GOLD(III) MEDIATED BIARYL FORMATION OF UNFUNCTIONALISED AROMATICS AND THE TOTAL SYTHESIS OF (±)-POLYSIPHENOL

A thesis submitted by

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ABSTRACT

This thesis describes the studies towards the functionalisation of arenes using gold(III) chloride and the total synthesis of (±)-polysiphenol, a naturally occurring bromophenol, isolated from *Polysiphonia urceolata*, a red alga of the family of Rhodomelaceae found in Chinese coastal waters.

The first chapter details the optimisation of the auration reaction of benzene and trapping of the intermediate species, $PhAuCl_2$, with the use of a coordinating ligand. The isolation and characterisation of the aurated species, $PhAuCl_2 \cdot lut$, is also discussed. The intermediate aurated species is utilised to achieve oxidative homocoupling, yielding biphenyl. The reaction is further expanded to a number of electron rich and mildly electron deficient aromatics. Attempts to render the reaction catalytic and to achieve oxidative heterocoupling are also described.

The second chapter illustrates the total synthesis of (±)-polysiphenol, *via* a biomimetically inspired highly regioselective intramolecular oxidative coupling route. The two bromine atoms are installed prior to oxidative coupling, preventing further oxidation to a planar aromatized phenanthrene, however attempts to brominate the aromatic rings following oxidative coupling, have also been carried out. The first synthesis of 1,1'-ethane-1,2-diylbis(2,5,6-tribromobenzene-3,4-diol), another natural product belonging to the family of *Rhodomelaceae*, is also described.

The last section of each chapter details the experimental protocols and spectral characterisation of all the compounds synthesised in this study.

CONTENTS

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ABBREVIATIONS

Ac	acetyl
Anal.	analysis
app.	apparent (NMR)
aq.	aqueous
Ar	aryl
b.p.	boiling point
br	broad
Bu	butyl
Calcd.	calculated
cat.	catalytic
CI	chemical ionization
d	doublet
1,2-DCE	1,2-dichloroethane
DCM	dichloromethane
DMF	*N, N*-dimethyl formamide
DMSO	dimethyl sulfoxide
EI	electron ionisation
eq.	equivalent
Et	ethyl
g	gram(s)
GC	gas chromatography
h	hour(s)
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometery
Hz	Hertz
I	iso
IR	infrared
J	coupling constant
2,6-lut	2,5-lutidine
m	multiplet (NMR)
m	milli

m	*meta*
M	molar
Me	methyl
MHz	megaHertz
min	minute
mol	moles(s)
m.p.	melting point
MS	mass spectrometry
m/z	mass to charge ratio
NBS	*N*-bromosuccinimide
nm	nanometer
NMR	nuclear magnetic resonance
p	*para*
Ph	phenyl
PIFA	(trifluoroacetoxy)iodobenzene
ppm	part per million
Pr	propyl
Psi	pounds per square inch
py	pyridine
q	quartet
quin.	quintet
R	general substituent
RT	room temperature
s	singlet
sat.	saturated
t	triplet
t	tertiary
TBCO	2,4,4,6-tetrabromocyclohexa-2,5-dienone
TBHP	*tetra*-butyl hydrogen peroxide
TBME	*tert*-butylmethylether
THF	tetrahydrofuran
TLC	thin layer chromatography
TMG	*tetra*-methylguanidine
TON	turnover number

Tr	trityl
Wrt	with respect to

Chapter 1:

Gold(III)-mediated oxidative coupling of unfunctionalised aromatics

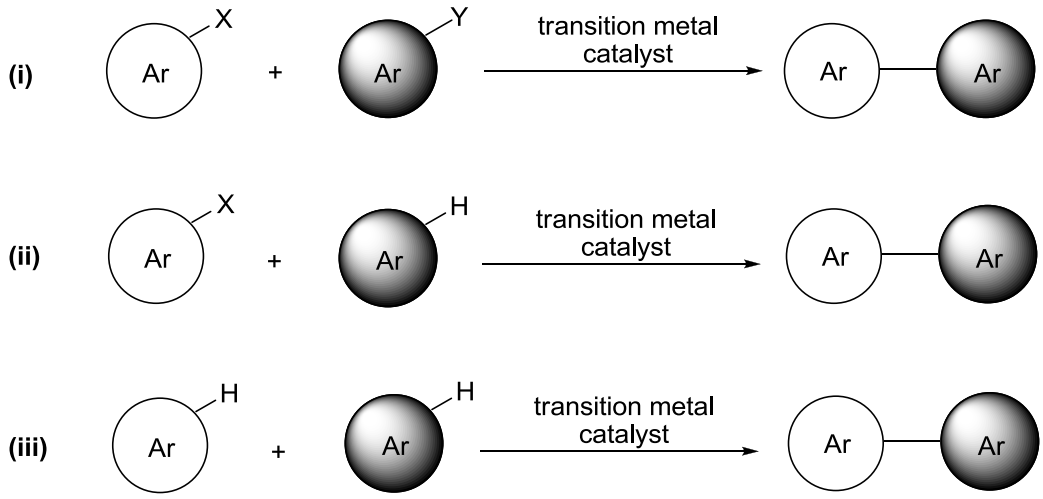
1. INTRODUCTION

The biaryl structural motif is a predominant feature in many pharmaceutically relevant and biologically active compounds as well as natural products.[1] Biaryls can also serve as versatile chiral ligands in synthetic chemistry.[2] It is for these reasons that, for over a century now,[3] chemists have focused their efforts in developing new and more efficient aryl-aryl bond forming methods.

Many methods of preparation already exist in literature but these mainly involve the use of transition metals and the coupling of a nucleophilic unit (Ar-M, where M= SnR_3, MgX, BR_2, ZnX, corresponding to Stille,[4] Kumada,[5] Suzuki[6] and Negishi[7] reactions respectively) with an electrophilic reagent (Ar-X, where X=halogen, sulphonate or diazonium salt).[8-9] The Nobel Prize in Chemistry 2010 was awarded jointly to Richard F. Heck, Ei-ichi Negishi and Akira Suzuki *"for palladium-catalyzed cross couplings in organic synthesis"* (http://www.nobelprize.org/nobel_prizes/chemistry/laureates/2010/), leaving no doubt of the significance of these methods. But whilst they have been highly successful, they suffer from certain drawbacks, those being either the type of substrate which needs to be used (the preparation of which is frequently troublesome since the installation of the activating group(s) often requires several steps), the use of harsh conditions and/or stoichiometric amounts of an expensive or moisture-sensitive organometallic compound, the usual regioselectivity problems as well as the secondary issues of generating waste from reagents, solvents and purifications. So the question remains: can we develop a method which will overcome these limitations and be able to achieve biaryl coupling of unfunctionalised arenes? Herein, we shall examine the evolution of direct arylation and the three main pathways (Scheme 1):

i. where both arenes are functionalised
ii. where one arene is functionalised only (direct arylation)
iii. where neither arene is functionalised

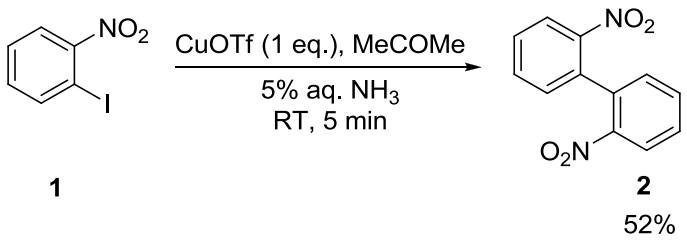
Particular focus will be placed on the latter method, direct arylation *via C-H* activation (oxidative coupling), since in principle, this is the most atom-economic, cost effective and environmentally friendly technique. Methods **(i)** and **(ii)** have been thoroughly reviewed[10-11] in previous years and will only be touched upon.



Scheme 1: The three main pathways of direct arylation

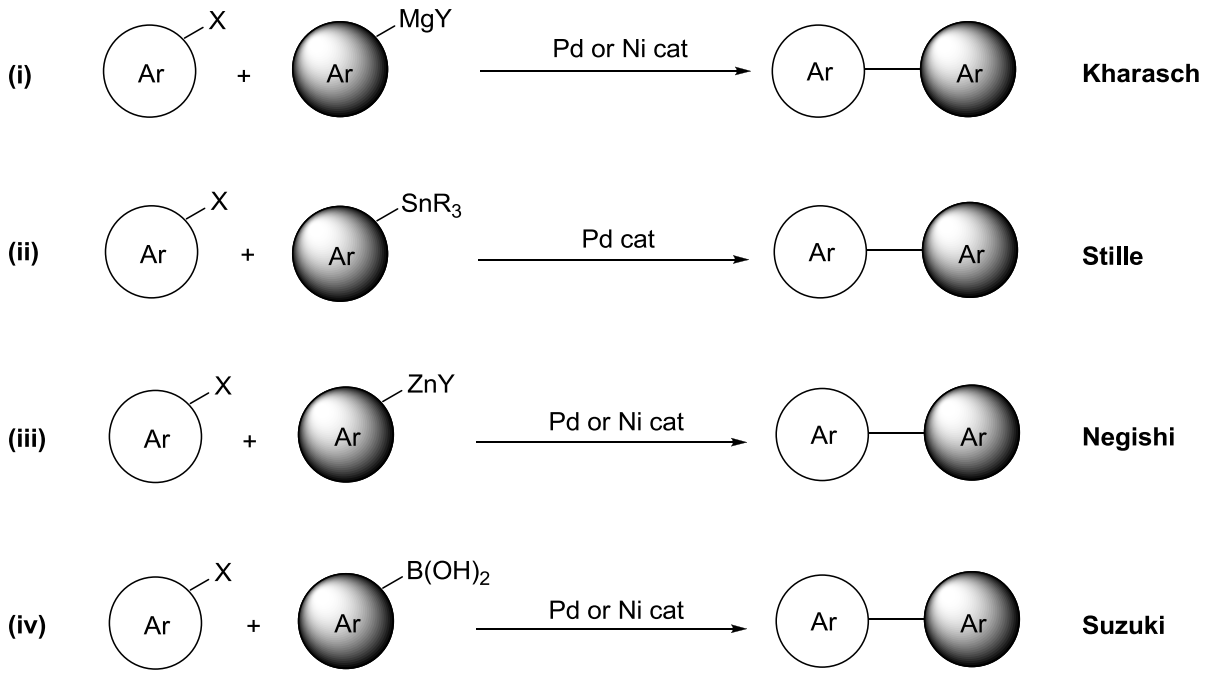
Research on the synthesis of biaryls dates back to 1901 when Ullmann and Bielecki[3] discovered the coupling between two aryl halides in the presence of equimolar amounts of copper powder, copper bronze, copper(I) salts or copper oxides, to form symmetrical biaryls. These reactions usually require long reaction times and high temperatures and often solvents such a DMF (b.p. 153 ^{o}C), pyridine (b.p. 115 ^{o}C) and quinoline (b.p. 110 ^{o}C) are employed to help solubilise the copper salt.

In more recent years, the Ullmann reaction has been improved to employ milder conditions and solvents such as acetone at 20 ^{o}C for 5 minutes (Scheme 2),[12] an example of which is shown in Scheme 2 that produces biaryl **2**. Mostly symmetrical biaryls were obtained, however in some cases, unsymmetrical biaryls have been synthesised by manipulating the different reactivity of various aryl halides.



Scheme 2: An improved Ullmann reaction with reduced reaction times and milder conditions

Whilst the Ullmann reaction employs two aryl halides, more conventional methods of biaryl coupling involve an aryl halide and an aryl Grignard/ arylstannane/ arylboronic acid/ arylzinc derivative in the presence of a Pd or Ni catalyst.[10] These state of the art methods are known as the Kharasch, the Stille, the Negishi and the Suzuki reactions respectively (Scheme 3).



Scheme 3: Traditional methods for biaryl coupling

For the reasons mentioned previously, there has been a shift in focus to using one or even two unfunctionalised arenes to form biaryls. Modern methods to synthesise compounds *via* C-H activation are among the "Wanted List" of top pharmaceutical companies.[13] The most atom-economic approach would involve treatment of the C-H bond as a functional group similar to a carbon-halide bond, and taking it a step further, the coupling of two aryl C-H bonds to give the corresponding biaryl product would seem ideal. However the strength of the C-H bond and the small difference in the electronegativities of carbon (2.5) and hydrogen (2.1) render this reaction thermodynamically disfavoured.[14]

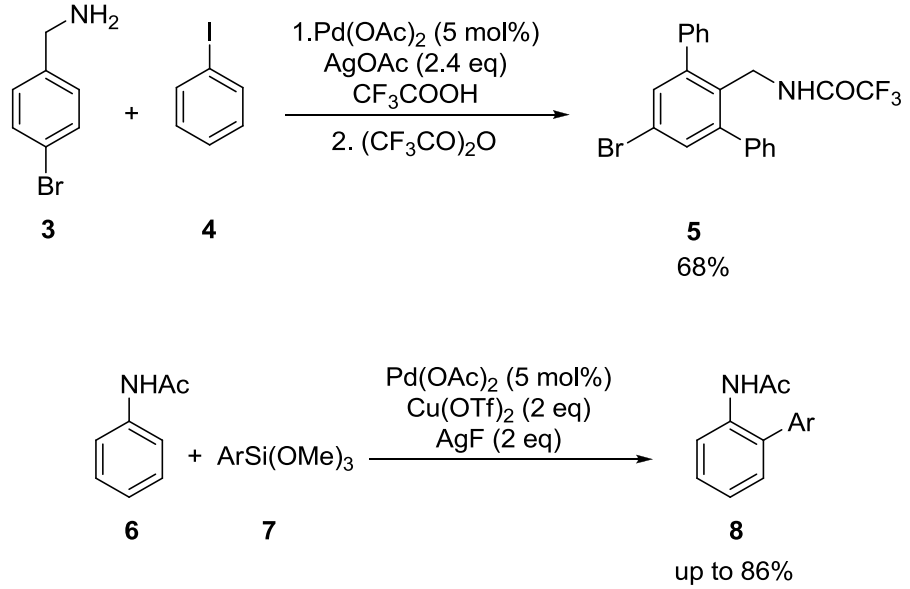
As a compromise the substitution of one preactivated species with a simple arene has been the most widely explored approach has been described in several ways including C-H activation and C-H functionalisation, although the term 'direct arylation' is generally preferred.

1.1 Intermolecular Direct Arylation

The great majority of direct arylation methods have been carried out by Ru, Rh or Pd catalysts with good turnover numbers allowing low catalytic loadings.[15] Usually aryl iodides and bromides are used and electron rich mono-phosphine ligands are often employed. Polar aprotic solvents such as DMF, NMP and even THF are employed at temperatures around 100 ^{o}C. Aryl-aryl bond formation can be either inter- or intramolecular and regioselectivity is induced by either the use of a directing group, by the electronics of the aryl group being used or occasionally by sterics.[11]

1.1.1 Intermolecular aryl-aryl bond formation in the presence of a directing tether

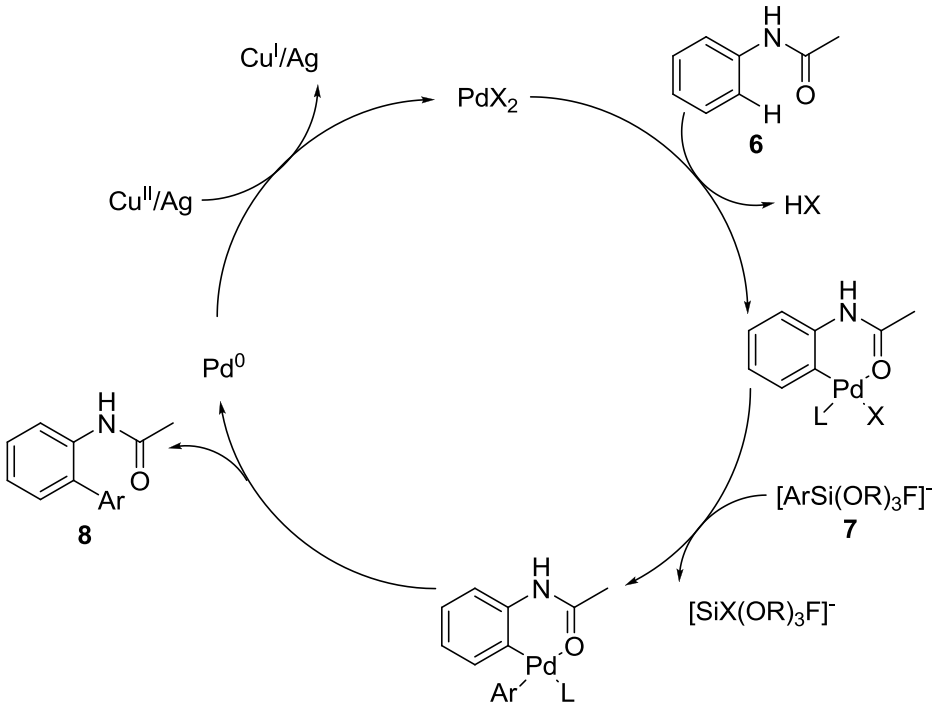
In 2006 Daugulis' group reported the double *ortho*-arylation of primary and secondary benzamines such as **3**, and aryliodides under Pd-catalysis in the presence of CF_3COOH and a silver salt,[16] and in 2007, Shi *et al.* carried out the oxidative *ortho*-arylation of acetanilides *via* Pd-catalysis in the presence of trialkoxyarylsilanes as coupling partners (Scheme 4).[17]



Scheme 4: Double *ortho*-arylation of primary and secondary benzamines and oxidative *ortho*-arylation of acetanilides *via* Pd-catalysis in the presence of trialkoxyarylsilanes as coupling partners

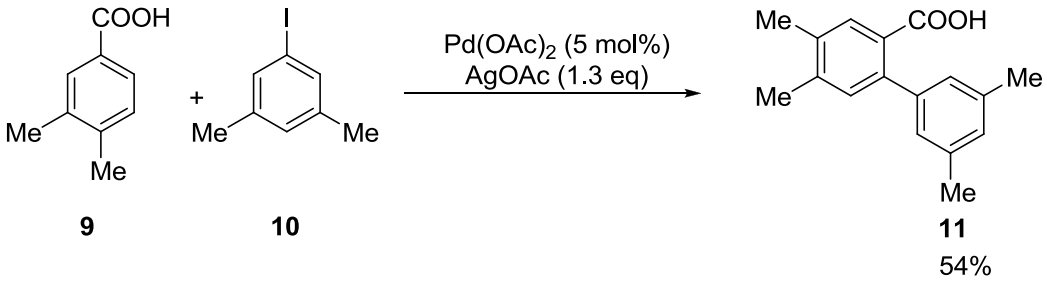
Shi's proposed mechanism involves *ortho* electrophilic attack on acetanilide **6** by a Pd(II) cation directed by the acetamino group and transmetallation of silicate **7** with the aid of fluoride to give a palladacycle. This is followed by reductive elimination to give coupled

product **8**. The catalyst is reoxidised from Pd(0) back to Pd(II) by either Ag(I) or Cu(II) or both, to complete the catalytic cycle (Scheme 5).

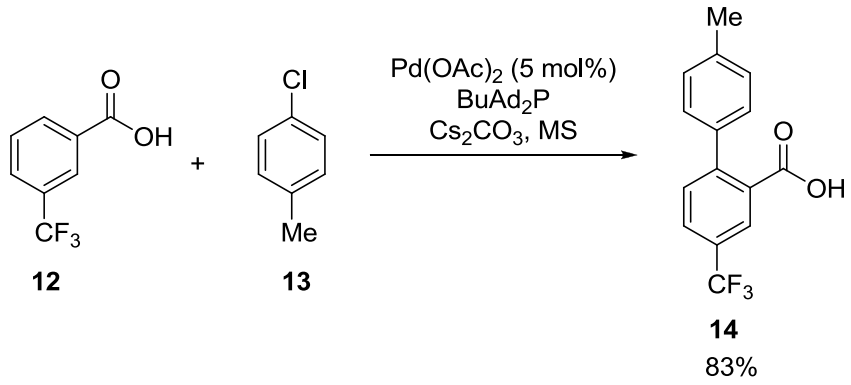


Scheme 5: Shi's proposed mechanism

In 2007, the direct *ortho*-arylation of benzoic acids such as **9** and **12** was reported,[18] by either the use stoichiometric amounts of silver acetate for iodide removal and aryl iodide **10** as the coupling partner (Scheme 6), or aryl chlorides **13**, caesium carbonate as the base, *n*-butyl-di-1-adamantylphosphine as ligand and DMF as the solvent with molecular sieves (Scheme 7). This development constitutes a milestone for the coupling of benzoic acids, as these previously needed to be protected, *ortho*-lithiated, transmetallated and deprotected, a process which required several steps.

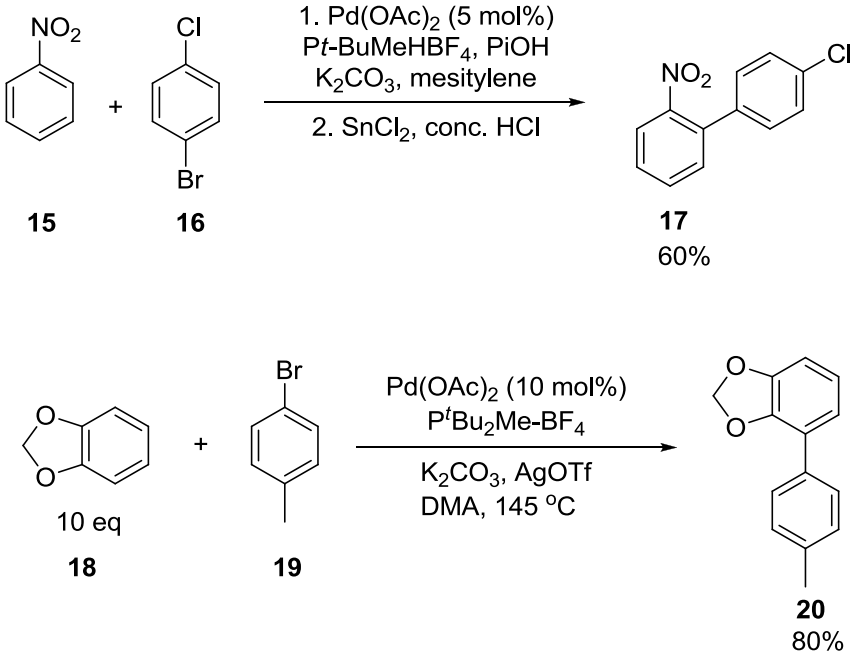


Scheme 6: Direct *ortho*-arylation of benzoic acids



Scheme 7: Direct *ortho*-arylation of aryl chlorides

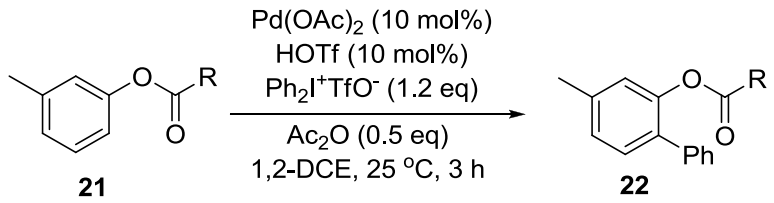
The late Keith Fagnou and his group have demonstrated the direct arylation of nitro-substituted aromatics such as **15** with aryl-halide **16** using 5 mol % $Pd(OAc)_2$ and P^tBuMe-HBF_4, as well that of benzodioxole **18** with bromide **19** using 10 mol % $Pd(OAc)_2$, 10-30 mol % of either P^tBu_2Me-BF_4 or PCy_3-BF_4, 1 equivalent of AgOTf, and 2 equivalents of K_2CO_3 in DMA at 145 °C (Scheme 8).[19]



Scheme 8: direct arylation of nitro-substituted aromatics with aryl-halides and benzodioxoles with bromides

Previously, in 2004, Xiao and co-workers have reported the Pd(II)-catalyzed C-H activation and aryl-aryl coupling of phenol esters,[20] where the ester moiety acts as the directing group

and directs at the *ortho* position (Scheme 9). Stirring solutions of phenol esters with 1.2 equivalents of Ph_2IOTf, 10 mol % $Pd(OAc)_2$ and 10 mol % HOTf in 1,2-DCE at room temperature for 3 hours afforded the *ortho*-arylated product. Addition of 0.5 equivalents of Ac_2O made the reaction insensitive to moisture.

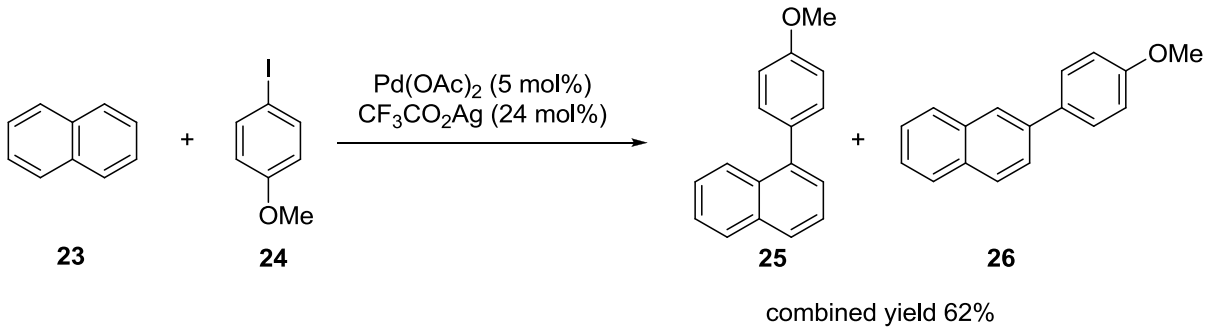


Scheme 9: Pd(II)-catalyzed C-H activation and aryl-aryl coupling of phenol esters

1.1.2 Intermolecular Direct Arylation in the absence of a directing tether

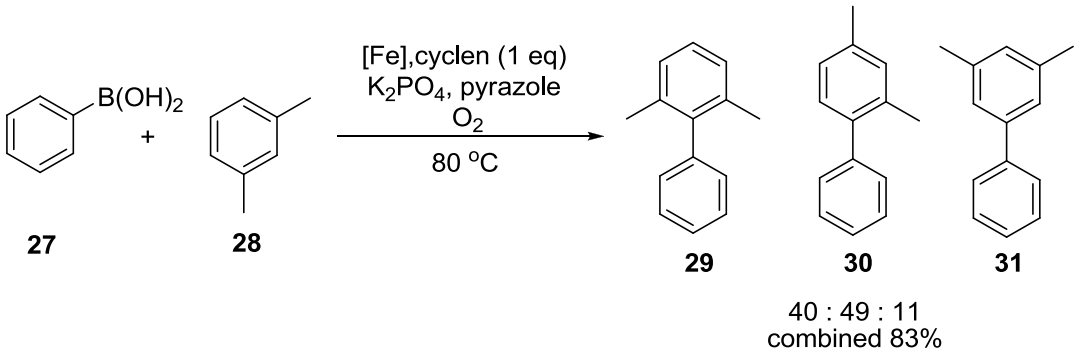
These couplings usually employ an unfunctionalised arene and an aryl halide/boronic acid/carboxylic acid in the presence of a catalyst, namely Pd, Rh or even Cu and they are the most common form of direct arylation.

A phosphane-free arylation of naphthalene (**23**) and benzene with aryl halides such as **24** in the presence of catalytic $Pd(OAc)_2$ and stoichiometric amounts of CF_3CO_2Ag has been described by Lu and Qin (Scheme 10).[21] A Pd(II)/Pd(IV) mechanism is proposed involving initial attack of the highly electrophilic Pd(II) complex on an aryl C–H bond to give an aryl-Pd(II) intermediate followed by oxidative addition of the aryl halide affording a diarylpalladium(IV) complex.



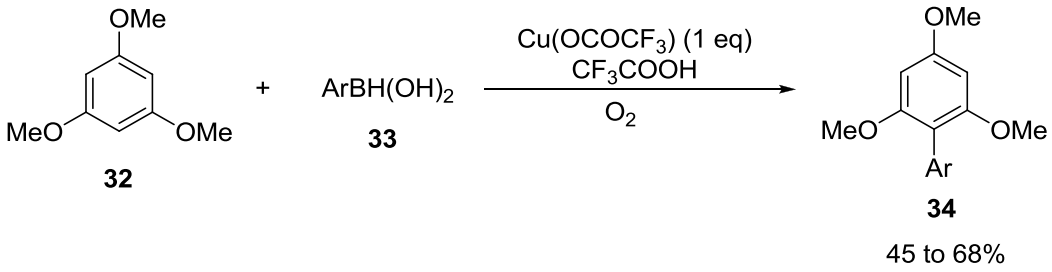
Scheme 10: Phosphane-free arylation of naphthalene with aryl halides

In 2008 Yu *et al*.[22] disclosed the first examples of iron-mediated direct arylations and showed that $Fe_2(SO_4)_3{\cdot}7H_2O$ in the presence of 1,5,7,10-tetraazacyclododecane (cyclen) and base can affect direct arylation at the relatively low temperature of 80 ^oC (Scheme 11). Surprisingly, pyrazole as an additive was necessary; however, its role remains unclear at this point. Good yields were obtained (up to 83%) with substrates such as **27** and **28** but lower yields were observed, for example, with *ortho*-substitution on the boronic acid. By contrast, steric hindrance on the arene led to greater reactivity. Molecular oxygen was a sacrificial oxidant in the reactions.



