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New Oxidants for

Arylations with Gold

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Declaration

I declare that the work in this thesis was carried out principally by me, with collaborators specifically acknowledged, under the supervision of Prof. Guy Lloyd-Jones FRS and is in accordance with the requirements of the University of Edinburgh. This work is original, except where indicated by special reference in the text, and no part of the thesis has been previously submitted for any other academic award.

06/04/2020

Acknowledgments

To my parents for encouraging, then allowing me to explore science; to my grandad Blib, for teaching me patience and believing that I had what it took to complete a PhD; to the lab group for teaching me countless practical, theoretical and philosophical lessons whilst simultaneously offering daily entertainment through this journey; and finally to Guy, for accepting me into his research group, teaching me how to be a careful and rigorous scientist and showing me how to lead people.

Abstract

Gold as an element, has been known for tens of thousands of years, though only recently has the chemistry of gold complexes emerged as an important field for synthetic organic chemistry research. One significant challenge when investigating the chemistry of gold complexes is the oxidation of gold(I) to gold(III), gold(I) having a very high oxidation potential. This thesis comprises an investigation of gold through a homogeneous oxidative arylation of arenes using arylsilanes. Chapter 2 examines the nature of ligands on gold through a gold catalysed arylation reaction and the application of this to synthesise chiral biaryls. The investigation realises that strongly coordinating L type ligands inhibit catalyst turnover and discovers that transient, enantiopure, chiral additives have no effect on the distribution of enantiomers of the chiral biaryl. Chapter 3 explores new, inorganic oxidants for the oxidation of gold(I) to gold(III) and investigates aryl iodide cocatalysts for gold catalysed arylation. It is discovered that periodic acid allows turnover of the gold catalyst and produces a biaryl product from an arylsilanes substrate. Through MALDI-MS, gold is also discovered to react with acetonitrile in the presence of periodic acid, in a novel oxidative reaction for gold, to form a gold(I) cyanide polymer. In Chapter 4, NMR kinetics and stoichiometric experiments are utilised in the investigation of mechanistic details of periodic acid as an oxidant for gold catalysed direct arylation. The six-electron reduction pathway for periodic acid to an iodonium species and the mechanism of formation of aryl iodide from the starting arylsilane is probed. Iodonium is proposed to be the intermediate that forms the aryl iodide byproduct. Further evidence for a reactive iodonium species is found using a chemospecific, nucleophilic trap that prevents the non-productive iodination of aryl silane. A substrate scope of the new arylation conditions using the trap is assessed and the reaction was found to tolerate substrates that generated 5 membered rings. This thesis aims to establish new conditions for gold catalysed arylation of arenes using arylsilanes and describes interactions of oxyiodine species with arylsilanes, nitrile solvents and gold.

Lay Summary

Through carefully planned routes, desired compounds can be fabricated for use in materials, technological devices, pharmaceuticals, food and many other applications. Reactions that form bonds between two carbon atoms (carbon-carbon bond forming) lie at the heart of this science as they allow for the extension of molecular structures; the discovery of metal catalysed cross coupling at the end of the 20th century enabled chemists to assemble complex structures in a way analogous to a jig-saw puzzle. Following their discovery, dramatic improvements to cross coupling methodologies were made, such as reducing the amount of expensive metals required to catalyse the coupling, replacing previously used solvents with water, allowing more challenging reactions to proceed, or replacing the platinum group catalysts with cheaper, more environmentally benign catalysts.

Previous work in the Lloyd-Jones group has identified gold as a catalyst for the coupling of arylsilanes, containing silicon, and arenes. The product, a biaryl, is a desirable molecular motif for many chemical industries. Arylsilanes, as a reagent in the formation of biaryls, provide significant benefits over many of the reagents used previously for this kind of reaction: they have low toxicity, can be stored under air and do not react with water, and can be stored at room temperature for long periods of time.

The work in this thesis aims to improve the understanding of this biaryl forming reaction. The interaction of additives in the reaction with gold is poorly understood and some of the compounds required to progress the reaction can consume the aryl silane and arene starting materials as well as the biaryl product. Replacing these components and investigating the new additives activity in the reaction system may allow for further improvements to the methodology.

Abbreviations

Å	ångström
ρ	Hammett reaction constant
σ	Hammett substituent constant
σ	BM σ-bond metathesis
μL	microlitre
Ac	acetyl
Ar	aryl substituent
Bn	benzyl
Bu	butyl
CI	chemical ionisation
CSA	camphorsulfonic acid
Cy	cyclohexyl
DCE	1,2-dichloroethane
DMF	N,N-dimethylformamide
DMSO	dimethyl sulfoxide
E, E$^+$	electrophile
EI	electron impact ionisation
eq	molar equivalents
ESI-MS	electrospray ionisation mass spectrometry
e.r.	enantiomeric ratio
Et	ethyl
g	gram

HCIB	[hydroxy(camphorsulfonyloxy)iodo]benzene
HFIP	hexafluoroisopropanol
HTIB	[hydroxy(tosyloxy)iodo]benzene
IBDA	iodobenzene diacetate
KIE	kinetic isotope effect
k	rate constant
L	neutral ligand
m-CPBA	*meta*-chloroperbenzoic acid
M	molar
Me	methyl
mg	milligram
MHz	megahertz
mL	millilitre
mmol	millimole
mol%	mole percent
m.p.	melting point
MS	molecular sieve
m/z	mass-to-charge ratio
NBS	N-bromosuccinimide
NMR	nuclear magnetic resonance
Nu, Nu$^-$	nucleophile
Ph	phenyl
PIDA	Phenyl iodine(III) diacetate
ppm	parts per million

Pin	Pinacol
Pr	propyl
Piv, pivalyl	trimethylacetyl
R	alkyl, aryl or heteroaromic substituent
rt	room temperature
S_EAr	electrophilic aromatic substitution
TBA	tetrabutylammonium
TBHP	tert-butyl hydroperoxide
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
tfe	2,2,2-trifluoroethanol
THF	tetrahydrofuran
tht	tetrahydrothiophene
TLC	thin-layer chromatography
TM	transition metal
WI	Wheland intermediate
X	(halogen) substituent, or anionic ligand

Contents

1 - Introduction

1.1 - Gold-catalysed Oxidative Cross Coupling

Transmetalation/C-H activation

The first example of gold being used as an electrophile in arene C-H activation was published by Kharasch, in 1931, documenting the addition of gold(III) chloride to benzene resulting in long yellow crystals of phenyl auric dichloride **1** (Scheme 1).[1] In the subsequent 70 years, four further reports were published in which the formation of aryl gold complexes via electrophilic aromatic substitution of arenes with gold salts was investigated.[2-5]
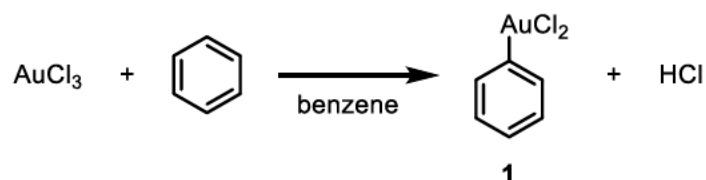
Scheme 1. Auration of benzene using AuCl$_3$.[1]

Gold salts, being electrophilic, react regioselectively with arenes, following standard electrophilic aromatic substitution patterns.[6]

In order to form aryl gold complexes in which the arene was substituted in a position that was not inherently nucleophilic, organometallic aryl mercury compounds (Ar$_2$Hg or ArHgX) such as **2** were used. Aryl mercury compounds were shown to transmetalate at the C-Hg bond to form aryl gold complexes **3** (Scheme 2).[7-12]
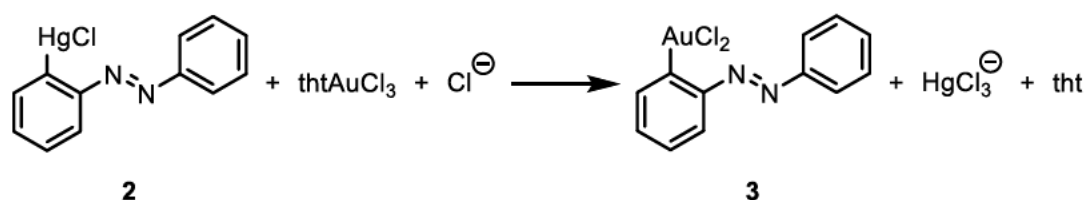
Scheme 2. Transmetalation of aryl mercury compound to gold.[12]

When two, structurally distinct, aryl mercury compounds, **4** and **5**, were added sequentially to a gold complex, bisaryl gold complexes containing two distinct aryl groups were formed **6** (Scheme 3).[9-11]
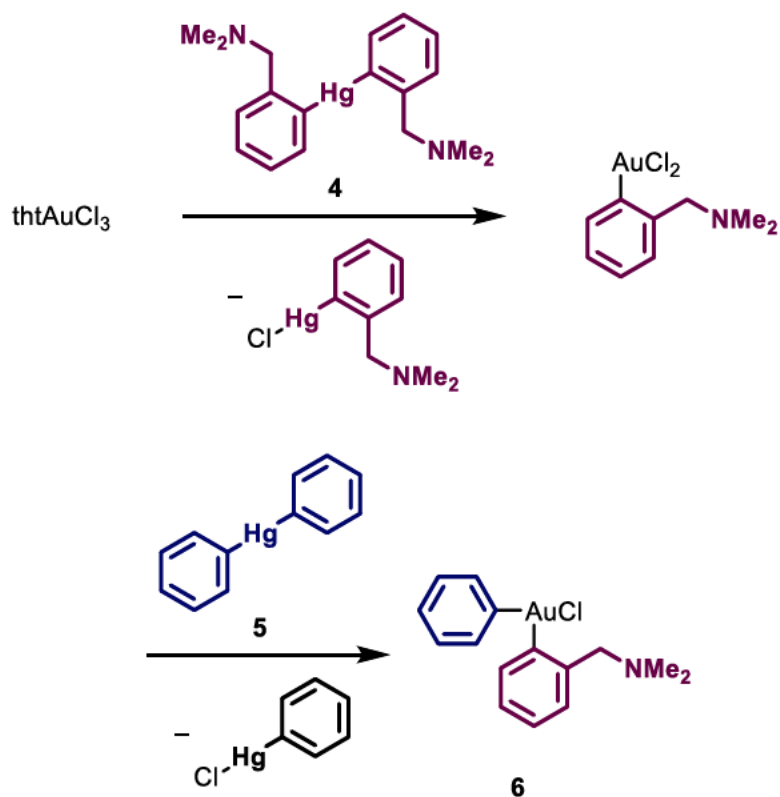
Scheme 3. Formation of hetero-bisaryl gold complexes.[10]

Alternative transmetallation procedures, utilising aryl tin,[13] lithium,[14] silver,[14] and boron[15] compounds to synthesise aryl gold complexes were subsequently reported.

Reductive Elimination

Vincente and co-workers demonstrated that bisaryl gold chloride complexes **6**, when ligated with triphenylphosphine or an extra equivalent of chloride, undergo reductive elimination to form either homo- or heterocoupled biaryls **7** corresponding to the bisaryl gold complex used (Scheme 4).[11]
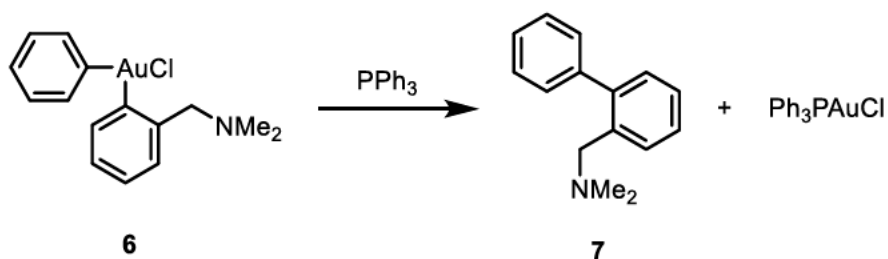
Scheme 4. Formation of heterocoupled biaryls by reductive elimination from bisaryl gold complexes.[11]

Kochi and co-workers in the 1970s, reported that the reductive elimination from neutral, square planar, gold(III) complexes is slow, whereas, upon the loss of a neutral L type ligand, the reductive elimination from a T shaped complex is fast (Scheme 5).[16-18]
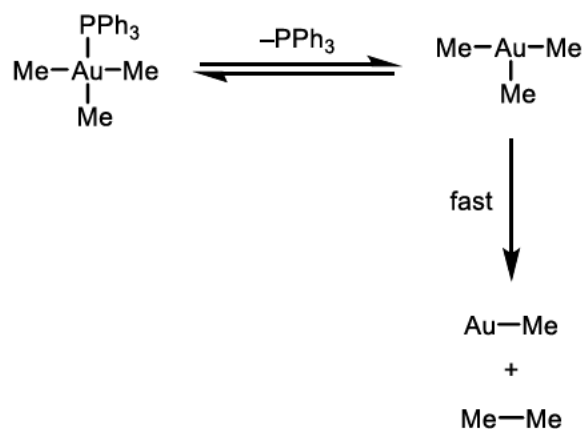
Scheme 5. Reductive elimination from gold(III).[16]

Toste and co-workers have extensively explored the mechanisms of reductive elimination of bisaryl gold complexes in the presence of phosphine ligands.[19] Reductive elimination from a cationic, square planar gold complex is faster than that of a neutral square planar complex (Scheme 6).
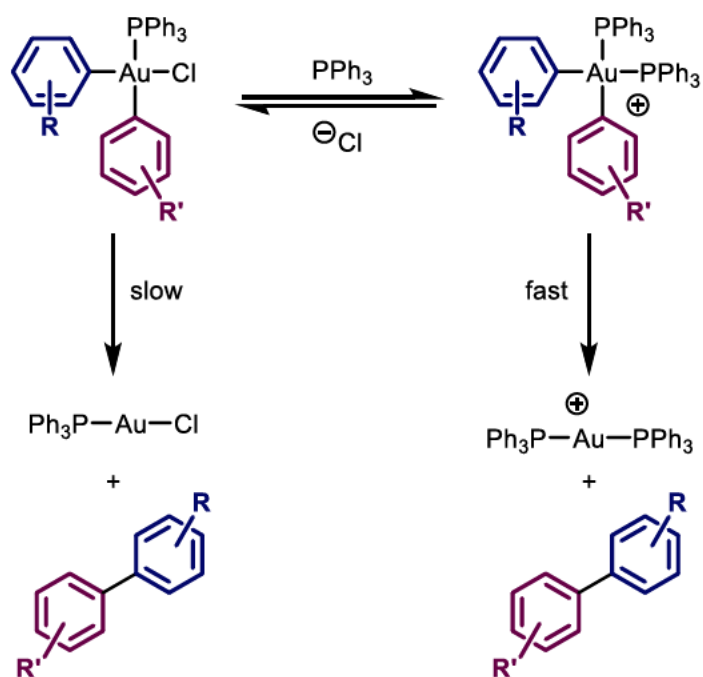
Scheme 6. Ligand promoted reductive elimination.[19]

2

Oxidative Addition

In contrast to the isoelectronic platinum(0), there are few reports of oxidative addition of aryl halides or aryl pseudohalides to gold(I). This can be explained by the high oxidation potential of gold(III) compared to platinum(II).[20, 21] Through the use of *cis*-chelating bidentate ligands,[22] hemilabile P,N-ligands,[23] intramolecular delivery (Scheme 7),[24] and photoactivation,[25-28] oxidative addition has been achieved with organo-iodides and gold(I).
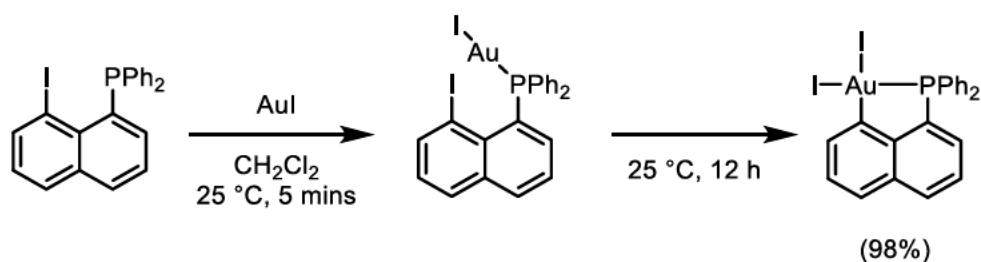
Scheme 7. Intramolecular delivery of gold(I) facilitating oxidative addition.[24]

Bower and co-workers combined oxidative addition, transmetallation and reductive elimination to synthesise biaryls with stoichiometric gold (Scheme 8). A gold complex **8** containing *cis*-chelating ligand based on 2,2'-bipyridine allowed for the reversible oxidative addition of aryl iodides to form the aryl gold complex **9**. Transmetalation of an aryl zinc with gold complex **9** formed the bisaryl gold complex **10** that subsequently underwent facile reductive elimination.
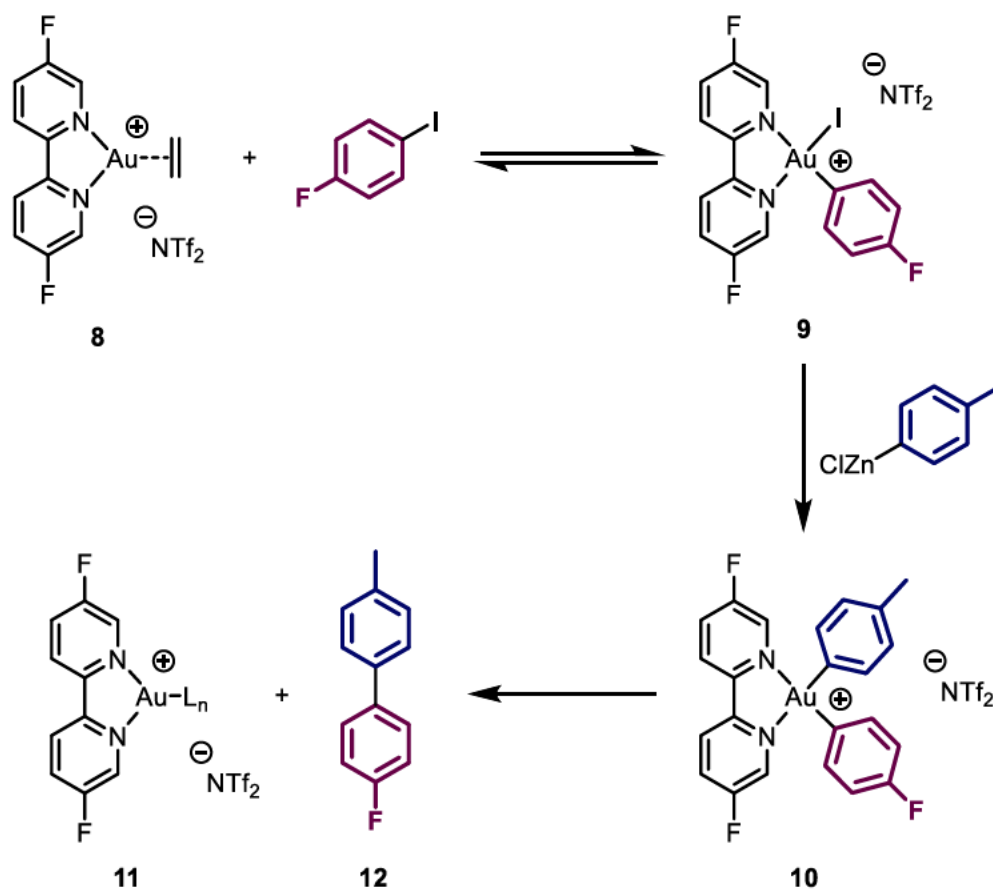
Scheme 8. Oxidative addition, transmetalation, and reductive elimination on gold.[22]

Gold(III) is commonly used in catalysis, however, it is often formed from gold(I) via a sacrificial oxidant,[29-31] such as a fluoronium source like selectfluor[32, 33] or hypervalent aryliodine oxidant.[34-36] Fluoronium and hypervalent iodine oxidants can be used in stoichiometric reactions[35] or under catalytic conditions.[32-34, 36]

Oxidative addition is easier into strained bonds. Toste and co-workers reported the oxidative addition of gold(I) into the strained carbon-carbon bonds of biphenylene substrates (Scheme 9).[37]
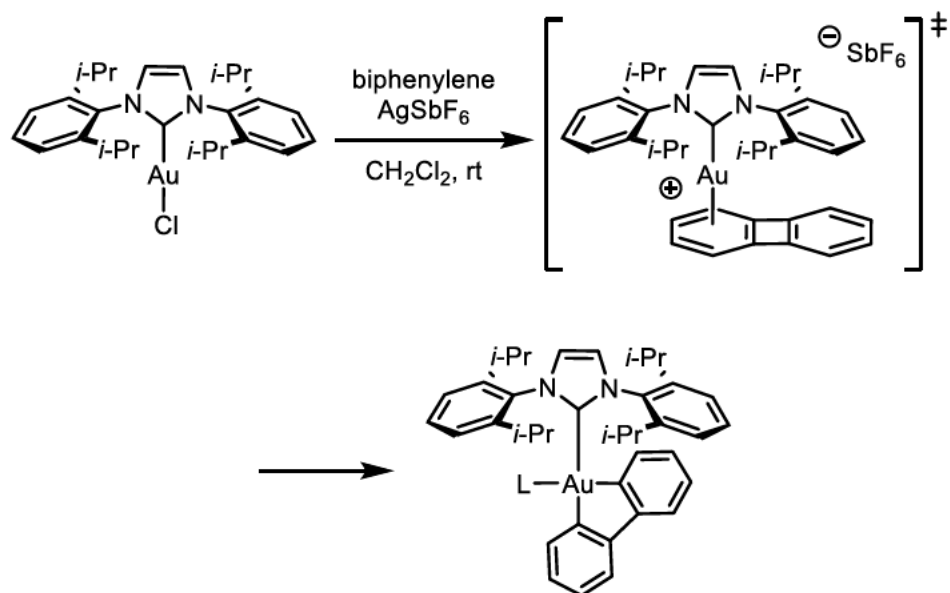
Scheme 9. Oxidative addition to biphenylene.[37]

Stoichiometric Coupling Reactions

In 1999, Lippert reported the homodimerization of alkylated uracil moieties using stoichiometric NaAuCl$_4$ (Scheme 10).[38] Gold(0) was observed to be the byproduct of this oxidative coupling reaction.
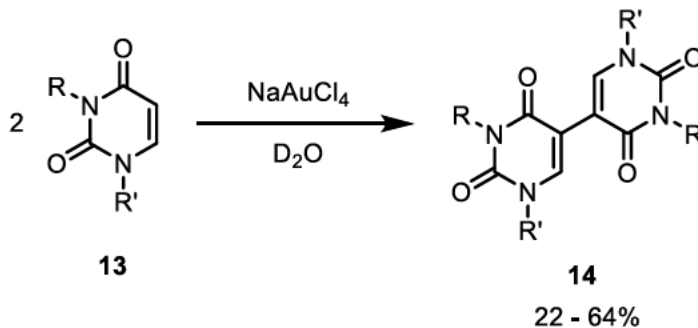
Scheme 10. Gold mediated homodimerisation of uracil derivatives.[38]

Hashmi and co-workers reported the formation of homocoupled byproducts during a gold(III) catalysed intramolecular cycloisomerisation of allenyl alcohols; it was suspected that the reductive elimination, required for dimerization could form the more active gold(I) species required for the catalysis.[39]
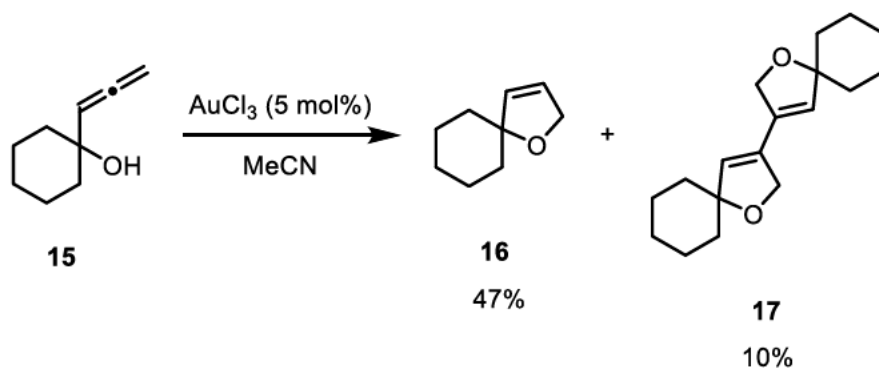
Scheme 11. Stoichiometric dimerisation of dihydrofuran with gold(III). [39]

Catalytic Coupling Reactions

In 2007, Tse and co-workers reported the first gold-catalysed homocoupling of electron rich arenes to form symmetrical biaryls such as **18** (Scheme 12).[40, 41] A hypervalent aryliodine oxidant is required to re-oxidise the gold(I) back to gold(III). Aryl halides were tolerated by the gold-catalysed homocoupling even at 95 °C in acetic acid, allowing for complementarity between gold and other metal-catalysed transformations.
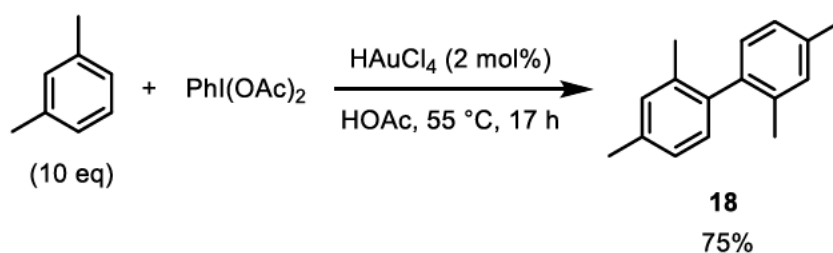
Scheme 12. Gold(III) catalysed homocoupling of electron rich arenes. [40]

By mixing arenes, Tse and co-workers could produce statistical mixtures of cross coupled biaryls.[41]

Zhang and co-workers reported heterocoupling using gold(III), in which alkenes were reacted with tethered alcohols or amines (**19**) intramolecularly, as well as aryl boronic acids such as **20** to make saturated heterocycles (**21**) (Scheme 13).[32]

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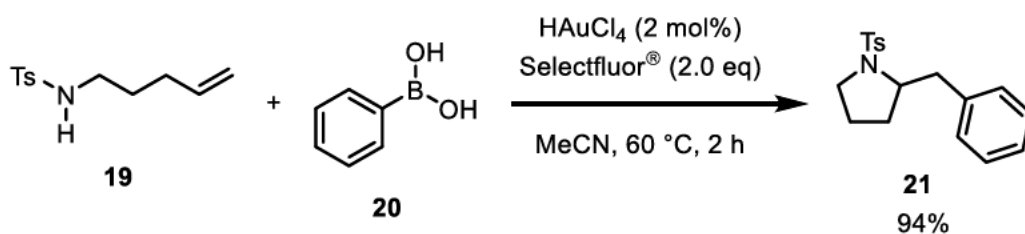
Scheme 13. Aminoarylation using gold(III) and phenylboronic acid.[32]

Selectfluor® was used as the terminal oxidant in the oxidative gold catalysis; proposed to oxidise gold(I) to gold(III), with potentially two possible mechanisms (Scheme 14).[32]
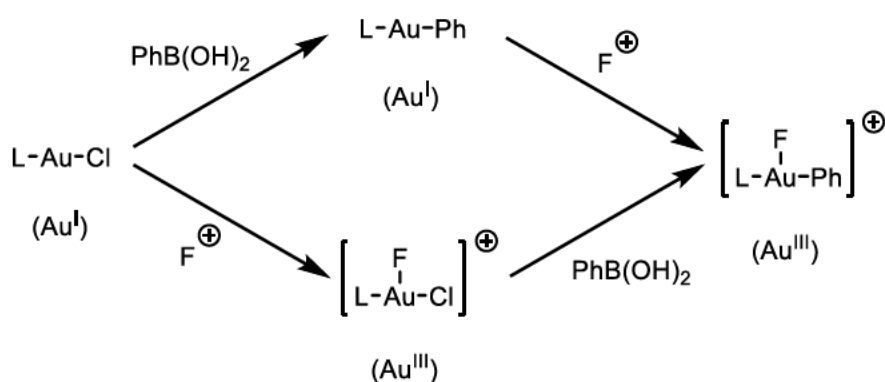
Scheme 14. Potential oxidations pathways for gold(I).[32]

Toste and co-workers investigated the mechanism of the formation of the aminoarylated product 21.[42] The reaction of PhAuPPh$_3$ and tosyl protected amine tethered alkene in the presence of Selectfluor® did not proceed without the addition of phenylboronic acid. The importance of the aryl boronic acid in the formation of 21 was attributed to a 5-membered transition state 22 (Scheme 15).
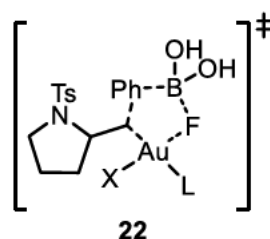
Scheme 15. 5-Membered transition state proposed to be key in the formation of compound 21. [42]

Toste et al published an example of gold-catalysed oxyarylation in which the alcohol nucleophile and alkene 23 could couple with the aryl boronic acid 24 without the aid of a

tether (Scheme 16) giving complex products (such as **25**) from three simple reagents.[33] This oxidative coupling also used Selectfluor® as the stoichiometric oxidant.
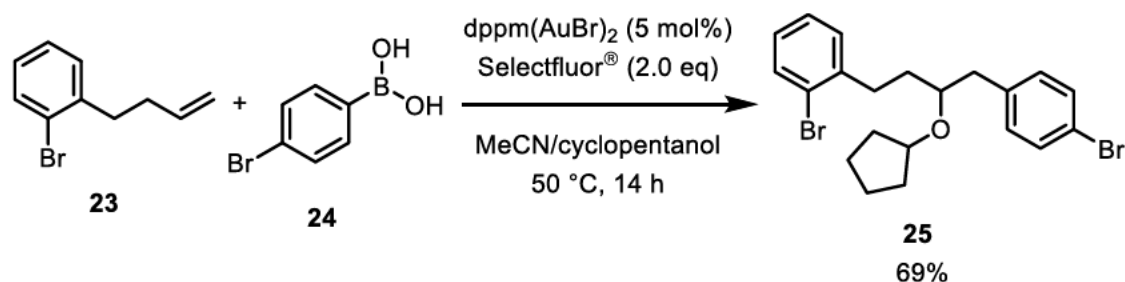
Scheme 16. Three component oxyarylation.[33]

The scope of gold-catalysed nucleophile-arylation reactions was expanded to aryl trimethyl silanes simultaneously by Toste[43] and Lloyd-Jones.[44] The oxyarylation of alkenes with aryl trimethyl silanes has broad scope due to its mild reaction conditions.

Toste and co-workers proposed the oxidative oxyarylation transition state **26** (Scheme 17) that was based on the related aryl boronic acid nucleoarylation transition state **22**.[43]
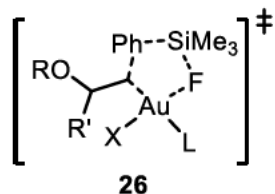
Scheme 17. Proposed oxyarylation transition state using aryl trimethyl silanes.[43]

During the coupling of alkenes **27** with alcohols **28** and aryl trimethyl silanes **29** to form arylated alkanes **30**, Lloyd-Jones and co-workers observed the formation of symmetrical biaryls **31** as a byproduct derived from the homocoupling of aryl trimethyl silanes **28** (Scheme 18).[44]
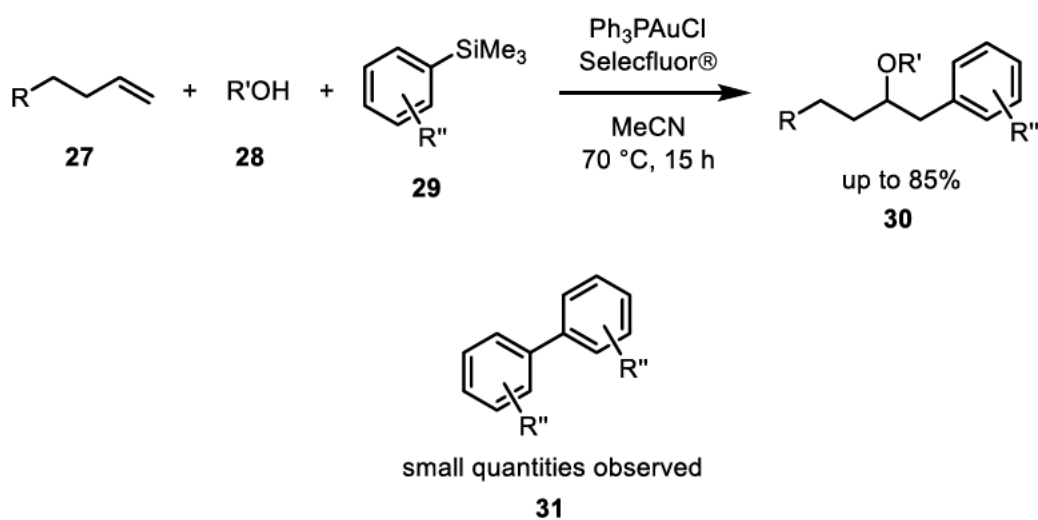
Scheme 18. Three component oxyarylation using aryl trimethyl silanes.[44]

1.2 - Direct arylation of Aryl Silanes – Previous Work in the Lloyd-Jones Group

Lloyd-Jones *et al* continued to investigate the byproduct, biaryl (31) forming, reaction.[45] Aryl trimethyl silanes and arenes were discovered to couple in the presence of a gold catalyst and an aryliodine oxidant; camphorsulfonic acid (CSA) was observed to be an effective additive in improving the reaction rate and yield (Scheme 19). Methanol was required to solvate the oxidant as well as sequester the silane byproduct. A wide variety of functional groups were tolerated, including oxidatively sensitive groups such as alcohols (32), aldehydes (33) and naphthalenes (34) as well as aryl halides (32 and 33)
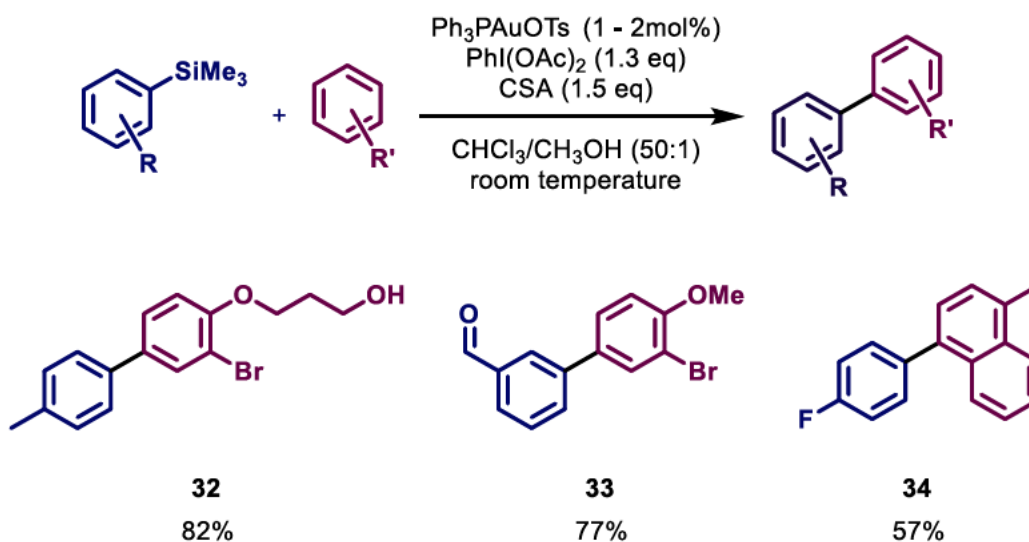
The importance of gold-catalysed direct arylation tolerating aryl halides was highlighted in the total synthesis of Diflunisal (Scheme 20), the initial cross coupling tolerates the aryl iodide **35**, the biaryl **36** can subsequently be carboxymethylated using a palladium catalysed methodology. Demethylation of intermediate **37** gave Diflunisal in 68% overall yield.
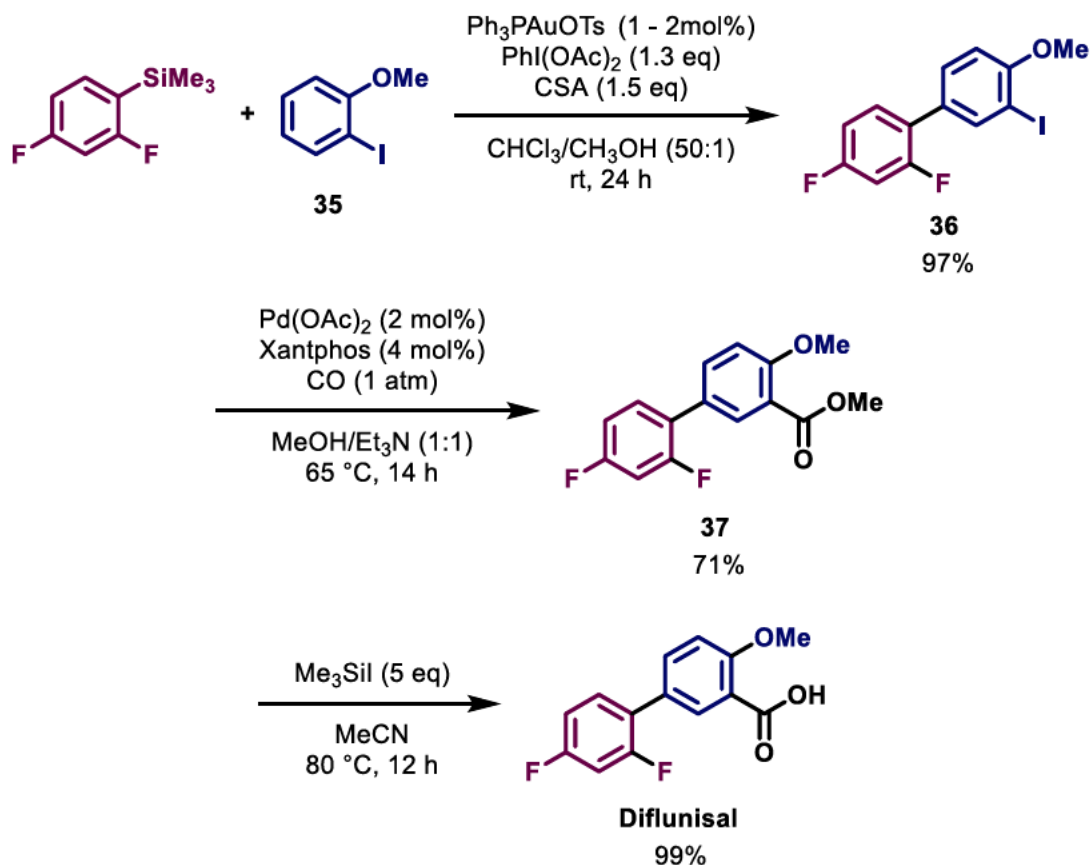
Scheme 20. Using gold-catalysed direct arylation to synthesise Diflunisal. [45]

Subsequent research from the Lloyd-Jones group investigated the mechanism of gold-catalysed arylation of arenes. [46]

The stoichiometric reaction of mesitylene and/or *p*-fluorophenyl trimethyl silane with two sources of gold(I) (Ph₃PAuOTs and thtAuCl/AgOTf) showed no reaction whereas the same silane reacted with gold(III) to form an aryl gold complex (Scheme 21), indicating that the first step in the catalytic cycle may be transmetalation of the aryl silane arene onto gold. [46]
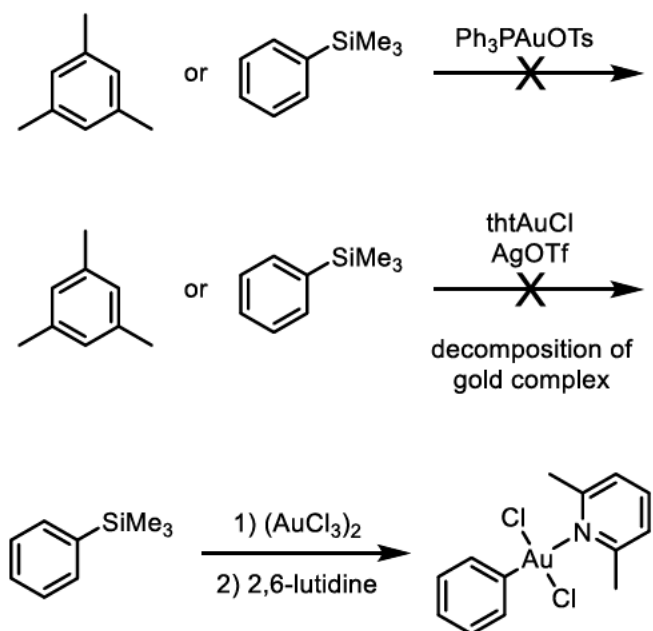
Scheme 21. Stoichiometric reactions with gold. [46]

Based on the observed consumption of 2 equivalents of oxidant with respect to the gold precatalyst during the initiation, the rates of consumption of the oxidant, and the dependence of the rate of oxidation on the nature of the phosphine ligand, it was concluded that the gold(I) complex was first oxidised to a phosphine ligated gold(III) complex, followed by reductive elimination of a phosphonium salt and subsequent reoxidation of gold(I) (Scheme 22).[46]
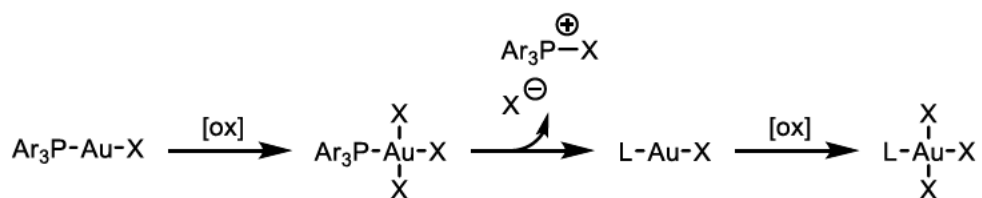
Scheme 22. Proposed gold precatalyst activation mechanism.[46]

The Hammett plot for the competition of different aryl trimethyl silanes coupling with mesitylene showed correlation with σ. The value of $\rho = -1.6$ (Figure 1) is consistent with electrophilic aromatic substitution mechanism of aurodesilylation.[46]
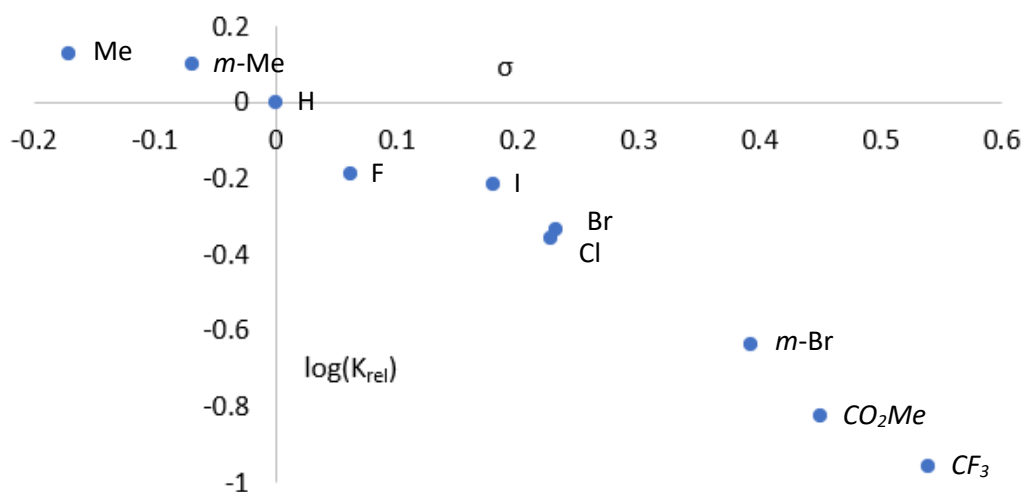
Figure 1. Hammett plot for the gold-catalysed coupling of p-substituted (unless otherwise stated) aryl trimethyl silanes with mesitylene.[46]

Turn-over limiting step

Arylation was observed to exhibit first order dependence on the concentration of the gold precatalyst, arene and CSA; the rate was independent of silane concentration and showed an inverse half order dependence on methanol (Equation 1).[46] The inverse half order dependence on methanol implies that methanol exists as a dimer in chloroform and that it is an inhibitor for turnover.

$$rate \cong k_{obs} \frac{[Au][Ar][CSA]}{[MeOH]^{1/2}}$$

Equation 1. Rate equation for gold-catalysed direct arylation of aryl silanes.[46]

Activation parameters of ΔH = 15.2 ± 0.5 kcal mol^{-1} and ΔS = −26.5 ± 0.5 cal K^{-1} mol^{-1} were calculated over the range 25-55 °C. The large negative entropy value associated with a large increase in order during the turnover limiting step. [46]

The kinetic isotope effect for the C-H auration was calculated to be k(H/D) = 0.97. The closeness of the k(H/D) to 1 indicates that the C-H/D cleavage is not turnover limiting for this substrate. [46]

To gain further insight into the mechanism of C-H auration and its relation to the turnover limiting step, the arylation of methylated benzene substrates were investigated. The rates of auration of differently substituted methyl arenes provides insight into whether the formation of the π-complex or Wheland intermediate were the turnover limiting steps (Figure 2).

