl(2)–C(29)–Cl(3)	34.7(10)	C(29)–Cl(2)–C(29A)–Cl(3A)	−47.7(11)

Symmetry operations for equivalent atoms
A −x+1,y,−z+1/2

7.3 [(OMe-CATPHOS)$(AuCl)_2$]

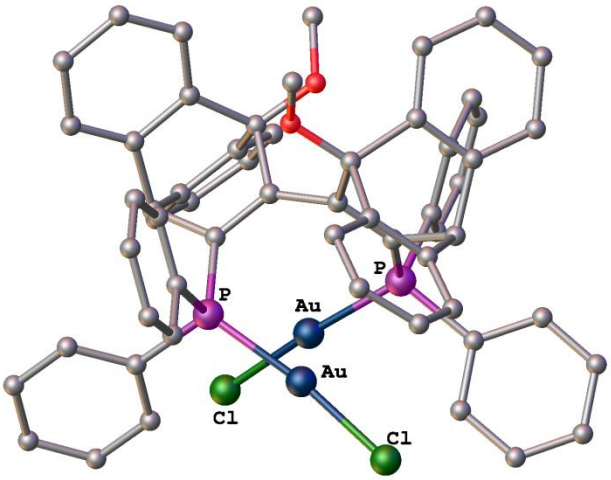

Table 1. Crystal data and structure refinement for sd315.

Identification code	sd315	
Chemical formula (moiety)	$C_{58}H_{44}P_2O_2Au_2Cl_2 \cdot 2CH_2Cl_2$	
Chemical formula (total)	$C_{60}H_{48}Au_2Cl_6O_2P_2$	
Formula weight	1469.56	
Temperature	150(2) K	
Radiation, wavelength	MoKα, 0.71073 Å	
Crystal system, space group	monoclinic, C12/c1	
Unit cell parameters	a = 15.6806(6) Å	α = 90°
	b = 15.6099(4) Å	β = 104.607(3)°
	c = 22.3455(6) Å	γ = 90°
Cell volume	5292.8(3) Å^3	
Z	4	
Calculated density	1.844 g/cm^3	
Absorption coefficient μ	5.946 mm^{-1}	
F(000)	2856	
Crystal colour and size	colourless, 0.20 × 0.20 × 0.20 mm^3	
Reflections for cell refinement	10232 (θ range 2.9 to 28.6°)	
Data collection method	Xcalibur, Atlas, Gemini ultra thick-slice ω scans	
θ range for data collection	2.9 to 28.6°	
Index ranges	h –19 to 20, k –21 to 17, l –29 to 26	
Completeness to θ = 25.0°	99.8 %	
Reflections collected	20325	
Independent reflections	5785 (R_{int} = 0.0299)	
Reflections with $F^2>2\sigma$	5212	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.3826 and 0.3826	
Structure solution	direct methods	
Refinement method	Full-matrix least-squares on F^2	
Weighting parameters a, b	0.0221, 14.4567	
Data / restraints / parameters	5785 / 0 / 299	
Final R indices [$F^2>2\sigma$]	R1 = 0.0240, wR2 = 0.0564	
R indices (all data)	R1 = 0.0282, wR2 = 0.0581	
Goodness-of-fit on F^2	1.096	
Largest and mean shift/su	0.003 and 0.000	
Largest diff. peak and hole	1.64 and –0.76 e Å^{-3}	

