

Routes to organogold compounds and gold catalysed A³-coupling reactions

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Additional Material:

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Abbreviations

Å	Angstrom
Ac	Acetate
acac	acetylacetoneate
Au-np	gold nanoparticles
bipy	2,2-bipyridine
bmim	1-butyl-3-methylimidazolium
Bn	benzyl
box	bis oxazoline
Bpin	2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane
<i>n</i> -Bu	<i>n</i> -butyl
<i>n</i> BuLi	<i>n</i> -butyllithium
'Bu	tertiary butyl
'BuLi	tertiary butyllithium
COD	1,5-Cyclooctadiene
Cy	cyclohexyl
damp	2- <i>N,N</i> -dimethylaminomethylphenyl
DEAD	diethyl azodicarboxylate
(-)-DIOP	(-)-2,3-O-i-propylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethylsulfoxide
dppe	1,2-bis(diphenylphosphino)ethane

Et	ethyl
EtOH	ethanol
eq	equivalent
h	hour
Hz	hertz
Hptp	2-phenyl-6- <i>p</i> -toluidinopyridazine
ⁿ Hex	<i>n</i> -hexyl
hmim	1-hexyl-3-methylimidazolium
H ₂ TPP	<i>meso</i> -tetr phenylporphyrin
HPLC	High-performance Liquid Chromatography
IMes	1,3-bis(2,4,6-trimethylphenyl)-imidazolin-2-ylidene
IPr	1,3-bis(2,6-diisopropylphenyl)-imidazolin-2-ylidene
M	molar
MAO-B	monoamine oxidase type B
MCM	mobile crystalline material
Me	methyl
mg	milligram
MHz	megahertz
min	minute
mL	millilitre
mm	millimetre
mmHg	millimetre of mercury
mmol	millimole

MOF	metal-organic framework
mol	mole
μL	microlitre
NBS	<i>N</i> -bromosuccinimide
NHC	<i>N</i> -heterocyclic carbene
nm	nanometre
NMR	Nuclear Magnetic Resonance
octmim	1-octyl-3-methylimidazolium
ODG	ortho directing group
ORTEP	Oak Ridge Thermal Ellipsoid Plot
PEG	polyethylene glycol
Ph	phenyl
PhLi	phenyllithium
Piv	pivalate
ppm	parts per million
ⁿ Pr	<i>n</i> -propyl
ⁱ Pr	isopropyl
ⁱ PrOH	isopropyl alcohol
py	pyridine
pybox	bis(oxazolinyl)pyridine
PVC	polyvinyl chloride
QELS	quasi elastic light scattering
RA	rheumatoid arthritis

r.t.	room temperature
TEMPO	2,2,6,6-tetramethylpiperidine-1-oxyl
TIPSCl	triisopropylsilylchloride
THT	tetrahydrothiophene
TMEDA	<i>N,N,N,N-</i> tetramethylethylenediamine
TMSCl	trimethylsilylchloride
TOF	turnover frequency
TON	turnover number
Ts	tosyl
UV	ultra violet

Abstract

The University of Manchester

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PhD

Routes to organogold compounds and gold catalysed A³-coupling reactions

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A new route to the synthesis of cyclometallated gold(III) complexes containing functionalised (2-dimethylaminomethyl)phenyl ligands is described. The synthesis of 2-Me₂NCH₂-C₆H₄AuCl₂ (**8a**), 2-Me₂NCH₂-5-CH₃-C₆H₃AuCl₂ (**49**), 2-Me₂NCH₂-5-CF₃-C₆H₃AuCl₂ (**50**) and 2-Me₂NCH₂-5-OMe-C₆H₃AuCl₂ (**51**) has been accomplished *via* transmetallation from the corresponding boroxines to sodium tetrachloroaurate in aqueous acetonitrile. This protocol gives comparable yields to those obtained *via* transmetallation from an organomercurial. However this route is advantageous as it avoids the use of extremely toxic mercury compounds.

The novel bimetallic tin(IV) complexes 1,4-(SnPh₃)₂-2,5-(NMe₂CH₂)₂-C₆H₂ (**66**), 1,4-(SnMe₃)₂-2,5-(NMe₂CH₂)₂-C₆H₂ (**67**) and 1,4-(SnMe₂Cl)₂-2,5-(NMe₂CH₂)₂-C₆H₂ (**68**) have been synthesised by *in-situ* quenching of 1,4-(Li)₂-2,5-(NMe₂CH₂)₂-C₆H₂ (**57**) with two equivalents of ClSnPh₃, ClSnMe₃ or Cl₂SnMe₂ respectively. Transmetallation from 1,4-(SnMe₂Cl)₂-2,5-(NMe₂CH₂)₂-C₆H₂ (**68**) with two equivalents of sodium tetrachloroaurate in refluxing acetonitrile resulted in the formation of the relatively insoluble di-gold(III) complex 1,4-(AuCl₂)₂-2,5-(NMe₂CH₂)₂-C₆H₂ (**71**).

The novel bisphosphine 1,4-(PPh₂)₂-2,5-(NMe₂CH₂)₂-C₆H₂ (**69**) has also been prepared by *in-situ* quenching of 1,4-(Li)₂-2,5-(NMe₂CH₂)₂-C₆H₂ (**57**) with two equivalents of ClPPh₂. **69** was reacted with ClAu(THT) to form the novel di-gold(I) phosphine complex 1,4-(ClAuPPh₂)₂-2,5-(NMe₂CH₂)₂-C₆H₂ (**70**) in excellent yield.

The catalytic activity of a variety of gold(I) and gold(III) complexes in the A³-coupling of aldehydes, amines and alkynes has been investigated. 2-Me₂NCH₂-C₆H₄AuCl₂ (**8a**) was found to be an effective catalyst for A³-couplings, with H₂O as solvent, giving essentially quantitative conversions after 24 h. The couplings were tolerant to a diverse range of substrates. A range of chiral Au(III) and Au(I) complexes were prepared and screened in the reaction of benzaldehyde, dibenzylamine and phenylacetylene. In all cases no discernible ee was observed. A series of A³-coupling reactions catalysed by **8a**, Na[AuCl₄].2H₂O and [AuCCPh]_n (**139**) were also monitored by ¹H NMR spectroscopy and this data suggests a common, catalytically active species, is formed during these reactions. The addition of PPh₃ to the gold catalysed couplings was found to severely retard the reactions. In contrast the use of chloroform as the solvent resulted in significant improvements to the rate of reaction. Overall the data collected provides a mechanistic insight into the development of asymmetric A³-coupling reactions. The evidence suggests that a single universal catalytically active acetylide species is formed from both Au(I) and Au(III) precursors.

Declaration

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1 The Chemistry of Gold

1.1 Introduction

Gold is a third row transition metal located in Group 11 of the periodic table, along with copper and silver, and has an outer shell electron configuration of $5d^{10}6s^1$. Gold is a noble metal that is widely found in metallic form in nature, and is endowed with a high ductility and malleability.^{1,2} Metallic gold is relatively chemically inert and does not react with common chemical reagents or light explaining its prevalence in jewellery.³ The chemistry of gold is remarkably different to that of other metals, and is dominated by relativistic effects.⁴ Relativistic effects arise from the high speeds attained by electrons when they move near a heavy nucleus.⁵⁻⁷ This results in a stabilisation and relativistic contraction of the 6s orbitals in gold. This in turn leads to an expansion and de-stabilisation of the 5d orbitals which enables access to higher oxidation states. Due to gold's unique position in the periodic table, a relativistic maximum exists for this element, which can cause as much as 20% 6s orbital contraction.⁸ Figure 1.1.1 illustrates the special position of gold in the periodic table and the contribution of relativistic effects to the radii of the 6s orbital. The contraction of the 6s shell in gold confers a greater stability on the metallic state, and also explains the higher than expected electron affinity of gold.^{4,9} Relativistic effects also help to explain many of the similarities and differences between the 5th and 6th row of the periodic table. One striking example is that the covalent radius of gold(I) is smaller than that for silver(I).¹⁰

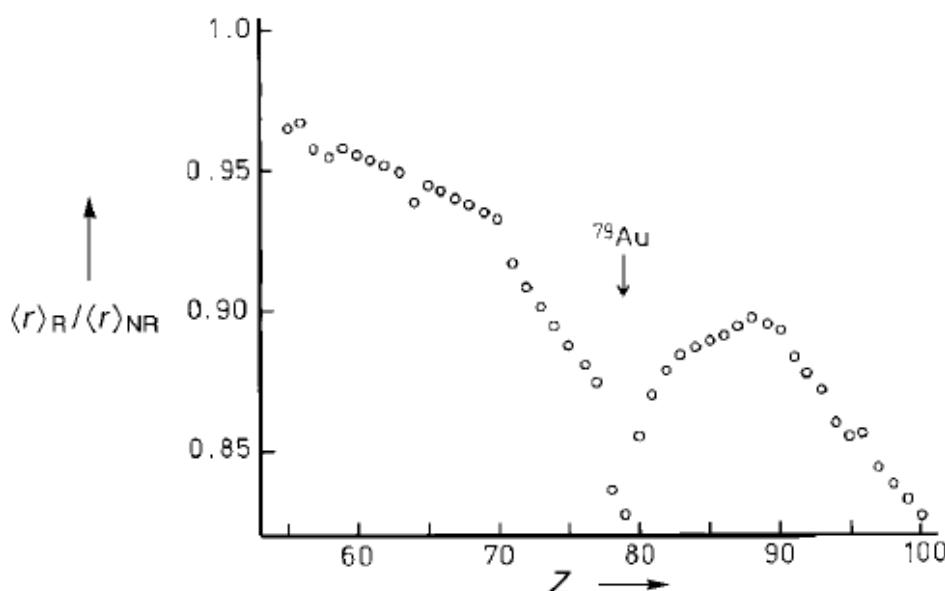


Figure 1.1.1: The relativistic contraction of the 6s shell in elements Cs to Fm. Taken from Pyykko and Desclaux,⁸ with the numbers taken from the Dirac-Fock and Hartree-Fock calculations of Desclaux.¹¹

1.2 Oxidation states of gold

1.2.1 Gold(I) complexes

Gold(I) is the most prevalent, and well studied oxidation state of the metal.⁴ Ligands utilising soft sulfur and phosphorus donor sets are favoured due to the “soft” Au(I) cation.¹² Gold(I) organometallics and *N*-heterocyclic carbene complexes are also well known,^{13,14} and interest in these areas has intensified recently due to the excellent catalytic activity and medicinal properties that these compounds display.^{15–18} The electronic configuration of Au(I) is [Xe] 4f¹⁴ 5d¹⁰ and the most common geometry for gold(I) complexes is linear, two coordinate, with angles around the Au centre approaching 180 °. One of the most intensely investigated and hotly debated topics in modern gold chemistry is that of Au⋯⋯Au contacts. The aurophilic interaction or aurophilicity as coined by Schmidbaur *et al.*¹⁹ is the tendency of gold in some of its compounds to be ‘attracted’ to other gold atoms. This unusual interaction was first reported by Jones during the course of his X-ray crystallographic investigations of gold compounds,^{20–22} and predominately occurs between closed shell d¹⁰ gold(I) centres. The interaction is reported to be similar in strength to hydrogen bonding,^{6,23} and is believed to be due to a combination of correlation and relativistic effects.²⁴ The typical range of distances quoted for Au⋯⋯Au contacts in the literature is generally between 2.8 and 3.5 Å,^{25,26} although recently it has been suggested that gold(I)-gold(I) contacts can be justified up to a distance of 4 Å.²⁷ Numerous examples of aurophilic interactions now exist, and the reader’s attention is directed towards the excellent reviews of Schmidbaur and Schier,²⁵ and Tiekkink *et al.*²⁸ for a more comprehensive overview.

1.2.2 Gold(III) complexes

Compounds with gold in the +3 oxidation state are also common and have received extensive investigation. Au(III) is a “harder” metal cation than gold(I),¹² and so forms stable complexes with nitrogen, sulfur, phosphorus, carbon and oxygen based ligands.⁴ However due to the relative instability of gold(III) compounds with respect to reduction,²⁹ complexes are typically prepared utilising multidentate ligands in a bid to stabilise the gold(III) centre. Gold(III) has an electronic configuration of [Xe] 4f¹⁴ 5d⁸, and its compounds usually assume a square planar coordination geometry.³⁰ This means that

Au(III) and Pt(II) are essentially isostructural and isoelectronic, thus many gold(III) compounds have been investigated for their antitumour properties due to the clinical success of Pt(II) based drugs.³¹

1.2.3 Other oxidation states

Complexes of gold with metal oxidation states other than +1 and +3 are known in the literature, however they are rare in comparison to the abundance of reports on gold(I) and gold(III) complexes. Currently complexes with gold oxidation states of 0,^{32,33} -1,³⁴ +2,^{35,36} and +5^{37,38} have been described, although many of these are outside the scope of this report, and are therefore not discussed further. The excellent article by Laguna *et al.*⁴ gives a more detailed overview of the various oxidation states of gold in Au complexes.

1.3 Uses of gold complexes

Gold complexes have been investigated for use in a wide range of potential applications. Chief among these is their use as efficient catalysts, for an ever-growing number of organic reactions, and also their efficacy as anticancer drugs. What follows is a brief overview of some of the key developments in these areas, highlighting the unique properties of gold.

1.3.1 Medicinal applications

The first known examples of gold being used in medicine date back as far as 2500 BC, and originate from Ancient China, where gold elixirs were taken to provide ‘eternal life’ and also used to treat a range of ailments.³⁹ The modern day use of gold in medicinal applications began with the observations of Robert Koch in 1890.⁴⁰ Koch discovered that dilute solutions of gold cyanide ($K[Au(I)(CN)_2]$) exhibited antibacterial activity against tuberculosis,⁴⁰ although later studies showed this was not a particularly effective treatment.⁴¹ This led to numerous therapeutic trials being carried out with gold salts, before Forestier found that gold drugs may provide treatment for rheumatoid arthritis (RA).^{42,43} Currently much of the biological work with gold complexes is directed towards their interesting anticancer properties. A detailed examination of the medicinal properties of

gold compounds is beyond the scope of this report, however a number of reviews on the topic have been compiled.^{18,30,31,44,45} Here a brief summary of the major breakthroughs and recent studies are described. Preliminary work on the anticancer activity of gold(I) complexes was carried out by Mirabelli *et al.*⁴⁶ who prepared 63 gold(I) compounds (selected examples displayed in Figure 1.3.1) and investigated their cytotoxicity in melanoma and leukaemia models. Gold(I) thiolates exhibited a low activity, while the presence of a phosphine ligand improved the compounds activity.

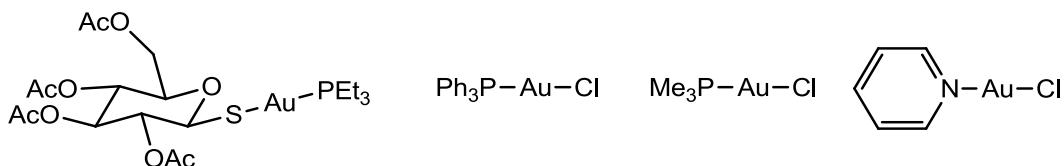


Figure 1.3.1: Examples of gold(I) complexes investigated by Mirabelli and co-workers.⁴⁶

Subsequently a number of gold(I) compounds have demonstrated anticancer activity across a range of tumour cell-lines.^{47–49} A large body of work has also been carried out on the anticancer properties of gold(III) complexes. This is mainly due to the observation that gold(III) is isostructural and isoelectronic with platinum(II), and therefore gold(III) complexes analogous to cisplatin [$\text{Pt}(\text{NH}_3)_2\text{Cl}_2$]⁵⁰ can be prepared. A number of complexes containing nitrogen,^{51,52} sulfur^{53,54} and carbon based ligands have demonstrated anticancer activity. Recently Ronconi *et al.* have demonstrated very promising results with the use of gold(III) dithiocarbamate complexes as antitumour agents.^{53,54} These complexes displayed a higher activity than cisplatin in the prostate cancer cell lines tested, and *in-vivo* testing in mice gave a remarkable *ca.* 85% reduction in tumour cell mass after 19 days treatment. The most detailed work in this area has concerned the use of complexes of the type $[\text{AuX}_2(\eta^2\text{-C,N-C}_6\text{H}_4\text{-2-CH}_2\text{NMe}_2)]$, containing the bidentate *N,N*-dimethylbenzylamine ligand. A range of compounds with X = Cl, O₂CMe, SCN or X₂ = oxalate or malonato have been screened with the complexes displaying a similar activity to that of cisplatin.^{55–57} The acetate and malonato derivatives generally displayed the best activity. It was thought that the C,N chelate stabilised the gold(III) centre towards reduction. Furthermore mechanistic studies indicated a distinct mode of action from cisplatin.⁵⁸ The acetate complex was found to readily hydrolyse in solution, so it was concluded that the active species was not the original complex.⁵⁵ Subsequently Henderson and co-workers⁵⁹ demonstrated the activity of gold(III) complexes that contain a C,N chelate derived dimethylbenzylamine and a second metallacyclic ring. Other cycloaurated complexes

possessing the 2-phenylpyridine template have been investigated,⁶⁰ and found to have a higher activity than cisplatin in human leukaemia cell lines. Furthermore Che *et al.*⁶¹ have also prepared cyclometallated complexes with the C^NC (2,6-diphenylpyridine) ligand. The resultant [Au(C^NC)X]ⁿ⁺ complexes displayed anticancer activity comparable to that of cisplatin across a range of cell lines. The complexes were observed to induce apoptosis in cancer cells and bind strongly to DNA by intercalation. Figure 1.3.2 displays some of the gold(III) compounds that have been investigated for their anticancer properties.

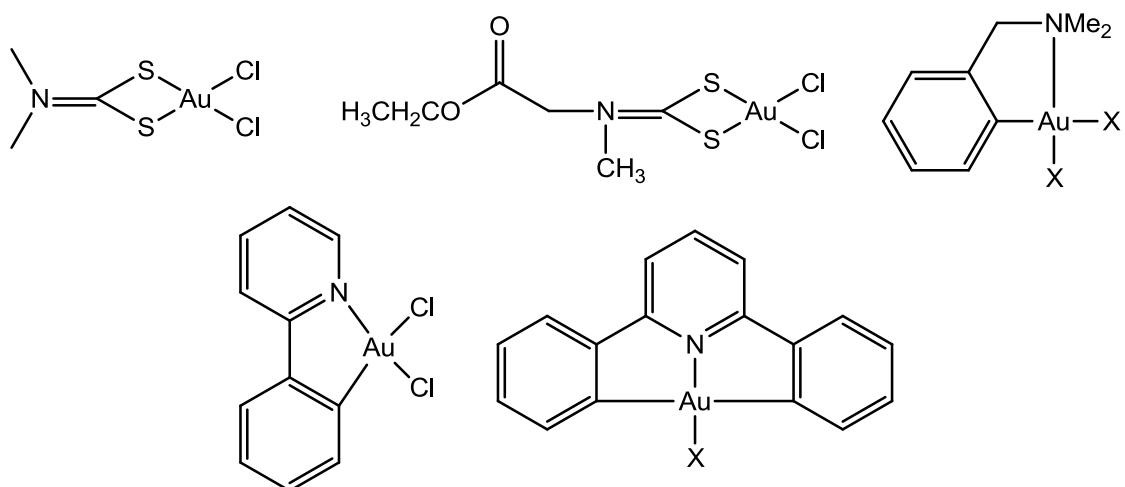
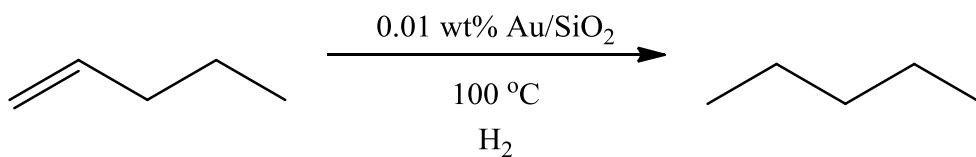


Figure 1.3.2: Selected examples of gold(III) compounds that show promising anticancer activity. X = Cl, O₂CMe, SCN.

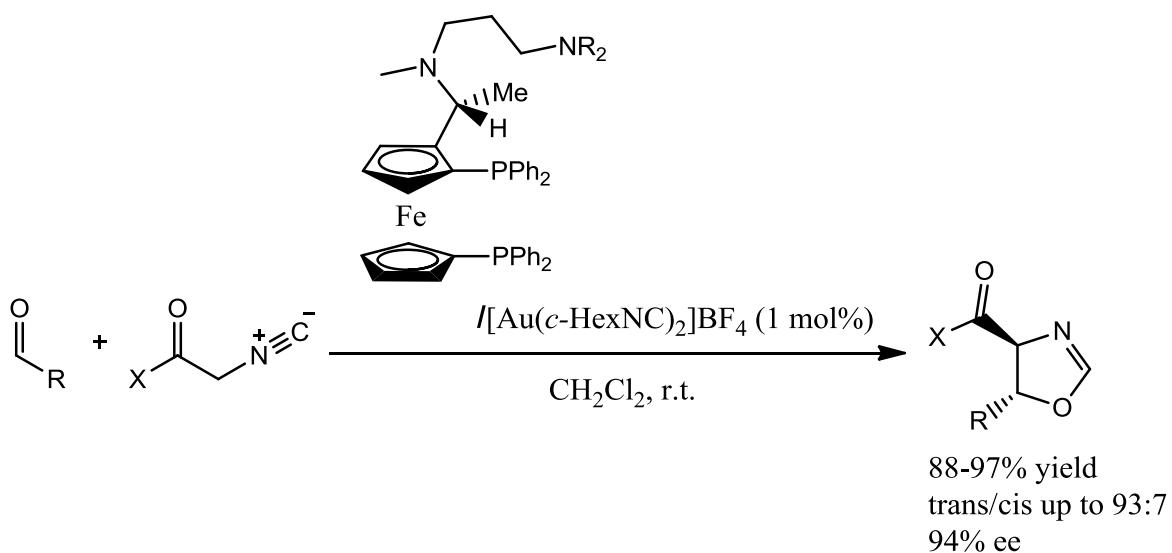
1.3.2 Catalysis using gold complexes

For many years gold was believed to have little or no potential for catalytic activity and so the element was somewhat neglected in the field of transition metal catalysis.¹⁵ Recently however the use of gold in both homogeneous and heterogeneous catalysis has undergone rapid expansion. The key developments in this area were the reports by Bond *et al.*,^{62,63} who in 1973 demonstrated gold catalysed hydrogenation of alkenes (Scheme 1.3.1). Hydrogenation was possible at 100–217 °C with gold on silica, γ-alumina or boehmite.



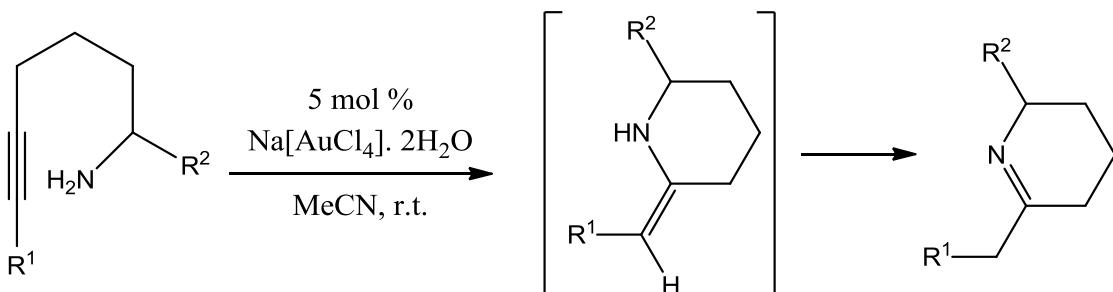
Scheme 1.3.1: Gold catalysed hydrogenation of pent-1-ene as reported by Bond and co-workers.⁶³

Subsequently Haruta *et al.*⁶⁴ and Hutchings⁶⁵ simultaneously reported the use of heterogeneous gold catalysts for the oxidation of carbon monoxide at low temperature, and the hydrochlorination of acetylene. The major breakthrough in homogeneous gold catalysis came when Ito and co-workers⁶⁶ used a chiral ferrocenylphosphine-gold(I) catalyst for the asymmetric synthesis of oxazolines (Scheme 1.3.2).



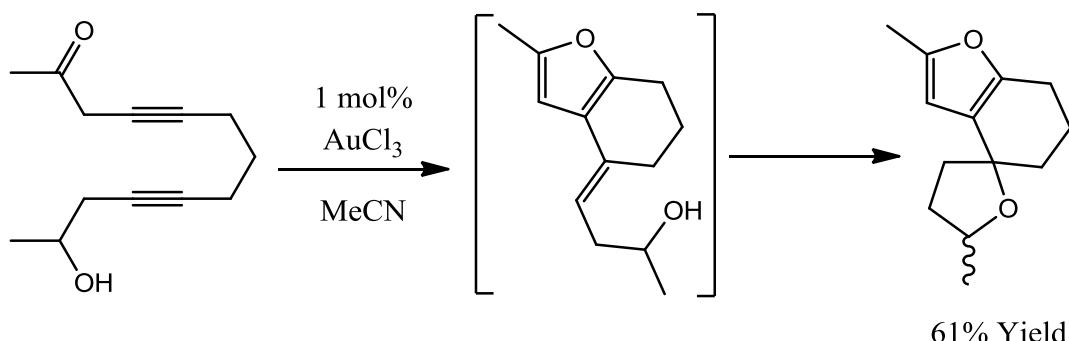
Scheme 1.3.2: Asymmetric synthesis of oxazolines using a chiral ferrocenylphosphine-gold(I) catalyst.⁶⁶

Generally the most common gold catalysed reactions are nucleophilic additions to C-C multiple bonds, be that alkynes, alkenes or allenes.^{15,67} These reactions proceed via prior coordination of the electrophilic gold centre to C-C multiple bonds which activates them, making them susceptible to nucleophilic attack. An early example in this area is that of Utimoto *et al.*^{68,69} who used Na[AuCl₄] to catalyse the intramolecular hydroamination of 5-alkynylamines (Scheme 1.3.3). The first step involves the addition of the amine to the alkyne, followed by tautomerization of the intermediate enamine to give the imine product in quantitative yield.



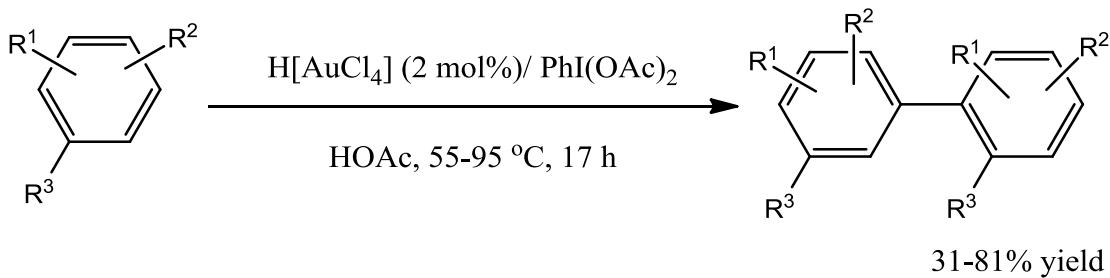
Scheme 1.3.3: Intramolecular hydroamination of 5-alkynylamines catalysed by Na[AuCl₄].^{68,69}

Following this Hashmi and co-workers⁷⁰ extended the scope of nucleophilic addition reactions to cover the intramolecular addition of alcohols to alkenes (Scheme 1.3.4).



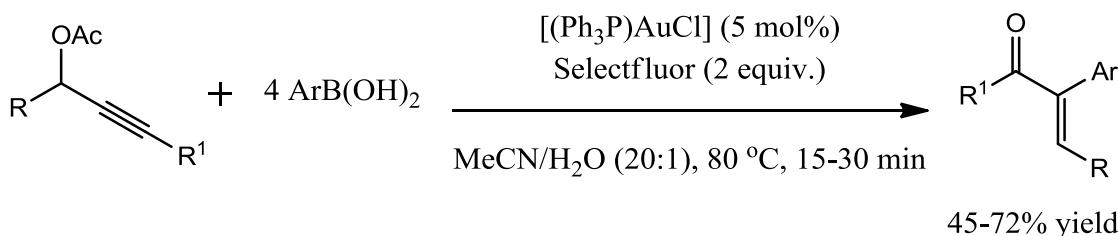
Scheme 1.3.4: First intramolecular addition of hydroxy group to alkene.⁷⁰

Gold catalysed nucleophilic additions to C-C multiple bonded species remain an active area of research, with much work being undertaken in order to expand the range of substrates available for reaction. Recently progress has been made in the area of gold catalysed C-C cross coupling reactions. Homo- and cross-coupling reactions are useful tools in organic synthesis as they enable the synthesis of important functionalised organic compounds. Palladium catalysed couplings are well-known^{71,72} although gold catalysed couplings have begun to receive increased attention. The coupling reactions are presumed to proceed *via* a Au(I)/Au(III) redox cycle, and it has been found that an external oxidant is required in order to oxidise from Au(I) to Au(III) in homogeneous systems.^{73–75} The first gold catalysed C-C coupling reaction was reported by Tse *et al.*⁷⁶ in 2008 who described the oxidative homo-coupling of a range of arenes (Scheme 1.3.5). The biaryls were obtained in moderate to good yields using 2 mol% loading of H[AuCl₄] and phenyliodinium diacetate as the external oxidant.



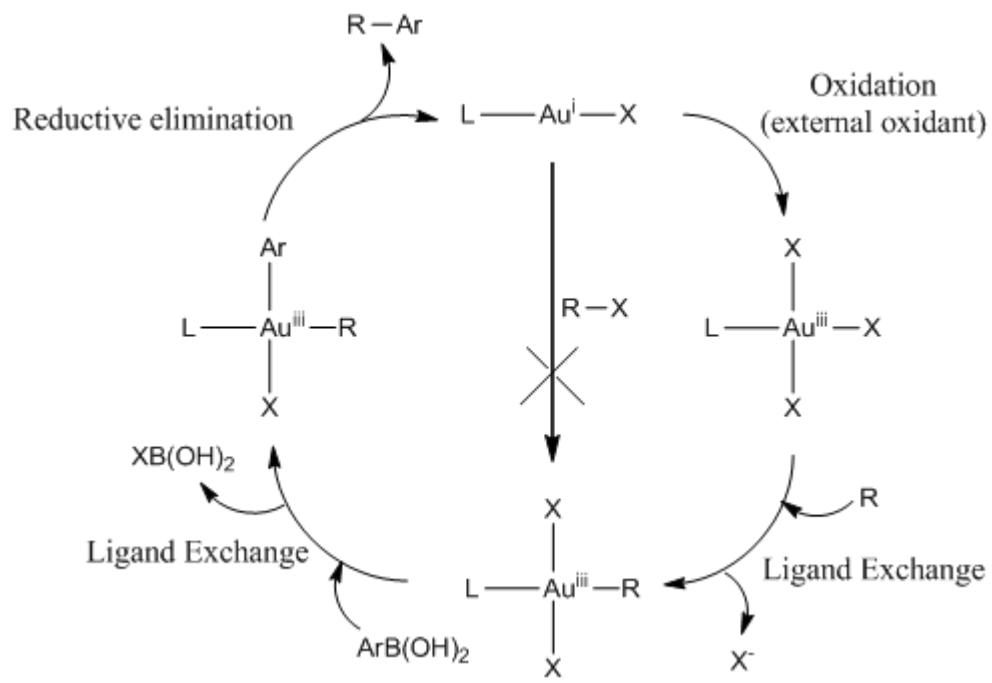
Scheme 1.3.5: Homo-coupling reactions catalysed by H[AuCl₄] as reported by Tse and co-workers.⁷⁶

Subsequently gold catalysed Suzuki and Sonogashira couplings have been explored.^{77,78} Couplings utilising arylboronic acids and a gold catalyst in combination with Selectfluor® are generally the most popular reactions. Zhang *et al.*⁷⁹ used a triphenylphosphine gold(I) chloride/ Selectfluor® system for the cross-coupling of propargylic acetates and aryl boronic acids (Scheme 1.3.6).



Scheme 1.3.6: Gold catalysed coupling utilising arylboronic acids, as reported by Zhang and co-workers.⁷⁹

The exact mechanism of these gold catalysed C-C coupling reactions has not been established, but a tentative proposal has been made (Scheme 1.3.7).⁸⁰⁻⁸² The first step in the catalytic cycle is the oxidation of Au(I) to Au(III) utilising an external oxidant. Given that gold(I) complexes tend to be unreactive with respect to C-X oxidative addition⁸³ an external oxidant is required to enable access to gold(III) intermediates that participate in C-C couplings. The LAuX₃ complex formed from oxidation undergoes ligand exchange with organic group to give LAuX₂R. Transmetallation with an aryl boronic acid then takes place followed by reductive elimination to give the C-C coupled product. One of the key intermediate steps is believed to involve transmetallation from an arylboronic acid to a gold(III) centre, however no direct evidence of the transmetallation has been presented. The field of gold-catalysis has undergone enormous expansion in recent years and now covers a large number of organic transformations. Originally, gold was used as a Lewis acid catalyst for the addition of nucleophiles to alkynes and olefins, however new methodologies such as C-C coupling are rapidly emerging and it is expected that the area of gold catalysis will continue to expand apace. For a detailed examination of gold catalysis the reader is referred to reviews by Hashmi,^{15,67,84,85} Hopkinson,⁸¹ Wegner⁸⁰ and Toste.⁸⁶

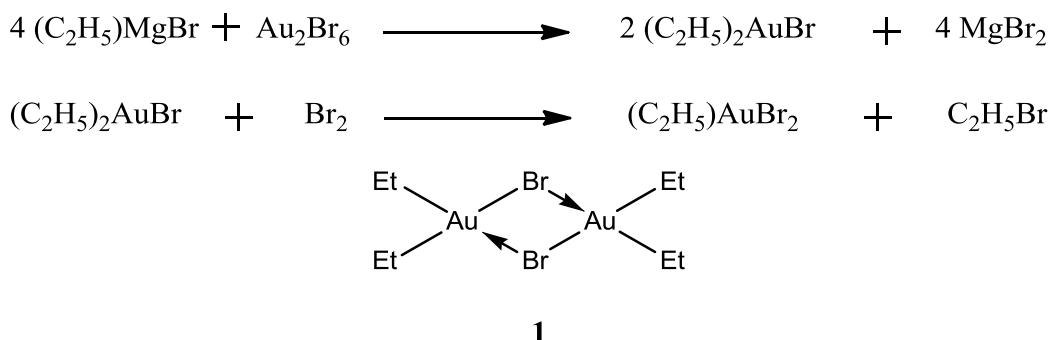


Scheme 1.3.7: Proposed mechanism for C-C coupling catalysed by Au/Selectfluor[®].⁸¹

2 Gold Organometallics

2.1 Introduction

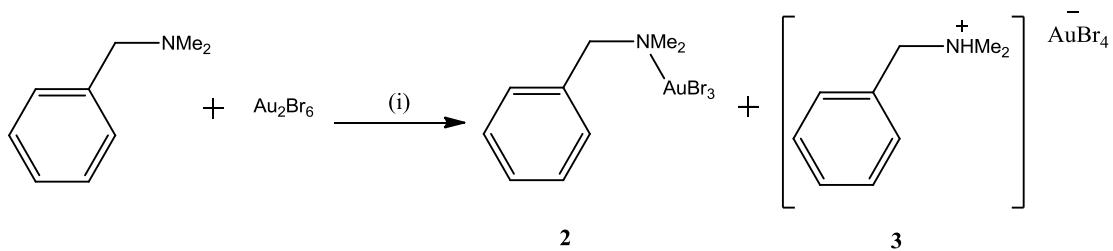
In 1907 Pope and Gibson prepared the first examples of gold complexes containing Au-C σ bonds.^{87,88} These authors described the reaction between ethylmagnesium bromide and auric bromide in dry diethyl ether to give diethylauric bromide (**1**) albeit in low yield, where the identity of the product was established by elemental analysis (Scheme 2.1.1). Subsequent investigations over thirty years later by Gibson suggested that the auric bromide used was in fact $\text{HAuBr}_4 \cdot 3\text{H}_2\text{O}$ and that the diethylauric bromide product was dimeric with bridging bromine atoms.^{89,90}



Scheme 2.1.1: First reported examples of organometallic gold complexes.

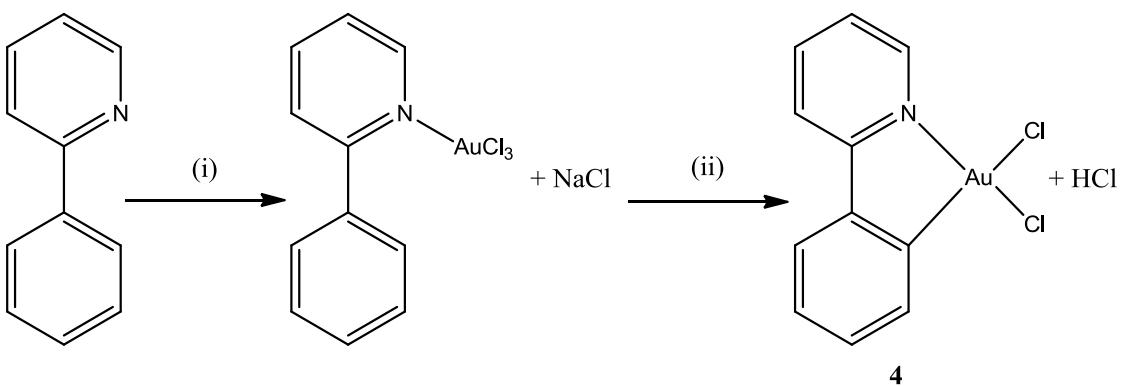
Aryl gold compounds were first prepared in 1931 by Kharasch and Isbell who synthesised the unstable compounds $[\text{C}_6\text{H}_5\text{AuCl}_2]_2$ and $[(\text{C}_6\text{H}_5)_2\text{AuCl}]$ via the direct auration of dry benzene with anhydrous AuCl_3 .⁹¹ Previously these authors had attempted to prepare aryl gold(III) complexes using Grignard reagents, but all attempts failed.^{92,93} This led them to conclude that the direct auration of aromatics was the only available method to prepare aryl gold(III) complexes, and that the reaction between Grignard reagents and AuCl_3 was also of limited use. These authors also investigated the auration reaction of a variety of different organic substrates and concluded that direct auration was a “general” and versatile reaction.⁹¹ Subsequently Liddle and Parkin⁹⁴ addressed the instability of the dimeric gold(III) compounds by preparing and characterising a series of air-stable RAuCl_2L (where R = Ph, *p*-MeC₆H₄, *p*-ClC₆H₄; L = SⁿPr₂, PPh₃, PMe₃, py) complexes, obtained from the addition of ligand (L) to $[\text{RAuCl}_2]_2$. In the 1970’s the work of Kharasch was re-visited by Calderazzo,⁹⁵ de Graaf *et al.*⁹⁶ and Puddephatt and Monaghan⁹⁷ who outlined some of the limitations of the direct auration reaction. During the course of these studies it was

observed that the auration reaction was not a versatile synthetic tool, and was inhibited by the presence of a weakly co-ordinating group on the arene.^{96,97} Indeed the attempted auration of *N,N*-dimethylbenzylamine with anhydrous AuCl₃ or AuBr₃ gives some decomposition to metallic gold, and mixtures of either tri-halo gold(III) adducts (**2**) containing the amine as a ligand,⁹⁷ or ammonium salts (**3**) containing the tetra-halo gold aurates rather than the desired *ortho*-metallated complex (Scheme 2.1.2).



Scheme 2.1.2: Products from the auration reaction of *N,N*-dimethylbenzylamine and AuBr₃. (i) Dichloromethane, r. t.

All attempts to re-arrange **2** and **3** into the cyclometallated gold complex resulted in the precipitation of metallic gold and similar results were obtained upon substituting the amine ligand for azobenzene.⁹⁷ Recently however the direct auration reaction has been re-investigated by a number of research groups and progress has been made through the use of different cyclometallated C,N ligands.^{98–100} Direct cycloauration reactions typically provide products containing five or six-membered chelates, possessing an anionic carbon donor and a neutral nitrogen donor ligand. These C,N chelates stabilise the Au(III) centre towards reduction. Complexes of the type Cl₂Au(C,N) exhibit square planar geometry, typical for d⁸ electronic configurations.⁹⁸ The first example of a direct C,N cycloauration reaction is that of Constable and Leese¹⁰¹ who used Na[AuCl₄] and H[AuCl₄] to cycloaurate 2-phenylpyridine. The reaction proceeds *via* the formation of a tri-chloro gold(III) adduct which upon heating in aqueous acetonitrile gives the cyclometallated complex AuCl₂(η²-C,N-C₆H₄-2-C₅H₄N) **4** in 80 % yield (Scheme 2.1.3).



Scheme 2.1.3: The cycloauration of 2-phenylpyridine. (i) $\text{Na}[\text{AuCl}_4] \cdot 2\text{H}_2\text{O}$, $\text{MeCN}/\text{H}_2\text{O}$ (1:1), r.t.; (ii) $\text{MeCN}/\text{H}_2\text{O}$ (1:1), reflux, 3 h.¹⁰¹

Despite the straightforward nature of the methodology this route suffers from poor reproducibility, which has been commented upon by Eisenberg and co-workers.¹⁰² This led Shaw *et al.*¹⁰³ to explore the use of microwave irradiation for the synthesis of **4**. Conducting these reactions in a microwave reactor using water as solvent resulted in reduced reaction times, higher product yields and a better reproducibility when compared to conventional methods of heating. Many different examples of this direct cyclometallation reaction now exist and a detailed overview is provided in a review by Henderson.⁹⁸

Nonoyama *et al.* have also investigated the preference of Au(III) for forming five or six-membered chelates during the auration process.¹⁰⁴ These authors prepared the ambidentate 3-phenyl-6-*p*-toluidinopyridazine (Hptp) ligand which has the potential to form five or six-membered cyclometallated rings. When Hptp was refluxed with $\text{AuBr}_3 \cdot 2\text{H}_2\text{O}$ in $\text{EtOH}/\text{H}_2\text{O}$ (1:1) overnight, the isolated complex was $[\text{Au}(\text{ptp})\text{Br}_2]$ (**5**) which contained the six-membered cycloaurated ring rather than a five-membered metallacycle (Figure 2.1.1). This is in contrast to cyclopalladation and cyclorhodation which exclusively gave products containing five-membered rings. It should be noted that although gold(III) prefers to form six-membered chelates, five-membered auracycles are still far more prevalent throughout the literature. Although progress has been made with the direct auration reaction low yields are obtained with some ligands, and several reagents (notably *N,N*-dimethylbenzylamine and azobenzene) are incompatible with the reaction.

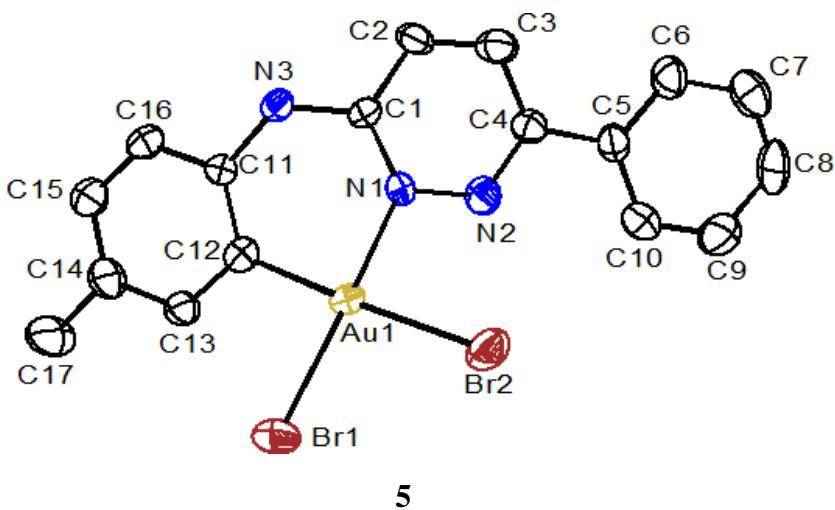
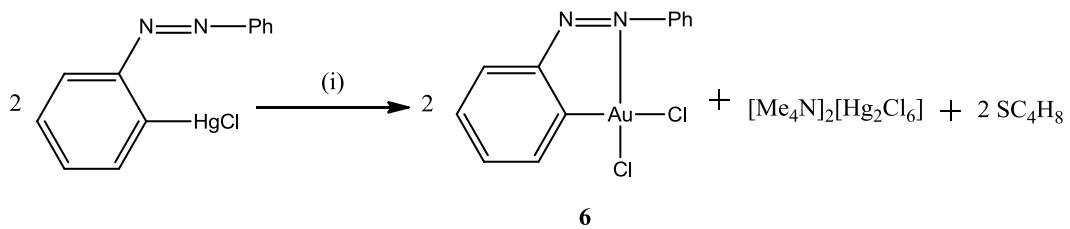


Figure 2.1.1: ORTEP¹⁰⁵ representation of $[\text{Au}(\text{ptp})\text{Br}_2]$ (5).(CH₃)₂SO. Hydrogen atoms and (CH₃)₂SO solvate are omitted for clarity; Thermal ellipsoids at 40 % probability level.¹⁰⁴

Currently the most common and versatile method of preparing cyclometallated aryl gold(III) complexes is *via* transmetallation from the analogous organomercurial complex.^{106,107} This reaction was used by Vicente and co-workers to prepare cycloaurated complexes of azobenzene and dimethylbenzylamine,^{108,109} which are inaccessible by direct auration reactions. The 2-[(phenylazo)-phenyl] gold(III) complexes are prepared by reacting the appropriate organomercurial [HgCl(C₆H₄-2-N=N-Ph)] with [AuCl₃(SC₄H₈)] in the presence of [Me₄N]Cl (Scheme 2.1.4).^{108,110} The addition of [Me₄N]Cl facilitates the formation of [Hg₂Cl₆][Me₄N]₂ which is insoluble, and thus easily separated from the cycloaurated complex.



Scheme 2.1.4: The preparation of $[\text{AuCl}_2(\eta^2\text{-C}_6\text{H}_4\text{-2-N=N-Ph})]$ (6) by organomercury transmetallation. (i) 2 $\text{AuCl}_3(\text{SC}_4\text{H}_8)$, 2 $[\text{Me}_4\text{N}]\text{Cl}$, r.t., (CH₃)₂CO or CH₂Cl₂, 24 h.¹⁰⁸

Numerous cycloaurated derivatives of azobenzene, containing *para* substituents on the phenyl rings, have been prepared *via* this route,¹¹¹ with the structure of the methyl substituted compound shown in Figure 2.1.2.

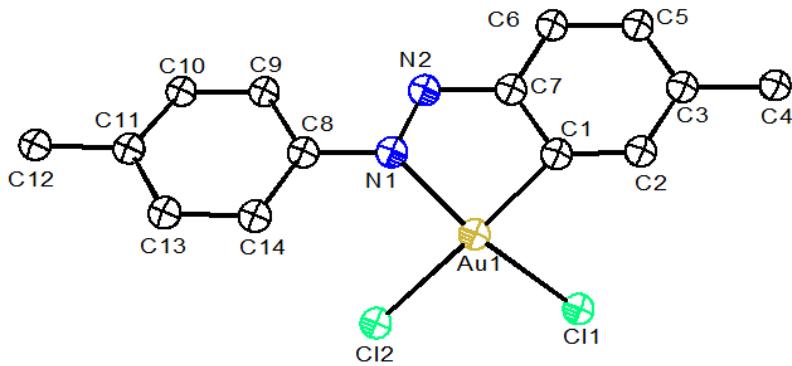
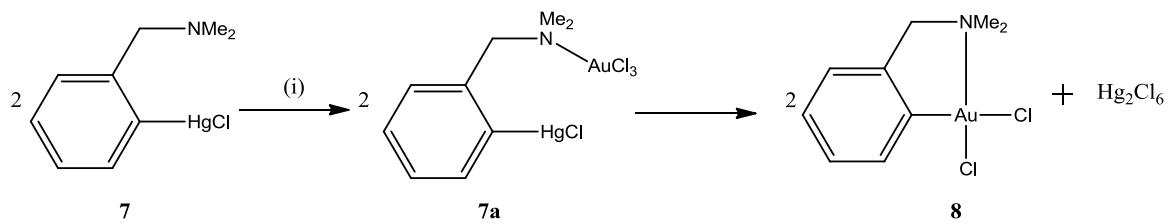


Figure 2.1.2: ORTEP representation of $[\text{AuCl}_2(\eta^2\text{-C},\text{N-}\text{C}_6\text{H}_3\text{-}2\text{-N=N-}p\text{-tolyl-}5\text{-CH}_3)]$. Hydrogen atoms omitted for clarity. Thermal ellipsoids at 40 % probability.¹¹²

Cycloaurated complexes containing the 2-(*N,N*-dimethylaminomethyl)phenyl (damp) ligand have been extensively studied.^{109,113} The gold(III) complex $[\text{AuCl}_2(\eta^2\text{-C},\text{N-}\text{C}_6\text{H}_4\text{-}2\text{-CH}_2\text{NMe}_2)]$ (**8**) has been prepared in ~80% yield from the reaction between the HgCl (damp) with $[\text{AuCl}_3(\text{SC}_4\text{H}_8)]$, $[\text{Me}_4\text{N}][\text{AuCl}_4]$ or $\text{Na}[\text{AuCl}_4]$.^{56,109} The organomercurial precursor $[\text{HgCl}(2\text{-C}_6\text{H}_4\text{CH}_2\text{NMe}_2)]$ (**7**) is readily prepared from the *ortho*-directed lithiation of dimethylbenzylamine using *n*-butyllithium followed by transmetallation with HgCl_2 at -78 °C.¹¹⁴ Attempts to react the lithium reagent $[\text{Li}(\text{C}_6\text{H}_4\text{-}2\text{-CH}_2\text{NMe}_2)]$ directly with $\text{AuCl}_3(\text{SC}_4\text{H}_8)$ or $[\text{Me}_4\text{N}][\text{AuCl}_4]$ resulted in the precipitation of metallic gold.¹⁰⁹ The proposed mechanism for the transmetallation is shown in Scheme 2.1.5.⁹⁸ The first step is coordination of the nitrogen donor of the amine to the gold centre, to form an intermediate tri-chloro gold(III) adduct **7a**. Over twenty four hours the aryl group is transferred to the gold(III) centre with elimination of Hg_2Cl_6 . The bis-organomercurial $[\text{Hg}(\text{C}_6\text{H}_4\text{CH}_2\text{NMe}_2)_2]$ can also be used to prepare **8**.¹¹⁵



Scheme 2.1.5: The proposed mechanism of organomercurial transmetallation to give $[\text{AuCl}_2(\eta^2\text{-C},\text{N-}\text{C}_6\text{H}_4\text{-}2\text{-CH}_2\text{NMe}_2)]$ (**8**). (i) 2 $\text{Na}[\text{AuCl}_4]$ · $2\text{H}_2\text{O}$, MeCN or $(\text{CH}_3)_2\text{CO}$, r.t., 24 h.⁹⁸

The molecular structure of **8**, shown in Figure 2.1.3, has been determined by a single crystal X-ray diffraction study.¹¹⁶ This complex contains the expected five-membered gold chelate, with a square planar arrangement around the gold centre and a Au(1)-C(1) bond length of 2.046(8) Å. The strong *trans* influence of the aryl group lengthens the Au(1)-

Cl(2) bond to 2.387(2) Å compared to an Au(1)-Cl(1) bond length of 2.285(2) Å for the chloride *trans* to the NMe₂ group.

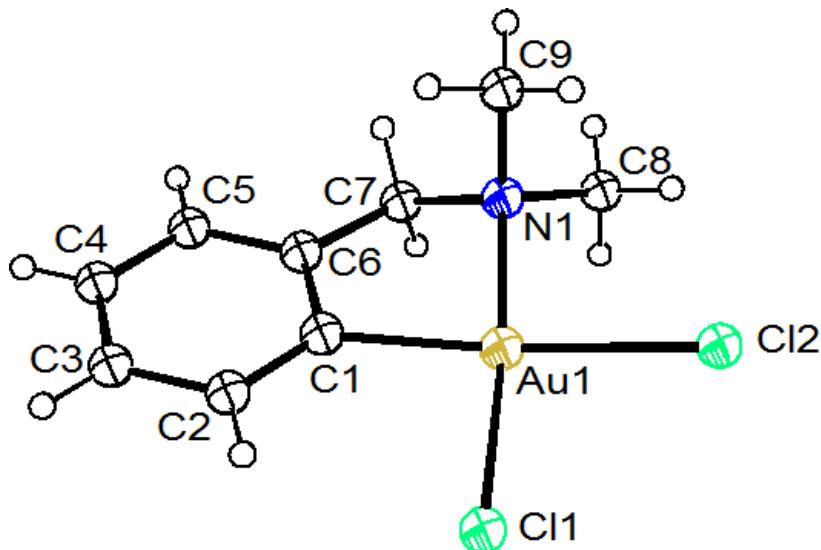


Figure 2.1.3: ORTEP representation of $[\text{AuCl}_2(\eta^2\text{-C},\text{N-}\text{C}_6\text{H}_4\text{-2-CH}_2\text{NMe}_2)]$ (8). Thermal ellipsoids at 40 % probability level.¹¹⁶

Subsequently Parish and co-workers^{113,117} prepared and characterised a wide range of organomercury, and cycloaurated gold(III) complexes containing analogues of the dimethylbenzylamine ligand. The authors also used organomercurials to synthesise a variety of oxazoline containing auracycles.¹¹³ More recently transmetallation from organomercurials has been used by Henderson *et al.*^{118–120} to prepare cycloaurated gold(III) complexes containing iminophosphorane ligands. The cyclometallated gold complex $\text{AuCl}_2(\eta^2\text{-C},\text{N-}\text{C}_6\text{H}_4\text{-2-C}_5\text{H}_4\text{N})$ (4) prepared by direct cycloauration (Scheme 2.1.3) can also be prepared from the relevant organomercury compound; $[\text{HgCl}(\text{C}_6\text{H}_4\text{-2-C}_5\text{H}_4\text{N})]$.¹⁰¹ The organomercurial pathway provides a more convenient, and reproducible route to the 2-phenylpyridine Au(III) complex than direct auration. Mixed diaryl gold(III) complexes can also be obtained using organomercurial transmetallation reactions.¹²¹ For example the reaction between $\text{AuCl}_2(\eta^2\text{-C},\text{N-}\text{C}_6\text{H}_4\text{-2-CH}_2\text{NMe}_2)$ (8) and $[\text{Hg}(2\text{-C}_6\text{H}_4\text{N=N-Ph})_2]$ proceeded in acetone over 6 hours to afford $[(2\text{-PhN=NC}_6\text{H}_4)\text{Au}(\eta^2\text{-C},\text{N-}\text{C}_6\text{H}_4\text{-2-CH}_2\text{NMe}_2)\text{Cl}]$ (9) in 85% yield. The dimethylbenzylamine ligand binds in a η^2 -fashion and forms the 5-membered cycloaurated ring, while the azobenzene ligand acts as a monodentate ligand, bonded by the phenyl group. Reaction of 9 with silver perchlorate affords the *bis*-cycloaurated complex $[(\eta^2\text{-C},\text{N-}\text{C}_6\text{H}_4\text{-2-N=NPh})\text{Au}(\eta^2\text{-C},\text{N-}\text{C}_6\text{H}_4\text{-2-CH}_2\text{NMe}_2)]\text{ClO}_4$ (10). The perchlorate salt can be converted to the tetrachloroaurate salt

upon reaction with $\text{Me}_4\text{N}[\text{AuCl}_4]$, and the molecular structure of the cation has been confirmed by a single crystal X-ray diffraction study (Figure 2.1.4).

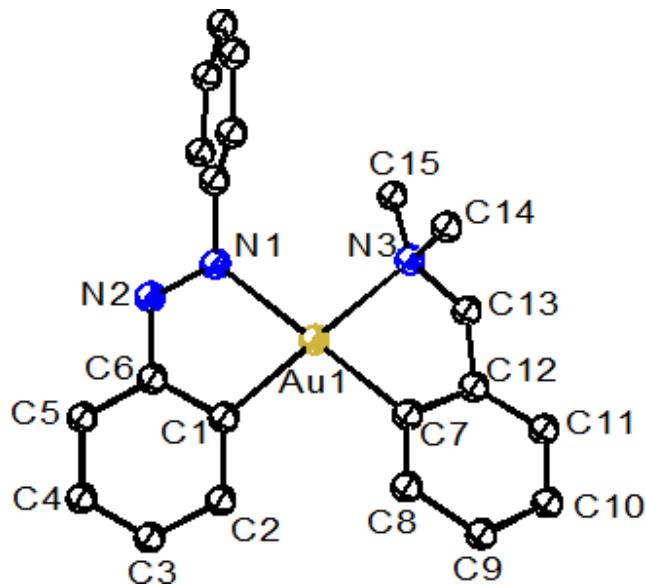
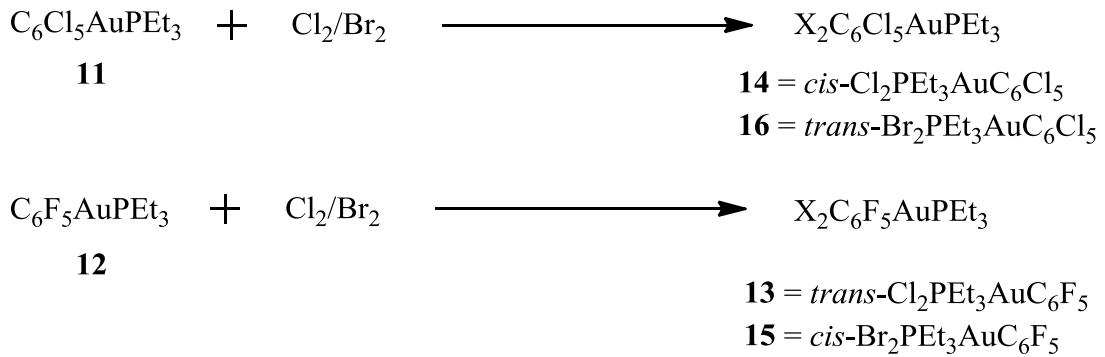


Figure 2.1.4: ORTEP representation of the bis-cycloaurated cation $[(\eta^2\text{-C}_6\text{H}_4\text{-2-N=NPh})\text{Au}(\eta^2\text{-C}_6\text{H}_4\text{-2-CH}_2\text{NMe}_2)]\text{AuCl}_4$. Hydrogen atoms and $[\text{AuCl}_4]$ omitted for clarity. Thermal ellipsoids at 40 % probability.¹²¹

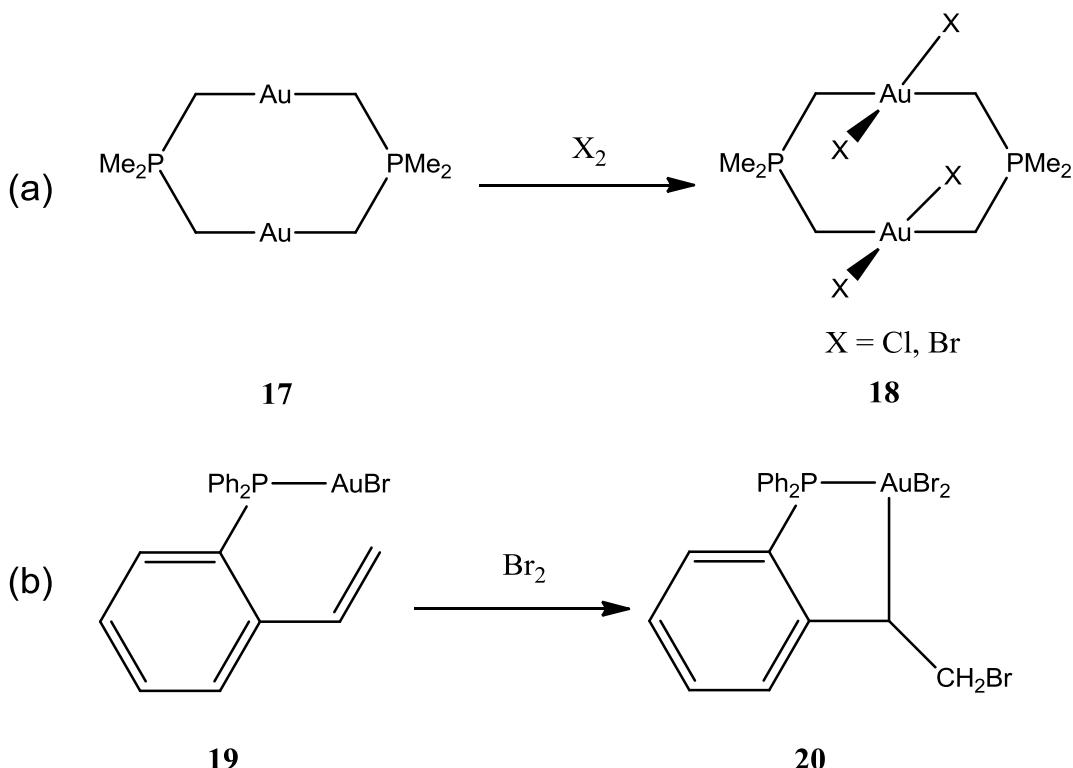
Numerous cyclometallated gold(III) complexes have been prepared *via* the organomercury route,^{98,107,110,119,122,123} and many show promising *in-vitro* activity in cancer cell lines.⁵⁶ However the use of severely toxic organomercury compounds would preclude their potential use as therapeutic agents.

Another method by which aryl gold(III) complexes can be prepared utilises the oxidative addition of a halogen to a preformed aryl gold(I) complex. This pathway has been utilised by Usón *et al.*^{124–126} for the synthesis of dihaloperhalophenyl gold(III)triethylphosphine complexes in high yield (Scheme 2.1.6). Curiously oxidation of the pentfluorophenyl gold(I) compound (**12**), with Cl_2 at room temperature afforded the *trans*-isomer (**13**), while the pentachlorophenyl ligand (**11**) afforded the *cis*-isomer (**14**). This outcome is reversed when bromine is used in the oxidation reaction, where the initial C_6F_5 -complex **12** now affords the *cis*-Au(III) compound (**15**), and the C_6Cl_5 -complex **11** affords the *trans*-product (**16**).¹²⁵ Substituting triethylphosphine for triphenylphosphine in the initial gold(I) complex results in cleavage of the Au-C₆F₅ bond when either bromine or chlorine is used as the oxidising agent. Thallium(III) chloride has also been used as a chlorinating agent in the oxidation of aryl gold(I) complexes to aryl gold(III) complexes.¹²⁴



Scheme 2.1.6: The oxidative addition of halogen to pentafluoro- and pentachloro-phenyl gold(I) triethylphosphine complexes. Where X = Cl/Br or I.¹²⁴⁻¹²⁶

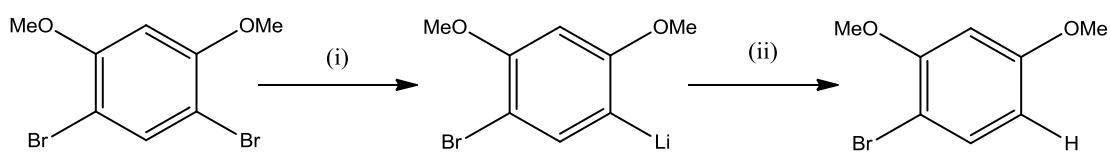
The oxidation of a dinuclear gold(I) complex has also been reported by Schmidbaur and Franke.¹²⁷ These authors were able to prepare the cyclic Au(I) dimer, $[(\text{CH}_3)_2\text{P}(\text{CH}_2)_2\text{Au}]_2$ (**17**) and effect its oxidation with two equivalents of Cl₂ or Br₂ to give a dinuclear gold(III) complex (**18**) with a *trans*-arrangement around the gold centres (Scheme 2.1.7, (a)). An unusual example of Au(I) oxidation to gold(III) has also been observed with olefinic tertiary phosphines as ligands.¹²⁸ It was found that the bromination of the *ortho*-styryldiphenylphosphine gold(I) bromide complex (**19**) resulted in the overall bromocarbometallation of the double bond affording the novel complex **20** (Scheme 2.1.7, (b)). This route to aryl gold(III) complexes is fairly uncommon, and has only been demonstrated with a very small number of compounds, although high yields of Au(III) products are obtained.



Scheme 2.1.7: (a) The oxidative addition of Cl_2 or Br_2 to $[(\text{CH}_3)_2\text{P}(\text{CH}_2)_2\text{Au}]_2$ (**17**);¹²⁷ (b) The oxidative addition of Br_2 to *o*-styryldiphenylphosphine gold(I) bromide (**19**).¹²⁸

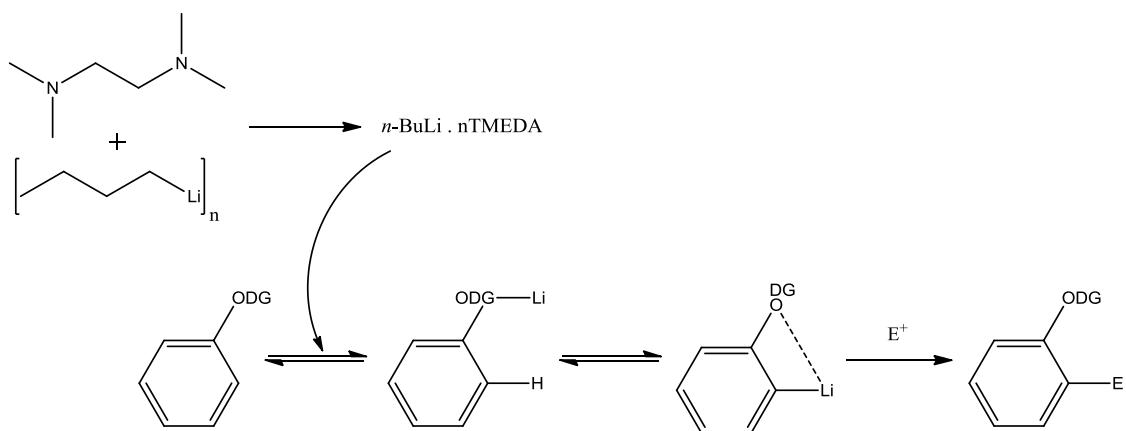
2.2 Organolithium reagents

Organolithium compounds are extremely useful reagents that are easily prepared, and able to undergo reaction with a wide range of substrates. One common method for the preparation of organolithiums is the lithium-halogen exchange reaction, which was first described by Wittig and co workers in 1938.¹²⁹ The initial report detailed the reaction of 4,6-dibromo-1,3-dimethoxybenzene with phenyllithium in diethyl ether followed by protonolysis with water (Scheme 2.2.1).



Scheme 2.2.1: The reaction of 4,6-dibromo-1,3-dimethoxybenzene. (i) $\text{PhLi}, \text{Et}_2\text{O}$; (ii) H_2O .¹²⁹

Following on from this Henry Gilman carried out many studies on the lithium-halogen exchange reaction,^{130–132} and today the reaction is widely used for the preparation of organolithium compounds. Organolithium reagents can also be prepared by *ortho*-directed lithiation reactions which allow the introduction of functional groups onto aromatic compounds. In 1939–1940 both Gilman and Bebb¹³³ and Wittig and Fuhrman¹³⁴ working independently discovered the *ortho*-lithiation of anisole using *n*-butyllithium (*n*-BuLi). Subsequently Gilman¹³⁵ and Hauser¹³⁶ expanded the scope of the *ortho*-directed lithiation reaction and investigated a range of different *ortho*-directing groups (ODG). The general course of the reaction is shown in Scheme 2.2.2.



Scheme 2.2.2: Simplified view of the *ortho*-directed lithiation mechanism using *n*-BuLi·TMEDA.¹³⁷

Firstly *n*-BuLi and *N,N,N,N*-tetramethylethylenediamine (TMEDA) are stirred together to break-up the *n*-BuLi aggregates, and form a more reactive *n*-BuLi·TMEDA species. Anisole is then added and the lithium reagent co-ordinates to the ODG. Deprotonation at the *ortho*-position then gives the *ortho*-lithiated species which can be reacted with a range of electrophiles. *Ortho*-directed lithiation is now an extremely important and powerful tool for the synthesis of substituted aromatic compounds.

2.3 Attempted Oxidation of gold(I) compounds

2.3.1 Preparation of Organolithium reagents

The organolithium reagents shown in Figure 2.3.1 were prepared for use as organic ligands for gold(I) complexes. 1-Li-2-OMe-C₆H₄ (**21**) was prepared using a modification of the method of Crowther *et al.*,¹³⁸ treatment of anisole with a 1:1 mixture of *n*-BuLi and TMEDA gave **21** as a white solid. The number of moles of TMEDA of crystallisation was

then determined by quenching a known mass of **21** with trimethylsilyl chloride in diethyl ether and assuming quantitative conversion to [1-(SiMe₃)-2-OMe-C₆H₄] (**21a**). The formula weight of **21** was then back-calculated using Equation 2.3.1.

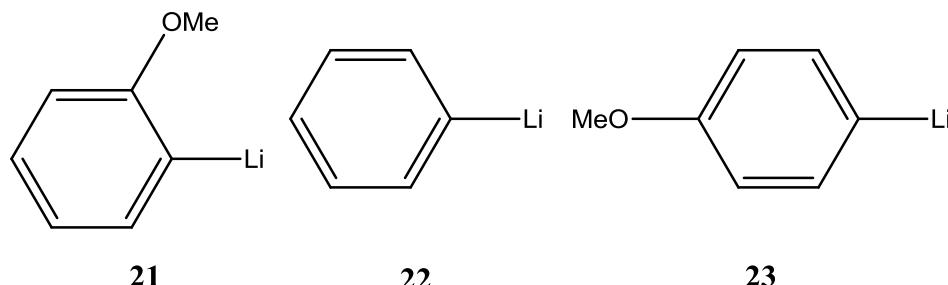


Figure 2.3.1: The organolithium reagents prepared for Au(I) oxidation experiments.

$$\frac{\text{Product Mass}}{\text{Product Formula Weight}} = \frac{\text{Lithium Salt Mass}}{\text{Lithium Salt Formula Weight}}$$

Equation 2.3.1: Equation to determine the formula weight of lithium reagent.

Lithium salts **22** and **23** were prepared by lithium-halogen exchange with the corresponding aryl-bromide compounds. Equimolar quantities of *n*-BuLi were used, and the reactions were carried out at -78 °C in hexane.¹³⁹ TMEDA was added to precipitate the lithium reagents which were isolated as white powders and stored in a glove box under nitrogen. The composition of **22** and **23** was determined by preparation of the silyl derivatives [(SiMe₃)-C₆H₅] (**22a**) and [1-(SiMe₃)-4-OMe-C₆H₄] (**23a**) and back calculation using Equation 2.3.1.

2.3.2 Preparation of gold(I) complexes

The monodentate phosphine chloride complex [ClAuPPh₃]¹⁴⁰ (**25**) was prepared by reaction of [ClAu(THT)] (**24**) (THT = SC₄H₈) with 1.1 equivalents of triphenyl phosphine in CH₂Cl₂. Recrystallisation from CH₂Cl₂/hexane gave the pure compound. The gold precursor [ClAu(THT)] (**24**) was prepared by reacting Na[AuCl₄] or K[AuCl₄] with 2.12 equivalents of THT in H₂O/EtOH (1:1) as outlined by Usón and co-workers.¹⁴¹ The previously reported organometallic gold(I) complexes [Ph₃PAu-(2-OMe-C₆H₄)]¹⁴² (**26**), [Ph₃PAu-(4-OMe-C₆H₄)]¹⁴³ (**27**), and [Ph₃PAu-C₆H₅]¹⁴⁰ (**28**) were prepared by reaction of [ClAuPPh₃] (**25**) with the appropriate lithium reagent in THF. The complexes were

isolated as white crystalline solids in good yield, and the analytical and spectroscopic data given in section 8.3 are in good agreement with the data found in the literature.

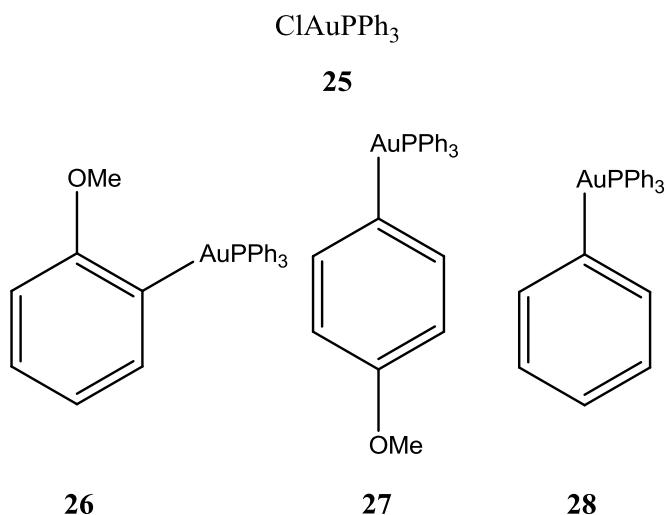


Figure 2.3.2: Gold (I) complexes prepared for oxidation reactions.

2.3.3 Attempted Oxidation of gold(I) complexes

Iodobenzene dichloride as prepared, according to the procedure of Zhao and Zhang,¹⁴⁴ was employed as the stoichiometric chlorine source for oxidative addition to Au(I) complexes **26-28**. PhICl_2 was isolated as a light and heat sensitive yellow powder that was identified by its melting point; 109-111°C.¹⁴⁴ The oxidative addition of Cl_2 and Br_2 to aryl gold(I) complexes (**26-28**) was carried out in CH_2Cl_2 with 1.3 equivalents of halogen or halogen reagent, as detailed in the experimental section 8.3.6. No gold(III) oxidative addition products were isolated or observed in the $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum. A representative phosphorus NMR spectrum, after the reaction of **26** with PhICl_2 is shown in Figure 2.3.3. Unreacted **26** was found to be present in the reaction mixture (resonance at δ 43.67 ppm), even when treated with an excess of chlorinating agent. The appearance of a resonance at δ 33.14 ppm was indicative of the formation of ClAuPPh_3 (**25**).

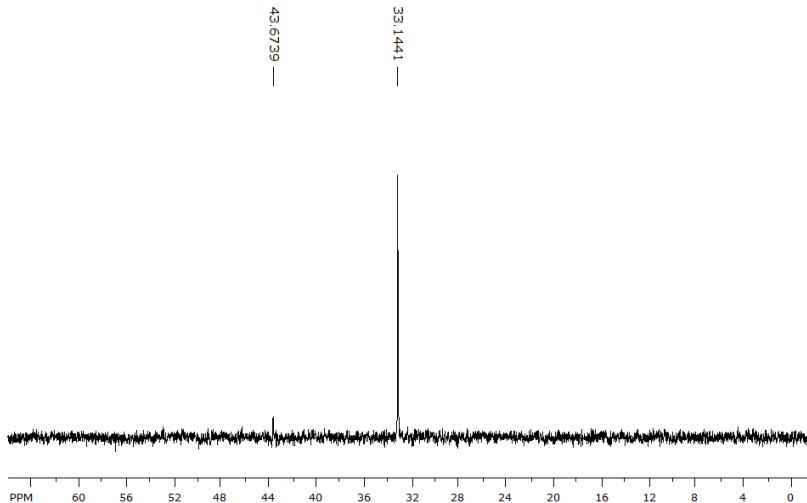


Figure 2.3.3: $^{31}\text{P}\{\text{H}\}$ NMR spectrum after the reaction of **26** with PhICl_2 .

When an excess of Br_2 was added to complexes **26-28**, the starting material was completely consumed and two new signals appear in the ^{31}P NMR spectrum as shown in Figure 2.3.4. The resonance at δ 31.35 ppm corresponds to BrAuPPh_3 , while the signal at δ 35.25 ppm was ascribed to the formation of $\text{Br}_3\text{AuPPh}_3$ after comparison with literature values.^{145,146}

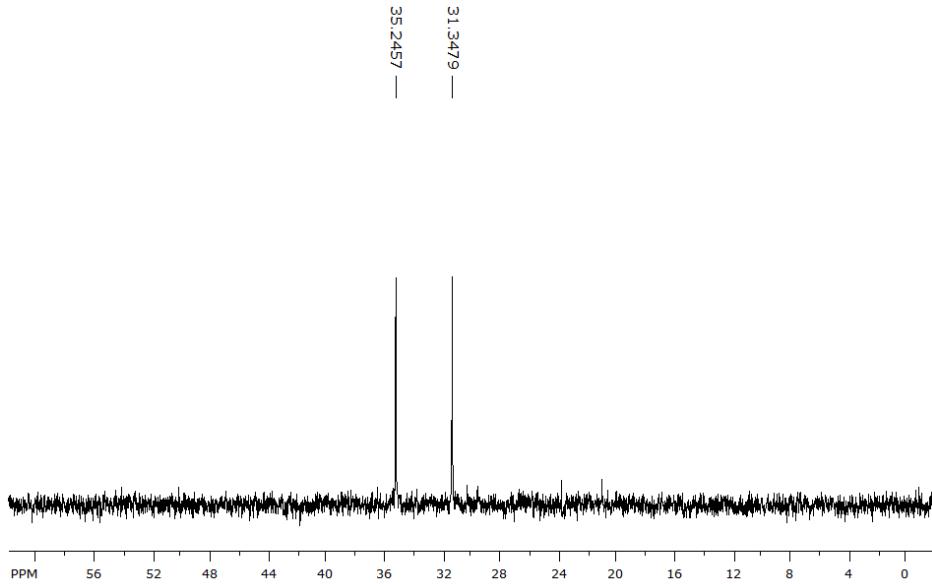
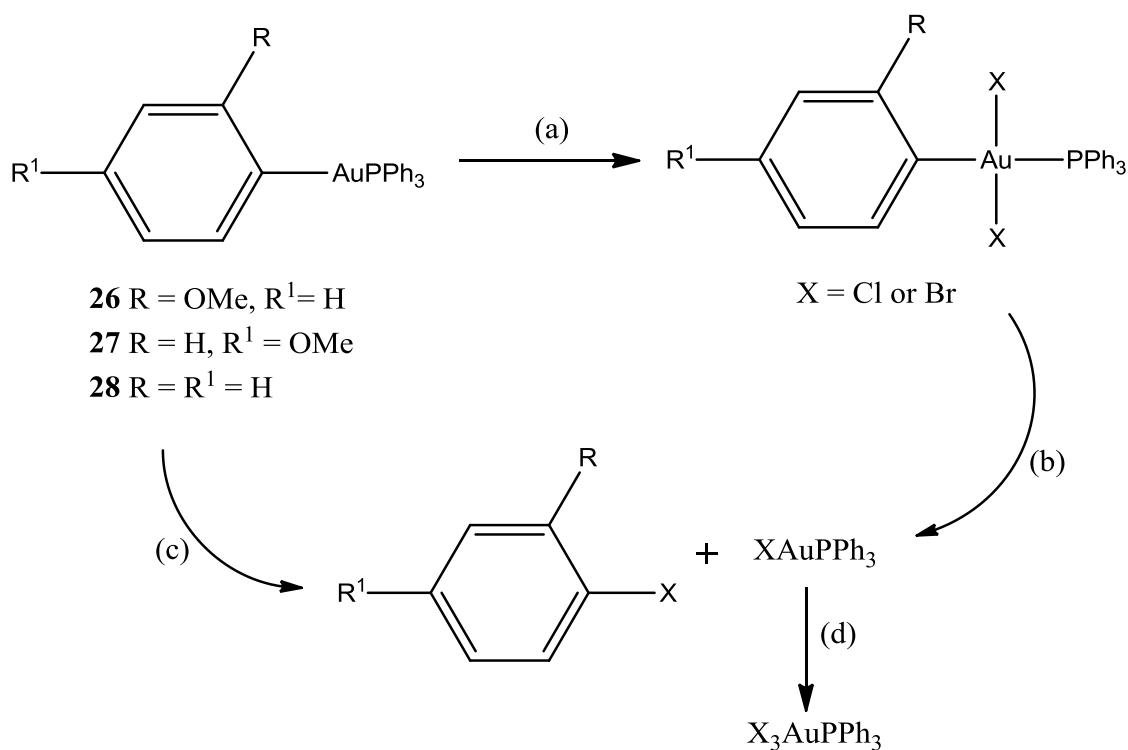


Figure 2.3.4: The resulting $^{31}\text{P}\{\text{H}\}$ NMR spectrum when an excess of Br_2 is reacted with compounds **26-28**.