π-complex   Wheland intermediate

Figure 2

Comparing the rates of arylations to the relative stability of reference π-complexes or Wheland intermediates indicated that, for arenes with one or no *ortho*-methyl groups relative to the reactive C-H site, the formation of the π-complex is the turnover limiting step, however, when two methyl groups are in the *ortho*-position to the reactive C-H site, Wheland intermediate formation is turnover limiting.[46]

From the data above, it was proposed that the mechanism of the turnover limiting step is as shown in Figure 3. An aryl gold complex reversibly reacts with CSA prior to π-complexation of the arene, the π-complex can react to form the bisaryl gold complex.
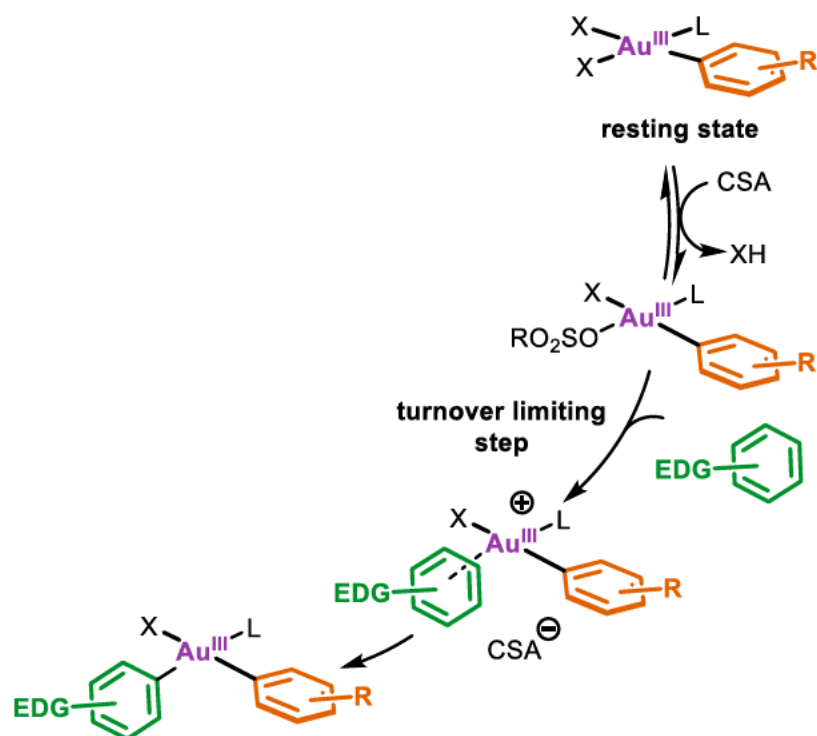
Figure 3. Detailed intermolecular turnover limiting step. [46]

In a subsequent study on intramolecular arylation of aryl silanes,[47] it was discovered that reductive elimination is the turnover limiting steps when preparing cyclic biaryls of 5

13

membered rings; arene π-complexation remained the turnover limiting step when preparing cyclic biaryls (Figure 4).
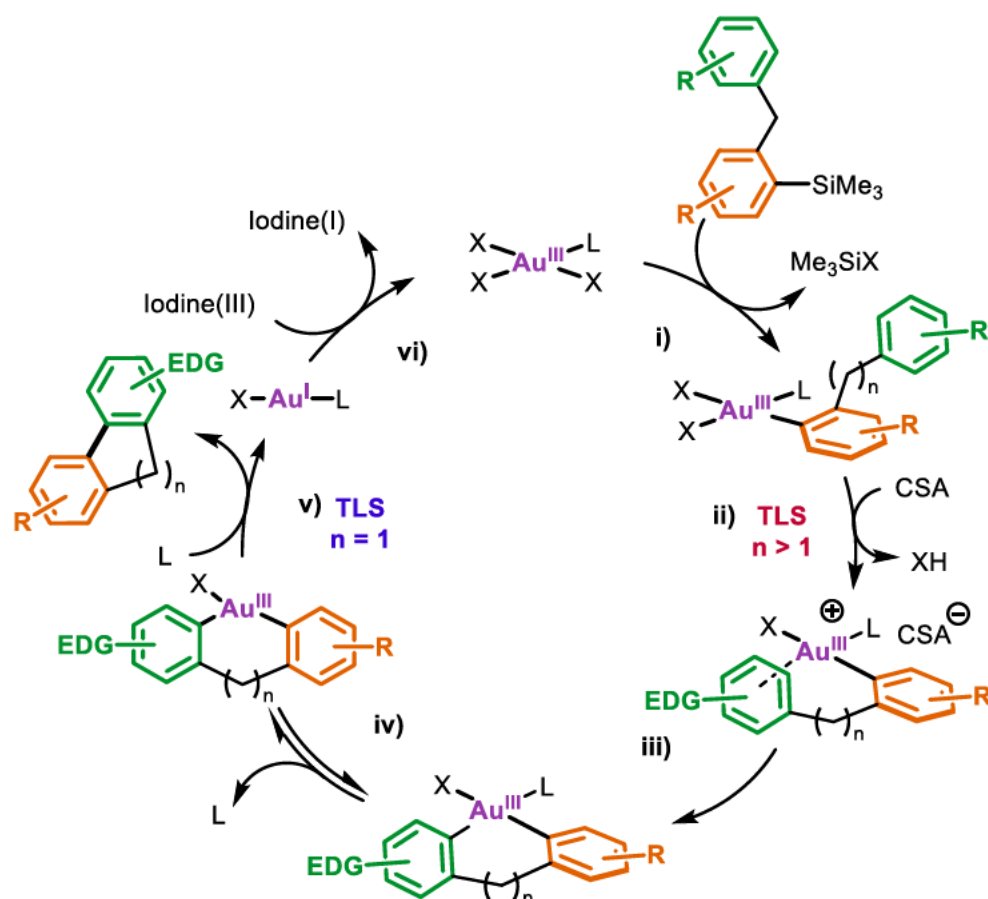
Figure 4. Simplified catalytic cycle for gold-catalysed direct arylation of tethered aryl trimethyl silanes.[47]

Methanol

Methanol acts as an inhibitor to the reductive elimination, however it is required as an additive to gold-catalysed direct arylation of aryl trimethyl silanes as it sequesters the silane moiety and helps solvate both oxidant and CSA. Coordinating solvents have been shown to reduce the rate of reductive elimination of gold.[16-18] In an effort to increase the rate of coupling and therefore reduce the amount of byproduct formation, Lloyd-Jones and co-workers developed the alcohol tethered silane coupling functionality, 3-hydroxypropyldimethylsilyl (HPDMS) group (Figure 5) that removes the need for the addition of methanol.
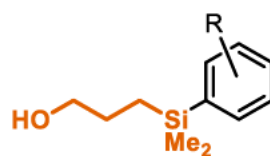
Figure 5. 3-Hydroxypropyldimethylsilyl arene.

This alcohol substituted silane allowed for the arylation of heterocycles (Scheme 23).[48] Aryl pinacol boranes (**40**) were discovered to be tolerated by the gold-catalysed coupling conditions. Aryl pinacol boranes allow for subsequent palladium catalysed coupling reactions to be performed.
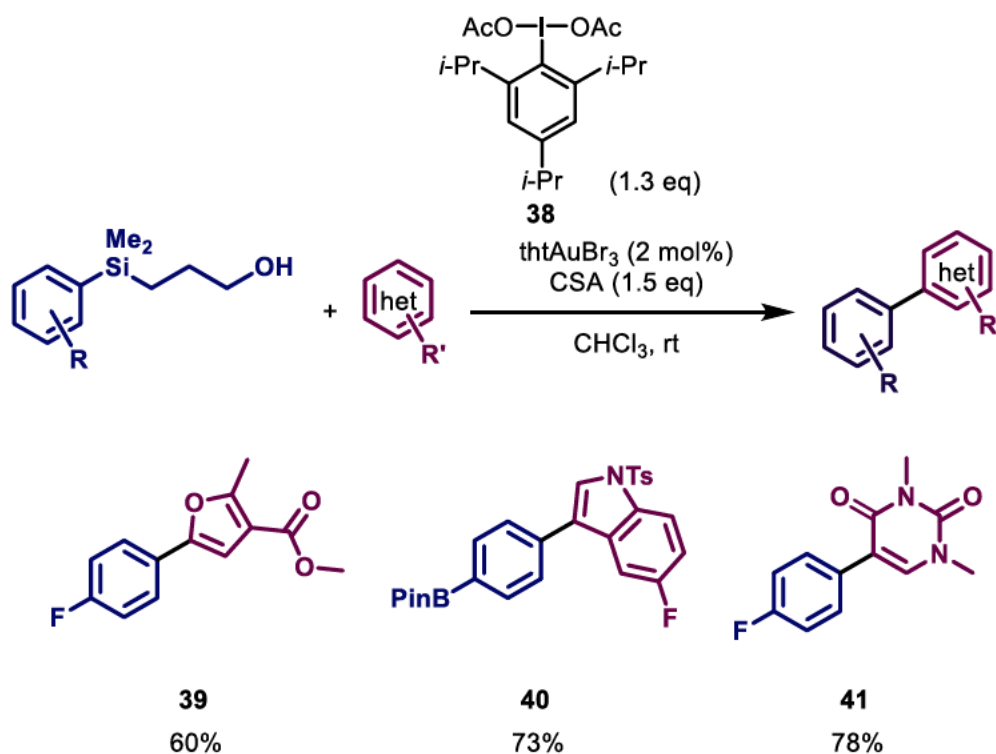
Scheme 23. Aryl HPDMS coupling with arenes.[48]

Hypervalent Iodine Oxidant

Phenyl iodine(III) diacetate (PIDA) is a hypervalent aryl iodine oxidant, known for its mild nature and functional group tolerance that can be seen in the substrate scope of the gold-catalysed direct arylation.

A drawback with hypervalent aryl iodine oxidants is that they are electrophilic on the iodine, meaning that the iodine can react with electron rich arenes[49, 50] and aryltrimethylsilanes[50, 51] to form diaryliodonium salts as shown in Figure 35.

15

i)

ii)

iii)
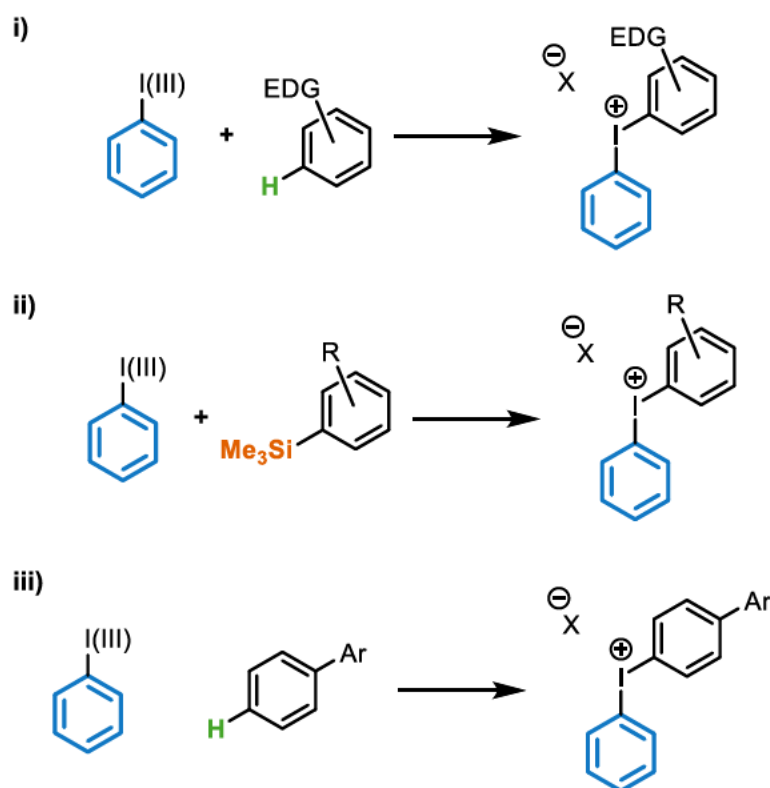
Figure 6. Reactions of hypervalent aryliodine oxidants with arenes and arylsilanes.

PIDA **42** is known to react with CSA (Scheme 24) to form a variant of Koser's reagent **43** that is more electrophilic than PIDA itself.[50, 52-56]

42   **43**
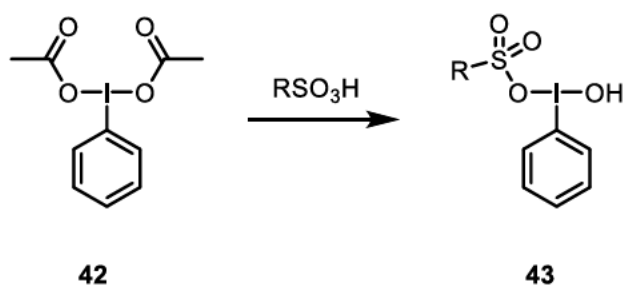
Scheme 24. PIDA reacting with sulfonic acid to form variations of Koser's reagent.

The formation of bisaryl iodonium salts can be more detrimental than simply consuming the starting material or product. The reaction of hydroxy(sulfonoxy)iodobenzenes **43** with the electron rich arene of **44** in the synthesis of (±)-allocolchicine formed the catalyst inhibitor, diaryliodonium salt **46** (Scheme 60) that significantly reduced the yield of desired product **45**.[49]

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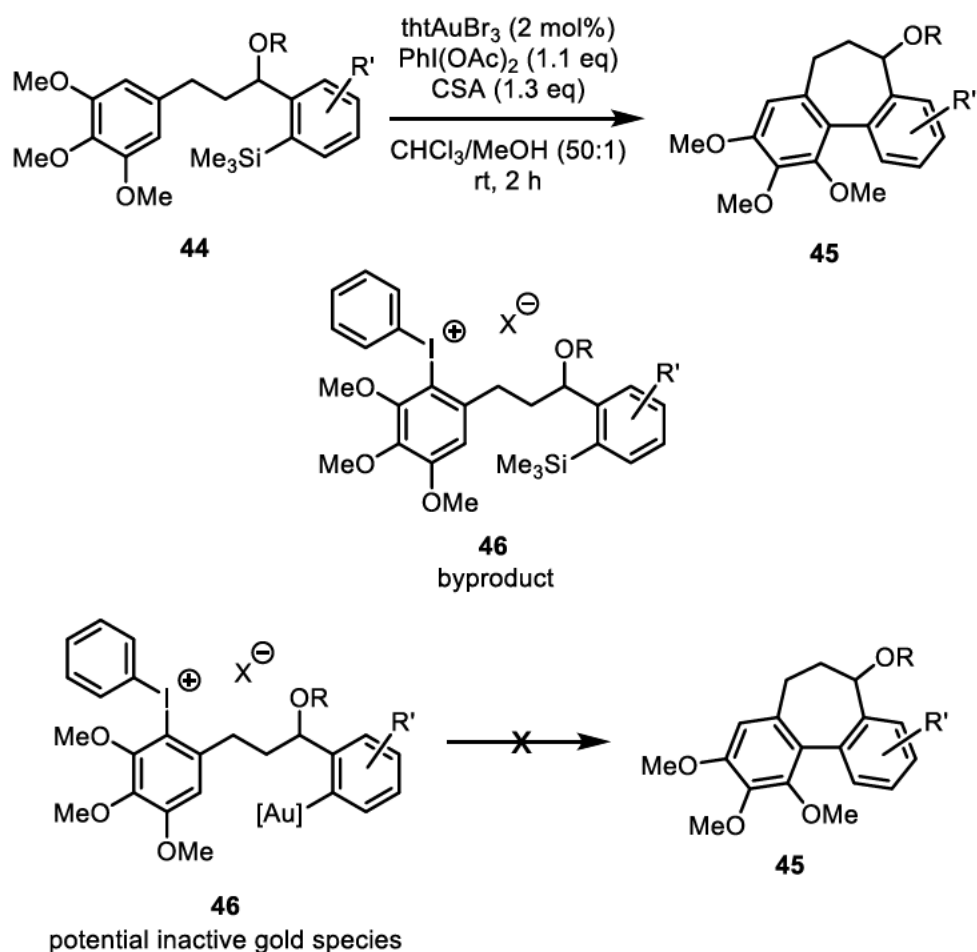
Scheme 25. Potential byproduct formation and deactivation of gold in the synthesis of (±)-allocolchicine.[49]

Phenyliodine bis(trifluoroacetate) (PIFA) **47** can be used in place of PIDA **43** to reduce the amount of diaryliodonium salt formed.[49] Another method to prevent diaryl iodonium formation is the use of aryliodine oxidants with bulky *ortho*-groups preventing reaction at iodine. 2,4,6-Triisopropyl(diacetoxy)iodobenzene **38** (Scheme 23 and Figure 7), alongside the use of aryl HPDMS to increase the rate of coupling, allowed for the arylation of heterocycles that had previously been substrates that give low yields (Scheme 23).[48]
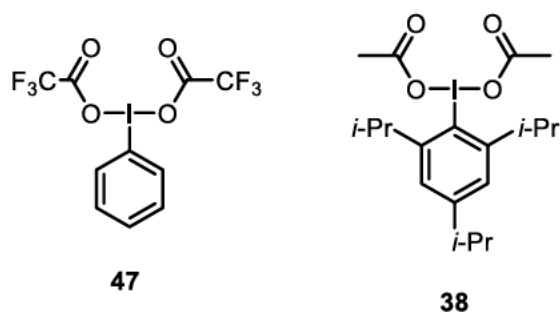
Sulfonic Acid

Lloyd-Jones and co-workers originally reported the use of camphorsulfonic acid as an additive required to activate the hypervalent iodine oxidant (PIDA) in the coupling of aryl trimethyl silanes.[45] When camphorsulfonic acid and phenyl iodine diacetate oxidant are combined in solution, they can form the more powerful oxidant, Koser's reagent.[50, 52-56]

As mentioned above, acidic conditions are important for the turnover of the catalyst as, for untethered substrates or substrates that form rings of 6 or more atoms, it is required to remove an X-type ligand and promote aurodeprotonation of the arene (Figure 3).[46]

1.3 - Coupling of Other Aryl Substrates

Since the seminal work by Lloyd-Jones and co-workers in 2012, other aryl substrates have been cross coupled using gold catalysis.

Larrosa and co-workers reported the cross coupling of electron rich arenes and heteroarenes with polyfluorinated arenes and pyridines (Scheme 26).[57] Gold(I) is known to aurate carbon-hydrogen bonds in polyfluoroarenes[58-60] and fluorinated pyridines[59] to form (hetero)aryl gold complexes. The reactive site on the fluorinated coupling partner is the most acidic C-H bond. The position of substitution of the electron rich arene is in the most nucleophilic position and follows S_EAr substitution rules.
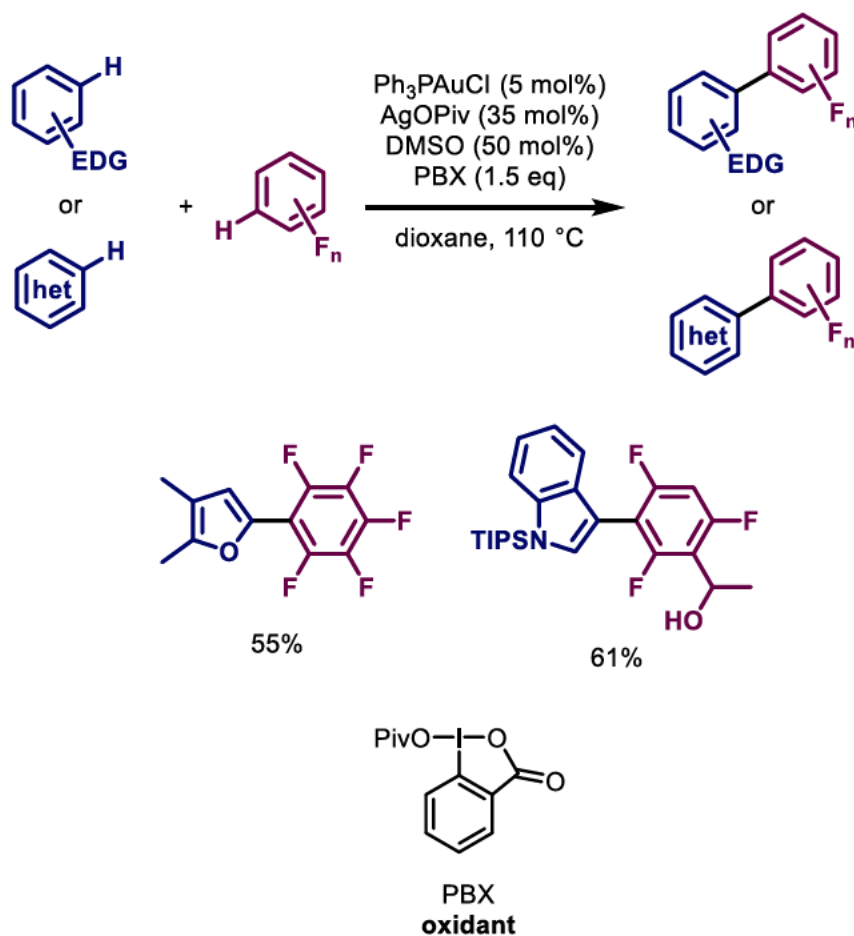
Scheme 26. Gold-catalysed dehydrogenative coupling to form biaryls.[57]

Silver pivalate (AgOPiv) was essential for catalyst turnover and its role was proposed to be conjointly, halide abstraction and C-H activation. The import of DMSO was tentatively attributed to increase the solubility of AgOPiv and/or to stabilise a gold(I) intermediate.[57]

The proposed mechanism was reported to be that a gold(I) salt initially reacts with the fluorinated arene to form an aryl gold(I), the gold complex is subsequently oxidised by the external oxidant PBX, forming the aryl gold(III) complex that can perform the auration of the second arene prior to reductive elimination reforming gold(I) (Figure 8).
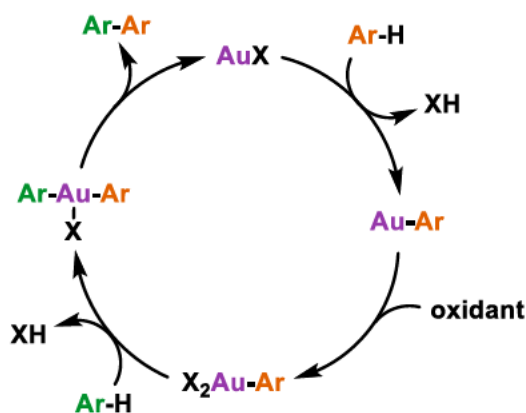
Figure 8. Proposed catalytic cycle for cross arene coupling.[57]

Nevado and co-workers reported the gold-catalysed coupling of fluorinated aryl boronic acids and electron rich arenes.[61] Highly electron deficient aryl boron reagents are synthetically challenging to use due to their propensity to protodeboronate when under the basic conditions that are usually required for transmetalation.[62]
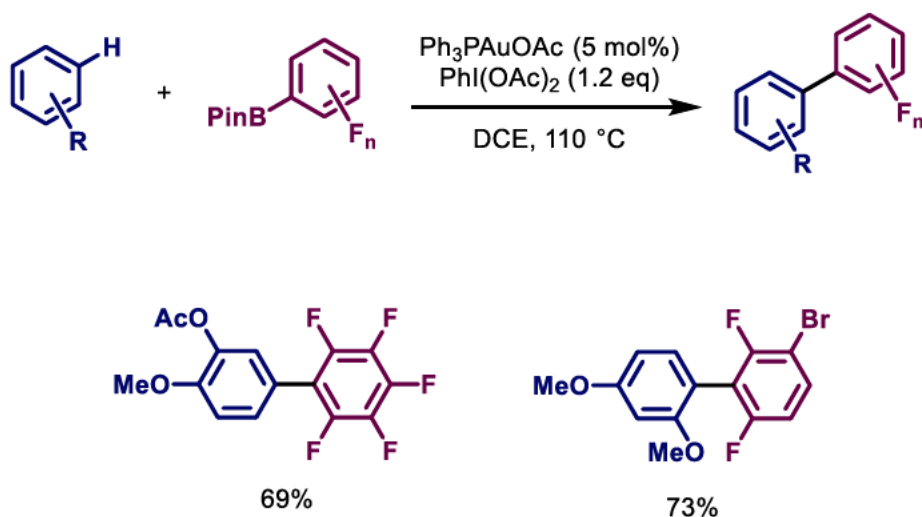
Scheme 27. Gold-catalysed cross coupling of aryl boron reagents and arenes.[61]

A gold acetate precatalyst allowed the coupling when others tested did not, the acetate was proposed to act as an 'internal base', promoting transmetalation of the aryl boron reagent to gold(I). The stoichiometric reaction of (triphenylphosphine)gold(I) acetate with pentafluorophenyl pinacolborane showed transmetalation where a gold(I) chloride did not (Scheme 28).
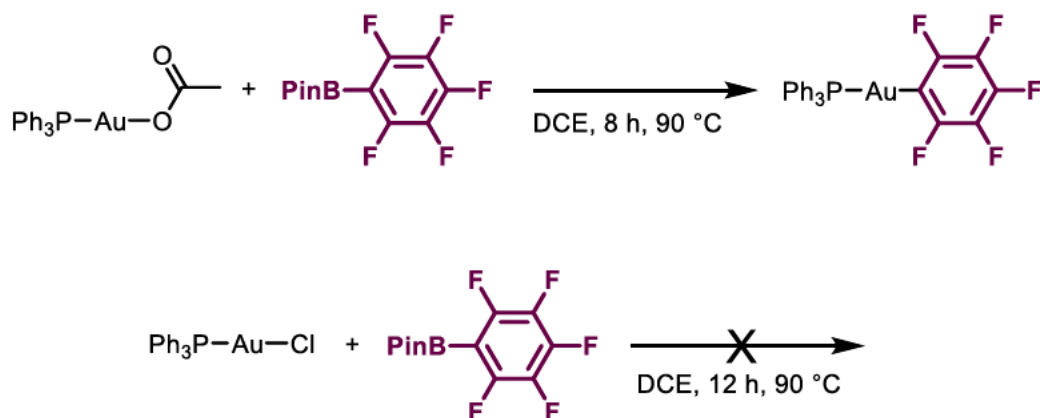
Scheme 28. Stoichiometric transmetalation reactions.[61]

Shi and co-workers reported the cross coupling of aryl diazonium salts with aryl boronic acids using a 1-methylbenzyltriazole ligated gold(I) precatalyst **48** (Scheme 26).[63] The use of aryl diazonium salts as aryl electrophiles bypasses the requirement for external oxidants to oxidise gold(I) to gold(III).
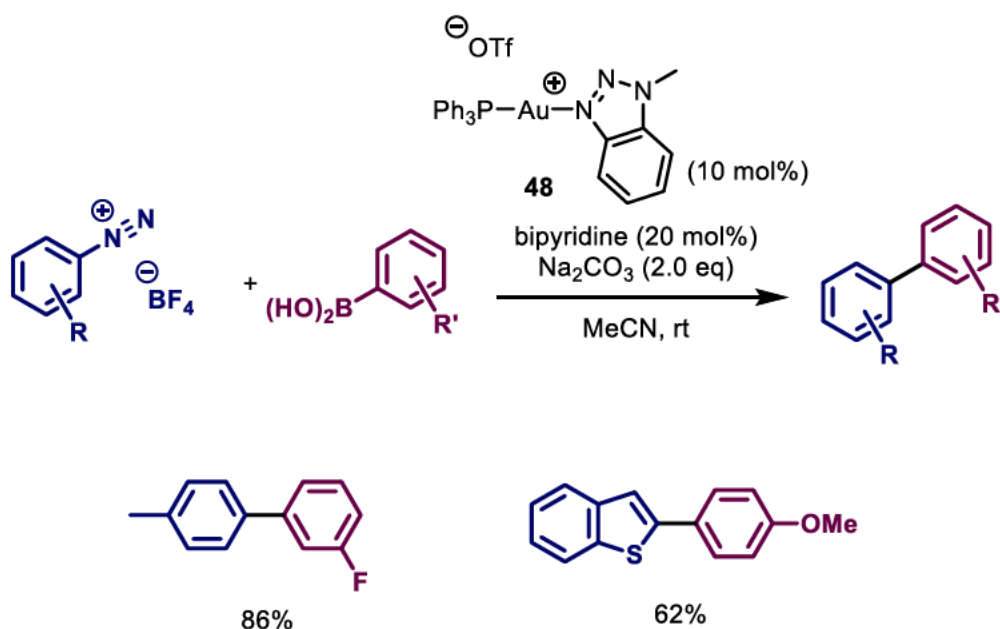
Scheme 29. Gold-catalysed cross coupling of aryl boronic acids with aryl diazonium salts.[63]

The reaction between gold and aryldiazonium salt is a formal oxidative addition. In stoichiometric reactions, *para*-fluorophenyl diazonium tetrafluoroborate was shown to react with a gold(I) complex in the presence of bipyridine to form a tetraaryl phosphonium cation, this was concluded to be the decomposition product of the gold arene complex (Scheme 30).

In the absence of bipyridine, no reaction occurred. Toste and co-workers subsequently explored the mechanism reductive elimination of aryl gold triaryl phosphine complexes.[10]
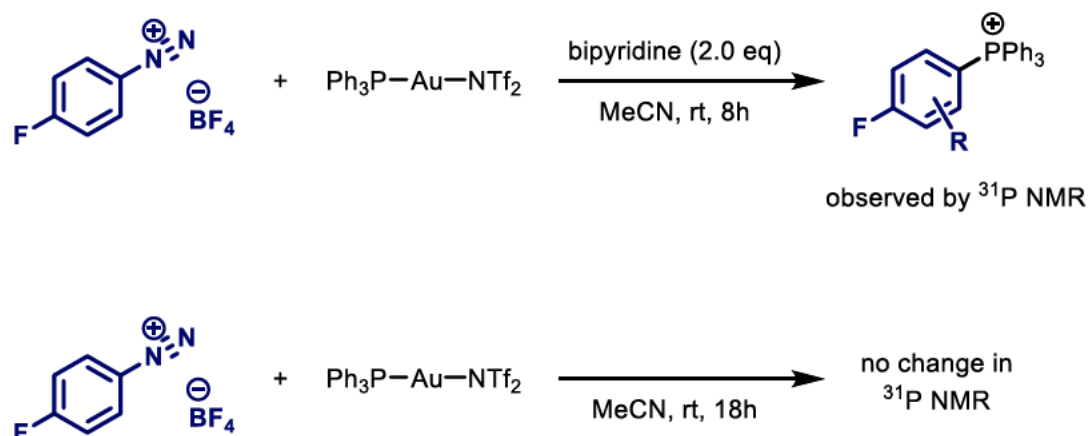
Scheme 30. Stoichiometric oxidative addition reactions with gold.[63]

Radical trapping experiment indicated that no free aryl radical was generated and that the gold(I) was required for the formation of the reactive arylating species.

Aryl radicals from aryldiazonium salts were developed to perform similar coupling reactions with gold. Both the Lee[64] and Fouquet[65] groups reported photoredox methodologies to synthesise biaryls using a gold catalyst.

Lee and co-workers published the ruthenium photocatalysed cross-coupling of aryldiazonium salts with aryl boronic acids (Scheme 31).[64]
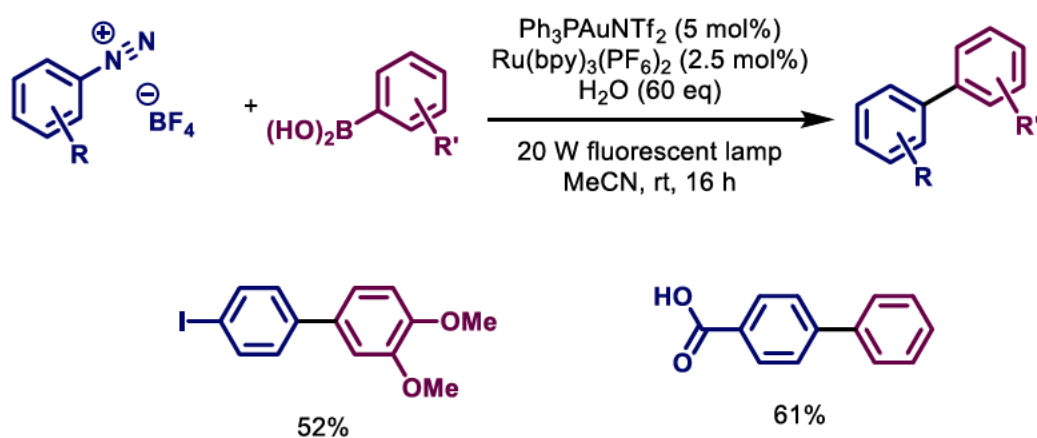
Scheme 31. Photoredox assisted, gold-catalysed, biaryl formation.[64]

Fouquet and co-workers published both the organo- (49) and ruthenium-photocatalytic and gold dual catalysis cross coupling of aryldiazonium salts and aryl boronic acids to make biaryls (Scheme 32).[65]
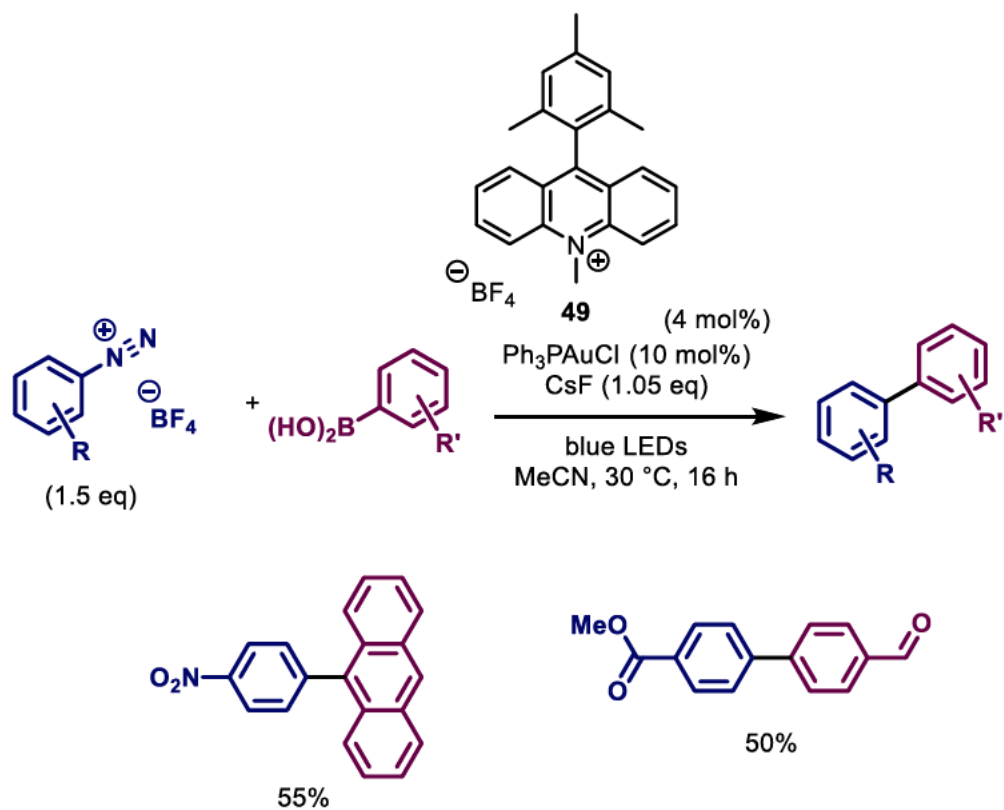
Scheme 32. Organophotocatalysed biaryl forming reaction.[65]

Hashmi and co-workers subsequently reported the gold-catalysed coupling of aryl diazonium salts and aryl boronic acids using photosensitiser free conditions (Scheme 33).[66] Reactions run in the dark gave no product.
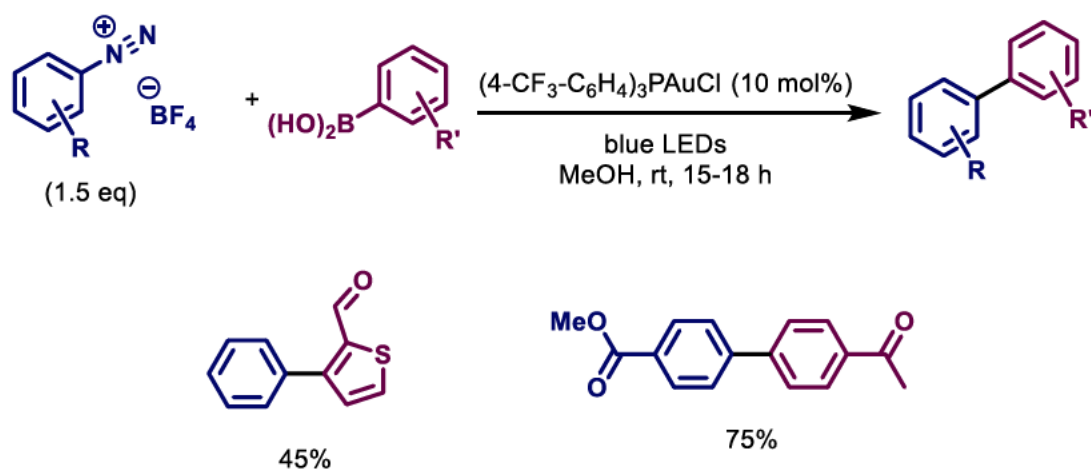
Scheme 33. Photosensitiser-free, gold-catalysed biaryl formation.[66]

Schoenebeck and co-workers have developed the coupling of arenes with aryl triethyl germanes (Scheme 34).[67, 68] The coupling reactions of aryl triethyl germanes have similar functional group tolerances as that of aryl trimethyl silanes. The coupling of polyfluorinated arenes is of interest as it bypasses the requirement for reactive polyfluorinated aryl organometallic reagents.
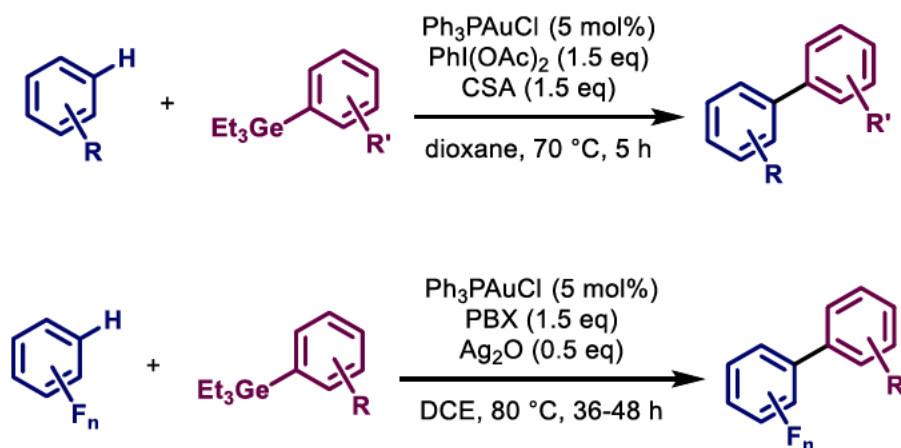
Scheme 34. Cross coupling of arenes[67] and polyfluorinated arenes[68] with aryl triethyl germanes.

1.4 – Summary and Aims

Despite the applications of gold(I)/gold(III) catalysis for the synthesis of biaryls, little is understood about the ligands on gold throughout the catalytic cycle and the oxidation of gold(I) to gold(III). The lack of knowledge surrounding the oxidation step can be attributed to the challenging nature of this process.