Table 2. Atomic coordinates and equivalent isotropic displacement parameters ($Å^2$) for sd315. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
Au	–0.080428(8)	0.990080(8)	0.297264(5)	0.01705(5)
P	–0.14540(5)	1.06619(5)	0.21425(3)	0.01339(16)
Cl	–0.03495(6)	0.90413(6)	0.38146(4)	0.0282(2)
O	0.07609(15)	1.31345(14)	0.21753(10)	0.0176(5)
C(1)	–0.0810(2)	1.14178(19)	0.18241(13)	0.0126(6)
C(2)	–0.0187(2)	1.19288(19)	0.21625(13)	0.0125(6)
C(3)	0.0130(2)	1.2623(2)	0.17747(13)	0.0133(6)
C(4)	–0.0716(2)	1.3088(2)	0.14291(13)	0.0156(6)
C(5)	–0.0917(3)	1.3948(2)	0.14711(15)	0.0231(7)
C(6)	–0.1736(3)	1.4240(3)	0.11457(17)	0.0319(9)
C(7)	–0.2358(3)	1.3697(3)	0.07925(16)	0.0327(9)
C(8)	–0.2162(2)	1.2830(2)	0.07595(15)	0.0248(8)
C(9)	–0.1336(2)	1.2536(2)	0.10740(13)	0.0164(7)
C(10)	–0.1036(2)	1.1614(2)	0.11239(13)	0.0157(7)
C(11)	–0.0176(2)	1.15826(19)	0.09417(13)	0.0138(6)
C(12)	0.0018(2)	1.1091(2)	0.04796(14)	0.0211(7)
C(13)	0.0857(3)	1.1105(2)	0.03882(15)	0.0249(8)
C(14)	0.1512(2)	1.1598(2)	0.07654(15)	0.0233(8)
C(15)	0.1316(2)	1.2104(2)	0.12270(14)	0.0189(7)
C(16)	0.0469(2)	1.21104(19)	0.13007(13)	0.0135(6)
C(17)	0.1137(3)	1.3817(2)	0.18969(17)	0.0269(8)
C(18)	–0.1992(2)	0.9962(2)	0.15094(14)	0.0161(7)
C(19)	–0.1643(2)	0.9163(2)	0.14667(16)	0.0226(7)
C(20)	–0.2027(3)	0.8623(3)	0.09764(18)	0.0325(9)
C(21)	–0.2756(3)	0.8886(3)	0.05377(16)	0.0314(9)
C(22)	–0.3115(3)	0.9679(3)	0.05800(16)	0.0314(9)
C(23)	–0.2739(2)	1.0221(2)	0.10640(16)	0.0237(7)
C(24)	–0.2353(2)	1.1275(2)	0.23052(14)	0.0176(7)
C(25)	–0.2906(2)	1.0845(2)	0.26052(16)	0.0261(8)
C(26)	–0.3608(3)	1.1267(3)	0.27404(19)	0.0355(10)
C(27)	–0.3751(2)	1.2126(3)	0.25917(18)	0.0354(10)
C(28)	–0.3209(3)	1.2551(3)	0.23048(17)	0.0307(9)
C(29)	–0.2504(2)	1.2133(2)	0.21578(15)	0.0221(7)

Table 3. Bond lengths [Å] and angles [°] for sd315.

Au–P	2.2219(8)	Au–Cl	2.2741(8)
P–C(1)	1.811(3)	P–C(18)	1.818(3)
P–C(24)	1.815(3)	O–C(3)	1.404(4)
O–C(17)	1.433(4)	C(1)–C(2)	1.338(4)
C(1)–C(10)	1.545(4)	C(2)–C(2A)	1.474(6)
C(2)–C(3)	1.546(4)	C(3)–C(4)	1.538(4)
C(3)–C(16)	1.527(4)	C(4)–C(5)	1.387(5)
C(4)–C(9)	1.388(5)	C(5)–H(5A)	0.950
C(5)–C(6)	1.385(5)	C(6)–H(6A)	0.950
C(6)–C(7)	1.380(6)	C(7)–H(7A)	0.950
C(7)–C(8)	1.393(5)	C(8)–H(8A)	0.950
C(8)–C(9)	1.387(5)	C(9)–C(10)	1.510(5)
C(10)–H(10A)	1.000	C(10)–C(11)	1.504(4)
C(11)–C(12)	1.380(4)	C(11)–C(16)	1.392(4)
C(12)–H(12A)	0.950	C(12)–C(13)	1.383(5)
C(13)–H(13A)	0.950	C(13)–C(14)	1.385(5)
C(14)–H(14A)	0.950	C(14)–C(15)	1.393(5)
C(15)–H(15A)	0.950	C(15)–C(16)	1.380(5)
C(17)–H(17A)	0.980	C(17)–H(17B)	0.980
C(17)–H(17C)	0.980	C(18)–C(19)	1.376(5)
C(18)–C(23)	1.392(5)	C(19)–H(19A)	0.950
C(19)–C(20)	1.393(5)	C(20)–H(20A)	0.950
C(20)–C(21)	1.368(6)	C(21)–H(21A)	0.950
C(21)–C(22)	1.371(6)	C(22)–H(22A)	0.950
C(22)–C(23)	1.383(5)	C(23)–H(23A)	0.950
C(24)–C(25)	1.395(5)	C(24)–C(29)	1.384(5)
C(25)–H(25A)	0.950	C(25)–C(26)	1.379(5)
C(26)–H(26A)	0.950	C(26)–C(27)	1.386(6)
C(27)–H(27A)	0.950	C(27)–C(28)	1.361(6)
C(28)–H(28A)	0.950	C(28)–C(29)	1.393(5)
C(29)–H(29A)	0.950		