Scheme 11: Iron-mediated direct arylation

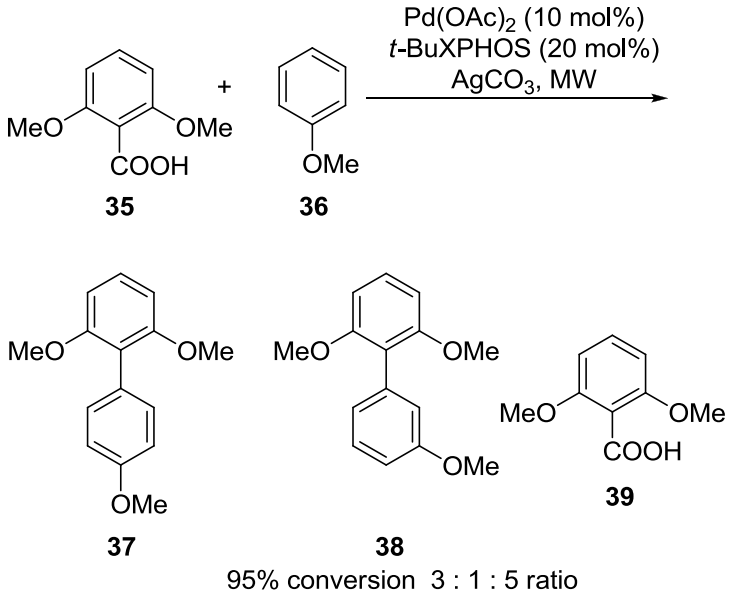
In 2008 Itami and co-workers[23] used an anionic ligand approach for C–H/C–B coupling *via* copper-catalysis. Substituted aryl **32** could be arylated using the boronic acid **33** in moderate yields (Scheme 12). Perarylated *N*-pyrrole and doubly arylated *N*-methylindole could be furnished by this method also. This good turnover by copper-catalysis suggests that the role of copper in other Pd-catalysed oxidative couplings may not be limited to the oxidation of Pd(0).



Scheme 12: C–H/C–B coupling *via* copper-catalysis using an anionic ligand approach

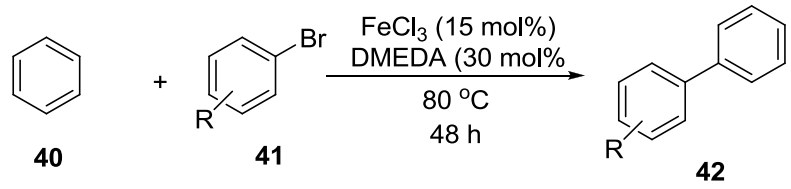
The Crabtree group[24] described the palladium-catalysed decarboxylative coupling of aromatic acids such as **35** with unactivated arenes such as **36** in moderate to good yield under

microwave conditions (Scheme 13). They also report an example using the 2-pyridine directing group.



Scheme 13: Palladium-catalysed decarboxylative coupling of aromatic acids

In 2010, the Lei group reported the iron-catalysed direct arylation of unactivated arenes, the simplest of them being benzene (**40**) with aryl halides (iodides, bromides and chlorides) such as bromide **41** (Scheme 14).[25]



Scheme 14: Iron-catalysed direct arylation of benzene using aryl bromide

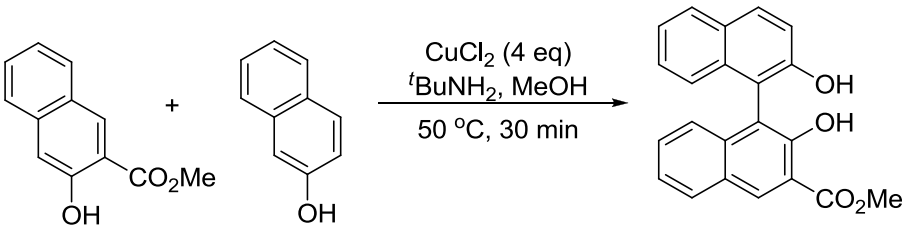
1.2 Biaryl formation *via* coupling of unfunctionalised arenes

This type of biaryl coupling is inherently the most potentially efficient and atom-economic of the three coupling modes and hence is the main focus of much research. However, though elegant, it is also the most challenging due to the great strength and lack of polarity of the C-H bond. The field is mainly dominated by Pd catalysis, nevertheless there exist other methods which even though not as widely known, give good to excellent results.

Herein we shall discuss the recent developments in this field and some state-of-the-art methods that exist, both for homo- and heterocoupling of arenes. Even though there exist methods for the coupling of heteroaromatics,[11] this section will review benzenoid reactions only.

Oxidative dimerization of phenols is one of the most well-known reactions for the formation of aryl-aryl bonds, and in most cases (depending on the reaction conditions) it is known to proceed *via* a radical mechanism.[12,26] However, cross-coupling of phenols as well as coupling of arenes which do not contain the hydroxyl moiety have proved to be more troublesome.

An early example of cross-coupling of phenols was provided by Hovorka and co-workers[27] who achieved the oxidative cross-coupling of naphthols such as **43** and **44** with excess $CuCl_2$ and either $^tBuNH_2$ or $EtNH_2$ in anaerobic methanol to obtain high yields of the coupled products, provided one component contained an electron-withdrawing ester moiety (Scheme 15).



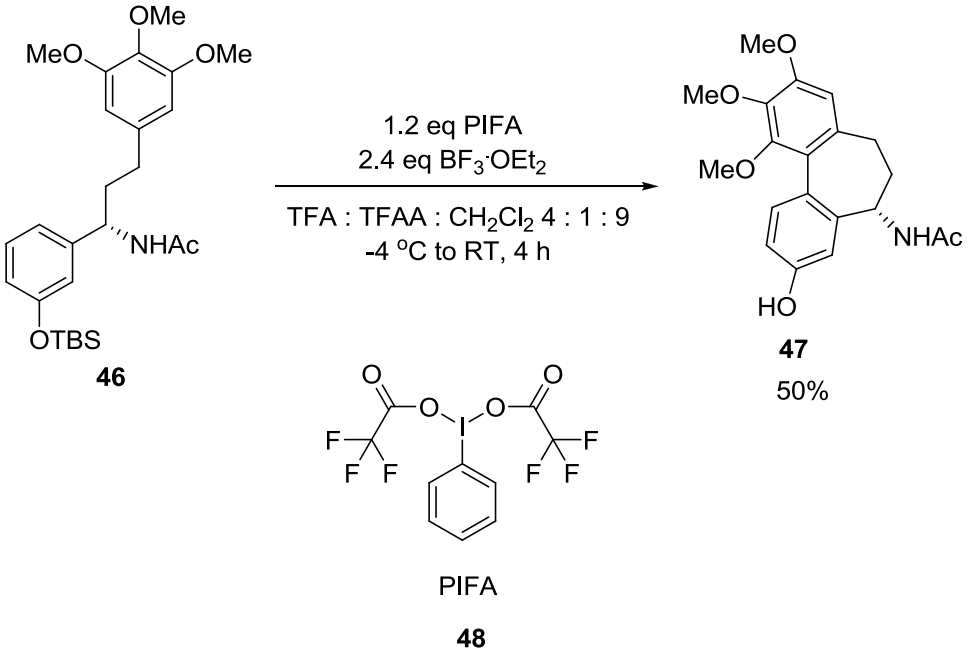
43 **44** **45**

91%

Scheme 15: Cu(II)-mediated oxidative coupling of naphthols

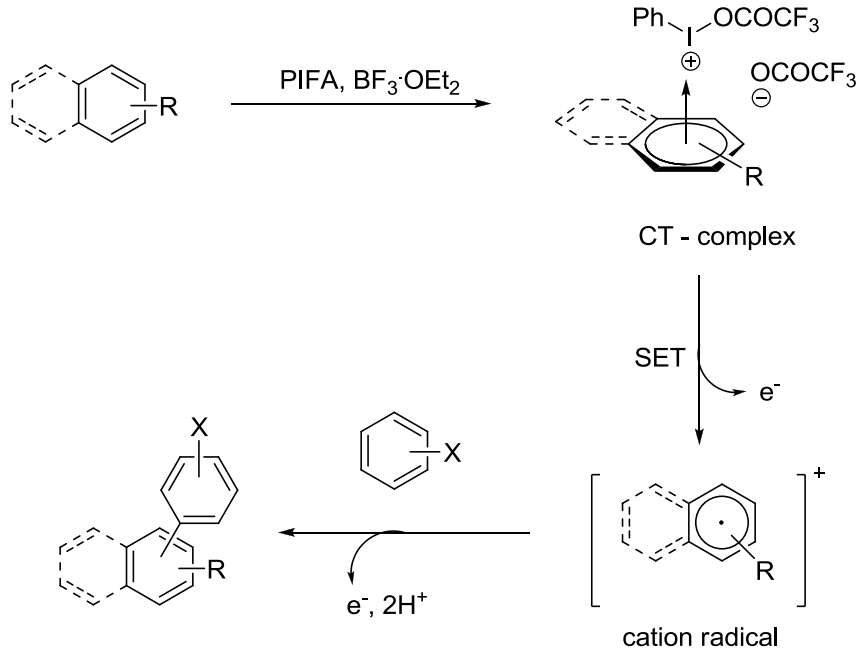
Radical oxidative biaryl coupling has also been achieved using the hypervalent iodine 'PIFA' reagent ((trifluoroacetoxy)iodobenzene, **48**). There have been numerous reports of intra- and

intermolecular coupling, and this method has been employed in the synthesis of natural products containing the biaryl motif (Scheme 16).[28]

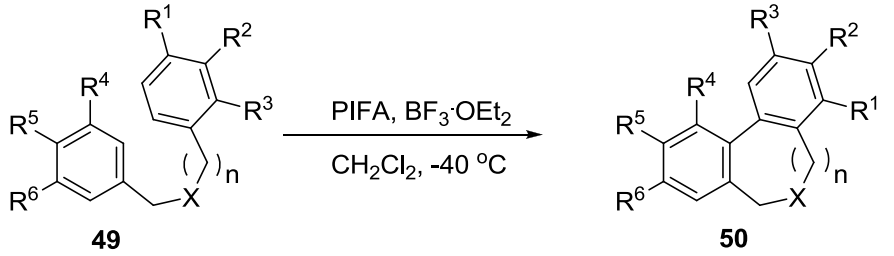


Scheme 16: Radical oxidative biaryl coupling using the hypervalent iodine 'PIFA' reagent

In this process, PIFA is proposed to coordinate to the electron-rich arene to form a π complex. After single electron transfer occurs, the cationic radical undergoes nucleophilic attack by the second arene to provide the coupled product (Scheme 17). By this method, several electron-rich arene systems have been coupled (Scheme 18).[29]



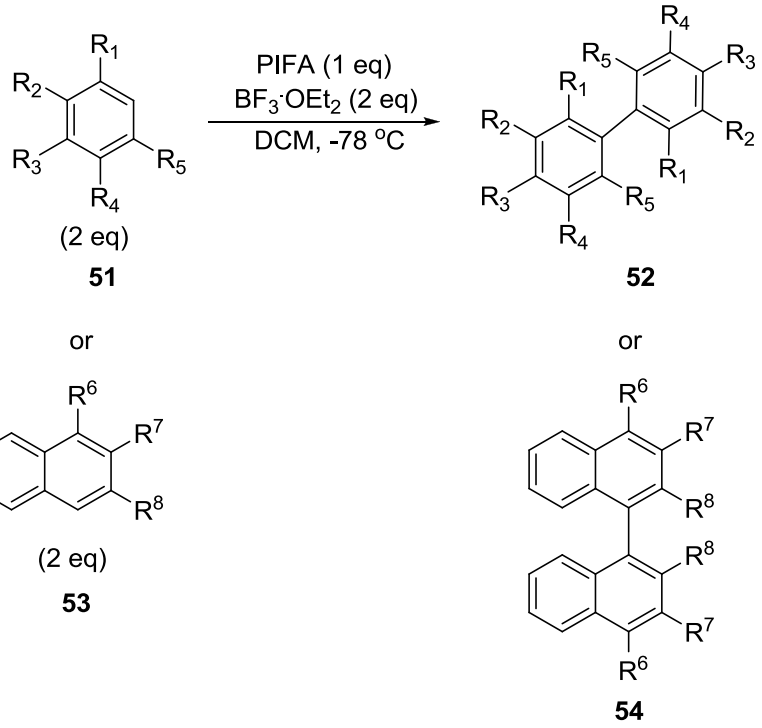
Scheme 17



R^{1-6} = H, OMe, OCH_2O, OAc etc.; X = CH_2, $NCOCF_3$, SiR_2, SO, O etc.; n = 0,1

Scheme 18: Single electron transfer mechanism for PIFA oxidative coupling

One noteworthy achievement using the PIFA-BF_3·OEt_2 reagent combination, is that of coupling of highly substituted arenes[30] to produce various alkylbiphenyls and binaphthyls (Table 1). Oxidation of inactive monoalkylbenzenes such as toluene and *tert*-butylbenzene did not proceed under these conditions, but reactions of mesitylene, triethylbenzene, xylene (entries 1-3) and alkylnaphthalenes (entries 8-12) with PIFA–BF_3·Et_2O proceeded smoothly to afford the corresponding biphenyl and binaphthyl compounds including tetra-*ortho*-substituted biaryls in moderate to high yields.



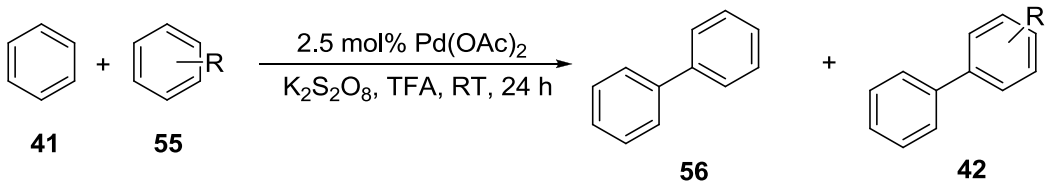
Entry	R^1	R^2	R^3	R^4	R^5	Yield (%)[a]
1	Me	H	Me	H	Me	90
2	Et	H	Et	H	Et	74
3	Me	H	Me	H	H	75[b]
4	Me	H	Me	H	I	84
5	Me	Me	Me	H	H	64[c]
6	Me	Me	H	Me	Me	46
7	Me	Me	Me	Me	Me	20

	R^6	R^7	R^8	
8	Me	H	H	82
9	Et	H	H	89
10	^{n}Bu	H	H	80
11	Me	Me	H	94
12	Me	H	Me	96

a. Isolated yields.
b. 10 eq. of substrate used at -40 °C
c. 10 eq. of substrate used at 0 °C

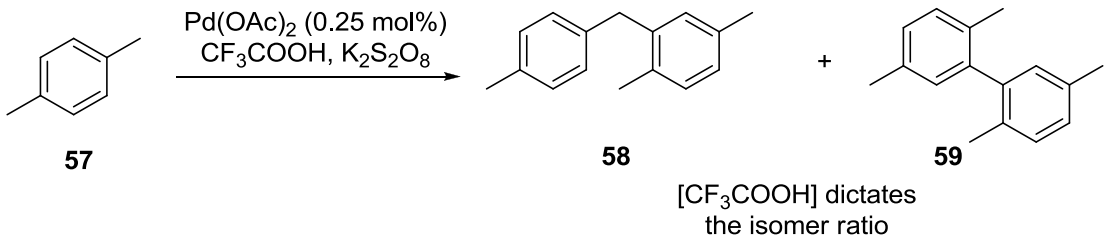
Table 1

Moving away from radical mechanisms, VanHelden and Verberg disclosed the formation of biphenyl from benzene by using a stoichiometric amount of $PdCl_2$.[31] More recently,[32] formation of unsymmetrical biaryls from simple arenes such as benzene (**41**) and several mono-substituted arenes (**55**) has been achieved successfully in a catalytic system of $Pd(OAc)_2/CF_3CO_2H(TFA)/K_2S_2O_8$ just by tuning the concentrations of arenes and TFA under mild conditions (Scheme 19).



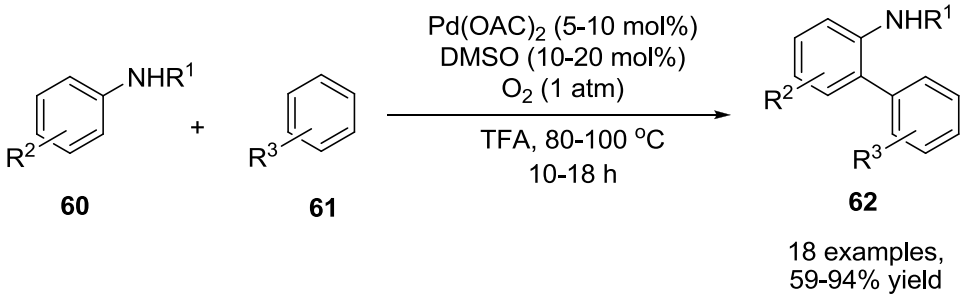
Scheme 19: Formation of unsymmetrical biaryls from simple arenes

In 2007 Lu *et al.* reported the Pd(II)-catalysed homocoupling of *p*-xylene **57** in CF_3COOH, with excellent regioselectivity.[33] Diarylmethane **58** was formed as the undesired side product, however formation of this product could be suppressed by tuning the concentration of CF_3COOH (Scheme 20). Generally, a low concentration of TFA resulted in more of the desired product being formed, whilst higher TFA concentrations afforded more of the undesired product.



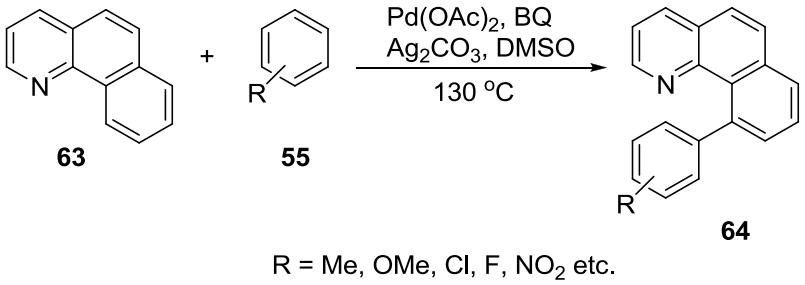
Scheme 20: Pd(II)-catalysed homocoupling of *p*-xylene

Buchwald *et al.*[34] have developed the *ortho*-arylation of anilides such as **60** to form biphenyls **62** in the presence of $Pd(OAc)_2$ in TFA under an atmosphere of O_2 and 10-20% DMSO and with no need for a metal co-catalyst such as Cu or Ag (Scheme 21).



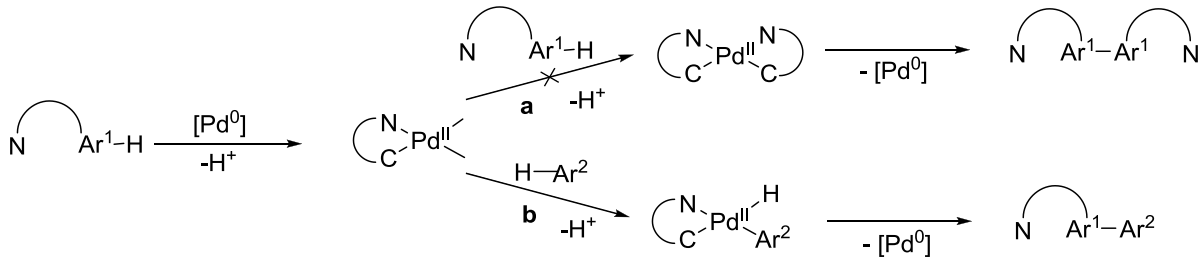
Scheme 21: *Ortho*-arylation of anilides to form biphenyls

Sanford and Hull have reported a method for Pd-catalysed oxidative cross-coupling of arenes based on ligand-directed C-H activation (Scheme 22).[35] It was demonstrated in previous work that treatment of heterocyclic arenes with $Pd(OAc)_2$ resulted in facile, regioselective C-H activation to form a cyclometallated intermediate which upon treatment with an arene, cross-couples to give the desired biaryl product.



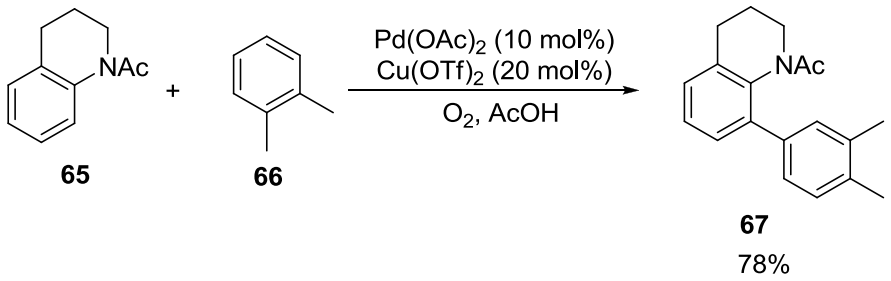
Scheme 22: Pd-catalysed oxidative cross-coupling of arenes based on ligand-directed C-H activation

In designing the reaction Sanford and co-workers utilised the knowledge that mono-cyclometalated Pd(II) products are typically unreactive toward a second ligand-directed C-H activation event under Pd(0/II) conditions, which limits competitive homocoupling (Scheme 23, path a). As such, the desired cross-coupling between the arene containing the directing ligand and a simple arene is possible, since the cyclopalladated complex has participated in a second, nondirected C-H activation reaction with Ar-H (Scheme 23, path b).



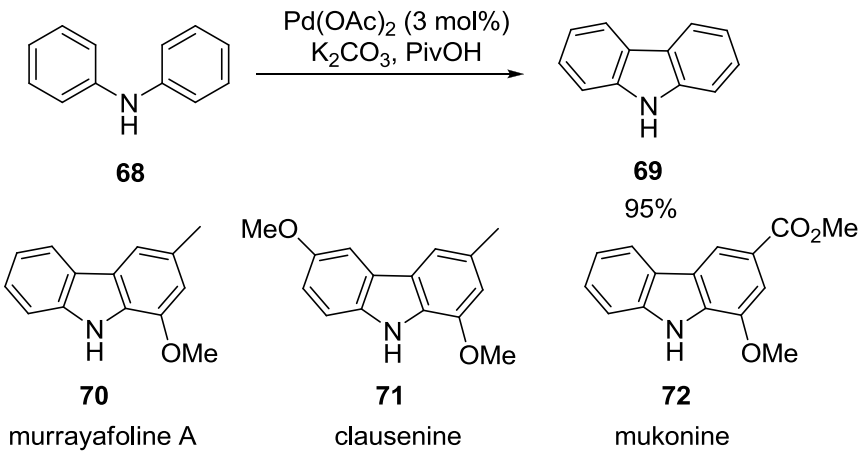
- **Scheme 23:** Suppressing homocoupling

In a 2005 publication, Shi and co-workers reported an environmentally friendly route to the construction of biaryls.[36] Biologically active molecules have been put together using methods completely free of organohalogen and organometallic components such as **65** and **66**, but based on catalytic amounts of $Pd(OAc)_2$, and $Cu(OTf)_2$ as the co-oxidant. Directing groups such as the *N*-acetyl group were used together with the steric hindrance of the aryl coupling partner to achieve regioselectivity (Scheme 24).



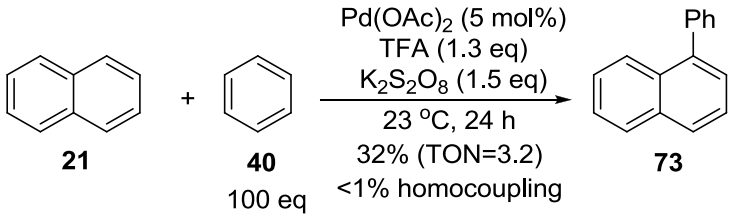
Scheme 24: Construction of biaryls using organohalogen and organometallic-free components

A particularly interesting example has been provided by Fagnou *et al.* in 2008 who reported the intramolecular Pd(II)-catalysed oxidative biaryl synthesis in air with pivalic acid as the solvent, which has been applied to the synthesis of a number of natural products[37] such as murrayfoline A (**70**), clausenine (**71**) and mukonine (**72**) (Scheme 25).



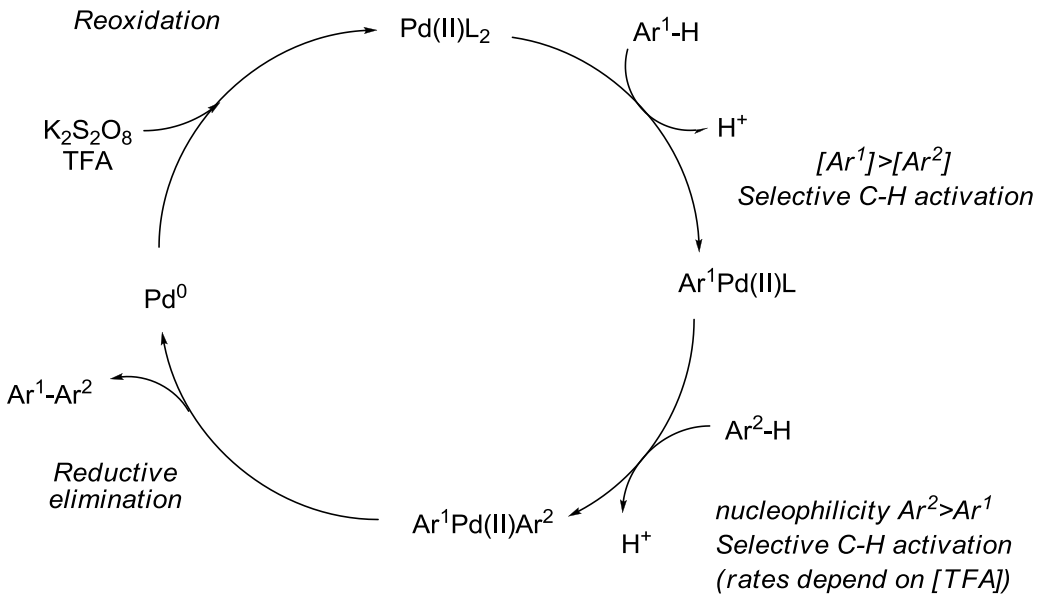
Scheme 25: Pd(II)-catalysed oxidative biaryl synthesis in air with pivalic acid as the solvent and its use to the synthesis of natural products

In 2006 Lu and co-workers[38] reported the $Pd(OAc)_2$-catalysed cross coupling of benzene (**40**) and naphthalene (**21**) in the presence of TFA at room temperature with TON of 3.2. Isotopic labelling studies suggested that the reaction proceeds by a rate-determining S_EAr palladation of benzene (Scheme 26). The lower the concentration of TFA the higher the ratio of heterocoupled: homocoupled product was.



Scheme 26: $Pd(OAc)_2$-catalysed cross coupling of benzene (**40**) and naphthalene (**21**) in the presence of TFA

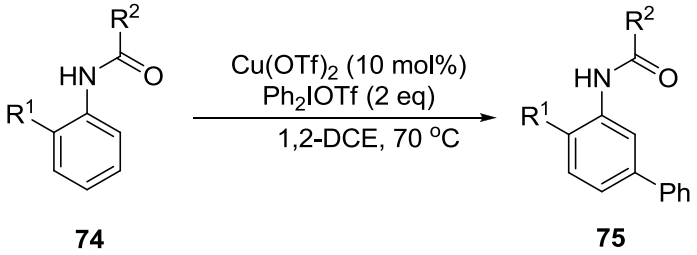
The proposed mechanism (Scheme 27) involves (i) first, electrophilic attack of $Pd(II)L_2$ on Ar^1H, which is in excess in the mixture, mainly produces an arylpalladium(II) species, $Ar^1Pd(II)L$; (ii) the second electrophilic attack of $Ar^1Pd(II)L$ on the electron-rich arene Ar^2H generates the species $Ar^1Pd(II)Ar^2$; (iii) after a reductive elimination, the unsymmetrical biaryl Ar^1Ar^2 is produced, and Pd(0) is formed as well; (iv) finally, Pd(0) is reoxidised by an oxidant in the presence of HL to give $Pd^{II}L_2$ again and the catalytic cycle is complete.



Scheme 27: Proposed catalytic cycle

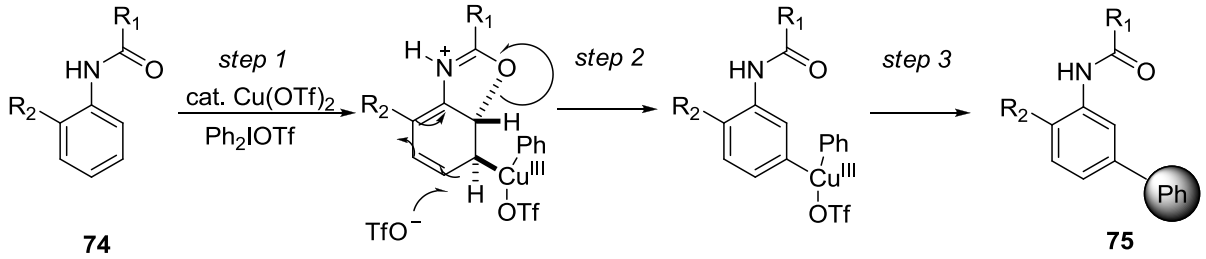
In this process, the use of TFA, in comparison with AcOH, improves the reactivity of Pd(II) catalysts strongly. In contrast, decreasing the amount of TFA mainly leads to the less electrophilic catalyst $Ar^1Pd^{II}L$, which displays preferential attack of the electron-rich arene in step (ii). However, if the difference in arene activity between Ar^1H and Ar^2H is not large enough or the concentration of TFA is too high, the homocoupling product Ar^1Ar^1 from the relatively electron-poor arene Ar^1H will be produced in those reactions. Therefore, through the concentration selection of step (i) and the activity selection of step (ii), an unsymmetrical biaryl is obtained from this cross-coupling reaction.

One of the most recent, and perhaps exciting, developments in the field of C-H activation is the work published by Gaunt *et al.* in Science.[39] It describes the development of a reactivity concept for a metal-catalyzed aromatic C–H bond functionalisation strategy that selectively generates the elusive *meta* isomer **75** (Scheme 28). The outcome is not predicted by the conventional rules associated with electronic factors, directing groups, or steric effects, and provides direct access to the *meta* isomer on highly versatile electron-rich aromatic structures. The process is simple, proceeds under mild conditions, uses inexpensive copper catalysts, and forms valuable products that would be difficult to synthesize by other methods.



Scheme 28: M*eta*-Selective Copper-catalyzed C–H bond arylation

The proposed mechanism (Scheme 29) involves the highly electrophilic Cu(III)-aryl species activating the aromatic ring sufficiently to permit an *anti*–oxy-cupration of the carbonyl group of an acetamide across the 2,3 positions on the arene ring (step 1). This dearomatizing transformation would place the Cu(III)-aryl species at the *meta* position, and rearomatizing deprotonation (step 2) followed by reductive elimination (step 3) would deliver *meta* product **75**.