Very few oxidants have been utilised for the oxidation of gold(I) to gold(III) in catalytic reactions. With more understanding of the tolerances of gold-catalysed direct arylation should come improvements to the methodology and more applications.

One aim of this work is to investigate the impact of ligands on key steps of the biaryl forming process of the gold-catalysed direct arylation with the aim to prepare enantioenriched chiral biaryls. There may be potential to improve other features of the coupling such as the Au(I)/Au(III) oxidation potential, substrate scope, replace or remove additives and

Through screening, the discovery and mechanistic analysis of new oxidising agents for gold-catalysed oxidative coupling may be investigated. This has the potential to improve the gold catalysed direct arylation methodology's general applicability if inorganic oxidants could replace the organic hypervalent aryl iodine oxidants currently used. Other advantages could be the widening of the substrate scope, the replacement of solvents or the discovery of other reactions utilising a homogeneous gold catalyst under oxidative conditions.

1.5 - References

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2 - Enantioselective Gold-Catalysed Cross-Coupling

2.1 - Introduction

Ligands on Gold

Little is known of the ligands on the gold through the direct arylation catalytic cycle (Figure 9). With increased understanding of the catalyst species, the coupling of arylsilanes with arenes could potentially be further optimised, or other reactions discovered. To improve understanding of this reaction and the gold environment throughout the reaction, enantiopure, chiral ligands could be used to make chiral biaryls. This could provide valuable information about the gold environment at the step where the product chirality is set as well as providing desirable products that are hard to synthesise by other means.

Due to the oxidising and acidic reaction conditions, potential ligands on gold must be carefully chosen. Phosphines and thiols are oxidised, and amines protonated.

Ligands with high bond dissociation energies, those which strongly coordinate the metal throughout the catalytic cycle such as N-heterocyclic carbenes (NHCs), are of particular interest. These may be stable to the reaction conditions and may also affect the reactivity of the gold. Altering the electronics of the gold through ligation may allow for more trivial oxidation of the gold centre, enabling the use of milder oxidants. Furthermore, if a ligand is always present then additives such as CSA or methanol may not be required, lending to milder reaction conditions and a broader substrate scope.

Research into the interactions between additives and gold, throughout the catalytic cycle (Figure 9) could lead to the preparation of synthetically valuable enantioenriched chiral biaryls.

Chiral Biaryls

As well as the most well-known chirality type, point chirality, biaryl compounds may possess at least two other types of chirality, atropisomerism and planar chirality, that can be created through the formation of a biaryl bond (red - Figure 10).
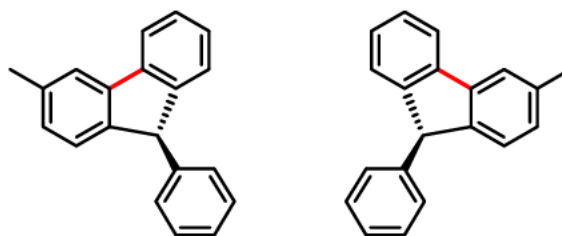
Point Chirality
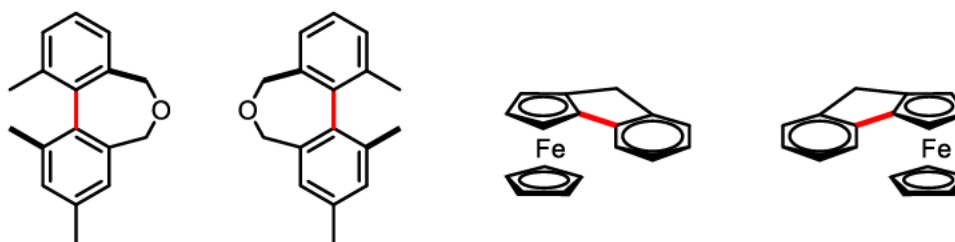
Axial Chirality   Planar Chirality

1

Figure 10. Chirality resulting from a biaryl bond.

2.2 - Background

Axial Chirality

Axial chirality results from substituents being arranged around an axis in such a way as to form a molecule whose mirror image is not superimposable on the original structure. Atropisomers are a subset of axial chirality, defined by isomers that arise from the restricted rotation around a single bond. To be isolable ($t_{1/2}$ of at least 1000s) at 300 K, they require an energy barrier to rotation of at least 93 kJ mol^{-1} (Scheme 35).[2]
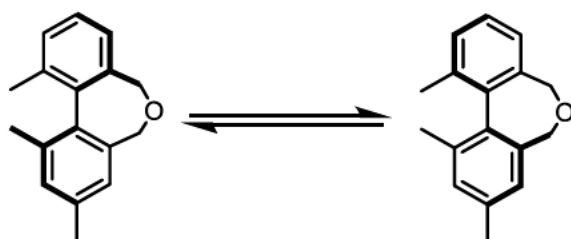
Scheme 35. Racemisation of an atropisomeric compound.

Atropisomerism is found in nature and biologically active compounds. Naturally occurring atropisomers of interest include (*P*)-dioncophylline C **1** and (*M*)-gossypol **2** (Figure 11). (*P*)-Dioncophylline C **1** is an antiplasmodial compound and (*M*)-gossypol **2** is under development as a male contraceptive and a chemotherapy drug.
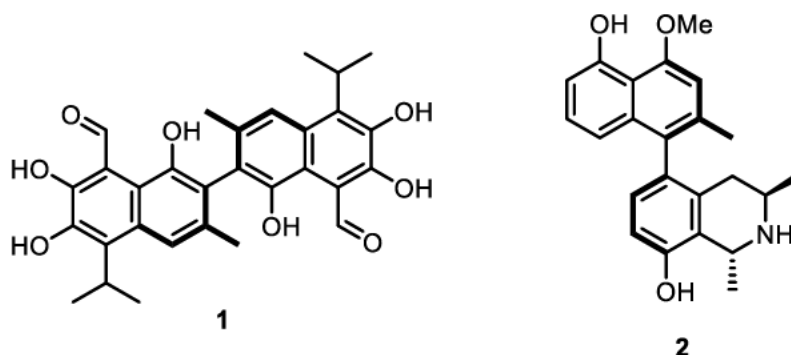
Figure 11. Naturally occurring atropisomers.

In synthetic chemistry, atropisomeric compounds find extensive use as chiral ligands in enantioselective catalysis.[3-7] Typical of this group are the 2,2'-disubstituted 1,1'-binaphthyls, including BINOL **3** and BINAP **4** (Figure 12). Atropisomeric biaryls also find use in materials and physical chemistry.[3, 8]
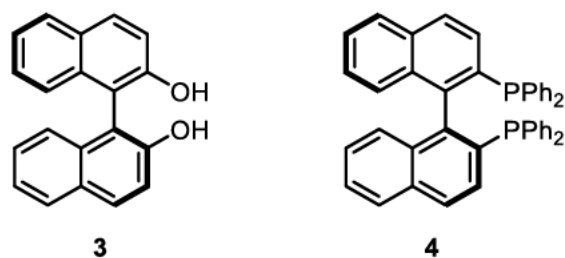
Figure 12. (S)-BINOL and (S)-BINAP.

Despite their utility in multiple fields, literature on their synthesis is sparse and often very specific to certain substrates.[9-11] Very few general procedures exist for the preparation of chiral biaryls.[9, 11]

One method for the synthesis of the ubiquitous binaphthol (BINOL) core involves the oxidative, diamine ligated copper catalysed, coupling of 2-naphthols (Figure 13).[12]
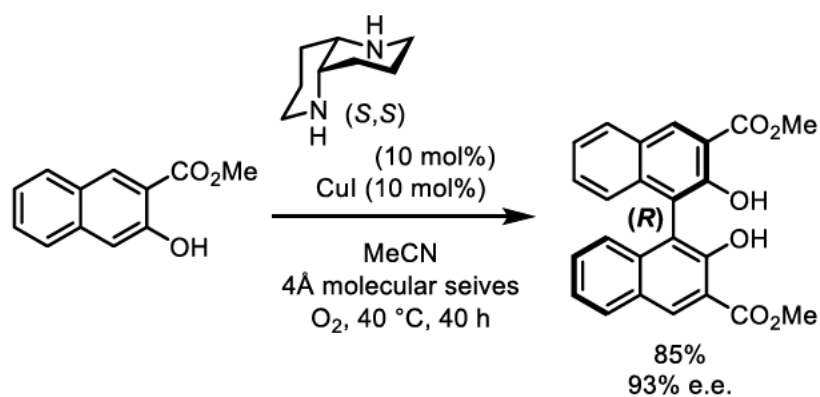
Figure 13. Copper catalysed homocoupling of 2-naphthols using a chiral diamine ligand. [12]

A common method to prepare atropisomeric biaryls is using a chiral tether, making the product diastereomeric. Lipshutz and co-workers utilised a copper mediated oxidative coupling of tethered 2-substituted naphthalenes using racemic (rac) α-methylbenzylamine (Figure 14).[13]
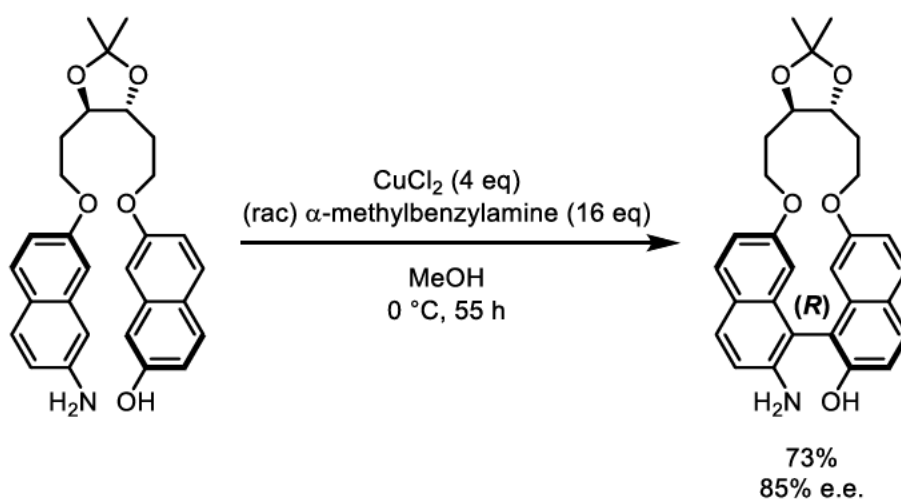
Figure 14. Oxidative coupling of 2-substituted naphthalenes containing an enantioenriched chiral tether.[13]

Buchwald and co-workers reported a method for the preparation of chiral biaryls using a palladium catalysed asymmetric Suzuki-Miyaura coupling reaction (Figure 15).[9]
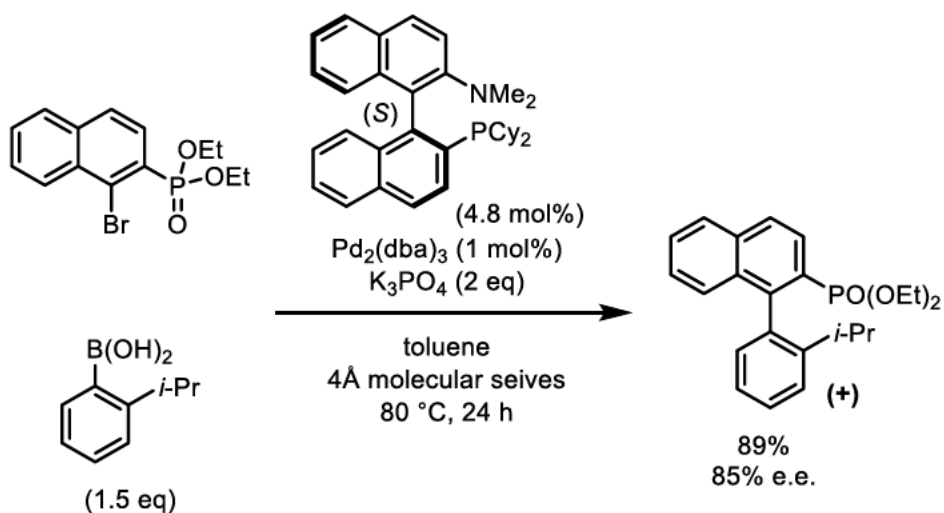
Figure 15. Suzuki-Miyaura cross coupling, using an atropisomerically pure ligand, to prepare enantioenriched atropisomeric products.[9]

Planar Chirality

Less commonly encountered in small molecule chemistry, planar chiral compounds are isomers that result from the arrangement of out of plane groups with respect to a plane. Isomerisation of planar chiral compounds depends on the type of bond that holds the two parts of the planar chiral compound together.

Planar chiral compounds generally exist in two main groups, those with organic tethers that are out of the plane or metal atoms, such as iron or cobalt, that bind to one face of a compound.

A rare example of planar chirality that occurs in nature is cavicularin 5 (Figure 16). Cavicularin contains a tether that reaches over the plane of the bis(bibenzyl) and is in a class of compounds under investigation as antifungals.
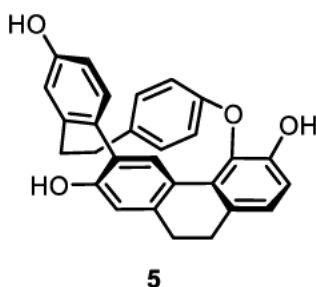
Figure 16. Cavicularin.

In the synthetic organic chemistry community, planar chiral compounds are used as chiral ligands and organic catalysts. Examples being the Josiphos family of ligands 6[14] and Fu's nucleophilic organocatalyst 7[15] (Figure 17).
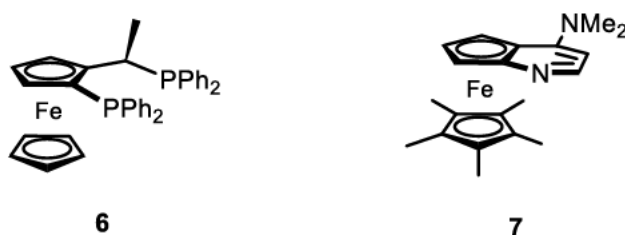
Figure 17. Planar chiral compounds, 6[14] and 7,[15] used in synthesis.

2.3 - General Consideration

Synthetic challenges are associated with making chiral biaryls. Some associated with the synthesis of substrates and some with the gold catalysed direct arylation itself.

Atropisomeric Compounds

Commonly, at least three ortho-substituents are required to provide a substantial barrier to rotation around the biaryl bond (Figure 18).
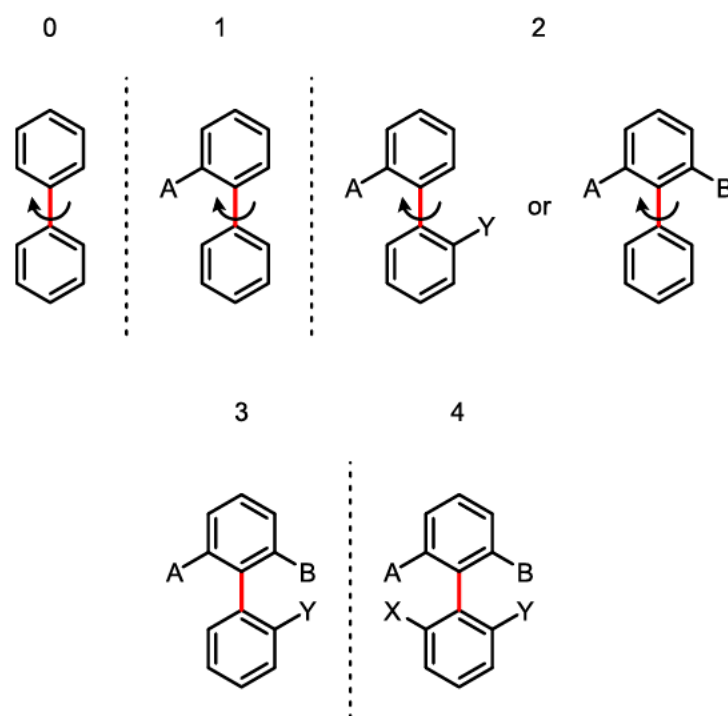
Figure 18. Rotation around the biaryl bond for differently ortho-substituted biaryls.

Substrates with *ortho*-substituents are known to undergo aurodesilylation faster that those without,[16] however, they are also more reactive to other electrophiles such as protons.[17-19] As the aurodesilylation is not the turnover-limiting step,[20] increasing the reactivity of the C-Si bond too much, through *ortho*-substitution will result in protodesilylation outcompeting the desired coupling. Step i) in the catalytic cycle (Figure 19), the productive aurodesilylation, is in competition with protodesilylation.

As the majority of the gold in solution is in its resting state, the form of the complex prior to the turnover limiting step, increasing the reactivity of the silane towards electrophiles can quickly overwhelm the amount of gold that is available for productive coupling, resulting in large amounts of protodesilylated byproduct. Multiple *ortho*-substituents could also drastically reduce further the rate of electrophilic substitution of the arene or reductive elimination.
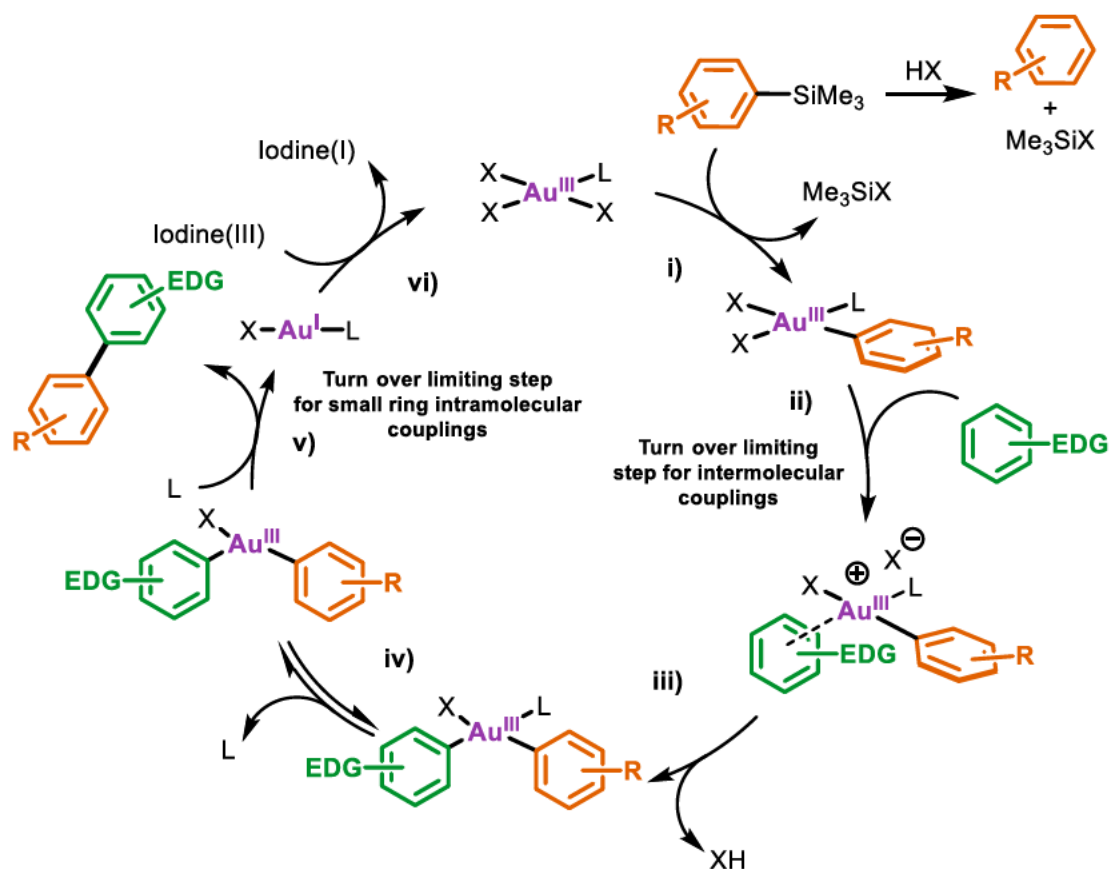
Figure 19. Catalytic cycle showing desilylation competition.

Planar Chiral Compounds

Utilising a ferrocene core for planar chiral compounds allowed for simple synthesis and fast screening of reaction conditions. The drawback of these structural motifs is that they can undergo facile redox chemistry.

2.4 - Project Aims and Initial Hypothesis

The aim of this project is to synthesise enantioenriched atropisomeric or planar chiral biaryls using a gold catalysed direct arylation of aryl trimethyl silanes. This could be performed using enantiopure ligands or additives designed to induce chirality at the enantiodetermining step.

Through producing enantioenriched product biaryls, the nature of the gold species at the enantiodetermining step could potentially be probed.

The initial hypothesis of this project is that, through the use chiral, enantioenriched additives that can act as ligands, enantioenriched chiral biaryls could be produced using the gold catalysed direct arylation methodology. Through the optimisation of conditions and

7

additives, it is hoped that a general methodology could be discovered that allows enantioenriched chiral biaryls to be constructed using gold catalysed direct arylation.

2.5 - References

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2.6 - Results and Discussion

Designing Prochiral Coupling Partners

Atropisomeric biaryls are the prototypical chirality mode when thinking of chiral biaryls and, in order to form atropisomeric biaryls, careful substrate design is necessary. *Ortho*-substituted arene and aryl silane coupling partners are required. This introduces several practical challenges:

1) Finding coupling partners that, for each ring, have *ortho*- groups that are different from each other; A ≠ B and X ≠ Y, otherwise the product biaryl will not be an atropisomer.

2) Finding *ortho*-substituents that are bulky enough to prevent rotation around the biaryl bond at room temperature.

3) Ensuring that the arene reacts at the position desired. Regioselective arylation may be a challenge as the coupling is desired at a sterically congested position.

4) Inserting the bulky silane group adjacent to at least one *ortho*-substituent on an arene and preventing it from protodesilylating before the productive reaction can occur. Protodesilylation is easier with substituents *ortho*- to the silane due to steric decompression, the effect where *ortho*-substituents push on the silane, destabilising the ground state.[1-3]
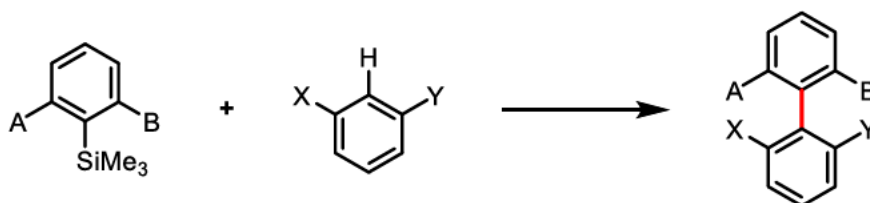
Figure 20. General scheme for the synthesis of atropisomeric biaryls.

Prochiral Starting Material

Naphthalene coupling partners provide low steric hindrance to the reactive site (position 1), whilst simultaneously having high barriers to racemisation in the product binaphthyls. **1** was expected to react at the most nucleophilic C-H bond (Scheme 36, highlighted) to couple with **2** as the aryl trimethyl silane coupling partner, to provide atropisomer **3**.

Naphthols are reactive towards PIDA$_2$,[4] so pivalate protecting groups were chosen.[5] Coupling arene **1** with aryl trimethyl silane **2** was expected to provide the desirable binaphthyl **3**, the

protected version of the privileged chiral ligand BINOL that is also the core of many more chiral ligands.[6, 7]
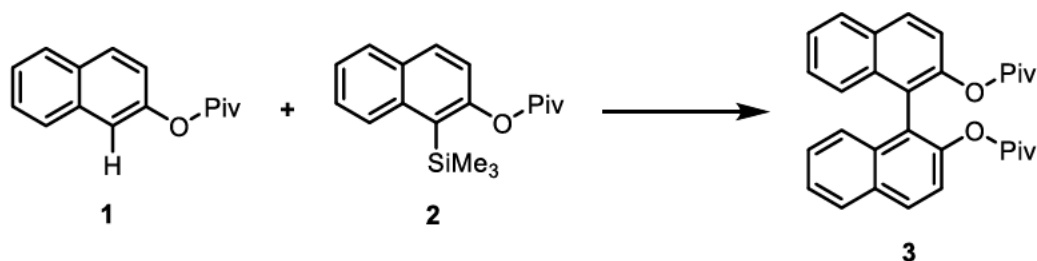
Scheme 36. Substrates and product for probing enantioselectivity of gold catalysed direct arylation.

Synthesis of Naphthyl Pivalate Starting Material

Initially, the synthesis of 1-trimethylsilyl-2-naphthyl pivalate **2** was attempted by silylating the phenol of 1-bromo-2-naphthol **4**, followed by retro-Brook rearrangement, via **5**, to give crude 1-trimethylsilyl-2-naphthol **6**. Silane **6** underwent protodesilylation on isolation. Two factors promoting the facile protodesilylation of **6** are: the electron rich arene stabilising the Wheland intermediate formed when the silane is electrophilically substituted, and that naphthalenes are less aromatic than a benzene-based system.
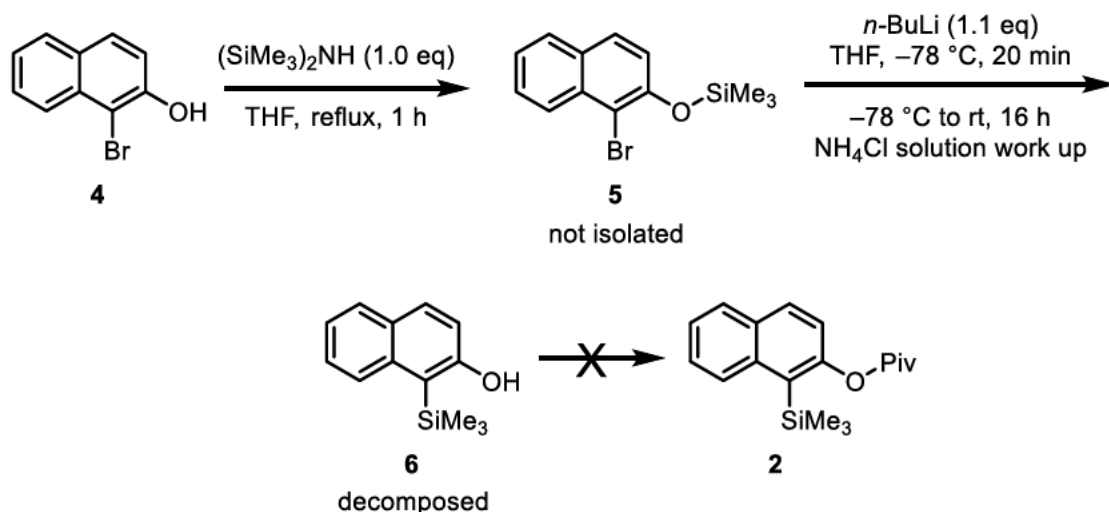
Scheme 37. Attempted synthesis of 1-trimethylsilyl-2-naphthyl pivalate.

Although the synthesis shown in Scheme 37 was not successful, it was suspected that **2** would be isolable. The electron withdrawing effect of the pivalate ester on the aromatic ring of **2** relative to the phenol of **6** should stabilise the aryl silane C-Si bond to electrophilic attack.

A new synthesis of **2** was devised (Scheme 38), in which the phenoxide intermediate formed from the retro-Brook is quenched directly at −78 °C with the electrophilic pivaloyl chloride. This method allowed for the synthesis of **2** in high overall yield.
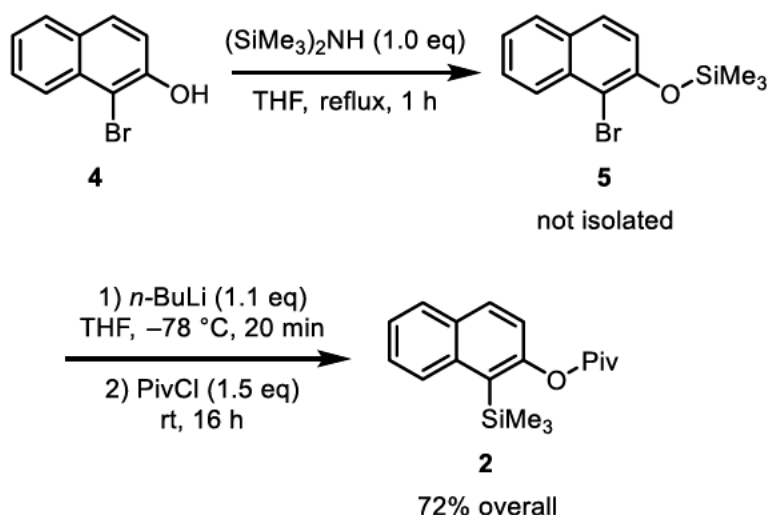
Scheme 38. Successful synthesis of 1-trimethylsilyl-2-naphthyl pivalate **2**.

Attempts to couple silane **2** to arene **1** were monitored by ^{1}H NMR. Upon subjection of silane **2** and arene **1** to coupling conditions (Scheme 39), aryl silane **2** underwent protodesilylation to form **1**.
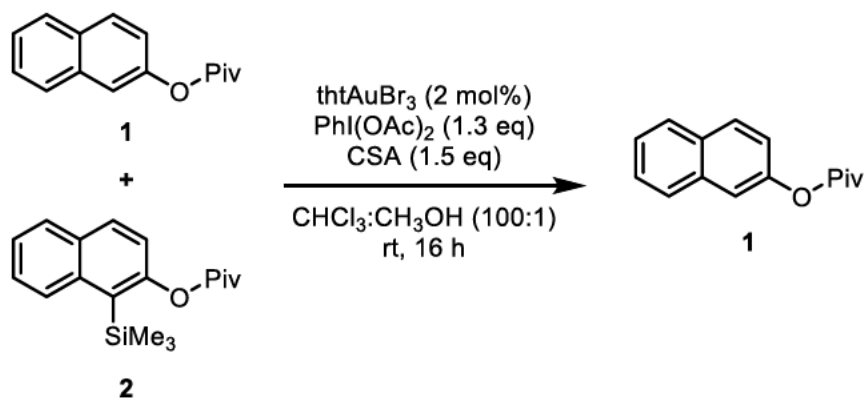
Scheme 39. Protodesilylation of **2**.

Two factors affecting the lack of coupling to form binaphthyl **3** are: the slow rate of coupling due to sterically hindered reaction positions, and the high rate of protodesilylation as aryl silane **2** is electron rich and weakly aromatic compared to related benzene rings. Adjusting either of these factors may influence the outcome of the coupling reaction.

2

Tethered Prochiral Starting Materials

New substrates were chosen with the idea of increasing the rate of coupling and/or reducing the rate of protodesilylation in order to improve the prospects of achieving a coupling.

Tethering the aryl silane to the arene provide multiple benefits; the reactive C-H bond is placed closer to the C-Si position, over arylation is hindered as intermolecular reaction is slower than intra-, and the regioselectivity of arylation on the arene is simpler to predict.

Dinaphthyl ether **7** was identified as a similar substrate to that of the partners **1** and **2**. Dibenzyl ether **8** was selected as it resembles other substrates that have been published for this reaction.[5] Benzyl ferrocene **9a** was of interest as it had the potential to give a planar chiral product instead of atropisomeric compounds. Additionally, ferrocene substrates had not been attempted with this reaction. Ferrocene is more reactive to electrophiles than most aromatic systems and is also redox active with many applications in materials chemistry and as chiral ligands.
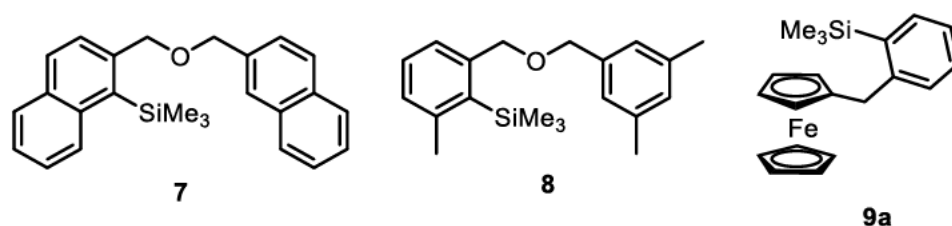
Figure 21. Tethered prochiral substrates.

Each of these substrates were novel compounds that, although functionally simple, required multiple step synthesis that considers many properties of each compound in the synthetic procedure:

1) Installation of the Me_3Si- group in a sterically congested position.

2) The installation of the Me_3Si- group usually requires the formation of a nucleophilic and basic aryl lithium intermediate.

3) Lack of polar functional groups makes for challenging isolation of the intermediates and products by flash column chromatography.

Synthesis of the Dinaphthyl Ether Substrate

The dinaphthyl ether **7** was synthesised from commercially available 1-bromo-2-methyl naphthalene **10** in 3 steps (Scheme 40). Initially, a benzylic C-H bond was radically

brominated, forming **11** followed by a Williamson etherification to create the tethered dinaphthyl ether **13**. Lithium halogen exchange followed by quench with Me$_3$SiCl gave the desired product **7** in high overall yield. A recrystallisation of **7** provided high product purity.
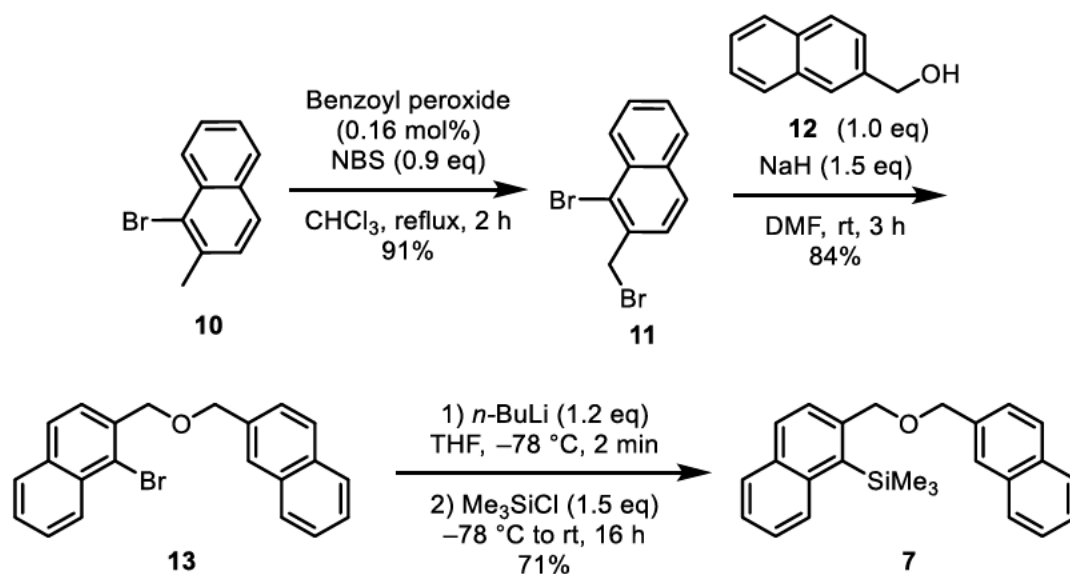
Scheme 40. Synthesis of dinaphthyl ether substrate.

Synthesis of the Dibenzyl Ether Substrate

The dibenzyl ether **8** was produced from 2-bromo-3-methyl benzoic acid **14** that was reduced with LiAlH$_4$ to give the benzyl alcohol **15**. Ether formation was performed via a Williamson etherification with benzyl bromide **16** forming the dibenzyl ether **17**. Performing lithium halogen exchange on **17** followed by quenching with Me$_3$SiCl gave the product **8**. When the silane was inserted before the etherification, the product was challenging to isolate due to similarly polar byproducts.
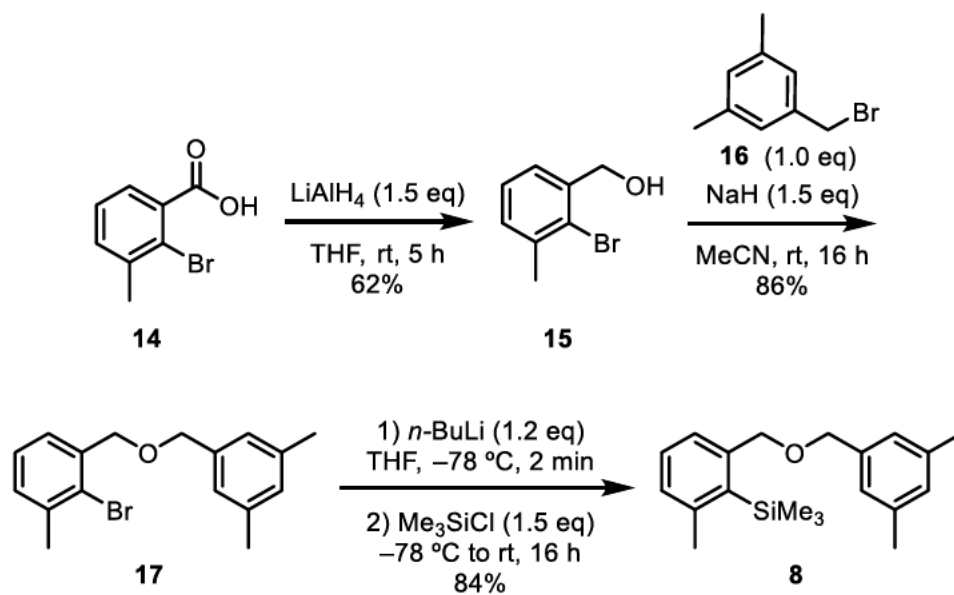
Scheme 41. Synthesis of dibenzyl ether substrate.

Synthesis of the Benzyl Ferrocene Substrate

Ferrocene was first acylated with 2-bromobenzoyl chloride **18**. The ketone **19** which was then reduced using a mixed aluminium hydride-chloride reagent to give the benzyl ferrocene **20**. Lithium/halogen exchange on **20** followed by quenching with Me₃SiCl gave the crude product **9a**. This was purified by column chromatography and recrystallisation.
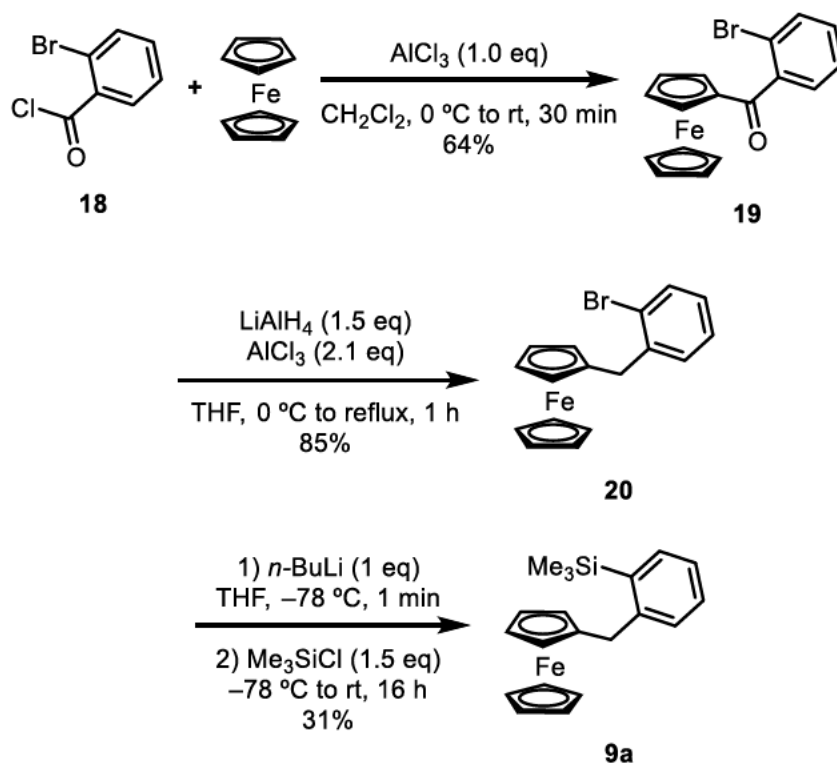
Scheme 42. Synthesis of benzyl ferrocene substrate.

Non-enantioselective Coupling Reactions

With three model substrates in hand, testing the gold catalysed direct arylation under non-enantioselective conditions began.

The coupling reactions of 7 and 8 were expected to be challenging because of the steric congestion around the reactive sites, reaction conditions were selected that had been used to overcome challenging gold catalysed arylations previously.

The standard solvent mixture for gold catalysed aryl silane/arene coupling is 50:1 chloroform/methanol.[5, 8-10] In order to provide the most favourable conditions for successful reaction with challenging substrates a solvent mixture of 100:1 chloroform/methanol was used. Although methanol is required to solvate the oxidant and sequester the Me_3Si- group, polar additives slow down the rate of reaction due to inhibition of reductive elimination.[9]

A temperature of 50 °C was chosen because the coupling of 7 and 8 were challenging, containing congested reactive sites. Temperatures up to 65 °C have been used to increase the rate of slow reactions of similar type.[8]

Dibenzyl Substrate

The dibenzyl ether **8** successfully coupled to give biaryl **21** using the conditions shown in Scheme 43, with 64% yield estimated by ^{1}H NMR using CSA as an internal standard (Scheme 43).
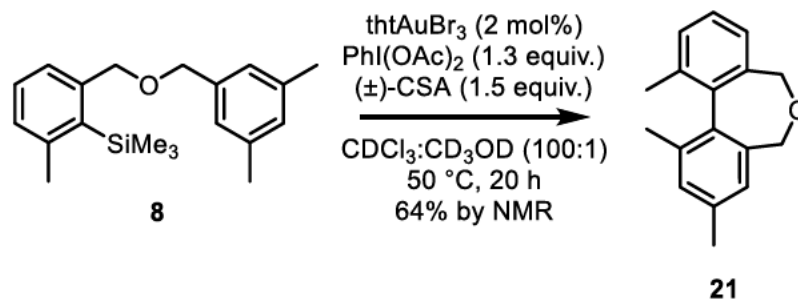
Scheme 43. Coupling of dibenzyl substrate.