P–Au–Cl	171.19(3)	Au–P–C(1)	119.52(10)
Au–P–C(18)	110.72(11)	Au–P–C(24)	109.31(10)
C(1)–P–C(18)	106.31(14)	C(1)–P–C(24)	105.83(15)
C(18)–P–C(24)	103.97(15)	C(3)–O–C(17)	116.5(2)
P–C(1)–C(2)	124.5(2)	P–C(1)–C(10)	121.3(2)
C(2)–C(1)–C(10)	113.7(3)	C(1)–C(2)–C(2A)	128.6(3)
C(1)–C(2)–C(3)	113.2(2)	C(2A)–C(2)–C(3)	118.1(2)
O–C(3)–C(2)	108.4(2)	O–C(3)–C(4)	115.6(3)
O–C(3)–C(16)	115.3(3)	C(2)–C(3)–C(4)	104.7(2)
C(2)–C(3)–C(16)	103.8(2)	C(4)–C(3)–C(16)	107.8(2)
C(3)–C(4)–C(5)	127.1(3)	C(3)–C(4)–C(9)	112.7(3)
C(5)–C(4)–C(9)	120.0(3)	C(4)–C(5)–H(5A)	120.7
C(4)–C(5)–C(6)	118.7(3)	H(5A)–C(5)–C(6)	120.7
C(5)–C(6)–H(6A)	119.2	C(5)–C(6)–C(7)	121.7(4)
H(6A)–C(6)–C(7)	119.2	C(6)–C(7)–H(7A)	120.2
C(6)–C(7)–C(8)	119.6(3)	H(7A)–C(7)–C(8)	120.2
C(7)–C(8)–H(8A)	120.5	C(7)–C(8)–C(9)	119.0(3)
H(8A)–C(8)–C(9)	120.5	C(4)–C(9)–C(8)	121.0(3)
C(4)–C(9)–C(10)	112.9(3)	C(8)–C(9)–C(10)	125.9(3)
C(1)–C(10)–C(9)	104.5(2)	C(1)–C(10)–H(10A)	112.8
C(1)–C(10)–C(11)	106.0(2)	C(9)–C(10)–H(10A)	112.8
C(9)–C(10)–C(11)	107.1(3)	H(10A)–C(10)–C(11)	112.8
C(10)–C(11)–C(12)	127.0(3)	C(10)–C(11)–C(16)	113.3(3)
C(12)–C(11)–C(16)	119.6(3)	C(11)–C(12)–H(12A)	120.0

C(11)–C(12)–C(13)	120.0(3)	H(12A)–C(12)–C(13)	120.0
C(12)–C(13)–H(13A)	119.8	C(12)–C(13)–C(14)	120.3(3)
H(13A)–C(13)–C(14)	119.8	C(13)–C(14)–H(14A)	120.1
C(13)–C(14)–C(15)	119.9(3)	H(14A)–C(14)–C(15)	120.1
C(14)–C(15)–H(15A)	120.3	C(14)–C(15)–C(16)	119.4(3)
H(15A)–C(15)–C(16)	120.3	C(3)–C(16)–C(11)	112.4(3)
C(3)–C(16)–C(15)	127.0(3)	C(11)–C(16)–C(15)	120.6(3)
O–C(17)–H(17A)	109.5	O–C(17)–H(17B)	109.5
O–C(17)–H(17C)	109.5	H(17A)–C(17)–H(17B)	109.5
H(17A)–C(17)–H(17C)	109.5	H(17B)–C(17)–H(17C)	109.5
P–C(18)–C(19)	118.9(3)	P–C(18)–C(23)	121.6(3)
C(19)–C(18)–C(23)	119.4(3)	C(18)–C(19)–H(19A)	119.9
C(18)–C(19)–C(20)	120.1(3)	H(19A)–C(19)–C(20)	119.9
C(19)–C(20)–H(20A)	120.0	C(19)–C(20)–C(21)	120.0(4)
H(20A)–C(20)–C(21)	120.0	C(20)–C(21)–H(21A)	119.9
C(20)–C(21)–C(22)	120.3(3)	H(21A)–C(21)–C(22)	119.9
C(21)–C(22)–H(22A)	119.8	C(21)–C(22)–C(23)	120.3(4)
H(22A)–C(22)–C(23)	119.8	C(18)–C(23)–C(22)	119.9(3)
C(18)–C(23)–H(23A)	120.1	C(22)–C(23)–H(23A)	120.1
P–C(24)–C(25)	116.8(3)	P–C(24)–C(29)	123.9(3)
C(25)–C(24)–C(29)	119.3(3)	C(24)–C(25)–H(25A)	119.9
C(24)–C(25)–C(26)	120.2(4)	H(25A)–C(25)–C(26)	119.9
C(25)–C(26)–H(26A)	120.0	C(25)–C(26)–C(27)	119.9(4)
H(26A)–C(26)–C(27)	120.0	C(26)–C(27)–H(27A)	119.9
C(26)–C(27)–C(28)	120.2(4)	H(27A)–C(27)–C(28)	119.9
C(27)–C(28)–H(28A)	119.7	C(27)–C(28)–C(29)	120.6(4)
H(28A)–C(28)–C(29)	119.7	C(24)–C(29)–C(28)	119.7(3)
C(24)–C(29)–H(29A)	120.1	C(28)–C(29)–H(29A)	120.1