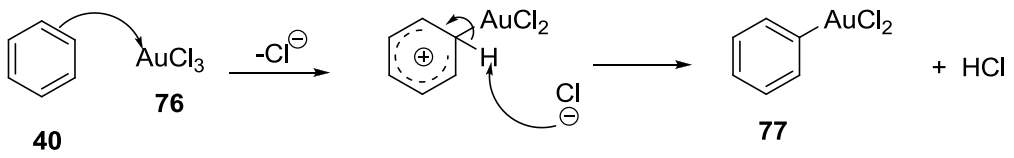
Scheme 29: Proposed mechanism leading to *meta*-selectivity

1.3 Using Gold for C-H activation

It is evident from the literature presented above that coupling of unfunctionalised arenes *via* C-H activation constitutes a challenge for chemists. From the myriad of examples where one of the two coupling partners is pre-activated, compared to a hand-full of examples where both coupling partners are unfunctionalised, one can see the need for further development in this field.

Interestingly, the use of gold to achieve C-H activation of unfunctionalised arenes was reported as early as 1931 by Kharasch and Isbell.[40] They reported the reaction between benzene and gold(III) chloride (in actual fact a dimer, $(AuCl_3)_2$, in both the solid and vapour state) which yielded phenylauryl dichloride ($PhAuCl_2$) as "beautiful, long, narrow crystals".

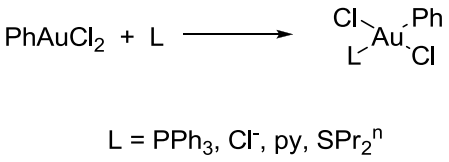
Despite the authors not proposing a mechanism it seems reasonable to presume that the reaction proceeds *via* electrophilic aromatic substitution, gold(III) chloride **76** being attacked by the aromatic ring to yield a Wheland intermediate. Aromaticity is then restored by loss of the proton which is picked up by the chloride anion to produce HCl (Scheme 30).



Scheme 30: Kharasch and Isbell's proposed mechanism of electrophilic substitution

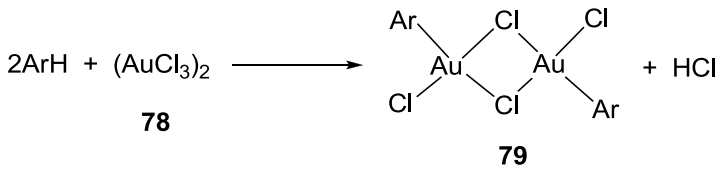
Kharasch found the product to be more unstable than the products of nitration, halogenation and mercuration, readily decomposing to the mono-, di- and tetrachloro-substituted phenyls. The reaction was performed under anhydrous conditions due to the hygroscopic nature of the $AuCl_3$ and it was found that in order to obtain the desired aryl gold intermediate and not any chlorinated aryl product (presumably by reductive elimination from $PhAuCl_2$), the anhydrous gold(III) chloride had to be added slowly to a large quantity of dry benzene and the reaction stopped at the point where the brown precipitate was formed, by addition of ether. Product **77** was characterised by microanalysis (Calculated for $Au(C_6H_5)Cl_2$: Au, 57.14%. Found: Au, 57.17%).

Nothing more about this reaction was reported for forty years until 1972,[41] when Liddle and Parkin reinvestigated the use of $AuCl_3$ for electrophilic auration of aromatics. The instability of the arylgold(III) dichloride led them to investigate the complexation of the original phenylauryl dichloride with coordinating ligands L (Scheme 11), the stability of the complex decreasing along the series L = PPh_3 > Cl^- > py > SPr_2. This was carried out by addition of the ligand to the unstable product of the auration reaction ($PhAuCl_2$) and the products were found to be monomeric (Scheme 31).



Scheme 31: Different ligands used to increase the stability of the gold(III) complex

Following this, a paper questioning the results of both the above research groups, was published in 1976.[42] It reported the reaction between gold(III) chloride (**78**) and a series of substituted benzenes in the absence of stabilizing ligands to yield thermally stable *para*-substituted arylgold(III) dichlorides **79** formed by electrophilic substitution on the aromatic ring (Scheme 32). Characterisation of these products by molecular weight determination showed that these were in fact dimeric and not monomeric as suggested by Kharasch *et al.*[40] back in 1931, probably involving intramolecular gold-chlorine coordination as deduced by IR data.

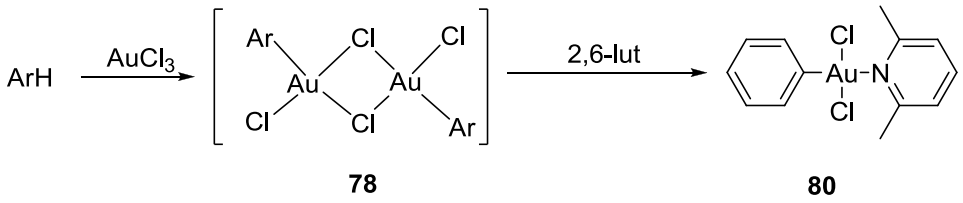


Scheme 32: The dimeric form of gold(III) chloride

This group also examined the properties of these dimeric complexes and found that they were indeed more thermally unstable than their ligand-coordinated equivalents, decomposing to give mono, di and tetra-chlorosubstituted aryl products. The low preparative yields were also attributed to the thermal instability and it was believed that if the reaction was allowed to proceed any further then the intermediate decomposed to the chlorosubstituted aryls. This is

in agreement with the findings of Kharasch *et al.*[40] Furthermore, it was found that addition of coordinating ligands to the dimeric products yielded the stable complexes of the type $ArAuCl_2 \cdot L$, identical to those described by Liddle and Parkin[41] in 1972.

In an attempt to improve the synthesis of arylgold(III) compounds, Fuchita *et al.*[43] carried out the auration of benzoids with $AuCl_3$ in solvents such as THF, hexane and diethyl ether. They concluded that the reaction proceeded heterogeneously at 20 ^oC in hexane and homogeneously in diethyl ether. However, in diethyl ether $AuCl_3$ did not react with benzene and toluene but did react with 2,5-xylene and anisole. This was proposed to be due to the formation of the adduct $[AuCl_3(OEt_2)]$, which is of lower electrophilicity than $AuCl_3$ and as the mechanism of C-H activation proceeds *via* electrophilic aromatic substitution, this adduct fails to add to the aromatic ring. In the case of 2,5-xylene and anisole, the aromatic ring is more electron rich and hence a better nucleophile. As a result it successfully attacks the $[AuCl_3(OEt_2)]$ adduct, which is otherwise inert, to yield 2,5-xylyl- and 4-methoxy-phenylgold(III) dichloride. The dimeric products were isolated but were once again found to be unstable and as a result 2,6-lutidine was used as a stabilizing ligand yielding the mononuclear species $[AuArCl_2(lut)]$ (**80**) (Scheme 33).



78 **80**

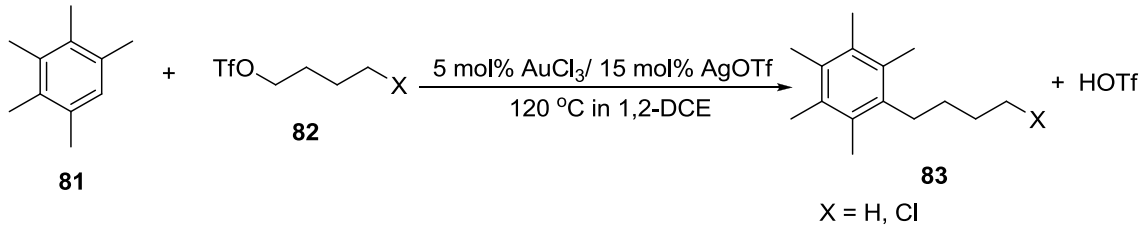
Ar = Ph, 4-tolyl, 3,4-xylyl, 2,5-xylyl, mesityl, 4-cumenyl, 4-methoxyphenyl, 4-chlorophenyl

Scheme 33: Unstable dimeric products isolated using 2,6-lutidine as a stabilising ligand

These complexes were found to be stable and were analysed by means of melting point determination, IR Spectroscopy, as well as ^1H NMR and ^1H-^1H correlation spectroscopy. Single-crystal X-ray analysis and IR data of $[Au(2,5\text{-}Me_2C_6H_3)Cl_2(lut)]$ showed a *trans*-configuration for the two chloro ligands. Furthermore, the yield of the reaction was more than doubled by addition of a base which neutralises the HCl produced during the auration, hence suppressing its reaction with the arylgold(III) compounds to produce the undesirable chlorinated aryl compound, as well as destruction of the catalyst when HCl reacts with it to

produce $AuCl_4^-$ H^+. Organic bases such as amines were found to be unsuitable, alkali metal carbonates however were found to be most effective.

Having prepared, isolated and fully characterised these arylgold(III) compounds it was then a matter of time before they were used in organic synthesis. 2004 and 2005 saw a flourish of activity involving these compounds, in all cases as a means of functionalisation of arenes and other aromatic systems. Shi[44] reported the functionalisation of arenes by a gold(III)-catalyzed process that can access 3-chromanol through direct cycloalkylation of electron-rich arenes with the tethered epoxides. The *endo* addition products were obtained exclusively, and the reaction is stereospecific. He then proceeded to report the functionalisation of electron-rich arenes like **81** with primary alcohol sulphonate esters such as **82** (Scheme 34); Nair[45-46] and Hashmi[47] reported the functionalisation of furans and indoles. In the case of Shi, it was observed that only electron-rich arenes yielded the desired product, the second step of the reaction proceeding *via* an S_N2 type mechanism, giving linear products.

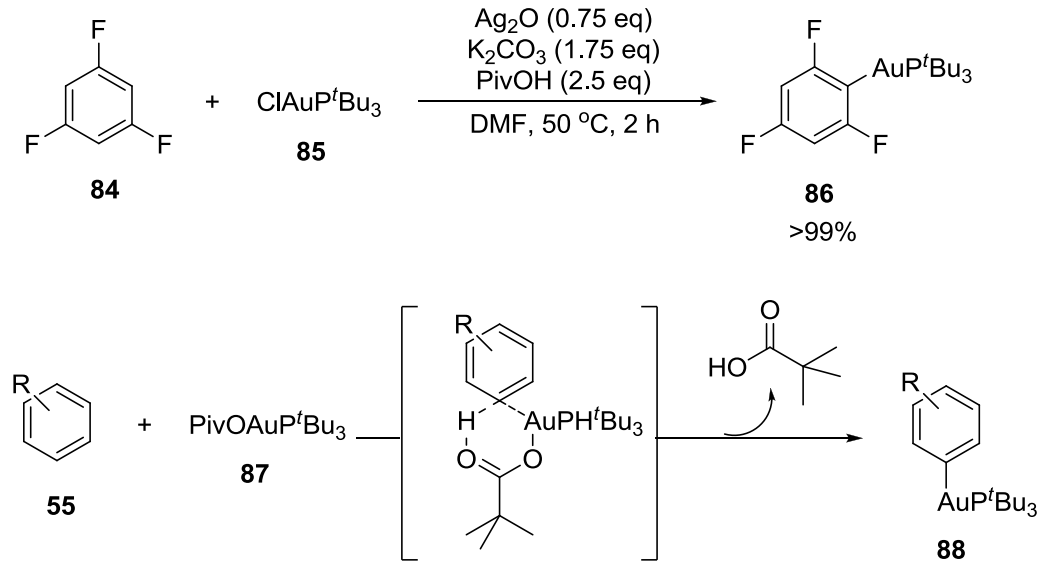


Scheme 34: Functionalisation of arenes by gold(III)

When less electron-rich arenes such as benzene were employed, more of the branched rather than the linear product was observed suggesting that the reaction proceeds *via* a Friedel-Crafts pathway by 1, 2-hydride shift and formation of the more stable secondary carbocation. This was confirmed by the reaction of electron-rich indoles, pyrroles and furans which also yielded the linear products and for which the usual laws of electrophilic substitution applied: 2-substitution on pyrroles and furans and 3-substitution on indoles.

The functionalisation of an arene, following auration, is now an acknowledged route to diversification of the aryl nucleus with the observation and isolation of aryl gold(III) reaction intermediates leading substantial support to such proposed mechanisms. However, there have only been isolated examples and the area requires more research to realise its full potential. In most cases, Au(III) has been used for the auration, but recently C-H activation of an arene

with Au(I) has been demonstrated for the first time.[48] Several arylgold(I) complexes have been generated in high yields under mild conditions. The Au(I) centre appears to show selectivity complementary to that of Au(III), with electron-deficient arenes such as **84** favoured over electron-rich. A number of ligands on the Au(I) were surveyed, those with superior electron-donating ability producing the best yield. The high primary isotope effect strongly suggests that the reaction proceeds *via* a concerted metallation-deprotonation pathway to generate stable arylgold(I) compounds (Scheme 35) which were easily isolated and characterised by X-ray crystallography.



Scheme 35: C-H activation of an arene with gold(I)

The group have not further investigated the reactivity of these arylgold(I) complexes but they postulate that this simple method opens the door to novel Au(I)-mediated transformations, including biaryl coupling.

2. RESULTS AND DISCUSSION

As previously established, only limited literature precedent exists of $AuCl_3$ used in C-H activation of aromatic systems with the prospect of direct functionalisation of arenes. Hence, research was aimed at broadening the scope of this reaction and making it applicable to a wider variety of substrates including less electron-rich arenes than the ones already used.

Research was aimed at investigating the nucleophilicity of arenes once complexed to a gold centre. However, the challenge lay in functionalising not only electron-rich aromatics but also electron-poor systems. It was envisaged that the difficulty in the functionalisation of the arenes lies in the intermediate's inability to nucleophilically attack another carbon centre (hard or soft) and this arises from the small difference in the electronegativities of gold and carbon (2.55 for C and 2.54 for Au) making the C-Au bond extremely unpolar and hence less likely to function as a nucleophile. By using an electron rich arene, the difference between the electronegativity of the carbon and the gold was increased, making the carbon adjacent to the gold, more susceptible to electrophilic attack. However, functionalisation of not only electron-rich but also electron-poor systems was aimed at and was believed to constitute a big challenge.

In our initial studies it was considered appropriate to re-examine Kharash and Isbell's[40] reported reaction between benzene and gold(III) chloride, using the modification of Liddle[41] and Fuchita[43] who had previously shown that aryl gold(III) dichloride compounds could be prepared and characterised as their Lewis acid-Lewis base adducts. Thus initial studies focussed on proving the initial auration was reproducible and so trapping the intermediate gold adduct with a ligand to form an isolable and stable complex was defined as the first research milestone.

In an attempt to choose the best ligand for complexation with the $PhAuCl_2$ adduct, it was found that Liddle's work did not include an experimental section but rather simply reported the results and characterisation of the $PhAuCl_2L$ compounds.[41] The group synthesised a number of air stable dichloro(aryl)gold(III) compounds by complexation of the original phenylauryl dichloride with coordinating ligands, the stability of the complex decreasing along the series $L = PPh_3 > Cl^- > py > SPr_2^n$ .This was carried out by addition of the ligand to the unstable product of the auration reaction ($RAuCl_2$) and the products were found to be monomeric. As no details of these reactions were included in the literature, consequently,

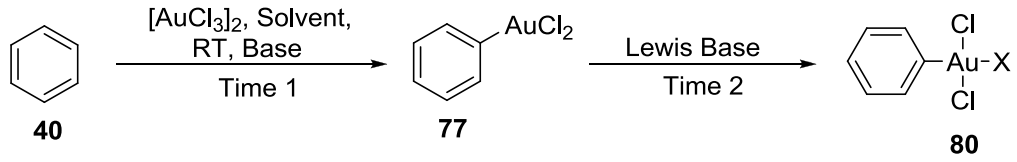
repeating his work was deemed necessary, where solvent, base, reaction times and Lewis base would be screened.

2.1 Optimisation of the initial auration reaction

2.1.1 Experimenting with the ligand and the reaction time

The reaction conditions described by Fuchita for the synthesis of the 2,6-lutidine adduct of arylgold(III)dichloride, $ArAuCl_2 \cdot lut$, were first used to form the $PhAuCl_2$ intermediate. He reports the reactions being carried out under a nitrogen atmosphere, using 6.0 mmol of benzene in a suspension of $[AuCl_3]_2$ in hexane, at 20 ^oC. After stirring for 30 minutes, diethyl ether was added, the resulting suspension was filtered and then treated with a diethyl ether solution (2 cm^3) of 2,6-lutidine (0.30 mmol) whereupon a pale yellow precipitate was formed. The reaction mixture was stirred for a further one hour at room temperature and the volatile material were removed *in vacuo*. Following chromatography, the $PhAuCl_2 \cdot lut$ product was isolated in 30% yield. The use of hexane as a solvent was reported to yield the best results and, it is specified that diethyl ether should be avoided as a solvent due to its coordinating ability. PPh_3 was the ligand of choice, based on Liddle's work.[41]

However, initial auration attempts using Fuchita's procedure for the formation of the $PhAuCl_2$ intermediate (vide supra), followed by trapping with PPh_3 were unsuccessful and only PPh_3 was isolated (Table 2, entries 1-4) as observed by ^1H NMR of the crude reaction mixture. Reactions were originally carried out on 50 mg scale which was later increased to 100 mg for purposes of ease of manipulation, and whilst promising colour changes (from yellow to brown upon addition of the benzene) were observed, only PPh_3 was isolated, quite possibly due to its insolubility in hexane preventing it from coordinating to the gold(III) centre.



40 **77** **80**

80a: X= PPh_3
80b; X=2,6-lut

Entry	Solvent	Base	Time 1	Lewis Base (1 eq., 0.16 mmol)	Time 2	Isolated Yield	Side-product
1	Hexane	K_2CO_3	30 min	PPh_3 in Et_2O	1 h	0%	PPh_3
2	Hexane	K_2CO_3	1 h	PPh_3 in Et_2O	1 h	0%	PPh_3
3	Hexane	none	1 h	PPh_3 in Et_2O	3 h	0%	PPh_3
4	Hexane	none	1 h	PPh_3 (no solvent)	1 h	0%	PPh_3
5	Hexane	K_2CO_3	1 h	2,6-lutidine in Et_2O	1 h	undetermined	2,6-lutidine
6	Hexane	none	3 h	2,6-lutidine in Et_2O	1 h	8% (**80b**)	$Cl_3Au{\cdot}lut$ (27%)
7	Hexane	none	1 h	2,6-lutidine in Et_2O	6 h	0%	$Cl_3Au{\cdot}lut$
8	Hexane	none	3 h	2,6-lutidine in Et_2O	1 h	0%	$Cl_3Au{\cdot}lut$

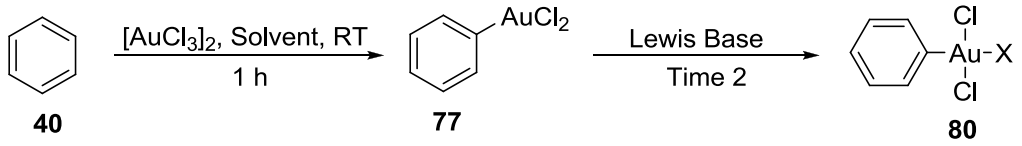
Table 2

The use of 2,6-lutidine as a coordinating ligand, in hexane, according to Fuchita's reaction conditions, also proved unsuccessful as only 2,6-lutidine was observed by ^{1}H NMR analysis of the crude reaction mixture (Table 1, entry 5), and upon excluding the base, K_2CO_3, from the reaction mixture, only $Cl_3Au{\cdot}lut$ could be observed (Table 1, entries 7-8). This was characterised by ^{1}H NMR spectroscopy only displaying signals at δ 7.95 (t, J = 7.7 Hz, 1H, *para*-pyridine proton), 7.45 (d, J = 7.7 Hz, 2H, 2 x *meta*-pyridine protons) and 3.11 (s, 6H, 2 x CH_3), and no resonances in the 7.0-7.5 ppm region which are characteristic of the aurated phenyl ring were observed.

Pleasingly, use of extended reaction times (Table 2, entry 6) yielded very small amounts of desired product **80b**, $PhAuCl_2{\cdot}lut$ and mostly $Cl_3Au{\cdot}lut$ as observed firstly by TLC analysis followed by ^{1}H NMR analysis of the crude reaction mixture. This was followed by isolation of the desired product by flash chromatography and characterisation by both ^{1}H and ^{13}C NMR. The desired product was stable both at room temperature and on silica and this made isolation and characterisation feasible. The ^{1}H NMR spectrum displayed signals at δ 7.75 (m, 3H, pyridine protons), 7.1-7.44 (m, 5H, PhH), 3.08 (s, 6H, CH_3), which this time, included the characteristic phenyl protons. The ^{13}C NMR was in agreement with the ^{1}H NMR, showing signals at δ 24.6, 124.6, 127.0, 129.1, 130.1, 131.8, 139.9 and 157.3 ppm. As the sample was stable, it was also submitted to Mass Spectroscopy to give HR-MS (FAB): m/z=452.0201, calculated for $C_{13}H_{15}N^{35}Cl_2Au$ $(M+H)^+$: 452.0247; m/z=454.0274, calculated for $C_{13}H_{15}N_{35}Cl^{37}ClAu$ $(M+H)^+$: 454.0218. Thus the desired $PhAuCl_2{\cdot}lut$ complex has been satisfactorily characterised.

2.1.2 Solvent screen

Fuchita describes the auration reaction as proceeding under heterogeneous conditions in hexane. Since only small quantities of the desired product had been obtained by use of hexane, it was thought that switching to a coordinating solvent in which $AuCl_3$ is soluble (and thus homogeneous conditions), the reaction would yield more of the desired product, $PhAuCl_2{\cdot}lut$. Efforts to solve the solubility issues, saw the reaction attempted in a variety of solvents. As before, the expected $PhAuCl_2$ intermediate **77**, was to be trapped with a Lewis base, namely PPh_3 or 2,6-lutidine. The results are tabulated below (Table 3).



40 **77** **80**

80a: X= PPh_3
80b; X=2,6-lut

Entry	Solvent	Lewis Base (1 eq., 016 mmol)	Time 2	Isolated Yield	Side-product
1	Et_2O	2,6-lutidine	1 h	28% (**80b**)	$Cl_3Au{\cdot}lut$ (9%)
2	Et_2O	PPh_3 in Et_2O	1 h	22% (**80a**)	-
3	THF	2,6-lutidine	18 h	0%	-
4	Dioxane	2,6-lutidine	18 h	Undetermined (**80b**)	-
5	TBME	2,6-lutidine	18 h	0%	-
6	Isopropyl ether	2,6-lutidine	18 h	0%	-
7	CH_2Cl_2	2,6-lutidine	18 h	0%	-
8	1,2-DCE	2,6-lutidine	18 h	0%	-
9	none	2,6-lutidine	18 h	18%	-

Table 3

Initial attempts involved carrying out the reaction in Et_2O (entry 1). It was immediately qualitatively observed when Et_2O was added to gold(III) chloride, a yellow solution rather than a brown suspension in a colourless solution was seen. Pleasingly, after carrying out the reactions as before, the desired $PhAuCl_2$·lut adduct was isolated in 28% yield after work-up and chromatography.

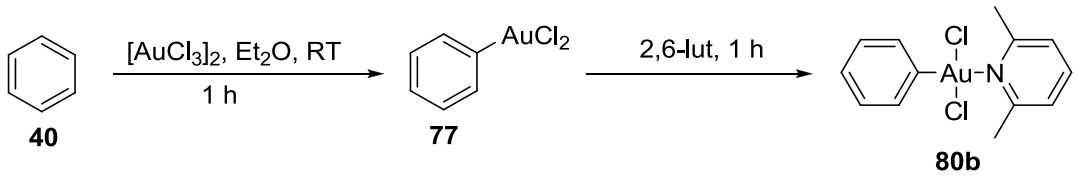
A reaction in Et_2O was also carried out but now trapping the initial $PhAuCl_2$ adduct with PPh_3 (entry 2). This gave the PPh_3 complex in 22% yield. Characterisation of this adduct was attempted by ^1H NMR and ^{13}C NMR, however, the overlapping signals of all the aryl groups in the spectra does not provide a convenient system for study and the use of the 2,6-lutidine adduct is preferred. Mass Spectrometry only led to the decomposition of the product, giving PPh_3 as the molecular ion. Some recent literature suggests that in fact it was not the $PhAuCl_2PPh_3$ adduct that was formed but rather the chloride salt of the $PhAuCl(PPh_3)_2$ adduct.

Having established that the reaction works in Et_2O, test reactions in solvents such as THF, dioxane, TBME and isopropyl ether (entries 3-6) were also attempted. Whilst the reaction in THF gave a black residue which did not contain any product due to a possible polymerisation of THF, reaction in dioxane yielded results similar to those using Et_2O as observed by TLC, but it was not further pursued due to the difficulty in removing dioxane from the reaction mixture due to its high boiling point (102 ^oC). However, attempted reactions in TBME and isopropylether yielded no product as judged by TLC analysis as indeed they suffered from the same solubility issues as those in hexane, giving a brown suspension.

CH_2Cl_2 and 1,2-DCE were also tested but solubility problems were once again encountered as these did not dissolve $[AuCl_3]_2$ and only a baseline spot was observed by TLC. The reaction was also carried out in neat benzene and this gave product **80b** in 18% yield (entry 9). However this was not considered appropriate as other aryl substrates, in their majority, are solid and require the use of solvent. The solvent search was then discontinued, having established that the use of Et_2O as the solvent gave the desired product in the highest yields.

2.1.3 Screening the concentration and the reaction temperature

The concentration of the reaction mixture was also increased and this gave the highest yield observed by that point (37%, Table 4, entry 3).



40 **77** **80b**

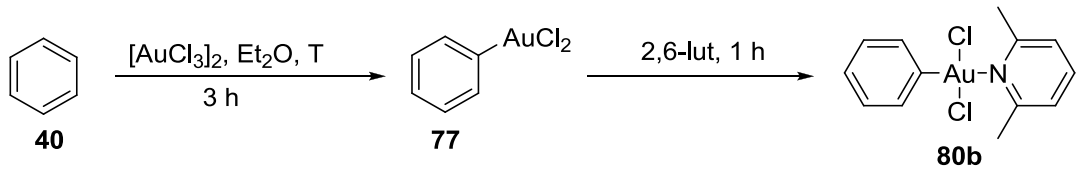
Entry[a]	**Concentration (M)**	**Isolated Yield**[b]
1	0.01	7%
2	0.02	13%
3	0.04	37%

a. All reactions carried out on 50 mg (0.08 mmol) of $[AuCl_3]_2$ in Et_2O at room temperature using 1 equivalent of 2,6-lutidine (0.16 mmol).

b. No side product observed

Table 4

Further studies to establish an optimum temperature for the reaction were carried out. Attempts to carry out the reaction originally at -20^{o}C (Table 5, entry 2) and then under reflux at 40 ^{o}C (entry 3), proved unsuccessful and only a baseline spot was observed by TLC analysis which is believed to be $AuCl_3$. This resulted in the reaction temperature being kept at room temperature.



40 **77** **80b**

Entry[a]	Temperature	Isolated Yield[b]
1	RT	37%
2	-20 ^{o}C.	0%
3	40 ^{o}C	0%

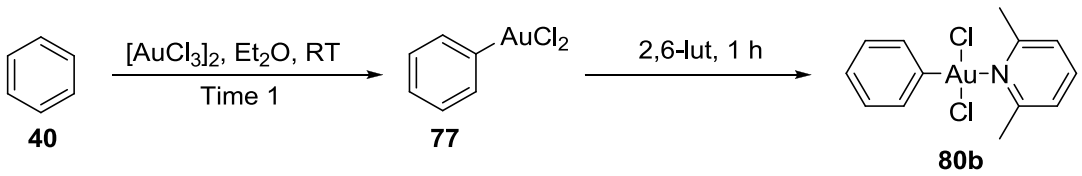
a. All reactions carried out on 50 mg (0.08 mmol) of $[AuCl_3]_2$ in Et_2O (0.04 M based on Au) using 1 equivalent of 2,6-lutidine (0.16 mmol).

b. No side product observed

Table 5

2.1.4 Screening the reaction time (time 1)

Since the auration of the benzene ring was suspected to be an equilibrium one, as judged by the significant change in yield upon changing the reaction time, and once it was established that performing the reaction at room temperature and using a concentration of 0.04M (based on $AuCl_3$) and twenty equivalents of benzene, yielded the best results, the first reaction time was varied, carrying out parallel reactions and adding the 2,6-lutidine at different intervals. Reaction times of 30 min, 1 hour, 2 hours and 3 hours were initially attempted and once it was established that the highest yield obtained was at 2 hours (Table 5, entry 3), further optimisation (reaction times of 1 hour 30min, 1 hour 45min, 2 hours, 2 hours 15min and 2 hours 30min) was carried out. In all cases, the product was isolated by flash chromatography and its identity verified by ^{1}H NMR. From the results tabulated below (Table 6) it was evident that the highest yield (57%, entry 6) obtained was at 2 hours.



40 **77** **80b**

Entry[a]	**Time 1**	**Isolated Yield**[b]
1	30 min	0%
2	1 h	21%
3	2 h	39%
4	1 h 30min	13%
5	1 h 45min	16%
6	2 h	57%
7	2 h 15min	48%
8	2 h 30min	43%
9	3 h	20%

a. All reactions carried out on 50 mg (0.08 mmol) of $[AuCl_3]_2$ at 0.04 M (based on Au) using 1 equivalent of 2,6-lutidine (0.16 mmol).

b. No side-product observed.

Table 6

The above results indicate that there is an induction period to the reaction after which the $PhAuCl_2$ adduct is formed but then starts decomposing. The optimum time was found to be 2 hours and all reactions from then onwards were carried out in this manner.

2.1.5 Screening additives

The auration reaction of benzene followed by trapping with 2,6-lutidine was also carried out in the presence of silver salts in an attempt to potentially form a more reactive gold(III) species (Figure 1).