The proposed scheme for the addition of halogens to gold(I) complexes **26-28** is shown in Scheme 2.3.1.

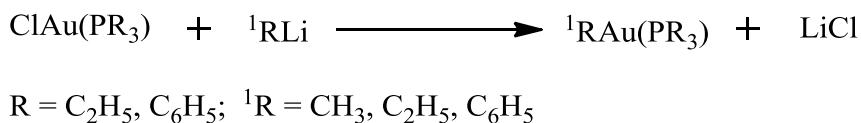


Scheme 2.3.1: The proposed reaction scheme for the addition of halogens to aryl gold(I) complexes.

The oxidative addition of halogen to compounds **26-28** could take place to yield the desired Au(III) complex, which then undergoes rapid reductive elimination to give the halogenated aryl and XAuPPh₃, observed by ³¹P{¹H} NMR spectroscopy (pathways (a) and (b)). Another possibility is that the addition of halogen directly cleaves the gold-carbon bond as in pathway (c) leading to the same products. The addition of an excess of halogen as in pathway (d) gives the trihalogold(III) phosphine complexes. At present both are plausible mechanisms and further low temperature *in-situ* NMR experiments would need to be carried out to see if oxidative addition was indeed taking place. These results essentially confirm those obtained by Usón and Laguna in 1974;¹²⁴ that the reaction of C₆H₅AuPPh₃ with Br₂ leads to mixtures of C₆H₅Br, BrAuPPh₃ and Br₃AuPPh₃. Given these unsuccessful attempts to prepare aryl gold(III) complexes by oxidation of Au(I) complexes, and the drawbacks of the other known methods for preparing gold(III) complexes, detailed above, it is clear that more general methods for the synthesis of aryl gold(III) complexes are required.

2.4 New Transmetallation routes to gold complexes

Aryl gold(I) complexes are commonly prepared by reacting organolithium or Grignard reagents with an appropriate gold(I) precursor.^{13,147} The first aryl gold(I) complexes were reported by Coates *et al.*^{148,149} who reacted phosphine gold(I) halide complexes with organolithium reagents (Scheme 2.4.1). A large number of Au(I) complexes have been prepared *via* this classical route, which is now ubiquitous in modern organogold(I) chemistry.



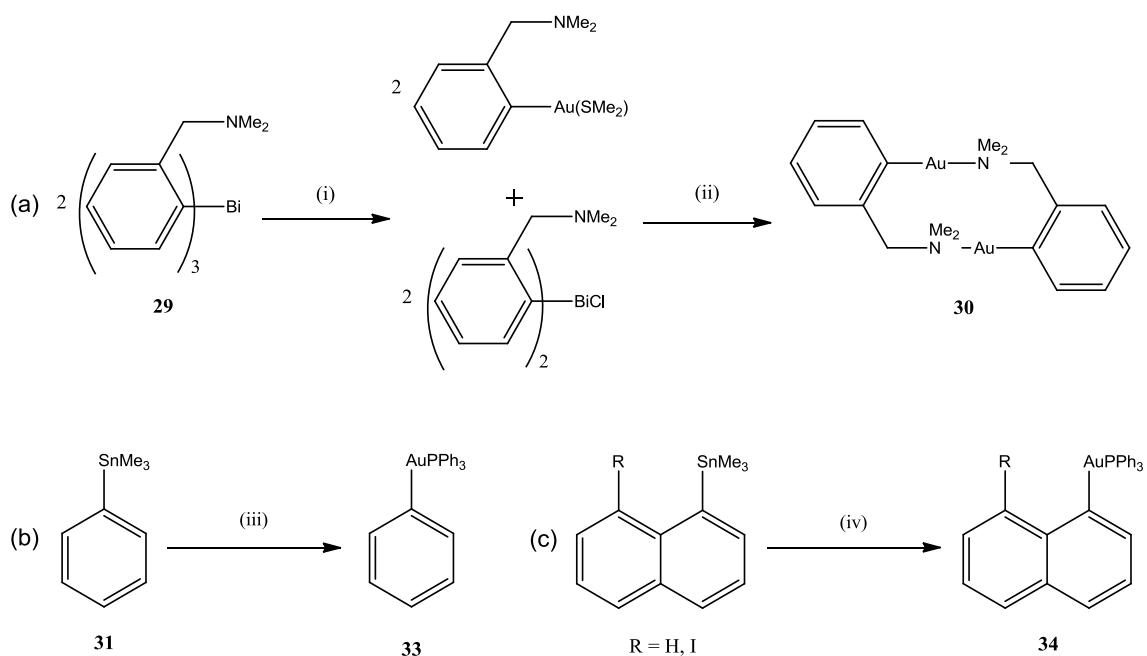
Scheme 2.4.1: The preparation of aryl gold(I) complexes using organolithium reagents.¹⁵⁰

Mononuclear organogold(I) species are among the most stable transition metal organometallics which possess a M-C σ-bond.¹⁵¹ This stability is due to the low polarity of the Au-C bonds, which would explain the resistance of these compounds to nucleophilic and electrophilic cleavage.¹⁵¹ Thus gold(I) organometallics are easier to prepare and handle than their gold(III) counterparts, making them ideal candidates for the testing of new transmetallation reagents.

In the past twenty years a number of new routes to aryl gold(I) complexes have been discovered. Schmidbaur *et al.*¹⁵² have demonstrated the facile transmetallation of the aryl groups to gold(I) centres from bismuth in aryl bismuthines (Scheme 2.4.2, (a)). At low temperature (-78 °C) the authors reacted (Me₂S)AuCl with Ph₃Bi to give the unstable gold complex (Me₂S)AuPh and Ph₂BiCl as the by-product. Substitution of the dimethylsulfide ligand for tetrahydrothiophene enabled preparation of the analogous (THT)AuPh complex, but again the complex was unstable and so could not be isolated. Only when [Bi(C₆H₄-2-CH₂NMe₂)₃] (**29**) was used in the transmetallation step was a stable organogold complex isolated, which was subsequently shown to be the dinuclear gold(I) complex [Au(C₆H₄-2-CH₂NMe₂)₂] (**30**). The main drawback of using this route is the difficulty in separating the desired gold complexes from the organobismuth by-products.¹⁵²

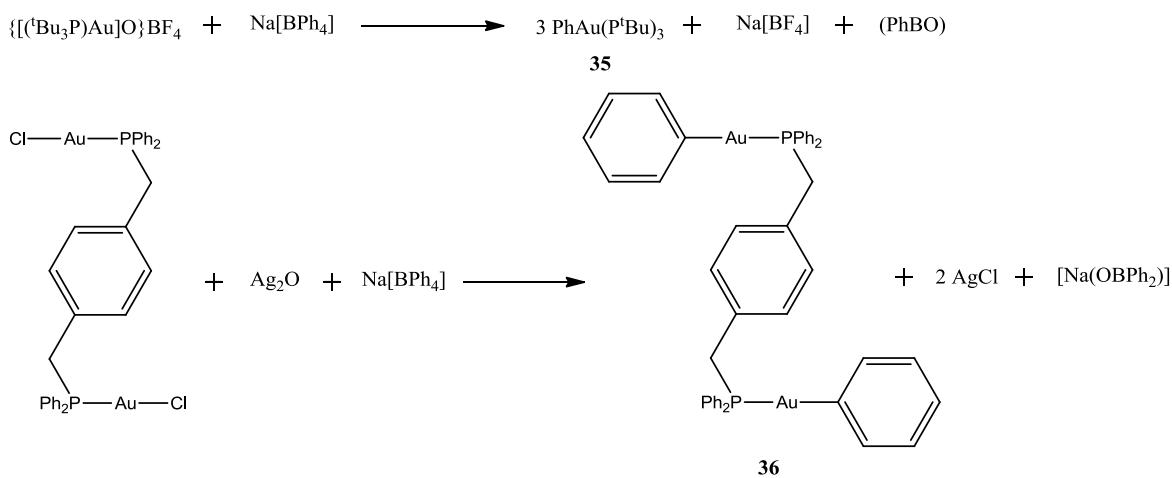
Organotin reagents have also been used in the transfer of aryl groups to Au(I). Mohr *et al.* have shown that 1,8-bis(trimethylstannyl)naphthalene readily transfers the 1,8-naphthalene

ligand to a dinuclear gold complex, $[\text{Cl}_2\text{Au}_2(\mu\text{-}1,2\text{-}(\text{PPh}_2)\text{-C}_2\text{H}_4)]$ in good yield.¹⁵³ The same authors also investigated phenyl group transfer to ClAuPPh_3 using PhSnMe_3 (**31**) and PhSn^nBu_3 (**32**).¹⁵⁴ They found that the butyl-derivative does not undergo transmetallation even when refluxing in toluene for 18 hours. In contrast the transfer of a phenyl group to Au(I) with the methyl-compound occurs in just two hours under the same conditions, to give **33** (Scheme 2.4.2, (b)).¹⁵⁴ This method was also used to prepare an iodo-functionalised naphthylgold(I) complex (**34**) which cannot be prepared by other routes. The disadvantage of using tin transmetallation reagents is that the organotin compounds and the reaction by-products, namely ClSnMe_3 , are deemed to be extremely toxic.



Scheme 2.4.2: Transmetallation routes to aryl gold(I) complexes: (a) transmetallation with aryl bismuth reagents,¹⁵² (i) 2 $(\text{Me}_2\text{S})\text{AuCl}$, CH_2Cl_2 , -78°C , 6 h; (ii) 2 Me_2S , 2 Ar_2BiCl , -78°C . (b) transmetallation with organotin reagents;¹⁵⁴ (iii) ClAuPPh_3 , $-\text{Me}_3\text{SnCl}$, Toluene, reflux, 2 h; (c) (iv) ClAuPPh_3 , $-\text{Me}_3\text{SnCl}$, CH_2Cl_2 , r.t. 2 h.

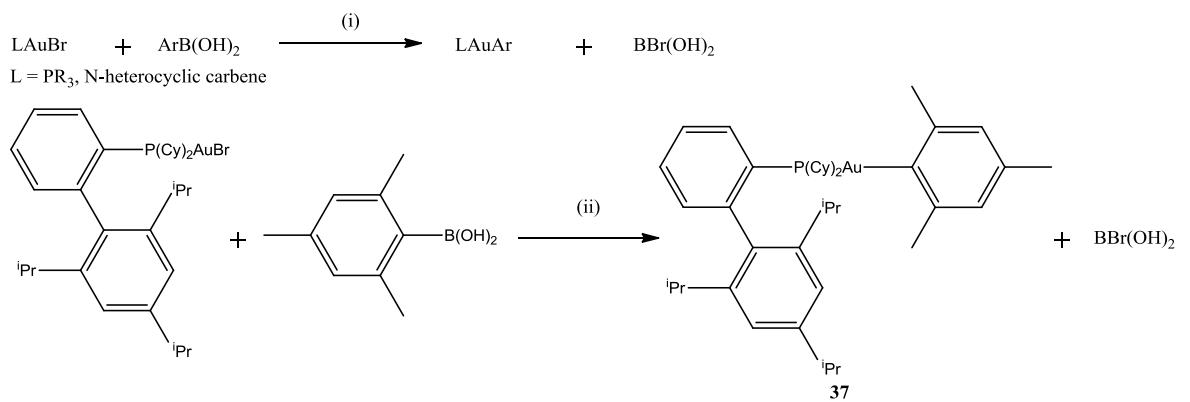
In the past twenty years transmetallation from boron reagents has developed as an alternative strategy for the synthesis of aryl gold(I) complexes. Schmidbaur *et al.*¹⁵⁵ and Fackler *et al.*¹⁵⁶ independently showed that sodium tetraphenylborate acted as a phenylating agent towards gold(I). The group of Schmidbaur reported the preparation of both PhAu(P'Bu)_3 (**35**), and 1,4-[$(\text{PhAu})\text{Ph}_2\text{PCH}_2$] $_2\text{C}_6\text{H}_4$ (**36**) utilising this method (Scheme 2.4.3).



Scheme 2.4.3: Examples of sodium tetraphenylborate as a transfer agent.¹⁵⁵

More recently Gray *et al.* have shown that aryl gold(I) compounds can be prepared *via* transmetallation from boronic acids under mild conditions.^{157–160} The reactions are carried out in isopropyl alcohol at 50 °C, in the presence of a strong base, and high yields (60–94%) are usually obtained (Scheme 2.4.4). These reactions tolerate a wide range of functional groups, including those that are incompatible with organolithium and Grignard reagents. The method also allows the formation of sterically crowded organogold(I) complexes in good yield. Indeed the preparation of complexes containing bulky dialkylbiarylphosphines has been reported¹⁵⁸ (Scheme 2.4.4). Furthermore *N*-heterocyclic carbene gold(I) halides can be arylated under the same conditions as those used for the phosphine complexes.¹⁵⁹ Transmetallation can also be effected from pinoccol boronate esters, with these precursors being used to prepare aromatics containing two gold(I) centres.¹⁵⁹

The recently reported homogeneous gold-catalysed cross-coupling reactions make use of proposed gold(I)/gold(III) redox cycles to enable C-C coupling with aryl boronic acids.⁸² Interestingly one of the proposed coupling pathways involves transmetallation from the aryl boronic acid to gold(III) (Scheme 1.3.7), although direct proof of this mechanism has yet to be established.



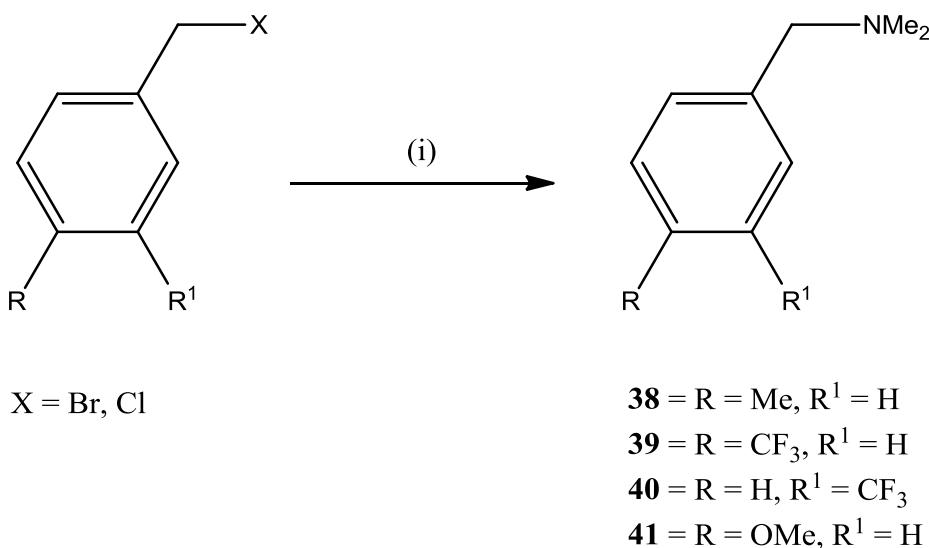
Scheme 2.4.4: Transmetalation from aryl boronic acids to gold(I) phosphines and N-heterocyclic carbene complexes. (i) Cs₂CO₃, ⁱPrOH, 50 °C, 24 h; (ii) Cs₂CO₃, ⁱPrOH, 55 °C, 24h.

3 The preparation of gold(III) organometallics *via* transmetallation from boroxines

A major objective of this research project was to establish a general method for the synthesis of aryl gold(III) complexes. The most widely studied of all gold(III) cycloaurated complexes is the compound $[\text{Au}(\text{damp})\text{Cl}_2]$ (**8**) (where damp is the 2-(*N,N*-dimethylaminomethyl)phenyl ligand), which is prepared from the organomercury precursor (*damp*)HgCl **7** as outlined previously in section 2.¹⁰⁹ Therefore this cyclometallating ligand was chosen as the model system to investigate the preparation of gold(III) complexes *via* boron transmetallation.

3.1 The synthesis of amines

To begin with the amines 1-Me₂NCH₂-4-CH₃-C₆H₄ (**38**), 1-Me₂NCH₂-4-CF₃-C₆H₄ (**39**) and 1-Me₂NCH₂-3-CF₃-C₆H₄ (**40**) were prepared by nucleophilic attack of dimethylamine hydrochloride (generated *in-situ*) on the requisite benzylic bromide precursor.¹⁶¹ 1-Me₂NCH₂-4-OMe-C₆H₄ (**41**) was prepared by the same methodology starting from 4-methoxybenzyl chloride.¹⁶¹ The yields and analytical data for compounds **38-41** are listed in Table 3.1.1, with the NMR data presented in section 8.4.1.



Scheme 3.1.1: General Scheme for the preparation of substituted *N,N*-dimethylbenzylamine derivatives. (i) Me₂NH ·HCl, CH₂Cl₂, KOH, r.t., 4.5 h.

Table 3.1.1: Yield and Microanalytical Data for *N,N*-dimethylbenzylamine derivatives.

Compound	Yield (%)	Microanalytical Data (%) ^a		
		C	H	N
38	61	79.9 (80.5)	10.0 (10.1)	9.1 (9.4)
39	89	59.2 (59.1)	5.6 (6.0)	6.9 (6.9)
40	90	59.2 (59.1)	6.1 (6.0)	6.9 (6.9)
41	85	72.4 (72.7)	9.5 (9.2)	8.4 (8.5)

^aCalculated values given in parentheses.

3.2 Synthesis and isolation of organolithium reagents

With the amines **38–41** in hand, the organolithium reagents 2-(Me₂NCH₂)C₆H₄Li (**42**), 2-(Me₂NCH₂)-5-CH₃-C₆H₄Li (**43**), and 2-(Me₂NCH₂)-5-CF₃-C₆H₄Li (**44**), were prepared *via ortho*-directed lithiation reactions on the parent amines, as outlined by Manzer.¹⁶² All organolithium intermediates were isolated as air- and moisture-sensitive solids and stored in an MBraun Unilab glovebox under a nitrogen atmosphere. Isolation and storage of the lithium reagents is of practical benefit as it allows the lithium compounds to be used as off-the-shelf stoichiometric reagents, and also results in cleaner subsequent reactions with no starting aromatic present in the product.

Table 3.2.1: Structure and Yield of isolated organolithium reagents.

Compound	Lithium Salt	Yield (%)
42		89
43		61
44		70

Unfortunately the preparation and isolation of the lithium reagent 2-(Me₂NCH₂)-6-CF₃-C₆H₃Li was unsuccessful where the presence of an *ortho* CF₃ group results in instability of this intermediate.

3.3 Synthesis of boroxines

Following the preparation of the lithium salts **42-44**, the boroxines [2-(Me₂NCH₂)C₆H₄BO]₃¹⁶³ (**45**), [2-(Me₂NCH₂)-5-CH₃-C₆H₃BO]₃ (**46**) and [2-(Me₂NCH₂)-5-CF₃-C₆H₃BO]₃ (**47**) were prepared by reacting the pre-formed and purified organolithium reagents **42**, **43** or **44** with an excess of trimethylborate in THF at -78 °C. Hydrolysis of the boronate ester followed by aqueous workup afforded the cyclic trimers shown in Figure 3.3.1 rather than the monomeric boronic acids. The boroxine [2-(Me₂NCH₂)-5-OMe-C₆H₃BO]₃ (**48**) was prepared by an *in-situ* quench of the lithium reagent 2-Me₂NCH₂-5-OMe-C₆H₃Li (formed by reaction of 1-Me₂NCH₂-4-OMe-C₆H₄ (**41**) with *n*-BuLi). The spectroscopic and analytical data for compounds **45-48** are presented in Section 8.4.3.

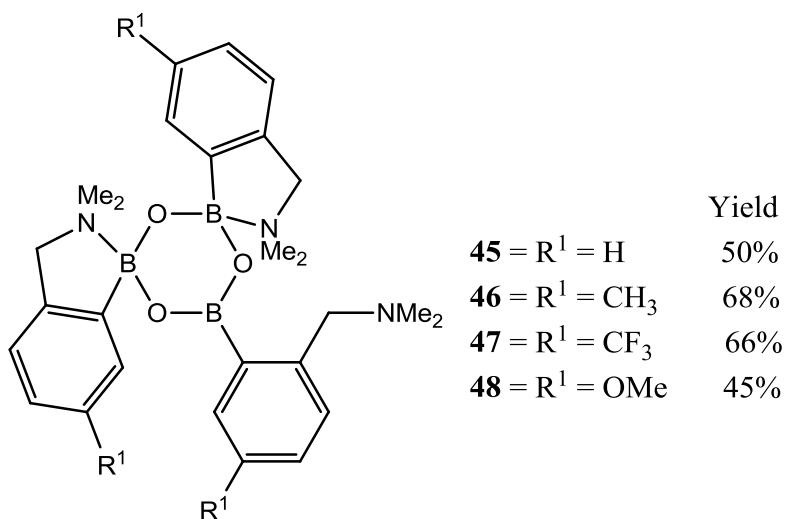


Figure 3.3.1: The proposed structure of the boroxine compounds

The molecular structure of [2-(Me₂NCH₂)C₆H₄BO]₃ (**45**)¹⁶³ has been determined previously by Norrild and Søtofte in a single crystal X-ray diffraction study.¹⁶⁴ However single crystals of **45** were grown from CH₂Cl₂/hexane in this study in order to confirm the absolute structure of the boroxine. The data collected for **45** showed that the unit cell was equivalent to that previously reported;¹⁶⁴ see Table 3.3.1 for comparison of the unit cell

data. A preliminary isotropic solution was carried out to confirm connectivities (Figure 3.3.2).

Table 3.3.1: Comparison of the Unit cell dimensions for compound 45.

	[2-(Me ₂ NCH ₂)C ₆ H ₄ BO] ₃ (45)	Literature Data from Norrild and Søtofte ¹⁶⁴
Formula	(C ₂₇ H ₃₆ N ₃ B ₃ O ₃)	(C ₂₇ H ₃₆ N ₃ B ₃ O ₃)
Formula Weight	483.3	483.02
Crystal System	Orthorhombic	Orthorhombic
Space group	P2 ₁ 2 ₁ 2 ₁	P2 ₁ 2 ₁ 2 ₁
a (Å)	8.9650(6)	8.9765(3)
b (Å)	14.709(11)	14.6975(4)
c (Å)	19.517(2)	19.6627(6)
T/K	100	120(2)

The solid state structure of **45** contains two intramolecular boron-nitrogen bonds, with B-N bond lengths of 1.758(1) Å and 1.726(1) Å. The third uncoordinated B-N distance is 3.162 Å. The co-ordination of only two NMe₂ to their Boron atoms is thought to be due to steric crowding around the central 6-membered (B-O)₃ ring.¹⁶⁴

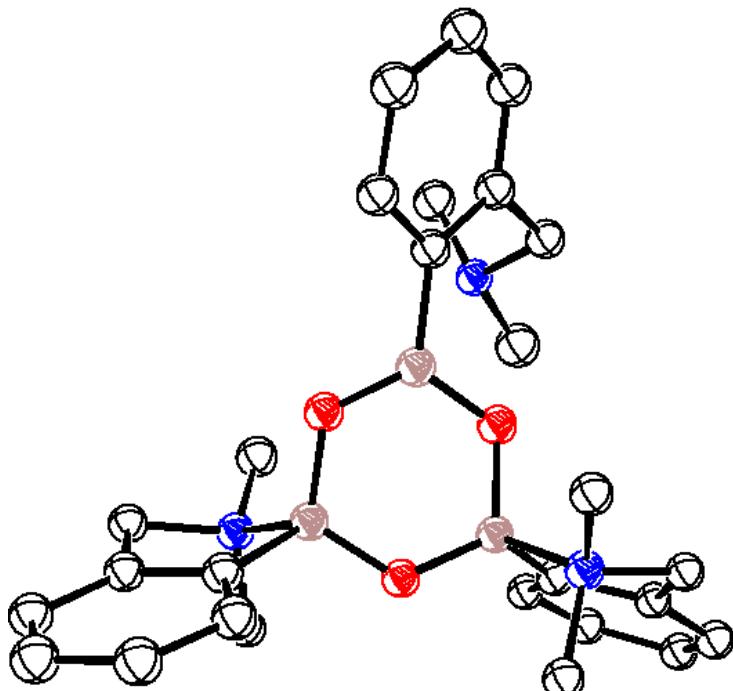


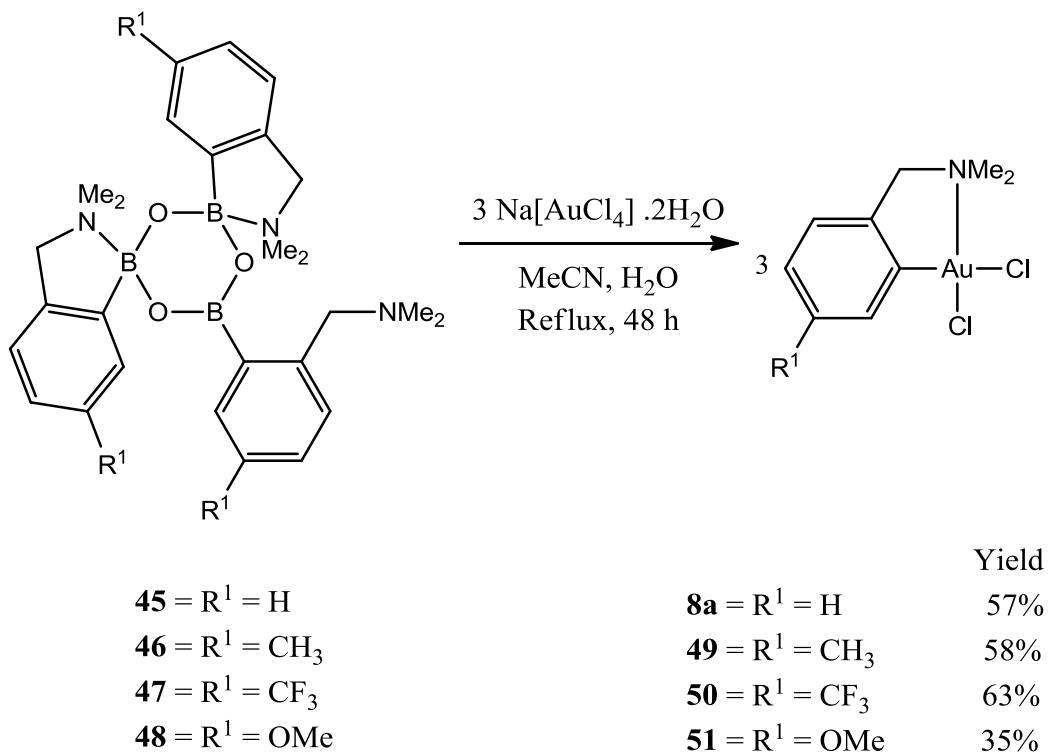
Figure 3.3.2: The molecular structure of **45** with thermal ellipsoids at 40% probability level. Hydrogen atoms are omitted for clarity.

The ¹H NMR spectra for compounds **45-48** are in good agreement with those reported in the literature for compounds of this type.¹⁶³ The ¹³C{¹H} NMR spectra each contain five resonances in the aromatic region, and also singlets for the CH₂ and NMe₂ carbons. The *ipso* carbon is NMR silent in all four of the compounds, due to the proximity to the

quadrupolar boron nucleus. Broad singlets centred around *ca.* 15 ppm are observed in the $^{11}\text{B}\{\text{H}\}$ NMR spectrum. The NMR data indicate that in solution the three units comprising the cyclic trimer are equivalent on the NMR timescale. This phenomenon has been reported previously and it is well-established that rapid B-N bond formation and cleavage can occur at room temperature in solution with boroxines and boronic esters of this type.¹⁶⁵

3.4 Gold(III) complexes prepared *via* transmetallation with boroxines

Gold(III) complexes [2-Me₂NCH₂-C₆H₄AuCl₂] (**8a**), [2-Me₂NCH₂-5-CH₃-C₆H₃AuCl₂] (**49**), [2-Me₂NCH₂-5-CF₃-C₆H₃AuCl₂] (**50**) and [2-Me₂NCH₂-5-OMe-C₆H₃AuCl₂] (**51**) were prepared by the addition of an aqueous solution of sodium tetrachloroaurate to the corresponding boroxine in acetonitrile (Scheme 3.4.1).¹⁶⁶ A yellow suspension was formed on stirring, which after 48 hours at reflux afforded the cyclometallated gold(III) complexes in moderate to good yields. The white products separated from the reaction mixture and were subsequently recrystallised from CH₂Cl₂/hexane. The reaction also proceeds in a similar fashion in aqueous ethanol under reflux. The microanalytical and spectroscopic data for **8a**, **49**, **50** and **51** is listed in section 8.4.4 of the experimental.



Scheme 3.4.1: The synthesis of gold(III) compounds from boroxines.

The ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR spectra of the gold complexes are consistent with the previously reported spectroscopic data for **8a** and derivatives.¹¹³ Upon coordination to Au(III) the signals corresponding to the CH_2 and NMe_2 groups in the cyclometallated ligands experience a significant downfield shift, in the ^1H NMR spectrum, relative to the free amine (**38-41**) and the boroxine (**45-48**) (Figure 3.4.1). A similar strong downfield shift of the signals is also observed in the $^{13}\text{C}\{^1\text{H}\}$ NMR spectra, and the *ipso* carbon is now visible for all four gold complexes.

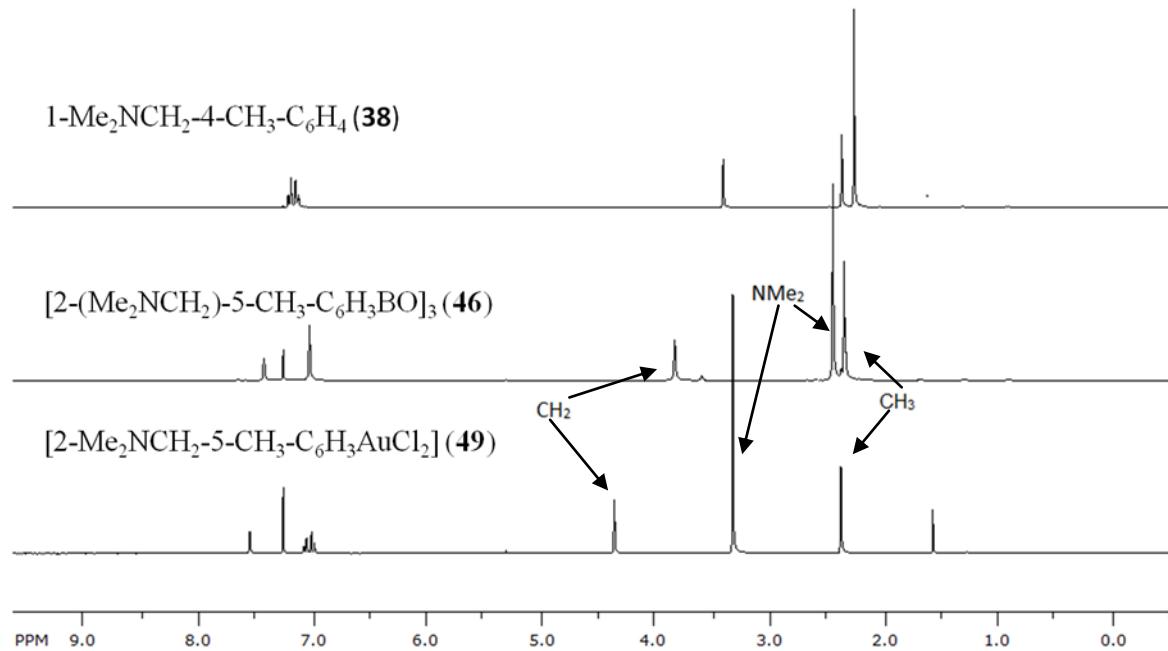


Figure 3.4.1: Illustration of the downfield shift that binding to gold(III) has on the proton resonances of the cyclometallating ligand in $[2-\text{Me}_2\text{NCH}_2-\text{5-CH}_3-\text{C}_6\text{H}_3\text{AuCl}_2]$ (**49**) in the ^1H NMR spectrum.

It has been well documented that transmetallation reactions involving Au(III) are extremely sensitive to the reaction conditions, especially the solvent used. Parish and co-workers routinely ran such reactions in dimethyl sulfoxide, acetonitrile and acetone.¹¹³ The boroxine transmetallation reaction to form **8a** was also carried out in both MeCN and EtOH, in the absence of H_2O . The ^{13}C NMR data from the crude reaction mixtures, see Figure 3.4.2, provided evidence for the formation of $[\text{AuCl}_2(\text{damp})]$ (**8a**) however the isolation of an analytically pure product could not be effected by a simple aqueous work-up and $\text{CH}_2\text{Cl}_2/\text{hexane}$ recrystallisation. It appears that the best solvent system for this new transmetallation reaction is aqueous acetonitrile, as the reaction proceeds with minimal deposition of metallic gold and allows simple isolation of the gold(III) complexes. It is believed that water plays a key role in transmetallation by hydrolysing the cyclic boroxine trimer. This allows coordination of the free nitrogen to the gold centre prior to

transmetallation.¹⁶⁶ This would be a similar mechanism to that proposed for organomercurial transfer (Scheme 2.1.5),⁹⁸ involving initial coordination of Au(III) to the amine donor followed by cycloauration.

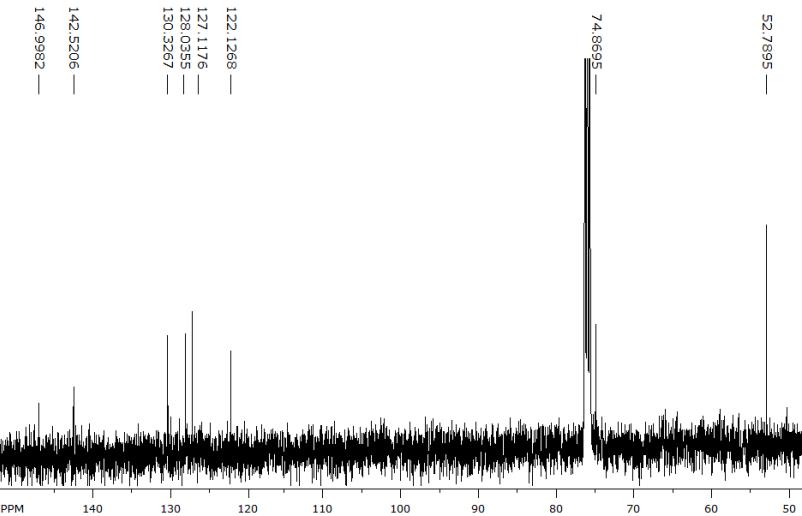


Figure 3.4.2: Crude $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of $(2\text{-Me}_2\text{NCH}_2)\text{-C}_6\text{H}_4\text{AuCl}_2$ (**8a**) formed by transmetallation of **45** with sodium tetrachloroaurate in MeCN, in the absence of water.

Single crystals of $(2\text{-Me}_2\text{NCH}_2)\text{-C}_6\text{H}_4\text{AuCl}_2$ (**8a**) were grown from $\text{CH}_2\text{Cl}_2/\text{hexane}$ in order to confirm formation of the gold(III) complex *via* boroxine transmetallation. The data collected in the single crystal X-ray diffraction study showed that the unit cell was equivalent to that previously reported,¹¹⁶ see Table 3.4.1. A preliminary isotropic solution of the data was carried out to confirm connectivities (Figure 3.4.3).

Table 3.4.1: Comparison of the unit cell data for $(2\text{-Me}_2\text{NCH}_2)\text{-C}_6\text{H}_4\text{AuCl}_2$ (**8a**) with that reported previously.

	$(2\text{-Me}_2\text{NCH}_2)\text{-C}_6\text{H}_4\text{AuCl}_2$ (8a)	Literature data for $[\text{AuCl}_2(\text{damp})]$ ¹¹⁶
Formula	$\text{C}_9\text{H}_{12}\text{NCl}_2\text{Au}$	$\text{C}_9\text{H}_{12}\text{NCl}_2\text{Au}$
Formula Weight	402.06	402.06
Crystal System	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/c$
a (Å)	7.7340(3)	7.896(3)
b (Å)	9.4210(3)	9.487(2)
c (Å)	15.0630(7)	15.107(6)
β (°)	100.2530(10)	100.22(3)
Crystal Size (mm)	0.2 x 0.14 x 0.14	0.5 x 0.35 x 0.2
T (K)	100	-

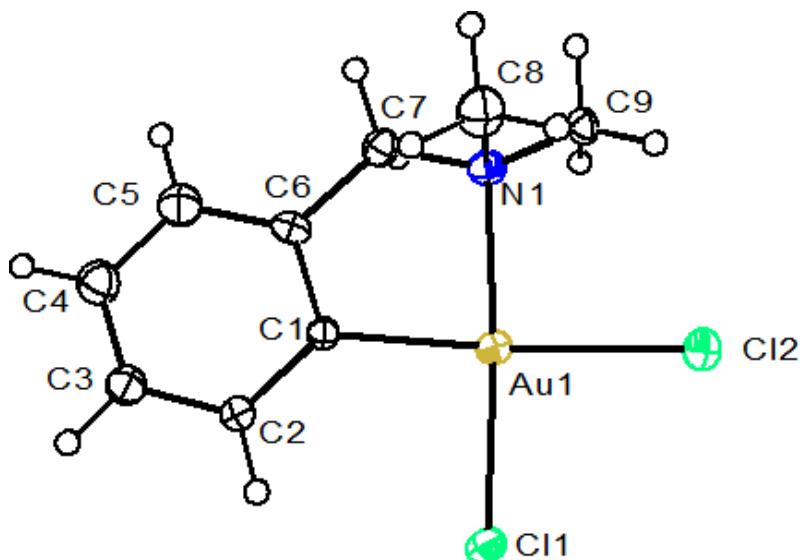


Figure 3.4.3: ORTEP representation of the preliminary isotropic solution of (2-Me₂NCH₂)-C₆H₄AuCl₂ (8a). Thermal ellipsoids at 40% probability.

Slow diffusion of hexane into a CH₂Cl₂ solution of [2-Me₂NCH₂-5-CH₃-C₆H₃AuCl₂] (**49**) resulted in the formation of colourless single crystals which were suitable for X-ray diffraction studies. Solution of the data obtained resulted in the molecular structure shown in Figure 3.4.4.

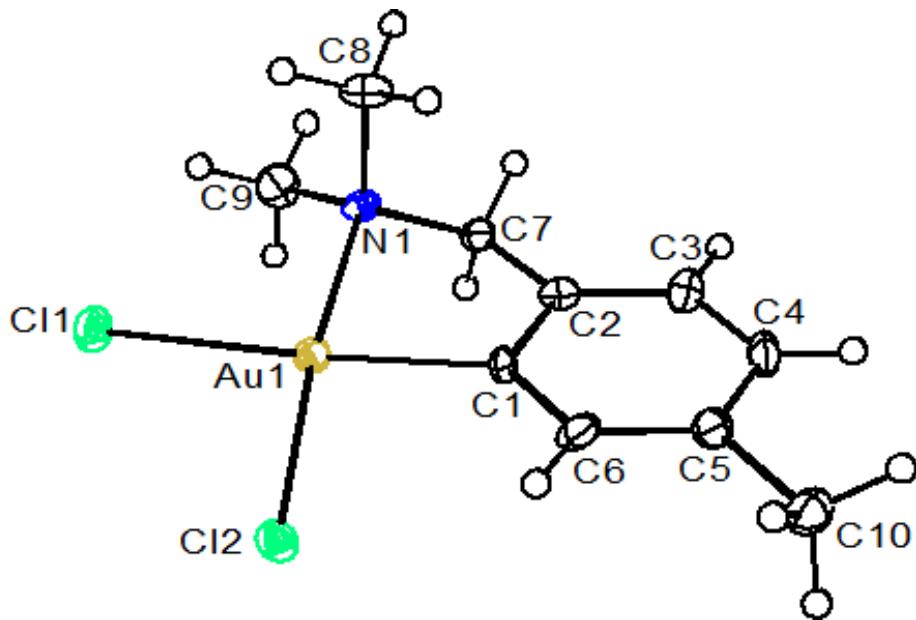


Figure 3.4.4: ORTEP representation of 2-Me₂NCH₂-5-CH₃-C₆H₃AuCl₂ (**49**). Thermal ellipsoids at 40% probability level.

Compound **49** crystallizes in the monoclinic space group *P2₁/c* and contains four molecules in the asymmetric unit cell. The gold-chlorine bond lengths (see Table 3.4.2 for

bond lengths and bond angles) show the characteristic differences associated with the strong *trans*-effect of the phenyl group relative to the NMe₂ group.¹¹⁶ Indeed the Au1-Cl1 bond is 0.098(4) Å longer than the Au1-Cl2 bond. The angles around the gold centre are approaching 90 °, and are typical of those for gold(III) in a square planar environment.

Table 3.4.2: Selected Bond Lengths (Å) and bond angles (°) for 49.

Dimension	Value	Dimension	Value
Au1-Cl1	2.385 (3) Å	Cl1-Au1-N1	94.1 (3) °
Au1-Cl2	2.287 (3) Å	Cl1-Au1-C1	175.6 (3) °
Au1-N1	2.091 (10) Å	Cl2-Au1-N1	173.8 (3) °
Au1-C1	2.028 (10) Å	Cl2-Au1-C1	92.4 (3) °
Cl1-Au1-Cl2	91.99 (9) °	N1-Au1-C1	81.5 (4) °

Table 3.4.3: Crystallographic data for 49.

Formula	C ₁₀ H ₁₄ NCl ₂ Au	T (K)	100 (2)
Formula Weight	416.09	D_c (g cm⁻³)	2.367
Crystal System	Monoclinic	Crystal Size (mm)	0.05 x 0.12 x 0.16
Space group	P2 ₁ /c	Mo K_a λ (Å)	0.71073
a (Å)	8.7402(3)	Total reflections	8932
b (Å)	11.1657(5)	Unique reflections (R_{int})	2663 (0.0531)
c (Å)	16.9401(5)	Goodness of Fit on F²	1.096
α (°)	90	Observed Reflections [I > 2σ(I)]	2372
β (°)	135.074(2)	Final R indices [I > 2σ(I)]	R 0.0469 wR ₂ 0.1202
γ (°)	90	Parameters	129
Z	4	S	1.10
V (Å³)	1167.47(8)	μ (mm⁻¹)	13.019

To summarise a new protocol for the preparation of gold(III) cyclometallated complexes containing dimethylbenzylamine derivatives is described. The reaction demonstrates that transmetallation from a boroxine to Au(III) in aqueous acetonitrile is an effective method of preparing cycloaurated gold(III) complexes with gold-carbon bonds.¹⁶⁶ The yields are comparable to those obtained *via* organomercury transmetallation. Additionally the boroxine route is advantageous as it avoids the use of extremely toxic mercury compounds, and therefore may enable development of organometallic gold(III) drugs free from contamination with other, toxic, heavy metals.

4 The Preparation of novel di-tin(IV) organometallics and their application to the synthesis of a di-gold(III) complex

The next aim of this research project was to prepare a digold(III) complex *via* transmetallation from novel transfer agents.

4.1 Dinuclear organogold complexes

Reports of dinuclear organogold complexes where the organic group acts as a spacer between the two gold centres are rare. Currently, the majority of examples concern digold(I) complexes bridged by highly substituted or branched organic groups.^{151,167,168} However recently progress has been made with Schmidbaur *et al.* reporting the preparation of bis(triphenylphosphine)gold(I) hydrocarbon species by reacting *in-situ* generated organolithium reagents with ClAuPPh₃.¹⁵¹ During these studies the authors found that digold(I) arenes that possess unsubstituted aryl groups (benzene and naphthalene) were difficult to prepare in a clean and efficient way using conventional approaches. Consequently Flower *et al.*^{27,47} developed a reproducible and efficient route to dilithio-benzene derivatives, which involved a lithium/iodine exchange, followed by isolation of the dilithio-compounds, before quenching with ClAuPPh₃. Figure 4.1.1 contains examples of digold(I) complexes synthesised *via* this route.

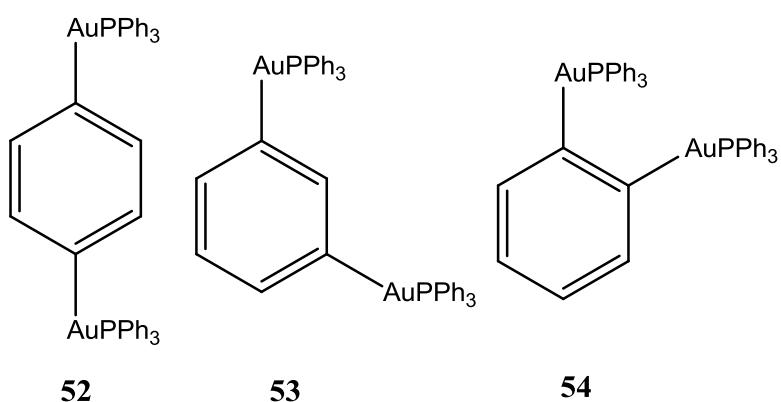


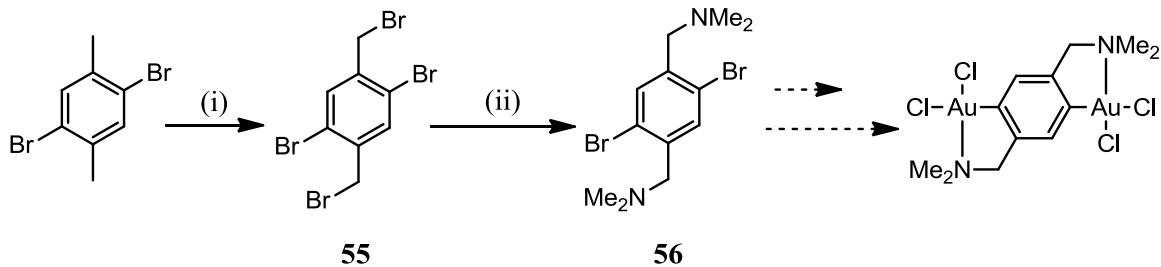
Figure 4.1.1: Digold(I) complexes synthesised via isolation of the dilithio reagent generated from lithium/iodine exchange, followed by quenching with ClAuPPh₃.

The digold(I) complexes prepared by both Schmidbaur and Flower exhibit interesting structural properties, in addition to the fact that the complexes synthesised by Flower have been shown to be highly cytotoxic in a range of cancer cell lines.⁴⁷ Therefore an attempt to

prepare a novel digold(III) complex, analogous to complexes **52-54** reported by Flower, was undertaken.

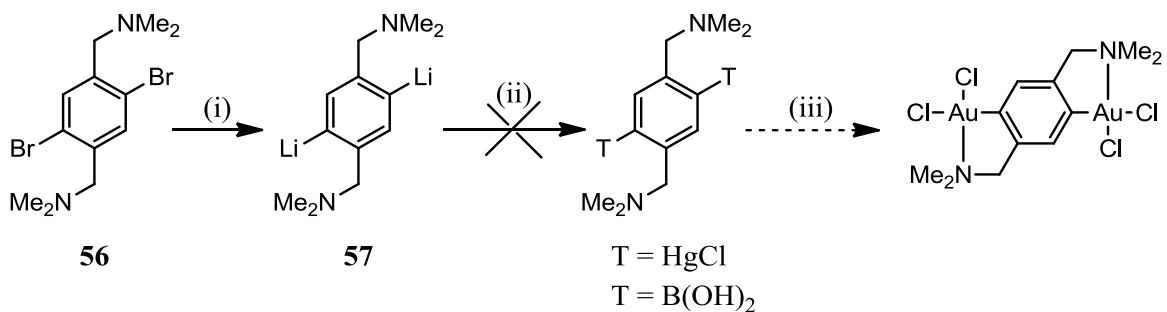
4.2 Preparation of amine ligand and established transmetallation reagents

The initial route investigated to synthesise a digold(III) complex is outlined in Scheme 4.2.1. Radical bromination of 2,5-dibromo-*p*-xylene with *N*-bromosuccinimide (NBS) in CHCl₃ in a modification of the method of Vicente *et al.*¹⁶⁹ and Swager and Izuhara¹⁷⁰ afforded 1,4-dibromo-2,5-bis(bromomethyl)-benzene (**55**) in 40% yield. 1,4-Dibromo-2,5-bis{(dimethylamino)methyl}-benzene (**56**) was prepared in 93% yield by nucleophilic substitution of **55** with dimethylamine in Et₂O according to the method described by Von Koten and co-workers.¹⁷¹



Scheme 4.2.1: Preparation of bisamines leading to digold(III) complex. (i) NBS, 1,1'-azobis(cyclohexanecarbonitrile), CHCl₃, reflux, 5 h; (ii) HNMe₂, EtOH, Et₂O, 3 h.

1,4-Dibromo-2,5-bis{(dimethylamino)methyl}-benzene (**56**) was originally used in the synthesis of platinum complexes,¹⁷¹ however the ligand could also be used for the preparation of the first di-gold(III) complex. Reaction of **56** with two equivalents of *n*-BuLi at -78 °C should result in double-lithium halogen exchange to give 1,4-(Li)₂-2,5-(NMe₂CH₂)₂-C₆H₂ (**57**) as reported by Van Koten and co-workers.¹⁷¹ The bromides *ortho* to the amine groups are used to ensure selective metalation occurs at those positions. The dilithio reagent can then be quenched, *in-situ*, with common transmetallation groups used to prepare gold(III) complexes, namely mercury or boron-centred electrophiles (Scheme 4.2.2). The resultant main group organometallics could then be utilised as transmetallation reagents in order to transfer the aryl bis-C,N chelating ligand to the gold(III) centres.



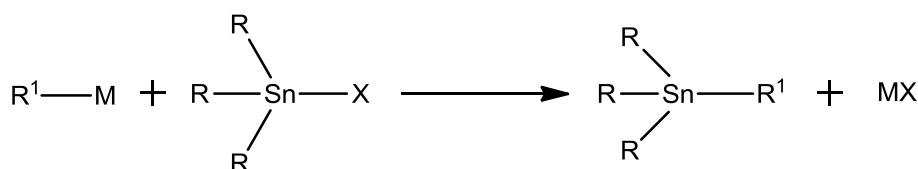
Scheme 4.2.2: Reaction scheme for the preparation of 1,4-(AuCl₂)₂-2,5-(Me₂NCH₂)₂-C₆H₂. (i) 2 *n*-BuLi, Et₂O, -78 °C to r.t.; (ii) HgCl₂ or B(O*i*Pr)₃, -78 °C to r.t.; (iii) transmetallation with 2 Na[AuCl₄] · 2H₂O.

This study would necessitate the preparation of the di-lithio reagent **57** in order to access the pivotal transfer agents “T”. To assess the potential of installing two transmetallation groups *ortho* to the amine substituents in **56** the dilithio reagent 1,4-(Li)₂-2,5-(NMe₂CH₂)₂-C₆H₂ (**57**) was prepared, using a modification of the method of Van Koten *et al.*,¹⁷¹ and quenched *in-situ* with trimethylsilyl chloride (TMSCl). After workup 1,4-(SiMe₃)₂-2,5-(Me₂NCH₂)₂-C₆H₂ (**58**) was isolated in 60% yield. ¹H and ¹³C{¹H} NMR data are contained in experimental section 8.5.3 and confirm formation of the bis-trimethylsilyl compound. Subsequently the preparation of 1,4-(HgCl)₂-2,5-(Me₂NCH₂)₂-C₆H₂ (**59**) and 1,4-(B(OH)₂)₂-2,5-(Me₂NCH₂)₂-C₆H₂ (**60**) was attempted by *in-situ* quenching of the organolithium reagent. A reverse quenching procedure was utilised, where the organolithium mixture was pre-cooled to -78 °C and added *via* cannula transfer to a vigorously stirred solution of HgCl₂ or B(O*i*Pr)₃ in Et₂O at -78 °C. This procedure was adopted in order to minimise side reactions and to prevent formation of polymeric species. Tri-isopropyl borate was used instead of trimethyl borate to further curtail unwanted side reactions in the case of **60**, although no boron-containing compound could be isolated from the reaction mixture. The reaction conditions used may have led to the formation of a boroxine as with **45-48** in section 3.3. Due to the symmetry of the chelating amine ligand the boroxine may be oligomeric or polymeric in nature,¹⁷² rather than the cyclic trimer observed for the boroxines in section 3.3, making isolation and identification of the pure product challenging. In an attempt to negate formation of polymeric species the lithium reagent was quenched with 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Bpin), however again no pure boron containing product could be isolated from the reaction mixture. A white powder was isolated from the reaction of HgCl₂ and organolithium reagent solution; however the material was completely insoluble in common laboratory solvents. There have been several literature reports outlining the synthesis of some aryl bis-

and poly-mercurial species^{173,174} and all have low solubility in common laboratory solvents including DMSO and DMF. It is possible that **59** cannot be formed directly from the organolithium reagent in this system due to the facile formation of oligomeric complexes, in which several amine ligands are linked by mercury centres. This would result in extremely insoluble compounds that could not be used in transmetallation with gold(III). The potential of Sn(IV) compounds as transfer agents in reactions with gold(III) salts was then explored as an alternative to the mercury and boron transmetallation routes.

4.3 Organotin(IV) Chemistry

The first organotin compound was reported by Frankland in 1849 who prepared diethylditin diiodide.¹⁷⁵ The area of organotin chemistry rapidly expanded from the 1940's onwards due to the commercial use of organotin compounds as stabilisers of polyvinyl chloride (PVC).^{176,177} Organotin(IV) compounds are typically prepared through the reaction of organometallics, commonly organolithiums and Grignard reagents, with tin precursors^{178,179} (Scheme 4.3.1).

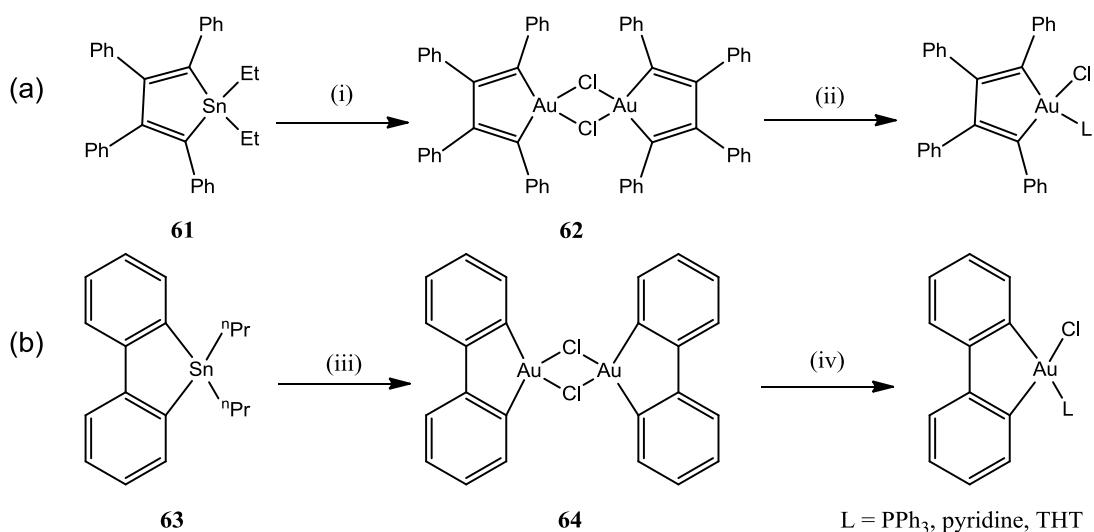


Scheme 4.3.1: The synthesis of Sn(IV) complexes through organometallic reagents. M = Li, Mg, Al or Zn, X = halide.

Organotin compounds have a wide range of uses in organic synthesis including their utility in promoting radical reactions.^{176,180} Additionally organotin compounds are key components in Stille reactions,^{181,182} however these uses are beyond the scope of this report. Organotin(IV) compounds have also been used as transmetallation reagents for the preparation of a variety of different metal complexes.^{183,184} Indeed polymercurated aromatics, that cannot be prepared directly from organolithium or Grignard reagents, have been synthesised *via* transmetallation with organotin compounds.^{173,185} The method involves the preparation of the relevant organotin compound, typically $(R\{SnMe_3\}_x)$, which is normally a well-defined monomeric species, and then substitution of the stannyl groups with chloromercurio groups.

Transmetallation reactions between Sn(IV) and Au(III) were first demonstrated by Vicente and co-authors in the early 1980's.^{123,186-188} For example the reaction between 1,1-diethyl-

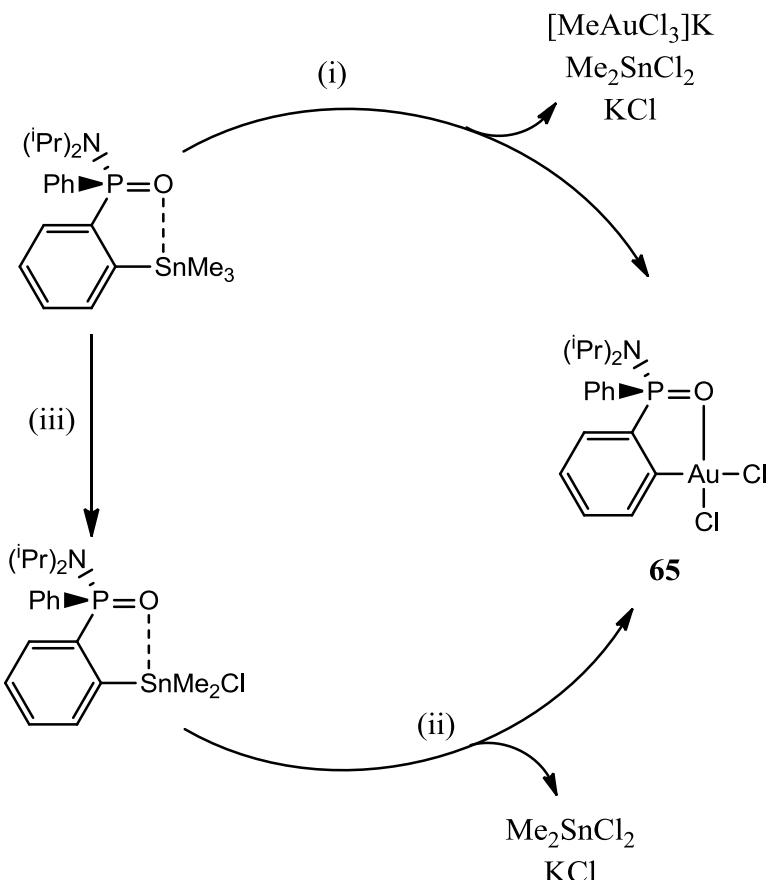
2,3,4,5-tetraphenyl-stannole (**61**) and $\text{Cl}_3\text{Au}(\text{THT})$ in Et_2O yields the 1-chloro-2,3,4,5-tetraphenylaura-cyclopentadiene dimer (**62**), in 75% yield¹⁸⁶ (Scheme 4.3.2). Release of monomeric complexes from these bridged dimeric compounds can be accomplished by further reaction with neutral monodentate ligands (PPh_3 , pyridine, THT) or by anionic bidentate ligands such as acetylacetoneate ([acac]). The 2,2-biphenyl moiety has also been transferred to gold(III) using a di-*n*-propyl-dibenzostannole (**63**).¹⁸⁷ Again the complex was isolated as the insoluble chloride bridged dimer (**64**), which could be split (Scheme 4.3.2) to give soluble monomeric compounds.



Scheme 4.3.2: The first reported Sn to Au(III) transmetallation reactions. (a) Synthesis and bridge splitting of the 1-chloro-2,3,4,5-tetraphenylaura-cyclopentadiene dimer. (i) $\text{Cl}_3\text{Au}(\text{THT})$, Et_2O , r. t., 20 mins; (ii) CH_2Cl_2 , L ; (b) Synthesis of the 2,2-biphenylgold(III) auracycle. (iii) $\text{Cl}_3\text{Au}(\text{THT})$, CH_2Cl_2 , 45 mins; (iv) CH_2Cl_2 , L .

Despite these promising results with tin transfer agents the advent of organomercurial transmetallation to gold(III) meant that this route to Au(III) complexes remained relatively unexplored until a recent example highlighted the utility of this method. Ortiz *et al.*¹⁸⁹ have demonstrated both ArSnMe_3 and ArSnMe_2Cl compounds behave as transfer agents in their synthesis of a gold phosphinamide complex (**65**), in 86% yield (Scheme 4.3.3). The tin reagents can be readily prepared by way of an *ortho*-directed lithiation of *N,N*-diisopropyl-*P,P*-diphenyl phosphinic amide followed by quenching at -78 °C with either ClSnMe_3 or Cl_2SnMe_2 . During the course of these studies it was found that aryl transfer from the ArSnMe_2Cl species was more efficient. This is because chlorine-methyl exchange takes place at the Sn-centre in the trimethyl stannyly compound when only one equivalent of potassium tetrachloroaurate is added per trimethyl stannyly group. Dimethyl tin dichloride is produced in the transmetallation reactions as a by-product. The synthesis of gold(III) complexes *via* transmetallation from organotin precursors offers a simple and high yielding

alternative to transmetallation from organomercurials. Coupled with this is the fact that organotin compounds, although toxic, are significantly less-toxic than the corresponding organomercury compounds.



Scheme 4.3.3: General Scheme for the preparation of gold(III) phosphorinamide (**65**) using Sn(IV) transfer agents.
 (i) 2 K[AuCl₄], CH₃CN, 90°C, 2 h; (ii) K[AuCl₄], CH₃CN, 90°C, 2 h; (iii) K[AuCl₄], CH₃CN, r.t., < 5 mins.

4.4 The preparation of organo-ditin(IV) compounds

The organotin compounds 1,4-(SnPh₃)₂-2,5-(Me₂NCH₂)₂-C₆H₂ (**66**), 1,4-(SnMe₃)₂-2,5-(Me₂NCH₂)₂-C₆H₂ (**67**), and 1,4-(SnMe₂Cl)₂-2,5-(Me₂NCH₂)₂-C₆H₂ (**68**), shown in Figure 4.4.1, were prepared by the *in-situ* quenching of 1,4-(Li)₂-2,5-(NMe₂CH₂)₂-C₆H₂ (**57**), with the appropriate tin chloride, in 51, 44 and 53% yield respectively. The analytical and spectroscopic data for **66**, **67**, and **68** is contained in experimental sections 8.5.4-8.5.6.

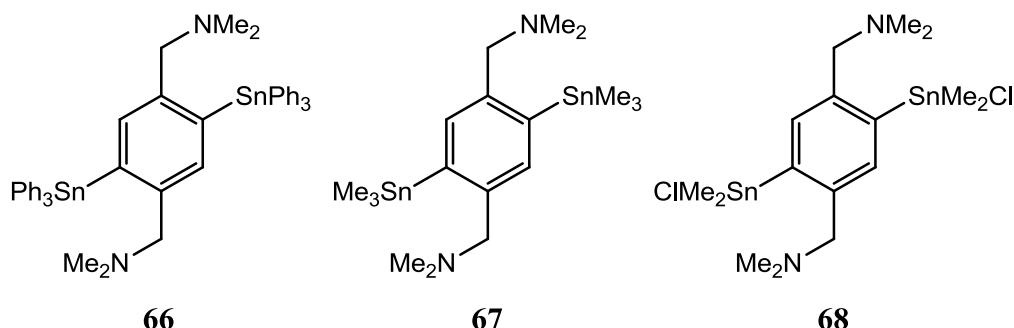


Figure 4.4.1: The organotin complexes prepared from 1,4-(Li)₂-2,5-(NMe₂CH₂)₂-C₆H₄ (**57**).

The ¹H and ¹³C{¹H} NMR spectra are similar to that of 1,4-(Me₂NCH₂)₂-C₆H₄ with singlets observed for all the benzylic-CH₂ and NMe₂ groups. This is consistent with either a tetrahedral Sn atom or a pentacoordinate Sn centre where intramolecular N → Sn dissociation and re-coordination is fast.¹⁹⁰ ¹¹⁹Sn{¹H} NMR spectroscopy is well established as a valuable tool for the elucidation of the structures of organotin compounds in solution.¹⁹¹ This is because the ¹¹⁹Sn chemical shift is dependent on the oxidation state of tin, and the type and number of substituents bound to the Sn centre, and the co-ordination geometry at the tin centre. Table 4.4.1 contains the ¹¹⁹Sn{¹H} chemical shifts for **66**, **67**, **68** and a range of reference compounds. It is generally found that an increase in coordination number at the metal centre results in a large upfield shift in the ¹¹⁹Sn signal relative to the corresponding tin reference samples, Table 4.4.1, entries 7-11.^{190,191} For **66** the ¹¹⁹Sn{¹H} shift is similar to that reported for the mononuclear tin complex (entry 4). An upfield shift of 36 ppm is observed when compared to the SnPh₄ reference sample (entry 11) indicating that only a weak intramolecular interaction between tin and nitrogen takes place in solution. For **67** the ¹¹⁹Sn{¹H} chemical shift is similar to that reported for the related mononuclear complex, entry 5. An upfield shift of 23 ppm is observed relative to the Me₃SnPh reference (entry 10) which again indicates that only a weak N → Sn interaction is present. In the case of **68** a large upfield shift of *ca.* 100 ppm is clearly visible relative to PhMe₂SnCl (entry 8). This suggests that for **68** the tin is now pentacoordinate with a strong intramolecular nitrogen-tin coordination in solution. The ¹¹⁹Sn{¹H} chemical shift is similar to that reported for the analogous mononuclear tin species (entry 6).

Table 4.4.1: $^{119}\text{Sn}\{^1\text{H}\}$ NMR shifts for a range of tin compounds.

Entry	Compound	$^{119}\text{Sn}\{^1\text{H}\} \delta$ (ppm)	Reference
1	66	-164.1	This work
2	67	-52.0	This work
3	68	-49.8	This work
4	(2-Me ₂ NCH ₂ C ₆ H ₄)Ph ₃ Sn	-164.1	¹⁹²
5	(2-Me ₂ NCH ₂ C ₆ H ₄)Me ₃ Sn	-50.0	¹⁹¹
6	(2-Me ₂ NCH ₂ C ₆ H ₄)Me ₂ SnCl	-48.7	¹⁹⁰
7	Ph ₂ SnCl ₂	-53.5	¹⁹³
8	Me ₂ PhSnCl	48.3	¹⁹⁴
9	Ph ₃ SnCl	-44.8	¹⁹⁵
10	Me ₃ PhSn	-28.7	¹⁹⁶
11	SnPh ₄	-128.1	¹⁹⁷

The formation of the dinuclear tin reagents was confirmed by single crystal X-ray diffraction studies. Single crystals of **66** suitable for X-ray diffraction studies were grown by slow diffusion of hexane into a saturated CH₂Cl₂ solution. **66** crystallises in the triclinic space group *P-1* with a dichloromethane molecule of crystallisation disordered about a site of special symmetry. An ORTEP representation of **66** is displayed in Figure 4.4.2. The Sn-N distance of 2.913(4) Å suggests that a weak intramolecular interaction between the nitrogen atoms and the Sn centres is present, mirroring the $^{119}\text{Sn}\{^1\text{H}\}$ NMR data obtained in solution.

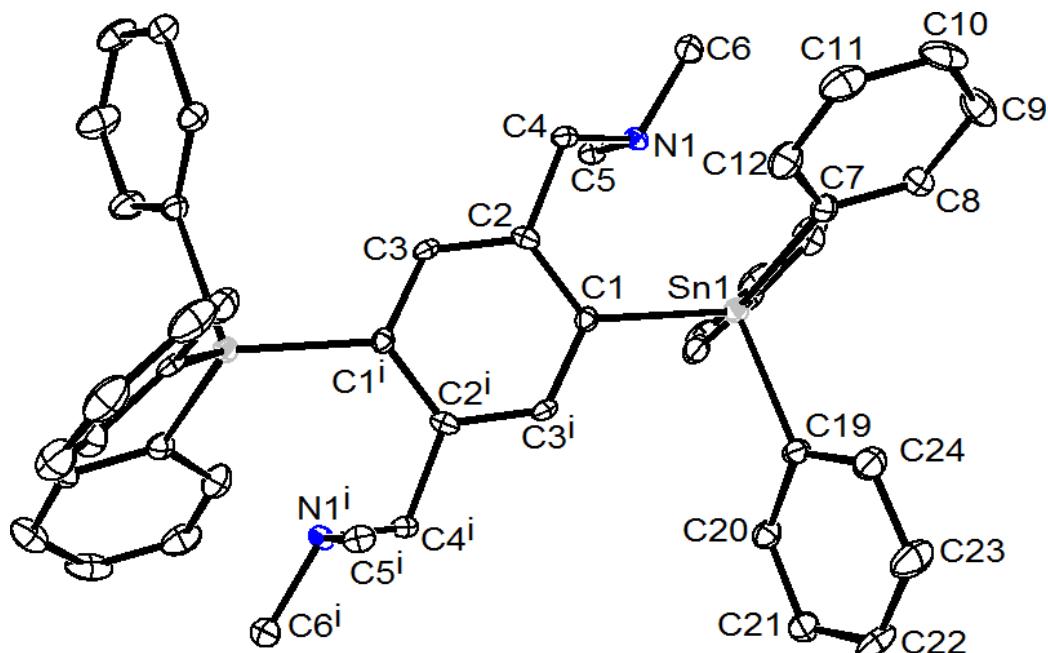


Figure 4.4.2: ORTEP representation of 1,4-(SnPh₃)₂-2,5-(Me₂NCH₂)₂-C₆H₂ (**66**). Hydrogen atoms and CH₂Cl₂ of crystallisation omitted for clarity. Thermal ellipsoids at 40% probability level.

Table 4.4.2: Selected bond lengths (Å) and bond angles (°) for 1,4-(SnPh₃)₂-2,5-(Me₂NCH₂)₂-C₆H₂ (66).

Dimension	Value	Dimension	Value
C1-Sn1	2.145(4) Å	C7-Sn1-C13	115.58(18) °
C7-Sn1	2.144(5) Å	C1-Sn1-C7	114.18(17) °
C13-N1	2.141(4) Å	C13-Sn1-C19	105.83(17) °
C19-Sn1	2.173(5) Å	C7-Sn1-C19	103.12(18) °
C1-Sn1-C13	112.47(17) °	C1-Sn1-C19	104.08(17) °

Table 4.4.3: Crystallographic data for 1,4-(SnPh₃)₂-2,5-(Me₂NCH₂)₂-C₆H₂ (66).

Formula	[C ₄₈ H ₄₈ N ₂ Sn ₂] .CH ₂ Cl ₂	T (K)	102(2)
Formula Weight	975.19	D_c (g cm⁻³)	1.490
Crystal System	triclinic	Crystal Size (mm)	1.0 x 0.1 x 0.1
Space group	<i>P</i> -1	Mo K_a λ (Å)	0.7107
a (Å)	8.1724(5)	Total reflections	6940
b (Å)	10.6414(5)	Unique reflections (R_{int})	4442 (0.0616)
c (Å)	13.2207(7)	Goodness of Fit on F²	1.024
α (°)	79.971(4)	Observed Reflections [I > 2σ(I)]	3819
β (°)	89.438(4)	Final R indices [I > 2σ(I)]	R 0.0506 wR ₂ 0.1291
γ (°)	73.889(5)	Parameters	255
Z	1	S	1.033
V (Å³)	1086.81(10)	μ (mm⁻¹)	1.307

Slow cooling of a saturated methanol solution of **67** resulted in the formation of colourless needles which were suitable for X-ray diffraction studies. **67** crystallises in the triclinic space group *P*-1 with one molecule in the asymmetric unit. An ORTEP representation of **67** is displayed in Figure 4.4.3. The Sn-N distance of 2.948 Å suggests that a weak intramolecular interaction between the nitrogen atoms and the Sn centres is present, mirroring the ¹¹⁹Sn{¹H} NMR data obtained in solution.

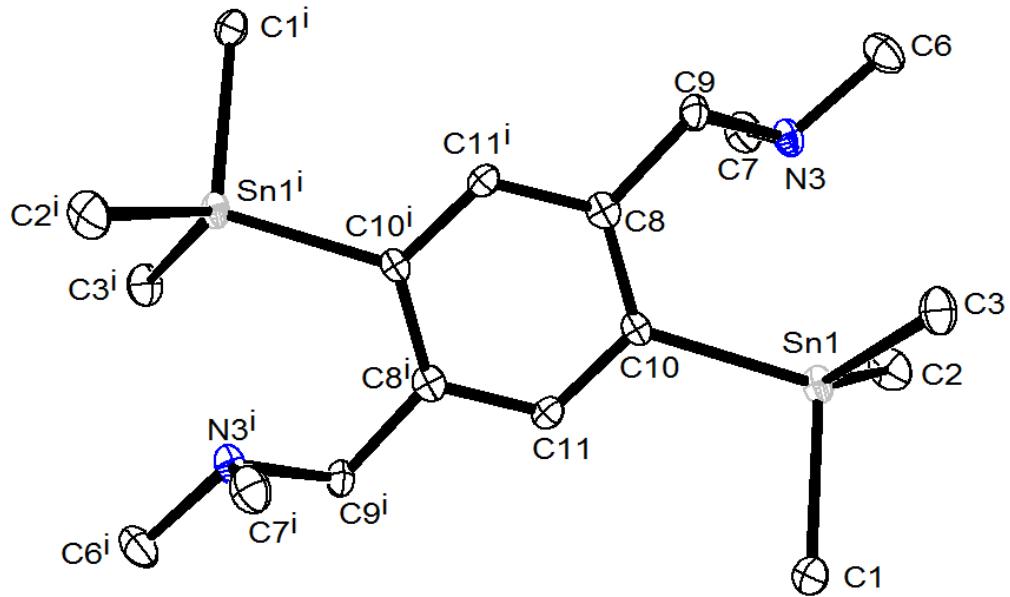


Figure 4.4.3: ORTEP representation of 1,4-(SnMe₃)₂-2,5-(Me₂NCH₂)₂-C₆H₂ (67). Hydrogen atoms omitted for clarity. Thermal ellipsoids at 40% probability level.

Table 4.4.4: Selected bond lengths (Å) and bond angles (°) for 1,4-(SnMe₃)₂-2,5-(Me₂NCH₂)₂-C₆H₂ (67).

Dimension	Value	Dimension	Value
Sn1-C10	2.153(6) Å	C2-Sn1-C1	103.8(2) °
Sn1-C1	2.160(6) Å	C3-Sn1-C1	106.5(2) °
Sn1-C2	2.136(6) Å	C3-Sn1-C2	112.2(2) °
Sn1-C3	2.134(6) Å	C10-Sn1-C2	116.8(2) °
C10-Sn1-C1	103.4(2)°	C10-Sn1-C3	112.7(2) °

Table 4.4.5: Crystallographic data for 1,4-(SnMe₃)₂-2,5-(Me₂NCH₂)₂-C₆H₂ (67).

Formula	C ₁₈ H ₃₆ N ₂ Sn ₂	T (K)	100(2)
Formula Weight	517.87	D_c (g cm⁻³)	1.572
Crystal System	Triclinic	Crystal Size (mm)	0.3 x 0.1 x 0.05
Space group	P-1	Mo K_a λ (Å)	0.7107
a (Å)	6.3767(11)	Total reflections	4047
b (Å)	7.6481(12)	Unique reflections (R_{int})	2042 (0.0499)
c (Å)	11.9372(19)	Goodness of Fit on F²	1.056
α (°)	107.094(14)	Observed Reflections [I > 2σ(I)]	1879
β (°)	95.128(14)	Final R indices [I > 2σ(I)]	R 0.0465 wR ₂ 0.1153
γ (°)	97.173(14)	Parameters	105
Z	1	S	1.056
V (Å³)	547.19(16)	μ (mm⁻¹)	2.282

Slow diffusion of hexane into a saturated CH_2Cl_2 solution of **68** resulted in the formation of single crystals suitable for X-ray diffraction studies. **68** crystallises in the triclinic space group $P-1$ with four molecules in asymmetric unit cell, see Figure 4.4.4 for an ORTEP representation. The Sn atoms are intramolecularly coordinated by the nitrogen on the pendant arm resulting in a distorted trigonal bipyramidal coordination geometry at tin in which the chloride ligand adopts a *trans* disposition with respect to the NMe_2 group. The bond lengths are comparable to those found in the related mononuclear compound,^{190,198} with an Sn-N bond length of 2.463(5) Å. The Sn-N distance is greater than the sum of the covalent radii for tin and nitrogen ($\Sigma_{\text{covalent radii}} = 2.1$ Å for Sn-N¹⁹⁹) which is common for this type of complex.

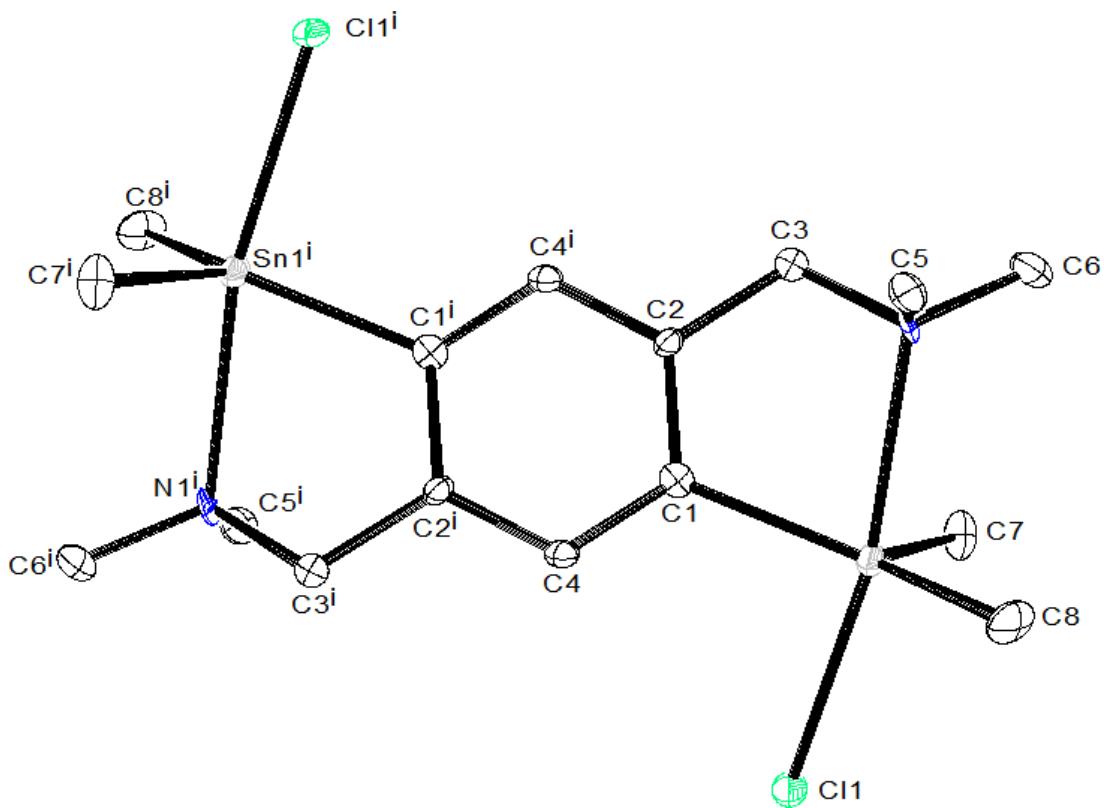


Figure 4.4.4: ORTEP representation of $1,4-(\text{SnMe}_2\text{Cl})_2 \cdot 2,5-(\text{Me}_2\text{NCH}_2)_2 \cdot \text{C}_6\text{H}_2$ (**68**). Hydrogen atoms omitted for clarity. Thermal ellipsoids at 40% probability level.

The extended structure shown in Figure 4.4.5 revealed intermolecular hydrogen bonding interactions between chloride atoms and hydrogen atoms from adjacent nitrogen methyl groups. The typical distances of 2.877(16) Å and 2.853(16) Å are shorter than the sum of the corresponding van der Waals radii ($\Sigma_{\text{vdW radii}} = \sim 3.0$ Å for $\text{Cl} \cdots \text{H}$ ¹⁹⁹). This results in a layered network throughout the structure with $\text{Cl} \cdots \text{H}$ contacts between layers.