Symmetry operations for equivalent atoms
A −x,y,−z+1/2

Table 4. Anisotropic displacement parameters ($Å^2$) for sd315. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ...+ 2hka^*b^*U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Au	0.01894(8)	0.01636(8)	0.01422(7)	0.00437(4)	0.00116(5)	–0.00354(5)
P	0.0151(4)	0.0132(4)	0.0115(3)	0.0014(3)	0.0026(3)	–0.0031(3)
Cl	0.0323(5)	0.0283(5)	0.0204(4)	0.0111(3)	–0.0003(3)	–0.0014(4)
O	0.0219(13)	0.0155(12)	0.0152(10)	–0.0018(9)	0.0048(9)	–0.0085(9)
C(1)	0.0158(16)	0.0123(15)	0.0091(13)	0.0029(11)	0.0021(12)	–0.0002(12)
C(2)	0.0133(16)	0.0129(15)	0.0127(14)	0.0023(12)	0.0060(12)	0.0030(12)
C(3)	0.0160(16)	0.0139(15)	0.0105(14)	–0.0006(11)	0.0044(12)	–0.0045(12)
C(4)	0.0196(17)	0.0188(17)	0.0102(14)	0.0057(12)	0.0072(12)	0.0024(13)
C(5)	0.034(2)	0.0202(18)	0.0172(15)	0.0026(13)	0.0101(14)	0.0008(15)
C(6)	0.042(2)	0.025(2)	0.031(2)	0.0089(16)	0.0134(18)	0.0165(18)
C(7)	0.033(2)	0.042(2)	0.0229(18)	0.0139(17)	0.0067(16)	0.0178(19)
C(8)	0.0239(19)	0.035(2)	0.0164(16)	0.0060(14)	0.0059(14)	–0.0010(16)
C(9)	0.0214(18)	0.0197(17)	0.0086(13)	0.0064(12)	0.0047(12)	0.0016(14)
C(10)	0.0167(17)	0.0182(16)	0.0103(14)	0.0021(12)	–0.0002(12)	–0.0058(13)
C(11)	0.0166(17)	0.0136(15)	0.0101(13)	0.0045(11)	0.0016(12)	–0.0026(13)
C(12)	0.034(2)	0.0166(17)	0.0129(15)	–0.0025(12)	0.0060(14)	–0.0062(15)
C(13)	0.038(2)	0.0194(18)	0.0202(16)	–0.0043(14)	0.0131(15)	0.0020(16)
C(14)	0.0225(19)	0.028(2)	0.0225(17)	–0.0007(14)	0.0120(14)	0.0007(15)
C(15)	0.0203(18)	0.0206(18)	0.0166(15)	–0.0008(13)	0.0066(13)	–0.0039(14)
C(16)	0.0215(17)	0.0096(15)	0.0094(13)	0.0028(11)	0.0035(12)	0.0010(13)
C(17)	0.034(2)	0.0200(19)	0.0309(19)	–0.0018(15)	0.0156(16)	–0.0124(16)
C(18)	0.0183(17)	0.0183(17)	0.0131(14)	–0.0008(12)	0.0068(12)	–0.0080(13)
C(19)	0.0240(19)	0.0209(18)	0.0240(17)	–0.0031(14)	0.0084(15)	–0.0042(15)
C(20)	0.036(2)	0.026(2)	0.038(2)	–0.0121(17)	0.0152(18)	–0.0055(17)
C(21)	0.037(2)	0.036(2)	0.0227(18)	–0.0127(16)	0.0095(17)	–0.0172(18)
C(22)	0.030(2)	0.041(2)	0.0196(17)	–0.0016(16)	–0.0010(15)	–0.0136(19)
C(23)	0.025(2)	0.0229(18)	0.0218(16)	0.0006(14)	0.0033(14)	–0.0039(15)
C(24)	0.0147(16)	0.0222(17)	0.0147(14)	–0.0026(13)	0.0017(12)	–0.0010(13)
C(25)	0.027(2)	0.0251(19)	0.0294(18)	–0.0065(15)	0.0139(16)	–0.0095(16)
C(26)	0.027(2)	0.044(3)	0.042(2)	–0.0093(19)	0.0198(18)	–0.0097(19)
C(27)	0.0142(19)	0.053(3)	0.038(2)	–0.0094(19)	0.0053(16)	0.0035(18)
C(28)	0.028(2)	0.033(2)	0.0280(19)	0.0022(16)	0.0014(16)	0.0092(17)
C(29)	0.0233(19)	0.0279(19)	0.0159(15)	0.0049(13)	0.0064(14)	0.0031(15)