Dinaphthyl Substrate

Whilst investigating the intramolecular coupling of dinaphthyl ether **7** (Scheme 44), protodesilylation to form **22** and oxidative cleavage giving aldehyde **23** was observed. Oxidative cleavage of the dinaphthyl ether was not expected and is not reported with aryl iodine(III) oxidants, however the 2-naphthyl methanol protecting group for alcohols and acids is known and its deprotection can be performed by oxidising agents in a similar manner to that of the PMB ether.[11]
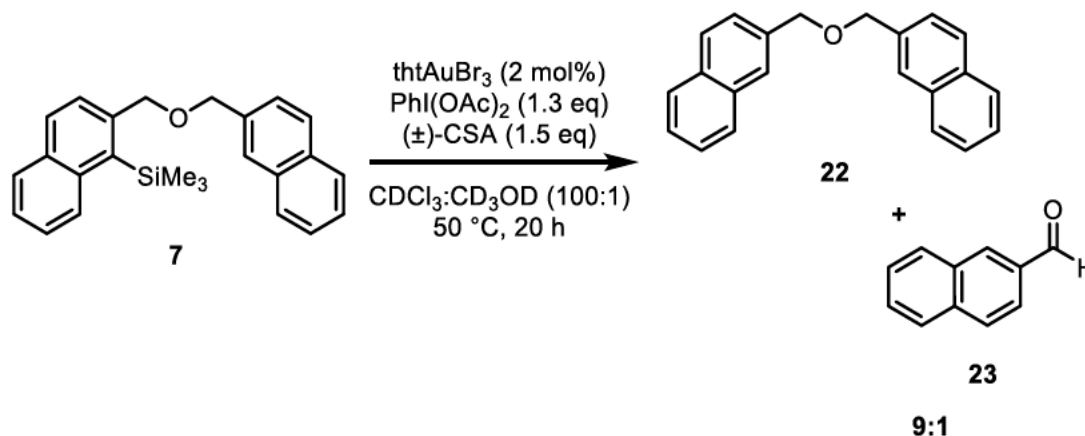
Scheme 44. Unsuccessful coupling of dinaphthyl substrate.

To learn more about the protodesilylation and oxidative cleavage of dinaphthyl ether **7** and to identify whether adjusting the additives (CSA and methanol) would allow for formation of binaphthyl product **24**, a series of reaction conditions were tested (Scheme 45 and Table 1).
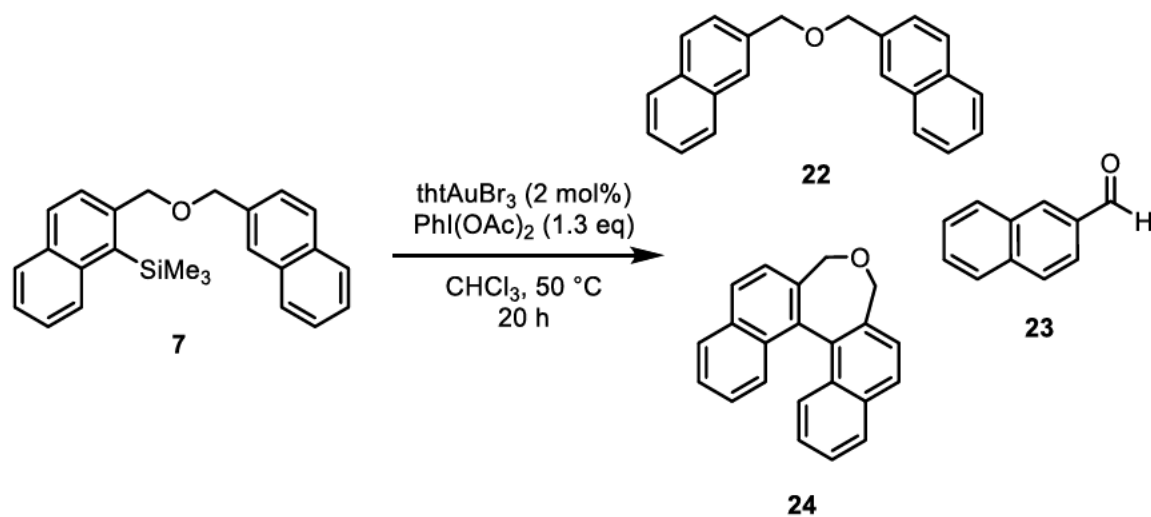
Scheme 45. Additive screening on dinaphthyl coupling.

Table 1. NMR conversions (Scheme 45).

Entry	Conditions	NMR Conversions (%)		
		22	23	24
1	No additives	0	5	90
2	CSA (1.5 eq)	40	27	28
3	CHCl$_3$:MeOH (100:1)	0	2	94
4	CSA (1.5 eq) and CHCl$_3$:MeOH (100:1)	88	10	0

The reaction conditions with CSA gave lower yields of coupled product **24** due to protodesilylation (**22**), a reaction that is known to be accelerated under acidic conditions.[12] Although CSA has been proposed to protonate X type ligands, removing them from gold, thus making the gold cationic and electrophilic enough to perform a substitution of the arene,[9] and for the activation of the oxidant,[9] under these reaction conditions with this substrate CSA is not required for successful coupling of substrate **7** to binaphthyl **24** (Table 1, entry 3).

Intermolecular Ferrocene Coupling

The coupling of ferrocene had not been attempted for this reaction. As ferrocene is very electron rich and undergoes facile redox chemistry, the simple intermolecular coupling reaction of ferrocene and an untethered aryl trimethyl silane **25** was tested.

Upon mixing the ferrocene with the gold precatalyst, a reaction occurred that immediately precipitated gold metal and caused a vivid blue precipitate to form that was suspected to be the ferrocenium cation.
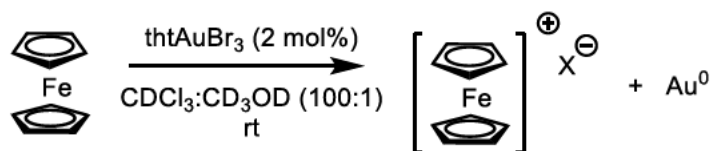
Scheme 46. Suspected reaction of ferrocene and thtAuBr₃.

In order to prevent this oxidation, the coupling with aryl trimethyl silane **25** was tested on the oxidised ferrocenium tetrafluoroborate. Because this was expected be a challenging reaction, both room temperature and heating to 50 °C were attempted to induce coupling. After 16 hours reaction for each temperature, no substrate **25** had been converted and no product **26** was observed by ^{1}H NMR (Scheme 47).
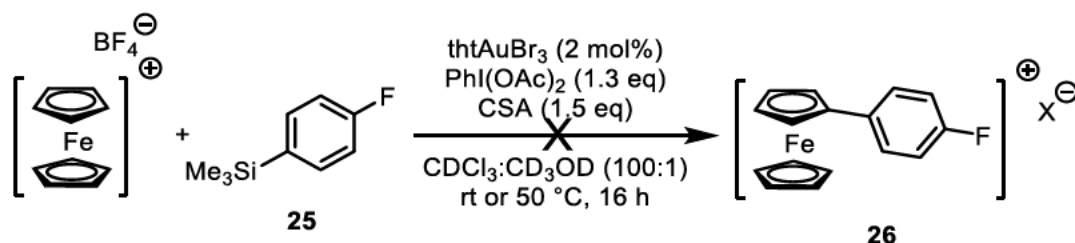
Scheme 47. Attempted coupling of ferrocenium tetrafluoroborate with p-fluorophenyl trimethyl silane.

Benzylferrocene Substrate

Although the intermolecular couplings of ferrocene and ferrocenium had not been successful, the intramolecular coupling of ferrocene substrate **9a** was suspected to be more facile. Once again, upon mixing the gold precatalyst with substrate **9a**, Au⁰ precipitated (Scheme 48a). When testing the benzylferrocinium substrate **9b** at room temperature and 50 °C, no reaction occurred (Scheme 48b).

a)

thtAuBr$_3$ (2 mol%)
PhI(OAc)$_2$ (1.3 eq)
CSA (1.5 eq)

CDCl$_3$:CD$_3$OD (100:1)
rt or 50 °C, 16 h

9a

b)

thtAuBr$_3$ (2 mol%)
PhI(OAc)$_2$ (1.3 eq)
CSA (1.5 eq)

CDCl$_3$:CD$_3$OD (100:1)
rt or 50 °C, 16 h

9b
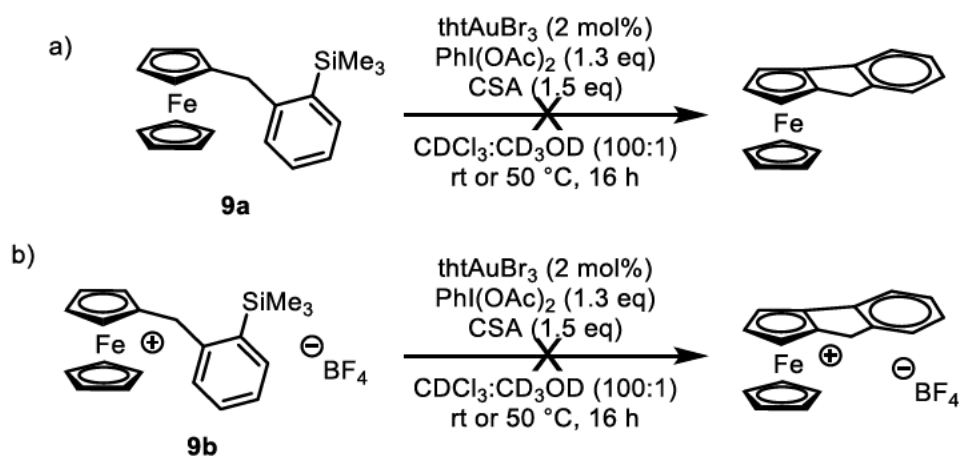
Scheme 48. Attempted coupling of benzylferrocene substrates.

Based on this lack of coupling, benzyl ferrocene **9** was excluded as a prochiral substrate for future experiments.

Method of Analysis

Having identified that two substrates (**7** and **8**) for the gold catalysed arylation that could be coupled to form biaryls, it was necessary to find a method to determine if the coupled products had a high enough barrier to rotation to be isolated at room temperature, and to determine the enantiomeric excess in future experiments involving enantiopure additives. HPLC with a chiral stationary phase was selected as the method of analysis.

Chiral separation of the racemic mixtures of products **24** and **21** was performed by HPLC using a CHIRALPAK OD-H column. Both enantiomers of products **24** and **21** were separable showing that they do not undergo fast rotation around the biaryl bond. Chiral HPLC confirmed that the test reactions (Scheme 43 and Table 1, entry 3) produced biaryls **24** and **21** as racemic mixtures. With conditions for the separation of enantiomers in hand, a variety of chiral ligands and additives were investigated to determine if the couplings could be made enantioselective.

N-Heterocyclic Carbene Gold Complexes

NHC gold complexes were selected because the NHC-gold bond was expected to be the most stable of common ligand-gold bonds under acidic, oxidative conditions. In 2015, Itami reported the use of a triarylpyridylidene based NHC ligand **27** (Figure 22) in gold catalysed direct arylation reaction.[13] This inspired the investigation into chiral NHC ligands for this reaction.

27
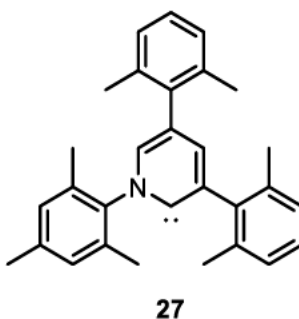
Figure 22. Triarylpyridylidene NHC ligand.

Achiral NHC ligands

Although the goal was to prepare enantioenriched, chiral atropisomers, achiral NHCs were initially used to test the applicability of NHCs as ligands for gold in direct arylation. IPr and ICy were chosen as two sterically different ligands, IPr is much bulkier than ICy.

The steric parameter of NHC ligands is commonly quoted at percent buried volume, defined as the percent of a sphere, extending from the atom bound by the NHC, that the ligand occupies.[14] IPr has a 39.0% 'buried volume' at 2.28 Å,[15] where ICy has a 23.6% 'buried volume' with the same bond length.[16] It should also be noted that ICy is also slightly more electron donating than IPr.[17]

Chloride and bromide were chosen as X type ligands in these complexes to probe their effect on the catalyst activation step. It has been shown that the chloride anion can bind more strongly to gold than bromide, increasing the activation time required and reducing the rate of reaction for gold chloride precatalysts relative to gold bromide precatalysts.[9] A simple intramolecular test reaction, coupling diphenylmethane substrate **28** to form fluorene **29**, was devised to examine the efficacy of these complexes (Scheme 49).

IPr

ICy

IPr—Au—Cl   IPr—Au—Br   ICy—Au—Cl   ICy—Au—Br

30   **31**   **32**   **33**
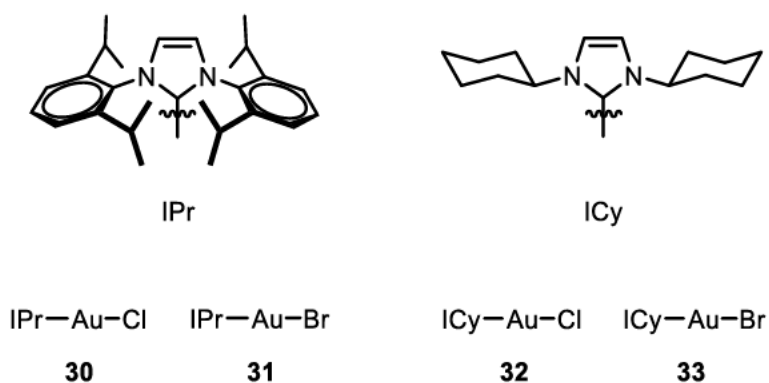
Figure 23. NHC)AuX complexes.
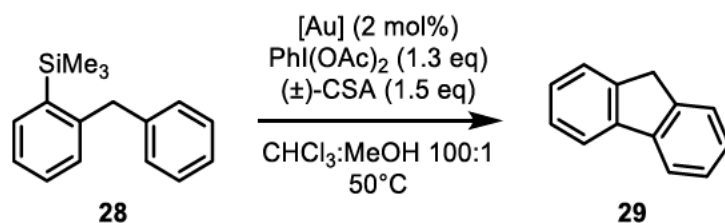
Scheme 49. NHCAuX precatalyst screening.

Table 2

Entry	Precatalyst	NMR Yield 29 (%)/ 30 mins	NMR Yield 29 (%)/ 18 h
1	thtAuBr$_3$	93	93
2	30	0	2
3	31	1	5
4	32	0	84
5	33	4	80

The reaction using thtAuBr$_3$ had reached maximum conversion by the 30-minute time point. The ICyAuX (**32** and **33**) complexes provided high conversions over a longer period of time (Table 2, entries 4 and 5), although ICyAuCl **32** appeared to initiate more slowly than ICyAuBr **33**. Both ICyAuX complexes (**32** and **33**) gave reasonable conversion to the product. Both IPrAuX (**30** and **31**) complexes gave low conversion, which could be due to the increased steric bulk of the IPr ligand compared to ICy.

Kinetics of the reaction involving ICyAuBr **33** (Figure 24) showed an increasing rate of conversion over time which indicated a slow activation of the catalyst. The catalyst loading for the kinetic study was increased to 5 mol% to follow the ICy ligand by ^{1}H NMR in the reaction (Scheme 50). In this case, the reaction was complete before 75 minutes and the increasing rate of reaction was observed (Figure 24).
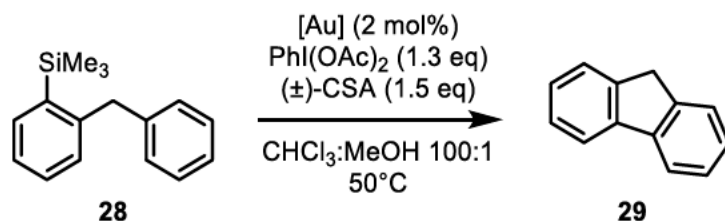
Scheme 50. Investigation of fluorene formation using ICyAuBr (5 mol%).
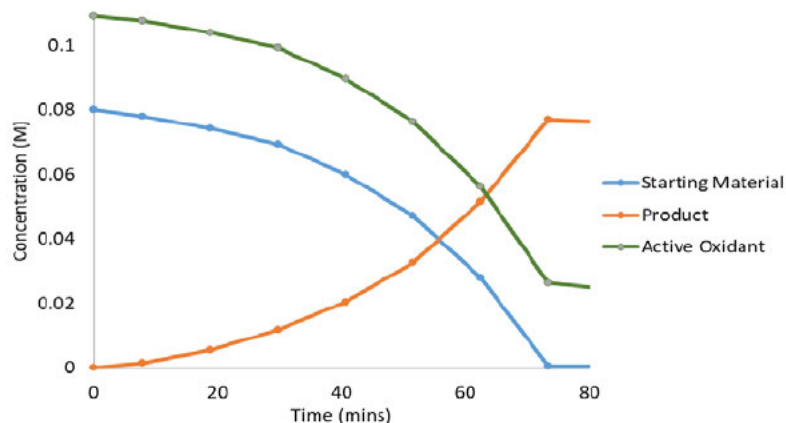
*Figure 24. Following the reaction of substrate **28** with ICyAuBr **33** (5 mol%) (Scheme 50).*

The backbone of the ICy ligand (Figure 25) in complex **33** can be seen in ^{1}H NMR, spectrum 1 (Figure 26), when following the reaction (Figure 26, spectra 2-11, δ_H 5.29), this peak splits and shifts without significant change in integration, indicating that there may be two species being observed. These NMR signal may be an active, or off cycle, gold species, or a decomposed ICy based fragment.
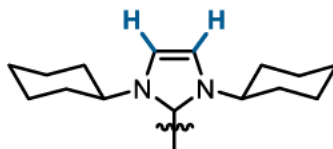
Figure 25. ICy backbone C-H bonds.

Because achiral ICyAuX complexes **32** and **33** successfully coupled the model intramolecular
substrate **28** (Table 2), two enantiopure NHC gold complexes **34** and **35** were prepared and
used as catalysts for the coupling of both substrates **7** and **8**.

Chiral NHC Ligands

To determine whether chiral, enantiopure NHC gold complexes could cause enantioinduction
in the chiral biaryl products **21** and **24**, gold complexes **34** and **35** were prepared and tested
in the arylation reactions using substrates **8** and **7**.

34   **35**
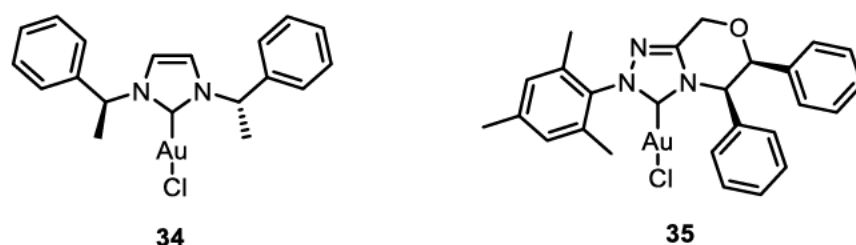
Figure 27. Enantiopure NHCAuCl complexes.

[Au] (2 mol%)
PhI(OAc)₂ (1.3 eq)
(±)-CSA (1.5 eq)

CDCl₃:CD₃OD (100:1)
50 °C, 5 days

8

21
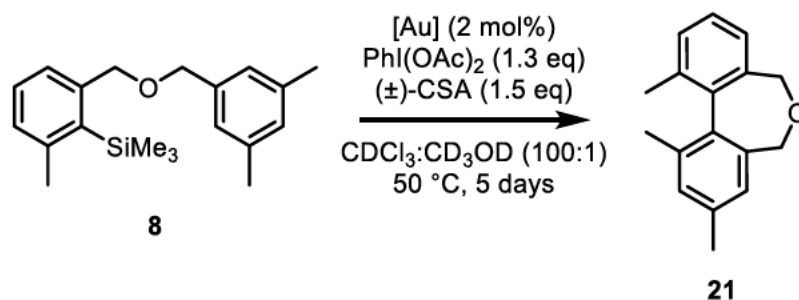
Scheme 51. Conditions for Enantiopure NHCAuCl Catalysts.

Table 3

Catalyst	NMR Yield 21 (%)	e.e.
34	0	0%
35	34	0%

14

For substrate **8**, catalyst **34** showed no conversion at 50 °C over 5 days, and **35** only turned over slowly, giving a low yield of product **21**. Upon chiral HPLC analysis of the product **21** it was found to be racemic.
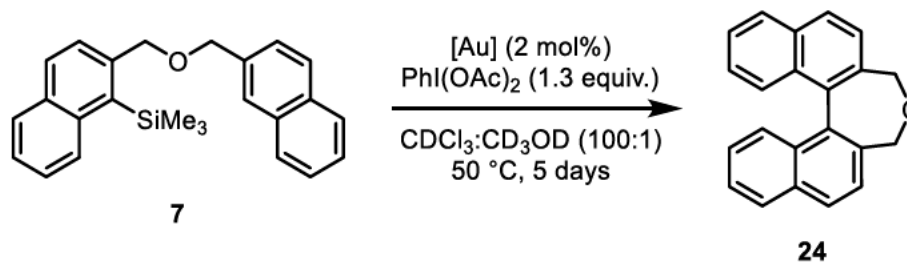
Scheme 52. Conditions for enantiopure NHCAuCl catalysts.

Table 4

Catalyst	NMR Yield 24 (%)	e.e.
34	0	0%
35	27	0%

The coupling of the dinaphthyl substrate **7** to **24** gave similar results of no conversion for catalyst **34** and racemic product for catalyst **35**.

Based on the kinetic profile (Figure 24) and the lack of enantioinduction from the enantiopure ligands (Table 3 and Table 4), it was hypothesised that the ligand inhibits the coupling reaction and that the successful coupling is only achievable once the NHC has been removed from the gold centre. Although many bond dissociation enthalpies have been determined,[18] conditions may change the mechanism of ligand dissociation. For example, protonation, reductive elimination, oxidation or complete degradation of the ligand could result in the loss of the NHC.

As NHCs (strong L type ligands) seemed to inhibit catalyst turnover, transient ligands were investigated. Ligands that can coordinate and decoordinate would not have such a strong effect on the mechanism of the reaction, making it more likely to have successful coupling of the aryl silane and arene.

Enantiopure Alcohols

Previous work has reported that methanol coordinates to gold and inhibits reductive elimination.[9] The investigation of enantiopure alcohol additives for the enantioinduction was based on the interaction of methanol and gold at a potentially enantiodetermining step.

A ratio of 100:1 chloroform/methanol with a substrate concentration of 0.1 M, supplies 5 eq. of methanol with respect to the silane. When replacing methanol for an enantiopure alcohol 5 eq. of each enantiopure alcohol was added to each reaction. Alcohols were chosen to be varied in structure: primary, secondary, benzylic.
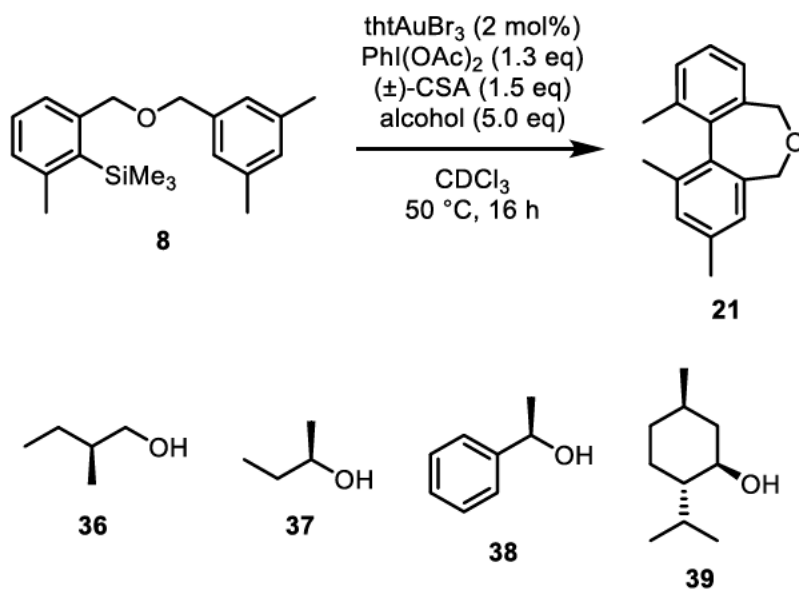
Figure 28. Reaction conditions and enantiopure alcohol additives.

Table 5

Alcohol	NMR Yield 21 (%)	e.e.
(S)-Methyl butanol 36	95	0%
(R)-2-Butanol 37	96	0%
(R)-Phenyl ethanol 38	95	0%
(−)-Menthol 39	62	0%

Although high conversions were seen for the coupling of substrate 8 to biaryl 21 with all alcohol additives, none gave enantioinduction. This is likely to do with the transient nature

of the alcohol coordination and that catalytic cycle completion depends on the decoordination of L type ligands (Figure 29, steps iv and v).
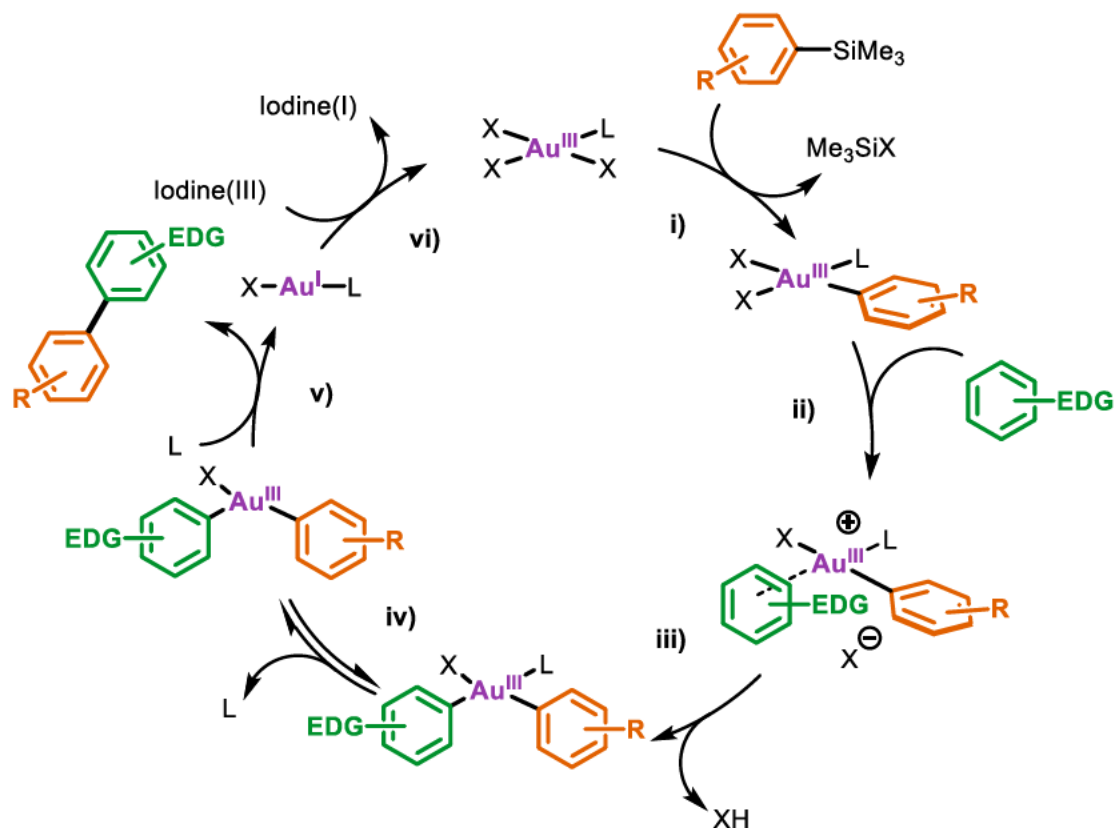
Figure 29. Proposed catalytic cycle.[5]

The proposed catalytic cycle (Figure 29) does show that an X type ligand may be present throughout the cycle. Although the identity of this X type ligand is unknown, it may be a camphor sulfonate anion.

Enantiopure CSA

In the same vein as alcohol additives, the already chiral CSA that has been utilised in racemic form could be replaced by enantiopure CSA. The effect of CSA on the gold centre was predicted to be stronger than that of the alcohols as it could act as either an X type sulfonate ligand, an L type sulfonic acid or carbonyl ligand or and X L or L L bidentate ligand.

Figure 30. Potential coordination modes of (+)-CSA.

If CSA bound as an X type ligand, then it could remain bound as the sulfonate throughout the cycle (Figure 29), causing enantioinduction at the key step. If the CSA bound in the X L style, then the ketone coordination that is the L type ligand could decoordinate to allow for reductive elimination from the bisaryl gold complex (Figure 29, steps iv and v).

(+)-CSA was used in place of (±)-CSA under standard conditions (as in Scheme 49) and a 93% yield of **21** was observed by ^{1}H NMR, although no enantioinduction was detected (Scheme 53, **Error! Reference source not found.**).

Scheme 53. Conditions for enantiopure (+)-CSA coupling.

Chiral *Ortho*-Directing Groups

Ortho-coordinating groups have been found to accelerate the rate of coupling compared to that of similarly sterically bulky but non-coordinating groups, this has been attributed to gold coordination removing the blocking interaction between the ortho group and the incoming arene coupling partner (Figure 31).[10]

Fast arylation   Slow arylation
ortho-group blocking

Figure 31. Coordinating and non-coordinating ortho-groups.

Taking advantage of the closeness of a coordinating chiral group on the silane coupling partner, chiral *ortho*-coordinating groups could be utilised to induce asymmetry. Initially, compound **40** was chosen to be the chiral substrate. Enantiopure sulfoxides have been utilised as chiral *ortho*-coordinating groups to direct enantioselective coupling reactions.[19] The electron-withdrawing nature of the sulfoxide *ortho*-coordinating group was suspected to be beneficial in tempering the rate of protodesilylation.

40
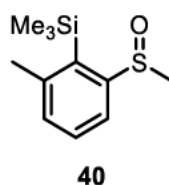
41 was selected as the most viable substrate to synthesise substrate **40**. The synthesis plan involved diazotisation of the aniline, followed by thiomethylation to give **42,** then either direct lithium-halogen exchange and quench with Me₃SiCl to form **43,** or oxidation of the thioether to give sulfoxide **44** before silane insertion producing the substrate **45**. However, the lithium-halogen exchange followed by Me₃SiCl quench on the methyl on the thioanisole **42** or methyl sulfoxide **44** were unsuccessful (Scheme 54). Compounds resembling **46** and **47** were observed, which indicate that the methyl C-H bonds were deprotonated. Grignard formation from **42** and **44** instead of lithium halogen exchange was also unsuccessful.
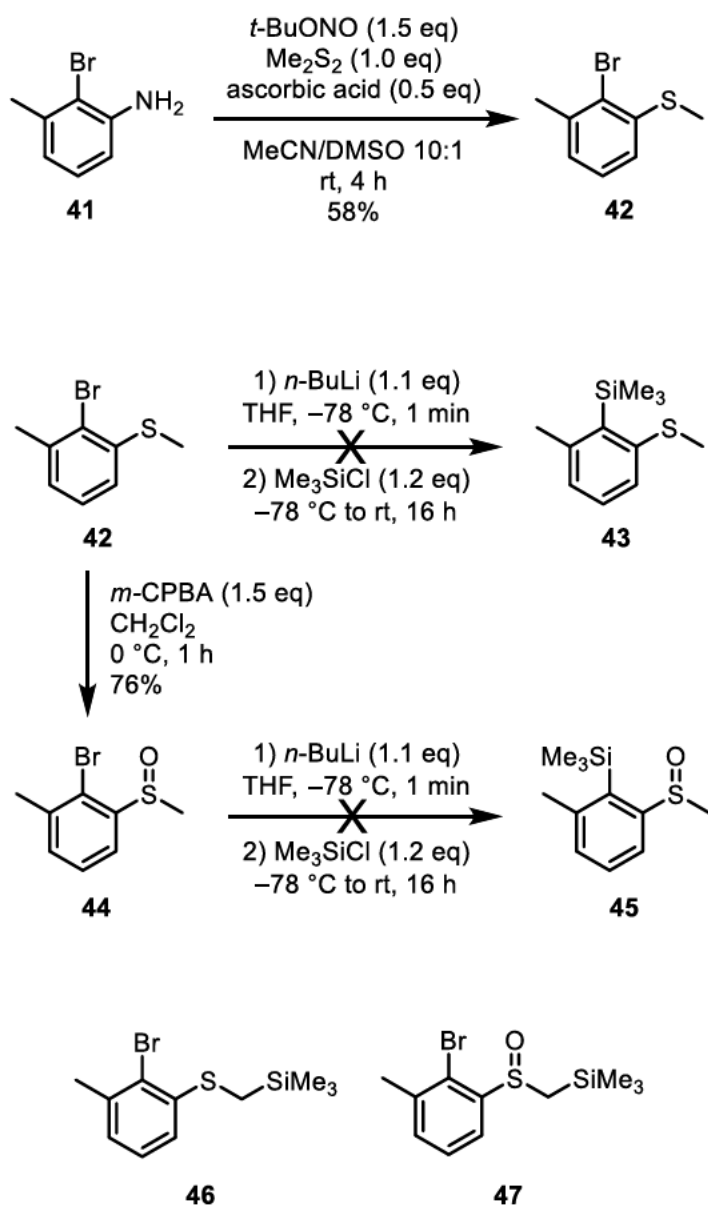
Scheme 54. Unsuccessful ortho-sulfoxide aryl silane synthesis.

Swapping the methyl sulfoxide for a *tert*-butyl sulfoxide group allowed for *ortho*-lithiation methodologies to be used as there are no protons acidic enough on the *tert*-butyl group to react with any organolithium species. This allowed for a successful synthesis of 1-trimethylsilyl-2,4-dimethyl-6-(*tert*-butylsulfinyl)benzene **50** from 3,5-dimethylbromobenzene **48**.
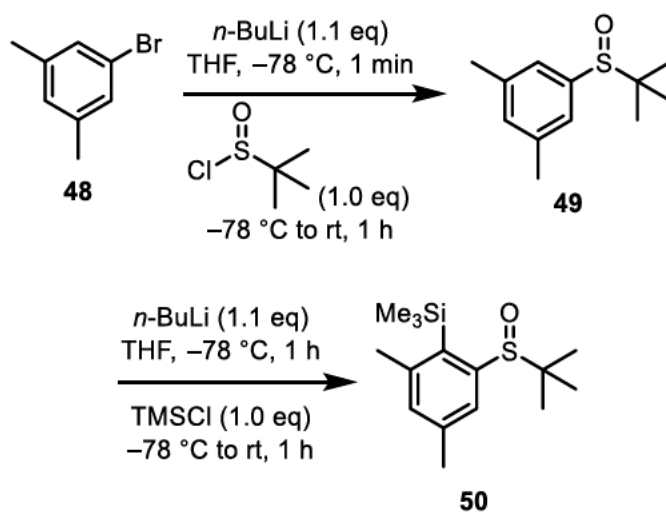
Scheme 55. Successful strategy to ortho-substituted aryl silane.

Standard conditions were employed to couple **50** to naphthalene or 2-bromothiophene. The naphthyl product **51** was expected to be an isolable atropisomeric compound and 2-bromothiophene is known to be a particularly reactive arene coupling partner to test for reactivity.[8]
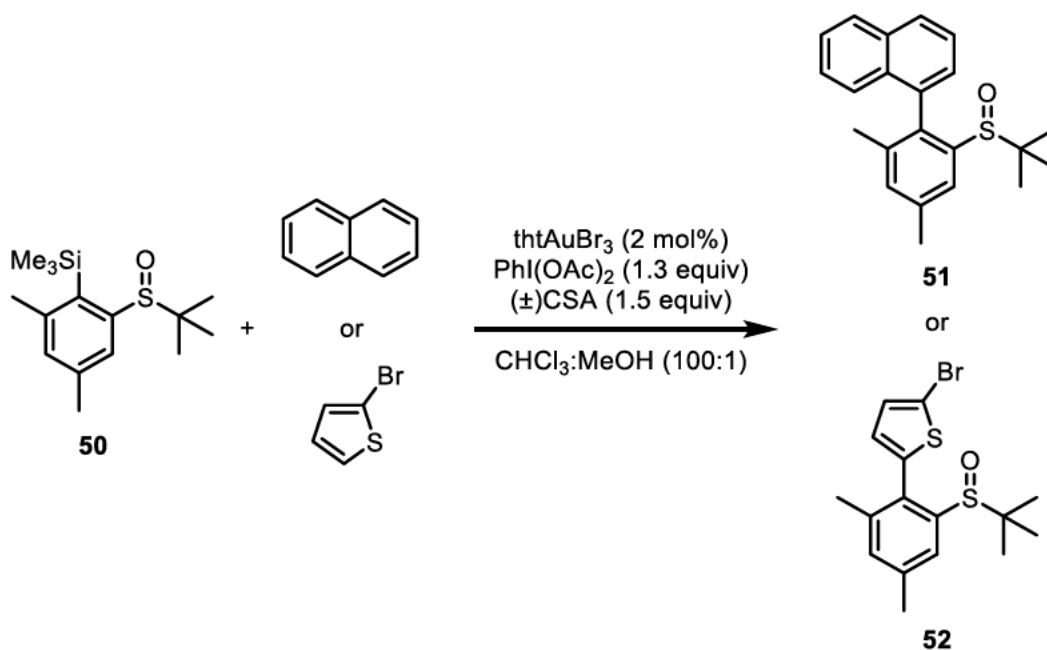
Scheme 56. Silane **50** coupling with naphthalene or 2-bromothiophene.

Table 6

Arene	NMR Conversion 50 (%)	NMR Conversion PhI(OAc)$_2$ (%)	NMR Yield 51/52 (%)
Naphthalene[a]	12	100	0
2-bromothiophene[b]	52	100	0

[a] 50 °C for 10 h, [b] room temperature for 12 h.

As PhI(OAc)$_2$ appeared to be consumed in an unproductive side reaction, other oxidising conditions were investigated.
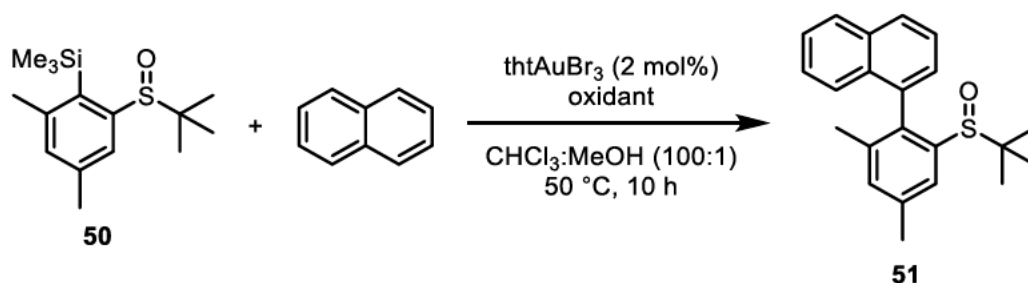
Scheme 57. Varying the oxidant in silane **50** coupling with naphthalene.

Table 7

Oxidant	NMR Conversion 50 (%)	NMR Yield 51 (%)
CSA (5.0 eq) + IBDA (4.5 eq)	63	0
CSA (1.3 eq) + IBA (1.1 eq)	38	0
PIFA (1.1 eq)	14	0

The small screen of aryl iodine oxidants shows that none of the ones tested allow for successful coupling of 50 and naphthalene to give 51.

Aryl iodine oxidants are known to react with naphthalene in the presence of metal catalyts,[20] and, although unreported, hypervalent aryl iodine oxidants may oxidise sulfoxides to sulfones. However, neither naphthalene nor sulfoxide oxidation were observed by [1]. The silane seems to be protodesilylated, but the fate of the oxidant is unknown. These conditions did not lead to successful couplings.

The slow unproductive consumption of oxidant is a symptom of coupling partners (**50** and naphthalene) that have a slow productive coupling reaction, likely due to sterics on the aryl silane.

2.7 - Conclusions and Future Work

The formation of enantioenriched biaryls through the methods attempted failed. However, the coupling of tethered substrates was successful in creating atropisomeric biaryls, some conclusions can be drawn:

1) Multiple ortho groups around the trimethyl silyl group on the aryl silane increase the rate of non-productive side reactions that consume the aryl silane.

2) Bulky substituents on the arene coupling partners significantly reduce the rate of coupling.

3) The NHC ligands tested strongly inhibit the reaction turnover.

4) Ferrocene and ferrocenium substrates are not tolerated by the conditions utilised in these coupling reactions.

5) Enantiopure CSA and chiral alcohols have no effect on the enantiodetermining step.

Although the formation of enantioenriched biaryls using gold catalysed direct arylation has been unsuccessful to date, there is the possibility that strongly coordinating, bidentate, L L type ligands could allow for enantioinduction. Toste has shown that cationic, tetracoordinate gold complexes undergo rapid reductive elimination.[21] Where monodentate L type ligands suppress reactivity, bidentate L L ligands could force the gold centre to be cationic through most of the cycle, potentially making it more electrophilic. This may then accelerate the reductive elimination, and, if the bidentate ligand has the correct bite angle, more rapid oxidation.[22]
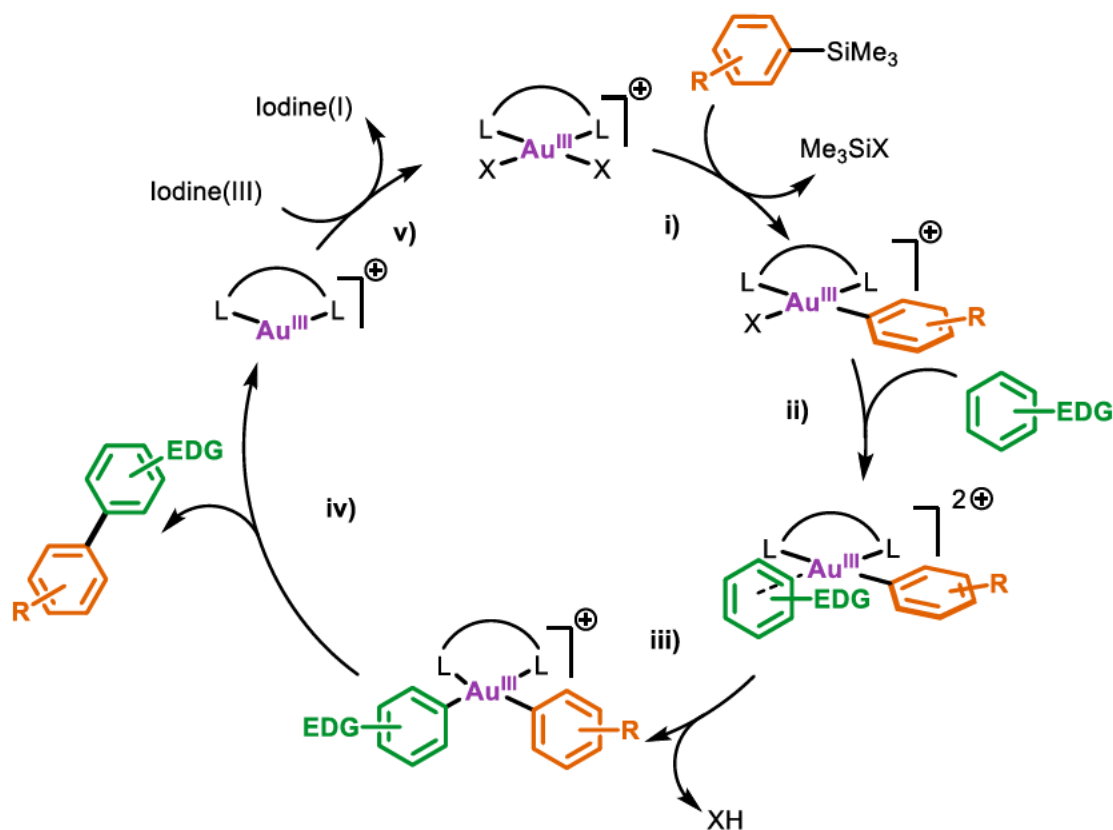
Figure 32. Potential catalytic cycle utilising bidentate L L type ligands.