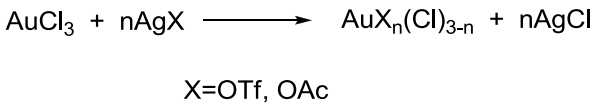
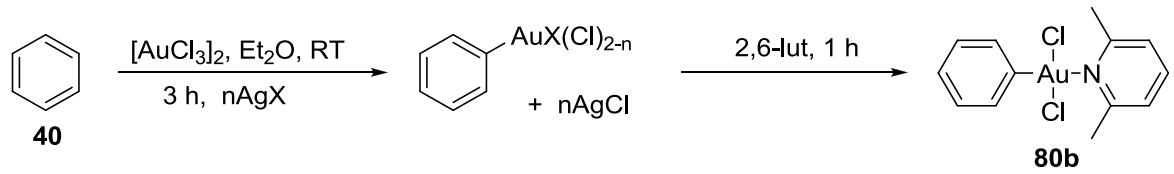


Figure 1

Reactions were carried out using one, two and three equivalents of the silver salt. Depending on the number of equivalents used, the appropriate gold(III) species was expected to form ($AuCl_2X$, $AuClX_2$ and AuX_3). The results are tabulated below (Table 7).



40 **80b**

Entry[a]	**Silver salt**	**Isolated Yield**[b]
1	AgOTf (1 eq.)	0 and 13%
2	AgOTf (2 eq.)	0%
3	AgOTf (3 eq.)	undetermined
4	AgOAc (3 eq.)	18%

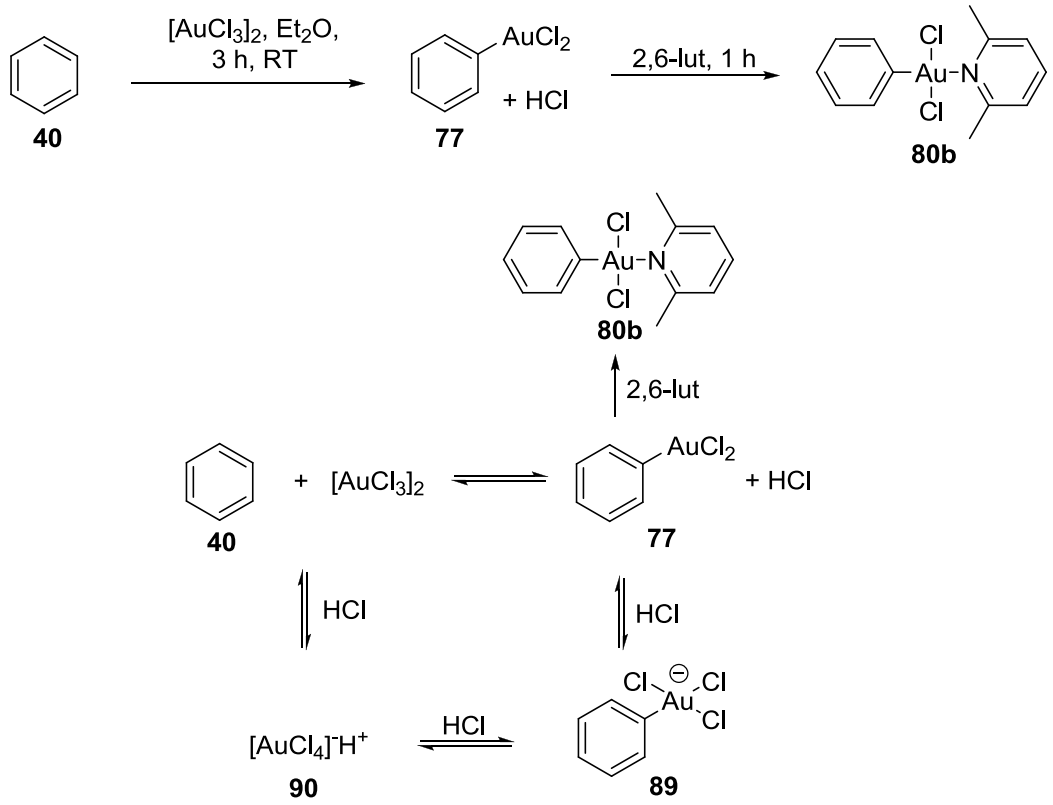
a. All reactions carried out on 50 mg (0.08 mmol) of $[AuCl_3]_2$ in Et_2O (0.04 M based on Au) using 1 equivalent of 2,6-lutidine (0.16 mmol).

b. No side product observed.

Table 7

When using silver salts, these were added to the gold(III) chloride as a solution in ether, with the exception of silver acetate which was loaded in the vial along with the gold(III) chloride as it is insoluble in ether. The reactions were carried out in the dark to avoid decomposition of the silver salts. Whilst carrying out the reaction using one equivalent of silver triflate initially gave no product (entry 1), repeating the experiment but reversing the order of addition of the benzene and the silver triflate (initially the silver triflate was added as a solution in ether, prior to the benzene, then it was added simultaneously as the benzene), gave product **80b** in 13% yield. The best result obtained was when three equivalents of silver acetate were used (entry 4). However, the yield was comparable to the ones obtained without the use of silver salts, so this modification was abandoned.

From a consideration of our findings, it was evident that the yield variability is attributed to the HCl produced in the reaction. This is evident by inspecting the potential equilibria of the entire process (Scheme 37), where the HCl can interfere with the$AuCl_3$ itself (to form $AuCl_4^-H^+$, **90**). A negatively charged species is then formed which can potentially protodeaurate to give the starting materials, $AuCl_3$ and benzene.

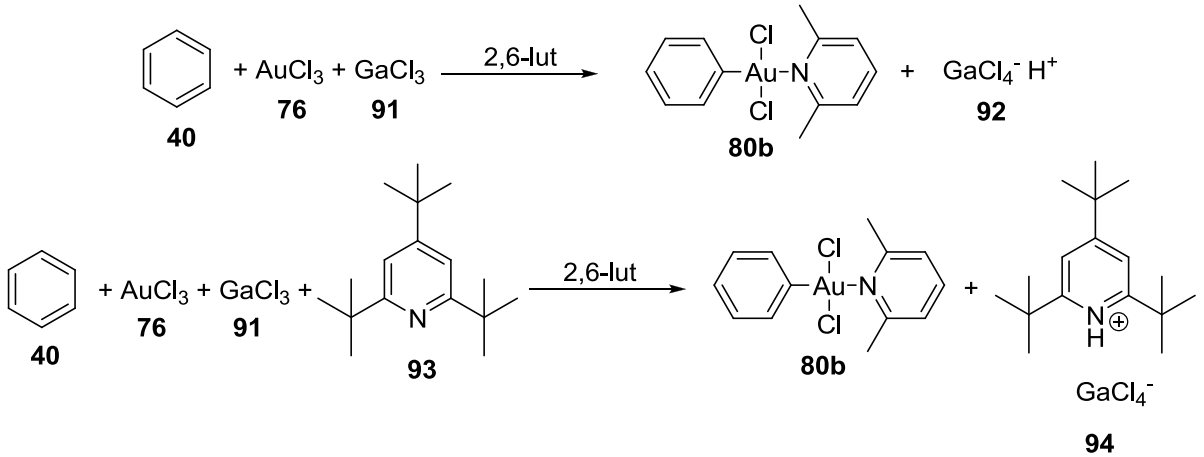


Scheme 37: Proposed mechanism for the formation of HCl and subsequent protodeauration

This is further complicated by the potential loss of HCl gas from the reaction mixture which is likely to depend on the temperature, the stirring speed and the shape of the reaction flask.

To test this theory, 1 equivalent of HCl (1M in Et_2O) was added to the reaction mixture once the $PhAuCl_2$ adduct is formed and prior to the addition of 2,6-lutidine. This led to no product formation. Consequently, the idea of using a base to neutralise the HCl was revisited. An organic base was firstly used, which would not have the solubility problems encountered by the inorganic bases attempted earlier on in the course. A non-nucleophilic base, 2,4,6-tri^{t}butylpyridine was chosen as the first candidate, and two attempts were carried out. Upon addition to the reaction mixture (addition of base was done simultaneously to the benzene) a yield of 20% of the desired product was first obtained which increased to 36% when the reaction was repeated. Clearly, as the yields were still fluctuating, it is believed that the free chloride ion is responsible for this. Attempting the reaction using an inorganic base K_2CO_3[43] would remove the chloride ion as the precipitate KCl. This gave product **80b** in only 13% yield presumably as once again solubility problems were encountered.

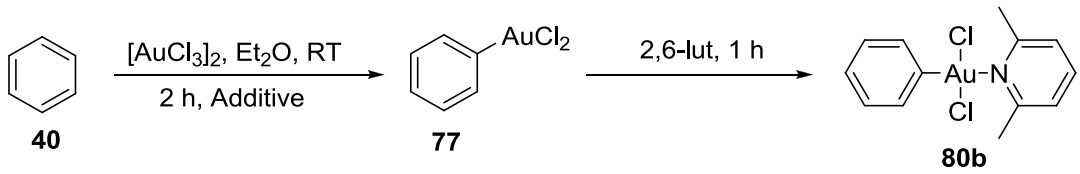
In effort to find a suitable chloride ion abstractor which would be soluble in ether but not interfere with any of the reagents or substrates, literature which reports the use of gallium(III) chloride as a chloride abstractor was discovered.[49] Ga is in group III of the periodic table and behaves similarly to Al. $GaCl_3$ is dimeric in the same way as $AlCl_3$. The perceived advantage with this method was that gallium(III) chloride had previously been used in conjunction with gold(I) and it was used to abstract the chloride ion to form $GaCl_4^-$.[49] The chloride ion was then replaced with a phosphorus-containing ligand. The method showed no interaction between Ga and Au, with and an additional benefit that $GaCl_3$ is soluble in benzene.



Scheme 38: Use of $GaCl_3$ as a chloride ion abstractor

The reaction with $GaCl_3$ was carried out similarly to all other auration reactions, where the $AuCl_3$ is first dissolved in Et_2O and then benzene was added. The only deviation was the $GaCl_3$ which was dissolved in benzene and then added to the $AuCl_3$ solution in Et_2O. A variation of this reaction was carried out, where 2,4,6-tri-*tert*-butylpyridine was also added to the reaction mixture in order to scavenge the H^+ produced. Unfortunately neither of these reactions was successful and gave only a baseline spot and no product as observed by TLC analysis. However, the idea of using $GaCl_3$ as a chloride abstractor was not abandoned as after careful inspection of the reactions carried out, it was suspected that the reason for the failure of the reaction was dissolving the $GaCl_3$ in benzene, as the $GaCl_3$ could be potentially undergoing substitution on the benzene ring in a mechanism similar to that of Friedel-Crafts. The reaction was repeated, however this time the $AuCl_3$ and $GaCl_3$ were loaded jointly in the vial (in order to avoid any unwanted interactions), dissolved in ether and then benzene was added. The product **80b** was obtained in 17% yield and as this was not satisfactory the reaction was abandoned.

The use of additives such as ^{n}BuLi, ^{t}BuLi, NaH, LDA, KHMDS and $NaNH_2$ to remove the HCl were then considered. These were added to the reaction mixture simultaneously to the benzene (if they were in solution) or loaded into the vial concurrently to the $[AuCl_3]_2$ (if they were solid). The results are tabulated below (Table 8).



40 **77** **80b**

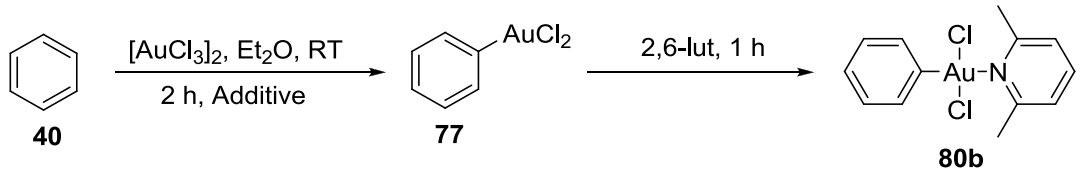
Entry[a]	Additive (2 eq.)	Isolated Yield
1	KOAc	79%
2	NaH	48%
3	KHMDS	0%
4	^{n}BuLi	0%
5	$NaNH_2$	5%
6	LDA	0%

a. All reactions carried out on 50 mg (0.08 mmol) of $[AuCl_3]_2$ in Et_2O (0.04 M based on Au) using 1 equivalent of 2,6-lutidine (0.16 mmol).

Table 8

As seen above, the use of KOAc and NaH as additives gave very good results (entries 1 and 2), whilst others (perhaps unexpectedly) proved too harsh for the reaction and presumably interfered with the $[AuCl_3]_2$, giving only baseline components by TLC. The reaction with KOAc gave the best results obtained so far, however when the reaction was repeated the yield dropped to 58%, showing the inherent variability of these results. However, the good yield confirms the fact that the problem lies with the presence of HCl in the reaction mixture. The most simplistic way of removing the HCl was also attempted: N_2 was bubbled through the solution for two hours during the reaction to drive off the HCl. This resulted in a 58% isolated yield, which is comparable to previous results. However this method was abandoned as invariably the solvent also evaporated to a certain extent during the reaction causing a change in the concentration of the reaction mixture.

Having established that KOAc was the best additive for the reaction giving the highest yield observed so far, it was decided best to pursue that route by testing other group I acetates: NaOAc, LiOAc and CsOAc. These were prepared by reaction of the group I hydroxide with acetic acid and were dried under vacuum to constant weight to ensure they did not contain any traces of water. The results are tabulated below (Table 9).



40 **77** **80b**

Entry[a]	**Additive (2 eq.)**	**Isolated Yield**[b]
1	KOAc	79%
2	NaOAc	23%
3	LiOAc	41%
4	CsOAc	15%

a. All reactions carried out on 50 mg (0.08 mmol) of $[AuCl_3]_2$ in Et_2O (0.04 M based on Au) using 1 equivalent of 2,6-lutidine (0.16 mmol).

b. No side product observed.

Table 9

It was obvious from the findings that KOAc was the best additive and as a natural progression the number of equivalents of KOAc added was varied. It was observed that the reaction gave the highest yield with two equivalents of KOAc (Table 10, entry 2). When five and especially ten equivalents (entries 3 and 4) were used the reaction mixture is too dense and not stirring properly which might contribute to the low yield of the reaction.

Entry[a]	No. of eq. of KOAc	Isolated Yield[b]
1	1	12%
2	2	79%
3	5	25%
4	10	1%

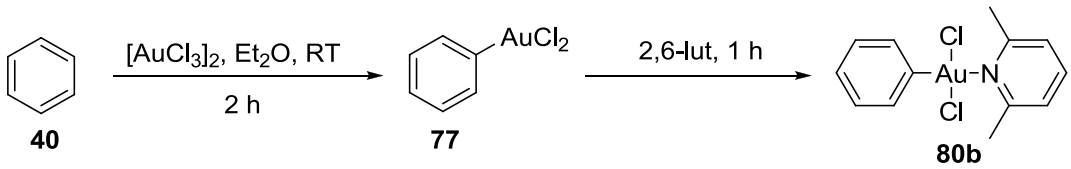
a. All reactions carried out on 50 mg (0.08 mmol) of $[AuCl_3]_2$ in Et_2O (0.04 M based on Au) using 1 equivalent of 2,6-lutidine (0.16 mmol).

b. No side product observed.

Table 10

2.1.6 Varying the number of equivalents of benzene

To this point, forty equivalents of benzene relative to Au were being used and even though this is not a problem when benzene is used as a substrate (it is a liquid with boiling point of 80 ^{o}C and hence the excess can be easily removed *in vacuo*) but to make this reaction more general obviously requires consideration. Where other substrates which are often solid would be used, the number of equivalents of substrate needed to be minimised to make the purification process easier. Furthermore, using less equivalents of substrate is not only more economical but it also reduces the amount of solvent needed to dissolve the starting material. Thus, the number of equivalents of benzene used were varied everything else being kept constant. The results are tabulated below (Table 11).



Entry	No. of eq. of benzene	Isolated Yield[b]
1	1	3%
2	2	5%
3	5	2%
4	10	3%
5	20	40%

a. All reactions carried out on 50 mg (0.08 mmol) of $[AuCl_3]_2$ in Et_2O (0.04 M based on Au) using 1 equivalent of 2,6-lutidine (0.16 mmol).

b. No side product observed.

Table 11

At low numbers of equivalents of benzene (entries 1-4) the reaction gave very low yields, however at twenty equivalents, similar yields to those using forty equivalents were observed. This result is related to the concentration of the reaction mixture; the more concentrated the reaction mixture the higher the observed yield. Above twenty equivalents the reaction mixture is sufficiently concentrated that the maximum yield is observed.

In conclusion, after these preliminary studies, it was established that the maximum yield and least amount of side-product is observed when the reaction is carried out in Et_2O, using twenty equivalents of benzene, at room temperature, using 2,6-lutidine as the coordinating ligand. Despite the fact that addition of KOAc appeared to increase the yield in certain occasions, after more experience was gained with the purification and handling of the

product, it was observed that it was unnecessary and was omitted from the reactions which follow. The optimum yield of $PhAuCl_2$·lut obtained in our hands (79%) constitutes to the best of our knowledge the highest yield obtained in the literature so far.

2.2 Mechanistic Studies

The reaction was attempted in Et_2O on a 50:50 mixture of benzene and hexadeuterated benzene in order to establish the rate determining step (RDS) of the reaction and obtain an insight about the mechanism *via* which it proceeds. If it proceeds through a standard electrophilic substitution mechanism, *via* a Wheland intermediate where the activation barrier of the second step is lower than that of the first step we expected a 50:50 mixture of the two products, where the RDS will not be the breaking of the C-H or C-D bond but rather the addition of the gold centre to the aromatic ring. Alternatively, if the product was richer in the non-deuterated isomer, this could be interpreted as the first step of the reaction being reversible. (Figure 2)

Carrying out the kinetic isotope experiment (using a 50:50 mixture of benzene and hexadeuterated benzene) several times the results obtained were consistent, giving 79:21 composition (cf. 72:28 and 73:27 composition from previous experiments) in favour of the non-deuterated product. Interpretation of the results suggests that the first step, the auration of the benzene ring is reversible, with the optimum result achieved with a reaction time of two hours.

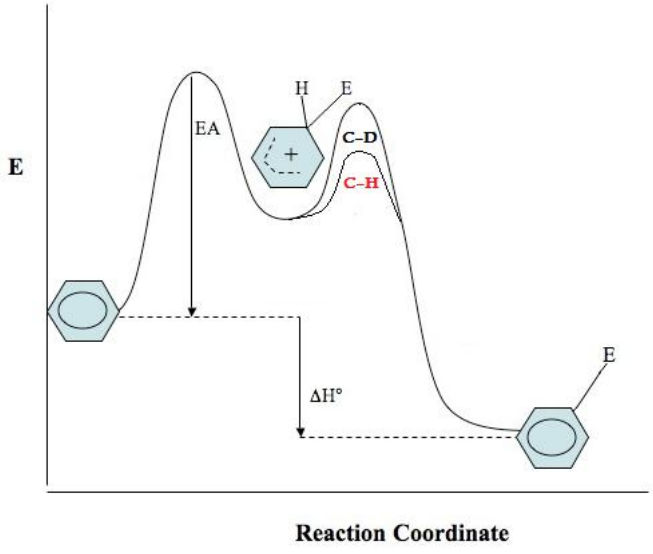


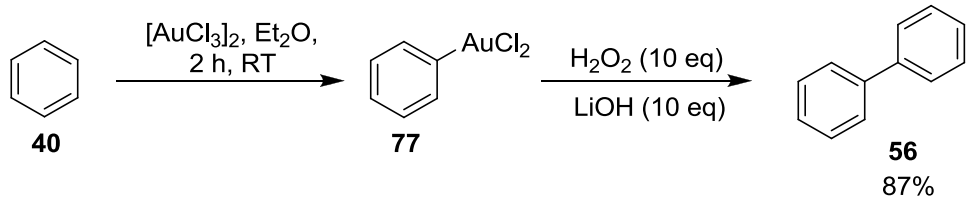
Figure 2: Reaction profile for benzene and hexadeuterated benzene

What can be concluded from the above results is that the reaction involves at least two steps, with the second being the RDS, the first step is reversible and it is consistent with an electrophilic substitution process *via* a Wheland intermediate.

2.3 Exploring the scope of the reaction

2.3.1 Biaryl heterocoupling

With an optimised method to aurate benzene in hand, the chemistry of the $PhAuCl_2$ adduct produced *in situ* was explored. By analogy with chemistry of trivalent aryl borons in mind, and with the expectation of forming phenol, the reaction with basic hydrogen peroxide was explored. Accordingly, upon addition of aqueous LiOH solution followed by H_2O_2 a violent exothermic reaction with gas evolution was observed and the solution turned black. and a new high running spot was immediately observed by TLC. ^1H NMR analysis of the crude reaction mixture displayed signals of a substituted benzene and Mass spectrometry showed that the product was biphenyl **56** (Scheme 39) with *m/z* 154 (M+), and it was isolated in 87% yield.

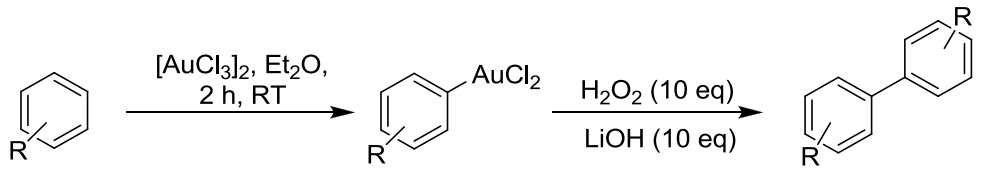


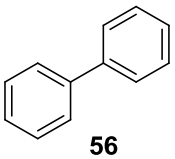
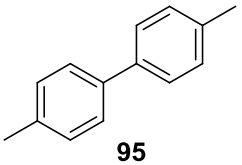
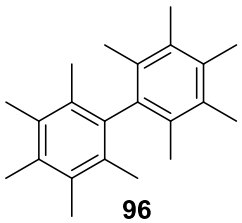
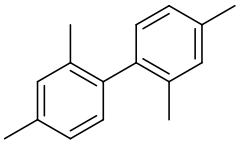
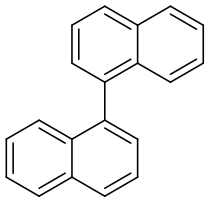
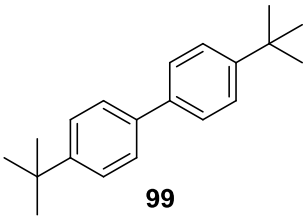
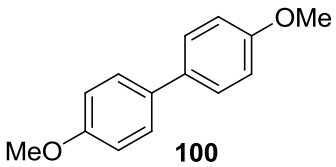
Scheme 39: Treatment of $PhAuCl_2$ adduct with basic hydrogen peroxide

Thus, albeit by serendipity, a new C-C bond forming method has been discovered, and the scope was therefore explored (vide infra).

Control experiments were also carried out to establish the necessity of both LiOH and H_2O_2 in the reaction, where one or the other reagent were excluded from the reaction. These yielded no signs of biphenyl product and confirm that both LiOH and H_2O_2 are essential for the reaction to proceed. This suggests that the active species in the reaction is in fact the peroxide anion HOO^-.

Initially, electron-rich aromatics were chosen as substrates (toluene, ^{t}butylbenzene, *m*-xylene, pentamethylbenzene, naphthalene and anisole, Table 12, entries 2-7). The reaction conditions used were the ones previously found to yield the best results: using Et_2O at room temperature. Pleasingly, the reaction proved general in scope and yielded the biaryl products in good to excellent yields (based on Au). In cases where the substrate was solid, only 2 equivalents were used. Additionally, positional selectivity was found to be exclusive at the *para*-position, except in the case of *m*-xylene (entry 4), where a mixture of regioisomers was observed. In the case of naphthalene (entry 5), both the 1,1- and the 2,2- biaryl product were observed, the 2,2- being more dominant.



Entry[a,b]	Product	Yield	Entry[a,b]	Product	Yield
1	 **56**	44%	2	 **95**	50%
3	 **96**	17% (by NMR)	4	 **97**	17%
5	 **98**	50%	6	 **99**	38%
7	 **100**	46%			

a. All reactions were carried out at room temperature, using a concentration of 0.04M (based on Au) in Et_2O.

b. Initial auration reaction time was 2 hours; then basic H_2O_2 solution added and stirred for 5 minutes.

Table 12

In the course of the above experiment, the isolation of the ^{t}BuPhAuCl$_2$·lut (**101**), was attempted by addition of 2,6-lutidine after the initial auration step. This was indeed produced and once isolated it was purified by flash chromatography and recrystallised from a 50:50 mixture of Et_2O and petroleum ether 40:60. The complex displays a slightly distorted square planar geometry with the two chlorine atoms around the Au(III) centre *trans*- to each other (Figure 3).

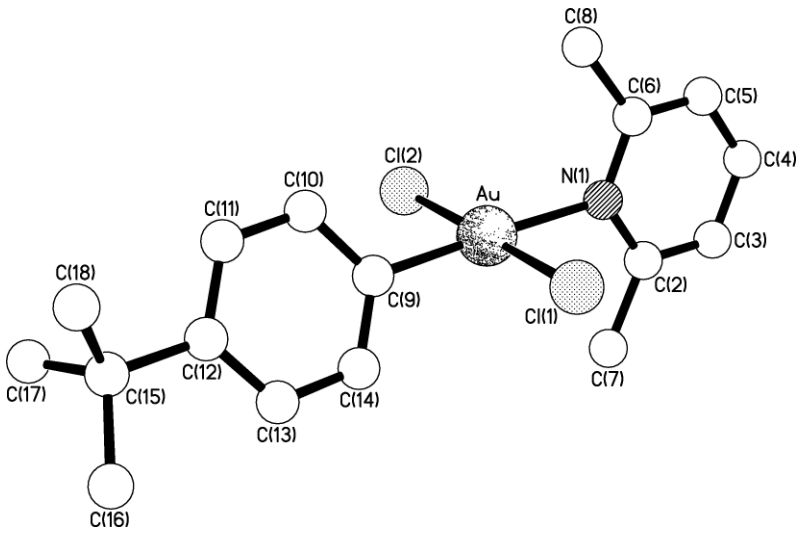
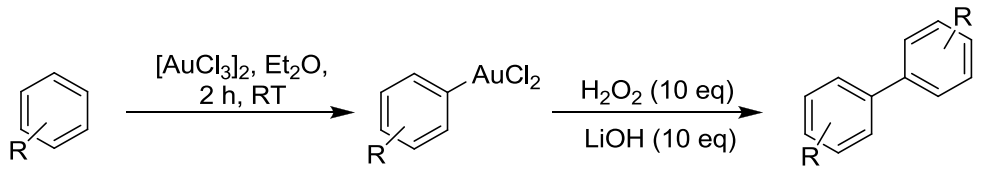
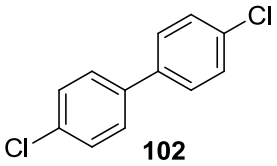
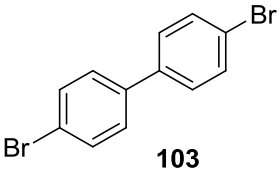
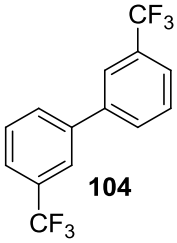
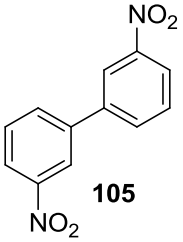
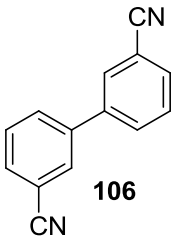
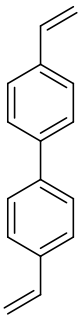


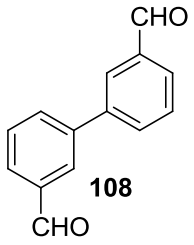
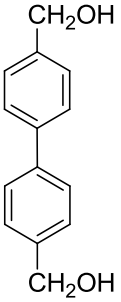
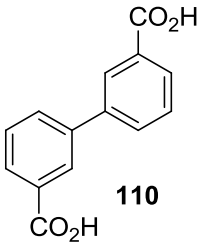
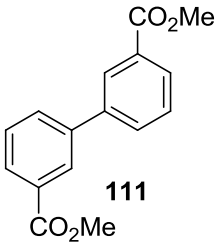
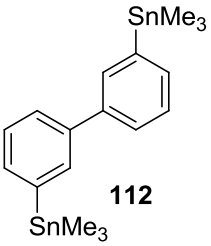
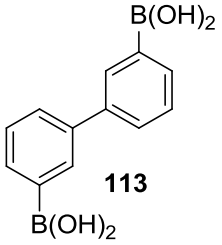
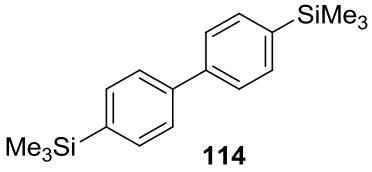
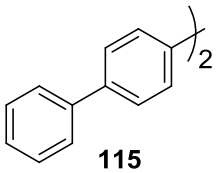
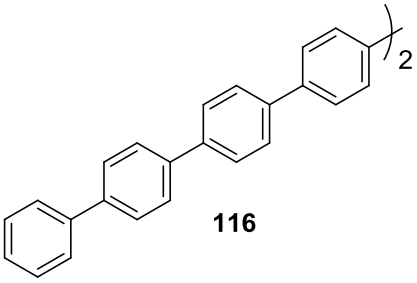
Figure 3: X-Ray structure of ^{t}BuPhAuCl$_2$·lut (**101**). Hydrogen atoms have been omitted for clarity. Selected bond lengths (Å): Au-C9 2.016, Au-N1 2.171, Au-Cl1 2.277. Selected bond angles (^{o}): N1-Au-C9 180.0, Cl1-Au-Cl2 178.85, N1-Au-Cl1 91.08, C9-Au-Cl1 88.95.

The isolation of this adduct confirms auration of benzenoids where the rules of electrophilic substitution are obeyed.

Attention then turned to the use of electron deficient aromatics, and those with other functional groups.