Table 5. Hydrogen coordinates and isotropic displacement parameters ($Å^2$) for sd315.

	x	y	z	U
H(5A)	–0.0500	1.4328	0.1718	0.028
H(6A)	–0.1874	1.4831	0.1166	0.038
H(7A)	–0.2916	1.3912	0.0573	0.039
H(8A)	–0.2588	1.2447	0.0525	0.030
H(10A)	–0.1489	1.1215	0.0875	0.019
H(12A)	–0.0426	1.0744	0.0224	0.025
H(13A)	0.0986	1.0775	0.0065	0.030
H(14A)	0.2092	1.1591	0.0709	0.028
H(15A)	0.1763	1.2441	0.1489	0.023
H(17A)	0.1780	1.3754	0.2002	0.040
H(17B)	0.0983	1.4368	0.2052	0.040
H(17C)	0.0907	1.3794	0.1447	0.040
H(19A)	–0.1138	0.8979	0.1772	0.027
H(20A)	–0.1783	0.8073	0.0947	0.039
H(21A)	–0.3016	0.8519	0.0202	0.038
H(22A)	–0.3624	0.9856	0.0275	0.038
H(23A)	–0.2990	1.0768	0.1093	0.028
H(25A)	–0.2800	1.0260	0.2717	0.031
H(26A)	–0.3993	1.0969	0.2935	0.043
H(27A)	–0.4229	1.2418	0.2690	0.042
H(28A)	–0.3312	1.3140	0.2204	0.037
H(29A)	–0.2128	1.2434	0.1957	0.027

Table 6. Torsion angles [°] for sd315.