This avenue was not investigated as the idea came to me late in my PhD, at this time I had overlapping projects and focussed on my newer project.

The formation of enantioenriched, planar chiral compounds may be possible for substrates such as [2.2]paracyclophan 53. This would significantly reduce the steric hindrance problems that are innate to the coupling of substrates to make atropisomers, however, producing very niche products from potentially hard to construct substrates.
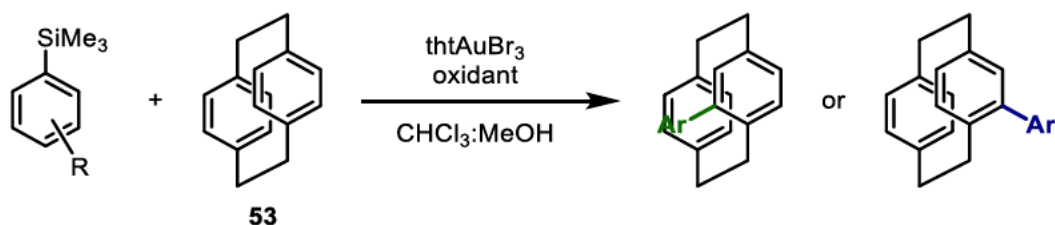
Scheme 58. Potential formation of 'metal free' planar chiral biaryls.

2.8 - References

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3 - Inorganic Oxidants for the Oxidation of Gold(I) to Gold (III) in Direct Arlyation

3.1 - Introduction

Oxidation of Gold(I) to Gold(III) in Direct Arylation

Throughout the majority of the catalytic cycle (Figure 33), gold exists in the stable 3+ state, however, after reductive elimination of the product biaryl (Figure 33, **v**) gold is in its +1 state. Gold(I), without strongly coordinating ligands, disproportionates to gold metal and gold(III).[1] Gold metal cannot then re-enter the catalytic cycle.

The oxidation of gold(I) to gold(III), although key, is poorly understood and little research has gone into understanding what requirements step **vi** has.
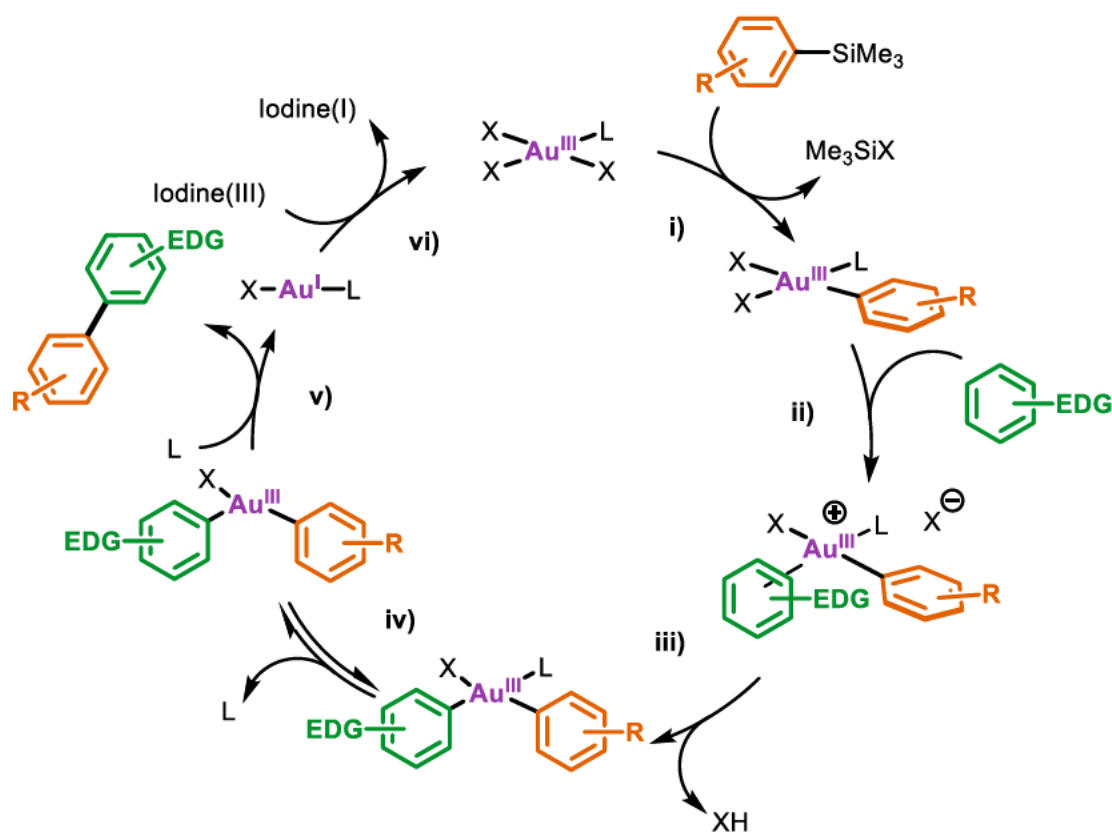
Figure 33. Proposed catalytic cycle.[2]

Phenyliodine Diacetate and CSA

Phenyliodine diacetate (PIDA) in conjunction with CSA, so far, has been found to be one of the most effective oxidants in oxidising gold(I) to gold(III) for this chemistry.[3] PIDA is a hypervalent iodine oxidant, known for its mild nature and functional group tolerance that can be seen in the substrate scope of the gold catalysed direct arylation. Alcohols and aldehydes are not oxidised under coupling conditions, allowing **1** and **2** to be synthesised in high yields using gold catalysed direct arylation.[3]
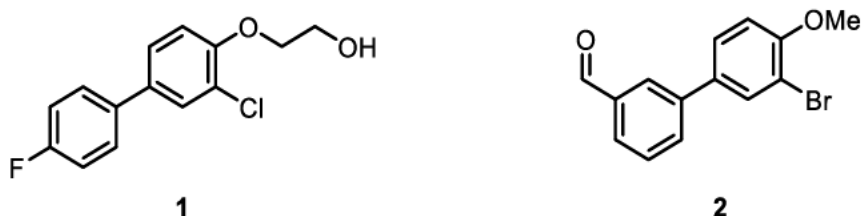
Figure 34. Biaryl products of oxidative gold catalysed direct arylation containing oxidisable functional groups.

PIDA, and oxidants related to it, do have drawbacks:

1) The aryl ring and acetate ligands on the iodine mean that, for the two-electron oxidation that it performs, PIDA has low atom economy.

2) Aryl iodine oxidants form significant quantities of aryl iodide as a waste product that can be challenging to separate from the desired product.

3) Hypervalent aryl iodine oxidants are electrophilic on the iodine, meaning that the iodine can react with electron rich arenes[4, 5] and aryltrimethylsilanes[5, 6] to form diaryliodonium salts as shown in Figure 35.
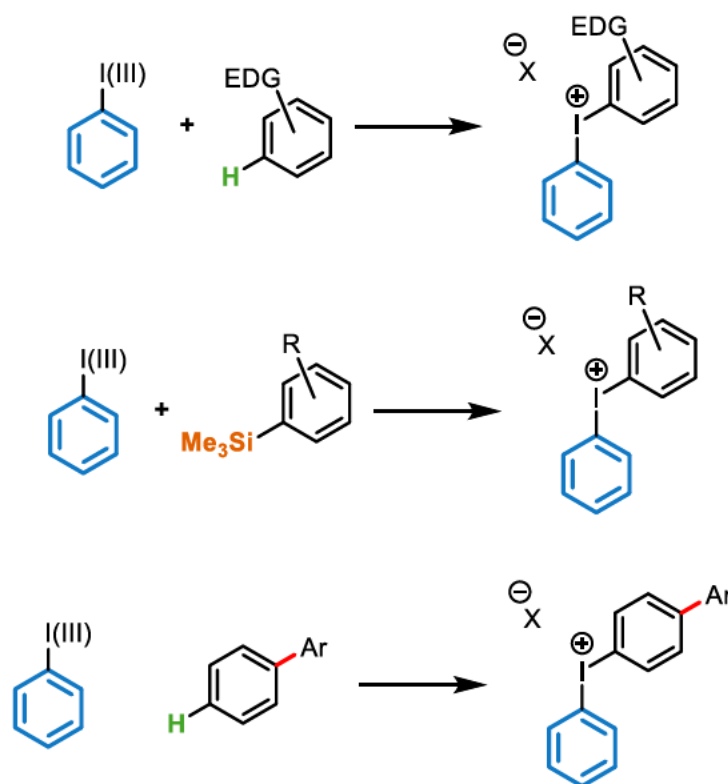
Figure 35. Reactions of hypervalent aryliodine oxidants with arenes and arylsilanes.

PIDA **3** is known to react with CSA to form a variant of Koser's reagent **4**.[7-10] Hydroxy(sulfonoxy)iodobenzenes **4** are more oxidising than PIDA **3** as well as being more electrophilic.[5, 11]
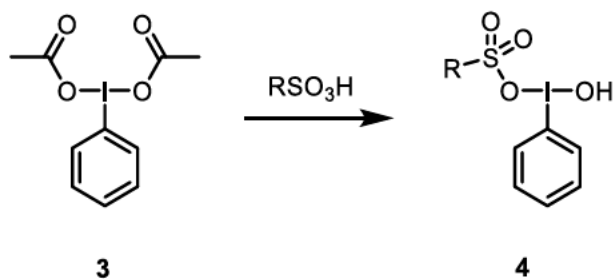
Scheme 59. PIDA reacting with sulfonic acid to form variations of Koser's reagent **4**.

The reaction of hydroxy(sulfonoxy)iodobenzenes **4** with electron rich arenes can be facile.[12] In the synthesis of (±)-allocolchicine, the electron rich trimethoxy arene in the starting arylsilane **5** reacted with hydroxy(camphorsulfonoxy)iodobenzene (HCIB) to form the catalyst inhibitor **7** (Scheme 60).[4]
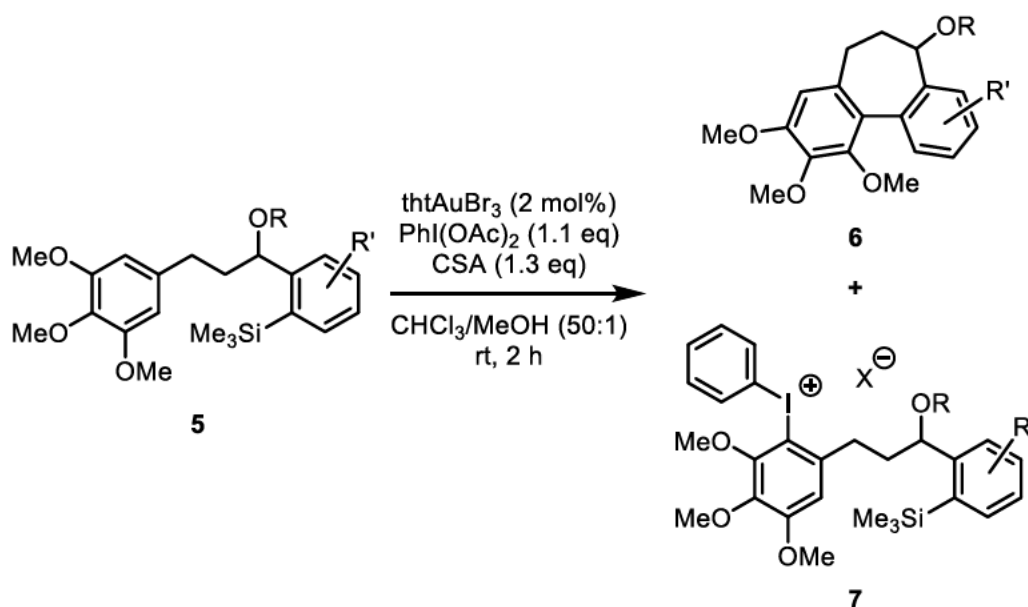
Scheme 60. Byproduct formation in the synthesis of (±)-allocolchicine.[4]

Strategies to Avoid Diaryliodonium Formation

Under certain circumstances, less reactive aryl iodine(III) oxidants, such as phenyliodine bis(trifluoroacetate) (PIFA) **8** can be used in place of PIDA **4**.[4] CSA is required to both activate the oxidant for step **vi**, Figure 33, and to protonate X type ligands that would prevent the electrophilic aromatic substitution of the arene in step **iii** of Figure 33. PIFA **8** is used without the addition of CSA, and, it does not allow for intermolecular direct arylations to occur.

Bulky 2,4,6-triisopropyl(diacetoxy)iodobenzene **9** have been developed to hinder the formation of diaryl iodonium salts and allow the arylation of challenging heterocycles.[13] The use of 2,4,6-triisopropyl(diacetoxy)iodobenzene **9** is limited by the fact that the oxidant is not commercially available and has even lower atom economy than PIDA.
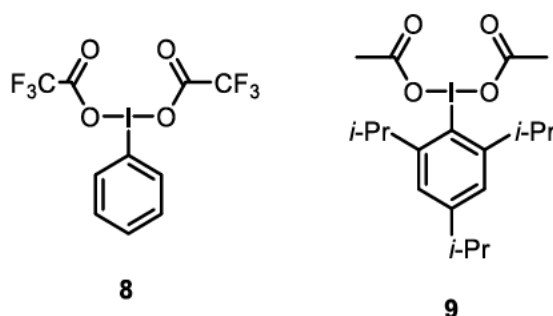
Figure 36. PIFA (left) and 2,4,6-triisopropyl(diacetoxy)iodobenzene (right).

Other Oxidants for Gold(I) to Gold(III)

Although hypervalent aryliodine(III) oxidants have limitations in gold catalysed direct arylation, very few practical useful oxidants are known to oxidise gold(I) complexes to gold(III), with even fewer being suitable for a wide variety of organic functional groups:

1) Aqua regia can be used for robust gold complex oxidation.[14]

2) Toste has utilised XeF_2 to synthesise gold(III) fluorides from gold(I) complexes.[15]

3) Some methodologies have relied on aryl radicals to oxidise gold(I) via diazonium salts and photoinitiation.[16]

4) Iodine, bromine and chlorine as elements[17-19] as well as the iodonium source, NIS,[20, 21] can oxidise gold complexes to the corresponding halide salt.

5) Recently, fluoronium sources such as selectfluor have been discovered to be potent oxidising agents for gold(I) to gold(III).[22]

XeF_2 and aqua regia as oxidants are no improvement over the hypervalent aryliodine based system using PIDA and CSA due to toxicity and explosion risk in organic solvents and photoredox initiate radical oxidation falls outside the remit of the gold catalysed direct arylation as shown in Figure 33.

Iodonium, bromonium and chloronium-based additives, including the halogens themselves are often used in conjunction with gold catalysis. However, they preferably form halogenated arenes instead of the desired biaryl product.[23, 24]

Selectfluor has been tested for oxidation activity in the gold catalysed direct arylation reaction, and showed no activity towards biaryl formation, although, selectfluor did not form fluorinated arenes.[3]

Requirements of the Oxidant

Based on all the information found in the literature, requirements of ideal oxidising agents can be concluded:

1) The oxidation step is required to be fast and produce a gold species that does not contain a chloride, bromide or iodide as this will likely produce undesired aryl halide side products.

2) For practical purposes, low toxicity oxidants that do not pose explosion hazards in organic solutions are easier to handle and use.

3) Improvements can be made with respect to isolation of biaryl products from the oxidant's reduction products.

3.2 - Project Aims and Initial Hypothesis

The aim of this project is to discover an alternative oxidant to PIDA, and by extension all organic hypervalent aryliodine oxidants, to improve the applicability of gold catalysed direct arylation reactions. Ideally an easily handled, inorganic oxidant or air could be utilised as the terminal oxidant.

The initial hypothesis for this project is that strong inorganic oxidants will be able to oxidise gold(I) to gold(III) in solution, allowing for the turnover of the gold catalytic cycle.

3.3 - References

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3.4 - Results and Discussion

General Considerations

Inorganic oxidants were chosen to test as replacements for PIDA in gold catalysed direct arylation because they are cheap, easy to handle, and often safer than organic oxidants that can pose an explosion risk. They do come with the drawback that they are commonly insoluble in organic solvents. In order to mediate this, acetonitrile, as a polar solvent, was tested alongside the standard chloroform/methanol solvent mixture.

Acetonitrile, as a solvent in the gold catalysed arylation reaction does have limitations. Step **iii** in Figure 37 shows the proposed cationic gold species that is required to allow for S_EAr aurodeprotonation of the arene.
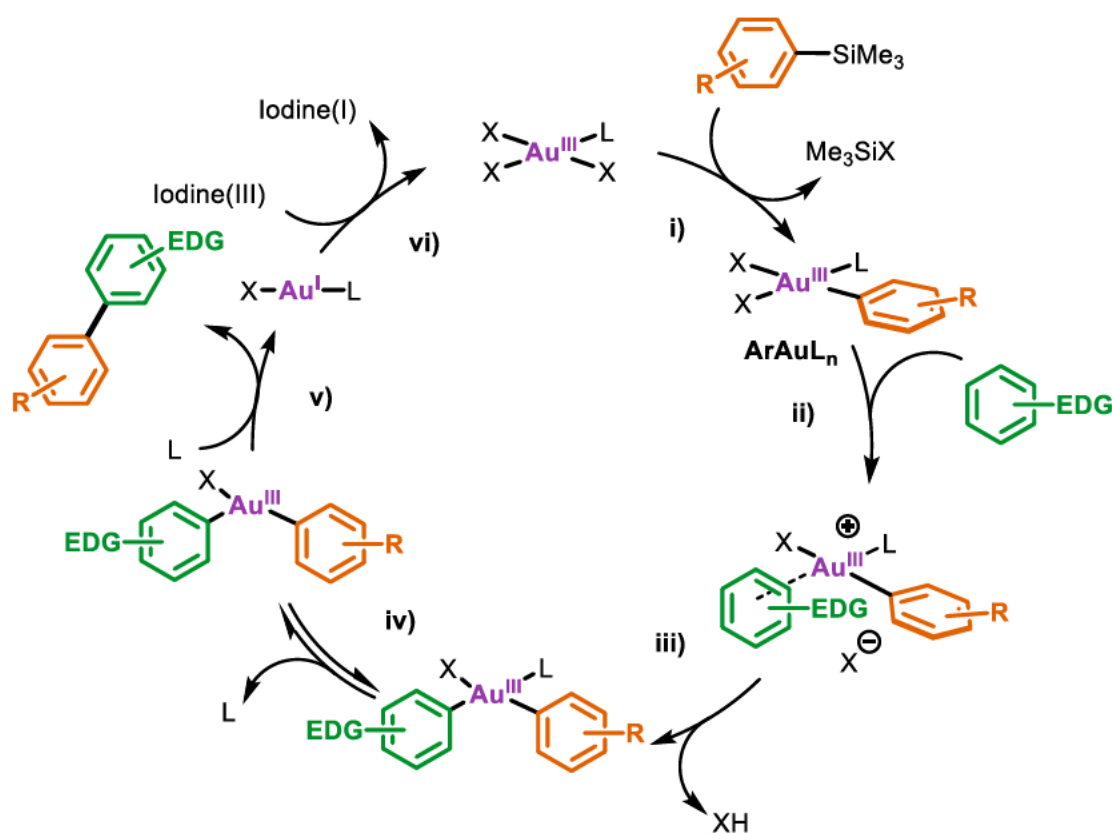
Figure 37. Proposed catalytic cycle.[1]

If the gold complex **ArAuL$_n$** is bound with coordinating solvent such as acetonitrile the reaction would likely be diverted away from the productive step in which the gold electrophilically adds to the arene.
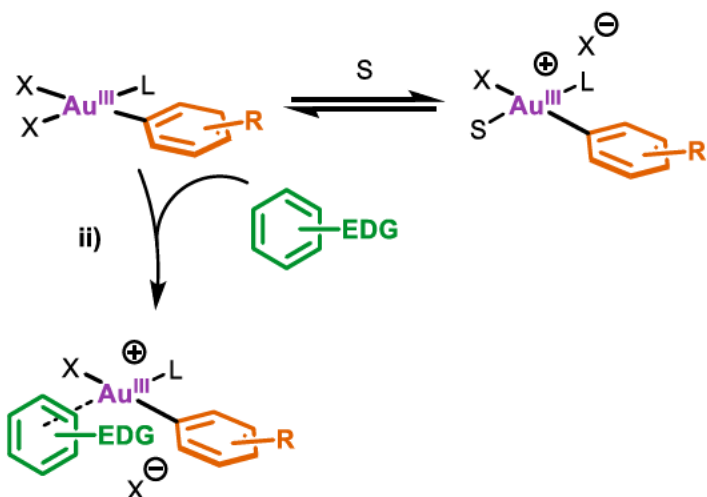
Figure 38

Methodology

Due to the heterogeneous nature of inorganic oxidants in gold catalysed direct arylation reactions, they were all stirred for 16 hours before filtering and analysing by ^{19}F NMR. Fluorinated substrate **1** allowed for fast and reliable determination of the success of the gold catalysed arylation reaction as the ^{19}F NMR signal for the silane **1** and coupled product **2** are separate in chemical shift (δ = -113.92 and -116.06 respectively) and have distinct splitting patterns.

Initial Oxidant Screening

The previously used oxidant, PIDA,[1-4] was directly substituted for an inorganic oxidant. Gold precatalyst (thtAuBr$_3$) and CSA concentrations were kept the same as in previous examples of gold catalysed direct arylation reactions[3] (Scheme 61) to have a direct comparison between the inorganic oxidants and PIDA.
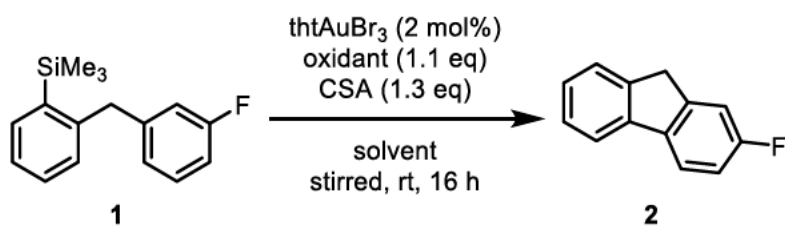
Scheme 61. Conditions for inorganic oxidant screening.

1

Halogens and aqua regia (3:1 conc. HCl/conc. HNO_3) are commonly used to oxidise gold metal to gold(III), and can be used to oxidise gold(I) complexes to gold(III) complexes.[5-10] Halonium and halogen oxidants inspired the use of oxyhalogenate salts; aqua regia inspired the use of nitrite and nitrate anions.

The oxidation of aryl iodides to aryl iodine(III) oxidants is often performed in a very polar solvent such as acetic acid or acetonitrile with inorganic oxidants, including $NaBO_3 \cdot 4H_2O$,[11] Oxone®,[12] $NaIO_4$,[13] and $K_2S_2O_8$[14]. As $NaBO_3 \cdot 4H_2O$, Oxone®, $NaIO_4$, and $K_2S_2O_8$ are strong enough to form hypervalent aryliodine oxidants from aryl iodides, and hypervalent aryliodine oxidants usually perform the oxidation of gold(I) to gold(III), they were included in the screen.

Table 8

Oxidant	2 NMR Yield (%)/ CDCl$_3$/CD$_3$OD (50:1)	2 NMR Yield (%)/ CD$_3$CN
NaClO$_3$	-	-
NaClO$_4$	-	-
NaBrO$_3$	-	-
NaIO$_3$	22	5
NaIO$_4$	2	2
NaNO$_2$	-	-
NaNO$_3$	-	-
NaBO$_3$·4H$_2$O	-	-
Oxone®	-	-
TBA Oxone®	< 1	-
K$_2$S$_2$O$_8$	-	-
Na$_2$S$_2$O$_8$	-	-

Both $NaIO_3$ and $NaIO_4$ show some conversion of substrate **1** to fluorene **2**. The lack of product **2** formed with the use of other oxidants highlights the challenges associated with the oxidation of gold(I) to gold(III) under catalytic direct arylation conditions. The lack of product formation with most oxidants in Table 8 may be due to:

1) Solubility issues associated with the inorganic oxidants.

2) That the oxidants do not interact with the gold(I) in a productive manner.

3) That the oxidising salts are inhibiting another key step in the arylation reaction.

Gold(I) can undergo disproportionation to gold(0) and gold(III).[15] If the oxidation of gold(I) to gold(III) is not fast enough to avert the formation of gold(0), that cannot re-enter the catalytic cycle, then the coupling will either not start, or will stall.

Aryl Iodide Co-Catalyst

To work around issues of oxidant solubility and the potential lack of favourable interaction between the oxidant and gold(I), aryl iodide oxidation co-catalysts were tested (Figure 39). Aryl iodides were used in conjunction with oxidants whose redox potentials are strong enough to oxidise aryl iodides to aryliodine oxidants ($NaBO_3 \cdot 4H_2O$, Oxone®, $NaIO_4$, and $K_2S_2O_8$), and have literature precedent for forming aryliodine oxidants when combined with aryl iodides.[11-14]
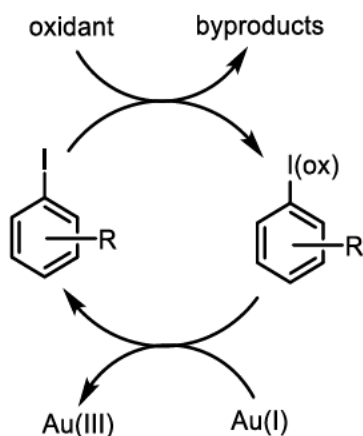
Figure 39. Aryl iodide oxidation co-catalyst.

The same conditions for coupling aryl silane **1** to form fluorene **2** were used as in Scheme 61, with both chloroform/methanol and acetonitrile as solvents. 5 mol% aryl iodide was added as an oxidation co-catalyst (Scheme 62).
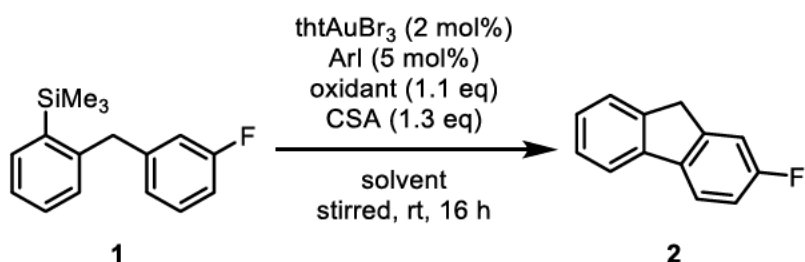
Scheme 62. Conditions for inorganic oxidant coupled with aryl iodide screening.

Oxone® showed no conversion without aryl iodide (Table 8) and thus would not exhibit any background reaction when used as the terminal oxidant with aryl iodide co-catalysts, it was thus tested with three electronically distinct aryl iodides. If one was successful, it may highlight a challenging step in the oxidation catalysis. For example, if the most electron rich aryl iodide, 4-iodoanisole, performed the best, then it may indicate that the most challenging step in the catalytic oxidation (Figure 39) is the oxidation of the aryl halide, rather than that of the gold(I). The oxidation of the 4-iodoanisole should be the easiest of the aryl halides selected, however it would be expected to form the weakest oxidant.

Table 9

Oxidant	2 NMR Yield (%)/ $CDCl_3/CD_3OD$ (50:1)	2 NMR Yield (%)/ CD_3CN
Oxone® + 4-iodoanisole	-	-
Oxone® + phenyl iodide	-	-
Oxone® + 4-iodotrifluorotoluene	-	-
$NaIO_4$ + phenyl iodide	3	1
$K_2S_2O_8$ + phenyl iodide	-	-
$NaBO_3 \cdot 4H_2O$ + phenyl iodide	-	-

No product **2** was seen for the Oxone®, $K_2S_2O_8$ and $NaBO_3 \cdot 4H_2O$ based oxidations and no improvement was observed over the background reaction for $NaIO_4$. These oxidants are known to react quickly with aryl iodides, under similar conditions, to form aryl iodine oxidants[11-14] and the aryl iodine oxidants are known to turn over the gold catalyst.[1-4, 16, 17] The lack of coupling may be attributed to some sort of inhibition in at least one of the processes key to this reaction. Inhibition may be coming from the anionic oxidant ions.

Oxygen

To avoid the use of stoichiometric salt-based oxidants and because the gold catalysed direct arylation is known to proceed in the presence of air, oxygen was considered as the terminal oxidant.

Oxygen, or air, are the ideal terminal oxidants from a 'green' perspective. Oxygen produces minimal waste and is enormously abundant, however, conducting oxidations in flammable solvents under an atmosphere of pure oxygen can lead to explosions.

Oxygen has been known to form peracids from aldehydes in the presence of copper, cobalt or manganese acetates since the early 1950s.[18] Peracids are strong oxidising agents that are known to oxidise aryl iodides to the corresponding aryliodine(III) oxidants.[19] The aerobic oxidation of aldehydes to form peracids and the peracid oxidation of aryl iodides to produce hypervalent aryliodine(III) oxidants have recently been combined by Powers in a one pot procedure.[20]

A screen of conditions was formulated (Scheme 63 and Table 10), in which acetaldehyde and air were key components, copper(II), cobalt(II) and manganese(III) acetates were used as radical initiator additives. All conditions were tested with and without phenyl iodide as an oxidation co-catalyst (Scheme 63 and Table 10).

Because of the explosion risk, acetonitrile was removed as a solvent for this oxidation screen. However, the methanol concentration in the mixed, chloroform/methanol solvent mixture required increasing to 9:1 to solubilise the metal acetates (Scheme 63).
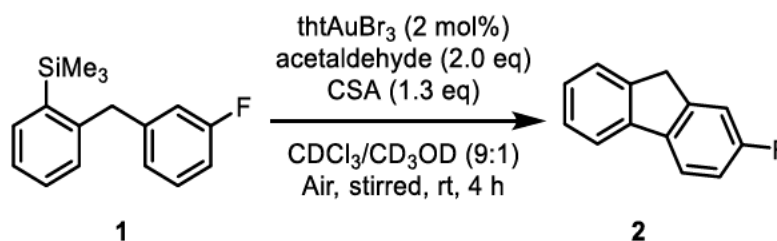
Scheme 63. Conditions for oxygen-based oxidation screening.

Table 10

Additives	2 NMR Yield (%)
-	-
Cu(OAc)$_2$·H$_2$O (2 mol%)	-
Co(OAc)$_2$·4H$_2$O (2 mol%)	-
Mn(OAc)$_3$·2H$_2$O (2 mol%)	-
phenyl iodide (15 mol%)	-
Cu(OAc)$_2$·H$_2$O (2 mol%) + phenyl iodide (15 mol%)	-
Co(OAc)$_2$·4H$_2$O (2 mol%) + phenyl iodide (15 mol%)	-
Mn(OAc)$_3$·2H$_2$O (2 mol%) + phenyl iodide (15 mol%)	-

None of the coupling conditions (Scheme 63 and Table 10) allow for successful coupling of **1** to **2**. The reason for the lack of gold catalysed arylation is unknown.

Oxyiodine Compounds

As the oxyiodine anions provided some success (Table 8), other oxyiodine compounds were tested. As many oxyiodine compounds are also acids, they were tested with and without the addition of CSA (Scheme 64, Table 11).
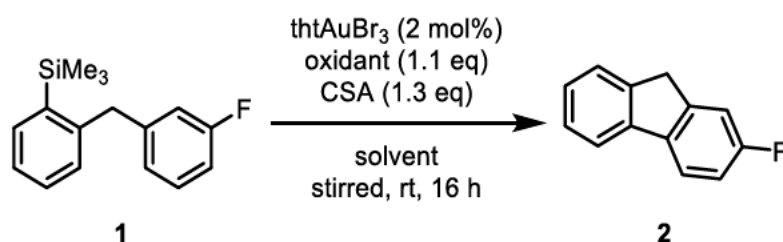
Scheme 64. Conditions for oxyiodine oxidant screening.

Table 11

Oxidant	2 NMR Yield (%)/ CDCl$_3$/CD$_3$OD (50:1)	2 NMR Yield (%)/ CD$_3$CN
H$_5$IO$_6$	9	47
I$_2$O$_5$ (0.55 eq)	4	3
HIO$_3$	4	-
(*n*-Bu$_4$N)IO$_4$	-	-
H$_5$IO$_6$[a]	3	58
I$_2$O$_5$ (0.55 eq)[a]	-	-
HIO$_3$[a]	-	-

[a]Without CSA

Periodic acid (H$_5$IO$_6$) in acetonitrile without CSA, gave reasonable yield of coupled product **2**. When investigating the reaction with periodic acid and without CSA further, it was apparent that the silane had been fully consumed and that a large quantity of a byproduct had been formed (26% by ^{19}F NMR).

6

Byproduct Identity

Upon GC-MS of the periodic acid reaction mixture (Table 11, entry 5), iodoarene **3** was hypothesised to be the byproduct. The byproducts identity was confirmed to be **3** through synthesis of a pure sample of **3** and doping the iodoarene into an NMR tube containing a sample of completed reaction mixture.
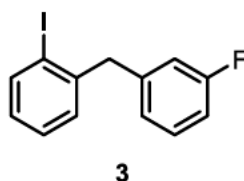
Figure 40. Aryl iodide byproduct.

The formation of aryl iodide **3** shows that periodic acid I(VII) is being reduced to I(I). The reduction of periodic acid past I(V) is rare in organic chemistry but gives us some insight into the mechanism of the redox processes going on.

Catalyst Activation

Iodic acid (HIO$_3$), although acidic and strongly oxidising, gave either no or very low conversions under the conditions tested in Scheme 64 and Table 11. One hypothesis as to why iodic acid is not allowing for an efficient coupling reaction was that iodic acid did not activate the catalyst.

Using the same conditions as Scheme 64, a mixture of iodic acid (0.1 equivalents) and periodic acid (1.0 equivalents) was tested (Table 12) and would show if iodic acid was an active oxidant, if unsuitable for an activation process.

Table 12

Oxidant	2 NMR Yield (%)
H$_5$IO$_6$ (1.1 eq)	58
HIO$_3$ (1.1 eq)	-
H$_5$IO$_6$ (0.1 eq) + HIO$_3$ (1.0 eq)	4
H$_5$IO$_6$ (0.1 eq)	7

Even with periodic acid activation, iodic acid did not turn over the coupling reaction (Table 12, entry 3); the NMR yield is negligible, much like that of 0.1 equivalents of periodic acid (Table 12, entry 4) on its own.

Substoichiometric Periodic Acid Oxidant

Based on the formation of aryl iodide **3** from periodic acid indicating that periodic acid is performing six electrons of oxidation, it was suspected that it could perform more than one turnover of the gold.
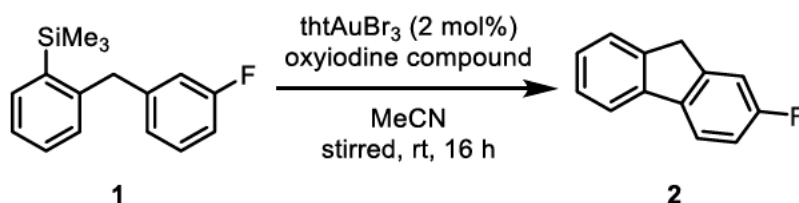
Scheme 65. Conditions for substoichiometric H_5IO_6 oxidant screening.

Table 13

Oxidant	2 NMR Yield (%)	1 NMR Conversion (%)
H_5IO_6 (1.1 eq)	58	100
H_5IO_6 (0.5 eq)	47	100

Although Table 13, entry 2 is not conclusive that the 0.5 equivalents of periodic acid are turning over the catalyst more than once per molecule of periodic acid, the small discrepancy in yield when comparing the two quantities of oxidant (Table 13, entries 1 and 2) indicate that substoichiometric equivalents of periodic acid are enough to fully convert the substrate, although providing more byproducts. The low yield for the reactions (Table 13), particularly that of the reaction with 0.5 equivalents of periodic acid (Table 13, entry 2), is explained by multiple side reactions that consume the oxidant, substrate and product. Multiple byproducts **4-7** were observed by GC-MS (Figure 41).
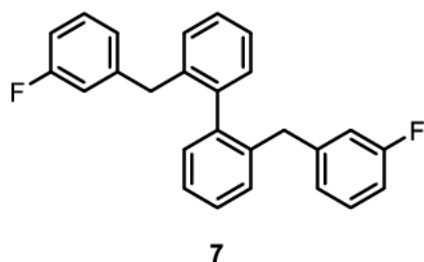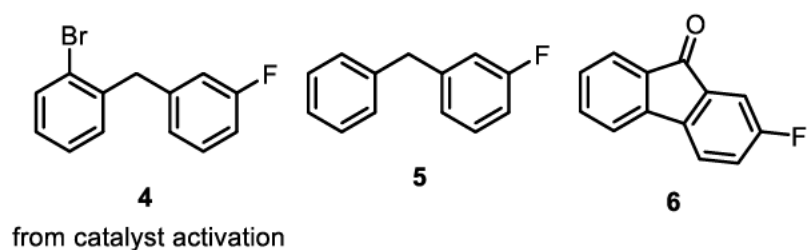
Figure 41. Byproducts identified by GC-MS.

Solvent Screening

To improve the selectivity of the gold-catalysed arylation reaction, and to investigate the dependence on acetonitrile, other solvents were tested for activity in the periodic acid mediated, gold-catalysed, arylation reaction (Scheme 66).

The reactions were stirred at room temperature for 16 hours, filtered and ^{19}F NMRs were run directly on the filtrate. This method meant that the reaction solvent did not require removal, reducing the chance of introducing an error in the results due to the evaporation of a product or the internal standard (trifluorotoluene).
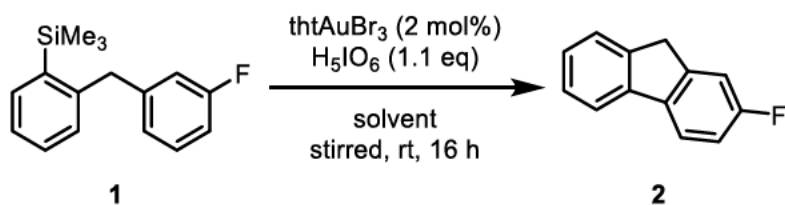
Scheme 66. Solvent screen for H_5IO_6 oxidation.

As polar solvents were suspected to be key (Table 11) due to their ability to dissolve periodic acid, a selection of mostly polar solvents were chosen to be screened as reaction solvents.

Entry	Solvent	2 NMR Yield (%)
1	MeCN	55
2	MeCN repeat	57
3	CHCl$_3$/MeOH (50:1)	-
4	CHCl$_3$/MeOH (25:1)	-
5	CHCl$_3$/MeOH (10:1)	-
6	THF	-
7	dioxane	1
8	DME	2
9	anisole	-
10	toluene	-
11	propylene carbonate	9
12	EtOAc	-
13	pyridine	-
14	NMP	-
15	DMF	-
16	MeOH	-
17	EtOH	-
18	*i*-PrOH	6
19	*t*-BuOH	-
20	*n*-PrOH	-
21	TFE	-
22	THF/EtOH (9:1)	2
23	THF/EtOH (8:2)	2

ᵃ Although a reference mixture containing the starting material, and all observed byproducts was added to the reaction mixtures, for the vast majority, the starting material ^{19}F or ^{1}H NMR peak could not be observed as an isolated signal. This prevents the conversion from being quoted.

Even though some solvents provided a small amount of conversion in 16 hours, acetonitrile was the most competent solvent for the coupling reaction in Scheme 66 (

Table 14). Chloroform/methanol, in all the ratios tested, provided no reaction. To explore why acetonitrile provided the fastest reaction rate, other nitrile-based solvents such as propionitrile and benzonitrile were tested.

One theory was that an impurity in acetonitrile, or acetonitrile itself was initiating the catalysis. In order to test for an impurity in acetonitrile or if acetonitrile was acting as an activator, mixtures of THF or dioxane with acetonitrile were used as solvent systems with the same conditions as in Scheme 66. THF and dioxane were chosen because they dissolved the periodic acid without providing much conversion when used as solvents on their own. It is key that 1% conversion was seen in dioxane (

Table 14), as this indicated that the reaction could turn over in an ether solvent.

Table 15

Solvent	2 NMR Yield (%)
MeCN	55
EtCN	18
trimethyl acetonitrile	-
benzonitrile	-
THF/MeCN (9:1)	-
THF/MeCN (8:2)	-
THF/MeCN (1:9)	38
THF/MeCN (1:19)	44
dioxane/MeCN (9:1)	2
dioxane/MeCN (8:2)	3

The large decrease in yield of **2** when going from acetonitrile to propionitrile, and with trimethyl acetonitrile and benzonitrile not providing any conversion could have at least two explanations:

1) There is an interaction between the nitrile solvent and gold that is very sterically sensitive.

2) The nitrile solvent requires a reactive C-H bond at the α-position, which is key for reaction turnover.

11
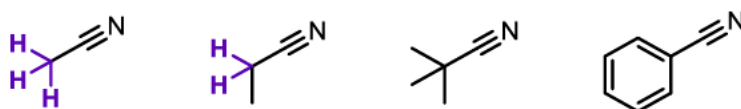
The mixtures of solvents show that low concentration of acetonitrile did not allow the reaction to proceed, which indicates that the effect of acetonitrile is not as an activator or reagent at a catalytic concentration. High concentrations of acetonitrile, containing small amounts of THF, allowed the gold catalysed arylation reaction to proceed in a similar manner to the pure acetonitrile solvent system.

Catalyst Deactivation

When mixing the gold precatalyst, periodic acid and acetonitrile, a white precipitate was observed to form. To investigate whether this was linked to a catalyst deactivation reaction, an experiment was performed using the same conditions for coupling as in Scheme 66, where a mixture of thtAuBr$_3$, periodic acid and acetonitrile was left to react at room temperature for 2 minutes before the addition of the substrate.