Table 4.4.6: Selected bond lengths (Å) and bond angles (°) for 1,4-(SnMe₂Cl)₂-2,5-(Me₂NCH₂)₂-C₆H₂ (68).

Dimension	Value	Dimension	Value
Sn1-C1	2.5254(16) Å	C1-Sn1-N1	75.5(2) °
Sn1-N1	2.463(5) Å	C1-Sn1-C11	93.79(17) °
Sn1-C11	2.136(6) Å	N1-Sn1-C11	168.36(12) °
Sn1-C7	2.152(7) Å	C1-Sn1-C7	117.7(2) °
Sn1-C8	2.149(6) Å	C1-Sn1-C8	126.0(2) °

Table 4.4.7: Crystallographic data for 1,4-(SnMe₂Cl)₂-2,5-(Me₂NCH₂)₂-C₆H₂ (68).

Formula	C ₁₆ H ₁₈ Cl ₂ N ₂ Sn ₂	T (K)	100(2)
Formula Weight	546.64	D_c (g cm⁻³)	1.711
Crystal System	triclinic	Crystal Size (mm)	0.6 x 0.4 x 0.25
Space group	P-1	Mo K_a λ (Å)	0.71073
a (Å)	7.5457(4)	Total reflections	6968
b (Å)	12.3249(6)	Unique reflections (R_{int})	4339 (0.0822)
c (Å)	12.4731(6)	Goodness of Fit on F²	1.043
α (°)	68.613(4)	Observed Reflections [I > 2σ(I)]	3645
β (°)	80.823(4)	Final R indices [I > 2σ(I)]	R 0.0499 wR ₂ 0.1341
γ (°)	81.496(4)	Parameters	203
Z	4	S	1.043
V (Å³)	1061.20(9)	μ (mm⁻¹)	2.603

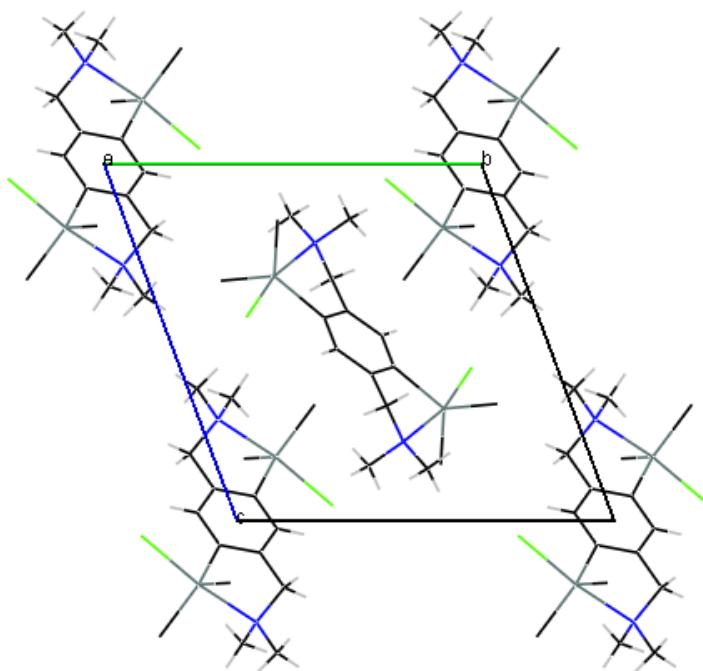
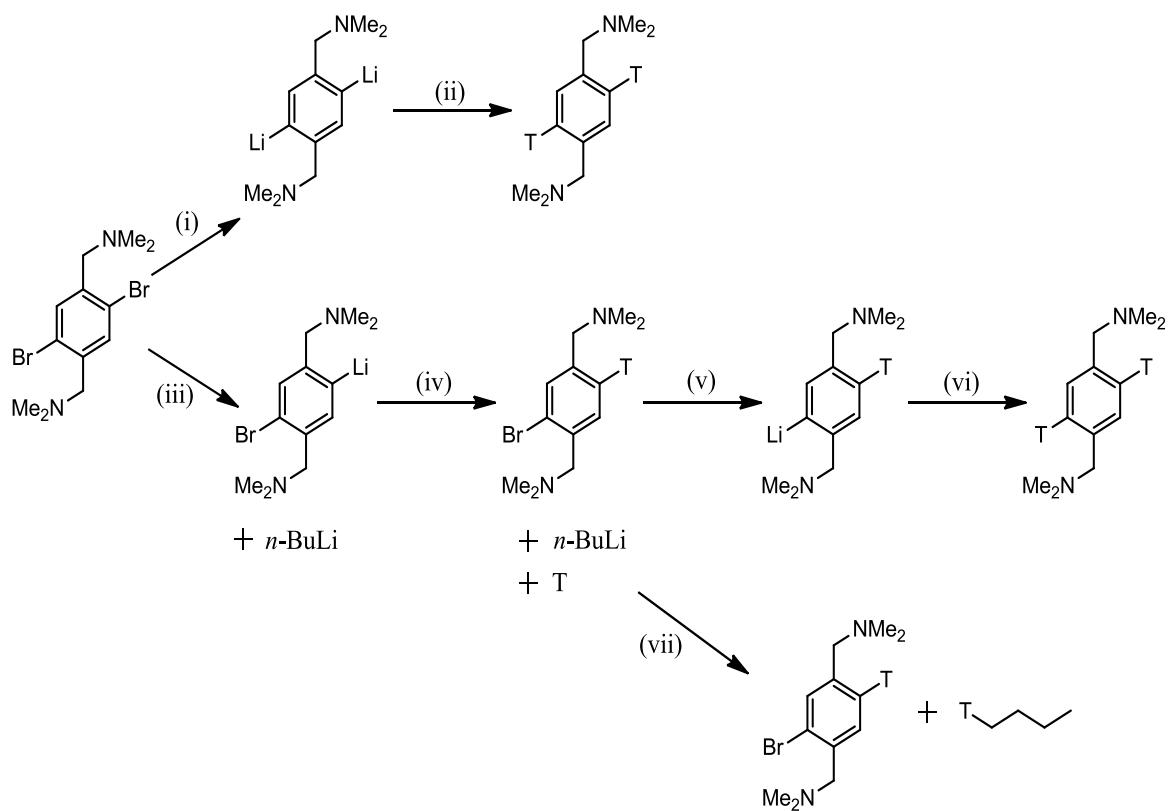


Figure 4.4.5: Packing diagram for $1,4\text{-}(\text{SnMe}_2\text{Cl})_2\text{-}2,5\text{-}(\text{Me}_2\text{NCH}_2)_2\text{-C}_6\text{H}_2$ (**68**) viewed down the **a** axis.

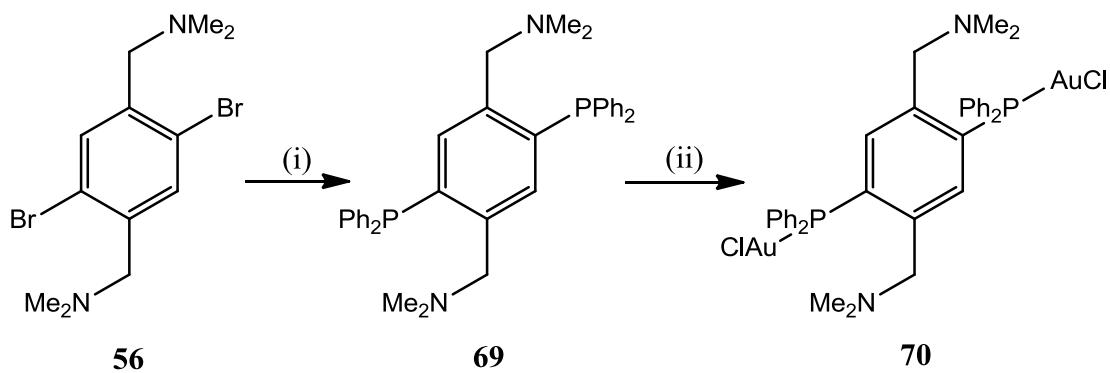
4.5 Discussion of lithium chemistry and preparation of phosphines

The preparation of **58**, **66**, **67** and **68** was based on the assumption of the *in-situ* formation of dilithio reagent $1,4\text{-}(\text{Li})_2\text{-}2,5\text{-}(\text{NMe}_2\text{CH}_2)_2\text{-C}_6\text{H}_2$ (**57**). However the moderate yields obtained for the silyl and tin derivatives (50–60%), coupled with the report of Fossatelli *et al.*²⁰⁰ suggest that this assumption may be flawed. Fossatelli indicated that when attempting to prepare $[1,4\text{-Li}_2\text{-C}_6\text{H}_4]$ from $[1,4\text{-Br}_2\text{-C}_6\text{H}_4]$ even when quenching with reactive electrophiles, *n*-BuLi and the electrophile may co-exist. The desired di-substituted product could thus be obtained after a sequence of alternating lithium-bromine exchange and derivatisations.²⁰⁰ The authors concluded that the key to achieving 100% double lithiation is the absolute need to keep the mono-lithium species in solution. Recent investigations by Flower *et al.*²⁷ have confirmed these observations and also suggest that isolation of dilithium reagents is advantageous, giving cleaner reactions. Scheme 4.5.1 outlines the possible routes to di-substituted products from lithium-bromine exchange on 1,4-dibromo-2,5-bis{(dimethylamino)methyl}-benzene (**56**). Attempts to isolate a clean sample of **57** were unsuccessful, and longer reaction times did not result in improved yields of di-substituted products. It is highly likely that the dilithio reagent is polymeric as reported for structurally related dilithium compounds.²⁰¹ In an effort to determine the extent of dilithiation the 1,4-dibromo-2,5-bis{(dimethylamino)methyl}-benzene/ *n*-BuLi reaction

mixture was quenched with 2 equivalents of chlorodiphenyl phosphine according to Scheme 4.5.2. ClPPh₂ reacts with any excess *n*-BuLi faster than reaction with the desired dilithium reagent, thereby giving an indication of the extent of dilithiation. The new bisphosphine 1,4-(PPh₂)₂-2,5-(Me₂NCH₂)₂-C₆H₂ (**69**) was obtained in 52% yield indicating that dilithiation occurs to ~50% under the reaction conditions used, which would explain the moderate yields obtained for quenching with Sn electrophiles. The analytical and spectroscopic data for **69** is contained in the experimental, section 8.5.7.



Scheme 4.5.1: Dilithiation of **56**. (i) 2.2 *n*-BuLi, Et₂O, 2 h, -78 °C to r.t.; (ii) 2 T, where T = ClSiMe₃, ClSnPh₃, ClSnMe₃, Cl₂SnMe₂, Et₂O, -78 °C; (iii) 2.2 *n*-BuLi, Et₂O, 2 h, -78 °C to r.t.; (iv) 2 T, where T = ClSiMe₃, ClSnPh₃, ClSnMe₃, Cl₂SnMe₂, Et₂O, -78 °C; (v) Lithium-bromine exchange with second equivalent of *n*-BuLi (sequential); (vi) quench of lithium reagent with second equivalent of T; (vii) Alternative pathway where reaction of *n*-BuLi and T is faster than the second lithium-bromine exchange.



Scheme 4.5.2: Quenching of 1,4-(Li)₂-2,5-(NMe₂CH₂)₂-C₆H₂ (**57**) with ClPPPh₂. (i) 2 *n*-BuLi, Et₂O, -78 °C to r.t., 2h , 2ClPPPh₂; (ii) 2 ClAu(THT), CH₂Cl₂, r.t., 24 h.

The solid state structure of **69** was confirmed by a single crystal X-ray diffraction study. Slow evaporation of a saturated CH₂Cl₂/hexane (2:1) solution of **69** resulted in the formation of colourless single crystals that were suitable for X-ray diffraction. **69** crystallises triclinic in the space group *P*-1 with one molecule in the asymmetric unit cell. Figure 4.5.1 contains an ORTEP representation of the solid state structure. The N-P distance of 2.855 Å indicates a weak intramolecular interaction with the nitrogen pendant arm pointing towards the phosphorus atoms. However the NMe₂ groups are twisted 27.22° out of the P1-C13-C15ⁱ-C16ⁱ plane.

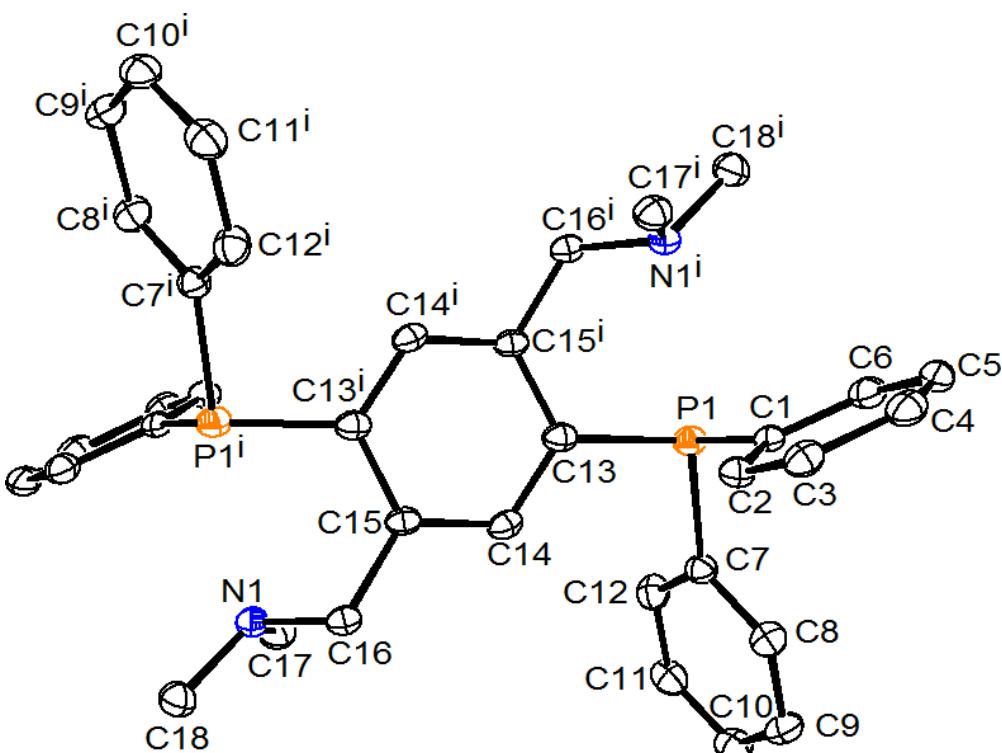


Figure 4.5.1: ORTEP representation of 1,4-(PPh₂)₂-2,5-(Me₂NCH₂)₂-C₆H₂ (**69**). Hydrogen atoms omitted for clarity. Thermal ellipsoids at 4% probability level.

Table 4.5.1: Selected bond lengths (\AA) and bond angles ($^{\circ}$) for 1,4-(PPh₂)₂-2,5-(Me₂NCH₂)₂-C₆H₂ (69).

Dimension	Value
P1-C7	1.838(3) \AA
P1-C1	1.832(3) \AA
P1-C13	1.842(3) \AA
C7-P1-C13	102.19(14) $^{\circ}$
C1-P1-C7	102.39(14) $^{\circ}$
C1-P1-C13	102.42(14) $^{\circ}$

Table 4.5.2: Crystallographic data for 1,4-(PPh₂)₂-2,5-(Me₂NCH₂)₂-C₆H₂ (69).

Formula	C ₃₆ H ₃₈ N ₂ P ₂	T (K)	100(2)
Formula Weight	560.62	D_c (g cm⁻³)	1.227
Crystal System	Triclinic	Crystal Size (mm)	0.4 x 0.2 x 0.1
Space group	<i>P</i> -1	Mo K_α λ (\AA)	0.71073
a (\AA)	8.0200(7)	Total reflections	3103
b (\AA)	9.9267(8)	Unique reflections (R_{int})	2069 (0.0689)
c (\AA)	10.5000(9)	Goodness of Fit on F²	1.035
α ($^{\circ}$)	76.447(7)	Observed Reflections [I > 2σ(I)]	3093
β ($^{\circ}$)	68.973(8)	Final R indices [I > 2σ(I)]	R 0.0689 wR ₂ 0.1778
γ ($^{\circ}$)	85.039(7)	Parameters	183
Z	1	S	1.035
V (\AA^3)	758.53(11)	μ (mm⁻¹)	0.171

The bisphosphine could undergo further reaction with ClAu(THT) (**24**) in CH₂Cl₂ to give the novel digold(I)-phosphine complex 1,4-(ClAuPPh₂)₂-2,5-(Me₂NCH₂)₂-C₆H₂ (**70**) in 87% yield. The ³¹P{¹H} NMR spectrum displays a significant downfield shift of ~42 ppm from -15.2 ppm for the parent bisphosphine to 26.9 ppm for the phosphine bound to AuCl. The solid state structure of **70** was determined by a single crystal X-ray diffraction study. **70** crystallises in the triclinic space group *P*-1 with one molecule in the asymmetric unit cell. The geometry around the gold(I) centre shows the expected approximately linear arrangement with a P1-Au1-Cl1 bond angle of 174.10(4) $^{\circ}$. The N-P distance has increased to 3.085(4) \AA relative to the distance in the free phosphine. An N-Au distance of 3.365(4) \AA indicates no intramolecular coordination between the atoms. In the extended structure (Figure 4.5.3) weak aurophilic contacts²⁵ are visible throughout the layered structure with typical Au-Au distances of 3.825(4) \AA . Also present are intermolecular hydrogen bonding

interactions between PAr-H and Cl. Each molecule is linked to two neighbouring molecules with Cl \cdots H distances of 2.797(12) Å and 2.848(11) Å, which are shorter than the sum of the van der Waals radii for chlorine and hydrogen.¹⁹⁹

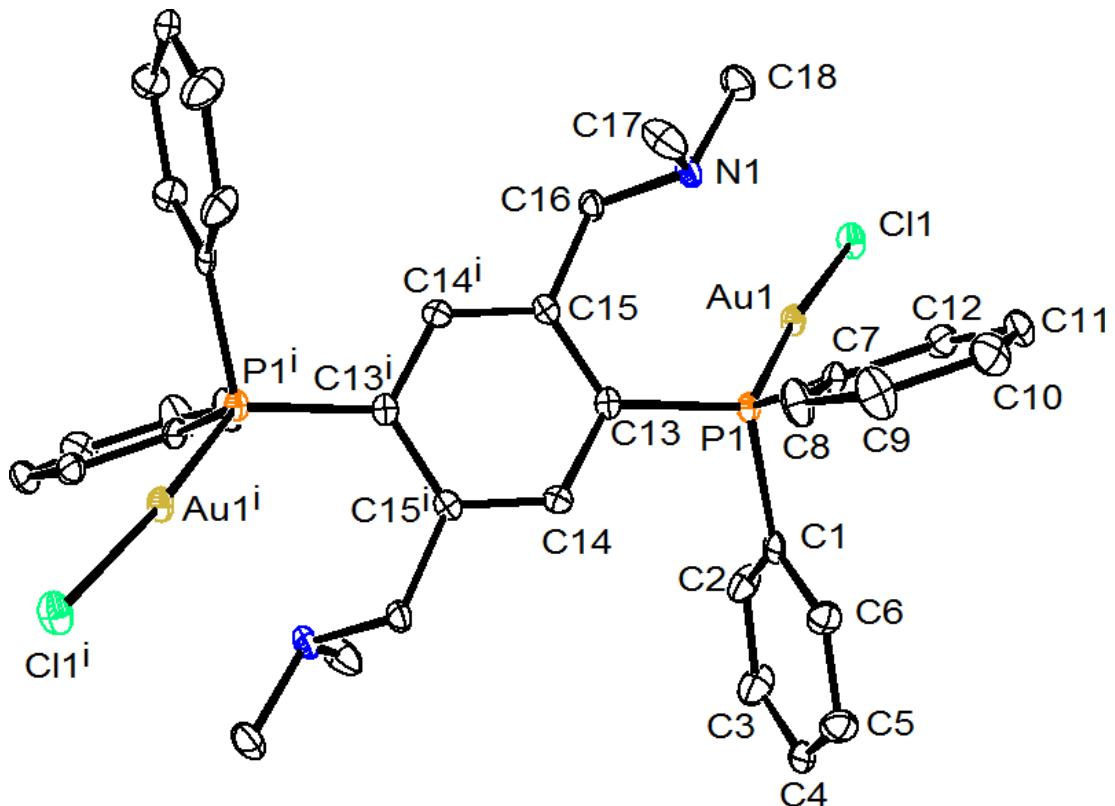


Figure 4.5.2: ORTEP representation of 1,4-(ClAuPPh₂)₂-2,5-(Me₂NCH₂)₂-C₆H₂ (70).

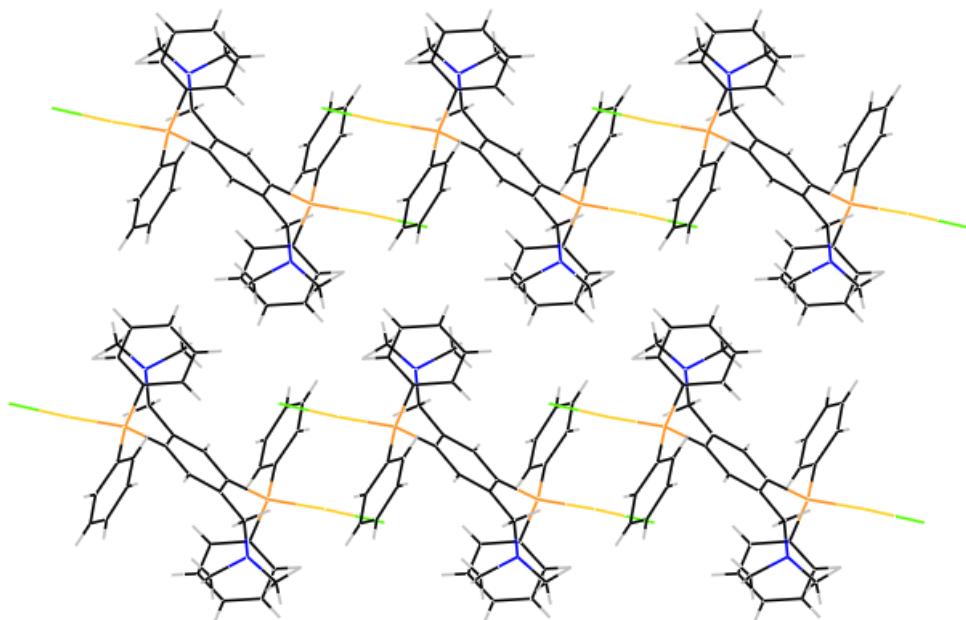


Figure 4.5.3: Extended structure of 1,4-(ClAuPPh₂)₂-2,5-(Me₂NCH₂)₂-C₆H₂ (70) viewed along the *a* axis.

Table 4.5.3: Selected bond lengths (Å) and bond angles (°) for 1,4-(ClAuPPh₂)₂-2,5-(Me₂NCH₂)₂-C₆H₂ (70).

Dimension	Value	Dimension	Value
Au1-P1	2.2309(11) Å	P1-Au1-C11	174.10(4) °
Au1-C11	2.2850(10) Å	C13-P1-Au1	118.88(3) °
P1-C13	1.826(5) Å	C7-P1-Au1	114.17(14) °
P1-C7	1.812(4) Å	C7-P1-C1	103.1(2) °
P1-C1	1.825(5) Å	C1-P1-Au1	107.84(14) °

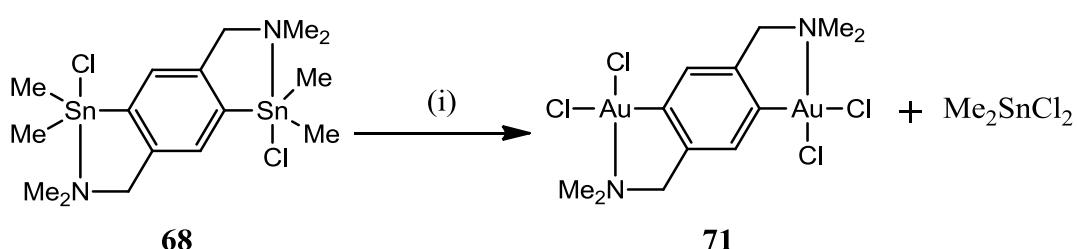
Table 4.5.4: Crystallographic data for 1,4-(ClAuPPh₂)₂-2,5-(Me₂NCH₂)₂-C₆H₂ (70).

Formula	C ₃₆ H ₃₈ Au ₂ Cl ₂ N ₂ P ₂	T (K)	103.7(6)
Formula Weight	1025.46	D_c (g cm⁻³)	1.944
Crystal System	triclinic	Crystal Size (mm)	0.4 x 0.2 x 0.1
Space group	<i>P</i> -1	Mo K_a λ (Å)	0.71070
a (Å)	9.1955(3)	Total reflections	3579
b (Å)	9.3658(4)	Unique reflections (R_{int})	3569 (0.0296)
c (Å)	10.8144(4)	Goodness of Fit on F²	0.962
α (°)	96.483(3)	Observed Reflections [I > 2σ(I)]	3311
β (°)	107.483(3)	Final R indices [I > 2σ(I)]	R 0.0266 wR ₂ 0.0655
γ (°)	94.689(3)	Parameters	201
Z	1	S	0.962
V (Å³)	876.07(6)	μ (mm⁻¹)	8.635

4.6 Synthesis of 1,4-(AuCl₂)₂-2,5-(Me₂NCH₂)₂-C₆H₂ (71) and substitution reactions

The digold(III) complex 1,4-(AuCl₂)₂-2,5-(Me₂NCH₂)₂-C₆H₂ (**71**) was synthesised by transmetallation of **68** with two equivalents of sodium tetrachloroaurate in refluxing acetonitrile (Scheme 4.6.1). The gold complex which separated from the reaction mixture was collected by filtration and washed with hexane. The complex was relatively insoluble in common solvents so characterisation by NMR spectroscopy could not be achieved. However the elemental analysis data confirmed the formation of the digold(III) complex. Further evidence for the formation of **71** was provided by isolation of the Me₂SnCl₂ by-

product. It should be noted that it is possible that **71** exists as a polymeric compound with chlorides acting as bridges between the Au(III) centres. This could account for the poor solubility of the complex in common solvents. The proposed reaction scheme is in good agreement with the mechanism reported by Ortiz *et al.*¹⁸⁹ who detected Cl₂SnMe₂ as a side product in their successful transmetallation reaction between tin(IV) and gold(III) (Scheme 4.3.3). Substitution of the chloride ligands may result in a soluble complex which can then be fully characterised.



Scheme 4.6.1: The proposed reaction scheme for the synthesis of 1,4-(AuCl₂)₂-2,5-(Me₂NCH₂)₂-C₆H₂(**71**). (i) 2 Na[AuCl₄] · 2H₂O, MeCN, 90 °C, 2 h.

Table 4.6.1: Analytical data for 1,4-(AuCl₂)₂-2,5-(Me₂NCH₂)₂-C₆H₂(**71**).

Compound	Yield (%)	Microanalytical Data (%) ^a			
		C	H	N	Cl
71	50.4	19.88 (19.84)	2.20 (2.50)	3.68 (3.86)	18.63 (19.54)

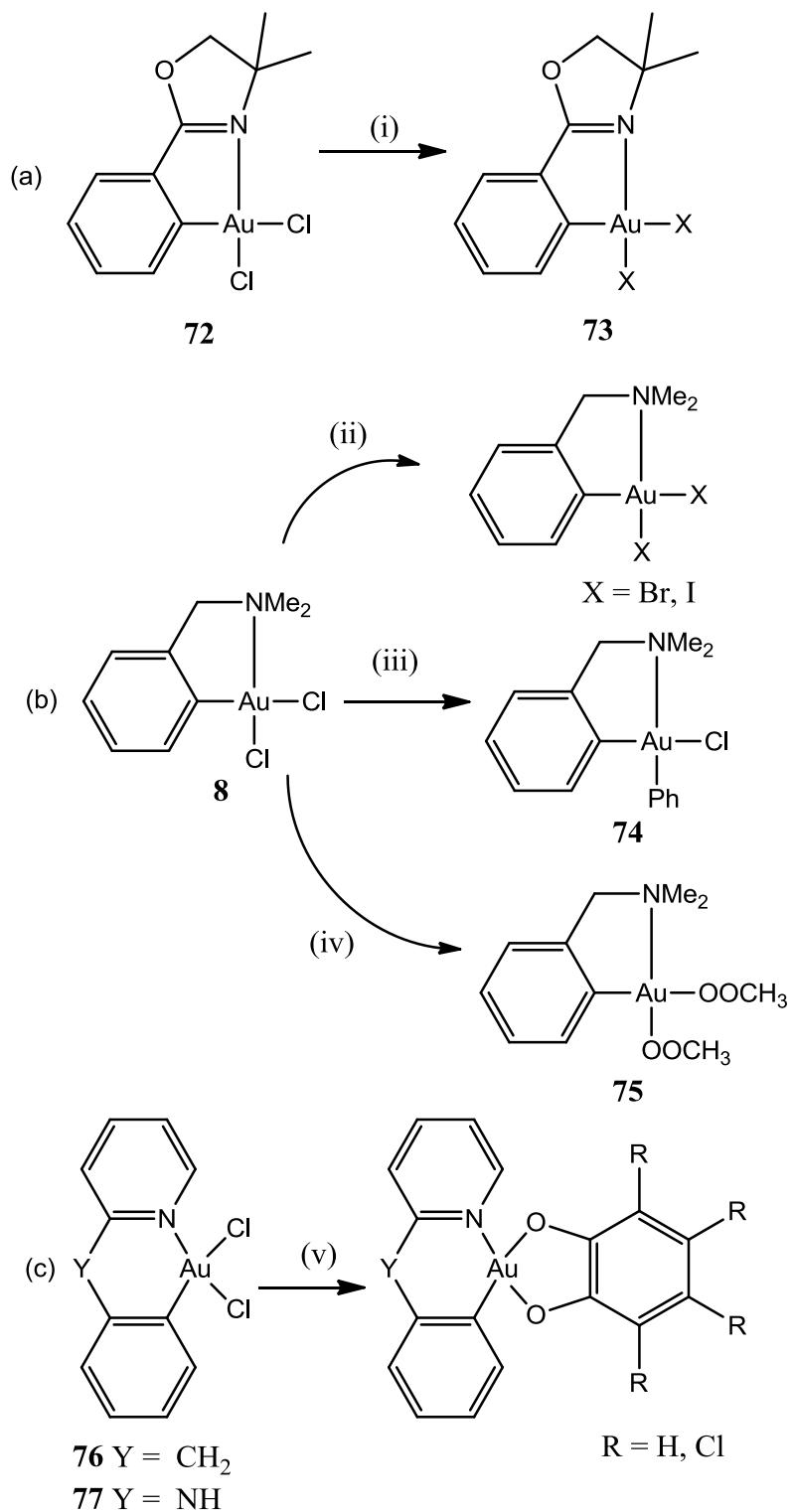
^a Calculated values shown in parentheses.

4.7 Ligand substitution in gold(III) complexes

Ligand substitution reactions on **71** were next investigated in order to obtain a digold(III) complex with an improved solubility in common laboratory solvents, thus allowing characterisation by NMR spectroscopy. Numerous ligand substitution reactions have been carried out on *cis*-dichloro organogold(III) complexes, and so only a summary of the most common reactions reported in the literature will be covered below. For a more detailed overview of the area the reader's attention is directed towards the excellent review of Henderson.⁹⁸

4.7.1 Substitution resulting in neutral complexes

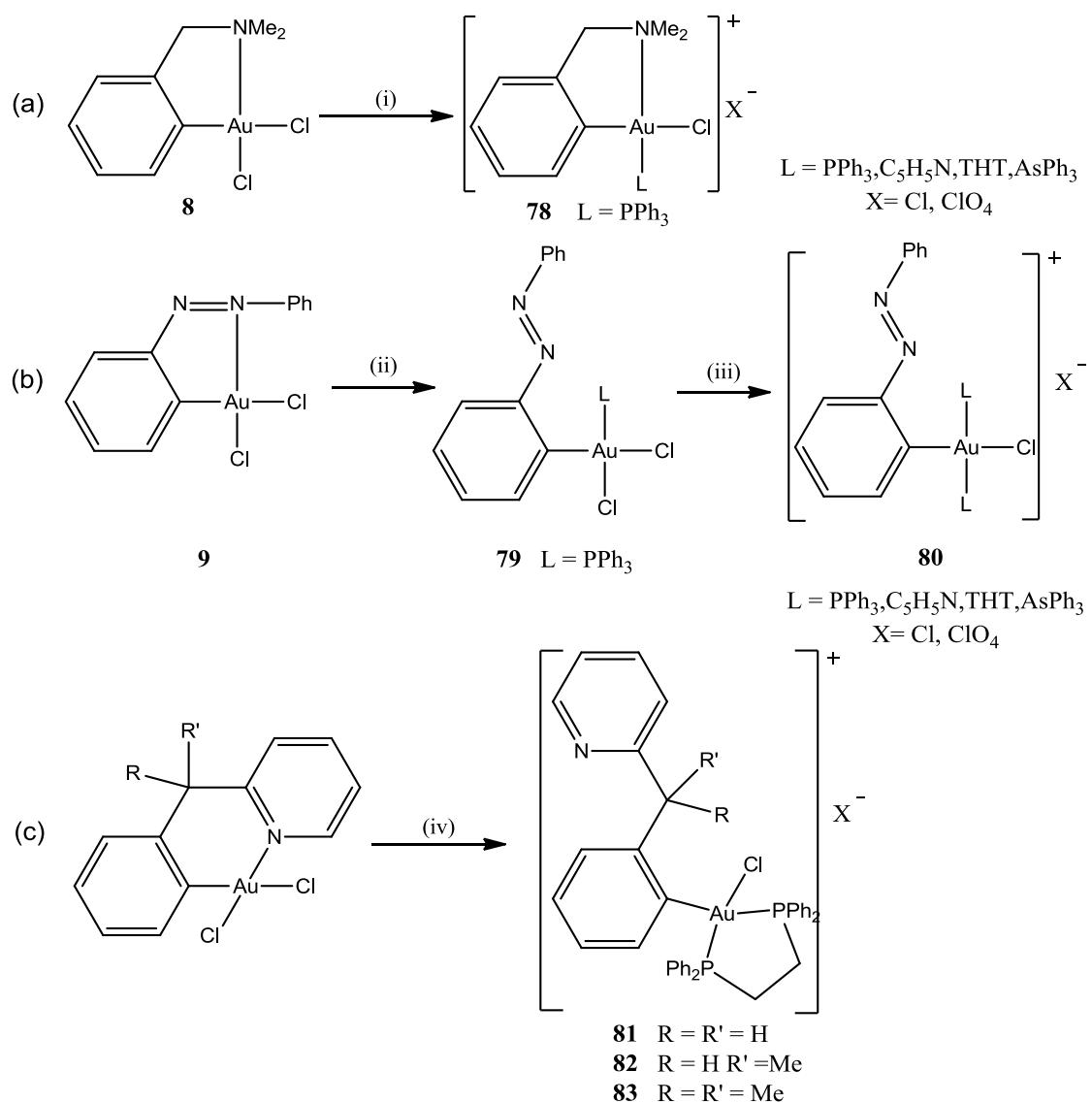
Cycloaurated gold(III) dichloro complexes generally undergo facile halogen exchange reactions with potassium bromide and potassium iodide. The complex $[\text{AuCl}_2(\text{damp})]$ (**8**) reacts to give the corresponding $[\text{AuX}_2(\text{damp})]$ derivatives in high yield.¹⁰⁹ The oxazoline complex **72** prepared by Parish *et al.*¹¹³ has also been subjected to halogen exchange resulting in the bromo- and iodo- compounds **73** (Scheme 4.7.1). Yields were far lower than those obtained with the damp compound **8**, leading the authors to conclude that this was due to nucleophilic attack at the oxazolinyl group.¹¹³ Formation of di-arylgold(III) complexes by displacement of one chlorine with a phenyl group has also been demonstrated by Vicente and co-workers.²⁰² **8** is stirred with one equivalent of $[\text{HgPh}_2]$ in chloroform at room temperature to give $[\text{AuCl}(\text{damp})\text{Ph}]$ (**74**) in 86 % yield. The structure of the aryl complex was obtained by single crystal X-ray diffraction studies, and the aryl groups were found to be *cis* to one another. Furthermore exchange of the remaining chloride ligand in the product has also been reported.²⁰² The most widely studied ligand substitution reaction with cyclometallated gold(III) chloride complexes, is acetate exchange.⁹⁸ The bis-acetate complexes are prepared by reacting the cyclometallated complex with silver acetate in acetone.^{109,203} The complexes generally have an improved solubility across a range of solvents compared to the parent dichloro-compounds. In addition the $[\text{Au}(\text{damp})(\text{OOCCH}_3)_2]$ (**75**) complex has shown promising anti-cancer activity.²⁰³ The preparation of the first gold(III) catecholate complexes has also been documented, with compounds containing either dimethylbenzylamine, 2-benzylpyridine, or 2-anilopyridine cyclometallating ligands.²⁰⁴ The reactions of the corresponding dichloride gold(III) compounds with an excess of catechol and triethylamine, in hot methanol gave the corresponding catecholate complexes (Scheme 4.7.1). With the benzylpyridine (**76**) and anilopyridine (**77**) complexes the tetrachlorocatecholate species could also be isolated, but they were found to be too insoluble in common deuterated solvents for characterisation by NMR spectroscopy.



Scheme 4.7.1: Ligand substitution reactions of *cis*-dichloro gold(III) complexes resulting in neutral complexes. (i) KBr or KI, (CH_3CO_2 , r.t., 30 mins; (ii) KBr or KI, r.t., 30 mins; (iii) $[\text{HgPh}_2]$, CHCl_3 , r.t., 1 h; (iv) 2.2 AgOOCH_3 , (CH_3CO_2 , r.t., 30 mins. (v) excess catechol or tetrachlorocatechol, NEt_3 , MeOH .

4.7.2 Substitution resulting in mono-cationic gold(III) compounds

The reactions of cycloaurated gold(III) complexes with phosphine ligands have been widely explored.⁹⁸ The reaction of one equivalent of triphenylphosphine with **8** in dichloromethane, results in the formation of the mono-cationic species $[\text{AuClPPh}_3(\eta^2\text{-C}_6\text{H}_4\text{-2-CH}_2\text{NMe}_2)]\text{Cl}$ (**78**) with the chloride ligand *trans* to the phenyl group on the basis of the Infra-red spectrum.¹⁰⁹ The chloride counter-ion can be replaced by the perchlorate anion on reaction with NaClO_4 . Even when an excess of triphenylphosphine is used no cleavage of the reasonably strong Au-N bond is observed. Attempting this substitution reaction with the 2-[(phenylazo)-phenyl] gold(III) dichloride complex (**9**) results in the formation of the neutral compound, $[(2\text{-PhN=NC}_6\text{H}_4)\text{AuCl}_2\text{PPh}_3]$ (**79**), with cleavage of the Au-N bond (Scheme 4.7.2 (b)).¹⁰⁸ This difference in reactivity is attributed to the strong Au-N bond present in the *N,N*-dimethylbenzylamine compound.¹⁰⁹ A variety of tertiary phosphine ligands have been reacted with the azobenzene compound and all result in gold-nitrogen bond cleavage. Using two equivalents of tertiary phosphine ligand in the presence of NaClO_4 , cationic bis-phosphine complexes of the type $[\text{Au}[(2\text{-PhN=NC}_6\text{H}_4)\text{AuClL}_2]]$ (**80**) (Scheme 4.7.2) can be isolated. In these complexes the phosphine ligands have a *trans*-arrangement. The reaction of **8** with weaker donor ligands, namely pyridine, THT or AsPh_3 , does not occur without the addition of sodium perchlorate. Conversely with the azobenzene derivative the reaction takes place, without the addition of sodium perchlorate, through cleavage of the Au-N bond to give neutral complexes.¹⁰⁸ Cycloaurated imine complexes also react with PPh_3 to yield neutral compounds with cleavage of the imine-gold nitrogen bond.¹²² Furthermore 2-benzylpyridine derivatives undergo reaction with PPh_3 in the presence of sodium tetrafluoroborate to give cationic complexes.²⁰⁵ Interestingly when the dichloride Au(III) precursors are stirred with one equivalent of 1,2-bis(diphenylphosphino)ethane (dppe), and NaBF_4 the cationic complexes, $[\text{AuCl(dppe)}\{\text{C}_6\text{H}_4\text{-2-CRR}'\text{-C}_5\text{H}_5\text{N}\}]\text{BF}_4$ (**81-83**) are obtained which contain an uncoordinated pyridine ligand (Scheme 4.7.2 (c)).²⁰⁵

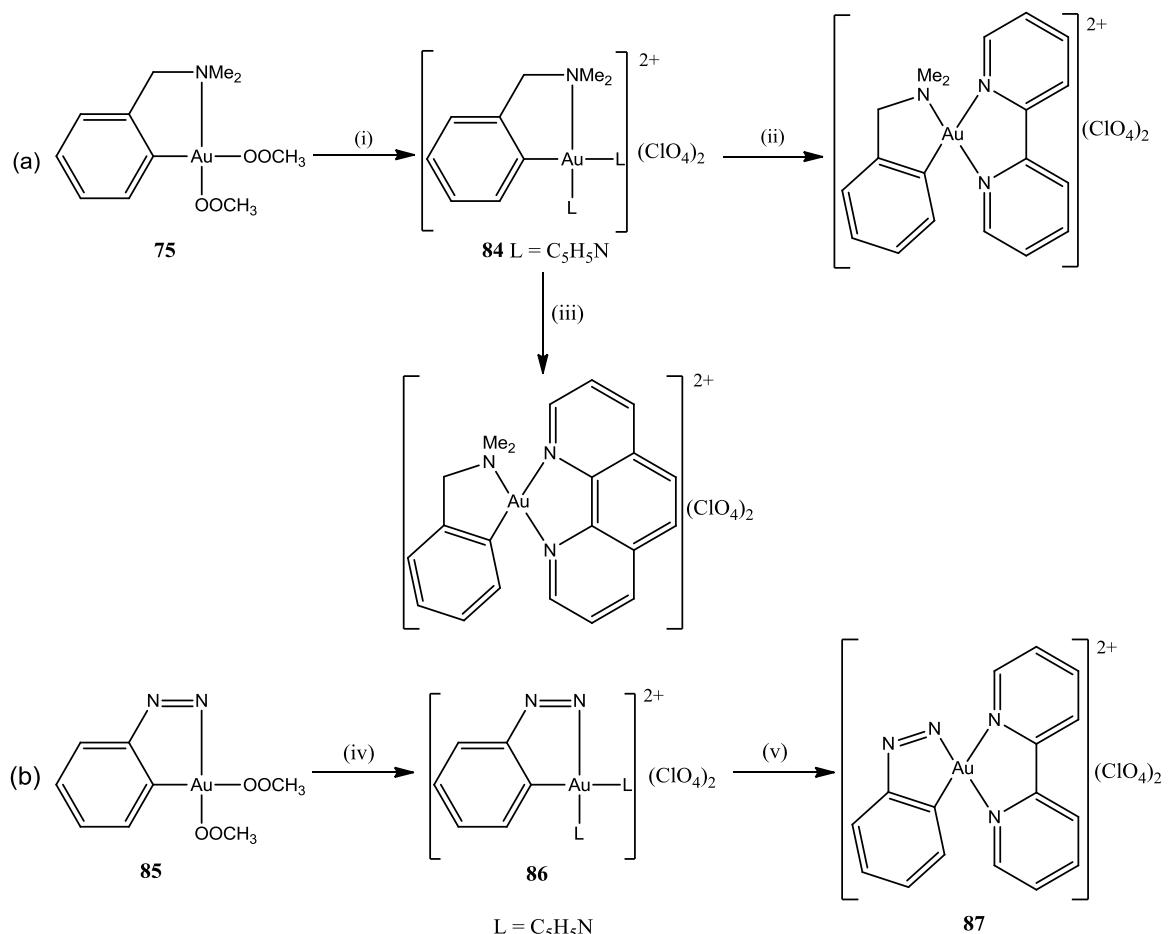


Scheme 4.7.2 : Ligand substitution resulting in mon-cationic complexes (a) (i) 1 L, CH_2Cl_2 , r.t., 30 min; (b) (ii) 1 L, $(\text{Me}_2)\text{CO}$, r.t., 4 h; (iii) 2 L, NaClO_4 , $(\text{Me}_2)\text{CO}$, r.t., 6 h; (c) (iv) dppe, NaBF_4 , $(\text{Me}_2)\text{CO}$, r.t., 6 h.

4.7.3 Substitution resulting in di-cationic gold(III) compounds

Generally dicationic gold(III) complexes cannot be prepared from their dichloride gold(III) precursors. The most common route to dicationic compounds involves substitution reactions on diacetate derivatives. The bis-pyridine complex, $[\text{Au}(\eta^2\text{-C}_5\text{N-C}_6\text{H}_4\text{-2-CH}_2\text{NMe}_2)(\text{C}_5\text{H}_5\text{N})_2](\text{ClO}_4)_2$ (**84**) has been prepared by reacting 2 equivalents of either pyridinium perchlorate or pyridinium tetrafluoroborate with $[\text{Au}(\text{damp})(\text{OOCH}_3)_2]$ (**75**) (Scheme 4.7.3 (a)).²⁰⁶ Facile substitution of the coordinated pyridine ligands for bidentate *N*-donor ligands such as 2,2-bipyridine and 1,10-phenanthroline has also been reported.²⁰⁶ Similarly the 2-[(phenylazo)-phenyl] gold(III) diacetate complex (**85**) can be prepared and then converted into the analogous bis-pyridine compound **86**.²⁰⁷ Reaction between **86** and

2,2-bipyridine gave the doubly charged complex $[\text{Au}(\eta^2\text{-C}_6\text{N}-2\text{-PhN=NC}_6\text{H}_4)(\text{bipy})](\text{ClO}_4)_2$ (**87**) (Scheme 4.7.3 (b)).



Scheme 4.7.3: Substitution reactions resulting in di-cationic complexes. (a) (i) 2 $[\text{pyH}] \text{ClO}_4$, $(\text{CH}_3)_2\text{CO}$, r.t., 14 h; (ii) 1 2,2-bipyridine, $(\text{CH}_3)_2\text{CO}$, r.t., 4 h; (iii) 1 1,10-phenanthroline, $(\text{CH}_3)_2\text{CO}$, r.t., 4 h; (b) (iv) 13 $\text{C}_5\text{H}_5\text{N}$, 3 $\text{NaOCl}_4 \cdot \text{H}_2\text{O}$, $(\text{CH}_3)_2\text{CO}$, r.t., 1 h; (v) 2,2'-bipyridine, , $(\text{CH}_3)_2\text{CO}$, r.t., 5 h.

4.7.4 Dithiocarbamate ligands

Dithiocarbamate ligands of general formula $(\text{R}_2\text{NCS}_2)^-$ are ambidentate ligands that are potentially bound through one or two of the soft sulfur donors. The nature of the binding depends on the molar ratio of dithiocarbamate used, with higher equivalents leading to displacement of the Au-N bond in most cycloaurated complexes studied.^{57,113,208} Parish and co-workers have reported the reaction of $[\text{AuCl}_2(\text{damp})]$ (**8**) reaction with one equivalent of sodium dimethyldithiocarbamate to give the cationic species $[(\text{damp})\text{Au}(\text{S}_2\text{CNMe}_2)]$ (**88**). The molecular structure of **88** was determined by a single crystal X-ray diffraction study,⁵⁷ and is shown in Figure 4.7.1 below. Both the dimethylbenzylamine and

dithiocarbamate ligands are η^2 -coordinated. The two gold-sulfur bond lengths differ significantly, with a bond length of 2.179 (9) Å for the sulfur *trans* to the nitrogen donor, and 2.340 (9) Å for the sulfur *trans* to the phenyl group. This difference can be explained by the strong *trans*-influence of the phenyl group.

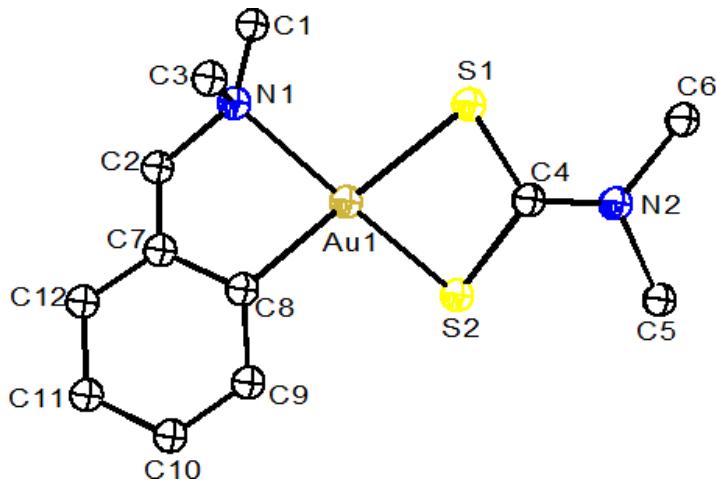


Figure 4.7.1: ORTEP representation of $[(\text{damp})\text{Au}(\text{S}_2\text{CNMe}_2)]$ (**88**). Hydrogen atoms and tetraphenyl borate removed for clarity. Thermal ellipsoids at 40% probability level.⁵⁷

With two equivalents of sodium diethyldithiocarbamate the neutral compound $[\text{Au}(\text{damp})(\text{S}_2\text{CNEt}_2)_2]$ (**89**) is isolated.⁵⁷ The solid state structure has been determined and is shown in Figure 4.7.2. **89** contains a monodentate dimethylbenzylamine ligand bound through the phenyl group, a monodentate dithiocarbamate, and a bidentate dithiocarbamate in a square planar arrangement around the gold centre. In the ^1H NMR spectrum only a single set of signals is observed for the two inequivalent dithiocarbamate methyl groups, indicating rapid exchange on the NMR-timescale between the two binding modes of the ligand. The 2-phenylpyridine gold(III) dichloride (**4**) complex and a variety of oxazoline derivatives display a similar reactivity towards dithiocarbamate ligands.^{113,208}

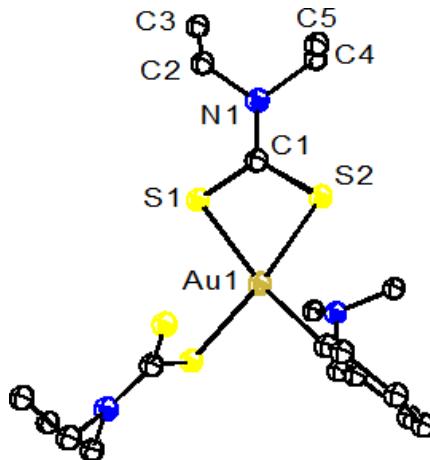
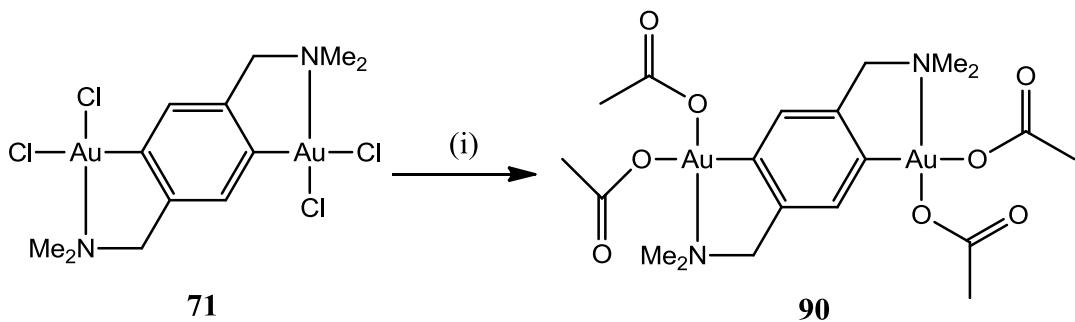


Figure 4.7.2: ORTEP representation of $[\text{Au}(\text{damp})(\text{S}_2\text{CNEt}_2)_2]$ (89).⁵⁷ Hydrogen atoms omitted for clarity. Thermal ellipsoids at 40% probability level.

4.8 Ligand substitution on 1,4-(AuCl_2)₂-2,5-(Me_2NCH_2)₂- C_6H_2 (71)

Given that substitution of the chloride ligands for acetate ligands is facile for the monogold(III) complex $[\text{AuCl}_2(\text{damp})]$ (8) exchange of the chlorides in **71** was attempted using silver acetate. Treatment of **71** with 4.4 equivalents of silver acetate in acetone resulted in substitution of all four chlorides to give 1,4-(O_2CMe)₂)₂-2,5-(Me_2NCH_2)₂- C_6H_2 (**90**), according to Scheme 4.8.1, in 97% yield.



Scheme 4.8.1: Ligand substitution on 1,4-(AuCl_2)₂-2,5-(Me_2NCH_2)₂- C_6H_2 (71). (i) 4.4 AgO_2CMe , $\text{CO}(\text{Me})_2$, 3 h, r.t., in the dark.

As expected **90** was found to have an improved solubility in common organic solvents relative to the chloride derivative, and so ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR spectra could be obtained. The ^1H NMR spectrum, displayed in Figure 4.8.1, has two resonances at *ca.* 2 ppm which correspond to two different environments for the acetate methyl groups. Singlets are observed at 3.1 ppm, 4.3 ppm and 6.7 ppm which correspond to NMe_2 , CH_2 and Ar-H

protons respectively. The $^{13}\text{C}\{\text{H}\}$ NMR spectrum highlights the non-equivalence of the acetate groups with two distinct signals observed for both the carbonyl carbon and the methyl groups. The non-equivalence of acetate groups is also observed in the NMR spectra of the mononuclear derivative $[\text{Au}\{\text{O}_2\text{CMe}\}_2(\eta^2\text{-C}_6\text{H}_4\text{-2-CH}_2\text{NMe}_2)]$ (**75**).²⁰³ **90**, although having improved solubility was found to decompose both in solution and as a powder, hence no elemental analysis or X-ray diffraction data has been obtained to date. In order to improve the stability of the complex exchange of the chlorides in the parent compound with diethyldithiocarbamate was attempted; however in all cases pure product could not be obtained.

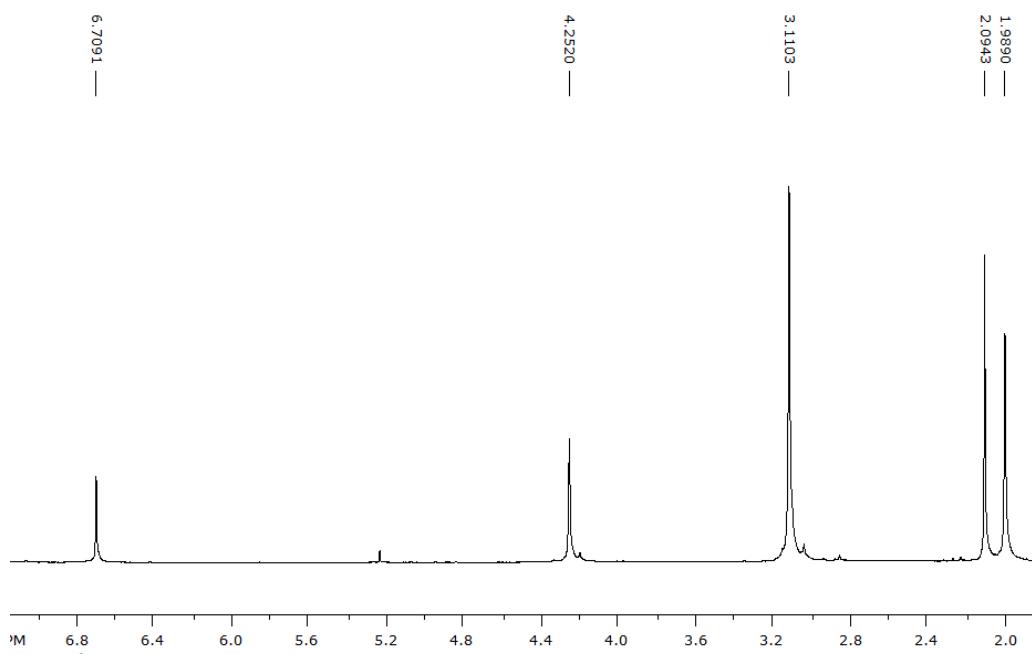


Figure 4.8.1: ^1H NMR spectrum of $1,4\text{-}(\text{Au}\{\text{O}_2\text{CMe}\}_2)_2\text{-}2,5\text{-}(\text{Me}_2\text{NCH}_2)_2\text{-C}_6\text{H}_2$ (**90**).

To summarise a range of novel di tin(IV) complexes have been prepared and characterised by NMR spectroscopy and X-ray crystallography. Transmetallation from $1,4\text{-}(\text{SnMe}_2\text{Cl})_2\text{-}2,5\text{-}(\text{Me}_2\text{NCH}_2)_2\text{-C}_6\text{H}_2$ (**68**) to two equivalents of $\text{Na}[\text{AuCl}_4]$ in refluxing acetonitrile resulted in the formation of relatively insoluble digold(III) complex, $1,4\text{-}(\text{AuCl}_2)_2\text{-}2,5\text{-}(\text{Me}_2\text{NCH}_2)_2\text{-C}_6\text{H}_2$ (**71**). Substitution of the chloride ligands in **71** for acetates gave $1,4\text{-}(\text{Au}\{\text{O}_2\text{CMe}\}_2)_2\text{-}2,5\text{-}(\text{Me}_2\text{NCH}_2)_2\text{-C}_6\text{H}_2$ (**90**) which could be characterised by NMR spectroscopy.

5 Propargylamines and the A³-coupling reaction

In this chapter, we aimed to apply the new gold complexes synthesised in chapters 2-4 as catalysts for the preparation of propargylamines. The A³-coupling reaction towards propargylamines was then chosen for this purpose.

5.1 Propargylamines

Propargylamines are compounds of the type R¹CH(NR²R³)CCR⁴ and have the general structure shown in Figure 5.1.1.

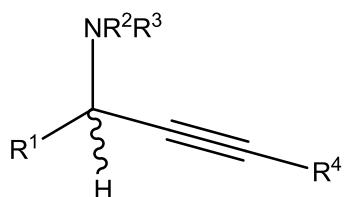
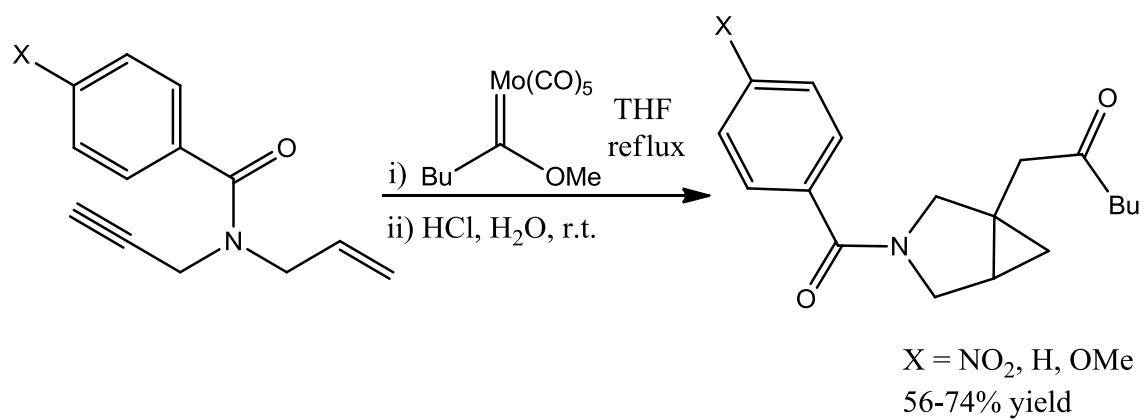


Figure 5.1.1: General structure of propargylamines.

Propargylic amines have been used extensively as important building blocks in synthetic organic chemistry since the structural motif is found in a wide range of natural products and biologically active compounds. They have been used as precursors to prepare oxazoles,²⁰⁹ pyrroles²¹⁰ and also by Harvey and Sigano²¹¹ to prepare cyclopropylpyrrolidines (Scheme 5.1.1). The propargylamines are cyclised using a molybdenum carbene complex in THF to give the cyclised products in good yield.



Scheme 5.1.1: The preparation of cyclopropylpyrrolidines from propargylamines.²¹¹

Furthermore propargylamines have been utilised as synthetic intermediates in the preparation of numerous natural products,^{212,213} pharmaceuticals^{214,215} and even herbicides

and fungicides.²¹⁶ Additionally some propargylamine derivatives display interesting biological activity, as potent inhibitors of the enzyme monoamine oxidase type B (MAO-B).^{217–220} A recent example of this class of drug is PF9601N, shown in Figure 5.1.2, which is a highly selective inhibitor of MAO-B and has excellent neuroprotective properties in *in vivo* and cellular models of Parkinson's disease.²¹⁹

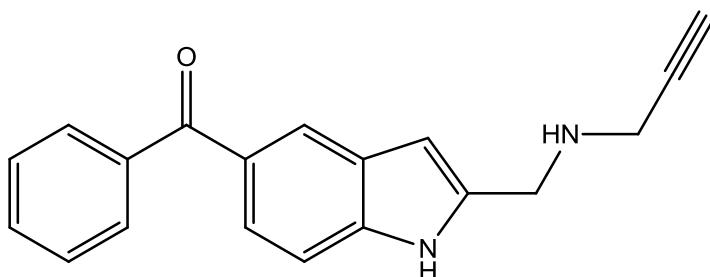
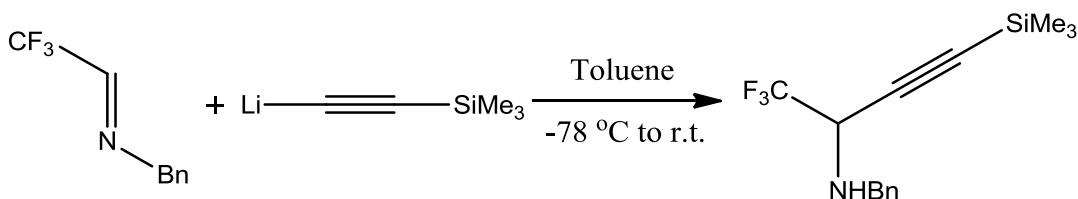


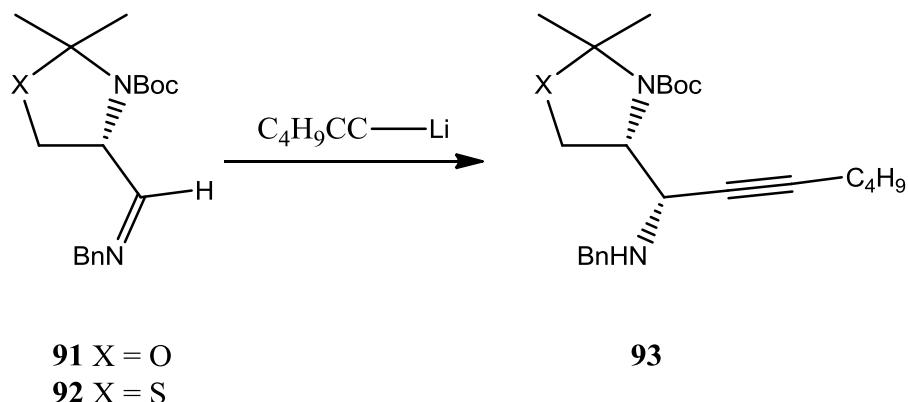
Figure 5.1.2: Structure of PF9601N, a propargylamine based MAO-B inhibitor.²¹⁹

The review article by Zani and Bolm²²¹ contains a more detailed overview of the potential uses of propargylamines in organic synthesis. Traditionally propargylamines are prepared *via* the addition of carbanions to the C=N bonds of imines.^{222–224} Due to the low acidity of the acetylinic C-H group ($pK_a \sim 25$) acetylinic lithium^{225–228} and magnesium²²⁹ organometallics are usually employed in the reaction with imines leading to propargylamines. Various compounds have been prepared in this way including novel amines with CF_3 substituents,²³⁰ as shown in Scheme 5.1.2.



Scheme 5.1.2: The preparation of CF_3 containing propargylamines through reaction of imines with organolithium reagents.²³⁰

In these reactions a new stereogenic centre is formed at the α -carbon, making it possible to carry out asymmetric syntheses. Chiral auxiliaries, incorporated into the imine substrate, have been used to direct the stereoselectivity of acetylide addition to the C=N bond. Fujisawa and co-workers²³¹ have reported the selective addition of acetylides to chiral imines derived from L-serine and L-cysteine (**91** and **92**) (Scheme 5.1.3). The *syn* addition product (**93**) was obtained in all cases.



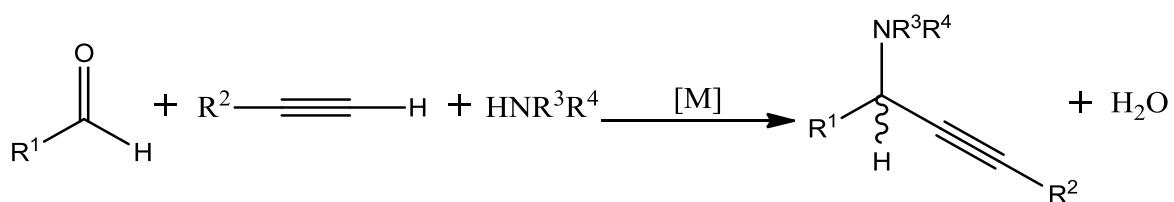
Scheme 5.1.3: The selective addition of acetylides to chiral imines as reported by Fujisawa and co-workers.²³¹

For a more detailed overview covering the preparation of propargylic amines using organometallic reagents, the reviews of Bloch,²²² Enders,²²³ and Bonin²²⁴ are recommended.

The main disadvantage of using metallic alkyne salts for the preparation of propargylamines is that stoichiometric quantities of organometallic reagent are required. Additionally the use of moisture sensitive lithium and Grignard reagents requires strict control of the reaction conditions, and an inert atmosphere. Consequently a milder and more atom efficient route to propargylamines has been developed.

5.2 The A³-coupling reaction

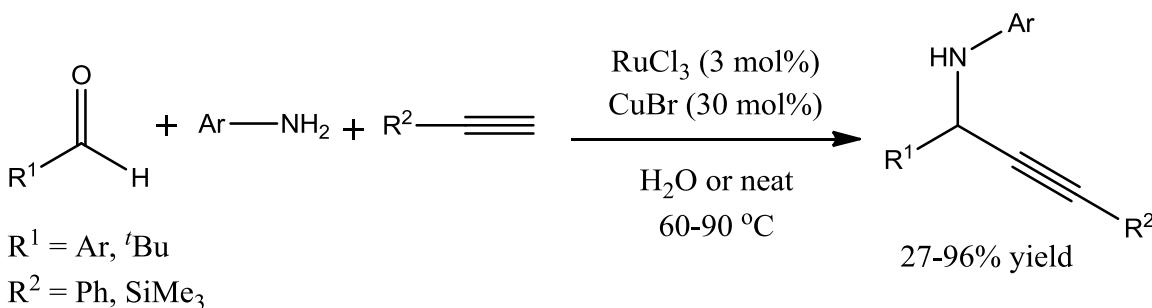
The A³-reaction is a multi-component reaction that enables the preparation of propargylamines from aldehydes, amines and terminal alkynes in a one-pot procedure (Scheme 5.2.1), using a transition metal catalyst with the only by-product being water.



Scheme 5.2.1: General scheme for the A³-reaction.

The first work on the A³-reaction was reported in 1998 when Dax and co-workers²³² described the solid-phase synthesis of propargylamines by a 3-component Mannich²³³-type condensation of an alkyne, aldehyde and secondary amine, catalysed by two equivalents of

CuCl. The amine or the aldehyde could be attached to the polymer resin, and the coupled products were prepared in good yields of over 80%. However this reaction does not meet the ideal requirements for an A³-reaction due to the use of stoichiometric amounts of copper chloride.²³⁴ Later in 1998 Rivero and Dyatkin²³⁵ reported a similar solid-phase coupling reaction, effected by a catalytic amount (10 mol %) of CuCl. This reaction procedure was the first reported example of an A³-coupling reaction. In this reaction any of the three substrates could be bound to the resin and the propargylamine products were obtained in high yield after cleavage from the polymer. In 2002 the group of Li²³⁶ reported an A³-coupling reaction using a bimetallic Ru-Cu catalyst system in water, and under solvent-free conditions. The authors found that the addition of phenylacetylene to an *in-situ* generated imine (formed from the condensation of aldehydes with anilines) was catalysed by copper complexes albeit in low conversion. Several copper complexes such as, CuCl, CuCl₂, CuBr, CuI and CuO all displayed moderate catalytic activity. However when RuCl₃ (3 mol%) was added as co-catalyst the yield of A³-coupled product increased from 30% to 90% (Scheme 5.2.2), though when RuCl₃ was used alone as the catalyst none of the desired product was obtained. The reaction was applicable to a broad range of aromatic and aliphatic imines and for imines that were easily hydrolysed in water the reaction could be carried out with no solvent. The yield of product decreased when aliphatic aldehydes were used; thought to be due to unwanted trimerization of the aldehydes.²³⁶



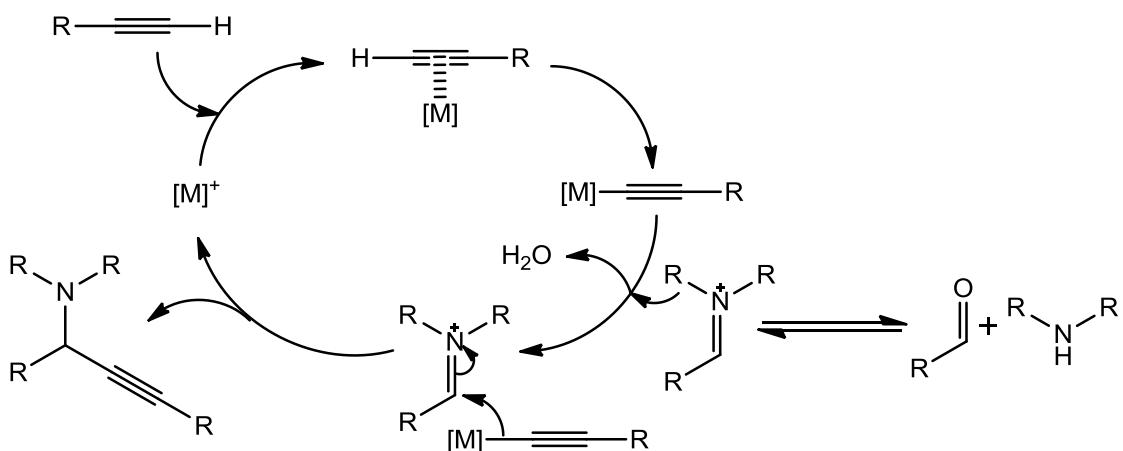
Scheme 5.2.2: The A³-reaction catalysed by Cu-Ru catalyst system.

It should be noted that A³-coupling does not proceed in the absence of a metal or main group catalyst.^{237,238} Since these initial reports, numerous transition metal complexes have demonstrated catalytic activity in the A³-coupling reaction and so a summary of the key developments in this area is given below. For a more detailed overview of A³-coupling reactions the reader's attention is directed towards the comprehensive reviews of Li *et*

al.^{239,240} and Eycken and co-workers.²³⁴ Typically the A³-coupling protocol has been optimised for use with anilines and secondary amines. Primary amines are generally considered to be difficult substrates due to a lower electrophilicity of the intermediate imine species.

5.3 Tentative mechanism for the A³-coupling reaction

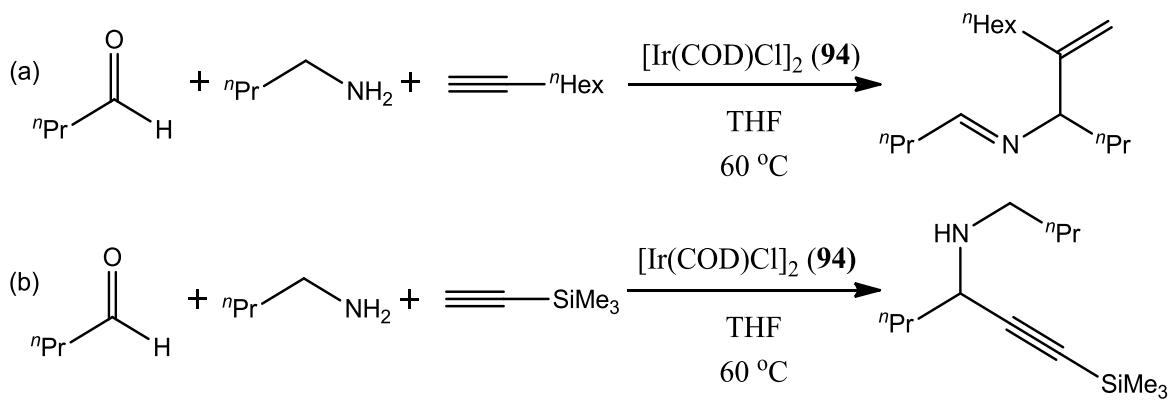
A simple generic mechanism for the A³-reaction has been proposed, see Scheme 5.3.1.²³⁴ The key mechanistic step in the reaction is the *in-situ* formation of a metal-acetylide species *via* C-H activation of the alkyne. The formation of this complex is poorly understood, and may proceed through a π -metal alkyne complex. The metal acetylide is then reacted with the imine or iminium ion (formed by *in-situ* reaction of the aldehyde and amine) to give the propargylamine with regeneration of the metal catalyst.



Scheme 5.3.1: Proposed general mechanism of the A³-coupling reaction.

5.4 Transition and Main Group Metals as homogeneous catalysts in the A³-reaction

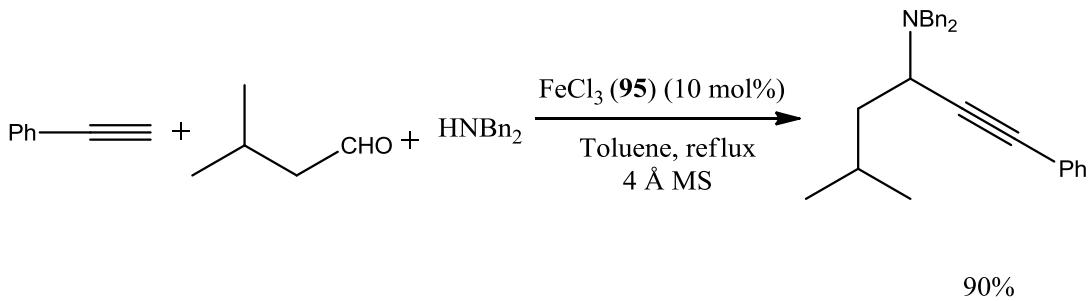
Iridium has been shown to be an effective catalyst for the A³-reaction. Ishii *et al.* found that [Ir(COD)Cl]₂ (**94**) in THF, effected a new type of C-H bond activation adjacent to the nitrogen atom of imines that led to allyl imines (Scheme 5.4.1 (a)).²⁴¹ However when trimethylsilyl acetylene was coupled with *n*-butyraldehyde and *n*-butylamine in THF at 60 °C, with **94** as the catalyst, the A³-coupled product was formed (Scheme 5.4.1 (b)).



Scheme 5.4.1: (a) $[\text{Ir}(\text{COD})\text{Cl}]_2$ (94) catalysed C-H activation to give allyl imines. (b) $[\text{Ir}(\text{COD})\text{Cl}]_2$ catalysed A^3 -coupling reaction.

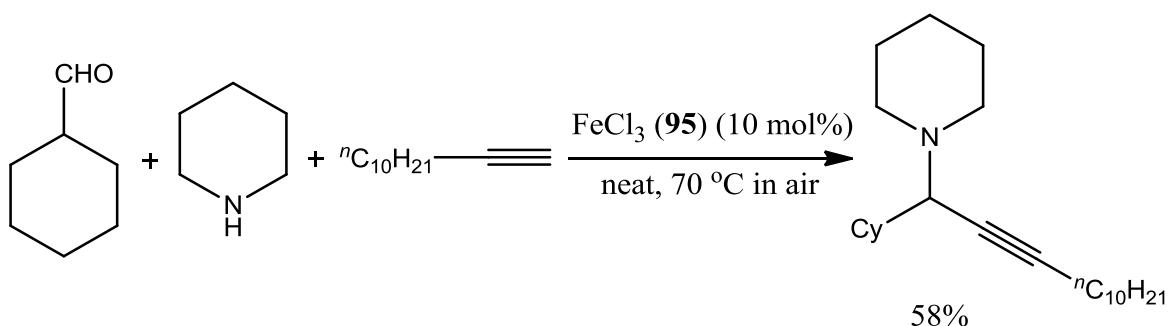
Subsequently Carreira²⁴² reported the preparation of a range of propargylamines *via* an A^3 -coupling reaction with an $[\text{Ir}(\text{COD})\text{Cl}]_2$ (94) (5 mol% loading) catalyst at room temperature in THF. The coupled products were obtained in good yields (69-85%). During the course of the investigation the authors found that only trimethylsilylacetylene underwent the addition reaction with imine species.

Iron catalysts are generally inexpensive and environmentally friendly, which make them extremely desirable for use in organic transformations. Both Li²⁴³ and Wang²⁴⁴ have independently demonstrated iron-catalysed A^3 -coupling of aldehydes, alkynes and amines. Wang used anhydrous FeCl_3 (95) (10 mol%), in toluene, at 120 °C in the presence of 4 Å molecular sieves to prepare propargylamines in good yield (Scheme 5.4.2).²⁴⁴ It was found that aliphatic aldehydes such as *n*-butyraldehyde, isobutyraldehyde, isovaleraldehyde, *para*-formaldehyde and cyclohexancarboxaldehyde display high reactivity and give high yields (70-98%) of the desired coupled product with phenylacetylene and dibenzylamine coupling partners. Aromatic aldehydes with electron withdrawing (Cl) and donating groups (OMe, Me), also underwent coupling in good yields.



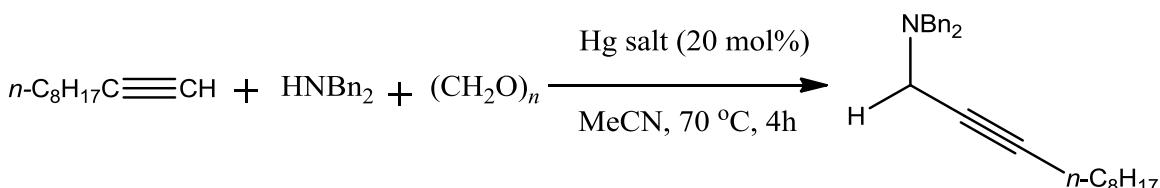
Scheme 5.4.2: Example of an Iron-catalysed A^3 -coupling of phenylacetylene, dibenzylamine and isovaleraldehyde as reported by Wang and co-workers.²⁴⁴

Li and co-workers²⁴³ developed a FeCl_3 (**95**) catalysed protocol in which the coupling reaction was carried out under neat conditions and in air at 70 °C (Scheme 5.4.3). It was observed that aliphatic aldehydes were in general considerably more reactive than aromatic aldehydes. Variation of the alkyne between aromatic and aliphatic substituents did not significantly affect the conversion; however variation of the amine had a more substantial effect on the yield. Cyclic dialkylamines such as piperidine, morpholine and azepane reacted smoothly under these standard conditions, but acyclic dialkylamines (diallylamine) were less effective.



Scheme 5.4.3: Example of an Iron-catalysed A^3 -coupling of cyclohexanecarbaldehyde, piperidine and 1-dodecyne, as reported by Li and co-workers.²⁴³

A novel investigation concerning the use of mercury salts as catalysts for the A^3 -reaction has been described by Pin-Hua and co-workers,²⁴⁵ in which the effect of mercuric or mercurous salts on the coupling reaction between dibenzylamine, 1-decyne, and *para*-formaldehyde at 70 °C in MeCN was investigated (Scheme 5.4.4). It was observed that Hg_2Cl_2 , $\text{Hg}_2(\text{NO}_3)_2$, HgCl_2 , HgI_2 , Hg_2Br_2 and Hg_2I_2 all catalysed the coupling reaction at a loading of 20 mol%.