Entry[a,b]	Product	Yield	Entry[a,b]	Product	Yield
1	 **102**	42%	2	 **103**	26%
3	 **104**	0%	4	 **105**	0%
5	 **106**	0%	6	 **107**	0%

7	 **108**	0%	8	 **109**	0%
9	 **110**	0%	10	 **111**	0%
11	 **112**	0%	12	 **113**	0%
13	 **114**	0% (biphenyl instead)	14	 **115**	17%
15	 **116**	0%			

a. All reactions were carried out at room temperature, using a concentration of 0.04M (based on Au) in Et_2O.

b. Initial auration reaction time was 2 hours; then basic H_2O_2 solution added and stirred for 5 minutes.

Table 13

Halobenzenes, namely chloro- and bromo- benzene (Table 13, entries 1 and 2) were used as substrates, and pleasingly these gave the expected biaryl product in good to excellent yields, with exclusive *para*- substitution. Exploring the scope of the reaction even further, substrates such as nitrobenzene, trifluorotoluene and benzonitrile (entries 3-5) were utilised, but perhaps unsurprisingly these deactivated and *meta*-directing substrates gave no products.

In order to gauge functional group tolerance, substrates such as styrene, benzaldehyde, benzyl alcohol, benzoic acid and benzene methyl ester were tested (entries 6-10). Unfortunately these functional groups were not tolerant of the conditions and the reactions gave a mixture of unidentifiable products.

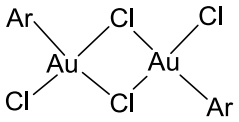
Trimethylphenyltin, phenyl boronic acid and trimethylsilylbenzene (entries 11-13) were also trialled as substrates. Whilst the first two gave a mixture of unidentifiable products, the latter gave biphenyl as the product. This suggests that the TMS group was substituted, possibly in the first step of the reaction *via* protodisilylation. This was confirmed by trapping the intermediate with 2,6-lutidine. The product was the 2,6-lutidine adduct of phenyl dichloro gold, confirming the fact that the TMS group was substituted following initial protonation at the *ipso*- position to produce benzene which then reacted with gold(III) chloride in the expected way.

The reaction was carried out on biphenyl and *p*-quaterphenyl (entries 14 and 15). Whilst the former yielded the *p*-quaterphenyl product in moderate yield, the latter gave only starting material, most probably owing to the low solubility of *p*-quaterphenyl in Et_2O.

2.3.2 Proposing a mechanism

In proposing a mechanism for this oxidative homocoupling reaction, the following key points were taken into considereation:

1. Due to its high normal potential, gold has the tendency to oxidise substrates, itself getting reduced during the process.[50]
2. The intermediate phenyl dichloride gold with six outer shell electrons is expected to function as a Lewis acid.
3. The intermediate phenyl dichloride gold has been reported in literature as a dimer with two bridging chlorine atoms (Figure 4).[42]

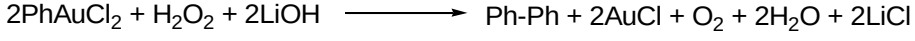


79

Figure 4

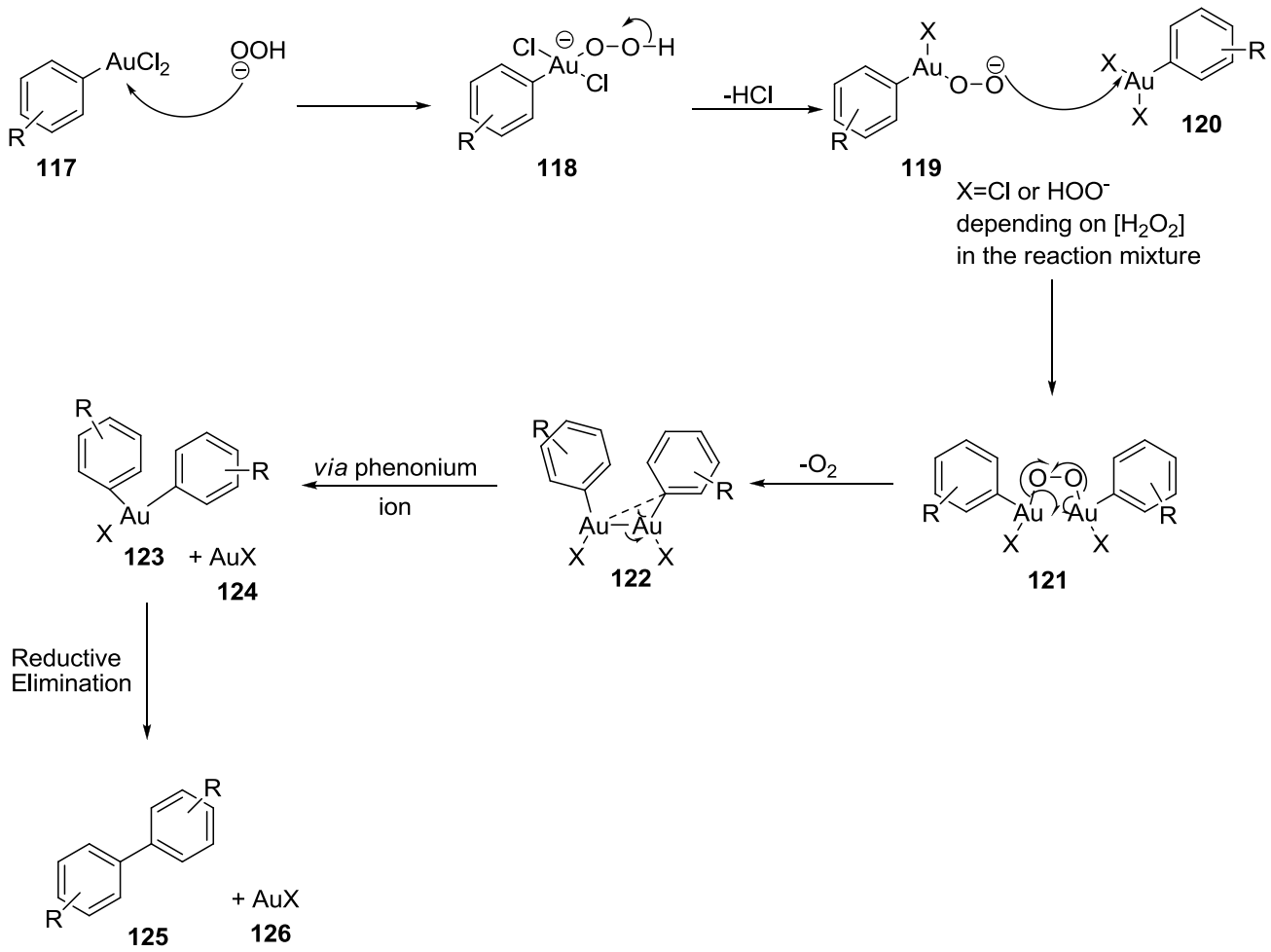
4. It has been established that both LiOH and H_2O_2 are essential for the reaction to proceed. This suggests that the active species in the reaction is in fact the peroxide anion HOO^-.
5. There have been reports of Au(II)-Au(II) bonds being formed which results in biphenyl coupling.[51-52]

By writing the overall equation for the reaction it is observed that the H_2O_2 is in fact acting as a reducing agent to the gold(III).



Scheme 40

Keeping all the above key points in mind a plausible mechanism is proposed (Scheme 41):



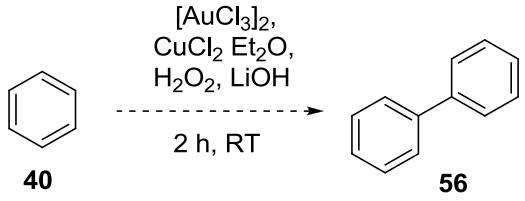
Scheme 41: Proposed mechanism for oxidative homocoupling involving phenonium ion formation

The reaction is proposed to proceed *via* initial nucleophilic attack of the peroxide anion on the gold centre followed by loss of the chloride and hydrogen to give an anionic species **119**. This in turn attacks another gold centre forming a bridging Au-O-O-Au bond (**121**). Upon homolytic Au-O bond dissociation, oxygen is released (this is in fact verified by observing strong effervescence and carrying out the glowing splint test) and a new Au-Au bond is formed (**122**). One phenyl group then migrates onto the other Au centre, possibly *via* phenonium ion formation. Finally, reductive elimination gives the biaryl product **125** and the gold(I) side product **126**.

The side product has not in fact been isolated so its exact nature is not known. It is however speculated that it is a gold(I) species where X can be chloride or peroxide, depending on the concentration of H_2O_2 in the reaction mixture.

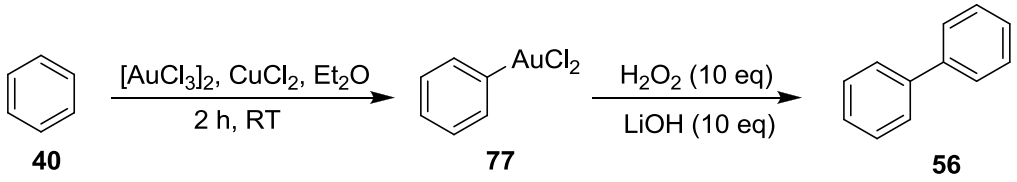
The above mechanism suggests that only one equivalent of H_2O_2 is required for the reaction to proceed. However, at least two equivalents of LiOH are necessary as one would be used to neutralise the HCl produced in the initial C-H activation. Hence in the future this needs to be examined by varying the number of equivalents of H_2O_2.

These reactions were all stoichiometric with respect to $[AuCl_3]_2$ so it was natural progression to attempt to make the reaction catalytic. As there was precedent in literature of $CuCl_2$ being used as a re-oxidant of Au(I), it was decided that this would be a good starting point. Initially a single-step reaction was attempted where $CuCl_2$, $AuCl_3$ and H_2O_2/LiOH were dissolved in diethyl ether and to that benzene was added. This did not give any product as the $AuCl_3$ was probably destroyed by the H_2O_2/LiOH prior to addition of benzene (Scheme 42).



Scheme 42

A different approach was then taken: that of repeating the conditions used in the biaryl coupling but decreasing the amount of $[AuCl_3]_2$ used whilst adding 1 equivalent of $CuCl_2$ w.r.t. benzene (Scheme 43).



Scheme 43

Pleasingly this showed an increase in the yield (from 44% to 198%, calculated w.r.t. $AuCl_3$).

Amount of $[AuCl_3]_2$ used	Yield	TON
100 mg	44%	0.44
50 mg	73%	0.73
25 mg	123%	1.23
12.5 mg	198%	1.98

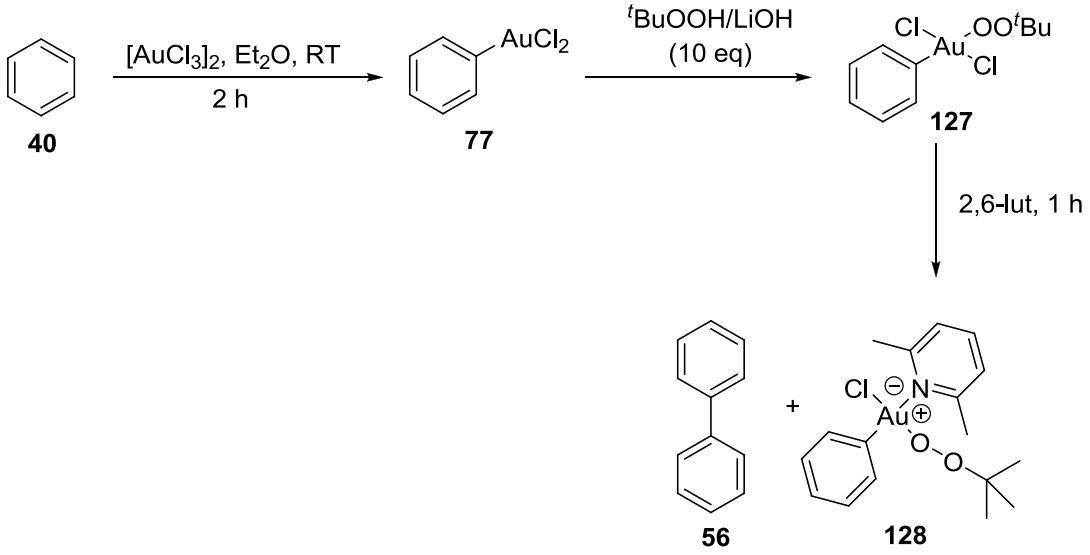
Table 14

At this point, it was best believed that the mechanism of the reaction should be elucidated, which in turn would help with making the reaction catalytic.

2.3.3 Investigating the mechanism by means of formation of intermediate analogues

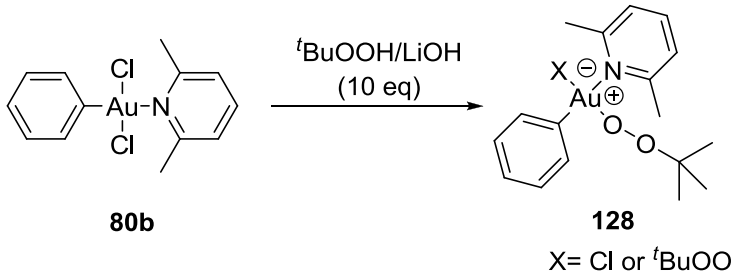
In order to investigate the proposed mechanism, stable analogues of the intermediates were targeted. Initial studies were focused on intermediate **128**, as it was considered that using ^{t}BuOOH instead of H_2O_2, would form a stable analogue as the ^{t}Bu linkage should be stable under basic conditions, which would then be trapped with 2,6-lutidine (Scheme 44).

Indeed, when carrying out the reaction, intermediate analogue **128**, PhAuCl($O_2{}^{t}$Bu)·lut, was isolated and characterised by ^{1}H NMR spectroscopy displaying a very evident ^{t}Bu signal at 1.03 ppm accounting for nine protons (Scheme 44). Surprisingly, a very small amount of biphenyl was also recovered.



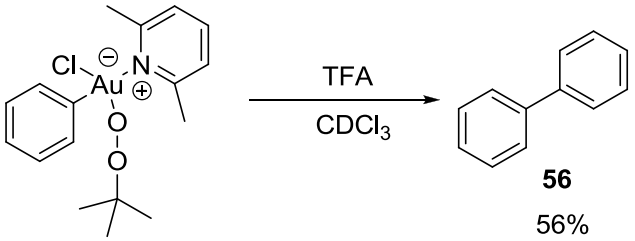
Scheme 44

The production of biphenyl must be due to small quantities of H_2O_2 in the ^{t}BuOOH. **128** was also obtained by reaction of Cl_2PhAu·lut (**80b**) with a mixture of ^{t}BuOOH/LiOH (Scheme 45).



Scheme 45

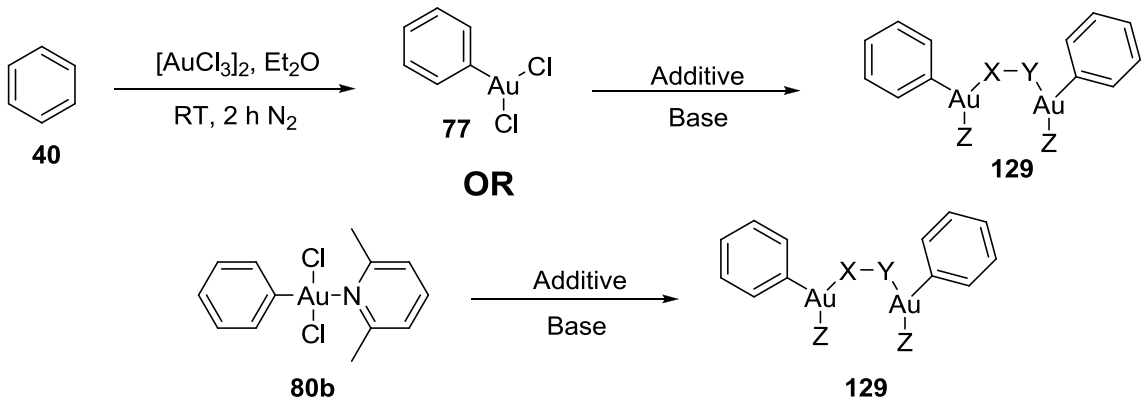
Analogue **128** was then treated with TFA, in order to remove the ^{t}butyl group, allowing the reaction to proceed and, according to the proposed mechanism, form biphenyl. This was indeed the case as biphenyl was observed in the ^{1}H-NMR of the crude reaction mixture and was isolated to 56% yield (Scheme 46), resulting to the first step of the proposed mechanism being confirmed.



128 **56** 56%

Scheme 46

Having successfully obtained analogue **128** of the proposed mechanism the next target was to obtain analogue 1**29** by using other peroxide equivalents (Scheme 47). The results are tabulated below (Table 15).



Scheme 47

Entry	Substrate	Additive (1 eq.)	Base (1 eq.)	Result
1	$PhAuCl_2$	H_2N-NH_2	-	Biphenyl (14%)
2	$PhAuCl_2$·lut	H_2N-NH_2	-	Biphenyl (8%)
3	$PhAuCl_2$	H_2N-OH	-	-
4	$PhAuCl_2$·lut	H_2N-OH	LiOH	-
5	$PhAuCl_2$·lut	H_2N-OH	-	-
6	$PhAuCl_2$	Me_2N-NH_2	-	-
7	$PhAuCl_2$·lut	Me_2N-NH_2	-	SM
8	$PhAuCl_2$	MeHN-NH_2	-	Biphenyl (17%)
9	$PhAuCl_2$	MeHN-OMe	-	-
10	$PhAuCl_2$	EtHN-NHEt	-	Biphenyl (12%)
11	$PhAuCl_2$	EtHN-NHEt	LiOH	Biphenyl (11%)

All reactions were carried out at room temperature, using a concentration of 0.04M (based on Au) in Et_2O.

Table 15

Despite the fact that analogue **129** could not be isolated, the results were consistent with the proposed mechanism as, with the exception of H_2N-OH, all reactions in which a double bond could be formed between the two heteroatoms (entries 1, 2, 8, 10 and 11) gave biphenyl as the product with the same observations as in the reaction with H_2O_2/LiOH; reaction turns black with effervescence and an exotherm. The yields, however, were noticeably lower.

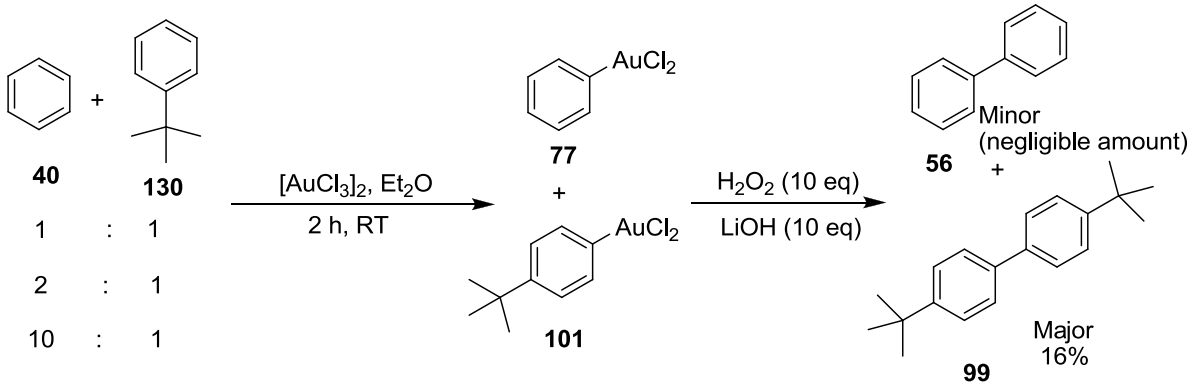
2.4 Biaryl Heterocoupling

The encouraging results obtained with the biaryl coupling described above led to further investigation of the formation of C-C bonds both in the form of aryl cross-coupling and aryl alkylation using various organometallic reagents. The aim was to achieve cross-coupling between *two different* aryl groups and/or functionalisation of the aromatic ring.

Cross-coupling using two different routes was attempted. The first was using $AuCl_3$ for auration of different aryl substrates followed by addition of H_2O_2/LiOH and subsequent heterocoupling. The second was by the use of phenyl/alkyl Grignards and organolithiums on the activated $ArAuCl_2$ species.

2.4.1 Using $AuCl_3$ and H_2O_2/LiOH

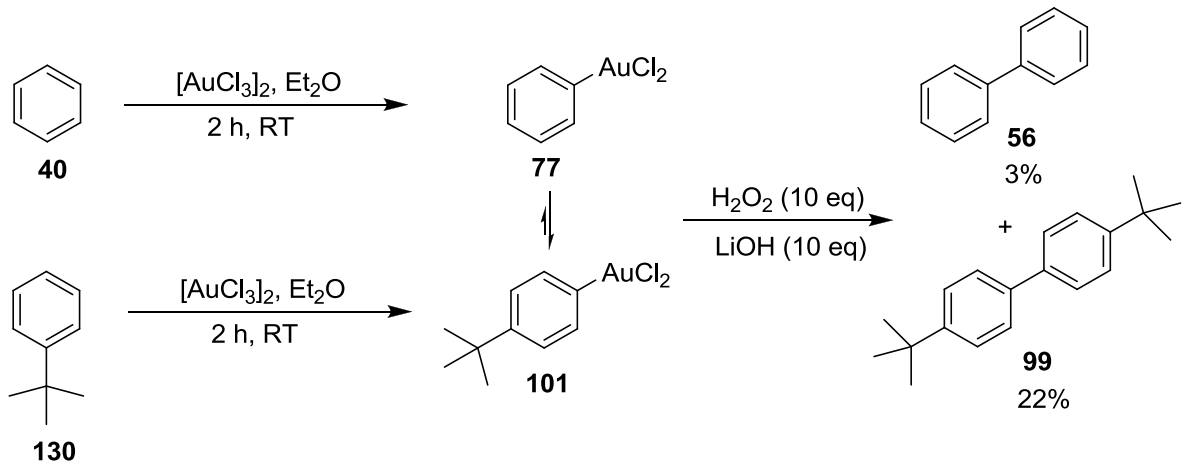
The concept behind this reaction was that once the $ArAuCl_2$ intermediate is formed with two different substrates (in this case Ar = ^{t}BuPhH and PhH) upon treatment with H_2O_2/LiOH a mixture containing a statistical distribution of all the possible products would be obtained. This was carried out in two ways. Firstly, having chosen benzene and ^{t}Bu-benzene as the two aryls to be coupled together, the reaction was carried out on a 50:50 mixture of the two substrates.



Scheme 48

The reaction showed one new component by TLC, but after isolation and GC-MS analysis it was observed that it was a mixture of biphenyl (**56**) and ^{t}Bubiphenyl^{t}Bu (**99**) where the latter dominated. Thus although homocoupling has proceeded, no heterocoupling is observed. The fact that a non-statistical product distribution is observed requires further investigation (vide infra). The reaction was further pursued using a 1:2 and a 1:10 mixture of the two substrates (in favour of benzene which is less reactive), however no change was observed in the product composition (Scheme 48).

A different method was then attempted, that of forming the $ArAuCl_2$ intermediate in two separate flasks for each substrate, mixing them together and then adding the H_2O_2/LiOH. However, this gave none of the desired cross-coupled product, ^{t}Bubiphenyl, and the two components observed by TLC, once isolated were found to be 4,4'-di-^{t}butylbiphenyl (22%) and traces of biphenyl (3%, Scheme 49). Interpretation of these results, suggests that, as the ^{t}butylbenzene is more activated than benzene, it reacts faster with gold.



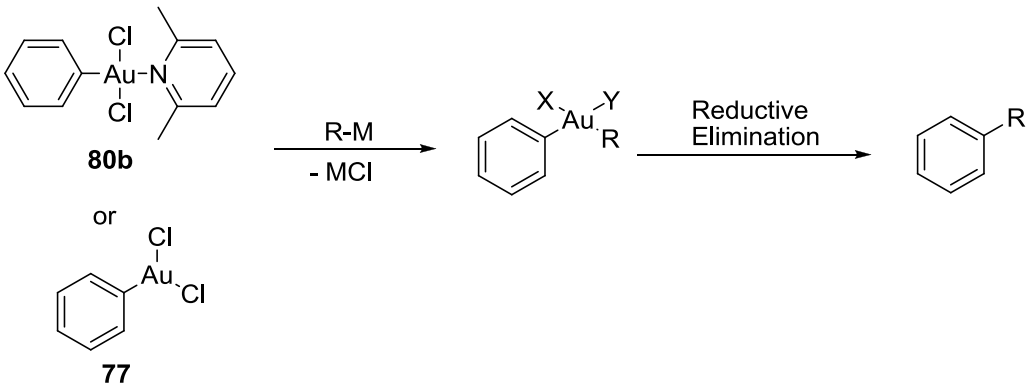
Scheme 49

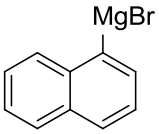
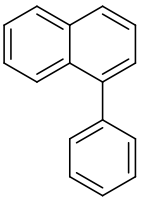
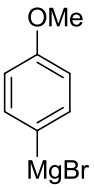
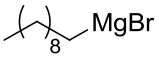
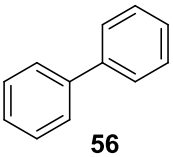
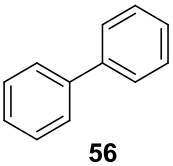
The above results of the first experiment is consistent with the idea that auration of the more reactive ^{t}butylbenzene is preferred and suggests that upon mixing the two adducts and stirring for 5 minutes, there is very rapid equilibration between the two $ArAuCl_2$ adducts, in favour of the $^{t}BuPhAuCl_2$. It was therefore decided that to overcome this problem, the second aryl group had to be introduced on the Au(III) centre by means of more forcing methods: using an organometallic nucleophilic reagent such as a Grignard or organolithium.

2.4.2 Using phenyl/alkyl Grignards and organolithiums

As the above method failed to give the desired cross-coupled product, the reaction of $PhAuCl_2$·lut with a phenyl or alkyl Grignard was pursued. Grignard reagents of bromobenzene, 1-bromonaphthalene and 4-bromoanisole were formed using conventional methods and the organolithiums were from commercial sources. Here it was expected direct attack of the gold(III) by the Grignard and as a result the Au centre would be arylated/alkylated. Reductive elimination would lead to carbon-carbon bond formation.

The results are tabulated below (Table 16).



Entry	R-M	Product	Yield
1		 **131**	8%
2	PhMgBr	-	0%
3		-	0%
4		-	0%
5	^{n}BuLi	 **56**	92%
6	PhLi	 **56**	47%

All reactions were carried out at room temperature, using a concentration of 0.04M (based on Au) in Et_2O and 1 equivalent of organometallic reagent.

Table 16

Reaction of the Grignard reagent of 1-bromonaphthalene with $PhAuCl_2 \cdot lut$ (Table 16, entry 1) furnished a complicated mixture from which the desired product, 1-phenylnaphthalene was observed by GC-MS analysis in approximately 8% yield. Its presence in the crude reaction mixture was also verified by Mass Spectroscopy. Naphthalene, 1-bromonaphthalene, 1-iodonaphthalene (due to the presence of residual I_2 from the Grignard formation), trinaphthyl and 1-naphthol were also observed as side products.

On the other hand when Grignard reagents of benzene (entry 2) and 4-bromoanisole (entry 3) were used the reaction did not proceed. Addition of more Grignard reagent and refluxing overnight did not push the reaction. The main products isolated were the $PhAuCl_2 \cdot lut$ starting material (in the case of phenyl Grignard) and anisole, 4-bromoanisole and 2,6-lutidine in the case of the 4-bromoanisole Grignard (35, 55 and 10% respectively as calculated by mass).

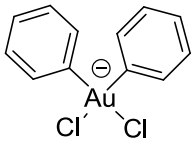
The use of sp^3 hybridised Grignard reagents instead of sp^2 (using 1-bromodecane, entry 4) was also attempted but the reaction only returned starting material when carried out at room temperature. After heating overnight under reflux at 40 ^{0}C, only starting material could be observed by TLC analysis and the reaction was stopped and starting material recovered.

From the results (with the exception of the 1-bromonaphthalene Grignard) it seemed that Grignard reagents are not potent enough nucleophiles to add onto the Au centre.

Furthermore, reacting the intermediate $PhAuCl_2$ with organolithiums such as ^{n}BuLi (entry 5), and stirring for 3 hours at room temperature, only returned starting material suggesting that sp^3 hybridised organolithiums were not nucleophilic enough to attack the Au(III) centre. Further stirring overnight gave biphenyl (92%) as the product but none of the desired ^{n}butylbenzene.

Combining findings from the reactions with Grignard and phenyl lithium reagents, the conclusion that the reaction is more likely to proceed with sp^2 hybridised organolithium reagents was reached. Indeed this was verified when the $PhAuCl_2 \cdot lut$ was reacted with phenyllithium (entry 6) and readily gave biphenyl in 47% yield (based on Au), which constituted the first success in oxidative coupling using aryl lithium reagents. However, heterocoupling had still not been achieved.

It was also evident that a strategy for biaryl heterocoupling was more likely to be successful *via* the nucleophilic attack of an organometallic reagent onto the Au centre rather to form intermediate **132** (Figure 5) than by the auration of two different aryls and subsequent reaction with H_2O_2/LiOH. We therefore moved on to investigate the former reaction and the factors affecting the reductive elimination step.