Table 16

Solvent	2 NMR Yield (%)
MeCN	55
MeCN repeat	57
MeCN (premix H$_5$IO$_6$ and thtAuBr$_3$ for 2 mins before SM addition)[a]	31

[a]White precipitate forms slowly upon mixing thtAuBr$_3$ and H$_5$IO$_6$ in acetonitrile.

Table 16, entry 3 shows lower conversion when premixing the catalyst and periodic acid in acetonitrile. As the conversion of arylsilane **1** to fluorene **2** was lower when gold, periodic acid and acetonitrile were premixed, the white precipitate was thought to be linked to a catalyst deactivation reaction.

White Precipitate from thtAuBr$_3$ and H$_5$IO$_6$ in Acetonitrile

The precipitate that was seen when thtAuBr$_3$ and periodic acid were dissolved in acetonitrile and allowed to react at room temperature was suspected to be a deactivated catalyst species due to the reduced reactivity when the substrate was added, after an incubation period, to this mixture (Table 16, entry 3). The only solvent that dissolved this solid was DMSO, which

allowed for NMRs to be recorded. No proton, carbon or silicon signal was seen in the samples, even after increased scan numbers.

Light was shed on the structure of the solid by MALDI-MS in negative mode, wherein repeating units of mass 223.08 daltons were observed. Masses of 174.90 (iodate), and 190.89 (periodate) daltons were observed to be the lowest mass units to which, a polymeric compound of repeating units of 223.08 daltons was added. The repeat unit was tentatively assigned as a gold(I) cyanide monomer, indicating that the acetonitrile was being cleaved to form cyanide, resulting in an insoluble gold cyanide polymer as a deactivation pathway as seen inTable 16, entry 3.

Exact Mass: 174.89   Exact Mass: 190.88   Exact Mass: 222.97
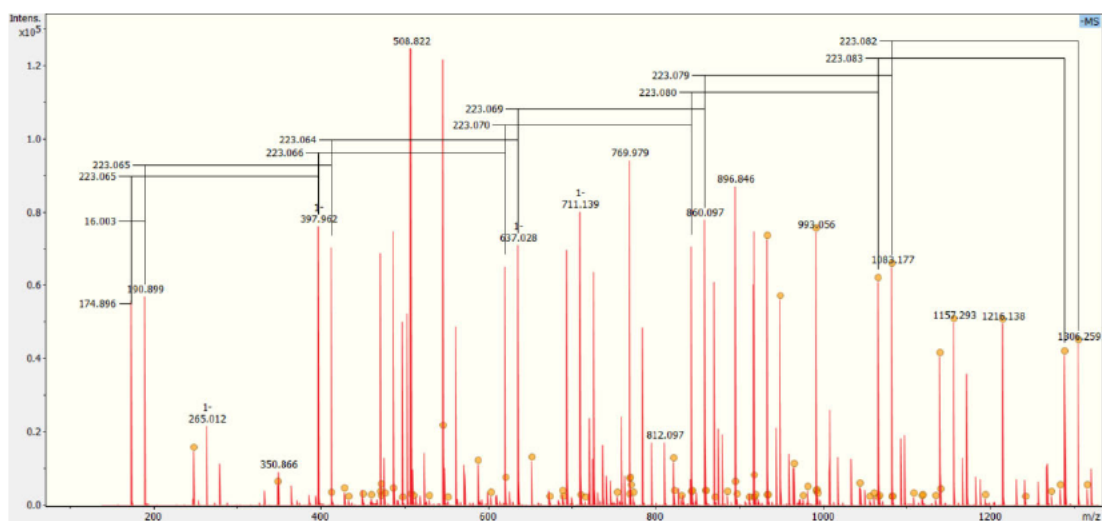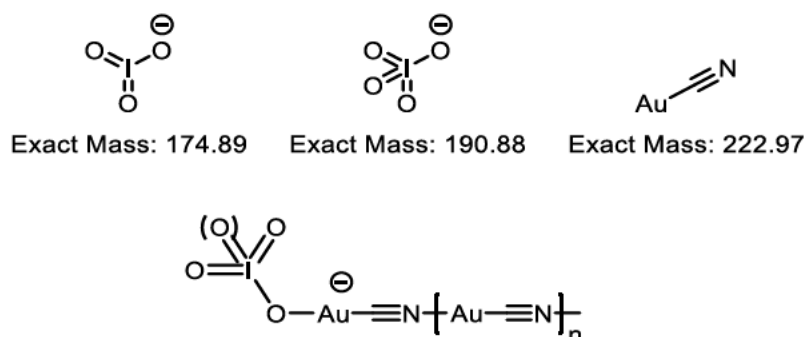
Figure 42. Gold cyanide MALDI-MS.

3.5 – Conclusions and Future Work

Few of the inorganic oxidants and none of the air-based oxidations allowed for the turnover of the direct arylation with gold. With the current information, it is hard to tell what is

preventing the catalysis, whether it be the solubility of the oxidant, oxidising power, or some other effect of the salt additives.

NaIO$_3$ gave reasonable conversion in CHCl$_3$/MeOH, however, periodic acid in acetonitrile gave the highest conversion of all the inorganic oxidants screened. Following this discovery, other solvents were tested although acetonitrile remained the most effective for gold catalysed direct arylation for the intramolecular substrate tested (**1**). Other nitrile-based solvents resulted in significantly slower coupling reactions, indicating that acetonitrile may be performing more functions than simply acting as a solvent.

Upon noticing a white precipitate forming when periodic acid, gold precatalyst and acetonitrile are combined at room temperature, and that this mixture was less catalytically active than when they were added to the substrate separately indicated that there was a reaction that produced a catalytically inactive gold species. Upon further investigation of this white precipitate it was tentatively assigned as a gold(I) cyanide polymer.

The dependence on acetonitrile and periodic acid for turnover and the observation of a gold cyanide polymer due to oxidative cleavage of acetonitrile inspired the mechanistic investigation of the periodic acid, acetonitrile and gold mediated direct arylation reaction (Chapter 3).

Shen and co-workers reported the use of acetonitrile as a cyanide source for the cyanation of aryl iodides.[21] Copper(II), TEMPO and hexamethyldisilane were key for the transformation, and they proposed the oxidised acetonitrile intermediate **8** (Figure 43).

8
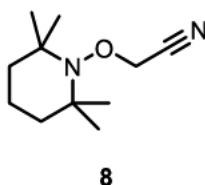
Figure 43. Proposed oxidised acetonitrile intermediate involved in copper catalysed cyanation.[21]

The conditions in the periodic acid, gold-catalysed direct arylation reactions are incidentally similar, consisting of a homogeneous gold species, an oxidant, and a silyl reagent in acetonitrile

3.6 - References

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4 - Periodic Acid in Gold Catalysed Direct Arylation

4.1 - Introduction

Oxidations using Periodate

The periodate anion has been used for many oxidative reactions in organic chemistry and is well known for its application in the cleavage of diols to form two aldehydes/ketones.[1] Periodate exists in two forms, the meta- or the ortho-periodate, shown as their corresponding conjugate acids in Figure 44.

	meta-	ortho-		
		$pK_a = 1.64$	$pK_a = 0.78$	$pK_a = -15$
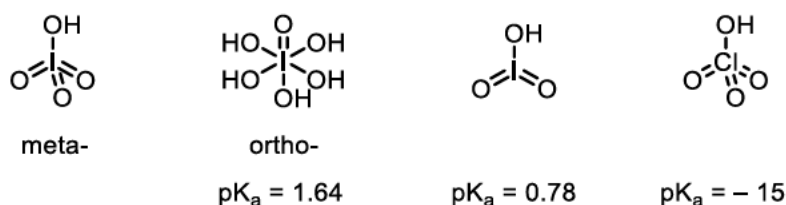
Figure 44. Acidity of oxyhalogen acids.

Metaperiodic acid has not been detected in water and is rarely used in practice due to its hygroscopic nature. Orthoperiodic acid has a $pK_a(H_2O)$ of 1.64 at 25 °C,[2] whereas iodic acid (HIO_3) under the same conditions has a $pK_a(H_2O)$ of 0.78.[2] Periodic acid, being less acidic than iodic acid is an anomaly in the trend of acidities for oxyhalogen compounds. Peroxyhalogenic acids are generally strong acids, for example perchloric acid has a calculated $pK_a(H_2O)$ of around -15.[3]

Periodate is also used to oxidise metals, often for catalysis. Two examples of periodate as an oxidant for metal centres is in the alkene oxidative cleavage methodology. The oxidative cleavage of alkenes using periodate with a manganese catalyst was developed by Lemieux.[4,5] To improve functional group tolerance of the oxidative cleavage reaction, Johnson developed the use of osmium as a catalyst.[6]
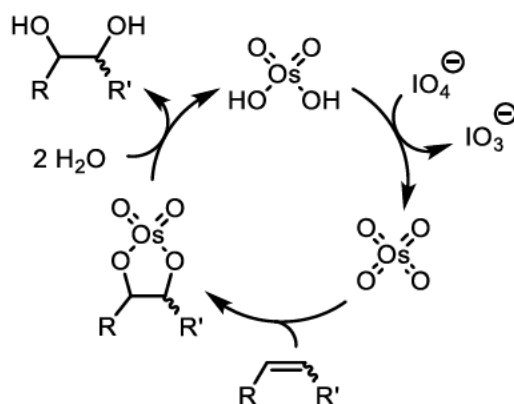
Figure 45. Osmium catalysed alkene oxidation.[6]

As in Figure 45, periodate is often reduced to iodate (IO_3^-). Although iodate is also an oxidising anion, it commonly does not continue to perform oxidation once formed.[1]

Redox Activity of Oxyiodine Species

The redox processes of iodine have been studied in water and are complex, involving disproportionation and comproportionation (Scheme 74a),[7-11] inter-reaction (Scheme 67b),[8] and ligand exchange.[12-15] Furthermore, the rate and equilibria of these processes are sensitive to pH.[16] The redox processes of oxyiodine compounds have yet to be studied in organic solvents.

a) $\quad 2\ HIO_2 \rightleftharpoons I^+ + HIO_3 + {}^-OH$

b) $\quad HIO_2 + HOI \rightleftharpoons HIO_3 + HI$
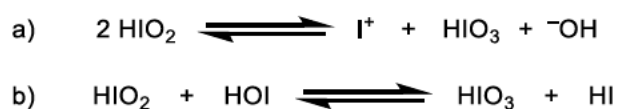
Scheme 67. Disproportionation and comproportionation of iodine species.

Iodites (IO_2^-) are unstable in water solution, undergoing rapid disproportionation.[17] Iodous acid (HIO_2) has not been isolated.

Combining the information above provides a simplified reduction pathway for periodic (Scheme 68). Six electrons are required to reduce periodic acid to iodonium.

$$H_5IO_6 \text{ (VII)} \xrightarrow{\quad 2\,H_2O \quad} HIO_4 \text{ (VII)} \xrightarrow{\quad 2\,e^- \quad} HIO_3 \text{ (V)} \xrightarrow{\quad 2\,e^- \quad} HIO_2 \text{ (III)}$$

$$2\,HIO_2 \text{ (III)} \longrightarrow I^+ \text{ (I)} + HIO_3 \text{ (V)}$$

Scheme 68. Simplified reduction pathway for periodic acid to iodonium.

Aromatic Iodinations

Iodonium (I^+) or iodonium sources, such as NIS, are common iodinating reagents for aryl nucleophiles, and typically react through an electrophilic aromatic substitution mechanism (Scheme 69).

Scheme 69. Electrophilic iodination of arenes.

Iodonium can be prepared by many methods, some examples of the iodination of arenes with iodonium are:

1) Aromatic iodination using silver sulfate and iodine.[18]

2) Halogenation of arenes using NBS and NIS in hexafluoroisopropanol.[19]

3) Imidazolium salt catalysed halogenation of electron-rich arenes.[20]

4) Silver salt catalysed iodination of arenes using NIS.[21]

5) Aromatic iodination via the oxidation of iodide to produce iodonium in situ.[22, 23]

6) *ipso*-halodeboronation by reacting NIS with aryl boronic acids.[24]

Aromatic Iodinations with Periodate

Periodate is known, under certain conditions, to perform iodination reactions. The arene iodination reactions that utilise periodate are proposed to go via an electrophilic aromatic substitution mechanism.[25-27] The conditions in which periodate can iodinate arenes are either in sulfuric acid solution,[25, 26] or with an iodine based reducing agent such as iodide or iodine itself.[27] In the case of iodination in sulfuric acid solution, it has been proposed that the

substrate (benzene) itself is oxidised to reduce the periodate to form the iodinating reagent (Scheme 70). Periodate, at low pH, is known to be a stronger oxidant than at high pH.[16]

48%
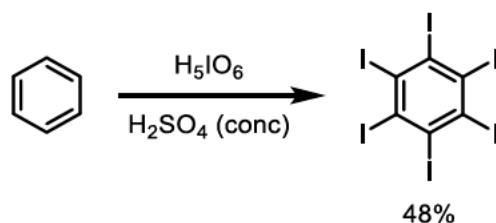
Scheme 70. Periodination of benzene using periodic acid. [25]

Gold Catalysed Aromatic Iodination

Aryl gold complexes are known to react with electrophiles.[28-30] When aryl gold complexes react with iodonium, aryl iodides are formed;[29-31] this is formally an electrophilic aromatic substitution in which gold is substituted for iodine (Scheme 71).
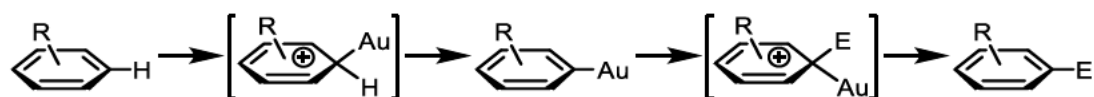
Scheme 71. General, gold catalysed S_EAr mechanism.

Gold catalysed iodination reactions are of synthetic interest as they can be performed on aryl boron reagents **1**, maintaining the carbon-boron bond in the product **2** (Scheme 72).[32]

AuCl$_3$ (1 mol%)
NIS (1.2 eq)

DCE, rt, 1 h

1

2
92%
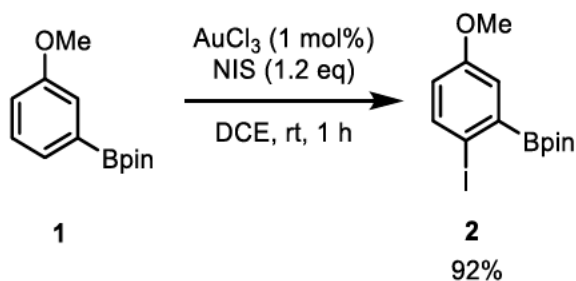
Scheme 72. Gold catalysed iodination of an aryl pinacolborane.[32]

Electrophilic Aromatic Substitution with Oxidised Iodine Species

Aryliodine oxidants react with nucleophilic arenes as described in Chapter 2, however this reactivity is not limited to aryliodine oxidants. Iodine(III) compounds are electrophilic and are known to react with nucleophilic arenes to form aryl iodine(III) compounds:

1) Aryl tributyl stannanes react with I(OAc)₃ via *ipso*-substitution of the tin to form (diacetoxyiodo)arenes.[33]

2) Aryl metals and metalloids including trimethyl silanes, trimethyl germanes and tributyl stannanes react with [I(tfa)₃]₂(tfa)NO, an iodine(III) trifluoroacetate dimer salt, via *ipso*-substitution of the metals to form [bis(trifluoroacetoxy)iodo]arenes 3 (Scheme 73).[34]

3) Iodination of coumarins occurs with I(tfa)₃, via a [bis(trifluoroacetoxy)iodo]arene, followed by reduction.[35]

Scheme 73. Iodination of an aryl trimethyl germane.[33]

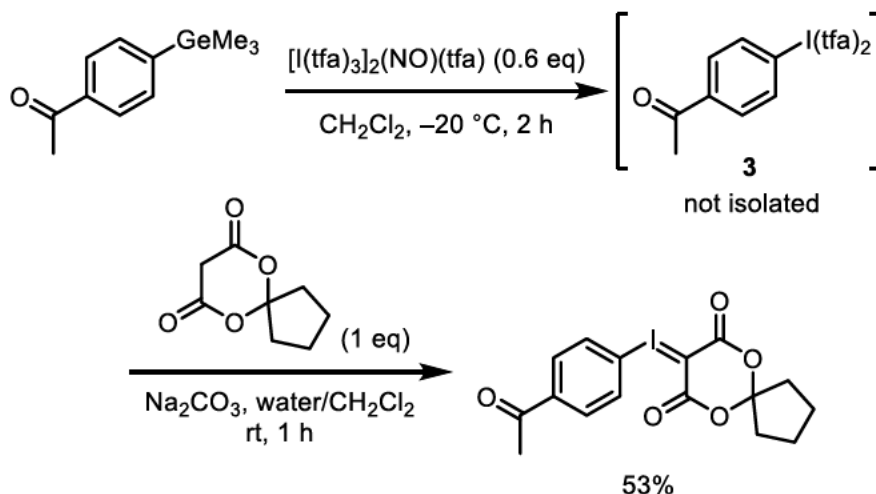Regarding the iodination of arenes using periodate, $ArIO_3$ is thought to be an intermediate in the iodination of arenes performed by $NaIO_4$, $H_2SO_4/AcOH/Ac_2O$ at 70 °C followed by aqueous Na_2SO_3 reduction, although there is no evidence for the intermediacy of $ArIO_3$.[26] $ArIO_3$ has also proposed as a potential intermediate in the periodination of benzene with $NaIO_4$ in H_2SO_4, although this claim was not investigated further.[25]

4.2 - Project Aims

The aim of this project is to investigate the mechanism of the oxidation of gold, and why periodic acid is particularly effective at this. The formation of aryl iodide byproducts from the reduction of periodic acid may be enlightening.

A secondary aim is to try to suppress the formation of the byproduct and increase the yield of the periodic acid mediated coupling of aryl silanes and arenes followed by substrate scope of this methodology.

4

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4.4 - Results and Discussion

The gold catalysed oxidative coupling of diarylmethane substrate **1** to fluorene **2** with periodic acid as the terminal oxidant gave significant quantities of aryl iodide **3** as a byproduct. Three hypotheses as to how the aryl iodide byproduct was generated were considered (Figure 46):

Path A) The trimethyl silane is electrophilically substituted for a highly-oxidised iodine species, resulting in an aryliodine oxidant **4**. The aryliodine oxidant can then oxidise the gold(I) species in the catalytic cycle, allowing another arylsilane and arene to be coupled.

Path B) The aryl iodide **3** could be made in a process that was not linked to catalyst turnover. This could then act as an oxidation cocatalyst, being oxidised by a highly oxidised iodine species to form an aryliodine oxidant **4**. The aryliodine oxidant **4** would then perform the oxidation as in path A.

Path C) The oxidation of gold(I) to gold(III) could be performed by an inorganic iodine oxidant in solution, which may continue to perform oxidations until iodonium is formed. Iodonium could then perform *ipso*- electrophilic aromatic substitution on the aryl trimethyl silane giving aryl iodide **3** as the byproduct.
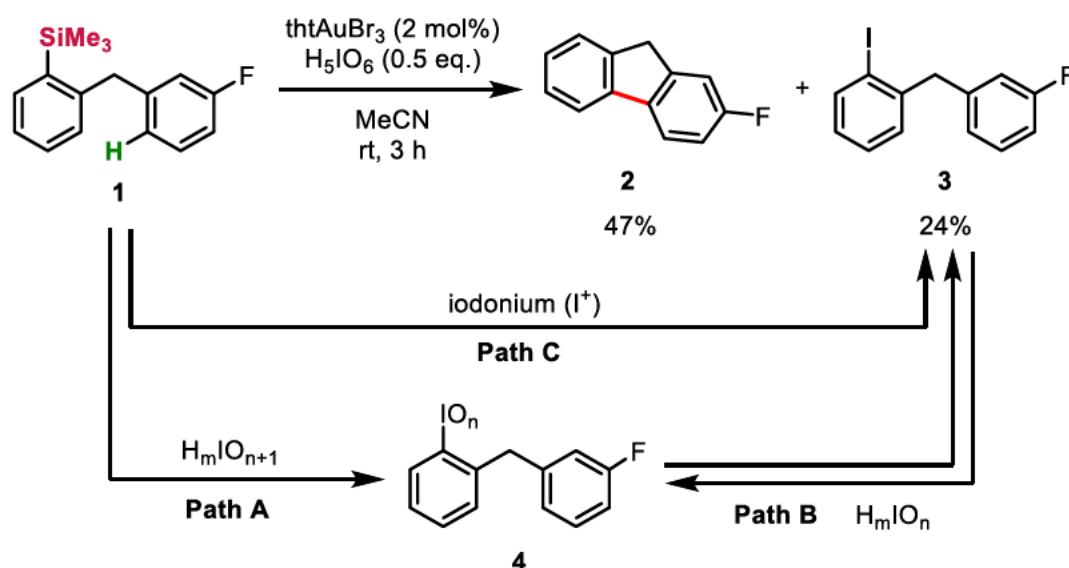

Figure 46. Potential H_5IO_6 oxidation pathways.

The redox processes of iodine have been studied in water and are complex and involve disproportionation,[1-4] comproportionation,[1-4] and ligand exchange[5-8] and are subject to pH.[9] The redox processes of oxyiodine compounds are unstudied in acetonitrile.

A potential reduction pathway for periodic acid can be seen in Scheme 74. Iodates and iodic acid are prone to disproportionation.[1-3] The overall reduction of periodic acid to iodonium requires six electrons.

$$H_5IO_6 \ (VII) \xrightarrow{\ 2\ H_2O\ } HIO_4 \ (VII) \xrightarrow[2\ e^-]{} HIO_3 \ (V) \xrightarrow[2\ e^-]{} HIO_2 \ (III)$$

$$2\ HIO_2 \ (III) \longrightarrow I^+ \ (I) \ + \ HIO_3 \ (V)$$

Scheme 74. Potential simplified reduction pathway of periodic acid to iodonium.

Pathway A

To investigate whether any of the isolable oxyiodine species could perform the direct electrophilic aromatic substitution of a highly oxidised oxyiodine species onto an aryl trimethyl silane, *p*-fluorophenyl trimethyl silane 5 was dissolved in CD_3CN and reacted with one of three commercially available oxyiodine compounds (Table 17) in the presence of thtAuBr$_3$ (Scheme 75).

p-Fluorophenyl trimethyl silane 5 was chosen because, unlike substrate 1, 5 is not capable of coupling to form biaryls under the conditions shown in Scheme 75. Five hours was chosen for the reaction because it was longer than the coupling reaction time (Figure 46), the reaction between the oxyiodine compound and the aryl trimethyl silane would have to be significant in these control reactions in order to indicate that this was the dominant pathway for the formation of aryl iodide.

Scheme 75. Experiment to investigate the potential formation of hypervalent aryl iodine oxidants in situ.

Iodic acid (HIO_3) (Table 17, entry 2) and diiodine pentoxide (I_2O_5) (Table 17, entry 3), both iodine(V) oxidants that are known to not turn over the gold catalyst in the direct arylation

1

reaction (see Chapter 2), were included in this study alongside periodic acid because they may be significant intermediates in the periodic acid reduction chain.

Oxyiodine Compound	NMR Conversion 5 (%)	NMR Yield 6 (%)
H_5IO_6	2	-
HIO_3	-	-
I_2O_5	-	-

None of the oxyiodine species reacted significantly with the aryl trimethyl silane (5) over the five-hour reaction time. Periodic acid reacts slowly with substrate 5 to form the proto- and iododesilylated byproducts, but no aryliodine oxidant species 6.

Based on this result, it was concluded that, under the conditions tested, the aryl trimethyl silanes do not react fast enough with an oxidised oxyiodine compound to form an aryliodine oxidant that could go on to perform the oxidation of gold(I) to gold(III). This makes path A unlikely as the mechanism for the formation of aryl iodide 3.

Pathway B

Aryl iodide 3 could be produced as a result of a side reaction and could then act as an oxidation cocatalyst. To test this theory, two reactions were performed, one without added aryl iodide 7 and another with 1 equivalent of aryl iodide 7 (Scheme 76, Table 18). Discrepancies between the results of the direct arylation without and with aryl iodide 7 would indicate a role in the mechanism for an aryl iodide.
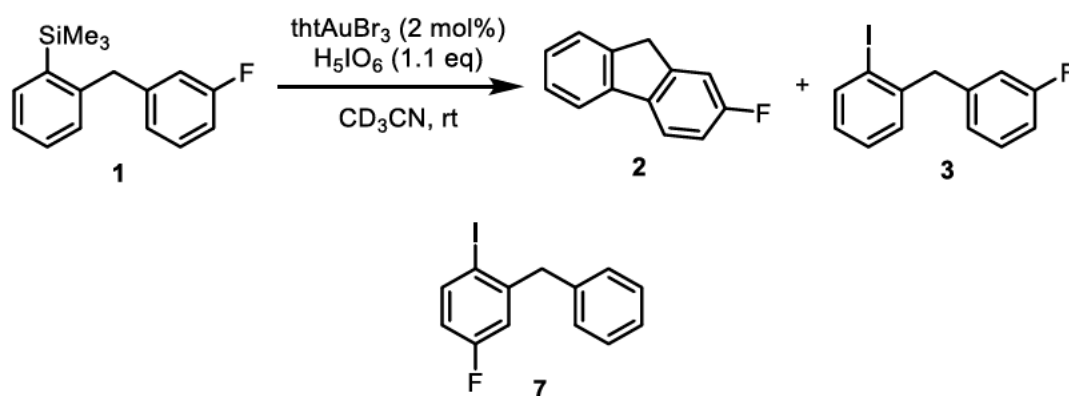

2

Table 18

Additive	NMR Yield 2 (%)	NMR Yield 3 (%)
None	57	26
7 (1 eq)	55	24

The yield of fluorene **2** and newly formed aryl iodide **3** is similar for the reaction without and with added aryl iodide **7** (Table 18). This indicates that the mechanism has not changed. However, the kinetics of the reaction (Figure 47) provide more detail.
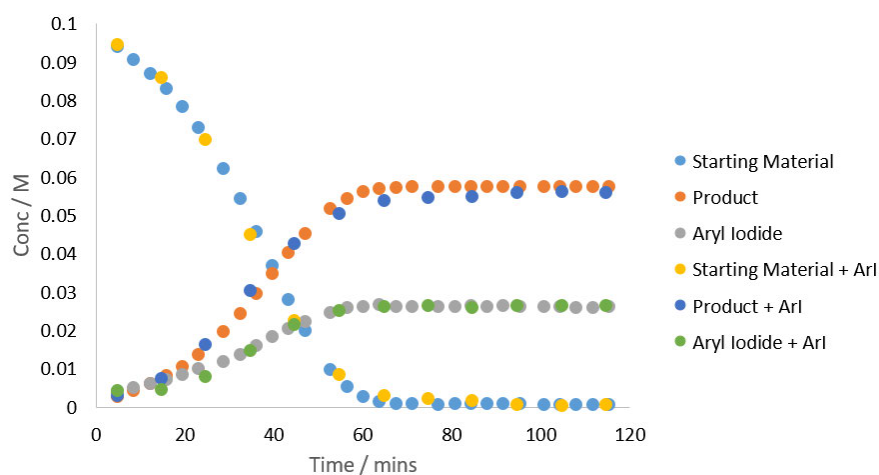

Figure 47. Kinetics of gold catalysed direct arylation with and without aryl iodide oxidation cocatalyst.

Both the coupling reaction without and with aryl iodide additive **7** show near-identical kinetic profiles, indicating that the aryl iodide **7** has no effect on the mechanism of the reaction.

Pathway C

To investigate pathway C, the feasibility of iododesilylation required testing. Iodonium (I^+) can be formed through the oxidation of iodine (I_2). The most appropriate oxidant in this case was decided to be periodic acid itself as it would form only water as a byproduct (Scheme 77).

3

$$7\,H^+ \;+\; \underset{\text{(periodic acid)}}{\text{HO—I(OH)(OH)(O)—OH}} \;+\; 3\,I_2 \;\longrightarrow\; 6\,H_2O \;+\; 7\,I^+$$
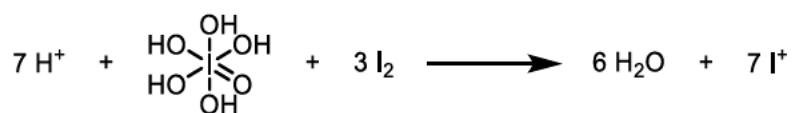
Scheme 77. Comproportionation of I(VII) and I(0) to form I(I) in situ.

p-Fluorophenyl trimethyl silane **5** was chosen as the substrate to react with iodine and periodic acid, the reagents chosen to form iodonium *in situ*.

Reagents: I_2 (1.1 eq), H_5IO_6 (1.1 eq), additive, CD_3CN, rt, 3 h. Substrate **5** (SiMe$_3$, F) → product **8** (I, F).
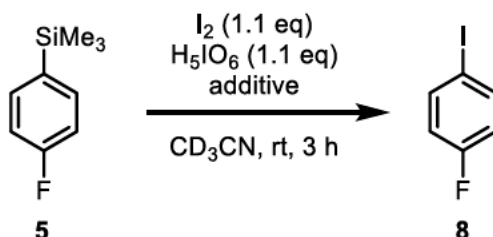
*Scheme 78. Investigation of the reactivity of aryl trimethyl silane **5** and I(I).*

Two control reactions were performed, one without and one with thtAuBr$_3$, the gold precatalyst used for the direct arylation reaction (Table 19). Iodination reactions on arenes are known to be catalysed by gold,[10] and aryl gold iodides are known to reductively eliminate to form aryl iodides.[11]

Table 19

Additives	NMR Conversion 5 (%)	NMR Yield 8 (%)
None	28	28
thtAuBr$_3$ (2 mol%)	100	96

The iodination of aryl trimethyl silane **5** to form aryl iodide **8** proceeded both without and with thtAuBr$_3$ (Table 19), however, the addition of a homogeneous source of gold(III) (thtAuBr$_3$) catalysed the iodination. From the control iodination experiment (Scheme 78 and Table 19) we cannot confirm that iodonium (I$^+$) is the reactive species that iodinates the aryl trimethyl silane. Based on the results from Table 17 and Table 19, it seems to be that a lower oxidation state of iodine, with a homogeneous gold catalyst, is key in the fast iodination of the aryl trimethyl silane that is observed in the coupling reaction.

Scheme 79 depicts a plausible mechanistic proposal that combines the evidence collected so far. **ArAuL$_n$** is formed through electrophilic aromatic auration at the *ipso*-position to the SiMe$_3$ group on the aryl silane. **ArAuL$_n$** can then either form the desired product, or, if there is iodonium present, react with iodonium to form the aryl iodide byproduct.
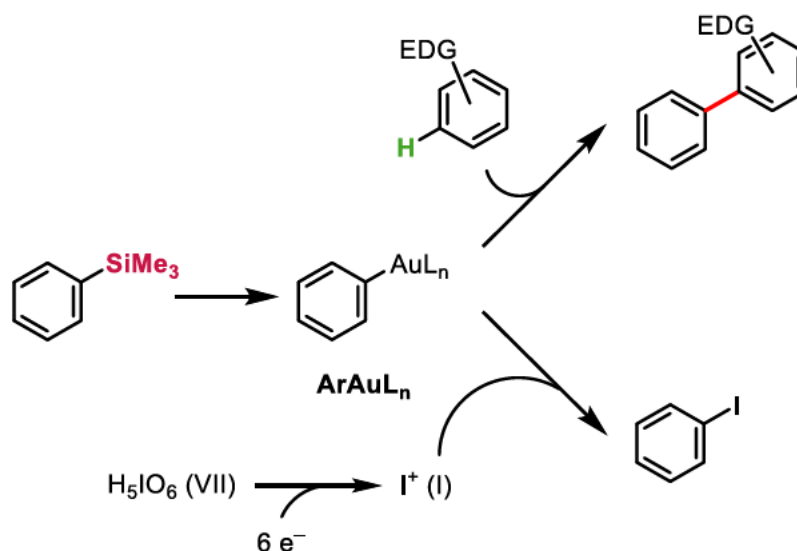
*Scheme 79. Proposed reaction pathway that describes the formation of product and aryl iodide.*

Iodonium Trapping

To increase the yield of biaryl product and reduce the quantity of byproduct aryl iodide formed, the reactive iodonium requires diversion away from **ArAuL$_n$** (Scheme 80).
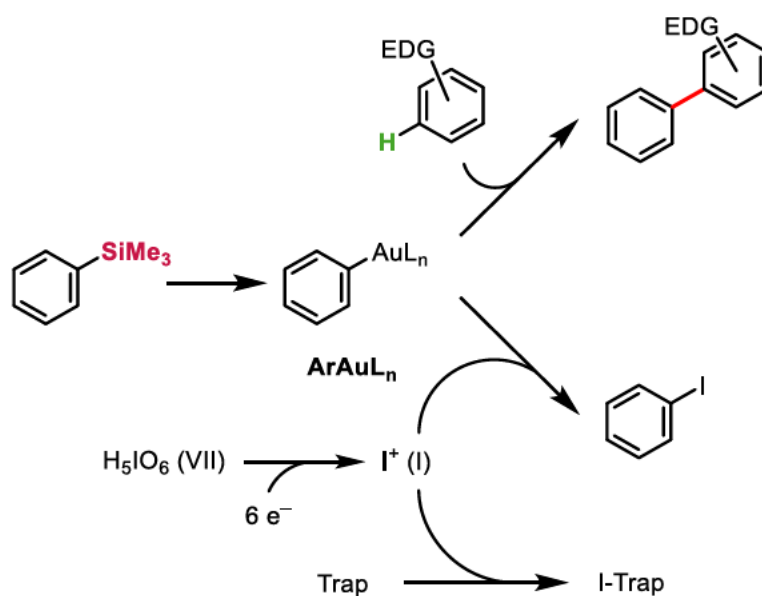
5

In order to direct the electrophilic iodonium intermediate, a nucleophilic trap was required. Because the gold catalysed direct arylation in acetonitrile does not allow for intermolecular biaryl couplings, *p*-fluorophenyl trimethyl silane **5** could be used as an iodonium trap. *p*-Fluorophenyl trimethyl silane **5** is known to react quickly with iodonium in the presence of gold in acetonitrile solution (Table 19). Five equivalents of silane **5** were used as an iodonium trap to investigate the effect of a sacrificial silane on the ratio of fluorene **2** and iodoarene **3** when performing the intramolecular coupling of silane **1** (Scheme 81).
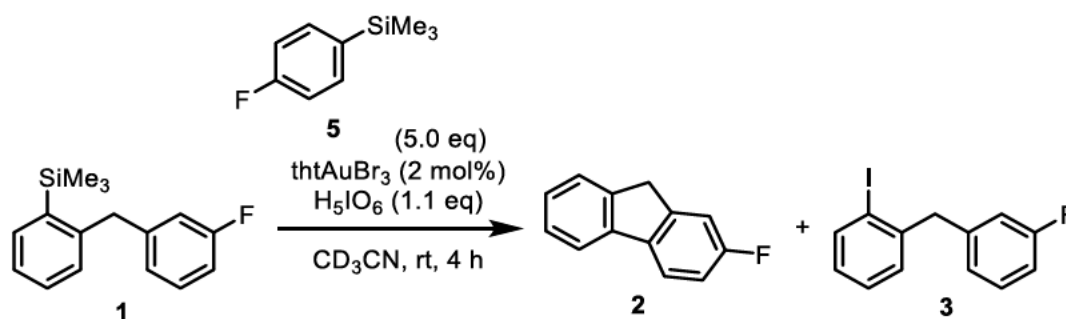
Scheme 81. Attempt at trapping I(I) using an aryl silane without a tethered arene (**4**).

Table 20

Trap	NMR Yield 2 (%)	NMR Yield 3 (%)
None	57	26
p-Fluorophenyltrimethylsilane (5.0 eq)	59	8

The addition of arylsilane **5** to the coupling of **1** showed a significant decrease in the NMR yield of iodoarene **3**, from 26% in the reaction with no additives down to 8% when arylsilane **5** is present. Although this initial result didn't improve the yield of desired product **2**, it showed that the trapping of the reactive iodonium ion and diverting it away from byproduct

6

formation was possible. Both *p*-fluorophenyl iodide and fluorobenzene were detected in the reaction mixture.

Five further traps were selected for screening (Figure 48): three silanes (**9**, **10** and **11**), a styrene **12** and anisole **13**. They were first screened for reactivity with iodonium and thtAuBr$_3$ in CD$_3$CN using the conditions described in Scheme 78.
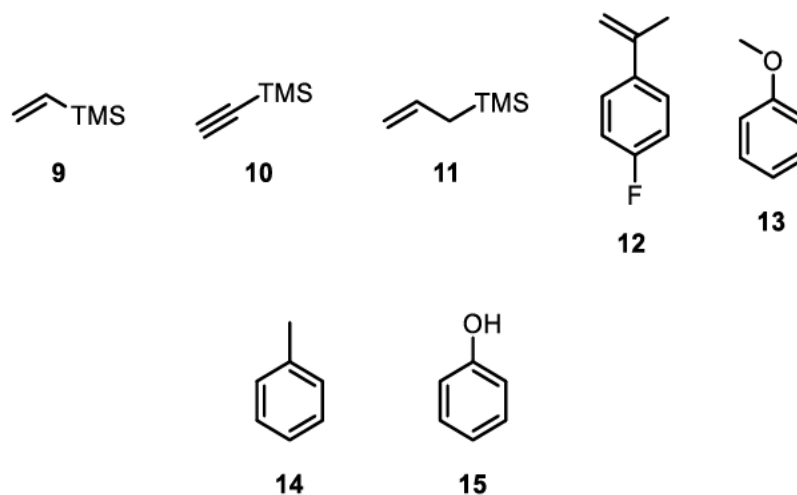

Figure 48. Proposed I(I) traps.

Vinyl trimethyl silane **9** and trimethyl silyl acetylene **10** reacted slowly with iodonium and gold in acetonitrile, meaning that they would not likely be efficient traps under coupling conditions. Allyl trimethyl silane **11**, *p*-fluoro-α-methyl styrene **12**, and anisole **13** all reacted fully in under 15 minutes with iodonium and gold in CD$_3$CN, highlighting them as potential iodonium traps under coupling conditions.

To test the effectiveness of nucleophilic additives as traps for iodonium, each was added to a coupling reaction of substrate **1** (Scheme 82), and the NMR yields of **2** and **3** were recorded. As well as traps **11**, **12** and **13**, toluene **14** and phenol **15** were also included. Based on the ability of anisole to trap iodonium: toluene was chosen because it is a cheap, electron rich aromatic solvent, and phenol because the iodophenol byproduct would be simple to separate from non-polar biaryls with a basic aqueous extraction (Table 21).
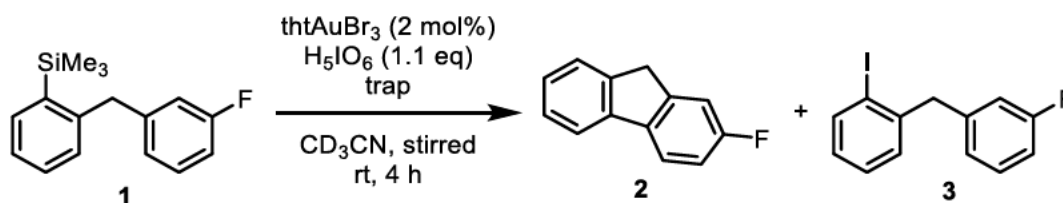

7

Scheme 82. Expanded trapping experiments,

Table 21

Trap	NMR Yield 2 (%)	NMR Yield 3 (%)
None	57	26
p-Fluorophenyl trimethyl silane (5.0 eq)	59	8
p-Fluoro-α-methyl styrene (1.1 eq)	-	-
Allyl trimethyl silane (1.1 eq)	-	-
Anisole (20 eq)	70	4
Toluene (20 eq)	45	22
Phenol (20 eq)	-	-

p-Fluoro-α-methyl styrene **12**, allyl trimethyl silane **11** and phenol **15** reacted quickly with periodic acid and the reactions with them as additives did not consume any substrate **1**. Anisole significantly increased the amount of fluorene **2** and simultaneously reduced the yield of aryl iodide **3**. Toluene had little impact on the yields of products **2** and **3**

To investigate whether temperature had any effect on the yield of fluorene **2** when using anisole as an iodonium trap, three reactions, at 4 °C, 20 °C, and 50 °C, were performed (Scheme 83 and Table 22); the reactions were run until the substrate was observed to be fully consumed by ^{19}F NMR.
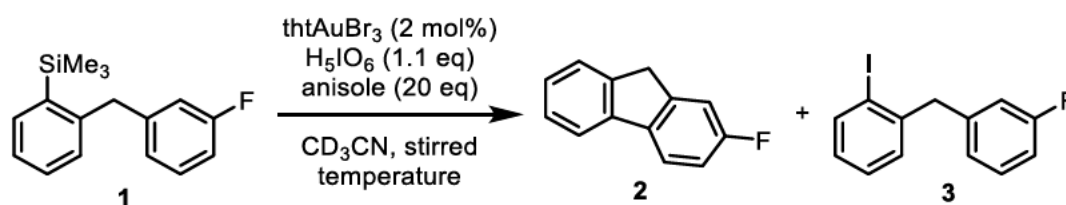
Scheme 83. Investigating the effect of temperature on product distribution.

Table 22

Temperature	NMR Yield 2 (%)	NMR Yield 3 (%)
4 °C	71	6
20 °C	70	4

| 50 °C | | 70 | 6 |

There was no observed difference between the yields of fluorene **2** at different temperatures.