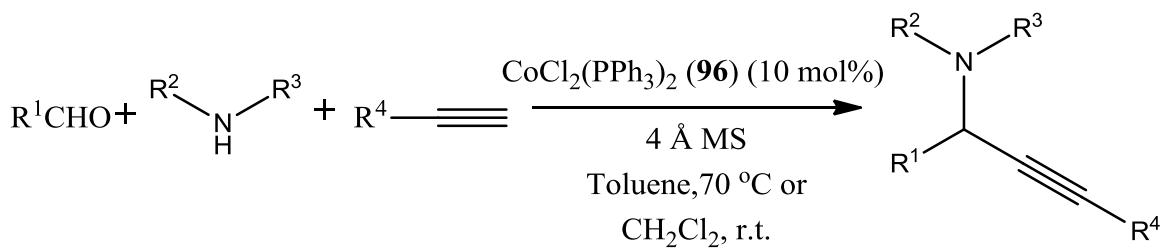


Scheme 5.4.4: Hg compound screening experiments.

Mercurous chloride (Hg_2Cl_2) was found to be the most efficient catalyst and so was selected for solvent optimisation studies. The choice of reaction solvent was found to influence the coupling reaction. A range of different solvents were screened in the presence of Hg_2Cl_2 (5 mol %) at 70 °C. Acetonitrile was the best solvent screened with a product yield of 90%, whereas DMSO, THF and EtOH gave only 70%, 10% and 35% yields

respectively. Interestingly no product was formed when benzene, dichloromethane or THF-H₂O mixtures were used as reaction solvents.

Recently cobalt complexes, particularly CoCl₂(PPh₃)₂ (**96**), have demonstrated catalytic activity in the A³-coupling reaction (Scheme 5.4.5).²⁴⁶ The reaction was moisture sensitive so 4 Å molecular sieves were added to improve the yield, by driving formation of the amine through removal of the H₂O by-product. Again a strong solvent effect on the reaction was observed. Toluene and CH₂Cl₂ gave the highest yields of 94% and 93% respectively. Other solvents such as THF, dioxane and hexane all gave significantly lower yields.



R¹, R⁴ = aryl, alkyl

R², R³ = alkyl

Scheme 5.4.5: CoCl₂(PPh₃)₂ (**96**) catalysed A³-coupling reaction.

The reaction was tolerant to a range of aliphatic and aromatic aldehydes, and various terminal aromatic alkynes, however higher temperatures (100 °C) were required for aliphatic alkynes. Other catalysts based upon nickel,²⁴⁷ indium²⁴⁸ and zinc^{249,250} have all shown the ability to catalyse the A³-reaction. Table 5.4.1 contains a comparison of the literature data for a range of transition metal and main group catalysts for the A³-coupling reaction. Complexes of the group 11 metals, copper, silver and gold have received the most attention, to date, as catalysts of the A³-coupling reaction.

Table 5.4.1: Comparison between different catalysts for the A³-coupling of piperidine, benzaldehyde and phenylacetylene.

Catalyst	Optimized Conditions					
	Loading (mol%)	Solvent	T (°C)	Time (h)	Yield for A ³ -coupling (%) ^a	Reference
FeCl ₃ (95)	10	Neat in air	70	14	34	²⁴³
FeCl ₃ (95)	10	Toluene under Ar in the presence of 4 Å MS	111	24	91	²⁴⁴
Hg ₂ Cl ₂	5	MeCN	70	4	81	²⁴⁵
CoCl ₂ (PPh ₃) ₂ (96)	10	Toluene under N ₂ with 4 Å MS	70	24	91	²⁴⁶
NiCl ₂	5	Toluene under Ar	111	8	95	²⁴⁷
Zn(OAc) ₂ .2H ₂ O	10	Toluene	111	7	92	²⁴⁹
Zn dust	15	MeCN	82	9	90	²⁵⁰
InCl ₃	10	Toluene under Ar with 4 Å MS	111	20	96	²⁴⁸

^a A³-coupling of piperidine, benzaldehyde and phenylacetylene.

5.5 Group 11 metal complexes as homogeneous catalysts in the A³-reaction

5.5.1 Copper Catalysts

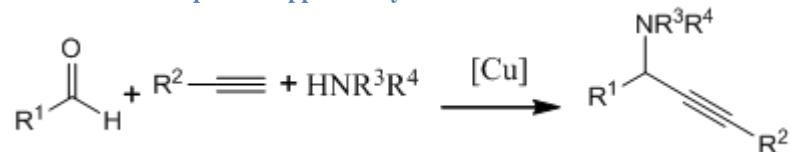
Since the initial report by Li²³⁶ in 2002, copper complexes have become the most extensively used catalysts for the A³-coupling reaction.²⁴⁰ Catalysis by Cu(I) complexes is by far the most prevalent in the literature, with the simple halides CuCl,²⁵¹ CuBr²⁵² and CuI^{253,254} commonly being reported as catalysts. The catalytic activity of CuBr₂ and CuCl₂ in the coupling reaction has also been noted by Knochel *et al.*²⁵² and Bieber and Silva²⁵³ respectively. Recently the development of copper catalysed processes that involve recycling of the catalyst and reaction solvent have been sought. Alper and Park²⁵⁵ and Yadav *et al.*²⁵⁶ independently used Cu complexes in the ionic liquid [bmim]PF₆ (1-butyl-3-methylimidazolium hexafluorophosphate) to catalyse the three component coupling reaction. Alper and Park screened a range of Cu complexes, including CuI, CuBr, CuCN and Cu(OAc)₂.H₂O in the reaction of benzaldehyde, piperidine and phenylacetylene at 120 °C for 2 hours. All the Cu(I) complexes examined showed excellent catalytic activity with conversions to product of 78-98%. CuCN and CuI catalysts were chosen for further studies to examine the recyclability of the A³-reaction in [bmim]PF₆. Using only 2 mol% of the copper complex, the catalyst could be easily recycled and re-used for 5 or 10 runs, with

only a slight drop in activity (86 % dropping to 78% after 10 runs).²⁵⁵ It was found that the reaction tolerated a wide range of functionalised aromatic aldehydes, both alkyl and aryl alkynes, and various amines. However it was observed that the reaction was sensitive to steric effects, with 2-methoxybenzaldehyde giving only trace amounts of coupled product, in contrast to the 3-methoxy-and 4-methoxy substituted aldehydes which reacted smoothly. Furthermore use of the sterically demanding amine, *cis*-2,6-dimethylpiperidine yielded no product. Yadav *et al.*²⁵⁶ reported a similar procedure using CuBr (30 mol%) at 60 °C also in [bmim]PF₆ for the preparation of an assortment of propargylamines in excellent yield (81-89%). The authors examined what effect changing the ionic liquid had on the reaction. It was found that changing the cation to [hmim] (1-hexyl-3-methylimidazolium) or [octmim] (1-octyl-3-methylimidazolium) had no effect on the reaction. However changing the anion from PF₆⁻ to Cl⁻ resulted in a significant drop in product yield (30-55%) leading the authors to conclude that the efficiency of the ionic liquid catalyst is influenced by the nature of the anion only.²⁵⁶ Chen *et al.*²⁵⁷ have explored Cu catalysed A³-reactions using polyethylene glycol (PEG) as solvent, due to it being inexpensive, non-halogenated and degradable. It was found that the reaction of benzaldehyde, morpholine and phenylacetylene at 100 °C under N₂ was catalysed by various copper complexes at a loading of 10 mol%. CuI gave the best results over a 12 h period with a yield of 92%. During the course of these studies it was observed that the substituents on the aldehyde had no effect on the coupling reaction, and that substituents on the alkyne could be varied with no significant loss in product yield. The PEG solvent containing CuI could be recycled and re-used for five runs with no significant drop in activity, illustrating an advantage of using PEG over conventional organic solvents. In an effort to lower reaction times microwave assisted A³-reactions with Cu catalysts have also been investigated. Tu and co-workers²⁵⁸ have used microwave irradiation of a three-component coupling reaction in H₂O in the presence of CuI (15 mol%) to decrease reaction times. Using this procedure aliphatic aldehydes gave similar yields to aromatic aldehydes, unlike standard Cu catalysed couplings, where trimerization of aliphatic aldehydes reduces product yield.²⁵⁸ This method could also be used to carry out highly diastereoselective A³-couplings when employing chiral amine precursors such as (*S*)-proline methyl ester (d.r. 95:5). Subsequently Varma *et al.*²⁵⁹ explored solvent free microwave assisted synthesis of propargylamines catalysed by CuBr (8 mol%). The method was applicable to both aromatic and aliphatic aldehydes and alkynes, although the reaction was restricted to the use of secondary amines. Again a significant decrease in reaction times was observed,

from days for normal Cu catalysed A³-reactions to minutes for the microwave assisted couplings. Leadbeater and co-workers²⁶⁰ have carried out a systematic investigation of the microwave promoted copper catalysed A³-reaction, using CuCl (10 mol%) in 1,4-dioxane-ionic liquid systems. It was found that even the slowest reactions between aromatic or aliphatic aldehydes, cyclic amines and aliphatic alkynes were complete after 10 mins at 150 °C, highlighting the utility of microwave heating for these couplings. Van der Eycken *et al.*²⁶¹ have also developed a microwave assisted synthesis of secondary alkylpropargylamines catalysed by CuBr (20 mol%), specifically for use with primary aliphatic amine.

Table 5.5.1 contains a summary of the copper catalysed reactions discussed above.

Table 5.5.1: Examples of copper catalysed A³-reactions



Entry	Catalyst	Catalyst Loading (mol%)	Reaction Conditions	R ¹ (aldehyde)	R ² (alkyne)	R ³ R ⁴ (amine)	Isolated yield (%)	Reference
1	CuCl	30	Dry THF, reflux, 10 h	Ph	C(CH ₃) ₂ OH	R ³ = C ₆ H ₄ - <i>p</i> -OMe R ⁴ = H	47	²⁵¹
2 ^a	CuBr	5	Dry Toluene, under Ar, r.t. or 60 °C, 24 h, 4 Å MS	C ₄ H ₉	Ph	R ³ = R ⁴ = Bn	75	²⁵²
3	CuI	2	DMSO, 30 °C, 10 h	H	Ph	(CH ₂) ₅	98	²⁵³
4	CuI	0.5	neat 25 °C, 1.5 h	H	Ph	(CH ₂) ₄	99 ^b	²⁵⁴
5	CuCl ₂	2	DMSO 30 °C, 2h	H	Ph	(CH ₂) ₂ O(CH ₂) ₂	59 ^b	²⁵³
6	CuCN	2	[bmim]PF ₆ Under N ₂ 120 °C, 4 h	Ph	Ph	(CH ₂) ₅	85	²⁵⁵
7	Cu(OAc) ₂ .H ₂ O	2	[bmim]PF ₆ Under N ₂ 120 °C, 4 h	Ph	Ph	(CH ₂) ₅	60 ^b	²⁵⁵
8	CuBr	30	[bmim]PF ₆ 60 °C, 5 h	3,4-(OMe) ₂ -C ₆ H ₃	Ph	R ³ = 4-F-C ₆ H ₄ R ⁴ = H	82	²⁵⁶
9	CuI	10	PEG-400 Under N ₂ ; 100 °C, 12 h	Ph	4-MeO-C ₆ H ₄	(CH ₂) ₂ O(CH ₂) ₂	88	²⁵⁷
10 ^c	CuI	15	H ₂ O Under Ar; 20 min in μW	Ph	Ph	(CH ₂) ₅	93	²⁵⁸

Entry	Complex	Catalyst Loading (mol%)	Reaction Conditions	R ¹ (aldehyde)	R ² (alkyne)	R ³ R ⁴ (amine)	Isolated yield (%)	Reference
11 ^c	CuI	15	H ₂ O Under Ar; 20 min in μW	Ph	Ph	(S)-(CH ₂ COOCH ₃)C ₄ H ₇	88 (d.r. 95:5) ^d	²⁵⁸
12 ^c	CuBr	8	Neat; 95 ± 5 °C in μW, 90 sec	C ₄ H ₉	Ph	(CH ₂) ₅	93	²⁵⁹
13 ^c	CuCl	10	1,4-dioxane/[1- ⁱ Pr-3-Me-imidazolium]PF ₆ ; 150 °C in μW, 6 min	Ph	Ph	(CH ₂) ₅	97	²⁶⁰
14 ^c	CuBr	20	Toluene under Ar; 100 °C in μW, 25 min	ⁱ Bu	Ph	R ³ = Pr R ⁴ = H	94	²⁶¹
15 ^c	CuBr	20	Toluene under Ar; 100 °C in μW, 25 min	ⁱ Bu	Ph	R ³ = CH ₂ (CH ₂) ₆ R ⁴ = H	72	²⁶¹

^a Preformed Enamine was used in the coupling reaction instead of *in-situ* reaction between aldehyde and amine.

^b Conversion (%) given as determined by ¹H NMR spectroscopy based upon aldehyde consumption.

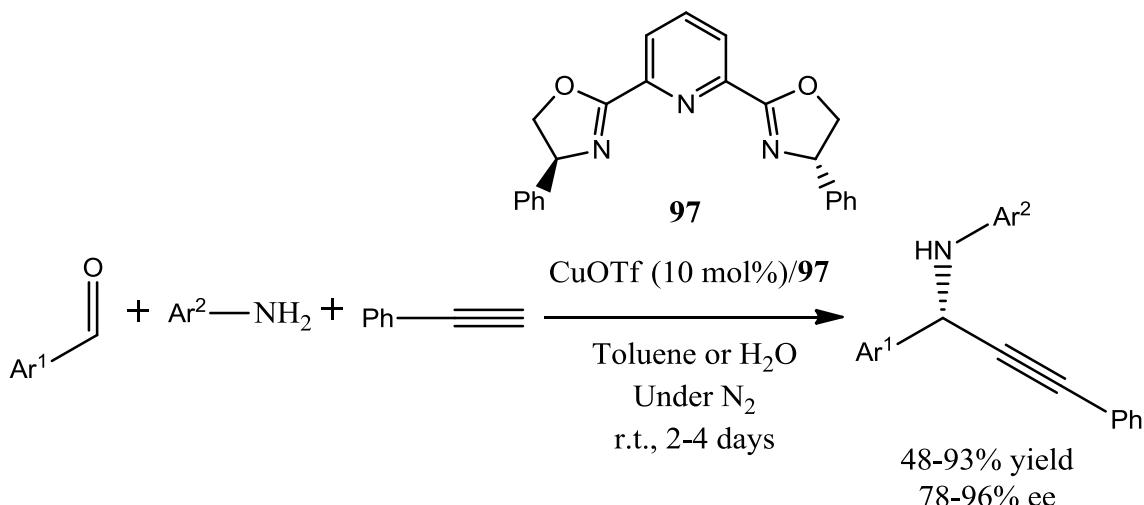
^c Reactions carried out under microwave conditions in sealed vessel.

^d Diastereomeric ratio of 95:5 determined by ¹H spectroscopy. The absolute configuration was not determined.

Bn = Benzyl

5.5.2 Copper catalysed asymmetric A³-(AA³) coupling reactions

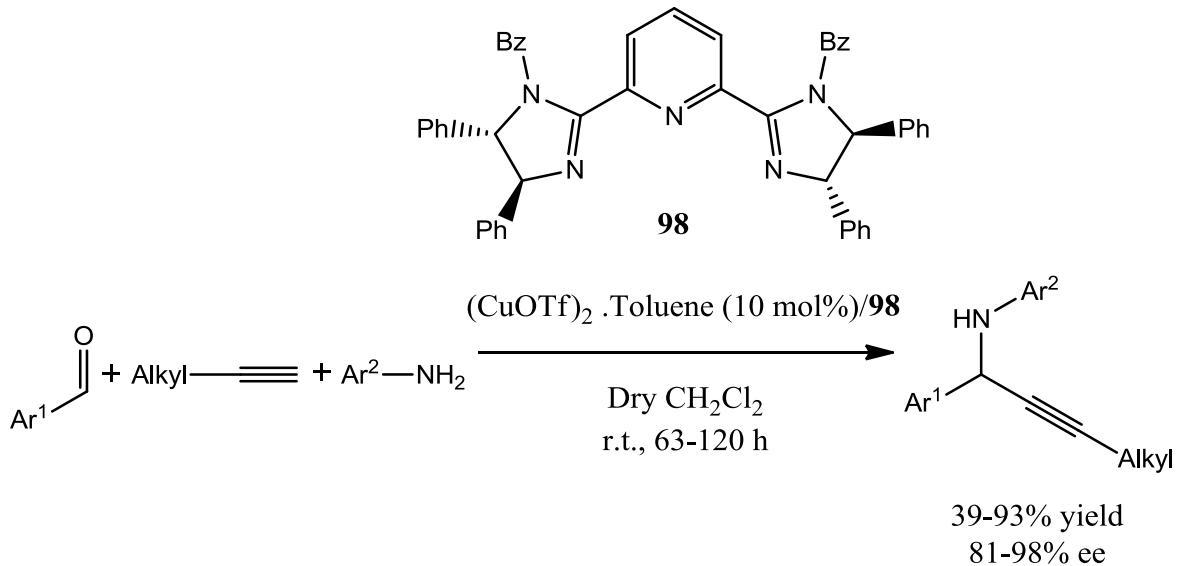
Optically active propargylamines are key components for many chiral biologically active molecules, and enantioselective A³-reactions provide a convenient route to this important class of compounds. During Li's original investigation of the Ru-Cu catalysed A³-reaction it was observed that CuBr alone gave the desired product in H₂O albeit in low conversions.^{236,239} The authors hypothesised that the low conversion may provide an opportunity to develop an asymmetric variant of the reaction. It was postulated that the low conversion was due to the low reactivity of the alkynyl C-Cu bond. It was thought that a strongly co-ordinating nitrogen based ligand would increase the reactivity. Moreover the use of a chiral ligand would produce a chiral environment around the C-Cu bond, which could then lead to asymmetric induction during addition of the alkyne to the imine.²³⁹ Several chiral bis(oxazolinyl) ligands were screened by Li *et al.*,²⁶² in combination with CuOTf, for the addition of phenylacetylene to *N*-arylimines. It was found that the desired enantioselective addition product was formed in low ee when bidentate bis(oxazoline) (box) ligands were used. However the use of tridentate bis(oxazolinyl) pyridine (pybox) ligand (**97**) gave the optimal conversion and enantioselectivity (71 % yield, 84% ee in H₂O), see Scheme 5.5.1. The yield and enantioselectivity could be further increased by using toluene as solvent (78% yield, 96% ee).^{262,263}



Scheme 5.5.1: CuOTf/pybox catalysed AA³-coupling reactions.²⁶²

Subsequently this catalytic system was extended to cover aliphatic alkyne addition to *N*-benzylideneaniline,²⁶³ although the yields of propargylamine and ee % were much lower than with standard phenylacetylene addition. During the course of these investigations it was noted that both the yield and enantiomeric excess were strongly affected by the choice of reaction solvent.^{239,263} Similar results were also reported by Bisai and Singh who utilized

a bulky Cu(I)-*i*Pr-pybox-diPh complex to carry out the enantioselective synthesis of propargylamines.²⁶⁴ More recently Nakamura and co-workers²⁶⁵ have developed an asymmetric copper catalysed protocol using a novel bis(imidazoline) pyridine (pybim) ligand (**98**), see Scheme 5.5.2. The reaction was optimised for use with aliphatic alkynes offering improved yields and enantioselectivities, compared to the earlier method of Li.²⁶³



Scheme 5.5.2: CuOTf/pybim (**98**) catalysed enantioselective A³-reactions.²⁶⁵

As with conventional copper catalysed A³-reactions the recycling and re-use of chiral Cu pybox complexes has been investigated. Portnoy *et al.*²⁶⁶ have prepared a range of chiral copper pybox complexes on polystyrene resins, as heterogeneous catalysts, see Figure 5.5.1. In general the yields and enantioselectivities were lower than those obtained with the homogeneous copper pybox complexes. The investigation did however demonstrate that the catalyst could be easily separated from the reaction medium, and recycled for at least three consecutive runs.

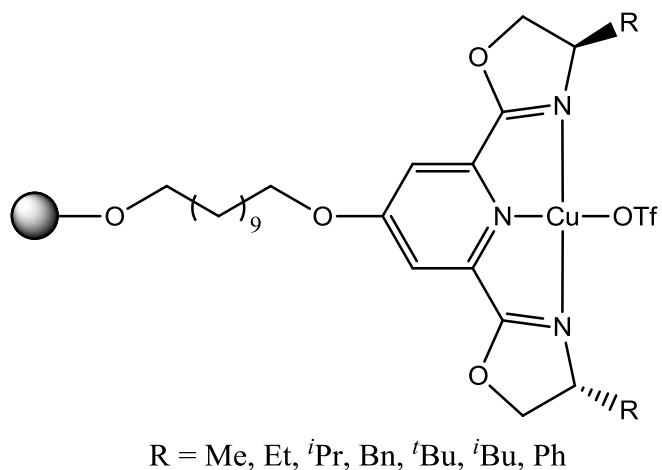


Figure 5.5.1: The heterogeneous Cu pybox catalysts screened by Portnoy and co-workers.²⁶⁶

Following this Li and co-workers²⁶⁷ synthesised an Fe₃O₄ nano-particle supported copper(I) pybox catalyst (**99**) which exhibited good activity and enantioselectivity. Indeed the yields and ee % were comparable to the homogenous copper pybox catalyst. The use of magnetic nano-particles enabled facile separation and recovery of the active catalyst from the reaction solvent, with the catalyst recycled for 6 consecutive runs with little decrease in reactivity and selectivity.

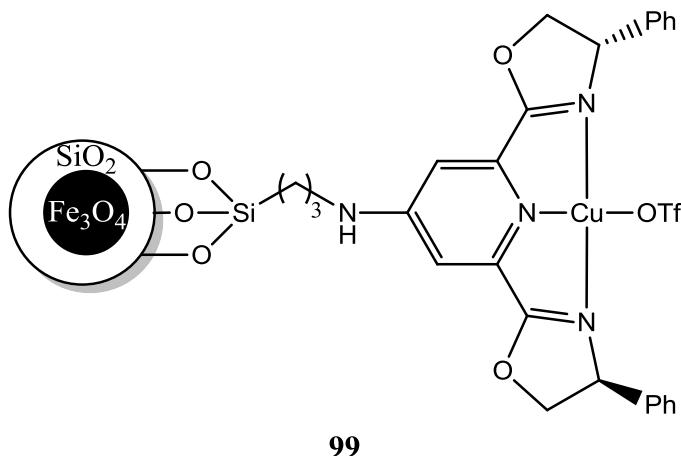
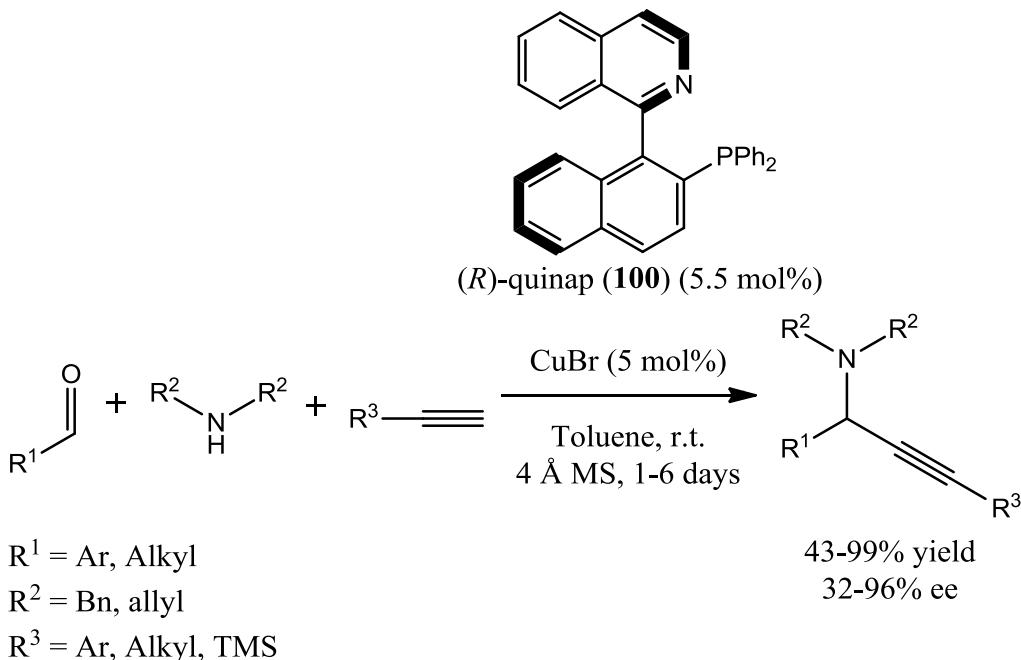


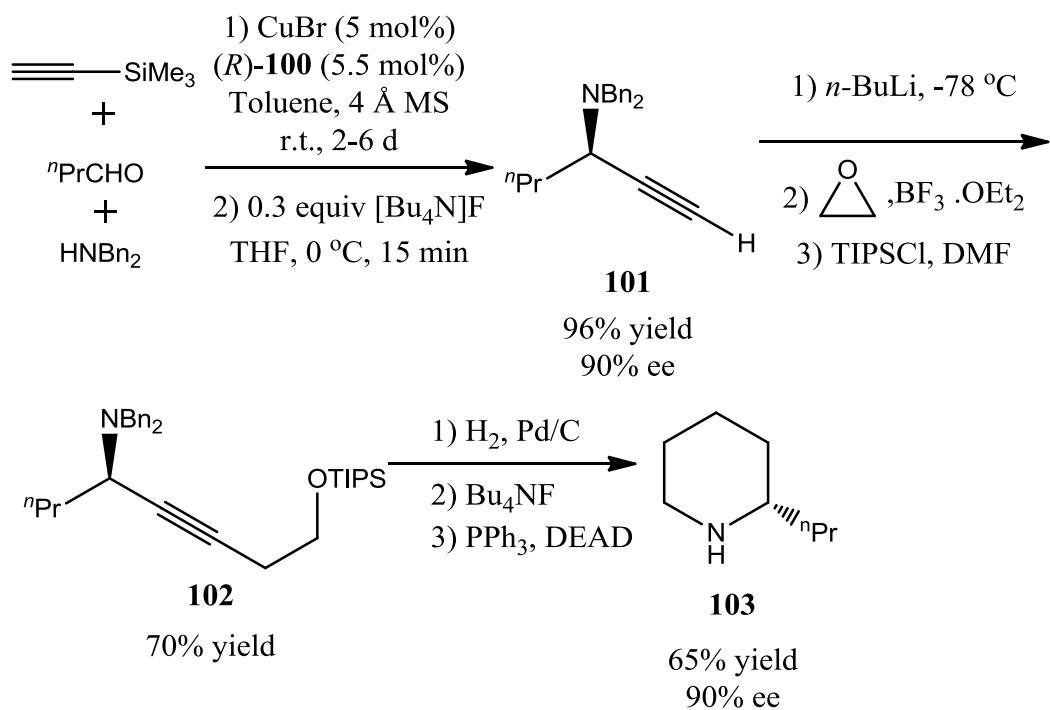
Figure 5.5.2: Fe₃O₄ nanoparticle-supported Cu(I) pybox (**99**) complex for AA³-reactions.²⁶⁷

The copper(I) pybox complexes detailed above have been used exclusively for the AA³-reaction of anilines. Using secondary amines as substrates in AA³-reactions requires the use of a different type of chiral ligand to achieve the desired asymmetric induction. In 2002 Knochel and co-workers²⁵² reported the asymmetric synthesis of tertiary propargylamines via the CuBr (*R*)- or (*S*)-Quinap (**100**) catalysed addition of alkynes to enamines. Subsequently the CuBr/Quinap catalytic system was applied to the related three component coupling of aldehydes, amines and alkynes (Scheme 5.5.3).²⁶⁸ Variations of the substituents on each component provided evidence that the reaction had a broad substrate scope.²⁶⁹ The reaction proceeds smoothly with both aromatic and aliphatic aldehydes, although aliphatic aldehydes gave higher enantioselectivities. With aromatic aldehydes the presence of an electron donating or withdrawing group in the *para*-position has only a moderate effect on the enantioselectivity; however the product yield dropped significantly (76% to 43%) upon changing from *p*-OMe to *p*-CF₃ due to a significant decrease in reactivity of the substrate.²⁵² Steric effects were found to be important in the coupling reaction with *ortho*-substituents on the aldehyde resulting in a dramatic decrease in the selectivity to 32% ee for *o*-methylbenzaldehyde.



Scheme 5.5.3: The CuBr/Quinap catalysed AA³-reaction.²⁶⁸

For the amine component secondary amines dibenzylamine and diallylamine were extensively examined. Dibenzylamine typically gave higher enantioselectivities due to the greater steric demand of the benzyl groups.²⁶⁹ The reaction was unsuccessful with anilines and amides. Variation of the alkyne substituent was also explored, with phenyl, alkyl and alkenyl groups giving high yields and enantioselectivities, but the best yields and enantioselectivities were obtained when trimethylsilylacetylene was used as the alkyne component (98% ee). In addition desilylation of the products with [Bu₄N]F in THF or KOH in MeOH gave the terminal triple bond containing propargylamines which could be further functionalised. Indeed the synthetic utility of this coupling protocol was demonstrated in the enantioselective synthesis of (*S*)-(+)coniine (**103**),²⁷⁰ see Scheme 5.5.4. Coniine is a highly toxic alkaloid inducing curare type paralysis.²⁷⁰ The synthesis of coniine, as depicted in Scheme 5.5.4, starts with an AA³-reaction followed by desilylation of the trimethylsilyl containing propargylamine to give **101**. Deprotonation of the terminal alkyne using *n*-BuLi followed by alkylation with ethylene oxide gave the alcohol which could then be silylated with TIPSCl (triisopropyl silylchloride) to give the TIPS protected alcohol (**102**). Hydrogenolysis of the benzyl groups and reduction of the triple bond gave the silyl protected amino alcohol which was desilylated with [Bu₄N]F and submitted to an intramolecular Mitsunobi reaction.²⁶⁹ (*S*)-(+)coniine(**103**) was prepared in an overall yield of 41% and with 90% ee.²⁷⁰



Scheme 5.5.4: The enantioselective synthesis of (S)-(+)-coniine (103).²⁷⁰

Following this Knochel and co-workers carried out a detailed mechanistic investigation of the AA³-reaction catalysed by CuBr/Quinap. During the course of these studies it was observed that the enantioselective reaction displays a strong positive non-linear effect²⁶⁸ (Figure 5.5.3). Accordingly when using a mixture of Quinap enantiomers (*R* and *S*) with only 5% ee, the propargylamine product is obtained with an enantiomeric excess of 50%. Furthermore the rate of AA³-coupling was found to be linearly correlated to the enantiomeric excess of the ligand.²⁶⁹

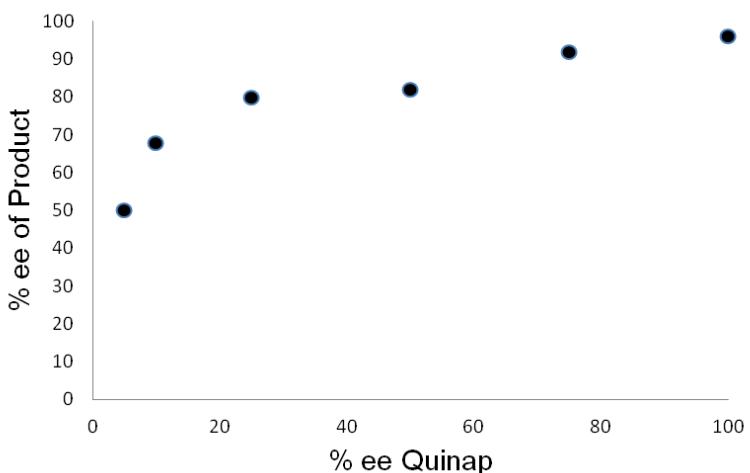


Figure 5.5.3: The non-linear effect in the CuBr/Quinap catalysed AA³-coupling reaction. Reproduced using the experimental data provided in reference.²⁶⁸

Both of these outcomes are believed to arise from the fact that CuBr and Quinap react *in-situ* to form a dimeric catalytically active Cu/Quinap species which is in good agreement with the reported crystal structure of $[\text{CuBr}\{(R)\text{-Quinap}\}]_2$ (**104**)²⁵² shown in Figure 5.5.4.

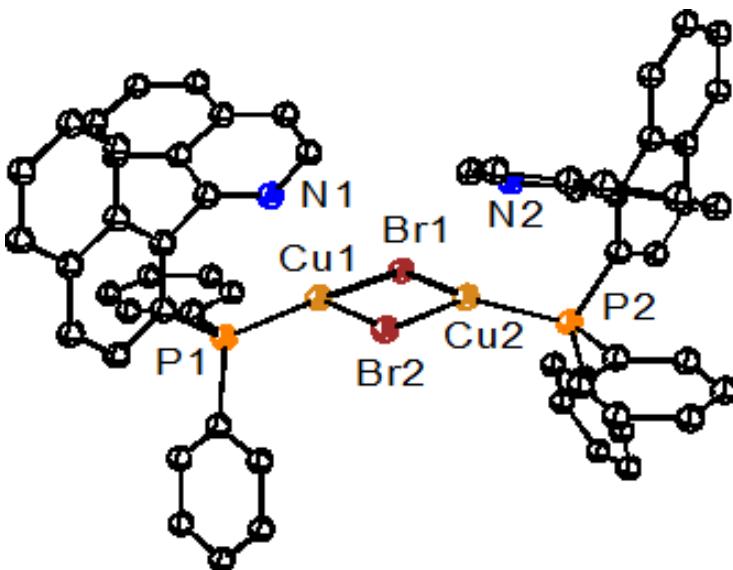
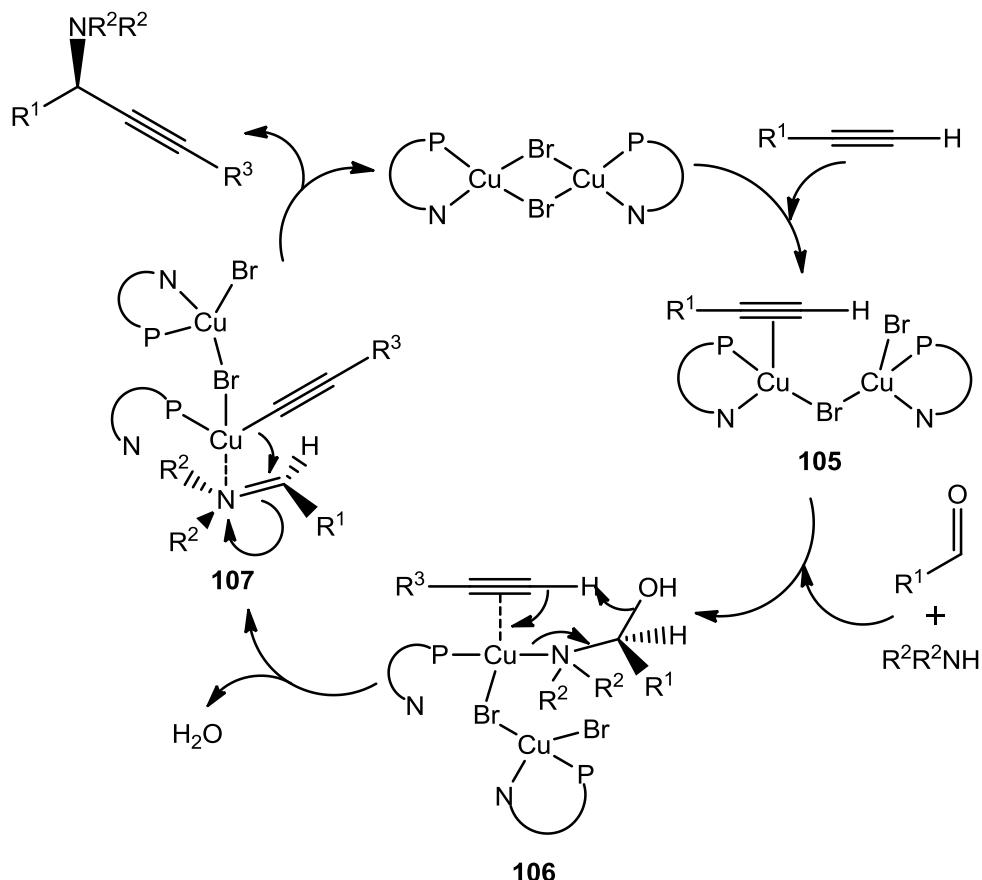


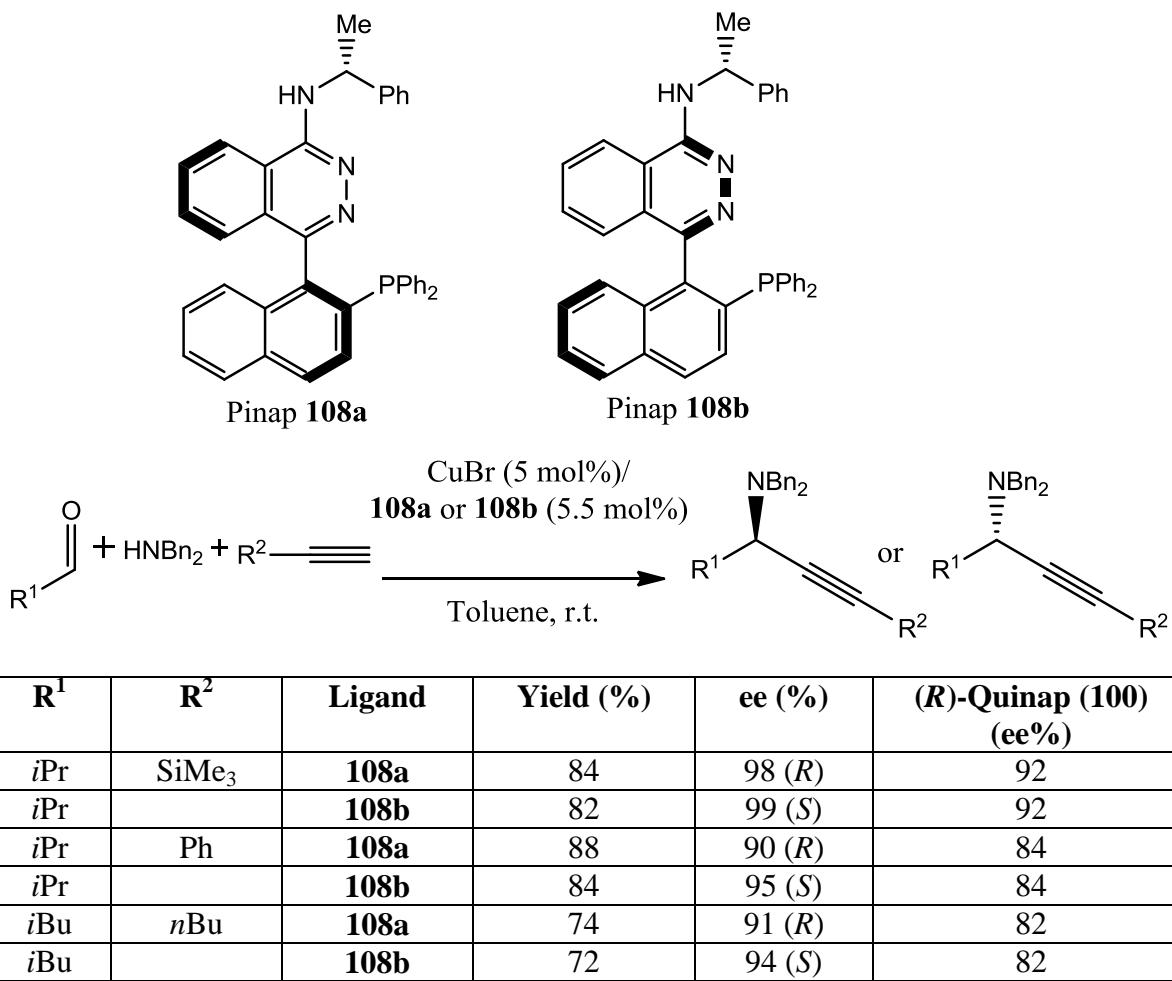
Figure 5.5.4: Solid state structure of $[\text{CuBr}\{(R)\text{-Quinap}\}]_2$ (**104**). Hydrogen atoms and crystallised solvent omitted for clarity. Thermal ellipsoids at 40% probability level.

The heterochiral complex $[\text{Cu}_2\text{Br}_2\{(R)/(S)\text{-Quinap}\}]$ (**104a**) is postulated to react at a much slower rate than the corresponding homochiral complex $[\text{Cu}_2\text{Br}_2\{(R)/(R)\text{-Quinap}\}]$ (**104**). Therefore this would explain the strong positive amplification seen in Figure 5.5.3.²⁶⁹ Additionally when the enantiomeric excess of the ligand is decreased the amount of reactive homochiral complex present also decreases relative to the amount of the more stable and less reactive heterochiral complex. This would explain why a reduction in the reaction rate is observed when the ee% of the ligand is decreased. Based on these results a reaction mechanism was proposed for the CuBr/Quinap catalysed AA³-reaction (Scheme 5.5.5). The first step in the mechanism is the formation of a ‘side-on’ alkyne complex (**105**), followed by coordination of the imine species (formed from the condensation of aldehyde and secondary amine) to the Cu atom (**106**). Deprotonation of the coordinated alkyne and the loss of H₂O give the ‘end-on’ acetylidate complex with a coordinated imminium ion (**107**). The final step is the addition of the acetylidate to the imine species, which takes place in the coordination sphere of the chiral Cu(I) complex. The catalyst is then regenerated in this last step.^{268,269}



Scheme 5.5.5: Proposed mechanism for the AA³-reaction catalysed by CuBr/Quinap. Adapted from ref²⁶⁸

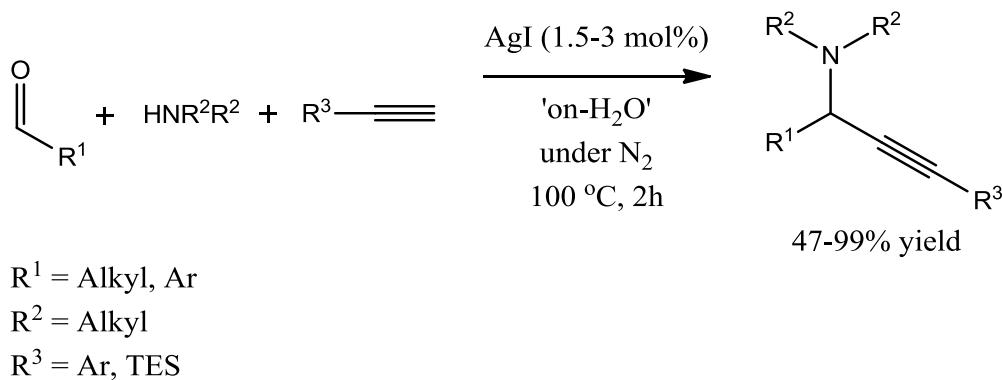
Quinap was prepared by Brown *et al.* in 1993 in a six-step procedure resulting in resolution of the enantiomeric atropisomers using a preformed chiral Pd-complex.²⁷¹ Due to this difficult preparation, Quinap although being commercially available is rather expensive. This led Carreira and co-workers to prepare a new class of P,N ligands called Pinap.²⁷² The biaryl back-bone of the Pinap ligands is readily prepared through the coupling of dichlorophthalazine with 2-naphthol. The two Pinap atropisomers (**108a** and **108b**) formed at the end of the synthesis could be conveniently separated by crystallisation or chromatography on silica gel. The new ligands were then screened in the CuBr/Pinap catalysed AA³-couplings to give both (*S*) and (*R*) propargylamines in excellent yields and enantioselectivities (Scheme 5.5.6). The CuBr/Pinap catalytic system affords higher ee% than the CuBr/Quinap method, and to date remains the benchmark for AA³-couplings.



Scheme 5.5.6: CuBr/Pinap catalysed AA³-coupling.²⁷²

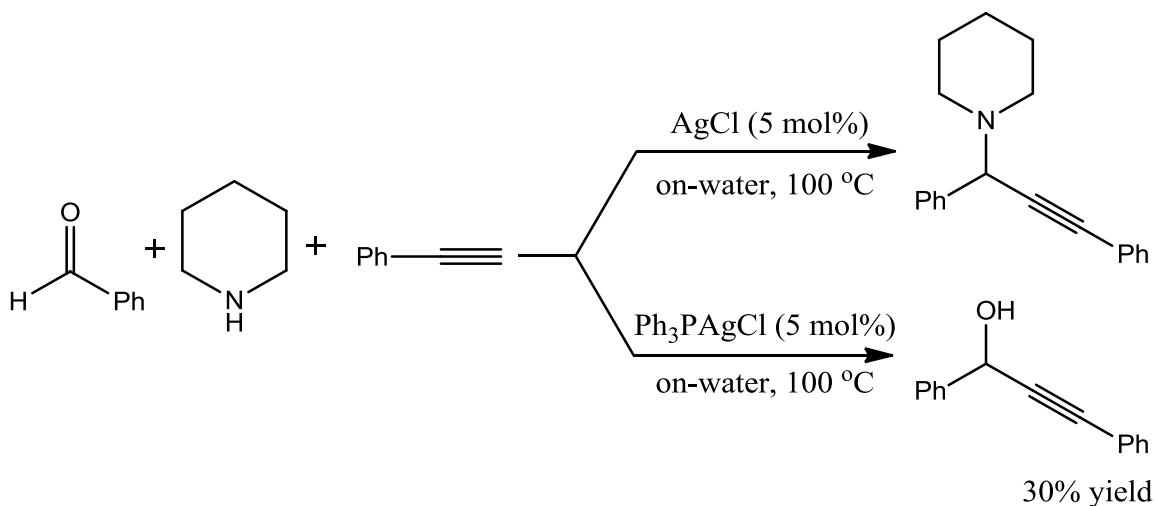
5.5.3 Silver catalysts

In 2003 Li *et al.*²⁷³ reported the first silver-catalysed coupling of aldehydes, amines and alkynes. Initially a range of water-soluble silver salts such as AgNO₃, Ag₂O, AgOAc, Ag₂SO₄, AgOTf and AgBF₄ were found to catalyse the reaction of benzaldehyde, piperidine and phenylacetylene albeit with low conversions (25-45 % after 14 hours in H₂O). It was found that the water-insoluble salts AgCl, AgBr and AgI gave higher conversions, with AgI proving to be the most effective catalyst (75% conversion, ‘on water’). Various aldehydes, terminal alkynes and cyclic dialkylamines reacted smoothly to give propargylic amines in good yields, see Scheme 5.5.7.



Scheme 5.5.7: AgI catalysed A^3 -coupling. TES = triethylsilyl.²⁷³

The reaction was found to be sensitive to aldehyde substituent, with aromatic aldehydes having a decreased reactivity, leading to lower conversions and yields. Aliphatic aldehydes displayed a higher reactivity and gave higher yields of the coupled product. The solvent could be varied to toluene and DMF with similar conversions to reactions carried out ‘on-water’. Subsequently Li and co-workers demonstrated a remarkable phosphine-triggered switch in the reactivity of AgCl in A^3 -reactions.²⁷⁴ When AgCl was used as a catalyst in the coupling of benzaldehyde, piperidine and phenylacetylene on-water the A^3 -coupled propargylamine was formed. However upon using $(\text{Ph}_3\text{P})\text{AgCl}$ as catalyst under the same conditions the A^2 coupling of aldehyde and alkyne to give the propargyl alcohol was observed (Scheme 5.5.8).



Scheme 5.5.8: Phosphine-triggered switch in reactivity of AgCl.

5.5.4 Gold catalysts

The first example of a gold catalysed A^3 -reaction was reported by Li and co-workers in 2003.²³⁷ The three component coupling of benzaldehyde, piperidine and phenylacetylene in H_2O was found to be catalysed by AuCl (5 mol%) to give quantitative conversion to propargylic amine in 12 h. Other gold salts such as AuI , AuBr , AuBr_3 and AuCl_3 were

screened and also exhibited excellent activity, see Table 5.5.2. The gold catalysed coupling was found to be highly efficient especially compared to the CuBr catalysed A³-reaction where a 10 mol% loading of CuBr gave only a 10 % conversion to coupled product under the same conditions.²³⁷ The gold(III) halides, AuBr₃ and AuCl₃ have slightly higher activity, and with AuBr₃ even low catalyst loadings of 0.25 mol% (Table 5.5.2, entry 6) gave the desired product in 99% yield. The reactions were found to be sensitive to the presence of air, so were carried out under a nitrogen atmosphere. Additionally the coupling was extremely sensitive to changes in the reaction solvent (Table 5.5.2, entries 4, 9-12). In H₂O clean reactions to give the propargylamine product took place, whereas in organic solvents, such as THF, toluene and DMF the conversion was significantly lower, and by-product formation was observed in the crude reaction mixture.

Table 5.5.2: Comparison of different gold salts and reaction conditions for the A³-coupling of benzaldehyde, piperidine and phenylacetylene adapted from reference ²³⁷

Entry	Catalyst (mol%)	Solvent/Temp (°C)/Time (h)	Conversion (%) ^a
1	AuCl (5)	H ₂ O/100/12	99
2	AuCl (1)	H ₂ O/100/12	99
3	AuI (1)	H ₂ O/100/12	99
4	AuBr ₃ (1)	H ₂ O/100/12	100
5	AuCl ₃ (1)	H ₂ O/100/12	100
6	AuBr ₃ (0.25)	H ₂ O/100/12	99
7	AuBr ₃ (0.01)	H ₂ O/100/12	13
8	AuBr ₃ (1)	H ₂ O/100/5.5	100
9	AuBr ₃ (1)	H ₂ O/r.t./72	81
10	AuBr ₃ (1)	THF/r.t./48	55 ^b
11	AuBr ₃ (1)	Toluene/100/12	78 ^b
12	AuBr ₃ (1)	DMF/100/12	62 ^b

All reactions carried out under N₂.

^a Conversion determined by ¹H NMR spectroscopy of the crude mixture with respect to aldehyde consumption.

^b By-products also formed.

Variation of the aldehyde and amine components was also carried out to determine the substrate scope of the gold-catalysed couplings. Both aromatic and aliphatic aldehydes underwent coupling, although aromatic aldehydes were generally more reactive and gave near quantitative yields. Aryl aldehydes containing electron rich groups such as *p*-MeO- and *p*-alkyl-benzaldehyde exhibited a slightly reduced reactivity. Propargylic amines comprising aliphatic aldehydes were obtained in reduced yields due to unwanted trimerization of the aliphatic aldehydes.²³⁷ The amine substrate also had an effect on reactivity with secondary dialkylamines giving high yields and *N*-alkylanilines and primary amines giving only trace amounts or no propargylamine. Table 5.5.3 lists some selected examples of the couplings carried out by Li and co-workers.

Table 5.5.3: Selected examples of coupling of aldehyde, amine with phenylacetylene carried out by Li and co-workers.²³⁷

Entry	Aldehyde	Amine	Product	Yield (%) ^a
1	PhCHO	piperidine		99
2	PhCHO	HN(Bn) ₂		99
3	PhCHO	HN(allyl) ₂		95
4	Ar-CH ₂ CH ₂ CHO	piperidine		75
5	<i>p</i> -MeO-PhCHO	piperidine		91
6	<i>p</i> -Me-PhCHO	piperidine		87

Coupling conditions: AuBr₃ (1 mol%), H₂O, 100 °C, 12 h, under N₂.

^a Isolated yields based on aldehyde.

A mechanism for the coupling was proposed, that is similar to the one featured previously in Scheme 5.3.1, whereby a gold acetylide (postulated by the authors to be a gold(I) species) reacts with an iminium ion (which is generated *in-situ*) to give the propargylamines.

Gold(III) salen complexes, prepared by the direct reaction of tetradentate Schiff base with [AuCl₄] salts,²⁷⁵ have also been shown to catalyse the A³-reaction.²⁷⁶ Five gold(III) salen complexes, **109a-b** and **110a-c** shown in Figure 5.5.5, were screened at a loading of 1 mol% in the coupling of benzaldehyde (2 mmol), piperidine (2.2 mmol) and phenylacetylene (3 mmol) in water, under N₂, at 40 °C for 24 hours.

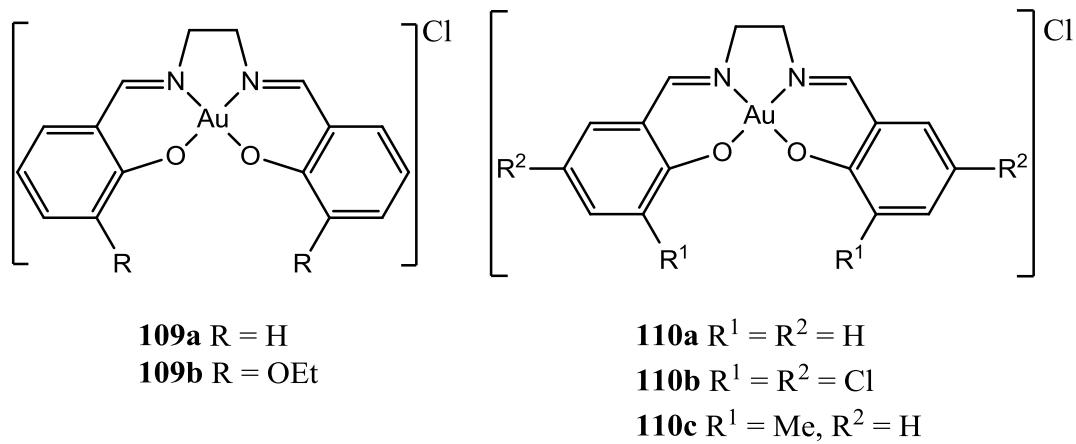
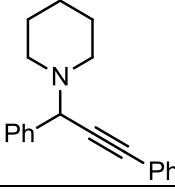
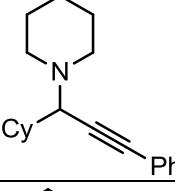
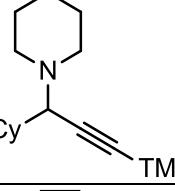
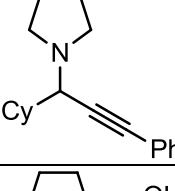
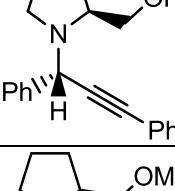
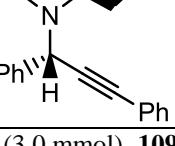


Figure 5.5.5: The structure of the gold(III) salen complexes investigated for A³-coupling.

109a was found to be the most effective catalyst under these conditions with a 94% isolated yield of propargylamine. The coupled product was still obtained in 84% isolated yield when the catalyst loading was reduced (0.05 mol%). The coupling reaction also took place at room temperature albeit at a slower rate (78% yield in 24 h). The reaction is compatible with a range of substrates with complete aldehyde conversion; see Table 5.5.4 for selected examples. Coupling reactions with chiral prolinol derivatives were also studied, and excellent diastereoselectivities were obtained (Table 5.5.4, entries 5 and 6). Indeed when (S)-prolinol was used as the amine component diastereomeric ratios of 99:1 were obtained, illustrating that chiral substituents on the amine are able to influence the reaction selectivity.

Recycling of **109a** was also investigated in the coupling of benzaldehyde, piperidine and phenylacetylene. After 1 reaction cycle an aliquot of the reaction mixture was removed from the reaction flask and an additional amount of starting materials was added and the reaction continued for 24 h. This demonstrated that the catalyst could be recycled, at least three times, with a slow loss in activity from 96% to 83 to 73% conversion after 3 cycles. Furthermore the utility of gold(III) salen complex catalysed A³-reactions was demonstrated through the propargylamine modified synthesis of Artemisinin derivatives.²⁷⁶

Table 5.5.4: Selected examples of coupling with complex 109a (1 mol%), H₂O, 40 °C, 24 h.

Entry	Aldehyde	Amine	Acetylene	Product	Yield ^a (%)	d.r.
1	PhCHO	piperidine	PhCCH		94	-
2	CyCHO	piperidine	PhCCH		99	-
3	CyCHO	piperidine	TMSCCH		90	-
4	CyCHO	pyrrolidine	PhCCH		97	-
5	PhCHO	(S)-prolinol	PhCCH		82	99:1
6	PhCHO	<i>O</i> -methyl-(S)-prolinol	PhCCH		74	95:5

Reaction conditions: aldehyde (2.0 mmol), amine (2.2 mmol), alkyne (3.0 mmol), **109a** (0.02 mmol), H₂O (1 mL), 40 °C, 24 h, under N₂.

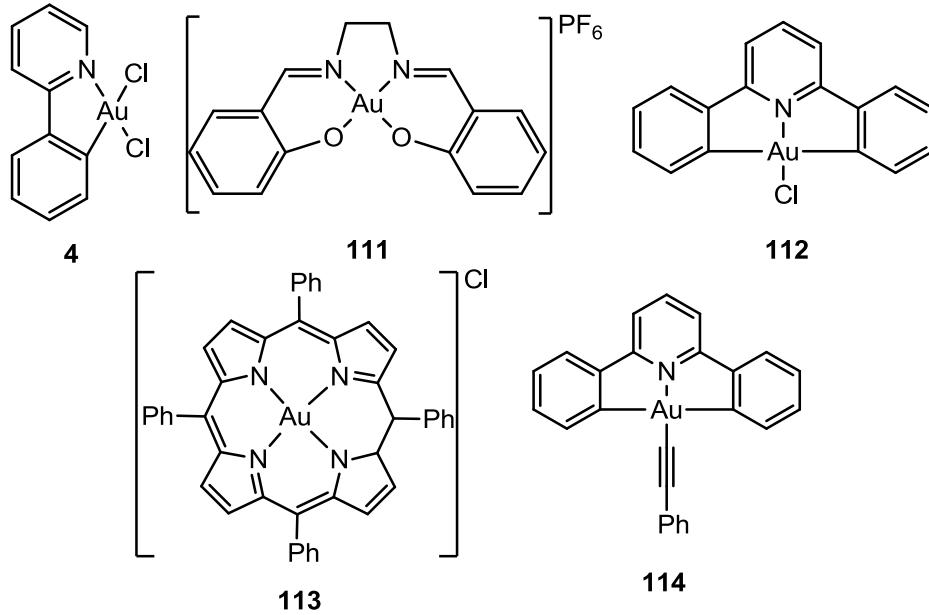
^a Isolated yields calculated based on aldehyde.

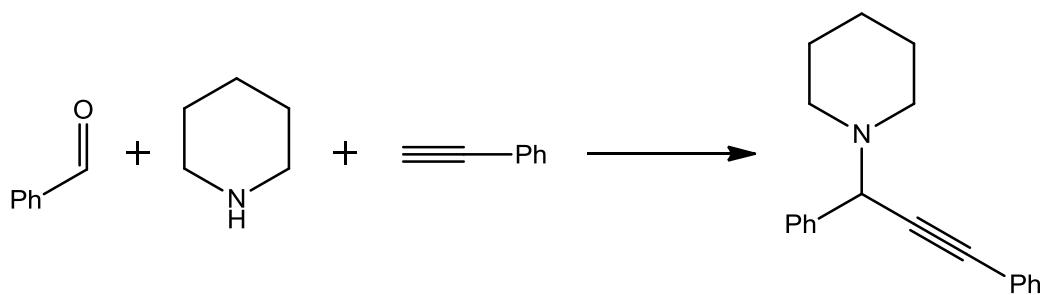
Cy = cyclohexyl; TMS= trimethylsilyl.

Che *et al.*²⁷⁷ have investigated the catalytic activity of the 2-phenylpyridine complex, AuCl₂(η²-C,N-C₆H₄-2-C₅H₄N) (**4**) in the three component coupling reaction. Initially four Au(III) complexes containing different nitrogen donors were screened in the reaction of benzaldehyde, piperidine and phenylacetylene at 40 °C in H₂O over 24 h (Table 5.5.5). The 2-phenylpyridine gold complex (**4**) was found to have comparable activity to the gold(III) salen complex (**111**), with 99% aldehyde conversion and an 82% isolated yield of the propargylamine. The 2,6-diphenylpyridine-derived complex (**112**) is much less reactive with only 10% conversion of the aldehyde under the same conditions. Interestingly a stable gold(III) acetylidyne complex was isolated from the reaction mixture after flash chromatography on silica.²⁷⁷ The ¹H NMR spectrum of this product is consistent with the

phenylacetylide substituted 2,6-diphenylpyridine complex (**114**).²⁷⁸ The porphyrin complex [Au(TPP)Cl] (**113**), where H₂TPP = *meso*-tetraphenylporphyrin, gave no conversion to product. Experiments with reduced loading of **4** were also carried out. With 0.25 mol% of **4** there is still complete conversion of benzaldehyde in 24 h, see Table 5.5.5, entry 5. A further reduction of catalyst loading to 0.1 mol% gives 74% benzaldehyde conversion over 24 h. Continuing the reaction for 48 h results in 97% conversion and a 70% isolated yield (Table 5.5.5, entries 6 and 7), giving a turnover number of 970 after 48 h. A variety of coupling reactions with chiral prolinol derivatives, as amine component, were carried out it in order to analyse the substrate scope of the AuCl₂(η²-C,N-C₆H₄-2-C₅H₄N) (**4**) catalysed A³-reaction. The coupling of prolinol methyl ester, benzaldehyde and phenylacetylene (Table 5.5.6, entry 1) gave the propargylamine in 83% yield with a diastereomer ratio of 94:6. The absolute configuration was determined as (*S*) by comparison to the relevant literature data.²⁶⁸ With (*S*)-prolinol diastereoselectivities of 96:4 were obtained with a 62% isolated yield of product. With (*R*)-prolinol the same diastereoselectivity was obtained, but an improved yield of 75% was obtained (Table 5.5.6, entries 2 and 3). Coupling reactions with (*S*)-prolinol were extended to various *para*-substituted aldehydes including Br and OMe substituents (Table 5.5.6, entries 4 and 5), with the propargylic amines obtained in high yield and excellent diastereoselectivities.

Table 5.5.5: Screening of gold(III) catalysts in the A³-reaction of benzaldehyde, piperidine and phenylacetylene.





Entry	Catalyst (mol%)	Conversion (%) ^c	Yield (%) ^d
1 ^a	4 (1)	99	82
2 ^a	111 (1)	99	94
3 ^a	112 (1)	10	-
4 ^a	113 (1)	0	-
5	4 (0.25)	100	-
6	4 (0.1)	74	-
7 ^b	4 (0.1)	97	70

^a Reaction conditions: benzaldehyde (1 mmol), piperidine (1.1 mmol), phenylacetylene (1.5 mmol), H₂O, 1 mol% catalyst, 40 °C, 24 h.

^b Reaction for 48 h.

^c Conversion determined by ¹H NMR spectroscopy of the crude reaction mixture based on aldehyde consumption.

^d Isolated yields based on aldehyde.

Different alkynes were also found to react with benzaldehyde and (*S*)-prolinol (Table 5.5.6, entries 6 and 7) to give excellent yields and diastereoselectivities of propargylamines. When isophthalaldehyde was reacted with (*S*)-prolinol and phenylacetylene two coupled products were formed in a total yield of 83% (Table 5.5.6, entry 8). The first product was formed by coupling of one of the aldehyde groups with prolinol and phenylacetylene in 52% yield. The other component in the mixture was the double coupled product obtained through reaction of both aldehyde groups.

Table 5.5.6: Selected examples of A³-couplings with 2-phenylpyridineAuCl₂ (4**).**

Entry	Aldehyde	Amine	Acetylene	Product	Yield (%) ^a	d.r. ^b
1	PhCHO	<i>O</i> -methyl-(<i>S</i>)-prolinol	PhCCH		83	94:6
2	PhCHO	(<i>S</i>)-prolinol	PhCCH		62	96:4
3	PhCHO	(<i>R</i>)-prolinol	PhCCH		75	96:4
4	<i>p</i> -OMe-PhCHO	(<i>S</i>)-prolinol	PhCCH		99	96:4
5	<i>p</i> -Br-PhCHO	(<i>S</i>)-prolinol	PhCCH		68	98:2
6	PhCHO	(<i>S</i>)-prolinol	C ₆ H ₉ CCH		84	96:4
7	PhCHO	(<i>S</i>)-prolinol	<i>p</i> -MeC ₆ H ₄ CCH		92	95:5
8 ^c	1,3-(CHO) ₂ -C ₆ H ₄	(<i>S</i>)-prolinol	PhCCH		83 (total yield)	96:4

Reaction conditions: aldehyde (1 mmol), amine (1.1 mmol), alkyne (1.5 mmol), 1 mol% **4**, H₂O, 40 °C, 24 h.

^a Isolated Yields based on aldehyde

^b Diastereomer ratio determined by ¹H NMR spectroscopy.

^c Mixture of products in 1.7:1 ratio. Major = single A³-coupled product.

Some preliminary mechanistic experiments were also carried out. The reaction between benzaldehyde (1 mmol), piperidine (1.1 mmol) and phenylacetylene (1.5 mmol) catalysed by **4**, in H₂O, at 40 °C was followed by monitoring benzaldehyde conversion against reaction time. At regular intervals an aliquot of the reaction mixture was removed and the conversion determined by ¹H NMR spectroscopy. Figure 5.5.6, taken from ref. ²⁷⁷ shows the reaction profile obtained. An induction period of around two hours was required for the catalyst to become active. The authors added AgNO₃ and NaCl, in the hope that abstraction of a chlorine atom from the catalyst may increase the rate; however neither reagent altered

the induction period. The recyclability of the catalyst was also examined by removing an aliquot of the reaction mixture after a 24 h reaction and then adding a fresh portion of the starting materials to the reaction mixture.

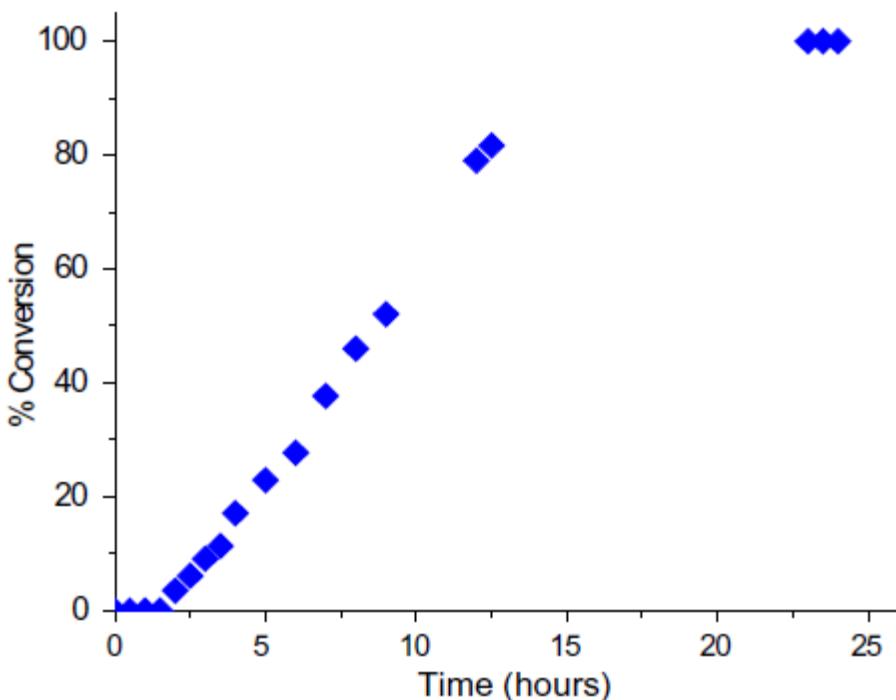


Figure 5.5.6: The reaction profile of $\text{AuCl}_2(\eta^2\text{-C}_5\text{N-C}_6\text{H}_4\text{-2-C}_5\text{H}_4\text{N})$ (4) (1 mol%) catalysed coupling of benzaldehyde, piperidine and phenylacetylene in H_2O at 40 °C. Taken from ref.²⁷⁷

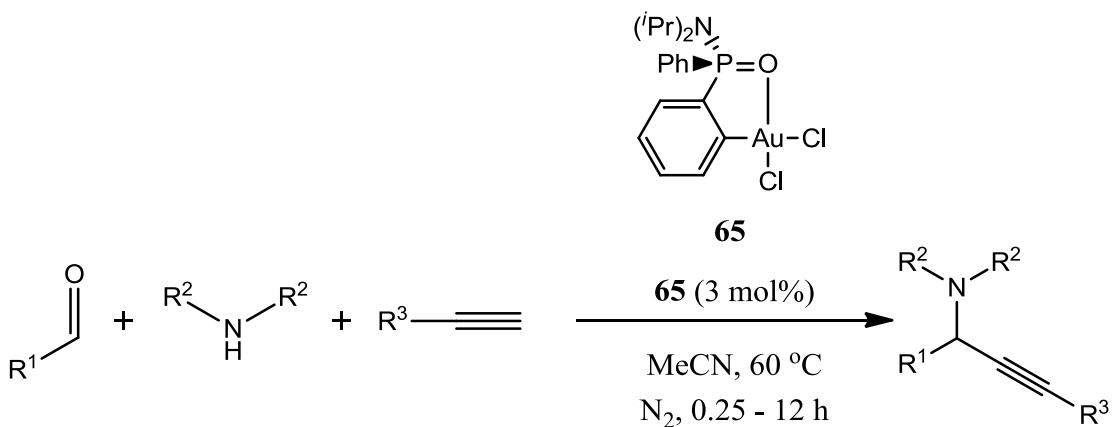
The catalyst could be recycled and re-used for 10 cycles giving 812 product turnovers in total, although the catalytic activity had decreased to give a conversion of 60% by run ten. These results contrast with gold(III) salen complex **111** where, after 3 cycles, the conversion of aldehyde had dropped to 73%.²⁷⁷ A mechanism analogous to the general mechanism of A^3 -coupling was proposed, whereby a gold-acetylidyne is the key intermediate for the formation of propargylic amines. The authors postulated that this complex was a gold(III) compound containing the 2-phenylpyridine ligand.

Table 5.5.7: Recyclability of the $\text{AuCl}_2(\eta^2\text{-C}_6\text{H}_4\text{-2-C}_5\text{H}_4\text{N})$ (4) in the coupling of benzaldehyde, piperidine and phenylacetylene.

Run	Conversion ^a (%)
1	100
2	100
3	92
4	89
5	84
6	76
7	73
8	70
9	67
10	60

^aConversion determined by ^1H NMR spectroscopy of the crude reaction mixture.

The gold(III) phosphinamidic complex (**65** as discussed in section 4.3) prepared by Ortiz *et al.* via organotin transmetallation has also demonstrated catalytic activity in A^3 -coupling reaction.¹⁸⁹ Typically low conversions have been reported for Au(III) catalysed couplings in organic solvents (Table 5.5.2),²³⁷ however **65** (3 mol%) was found to give the corresponding propargylamines in quantitative yield when coupling was carried out at 60 °C in acetonitrile under a nitrogen atmosphere (Scheme 5.5.9).



Scheme 5.5.9: A^3 -coupling catalysed by gold(III) phosphinamidic complex **65.**

With piperidine and morpholine as amine components the desired propargylamines were obtained in excellent conversions of 99%, see Table 5.5.8, entries 1 and 2. Reducing the catalyst loading from 3 to 1 mol% resulted in a *ca.* 20% decrease in conversion to 81% over 12 h. However with the addition of AgOTf (1 mol%) higher conversions can be achieved. This is most likely due to chloride abstraction from **65** to prepare a more active cationic species, as is well established in Au(I) catalysis.^{17,279–281} 4-Methoxybenzaldehyde

exhibited a reduced reactivity relative to benzaldehyde with a lower conversion of 80% over 24 h, whereas 3-phenylpropanal displayed a high reactivity (Table 5.5.8, entry 6) with conversions of 99% obtained after 15 min. The coupling of benzaldehyde, phenylacetylene and (*S*)-prolinol (Table 5.5.8, entries 7 and 8) yields propargylic amine product in near quantitative conversion, and with excellent diastereoselectivity (d.r. 99:1). Even at room temperature the coupled product is obtained in a high conversion of 91% in just 1 h. The recyclability of the catalyst was also probed, by carrying out four successive catalytic runs with piperidine, 3-phenylpropanal and trimethylsilylacetylene. Remarkably no loss of catalytic activity was observed after four cycles, and the reaction remained clean with no by-product formation observed. *In-situ* NMR experiments were carried out by monitoring aldehyde conversion (%) against reaction time (min), for the coupling of (*S*)-prolinol, benzaldehyde and phenylacetylene. 3 mol% of **65** was used and the reactions were conducted at room temperature in both MeCN and CHCl₃, see Figure 5.5.7 for the reaction profile. No induction period was found when either *d*³-MeCN or CHCl₃ was the solvent; however the reaction rate was significantly slower in chloroform. The authors hypothesised that the reason for this was due to aggregation of the catalyst in CHCl₃, whereas in *d*³-MeCN the catalyst remained monomeric.¹⁸⁹

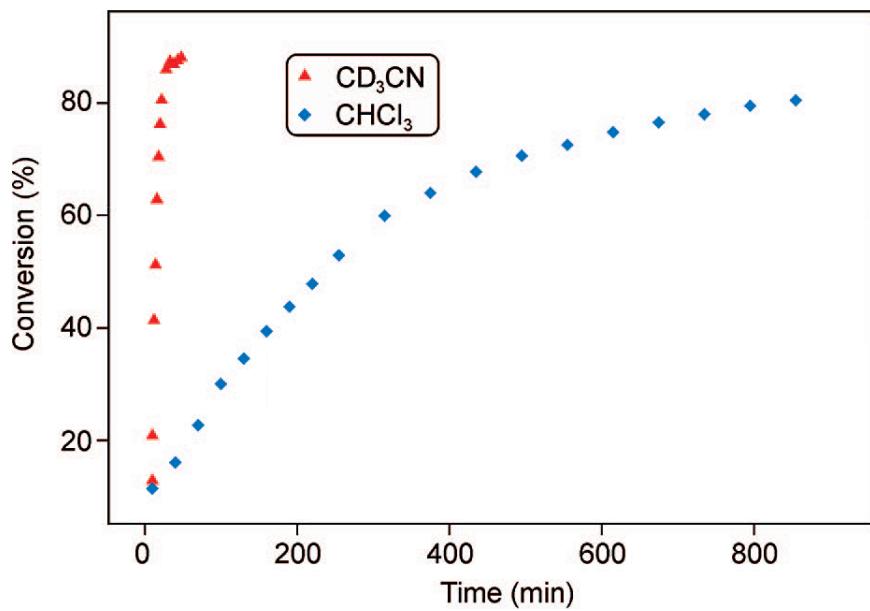


Figure 5.5.7: Reaction profile for the coupling of benzaldehyde, (*S*)-prolinol and phenylacetylene catalysed by **65**, carried out at room temperature in both *d*³-MeCN and CHCl₃. Taken from ref. ¹⁸⁹

Table 5.5.8: Selected examples of the coupling reactions with phenylacetylene as the alkyne component, carried out in ref¹⁸⁹

Entry	Aldehyde	Amine	65 (mol%)/Temp (°C)/time (h)	Product	Conversion (%) ^a
1	PhCHO	piperidine	3/60/6		>99
2	PhCHO	piperidine	1/60/12	As entry 1	81
3 ^b	PhCHO	piperidine	1/60/12	As entry 1	89
4	PhCHO	morpholine	3/30/9		>99
5	<i>p</i> -OMe-C ₆ H ₄ CHO	piperidine	3/60/24		80
6	PhCH ₂ CH ₂ CHO	piperidine	3/60/0.25		>99
7	PhCHO	(S)-prolinol	1/60/3		97 ^c
8	PhCHO	(S)-prolinol	1/25/3		91 ^c

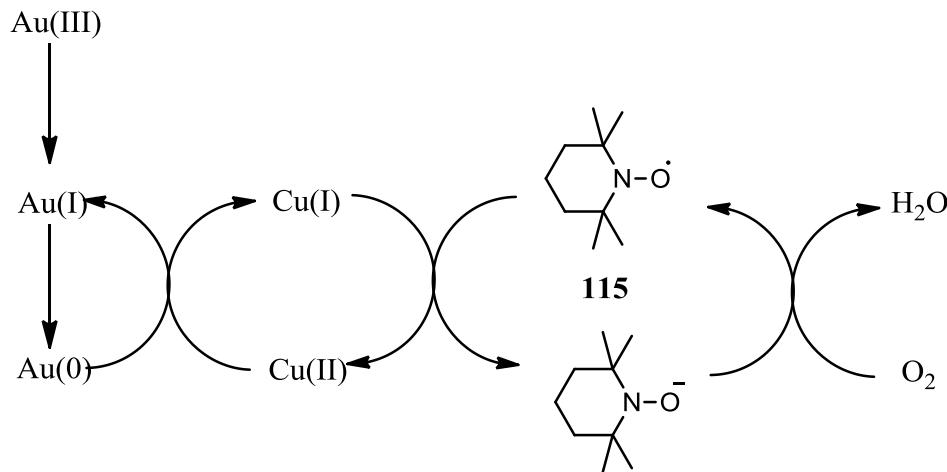
^a Conversion determined by ¹H NMR spectroscopy based on aldehyde.

^b AgOTf (1 mol%) added to increase conversion.

^c Diastereoselectivity determined by ¹H NMR spectroscopy on crude reaction mixture. (d.r. 99:1).

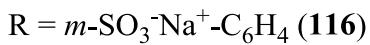
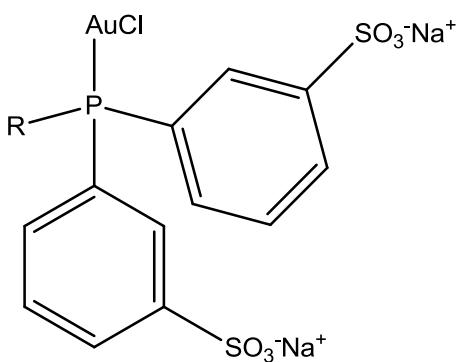
In a detailed study by Bowden and co-workers the recycling and re-use of gold(III) catalysts in the A³-reaction was investigated.²⁸² The authors repeated the AuCl₃ catalysed coupling of benzaldehyde, piperidine and phenylacetylene in H₂O, reported by Li and Wei.²³⁷ During a typical 12 hour reaction at 70 °C a dark solid precipitate formed in the

reaction flask, which was thought to be colloidal Au(0). The addition of another portion of starting materials at the end of the reaction resulted in no further conversion. By adding CuCl₂ (0.25 mol%) and TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl (**115**)) (60 mol%) the number of cycles could be dramatically increased so that quantitative conversions were achieved through 33 runs.²⁸² It should be noted that the authors reported that CuCl₂ and TEMPO showed no catalytic activity in the coupling reaction without the presence of gold(III).²⁸² It was also found that the presence of high amounts of O₂ in the reaction flask poisoned the gold catalyst, such that only one catalytic cycle could be carried out even in the reactions containing CuCl₂ and TEMPO. The difficulty of studying the reaction mechanism in these biphasic reactions was also commented on, nevertheless a general mechanism was proposed that is shown in Scheme 5.5.10. The authors believed that the Au(III) complex was reduced to a catalytically active Au(I) species which then underwent reduction and deactivation upon A³-coupling. The unreactive Au(0) species could be oxidised back to Au(I) by Cu(II) which increased the number of turnovers.²⁸² The Cu(I) species was then oxidised back to Cu(II) by TEMPO.



Scheme 5.5.10: Proposed general mechanism for the Au, Cu and TEMPO interact to increase lifetime of Au(III) catalysts in three component coupling reactions.

The majority of gold catalysts reported for the A³-reaction are gold(III) complexes. This is mainly due to the lower activity of gold(I) compounds such as AuCl and AuBr as reported by Li and Wei.²³⁷ However Contel and co-workers²⁸³ have detailed the preparation and use of gold(I) complexes containing water soluble phosphines (Scheme 5.5.11) as catalysts for A³-coupling.