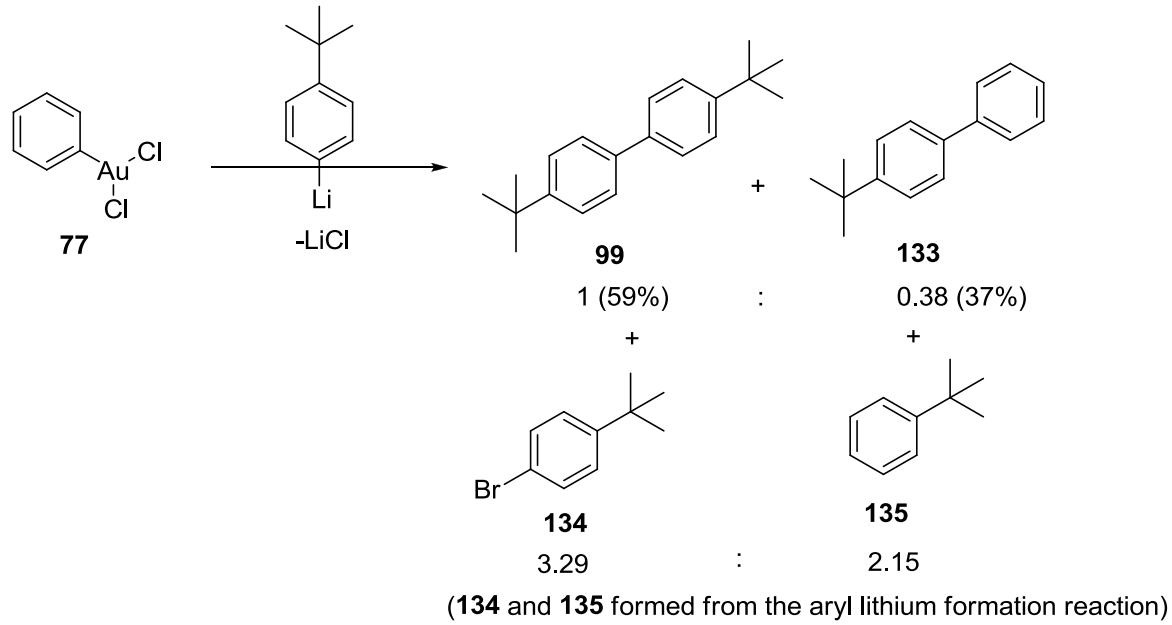


132

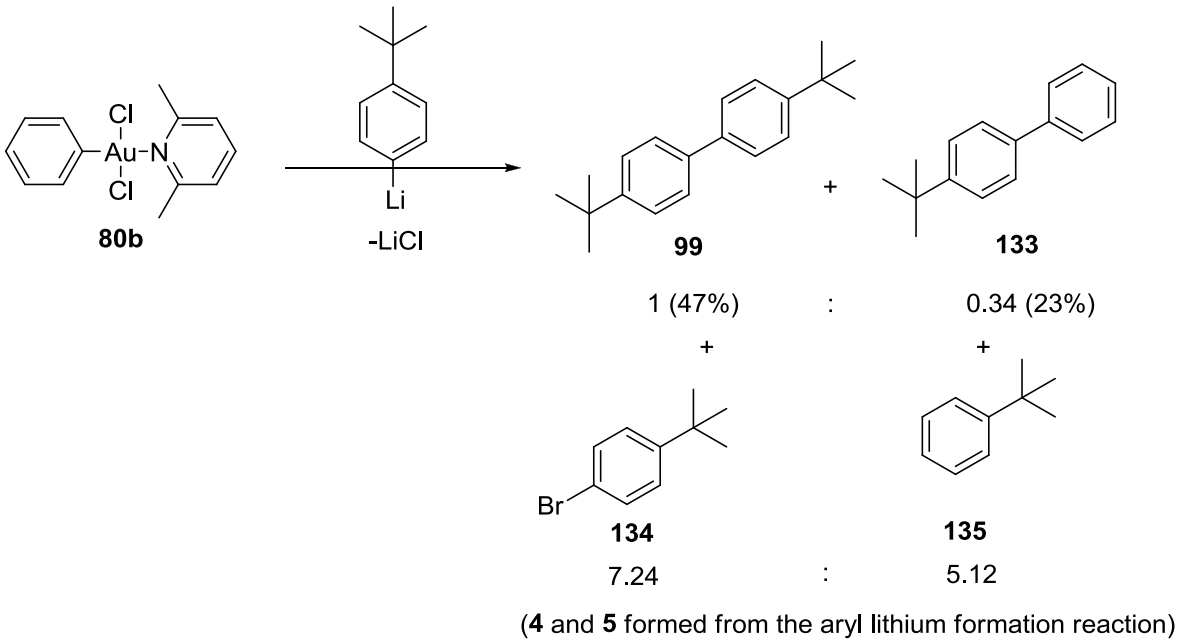
Figure 5

2.4.3 Forcing the Reductive Elimination

The first reaction attempted was treating both the $PhAuCl_2$ intermediate and the 2,6-lutidine adduct, $PhAuCl_2$·lut, with ^{t}BuPhLi (Schemes 50 and 51 respectively). Pleasingly, both reactions yielded the desired heterocoupled product in moderate yields. However, the homocoupled product, 4,4'-di-^{t}butylbiphenyl was also observed in higher yield.

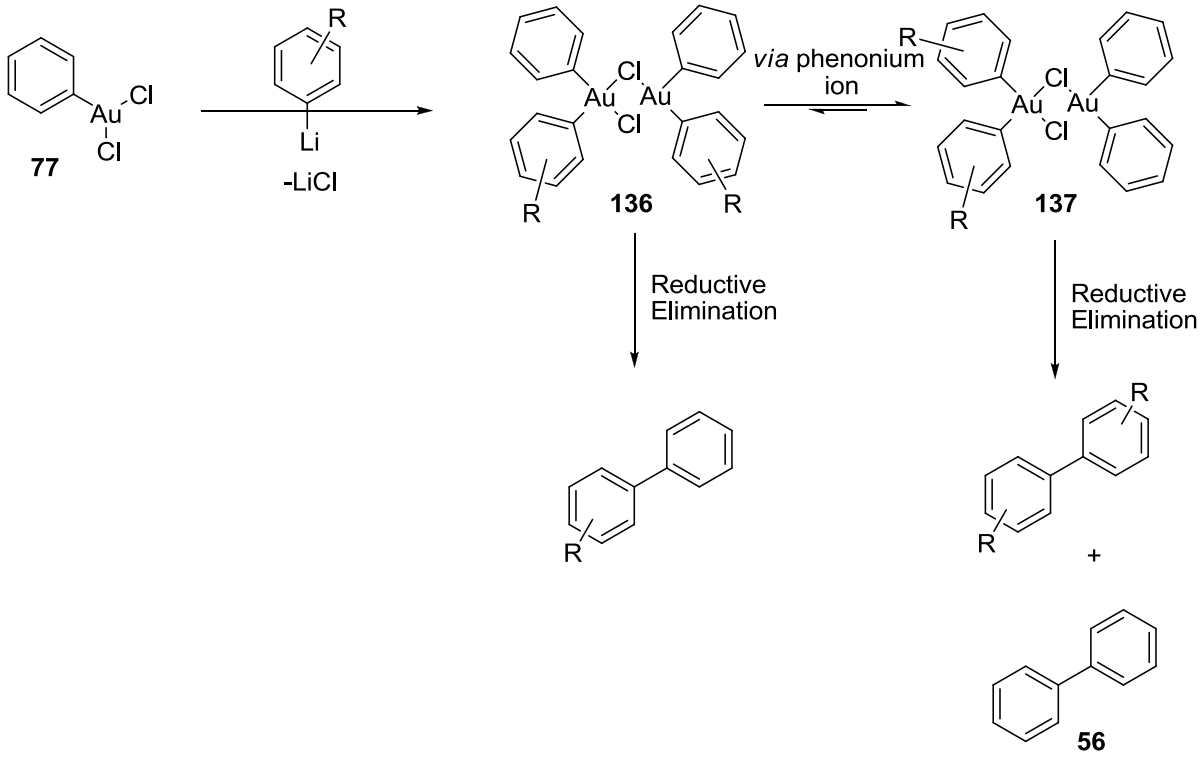


Scheme 50



Scheme 51

These two reactions gave very similar results and it was obvious that homocoupling was dominating the reaction (Schemes 50 and 51). From all the results so far, and based on the proposed mechanism which invokes the transfer of an aryl on the Au centre *via* a phenonium ion, it is proposed that once nucleophilic addition of the aryllithium occurs on the Au centre, there is scrambling of the aryl groups. This occurs firstly through the formation of an Au dimer, **136**, containing a 3-centre/2-electron bond (much like $[AuCl_3]_2$), followed by formation of a phenonium ion (Scheme 52).



Scheme 52

It is further proposed that the two dimers, **136** and **137**, are in equilibrium, and in this case we infer the equilibrium position to favour **137**, explaining the significantly higher yield of the homo-coupled product as compared to the hetero-coupled one. Alternatively, an irreversible reductive elimination step can be involved where ^{t}BuPhAuCl$_2$ undergoes faster irreversible reductive elimination than PhAuCl$_2$.

It became evident that equilibration of the two aryl fragments needed suppressing for controlled reductive elimination. One way of doing that would be by coordinating a bidentate ligand on the Au centre forcing the two aryl rings together to reductively eliminate prior to dimer formation and equilibration. Additionally, coordinative saturation around the Au centre is likely to prevent the formation of dimers and hence prevent scrambling. However this was not further pursued due to time limitations.

3. CONCLUSION

The following main conclusions can be drawn from the research outlined above regarding the auration of unfunctionalised aromatics and their subsequent homodimerisation and attempted heterodimerisation.

- The auration reaction proceeds *via* electrophilic substitution of the Au(III) centre to the aromatic ring.
- Auration is only feasible with electron-rich and mildly electron deficient aromatics.
- The substitution pattern follows the rules of electrophilic substitution.
- The first step (electrophilic addition) is reversible.
- Homocoupling is achievable through a phenonium ion intermediate which reductively eliminates to yield the homo-coupled biaryl product.
- Exclusive heterocoupling was not achieved, however, some homocoupled products have been obtained and the reaction requires further investigation.
- The reaction is not catalytic with respect to $AuCl_3$ due to the irreversible, in our hands, reduction of Au(III) to Au(I). However the first milestone in making it catalytic has been set by the use of Cu(II) as a re-oxidant and this also needs further exploration.

Concluding, a novel method for the homocoupling of unfunctionalised aromatics by the use of $AuCl_3$ has been developed. A possible mechanism has been elucidated and the reaction has proven to be general for electron rich and mildly electron deficient aromatics. The next challenges in the development of this method will be to render it catalytic, and to allow cross-couplings of different unfunctionalised aromatics.

4. EXPERIMENTAL

General Experimental

Reagents

All reagents were obtained from commercial sources (Acros, Sigma Aldrich, Lancaster, Degussa, Engelhard and Johnson Matthey). All solid reagents were used as received and all liquid reagents were distilled and stored over 4Å molecular sieves. Where $AuCl_3$ was used, it was loaded in a vial in the glovebox. Other solid reagents were loaded in the vial along with the $AuCl_3$ in the glovebox. The reactions were carried out in an atmosphere of N_2. Grignard reagents were either used from commercial sources or prepared according to the literature procedure.[53]

Solvents

Hexane, MeOH, 1,2-DCE and CH_2Cl_2 and NMP were distilled from CaH_2. THF was distilled from Ph_2CO/K, Et_2O , isopropylether and TBME from Ph_2CO/Na. Toluene and dioxane were distilled from Na. Extraction solvents and chromatography eluents were used as received. Pet. Ether refers to BDH Anal® petroleum spirit 40-60 °C. All other solvents were used as received. H_2O refers to distilled H_2O.

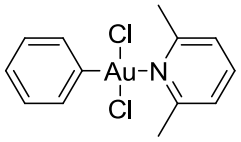
Experimental Techniques

Analytical thin-layer chromatography (TLC) was carried out on silica gel F254/366 60 Å plates with visualisation using UV light (254 nm) or potassium permanganate as appropriate. Chromatography was performed using BDH 33-70 μm grade silica gel. Air and moisture sensitive reagents were transferred *via* syringe or cannular and all reactions were carried out in oven dried flasks under a positive pressure of N_2. Reported reaction temperatures refer to the external bath temperature. Brine refers to saturated aqueous solution of NaCl. The term, concentrated *in vacuo*, refers to rotary evaporation.

Characterisation

Melting points were recorded on a Reichart Thermovar melting point apparatus and are uncorrected. Concentrations (*c*) are quoted in g/L. Infrared spectra were recorded on a Unicam FTIR spectrometer with automated background subtraction. Samples were prepared as thin films on sodium chloride plates. Reported absorptions are strong or medium strength unless stated otherwise and specified in wavenumbers (cm-1). ^{1}H NMR were recorded at 300 MHz on a 300 MHz Bruker RX spectrometer, at 400 MHz on a 400 MHz Bruker AV400 spectrometer and at 500 MHz on a 500 MHz Bruker AV500 spectrometer. ^{13}C NMR were recorded at 75 MHz on a 300 MHz Bruker DRX spectrometer respectively, at 100 MHz on a 400 MHz Bruker AV400 spectrometer and at 125 MHz on a 500 MHz Bruker AV500 spectrometer. NMR samples were run in the indicated solvents and were referenced internally. All chemical shift values are quoted in ppm and coupling constants quoted in Hz. The following abbreviations are used for the multiplicity of NMR signals: br = broad, s = singlet, d = doublet, dd = doublet of doublets, dt = doublet of triplets, t = triplet, td = triplet of doublets, ddd = doublet of doublet of doublets, tt = triplet of triplets, q = quartet, quin = quintet. Low Resolution Mass Spectra (MS) [EI, CI, ESI and FAB] and High Resolution Mass Spectra (HRMS) [EI, CI and ESI] were recorded by the Imperial College Department of Chemistry Mass Spectroscopy Service. X-ray crystal structures were obtained at Imperial College London Crystallographic Service (Dr Andrew White) using an OD Xcalibur 3 diffractometer or an OD Xcalibur PX Ultra diffractometer. HPLC was performed on a Perkin-Elmer series 200 machine, with UV detection (215 nm).

$PhAuCl_2$·lut (80b)[43]



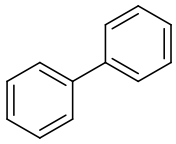
To a solution of gold(III) chloride (50 mg, 0.16 mmol) in Et_2O (2 mL) was added benzene (0.568 mL, 3.2 mmol) to give a bright yellow solution and the reaction mixture was stirred at room temperature for 2 hours. 2,6-Lutidine (0.038 mL, 0.16 mmol) was then added (white precipitate formed upon addition) and stirring was resumed for a further hour. The reaction was monitored by TLC and upon completion, the solvent was evaporated *in vacuo* and the residue was purified by flash chromatography using P.E and EtOAc gradient EtOAc 20-40% to yield product **80b** (57 mg, 79%) as a white solid: R_f 0.60 (P.E : EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (m, 3H, pyridine protons), 7.1-7.44 (m, 5H, PhH), 3.08 (s, 6H, CH_3); ^{13}C NMR (400 MHz, $CDCl_3$) δ 24.6, 124.6, 127.0, 129.1, 130.1, 131.8, 139.9 157.3; HR-MS (FAB): m/z=452.0201, calculated for $C_{13}H_{15}N^{35}Cl_2Au$ $(M+H)^+$: 452.0247; m/z=454.0274, calculated for $C_{13}H_{15}N_{35}Cl^{37}ClAu$ $(M+H)^+$: 454.0218.

The side product, Cl_3Au2,6-lut was also isolated as a white solid: R_f 0.30 (P.E : EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (t, J = 7.7 Hz, 1H, pyridine proton), 7.45 (d, J = 7.7 Hz, 2H, pyridine proton), 3.11 (s, 6H, CH_3).

General procedure for the synthesis of biaryls

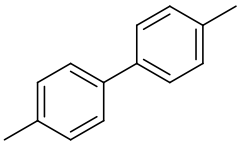
To a solution of gold(III) chloride (50 mg, 0.16 mmol) in Et_2O (2 mL), the arene (3.2 mmol) was added and the reaction mixture was stirred at room temperature for 2 hours. Lithium hydroxide (72 mg, 1.6 mmol) was added followed by hydrogen peroxide solution in water (0.146 mL, 1.6 mmol). Upon addition of hydrogen peroxide the reaction turned black with heat and gas evolution. The reaction was stirred at room temperature for 10 minutes under open atmosphere. The solvent was then evaporated *in vacuo* and the resulting black solid was extracted from EtOAc, washed with water (2 x 10 mL) and brine (2 x 10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography (P.E and EtOAc gradient EtOAc 0-10%) yielded the desired biaryl.

Biphenyl (56)[22]



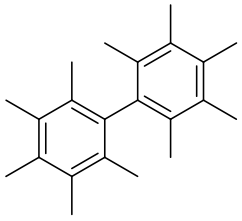
White solid (11 mg, 44% based on Au): R_f 0.70 (P.E : EtOAc, 95:5); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (dd, J = 8.3 Hz and 1.0 Hz, 4H), 7.45 (t, J = 7.8 Hz, 4H), 7.36 (t, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$,) δ 141.5, 128.9, 127.2, 127.3; EI-MS *m/z* 154 (M+).

4,4'-Dimethylbiphenyl (95)[30]



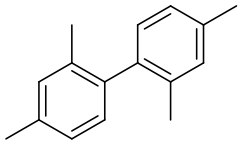
White solid (29 mg, 50%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 8.0 Hz, 4H), 7.25 (d, J = 8.0 Hz, 4H), 2.40 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2, 136.8, 129.4, 126.7, 21.1; EI-MS *m/z* 182 (M+).

Decamethylbiphenyl (96)



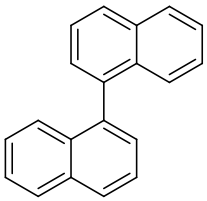
Purification from the starting material was not achieved and the product was only characterised by EI-MS *m/z* 294 (M+).

2,2',4,4'-Tetramethylbiphenyl (97)[54]



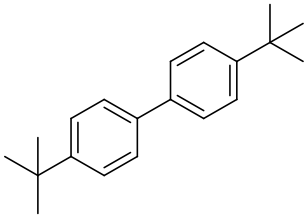
White solid (12 mg, 18%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (m, 6 H), 2.33 (s, 6 H), 2.00 (s,6 H); EI-MS *m/z* 210 (M+).

1,1'- Binaphthyl (98)[30]



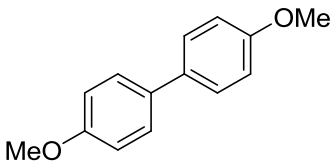
White solid (20 mg, 50%): R_f 0.41 and 0.43 (P.E : CH_2Cl_2, 95:5); ^{1}H NMR was far too complicated the product was mainly analyzed by EI-MS *m/z* 254 (M+).

4,4'-Di-^{t}butylbiphenyl (99)



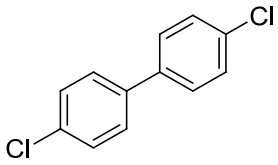
White solid (32 mg, 38%): R_f 0.48 (P.E); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J = 8.5 Hz, 4H), 7.44 (d, J = 8.5 Hz, 4H), 1.35 (s, 18H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 149.9, 138.2, 126.6, 125.6, 34.5 31.4; EI-MS *m/z* 266 (M+).

4,4'-Dimethoxybiphenyl (100)[5]



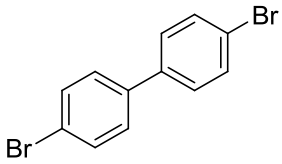
White solid (32 mg, 46%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J = 8.8 Hz, 4H), 6.87 (d, J = 8.8 Hz, 4H), 3.74 (s, 6H); ^{13}C NMR (100 MHz , $CDCl_3$) δ 158.5, 133.3, 127.6, 114.1, 55.3; EI-MS *m/z* 214 (M+).

4,4'-Dichlorobiphenyl (102)[5]



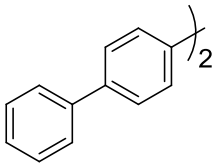
White solid (15 mg, 42%): R_f 0.49; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J = 8.4 Hz, 4H), 7.39 (d, J = 8.4 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 133.7, 129.0, 128.2; EI-MS *m/z* 223 (M+).

4,4'-Dibromobiphenyl (103)[29]



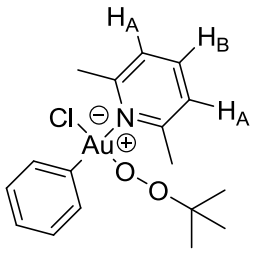
White solid (13 mg, 26%): R_f 0.42; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J = 8.4 Hz, 4H), 7.31 (d, J = 8.4 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$,) δ 138.9, 132.0, 128.5, 121.9; EI-MS *m/z* 312 (M+).

***p*-Quaterphenyl (115)**



White solid (8 mg, 17%): R_f 0.60 (P.E); EI-MS *m/z* 306 (M+).

PhAuCl(OO^{t}Bu)·lut (128)



To a solution of gold(III) chloride (50 mg, 0.16 mmol) in Et_2O (2 mL) benzene (0.568 mL, 3.2 mmol) was added and the reaction mixture was stirred at room temperature for 2 hours. Then LiOH (0.072 g, 3.2 mmol) was added followed by a 70% ww solution of ^{t}BuOOH in water (0.457 ml, 3.2 mmol). The reaction turned black with heat and gas evolution. After 5 minutes of stirring at room temperature, 2,6-lutidine (0.084 ml, 0.0352 mmol) was added and the reaction mixture was stirred for another 5 minutes. Repeated purification by chromatography gave the product in (0.029 g, 72%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (t, J = 7.7 Hz, 1H, H_B), 7.45 (m, 2H, H_A), 7.25-7.10 (m, 5H, Ph), 3.22 (s, 6H, CH_3); 1.03 (s, 9H, ^{t}Bu).

Alternatively, PhAuCl(OO^{t}Bu)·lut **(128)** was prepared by treating $PhAuCl_2$·lut (**80b**) (50 mg, 0.11 mmol) in Et_2O (2 mL) with a 70% ww solution of ^{t}BuOOH in water (0.163 ml, 1.1 mmol) followed by LiOH (48 mg, 1.1 mmol). The reaction mixture was stirred at room temperature for 5 minutes, the solvent was evaporated *in vacuo* and a crude ^{1}H NMR of the

crude mixture was taken, which, when compared to the spectrum of **128** from the previous procedure, showed signs of the desired product.

PhAuCl(OO^{t}Bu)·lut **(128)** (10 mg, 0.02 mmol) was then dissolved in Et_2O (0.5 mL) and treated with a qualitative amount of TFA (99%) at room temperature. After stirring for 2 hours, the solvent was removed *in vacuo* and ^{1}H NMR of the crude mixture revealed the formation of biphenyl (**56**). Following purification by flash chromatography (P.E and EtOAc gradient EtOAc 0-10%), biphenyl (**56**) was obtained as a white solid (0.002 g, 56%).

Forcing the reductive elimination

To a solution of gold(III) chloride (50 mg, 0.16 mmol) in Et_2O (2 mL) was added benzene (0.568 mL, 3.2 mmol) to give a bright yellow solution and the reaction mixture was stirred at room temperature for 2 hours. A qualitative amount of *tert*-butylphenyllithium (prepared by the author) was added and following stirring for 5 minutes at room temperature, the reaction mixture was quenched with distilled water and extracted from Et_2O (3 x 5 mL). The solvent was removed *in vacuo* and TLC analysis showed a single spot at R_f 0.70 (P.E : EtOAc, 95:5). The crude mixture was subjected to GC-MS which revealed four different compounds: 4,4'-Di-*tert*-butylbiphenyl (**99**) (59%), 4-*tert*-butylbiphenyl (**133**) (37%), 1-bromo, 4-*tert*-butyl benzene and *tert*-butyl benzene (yields calculated from GC-MS data).

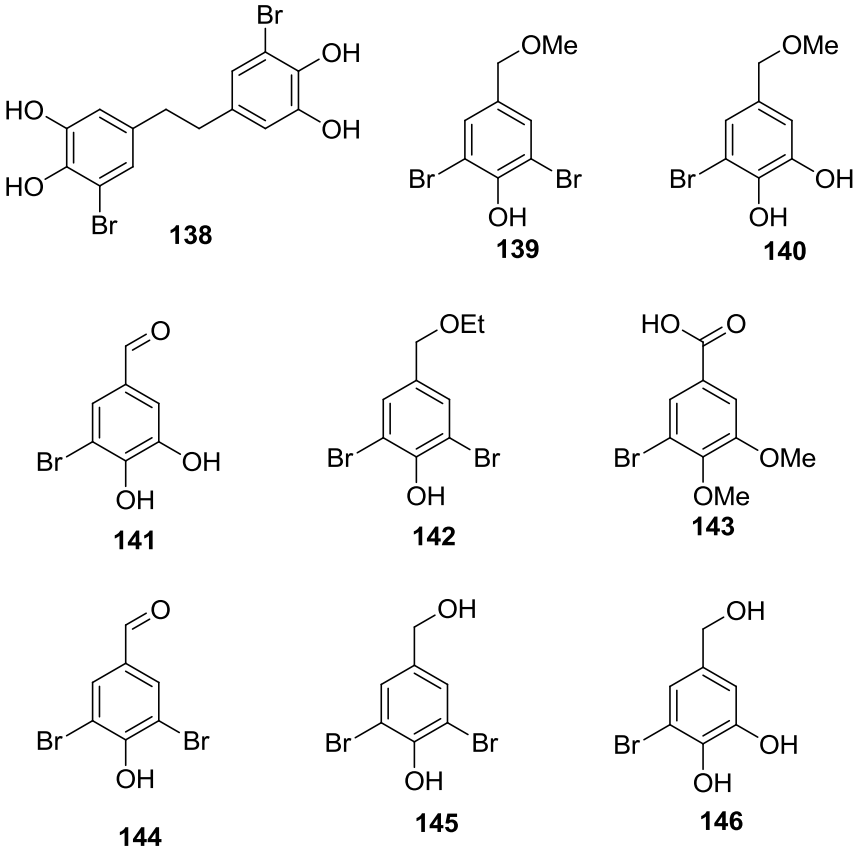
To a solution of PhAuCl$_2$·lut (**80b**) (72 mg, 0.16 mmol) in Et_2O (2 mL) was added a qualitative amount of *tert*-butylphenyllithium (prepared by the author) and following stirring for 5 minutes at room temperature, the reaction mixture was quenched with distilled water and extracted from Et_2O (3 x 5 mL). The solvent was removed *in vacuo* and TLC analysis showed a single spot at R_f 0.70 (P.E : EtOAc, 95:5). The crude mixture was subjected to GC-MS which revealed four different compounds: 4,4'-Di-*tert*-butylbiphenyl (**99**) (47%), 4-*tert*-butylbiphenyl (**133**) (23%), 1-bromo, 4-*tert*-butyl benzene and *tert*-butyl benzene (yields calculated from GC-MS data).

Chapter 2:

Total Synthesis of the Marine Metabolite (±)-Polysiphenol *via* Highly Regioselective Intramolecular Oxidative Coupling

1. INTRODUCTION

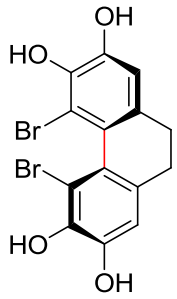
A number of naturally occurring bromophenols have been isolated from *Polysiphonia urceolata*, a red alga of the family of Rhodomelaceae,[55-62] belonging to the order of Ceramiales and found in Chinese coastal waters.[63-66] The first investigation dates back to 1966,[67] and the period from then until 1980 saw a rise in activity with bromophenols **138-146** all being isolated.



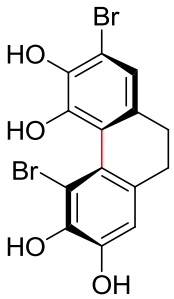
Activity studies of these compounds showed them to be antioxidants,[68-69] presumably due to the existence of the phenol/catechol moieties, which can form stabilised radicals on the oxygen atoms.

More recently, further bromophenols have been isolated from *Polysiphonia urceolata*. These, although containing the signature bromophenol moiety, were different to those previously isolated: a unique 9,10-dihydrophenanthrene skeleton (**147**,[56] **148**[56] and **149**[70]) or an unusual 5,7-dihydrodibenzo[*c*,*e*]oxepine structural feature (**150**). Finally, Urceolatol, a novel bromobenzaldehyde dimer which has been isolated, also has a rigid structure and has been determined to be (5*R*,10*R*)-2,7-dibromo-3,8-dihydroxy-5,10-dimethoxyl-5,10-dihydrochromeno[5,4,3-cde]chromene (**151**).[56] Compounds **147**, **148** and **149** were isolated

as single enantiomers due to restricted rotation about the aryl-aryl bond. Their absolute configurations were established on the basis of their CD spectrum as compared to a literature report, and were found to be *R*.[70]



147



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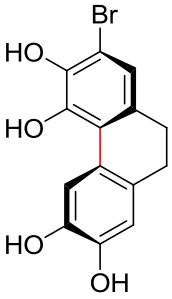
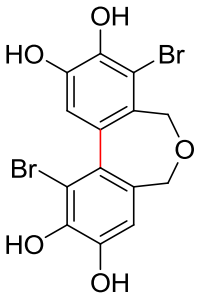


149



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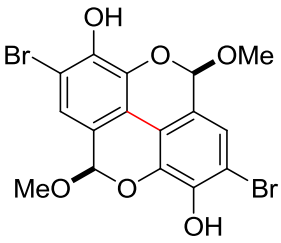


151

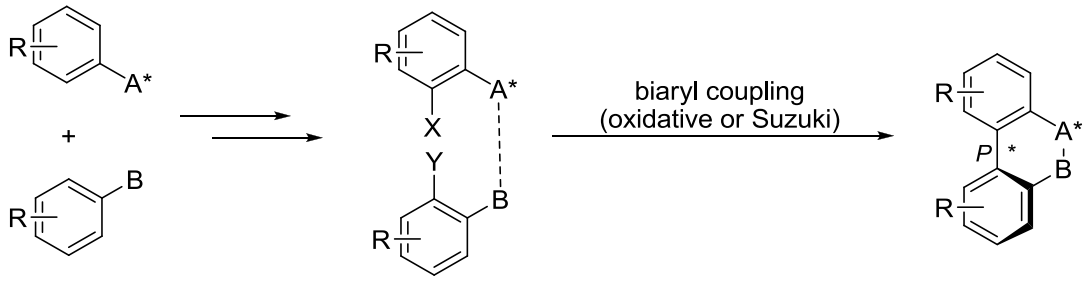
The biaryl motif is an important substructure of many bioactive and functional molecules and has been the focus of synthetic chemists for over one hundred years.[71] It is also found in many medicinally important compounds such as antibiotics,[72] anti-inflammatories and anti-hypertensives, as well as anticancer, antifungal and infertility treatments.[73] The motif is also an integral part of many agrochemicals, liquid crystal displays and has been incorporated into molecular switches and motors.[74]

Although a large number (certainly more than 1000) of biaryls equipped with a configurationally stable axis have so far been isolated from nature, and despite their other remarkable bioactivities, only a small portion of these chiral compounds has as yet been prepared by atroposelective total synthesis.[75] These have been divided into two categories: non-bridged and bridged. The existence or nonexistence of a bridge has a profound influence on the configurational stability of the biaryl and, in addition, on the method to be applied for the asymmetric induction at the axis. Since polysiphenol is a bridged biaryl, only the synthesis of these types of compounds shall be discussed within.