To confirm that anisole was trapping iodonium, 2-iodoanisole, 3-iodoanisole and 4-iodoanisole were doped into completed reaction mixture. 4-iodoanisole and 2-iodoanisole were observed by ^{1}H NMR in a ratio of 8:1 (Figure 49).
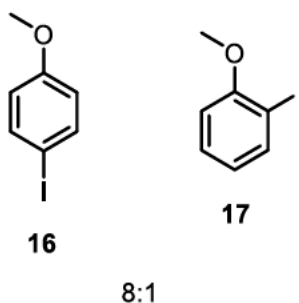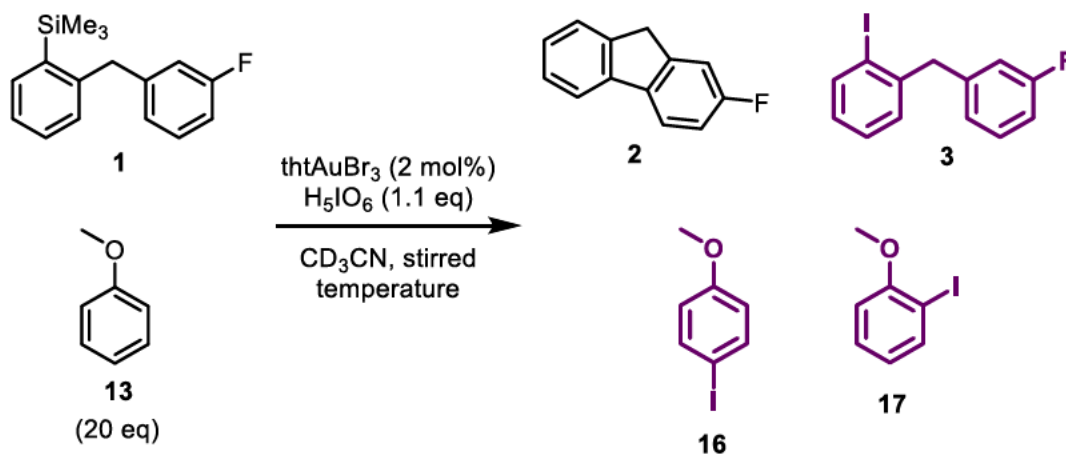

16   **17**

8:1

Figure 49. Iodoanisole byproducts

From the reaction of **1** in the presence of anisole **13** (Scheme 84), the ratio of product **2** to total aryl iodide (**3 + 16 + 17**) was calculated (Table 23) to determine whether anisole was affecting the amount of iodinating species being formed, or whether it was trapping what was being formed in the coupling reaction of **1**.

Scheme 84. Identifying byproducts.

Table 23

Trap	Product:Total ArI

| None | 2.2:1 |
| Anisole (20 eq) | 2.0:1 |

Table 23 shows no significant deviation from the 2.2:1 product to total aryl iodide ratio that is seen for no trap when 20 equivalents of anisole are used as a nucleophilic trap, indicating that anisole is not affecting the oxidation pathway and isn't being oxidised by a reactive oxidant species.

To produce the quantity of aryl iodide that is observed, it is required that periodic acid is the least reactive of the iodine oxidant species in the reduction pathway, the stoichiometric ratio of product to aryl iodide is 3:1 if no side reactions were occurring. There are three 2-electron oxidations that can be performed by periodic acid (iodine (VII)), for the gold catalytic cycle, before it is reduced to iodonium (iodine (I)).

A small amount of oxidant is required for the activation of the catalyst. The tetrahydrothiphene ligand is oxidised to the tetrahydrothiophene-1-oxide (as seen by GC-MS and ^{1}H NMR), and three bromide to bromonium oxidations occur (which performs bromodesilylayion on the aryl trimethylsilane substrate).

Four, two electron oxidations per molecule of gold catalyst are performed. The gold catalyst is present at 2 mol% so 8 mol% of a two electron reductant (8 mol% [O])is required for activation. The periodic acid an perform six electron oxidations (3[O]). This gives 2.66 mol% iodonium (assuming complete reduction from I(VII) to I(I)).

This accounts for 2.66% of the total aryl iodide formed, the remaining excess of aryl iodide over the 3:1 ratio is a result of side-reaction based oxidations.

Substrate Scope

Following the promising addition of anisole to reduce the quantity of unwanted aryl iodide byproduct, reaction conditions utilising periodic acid as the oxidant and anisole as an iodonium trap were tested on multiple substrates (Scheme 85).

Scheme 85. Substrate scope of gold catalysed direct arylation using periodic acid and anisole additives.

Isolated yield, conversion in parentheses.

[a] Isolated impure, yield calculated using dimethyl sulfone as an internal standard.

[b] Second addition of thtAuBr3 (2 mol%) at 1.5 h.

Successful coupling reactions were observed for diaryl methane substrates that contained aryl rings of similar electron richness (**18** and **19**) or where the aryl trimethyl silyl group was on the more electron-poor ring (**21** and **22**). Substrate **23** underwent fast protodesilylation that is common for electron rich aryl silanes in acidic environments. No product was observed for substrates **20**, **24**, and **25**; 6% conversion of the substrate would be expected for the bromodesilylated byproduct resulting from the bromine atoms on the thtAuBr$_3$ precatalyst.

Periodate Reduction Pathway

Figure 50 shows a plausible pathway for periodate reduction to iodonium prior to substitution onto an aryl ring.

Figure 50. Simplified periodic acid reduction pathway.

However, the iodic acid, when tested as an oxidant for the gold catalysed direct arylation does not turn over the reaction, even when a small quantity of periodic acid is added to overcome any initiation process (Chapter 2). The lack of reactivity when iodic acid is used as an oxidant is challenging to investigate in situ.

As iodonium is present in the product aryl iodides, iodine(VII) is being reduced to I(I). Some hypotheses for this were considered:

1) Periodate binds strongly with gold and is reduced to iodate. The iodate is already bound to the gold and can continue to oxidise gold due to its proximity to the gold centre.

2) Inter iodine clusters allow for redox reactions at iodine, meaning that iodate never oxidises gold, but is avoided altogether.

3) Oxyiodine species could be performing radical oxidations of gold(I), this may also bypass the iodine(V) species.

4) Iodic acid may be too insoluble to interact significantly with the homogeneous gold species. However, when iodic acid formed in small quantities in the reduction of the more

soluble periodic acid, it is either supersaturated in acetonitrile, allowing it to react, or of a small enough particle size to remain somewhat reactive.

5) Periodic acid undergoes esterification or some other form of ligand exchange to form a much more reactive oxidising species. This could form a similarly reactive iodine(V) species in place of unreactive iodic acid.

The real answer to why periodic acid is reduced to iodonium, but iodic acid remains unreactive may be a combination of two or more of these processes.

The kinetics of the gold catalysed coupling of substrate **1**, both without and with anisole, had been analysed by ^{1}H and ^{19}F NMR for potential reactive iodine species, however no reactive intermediate was observed. This could be the result of a fast reacting intermediate that obtains a low steady state concentration, or reaction via an intermediate species does not contain easily-identifiable protons or fluorine atoms.

[127]I NMR was found to be too insensitive to detect any iodine species in solution.

ESI-MS

ESI-MS was chosen as a method to investigate the active catalytic reaction. One significant drawback with MS compared to NMR is that MS is an invasive technique and the act of recording the spectrum may create species that are not present in the solution.

Initial results from coupling reactions followed by ESI-MS have indicated that trimethyl silyl periodate and iodate may be present in solution.
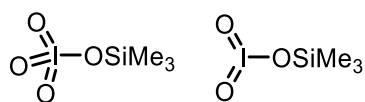
Figure 51. Potential active oxidant species.

Trimethyl silyl periodate or iodate could be a powerful oxidant. This may be the species that allows iodine(V) to continue to oxidise gold(I). The trimethyl silyl group may have a twofold effect, increasing the inherent reactivity of the iodine(V) and simultaneously keeping it in solution.

4.5 - Conclusions and Future Work

A likely mechanism for the formation of aryl iodide has been proposed (Scheme 79): the reduction of periodate to iodonium is concluded to occur before the substitution of the iodine onto the arene. The iodination of the arene is likely gold catalysed (Table 19) and the iodine source could be iodonium, however reactive species that are formed in low concentrations are not ruled out.

Although trimethyl silyl iodine oxidants have been found by ESI-MS, they may not be present in the reaction solution. To find evidence for or against the presence of trimethyl silyl iodine oxidants may be particularly challenging as the synthesis and isolation of organic periodate esters would likely be extremely dangerous and even the in-situ synthesis could pose a significant risk of explosion.

The formation of aryl iodide byproducts has been significantly reduced using the sacrificial nucleophile - anisole. Anisole improved the yield of coupled product 2 from 57% to 70%, whilst reducing the amount of aryl iodide **3** from 26% to 4%.

The periodic acid mediated direct arylation was found to have a limited substrate scope, partly due to the strongly coordinating solvent that prevents intermolecular coupling, and partly due to the fact that the conditions are very acidic that promote fast protodesilylation of electron rich aryl trimethyl silanes.

Further investigation into arylation using periodic acid as an oxidant by ESI-MS kinetics may provide more information about the mechanism of oxidation and potential reactive intermediates.

A key process may involve the oxidation of acetonitrile. Based on the ratios of product to aryl iodide formed during the coupling reactions (Table 23), the oxidant induces significant side oxidations. The formation of gold(I) cyanide when thtAuBr$_3$ reacts with acetonitrile in the presence of periodic acid (Chapter 2) may indicate why acetonitrile is the most effective solvent tested (Chapter 2).

4.6 - References

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5 - Experimental

5.1 - General Information

Procedures employing air or moisture-sensitive materials were performed with anhydrous solvents (*vide infra*) using standard Schlenk techniques, under an atmosphere of anhydrous nitrogen. Glassware necessary for these manipulations were previously oven dried (220 °C) and allowed to cool to room temperature under vacuum.

Analytical thin-layer chromatography was performed on precoated aluminium-backed plates (Silica Gel 60 F254; Merck), and visualised using a combination of UV light (254 nm) and aqueous basic potassium permanganate stain. Preparative thin-layer chromatography (for less than *ca* 15 mg of sample) was performed on precoated, analytical aluminium-backed plates (Silica Gel 60 F254; Merck). Column chromatography was performed using Davisil® 60A silica gel (35-70 μm; Fisher Scientific) or Geduran® Silica Gel 60 (40-63 μm; Merck). Chiral HPLC was performed using a Dionex U3000 fitted with a CHIRALPAK® OD-H column.

NMR spectra were recorded at 27 °C; ^{1}H, ^{19}F and ^{13}C{^{1}H} NMR spectra were recorded at 400 MHz, 375 MHz and 100 MHz respectively, using a Bruker Avance 400 spectrometer. ^{1}H NMR spectra were referenced to residual solvent peaks (CHCl$_3$, δ_H 7.26 ppm). ^{13}C{^{1}H} NMR spectra were referenced to deuterated solvent peak (CDCl$_3$, δ_C 77.16 ppm); chemical shifts are reported in ppm relative to tetramethylsilane standard. ^{19}F NMR chemical shifts are reported in ppm relative to 1,3,5-trifluorobenzene standard (δ_F −107.700). Coupling constants, *J*, were calculated using MestReNova Version 11, and are reported to the nearest 0.1 Hz. Coupling constants that did not match as a result of digitization are reported as rounded averages. The following abbreviations (and their combinations) are used to label the multiplicities: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad).

Dry solvents were obtained by passing solvent through a column of anhydrous alumina using an Anhydrous Engineering Grubbs-type system and stored under anhydrous nitrogen or by storing the solvent over 4 Å molecular sieves overnight.

5.2 - Section 2

Synthesis
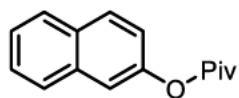
2-Naphthyl pivalate[1]

Following literature procedure.[1] 2-Naphthol (1.01 g, 7.00 mmol) and pivaloyl chloride (0.93 g, 7.70 mmol) were dissolved in dry CH_2Cl_2 (70 mL), this was cooled to 0 °C. Et_3N (2.00 mL, 14 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature and was stirred overnight. The solvent was removed *in vacuo*. Flash silica gel column chromatography (10% EtOAc in petroleum ether (40 – 60 °C)) afforded 2-naphthyl pivalate as a white crystalline powder (1.59 g, 6.96 mmol, 99%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.78 (m, 3H), 7.55 (d, *J* = 2.3 Hz, 1H), 7.54 – 7.45 (m, 2H), 7.22 (dd, *J* = 8.8, 2.3 Hz, 1H), 1.43 (s, 9H).
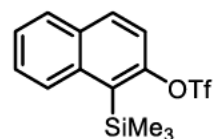
1-(Trimethylsilyl)naphthalen-2-yl triflate[2]

Under nitrogen, 1-bromo-2-naphthol (1.11 g, 5.00 mmol) was dissolved in dry THF (25 mL). Hexamethyldisilazane (1.05 mL, 5.00 mmol) was added and the reaction mixture was refluxed for 1 h. The solvent was removed *in vacuo*. The residue was dissolved in dry THF (25 mL) and cooled to −78 °C. *n*-BuLi (2.15 M in hexanes, 2.56 mL, 5.50 mmol) was added dropwise and the reaction mixture was stirred at −78 °C for 20 mins before warming to room temperature. Triflic anhydride (1.26 mL, 7.50 mmol) was added. The reaction mixture was stirred at room temperature for 1 h. The solvent was removed *in vacuo*. Flash silica gel column chromatography (10% EtOAc in petroleum ether (40 – 60 °C)) afforded 1-(trimethylsilyl)naphthalen-2-yl triflate as a pale yellow oil (383 mg, 1.10 mmol, 22%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.27 – 8.21 (m, 1H), 7.96 – 7.88 (m, 2H), 7.63 – 7.54 (m, 2H), 7.43 (d, *J* = 9.1 Hz, 1H), 0.62 (s, 9H).

1
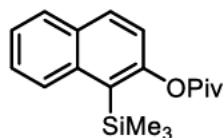
1-(Trimethylsilyl)naphthalen-2-yl pivalate

Prepared by modifying a literature procedure for the synthesis of *ortho*-trimethylsilyl triflates .[3] Under nitrogen, 1-bromo-2-naphthol (1.11 g, 5.00 mmol) was dissolved in dry THF (25 mL). Hexamethyldisilazane (1.05 mL, 5.00 mmol) was added and the reaction mixture was refluxed for 1 h. The solvent was removed *in vacuo*. The residue was dissolved in dry THF (25 mL) and cooled to −78 °C. *n*-BuLi (2.15 M in hexanes, 2.56 mL, 5.50 mmol) was added dropwise and the reaction mixture was stirred at −78 °C for 20 mins before warming to room temperature. Pivaloyl chloride (0.90 g, 7.50 mmol) was added and the reaction mixture was stirred at room temperature for 1 h. The solvent was removed *in vacuo*. Flash silica gel column chromatography (10% EtOAc in petroleum ether (40 − 60 °C)), followed by recrystallisation (10% water in EtOH) afforded 1-(trimethylsilyl)naphthalen-2-yl pivalate as large white crystals (1.08 g, 3.60 mmol, 72%).

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.28 − 8.21 (m, 1H), 7.88 − 7.82 (m, 2H), 7.55 − 7.43 (m, 2H), 6.96 (d, *J* = 8.8 Hz, 1H), 1.45 (s, 9H), 0.53 (s, 9H).

^{13}C NMR (400 MHz, CDCl$_3$) δ 178.2, 155.4, 137.7, 131.6, 131.5, 128.9, 128.1, 126.7, 125.9, 121.6, 39.3, 27.4, 2.5.

HRMS calcd. for [M]$^+$ 300.15401; Found (EI) 300.15381.

MP 72 − 74 °C.
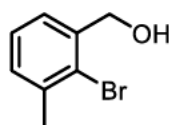
2-Bromo-3-methyl benzyl alcohol[4]

Following literature procedure.[4] Under nitrogen, crushed lithium aluminium hydride tablets (5.70 g, 150 mmol) were added to dry THF (400 mL). A solution of 2-bromo-3-methyl benzoic

acid (21.51 g, 100 mmol) in dry THF (100 mL) was added dropwise to the lithium aluminium hydride slurry. The reaction mixture was stirred at room temperature for 5 h. The reaction was quenched with water and partitioned with 3 M NaOH solution (1 L). The aqueous layer was extracted with Et$_2$O (3 × 200 mL). Combined organic layers were dried with MgSO$_4$, filtered, and concentrated *in vacuo*. The residue was then recrystallised (from hot 30% water in MeOH) to afford 2-bromo-3-methyl benzyl alcohol (12.82 g, 63.7 mmol, 64%).

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.35 − 7.31 (m, 1H), 7.25 (app. t, *J* = 7.4 Hz, 1H), 7.23 − 7.19 (m, 1H), 4.78 (d, *J* = 6.4 Hz, 2H), 2.45 (s, 3H), 2.11 (t, *J* = 6.4 Hz, 1H).
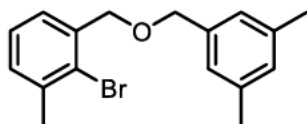
2-Bromo-1-(((3,5-dimethylbenzyl)oxy)methyl)-3-methylbenzene

Under nitrogen, 2-bromo-3-methyl benzyl alcohol (12.70 g, 63.8 mmol) and 3,5-dimethyl benzyl bromide (13.47 g, 67.0 mmol) were dissolved in dry MeCN (600 mL), NaH (60% in mineral oil, 3.83 g, 95.7 mmol) was added. The reaction mixture was stirred at room temperature overnight. The reaction was quenched with water, solvent removed *in vacuo*. Flash silica gel column chromatography (3% Et$_2$O in petroleum ether (40 − 60 °C)) afforded 2-bromo-1-(((3,5-dimethylbenzyl)oxy)methyl)-3-methylbenzene as a clear colourless oil (19.19 g, 60.1 mmol, 94%).

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.43 − 7.38 (m, 1H), 7.25 (app. t, *J* = 7.5 Hz, 1H), 7.22 − 7.18 (m, 1H), 7.05 (s, 2H), 6.97 (s, 1H), 4.67 (s, 2H), 4.61 (s, 2H), 2.46 (s, 3H) 2.36 (s, 6H).

^{13}C NMR (400 MHz, CDCl$_3$) δ 138.3, 138.1, 138.0, 138.0, 129.7, 129.3, 126.9, 126.5, 125.6, 125.3, 72.9, 72.2, 23.5, 21.3.

HRMS calcd. for [M]$^+$ 318.06138; Found (APPI) 318.06222.
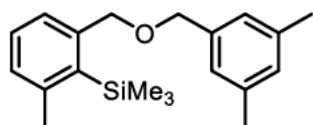
(2-(((3,5-Dimethylbenzyl)oxy)methyl)-6-methylphenyl)trimethylsilane

Under nitrogen, 2-bromo-1-(((3,5-dimethylbenzyl)oxy)methyl)-3-methylbenzene (10.00 g, 31.3 mmol) was dissolved in dry THF (150 mL), this was cooled to −78 °C. *n*-BuLi (2.4 M in hexanes, 15.6 mL, 37.6 mmol) was added and the reaction was stirred at −78 °C for 2 mins. Me₃SiCl (5.96 mL, 47.0 mmol) was added and the reaction mixture was allowed to warm to room temperature. The reaction mixture was stirred at room temperature for 3 h. The solvent was removed *in vacuo*. Flash silica gel column chromatography (40% CH_2Cl_2 in petroleum ether (40 − 60 °C)) afforded (2-(((3,5-dimethylbenzyl)oxy)methyl)-6-methylphenyl)trimethylsilane as a clear colourless oil (8.38 g, 26.7 mmol, 85%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 − 7.23 (m, 2H), 7.14 − 7.10 (m, 1H), 7.00 (s, 2H), 6.95 (s, 1H), 4.62 (s, 2H), 4.48 (s, 2H), 2.51 (s, 3H), 2.34 (s, 6H), 0.43 (s, 9H).

^{13}C NMR (400 MHz, $CDCl_3$) δ 144.4, 144.2, 138.2, 137.8, 137.2, 130.1, 129.1, 128.7, 127.0, 125.7, 73.0, 72.0, 24.7, 21.3, 3.1.

HRMS calcd. for [M]⁺ 312.19040; Found (EI) 312.19171.
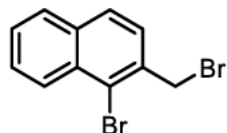
1-Bromo-2-(bromomethyl)naphthalene[5]

Prepared by modifying a literature procedure for the synthesis of benzyl bromides.[5] 1-Bromo-2-methylnaphthalene (90%, 12.28 g, 50.0 mmol) and benzoyl peroxide (100 mg, 0.04 mmol) were dissolved in $CHCl_3$ (75 mL) and refluxed. *N*-Bromosuccinimide (8.01 g, 45.0 mmol) and benzoyl peroxide (100 mg, 0.04 mmol) were suspended in $CHCl_3$ (75 mL) and added slowly to the refluxing solution. Once the addition was complete, the solution was refluxed for 1 h before quenching with saturated $NaHCO_3$ solution (50 mL). The reaction mixture was partitioned. The aqueous layer was washed with CH_2Cl_2 (3 × 50 mL). The organic layer was dried with $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was recrystallised

(heptane) affording 1-Bromo-2-(bromomethyl)naphthalene as pale yellow crystals (11.59 g, 38.6 mmol, 86%).

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.39 – 8.33 (d, J = 8.5 Hz, 1H), 7.84 (dd, J = 8.5, 8.1 Hz, 1H), 7.64 (ddd, J = 8.4, 6.9, 1.4 Hz, 1H), 7.57 (ddd, J = 8.1, 6.8, 1.4 Hz, 1H), 7.55 (d, J = 8.4 Hz, 1H), 4.89 (s, 2H).
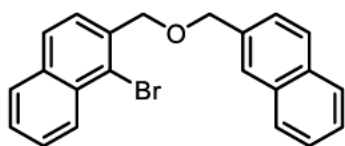
1-Bromo-2-((naphthalen-2-ylmethoxy)methyl)naphthalene

Under nitrogen, 1-bromo-2-(bromomethyl)naphthalene (10.41 g, 34.7 mmol) and 2-naphthyl methanol (5.48 g, 34.7 mmol) were dissolved in dry DMF (400 mL), NaH (60% in mineral oil, 2.08 g, 52.1 mmol) was added. The reaction mixture was stirred at room temperature for 3 h. The reaction was quenched with water. The reaction mixture was partitioned between Et$_2$O (500 mL) and water (1 L), the water layer was extracted with Et$_2$O (3 × 100 mL), the organic layers were dried with MgSO$_4$, filtered and concentrated *in vacuo*. The crude product was recrystallised (20% water in EtOH) affording 1-bromo-2-((naphthalen-2-ylmethoxy)methyl)naphthalene as white crystals (19.19 g, 60.1 mmol, 84%).

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.36 (d, J = 8.6 Hz, 1H), 7.94 – 7.83 (m, 6H), 7.75 (d, J = 8.4 Hz, 1H), 7.63 (ddd, J = 8.5, 6.9, 1.4 Hz, 1H), 7.60 – 7.48 (m, 4H), 4.97 (s, 2H), 4.87 (s, 2H).

^{13}C NMR (400 MHz, CDCl$_3$) δ 135.9, 135.6, 134.1, 133.3, 133.1, 132.2, 128.3, 128.2, 127.9, 127.8, 127.7, 127.4, 127.1, 126.6, 126.5, 126.2, 126.1, 125.9, 125.8, 122.7, 72.8, 72.4.

HRMS calcd. for [M]$^+$ 346.04583; Found (APPI) 376.04648.

MP 83 – 85 °C.
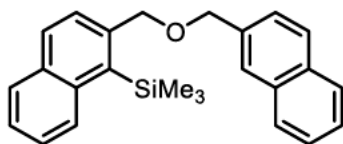
Trimethyl(2-((naphthalen-2-ylmethoxy)methyl)naphthalen-1-yl)silane

Under nitrogen, 1-bromo-2-((naphthalen-2-ylmethoxy)methyl)naphthalene (10.82 g, 28.7 mmol) was dissolved in dry THF (300 mL), and the mixture was cooled to −78 °C. *n*-BuLi (2.4 M in hexanes, 14.3 mL, 34.4 mmol) was added and the reaction was stirred at −78 °C for 2 mins. Me₃SiCl (5.46 mL, 43.0 mmol) was added, and the reaction mixture was allowed to warm to room temperature. The reaction mixture was stirred at room temperature overnight. Flash silica gel column chromatography (50% CH₂Cl₂ in petroleum ether (40 – 60 °C)) followed by recrystallisation from MeOH afforded trimethyl(2-((naphthalen-2-ylmethoxy)methyl)naphthalen-1-yl)silane as white crystals (7.56 g, 20.4 mmol, 71%).

^{1}H NMR (400 MHz, CDCl₃) δ 8.28 (m, 1H), 7.91 – 7.82 (m, 6H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.55 – 7.44 (m, 5H), 4.86 (s, 2H), 4.75 (s, 2H), 0.58 (s, 9H).

^{13}C NMR (400 MHz, CDCl₃) δ 142.9, 137.6, 136.5, 135.8, 133.3, 133.1, 133.0, 129.8, 128.9, 128.7, 128.7, 127.9, 127.7, 127.6, 126.6, 126.1, 125.9, 125.8, 125.1, 125.1, 72.9, 72.1, 3.6.

HRMS calcd. for [M]$^+$ 369.16692; Found (APPI) 369.16793.

MP 65 – 66 °C
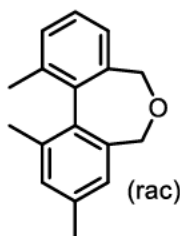
1,3,11-Trimethyl-5,7-dihydro-dibenzooxepine (rac)

(2-(((3,5-Dimethylbenzyl)oxy)methyl)-6-methylphenyl)trimethylsilane (780 mg, 2.50 mmol), (±)-camphorsulfonic acid (870 mg, 3.75 mmol), MeOH (500 µl) and (diacetoxyiodo)benzene (1.045 g, 3.25 mmol) were dissolved in CHCl₃ (50 mL). thtAuBr₃ (0.01 M in CHCl₃, 5.00 mL,

0.05 mmol) was added and the reaction was heated to 50 °C for 20 h. The solvent was removed *in vacuo*. Flash silica gel column chromatography (3% Et$_2$O in petroleum ether (40 – 60 °C)) afforded 1,3,11-trimethyl-5,7-dihydro-dibenzooxepine (rac) as a pale-yellow oil (159 mg, 0.67 mmol, 27%).

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.34 – 7.28 (m, 2H), 7.24 – 7.21 (m, 1H), 7.15 (s, 1H), 7.06 (s, 1H), 4.41 (d, *J* = 11.2 Hz, 1H), 4.37 (d, *J* = 11.2 Hz, 1H), 4.01 (d, *J* = 11.2 Hz, 1H), 4.03 (d, *J* = 11.2 Hz, 1H), 2.40 (s, 3H), 2.23 (s, 3H), 2.19 (s, 3H).

^{13}C NMR (400 MHz, CDCl$_3$) δ 138.6, 137.5, 135.9, 135.7, 135.6, 135.2, 135.1, 131.2, 130.5, 127.7, 127.4, 126.5, 67.5, 67.5, 21.1, 19.8, 19.7.

HRMS calcd. for [M]$^+$ 238.13522; Found (EI) 238.13600.
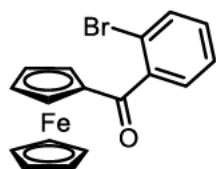
2-Bromobenzoylferrocene[6]

Following literature procedure.[6] Under nitrogen, ferrocene (1.86 g, 10.0 mmol) and 2-bromobenzoyl chloride (2.20 g, 10.0 mmol) were dissolved in dry CH$_2$Cl$_2$ (10 mL). This was cooled to 0 °C before portion-wise addition of AlCl$_3$ (1.33 g, 10 mmol). The reaction mixture was warmed to room temperature and stirred at room temperature for 1 h. The reaction mixture was quenched by pouring onto ice (*ca.* 100 g), partitioned, the water layer was extracted with CH$_2$Cl$_2$ (3 × 20 mL). Combined organic layers were dried with MgSO$_4$, filtered, passed through celite and concentrated *in vacuo*. Recrystallisation (10% EtOAc in petroleum ether (40 – 60 °C)) afforded 2-bromobenzoylferrocene as red crystals (2.37 g, 6.42 mmol, 64%).

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.66 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.52 (*J* = 7.5, 1.8 Hz, dd, 1H), 7.42 (app. td, *J* = 7.5, 1.2 Hz, 1H), 7.34 (ddd, *J* = 8.0, 7.5, 1.8 Hz, 1H), 4.76 (t, *J* = 2.0 Hz , 2H), 4.62 (t, *J* = 2.0 H, 2H), 4.31 (s, 5H).
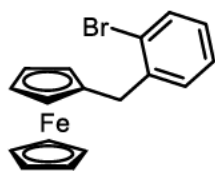
2-Bromobenzylferrocene[7]

Following literature procedure.[7] Under nitrogen, at -78 °C, AlCl$_3$ (820 mg, 6.15 mmol) was dissolved in dry THF (30 mL) followed by slow addition of LiAlH$_4$ (1 M in THF, 4.50 mL, 4.50 mmol). A solution of 2-bromobenzoylferrocene (1107 mg, 3.00 mmol) in dry THF (30 mL) was added slowly. The solution was allowed to warm to room temperature and then brought to reflux for 30 mins. The reaction was quenched with water partitioned with 3 M NaOH solution (200 mL). The aqueous layer was extracted with Et$_2$O (3 × 50 mL). The combined organic layers were dried with MgSO$_4$, filtered and concentrated *in vacuo*. Flash silica gel column chromatography (10% EtOAc in petroleum ether (40 – 60 °C)) afforded 2-bromobenzylferrocene as dark orange crystals (900 mg, 2.53 mmol, 85%).

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.54 (dd, J = 7.8, 1.3 Hz, 1H), 7.21 (ddd, J = 7.6, 7.3, 1.3 Hz, 1H), 7.13 (dd, J = 7.6, 1.7 Hz, 1H), 7.06 (ddd, J = 7.8, 7.3, 1.7 Hz, 1H), 4.20 (t, J = 1.9 Hz, 2H), 4.19 (s, 5H), 4.14 (t, J = 1.9 Hz, 2H).
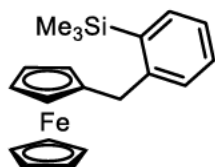
2-(Trimethylsilyl)benzylferrocene (53)

Under nitrogen, 2-bromobenzylferrocene (900 mg, 2.53 mmol) was dissolved in dry THF (25 mL). This was cooled to -78 °C. *n*-BuLi (2.4 M in hexanes, 1.05 mL, 2.53 mmol) was added slowly and the reaction mixture was stirred at -78 °C for 1 min before addition of Me$_3$SiCl (482 μl, 3.80 mmol). The reaction mixture was allowed to warm to room temperature and stirred overnight. The solvent was removed *in vacuo*. Flash silica gel column chromatography (10% Et$_2$O in petroleum ether (40 – 60 °C)) afforded 2-(trimethylsilyl)benzylferrocene as dark-orange crystals (273 mg, 0.78 mmol, 31%).

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.49 (dd, *J* = 7.4, 1.6 Hz, 1H), 7.32 – 7.25 (m, 1H), 7.22 – 7.12 (m, 2H), 4.19 (s, 5H), 4.13 (s, 4H), 3.92 (s, 2H), 0.41 (s, 9H).

^{13}C NMR (400 MHz, CDCl$_3$) δ 147.5, 137.8, 134.3, 129.3, 128.5, 125.3, 87.9, 69.5, 68.8, 67.7, 36.3, 0.7.

HRMS calcd. for [M+Na]$^+$ 371.0889; found (ESI) 371.0878.

MP 87 – 90 °C.
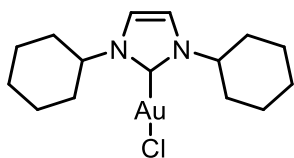
ICyAuCl[8]

Following literature procedure.[8] Under nitrogen, 1,3-dicyclohexylimidazolium chloride (134 mg, 0.50 mmol), chloro(dimethylsulfide)gold(I) (147 mg, 0.50 mmol) and K$_2$CO$_3$ (138 mg, 1.00 mmol) were suspended in dry acetone (1.5 mL) and stirred at 60 °C for 4 h. Solvent removed *in vacuo*, the residue was washed through a silica plug with CH$_2$Cl$_2$. Solvent was removed *in vacuo*, and the residue was triturated with pentane (3 mL) and the crystalline powder was washed with pentane (3 × 2 mL) to afford ICyAuCl as a crystalline white powder (208 mg, 0.46 mmol, 89%).

^{1}H NMR (400 MHz, CDCl$_3$) δ 6.98 (s, 2H), 4.67 – 4.57 (m, 2H), 2.17 – 2.08 (m, 4H), 1.96 – 1.86 (m, 4H), 1.84 – 1.75 (m, 2H), 1.67 – 1.42 (m, 8H), 1.30 – 1.15 (m, 2H).
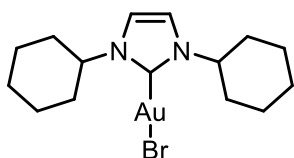
ICyAuBr[9]

Following literature procedure.[9] Under nitrogen, ICyAuCl (116 mg, 0.25 mmol) was dissolved in dry acetone (1 mL). LiBr (215 mg, 2.50 mmol) was added. The reaction mixture was stirred at room temperature for 24 h. The solvent was removed *in vacuo*. The residue was washed

through a silica plug with CH_2Cl_2. Solvent was removed *in vacuo* to afford ICyAuBr as a crystalline white solid (108 mg, 0.21 mmol, 85%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (s, 2H), 4.67 – 4.57 (m, 2H), 2.17 – 2.08 (m, 4H), 1.95 – 1.86 (m, 4H), 1.83 – 1.75 (m, 2H), 1.67 – 1.43 (m, 8H), 1.30 – 1.15 (m, 2H).
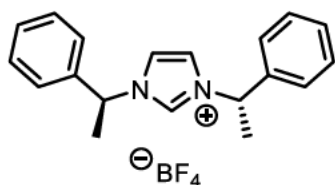
1,3-Bis[(1R)-1-phenylethyl]-2,3-dihydro-1H-imidazolium tetrafluoroborate[10]

Following literature procedure.[10] At 10 °C, paraformaldehyde (150 mg, 5.0 mmol) was added to a solution of (R)-α-methylbenzylamine (650 µL, 5.0 mmol) in toluene (10 mL) and the reaction mixture was stirred at 10 °C for 30 mins. The reaction was then cooled to 0 °C followed by another addition of (R)-α-methylbenzylamine (650 µL, 5.0 mmol). HBF_4 (630 µL, 8 M in water, 5 mmol) was added dropwise. The mixture was stirred at room temperature for 30 mins before heating to 40 °C and stirring for 12 h. CH_2Cl_2 (10 mL) and water (10 mL) were added and stirred together for 10 mins. The CH_2Cl_2 layer was separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated *in vacuo* to afford a brown amorphous solid (548 mg, 1.5 mmol, 30%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.46 (d, J = 1.7 Hz, 1H), 7.40 – 7.35 (m, 8H), 7.11 (d, J = 1.6 Hz, 2H), 1.96 (d, J = 7.0 Hz, 6H).
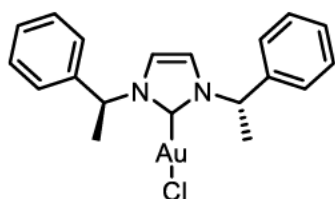
{1,3-Bis[(1R)-1-phenylethyl]-1,3-dihydro-2H-imidazol-2-ylidene}(chloro)gold[11]

Following literature procedure.[8] Under nitrogen, 1,3-Bis[(1R)-1-phenylethyl]-2,3-dihydro-1H-imidazolium tetrafluoroborate (134 mg, 0.50 mmol), chloro(dimethylsulfide)gold(I) (182 mg, 0.50 mmol) and K_2CO_3 (138 mg, 1.00 mmol) were suspended in dry acetone (1.5 mL) and

stirred at 60 °C for 4 h. The solvent was removed *in vacuo*, and the residue was washed through a silica plug with CH$_2$Cl$_2$. The solvent was removed *in vacuo*, and the residue was triturated with pentane (3 mL). The powder was washed with pentane (3 × 2 mL) to afford {1,3-Bis[(1*R*)-1-phenylethyl]-1,3-dihydro-2H-imidazol-2-ylidene}(chloro)gold as a white powder (6 mg, 0.01 mmol, 1 %).

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.42 – 7.31 (m, 10H), 1.84 (d, J = 7.1 Hz, 6H), 6.82 (s, 2H), 6.17 (q, J = 7.1 Hz, 2H).
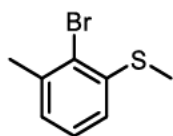
2-Bromo-3-methyl-thioanisole

Following literature procedure.[12] 2-Bromo-3-methyl-aniline (2.50 mL, 20 mmol) and Me$_2$S$_2$ (1.80 mL, 20 mmol) were dissolved in acetonitrile (100 mL) at room temperature. Ascorbic acid (1.76 g, 10 mmol) was dissolved in DMSO (10 mL). The DMSO solution was added slowly and the mixture was stirred at room temperature for 4 hours. Acetonitrile was removed *in vacuo*. Water (50 mL) was added and the mixture was extracted with Et$_2$O (3 × 50 mL). Combined organic layers were dried with MgSO$_4$, filtered and concentrated *in vacuo*. Flash silica gel column chromatography (3% Et$_2$O in petroleum ether (40 – 60 °C)) afforded the product as an orange oil (2.52 g, 11.6 mmol, 58%).

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.20 (t, J = 7.7 Hz, 1H), 7.04 – 6.99 (m, 1H), 6.96 (dd, J = 7.9, 1.5 Hz, 1H), 2.46 (s, 3H), 2.42 (d, J = 0.7 Hz, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 140.33, 139.00, 127.45, 126.84, 124.05, 122.75, 23.81, 16.26.

HRMS calcd. for [M]$^+$ 215.9608; found (ESI) 215.9608.
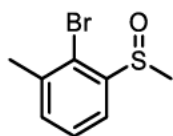
1-Bromo-2-methyl-6-(methylsulfinyl)benzene

Following literature procedure.[13] 2-Bromo-3-methyl-thioanisole (217 mg, 1.0 mmol) was dissolved in CH_2Cl_2 (10 mL) at 0 °C. *m*-CPBA (247 mg, 77%, 1.1 mmol) was added slowly over 15 mins. The reaction mixture was stirred at room temperature for 1 h. Sat. $NaHCO_3$ solution was added (50 mL) and the mixture was extracted with CH_2Cl_2 (3 × 50 mL) Combined organic layers were dried with $MgSO_4$, filtered and concentrated *in vacuo*. Flash silica gel column chromatography (20% Et_2O and 5% MeCN in petroleum ether (40 − 60 °C)) afforded the product as an orange oil (178 mg, 0.76 mmol, 76%).

^1H NMR (400 MHz, $CDCl_3$) δ 7.81 − 7.74 (m, 1H), 7.48 (t, J = 7.6 Hz, 1H), 7.38 (ddt, J = 7.5, 1.7, 0.7 Hz, 1H), 2.81 (s, 3H), 2.45 (d, J = 0.7 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 146.11, 139.30, 133.28, 128.60, 123.38, 120.75, 42.06, 22.49.

HRMS calcd. for $[M+H]^+$ 232.9557; found (ESI) 232.9634.
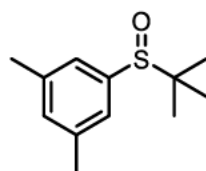
1,3-Dimethyl-5-(*tert*-butylsulfinyl)benzene

Under N_2, 3,5-dimethylbromobenzene (680 μL, 5.0 mmol) was dissolved in dry THF (50 mL) before cooling to −78 °C. *n*-BuLi (2.5 M in hexanes, 2.2 mL, 5.5 mmol) was added slowly followed by *tert*-butylsulfinyl chloride (620 μL, 5.0 mmol) before being warmed up to room temperature and stirred for 1 h. 50 ml of water was added slowly to the reaction mixture and the organic layer was removed and the aqueous phase was extracted with Et_2O (2 × 50 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated *in vacuo*. Flash silica gel column chromatography (20% Et_2O and 5% MeCN in petroleum ether (40 − 60 °C)) afforded the product as a colourless crystalline solid (662 mg, 3.2 mmol, 63%).

^1H NMR (400 MHz, $CDCl_3$) δ 7.18 (s, 2H), 7.10 (s, 1H), 2.37 (s, 6H), 1.17 (s, 9H).
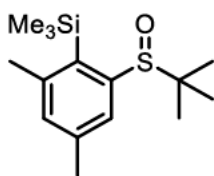
1-trimethylsilyl-2,4-dimethyl-6-(*tert*-butylsulfinyl)benzene

Under N_2, compound (633 mg, 3.0 mmol) was dissolved in dry THF (15 mL) before cooling to −78 °C. *n*-BuLi (2.5 M in hexanes, 1.3 mL, 3.3 mmol) was added slowly and the reaction mixture was stirred at −78 °C for 1 h. TMSCl (460 µL, 3.6 mmol) was added and the reaction mixture was allowed to warm to room temperature over 1 h. 30 ml of water was added slowly to the reaction mixture and the organic layer was removed and the aqueous phase was extracted with Et_2O (2 × 30 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated *in vacuo*. Flash silica gel column chromatography (20% Et_2O and 5% MeCN in petroleum ether (40 − 60 °C)) afforded the product as a colourless crystalline solid (236 mg, 0.84 mmol, 28%).

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.69 − 7.65 (s, 1H), 7.12 − 7.08 (s, 1H), 2.50 (s, 3H), 2.35 (s, 3H), 1.11 (s, 9H), 0.44 (s, 9H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 147.34, 144.40, 138.58, 135.61, 134.65, 123.67, 56.49, 23.81, 23.39, 21.04, 4.41.

HRMS calcd. for [M+H]$^+$ 283.1540; found (ESI) 283.1546.