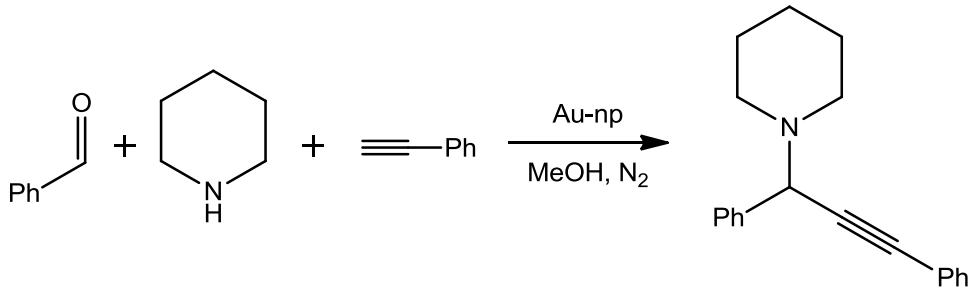


Scheme 5.5.11: Water soluble gold(I) phosphine complexes screened in the A^3 -reaction between benzaldehyde, piperidine and phenylacetylene.

The three complexes **116-118** were screened in the coupling of benzaldehyde, piperidine and phenylacetylene, varying the catalyst loading and temperature to determine the best reaction conditions. The best results (96 % conversion, 75% yield) were obtained with **116** (7 mol%) in H_2O at room temperature. The catalyst could also be recycled four times although a significant decrease in the conversion and yield (85% and 38% respectively) was observed.

The use of gold nanoparticles (Au-np) as catalysts for the A^3 -reaction was first reported by Kidwai and co-workers.²⁸⁴ Initially the catalytic activity of gold nanoparticles was probed using the coupling of benzaldehyde, piperidine and phenylacetylene as a coupling reaction. The couplings were carried out in methanol, under a nitrogen atmosphere by varying the temperature and loading of gold nanoparticles (18 \pm 2 nm diameter). At 35 °C with 10 mol% loading the propargylamine was isolated in 78% yield (Table 5.5.9, entry 1). Increasing the temperature to 75-80 °C resulted in higher conversions and improved yields (Table 5.5.9, entries 3, 4 and 5). Additionally increasing the catalyst loading beyond 10 mol% afforded only minimal improvements in the isolated yield; therefore the authors reported optimum conditions of 75-80 °C combined with 10 mol% loading of gold-nanoparticles.

Table 5.5.9: Variation of Au-np loading for A³-coupling.



Entry	Au-np (18 ± 2 nm) (mol%)	Time/h	Temp (°C)	Conversion ^a (%)	Yield (%)
1	10	12	35	91	78
2	5	12	75-80	66	83
3	10	5	75-80	97	92
4	30	3.5	75-80	88	95
5	50	2	75-80	93	96

Reaction conditions: benzaldehyde (1.0 equiv), piperidine (1.0 equiv), phenylacetylene (1.5 equiv), MeOH, under N₂.

^a Conversion determined from ¹H NMR spectrum of crude reaction mixture.

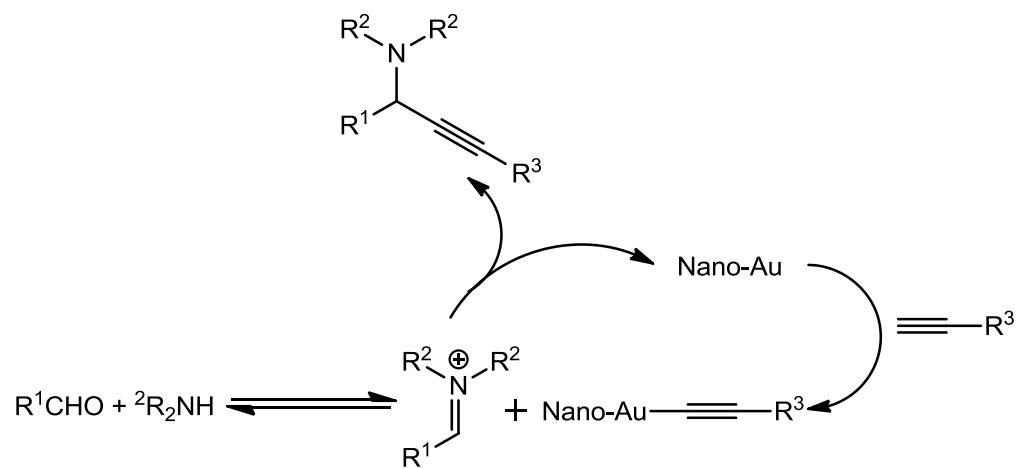
The effect of gold nanoparticle size on catalytic activity was also examined. Different sized Au-np, ranging from 10-70 nm in diameter, were prepared in an aqueous core of reverse micellar droplets.²⁸⁵⁻²⁸⁷ This was achieved by reducing an aqueous solution of Au³⁺ with hydrazine using *t*-octylphenoxy polyethoxyethanol as a surfactant.²⁸⁴ The nanoparticle size was determined by quasi-elastic light scattering (QELS) and transmission electron microscopy (TEM) studies. The best results were obtained with nanoparticles with a diameter of 20 nm, where after 5 h an isolated yield of 92% was achieved (Table 5.5.10, entry 2). For particles of between 30-70 nm a small decrease in reaction rate was observed (Table 5.5.10, entries 3,4 and 5), believed to be due to the increased particle size giving a lower surface area for adsorption, leading to a decrease in activity.²⁸⁴ With Au-nps of 10 nm diameter a slight decrease in reaction rate was observed postulated to be due to a downward shift of the Fermi level which increases the band gap energy. Therefore the particles require more energy to pump electrons to the adsorbed ions for electron transfer.²⁸⁴

Table 5.5.10: Effect of Au-np size on the A³-coupling of benzaldehyde, piperidine and phenylacetylene.

Entry	Au-np size (± 2 nm)	Time/ h	Conversion (%)	Yield (%)
1	10	11	94	87
2	20	5	97	92
3	30	8	87	85
4	50	12	91	73
5	70	15	78	67

Reaction Conditions: MeOH, 75-80 °C, under N₂.

Au-nps of 20 nm diameter could be recycled and re-used for four runs when the reaction was conducted in MeOH at 75-80 °C under N₂, although the yield dropped significantly from 92% to 63% by the fourth cycle. In addition the couplings also required longer reaction times (18 h) after recycling. This observed decrease in activity was thought to be caused by conglomeration of the gold nanoparticles.²⁸⁴ This was confirmed by separating the gold nanoparticles from the reaction mixture, by centrifugation, and carrying out QELS experiments. The choice of reaction solvent strongly influenced the Au-np catalysed coupling reactions. Acetonitrile as solvent gave the best results with a 96% yield of propargylamine in 5 h. The reaction also took place in MeOH and THF giving 92% and 87% yields respectively. The increased activity observed in MeCN was attributed to its high polarity and coordinating ability which could stabilise the gold-acetylide intermediate. In both cyclohexane and dichloromethane no product was obtained. The substrate scope of the nanoparticle catalysed couplings was also analysed by reacting different aromatic aldehydes with piperidine and phenylacetylene (Table 5.5.11). Aryl aldehydes with electron withdrawing groups such as *para*-Br and *meta*-Cl gave better yields, whereas the electron donating groups, *para*-Me and *para*-OMe, had a lower reactivity and required longer reaction times (Table 5.5.11, entries 1-4). Heterocyclic aldehydes such as 3-pyridinecarboxaldehyde and 2-furaldehyde also gave the corresponding propargylamines in good yield (Table 5.5.11, entries 6 and 7). A tentative mechanism for the Au-np catalysed A³-coupling reaction was proposed, and is shown in Scheme 5.5.12. The first step is C-H activation of the terminal alkyne by the gold nanoparticles. The Au-np acetylidyne species then reacts with the *in-situ* generated imminium ion to give propargylamines. Furthermore the role of Au-nps as redox catalysts in a free radical mechanism was not discounted.²⁸⁴



Scheme 5.5.12: Proposed mechanism of the Au-np catalysed A^3 -reaction.

Table 5.5.11: Selected examples of A³-couplings carried out the Au-np (10 mol%) with aldehydes, amines and phenylacetylene.

Entry	Aldehyde	Amine	Time/h	Product	Yield (%)
1	<i>p</i> -Me-C ₆ H ₄ CHO	piperidine	11		81
2	<i>p</i> -OMe-C ₆ H ₄ CHO	piperidine	8		87
3	<i>p</i> -Br-C ₆ H ₄ CHO	piperidine	7		95
4	<i>m</i> -Cl-C ₆ H ₄ CHO	piperidine	4		96
5	<i>p</i> -Me-C ₆ H ₄ CHO	morpholine	8.5		88
6	3-CHO-C ₅ H ₄ N	piperidine	6		93
7	2-CHO-C ₄ H ₃ O	piperidine	3		84

Reaction conditions: 10 mol% Au-np (18 ± 2 nm diameter), MeCN, 75–80 °C, N₂, phenylacetylene.

Due to some of the problems associated with recycling homogeneous catalysts, and the high cost of the gold complexes used for the A³-reaction a number of heterogeneous gold catalysts have been prepared and investigated for their catalytic activity in three component coupling reactions. Corma and Zhang have detailed the preparation and screening of supported Au(III) nanoparticle catalysts.²⁸⁸ Given that gold(III) and gold(I) species are thought to be the most active catalysts, the authors designed supported gold catalysts that

stabilise partially charged and electron deficient gold atoms. Six different supported gold catalysts were screened in the reaction of benzaldehyde, piperidine and phenylacetylene in H₂O at 100 °C. The results shown in Table 5.5.12 indicate that gold nanoparticles supported on carbon and silica lead to low conversions. Gold stabilised on titanium dioxide and iron(III) oxide showed moderate catalytic activity with conversions of 35% and 40% respectively. However it was found that excellent results could be achieved with gold (2-5 nm) supported on nanocrystalline CeO₂ (approximately 5 nm) and ZrO₂ (5-10 nm). As the diameter of the gold nanoparticles was similar for all the supported catalysts the authors concluded that there was no direct correlation between catalytic activity for the A³-reaction and gold particle size.²⁸⁸ The difference in catalytic activity was believed to be due to the stabilisation of cationic gold(III) species on both CeO₂ and ZrO₂, which has been well-documented.^{289–291} In contrast TiO₂, Fe₂O₃,²⁹² silica and carbon do not stabilise cationic gold species. By preparing Au/CeO₂ and Au/ZrO₂ catalysts with varying amounts of Au(III) and Au(I) species the cation effect on catalytic activity was monitored. The results suggested that the concentration of gold(III) species present was directly related to the catalytic activity. The activity of the Au/CeO₂ catalyst at a loading of 0.0003 mol% was then compared to that of the homogeneous catalyst AuCl₃ at a loading of 0.003 mol%. It was found that the reaction catalysed by AuCl₃ was initially faster giving 80% benzaldehyde conversion in 2 hours, however no further increase in conversion was observed over a 12 hour period. With Au/CeO₂ after 2 hours the benzaldehyde conversion was 59%, but a steady increase to 99% conversion was observed over 12 hours. It was thought that the AuCl₃ is deactivated by reduction after 2 h, as reported by Bowden and co-workers,²⁸² whereas the Au/CeO₂ was not deactivated. The results indicated that the Au/CeO₂ catalyst has higher turnover frequencies (TOF) (5674 h⁻¹ based on gold^{III} ions) than AuCl₃ (635 h⁻¹). Furthermore significantly higher turnover numbers (TON) are also observed with Au/CeO₂ (10760) than other catalysts reported for the A³-reaction (TON ≤ 100).^{236,237,258,273,276,277,284,293–295}

Table 5.5.12: Screening Results for supported Au catalysts in the reaction of benzaldehyde, piperidine and phenylacetylene.²⁸⁸

Entry	Catalyst (mass w.t. of gold on support)	Diameter of gold nanoparticles (nm)	Gold (mol%)	Conversion (%) ^a	Yield (%)
1	0.2% Au/SiO ₂	2-5	0.013	5	-
2	3.0% Au/C	2-5	0.081	13	-
3	1.5% Au/TiO ₂	2-5	0.075	35	-
4	4.5% Au/Fe ₂ O ₃	2-5	0.247	40	-
5	2.8% Au/ZrO ₂	2-5	0.142	95	93
6	2.5% Au/CeO ₂	2-5	0.127	100	99

Reaction conditions: benzaldehyde (1.0 mmol), piperidine (1.2 mmol), phenylacetylene (1.3 mmol) in H₂O at 100 °C.

^a Determined by ¹H NMR analysis of the crude reaction mixture.

Although the coupling reaction in water is very clean with no side product formation both Au/CeO₂ and Au/ZrO₂ are effective catalysts in organic solvents, with MeOH and THF, giving high conversions (80%). Additionally the major advantage of these supported catalysts is that no inert atmosphere is required for coupling, unlike homogeneous gold and unsupported gold nanoparticle catalysed procedures.^{237,284} The Au/CeO₂ catalyst could also be recycled four times, but a 25% drop in conversion was detected by the fourth run. Finally the substrate scope of the coupling was explored by varying the aldehyde, amine and alkyne components, see Table 5.5.13. Aromatic aldehydes reacted smoothly, with both electron withdrawing and donating functionalities well tolerated, although the strongly electron withdrawing *p*-NO₂ group resulted in decreased reactivity. Aliphatic aldehydes were generally well tolerated with the corresponding propargylamines obtained in high yield ($\geq 85\%$). This is in contrast to homogenous gold catalysed A³-reactions where aliphatic aldehydes generally display a low activity due to unwanted trimerization.²³⁷ Morpholine, pyrrolidine, dibenzylamine and diallylamine could be utilised to give the corresponding propargylamines in excellent yields. The chiral amine (*S*)-prolinol was also reacted with cyclohexanecarbaldehyde and phenylacetylene to give the propargylic amine in excellent yield (99%) and diastereoselectivity (d.r. 99:1). Aromatic alkynes gave high yields of product, although aliphatic alkynes such as *t*-butylacetylene were less reactive. The authors proposed a reaction mechanism for the supported catalysts that is broadly similar to the homogeneous mechanism (Scheme 5.2.1). The first step was thought to be C-H activation of the terminal alkyne by a Au(III) species stabilised by nanocrystalline CeO₂ or ZrO₂. The Au-alkyne species would then react with the *in-situ* generated imminium ion to give the corresponding propargylamines.

Table 5.5.13: Selected examples of Au/CeO₂ catalysed A³-coupling.

Entry	Aldehyde	Amine	Alkyne	Time/h	Product	Yield (%)
1	3,4-(OMe) ₂ -C ₆ H ₃ CHO	piperidine	PhCCH	12		90
2	<i>p</i> -CN-C ₆ H ₄ CHO	piperidine	PhCCH	12		99
3	<i>p</i> -NO ₂ -C ₆ H ₄ CHO	piperidine	PhCCH	14		26
4	CyCHO	piperidine	PhCCH	6		99
5	PhCHO	pyrrolidine	PhCCH	6		99
6	PhCHO	HN(Bn) ₂	PhCCH	6		92
7	CyCHO	(<i>S</i>)-prolinol	PhCCH	6		99 ^a
8	PhCHO	piperidine	(CH ₃) ₃ CCH	6		25

Reaction conditions: aldehyde (1.0 mmol), amine (1.2 mmol), alkyne (1.3 mmol), Au/CeO₂ (gold: 0.00127 mmol for entries 1–6 and 8; 0.0025 mmol for entry 7), H₂O (MiliQ, 1.0 mL), 100 °C.

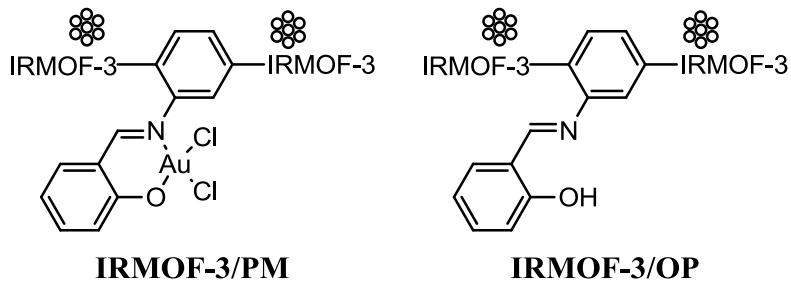
^a Diastereomer ratio of 99:1 obtained from ¹H NMR spectrum of crude reaction mixture.

Cy=cyclohexyl

Bn = Benzyl

A limited but growing number of heterogeneous gold catalysed A³-couplings have been reported,^{296–299} however most display a low catalytic activity compared to the supported Au(III) catalysts described by Corma and co-workers.²⁸⁸

In a novel study carried out by Chunming *et al.*³⁰⁰ metal-organic framework-(MOF) supported gold catalysts were prepared and screened for their catalytic activity in the A³-reaction. MOFs provide a number of potential advantages over traditional heterogeneous supports in that an extremely high surface area can be obtained, with a high degree of metal dispersion. In theory this means that there should be a high number of exposed active metal sites for catalysis to take place in. The MOF support used in the study was the well-known IRMOF-3 which consists of tetranuclear ZnO₄ clusters linked by a rigid 2-amino-1,4-benzenedicarboxylic acid linker.³⁰¹ The authors functionalised IRMOF-3 with gold utilising two different methods. Firstly post-covalent modification (PM) was used, where following solvothermal synthesis of the MOF, the free amino substituent of 2-amino-1,4-benzenedicarboxylic acid was reacted with salicylaldehyde to form salicylideneimine. Treatment with Na[AuCl₄] gave the gold(III) containing IRMOF-3 (**IRMOF-3/PM**) shown in Figure 5.5.7. The alternative ‘one-pot’ method (OP) involved heating a mixture of 2-amino-1,4-benzenedicarboxylic acid, Zn(NO₃)₂ · 6H₂O, salicylaldehyde, AuCl and Na[AuCl₄] in DMF at 100 °C for 24 hours to give **IRMOF-3/OP**.



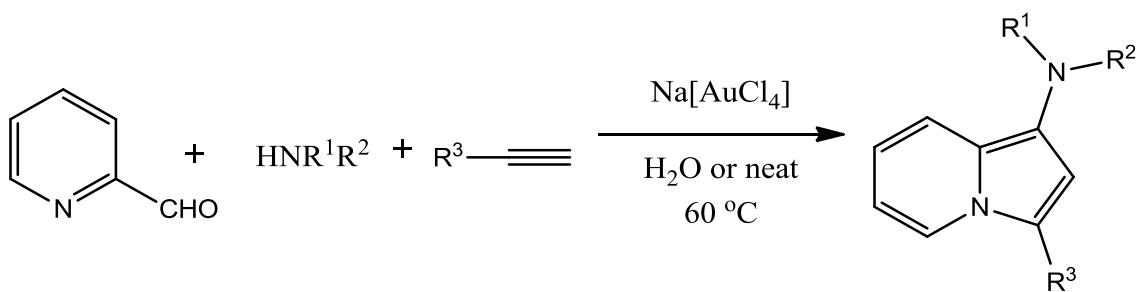
Where = gold nanoparticles.

Figure 5.5.8: Simplified structure of the Au(III) containing MOFs prepared by covalent modification with salicylaldehyde.

Characterisation studies revealed that **IRMOF-3/OP**, prepared *via* the one-pot procedure, led to metallic gold nanoparticles deposited on the surface of IRMOF-3 whereas with the post-covalent synthesis, **IRMOF-3/PM** contained both Au(III) species and metallic gold nanoparticles. The two types of MOF-supported gold catalysts were screened in the coupling of benzaldehyde, phenylacetylene and piperidine at 120 °C in 1,4-dioxane. It was found that **IRMOF-3/PM** was more active with 77% conversion of the aldehyde after 4 hours, while catalysts prepared through the ‘one-pot’ procedure attained maximum conversions of 8-16% after 12 hours. The low conversions could be overcome by

increasing the temperature to 150 °C where a conversion of 98% was obtained after 12 hours with **IRMOF-3/OP**. The higher rate of reaction observed for catalysts prepared by the post-covalent modification protocol was attributed to the presence of cationic gold(III) species present on the support, thus confirming the observations of Corma and co-workers.²⁸⁸ Additionally **IRMOF-3/OP** catalysts prepared in the one-pot protocol were reusable for 4 cycles with only a small drop in activity. **IRMOF-3/PM** could also be recycled for 4 runs but a 10% drop in activity was noted.³⁰⁰ After recycling experiments, aggregation of the gold nanoparticles was confirmed by TEM analysis in all the IRMOF-3 catalysts screened. Therefore it was inferred that the A³-coupling reaction is not sensitive to the size of the gold nanoparticles,³⁰⁰ and that the reduced activity seen for **IRMOF-3/PM** was due to reduction of the cationic gold species. Variation of the aldehyde component in the reaction was found to have a large effect on the conversion. As detailed previously, for many of the gold catalysed couplings electron donating groups on the aldehyde such as *p*-Me, and *p*-OMe result in reduced conversions, whereas electron withdrawing groups such as *m*-Cl showed greater activity. Coupling proceeded in good yield for piperidine, morpholine and pyrrolidine with benzaldehyde. Aromatic alkynes underwent smooth reactions, but upon increasing the steric hindrance around the alkyne the conversion dropped significantly. The authors speculated that the mechanism of their MOF-supported gold catalysts was the same as that of the homogeneous process whereby a gold-acetylide is formed and then reacts with the *in-situ* generated imminium ion.³⁰⁰

In a novel investigation Liu and Yan reported the three component coupling of heteroaryl-aldehydes, amines and alkynes followed by an *in-situ* cycloisomerisation to give aminoindolizines.³⁰² Indolizines have a structure featuring an *N*-bridgehead bicyclic ring system formed from a pyrrole and a pyridine ring (Scheme 5.5.13). They display interesting biological activities and potentially have broad applications in pharmaceuticals.^{303,304}



Scheme 5.5.13: The synthesis of aminoindolizines *via* a three component coupling reaction.³⁰²

A multi-component approach to aminoindolizines was designed, by utilising an A³-reaction of pyridine-2-carboxaldehyde, followed by *in-situ* metal catalysed cyclisation of the propargylamine (Scheme 5.5.13). The coupling of pyridine-2-carboxaldehyde, piperidine and phenylacetylene was used as the model reaction to screen various metal catalysts. With 1 mol% of Na[AuCl₄] .2H₂O in H₂O at 60 °C the coupled/cycloisomerised product was obtained in 85% yield over 3 hours. When 2 mol% of AuCl was used a yield of only 20% was obtained. It was found that improved yields of 95% could be obtained when 1 mol% of Na[AuCl₄] was used in the absence of solvent. The reactions could also be carried out at room temperature although this required longer reaction times (72 hours). The use of copper complexes CuBr and Cu(OTf)₂ resulted in no conversion to the desired product. A range of amines and alkynes were found to undergo coupling/rearrangement with 2-pyridine carboxyaldehyde (Table 5.5.14). Morpholine, dibenzylamine and piperidine gave coupled product in excellent yields ($\geq 95\%$), but lower yields were observed with pyrrolidine. It should be noted that the reaction was incompatible with primary amines. Alkynes with both electron donating (OMe) and electron withdrawing (Cl) groups gave the desired products in good yields (Table 5.5.14, entries 5 and 6). Piperazine could also be used to form a bridged indolizines in 52% yield (entry 7). A mechanism for the formation of indolizines through gold catalysed A³-couplings was proposed,³⁰² see Scheme 5.5.14. The initial step involves formation of the intermediate propargylamine *via* coupling of the aldehyde, amine and alkyne. The coordination of gold to the triple bond of the propargylic amine enhances the electrophilicity of the alkyne, so that nucleophilic attack of the pyridyl nitrogen occurs to produce the cationic species. Deprotonation and demetalation then lead to the indolizines.³⁰²

Table 5.5.14: Selected examples of aminoindolizines synthesis with 2-pyridine carboxyaldehyde.³⁰²

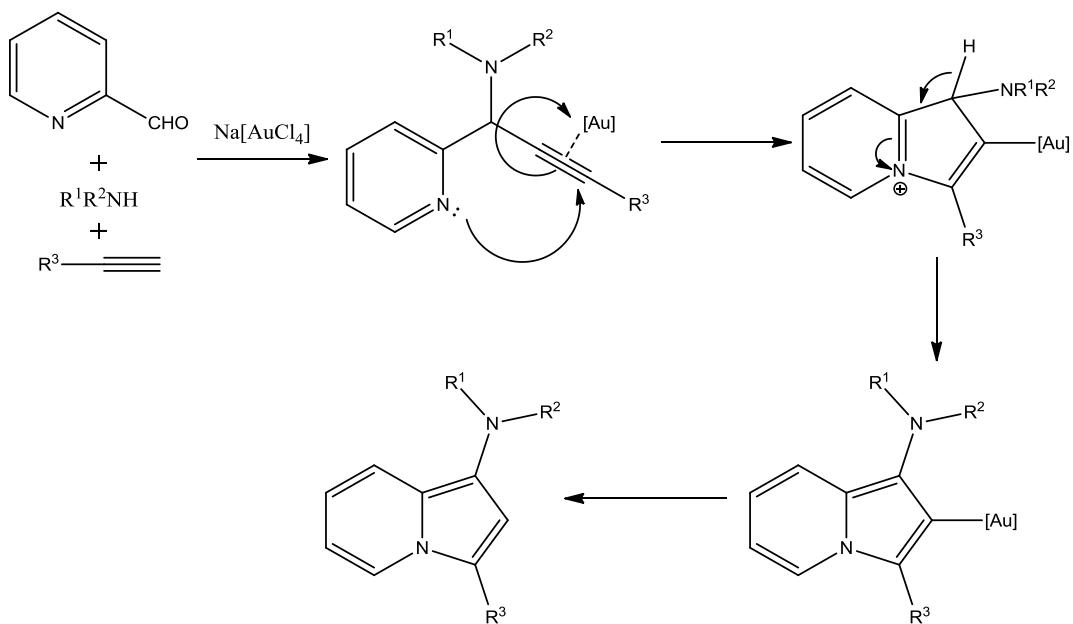
Entry	Amine	Alkyne	Product	Yield (%) ^a
1	piperidine	PhCCH		95
2	morpholine	PhCCH		96
3	HNBn ₂	PhCCH		98
4	pyrrolidine	PhCCH		68
5	piperidine	<i>p</i> -ClC ₆ H ₄ CCH		88
6	piperidine	<i>p</i> -OMeC ₆ H ₄ CCH		95
7 ^b	piperazine	PhCCH		52

Reaction conditions: 2-pyridine carboxyaldehyde (1.0 mmol), amine (1.1 mmol), alkyne (1.2 mmol) at 60 °C for 1-4 h, 1 mol% Na[AuCl₄] · 2H₂O.

^a isolated yields based on aldehyde.

^b 0.55 equivalents of piperazine

Bn = Benzyl



Scheme 5.5.14: Proposed mechanism for the one-pot synthesis of indolizines catalysed by $Na[AuCl_4]$.³⁰²

A^3 -coupling reactions with aldehydes are now well-established; however coupling of alkynes and amines with ketones is significantly more challenging. This is because the intermediate ketoimines are less reactive towards nucleophilic additions due to steric and electronic effects. Until recently very few examples of ketones being used in the A^3 -reaction were known, and all suffered from severe drawbacks. Che *et al.* developed a $[Au\{P('Bu)_2(o\text{-biphenyl})\}Cl/AgSbF_6$ catalysed addition of phenylacetylene to a ketoimine prepared from *N*-(4-methoxyphenyl)-5-aminopentan-2-one.³⁰⁵ The reaction was limited to ketoimines formed in an intramolecular manner. While Ramón *et al.* developed a $Cu(OH)_x\text{-Fe}_3O_4$ catalysed addition of phenylacetylene to ketoimines generated *in-situ* from 3-pentanone or acetophenone and piperidine.³⁰⁶ Low yields ($\leq 38\%$) were obtained and long reaction times *ca.* 7 days were required. The intermolecular *in-situ* generation of a ketoimine and reaction with an alkyne presents a synthetic challenge. To this end Ji and co-workers have developed a gold(III) catalysed direct addition of alkynes to ketoimines generated from ketones and secondary amines.³⁰⁷ Firstly the coupling of cyclohexanone, morpholine and phenylacetylene, in CH_2Cl_2 at room temperature, was explored in the presence of a range of metal catalysts. Au(I) and Au(III) complexes resulted in coupling whereas $CuBr$, $Cu(OTf)_2$, $AgNO_3$, $AgOTf$, $Zn(OTf)_2$, $In(OTf)_3$ and $InBr_3$ gave none of the desired product. The best results were obtained with $AuBr_3$ (4 mol%) which gave a 51% yield of product over 50 hours. Interestingly solvents were found to have a strong influence on the coupling reaction. Reactions in THF, toluene, MeCN and DMF at 60 °C resulted in

reduced yields of product; however in the absence of solvent the coupling proceeded smoothly. The best results were obtained with 4 mol% of AuBr₃ under neat conditions at 60 °C to give an 89% yield of the desired product in 8 hours. The scope and limitation of the coupling reaction was next examined using these optimised conditions. Both morpholine and piperidine gave high yields of product (Table 5.5.15, entries 1 and 3), although changing to the more sterically demanding dibenzylamine resulted in reduced yields of product (entry 2). It was found that aromatic alkynes generally gave higher yields of product, with both electron withdrawing (*p*-F) and donating substituents (*p*-OMe) well tolerated (entries 4 and 5). With aliphatic alkynes the isolated yield dropped considerably (entry 6 and 7). Variation of the ketone could also be carried out with aliphatic ketones, both cyclic and acyclic displaying high reactivity (entries 8-10). However it was found that aromatic ketones such as acetophenone, 4-methoxyacetophenone and 4-nitroacetophenone gave no conversion to the desired product.

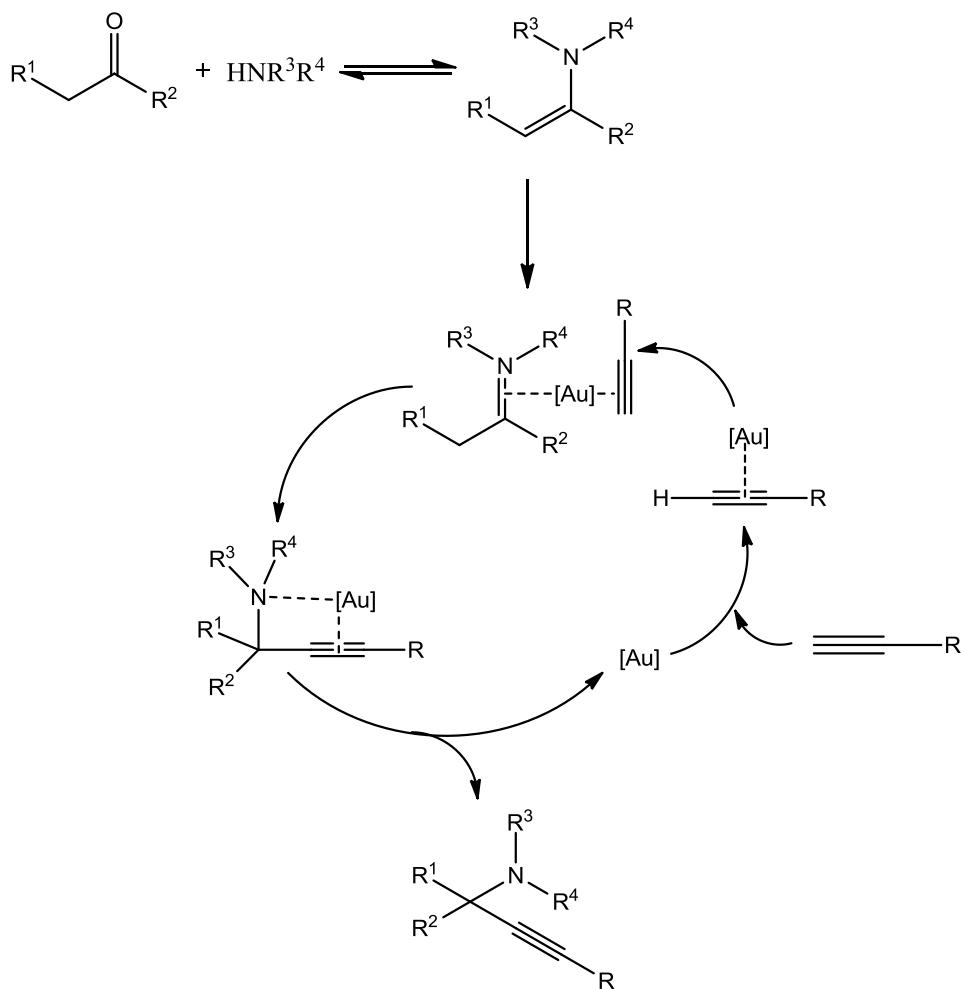
Table 5.5.15: Selected examples of ketone, amine and alkyne coupling.

Entry	Ketone	Amine	Alkyne	Product	Yield (%)
1	(CH ₂) ₅ CO	morpholine	PhCCH		89
2	(CH ₂) ₅ CO	HNBn ₂	PhCCH		29
3	(CH ₂) ₅ CO	piperidine	PhCCH		75
4	(CH ₂) ₅ CO	morpholine	HCCC ₆ H ₄ - <i>p</i> -OMe		96
5	(CH ₂) ₅ CO	morpholine	HCCC ₆ H ₄ - <i>p</i> -F		77
6	(CH ₂) ₅ CO	morpholine	HCC(CH ₂) ₃ CH ₃		45
7	(CH ₂) ₅ CO	morpholine	HCC(CH ₂) ₂ Ph		39
8	(CH ₂) ₄ CO	morpholine	PhCCH		82
9	Ph(CH ₂) ₂ COMe	morpholine	PhCCH		71
10 ^a	(CH ₃) ₂ CO	morpholine	PhCCH		84

Reaction Conditions: Ketone (1.5 mmol), amine (1.0 mmol), alkyne (1.5 mmol), AuBr₃ (4 mol%), neat, 60 °C.

^a Acetone (5 mmol) used. Bn = benzyl

A tentative mechanism was also proposed for this novel coupling reaction, see Scheme 5.5.15. The key intermediate is again a gold alkyne complex which undergoes reaction with the *in-situ* generated enamine.



Scheme 5.5.15: Tentative mechanism proposed for the gold catalysed coupling of ketones, amines and alkynes.

5.6 Summary

The three component coupling of aldehydes, amines and alkynes (A^3 -reaction) offers an attractive atom efficient route to propargylamines. Simple copper(I) halides exhibit good catalytic activity in this process across a diverse range of solvents such as H_2O , THF, DMSO, toluene and even ionic liquids.^{251–253,255} Microwave methods have also been used to improve coupling yields and facilitate reactions with difficult substrates including primary aliphatic amines.^{258,260,261} Asymmetric A^3 -reactions have also been reported utilising a chiral CuOTf/pybox catalyst system.²⁶² The coupled products were obtained in good yields and enantioselectivities, although the reaction was limited to the use of aryl

anilines. A heterogeneous variant was developed, by supporting the Cu(I) pybox complex on Fe₃O₄ nanoparticles, which could be recycled for six runs with good yields and selectivity.²⁶⁷ Furthermore Knochel demonstrated the use of the chiral phosphine (*R*) or (*S*)-Quinap (**100**) in tandem with CuBr for the asymmetric coupling of secondary amines.²⁶⁹ High yields and good enantioselectivities were reported and the catalyst system was used in the asymmetric synthesis of (*S*)-(+) -coniine (**101**).²⁷⁰ Subsequently Carreira and co-workers developed a CuBr/Pinap asymmetric catalyst system as a more cost effective alternative to CuBr/Quinap.²⁷² The Pinap/CuBr catalyst gives the propargylamine products in the highest yields and enantioselectivities reported to date. However gold complexes, notably gold(III), display the highest catalytic activity in the A³-reaction with secondary amine substrates. A diverse range of gold compounds have been screened from simple halide salts to organometallic complexes containing C,N and C,O chelate ligands and also gold nanoparticles. The choice of reaction solvent was found to be extremely important in the gold catalysed coupling reactions, with H₂O, MeCN and CHCl₃ reported to give the best conversions and yields.^{189,277} When chiral amines such as (*S*)-prolinol are used in the coupling reaction excellent diastereoselectivities of 96:4, and 99:1 were reported for a variety of gold complexes.²⁷⁶ Significantly this indicates that the nature of the complexes screened so far has little effect on the diastereoselectivity, with the chiral substituent on the amine influencing the selectivity. The mechanism of the A³-reaction with gold is generally believed to proceed *via* a gold acetylide, as the key intermediate, which undergoes reaction with an iminium ion to give the propargylamine. This would make the gold complex added at the start of the reaction a pre-catalyst which is transformed into the active catalytic species *in-situ*. However there is some disagreement over the oxidation state of the gold centre in the catalytically active species with some groups believing that a gold(I) complex is formed²³⁷ and some favouring a gold(III) complex.²⁷⁷ Additionally to date there have been no reports of asymmetric induction in gold catalysed A³-coupling.

6 A³-screening with N,N-dimethylbenzylamine catalyst

Given that *N,N*-dimethylbenzylamine based gold(III) complexes are well established in the literature it is perhaps surprising that this type of gold(III) complex has never been screened in A³-coupling. As the transmetallation routes outlined in sections 2.4 and 3.4 provide a convenient route to cyclometallated gold(III) complexes containing dimethylbenzylamine ligands [AuCl₂(η^2 -C,N-C₆H₄-2-CH₂NMe₂)] (**8a**) was screened in A³-coupling reactions. [AuCl₂(η^2 -C,N-C₆H₄-2-CH₂NMe₂)] (**8a**) was prepared via boroxine transmetallation as outlined *vide supra*, in section 3.4, and recently published.¹⁶⁶ Preliminary screening of **8a** was performed by reacting benzaldehyde and phenylacetylene with a range of cyclic secondary amines. The coupling reactions were carried out under the same conditions outlined by Che *et al.*²⁷⁷ for the 2-phenylpyridine gold(III) complex (**4**) as this compound is structurally similar to [AuCl₂(η^2 -C,N-C₆H₄-2-CH₂NMe₂)]. Aldehyde (1 mmol), secondary amine (1.1 mmol) and alkyne (1.5 mmol) were added to a reaction flask under nitrogen. [AuCl₂(η^2 -C,N-C₆H₄-2-CH₂NMe₂)] (**8a**) (1 mol%) was added followed by H₂O (2 mL) and the reaction heated at 40 °C for 24 hours. The reaction mixture was extracted with CH₂Cl₂, dried over MgSO₄ and the solvent removed *in vacuo* to give crude propargylamine. The product was purified by flash chromatography on silica gel using ethyl acetate/hexane as eluent. Table 5.6.1 contains the coupling data for the screening reactions. Excellent conversions and isolated yields are obtained for couplings with piperidine, pyrrolidine, morpholine and dibenzylamine (Table 5.6.1, entries 1-4). The results are comparable to those previously reported by Che *et al.*²⁷⁷ and Ortiz *et al.*¹⁸⁹ for other cyclometallated gold(III) complexes. Morpholine exhibits a slightly decreased reactivity due to the lower nucleophilicity of the amine.

In an effort to examine the scope of [AuCl₂(η^2 -C,N-C₆H₄-2-CH₂NMe₂)] catalysed A³-reactions various substrates were employed in the coupling reaction. Firstly (S)-prolinol was reacted with benzaldehyde and phenylacetylene to allow a comparison of the diastereoselectivity of the [AuCl₂(η^2 -C,N-C₆H₄-2-CH₂NMe₂)] catalysed process to the Au(III) salen (**109a**) catalysed reactions reported by Che and co-workers.²⁷⁶ The diastereoselectivity was calculated by ¹H NMR analysis of the crude reaction mixture. The 55% yield of propargylic amine (Table 5.6.1, entry 5) is lower than that previously reported, although crucially the diastereoselectivity is excellent with a diastereomeric ratio

of 96:4. This selectivity is the same as that obtained when Che *et al.* used gold(III) salen²⁷⁶ and 2-phenylpyridineAuCl₂ (**4**)²⁷⁷ complexes as catalysts, see Figure 5.6.1 for comparison.

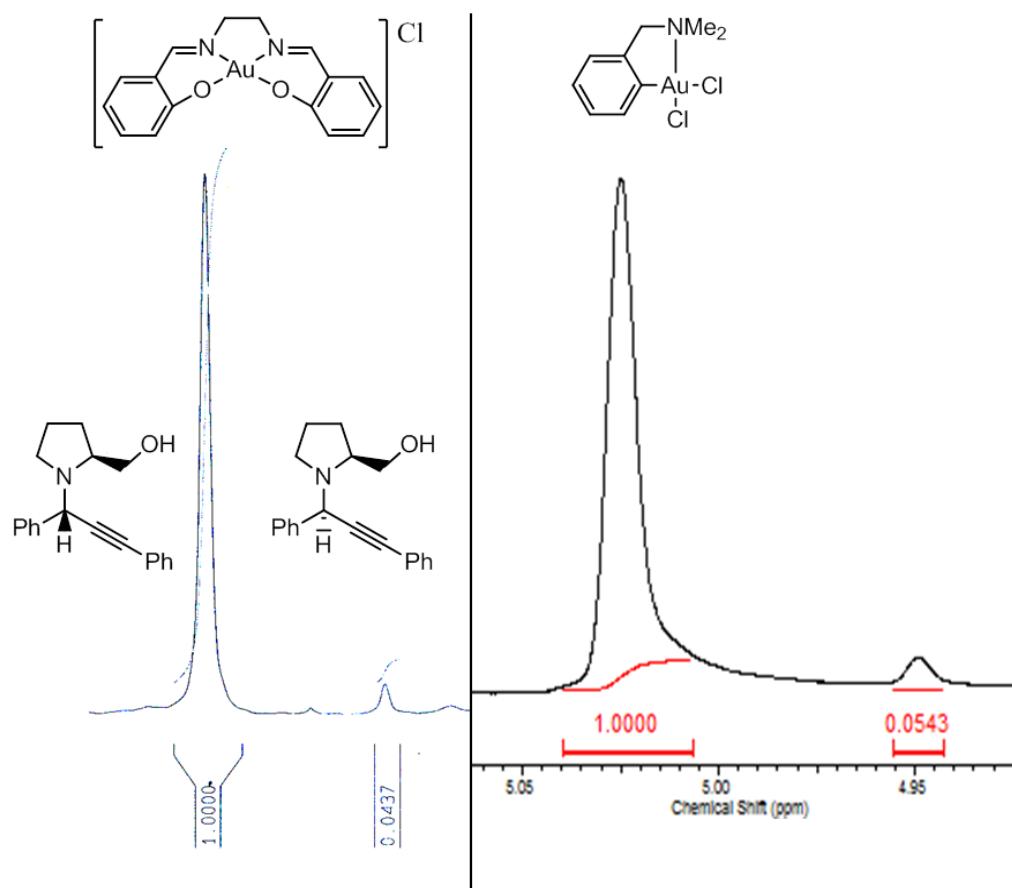
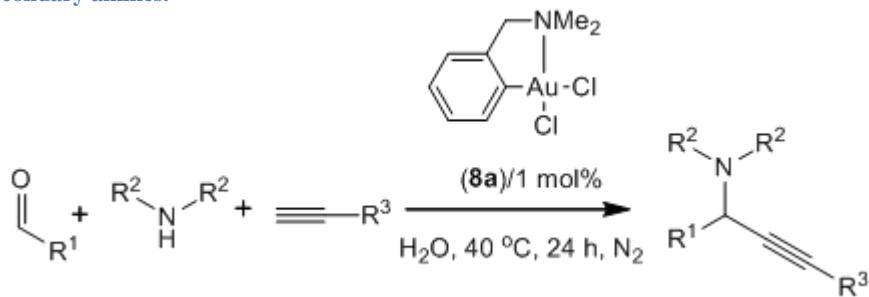


Figure 5.6.1: Comparison of the diastereoselectivity of gold(III) salen complex **109a** and $[\text{AuCl}_2(\eta^2\text{-C}_6\text{H}_4\text{-2-CH}_2\text{NMe}_2)]$ (**8a**) in the reaction of (S)-prolinol, benzaldehyde and phenylacetylene. Left side part of the NMR spectrum taken from supplementary information contained in ref²⁷⁶. Trace on right hand side this work.

Table 5.6.1: Preliminary screening of $[\text{AuCl}_2(\eta^2\text{-C}_6\text{H}_4\text{-2-CH}_2\text{NMe}_2)]$ (8a) in the A³-reaction of aldehydes, alkynes and secondary amines.



Entry	Aldehyde	Amine	Alkyne	Product	Conversion (%) ^a	Yield (%) ^b
1	PhCHO	piperidine	PhCCH		95	75
2	PhCHO	pyrrolidine	PhCCH		92	85
3	PhCHO	morpholine	PhCCH		90	72
4	PhCHO	HN(Bn) ₂	PhCCH		97	85
5 ^c	PhCHO	(S)-prolinol	PhCCH		83 (d.r. 96:4)	55
6	3-(CF ₃) ₂ -PhCHO	HN(Bn) ₂	PhCCH		98	80
7	C ₅ H ₄ N-2-CHO	HN(Bn) ₂	PhCCH		97	92

Entry	Aldehyde	Amine	Alkyne	Product	Conversion (%) ^a	Yield (%) ^b
8 ^d	1,4-(CHO)-C ₆ H ₄	HNBN ₂	PhCCH		98 (d.r. 1:1)	89
9 ^d	1,3-(CHO)-C ₆ H ₄	HNBN ₂	PhCCH		98 (d.r. 1:1)	85
10 ^d	PhCHO	Piperazine	PhCCH		95 (d.r. 1:1)	85
11 ^d	PhCHO	HNBN ₂	1,3-(HCC)-C ₆ H ₄		93 (d.r. 1:1)	75
12 ^d	Ferrocence-1,1'-dicarbaldehyde	HNBN ₂	PhCCH		99 (d.r. 1:1)	95
13 ^e	Cyclo-C ₆ H ₁₀ (O)	morpholine	PhCCH		-	60
14 ^f	PhCHO	HNBN ₂	PhCCH	PA-4	98	-
15 ^g	PhCHO	piperidine	PhCCH	-	0	0

Standard Reaction conditions: aldehyde (1 mmol), amine (1.1 mmol), alkyne (1.5 mmol), H₂O (2 mL), 40 °C, 24 h, 1 mol% catalyst, under N₂.

^a Conversion calculated based on benzaldehyde

^b Isolated yield based on benzaldehyde

^c d.r. determined by ¹H NMR analysis of the crude reaction mixture, with [AuCl₂(η²-C₆H₄-2-CH₂NMe₂)] (**8a**) found to be 96:4.

^d Reaction time increased to 48 h to give quantitative conversion. All ‘double A³’ -reactions give a 1:1 mixture of diastereomers which can be observed through doubling of some NMR signals.

^e 1.5 mmol cyclohexanone, 1 mmol morpholine, 1.5 mmol phenylacetylene, 5 mol% [AuCl₂(η²-C₆H₄-2-CH₂NMe₂)] (**8a**), neat, 60 °C, 8 h.

^f Na[AuCl₄] · 2H₂O (1 mol%) used as catalyst

^g uncatalysed

Efficient new routes to trifluoromethyl-containing synthetic intermediates are desirable due to the importance of the CF₃ group in pesticides and pharmaceutical products.^{308,309} Thus the coupling of 3-trifluoromethylbenzaldehyde, dibenzylamine and phenylacetylene was investigated, and found to proceed smoothly giving an excellent yield of the CF₃-containing propargylamine (**PA-6**) (Table 5.6.1, entry 6). Reaction of 2-pyridine carboxyaldehyde with dibenzylamine and phenylacetylene resulted in formation of the rearranged aminoindolizine (**PA-7**) in excellent yield (Table 5.6.1, entry 7). The conversion and yield is comparable to that previously reported by Liu and Yan for the Na[AuCl₄] .2 H₂O catalysed reaction.³⁰² Some novel ‘double A³’-couplings were also carried out with bis-aldehydes, bis-amines and bis-alkynes in order to determine if **8a** could facilitate coupling reactions with more challenging substrates. Terephthalaldehyde and isophthalaldehyde both undergo smooth coupling with phenylacetylene (2.6 equivalents) and dibenzylamine (2.1 equivs.) to give the corresponding propargylamines (**PA-8** and **PA-9**) in excellent yields (Table 5.6.1, entries 8 and 9). Piperazine reacted with benzaldehyde (2 equivs) and phenylacetylene (3 equivs) to give the bis-propargylamine (**PA-10**) in 85% isolated yield. The coupling reaction could also be extended to bis alkynes with 1,3-diethynylbenzene coupling with dibenzylamine and benzaldehyde to give the corresponding propargylic amine (**PA-11**) in good yield, see Table 5.6.1, entry 11. A novel double coupling of ferrocene-1,1’-dicarbaldehyde, dibenzylamine and phenylacetylene was also carried out (Table 5.6.1, entry 12). Ferrocene-1,1’-dicarbaldehyde was prepared using the procedure outlined by Connell *et al.*³¹⁰ ferrocene was treated with a *n*-butyllithium/TMEDA mixture (2.3 equivalents) and stirred overnight. Quenching of the dilithio-compound with DMF, followed by column chromatography on silica provided ferrocene-1,1’-dicarbaldehyde. The product was identified by ¹H, and ¹³C{¹H} NMR spectroscopy and elemental analysis, which were consistent with previously reported data.^{310,311} The propargylamine product (**PA-12**) was isolated as a red powder in excellent yield. The ¹H and C¹³{¹H} NMR spectra of the amine were complex, making assignment of all the signals challenging. However through the use of 2-D NMR experiments (COSY and HMQC) it was possible to identify the signals corresponding to the benzylic-CH₂ groups of the amine, the cyclopentadienyl protons and the CH at the α -positions, see Figure 5.6.2.

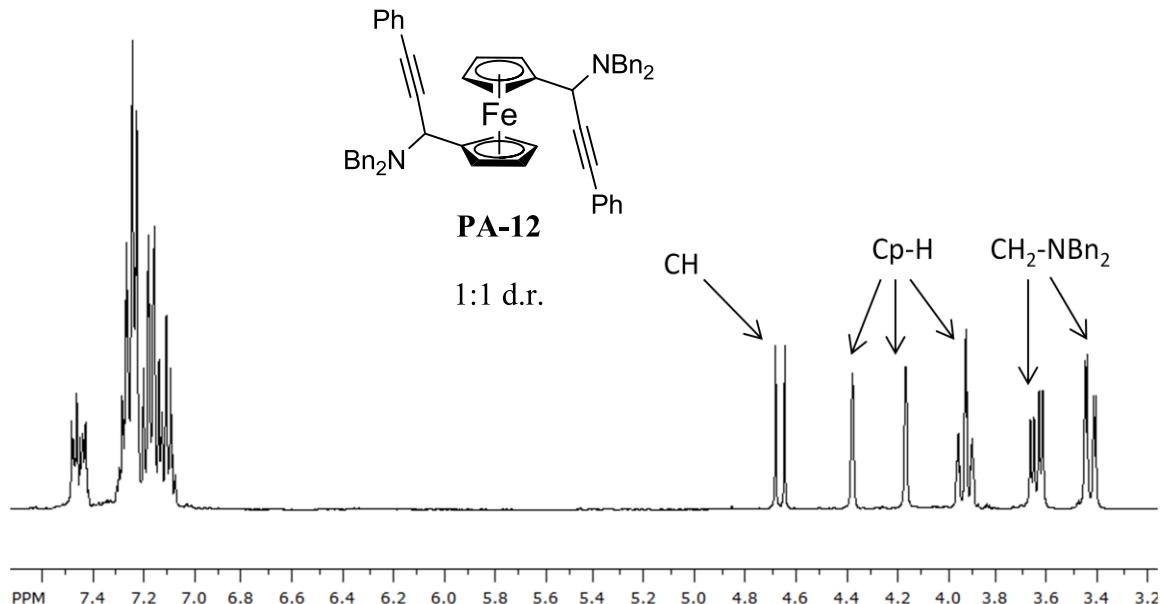
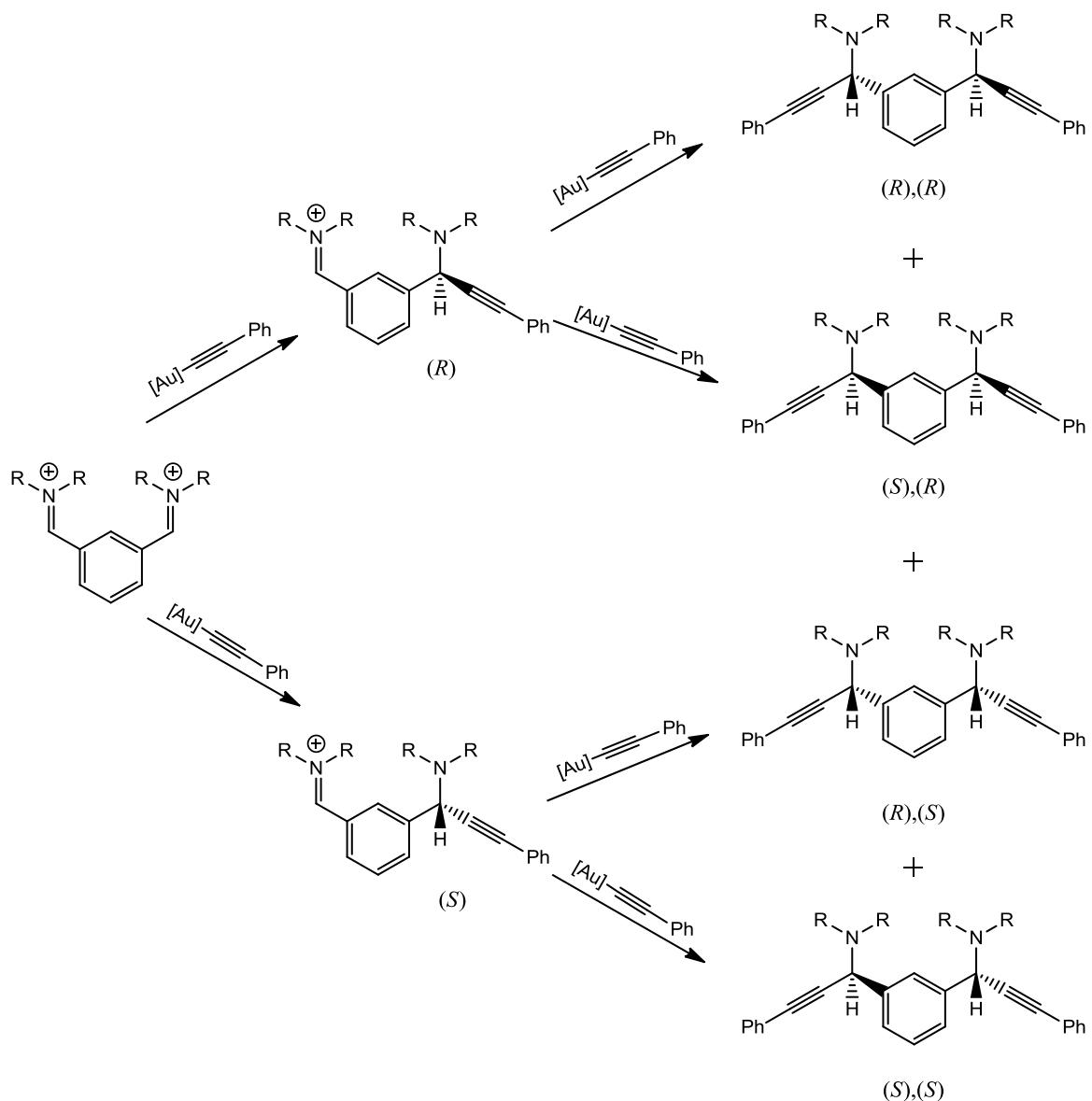


Figure 5.6.2: ^1H NMR spectrum of propargylamine PA-12, formed by A³-coupling of ferrocene-1,1'-dicarbaldehyde, dibenzylamine and phenylacetylene, Table 5.6.1, entry 12.

It should be noted that in all the ‘double A³-reactions’ (Table 5.6.1, entries 8-12) the products consisted of a 1:1 mixture of two diastereomers. This arises due to the step-wise nature of the acetylidyne addition to the intermediate iminium species, see Scheme 5.6.1. The first step in the double coupling is the addition of the gold-acetylidyne to one of the imine C=N bonds to give a racemic mixture of the mono-coupled product. Secondly the gold-acetylidyne reacts with the remaining iminium species C=N bond. The acetylidyne can react to give either *R* or *S* geometries at the second stereocentre, giving rise to four possible combinations. The four compounds are formed in a 1:1:1:1 ratio with an achiral catalyst therefore only two diastereomers are observed in the ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum.



Scheme 5.6.1: The possible combinations of acetylide addition to the iminium species in double A^3 -coupling of isophthalaldehyde. The four compounds are formed in a 1:1:1:1 ratio with an achiral catalyst, therefore two diastereomers are actually observed in the NMR spectrum.

All attempts to separate the diastereomers by HPLC failed, however separation of some signals could be observed in both 1H and $^{13}C\{^1H\}$ spectra, see Figure 5.6.3 for the signal doubling of **PA-9**, Table 5.6.1, entry 9.

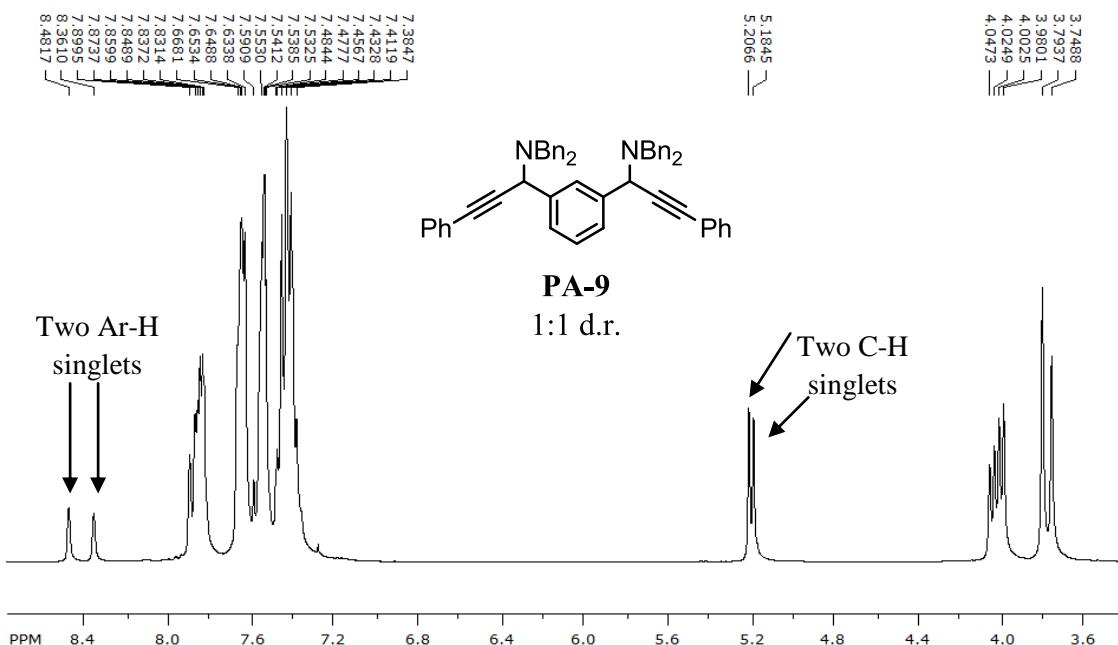


Figure 5.6.3: ^1H NMR spectrum of **PA-9**, from the coupling of isophthalaldehyde, phenylacetylene and dibenzylamine, Table 5.6.1, entry 9. Two C-H singlets are observed at ~ 5 ppm, and also two different downfield singlets are observed at 8.5 and 8.4 ppm corresponding to the Ar-H proton ortho to the amine substituents.

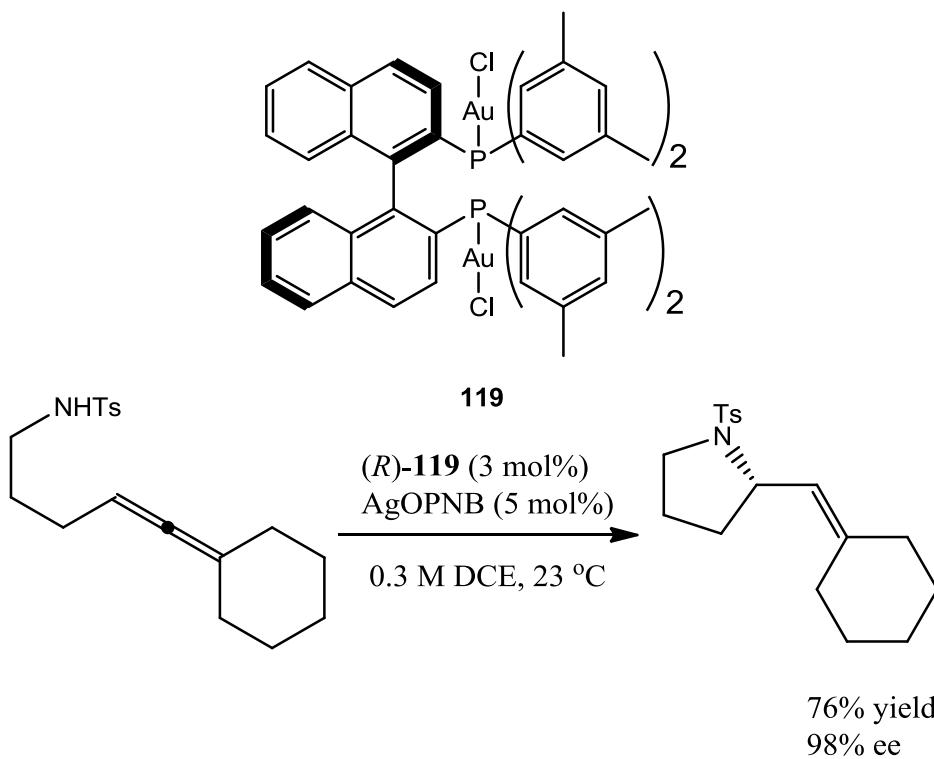
The three component coupling of acyclic and cyclic aliphatic ketones has been previously reported by Ji *et al.* who used an AuBr_3 catalyst in the absence of solvent.³⁰⁷ Attempts to carry out the $[\text{AuCl}_2(\eta^2\text{-C}_6\text{H}_4\text{-2-CH}_2\text{NMe}_2)]$ (**8a**) catalysed coupling of cyclohexanone, morpholine and phenylacetylene in water failed. However when the reaction was carried out at higher temperatures, with increased catalyst loading (5 mol%), in the absence of solvent, the coupling reaction proceeded smoothly to give propargylamine **PA-13** in 60% yield (Table 5.6.1, entry 13).

The use of $\text{Na}[\text{AuCl}_4] \cdot 2\text{H}_2\text{O}$ (1 mol%) as pre-catalyst was also investigated in the reaction of benzaldehyde, phenylacetylene and dibenzylamine to allow direct comparison between a simple gold halide salt and a cyclometallated complex. The reaction outcome was found to be qualitatively comparable to that obtained when **8a** was used as catalyst with a conversion of 98% after 24 hours (Table 5.6.1, entry 14). Furthermore in the absence of gold complex no A^3 -coupling takes place (Table 5.6.1, entry 15).

To summarise $[\text{AuCl}_2(\eta^2\text{-C}_6\text{H}_4\text{-2-CH}_2\text{NMe}_2)]$ (**8a**) was found to be an effective catalyst for A^3 -coupling reactions in water at 40 °C. A variety of substrates could be coupled, including some novel ‘double A^3 -couplings, which resulted in 1:1 mixtures of diastereomers.

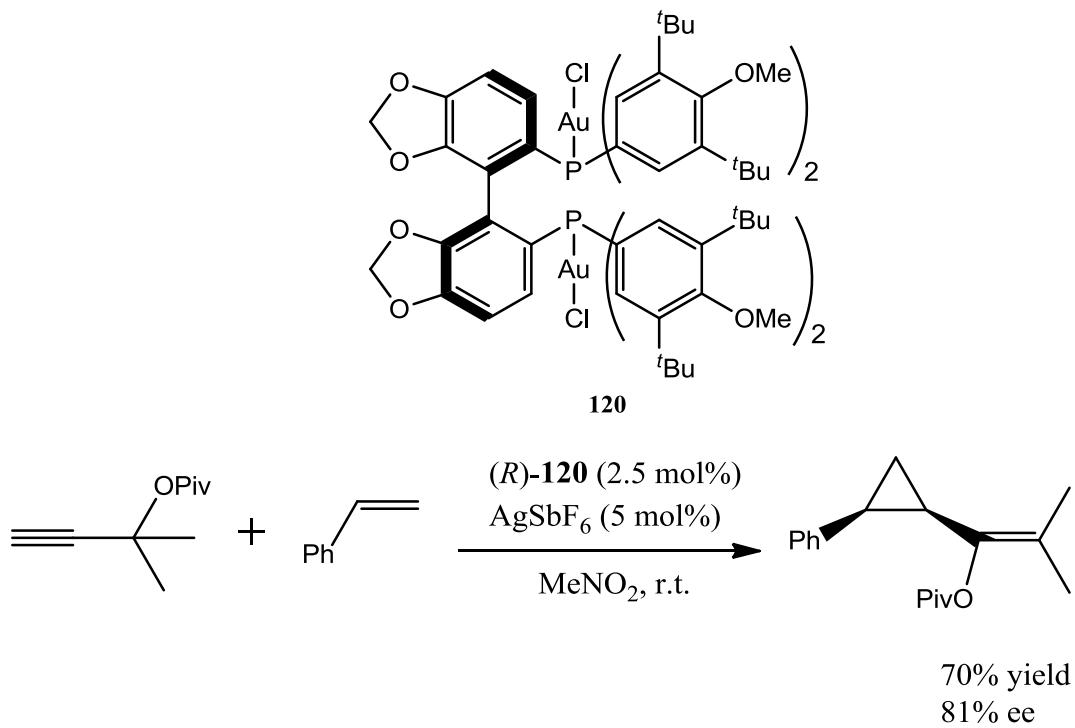
6.1 Introduction to chiral gold catalysts

The next aim was to extend the gold catalysed A³-coupling methodology to include enantioselective couplings. Currently, in the literature there are a small but growing number of asymmetric transformations catalysed by chiral gold complexes.³¹² Many of the examples make use of chiral gold(I) complexes where the chiral ligand is 180 ° from the reacting gold centre. Toste and co-workers have used a dinuclear chiral gold(I) complex, (*R*)-Xylyl-BINAP(AuCl)₂ (**119**) in combination with silver benzoate (AgOPNB) to catalyse the hydroamination of allenes with excellent enantioselectivities of 98% (Scheme 6.1.1).³¹³



Scheme 6.1.1: The asymmetric hydroamination of allenes catalysed by (*R*)-Xylyl-BINAP(AuCl)₂ (**119**) as reported by Toste and co-workers.³¹³ Ts = Tosyl.

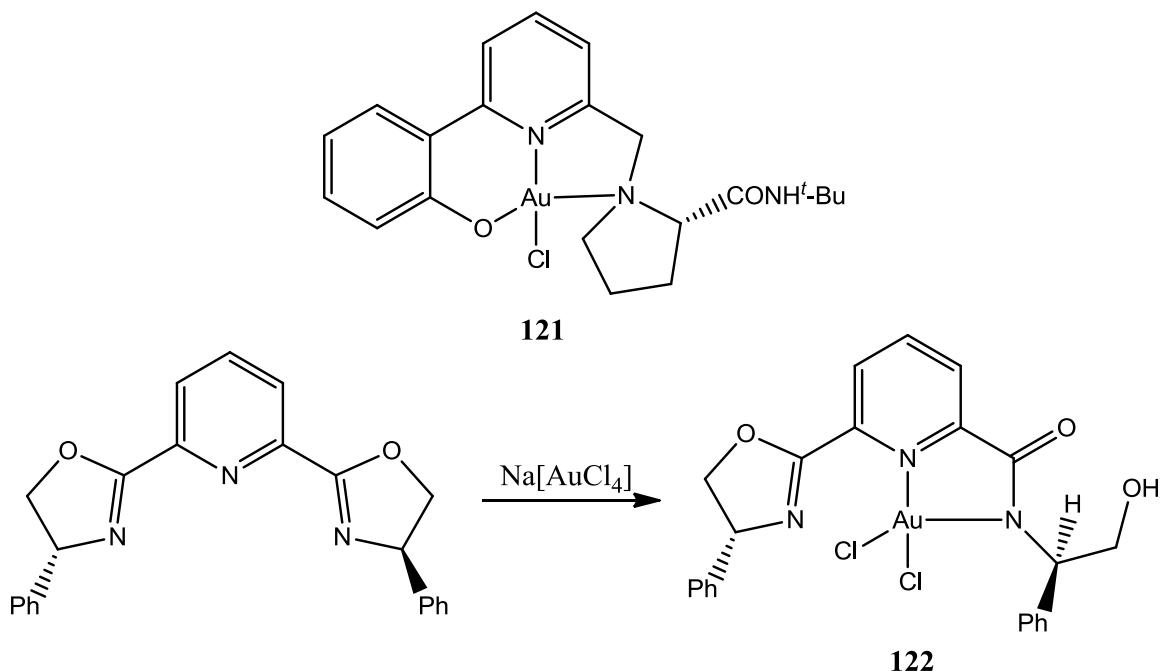
Toste and co-workers have also developed an asymmetric gold(I) catalysed olefin cyclopropanation.³¹⁴ The best catalyst was found to be (*R*)-DTBM-SEGPHOS(AuCl)₂ (**120**) which gave high enantioselectivity.



Scheme 6.1.2: Asymmetric olefin cyclopropanation catalysed by (*R*)-DTBM-SEGPHOS(AuCl)₂ (120**) as reported by Toste and co-workers.³¹⁴ Piv= Pivalate.**

For a detailed overview of the development of asymmetric gold catalysis and chiral gold complexes the review of Pradal *et al.* is recommended,³¹² along with previous review articles in this area.^{86,315,316}

Far fewer examples of chiral gold(III) complexes have been reported, although recently some progress has been made in this area. Sanchez *et al.* prepared a chiral Au(III) O,N,N-tridentate pincer complex (**121**) and evaluated its catalytic activity in the hydrogenation of diethylbenzylidene succinate. The complex was found to give excellent conversions (96%) with 80% enantioselectivity.³¹⁷ Corma and co-workers have synthesised a chiral gold(III) complex from the reaction of Na[AuCl₄] and 2,6-bis[(4*R*)-phenyl-2-oxazolin-2-yl]pyridine (pybox). Crystals suitable for X-ray structure determination could not be obtained and so the structure was assigned tentatively as the ring-opened pybox compound **122** based on Infra-red and UV-vis spectroscopies, and elemental analysis. **122** was screened in the asymmetric epoxidation of olefins with molecular oxygen, and found to give moderate enantioselectivities of 13-45%.

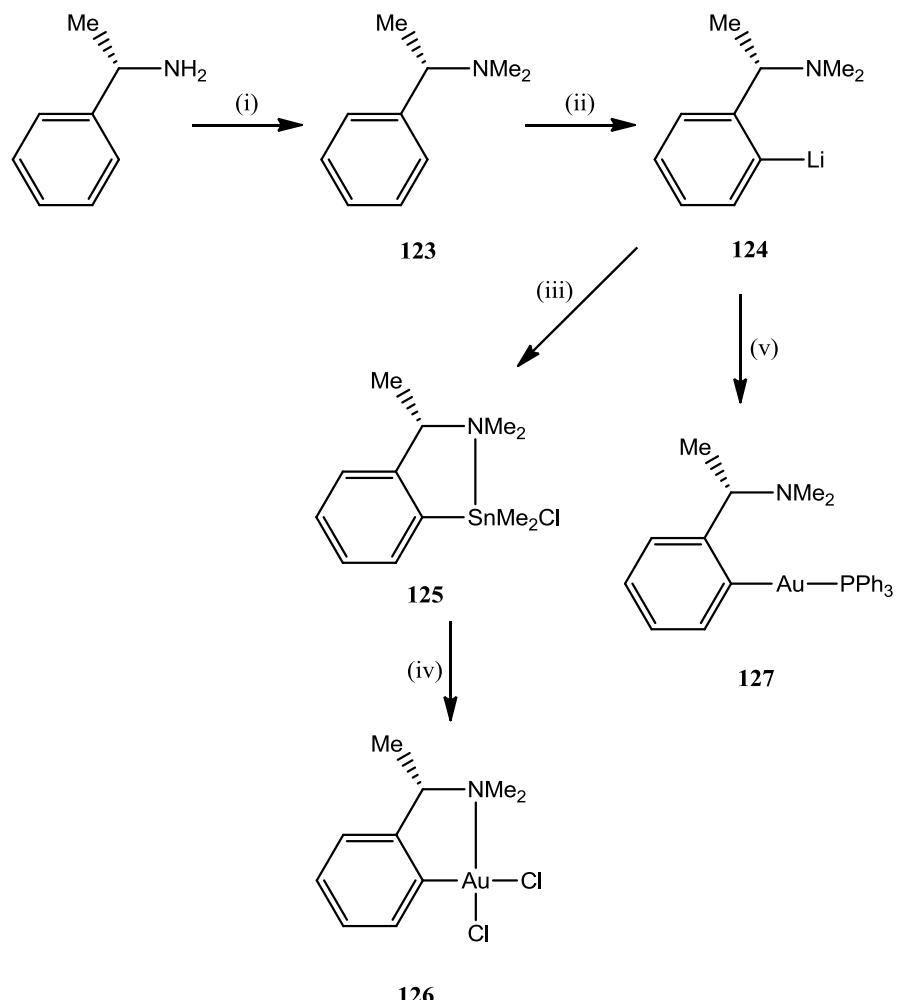


Scheme 6.1.3: Chiral gold(III) complexes prepared by Sanchez *et al.*³¹⁷ and Corma and co-workers.³¹⁸

6.2 Preparation of chiral gold complexes

Since $[\text{AuCl}_2(\eta^2\text{-C}_6\text{N-C}_6\text{H}_4\text{-2-CH}_2\text{NMe}_2)]$ (**8a**) proved to be an efficient catalyst for A^3 -coupling, it was thought that the preparation of a related chiral cyclometallated gold(III) complex, and a chiral gold(I) derivative, may offer an opportunity to develop an asymmetric variant of gold catalysed A^3 -coupling reactions. α -Methyl-*N,N*-dimethylbenzylamine was chosen as the cyclometallating ligand as it could be readily prepared and bound to both gold(I) and gold(III) (Scheme 6.2.1). The chiral ligand α -methyl-*N,N*-dimethylbenzylamine (**123**) was prepared by methylating the readily available (S)-(-)- α -methyl-benzylamine using formic acid and formaldehyde according to the procedure outlined by Ollis and co-workers.³¹⁹ Following the method of Van Koten *et al.*,³²⁰ **123** was lithiated with *tert*-butyllithium in hexane at room temperature overnight. It has been previously reported that the lithiation of α -methyl-*N,N*-dimethylbenzylamine (**123**) with *n*-butyllithium results in incomplete lithiation (50%) with the product also containing butyllithium-aryllithium aggregates.^{321,322} Further reactions of the aggregate mixtures would result in unwanted side-product formation; therefore the use of *t*-butyllithium is required in the lithiation step to afford optimum yields. The chiral lithium reagent $1\text{-LiC}_6\text{H}_4\text{CH(Me)NMe}_2$ (**124**) was isolated in 68% yield as an air- and moisture sensitive solid and stored in an MBraun glovebox working with nitrogen gas. The lithium

reagent could then be used as an off-the-shelf stoichiometric reagent. Quenching of **124** with dimethyltin dichloride at -78 °C in diethyl ether resulted in the formation of chiral stannane [$\text{SnMe}_2\text{Cl}(\eta^2\text{-C}_6\text{H}_4\text{CH(Me)NMe}_2)$] (**125**) in 86% yield. Transmetallation of **125** to a gold(III) centre was readily achieved by refluxing with $\text{Na}[\text{AuCl}_4] \cdot 2\text{H}_2\text{O}$ in MeCN for 24 hours. The Sn to gold(III) transmetallation reaction described by Ortiz *et al.*¹⁸⁹ was used to prepare the chiral gold(III) complex [$\text{AuCl}_2(\eta^2\text{-C}_6\text{H}_4\text{CH(Me)NMe}_2)$] (**126**) as this route was found to be very efficient giving excellent yields ($\geq 85\%$) of cyclometallated product in 24 hours. The analogous chiral gold(I) compound [$\text{Au}(\text{PPh}_3)(\eta^1\text{-C}_6\text{H}_4\text{CH(Me)NMe}_2)$] (**127**) was synthesised by quenching **124** with $\text{ClAu}(\text{THT})$ in diethyl ether at -78 °C, before adding PPh_3 to give the chiral organogold(I) phosphine complex **127**. Analytical and spectroscopic data for **123-127** is contained in experimental sections 8.7.1-8.7.5.



Scheme 6.2.1: Preparation of compounds **123-127**. Conditions: (i) 5.7 HCOOH, 2.4 HC(O)H, 2.5 h, reflux; (ii) 1.1 'BuLi, hexane, 24 h, r.t.; (iii) SnMe_2Cl_2 , Et_2O , -78 °C- r.t.; (iv) $\text{Na}[\text{AuCl}_4] \cdot 2\text{H}_2\text{O}$, MeCN, reflux; (v) $\text{ClAu}(\text{THT})$, PPh_3 , Et_2O , -78 °C-r.t.

Single crystals suitable for X-ray structure determination could not be obtained for the chiral Sn reagent **125**, however the solid state structures of both **126** and **127** were confirmed by single crystal X-ray diffraction studies. Slow diffusion of hexane into a saturated CH_2Cl_2 solution of **126** resulted in the formation of crystalline yellow plates that were suitable for X-ray structure determination. Compound **126** crystallises in the triclinic chiral space group *P*₁ with 1 molecule in the unit cell. An ORTEP representation of the structure is shown in Figure 6.2.1. Chirality at C7 was confirmed and the absolute configuration determined as the expected (*S*)-enantiomer. The gold(III) atom is in a typical square planar arrangement with angles approaching 90°. The Au1-C1 bond length of 2.004(14) Å is fairly standard for dimethylbenzylamine based gold(III) complexes, as is the Au1-N1 bond length of 2.09(4) Å. The gold-chlorine bond lengths exhibit the usual disparity caused by the differing trans-effects of the phenyl and NMe₂ groups, with bond lengths of 2.385(7) Å for Au1-Cl2 and 2.277(10) Å for Au1-Cl1.

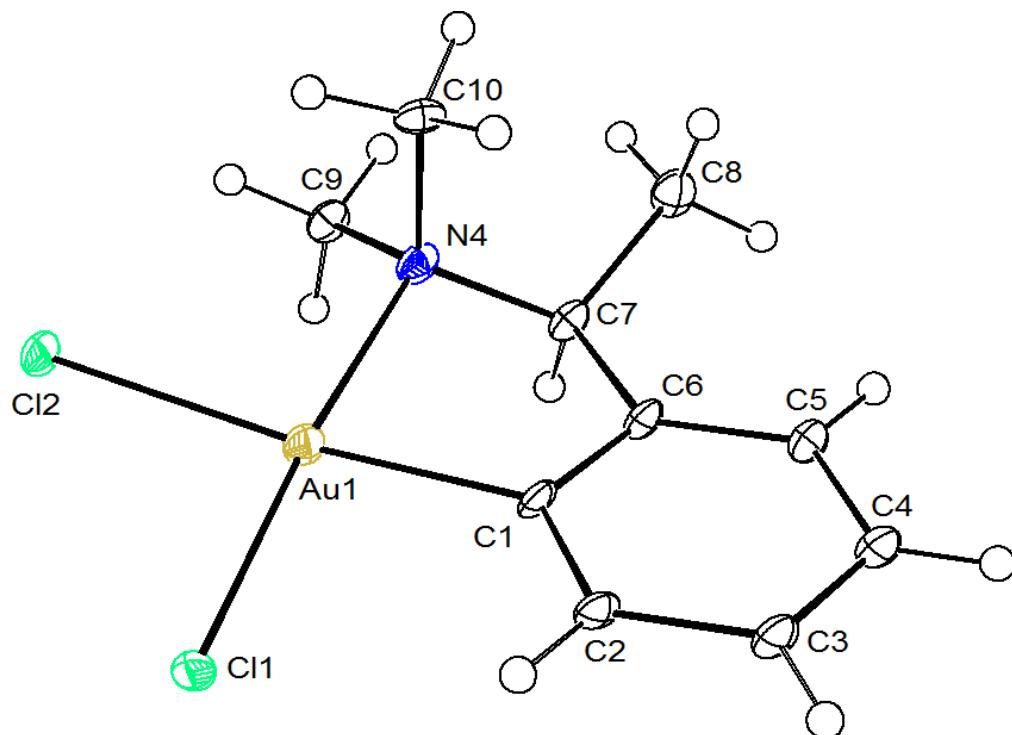


Figure 6.2.1: ORTEP representation of (*S*)-[AuCl₂(η^2 -C,N-C₆H₄CH(Me)NMe₂)] (**126**). Thermal ellipsoids at 40% probability.