The rapidly increasing interest in axially chiral biaryls has led to the development of a broad variety of highly successful methods for their atroposelective construction, of which, however, only few have so far been applied to the total synthesis of natural products. The most dominant one is the atropodiastereoselective biaryl coupling reactions of chirally modified arenes, either with internal asymmetric induction (stereogenic element remains in the target molecule) or by applying an artificial chiral bridge.

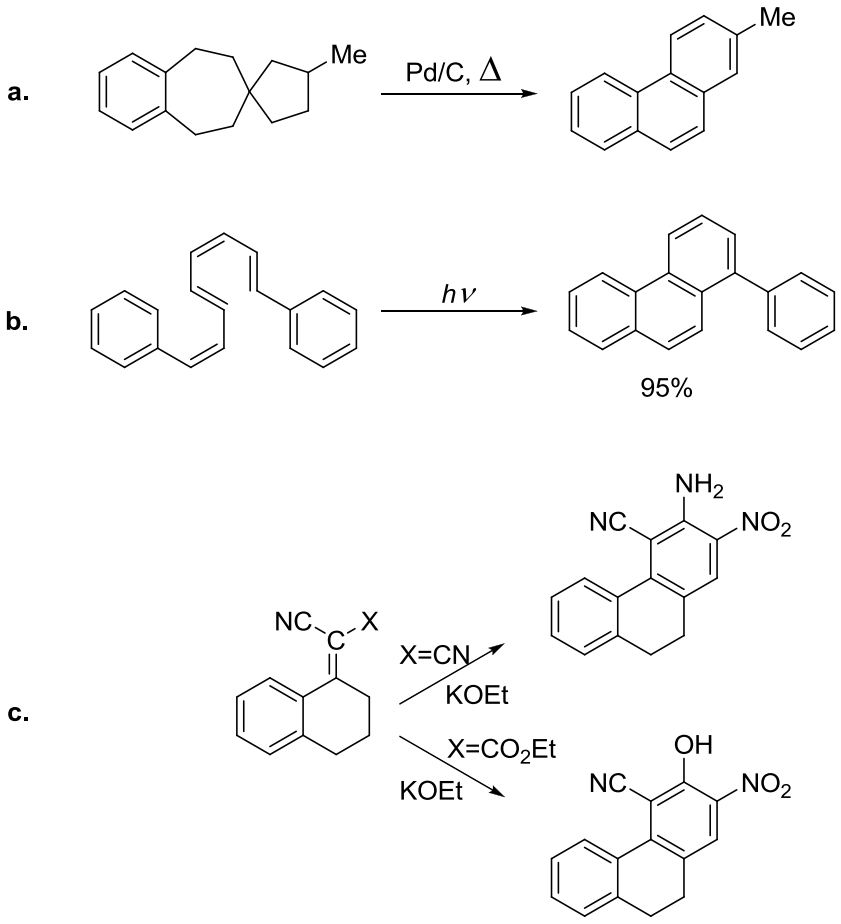
Atropodiastereoselective biaryl coupling with internal asymmetric induction, is well suited if the target biaryl itself bears additional stereogenic centers in the proximity of the axis. This concept has mainly been applied to the total synthesis of bridged natural biaryls. The optimum protocols for the construction of the aryl-aryl single bond, here generalized as 28 f (*P*)-29, depend on the actual system, and both oxidative procedures and Suzuki type couplings have been successful.

Atropodiastereoselective Biaryl Couplings with an Intrinsic Chiral Auxiliary



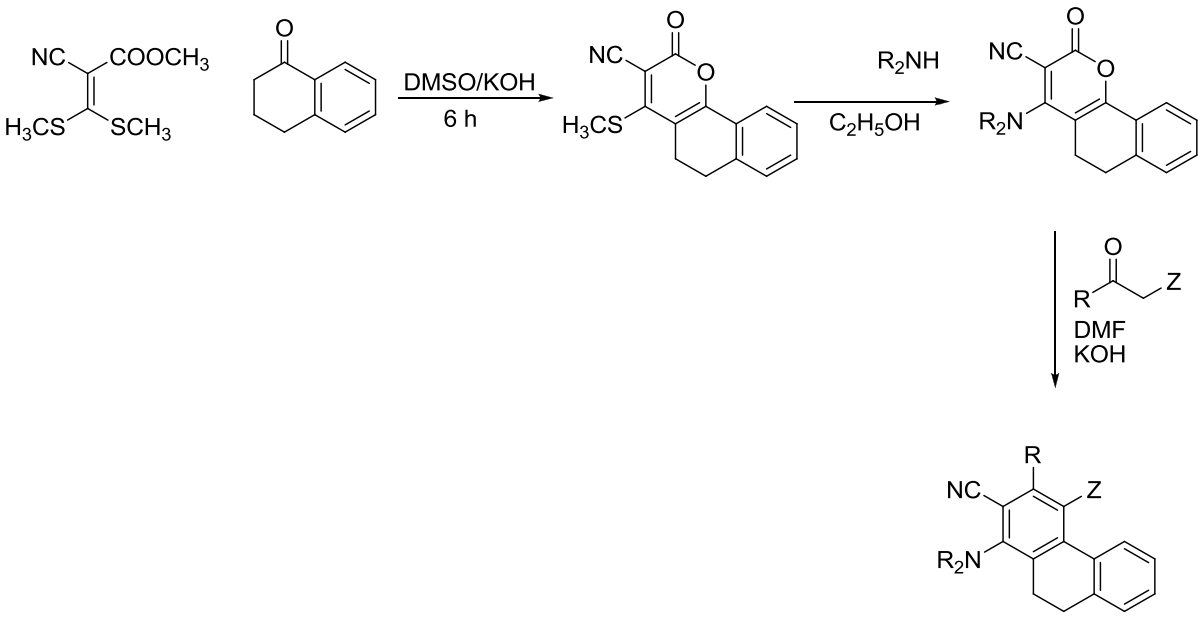
All these three auxiliary-based atropodiastereoselective coupling strategies permit access to axially chiral biaryls in reliably good to high chemical and optical yields. Restrictions are the required functionality patterns and the additional steps necessary to attach and remove the chiral auxiliary.

Numerous methods have been reported for the synthesis of non-chiral phenanthrenes[76] and dihydrophenanthrenes[77-84] through ring annulation[85] and intermolecular[86-88] and intramolecular[89-90] cyclization. A majority of the procedures have certain limitations of accessibility of the precursors, require multiple steps, have harsh reaction conditions, are incompatible with the presence of a functional group, have relatively low overall yield, and lack well-defined regiocontrol elements.



2,2'-Disubstituted biphenyls have been used as precursors for the preparation of phenanthrenes by intramolecular condensation,[86-88] cycloisomerization,[91] metal-catalyzed rearrangement of alkene-alkynes,[92] and photocyclization[93] depending upon the functionality present on the biphenyl moiety. Palladium-catalyzed cyclization of arynes with alkynes,[92] is also an alternative route for the synthesis of phenanthrenes. Recently, 9,10-disubstituted phenanthrenes[94] have been prepared from palladium-catalyzed reaction of *o*-substituted aryl iodides and diphenyl or alkylphenylacetylenes. These are also prepared through the ring transformation of methyl 6-aryl-4-methylsulfanyl- 2*H*-pyran-2-one-3-carboxylates by 1-tetralone in 59-67% yields.[80,95]

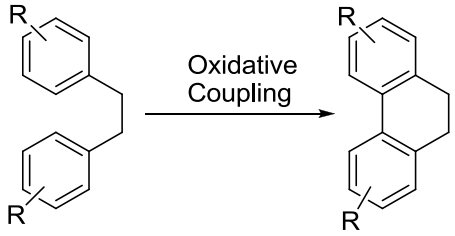
An efficient and novel approach to the synthesis of highly congested 3-alkyl-, 4-alkyl-, 3-aryl-, 3,4-dialkyl-, 4-alkyl-3-aryl-, and 3,4-diaryl-9,10-dihydro-1-*sec*-aminophenanthrene-2-carbonitriles has been delineated through the base-catalyzed ring transformation of 5,6-dihydro-2-oxo-4-*sec*-amino-2*H* benzo[*h*]chromene-3-carbonitrile by carbanion derived *in situ* from various ketones in moderate to good yields[96] (Scheme 53).



Scheme 53: Base-catalyzed ring transformation of 5,6-dihydro-2-oxo-4-*sec*-amino-2*H* benzo[*h*]chromene-3-carbonitrile by carbanion derived *in situ* from various ketones

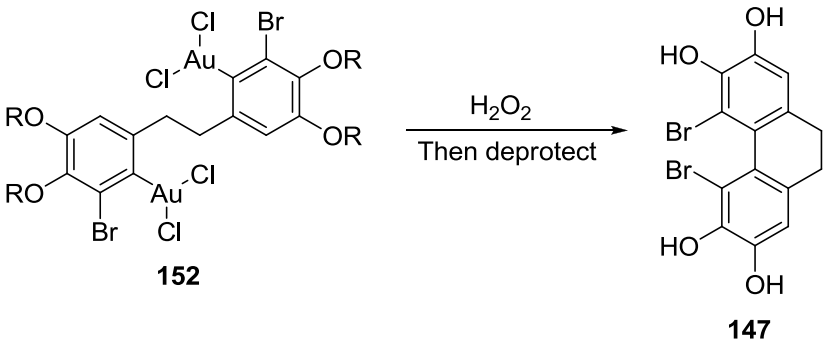
1.1 Retrosynthesis

To the best of our knowledge, there has been no synthesis of any of the above highlighted dihydrophenanthrene bromophenols to date and we have targeted polysiphenol **147**. The synthetic approach we were to take would be one where the ethylene chain would be constructed first and then the two ends of the molecule would be stitched together by formation of the aryl-aryl bond (Scheme 54). This would be achieved by the formation of an appropriate dihydrostilbene, C-C double bond hydrogenation and subsequent oxidative coupling of the two unfunctionalised arenes.



Scheme 54

Due to the inherent symmetry in polysiphenol **147**, earlier research on gold(III)-mediated aryl homocoupling could also potentially be utilised, where the biaryl bond would be formed by the oxidative coupling of the gold-adduct **152**; the prerequisite for this though, is that the gold(III) attaches itself to the aryl ring *via* electrophilic substitution (Scheme 55)

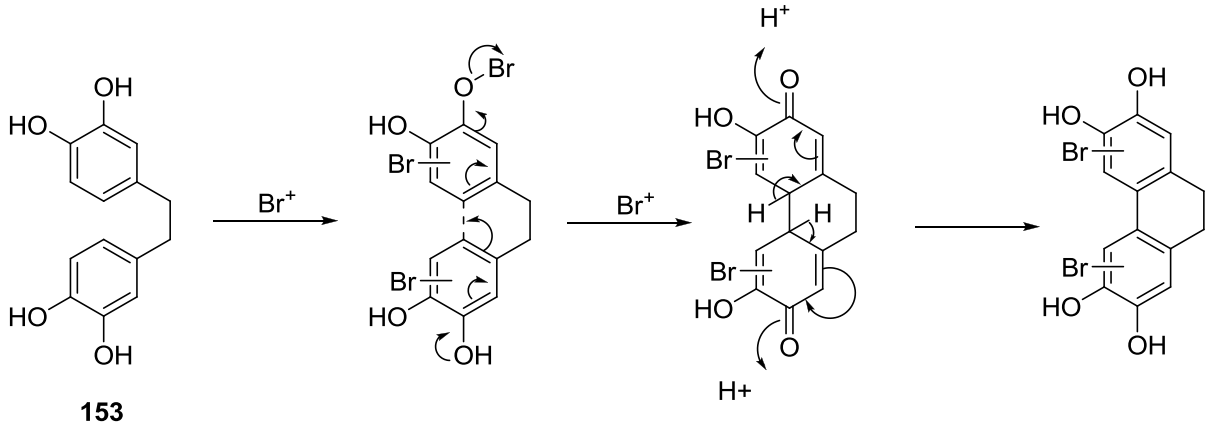


Scheme 55: Exploiting previously developed methodology in the biaryl coupling step

These methods would, of course, lead to the desired product, polysiphenol **147**, being synthesised racemically.

Our original approach was biomimetic in design. Due to the fact that (±)-polysiphenol exists in a marine environment where there is an abundance of Br^+ ions (converted from Br^- by the

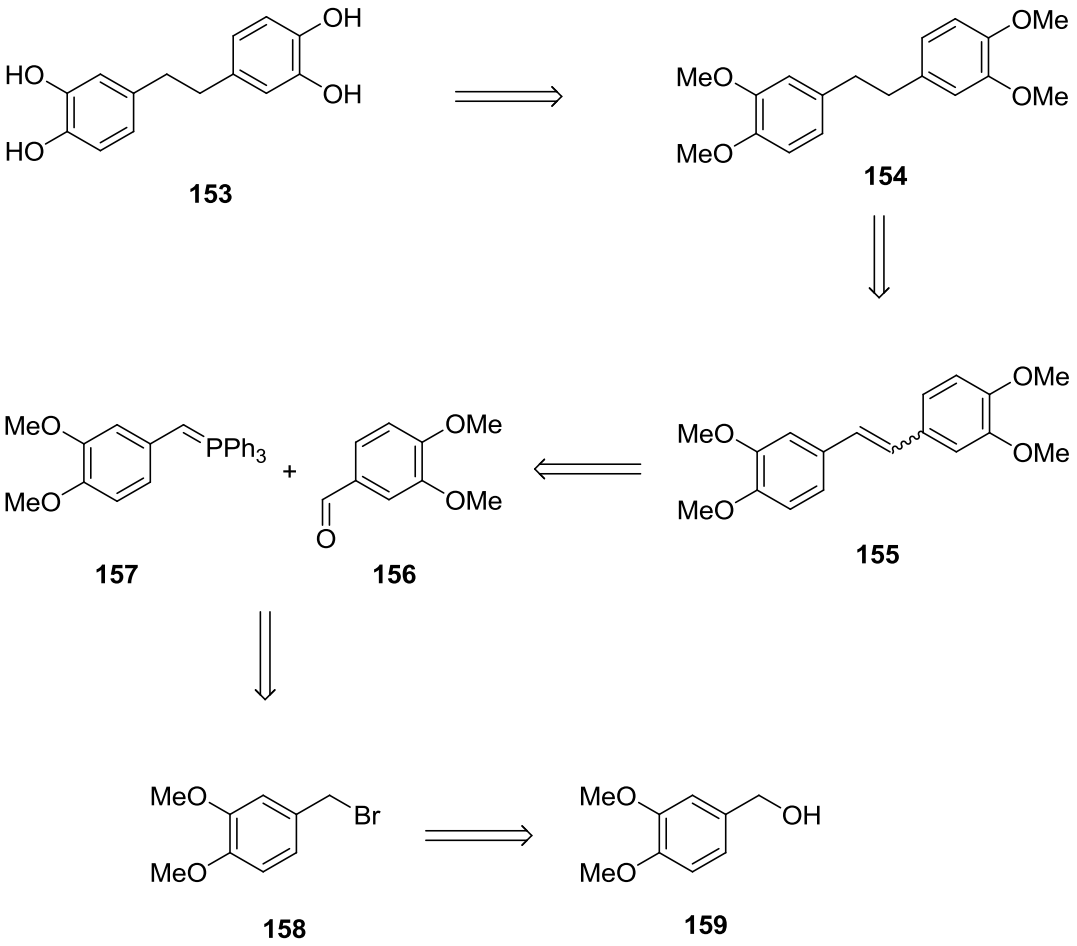
enzyme Vanadium Bromoperoxidase),[97] we conjectured that the biogenesis was oxidative coupling of dihydrostilbene **153** which upon exposure to a source of electrophilic bromine would brominate in the ring as well as form the desired aryl-aryl bond. This tactic seemed logical as there have been numerous reports in literature of dihydrostilbenes undergoing oxidative phenolic coupling.[98] We also envisaged that bromination of the phenyl rings and oxidative coupling would occur first (step 1, Scheme 56) thus preventing complete aromatisation to the corresponding phenanthrene. Even though there is no literature precedent for Br^+ mediated oxidative phenolic coupling, this strategy seems appealing.



Scheme 56: Proposed one-step bromination/oxidative coupling

Dihydrostilbene **153** can be retrosynthetically disconnected into two components: the methoxy-protected alcohol **159** and the methoxy-protected aldehyde **156** (Scheme 57), both of which are cheap and commercially available. Alcohol **159** could also be prepared by $NaBH_4$ reduction of the aldehyde in quantitative yield. This results in the proposed synthesis being highly convergent, and it relies only on one inexpensive starting material.

We also considered that this strategy would allow us flexibility should the formation of the aryl-aryl bond *via* bromination fail, as other means of oxidative coupling[99] could be employed on the same substrate. The C-C bond could be constructed by the use of hypervalent iodine and opens up the possibility of using gold(III) substitution-oxidation method to construct the biaryl motif.



Scheme 57: Proposed retrosynthetic route

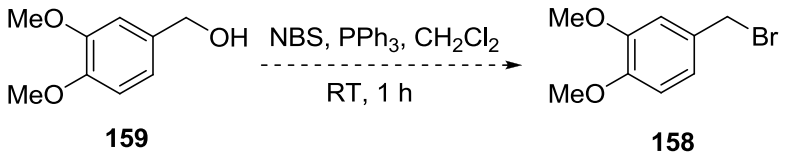
Accordingly, alcohol **159** will be converted to phosphonium ylide **157** *via* primary bromide **158**, and then reacted with aldehyde **156** in a Wittig reaction to give alkene **155**. This is in turn will be reduced by hydrogenation to the symmetric alkane **154**. The methoxy groups will finally be removed to give the desired dihydrostilbene **153** and the proposed biomimetic bromination will be tested.

2. RESULTS AND DISCUSSION

2.1 Formation of the Wittig salt

*2.1.1 From alcohol **159** to bromide **158***

This reaction was carried out by the author in the Process Development Department of GSK Tonbridge. The aim was to synthesise large quantities of the tetrol precursor **153** *via* a facile, cheap route. 3,4-Dimethoxyphenyl)methanol (**159**) was chosen as the starting material as it is commercially available and inexpensive (Scheme 58)



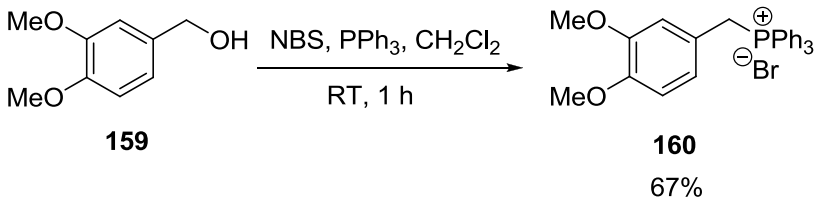
Scheme 58: Apple bromination

According to literature procedures,[100] it would be possible to convert benzyl alcohol **159** to bromide **158** *via* an Appel bromination reaction using NBS and PPh_3 in CH_2Cl_2 at room temperature.

The literature procedure was followed and to a solution of alcohol **159** in CH_2Cl_2, 1.1 equivalents of PPh_3 was added followed by 1.2 equivalents of NBS and the reaction mixture was stirred for one hour at room temperature. The progress of the reaction was monitored by HPLC. After one hour it had not reached completion but a single product was observed. It was further stirred for an additional 12 hours with constant monitoring by HPLC, but starting material could still be observed. Then an additional 0.6 equivalents of PPh_3 was added followed by 0.6 equivalents of NBS and stirring was resumed for 5 hours at the end of which starting material was still present. The reaction was finally driven to completion by addition of a total of 2.2 equivalents of PPh_3 and 2.1 equivalents of NBS, to give a single product as observed by HPLC monitoring. After reduction of the reaction volume by evaporation, the mixture was passed through a silica gel column (eluent, CH_2Cl_2) to remove PPh_3O, yielding a white solid as the product. When the crude mixture was submitted to ^1H NMR analysis, the spectrum did not match that of literature as it was missing the expected resonance for the benzylic protons α- to the bromine at δ_H 4.5 ppm. Instead a singlet at δ_H 2.71 ppm appeared. LC-MS analysis instead showed a molecular ion consistent with phosphonium salt **160** rather than that of the desired bromide. Since this was the desired product of the next reaction, it

was isolated and recrystallised from isopropyl alcohol to give phosphonium salt **160** in 67% yield (Scheme 59).

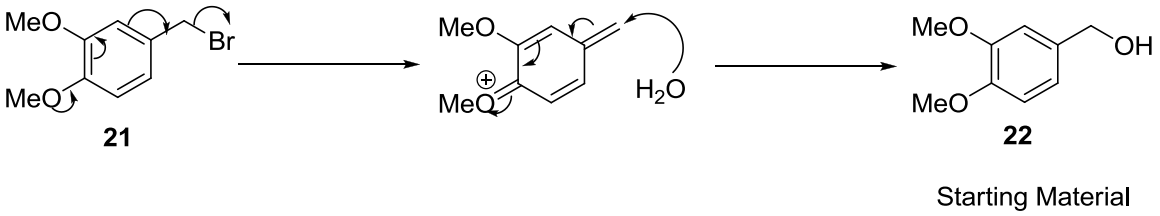
Upon careful examination of the reaction, it came to our attention that the solvent used for HPLC analysis was a 50:50 mixture of water and methanol. It was therefore rationalised that upon monitoring the reaction by HPLC analysis, bromide **158** was initially formed in the reaction but was reconverted on the HPLC column to alcohol **159**, hence was not observed. Subsequently the reaction was further pushed by addition of excess NBS and PPh_3 which resulted in bromide **158** being converted to phosphonium salt **160**. We envisage that should the reaction not have been monitored by HPLC analysis, bromide **158** would have been isolated as in the literature, however, since the phosphonium salt was the target, this reactivity was taken advantage of to reduce the number of steps in the synthesis.



159 **160** 67%

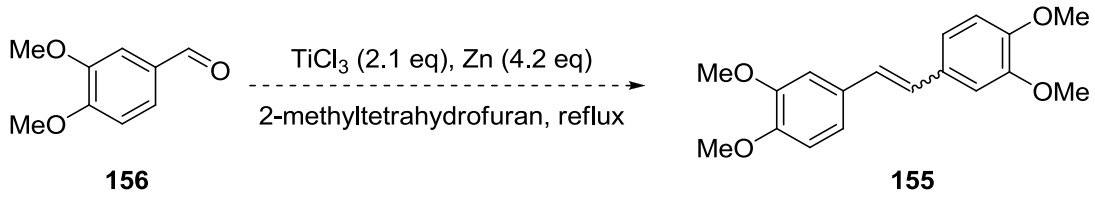
Scheme 59: Formation of phosphonium salt

Whilst this reaction was under investigation, other methods of bromination were also attempted.[101-102] Use of CBr_4/PPh_3 or PBr_3 in CH_2Cl_2 solution both yielded starting material despite the addition of more than one equivalents of reagent. Originally, it was also thought that the desired bromide **158** was decomposing due to the strong activating effect of the methoxy moieties on the benzene ring and then subsequently attacked by water to regenerate the starting material (Scheme 60). To eliminate this possibility, extra care was taken to use dry reagents and the solvent was degassed. However the same observations as before were made despite the fact that the literature preparation that was followed did not involve an aqueous work-up. However, upon careful examination, we established that the problem lay with the chosen method of analysis, the HPLC, which, as previously mentioned, caused the decomposition of the desired bromide product **158** upon exposure to the eluent system.



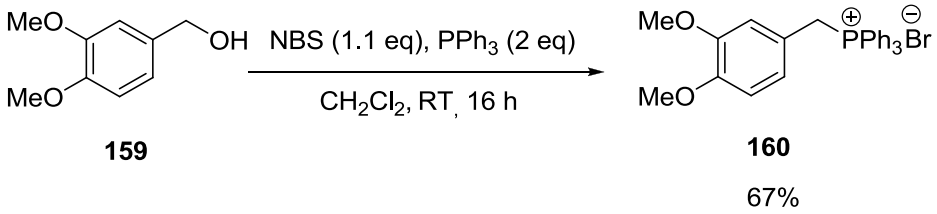
Scheme 60: Decomposition of desired product by water

Whilst investigation of the reaction to form bromide **158** was undergoing, alternatives to the proposed Wittig synthesis were also examined. McMurry coupling was considered.[103] It is the reaction between two aldehydes (or ketones) to give an alkene using $TiCl_4$ as a reagent. The reaction was attempted using a literature procedure with $TiCl_3$ and Zn metal[104-105] (Scheme 61) and monitored by HPLC and LC-MS which only showed only decomposition of aldehyde **156** and unreacted starting material. Hence this method was abandoned.



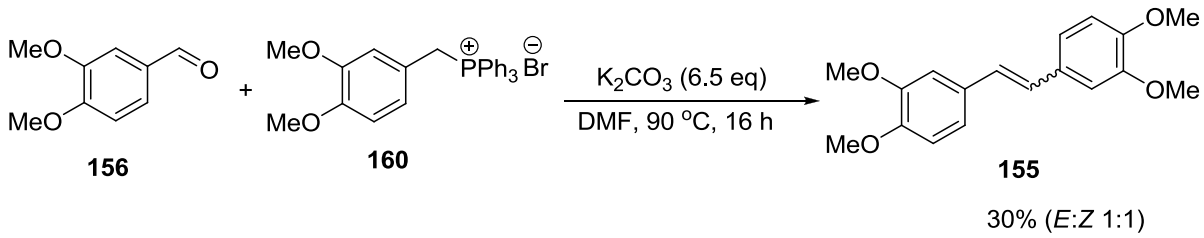
Scheme 61: McMurry coupling

After the product of the initial reaction with alcohol **159** and excess PPh_3 and NBS was characterised and found to be the phosphonium salt **160**, the reaction was scaled up (5 g) and it was found that addition of 2 equivalents of PPh_3 and 1.1 equivalents of NBS, drives the reaction to completion (67% yield after recrystallisation, Scheme 62).



Scheme 62: One-step synthesis of phosphonium salt from alcohol

*2.1.2 From Wittig salt **23** to alkene **18***

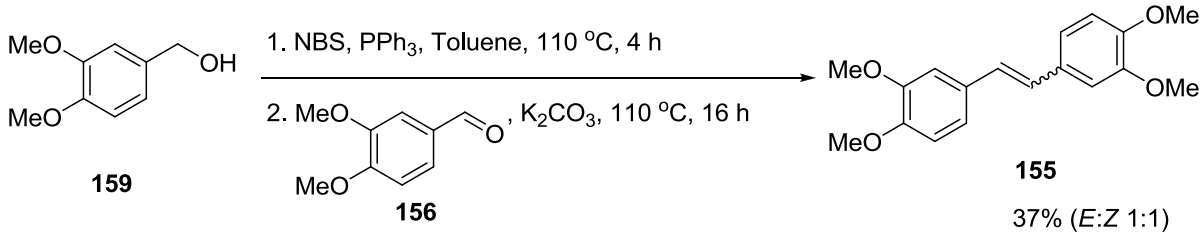


Scheme 63: Wittig reaction

The first attempt at a Wittig reaction was following a literature procedure[106] which involved mixing the phosphonium salt **160** and benzaldedyde **156** (Scheme 63) at room temperature in DMF, adding K_2CO_3 and heating under reflux at 90 ^oC. The progress of the reaction was monitored by HPLC and upon complete consumption of the starting material, the solvent was evaporated *in vacuo* and an aqueous work-up was carried out to yield a light brown solid which was then recrystallised from IPA to furnish the product, 1,2-bis(3,4-dimethoxyphenyl)ethene (**155**) as a 1:1 mixture of the *E* and *Z* double bond isomers (observed by ^1H NMR), as white crystals in 30% yield. The whole procedure was not further optimised as it was later telescoped (*vide infra*).

*2.1.3 From alcohol **22** to alkene **18** in one pot*

Having carried out the first two transformations of alcohol **159** to phosphonium salt **160** *via* bromide **158** and then phosphonium salt **160** to stilbene **155**, it was noted that a benzylic bromide is not formed but rather the phosphonium salt **160** is formed directly. NBS and PPh_3 are the common reagents, and the by-product of the reaction for the formation of the phosphonium salt **160** (Ph_3PO) is unreactive and could be carried through to the next step. For this reason it was decided to try and telescope the reactions and combine all three steps into a one-pot procedure (Scheme 64).



Scheme 64: One pot alkene synthesis from alcohol

It was decided to use a high boiling solvent which would dissolve both the starting materials and the reagents at high temperature and after testing several solvents toluene was chosen as the most appropriate. Hence a one-pot reaction was attempted where the steps were carried out sequentially with no work-up or purification. The reaction conditions previously discovered for the formation of the phosphonium salt were used, the only difference being that the reaction was heated under reflux to both push the reaction to completion faster (4 hours required rather than 24 hours) and to also solubilise the NBS. The progress of the reaction was monitored by ^{1}H NMR and upon completion the reaction mixture was cooled to room temperature and aldehyde **156** followed by the K_2CO_3 were added. Heating under reflux was resumed overnight to yield the alkene product **155** as a light brown solid after aqueous work-up. The product was purified by recrystallisation from isopropyl alcohol to furnish 1,2-bis(3,4-dimethoxyphenyl)ethene **155** (1:1 mixture of the *E* and *Z* double bond isomers as observed by ^{1}H NMR) as white crystals in 35% yield over three steps. This procedure was also carried out on a 150 mmol scale and 16.6 g (37%) of the desired product could be obtained.