Cl–Au–P–C(1)	176.6(2)	Cl–Au–P–C(18)	–59.4(2)
Cl–Au–P–C(24)	54.5(2)	Au–P–C(1)–C(2)	–40.2(3)
Au–P–C(1)–C(10)	148.6(2)	C(18)–P–C(1)–C(2)	–166.3(3)
C(18)–P–C(1)–C(10)	22.5(3)	C(24)–P–C(1)–C(2)	83.6(3)
C(24)–P–C(1)–C(10)	–87.6(3)	P–C(1)–C(2)–C(2A)	8.1(5)
P–C(1)–C(2)–C(3)	–169.1(2)	C(10)–C(1)–C(2)–C(2A)	179.8(3)
C(10)–C(1)–C(2)–C(3)	2.6(4)	C(17)–O–C(3)–C(2)	179.7(3)
C(17)–O–C(3)–C(4)	–63.2(4)	C(17)–O–C(3)–C(16)	63.9(4)
C(1)–C(2)–C(3)–O	178.4(3)	C(1)–C(2)–C(3)–C(4)	54.4(3)
C(1)–C(2)–C(3)–C(16)	–58.5(3)	C(2A)–C(2)–C(3)–O	0.9(4)
C(2A)–C(2)–C(3)–C(4)	–123.1(3)	C(2A)–C(2)–C(3)–C(16)	124.0(3)
O–C(3)–C(4)–C(5)	0.1(4)	O–C(3)–C(4)–C(9)	–175.9(2)
C(2)–C(3)–C(4)–C(5)	119.3(3)	C(2)–C(3)–C(4)–C(9)	–56.7(3)
C(16)–C(3)–C(4)–C(5)	–130.6(3)	C(16)–C(3)–C(4)–C(9)	53.4(3)
C(3)–C(4)–C(5)–C(6)	–176.7(3)	C(9)–C(4)–C(5)–C(6)	–1.0(5)
C(4)–C(5)–C(6)–C(7)	1.2(5)	C(5)–C(6)–C(7)–C(8)	0.0(6)
C(6)–C(7)–C(8)–C(9)	–1.3(5)	C(7)–C(8)–C(9)–C(4)	1.5(5)
C(7)–C(8)–C(9)–C(10)	175.6(3)	C(3)–C(4)–C(9)–C(8)	176.0(3)
C(3)–C(4)–C(9)–C(10)	1.2(4)	C(5)–C(4)–C(9)–C(8)	–0.3(5)
C(5)–C(4)–C(9)–C(10)	–175.1(3)	C(4)–C(9)–C(10)–C(1)	55.7(3)
C(4)–C(9)–C(10)–C(11)	–56.5(3)	C(8)–C(9)–C(10)–C(1)	–118.8(3)
C(8)–C(9)–C(10)–C(11)	129.0(3)	P–C(1)–C(10)–C(9)	113.2(3)
P–C(1)–C(10)–C(11)	–133.8(2)	C(2)–C(1)–C(10)–C(9)	–58.8(3)
C(2)–C(1)–C(10)–C(11)	54.2(3)	C(1)–C(10)–C(11)–C(12)	125.4(3)
C(1)–C(10)–C(11)–C(16)	–53.7(3)	C(9)–C(10)–C(11)–C(12)	–123.4(3)
C(9)–C(10)–C(11)–C(16)	57.5(3)	C(10)–C(11)–C(12)–C(13)	–176.9(3)
C(16)–C(11)–C(12)–C(13)	2.0(5)	C(11)–C(12)–C(13)–C(14)	1.1(5)
C(12)–C(13)–C(14)–C(15)	–2.0(5)	C(13)–C(14)–C(15)–C(16)	–0.4(5)
C(14)–C(15)–C(16)–C(3)	–179.6(3)	C(14)–C(15)–C(16)–C(11)	3.6(5)
C(10)–C(11)–C(16)–C(3)	–2.6(4)	C(10)–C(11)–C(16)–C(15)	174.7(3)
C(12)–C(11)–C(16)–C(3)	178.3(3)	C(12)–C(11)–C(16)–C(15)	–4.4(4)
O–C(3)–C(16)–C(11)	176.7(2)	O–C(3)–C(16)–C(15)	–0.4(4)
C(2)–C(3)–C(16)–C(11)	58.2(3)	C(2)–C(3)–C(16)–C(15)	–118.8(3)
C(4)–C(3)–C(16)–C(11)	–52.4(3)	C(4)–C(3)–C(16)–C(15)	130.6(3)
Au–P–C(18)–C(19)	–30.5(3)	Au–P–C(18)–C(23)	150.4(3)
C(1)–P–C(18)–C(19)	100.7(3)	C(1)–P–C(18)–C(23)	–78.3(3)
C(24)–P–C(18)–C(19)	–147.8(3)	C(24)–P–C(18)–C(23)	33.1(3)
P–C(18)–C(19)–C(20)	–178.2(3)	C(23)–C(18)–C(19)–C(20)	0.9(5)
C(18)–C(19)–C(20)–C(21)	–0.3(6)	C(19)–C(20)–C(21)–C(22)	–0.3(6)
C(20)–C(21)–C(22)–C(23)	0.4(6)	C(21)–C(22)–C(23)–C(18)	0.2(6)
P–C(18)–C(23)–C(22)	178.2(3)	C(19)–C(18)–C(23)–C(22)	–0.9(5)
Au–P–C(24)–C(25)	–44.8(3)	Au–P–C(24)–C(29)	134.2(3)
C(1)–P–C(24)–C(25)	–174.8(2)	C(1)–P–C(24)–C(29)	4.2(3)
C(18)–P–C(24)–C(25)	73.5(3)	C(18)–P–C(24)–C(29)	–107.6(3)
P–C(24)–C(25)–C(26)	–179.5(3)	C(29)–C(24)–C(25)–C(26)	1.5(5)
C(24)–C(25)–C(26)–C(27)	–1.6(6)	C(25)–C(26)–C(27)–C(28)	0.9(6)
C(26)–C(27)–C(28)–C(29)	–0.1(6)	P–C(24)–C(29)–C(28)	–179.6(3)
C(25)–C(24)–C(29)–C(28)	–0.6(5)	C(27)–C(28)–C(29)–C(24)	0.0(5)

Symmetry operations for equivalent atoms
A –x,y,–z+1/2