Table 6.2.1: Selected bond lengths (Å) and bond angles (°) for (S)-[AuCl₂(η²-C,N-C₆H₄CH(Me)NMe₂)] (126).

Dimension	Value	Dimension	Value
Au1-Cl1	2.277(10) Å	Cl1-Au1-N1	174.1(11) °
Au1-Cl2	2.385(7) Å	Cl1-Au1-C1	93.6(6) °
Au1-N1	2.09(4) Å	Cl2-Au1-N1	95.6(12) °
Au1-C1	2.004(14) Å	Cl2-Au1-C1	174.0(6) °
Cl1-Au1-Cl2	90.2(3) °	N1-Au1-C1	8.06(13) °

Table 6.2.2: Crystallographic data for (S)-[AuCl₂(η²-C,N-C₆H₄CH(Me)NMe₂)] (126).

Formula	C ₁₀ H ₁₄ AuCl ₂ N	T (K)	100 (2)
Formula Weight	416.09	D_c (g cm⁻³)	2.417
Crystal System	Triclinic	Crystal Size (mm)	0.03 x 0.10 x 0.20
Space group	<i>P</i> 1	Mo K_a λ (Å)	0.71069
a (Å)	6.120(5)	Total reflections	1688
b (Å)	6.699(5)	Unique reflections (R_{int})	1441 (0.067)
c (Å)	7.192(5)	Goodness of Fit on F²	1.083
α (°)	76.140(5)	Observed Reflections [I > 2σ(I)]	1426
β (°)	87.943(5)	Final R indices [I > 2σ(I)]	R 0.0621 wR ₂ 0.1564
γ (°)	87.303(5)	Parameters	118
Z	1	S	1.08
V (Å³)	285.9(4)	Flack x	-0.02(4)

Slow diffusion of hexane into a saturated CH₂Cl₂ solution of **127** resulted in the formation of colourless single crystal prisms which were suitable for X-ray structure determination. Compound **127** crystallises in the monoclinic chiral space group *P*2₁ with two molecules in the unit cell. Figure 6.2.2 contains an ORTEP representation of **127**. Chirality at C7 was confirmed, and the absolute configuration determined as the expected (*S*)-enantiomer. The gold(I) atom is in an approximately linear arrangement with a C1-Au1-P1 bond angle of 176.2(2) °. The Au1-C1 bond length of 2.041(9) Å and Au1-P1 bond length of 2.295(3) Å are comparable to those reported in the literature for this type of complex.²⁷ Interestingly in **127** the nitrogen is rotated away from the Au(I) centre having no interaction with the metal atom, contrasting with **126** where the nitrogen is co-ordinated to the gold(III) metal centre forming a C,N chelate. It should also be noted that in the extended structure of **127** no aurophilic contacts^{25,26} are observed.

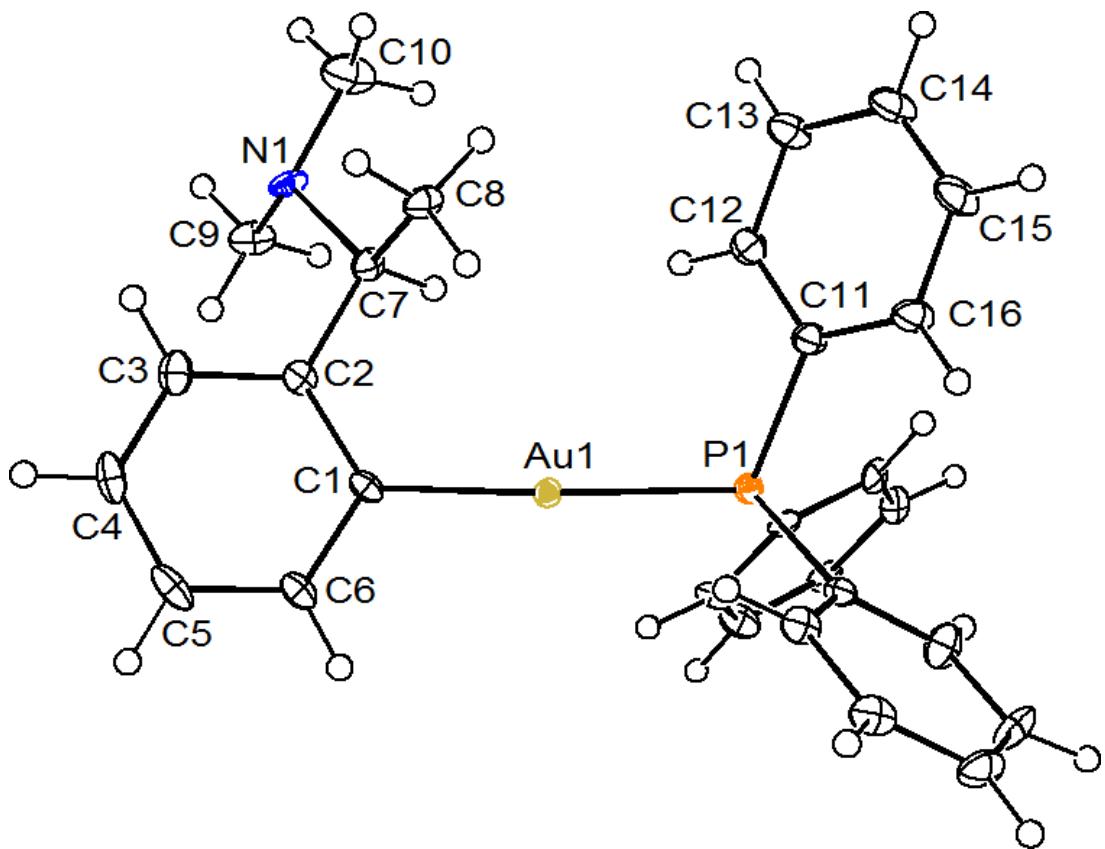


Figure 6.2.2: ORTEP representation of (S)-[Au(PPh₃)(η¹-C₆H₄CH(Me)NMe₂)] (127). Thermal ellipsoids at 40% probability level.

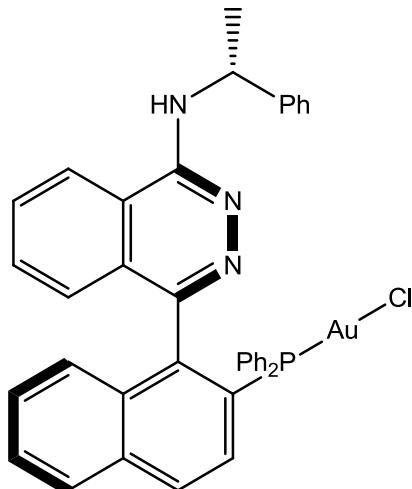
Table 6.2.3: Crystallographic data for (S)-[Au(PPh₃)(η¹-C₆H₄CH(Me)NMe₂)] (127).

Formula	C ₂₈ H ₂₉ AuNP	T (K)	100(2)
Formula Weight	607.46	D_c (g cm⁻³)	1.605
Crystal System	Monoclinic	Crystal Size (mm)	0.08 x 0.40 x 0.60
Space group	P2 ₁	Mo K_a λ (Å)	0.71069
a (Å)	8.784(5)	Total reflections	8056
b (Å)	10.646(5)	Unique reflections (R_{int})	4087 (0.050)
c (Å)	13.540(5)	Goodness of Fit on F²	1.042
α (°)	90	Observed Reflections [I > 2σ(I)]	3740
β (°)	96.837(5)	Final R indices [I > 2σ(I)]	R 0.0381 wR ₂ 0.0830
γ (°)	90	Parameters	283
Z	2	S	1.042
V (Å³)	1257.2(10)	Flack x	-0.034(12)

Table 6.2.4: Selected bond lengths (Å) and bond angles (°) for (*S*)-[Au(PPh₃)(η¹-C₆H₄CH(Me)NMe₂)] (127).

Dimension	Value
A1-C1	2.041(9) Å
Au1-P1	2.295(3) Å
C1-Au1-P1	176.2(2) °

Next the complex {(*R*)-(+)4-[2-(diphenylphosphenyl)-1-naphthyl]-*N*-[(*R*)-1-phenylethyl]-1-phthalazinamine}gold(I) chloride [(PINAP)AuCl] (**128**) was prepared following the method of Hashmi *et al.*,³²³ reaction ClAu(THT) with (*R*)-PINAP in CH₂Cl₂ over 24 hours. The chiral complex was prepared as the CuBr/PINAP catalyst system has exhibited excellent enantioselectivity in the A³-coupling of aldehydes, amines and alkynes,²⁷² so it was thought that a Au/PINAP system may also lead to asymmetric A³-reactions. The spectroscopic and analytical data of **128** was comparable to that previously reported.³²³

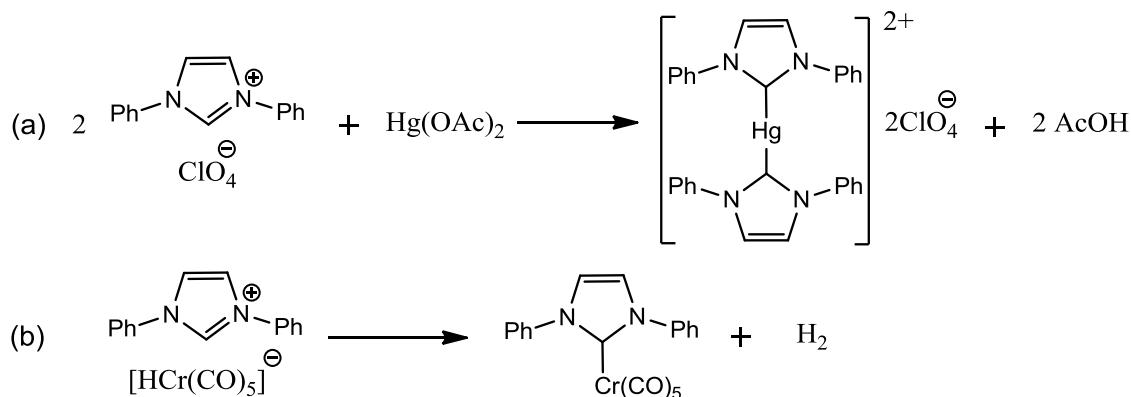


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6.3 Introduction to *N*-heterocyclic carbenes

N-heterocyclic carbenes are routinely used in modern organometallic chemistry, and have come to replace phosphines in many organometallic and organic reactions. Due to their facile preparation and structural versatility the preparation of new chiral gold(I) NHC complexes was attempted. Carbenes are neutral electron deficient divalent carbon compounds that have two non-bonding electrons. The two non-bonding electrons can occupy two different orbitals with parallel spins leading to a triplet state, or reside in the

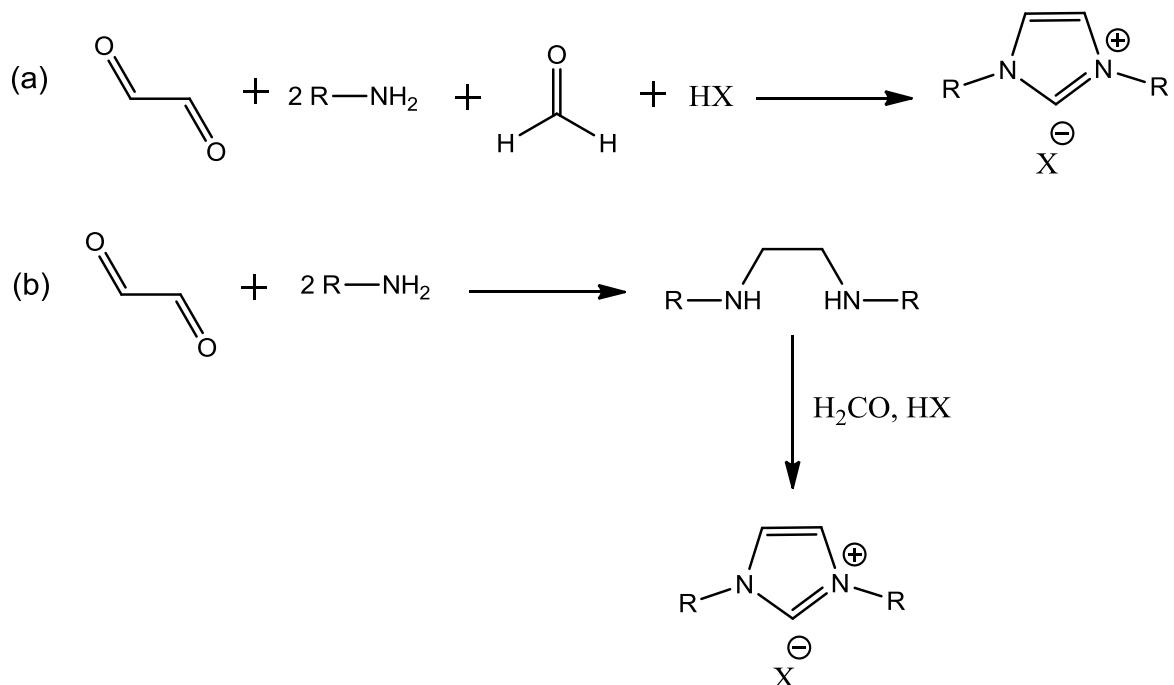
same orbital with anti-parallel spins giving a singlet state.^{324,325} *N*-heterocyclic carbenes (NHCs) are the most common and important class of stable singlet carbenes.³²⁵ Their structures are based around incorporation of the carbene carbon into a nitrogen containing heterocycle. The early work in this area was carried out by Wanzlick *et al.*³²⁶ and Öfele³²⁷ who both independently reported the synthesis of the first NHC complexes (Scheme 6.3.1).



Scheme 6.3.1: Early NHC complexes prepared by Wanzlick *et al.*³²⁶ (a), and Ofele (b).³²⁷

The pioneering work in this area was carried out by Arduengo *et al.*³²⁸ who in 1991 reported the isolation of the first stable NHC, 1,3-diadamantyl-imidazol-2-ylidene. Since this important breakthrough numerous different free NHCs have been prepared and investigated, with the most common being five-membered ring imidazolylidenes which are typically stable under an inert atmosphere. *N*-heterocyclic carbene precursors, imidazolium salts, are generally prepared *via* multi-component reactions between glyoxal, formaldehyde and primary amines in the presence of an acid Scheme 6.3.2 (a)).^{325,329} Variation of the amine enables the preparation of structurally diverse imidazolium salts. Synthesis and isolation of the bisimine, before ring closure with formaldehyde and acid, in a two-step procedure enables access to imidazolium salts derived from bulky anilines Scheme 6.3.2 (b)).^{330,331} Due to the facile preparation of NHCs and their excellent properties as ligands, *N*-heterocyclic carbene complexes are now ubiquitous in modern organometallic chemistry. *N*-heterocyclic carbenes behave like typical two electron σ -donor ligands, analogous to phosphines.³²⁹ Indeed early studies by Öfele and co-workers³³² reported that *N*-heterocyclic carbenes have similar bonding properties to those of electron rich tertiary phosphines. However detailed investigations by the group of Nolan into the steric and electronic effects of NHC binding to metal centres determined that in general NHCs behave as better donors than the best phosphine ligands.^{324,333–336} Thus transition metal-

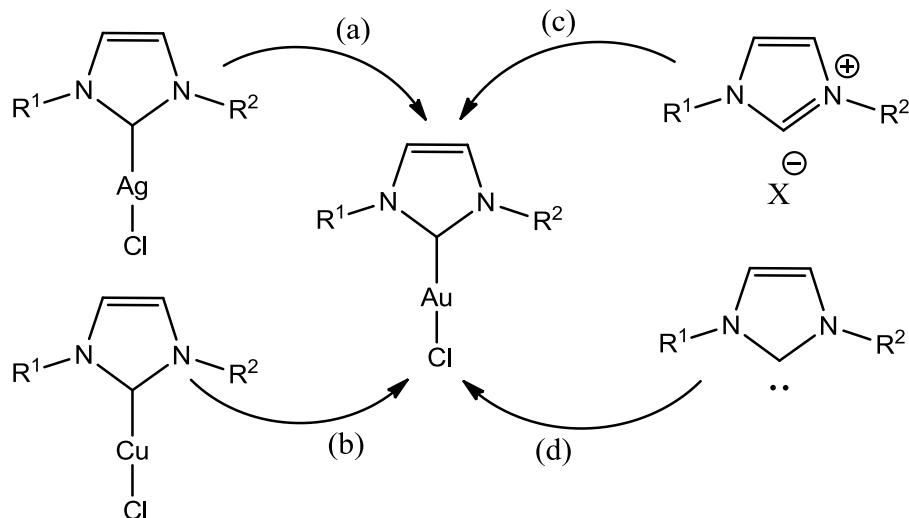
NHC complexes have received enormous attention for their use as catalysts in a wide variety of transformations.^{16,337} This utility is attributed to the strong σ -donor properties of NHCs^{324,338} which in turn gives strong M-NHC bonds and a strong *trans*-effect.^{339–341}



Scheme 6.3.2: Synthesis of imidazolium salts. (a) one-pot reaction of glyoxal, primary amines, formaldehyde in the presence of acid; (b) two step preparation of imidazolium salts.

For a more extensive overview on the chemistry of *N*-heterocyclic carbenes the reader's attention is directed towards the comprehensive reviews of Herrmann,^{329,342,343} Kirmse,³⁴⁴ Crudden,³⁴⁵ Glorius³⁴⁶ and Nolan.¹⁶ Interest in preparing Au(I) and Au(III)-NHCs has rapidly expanded in recent years due to the increasing use of gold-NHC complexes in homogeneous catalysis.¹⁷ Au(I)-NHCs, are far more common than their gold(III) counterparts, and have also been investigated in biological applications.³⁴⁷ A number of synthetic routes have been developed for the synthesis of Au(I)-NHCs, and the most commonly used routes are shown in Scheme 6.3.3. Transmetallation from Ag(I)-NHCs is currently the most popular method of preparing Au(I)-NHCs (Scheme 6.3.3 (a)). This method of preparing gold-NHC complexes is widely known,³⁴⁸ as Ag-NHC's have been extensively used as carbene transfer agents.^{349–353} The Ag-NHC is typically synthesised by stirring the corresponding imidazolium-chloride salt with Ag₂O. Normally the Ag-NHC is reacted *in-situ* with a gold(I) precursor rather than isolation of the silver complex.³⁴⁹ This protocol accounts for the preparation of *ca.* 70% of the published Au(I)-NHCs,¹⁶ and

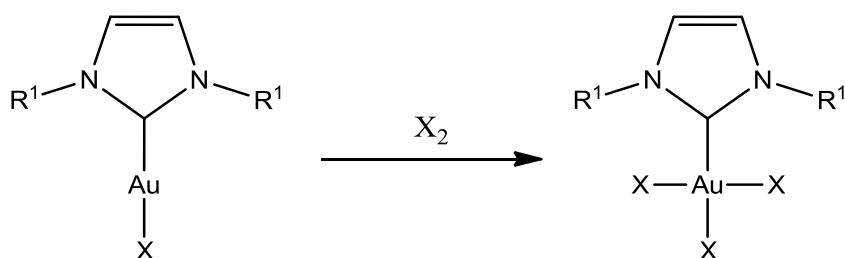
exhibits a wide applicability for various substituted NHCs. Transmetallation from Cu(I)-NHCs to Au(I) has recently been developed,³⁵⁴ however this method has, to date, only been used to prepare a small number of complexes (Scheme 6.3.3 (b)). The direct reaction of imidazolium salts with K[AuCl₄] or Na[AuCl₄] in the presence of K₂CO₃ and 3-chloropyridine offers an alternative to the silver transmetallation route (Scheme 6.3.3 (c)).^{355,356} High yields of the desired product are obtained and the reaction proceeds in air. Additionally the use of silver oxide, which is relatively expensive, is avoided. The final route to Au(I)-NHCs is through the direct reaction of gold(I) precursor with the free *N*-heterocyclic carbene (Scheme 6.3.3 (d)).^{16,357} The free NHC is typically prepared under an inert atmosphere using strong bases for example potassium t-butoxide. The reaction usually results in high yields of the desired Au-NHC, however preparation of the free carbene can be challenging in some instances. Furthermore this protocol is unsuccessful for the synthesis of some common Au-NHCs, namely 1,3-bis(2,4,6-trimethylphenyl)imidazolin-2-ylidene gold chloride which is prepared *via* transmetallation with the silver carbene.³⁴⁸



Scheme 6.3.3: Most common routes to Au(I)-NHC complexes. (a) Transmetallation of corresponding silver-NHC with ClAuS-R;³⁴⁹ (b) Transmetallation of corresponding copper-NHC with ClAuS-R;³⁵⁴ (c) Direct reaction of imidazolium salt with K[AuCl₄] or Na[AuCl₄];^{355,356} (d) Reaction of free carbene with ClAuS-R.^{17,357}

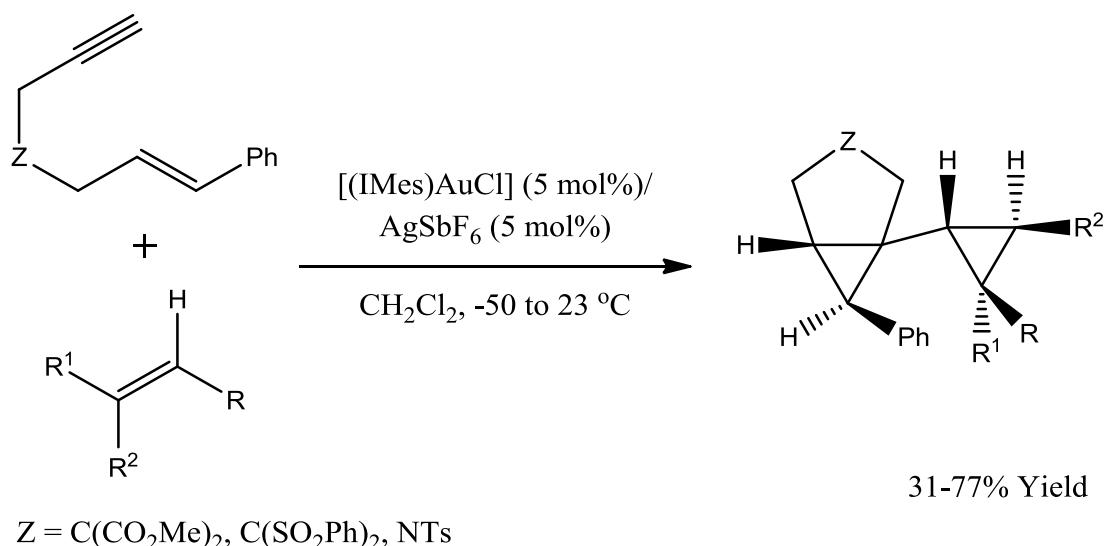
Au(III)-NHCs are less common in the literature and only a handful of routes are available for their preparation. The most widely used method to prepare Au(III)-NHCs involves oxidative addition of halogens to the corresponding Au(I) complexes (Scheme 6.3.4).^{358–360} It has been reported that attempts to prepare Au(III)-NHCs by the direct reaction of Au(III)

salts with the free carbene resulted in precipitation of metallic gold, decomposition of the carbene and the formation of Au(I)-NHC.³⁵⁹



Scheme 6.3.4: Oxidative addition of halogen to Au(I)-NHCs.

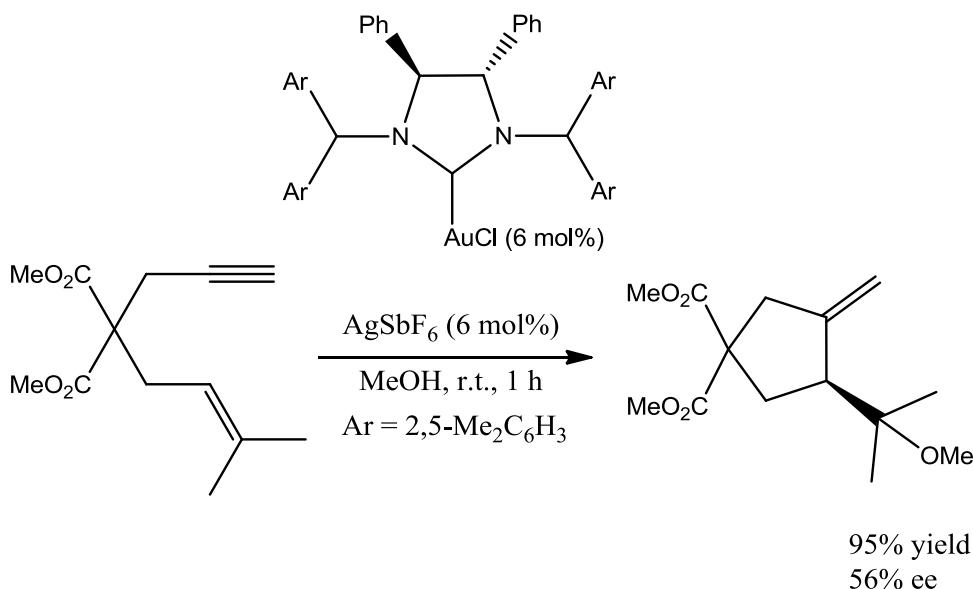
Gold-NHC complexes have demonstrated the ability to catalyse an increasing number of organic transformations,¹⁷ with the rearrangement of enynes the most popular reaction. Echavarren *et al.* have reported the cyclopropanation of 1,6-enynes catalysed by a 1,3-bis(2,4,6-trimethylphenyl)-imidazolin-2-ylidene gold(I) chloride [(IMes)AuCl]/ AgSbF₆ system in moderate yields²⁸⁰ (Scheme 6.3.5). The silver salt is used as a chloride abstractor to generate the active catalyst.



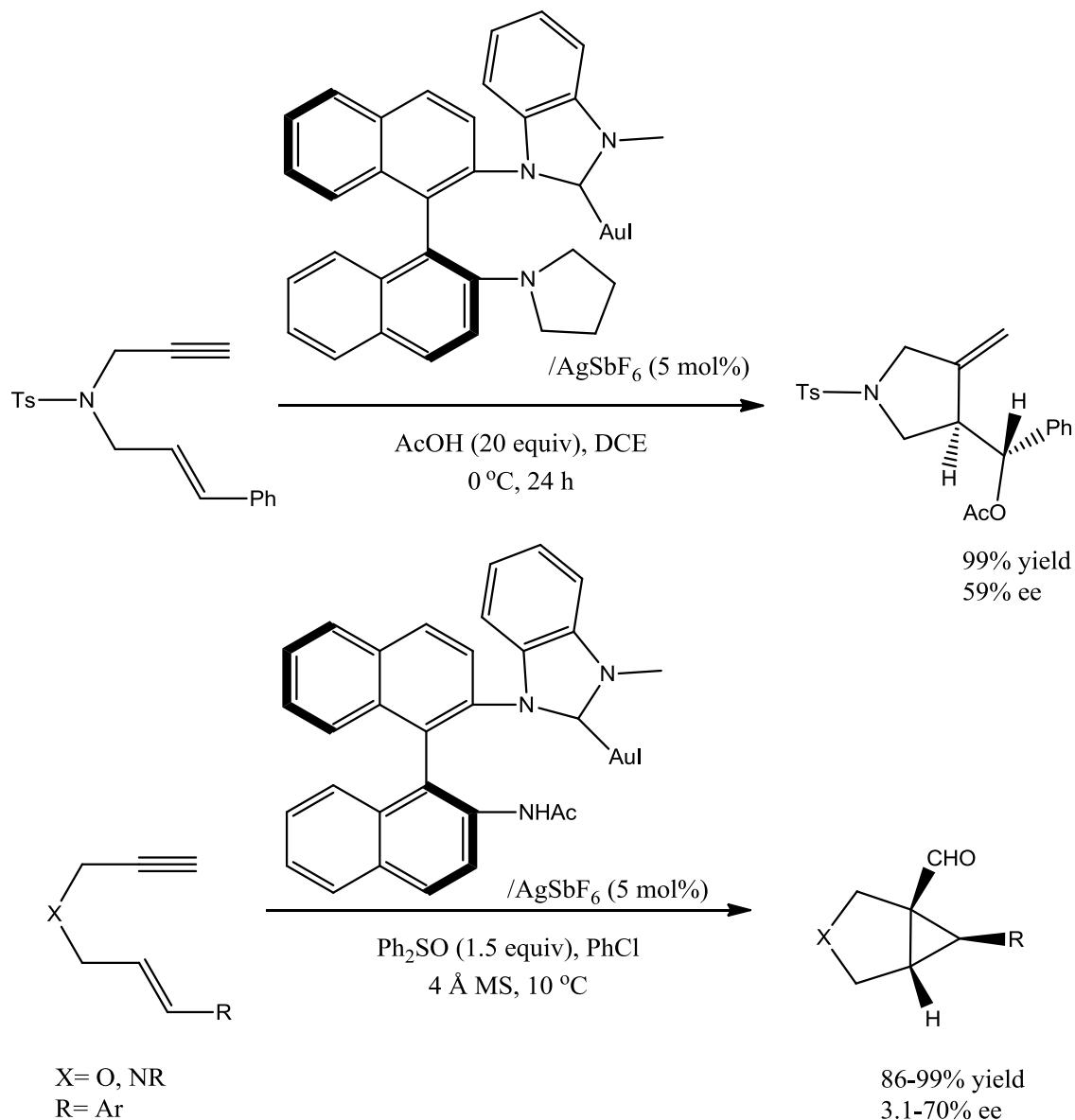
Scheme 6.3.5: Cyclization of enynes with alkenes as reported by Echavarren and co-workers.²⁸⁰

Subsequently Toste *et al.*³⁶¹ demonstrated the cyclization of a variety of 1,6-enynes, to give cyclopropylaldehydes, catalysed by 1,3-bis(2,6-diisopropylphenyl)-imidazolin-2-ylidene gold(I) chloride [(IPr)AuCl]/ AgSbF₆. Reports of chiral NHCAu(I) complexes and their use as catalysts are extremely rare, however recently progress has been made in this area. Firstly Tomioka and co-workers³⁶² reported the synthesis and use of (4*S*,5*R*)-1,3-bis-(bis-

2,5-dimethylphenyl)methyl-4,5-diphenylimidazolin-2-ylidene gold(I) chloride in the asymmetric cyclization of 1,6-enynes (Scheme 6.3.6). Moderate enantioselectivities were obtained (56% ee) and the *N*-substituents on the NHC ring were found to significantly affect enantioselectivity.³⁶³ Shi *et al.*³⁶⁴ have synthesised a range of axially chiral Au(I) NHCs and screened them in the asymmetric acetoxycyclization of 1,6-enynes and the asymmetric oxidative rearrangement of 1,6-enynes (Scheme 6.3.7). Excellent yields were obtained, but with moderate enantioselectivities.



Scheme 6.3.6: The asymmetric cyclization of 1,6-enynes to give cyclopentanes as reported by Tomioka and co-workers.³⁶²



Scheme 6.3.7: Asymmetric acetoxycyclization of 1,6-enynes and asymmetric oxidative rearrangement of 1,6-enynes giving aldehydes, as reported by Shi and co-workers.³⁶⁴

6.3.1 Gold NHCs as catalysts for A^3 -coupling

Gold *N*-heterocyclic carbene complexes are now commonly used as catalysts in a variety of organic transformations,^{17,365} however there remain only a handful of examples of their use in the A^3 -reaction. Recently Corma and co-workers have reported the use of different homogeneous and heterogeneous *N*-heterocyclic carbene-dioxolane and pincer type (NHC)NN gold complexes as catalysts for A^3 -coupling.²³⁸ The chiral dioxolane complexes (*S,S*)-**129**, (*S,S*)-**130**, (*S,S*)-**132** and (*S,S*)-**133** were prepared according to Scheme 6.3.8, (a),³⁶⁶ with the chiral pincer complexes (*S*)-**131** and (*S*)-**134** prepared by two successive nucleophilic substitutions as outlined in Scheme 6.3.8, (b).³⁶⁷ Complexes **129**, **130** and **131**

containing triethoxysilyl groups were covalently bound to a MCM-41 mesoporous silica support. MCM-41 or Mobil crystalline material is a short range amorphous silicate that contains a large number of silanol groups available for binding.^{238,367} The gold complexes were refluxed with a dispersion of MCM-41 in toluene over 24 h to afford the supported catalysts. Solvent screening experiments were carried out for the reaction of benzaldehyde, piperidine and phenylacetylene. Chloroform was found to be the best solvent giving the highest yields of product (Table 6.3.1). When EtOH and MeCN were used, only poor to moderate yields of the propargylic amine could be obtained. From Table 6.3.1 it can be clearly seen that the reaction temperature strongly influences the outcome of the reaction, with increased yields achieved at higher temperatures. This led the authors to conclude that A³-couplings with these catalysts was more affected by temperature than reaction solvent.²³⁸ The coupling reaction proceeds to only 63% with K[AuCl₄] as the catalyst, and importantly when no catalyst is used there is no observed conversion in refluxing chloroform. Additionally it can be seen that in general the homogenous catalysts **132**, **133** and **134** are more active than their analogous MCM-41 bound derivatives.

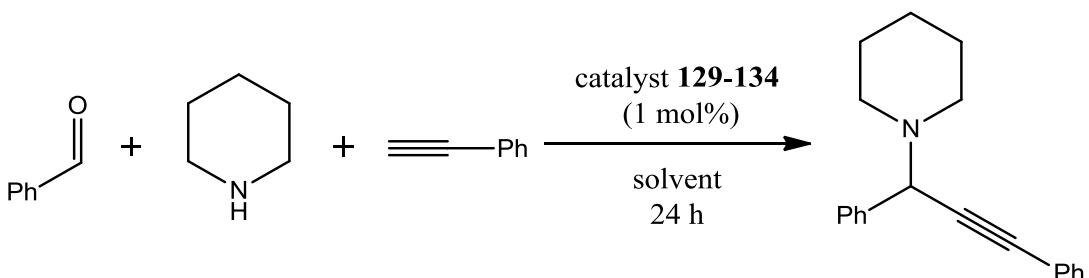
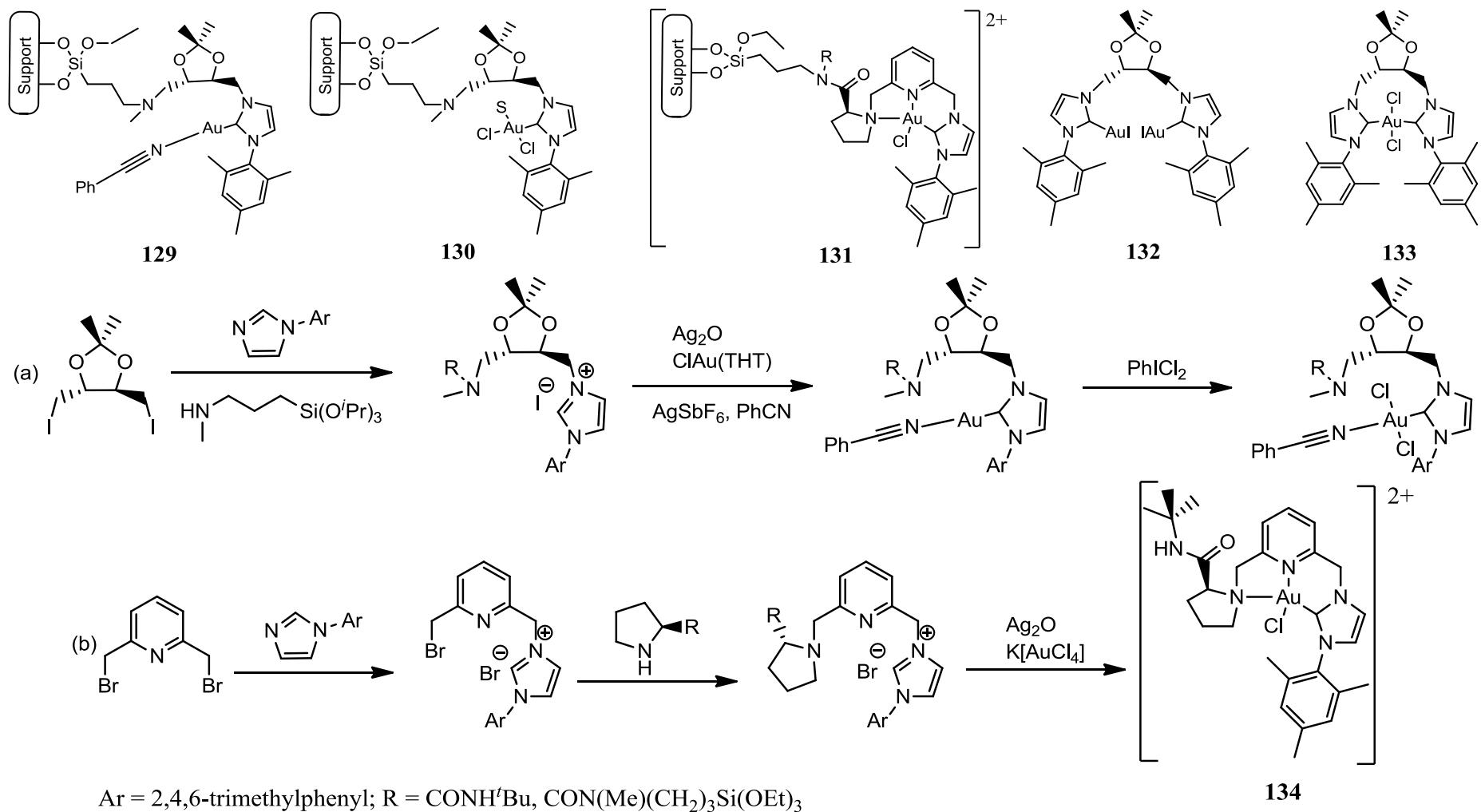


Table 6.3.1: Solvent screening experiments for the homogeneous and heterogeneous NHC catalysts.

Entry	Catalyst	Solvent	T/°C	Yield (%) ^a
1	129	EtOH	r.t.	trace
2	129	EtOH	reflux	41
3	129	CHCl ₃	reflux	85
4	130	EtOH	reflux	trace
5	130	CHCl ₃	reflux	80
6	131	EtOH	50	64
7	131	CHCl ₃	reflux	65
8	132	EtOH	reflux	trace
9	132	CHCl ₃	reflux	99
10	133	EtOH	50	trace
11	133	EtOH	reflux	22
12	133	CHCl ₃	reflux	99
13	134	EtOH	50	33
14	134	CHCl ₃	reflux	94
15	K[AuCl ₄]	CHCl ₃	reflux	63
16	uncatalysed	CHCl ₃	reflux	0

Reaction Conditions: benzaldehyde (0.19 mmol), piperidine (0.22 mmol), phenylacetylene (0.28 mmol), catalyst (1 mol% loading), inert atmosphere, 24 h.

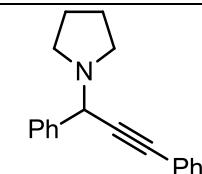
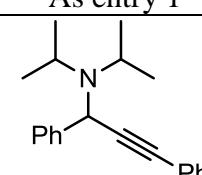
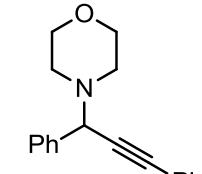
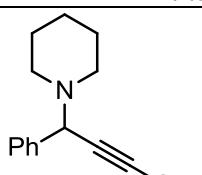
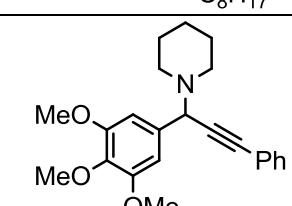
^a Isolated yield calculated based on benzaldehyde.

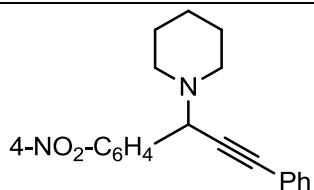
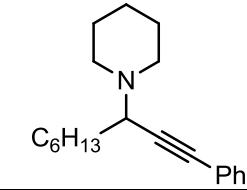
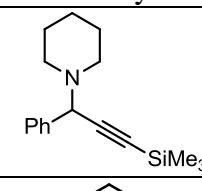
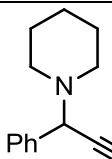


Scheme 6.3.8: The homogeneous and heterogeneous gold NHC complexes prepared by Corma and co-workers. (a) The preparation of dioxolane NHC compounds. (b) The preparation of pincer type (NHC)₂N gold complexes.²³⁸

The reaction was explored with various aldehyde, amine and alkyne substituents (Table 6.3.2). Substitution of piperidine for pyrrolidine resulted in moderate yields of the desired propargylamine (Table 6.3.2, entries 1 and 2). The reaction of benzaldehyde and phenylacetylene with either diisopropylamine or morpholine resulted in only trace amounts of coupled product when **129** was employed as catalyst. However the reaction between 1-decyne, benzaldehyde and piperidine (Table 6.3.2, entry 5) gave high yields of coupled propargylic amine product. Different aldehyde substituents also underwent coupling although the best yields were obtained when benzaldehyde was used. It was found that 3,4,5-(OMe)₃-C₆H₂CHO underwent coupling with phenylacetylene and piperidine in 64% yield when the reaction was catalysed by **134**. In the presence of the heterogeneous catalyst **129** and **131** the yields were significantly lower, again highlighting the greater activity of the homogeneous catalysts. When the strongly electron withdrawing nitro group was present only trace quantities of the desired product could be obtained with both **131** and **134** as catalysts. The aliphatic aldehyde heptanal could be coupled with piperidine and phenylacetylene in good yields of 80% and 74% when catalysed by **129** and **131** respectively. It was also found that coupling reactions with trimethylsilylacetylene proceeded smoothly. Trimethylsilyl substituents can be readily removed after the coupling reaction to obtain terminal propargylamines that can be further functionalised. Interestingly it was found that the MCM-41 support was able to desilylate the A³-product *in-situ* (Table 6.3.2 entry 14), whereas the homogeneous catalyst **134** gave the silyl protected product (Table 6.3.2, entries 13 and 14). This effect was believed to be due to the acidity of the silica support which acts as an acid catalyst to facilitate removal of the silyl group. The reusability of the supported catalysts **129**, **130** and **131** was investigated by performing the coupling of benzaldehyde, piperidine and phenylacetylene several times with the same solid support. It was found that a regeneration step, where the solid catalyst was treated with benzonitrile at 70 °C for 5 hours, was needed after the first cycle, subsequently the catalyst could be recycled for at least six cycles. The recycling of the dioxolane catalysts **129** and **130** resulted in a *ca.* 30% decrease in activity by the fifth run, whereas **131** could only be used for one cycle.

Table 6.3.2: Selected results of A³-coupling with heterogeneous and homogeneous NHC complexes.

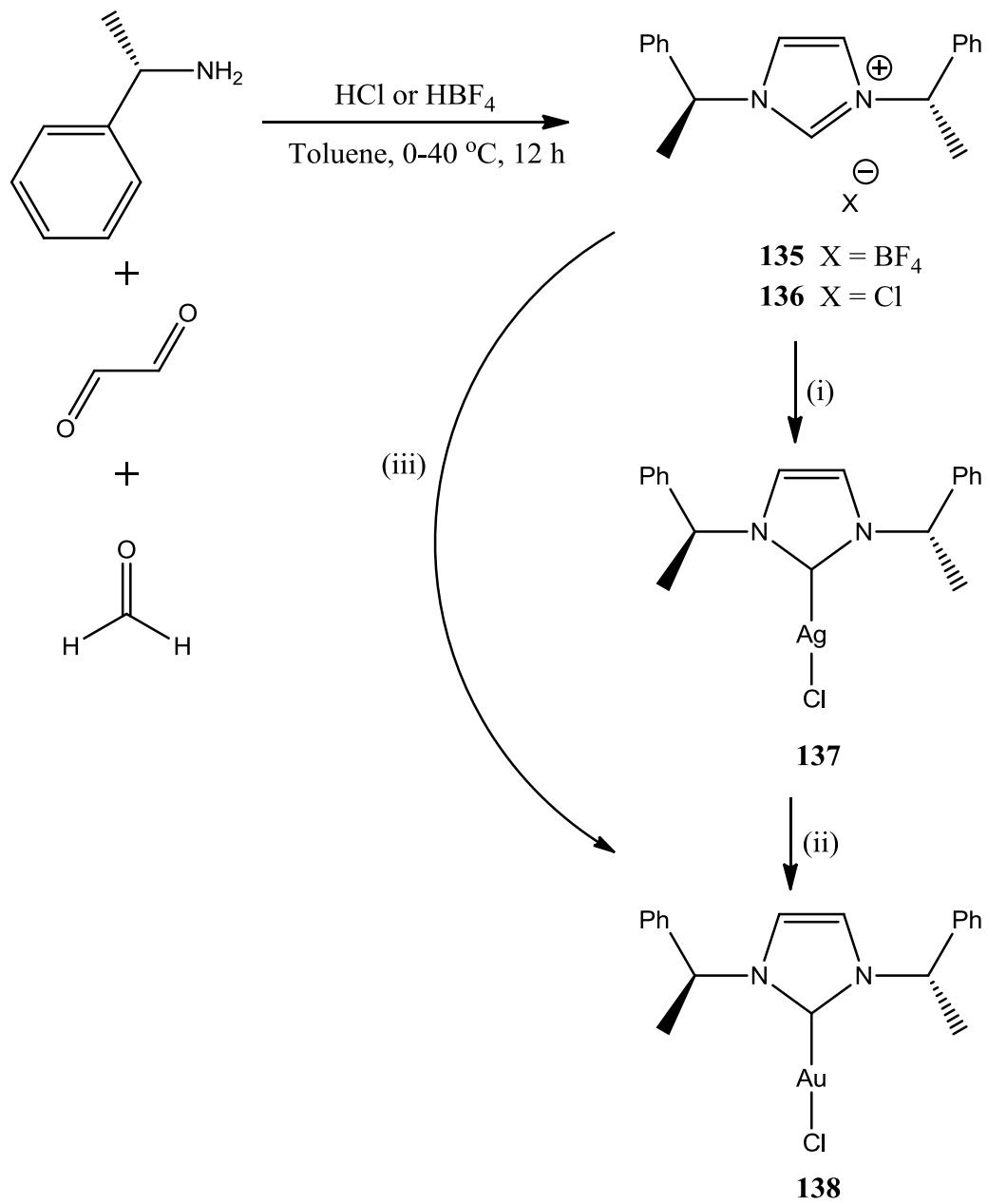
Entry	Catalyst	Aldehyde	Amine	Alkyne	Product	Yield(%)
1	129	PhCHO	pyrrolidine	PhCCH		40
2	134	PhCHO	pyrrolidine	PhCCH	As entry 1	93
3	129	PhCHO	HN(C(CH ₃) ₂) ₂	PhCCH		trace
4	129	PhCHO	morpholine	PhCCH		trace
5	129	PhCHO	piperidine	C ₈ H ₁₇ CCH		97
6	129	3,4,5-(OMe) ₃ -PhCHO	piperidine	PhCCH		3

Entry	Catalyst	Aldehyde	Amine	Alkyne	Product	Yield(%)
7	131	3,4,5-(OMe) ₃ -PhCHO	piperidine	PhCCH	As entry 6	30
8	134	3,4,5-(OMe) ₃ -PhCHO	piperidine	PhCCH	As entry 6	64
9	131	4-NO ₂ -PhCHO	piperidine	PhCCH	 4-NO ₂ -C ₆ H ₄ -C≡CH-Ph	0
10	134	4-NO ₂ -PhCHO	piperidine	PhCCH	As entry 9	5
11	129	C ₆ H ₁₃ CHO	piperidine	PhCCH	 C ₆ H ₁₃ -C≡CH-Ph	80
12	131	C ₆ H ₁₃ CHO	piperidine	PhCCH	As entry 11	74
13	134	PhCHO	piperidine	Me ₃ SiCCH	 Ph-C≡CH-SiMe ₃	60
14	131	PhCHO	piperidine	Me ₃ SiCCH		39.2

Reaction Conditions: aldehyde (0.19 mmol), amine (0.22 mmol), alkyne (0.28 mmol), catalyst (1 mol%), 24 h.

6.4 Preparation of 1,3-bis-(1(S)-1-phenyl-ethyl)-imidazolin-2-ylidene gold(I) chloride (138)

In order to extend the number of chiral gold complexes available for A³-couplings the preparation of a chiral gold N-heterocyclic carbene complex was attempted. A chiral N-heterocyclic carbene gold(I) complex, 1,3-bis-(1(S)-1-phenyl-ethyl)-imidazolin-2-ylidene gold(I) chloride (138) was prepared (Scheme 6.4.1) and screened in the A³-coupling reaction. The imidazolium salts **135** and **136** were synthesised by the ‘one-pot’ procedures of Alexakis *et al.*³⁶⁸ and Hermann and co-workers³⁶⁹ respectively. (S)-(-)-α-methylbenzylamine, glyoxal, paraformaldehyde and either HCl or HBF₄ were heated at 40 °C in toluene overnight. Compound **135** was isolated as a viscous orange oil after aqueous workup and trituration with diethyl ether, similarly complex **136** was isolated as an extremely hygroscopic off-white powder. The (S)-(-)-α-methylbenzylamine system was chosen due to previous reports of enantioselective 1,4-conjugate addition reactions and the acylation of secondary alcohols catalysed by simple copper salts in combination with the chiral imidazolium salts **135** and **136**.^{368,370,371} The chiral Ag(I) complex 1,3-bis-(1(S)-1-phenyl-ethyl)-imidazolin-2-ylidene silver chloride (**137**) was prepared according to the procedure of Alexakis *et al.*³⁶⁸ in 85% yield by stirring **136** with Ag₂O in refluxing CH₂Cl₂ for 24 hours. The silver complex was prepared as a transmetallation reagent in order to transfer the chiral NHC ligand to an Au(I) centre. Complex **137** was isolated as a white powder after recrystallisation from CH₂Cl₂/hexane. Transmetallation from **137** to a gold(I) centre was effected by reaction with ClAu(THT) in CH₂Cl₂. Filtration through a plug of silica followed by recrystallisation from CH₂Cl₂/hexane gave analytically pure 1,3-bis-(1(S)-1-phenyl-ethyl)-imidazolin-2-ylidene gold chloride (**138**) in 92% yield. The chiral gold complex could also be prepared by heating a mixture of **135**, K₂CO₃ and ClAu(THT) in 3-chloropyridine at 90 °C, in a modification of the general method reported by Zhu and co-workers.^{355,356} This direct route to Au(I)-NHC complexes is attractive as it avoids the use of silver transfer reagents, however the method results in substantially lower yields (44%) of **138**. Analytical and spectroscopic data for **135-138** is contained in experimental sections 8.7.7-8.7.11.



Scheme 6.4.1: Preparation of compounds **135-138**. (i) **136**, Ag₂O, CH₂Cl₂, 40 °C, 24 h; (ii) ClAu(THT), CH₂Cl₂, r.t., 24h; (iii) **135**, 3-Chloropyridine, K₂CO₃, 80 °C, 42 h.

Single crystals of 1,3-bis-(1(*S*)-1-phenyl-ethyl)-imidazolin-2-ylidene silver chloride (**137**) suitable for X-ray diffraction studies were grown by slow diffusion of pentane into a saturated CHCl₃ solution. Compound **137** crystallizes in the orthorhombic chiral space group *P*2₁2₁2₁ with 4 molecules in the asymmetric unit cell. Figure 6.4.1 displays an ORTEP representation of **137**. Chirality at C4 and C12 was confirmed and the absolute configuration at both stereocenters was determined to be (*S*).

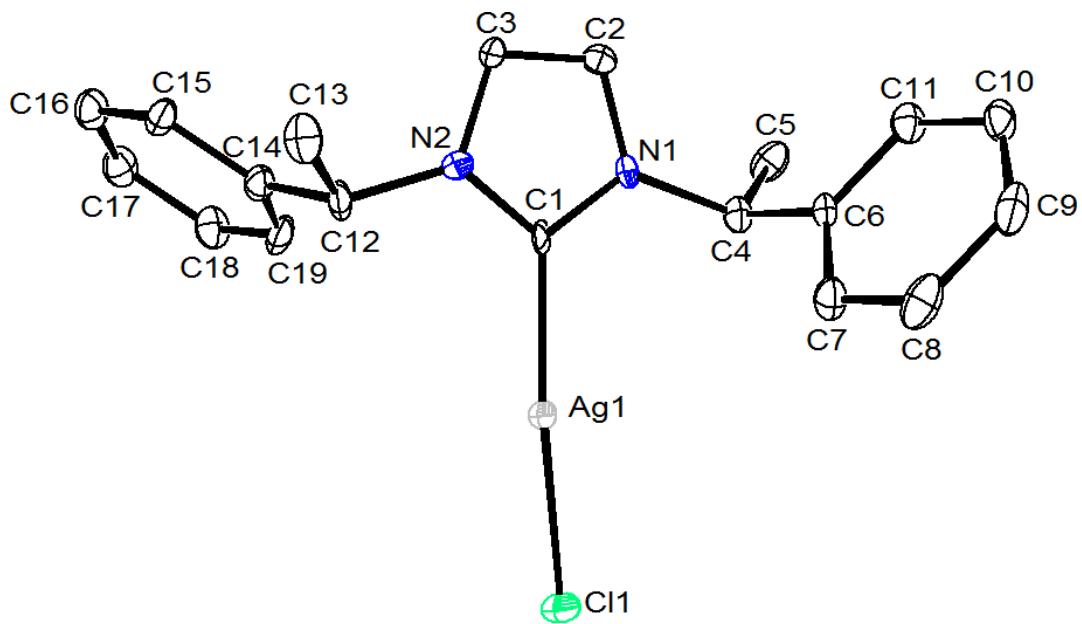


Figure 6.4.1: ORTEP representation of 1,3-bis-(1(S)-1-phenyl-ethyl)-imidazolin-2-ylidene silver chloride (137). Hydrogen atoms are omitted for clarity. Thermal ellipsoids at 40% probability level.

Table 6.4.1: Crystallographic data for 1,3-bis-(1(S)-1-phenyl-ethyl)-imidazolin-2-ylidene silver chloride (137).

Formula	$C_{19}H_{20}AgClN_2$	T (K)	99.95(10)
Formula Weight	419.69	$D_c (\text{g cm}^{-3})$	1.623
Crystal System	orthorhombic	Crystal Size (mm)	0.5 x 0.4 x 0.4
Space group	$P2_12_12_1$	Mo K_a λ (Å)	0.7107
a (Å)	9.5786(6)	Total reflections	8715
b (Å)	9.8045(6)	Unique reflections (R_{int})	5024 (0.0665)
c (Å)	18.2878(11)	Goodness of Fit on F^2	1.119
α (°)	90	Observed Reflections [$I > 2\sigma(I)$]	4788
β (°)	90	Final R indices [$I > 2\sigma(I)$]	R 0.0644 wR ₂ 0.1770
γ (°)	90	Parameters	210
Z	4	S	1.119
V (Å³)	1717.48(18)	Flack x	0.04(8)

Table 6.4.2: Selected bond lengths (Å) and angles (°) for of 1,3-bis-(1(S)-1-phenyl-ethyl)-imidazolin-2-ylidene silver chloride (137).

Dimension	Value	Dimension	Value
Ag1-C1	2.106(6) Å	N1-C2	1.381(9) Å
Ag1-Cl1	2.3408(16) Å	C3-C2	1.343(9) Å
C1-N1	1.338(9) Å	N1-C1-Ag1	125.6(5) °
C1-N2	1.356(8) Å	N1-C1-N2	110.5(6) °
N2-C3	1.402(8) Å	C1-Ag1-Cl1	171.67(18) °

Single crystals of 1,3-bis-(1(S)-1-phenyl-ethyl)-imidazolin-2-ylidene gold chloride (**138**) suitable for X-ray diffraction studies were grown by slow diffusion of pentane into a saturated THF/toluene solution. Compound **138** crystallizes in the monoclinic chiral space group *C121* with 4 molecules in the asymmetric unit cell. Additionally the unit cell contains a molecule of toluene. Figure 6.4.2 displays an ORTEP representation of **138**. Chirality at C4 and C12 was confirmed and the absolute configuration at both stereocenters was determined to be (*S*). The Au1-C1 and Au1-Cl1 bond lengths of 1.971(7) Å and 2.285(2) Å respectively are comparable to those reported previously for other Au(I)-NHC complexes.^{348,372–374} The gold(I) atom is in a linear coordination environment with a C1-Au1-Cl1 bond angle approaching 180 °.

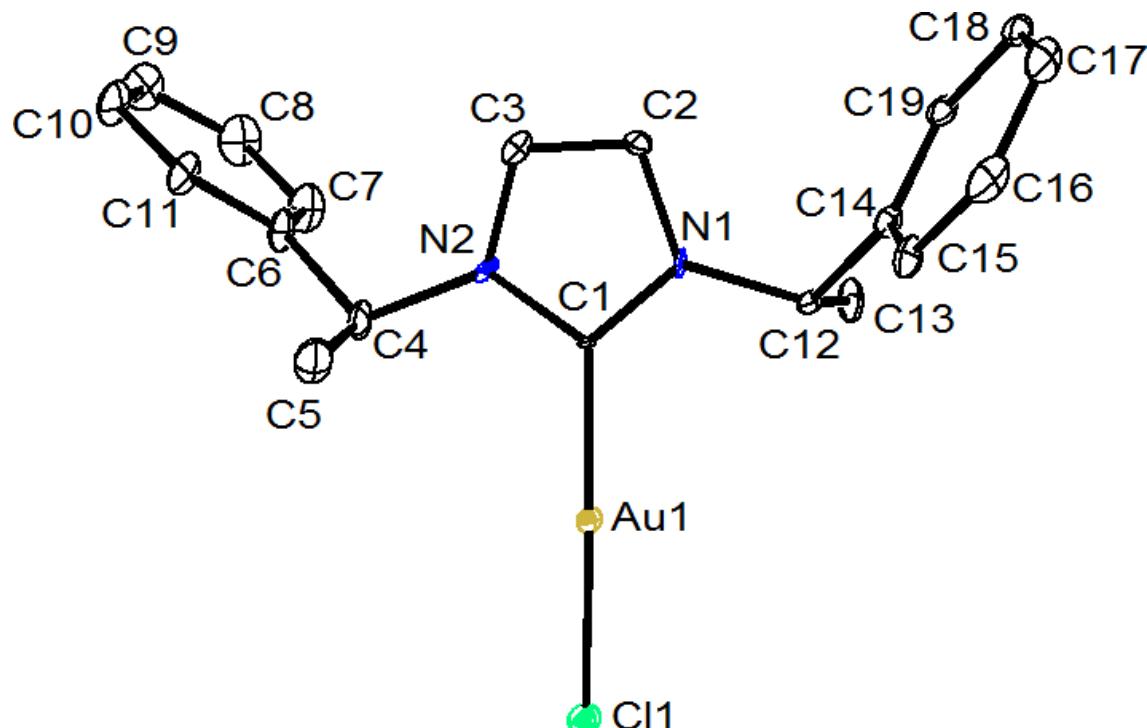


Figure 6.4.2: ORTEP representation of 1,3-bis-(1(S)-1-phenyl-ethyl)-imidazolin-2-ylidene gold chloride (138). Hydrogen atoms and toluene of crystallisation omitted for reasons of clarity. Thermal ellipsoids at 40% probability level.

Table 6.4.3: Selected bond lengths (Å) and bond angles (°) for 1,3-bis-(1(S)-1-phenyl-ethyl)-imidazolin-2-ylidene gold chloride (138).

Dimension	Value	Dimension	Value
Au1-Cl1	2.285(2) Å	N1-C2	1.397(11) Å
Au1-C1	1.971(7) Å	C3-C2	1.339(12) Å
C1-N1	1.334(10) Å	N1-C1-Au1	129.9(6) °
C1-N2	1.372(10) Å	N1-C1-N2	104.2(6) °
N2-C3	1.388(11) Å	C11-Au1-C1	175.1(2) °

Table 6.4.4: Crystallographic data for 1,3-bis-(1(S)-1-phenyl-ethyl)-imidazolin-2-ylidene gold chloride (138).

Formula	(C ₁₉ H ₂₀ AuClN ₂) ₃ C ₇ H ₈	T (K)	150(2)
Formula Weight	1618.49	D_c (g cm⁻³)	1.757
Crystal System	monoclinic	Crystal Size (mm)	0.20 x 0.10 x 0.05
Space group	<i>C121</i>	Cu K_a λ (Å)	1.54178
a (Å)	17.3720(4)	Total reflections	52153
b (Å)	10.4063(2)	Unique reflections (R_{int})	11399 (0.0413)
c (Å)	33.8614(7)	Goodness of Fit on F²	1.118
α (°)	90.00	Observed Reflections [I > 2σ(I)]	11363
β (°)	91.3460(10)	Final R indices [I > 2σ(I)]	R 0.0413 wR ₂ 0.1076
γ (°)	90.00	Parameters	693
Z	4	S	1.113
V (Å³)	6119.7(2)	Flack x	0.097(11)

In the extended structure **138** is associated into dimer pairs, see Figure 6.4.3. The dimers are separated by a toluene of crystallisation. Between the dimers short Au—Au distances of *ca.* 3.4 Å are observed, well within the acceptable range for aurophilic contacts.²⁷ Also present are intramolecular hydrogen bonding interactions between chlorides and adjacent hydrogen atoms. H—Cl distances of ~ 2.9 Å are within the sum of the van der Waals radii for the corresponding atoms.¹⁹⁹

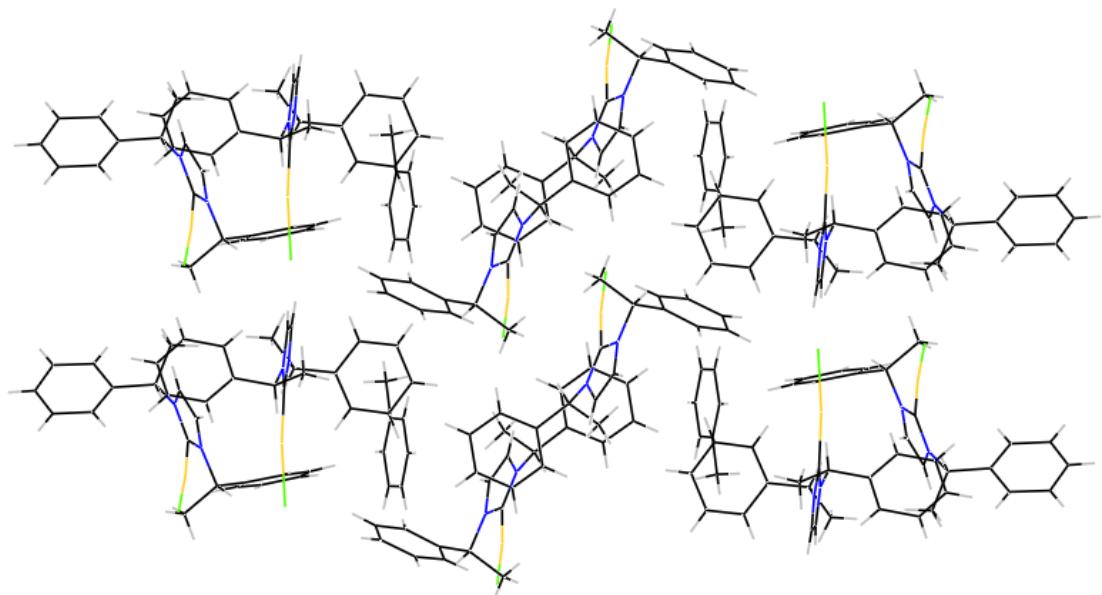


Figure 6.4.3: Extended structure of **138** viewed down the **b** axis.

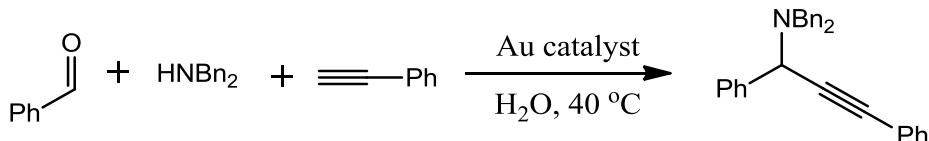
6.5 Screening of chiral gold complexes in A³-coupling reactions

With the chiral gold complexes **126**, **127**, **128** and **138** in hand, these were next investigated in the A³-coupling reaction, with a view to developing enantioselective reactions. Chiral compounds **126**, **127** and **128** were found to be effective catalysts for the A³-reaction. The catalytic activity of **126** was found to be the same as that for achiral [AuCl₂(η²-C,N-C₆H₄-2-CH₂NMe₂)] (**8a**), for all the screened couplings listed in Table 5.6.1. Generally all three of the gold(I) complexes screened showed poorer activity in A³-coupling reactions, in H₂O, when compared to gold(III) complexes over a 24 hour period. While **127** and **128** did catalyse the A³-reaction they were found to be much less effective, requiring higher catalyst loadings (3 mol% and 2 mol% respectively), and extended reaction times (336 hours and 168 hours respectively) to afford similar conversions. The chiral gold NHC complex **138** was found to have a very low catalytic activity for the A³-reaction in water, with low conversions (~6%) even after prolonged reaction times.

Attempts to separate the two propargylic amine enantiomers formed from the coupling reactions in Table 5.6.1, entries 1-3, were unsuccessful. However it was found that when dibenzylamine was reacted with phenylacetylene and benzaldehyde, the coupling reaction proceeded smoothly and baseline separation of the enantiomers could be achieved by chiral HPLC using a CHIRALPAK AD-H or CHIRALPAK IA column and eluting with

hexane/ⁱPrOH (Table 6.5.1). As can be seen from Table 6.5.1 none of the chiral gold complexes resulted in any discernible enantioselectivity as shown by HPLC, and the reaction afforded a racemic mixture of products, see Figure 6.5.1 for copies of the HPLC traces.

Table 6.5.1: Coupling reaction between benzaldehyde, phenylacetylene and dibenzylamine catalysed by range of chiral Au complexes.



Entry	Catalyst	Loading(mol%)/ reaction time (h)	Conversion (%) ^a	Yield(%) ^b	ee (%) ^c
1	8a	1 mol%/ 24 h	97	85	0
2	126	1 mol%/ 24 h	97	85	0
3	127	3 mol%/ 336 h	44	-	0
4	128	2 mol%/ 168 h	55	-	0
5	138	2 mol%/ 168 h	6	-	0

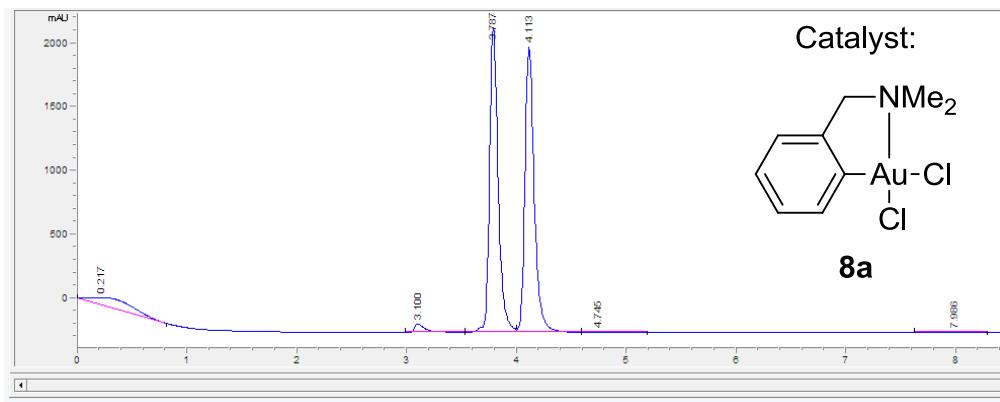
Reaction conditions: 1 mmol aldehyde, 1.1 mmol amine, 1.5 mmol alkyne, Au catalyst, H₂O, 40 °C.

^a Conversion determined by ¹H NMR analysis of crude reaction mixtures based benzaldehyde conversion.

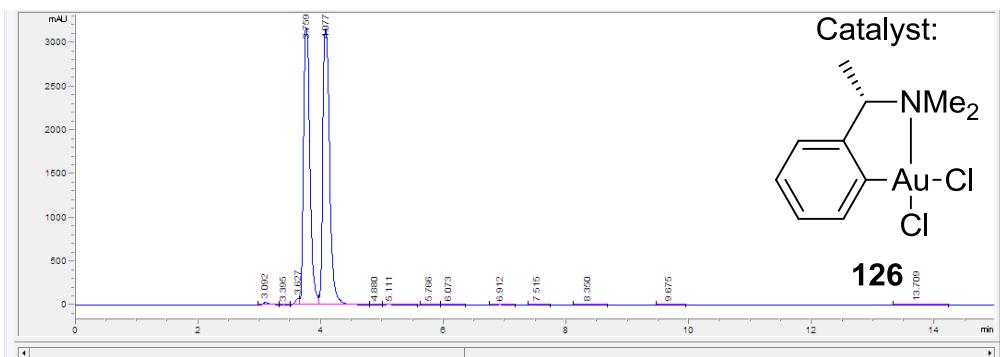
^b Isolated yield.

^c enantiomeric excess determined by chiral HPLC using either CHIRALPAK AD-H or CHIRALPAK IA column eluting with hexane/ⁱPrOH.

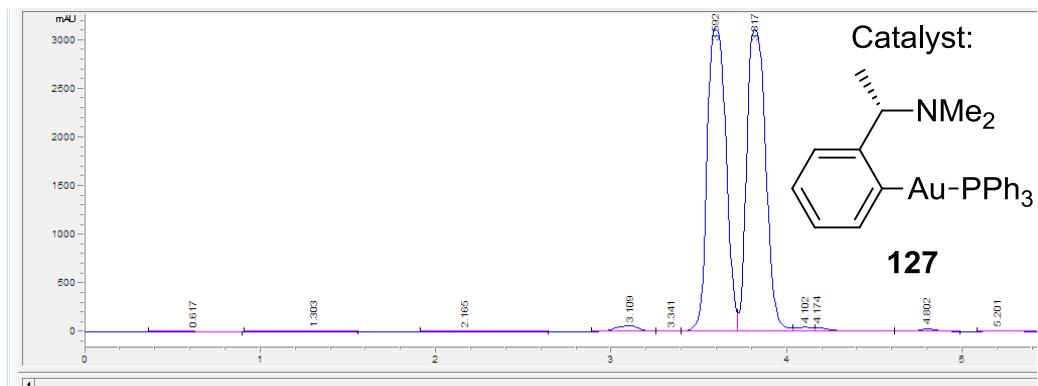
Interestingly it was observed that for the reaction of (*S*)-prolinol with benzaldehyde and phenylacetylene the conversion, yield and diastereoselectivity obtained with the chiral complex **126** was the same (96:4) as that obtained with achiral complex **8a** see Table 5.6.1, entry 5. Additionally with the double coupling reactions (Table 5.6.1, entries 8-12) the same 1:1 ratio of observable diastereomers was obtained. This suggests that the nature of the *N,N*-dimethylbenzylamine ligand bound to the gold(III) centre does not have any effect on the selectivity, therefore the sense of induction is controlled solely by the substrate. However it may be the case that the dimethylamino group with a chiral centre on a distal carbon atom, containing only a methyl substituent, is not an ideal ligand system for attaining asymmetric induction in gold catalysed A³-couplings.



HPLC trace when **8a** is used as catalyst. Conditions: 95 % hexane/ 5 % $^i\text{PrOH}$, 1 mL/min, 5 μL injection, $t_r(\text{min}) = 3.787, 4.113$, Diode array detector (DAD).



HPLC trace when $(S)-[\text{AuCl}_2(\eta^2-\text{C}_6\text{H}_4\text{CH}(\text{Me})\text{NMe}_2)]$ **126** is used as catalyst. Conditions: 95 % hexane/ 5 % $^i\text{PrOH}$, 1 mL/min, 5 μL injection, $t_r(\text{min}) = 3.759, 4.077$, Diode array detector (DAD).



HPLC trace when $(S)-[\text{Au}(\text{PPh}_3)(\eta^1-\text{C}_6\text{H}_4\text{CH}(\text{Me})\text{NMe}_2)]$ **127** is used as catalyst. Conditions: 90 % hexane/ 10 % $^i\text{PrOH}$, 1 mL/min, 5 μL injection, $t_r(\text{min}) = 3.592, 3.817$, Diode array detector (DAD).

Figure 6.5.1: Chiral HPLC traces of the products of the coupling of benzaldehyde, dibenzylamine and phenylacetylene.

The (*R*)-PINAP gold chloride complex **128** gave no asymmetric induction in the A³-reaction in contrast to the CuBr/PINAP catalysed A³-couplings reported by Carreira *et al.*²⁷² where excellent enantioselectivities were obtained.

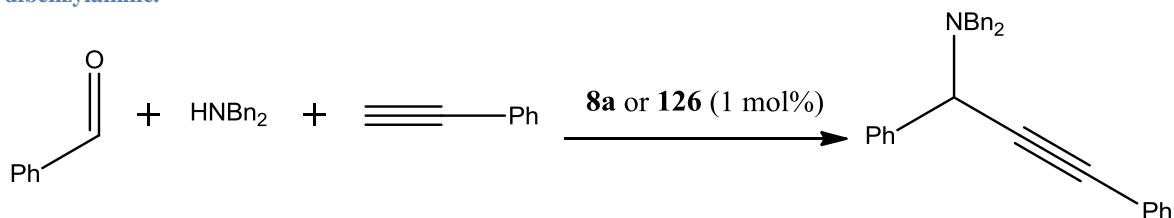
The NHC-gold complex **138** was a particularly poor catalyst with only a 6% conversion after 1 week. It is well-known that gold(I) compounds are more stable than gold(III) complexes,² so on the basis of these preliminary results it was hypothesised that catalytic activity may be related to the stability of the gold pre-catalyst.

Therefore to evaluate this theory a range of different gold compounds were prepared and screened under different conditions in A³-reactions. This would enable optimisation of the catalyst and reaction conditions whilst also giving important insight into the mechanistic aspects of the reaction.

6.6 Reactions in Acetonitrile and ¹H-NMR Experiments

The coupling of benzaldehyde, phenylacetylene and dibenzylamine catalysed by **8a**, was investigated in acetonitrile, due to previous reports by Ortiz *et al.*¹⁸⁹ and Kidwai and co-workers²⁸⁴ that acetonitrile is an effective solvent medium for A³-reactions. It was found that similar conversions to those obtained in H₂O could be achieved, over 24 hours by increasing the catalyst loading and reaction temperature, see Table 6.6.1 for a comparison between H₂O and MeCN as solvent. With both chiral and achiral cyclometallated gold(III) complexes (**126** and [AuCl₂(η²-C₆N-C₆H₄-2-CH₂NMe₂)] (**8a**)) there is no discernible ee observed for the coupling reactions in MeCN.

Table 6.6.1: Comparison between H₂O and MeCN for the coupling of benzaldehyde, phenylacetylene and dibenzylamine.



Catalyst	Solvent	T/(°C)	Loading (mol%)	Reaction time (h)	Conversion (%)	ee%
8a	H ₂ O	40	1	24	97	0
8a	MeCN	60	3	24	95	0
126	H ₂ O	40	1	24	97	0
126	MeCN	60	3	24	93	0

Additionally the product distribution is the same as that observed for reactions in water when (*S*)-prolinol is used as the amine component, giving a diastereomeric ratio of 96:4. Thus it would appear that in the [AuCl₂(η²-C,N-C₆H₄-2-CH₂NMe₂)] (**8a**) catalysed A³-reaction, changing the solvent from H₂O to acetonitrile has no effect on the reaction outcome. The advantage of using MeCN as a solvent is that the substrates, products and gold catalysts have an enhanced solubility compared to the biphasic systems in H₂O. This enables the reaction to be easily followed by *in-situ* NMR experiments, providing insight into the reaction mechanism.

The relative activity of both Na[AuCl₄] ·2H₂O and **8a** was investigated by ¹H-NMR spectroscopy in deuteroacetonitrile (Figure 6.6.1). The experiments were performed by loading benzaldehyde (1 mmol), dibenzylamine (1 mmol), phenylacetylene (1.5 mmol), *d*³-MeCN and gold pre-catalyst (3 mol%) into a J. Young NMR tube under a nitrogen atmosphere. The solution was vigorously shaken and then heated to 60 °C in a Bruker Avance III (400.1 MHz) NMR machine. The first ¹H-NMR spectrum was recorded immediately, and then subsequent spectra were recorded at five minute intervals. For both compounds there appears to be no measurable induction period, on the NMR-timescale, with product formation observable in the first ¹H-NMR spectrum. In addition the rate of product formation, under these coupling conditions, appears to be equivalent within experimental error. This contrasts with results obtained by Ortiz and co-workers¹⁸⁹ who reported that the performance of their C,O cyclometallated phosphinamidic gold(III) complex (**65**, see section 5.5.4) was “superior to that of Au salts in analogous

transformations.” Given that a gold acetylide containing complex is presumed to be the active catalytic species in both gold(III) and gold(I) catalysed reactions^{237,277} it was thought that there might be a common acetylide containing intermediate generated from Na[AuCl₄] · 2H₂O and **8a**. This would then explain the similar ¹H-NMR data collected for both complexes. If there is a common intermediate then the C,N cyclometallating ligand would have to de-complex from the gold centre prior to C-C bond formation. Therefore this could account for the lack of asymmetric induction observed with the chiral complexes **126** and **127**. To test this hypothesis the polymeric acetylide [Au(C≡CPh)]_n (**139**) was synthesised and used in the A³-coupling reaction. **139** was prepared by reacting ClAu(THT) with phenylacetylene and triethylamine in CH₂Cl₂ according to the method outlined by Crowley and co-workers.³⁷⁵ The polymeric product precipitates out from solution during the reaction and can be collected by filtration. **139** was found to be an efficient catalyst for the A³-reaction giving comparable conversions (*ca.* 96%) to **8a** and **126** for the coupling of benzaldehyde, phenylacetylene and piperidine in H₂O at 40 °C. The A³-reaction, catalysed by **139**, was also followed by ¹H-NMR spectroscopy (Figure 6.6.1) and the data was found to mirror that obtained for both **8a** and Na[AuCl₄]. The rate is comparable to the Au(III) complexes screened and again there is no observable induction period. This data suggests that under the studied reaction conditions **8a**, **126**, Na[AuCl₄] and **139** appear to catalyse the A³-coupling reaction through a common intermediate. When the chiral amine (S)-prolinol is used as the amine component, and **139** used as gold pre-catalyst the same ratio of diastereomers is obtained (96:4) as with all the Au complexes screened in this work and in the literature.^{189,276,277} This would suggest that the stereochemical selectivity is invariant with respect to the catalyst system chosen, and the diastereoselectivity is controlled by the substrate and not the gold catalyst. Additionally, the formation of a common achiral catalytically active species, that does not result in asymmetric induction would account for the lack of enantioselectivity observed with all the chiral gold catalysts.