13

Separation of Atropisomers

1,3,11-Trimethyl-5,7-dihydro-dibenzooxepine (rac)
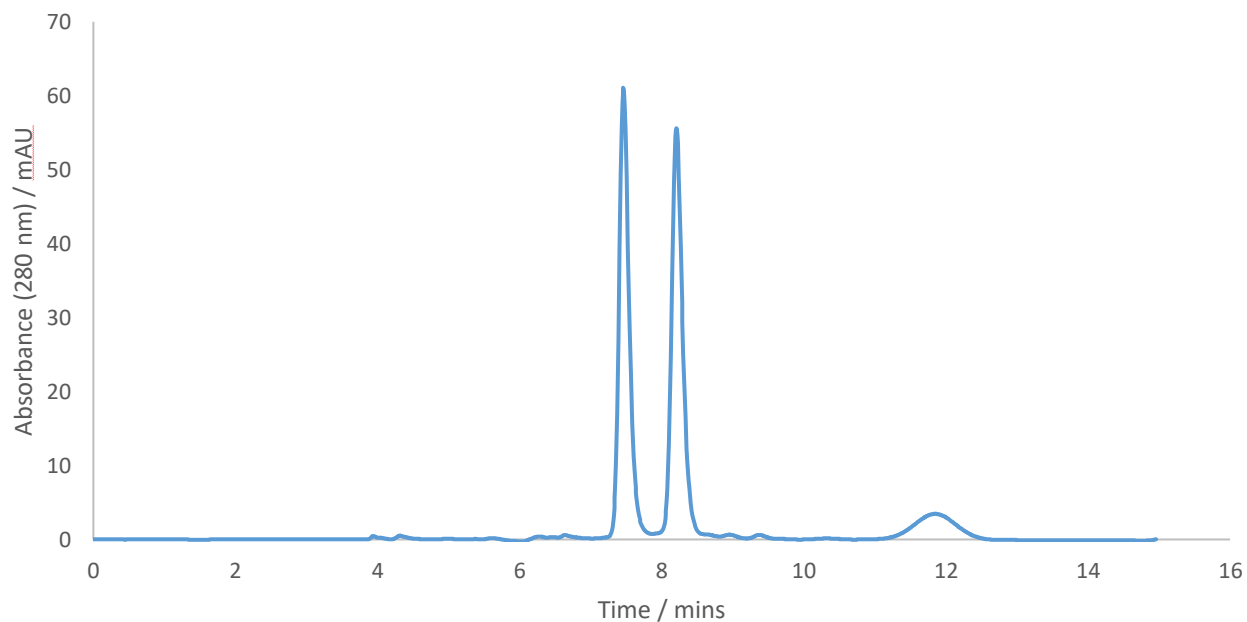
Area percentage: 1) 50.09, 2) 49.91.

5,7-dihydro-dinaphthooxepine (rac)
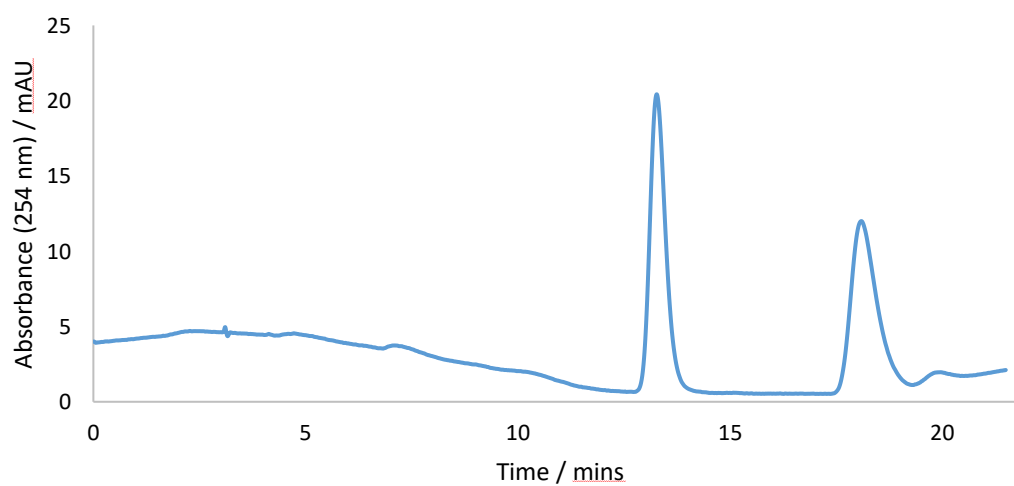
Area percentage: 1) 50.00, 2) 50.00.

5.3 - Sections 3 and 4

Some compounds below were kindly donated by Matthew Robinson[14] and Tom Corrie.[15, 16]
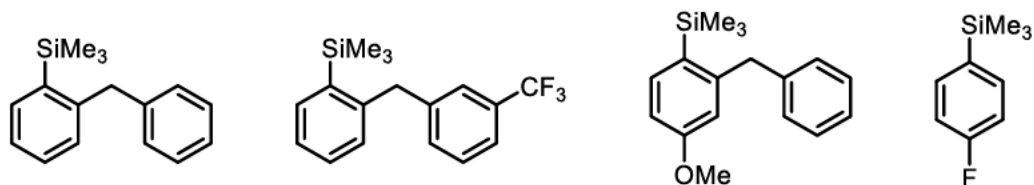
General Procedures
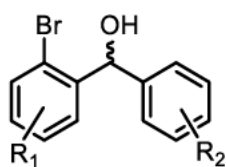
General procedure 1 – Synthesis of 2-bromodiarylmethanols[17]

Under nitrogen, bromoarene (1 eq) was dissolved in dry THF (0.2 M) and cooled to -78 °C. *n*-BuLi (in hexanes, 1.1 eq) was added slowly and the reaction mixture was stirred at -78 °C for 1 min before the slow addition of substituted 2-bromobenzaldehyde (1 eq). The mixture was warmed to room temperature over an hour. The reaction was quenched with water and the aqueous phase was extracted with Et_2O (3 ×). Combined organic phases were dried with $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product.
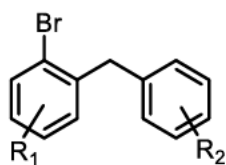

General procedure 2 – Synthesis of 2-bromodiarylmethanes[17]

2-bromodiarylmethanol (1 eq) was dissolved in TFA (4 eq) at room temperature. Et_3SiH (2 eq) was added slowly and the reaction mixture was stirred at room temperature overnight. The reaction was quenched with water and the aqueous phase was extracted with Et_2O (3 ×). Combined organic phases were dried with $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product.
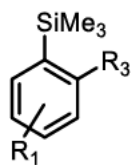
General procedure 3 – Synthesis of trimethylsilyl arenes[17]

Under nitrogen, bromoarene (1 eq) was dissolved in dry THF (0.2 M) and cooled to -78 °C. *n*-BuLi (in hexanes, 1.1 eq) was added slowly and the reaction mixture was stirred at -78 °C for 1 min before the slow addition of TMSCl (1.2 eq). The mixture was warmed to room temperature over an hour. The reaction was quenched with water and the aqueous phase was extracted with Et$_2$O (3 ×). Combined organic phases were dried with MgSO$_4$, filtered and concentrated *in vacuo* to give the crude product.

Synthesis
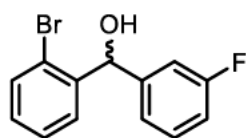
(2-Bromophenyl)(3-fluorophenyl)methanol[17]

Following general procedure 1, using 3-fluoro-bromobenzene (9.25 g, 50 mmol), *n*-BuLi (2.5 M) and 2-bromobenzaldehyde (9.75 g, 50 mmol). Purified by flash silica gel column chromatography (20% EtOAc in petroleum ether (40 – 60 °C)) afforded (2-bromophenyl)(3-fluorophenyl)methanol as a viscous pale green oil (11.89 g, 42.3 mmol, 85%).

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.56 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.53 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.35 (td, *J* = 7.8, 1.4 Hz, 1H), 7.32 – 7.27 (m, 1H), 7.21 – 7.11 (m, 3H), 6.97 (tdd, *J* = 8.3, 2.6, 1.1 Hz, 1H), 6.21 (d, *J* = 4.0 Hz, 1H), 2.40 (*OH*, d, *J* = 4.0 Hz, 1H).
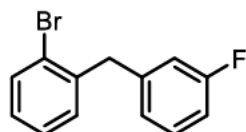
1-Bromo-2-(3-fluorobenzyl)benzene[17]

Following general procedure 2, using (2-bromophenyl)(3-fluorophenyl)methanol (11.89 g, 42.3 mmol). Purified by flash silica gel column chromatography (3% Et$_2$O in petroleum ether (40 – 60 °C)) afforded 1-bromo-2-(3-fluorobenzyl)benzene as a mobile colourless oil (7.19 g, 27.1 mmol, 77%).

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.58 (dd, J = 8.0, 1.3 Hz, 1H), 7.28 – 7.22 (m, 2H), 7.15 (dd, J = 7.7, 1.8 Hz, 1H), 7.11 (td, J = 7.6, 1.9 Hz, 1H), 6.98 (ddd, J = 7.6, 1.7, 0.8 Hz, 1H), 6.94 – 6.85 (m, 2H), 4.12 (s, 2H).
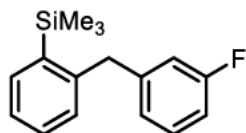
(2-(3-Fluorobenzyl)phenyl)trimethylsilane[17]

Following general procedure 3, using 1-bromo-2-(3-fluorobenzyl)benzene (7.19 g, 27.1 mmol) and n-BuLi (2.5 M). Purified by flash silica gel column chromatography (3% Et$_2$O in petroleum ether (40 – 60 °C)) afforded (2-(3-fluorobenzyl)phenyl)trimethylsilane as a mobile colourless oil (5.59 g, 21.6 mmol, 80%).

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.57 – 7.52 (dd, J = 7.3, 1.4 Hz, 1H), 7.30 (td, J = 7.5, 1.6 Hz, 1H), 7.23 (ddd, J = 7.6, 6.6, 1.6 Hz, 2H), 7.01 (m, 1H), 6.88 (m, 2H), 6.79 – 6.75 (m, 1H), 4.15 (s, 2H), 0.30 (s, 9H).
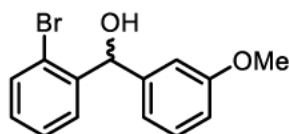
(2-Bromophenyl)(3-methoxyphenyl)methanol[17]

Following general procedure 1, using 3-methoxy-bromobenzene (1.87 g, 10 mmol), n-BuLi (2.5 M) and 2-bromobenzaldehyde (1.85 g, 10 mmol). Purified by flash silica gel column chromatography (20% EtOAc in petroleum ether (40 – 60 °C)) afforded (2-bromophenyl)(3-methoxyphenyl)methanol as a clear colourless oil (2.21 g, 7.54 mmol, 75%).

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.57 (td, J = 8.0, 1.5 Hz, 2H), 7.42 – 7.32 (m, 1H), 7.32 – 7.23 (m, 1H), 7.17 (ddd, J = 7.9, 7.3, 1.7 Hz, 1H), 7.04 – 6.95 (m, 2H), 6.84 (ddd, J = 8.2, 2.4, 1.2 Hz, 1H), 6.21 (d, J = 3.5 Hz, 1H), 3.82 (s, 3H), 2.39 (d, J = 3.9 Hz, 1H).
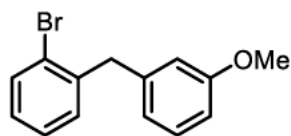
1-Bromo-2-(3-fluorobenzyl)benzene[17]

Following general procedure 2, using (2-bromophenyl)(3-methoxyphenyl)methanol (2.14 g, 7.30 mmol). Purified by flash silica gel column chromatography (3% Et$_2$O in petroleum ether (40 – 60 °C)) afforded 1-bromo-2-(3-fluorobenzyl)benzene as a mobile colourless oil (1.16 g, 4.18 mmol, 77%).

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.59 (dd, J = 7.9, 1.3 Hz, 1H), 7.25 (tdd, J = 7.5, 4.1, 1.0 Hz, 2H), 7.20 – 7.14 (m, 1H), 7.11 (ddd, J = 7.9, 7.2, 1.8 Hz, 1H), 6.85 – 6.75 (m, 3H), 4.12 (s, 2H), 3.80 (s, 3H).
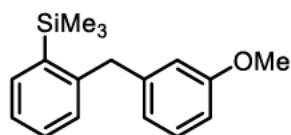
(2-(3-Methoxybenzyl)phenyl)trimethylsilane[17]

Following general procedure 3, using 1-bromo-2-(3-methoxybenzyl)benzene (1.11 g, 4.00 mmol) and n-BuLi (2.5 M). Purified by flash silica gel column chromatography (3% Et$_2$O in petroleum ether (40 – 60 °C)) afforded (2-(3-methoxybenzyl)phenyl)trimethylsilane as a mobile colourless oil (243 mg, 0.90 mmol, 23%).

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.56 (ddd, J = 7.3, 1.7, 0.5 Hz, 1H), 7.30 (td, J = 7.5, 1.6 Hz, 1H), 7.26 – 7.15 (m, 2H), 7.05 (ddd, J = 7.7, 1.4, 0.7 Hz, 1H), 6.82 – 6.74 (m, 1H), 6.72 (ddt, J = 7.5, 1.6, 0.8 Hz, 1H), 6.73 – 6.64 (m, 1H), 4.16 (s, 2H), 3.79 (s, 3H), 0.34 (s, 9H).
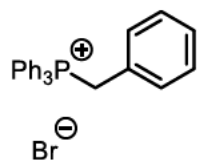
Benzyltriphenylphosphonium bromide

Under nitrogen, triphenyl phosphine (2.62 g, 10.00 mmol) and phenethyl bromide (1.85 g, 10.00 mmol) were dissolved in toluene (10 ml) and heated to 100 °C for 16 h. Solvent was

decanted and the solid was washed with petroleum ether (40 – 60 °C) (20 ml, 2 ×). The solid was used directly in the subsequent reaction.

and
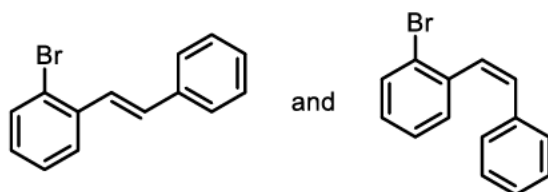
1-Bromo-styrylbenzene[18]

Under nitrogen, crude benzyltriphenylphosphonium bromide was dissolved in THF (50 ml) and cooled to 0 °C. *t*-BuOK (1.12 g, 10.0 mmol) was added and the reaction was stirred at 0 °C for 30 mins. 2-bromobenzaldehyde (1.85 g, 10.0 mmol) was added dropwise and then the reaction mixture was allowed to warm to rt and stirred at rt for 16 h. The crude reaction mixture was dried onto silica and purified by flash silica gel column chromatography (petroleum ether (40 – 60 °C)) afforded 1-bromo-styrylbenzene as a clear colourless oil (2.27 g, 8.76 mmol, 88%). The compound was used in the subsequent reaction as a mixture of *E:Z* isomers in the ratio 1:4.76.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.74 – 7.04 (m, 13H), 6.72 (d, J = 12.1 Hz, 1H), 6.65 (d, J = 12.1 Hz, 1H).

and
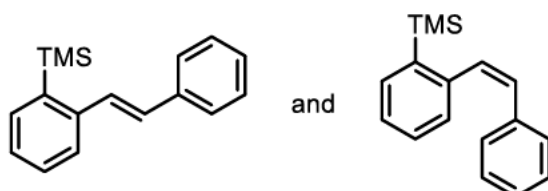
Trimethyl(2-styrylphenyl)silane

Following general procedure 3, using 1-bromo-styrylbenzene (2.14 g, 8.25 mmol) and *n*-BuLi (2.5 M). Purified by flash silica gel column chromatography (petroleum ether (40 – 60 °C)) afforded trimethyl(2-styrylphenyl)silane as a colourless oil (2.14 g, 8.03 mmol, 99%). The compound was used in the subsequent reaction as a mixture of *E:Z* isomers in the ratio 1:4.76.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.75 – 7.07 (m, 9H), 7.04 – 6.57 (m, 2H), 0.38 (d, J = 26.7 Hz, 9H).
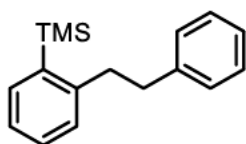
Trimethyl(2-phenethylphenyl)silane[17]

Compound trimethyl(2-styrylphenyl)silane (2.02 g, 8.00 mmol) and 10% Pd/C (43 mg, 0.04 mmol) were dissolved in EtOH (20 ml). This solution and flask was purged with nitrogen before flushing with hydrogen. The reaction was stirred at room temperature under hydrogen atmosphere for 16 h. Purified by flash silica gel column chromatography (petroleum ether (40 – 60 °C)) afforded trimethyl(2-phenethylphenyl)silane as a colourless oil (1.76 g, 6.92 mmol, 87%).

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.54 (ddd, J = 7.5, 1.6, 0.6 Hz, 1H), 7.39 – 7.29 (m, 5H), 7.28 – 7.20 (m, 3H), 3.11 – 3.04 (m, 2H), 2.98 – 2.94 (m, 2H), 0.38 (s, 9H).
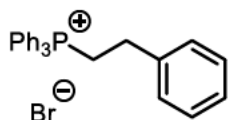
Phenethyltriphenylphosphonium bromide

Under nitrogen, triphenyl phosphine (2.62 g, 10.00 mmol) and phenethyl bromide (1.85 g, 10.00 mmol) were dissolved in toluene (10 ml) and heated to 100 °C for 16 h. Solvent was decanted and the solid was washed with petroleum ether (40 – 60 °C) (20 ml, 2 ×). The solid was used directly in the subsequent reaction.
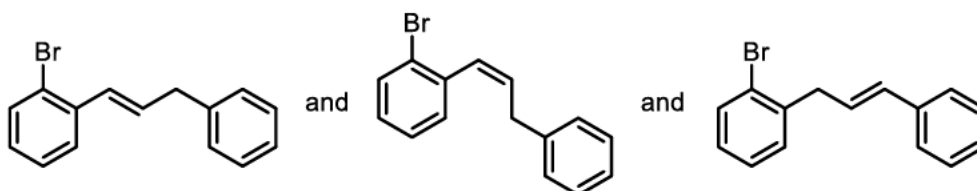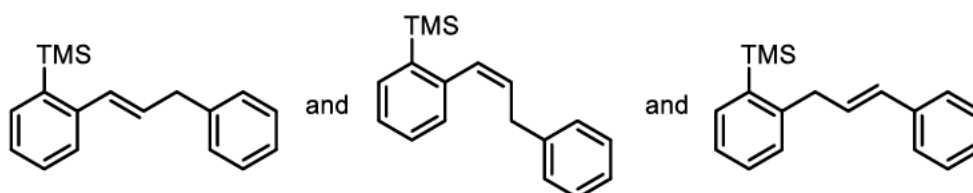

1-Bromo-2-(phenylpropenyl)benzene

Under nitrogen, crude phenethyltriphenylphosphonium bromide was dissolved in EtOH (40 ml) and cooled to 0 °C. EtONa (1 M, prepared by dissolving 230 mg, 10.0 mmol of Na in 10 ml of EtOH) was added and the reaction was stirred at 0 °C for 30 mins. 2-bromobenzaldehyde (1.85 g, 10.0 mmol) was added dropwise and then the reaction mixture was allowed to warm

to rt and stirred at rt for 16 h. The crude reaction mixture was dried onto silica and purified by flash silica gel column chromatography (petroleum ether (40 – 60 °C)) afforded 1-bromo-2-(phenylpropenyl)benzene as a clear colourless oil (2.40 g, 8.78 mmol, 88%). The compound was used in the subsequent reaction as a mixture of three isomers in the ratio 1:1.74:2.44.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.72 – 7.05 (m, 9H), 6.91 – 6.46 (m, 1H), 6.43 – 6.28 (m, 1H), 3.76 – 3.53 (m, 2H).

Trimethyl(2-(3-phenylpropenyl)phenyl)silane

Following general procedure 3, using 1-bromo-2-(phenylpropenyl)benzene (2.32 g, 8.50 mmol) and ^{n}BuLi (2.5 M). Purified by flash silica gel column chromatography (petroleum ether (40 – 60 °C)) afforded trimethyl(2-(3-phenylpropenyl)phenyl)silane as a colourless oil (2.14 g, 8.03 mmol, 94%). The compound was used in the subsequent reaction as a mixture of three isomers in the ratio 1:1.46:2.30.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.67 – 7.05 (m, 9H), 6.93 – 6.44 (m, 1H), 6.43 – 6.22 (m, 1H), 3.76 – 3.48 (m, 2H), 0.41 – 0.27 (m, 9H).
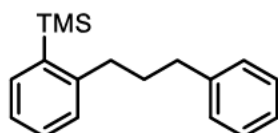
Trimethyl(2-(3-phenylpropyl)phenyl)silane[17]

Trimethyl(2-(3-phenylpropenyl)phenyl)silane (2.13 g, 8.00 mmol) and 10% Pd/C (43 mg, 0.04 mmol) were dissolved in EtOH (20 ml). This solution and flask was purged with nitrogen before flushing with hydrogen. The reaction was stirred at room temperature under hydrogen atmosphere for 16 h. Purified by flash silica gel column chromatography (petroleum ether (40 – 60 °C)) afforded trimethyl(2-(3-phenylpropyl)phenyl)silane as a colourless oil (2.14 g, 8.03 mmol, 94%).

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.50 (ddd, J = 7.5, 1.5, 0.5 Hz, 1H), 7.37 – 7.29 (m, 3H), 7.26 – 7.18 (m, 5H), 2.82 – 2.75 (m, 3H), 2.73 – 2.66 (m, 1H), 2.05 – 1.93 (m, 2H), 0.31 (s, 9H).
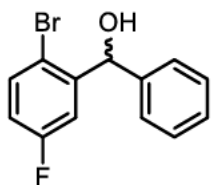
(2-Bromo-4-fluorophenyl)phenylmethanol[17]

Following general procedure 1, using bromobenzene (1.80 mL, 17.2 mmol), *n*-BuLi (2.5 M) and 2-bromo-4-fluoro-benzaldehyde (3.49 g, 17.2 mmol). Purified by flash silica gel column chromatography (20% EtOAc in petroleum ether (40 – 60 °C)) afforded (2-Bromo-4-fluorophenyl)phenylmethanol as a clear colourless oil (3.52 g, 12.52 mmol, 73%).

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.48 (dd, J = 8.8, 5.2 Hz, 1H), 7.42 – 7.27 (m, 6H), 6.89 (ddd, J = 8.7, 7.7, 3.1 Hz, 1H), 6.15 – 6.10 (m, 1H), 2.34 (d, J = 3.7 Hz, 1H).
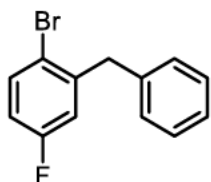
1-Bromo-2-benzyl-4-fluorobenzene[17]

Following general procedure 2, using (2-Bromo-4-fluorophenyl)phenylmethanol (3.33 g, 12.6 mmol). Purified by flash silica gel column chromatography (3% Et$_2$O in petroleum ether (40 – 60 °C)) afforded 1-Bromo-2-benzyl-4-fluorobenzene as a mobile colourless oil (2.93 g, 11.1 mmol, 88%).

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.56 – 7.48 (m, 1H), 7.37 – 7.15 (m, 5H), 6.87 – 6.77 (m, 2H), 4.09 (s, 2H).
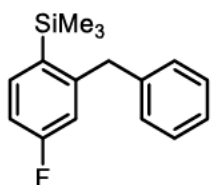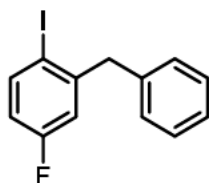

(2-Benzyl-5-fluorophenyl)trimethylsilane[17]

Following general procedure 3, using 1-Bromo-2-benzyl-4-fluorobenzene (2.81 g, 11.2 mmol) and *n*-BuLi (2.5 M). Purified by flash silica gel column chromatography (3% Et$_2$O in petroleum

ether (40 – 60 °C)) afforded (2-Benzyl-5-fluorophenyl)trimethylsilane as a mobile colourless oil (1.85 g, 7.16 mmol, 64%).

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.49 (dd, J = 8.3, 6.7 Hz, 1H), 7.35 – 7.27 (m, 2H), 7.25 – 7.20 (m, 1H), 7.10 (ddt, J = 7.4, 1.3, 0.7 Hz, 2H), 6.90 (td, J = 8.5, 2.6 Hz, 1H), 6.69 (dd, J = 10.8, 2.5 Hz, 1H), 4.14 (s, 2H), 0.32 (s, 9H).
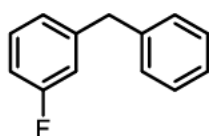

1-Iodo-2-benzyl-4-fluorobenzene

At room temperature, under air, (2-Benzyl-5-fluorophenyl)trimethylsilane (260 µL, 1.0 mmol), was dissolved in AcOH (10 mL) followed by *N*-iodosuccinimide (270 µL, 1.1 mmol), this was stirred at room temperature for 16 h. Solvent was removed in vacuo. Purified by flash silica gel column chromatography (petroleum ether (40 – 60 °C)) afforded 1-Iodo-2-benzyl-4-fluorobenzene as pale purple oil (262 mg, 0.84 mmol, 84%).

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.79 (dd, J = 8.7, 5.7 Hz, 1H), 7.37 – 7.29 (m, 2H), 7.28 – 7.22 (m, 1H), 7.21 – 7.15 (m, 2H), 6.80 (dd, J = 9.8, 3.0 Hz, 1H), 6.69 (td, J = 8.3, 3.0 Hz, 1H), 4.07 (s, 2H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 164.5, 146.2 (d, J = 7.2 Hz), 140.6 (d, J = 7.8 Hz), 138.9, 129.3, 128.8, 126.8, 117.6 (d, J = 22.6 Hz), 115.6 (d, J = 21.8 Hz), 94.0 (d, J = 3.1 Hz), 46.7 (d, J = 1.5 Hz).

^{19}F NMR (375 MHz, CDCl$_3$) δ -113.67 (m)

HRMS calcd. for [M−H]$^-$ 310.9811; found (ESI) 310.9727.


1-benzyl-3-fluorobenzene[19]

Prepared by modifying a literature procedure for the protodesilylation of aryl trimethyl silanes.[20] At room temperature, under air, (2-Benzyl-5-fluorophenyl)trimethylsilane (260 µL, 1.0 mmol), was dissolved in AcOH (10 mL) followed by H_2SO_4 (1 mL, 20 mmol), this was stirred at room temperature for 16 h. Solvent was removed in vacuo. Purified by flash silica gel column chromatography (petroleum ether (40 – 60 °C)) afforded 1-benzyl-3-fluorobenzene as clear colourless oil (69 mg, 0.37 mmol, 37%).

^1H NMR (400 MHz, CDCl$_3$) δ 7.34 – 7.28 (m, 2H), 7.27 – 7.21 (m, 2H), 7.21 – 7.16 (m, 2H), 7.01 – 6.95 (m, 1H), 6.94 – 6.84 (m, 2H), 3.98 (s, 2H).

Oxidant/Solvent Screening
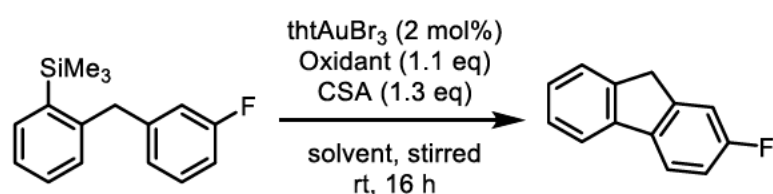
Under air, oxidant (0.055 mmol) and CSA (15 mg, 0.065 mmol) were added to a screw cap vial and suspended in solvent (400 µL), aryl silane (13 mg, 0.050 mmol) was then added followed by thtAuBr$_3$ solution (100 µL, 0.01 M, 0.001 mmol). The reaction was stirred at rt for 16h before filtering through cotton wool and recording ^1H and ^{19}F NMR.
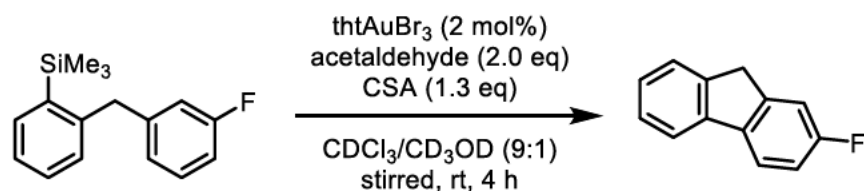

Under air, CSA (0.13 mmol), solvent (800 µL), aryl silane (26 mg, 0.10 mmol) and, if required, phenyl iodide (3 mg, 0.015 mmol) were added to a screw cap vial, followed by acetaldehyde (9 mg, 0.20 mmol), if required, transition metal salt solution (200 µL, 0.01 M, 0.002 mmol) then thtAuBr$_3$ solution (200 µL, 0.01 M, 0.002 mmol). The reaction was stirred in a vial with an attached air balloon at rt for 4 h, before filtering through cotton wool and acquiring ^1H and ^{19}F NMR spectra.
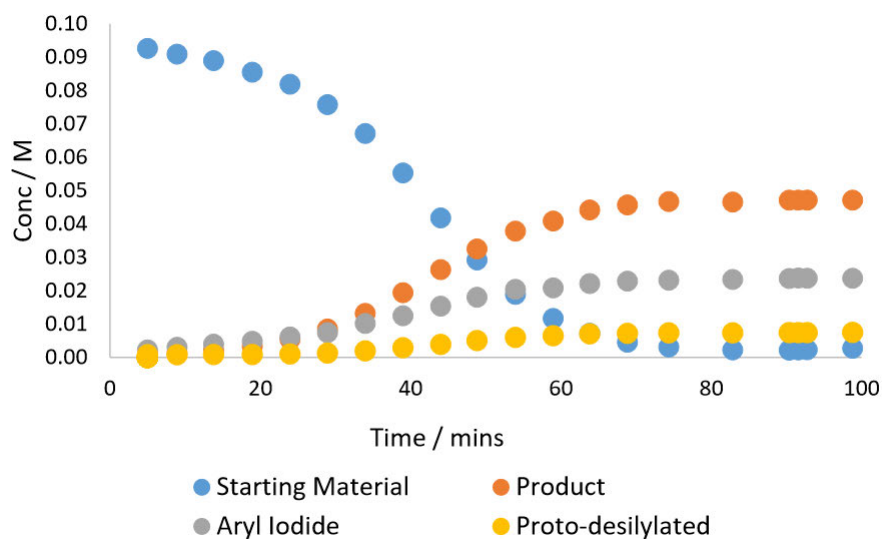
H$_5$IO$_6$ Oxidant in CD$_3$CN Kinetics

Under air, CD$_3$CN (500 μL) and aryl silane (26 mg, 0.10 mmol) were added to an NMR tube, followed by H$_5$IO$_6$ solution in CD$_3$CN (300 μL) then thtAuBr$_3$ solution in CD$_3$CN (200 μL). The reaction was followed by ^{1}H NMR spectroscopy.

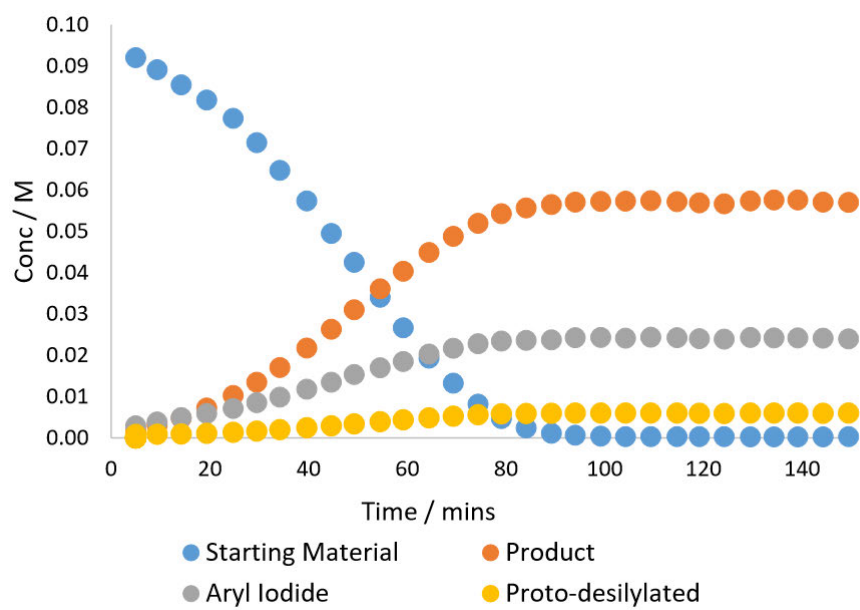0.11 M H$_5$IO$_6$ and 0.002 M thtAuBr$_3$
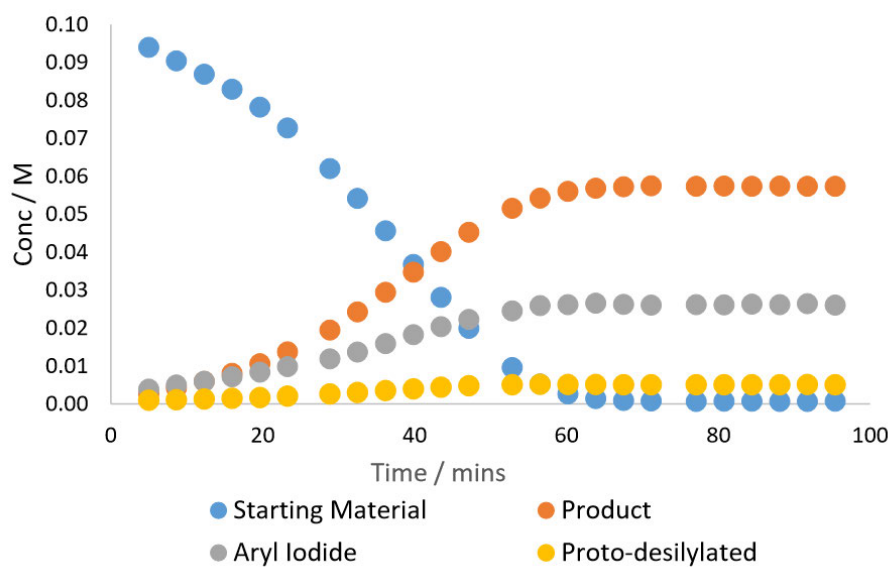
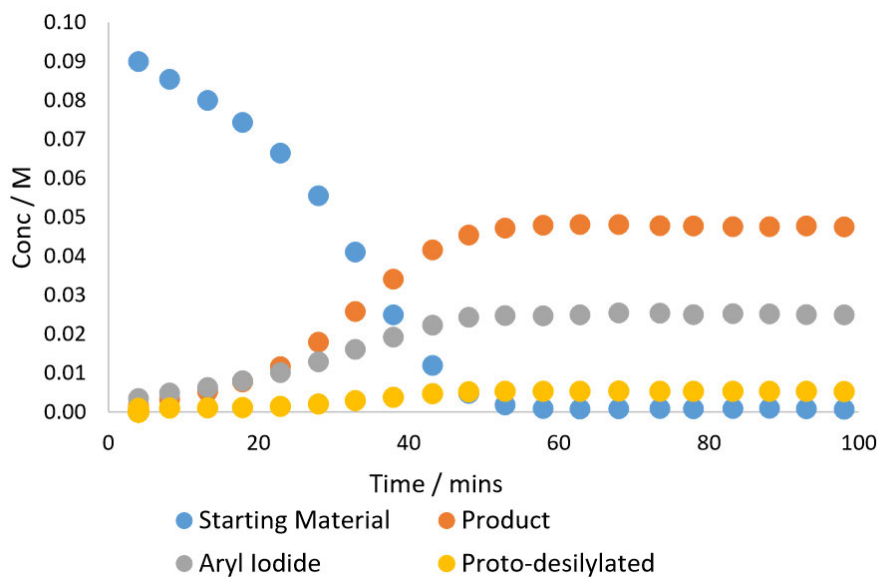0.05 M H$_5$IO$_6$ and 0.002 M thtAuBr$_3$

0.01 M H_5IO_6 and 0.002 M thtAuBr$_3$
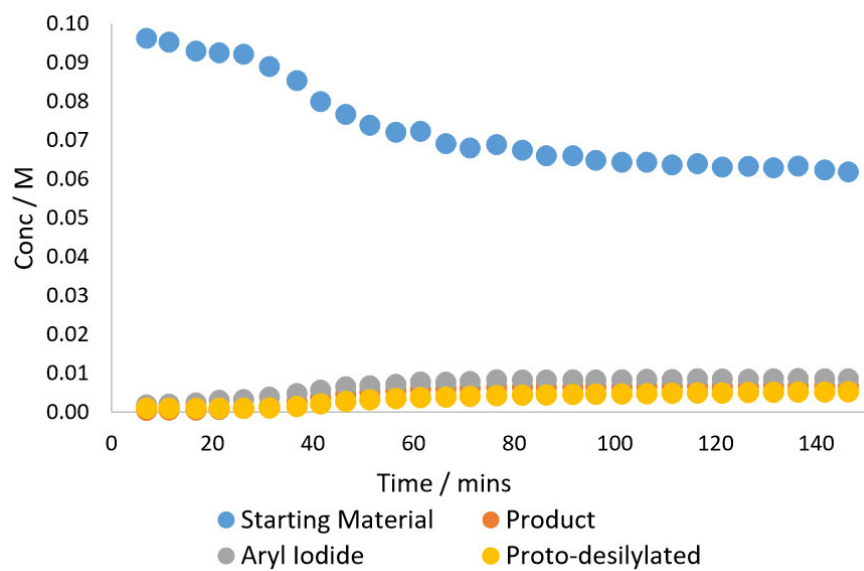
0.11 M H_5IO_6 and 0.001 M thtAuBr$_3$

0.11 M H_5IO_6 and 0.004 M thtAuBr$_3$

Iodonium Control Experiments

Under air, I_2 (25 mg, 0.10 mmol), internal standard (1,3,5-trifluorobenzene, 3.4 μL, 0.33 mmol) then aryl silane (0.10 mmol) were dissolved in CD_3CN (1000 μL – the volume of subsequent stock solutions to be added) in an NMR tube. H_5IO_6 solution in CD_3CN (2.3 mg in 300 μL, 0.01 mmol) was added if required, then tht$AuBr_3$ solution in CD_3CN (200 μL, 0.01 M, 0.002 mmol) if required. The reaction was followed ^{1}H and/or ^{19}F NMR spectroscopy.

Iodonium Trapping

Under air, trap in solvent (500 μL) and aryl silane (26 mg, 0.10 mmol) were added to a screw cap vial, followed by H_5IO_6 solution in CD_3CN (25 mg in 300 μL, 0.11 mmol) then tht$AuBr_3$ solution in CD_3CN (200 μL, 0.01 M, 0.002 mmol). The reaction was stirred in a vial at rt for 4 h before filtering through cotton wool and acquiring ^{1}H and ^{19}F NMR spectra.
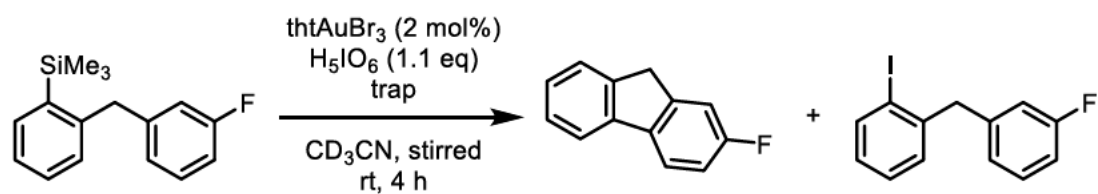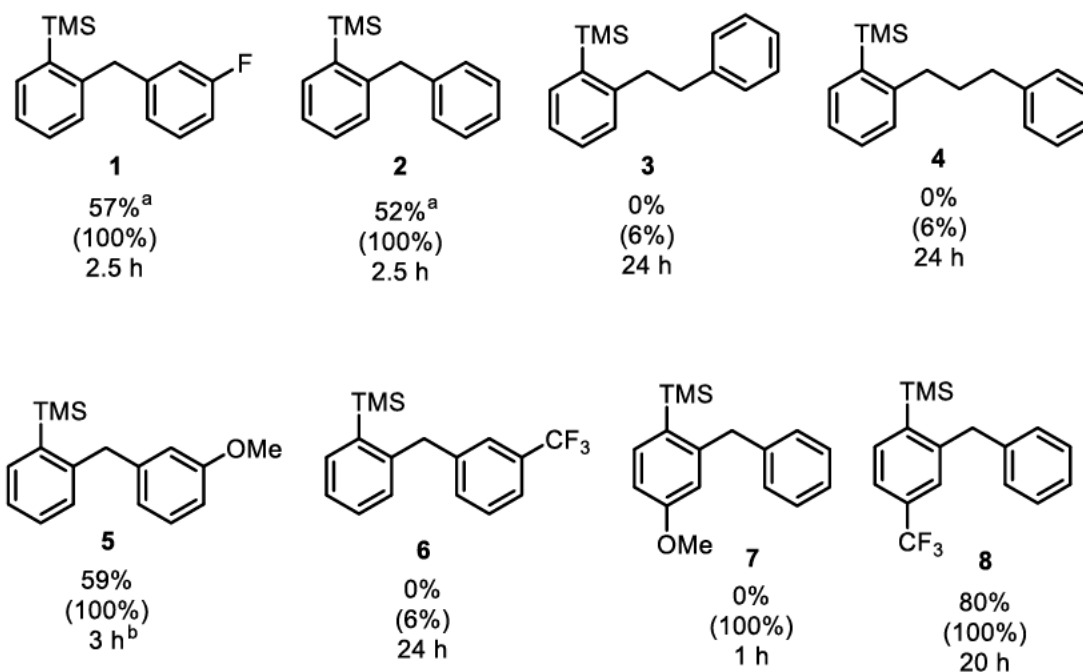
Trap	NMR Yield Product (%)	NMR Yield ArI (%)
none	57	26
p-fluoro-α-methyl styrene (1.1 eq)	-	-
Allyl trimethylsilane (1.1 eq)	-	-
Toluene (20 eq)	45	22
Phenol (20 eq)	-	-
Anisole (20 eq)	70	4
Anisole (20 eq)[a]	70	6
Anisole (20 eq)[b]	71	6

[a]4 °C, 7 days

[b]50 °C, 30 mins

Substrate Scope

Under air, anisole (1.0 mL) and aryl silane (0.50 mmol) were added to a screw cap vial, followed by H_5IO_6 solution in CD_3CN (125 mg in 3.0 mL, 0.55 mmol) then thtAuBr$_3$ solution in CD_3CN (1.0 mL, 0.01 M, 0.01 mmol). The reaction was stirred in a vial at rt before separation between water (50 mL) and ether (50 mL), the water layer was extracted with ether (2 × 50 mL). Organic layers were combined and dried over Na_2SO_4 before being concentrated *in vacuo*. The crude was purified by flash silica gel column chromatography (petroleum ether (40 – 60 °C)).

1
57%[a]
(100%)
2.5 h

2
52%[a]
(100%)
2.5 h

3
0%
(6%)
24 h

4
0%
(6%)
24 h

5
59%
(100%)
3 h[b]

6
0%
(6%)
24 h

7
0%
(100%)
1 h

8
80%
(100%)
20 h

Isolated yield, conversion in parentheses.

[a]Isolated impure, yield calculated using dimethyl sulfone as an internal standard.

[b]Second addition of thtAuBr$_3$ (2 mol%) at 1.5 h.

5.4 - References

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