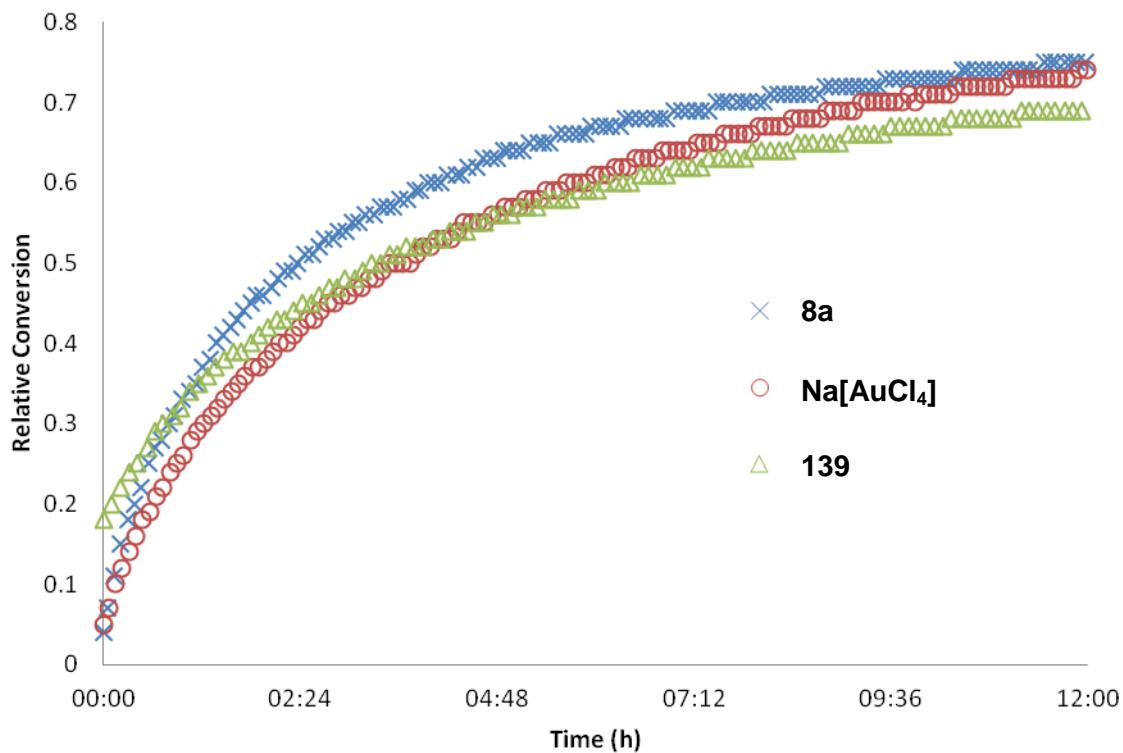
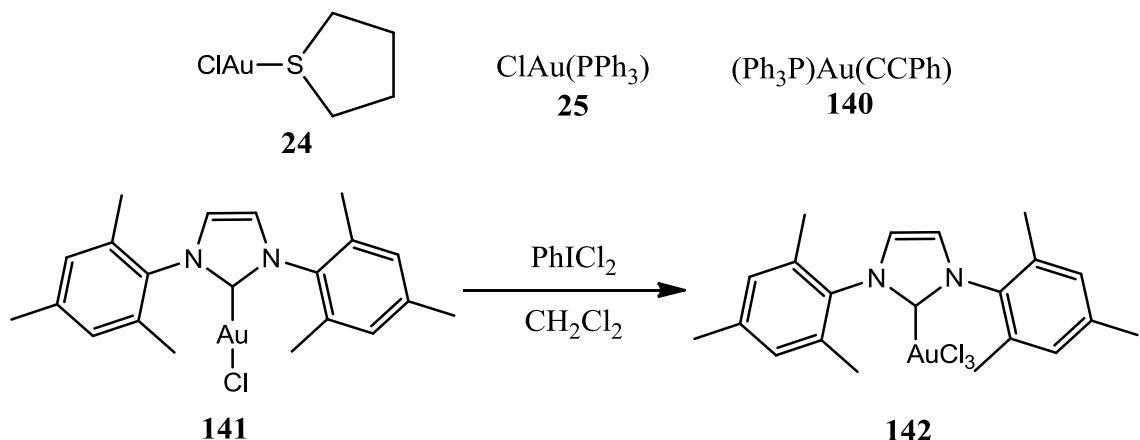


Figure 6.6.1: A plot of relative conversion versus time for A^3 -coupling of benzaldehyde (1 mmol), dibenzylamine (1 mmol) and phenylacetylene (1.5 mmol), d^3 -MeCN, 60 °C, 3 mol% Au catalyst. X= 8a , o = $\text{Na}[\text{AuCl}_4] \cdot 2\text{H}_2\text{O}$, Δ = 139.

6.7 Catalyst and Solvent screening studies

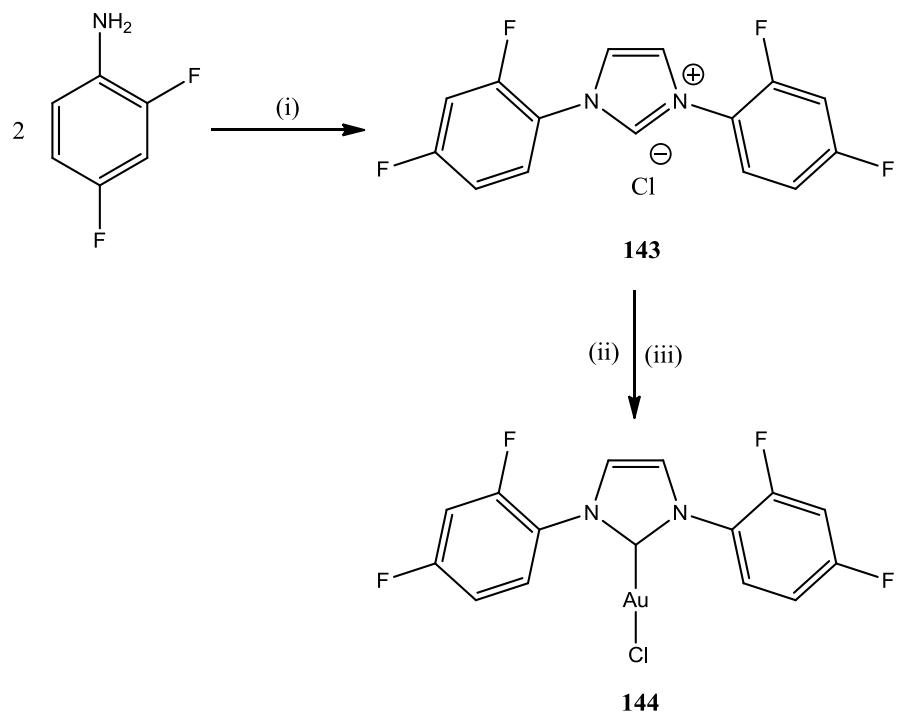
To provide further insight into the reaction mechanism a range of gold complexes were synthesised and screened in the A^3 -reaction (Scheme 6.7.1). ClAu(THT) (**24**) was prepared by reacting $\text{Na}[\text{AuCl}_4] \cdot 2\text{H}_2\text{O}$ with THT in $\text{H}_2\text{O}/\text{EtOH}$.¹⁴¹ ClAu(PPh_3) (**25**) was prepared by reacting ClAu(THT) with PPh_3 in CH_2Cl_2 according to the method described by Omary and co-workers.³⁷⁶ The acetylide ($\text{Ph}_3\text{P}\text{Au}(\text{C}\equiv\text{CPh})$) (**140**) was synthesised by reacting **25** with lithium phenylacetylide in diethyl ether.³⁷⁷ The gold(I) *N*-heterocyclic carbene, 1,3-bis(2,4,6-trimethylphenyl)imidazolin-2-ylidene gold(I) chloride (IMesAuCl, **141**) was prepared by the direct reaction of $\text{K}[\text{AuCl}_4]$ with the imidazolium salt 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride in the presence of 3-chloropyridine and excess K_2CO_3 .^{355,356} **141** could be oxidised with PhICl_2 in CH_2Cl_2 to give the gold(III)-NHC, 1,3-bis(2,4,6-trimethylphenyl)imidazolin-2-ylidene gold(I) trichloride (IMesAuCl₃, **142**), according to Scheme 6.3.4.³⁵⁸



Scheme 6.7.1: Gold complexes prepared and screened in the A³-reaction.

Additionally the novel fluorinated-NHC gold(I) complex, 1,3-bis(2,4-difluorophenyl)imidazolin-2-ylidene gold(I) chloride (**144**) was synthesised for use in A³-reactions (Scheme 6.7.2). The imidazolium precursor **143** was prepared by the one-pot reaction of 2,4-difluoroaniline with glyoxal, paraformaldehyde and HCl in toluene at 100 °C as described by Hope and co-workers.³⁷⁸ The gold complex **144** was synthesised in 81% yield by treating **143** with Ag₂O, followed by *in-situ* transmetallation with ClAu(THT). Disappointingly the direct route to **144**, whereby **143** is heated at 80 °C with K[AuCl₄] and K₂CO₃ in 3-chloropyridine did not yield any of the desired product. Likewise attempted *in-situ* generation of the free carbene by treatment of **143** with potassium *tert*-butoxide and subsequent reaction with ClAu(THT) did not afford the desired gold-NHC product.

The solid state structure of **144** was confirmed by a single crystal X-ray diffraction study. Single crystals were obtained by slow diffusion of hexane into a saturated CH₂Cl₂ solution of **144**. Compound **144** crystallises in the monoclinic space group *P*2₁/*n* with 4 molecules in the asymmetric unit cell. An ORTEP representation of **144** is shown in Figure 6.7.1. The Au1-C1 bond length of 1.982(6) Å is comparable to that reported for other gold(I) NHC complexes.^{348,372–374} There is no apparent intramolecular F-Au interaction in this complex.



Scheme 6.7.2: The preparation of 1,3-bis(2,4-difluorophenyl)imidazolium gold chloride (**144**). (i) glyoxal (1 equiv.), paraformaldehyde (1 equiv), HCl (1 equiv), toluene, 100 °C, 8h; (ii) Ag_2O (0.6 equiv.), CH_2Cl_2 , 24 h; (iii) $\text{ClAu}(\text{THT})$ (1 equiv.), CH_2Cl_2 , 24 h.

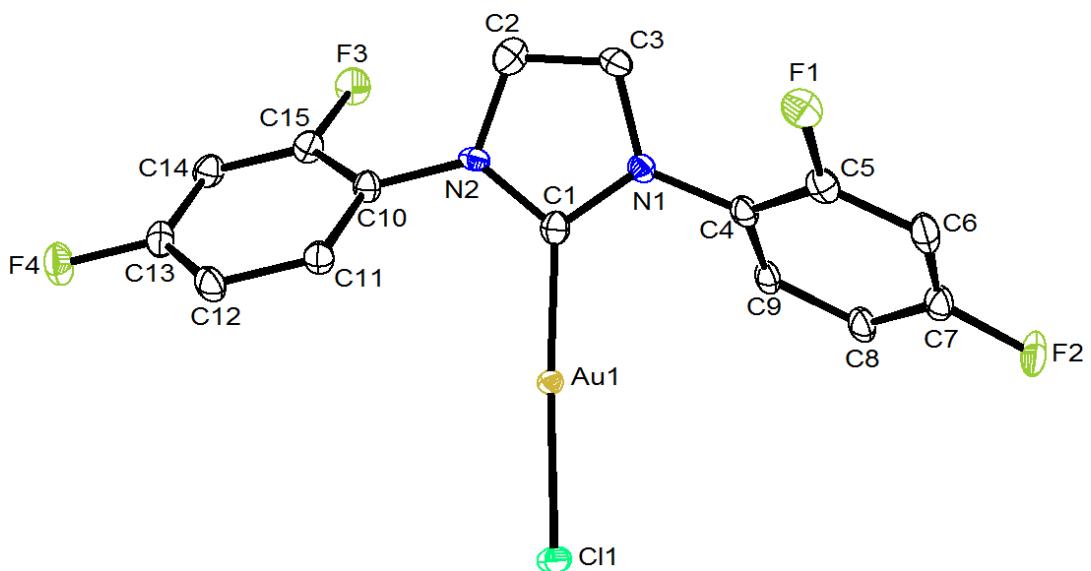


Figure 6.7.1: ORTEP representation of 1,3-bis(2,4-difluorophenyl)imidazolin-2-ylidene gold(I) chloride (**144**). Thermal ellipsoids at 40% probability. Hydrogen atoms are omitted for clarity.

Table 6.7.1: Selected Bond lengths (Å) and bond angles (°) for 1,3-bis(2,4-difluorophenyl)imidazolin-2-ylidene gold(I) chloride (144).

Dimension	Value	Dimension	Value
Au1-C1	1.982(6) Å	N2-C1	1.358(8) Å
Au1-Cl1	2.2746(14) Å	C2-C3	1.348(8) Å
C15-F3	1.348(7) Å	N1-C1-N2	105.0(5) °
C13-F4	1.346(7) Å	N1-C1-Au1	126.3(4) °
N1-C1	1.348(7) Å	C1-Au1-Cl1	176.54(17) °

Table 6.7.2: Crystallographic data for 1,3-bis(2,4-difluorophenyl)imidazolin-2-ylidene gold(I) chloride (144).

Formula	$C_{15}H_8AuClF_4N_2$	T (K)	102(4)
Formula Weight	524.65	$D_c \text{ (g cm}^{-3})$	2.315
Crystal System	Monoclinic	Crystal Size (mm)	0.6 x 0.5 x 0.05
Space group	$P2_1/c$	Mo K_a λ (Å)	0.7107
a (Å)	9.6772(3)	Total reflections	25951
b (Å)	10.2216(3)	Unique reflections (R_{int})	4233 (0.0457)
c (Å)	15.3169(4)	Goodness of Fit on F^2	1.137
α (°)	90	Observed Reflections [$I > 2\sigma(I)$]	3614
β (°)	96.553(3)	Final R indices [$I > 2\sigma(I)$]	$R = 0.0398$ $wR_2 = 0.1233$
γ (°)	90	Parameters	208
Z	4	S	1.137
V (Å³)	1505.20(8)	μ (mm⁻¹)	9.992

Firstly the complexes were screened in the reaction of benzaldehyde and phenylacetylene with dibenzylamine or piperidine in H₂O at 40 °C over 24 hours with 1 mol% loading of the complex (Table 6.7.3, entries 1-8). Complexes **25**, and **140-144** generally display a poor catalytic activity relative to the gold(III) complexes [AuCl₂(η²-C,N-C₆H₄-2-CH₂NMe₂)] (**8a**) and **126**. However ClAu(THT) (**24**) displays excellent activity with a conversion of 99% after 24 hours. This may be due to the relative instability of the complex, so that under the reaction conditions **24** is rapidly transformed into the catalytically active gold-acetylide species. The presence of a triphenylphosphine or *N*-heterocyclic carbene ligand in the complex would appear to severely retard the activity of the catalyst, see entries 2-8. During the course of these studies it was observed that the use of chloroform as solvent in place of water has a dramatic effect on the rate of conversion. The A³-reaction catalysed by ClAuPh₃ (**25**) in a biphasic H₂O system gave a conversion of only 18% after 24 h (entry 2), however on switching to a homogeneous reaction in

chloroform at 60 °C the conversion was increased to 100% over the same time period. The large difference in activity arises because of a solvent effect, and is not due to the increased temperature of the reactions in chloroform. Indeed even when the reaction in water is carried out at 100 °C the reaction does not reach completion, see entries 11-13.

A reaction was carried out with water as solvent, in the presence of concentrated HCl (entry 13). The conversion obtained was, within experimental error, equal to that without the addition of HCl (entry 11). This indicates that the improved rate observed for reactions in chloroform is not due to HCl present in the solvent. Remarkably even the gold-NHC complexes, which have a low activity for A³-reactions in water, display good catalytic activity when the couplings are performed in refluxing chloroform (entries 14-17, 20). PINAPAuCl (**128**) also displays improved conversions (55% vs. 13%) when the A³-reactions are carried out in chloroform instead of water. The two gold(III) *N,N*-dimethylbenzylamine based complexes, **8a** and **126** both give quantitative conversion for the couplings in CHCl₃ (entries 18,19). Screening was also carried out in the fluorinated solvents 2,2,2-trifluoroethanol and α,α,α -trifluorotoluene (entries 26-29) to evaluate the effects of solvent polarity on A³-coupling. Quantitative conversions were obtained for the ClAuPPh₃ (**25**) catalysed couplings in 2,2,2-tifluoroethanol, whereas in α,α,α -trifluorotoluene low conversions of 8% were obtained. Furthermore the use of α,α,α -trifluorotoluene as solvent was found to inhibit the coupling reaction catalysed by [AuCl₂(η^2 -C₆H₄-2-CH₂NMe₂)] (**8a**) with only a 35 % conversion achieved after 24 hours at reflux (entry 29). This compares to reactions in water, acetonitrile and chloroform where essentially quantitative conversion was obtained after 24 hours with **8a** as catalyst. It should be noted that due to the high catalytic activity observed in chloroform for all gold complexes tested thus far, the study requires scrupulous cleaning of glassware in order to prevent false positives. Furthermore in the absence of a gold species the reaction does not turnover in chloroform (entry 30).

When chiral complexes **126-128** and **138** are used as pre-catalysts for the coupling of benzaldehyde, phenylacetylene and dibenzylamine in chloroform there is no discernible enantiomeric excess. In addition when **8a** and **126** are used to catalyse the reaction with the chiral amine component (*S*)-prolinol, in chloroform, the product distribution is the same (96:4) as that for the analogous reactions in water and acetonitrile indicating that the reaction solvents examined have no effect on the product distribution.

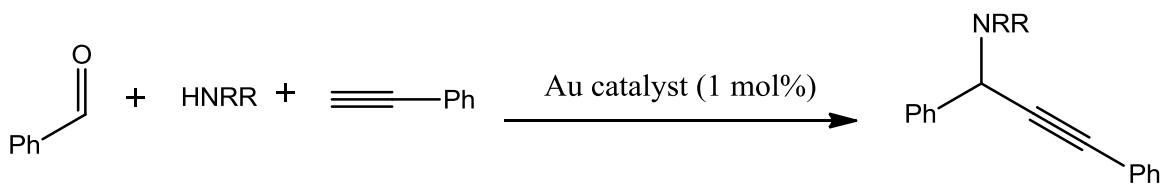


Table 6.7.3: The screening of gold complexes in the A^3 -reaction of benzaldehyde and phenylacetylene with either piperidine or dibenzylamine.

Entry	Catalyst	Solvent/temperature	Time	Amine	Conversion (%) ^a
1	ClAu(THT) (24)	$\text{H}_2\text{O}/40^\circ\text{C}$	24 h	piperidine	99
2	ClAuPPh ₃ (25)	$\text{H}_2\text{O}/40^\circ\text{C}$	24 h	piperidine	18
3	(Ph ₃ P)Au(CCPh) (140)	$\text{H}_2\text{O}/40^\circ\text{C}$	24 h	HNBN ₂	14
4	IMesAuCl (141)	$\text{H}_2\text{O}/40^\circ\text{C}$	24 h	Piperidine	0
5	IMesAuCl (141)	$\text{H}_2\text{O}/40^\circ\text{C}$	24 h	HNBN ₂	2
6	IMesAuCl ₃ (142)	$\text{H}_2\text{O}/40^\circ\text{C}$	24 h	piperidine	8
7	IMesAuCl ₃ (142)	$\text{H}_2\text{O}/40^\circ\text{C}$	24 h	HNBN ₂	0
8	144	$\text{H}_2\text{O}/40^\circ\text{C}$	24 h	HNBN ₂	9
9	ClAuPPh ₃ (25)	CHCl ₃ / reflux	24 h	Piperidine	100
10	ClAuPPh ₃ (25)	CHCl ₃ / reflux	24 h	HNBN ₂	60
11	ClAuPPh ₃ (25)	$\text{H}_2\text{O}/60^\circ\text{C}$	24 h	Piperidine	33
12	ClAuPPh ₃ (25)	$\text{H}_2\text{O}/100^\circ\text{C}$	24 h	Piperidine	75
13 ^b	ClAuPPh ₃ (25)	$\text{H}_2\text{O}/\text{HCl}/60^\circ\text{C}$	24 h	piperidine	29
14	IMesAuCl (141)	CHCl ₃ / reflux	24 h	Piperidine	93
15	IMesAuCl (141)	CHCl ₃ / reflux	24 h	HNBN ₂	95
16	IMesAuCl ₃ (142)	CHCl ₃ / reflux	24 h	HNBN ₂	80
17	144	CHCl ₃ / reflux	24 h	HNBN ₂	65
18	8a	CHCl ₃ / reflux	24 h	HNBN ₂	100
19	126	CHCl ₃ / reflux	24 h	HNBN ₂	100
20	138	$\text{H}_2\text{O}/40^\circ\text{C}$	24 h	HNBN ₂	0
21	138	CHCl ₃ / reflux	24 h	HNBN ₂	40
22	127	$\text{H}_2\text{O}/40^\circ\text{C}$	336 h	HNBN ₂	45
23	127	CHCl ₃ / reflux	24 h	HNBN ₂	45
24	PINAPAuCl (128)	$\text{H}_2\text{O}/40^\circ\text{C}$	24 h	HNBN ₂	13
25	PINAPAuCl (128)	CHCl ₃ / reflux	24 h	HNBN ₂	55
26	ClAuPPh ₃ (25)	CF ₃ CH ₂ OH/60°C	24 h	piperidine	100
27	ClAuPPh ₃ (25)	CF ₃ CH ₂ OH/60°C	24 h	HNBN ₂	100
28	ClAuPPh ₃ (25)	Ar-CF ₃ /60°C	24 h	HNBN ₂	8
29	8a	Ar-CF ₃ / reflux	24 h	HNBN ₂	35
30	uncatalysed	CHCl ₃	24 h	Piperidine or HNBN ₂	0

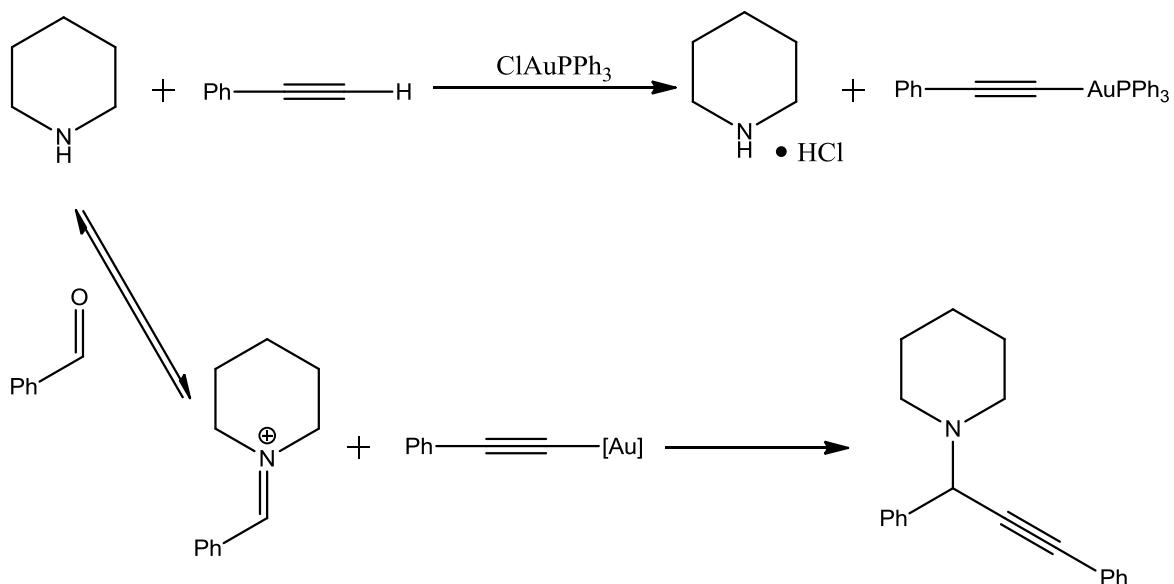
Reaction conditions: benzaldehyde (1 mmol), phenylacetylene (1.5 mmol) and either dibenzylamine (1.1 mmol) or piperidine (1.1 mmol), 1 mol% Au catalyst, H_2O (2 mL) or CHCl₃ (2 mL). Reactions in H_2O carried out under N₂.

^a Conversion determined by ¹H NMR analysis of crude reaction mixtures based on benzaldehyde conversion.

^b 1 drop of conc. HCl was added to the reaction mixture.

6.8 Monitoring reaction by $^{31}\text{P}\{^1\text{H}\}$ and $^{19}\text{F}\{^1\text{H}\}$ NMR spectroscopy

The catalytic activity of gold complexes containing phosphine and *N*-heterocyclic carbene ligands appears to be severely retarded, in water, relative to complexes without these types of ligand (Table 6.7.3). To determine why this is the case the A³-reactions catalysed by ClAuPPh₃ (**25**), (Ph₃P)Au(C≡CPh) (**140**), (S)-[Au(PPh₃)(η¹-C₆H₄CH(Me)NMe₂)] (**127**) and 1,3-bis(2,4-difluorophenyl)imidazolin-2-ylidene gold(I) chloride (**144**) were followed by $^{31}\text{P}\{^1\text{H}\}$ and $^{19}\text{F}\{^1\text{H}\}$ NMR spectroscopy respectively. In all the reactions catalysed by phosphine containing complexes the appearance of signals at ~42 ppm and ~29 ppm is observed in the $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum. The resonance at 42 ppm corresponds to (Ph₃P)Au(C≡CPh) (**140**), while the resonance at 29 ppm corresponds to triphenyl phosphine oxide (OPPh₃). The identity of the signals was established through spiking of the reaction mixtures with pure samples of **140** and OPPh₃. For ClAuPPh₃ (**25**), when the reaction was carried out in the absence of aldehyde, with just piperidine and phenylacetylene, the acetylidic complex (Ph₃P)Au(C≡CPh) (**140**) is rapidly formed along with the ammonium salt. As imminium ion formation is an equilibrium process it is likely that the acid/base reaction between the alkyne and amine is faster than gold activation of the terminal C-H bond in the alkyne. The deprotonated alkyne would then bind to the gold center, and the hydrochloride salt of the amine would be formed. This would then force the equilibrium for imminium ion formation in the less favoured direction (Scheme 6.8.1).



Scheme 6.8.1: Acid/base reaction between alkyne and amine rather than C-H activation of the terminal alkyne bond.

In the case of the A³-coupling of benzaldehyde, dibenzylamine and phenylacetylene catalysed by **127** a similar process occurs. The formation of (Ph₃P)Au(C≡CPh) (**140**) and OPPh₃ is observed in the ³¹P{¹H} NMR spectrum along with complete disappearance of the signal for **127** (Figure 6.8.1). The loss of the chiral cyclometallated ligand is presumably facilitated by the non-coordination of the NMe₂ group. This would explain why no asymmetric induction is obtained with this catalyst, as losing the chiral ligand results in the formation of a common achiral intermediate.

Table 6.8.1: ³¹P{¹H} and ¹⁹F{¹H}-NMR signals observed after A³-coupling.

Entry	Reaction conditions	Catalyst	³¹ P{ ¹ H} shift of catalyst/ ppm	Conversion (%)	³¹ P{ ¹ H} shifts after A ³ -coupling / ppm
1	piperidine, CHCl ₃ , reflux	ClAuPPh ₃ (25)	33.19	100	42.35, 29.11
2	piperidine, H ₂ O, 40 °C	ClAuPPh ₃ (25)	33.19	18	42.31
3	HN(Bn) ₂ , H ₂ O, 40 °C	Ph ₃ PAuCCPh (140)	42.28	12	42.37
4	HN(Bn) ₂ , CHCl ₃ , reflux	127	44.09	45	42.36, 29.33

Reaction conditions: benzaldehyde (1 mmol), phenylacetylene (1.5 mmol), dibenzylamine or piperidine (1 mmol), 1 mol% Au catalyst.

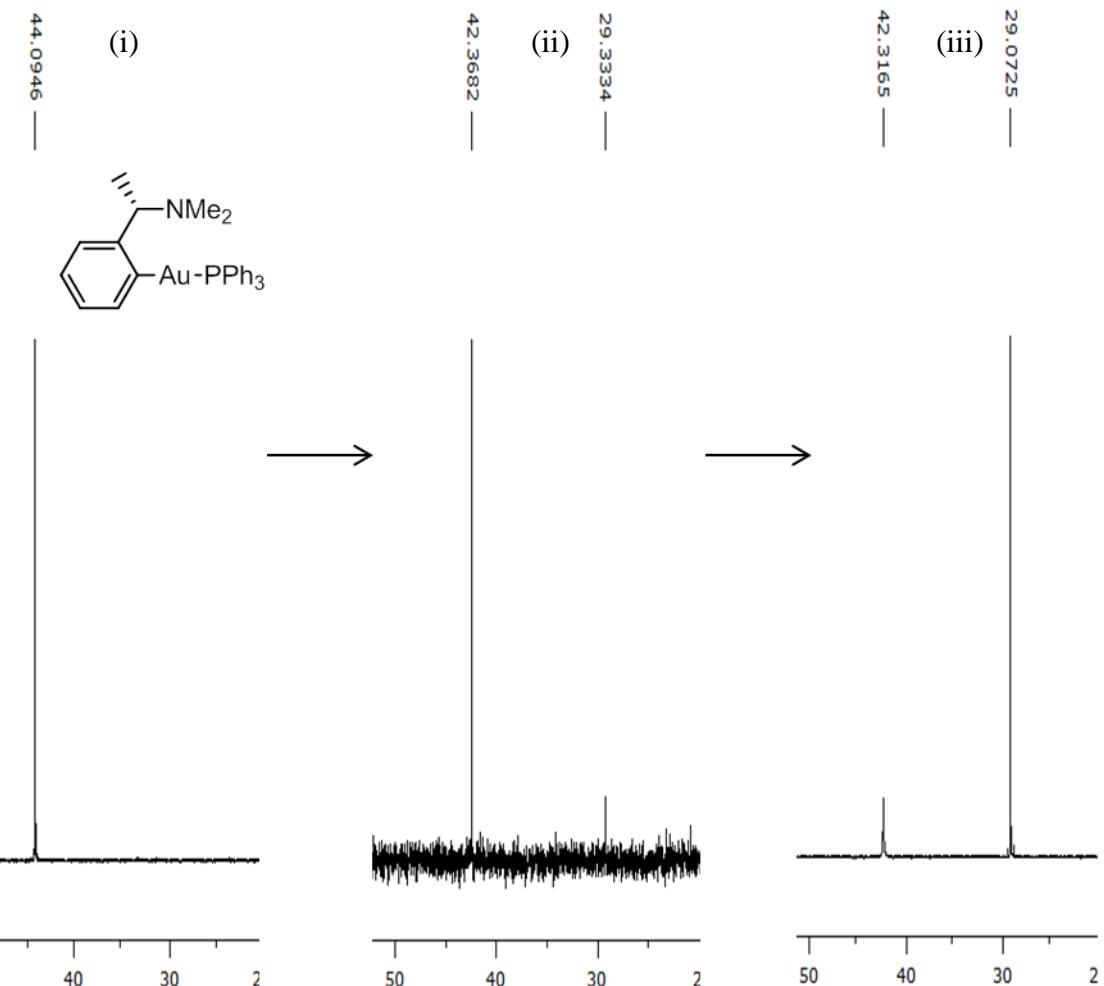


Figure 6.8.1: $^{31}\text{P}\{^1\text{H}\}$ NMR spectra illustrating decomposition of catalyst 127 into acetylide ($\text{Ph}_3\text{PAu}(\text{C}\equiv\text{CPh})$) (140) and OPPh_3 during the course of the A^3 -coupling of dibenzylamine, benzaldehyde and phenylacetylene. (i) : $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum of pure 127, singlet at 44.1 ppm; (ii) : $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum of crude reaction mixture after A^3 -coupling with 127; (iii) : $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum of crude reaction mixture spiked with pure samples of OPPh_3 and $(\text{Ph}_3\text{PAu}(\text{C}\equiv\text{CPh}))$ (140).

The decreased rate for reactions containing PPh_3 ligands can be explained by the increased stability of the gold-acetylide intermediate upon binding of the phosphine ligand to the active gold center. Therefore it would appear that phosphines in the reaction mixture act as a sink for the catalytically active species. Presumably to achieve the catalytically active species the phosphine must be lost from the $(\text{Ph}_3\text{PAu}(\text{C}\equiv\text{CPh}))$ (140) intermediate. Subsequent oxidation of the free phosphine would prevent re-coordination and yield the catalytically active species. To test this hypothesis PPh_3 was added to the coupling reactions effected by the gold(III) complexes $[\text{AuCl}_2(\eta^2\text{-C}_6\text{H}_4\text{-2-CH}_2\text{NMe}_2)]$ (8a) and $\text{Na}[\text{AuCl}_4]\cdot 2\text{H}_2\text{O}$ and found to retard them significantly, see Table 6.8.2. With 1 mol% of PPh_3 added to the reactions the conversion after 24 hours with both 8a and $\text{Na}[\text{AuCl}_4]\cdot 2\text{H}_2\text{O}$ are reduced from near quantitative conversions to 77% and 31% respectively. In the

$^{31}\text{P}\{\text{H}\}$ NMR spectrum of the crude reaction mixtures a signal corresponding to $(\text{Ph}_3\text{P})\text{Au}(\text{C}\equiv\text{CPh})$ (**140**) is clearly seen at 42 ppm, and indicates that the gold(III) complexes are reduced to gold(I) species under the reaction conditions. When 10 mol% of PPh_3 is added to the reaction no conversion to propargylamine is observed after 24 hours (entries 2,3,5). In the $^{31}\text{P}\{\text{H}\}$ NMR spectrum of the crude reaction mixture a signal at 29 ppm, corresponding to OPPh_3 , is observed along with a broad resonance centred around -1 ppm, see Figure 6.8.2. This broad resonance most likely arises due to rapid phosphine exchange between free triphenylphosphine (typical $^{31}\text{P}\{\text{H}\}$ NMR shift \sim -8 ppm) and $(\text{Ph}_3\text{P})\text{Au}(\text{C}\equiv\text{CPh})$ (**140**) ($^{31}\text{P}\{\text{H}\}$ NMR shift \sim 42 ppm). Attempts to confirm this by resolving the signal at low temperature (*ca.* -80 °C) were however unsuccessful.

Table 6.8.2: Addition of phosphines to A³-reactions catalysed by $[\text{AuCl}_2(\eta^2\text{-C}_6\text{NMe}_2)]$ (8a**) and $\text{Na}[\text{AuCl}_4]\cdot 2\text{H}_2\text{O}$.**

Entry	Catalyst (mol%)	Phosphine (mol%)	Reaction time	Conversion (%)
1	8a (1 mol%)	PPh_3 (1 mol%)	24 h	77
2	8a (1 mol%)	PPh_3 (10 mol%)	24 h	0
3	8a (1 mol%)	PPh_3 (10 mol%)	168 h	10
4	$\text{Na}[\text{AuCl}_4]\cdot 2\text{H}_2\text{O}$ (1 mol%)	PPh_3 (1 mol%)	24 h	31
5	$\text{Na}[\text{AuCl}_4]\cdot 2\text{H}_2\text{O}$ (1 mol%)	PPh_3 (10 mol%)	24 h	0
6	8a (1 mol%)	dppe (1 mol%)	24 h	6
7	8a (1 mol%)	(-)DIOP (1 mol%)	24 h	9

Reaction conditions: benzaldehyde (1 mmol), dibenzylamine (1 mmol), phenylacetylene (1.5 mmol), Au catalyst (mol%), H_2O , 40 °C.

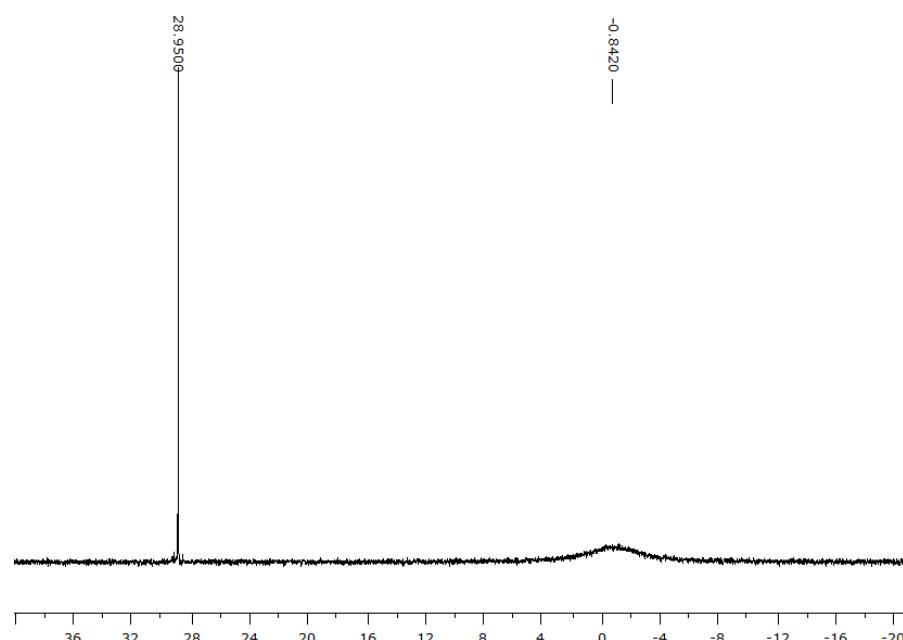


Figure 6.8.2: $^{31}\text{P}\{\text{H}\}$ NMR spectrum of the crude reaction mixture after catalysis with $\text{Na}[\text{AuCl}_4]\cdot 2\text{H}_2\text{O}$ (1 mol%) and PPh_3 (10 mol%).

Addition of one equivalent of the bidentate phosphines 1,2-bis(diphenylphosphino)ethane (dppe) or (*-*)-2,3-*O*-*i*-propylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane ((*-*)-DIOP) also results in reduced conversions (entries 6,7). In the $^{31}\text{P}\{\text{H}\}$ NMR spectrum new resonances appear around 20 ppm which correlate with the formation of stable tetrahedral gold(I) cations $[\text{Au}(\text{L-L})_2]^+$.³⁷⁹ Even when the reaction time is extended to seven days no appreciable conversion is observed.

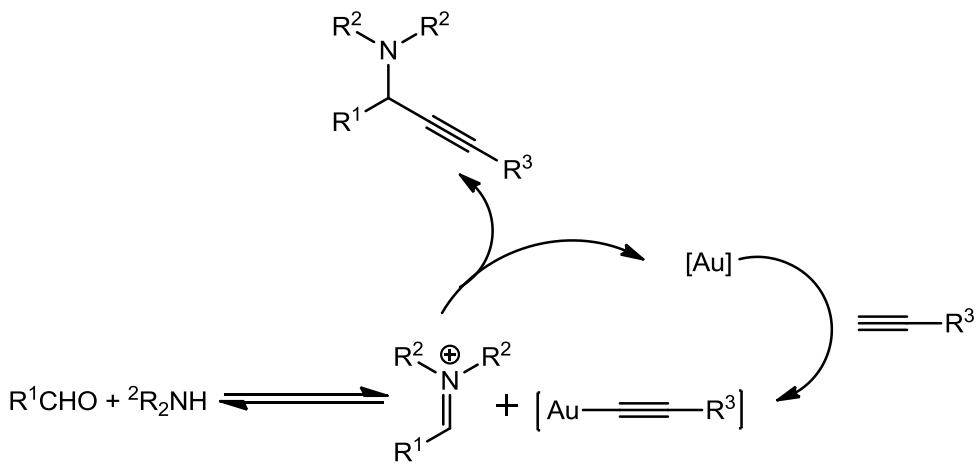
In the case of the fluorinated *N*-heterocyclic carbene complex **144** two new species are observed in the $^{19}\text{F}\{\text{H}\}$ NMR spectrum of the crude reaction mixture, along with the complete disappearance of signals corresponding to **144** (this was again confirmed by spiking experiments). If the reaction proceeds in an analogous route to the gold(I) phosphine complexes, which is not unreasonable considering the similarities between *N*-heterocyclic carbene ligands and phosphine ligands,^{332,380} then one set of doublets corresponds to the acetylidyde $(\text{PhCC})\text{Au}(\text{NHC})$ whilst the other doublet would correspond to the free carbene.

Table 6.8.3: $^{19}\text{F}\{\text{H}\}$ NMR data after A³-coupling with **144**.

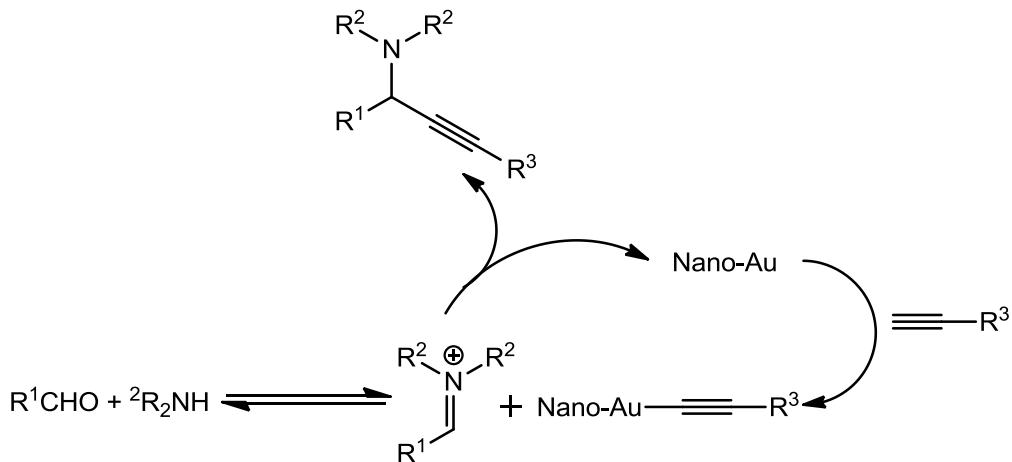
Reaction conditions	Catalyst	$^{19}\text{F}\{\text{H}\}$ shift of catalyst/ppm	Conversion (%)	$^{19}\text{F}\{\text{H}\}$ shift of crude reaction mixture / ppm
HNBN ₂ , CHCl ₃ , reflux	144	-105.0 (d, $^4J_{\text{FF}}= 8.3$ Hz), -117.9 (d, $^4J_{\text{FF}}= 8.3$ Hz).	65	-105.46 (d, $^4J_{\text{FF}}= 8$ Hz), -118.16 (d, $^4J_{\text{FF}}= 8$ Hz) and -104.61 (d, $^4J_{\text{FF}}= 8.2$ Hz), -117.62 (d, $^4J_{\text{FF}}= 8.2$ Hz).

Reaction conditions: benzaldehyde (1 mmol), phenylacetylene (1.5 mmol), dibenzylamine or piperidine (1 mmol), 1 mol% Au catalyst.

Taken together the data collected suggests that a common catalytically active species is formed from all the gold complexes. The species is likely to be an intermediate gold acetylidyde formed *in-situ*, as evidenced from the addition of PPh₃ to couplings catalysed by $[\text{AuCl}_2(\eta^2\text{-C}_6\text{H}_4\text{-2-CH}_2\text{NMe}_2)]$ (**8a**) and Na[AuCl₄] · 2H₂O. Therefore it is possible that the active species is a monomeric gold acetylidyde as in Scheme 6.8.2, or an analogous system based on a gold nanoparticle as in Scheme 6.8.3.



Scheme 6.8.2: A^3 -coupling catalysed by monomeric gold acetylide.



Scheme 6.8.3: A^3 -reaction catalysed by gold nanoparticles.

Differentiating metal-complex homogeneous catalysis, as in a monomeric gold acetylide catalysed process, from gold nanoparticle catalysis is particularly challenging.³⁸¹ A number of methods have been used, mainly in hydrogenation catalysis, in an attempt to determine the identity of the catalytically active species. Amongst the techniques utilised is the mercury poisoning or Whitesides test.³⁸² It is well-known that elemental mercury poisons metal particle heterogeneous catalysts by forming amalgams with metals.^{383,384} Therefore, given the recent developments in the field of mercury detection utilising gold nanoparticles^{385–387} it was postulated that the mercury poisoning test could provide mechanistic insight into gold-catalysed A^3 -coupling. Typically the test is performed by adding an excess of $\text{Hg}(0)$ to the reaction mixture; if the reaction is inhibited then this provides evidence for a heterogeneous/nanoparticle catalysed process. It should be noted

that no single test exists for the determination of whether a reaction is catalysed homogeneously or heterogeneously, instead a combination of experiments are used to reach a conclusion about the state of the active species.³⁸¹ Unfortunately elemental mercury was found to react with pre-catalyst $[\text{AuCl}_2(\eta^2\text{-C}_6\text{N-C}_6\text{H}_4\text{-2-CH}_2\text{NMe}_2)]$ (**8a**) at room temperature to give the organomercurials, $[\text{HgCl}(\text{2-C}_6\text{H}_4\text{CH}_2\text{NMe}_2)]$ or $[\text{Hg}(\text{2-C}_6\text{H}_4\text{CH}_2\text{NMe}_2)_2]$. This means that the Hg(0) poisoning test is not applicable to this system.

7 Conclusion

This thesis describes a new route to cyclometallated gold(III) complexes containing a functionalised dimethylbenzylamine ligand. Gold complexes [2-Me₂NCH₂-C₆H₄AuCl₂] (**8a**), [2-Me₂NCH₂-5-CH₃-C₆H₃AuCl₂] (**49**), [2-Me₂NCH₂-5-CF₃-C₆H₃AuCl₂] (**50**) and [2-Me₂NCH₂-5-OMe-C₆H₃AuCl₂] (**51**) have been prepared via transmetallation from boroxines (**45-48**) to sodium tetrachloroaurate in aqueous acetonitrile. The yields are comparable to those obtained from the traditional organomercury route, however the new method is advantageous, as non-toxic reagents are utilised, and therefore could be used in the preparation of gold(III) drugs. Further development of the methodology is required so that the reaction can be extended to different cyclometallating ligand systems.

The preparation of dinuclear Sn(IV) complexes, 1,4-(SnPh₃)₂-2,5-(NMe₂CH₂)₂-C₆H₂ (**66**), 1,4-(SnMe₃)₂-2,5-(NMe₂CH₂)₂-C₆H₂ (**67**) and 1,4-(SnMe₂Cl)₂-2,5-(NMe₂CH₂)₂-C₆H₂ (**68**) has been achieved by *in-situ* quenching of the dilithium reagent 1,4-(Li)₂-2,5-(NMe₂CH₂)₂-C₆H₂ (**57**) (formed by reaction of 1,4-dibromo-2,5-bis{(dimethylamino)methyl}-benzene (**56**) with two equivalents of *n*-BuLi in diethyl ether at -78 °C) with the appropriate tin precursor. The new compounds have been fully characterised by NMR spectroscopy, elemental analysis and single crystal X-ray diffraction studies. Intramolecular coordination of nitrogen to tin in solution has been probed by ¹¹⁹Sn{¹H} NMR spectroscopy. It was found that in **66** and **67** only a weak N → Sn interaction exists, whereas strong intramolecular N → Sn coordination is present in **68**. Additionally quenching of 1,4-(Li)₂-2,5-(NMe₂CH₂)₂-C₆H₂ (**57**) with 2 equivalents of PPh₂Cl resulted in the formation of bisphosphine 1,4-(PPh₂)₂-2,5-(NMe₂CH₂)₂-C₆H₂ (**69**). It was found that lithiation of **56** with two equivalents of *n*-BuLi proceeds to ~50% completion, under the conditions used. Reaction of **69** with 2 equivalents of ClAu(THT) gives after workup 1,4-(AuClPPh₂)₂-2,5-(NMe₂CH₂)₂-C₆H₂ (**70**). **70** has been fully characterised, including determination of the structure in the solid state.

A novel digold(III) complex 1,4-(AuCl₂)₂-2,5-(Me₂NCH₂)₂-C₆H₂ (**71**) has been synthesised *via* transmetallation from 1,4-(SnMe₂Cl)₂-2,5-(NMe₂CH₂)₂-C₆H₂ (**70**) to two equivalents of sodium tetrachloroaurate in refluxing acetonitrile. **71** was found to be relatively insoluble in common laboratory solvents, so formation was confirmed by elemental analysis.

Reaction of **71** with 4.6 equivalents of silver acetate resulted in exchange of all chloride ligands for acetate ligands. The acetate compound 1,4-(Au{O₂CMe₂})₂-2,5-(NMe₂CH₂)-C₆H₂ (**90**) had improved solubility and so was characterised by ¹H and ¹³C{¹H}-NMR spectroscopy. However **90** decomposed rapidly preventing further characterisation. Further work could involve exchange of the chlorides with bidentate ligands to give complexes that have improved stability and solubility so that characterisation by single crystal X-ray diffraction can be achieved.

A range of gold compounds have been investigated for their catalytic activity in the A³-reaction of aldehydes, amines and alkynes. [AuCl₂(η²-C,N-C₆H₄CH₂NMe₂)] (**8a**) (1 mol%) was found to be an effective catalyst for A³-coupling, in water at 40 °C, giving quantitative conversion after 24 hours. A variety of substrates could be coupled, and novel ‘double-A³’-couplings could also be carried out in 48 hours (Table 5.6.1). Coupling of cyclohexanone, morpholine and phenylacetylene was also achieved using **8a** (5 mol%) under neat conditions.

The chiral complexes (S)-[AuCl₂(η²-C,N-C₆H₄CH(Me)NMe₂)] (**126**), (S)-[Au(PPh₃)(η¹-C₆H₄CH(Me)NMe₂)] (**127**) and 1,3-bis((S)-1'-phenylethyl) imidazolin-2-ylidene gold chloride (**138**) were prepared and fully characterised by multinuclear NMR spectroscopy and X-ray diffraction studies. Screening in the A³-reaction of benzaldehyde, dibenzylamine and phenylacetylene was found to give no discernible ee for any of the chiral complexes tested. Gold(I) complexes were generally found to be less active than gold(III) compounds. Using acetonitrile as solvent gave broadly similar results to couplings in H₂O when catalyst loading was increased to 3 mol% and the temperature was increased to 60 °C. The reaction of benzaldehyde, dibenzylamine and phenylacetylene in acetonitrile, catalysed by Na[AuCl₄], **8a** and [AuCCPh]_n (**139**) was monitored by ¹H NMR spectroscopy. All three complexes displayed broadly the same rate of product formation, within experimental error, suggesting that under the studied reaction conditions compounds Na[AuCl₄], **8a** and **41** catalyse the A³-reaction through a common intermediate. Additionally when the chiral amine (S)-prolinol was used as the amine component **126**, **8a** and **139** were found to give the same diastereoselectivity (96:4) as that reported for gold salen complex **111** and 2-phenylpyridine complex **4**.^{276,277}

Solvent screening studies revealed chloroform and 2,2,2-trifluoroethanol to be the best solvents giving the highest conversions with a variety of gold complexes after 24 hours.

Even ClAuPPh₃ (**25**) and *N*-heterocyclic carbene complexes 1,3-bis((*S*)-1'-phenylethyl)imidazolin-2-ylidene gold chloride (**138**) and 1,3-bis(2,4-difluorophenyl)imidazolin-2-ylidene gold(I) chloride (**144**) which gave low conversions (20% \leq) in H₂O afforded greatly improved conversions (> 50%) when the reaction was carried out in CHCl₃. The variation of solvent had no effect on the selectivity of the coupling reaction for any of the complexes tested. The use of **25**, **127** and **144** enabled monitoring of the pre-catalyst by ³¹P{¹H} and ¹⁹F{¹H}-NMR spectroscopy respectively. For ClAuPPh₃ (**25**) and (*S*)-[Au(PPh₃)(η^1 -C₆H₄CH(Me)NMe₂)] (**127**) the appearance of resonances at ~29 ppm and 42 ppm was observed in the ³¹P{¹H}-NMR spectra along with the complete disappearance of **25** and **127**. The resonance at 29 ppm was subsequently identified as triphenylphosphine oxide while that at 42 ppm was identified as (Ph₃P)Au(C≡CPh) (**140**). The loss of the chiral cyclometallating ligand in (*S*)-[Au(PPh₃)(η^1 -C₆H₄CH(Me)NMe₂)] (**127**) would also explain why no asymmetric induction is observed in the A³-reaction. With 1,3-bis(2,4-difluorophenyl)imidazolin-2-ylidene gold(I) chloride (**144**) complete disappearance of the signal corresponding to the starting complex is observed. The data indicates that the gold complexes are pre-catalysts and that during the A³-coupling a common catalytically active species is formed. The addition of PPh₃ to A³-couplings effected by Na[AuCl₄] and **8a** was found to significantly retard them. In the ³¹P {¹H} NMR spectrum of the crude reaction mixtures a signal at 42 ppm that corresponds to **140** is clearly seen and indicates the gold(III) species is reduced to gold(I) under the reaction conditions. A similar retardation is observed when either the bidentate ligands dppe or (-)-DIOP are used. The data suggests that the mode of gold catalysed A³-coupling to produce propargylic amines in water is significantly different to that reported for copper. This indicates that chiral cyclometallated ligands are not suitable promoters of asymmetric induction as they appear to be decomplexed during the reduction process from gold(III) to give a catalytically active gold species. Overall the data presented provides mechanistic insight into the development of asymmetric A³-coupling reactions in water. It gives strong evidence for the generation of a single universal catalytically active species, from both gold(III) and gold(I) precursors, that contain an acetylide ligand. The species could either be monomeric or nanoparticulate in nature. To investigate this further TEM (transmission electron microscopy) or an analogous technique could be used to probe the crude reaction mixtures for the presence of gold nanoparticles. Furthermore the coupling of benzaldehyde, dibenzylamine and phenylacetylene, catalysed by gold nanoparticles, could be monitored by ¹H NMR spectroscopy to ascertain if the rate of reaction is the same as that observed for Na[AuCl₄],

8a and **139**. Additionally other structurally diverse chiral gold complexes could be synthesised that incorporate sterically bulky groups in an attempt to achieve gold catalysed AA³-couplings.

8 Experimental

8.1 General Considerations

Where required, solvents were dried by refluxing over an appropriate drying agent: toluene, Na; hexane, NaK; diethylether, NaK; tetrahydrofuran, K; dichloromethane, CaCl₂; acetonitrile, CaCl₂; and distilled under N₂ prior to use. Chemicals and compounds whose syntheses are not mentioned were obtained from commercial sources and used as received. ¹H-NMR spectra were recorded on either a Bruker Avance III (400.1 MHz), a Bruker DPX300 (300 MHz) or a Bruker Avance II+ (500 MHz). ¹³C {¹H} NMR spectra were recorded on either a Bruker Avance III (100.6 MHz), a Bruker DPX300 (75.4 MHz) or a Bruker Avance II+ (126 MHz), and ¹¹B{¹H} NMR spectra were recorded on a Bruker Avance III (128.4 MHz). ³¹P{¹H}-NMR spectra were recorded on a Bruker Avance III(161.9 MHz) and ¹⁹F{¹H} NMR spectra were recorded on a Bruker Avance III (376.5 MHz). ¹H NMR spectra were referenced to the residual protio impurity in the deuterated solvent used and {¹H}¹³C NMR spectra were referenced to the ¹³C signal of the solvent used. ¹¹B{¹H} NMR spectra were referenced externally to boric acid. ¹¹⁹Sn{¹H}, ³¹P{¹H} and ¹⁹F{¹H} NMR spectra were referenced externally to SnMe₄, 85% H₃PO₄ and CFCl₃ respectively. Optical rotation measurements were recorded on an Automatic Polarimeter AA-100. Chiral HPLC was performed on a Agilent 1260 infinity LC system, using a CHIRALPAK AD-H or CHIRALPAK IA column. All air and moisture sensitive procedures were carried out under an atmosphere of argon using standard Schlenk techniques. Elemental analyses were performed by the Microanalytical Service, The University of Manchester, Manchester, UK.

8.1.1 Crystallography

X-ray diffraction data was collected on a Bruker-Nonius Kappa CCD machine using MoK α radiation ($\lambda = 0.71073 \text{ \AA}$) or on an Oxford Excalibur 2 diffractometer, and were corrected for Lorentz, polarisation and absorption using the multi-scan method. The X-ray structural data were solved by direct methods, with full-matrix least-squares refinement of F^2 using the SHELXL³⁸⁸ or SHELXTL³⁸⁸ programs. Non-hydrogen atoms were refined with anisotropic thermal parameters; hydrogen atoms were placed in idealised locations. The programs MERCURY³⁸⁹ and ORTEP¹⁰⁵ were used to investigate the structures and generate the graphical representations.

8.2 Preparation of Organolithium reagents for oxidation experiments

8.2.1 Synthesis of [1-Li-2-OMe-C₆H₄] .n TMEDA (21)

To a Schlenk tube under an atmosphere of argon was added *n*-BuLi (10 mL, 16 mmol, 1.6M in hexanes) and TMEDA (2.4 mL, 16 mmol). The solution was stirred for 10 min, and then anisole (1.7 mL, 16 mmol) added dropwise. The reaction was stirred for 3 hours and the precipitate formed transferred *via* wide-bore cannula to a filtration unit under argon. The filtrate **21** was washed with hexane (3 x 10mL) and dried *in vacuo*. The white solid was then transferred to an MBraun Unilab glovebox. Typical yield 2.5 g, 69%.

The number of moles of TMEDA of crystallisation were calculated by quenching a known mass of **21** with excess ClSiMe₃ in Et₂O and assuming a quantitative conversion to [1-(SiMe₃)-2-OMe-C₆H₄] (**21a**). The formula weight was back calculated using Equation 2.3.1. ¹H NMR (CDCl₃, δ ppm): 7.31 (dd, *J*_{HH} = 7.1, 1.8 Hz, 1H, Ar-H), 7.28-7.24 (m, 1H, Ar-H), 6.87 (td, *J*_{HH} = 7.2, 0.8 Hz, 1H, Ar-H), 6.73 (d, ³*J*_{HH} = 8.1 Hz, 1H, Ar-H), 3.70 (s, 3H, OMe), 0.20 (s, 9H, SiMe₃).

8.2.2 Synthesis of [Li-C₆H₅] .n TMEDA (22)

To a solution of bromobenzene (0.85 mL, 8.0 mmol) in hexane (15 mL) under argon at -78 °C was added *n*-BuLi (5.0 mL, 8.0 mmol, 1.6 M in hexanes). The solution was vigorously stirred for 1 hour and then TMEDA (0.1 mL) was added to effect the precipitation of **22**. The precipitate was transferred to a filtration unit under argon. The filtrate was washed with hexane (3 x 10 mL) and dried *in vacuo*. The white solid was then transferred to an MBraun Unilab glovebox. Typical yield 0.55 g, 81%.

The number of moles of TMEDA of crystallisation were calculated by quenching a known mass of **22** ClSiMe₃ in Et₂O and assuming a quantitative conversion to [(SiMe₃)-C₆H₅] (**22a**). The formula weight was back calculated using Equation 2.3.1. ¹H NMR (CDCl₃, δ ppm): 7.59 - 7.74 (m, 2 H, Ar-H), 7.28 - 7.57 (m, 3 H, Ar-H), 0.35 - 0.49 (s, 9 H, SiMe₃).

8.2.3 Synthesis of [1-Li-4-OMe-C₆H₄] .n TMEDA (23)

4-Bromoanisole (8.0 mL, 63.7 mmol) was added to a Schlenk flask under an atmosphere of dry argon. Hexane (15 mL) was added, the solution cooled to -60 °C, and *n*-BuLi (40 mL, 64 mmol, 1.6 M in hexanes) added. The solution was vigorously stirred for 1 hour and then

TMEDA (0.1 mL) was added to effect the precipitation of **23**. The precipitate was transferred to a filtration unit under argon, washed with hexane (3 x 10 mL) and dried *in vacuo*. The white solid was then transferred to an MBraun Unilab glovebox for storage. Typical yield 7.2 g, 49%.

The number of moles of TMEDA of crystallisation were calculated in a similar manner to **21** detailed above, yielding [1-OMe-4-(SiMe₃)-C₆H₄] (**23a**). ¹H NMR (CDCl₃, δ ppm): 7.39-7.36 (m, 2H, Ar-H), 6.85- 6.83 (m, 2H, Ar-H), 3.73 (s, 3H, OMe), 0.17 (s, 9H, SiMe₃).

8.3 Preparation of gold(I) compounds

ClAu(THT) (**24**) was prepared according to the method described in the literature.¹⁴¹ To a stirred solution of Na[AuCl₄]. 2H₂O (1.0 g, 2.5 mmol) in H₂O/EtOH (20 mL, 1:1) was added tetrahydrothiophene (0.47 mL, 5.3 mmol) dropwise and the suspension stirred for 15 min. The precipitate was collected by filtration and washed with H₂O (2 x 10 mL) and air dried. Yield 0.71 g, 89 %.

8.3.1 Preparation of ClAuPPh₃ (**25**)³⁷⁶

To a solution of ClAu(THT) (**24**) (0.78 g, 2.4 mmol) in CH₂Cl₂ (15 mL) was added PPh₃ (0.72 g, 2.8 mmol), and the mixture stirred for 18 h. EtOH (10 mL) was added and the CH₂Cl₂ slowly removed under reduced pressure to give **25** which was filtered and washed with hexane (2 x 10 mL). The product **25** was collected as a white solid (0.98 g, 82 %). ¹H NMR (CDCl₃, δ ppm): 7.49-7.44 (m, 6H, Ar-H), 7.44-7.37 (m, 9H, Ar-H). ¹³C{¹H} NMR (CDCl₃, δ ppm) 134.2 (d, J_{CP} = 13.8 Hz,), 132.0 (d, J_{CP} = 2.8 Hz), 129.3 (d, J_{CP} = 11.1 Hz), 128.4 (d, J_{CP} = 62 Hz,). ³¹P{¹H} NMR (CDCl₃, δ ppm): 33.19 (s). Calculated for C₁₈H₁₅AuClP: C, 43.68; H, 3.06; P, 6.26; Found: C, 43.67; H, 2.67; P, 6.00.

8.3.2 Preparation of [Ph₃PAu(1-OMe-C₆H₄)] (**26**)¹⁴²

To **21** (0.16 g, 0.68 mmol) in THF (20 mL) was added ClAuPPh₃ (**25**) (0.15 g, 0.68 mmol) and the reaction stirred under argon for 18 hours. H₂O (0.1 mL) was added and the mixture stirred for an additional 10 min. The solvents were removed *in vacuo*, and CH₂Cl₂ (10 mL) was added and stirring continued for 10 min before drying over MgSO₄ and filtering through a plug of celite. Hexane (5 mL) was added to the filtrate and the CH₂Cl₂ slowly removed under reduced pressure to affect precipitation of **26** which was filtered and

washed with hexane (2×10 mL). The title product **26** was isolated as a white solid (0.27 g, 72%). ^1H NMR (CDCl_3 , δ ppm): 7.58-7.53 (m, 6H, Ar-H), 7.34-7.49 (m, 10H, Ar-H), 7.08-7.04 (m, 1H, Ar-H), 6.92-6.88 (t, $^3J_{\text{HH}} = 8$ Hz, 1H, Ar-H), 6.85-6.83 (m, 1H, Ar-H), 3.77 (s, 3H, OMe). $^{13}\text{C}\{\text{H}\}$ NMR (CDCl_3 , δ ppm): 139.8, 134.5 (d, $J_{\text{CP}} = 13.8$ Hz), 134.3, 131.2 (d, $J_{\text{CP}} = 49$ Hz), 131.1, 129.0 (d, $J_{\text{CP}} = 11.1$ Hz), 128.9, 126.7, 120.8, 110.0 (d, $J_{\text{CP}} = 4.6$ Hz), 55.6. $^{31}\text{P}\{\text{H}\}$ NMR (CDCl_3 , δ ppm): 43.86 (s). Calculated for $\text{C}_{25}\text{H}_{22}\text{AuOP}$: C, 53.0; H, 3.9; P, 5.5; Found: C, 52.7; H, 3.6; P, 5.0.

8.3.3 Preparation of $[\text{Ph}_3\text{PAu}(4\text{-OMe-C}_6\text{H}_4)]$ (**27**)¹⁴³

Prepared in an analogous fashion to **26** and isolated as a white solid (0.2 g, 72 %). ^1H NMR (CDCl_3 , δ ppm): 7.55-7.50 (m, 6H, Ar-H), 7.47-7.36 (m, 11H, Ar-H), 6.83 (d, $^3J_{\text{HH}} = 8.3$ Hz, 2H, Ar-H), 3.72 (s, 3H, OMe). $^{13}\text{C}\{\text{H}\}$ NMR (CDCl_3 , δ ppm): 157.9, 140.0, 134.4 (d, $J_{\text{CP}} = 13.8$), 131.1, 130.9, 129.0 (d, $J_{\text{CP}} = 11.1$), 113.4, 55.0. $^{31}\text{P}\{\text{H}\}$ NMR (CDCl_3 , δ ppm): 43.78. Calculated for $\text{C}_{25}\text{H}_{22}\text{AuOP}$: C, 53.0; H, 3.9; P, 5.5; Found: C, 52.8; H, 3.4; P, 5.0.

8.3.4 Preparation of $[\text{Ph}_3\text{PAu-C}_6\text{H}_5]$ (**28**)³⁹⁰

Prepared in an analogous fashion to **26** and isolated as a white solid (0.13 g, 79 %). ^1H NMR (CDCl_3 , δ ppm): 7.58-7.48 (m, 6H, Ar-H), 7.46-7.35 (m, 11H, Ar-H), 7.24-7.20 (t, $J_{\text{HH}} = 7.6$ Hz, 1H, Ar-H), 7.04-6.99 (m, 2H, Ar-H). $^{13}\text{C}\{\text{H}\}$ NMR (CDCl_3 , δ ppm): 139.6, 134.4 (d, $J_{\text{CP}} = 13$ Hz), 131.3, 131.1, 130.9, 129.0 (d, $J_{\text{CP}} = 11.1$ Hz), 127.6, 125.9. $^{31}\text{P}\{\text{H}\}$ NMR (CDCl_3 , δ ppm): 43.50 (s). Calculated for $\text{C}_{25}\text{H}_{22}\text{AuOP}$: C, 53.7; H, 3.8; P, 5.8; Found: C, 52.9; H, 3.2; P, 6.0.

8.3.5 Synthesis of PhICl_2 ¹⁴⁴

To iodobenzene (0.52 g, 2.55 mmol) in aqueous NaOCl (10-15%, 6.0 mL) at room temperature was added concentrated HCl (2 mL), and the mixture stirred for 10 min. The yellow solid was collected by filtration, washed with H_2O and Petroleum ether (40-60), and air-dried, (0.54 g, 78%). $\text{Mp} = 109\text{-}111$ °C.

8.3.6 Attempted oxidative addition to Au(I) complexes. (Typical procedure)

To **26** (0.05 g, 0.09 mmol) in CH₂Cl₂ (15 mL) at -20 °C was added PhICl₂ (0.032 g, 0.12 mmol) dropwise and the reaction stirred for 1 hour at this temperature. Stirring was continued for 2 hours whilst the reaction was allowed to warm to room temperature. After workup the expected Au(III) product was not isolated and ³¹P{¹H} signals corresponding to ClAuPPh₃ and **26** were observed in the NMR spectrum.

8.4 Synthesis of gold(III) compounds via boroxine transmetallation

8.4.1 Synthesis of Amines: General procedure

To a solution of 1-BrCH₂-4-CH₃-C₆H₄ (20.0 g, 0.1 mol) in dichloromethane (150 mL) was added an aqueous solution of dimethylamine hydrochloride (61.7 g, 0.8 mol) in the presence of KOH (84.9 g, 1.5 mol) at room temperature. After stirring for 4.5 h the organic phase was separated and dried over MgSO₄. Removal of the solvent afforded 1-Me₂NCH₂-4-CH₃-C₆H₄ (**38**)¹⁶¹ as a light yellow oil (10.0 g, 61 %). ¹H NMR (CDCl₃, δ ppm): 6.91 - 7.17 (m, 4 H, Ar-H), 3.29 (s, 2 H, CH₂), 2.25 (s, 3 H, CH₃), 2.14 (s, 6 H, NMe₂). ¹³C{¹H} NMR (CDCl₃, δ ppm): 136.6, 135.9, 129.1, 128.9, 64.2, 45.3, 21.1.

1-Me₂NCH₂-4-CF₃-C₆H₄ (**39**)¹⁶¹ prepared from 1-BrCH₂-4-CF₃-C₆H₄ (20.0 g, 84 mmol) and dimethylamine hydrochloride (52.0 g, 0.6 mol) in the presence of KOH (70.4 g, 1.3 mol) and isolated as a light yellow oil (15.2 g, 89 %). ¹H NMR (CDCl₃, δ ppm): 7.49 (d, J=8.1 Hz, 2 H, Ar-H), 7.35 (d, J=8.1 Hz, 2 H, Ar-H), 3.38 (s, 2 H, CH₂), 2.16 (s, 6 H, NMe₂). ¹³C{¹H} NMR (CDCl₃, δ ppm): 143.3 (q, J_{CF}= 1.35 Hz), 129.3 (q, ²J_{CF}=32.24 Hz,), 129.1, 125.1 (q, J_{CF}=3.84 Hz), 124.3 (q, ¹J_{CF}=271.83 Hz), 63.8, 45.4.

1-Me₂NCH₂-3-CF₃-C₆H₄ (**40**)¹⁶¹ prepared from 1-BrCH₂-3-CF₃-C₆H₄ (20.0 g, 84 mmol) and dimethylamine hydrochloride (51.2 g, 0.63 mol) in the presence of KOH (70.4 g, 1.3 mol) and isolated as a colourless oil (19.7 g, 89.5 %). ¹H NMR (CDCl₃, δ ppm): 7.48 (s, 1 H, Ar-H), 7.34 - 7.40 (m, 2 H, Ar-H), 7.25 - 7.31 (m, 1 H, Ar-H), 3.32 (s, 2 H, CH₂), 2.11 (s, 6 H, NMe₂). ¹³C{¹H} NMR (CDCl₃, δ ppm): 140.2, 132.2 (q, J_{CF}= 1.31 Hz), 130.7 (q, ²J_{CF}= 32.07 Hz), 128.6, 125.5 (q, J_{CF}= 3.83 Hz), 124.3 (q, ¹J_{CF}= 272.14 Hz), 123.8 (q, J_{CF}= 3.85 Hz), 63.7, 45.2.

1-Me₂NCH₂-4-OMe-C₆H₄ (**41**)¹⁶¹ prepared from 1-ClCH₂-4-OMe-C₆H₄ (20.0 g, 0.13 mol) and dimethylamine hydrochloride (78.1 g, 1 mol) in the presence of KOH (107.3 g, 1.9 mol) and isolated as a light yellow oil (17.7 g, 85 %). ¹H NMR (CDCl₃, δ ppm): 7.21 (d, *J*_{HH} = 8.7 Hz, 2 H, Ar-H), 6.85 (d, *J*_{HH} = 8.7 Hz, 2 H, Ar-H), 3.76 (s, 3 H, OMe), 3.34 (s, 2 H, CH₂), 2.21 (s, 6 H, NMe₂). ¹³C{¹H} NMR (CDCl₃, δ ppm): 158.7, 131.0, 130.2, 113.6, 63.7, 55.1, 45.2.

8.4.2 Synthesis and isolation of organolithium reagents

8.4.2.1 Preparation of 2-(Me₂NCH₂)C₆H₄Li (**42**)

Prepared following the procedure of Manzer.¹⁶² To *N,N*-dimethylbenzylamine (2.4 mL, 16 mmol) in Et₂O under argon was added *n*-butyllithium (10 mL, 16 mmol, 1.6 M in hexanes) and the mixture stirred for 24 h. The white precipitate was filtered under argon, washed with Et₂O (3 x 10 mL) and dried *in vacuo*. **42** was isolated as a white solid (1.95 g, 89%) and transferred to a glovebox for storage.

8.4.2.2 Preparation of 2-(Me₂NCH₂)-5-CH₃-C₆H₄Li (**43**)³⁹¹

To a solution of 4-(Me₂NCH₂)C₆H₄CH₃ (**38**) (7.2 g, 48 mmol) in Et₂O (125 mL) was added *n*-butyllithium (36.2 mL, 58 mmol, 1.6 M in hexanes) and the mixture was stirred for 3 days. The solution was concentrated to 30 mL and cooled to -20 °C for 24 h. The white precipitate that had formed was filtered under argon, washed with cold hexane (3 x 10 mL) and transferred to a glovebox for storage. **43** was isolated a white solid (4.5 g, 61%).

8.4.2.3 Preparation of 2-(Me₂NCH₂)-5-CF₃-C₆H₄Li (**44**)

To 4-(Me₂NCH₂)C₆H₄CF₃ (**39**) (12.4 g, 61.3 mmol) in hexane (30 mL) under argon was added *n*-butyllithium (42.1 mL, 67.4 mmol, 1.6 M in hexanes) and the mixture was stirred for 48 hours. The white precipitate was filtered under argon, washed with hexane (3 x 15 mL) and dried *in vacuo*. It was then transferred to a glovebox for storage. **44** was isolated as a white solid (9.0 g, 70%).

8.4.3 Preparation of boroxines

8.4.3.1 Synthesis of $(2-(Me_2NCH_2)C_6H_4BO)_3$ (**45**)¹⁶⁴

To a stirred solution of 2-(Me₂NCH₂)C₆H₄Li (**42**) (5 g, 35.5 mmol) in THF (20 mL) at -78 °C was added B(OMe)₃ (6.3 mL, 49.2 mmol) and the solution stirred for 1 h before warming to room temperature overnight. The solution was acidified with 1 M HCl and brine was added. The phases were separated, the aqueous layer washed with Et₂O (50 mL) and all organic phases combined and washed with saturated Na₂CO₃ solution and brine. The organic layer was dried over MgSO₄ and the solvent evaporated to give (2-(Me₂NCH₂)C₆H₄BO)₃ (**45**) which was recrystallised from CH₂Cl₂/hexane to give a white solid (2.9 g, 50%). ¹H NMR (CDCl₃, δ ppm): 7.65 (dd, J_{HH}=5.0, 3.5 Hz, 3H, Ar-H), 7.13 - 7.36 (m, 9H, Ar-H), 3.88 (s, 6H, CH₂), 2.46 (s, 18H, NMe₂). ¹³C{¹H}(CDCl₃, δ ppm): (C-B not observed) 141.4, 131.6, 127.2, 126.6, 124.9, 64.0, 45.1. ¹¹B{¹H} NMR (CDCl₃, δ ppm): = 16.6 (s). Calculated for C₂₇H₃₆N₃B₃O₃: C, 67.0; H, 7.5; N, 8.7; B, 6.8; Found: C, 66.4; H, 7.6; N, 8.6; B, 6.8.

8.4.3.2 Synthesis of $(2-(Me_2NCH_2)-5-CH_3-C_6H_4BO)_3$ (**46**)

To a stirred solution of 2-(Me₂NCH₂)-5-CH₃-C₆H₄Li (**43**) (2.8 g, 18 mmol) in THF (20 mL) at -78 °C was added B(OMe)₃ (3.0 mL, 27.1 mmol) and the solution stirred for 1 h before warming to room temperature overnight. The solution was acidified with 1 M HCl and brine was added. The phases were separated and the aqueous layer neutralised with 1 M NaOH. The aqueous layer was extracted with dichloromethane and the phases separated, and the combined organic fractions dried over MgSO₄. The solvent was removed *in vacuo* to give (2-(Me₂NCH₂)-5-CH₃-C₆H₄BO)₃ (**46**) which was recrystallised from CH₂Cl₂/hexane to give a white solid (2.2 g, 68%). ¹H NMR (CDCl₃, δ ppm): 7.36 (s, 3 H, Ar-H), 6.96 (s, 6 H, Ar-H), 3.75 (s, 6 H, CH₂), 2.35 (s, 18 H, NMe₂), 2.26 (s, 9 H, CH₃). ¹³C{¹H}(CDCl₃, δ ppm): (C-B not observed) 138.5, 135.7, 132.4, 127.9, 124.8, 63.8, 45.1, 21.5. ¹¹B{¹H} NMR (CDCl₃, δ ppm): 15.12 (s). Calculated for C₃₀H₄₂B₃N₃O₃: C, 68.5; H, 8.1; N, 8.0; Found: C, 68.3; H, 8.3; N, 7.9.

8.4.3.3 Synthesis of $(2-(Me_2NCH_2)-5-CF_3-C_6H_4BO)_3$ (**47**)

To a stirred solution of 2-(Me₂NCH₂)-5-CF₃-C₆H₄Li (**44**) (3.2 g, 15.3 mmol) in THF (20 mL) at -78 °C was added B(OMe)₃ (2.6 mL, 23 mmol) and the solution stirred for 1 h

before warming to room temperature overnight. The solution was acidified with 1 M HCl and brine was added. The phases were separated and the aqueous layer neutralised with 1M NaOH. The aqueous layer was extracted with dichloromethane and the phases separated, and the combined organic fractions dried over MgSO₄. The solvent was removed *in vacuo* to give (2-(Me₂NCH₂)-5-CF₃-C₆H₄BO)₃ (**47**) which was recrystallised from CH₂Cl₂/hexane to give a white solid (2.3 g, 66%). ¹H NMR (CDCl₃, δ ppm): 7.84 (s, 3 H, Ar-H), 7.50 (d, *J*_{HH}=7.7 Hz, 3 H, Ar-H), 7.27 (d, *J*_{HH}=8.3 Hz, 3 H, Ar-H), 3.89 (s, 6 H, CH₂), 2.45 (s, 18 H, NMe₂). ¹³C{¹H} NMR (CDCl₃, δ ppm): (C-B not observed), 145.08, 128.9 (q, ²J_{CF}=31.1 Hz,), 127.9 (q, *J*_{CF}=3.5 Hz,), 125, 124.9 (q, ¹J_{CF}= 272.1 Hz), 124.3 (q, ³J_{CF}=3.7 Hz), 74.3, 53.3. ¹¹B{¹H} NMR (CDCl₃, δ ppm): 14.32 (s). Calculated for C₃₀H₃₃B₃F₉N₃O₃: C, 52.4; H, 4.8; N, 6.1; Found: C, 52.6; H, 4.7; N, 6.1.

8.4.3.4 Synthesis of (2-(Me₂NCH₂)-5-OMe-C₆H₄BO)₃ (**48**)

To 1-Me₂NCH₂-4-OMe-C₆H₄ (**41**) (3.6 g, 21.6 mmol) in Et₂O (25 mL) was added *n*-butyllithium (14.8 mL, 23.7 mmol, 1.6 M in hexanes) and the mixture stirred for 18 h at room temperature. The solution was added to a vigorously stirred solution of B(OMe)₃ (3.6 mL, 32.3 mmol) in Et₂O (20 mL) at -78 °C and allowed to warm to room temperature overnight. The solution was acidified with 1 M HCl and brine was added. The phases were separated and the aqueous layer neutralised with 1 M NaOH. The aqueous layer was extracted with Et₂O the phases separated, and the combined organic fractions dried over MgSO₄. The solvent was removed *in vacuo* to give (2-(Me₂NCH₂)-5-OMe-C₆H₄BO)₃ (**48**) which was recrystallised from dichloromethane/hexane to give a white solid (1.9 g, 45%). ¹H NMR (CDCl₃, δ ppm): 7.18 (d, *J*_{HH}=2.6 Hz, 3 H, Ar-H), 7.08 (d, *J*_{HH}=8.1 Hz, 3 H, Ar-H), 6.77 (dd, *J*_{HH}=8.1, 2.6 Hz, 3 H, Ar-H), 3.81 (s, 15 H, CH₂ + OCH₃), 2.44 ppm (s, 18 H, NMe₂). ¹³C{¹H} NMR (CDCl₃, δ ppm): (C-B not observed), 158.5, 133.6, 125.9, 117.1, 112.3, 63.5, 55.2, 45.0. ¹¹B{¹H} NMR (CDCl₃, δ ppm): 16.84 (s). Calculated for C₃₀H₄₂B₃N₃O₆: C, 62.8; H, 7.4; N, 7.3; Found: C, 62.3; H, 7.4; N, 7.2.

8.4.4 Synthesis of Gold(III) compounds

8.4.4.1 Preparation of 2-Me₂NCH₂-C₆H₄AuCl₂ (**8a**)

To a solution of Na[AuCl₄]·2H₂O (0.2 g, 0.50 mmol) in H₂O (25 mL) was added (2-(Me₂NCH₂)C₆H₄BO)₃ (**45**) (0.08 g, 0.17 mmol) in MeCN (5 mL). The yellow mixture was

refluxed for 48 h. The acetonitrile was removed under reduced pressure, the mixture filtered and the solid extracted into CH₂Cl₂ (10 mL) and hexane (15 mL) added. The CH₂Cl₂ was removed slowly under reduced pressure to induce crystallisation of [Au(III)(damp-C,N)Cl₂] (**8a**) which was collected by filtration as an off-white solid (0.1 g, 57%). ¹H NMR (CDCl₃, δ ppm): 7.68 (d, *J_{HH}*=7.6 Hz, 1 H, Ar-H), 7.15 - 7.31 (m, 2 H, Ar-H), 7.04 - 7.14 (m, 1 H, Ar-H), 4.34 (s, 2 H, CH₂), 3.26 (s, 6 H, NMe₂). ¹³C{¹H} NMR (CDCl₃): 148.0, 143.6, 131.3, 129.1, 128.1, 123.2, 75.9, 53.8. Calculated for C₉H₁₂NAuCl₂: C, 26.9; H, 3.0; N, 3.5; Found: C, 26.9; H, 2.7; N, 3.2.

*8.4.4.2 Preparation of 2-Me₂NCH₂-5-CH₃-C₆H₃AuCl₂ (**49**)*

To Na[AuCl₄]. 2H₂O (0.2 g, 0.50 mmol) in H₂O (25 mL) was added (2-(Me₂NCH₂)-5-CH₃-C₆H₄BO)₃ (**46**) (0.1 g, 0.2 mmol) in acetonitrile (5 mL). The yellow mixture was refluxed for 48 h. The acetonitrile was removed under reduced pressure, the mixture filtered and the solid extracted into CH₂Cl₂ (10 mL) and hexane (15 mL) added. The CH₂Cl₂ was removed slowly under reduced pressure to induce crystallisation of 2-Me₂NCH₂-5-CH₃-C₆H₃AuCl₂ (**49**) which was collected by filtration as an off-white solid (0.12 g, 58%). ¹H NMR (CDCl₃, δ ppm): 7.49 (s, 1 H, Ar-H), 6.85 - 7.08 (m, 2 H, Ar-H), 4.28 (s, 2 H, CH₂), 3.24 (s, 6 H, NMe₂), 2.29 (s, 3 H, CH₃). ¹³C{¹H} NMR (CDCl₃, δ ppm): 148.1, 140.4, 138.4, 131.7, 129.6, 122.8, 75.7, 53.7, 21.5. Calculated for C₁₀H₁₄AuCl₂N: C, 28.9; H, 3.4; N, 3.4; Found: C, 29.9; H, 3.1; N, 3.4.

*8.4.4.3 Preparation of 2-Me₂NCH₂-5-CF₃-C₆H₃AuCl₂ (**50**)*

To a solution of Na[AuCl₄]. 2H₂O (0.2 g, 0.5 mmol) in H₂O (25 mL) was added (2-(Me₂NCH₂)-5-CF₃-C₆H₄BO)₃ (**47**) (0.1 g, 0.2 mmol) in MeCN (5 mL). The yellow mixture was refluxed for 48 h. The acetonitrile was removed under reduced pressure, the mixture filtered and the solid extracted into CH₂Cl₂ (10 mL) and hexane (15 mL) added. The CH₂Cl₂ was removed slowly under reduced pressure to induce crystallisation of 2-Me₂NCH₂-5-CF₃-C₆H₃AuCl₂ (**50**) which was collected by filtration as an off-white solid (0.1 g, 63%). ¹H NMR (d⁶-DMSO, δ ppm): 7.98 (s, 1 H), 7.47 (d, *J_{HH}*=7.9 Hz, 1 H), 7.10 - 7.30 (m, 1 H), 4.41 (s, 2 H, CH₂), 3.28 (s, 6 H, NMe₂). ¹³C{¹H} NMR (d⁶-DMSO, δ ppm): 151.1, 146.5, 126.9 (q, ²*J_{CF}* = 31.6 Hz, 125.8 (q, *J_{CF}* = 4.0 Hz), 125.3 (q, *J_{CF}* = 3.9 Hz),

124.6, 123.7 (q, $J_{\text{CF}}=272.7$ Hz), 74.2, 53.3. Calculated for $\text{C}_{10}\text{H}_{11}\text{AuCl}_2\text{F}_3\text{N}$: C, 25.5; H, 2.4; N, 3.0; Found: C, 25.5; H, 2.0; N, 2.9.

8.4.4.4 Preparation of 2-Me₂NCH₂-5-OMe-C₆H₃AuCl₂ (51)

To Na[AuCl₄]·2H₂O (0.2 g, 0.5 mmol) in H₂O (25 mL) was added (2-(Me₂NCH₂)-5-OMe-C₆H₄BO)₃ (**48**) (0.1 g, 0.2 mmol) in MeCN (5 mL) and the mixture refluxed for 48 h. The acetonitrile was removed under reduced pressure, the mixture filtered and the solid extracted into CH₂Cl₂ (10 mL) and hexane added (15 mL). The CH₂Cl₂ was removed slowly under reduced pressure to induce crystallisation of 2-Me₂NCH₂-5-OMe-C₆H₃AuCl₂ (**51**) which was collected by filtration as an off-white solid (0.08g, 35%). ¹H NMR (CDCl₃, δ ppm): 7.26 (d, $J_{HH}=2.4$ Hz, 1 H, Ar-H), 6.99 (d, $J_{HH}=8.3$ Hz, 1 H, Ar-H), 6.74 (dd, $J_{HH}=8.3$, 2.4 Hz, 1 H, Ar-H), 4.28 (s, 2 H, CH₂), 3.74 (s, 3 H, OCH₃), 3.23 (s, 6 H, NMe₂). ¹³C{¹H} NMR (CDCl₃, δ ppm): 157.9, 148.5, 135.5, 123.7, 115.7, 115.4, 75.5, 55.6, 53.7. Calculated for C₁₀H₁₄AuCl₂NO: C, 27.8; H, 3.3; N, 3.2; Found: C, 27.1; H, 3.0; N, 3.1.

8.5 Synthesis of Tin reagents and amines

8.5.1 Synthesis of 1,4-(Br)₂-2,5-(BrCH₂)₂-C₆H₂ (**55**)^{169,170}

N-Bromosuccinamide (15.4 g, 86.4 mmol) was added to a stirred solution of 2,5-dibromo-*p*-xylene (10.0 g, 37.9 mmol) and 1,1'-Azobis(cyclohexanecarbonitrile) (10.0 mg, 0.04 mmol) in CHCl₃ (150 mL) at room temperature. The reaction mixture was heated to reflux and stirred for 5 h. Upon cooling the mixture was filtered and the solvent removed *in vacuo*. The white solid was stirred in methanol (25 mL) for 10 min, and filtered to give crude 1,4-Br-2,5-(BrCH₂)-C₆H₂ (**55**) which was recrystallised from ethanol to yield **55** as a white solid (6.4 g, 40%). ¹H NMR (CDCl₃, δ ppm): 7.70 (s, 2 H, Ar-H), 4.55 (s, 4 H, CH₂). ¹³C{¹H} NMR (CDCl₃, δ ppm): 138.0, 134.3, 122.3, 30.4. Calculated for C₈H₆Br₄: C, 22.77; H, 1.43; Br, 75.80; Found: C, 22.94; H, 0.97; Br, 75.80.

8.5.2 Synthesis of 1,4-(Br)₂-2,5-(NMe₂CH₂)₂-C₆H₂ (**56**)¹⁷¹

A solution of HNMe₂ (209 mL, 0.42 mol, 2M in ethanol) was added to a suspension of **55** (11.0 g, 26.2 mmol) in Et₂O (250 mL). The mixture was stirred for 3 h at room temperature, filtered, washed with brine and then 2M NaOH. The organic phase was

separated and the solvent removed *in vacuo* to afford 1,4-(Br)₂-2,5-(NMe₂CH₂)₂-C₆H₂ (**56**) as a white solid (8.48 g, 93%). ¹H NMR (CDCl₃, δ ppm): 7.55 (s, 2 H, Ar-H), 3.39 (s, 4 H, CH₂), 2.23 (s, 12 H, NMe₂). ¹³C{¹H} NMR (CDCl₃, δ ppm): 138.6, 134.3, 123.3, 62.6, 45.6. Calculated for C₁₂H₁₈Br₂N₂: C, 41.26; H, 5.15; N, 8.02; Found: C, 41.02 ; H, 5.08; N, 7.92.

8.5.3 Synthesis of 1,4-(SiMe₃)₂-2,5-(NMe₂CH₂)₂-C₆H₂ (**58**)

To a solution of **56** (0.2 g, 0.6 mmol) in Et₂O (10 mL) was added *n*-BuLi (0.75 mL, 1.2 mmol, 1.6 M in hexanes) at -78 °C. The reaction mixture was stirred for 15 min at this temperature, and then the suspension allowed to reach room temperature and stirred for 45 min. The mixture was cooled to -78 °C and trimethyl silylchloride (0.16 mL, 1.3 mmol) added and the reaction allowed to warm to room temperature overnight. H₂O (0.1 mL) was added and the mixture stirred for 10 min, before drying over MgSO₄. The mixture was filtered and the solvent removed *in vacuo* to afford 1,4-(SiMe₃)₂-2,5-(NMe₂CH₂)₂-C₆H₂ (**58**) as a light yellow solid (0.12 g, 60%). ¹H NMR (CDCl₃, δ ppm): 7.41 (s, 2 H, Ar-H); 3.39 (s, 4 H, CH₂), 2.10 (s, 12 H, NMe₂), 0.23 (s, 18 H, SiMe₃). ¹³C{¹H} NMR (CDCl₃, δ ppm): 141.7, 138.4, 134.6, 63.7, 44.2, -0.6.

8.5.4 Synthesis of 1,4-(SnPh₃)₂-2,5-(NMe₂CH₂)₂-C₆H₂ (**66**)

To a solution of **56** (0.5 g, 1.43 mmol) in Et₂O (10 mL) was added *n*-BuLi (1.97 mL, 3.2 mmol, 1.6 M in hexanes) at -78 °C. The reaction mixture was stirred for 15 min at this temperature, and then the suspension allowed to reach room temperature and stirred for 45 min. The reaction mixture was cooled to -78 °C and then transferred to a Schlenk flask containing a stirred solution of triphenyltin chloride (1.3 g, 3.29 mmol) in Et₂O (20 mL) at -78 °C, and the reaction allowed to warm to room temperature slowly overnight. The solvent was removed *in vacuo* and the residue extracted with THF (30 mL). The THF was removed under reduced pressure and the mixture extracted into CH₂Cl₂ (10 mL). Addition of hexane (10 mL) and slow removal of CH₂Cl₂ under reduced pressure afforded 1,4-(SnPh₃)₂-2,5-(NMe₂CH₂)₂-C₆H₂ (**66**) as a white solid (0.65 g, 51%) which was collected by filtration. ¹H NMR (CDCl₃, δ ppm): 7.45 - 7.66 (m, 12 H, Ar-H), 7.12 - 7.39 (m, 20 H, Ar-H), 3.17 (s, 4 H, CH₂), 1.46 ppm (s, 12 H, NMe₂). ¹³C{¹H} NMR (CDCl₃, δ ppm): 144.7, 142.1 (s, ¹J_C^{117/119}Sn = 543.27/517.96 Hz), 139.3, 139.0, 136.8 (s, ¹J_C^{117/119}Sn = 34.16/35.75

Hz), 128.1 (s, $J_{\text{C}}^{117/119}\text{Sn}$ = 48.73/50.93 Hz), 128.1, 65.0, 44.9. $^{119}\text{Sn}\{\text{H}\}$ NMR (CDCl_3): - 164.1 ppm. Calculated for $\text{C}_{48}\text{H}_{48}\text{N}_2\text{Sn}_2$: C, 64.73; H, 5.44; N, 3.15; Found: C, 64.31 ; H, 5.35; N, 3.09.

8.5.5 Synthesis of 1,4-(SnMe_3)₂-2,5-(NMe_2CH_2)₂- C_6H_2 (67)

To a solution of **56** (1.83 g, 5.23 mmol) in Et_2O (10 mL) was added *n*-BuLi (7.5 mL, 12 mmol, 1.6 M in hexanes) at -78 °C. The reaction mixture was stirred for 15 min at this temperature, and then the suspension allowed to reach room temperature and stirred for 45 min. The reaction mixture was cooled to -78 °C and then transferred to a Schlenk flask containing a stirred solution of trimethyltin chloride (2.23 g, 11.2 mmol) in Et_2O (20 mL) at -78 °C, and the reaction allowed to warm to room temperature slowly overnight. The solvent was removed *in vacuo* and the residue extracted with THF (30 mL). The THF was removed under reduced pressure and the mixture extracted into CH_2Cl_2 (10 mL). Addition of MeOH (15 mL) and slow removal of CH_2Cl_2 under reduced pressure afforded 1,4-(SnMe_3)₂-2,5-(NMe_2CH_2)₂- C_6H_2 (**67**) which was collected by filtration. The white solid was then recrystallised from MeOH (1.2 g, 44%). ^1H NMR (CDCl_3 , δ ppm): 7.09 (s, $^3J_{\text{H}}^{117/119}\text{Sn}$ = 18.53/53.67, 2H, Ar-H), 3.22 (s, 4 H, CH_2), 1.94 (s, 12 H, NMe_2), 0.00 (s, $^2J_{\text{H}}^{117/119}\text{Sn}$ = 51.60/53.76 Hz, 18 H, SnMe_3). $^{13}\text{C}\{\text{H}\}$ NMR (CDCl_3 , δ ppm): 143.7, 142.1, 136.6, 65.8, 45.2, -8.5 (s, $^1J_{\text{C}}^{117/119}\text{Sn}$ = 345.09/361.71 Hz). $^{119}\text{Sn}\{\text{H}\}$ NMR(CDCl_3): -52.0 ppm. Calculated for $\text{C}_{18}\text{H}_{36}\text{N}_2\text{Sn}_2$: C, 41.72; H, 7.01; N, 5.41; Found: C, 41.69 ; H, 7.28; N, 5.40.

8.5.6 Synthesis of 1,4-(SnMe_2Cl)₂-2,5-(NMe_2CH_2)₂- C_6H_2 (68)

To a solution of **56** (2.0 g, 5.7 mmol) in Et_2O (50 mL) was added *n*-BuLi (8.3 mL, 13.2 mmol, 1.6 M in hexanes) at -78 °C. The reaction mixture was stirred for 15 min at this temperature, and then the suspension allowed to reach room temperature and stirred for 45 min. The reaction mixture was cooled to -78 °C and then transferred to a Schlenk flask containing a stirred solution of dimethyltin dichloride (2.7 g, 12.1 mmol) in Et_2O (20 mL) at -78 °C, and the reaction allowed to warm to room temperature slowly overnight. The solvent was removed *in vacuo* and the residue extracted with THF (30 mL). The THF was removed under reduced pressure and the mixture extracted into CH_2Cl_2 (10 mL). Addition of hexane (15 mL) and slow removal of CH_2Cl_2 under reduced pressure afforded 1,4-(SnMe_2Cl)₂-2,5-(NMe_2CH_2)₂- C_6H_2 (**68**) which was collected by filtration as a white solid

(1.7 g, 53%). ^1H NMR (CDCl_3 , δ ppm): 7.91 (s, $^3J_{\text{H}}^{117/119}\text{Sn} = 25.35/66.98$ Hz, 2 H, Ar-H), 3.62 (s, 4 H, CH_2), 2.3 (s, 12 H, NMe_2), 0.7 ppm (s, $^2J_{\text{H}}^{117/119}\text{Sn} = 64.39/67.14$ Hz, 12 H, SnMe_2Cl). $^{13}\text{C}\{\text{H}\}$ NMR (CDCl_3 , δ ppm): 142.6, 141.8, 135.5, 64.8, 45.5, 0.0 (s, $^1J_{\text{C}}^{117/119}\text{Sn} = 494.91/517.95$ Hz). $^{119}\text{Sn}\{\text{H}\}$ NMR (C_6D_6): -49.8 ppm. Calculated for $\text{C}_{16}\text{H}_{30}\text{Cl}_2\text{N}_2\text{Sn}_2$: C, 34.37; H, 5.41; N, 5.01; Found: C, 34.07; H, 5.19; N, 4.75.

8.5.7 Synthesis of 1,4-(PPh₂)₂-2,5-(NMe₂CH₂)₂-C₆H₂ (69)

To a solution of 1,4-(Br)₂-2,5-(NMe₂CH₂)₂-C₆H₂ (**56**) (0.85 g, 2.42 mmol) in Et₂O (10 mL) was added *n*-BuLi (3 mL, 4.8 mmol, 1.6 M in hexanes) at -78 °C. The reaction mixture was stirred for 15 min at this temperature, and then the suspension allowed to reach room temperature and stirred for 45 min. The reaction mixture was cooled to -78 °C and Ph₂PCl (0.94 mL, 5.2 mmol) added and the reaction allowed to warm to room temperature slowly overnight. The solvent was removed *in vacuo* and the residue extracted with CH₂Cl₂ (20 mL). Addition of hexane (15 mL) and slow removal of CH₂Cl₂ under reduced pressure afforded 1,4-(PPh₂)₂-2,5-(NMe₂CH₂)₂-C₆H₂ (**69**) which was collected by filtration as a white solid (0.7 g, 52%). ^1H NMR (CDCl_3 , δ ppm): 7.48 - 7.61 (m, 1 H, Ar-H), 7.32 - 7.48 (m, 2 H, Ar-H), 7.10 - 7.26 (m, 17 H, Ar-H), 6.86 (t, $J=4.4$ Hz, 2 H, Ar-H), 3.36 (s, 4 H, CH₂), 1.80 (s., 12 H, NMe₂). $^{13}\text{C}\{\text{H}\}$ NMR (CDCl_3 , δ ppm): 138.0 (d, $J_{\text{CP}}=10.20$ Hz), 137.6 (d, $J_{\text{CP}}=16.84$ Hz), 135.1, 133.6 (d, $J_{\text{CP}}=19.72$ Hz), 131.6 (d, $J_{\text{CP}}=9.62$ Hz), 128.2, 128.2 (d, $J_{\text{CP}}=6.93$ Hz), 62.2, 44.1. $^{31}\text{P}\{\text{H}\}$ NMR (CDCl_3): -15.2 ppm. Calculated for C₃₆H₃₈N₂P₂: C, 77.11; H, 6.84; N, 5.00; Found: C, 76.61; H, 6.90; N, 5.08.

8.5.8 Synthesis of 1,4-(AuClPPh₂)₂-2,5-(NMe₂CH₂)₂-C₆H₂ (70)

To a stirred solution of **69** (0.21 g, 0.37 mmol) in CH₂Cl₂ (10 mL) was added ClAu(THT) (0.23 g, 0.72 mmol) and the mixture stirred for 18 h. Hexane (15 mL) was added and the CH₂Cl₂ removed *in vacuo* to precipitate 1,4-(AuClPPh₂)₂-2,5-(NMe₂CH₂)₂-C₆H₂ (**70**) as a white solid which was collected by filtration (0.33 g, 87%). ^1H NMR (CDCl_3 , δ ppm): 7.37 - 7.51 (m, 20 H, Ar-H), 6.84 - 7.02 (m, 2 H, Ar-H), 3.53 (s, 4 H, CH₂), 1.63 ppm (s, 12 H, NMe₂). $^{13}\text{C}\{\text{H}\}$ NMR (CDCl_3 , δ ppm): 143.1 (t, $J_{\text{CP}}=9.23$ Hz), 136.3 (t, $J_{\text{CP}}=8.31$ Hz), 133.9 (d, $J_{\text{CP}}=14.33$ Hz), 132.2 (d, $J_{\text{CP}}=2.80$ Hz), 131.7 (t, $J_{\text{CP}}=1.21$ Hz), 129.19 (d, $J_{\text{CP}}=64.57$ Hz), 129.2 (d, $J_{\text{CP}}=12.20$ Hz), 63.2, 44.0. $^{31}\text{P}\{\text{H}\}$ NMR (CDCl_3): 26.9 ppm.

Calculated for C₃₆H₃₈Au₂Cl₂N₂P₂: C, 42.14; H, 3.74; N, 2.73; Found: C, 42.28 ; H, 3.46; N, 2.65 .

8.5.9 Synthesis of 1,4-(AuCl₂)₂-2,5-(NMe₂CH₂)₂-C₆H₂ (71)

To a suspension of **68** (0.2 g, 0.36 mmol) in acetonitrile (20 mL) was added Na[AuCl₄] ·H₂O (0.29 g, 0.72 mmol) and the mixture refluxed for 3 h. After cooling the insoluble solid was filtered off, and washed with H₂O (10 mL) and hexane (2 x 10 mL) to give 1,4-(AuCl₂)₂-2,5-(Me₂NCH₂)₂-C₆H₂ (**71**) as a red powder (0.2 g, 50%).

The organic filtrate was collected and the solvent removed *in vacuo* to give dimethyltin dichloride. ¹H NMR (CDCl₃, δ ppm): 1.23 (s, ²J_H^{117/119}_{Sn}=65.56/68.57 Hz, 6 H). ¹³C{¹H} NMR (CDCl₃, δ ppm): 5.6 (s, ¹J_C^{117/119}_{Sn}=458.31/479.56 Hz).

8.5.10 Synthesis of 1,4-(Au{O₂CMe})₂-2,5-(NMe₂CH₂)₂-C₆H₂ (90)

To a suspension of **71** (0.1 g, 0.14 mmol) in acetone (15 mL) was added silver acetate (0.11g, 0.66 mmol) and the mixture stirred for 3 hours in the dark. The mixture was filtered and the solvent removed *in vacuo*. The residue was recrystallised from CH₂Cl₂/hexane to give **90** as an off-white solid which was collected by filtration (0.11g, 97%). ¹H NMR (CDCl₃, δ ppm): 6.71 (s, 2 H, Ar-H), 4.25 (s, 4 H, CH₂), 3.11 (s, 12 H, NMe₂), 2.09 (s, 6 H, O₂CMe), 1.99 ppm (s, 6 H, O₂CMe). ¹³C{¹H} NMR (CDCl₃, δ ppm): 177.4, 175.0, 142.2, 136.3, 123.3, 74.7, 53.2, 24.3, 22.0.

8.6 A³-screening with [AuCl₂(η²-C,N-C₆H₄-2-CH₂NMe₂)] (8a)

[AuCl₂(η²-C,N-C₆H₄-2-CH₂NMe₂)] (**8a**) was prepared as outlined in section 8.4.4.1.¹⁶⁶

Preparation for ferrocene-1-1-'dicarbaldehyde³¹⁰

To a solution of ferrocene (6.0 g, 32 mmol) in hexane (100 mL) was added tetramethylethylenediamine (TMEDA) (10.6 mL, 71 mmol) and *n*-butyllithium (46.4 mL, 74 mmol) and the mixture stirred overnight at room temperature. The reaction was cooled to -78°C and a solution of DMF (5.5 mL, 71 mmol) in Et₂O (100 mL) was added. The mixture was allowed to warm to room temperature and stirred for 4 h. The reaction was quenched with brine (100 mL) and extracted with CH₂Cl₂ (100 mL). The organic phase

was dried over MgSO₄ and the solvent removed *in vacuo*. The product was purified by column chromatography on silica gel using hexane/ether followed by hexane/ether/ethyl acetate to give ferrocene-1-1-'dicarbaldehyde as a red solid (4.3 g, 56 %). ¹H NMR (CDCl₃, δ ppm): 9.88 (s, 2 H, HC=O), 4.82 (t, J_{HH}=1.8 Hz, 4 H, Cp-H), 4.61 (t, J_{HH}=1.8 Hz, 4 H, Cp-H). ¹³C{¹H} NMR (CDCl₃, δ ppm): 192.8, 80.3, 74.2, 70.9. Calculated for C₁₂H₁₀FeO₂: C, 59.53; H, 4.17; Found: C, 59.65, H, 3.87.

8.6.1 Typical A³-coupling procedure for single coupling

A mixture of aldehyde (1 mmol), amine (1.1 mmol), alkyne (1.5 mmol) and Au catalyst (0.01 mmol) in water (2 mL) was stirred at 40°C for 24 h in an N₂ flushed flask. The reaction mixture was extracted with CH₂Cl₂, dried over MgSO₄ and concentrated under reduced pressure. The product was purified on silica gel using ethyl acetate/hexane as eluent.

8.6.2 Synthesis of PA-1²³⁷

To a dry nitrogen flushed Schlenk flask was added benzaldehyde (100 μL, 1 mmol) piperidine (116 μL, 1.1 mmol), phenylacetylene (162 μL, 1.5 mmol), H₂O (2 mL) and [AuCl₂(η²-C₆H₄-2-CH₂NMe₂)] (**8a**) (4 mg, 1 mol %). The mixture was stirred at 40°C for 24 h, then extracted with CH₂Cl₂, dried over MgSO₄ and concentrated *in vacuo*. The product was purified by column chromatography on silica gel using hexane/EtOAC eluent to give **PA-1** as a colourless oil (0.20 g, 75%). ¹H NMR (CDCl₃, δ ppm): 7.53 - 7.59 (m, 2 H, Ar-H), 7.39 - 7.46 (m, 2 H, Ar-H), 7.23 - 7.29 (m, 2 H, Ar-H), 7.15 - 7.23 (m, 4 H, Ar-H), 4.71 (s, 1 H, C-H), 2.39 - 2.55 (m, 4 H, CH₂), 1.41 - 1.61 (m, 4 H, CH₂), 1.29 - 1.40 (m, 2 H, CH₂). ¹³C{¹H} NMR (CDCl₃, δ ppm): 137.5, 130.7, 127.4, 127.2, 127.0, 126.9, 126.4, 122.3, 86.8, 85.0, 61.3, 49.6, 25.1, 23.4. ESMS m/z : 276 (M⁺ +H); HRMS: calculated for C₂₀H₂₁N (M⁺ + H): 276.1747, found: 276.1745.

8.6.3 Synthesis of PA-2²⁷³

To a dry nitrogen flushed Schlenk flask was added benzaldehyde (100 μL, 1 mmol) pyrrolidine (80 μL, 1 mmol), phenylacetylene (162 μL, 1.5 mmol), and [AuCl₂(η²-C₆H₄-2-CH₂NMe₂)] (**8a**) (4 mg, 1 mol %). The mixture was stirred at 40°C for 24 h, then extracted with CH₂Cl₂, dried over MgSO₄ and concentrated *in vacuo*. The product was

purified by column chromatography on silica gel using hexane/EtOAC eluent to give **PA-2** as a brown oil (0.22 g, 85%). ^1H NMR (CDCl_3 , δ ppm): 7.47 - 7.53 (m, 2 H, Ar-H), 7.34 - 7.41 (m, 2 H, Ar-H), 7.12 - 7.28 (m, 6 H, Ar-H), 4.77 (s, 1 H, C-H), 2.52 - 2.62 (m, 4 H, CH_2), 1.60 - 1.74 (m, 4 H, CH_2). $^{13}\text{C}\{\text{H}\}$ NMR (CDCl_3 , δ ppm): 139.7, 131.9, 128.4 (2 C), 128.2, 127.6, 123.4, 87.0, 86.9, 59.2, 50.4, 23.6. ESMS m/z: 262 (M^++H); HRMS calculated for $\text{C}_{19}\text{H}_{19}\text{N}$ (M^++H): 262.1591, found: 262.1589.

8.6.4 Synthesis of **PA-3**³⁹²

To a dry nitrogen flushed Schlenk flask was added benzaldehyde (100 μL , 1 mmol) morpholine (87 μL , 1 mmol), phenylacetylene (162 μL , 1.5 mmol), and $[\text{AuCl}_2(\eta^2\text{-C,N-C}_6\text{H}_4\text{-2-CH}_2\text{NMe}_2)]$ (**8a**) (4 mg, 1 mol %). The mixture was stirred at 40°C for 24 h, then extracted with CH_2Cl_2 , dried over MgSO_4 and concentrated *in vacuo*. The product was purified by column chromatography on silica gel using hexane/EtOAC eluent to give **PA-3** as a colourless oil (0.20 g, 72%). ^1H NMR (CDCl_3 , δ ppm): 7.50 - 7.61 (m, 2 H, Ar-H), 7.39 - 7.48 (m, 2 H, Ar-H), 7.14 - 7.35 (m, 6 H, Ar-H), 4.71 (s, 1 H, C-H), 3.57 - 3.73 (m, 4 H, CH_2), 2.56 (m, 4 H, CH_2). $^{13}\text{C}\{\text{H}\}$ NMR (CDCl_3 , δ ppm): 137.9, 131.8, 128.6, 128.3, 128.3, 128.3, 127.8, 123.0, 88.5, 85.1, 67.2, 62.1, 49.9. ESMS m/z: 278 (M^++H); HRMS calculated for $\text{C}_{19}\text{H}_{19}\text{NO}$ (M^++H): 278.1540, found: 278.1528.

8.6.5 Synthesis of **PA-4**²³⁷

To a dry nitrogen flushed Schlenk flask was added benzaldehyde (100 μL , 1 mmol) dibenzylamine (189 μL , 1.1 mmol), phenylacetylene (162 μL , 1.5 mmol), H_2O (2 mL) and $[\text{AuCl}_2(\eta^2\text{-C,N-C}_6\text{H}_4\text{-2-CH}_2\text{NMe}_2)]$ (**8a**) (4 mg, 1 mol %). The mixture was stirred at 40°C for 24 h, then extracted with CH_2Cl_2 , dried over MgSO_4 and concentrated *in vacuo*. The product was purified by column chromatography on silica gel using hexane/EtOAC eluent to give **PA-4** as white solid (0.32 g, 85%). ^1H NMR (CDCl_3 , δ ppm): 8.01 (d, $J_{HH}=8.0$ Hz, 2 H, Ar-H), 7.88 (dd, $J_{HH}=8.0$, 1.5 Hz, 2 H, Ar-H), 7.70 (d, $J=7.5$ Hz, 4 H, Ar-H), 7.53 - 7.63 (m, 9 H, Ar-H), 7.44 - 7.52 (m, 3 H, Ar-H), 5.22 (s, 1 H, C-H), 4.08 (d, $J_{HH}=13.5$ Hz, 2 H, CH_2), 3.82 (d, $J_{HH}=13.5$ Hz, 2 H, CH_2). $^{13}\text{C}\{\text{H}\}$ NMR (CDCl_3 , δ ppm): 138.4, 138.1, 130.9, 127.8, 127.3, 127.2, 127.1, 127.0, 126.4, 125.9, 122.2, 87.6, 83.6, 55.0, 53.6. ESMS m/z: 388 (M^++H); HRMS calculated for $\text{C}_{29}\text{H}_{25}\text{N}$ (M^++H): 388.2060, found: 388.2055.

HPLC: To a dry nitrogen flushed Schlenk flask was added benzaldehyde (100 μL , 1 mmol) dibenzylamine (189 μL , 1.1 mmol), phenylacetylene (162 μL , 1.5 mmol), H_2O (2 mL) and either **8a**, **126** or **127** (1 mol %). The mixture was stirred at 40 °C for 24 h, then extracted

with CH_2Cl_2 , dried over MgSO_4 and concentrated *in vacuo*. The crude reaction mixture then separated by HPLC.

8.6.6 Synthesis of PA-5²⁷⁶

To a dry nitrogen flushed Schlenk flask was added benzaldehyde (200 μL , 2 mmol) L-prolinol (189 μL , 2 mmol), phenylacetylene (324 μL , 3 mmol), H_2O (2 mL) and $[\text{AuCl}_2(\eta^2\text{-C}_6\text{H}_4\text{-2-CH}_2\text{NMe}_2)]$ (**8a**) (4 mg, 1 mol %). The mixture was stirred at 40°C for 24 h, then extracted with CH_2Cl_2 , dried over MgSO_4 and concentrated *in vacuo*. The product was purified by column chromatography on silica gel using hexane/EtOAC eluent to give **PA-5** as a pale yellow oil (0.16 g, 55%). ^1H NMR (CDCl_3 , δ ppm): 7.52 (d, $J_{\text{HH}}=7.3$ Hz, 2 H, Ar-H), 7.39 - 7.46 (m, 2 H, Ar-H), 7.16 - 7.32 (m, 6 H, Ar-H), 5.03 (s, 1 H, C-H), 3.74 (dd, $J_{\text{HH}}=10.9$, 3.6 Hz, 1 H, C-H), 3.45 (dd, $J_{\text{HH}}=10.9$, 2.3 Hz, 1 H, C-H), 3.11 - 3.25 (m, 1 H, C-H), 2.65 - 2.81 (m, 1 H, C-H), 2.46 - 2.62 (m, 1 H, C-H), 1.51 - 1.93 (m, 4 H, C-H). $^{13}\text{C}\{\text{H}\}$ NMR (CDCl_3 , δ ppm): 139.2, 131.9, 128.7, 128.5, 128.4, 128.3, 128.3, 128.1, 127.6, 123.0, 87.9, 85.4, 61.9, 61.8, 56.3, 47.9, 28.1, 23.6. ESMS m/z: 292 (M^++H); HRMS calculated for $\text{C}_{20}\text{H}_{21}\text{NO}$ (M^++H): 292.1696, found: 292.1693.

8.6.7 Synthesis of PA-6

To a dry nitrogen flushed Schlenk flask was added 3-(CF_3)- C_6H_4 (200 μL , 1.5 mmol) dibenzylamine (288 μL , 1.5 mmol), phenylacetylene (246 μL , 2.2 mmol), and $[\text{AuCl}_2(\eta^2\text{-C}_6\text{H}_4\text{-2-CH}_2\text{NMe}_2)]$ (**8a**) (4 mg, 1 mol %). The mixture was stirred at 40°C for 24 h, then extracted with CH_2Cl_2 , dried over MgSO_4 and concentrated *in vacuo*. The product was purified by column chromatography on silica gel using hexane/EtOAC eluent to give **PA-6** as a white solid (0.54 g, 80%). ^1H NMR (CDCl_3 , δ ppm): 7.92 (s, 1 H, Ar-H), 7.83 (d, $J=7.9$ Hz, 1 H, Ar-H), 7.51 - 7.59 (m, 2 H, Ar-H), 7.43 - 7.46 (m, 1 H, Ar-H), 7.23 - 7.41 (m, 12 H, Ar-H), 7.11 - 7.21 (m, 2 H, Ar-H), 4.87 (s, 1 H, C-H), 3.68 (d, $J=13.2$ Hz, 2 H, CH_2), 3.47 (d, $J=13.2$ Hz, 2 H, CH_2). $^{13}\text{C}\{\text{H}\}$ NMR (CDCl_3 , δ ppm): 140.5, 139.1, 132.0, 131.7, 130.5 (q, $J_{\text{CF}}=31.8$ Hz), 128.9, 128.6, 128.6, 128.5, 128.5, 127.3, 125.1 (q, $J_{\text{CF}}=3.84$ Hz), 124.4 (q, $J_{\text{CF}}=3.6$ Hz), 124.3 (q, $^1J_{\text{CF}}=272.48$ Hz), 122.9, 89.4, 83.6, 55.9, 54.8. ESMS m/z: 456 (M^++H); HRMS calculated for $\text{C}_{30}\text{H}_{24}\text{F}_3\text{N}$ (M^++H): 456.1934, found: 456.1928.

8.6.8 Synthesis of PA-7³⁰²

To a dry nitrogen flushed Schlenk flask was added C₅H₄N-2-CHO (150 µL, 1.6 mmol) dibenzylamine (300 µL, 1.6 mmol), phenylacetylene (260 µL, 2.4 mmol), and [AuCl₂(η²-C,N-C₆H₄-2-CH₂NMe₂)] (**8a**) (7 mg, 1 mol %). The mixture was stirred at 40°C for 24 h, then extracted with CH₂Cl₂, dried over MgSO₄ and concentrated *in vacuo*. The product was purified by column chromatography on silica gel using hexane/EtOAC eluent to give a brown oil (0.56 g, 92%). ¹H NMR (CDCl₃, δ ppm): 8.05 (d, *J*_{HH}=6.8 Hz, 1 H, Ar-H), 7.24 - 7.43 (m, 9 H, Ar-H), 7.05 - 7.24 (m, 7 H, Ar-H), 6.57 (s, 1 H, Ar-H), 6.40 (t, *J*_{HH}=7.2 Hz, 1 H, Ar-H), 6.25 (t, *J*_{HH}=6.5 Hz, 1 H, Ar-H), 4.11(s, 4 H, CH₂). ¹³C{¹H} NMR (CDCl₃, δ ppm): 138.4, 131.5, 127.7, 127.5, 127.0, 127.0, 126.6, 126.6, 125.7, 125.6, 121.4, 120.5, 116.7, 113.7, 109.6, 107.2, 58.3. ESMS m/z: 388 (M⁺+H); HRMS calculated for C₂₈H₂₄N₂ (M⁺+H): 389.2013, found: 389.2009.

8.6.9 Synthesis of PA-8

To a dry nitrogen flushed Schlenk flask was added terephthalaldehyde (0.1 g, 0.75 mmol) dibenzylamine (300 µL, 1.6 mmol), phenylacetylene (230 µL, 2 mmol), and [AuCl₂(η²-C,N-C₆H₄-2-CH₂NMe₂)] (**8a**) (3 mg, 1 mol %). The mixture was stirred at 40°C for 48 h, then extracted with CH₂Cl₂, dried over MgSO₄ and concentrated *in vacuo*. The product was purified by column chromatography on silica gel using hexane/EtOAC eluent and isolated as a white solid which was a 1:1 mixture of diastereomers (0.47 g, 89%). ¹H NMR (CDCl₃, δ ppm): 7.64 (m, 8 H, Ar-H), 7.55 (m, 2.0 Hz, 8 H, Ar-H), 7.09 - 7.38 (m, 52 H, Ar-H), 4.84 (br. s, 2H, C-H), 4.83 (br. s, 2H, C-H), 3.70 (d, *J*_{HH}=13.4 Hz, 8 H, CH₂), 3.45 (dd, *J*_{HH}=13.6, 2.8 Hz, 8 H, CH₂). ¹³C{¹H} NMR (CDCl₃, δ ppm): 139.6, 139.6, 138.6, 138.5, 132.0 132.0, 129.0, 128.9, 128.4, 128.4, 128.3, 128.3, 128.3, 128.1, 128.1, 127.0, 123.3, 88.6, 88.6, 84.9, 84.9, 55.9, 55.9, 54.7 (br. s.). ESMS m/z: 697 (M⁺+H); HRMS calculated for C₅₂H₄₄N₂ (M⁺+H): 697.3578, found: 697.3574.

8.6.10 Synthesis of PA-9

To a dry nitrogen flushed Schlenk flask was added isophthalaldehyde (0.1 g, 0.75 mmol) dibenzylamine (300 µL, 1.6 mmol), phenylacetylene (230 µL, 2 mmol), and [AuCl₂(η²-C,N-C₆H₄-2-CH₂NMe₂)] (**8a**) (3 mg, 1 mol %). The mixture was stirred at 40°C for 48 h, then extracted with CH₂Cl₂, dried over MgSO₄ and concentrated *in vacuo*. The product was purified by column chromatography on silica gel using hexane/EtOAC eluent and isolated as a light yellow solid which was a 1:1 mixture of diastereomers (0.44 g, 85%). ¹H

¹H NMR (CDCl₃, δ ppm): 8.48 (s, 1H, Ar-H), 8.36 (s, 1 H, Ar-H), 7.75 - 7.99 (m, 12 H, Ar-H), 7.35 - 7.68 (m, 54 H, Ar-H), 5.21 (s, 2 H, C-H), 5.18 (s, 2 H, C-H), 4.01 (dd, J_{HH}=13.5, 6.7 Hz, 8 H, CH₂), 3.77 (d, J_{HH}=13.6 Hz, 8 H, CH₂). ¹³C{¹H} NMR (CDCl₃, δ ppm): 139.7, 139.7, 139.3, 139.3, 132.2, 129.1, 129.0, 128.6, 128.5, 128.4, 128.4, 128.0, 127.8, 127.6, 127.1, 123.5, 123.5, 89.0, 88.9, 84.9, 84.9, 56.4, 56.3, 54.9, 54.8. ESMS m/z: 697 (M⁺+H); HRMS calculated for C₅₂H₄₄N₂ (M⁺+H): 697.3578, found: 697.3574.

8.6.11 Synthesis of PA-10

To a dry nitrogen flushed Schlenk flask was added benzaldehyde (200 μL, 2 mmol) piperazine (85 mg, 1 mmol), phenylacetylene (324 μL, 3 mmol), and [AuCl₂(η²-C₆N-C₆H₄-2-CH₂NMe₂)] (**8a**) (4 mg, 1 mol %). The mixture was stirred at 40°C for 48 h, then extracted with CH₂Cl₂, dried over MgSO₄ and concentrated *in vacuo*. The product was purified by column chromatography on silica gel using hexane/EtOAC eluent to give **PA-10** as a white solid which was a 1:1 mixture of diastereomers (0.39 g, 85%). ¹H NMR (CDCl₃, δ ppm): 7.49 - 7.59 (m, 8 H, Ar-H), 7.39 - 7.48 (m, 8 H, Ar-H), 7.19 - 7.35 (m, 24 H, Ar-H), 4.73 (br. s, 4 H, C-H), 2.60 (br. s, 16 H, CH₂). ¹³C{¹H} NMR (CDCl₃, δ ppm): 138.2, 138.2, 131.9, 128.6, 128.3, 128.1, 127.6, 123.2, 88.0, 87.9, 85.9, 85.8, 61.7, 61.7, 49.7 (br. s). ESMS m/z: 467 (M⁺+H); HRMS calculated for C₃₄H₃₀N₂ (M⁺+H): 467.2482, found: 467.2481.

8.6.12 Synthesis of PA-11

To a dry nitrogen flushed Schlenk flask was added benzaldehyde (153 μL, 1.5 mmol) dibenzylamine (290 μL, 1.6 mmol), 1,3-diethynylbenzene (0.1 g, 0.8 mmol), and [AuCl₂(η²-C₆N-C₆H₄-2-CH₂NMe₂)] (**8a**) (3 mg, 1 mol %). The mixture was stirred at 40°C for 48 h, then extracted with CH₂Cl₂, dried over MgSO₄ and concentrated *in vacuo*. The product was purified by column chromatography on silica gel using hexane/EtOAC eluent and isolated as a white solid which was a 1:1 mixture of diastereomers (0.41 g, 75%). ¹H NMR (CDCl₃, δ ppm): 7.78 (s, 2 H, Ar-H), 7.67 (d, J_{HH}=7.8 Hz, 8 H, Ar-H), 7.56 (dd, J_{HH}=7.8, 1.5 Hz, 4 H, Ar-H), 7.15 - 7.40 (m, 54 H, Ar-H), 4.90 (br. s, 4 H, Ar-H), 3.75 (d, J_{HH}=13.6 Hz, 8 H, CH₂), 3.50 (d, J_{HH}=13.6 Hz, 8 H, CH₂). ¹³C{¹H} NMR (CDCl₃, δ ppm): 139.5, 139.0, 135.1, 131.8, 128.9, 128.6, 128.4, 128.3, 128.2, 127.6, 127.1, 123.7, 87.9, 85.7, 56.1, 54.7. ESMS m/z: 697 (M⁺+H); HRMS calculated for C₅₂H₄₄N₂ (M⁺+H): 697.3578, found: 697.3574.

8.6.13 Synthesis of PA-12

To a dry nitrogen flushed Schlenk flask was added ferrocene-1-1'-dicarbaldehyde (0.12 g, 0.5 mmol) dibenzylamine (190 μ L, 1 mmol), phenylacetylene (131 μ L, 1.2 mmol), and [AuCl₂(η^2 -C,N-C₆H₄-2-CH₂NMe₂)] (**8a**) (3 mg, 1 mol %). The mixture was stirred at 40 °C for 48 h, then extracted with CH₂Cl₂, dried over MgSO₄ and concentrated *in vacuo*. The product was purified by column chromatography on silica gel using hexane/EtOAC eluent and isolated as a red solid which was a 1:1 mixture of diastereomers (0.38 g, 95%). ¹H NMR (CDCl₃, δ ppm): 7.38 - 7.61 (m, 8 H, Ar-H), 7.08 - 7.35 (m, 52 H, Ar-H), 4.68 (s, 2 H, C-H), 4.64 (s, 2 H, C-H), 4.27 - 4.47 (m, 4 H, Fc-H), 4.16 (d, J_{HH} =1.5 Hz, 4 H, Fc-H), 3.82 - 4.05 (m, 8 H, Fc-H), 3.65 (d, J_{HH} =5.8 Hz, 4 H, CH₂), 3.62 (d, J_{HH} =5.8 Hz, 4 H, CH₂), 3.44 (d, J_{HH} =3.5 Hz, 4 H, CH₂), 3.40 ppm (d, J_{HH} =3.5 Hz, 4 H, CH₂). ¹³C{¹H} NMR (CDCl₃, δ ppm): 138.8, 130.8, 130.8, 127.6, 127.6, 127.3, 127.3, 127.1, 127.1, 127.0, 127.0, 125.8, 25.7, 122.5, 122.5, 85.6, 85.6, 85.5, 84.5, 84.4, 69.2, 69.0, 68.8, 68.6, 68.6, 68.4, 68.3, 67.9, 54.4, 54.4, 52.9, 52.9. ESMS m/z: 804 (M⁺); HRMS calculated for C₅₆H₄₈N₂Fe (M⁺): 804.3162, found: 804.3177.

8.6.14 Synthesis of PA-13³⁰⁷

To a dry nitrogen flushed Schlenk flask was added cyclohexanone (150 μ L, 1.5 mmol) morpholine (84 μ L, 1 mmol), phenylacetylene (159 μ L, 1.5 mmol), and [AuCl₂(η^2 -C,N-C₆H₄-2-CH₂NMe₂)] (**8a**) (20 mg, 5 mol %). The mixture was stirred at 60°C for 8 h, then extracted with CH₂Cl₂, dried over MgSO₄ and concentrated *in vacuo*. The product was purified by column chromatography on silica gel using hexane/EtOAC eluent to give **PA-13** as a light brown oil (0.16 g, 60%). ¹H NMR (CDCl₃, δ ppm): 7.29 - 7.40 (m, 2 H, Ar-H), 7.15 - 7.24 (m, 3 H, Ar-H), 3.63 - 3.71 (m, 4 H, CH₂), 2.58 - 2.69 (m, 4 H, CH₂), 1.94 (m, 2 H, CH₂), 1.59 - 1.69 (m, 2 H, CH₂), 1.47 - 1.59 (m, 2 H, CH₂), 1.36 - 1.45 (m, 2 H, CH₂), 1.03 - 1.29 (m, 2 H, CH₂). ¹³C{¹H} NMR (CDCl₃, δ ppm): 130.7, 127.2, 126.8, 122.4, 88.8, 85.4, 66.4, 57.8, 45.6, 34.4, 24.7, 21.7. ESMS m/z: 270 (M⁺+H); HRMS calculated for C₁₈H₂₃NO (M⁺+H): 270.1853, found: 270.1855.

8.7 Preparation and screening of chiral gold complexes

8.7.1 Synthesis of (S)-(-)-N,N-Dimethyl-1-phenylethylamine (**123**)³¹⁹

(S)-(-)- α -Methylbenzylamine (16.8 g, 138.5 mmol) was added to formic acid (30 mL, 98-100%) and 37% aqueous formaldehyde (25 mL) and the mixture refluxed for 2.5 h. Concentrated HCl (12 mL) was added and the acidic layer separated then made alkaline

with K_2CO_3 (50% solution). The resulting solution was extracted with Et_2O (3 x 25 mL) and the organic phase separated and dried over MgSO_4 . Removal of the solvent afforded crude (*S*)-(–)-*N,N*-Dimethyl-1-phenylethylamine, which was purified by distillation (b.p. 70°C at 8 mmHg) to give **123** as a colourless oil (13.3 g, 64%). ^1H NMR (CDCl_3 , δ ppm): 7.08 - 7.38 (m, 5 H, Ar-H), 3.14 (q, $J_{HH} = 6.8$ Hz, 1 H, C-H), 2.10 (s, 6 H, NMe_2), 1.28(d, $J_{HH} = 6.6$ Hz, 3 H, CH_3). $^{13}\text{C}\{\text{H}\}$ NMR (CDCl_3 , δ ppm): 144.2, 128.2, 127.5, 126.9, 66.0, 43.3, 20.3. Calculated for $\text{C}_{10}\text{H}_{15}\text{N}$: C, 80.5; H, 10.1; N, 9.4; Found: C, 80.9; H, 10.1; N, 9.0. $\alpha_D^{25} = -65.8^\circ$ ($c = 1$, MeOH).

8.7.2 Preparation of (*S*)-2-[1-(dimethylamino)ethyl]phenyllithium (**124**) ³²⁰

To a solution of (*S*)-(–)-*N,N*-Dimethyl-1-phenylethylamine (**123**) (6.7 g, 44.6 mmol) in hexane (30 mL) under argon was added *t*-butyllithium (32 mL, 51.2 mmol, 1.6 M in pentane) and the mixture stirred for 24 h. The white precipitate was filtered under argon, washed with hexane (3 x 15 mL) and dried *in vacuo*. It was then transferred to a glovebox for storage. Yield 4.7 g, 68%.

8.7.3 Preparation of (*S*)-[$\text{SnClMe}_2(\eta^2\text{-C}_6\text{H}_4\text{CH(Me)NMe}_2)$] (**125**)

To dimethyltin dichloride (2.5 g, 11.2 mmol) in Et_2O (20 mL) at -78°C was added a solution of (*S*)-2-[1-(*N,N*-dimethylamino)ethyl]phenyllithium (**124**) (1.7 g, 11.2 mmol) in Et_2O (30 mL), and the mixture stirred for 1 h before warming to room temperature overnight. The solvent was removed *in vacuo* and the mixture extracted with CH_2Cl_2 . The CH_2Cl_2 was removed under reduced pressure to leave an oily residue. The oil was stirred in hexane to give a white solid which was collected by filtration. Recrystallisation from MeOH gave pure (*S*)-[$\text{SnClMe}_2(\eta^2\text{-C}_6\text{H}_4\text{CH(Me)NMe}_2)$] **125** as a white solid (3.2 g, 86%). ^1H NMR (CDCl_3 , δ ppm): 8.20 (dd, $J = 5.27, 3.39$ Hz, 1 H, Ar-H), 7.24 - 7.35 (m, 2 H, Ar-H), 7.03 - 7.15 (m, 1 H, Ar-H), 3.53 - 3.68 (q, $^3J_{HH} = 6.78$ Hz, 1 H, C-H), 2.28 (s, 3 H, NMe), 2.09 (s, 3 H, NMe), 1.33 (d, $^3J_{HH} = 6.78$ Hz, 3 H, CH_3), 0.75 (s, $^2J_{HSn} = 64.43/67.06$ Hz, 3 H, SnMe_2Cl), 0.68 (s, $^2J_{HSn} = 62.17/65.18$ Hz, 3 H, SnMe_2Cl). $^{13}\text{C}\{\text{H}\}$ NMR (CDCl_3 , δ ppm): 145.6 ($^2J_{CSn} = 38.83/40.88$ Hz), 137.4 ($^1J_{CSn} = 720.53/752.99$ Hz), 136.1 ($J_{CSn} = 44.79$ Hz), 127.8 ($J_{CSn} = 13.57$ Hz), 125.9 ($J_{CSn} = 67.01/70.10$ Hz), 123.8 ($J_{CSn} = 58.09/60.91$ Hz), 63.5 ($^2J_{CSn} = 28.34$ Hz), 43.2, 37.0, 13.2, 0.0 ($^1J_{CSn} = 501.48/524.73$ Hz), -2.0 ($^1J_{CSn} = 477.41/499.58$ Hz). $^{119}\text{Sn}\{\text{H}\}$ NMR (150 MHz, CDCl_3 , δ ppm): -52.29. Calculated for $\text{C}_{12}\text{H}_{20}\text{ClNSn}$: C, 43.33; H, 6.07; N, 4.2; Found: C, 43.24; H, 5.97; N, 4.19. $\alpha_D^{24} = +25.2^\circ$ ($c = 1$, MeOH).

8.7.4 Preparation of (*S*)-[AuCl₂(η^2 -C,N-C₆H₄CH(Me)NMe₂)] (**126**)

To (*S*)-[SnClMe₂(η^2 -C,N-C₆H₄CH(Me)NMe₂)] (**125**) (0.17 g, 0.5 mmol) in MeCN (5 mL) was added Na[AuCl₄]. 2H₂O (0.2 g, 0.5 mmol) and the mixture refluxed for 12 h. The solvent was removed *in vacuo* to leave an oily residue which was washed with H₂O and hexane. The remaining solid was extracted into CH₂Cl₂ (5 mL) and filtered, dried over MgSO₄ and hexane added (7 mL). The CH₂Cl₂ was slowly removed under reduced pressure to afford (*S*)-[AuCl₂(η^2 -C,N-C₆H₄CH(Me)NMe₂)] **126** as an off-white solid which was collected by filtration (0.18 g, 85%). ¹H NMR (CDCl₃, δ ppm): 7.73 - 7.84 (m, 1 H, Ar-H), 7.12 - 7.43 (m, 2 H, Ar-H), 7.07 (dd, J_{HH}=7.4, 1.4 Hz, 1 H, Ar-H), 4.37 (q, ³J_{HH}=6.5 Hz, 1 H, C-H), 3.34 (s, 3 H, NMe), 3.19 (s, 3 H, NMe), 1.71 (d, ³J_{HH}=6.6 Hz, 3 H, CH₃). ¹³C{¹H} NMR (CDCl₃, δ ppm): 148.9, 147.7, 131.4, 129.1, 128.3, 123.6, 79.3, 53.3, 48.8, 19.9. Calculated for C₁₀H₁₄AuCl₂N: C, 28.85; H, 3.39; N, 3.37; Found: C, 28.98; H, 3.15; N, 3.17. α_D²⁴ = +82.0° (c=1, CH₂Cl₂).

8.7.5 Preparation of (*S*)-[Au(PPh₃)(η^1 -C₆H₄CH(Me)NMe₂)] (**127**)

To [ClAu(THT)] (0.4 g, 1.3 mmol) in Et₂O (15 mL) at -78°C under argon was added (*S*)-2-[1-(*N,N*-dimethylamino)ethyl]phenyllithium (**124**) (0.25 g, 1.6 mmol) in Et₂O (25 mL) and the reaction stirred for 1.5 h. PPh₃ (0.34 g, 1.29 mmol) was added and the mixture stirred for 1.5 h before warming to room temperature overnight. The Et₂O was removed under reduced pressure and the residue extracted into CH₂Cl₂ and filtered. The solvent was then removed in vacuo and the crude mixture stirred in hexane to give a solid which was collected by filtration. Subsequent recrystallization of the powder with CH₂Cl₂/hexane gave pure (*S*)-[Au(PPh₃)(η^1 -C₆H₄CH(Me)NMe₂)] (**127**) as a off-white solid (0.64 g, 82%). ¹H NMR (CDCl₃, δ ppm): 7.53 (dd, J=7.8, 1.5 Hz, 3 H, Ar-H), 7.56 (dd, J=7.7, 1.6 Hz, 3 H, Ar-H), 7.32 - 7.50 (m, 11 H, Ar-H), 7.01 - 7.14 (m, 2 H, Ar-H), 3.83 (d, ³J_{HH}=6.6 Hz, 1 H, C-H), 2.18 (s, 6 H, NMe₂), 1.37 (d, ³J_{HH}=6.6 Hz, 3 H, CH₃). ¹³C{¹H} NMR (CDCl₃, δ ppm): 172.8 (d, J_{CP}=112.60 Hz), 153.6 (d, J_{CP}=2.77 Hz), 139.2, 134.4 (d, J_{CP}=13.84 Hz), 131.3 (d, J_{CP}=47.99 Hz), 131.1 (d, J_{CP}=1.85 Hz), 129.0 (d, J_{CP}=11.08 Hz), 125.9 (d, J_{CP}=6.46 Hz), 125.8 (d, J_{CP}=5.54 Hz), 125.7, 72.3 (d, J_{CP}= 1.76 Hz), 44.6, 22.4. ³¹P{¹H} NMR (CDCl₃, δ ppm): 44.09. Calculated for C₂₈H₂₉AuNP: C, 55.34; H, 4.81; N, 2.31; P, 5.10; Found: C, 55.32; H, 4.74; N, 2.24; P, 4.90. α_D²⁸ = -64.5° (c=1 CH₂Cl₂).

8.7.6 Synthesis of PINAPAuCl (**128**)³²³

To a stirred solution of ClAu(THT) (0.05 g, 0.16 mmol) in CH₂Cl₂ (10 mL) was added (*R*)-(+)-4-[2-(Diphenylphosphenyl)-1-naphthyl]-*N*-[(*R*)-1-phenyl-ethyl]-1-phthalazinamine (0.1 g, 0.18 mmol) and the mixture stirred for 18 h. The mixture was concentrated under reduced pressure and hexane (10 mL) added to precipitate PINAPAuCl (**128**) as a white solid(0.09 g, 72%). ¹H and ¹³C{¹H} NMR data were comparable to that previously reported.³²³ ³¹P{¹H} NMR (OC(CD₃)₂, δ ppm):= 30.48 (s). Calculated for C₃₈H₃₀AuClN₃P: C, 57.60; H, 3.82; N, 5.31; Found: C, 56.70; H, 4.01; N, 5.22. $\alpha_D^{26} = -60.48^\circ$ (c=0.835, CH₂Cl₂).

8.7.7 Preparation of 1,3-bis((S)-1'-phenylethyl)imidazolium tetrafluoroborate (**135**)³⁶⁸

To a vigorously stirred solution of (*S*)-(−)-α-methylbenzylamine (2.5 g, 20.6 mmol) in toluene (25 mL) was added paraformaldehyde (0.62 g, 20.6 mmol). After 30 min the solution was cooled to 0 °C and another equivalent of (*S*)-(−)-α-methylbenzylamine (2.5 g, 20.6 mmol) was added along with HBF₄ (3.6 g, 20.6 mmol, 50% aqueous solution) and the solution stirred for 15 min. The cooling bath was removed and glyoxal (3 g, 20.6 mmol, 40% aqueous solution) slowly added. The mixture was stirred for 30 min at room temperature then heated to 40 °C for 12 h. The mixture was cooled to room temperature, then diluted with Et₂O (15 mL) and saturated Na₂CO₃ (1.5 mL). The phases were separated, and the aqueous layer washed with CH₂Cl₂. The combined organic layers were washed with brine, dried over MgSO₄ and concentrated under reduced pressure. The oily residue was triturated with cold Et₂O to give pure 1,3-bis((*S*)-1'-phenylethyl)imidazolium tetrafluoroborate (**135**) as a orange oil (3.13 g, 43%). ¹H NMR (CDCl₃, δ ppm): 9.40 (br. s, 1 H, N₂C-H), 7.17 - 7.49 (m, 10 H, Ar-H), 5.76 (s, 2 H, N-CH), 3.48 (q, ³J_{HH}=7.0 Hz, 2 H, C-H), 1.76 - 2.08 (m, 6 H, CH₃). ¹³C{¹H} NMR (CDCl₃, δ ppm): 137.8, 134.3, 129.5, 129.4, 127.0, 121.1, 60.2, 20.8.

8.7.8 Preparation of 1,3-bis((S)-1'-phenylethyl)imidazolium Chloride (**136**)³⁶⁹

To a vigorously stirred solution of (*S*)-(−)-α-methylbenzylamine (2.5 g, 20.6 mmol) in toluene (25 mL) was added paraformaldehyde (0.62 g, 20.6 mmol). After 30 min the mixture was cooled to 0 °C and another equivalent of (*S*)-(−)-α-methylbenzylamine (2.5 g, 20.6 mmol) was added followed by HCl (6.88 mL, 20.6 mmol, 3 M). After 15 min the ice

bath was removed and glyoxal (3 g, 20.6 mmol, 40% aqueous solution) slowly added. The mixture was stirred for 12 h at 40 °C and then cooled to room temperature. Et₂O (25 mL) and saturated Na₂CO₃ (5 ml) was added, the phases separated and the aqueous layer washed with CH₂Cl₂ (30 mL). The organic phase was dried over MgSO₄ and concentrated *in vacuo*. The residue was triturated with Et₂O to give 1,3-bis((S)-1'-phenylethyl)imidazolium Chloride (**136**) as an off-white powder (4.4 g, 68%). ¹H NMR (CDCl₃, δ ppm): 11.28 (s, 1 H, N₂CH), 7.19 - 7.43 (m, 10 H, Ar-H), 7.00 - 7.19 (m, 2 H, NCH), 5.98 (q, ³J_{HH}=6.7 Hz, 2 H, N-CH-Ph), 1.95 (d, ³J_{HH}=7.0 Hz, 6 H, CH₃). ¹³C{¹H} NMR (CDCl₃, δ ppm): 138.0, 136.8, 129.4, 129.3, 127.1, 120.4, 59.9, 21.2. ESMS m/z: 347 (M⁺+HCl); HRMS calculated for C₁₉H₂₁N₂Cl₂ (M⁺+HCl): 347.1087, found: 347.1087.

8.7.9 Preparation of 1,3-bis((S)-1'-phenylethyl) imidazolin-2-ylidene silver chloride (137**)^{368,371}**

To a stirred solution of 1,3-bis((S)-1'-phenylethyl)imidazolium Chloride (**136**) (0.2 g, 0.64 mmol) in CH₂Cl₂ (15 mL) was added Ag₂O (0.096g, 0.4 mmol) and the mixture heated to 40 °C for 24 h in the dark. After cooling to room temperature the mixture was filtered through celite and concentrated under reduced pressure. Hexane (15 mL) was added to precipitate 1,3-bis((S)-1'-phenylethyl) imidazolin-2-ylidene silver chloride (**137**) as a white solid (0.2 g, 85%). ¹H NMR (CDCl₃, δ ppm): 7.11 - 7.38 (m, 10 H, Ar-H), 6.85 (s, 2 H, NCH), 5.70 (q, ³J_{HH}=7.2 Hz, 2 H, N-CH-Ph), 1.78 (d, ³J_{HH}=7.0 Hz, 6 H, CH₃). ¹³C{¹H} NMR (CDCl₃, δ ppm): 139.7, 129.1, 128.6, 126.6, 118.8, 61.0, 21.4. Calculated for C₁₉-H₂₀AgClN₂: C, 54.35; H, 4.80; N, 6.68; Found: C, 54.89; H, 4.86; N, 6.70. $\alpha_D^{28} = -165.54^\circ$ (c=0.74, CH₂Cl₂)

8.7.10 Preparation of 1,3-bis((S)-1'-phenylethyl) imidazolin-2-ylidene gold chloride (138**)**

To a stirred solution of 1,3-bis((S)-1'-phenylethyl)imidazolium silver chloride (**137**) (0.12 g, 0.29 mmol) in CH₂Cl₂ (15 mL) was added ClAu(THT) (0.09 g, 0.29 mmol) and the mixture stirred for 24 h. The solution was filtered through a Celite/silica plug and hexane added (10 mL). The CH₂Cl₂ was removed under reduced pressure to afford 1,3-bis((S)-1'-phenylethyl) imidazolin-2-ylidene gold chloride (**138**) as a off-white solid which was collected by filtration (0.13 g, 92%). ¹H NMR (CDCl₃, δ ppm): 7.24 - 7.43 (m, 10 H, Ar-H), 6.75 (s, 2 H, NCH), 6.10 (q, ³J_{HH}=7.2 Hz, 2 H, N-CH-Ph), 1.77 (d, ³J_{HH}=7.0 Hz, 6 H,

CH_3). $^{13}\text{C}\{\text{H}\}$ NMR (CDCl_3 , δ ppm): 170.0, 139.3, 129.0, 128.6, 126.8, 118.2, 60.1, 20.8. Calculated for $\text{C}_{19}\text{H}_{20}\text{AuClN}_2$: C, 44.83; H, 3.96; N, 5.51; Found: C, 44.85; H, 4.05; N, 5.47. ESMS m/z: 543 ($\text{M}^- + \text{Cl}$); HRMS calculated for $\text{C}_{19}\text{H}_{20}\text{N}_2\text{Cl}_2\text{Au}$ ($\text{M}^- + \text{Cl}$): 543.0674, found: 543.0668. $\alpha_D^{28} = -213^\circ$ ($c=1$, CH_2Cl_2).

8.7.11 Direct route to 1,3-bis((S)-1'-phenylethyl) imidazolin-2-ylidene gold chloride (138)

To 1,3-bis((S)-1'-phenylethyl)imidazolium tetrafluoroborate (**135**) (0.16 g, 0.43 mmol) was added K_2CO_3 (0.25 g, 1.8 mmol) and 3-chloropyridine (2 mL) and the mixture stirred at 80 °C for 2 h. After cooling to room temperature ClAu(THT) (0.14 g, 0.43 mmol) was added and the mixture stirred for 12 h before heating to 60 °C for 2 hours. The slurry was extracted with CH_2Cl_2 (15 mL) and filtered through a Celite/silica plug. The CH_2Cl_2 was removed *in vacuo* and the oily residue triturated with hexane (15 mL) to give 1,3-bis((S)-1'-phenylethyl) imidazolin-2-ylidene gold chloride (**138**) as an off-white powder which was collected by filtration (0.1 g 44%).

8.7.12 Screening of chiral complexes in A³-reaction

To a dry nitrogen flushed Schlenk flask was added benzaldehyde (100 μL , 1 mmol) dibenzylamine (189 μL , 1.1 mmol), phenylacetylene (162 μL , 1.5 mmol), H_2O (2 mL) and chiral-[Au complex] (1 mol %). The mixture was stirred at 40°C for 24 h, then extracted with CH_2Cl_2 , dried over MgSO_4 and concentrated *in vacuo*. The product was purified by column chromatography on silica gel using hexane/EtOAC eluent.

8.7.13 Preparation of [PhCCAu]_n (**139**)^{148,375}

To a stirred solution of [ClAu(THT)] (**25**) (0.22 g, 0.69 mmol) in CH_2Cl_2 (10 mL) was added phenylacetylene (76 μL , 0.69 mmol). NEt_3 (143 μL , 1.03 mmol) was added and a yellow precipitate was formed upon stirring for 1 h. The precipitate was filtered and washed with CH_2Cl_2 and Et_2O (0.13 g, 63%). Calculated for $\text{C}_8\text{H}_5\text{Au}$: C, 32.21; H, 1.69; Found: C, 31.97; H, 1.70.

8.7.14 A³-reactions in MeCN

To a dry nitrogen flushed Schlenk flask was added benzaldehyde (100 μ L, 1 mmol) dibenzylamine (189 μ L, 1 mmol), phenylacetylene (162 μ L, 1.5 mmol), acetonitrile (2 mL) and [AuCl₂(η^2 -C,N-C₆H₄CH₂NMe₂)] (**8a**) or (*S*)-[AuCl₂(η^2 -C,N-C₆H₄CH(Me)NMe₂)] (**126**) (3 mol %). The mixture was stirred at 60°C for 24 h, then concentrated *in vacuo*. The diastereoselectivity was determined by ¹H NMR analysis of the crude reaction mixture.

8.8 NMR-tube Experiments

To an oven-dried J-Young NMR tube was added benzaldehyde (100 μ L, 1 mmol), dibenzylamine (189 μ L, 1 mmol) and [Au] catalyst (0.03 mmol). Water (1.5 mL) and phenylacetylene (162 μ L, 1.5 mmol) were added, and the tube shaken and transferred to the NMR probe. The reaction was monitored by ¹H spectroscopy at 60 °C.

8.8.1 Preparation of [PhCCAuPPh₃] (**140**) ³⁷⁷

To phenylacetylene (110 μ L, 1 mmol) in Et₂O (15 mL) at 0°C was added *n*-butyllithium (0.68 mL, 1.1 mmol, 1.6 M in hexanes) and the solution stirred for 20 min. [ClAuPPh₃] (0.5 g, 1 mmol) was added and the mixture stirred at room temperature for 18 h. The Et₂O was removed *in vacuo* and the residue extracted into CH₂Cl₂ (15 mL) and filtered through celite. Hexane (10 mL) was added and the CH₂Cl₂ removed under reduced pressure to precipitate [PhCCAuPPh₃] (**140**) as a white solid which was collected by filtration (0.45 g, 80%). ¹H NMR (CDCl₃, δ ppm): 7.39 - 7.62 (m, 16 H, Ar-H), 7.12 - 7.37 (m, 4 H, Ar-H). ¹³C{¹H} NMR (CDCl₃, δ ppm): 134.3 (d, J_{CP} =13.6 Hz), 132.4, 131.6 (d, J_{CP} =2.2 Hz, 129.8 (d, J_{CP} =55.59 Hz), 129.2 (d, J_{CP} = 10.9 Hz), 127.9, 126.8, 124.9. ³¹P{¹H} NMR (CDCl₃, δ ppm): 42.28. Calculated for C₂₆H₂₀AuP: C, 55.70; H, 3.60; Found: C, 55.33; H, 3.45.

8.8.2 Synthesis of 1,3-bis(2,4,6-trimethylphenyl)imidazolin-2-ylidene gold(I) chloride (**141**)^{355,356}

The diazadiene precursor was prepared according to literature methods:³⁹³ Glyoxal (2.7 g, 18.5 mmol, 40% aqueous solution) was added to a vigorously stirred solution of 2,4,6-trimethylaniline (5 g, 37 mmol) in ⁱPrOH (50 mL) at 50 °C. One drop of acetic acid was added and the mixture stirred at room temperature for 10 h. The resulting suspension was filtered and washed with ⁱPrOH to give bis(2,4,6-trimethylphenyl)diazabutadiene as a

bright yellow solid (4 g, 74%). ^1H NMR (CDCl_3 , δ ppm): 8.02 (s, 2 H, NCH), 6.83 (s, 4 H, Ar-H), 2.22 (s, 6 H, CH_3), 2.04 - 2.12 (m, 12 H, CH_3). $^{13}\text{C}\{\text{H}\}$ NMR (CDCl_3 , δ ppm): 163.5, 147.5, 134.3, 129.0, 126.6, 20.8, 18.2.

1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride:³⁹³

1,3-bis(2,4,6-trimethylphenyl)diazabutadiene (1 g, 3.42 mmol) and paraformaldehyde (0.10 g, 3.43 mmol) were heated at 70 °C in EtOAc (20 mL). A solution of trimethylsilyl chloride (0.43 mL, 3.43 mmol) in EtOAc was added dropwise with vigorous stirring and the resulting mixture stirred for 2 h. After cooling to 10 °C the mixture was filtered and the solid washed with EtOAc to give 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride as an off-white powder (0.63 g, 53%). ^1H NMR (CDCl_3 , δ ppm): 11.00 (s, 1 H, N_2CH), 7.52 - 7.63 (m, 2 H, NCH), 7.05 (s, 4 H, Ar-H), 2.36 (s, 6 H, CH_3), 1.99 - 2.28 (m, 12 H, CH_3). $^{13}\text{C}\{\text{H}\}$ NMR (CDCl_3 , δ ppm): 141.2, 139.6, 134.1, 130.7, 129.9, 124.6, 21.1, 17.6.

Synthesis of 1,3-bis(2,4,6-trimethylphenyl)imidazolin-2-ylidene gold(I) chloride (**141**)

Potassium carbonate (0.26 g, 1.9 mmol), K[AuCl₄] (0.15 g, 0.4 mmol) and 3-chloropyridine (0.5 mL) were stirred at 80 °C for 24 h. After cooling the slurry was extracted with CH₂Cl₂ (15 mL) and filtered through a celite plug. Hexane was added (15 mL) and the CH₂Cl₂ removed slowly under reduced pressure to give 1,3-bis(2,4,6-trimethylphenyl)imidazolin-2-ylidene gold(I) chloride (**141**) as an off-white powder (0.14 g, 61%) which was collected by filtration. ^1H NMR (CDCl_3 , δ ppm): 7.02 (s, 2 H, NCH), 6.92 (s, 4 H, Ar-H), 2.28 (s, 6 H, CH_3), 2.03 ppm (s, 12 H, CH_3). $^{13}\text{C}\{\text{H}\}$ NMR (CDCl_3 , δ ppm): 173.5, 139.8, 134.7, 134.7, 129.5, 122.2, 21.1, 17.8. Calculated for C₂₁H₂₄AuN₂Cl: C, 46.96; H, 4.51; N, 5.22; Found: C, 46.87; H, 4.23; N, 5.20.

8.8.3 Synthesis of 1,3-bis(2,4,6-trimethylphenyl)imidazolin-2-ylidene gold(III) trichloride (**142**)³⁵⁸

To 1,3-bis(2,4,6-trimethylphenyl)imidazolin-2-ylidene gold(I) chloride (**141**) (0.1 g, 0.19 mmol) in CH₂Cl₂ (5 mL) was added PhICl₂ (0.06 g, 0.22 mmol) and the mixture stirred at room temperature overnight. The solution was filtered through a silica/celite plug and hexane added (10 mL). The CH₂Cl₂ was slowly removed under reduced pressure to give pure 1,3-bis(2,4,6-trimethylphenyl)imidazolin-2-ylidene gold(III) trichloride (**142**) as a pale yellow solid (0.1 g, 88%). ^1H NMR (CDCl_3 , δ ppm): 7.32 (s, 2 H, NCH), 7.05 (s, 4 H,

Ar-H), 2.39 (s, 6 H, CH₃), 2.28 ppm (s, 12 H, CH₃). ¹³C{¹H} NMR (CDCl₃, δ ppm): 145.1, 141.1, 135.3, 132.4, 130.0, 125.6, 21.2, 18.6. Calculated for: C₂₁H₂₄AuN₂Cl₃: C, 41.48; H, 3.98; N, 4.61; Found: C, 41.43; H, 3.81; N, 4.54.

8.8.4 Synthesis of 1,3-bis(2,4-difluorophenyl)imidazolium chloride (**143**)³⁷⁸

To a stirred solution of 2,4-difluoroaniline (5 g, 38.7 mmol) in toluene (20 mL) was added paraformaldehyde (0.58 g, 19.3 mmol) and the mixture heated to 100 °C until the solids were dissolved. The resulting solution was cooled to 40 °C and glyoxal was added (2.8 g, 19.3 mmol, 40% aqueous solution) and the solution stirred for 5 min, before HCl (6.5 mL, 19.3 mmol, 3 M) was added dropwise. The mixture was then heated to 100 °C for 12 h, before cooling to room temperature. The solvent was removed *in vacuo* to give a dark slurry, which was repeatedly washed with Et₂O and THF. Recrystallisation from DMSO/diethyl ether gave 1,3-bis(2,4-difluorophenyl)imidazolium chloride (**143**) as an off-white powder (3.84 g, 60%). ¹H NMR (DMSO-d₆, δ ppm): 10.36 (s, 1 H, N₂CH), 8.51 (s, 2 H, NCH), 8.14 (td, *J*=8.9, 5.7 Hz, 2 H, Ar-H), 7.87 (ddd, *J*=11.2, 8.8, 2.8 Hz, 2 H, Ar-H), 7.48 - 7.60 ppm (m, 2 H, Ar-H). ¹³C{¹H} NMR (DMSO-d₆): 162.9 (dd, ¹J_{CF}=239.47, ³J_{CF}= 11.60 Hz), 155.2 (dd, ¹J_{CF}=241.08, ³J_{CF}= 13.50 Hz), 138.84, 128.8 (d, *J*_{CF}=10.7 Hz), 123.9 (d, *J*_{CF}=2.39 Hz), 119.4 (dd, *J*_{CF}= 3.95, 7.47 Hz), 113.0 (dd, *J*_{CF}=19.47, 3.78 Hz), 106.0 (dd, *J*_{CF}=23.39, 4.44 Hz). ¹⁹F{¹H} NMR (DMSO-d₆, δ ppm): -105.4 (d, ⁴J_{FF}=8.5 Hz), -118.5 (d, ⁴J_{FF}=8.5 Hz).

8.8.5 Synthesis of 1,3-bis(2,4-difluorophenyl)imidazolin-2-ylidene gold(I) chloride (**144**)

To 1,3-bis(2,4-difluorophenyl)imidazolium chloride (**143**) (0.1 g, 0.3 mmol) in CH₂Cl₂ (10 mL) was added Ag₂O (0.045 g, 0.19 mmol) and the mixture stirred in the dark for 24 h. The suspension was filtered through celite and ClAu(THT) (0.09 g, 0.3 mmol) added. The resulting mixture was stirred for 24 h and filtered through a celite/silica plug, the solvent was removed *in vacuo*, and then CH₂Cl₂ (5 mL) added. Hexane (10 mL) was added to the solution and the CH₂Cl₂ removed under reduced pressure to afford 1,3-bis(2,4-difluorophenyl)imidazolin-2-ylidene gold(I) chloride (**144**) as a white solid which was collected by filtration (0.13 g, 81%). ¹H NMR (CDCl₃, δ ppm): 7.76 (td, *J*=8.8, 5.5 Hz, 2 H, Ar-H), 7.28 (d, *J*=1.3 Hz, 2 H, Ar-H), 7.19 (s, 2 H, NCH), 6.96 - 7.05 ppm (m, 2 H, Ar-H). ¹³C{¹H} NMR (CDCl₃, δ ppm): 172.9, 162.2 (dd, ¹J_{CF}=242.72, ³J_{CF}=12.00 Hz),

155.5 (dd, $^1J_{CF} = 242.72$, $^3J_{CF} = 12.92$ Hz), 128.6 (d, $J_{CF} = 10.15$ Hz), 121.9(m, 2C), 111.6 (dd, $J_{CF} = 18.46$, 4.61 Hz), 104.6 (dd, $J_{CF} = 23.07$, 3.69 Hz). $^{19}F\{^1H\}$ NMR ($CDCl_3$, δ ppm): -105.0 (d, $^4J_{FF} = 8.3$ Hz), -117.9 (d, $^4J_{FF} = 8.3$ Hz). Calculated for: $C_{15}H_8AuClF_4N_2$: C, 34.32; H, 1.54; N, 5.34; Found: C, 34.51; H, 1.84; N, 5.25. ESMS m/z: 559 ($M^- + Cl$); HRMS calculated for $C_{15}H_8N_2Cl_2F_4Au$ ($M^- + Cl$): 558.9671, found: 558.9655.

8.9 Solvent screening experiments

8.9.1 Reactions in $CHCl_3$

To a dry flask was added benzaldehyde (100 μ L, 1 mmol) dibenzylamine or piperidine (1 mmol), phenylacetylene (162 μ L, 1.5 mmol), $CHCl_3$ (2 mL) and Au catalyst (1 mol %). The mixture was heated to reflux and stirred for 24 h, then concentrated *in vacuo*. The conversion was determined by 1H NMR analysis of the crude reaction mixture.

8.9.2 Reactions in CF_3CH_2OH

To a dry flask was added benzaldehyde (100 μ L, 1 mmol) dibenzylamine or piperidine (1 mmol), phenylacetylene (162 μ L, 1.5 mmol), CF_3CH_2OH (2 mL) and Au catalyst (1 mol %). The mixture was heated to reflux and stirred for 24 h, then concentrated *in vacuo*. The conversion was determined by 1H NMR analysis of the crude reaction mixture.

8.9.3 Reactions in $C_6H_5CF_3$

To a dry flask was added benzaldehyde (100 μ L, 1 mmol) dibenzylamine or piperidine (1 mmol), phenylacetylene (162 μ L, 1.5 mmol), $C_6H_5CF_3$ (2 mL) and Au catalyst (1 mol %). The mixture was heated to reflux and stirred for 24 h, then concentrated *in vacuo*. The conversion was determined by 1H NMR analysis of the crude reaction mixture.

8.10 Catalytic Reactions carried out in the presence of PPh_3

To a dry nitrogen flushed Schlenk flask was added benzaldehyde (100 μ L, 1 mmol) dibenzylamine (189 μ L, 1 mmol), phenylacetylene (162 μ L, 1.5 mmol), and either $[AuCl_2(\eta^2-C_6H_4CH_2NMe_2)]$ **8a** (1 mol %) or $Na[AuCl_4] \cdot 2H_2O$ (1 mol %) and PPh_3 (2.6 mg, 1 mol%). The mixture was stirred at 40°C for 24 h, then extracted with CH_2Cl_2 , dried over $MgSO_4$ and concentrated *in vacuo*. The conversion was obtained by 1H NMR analysis of the crude reaction mixture.

8.10.1 Catalytic reactions carried out in the presence of 1,2-bis(diphenylphosphino)ethane (dppe) and (-)-2,3-O-i-propylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane ((-)- DIOP)

To a dry nitrogen flushed Schlenk flask was added benzaldehyde (100 μ L, 1 mmol) dibenzylamine (189 μ L, 1 mmol), phenylacetylene (162 μ L, 1.5 mmol), and either $[\text{AuCl}_2(\eta^2\text{-C}_6\text{H}_4\text{CH}_2\text{NMe}_2)]$ **8a** (1 mol %) or $\text{Na}[\text{AuCl}_4]\cdot 2\text{H}_2\text{O}$ (1 mol %) and either dppe or (-)-DIOP (1 mol%). The mixture was stirred at 40°C for 24 h, then extracted with CH_2Cl_2 , dried over MgSO_4 and concentrated *in vacuo*. The conversion was obtained by ^1H NMR analysis of the crude reaction mixture.

9 References

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