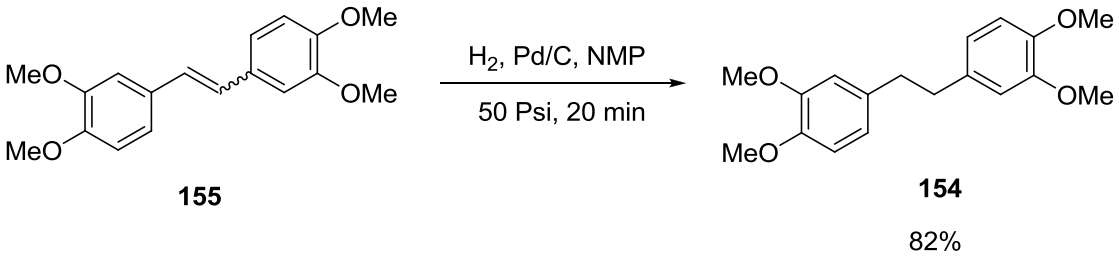
2.2 Alkene Hydrogenation

*2.2.1 Hydrogenation of alkene **155** to alkane **154***

The hydrogenation of *E/Z*-stilbene **155** into dihydrostilbene **154** was also carried out by the author at GSK Tonbridge where access to a high pressure hydrogenator was possible. The hydrogen uptake was electronically monitored and the reaction was stopped upon consumption of the starting material.

Literature procedure[106] suggested a 50:50 mixture of methanol and ethanol as the solvent for the reaction but we found that the starting material was only sparingly soluble in ethanol and

methanol. Alternatively, NMP was chosen as a solvent as it allowed for the reaction to be carried out at high concentration. The drawback with using NMP is that, much like DMF and DMSO, it is a high boiling solvent and requires an aqueous work-up to be completely removed, whereas other more volatile solvents can be removed *in vacuo*. Several test reactions were carried out on 50 mg scale, screening a range of Pd/C catalysts with different Pd loadings on carbon, as well as different amounts used in the reaction (Table 17).



Scheme 65: Alkene hydrogenation

Entry	Pd loading on C	Amount of catalyst used (w/w)	Reaction time	Yield (%)[a]
1	5%	0.1	1 hour	60
2	10%	0.05	40 min	73
3	20%	0.03	30 min	70
4	5%	0.5	20 min	80
5	10%	0.5	15 min	71

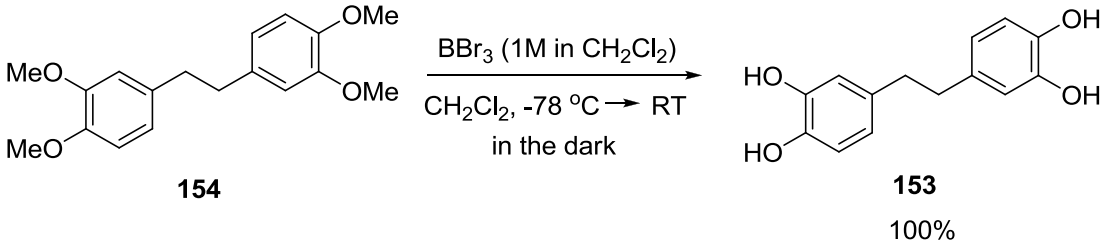
a. Following aqueous work-up and removal of solvent *in vacuo.*

Table 17

The best result was obtained when using a 5% Pd on carbon loading catalyst, with 0.5 wt used (Entry 4). The reaction reached completion within 20 minutes and following aqueous work-up and recrystallisation from isopropyl alcohol, the desired product, 1,2-bis(3,4-dimethoxyphenyl)ethane (**154**) was obtained as white crystals in 80% yield. The hydrogenation of ethene **155** was performed on a 55 mmol scale (16.6 g) affording the pure product **154** in 82% yield (13.7 g) after recrystallisation.

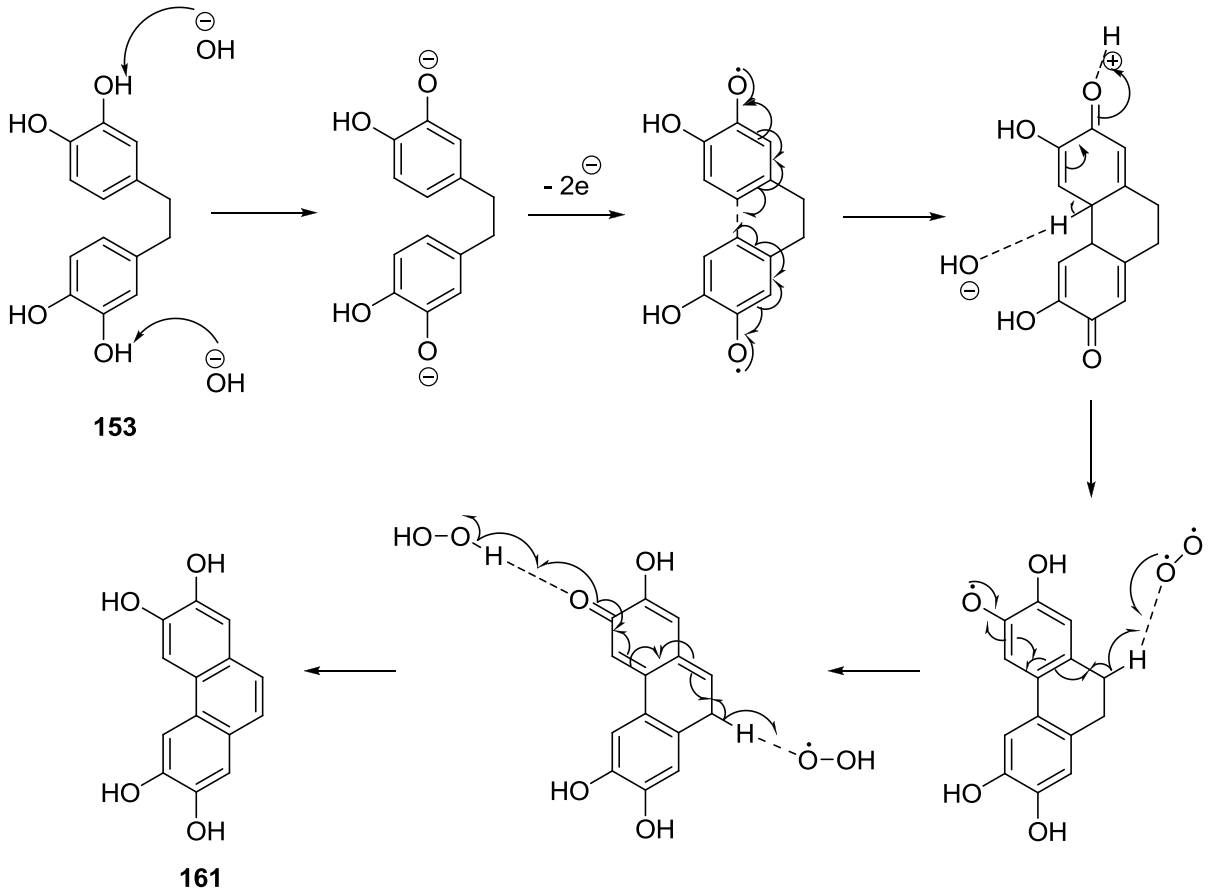
2.3 Methoxy Deprotection

*2.3.1 From tetramethoxy **154** to tetrol **153***



Scheme 66

For the deprotection of **154** to dihydrostilbene **153** a standard methoxy deprotection procedure was originally followed,[107] whereby the starting material **154** was dissolved in CH_2Cl_2, cooled down to -78 ^oC and then 4 equivalents of BBr_3 (1M in CH_2Cl_2) was added slowly over a period of 30 minutes. The BBr_3 (1M in CH_2Cl_2) solution was kept away from light by wrapping both the flask and the syringe used in the addition, in aluminium foil, in order to avoid decomposition of BBr_3. The progress of the reaction was monitored by HPLC and only starting material and formation of a single product were observed. Upon completion (3 hours), the reaction mixture was quenched by pouring into a cold NaOH (aq) solution and extracted with ethyl acetate. However, after this work-up procedure, HPLC analysis on the crude product mixture showed only a new peak at a different retention time than that observed prior to work-up. LC-MS analysis revealed that the product had a mass which was 4 amu lower than that of the desired product. The ^1H NMR spectrum, unexpectedly displayed three aromatic resonances (singlets at δ_H 7.76, 7.29 and 7.10 ppm, rather than the two expected doublets and one singlet), contained no signals for the benzylic protons which are normally expected in the δ_H 2-3 ppm region. The compound that had been formed was therefore identified as phenanthrene **161** and indicates that the desired product **153** is evidently sensitive to the conditions of the work-up procedure and upon work-up it both oxidatively couples and has undergone coupling and aromatisation to phenanthrene **161** (Scheme 67).

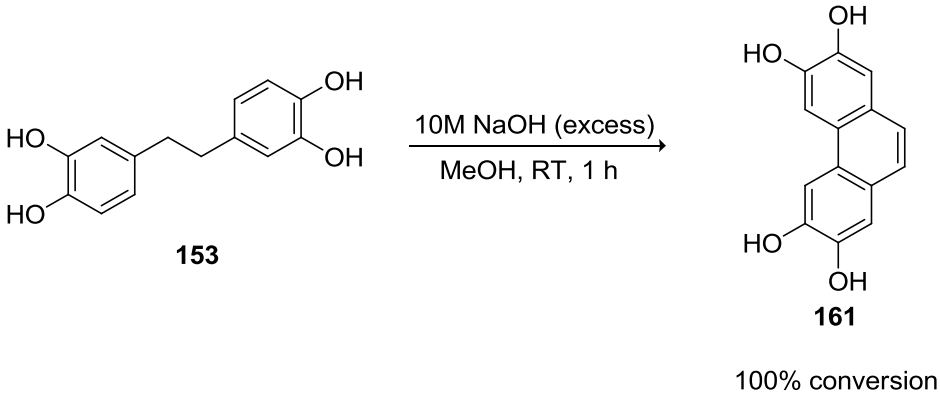


Scheme 67: Proposed mechanism justifying aromatisation upon methoxy-deprotection

Our theory was confirmed by carrying out a control demethylation reaction of tetramethoxystilbene **154** in deuterated chloroform, quenching with deuterated methanol and submitting directly the solution to ^{1}H NMR and LC-MS analysis, which showed exclusive formation of the desired product, 1,1'-ethane-1,2-diyldibenzene-3,4-diol (**153**). The deprotection was accordingly performed on larger scale (13.0 g) and following quenching with methanol, non-basic aqueous work-up and purification by recrystallisation from isopropyl alcohol the desired product **153** was obtained as an off-white solid in 100% yield.

Unequivocal proof to the instability of 1,1'-ethane-1,2-diyldibenzene-3,4-diol (**153**) to base under oxidising conditions was obtained by exposing it to aqueous NaOH solution open to the atmosphere. Thus dihydrostilbene **153** was dissolved in methanol and excess 10M NaOH solution was added with vigorous stirring. Upon addition of the base, the mixture immediately turned blue/green in colour, much like in the case of the original work-up.

Following work-up with ethyl acetate and water, the ^{1}H NMR spectrum of the crude mixture revealed 100% conversion to the fully aromatised product **161**, as expected (Scheme 68).



Scheme 68

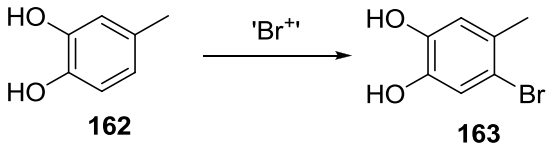
2.4 Brominations

With dihydrostilbene **153** in hand, we were now faced with three possible options: bromination prior to cyclisation, bromination after cyclisation and bromination to cause cyclisation. Potential issues with all possible routes could be identified: both bromination prior to and after cyclisation ran into the risk of bromination at the wrong position on the ring, and for the latter strategy it was feared that the cyclisation might suffer from the same problem as demethylation; aromatisation to the evidently thermodynamically stable phenanthrene.

2.4.1 Bromination prior to cyclisation

*2.4.1.1 Brominations of tetrol **153***

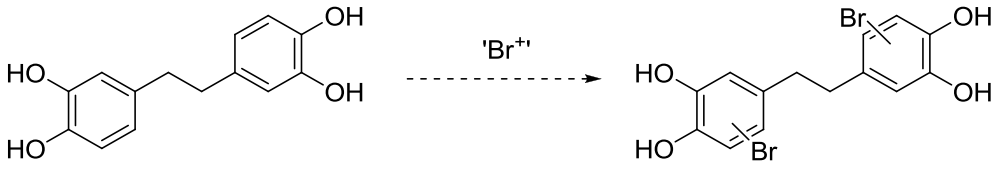
Based on the directing effects of the substituents on the aromatic ring, it was speculated that electrophilic bromination of dihydrostilbene **153** would direct to the undesired, 6- position on the benzene ring. Mataka and co-workers[108] previously reported the bromination of aromatic compound **162** with the same substitution pattern as our tetrol with regiocontrol at the undesired position to give bromide **163** (Scheme 69).



162 **163**

Scheme 69

Despite this concern it was decided to investigate the reaction of dihydrostilbene **153** with different sources of electrophilic bromine. The first problem that was faced with was that of solubility. 1,1'-Ethane-1,2-diyldibenzene-3,4-diol (**153**) is insoluble in most solvents with the exception of the alcohols such as ethanol, methanol and isopropyl alcohol; the latter however, are incompatible with electrophilic bromine reagents (they are potential oxidised). Several test reactions were attempted using 2, 4 and 10 equivalents of *N*-bromosuccinimide (NBS) and 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TBCO), with, and without catalytic amount of *tetra*-methylguanidine (TMG), in CH_2Cl_2, 1,2-DCE, water and toluene, the last three being heated at reflux. However, in all cases, only starting material could be observed by ^{1}H NMR after work-up. Reactions were also carried out in deuterated CH_2Cl_2, methanol and DMSO in order to monitor the progress by ^{1}H NMR. However only starting material was observed in all cases (Table 18). It was speculated that this result was due to the poor solubility of tetrol **153**.



153

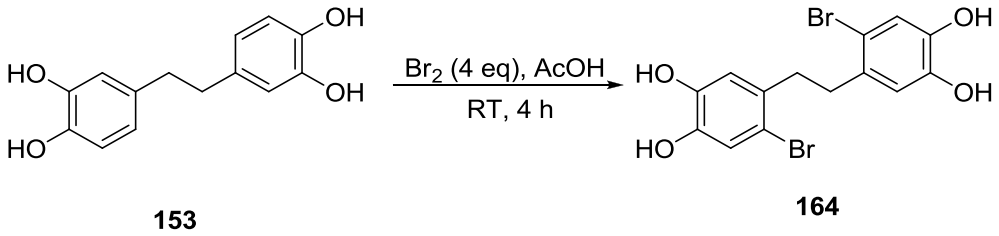
Entry	Solvent	Conditions	NBS	TBCO	TMG	Result
1	CH_2Cl_2	RT	1 eq.	-	5 mol %	**153**
2	CH_2Cl_2	RT	2 eq.	-	5 mol %	**153**
3	CH_2Cl_2	RT	3 eq.	-	5 mol %	**153**
4	$CDCl_3$	RT	3 eq.	-	5 mol %	**153**
5	MeOH	RT	3 eq.	-	5 mol %	**153**
6	DMSO	RT to reflux	3 eq.	-	5 mol %	**153**
7	CH_2Cl_2	-60 ^oC to reflux	-	1 eq.	-	**153**
8	CH_2Cl_2	-60 ^oC to reflux	-	2 eq.	-	**153**
9	CH_2Cl_2	-60 ^oC to reflux	-	3 eq.	-	**153**
10	$CDCl_3$	RT	-	1 eq.	-	**153**
11	MeOH	RT	-	2 eq.	-	**153**
12	DMSO	RT to reflux	-	3 eq.	-	**153**

Table 18

The use of molecular bromine in acetic acid, in which dihydrostilbene **153** is soluble, was then exploited. Use of 2 equivalents of bromine at room temperature resulted in an inseparable mixture of brominated compounds consisting of symmetric and unsymmetric brominated products, as judged by singlets and multiplets in the benzylic region (δ_H 2-3 ppm) of the ^{1}H NMR spectrum of the crude reaction mixture.

Having established that dihydrostilbene **153** reacts with molecular bromine in acetic acid, a series of test reactions to obtain controlled regioselective bromination were carried out. Seeing as two equivalents of Br_2 gave a mixture of compounds it was envisaged that the reaction had not gone to completion and addition of further equivalents of bromine would push the reaction to a single product.

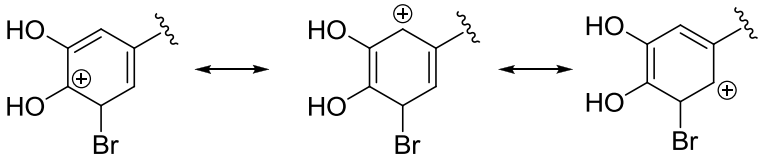
Addition of four equivalents of molecular bromine gave a single product (Scheme 70). This was identified as bromotetrol **164** as two bromide atoms could be deduced from the characteristic 1: 2: 1 isotopic pattern at *m/z* 476: 478: 480 in the MS spectrum, seven signals were observed in the ^{13}C NMR spectrum and two singlets in the ^{1}H NMR spectrum, confirming that it was symmetrical. The position of the Br atoms on the aromatic rings was established by the lack of any *meta*-coupling between the aromatic protons in the ^{1}H NMR spectrum placing them *para* to each other.



153 **164**

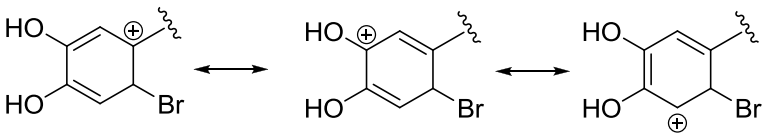
Scheme 70: Exclusive 6- bromination (undesired position)

This experiment confirmed our speculation that bromination of tetrol **153** would directed to the 6- position of the aromatic ring and it can be rationalised by inspection of the resonance forms of the Wheland intermediate (Figure 6). Substitution at the 6- position is favoured as it gives rise to a resonance form with tertiary carbocation character, whereas substitution at the 5- position does not. The tertiary carbocation character, evidently dominates the substitution entirely and no signs of other products are observed; the reaction proceeds with 100% regiocontrol.



Two secondary and one tertiary carbocations

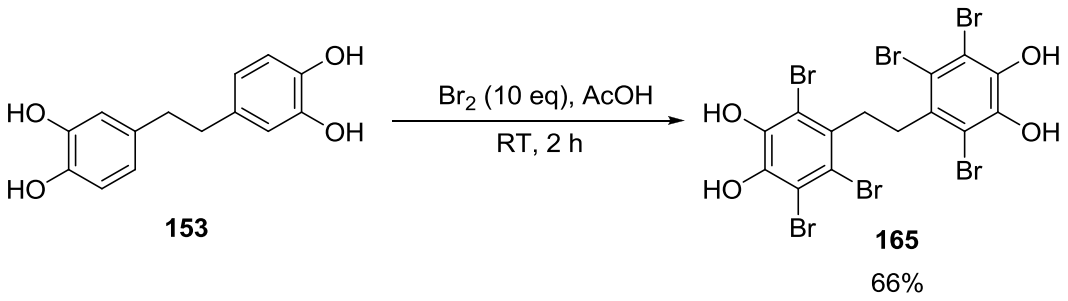
Vs



One secondary and two tertiary carbocations

Figure 6: The 6- position is preferentially brominated due to the formation of a tertiary carbocation

The use of excess bromine (6-10 equivalents) in acetic acid to brominate tetrol **153** resulted in exhaustive substitution of all available aromatic positions to yield hexabromotetrol **165** as a white solid (66% yield) following evaporation of the acetic acid (Scheme 71). Hexabromotetrol **165** is itself a natural product[68] belonging to the family of *Rhodomelaceae*, and to the best of our knowledge, has not been synthesised before. It is used as a food preservative and its isolation/extraction as well as its use as such has been patented in China.[109]

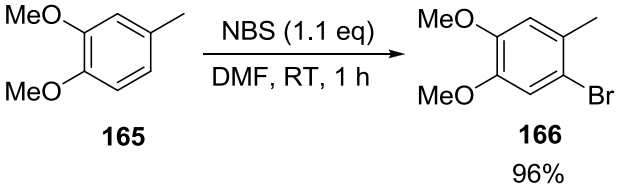


Scheme 71

Clearly, bromination of dihydrostilbene **153** could not be the route to (±)-polysiphenol; despite overcoming the solubility problem, bromination proceeds with 100% regiocontrol at the undesired 6- position.

*2.4.1.2 Bromination of tetramethoxy compound **154***

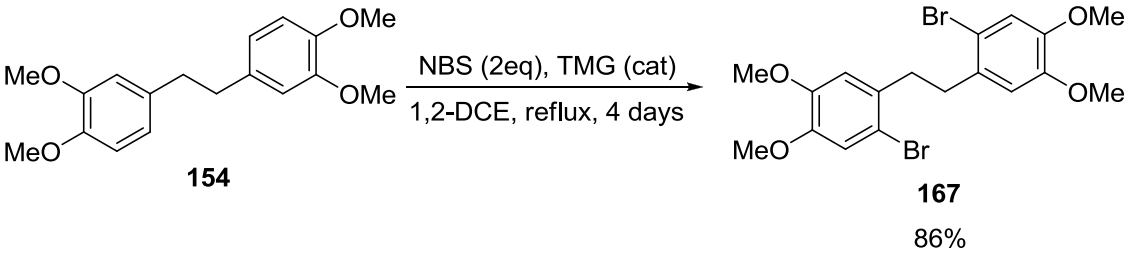
From our findings on the bromination of the tetrol, it was speculated that bromination of methoxybenzene **154** would yield similar results, where substitution will be once again dominated by tertiary carbocation character in the Wheland intermediate. Indeed, as part of their synthesis of both enantiomers of photoberberines, Fukuda and co-workers[110] reported the bromination of 1-methylbenzene-3,4-dimethoxytoluene **165** with NBS in DMF at room temperature to proceed with complete regiocontrol to give bromomethoxytoluene **166** in 96% yield (Scheme 72).



Scheme 72

However, the bromination of tetramethoxy compound **154** was attempted for a number of reasons: to compare the reactivity of dihydrostilbene **153** to that of tetramethoxy compound **154**, to attempt crystallisation of the methoxy compound in order to confirm the position of the bromine atom by X-ray crystallography, and finally to confirm our theory.

Bromination[111] of methoxybenzene **154** was attempted with two equivalents of NBS, catalytic TMG in 1,2-DCE and heated under reflux for 4 days (Scheme 73). A single product was observed and this was identified as 1,1'-ethane-1,2-diylbis(6-bromo-3,4-dimethoxybenzene) **167** (86% yield).



154 **167** 86%

Scheme 73

Dibromide **167** was recrystallised from a mixture of ethyl acetate, methanol and petroleum ether (40-60 ^{o}C) (83% yield after recrystallisation) and X-ray crystallography, the results of which verified the position of the bromine atoms, at the 6-positions (Figure 7). It is also apparent from inspection of the X-ray structure of **167**, that the dimethoxy groups lie co-planar to the aromatic rings.[111] It is possible that this enforced conformation leads to steric blocking of the 2- and 5- positions of the aromatic ring (*vide infra*).

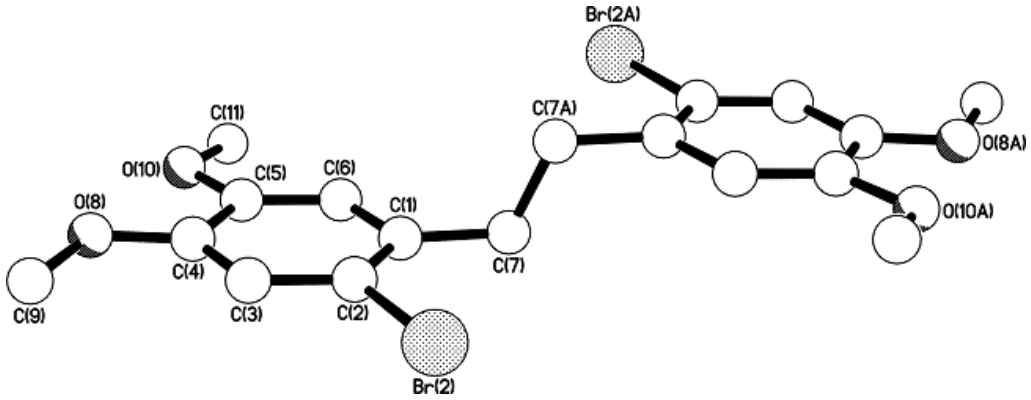
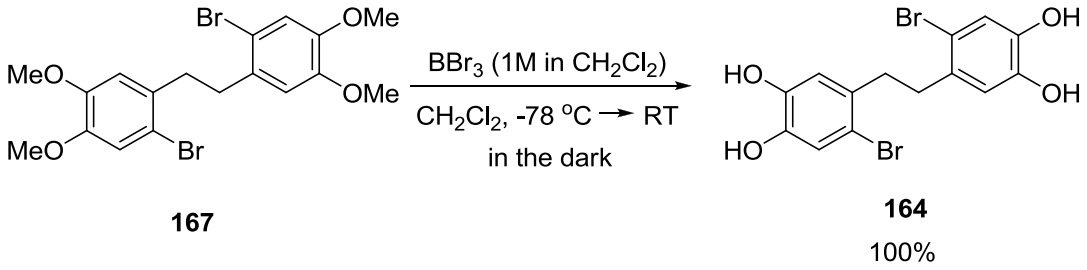


Figure 7: X-ray structure of 1,1'-Ethane-1,2-diylbis(6-bromo-3,4-dimethoxybenzene) (**167**)

Bromomethoxybenzene **31** was subjected to demethylation using BBr_3 in CH_2Cl_2 to furnish bromotetrol **27**. The spectra of which were compared to the product of the bromination of tetrol **16**, in order to confirm the position of the bromine atoms and were found to be identical (Scheme 74).



167 **164**

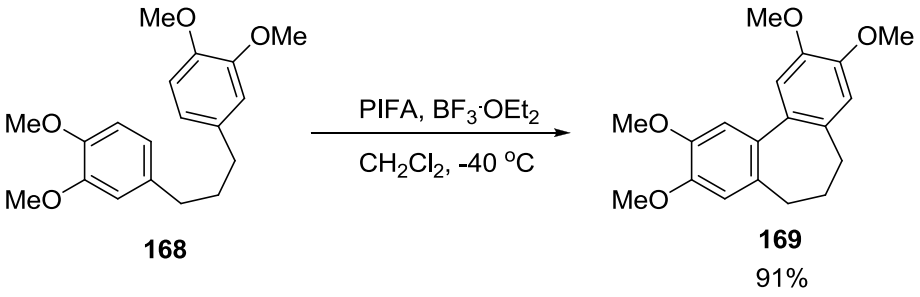
100%

Scheme 74

2.4.2 Biaryl coupling

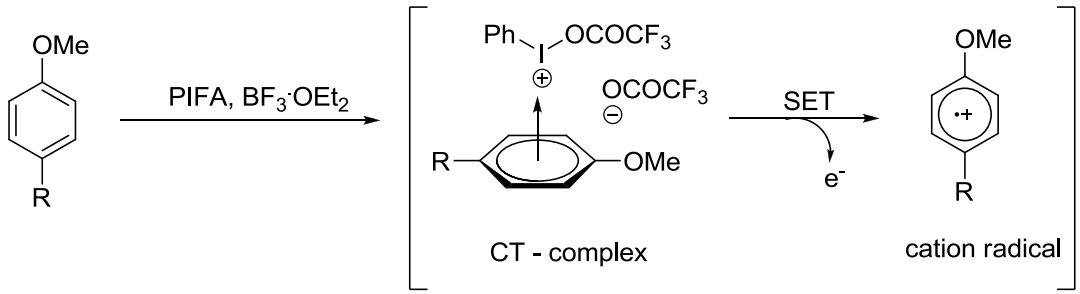
Having failed to introduce the bromine atoms at the desired position, we turned our attention to the possibility of introducing the bromine substituent following aryl coupling.

In the literature,[99] there has been precedent of oxidative coupling being achieved by the use of hypervalent iodine reagents (specifically PIFA in conjunction with boron trifluoride etherate), on similar substrates (Scheme 75).



Scheme 75: PIFA-mediated oxidative coupling

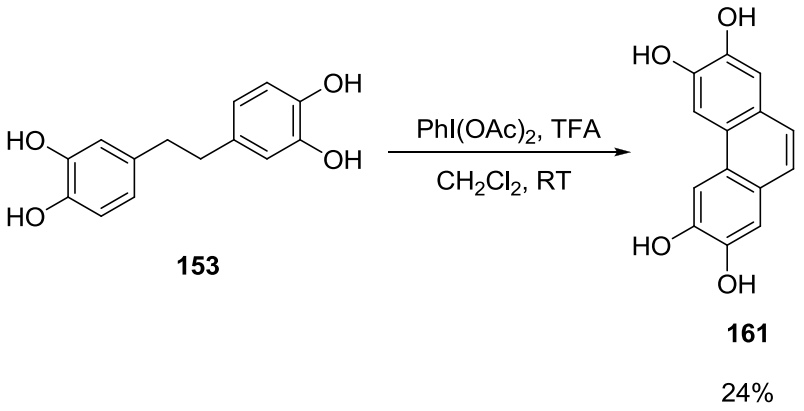
The reaction mechanism for the biaryl coupling reaction of phenol ether derivatives with PIFA possibly involves a one-electron oxidation step (Scheme 76).[112] It is assumed that the reaction of an electron-rich aromatic ring with the reagent PIFA-BF_3·OEt_2 results in the formation of a cation radical intermediate. The nucleophilic attack by the other aromatic ring on the cation radical then occurs to give the corresponding biaryl product.



Scheme 76: One-electron oxidation to form a cation radical

*2.4.3.1 Oxidative coupling of tetrol **153***

1,1'-Ethane-1,2-diyldibenzene-3,4-diol (**153**) was treated with one equivalent of diacetoxy-iodobenzene and two equivalents of trifluoroacetic acid in CH_2Cl_2 at room temperature and stirred for two hours whilst the progress of the reaction was monitored by HPLC. A new major product could be observed and upon disappearance of the starting material and basic work-up, LC-MS and ^{1}H NMR analysis of the crude mixture showed that although oxitative coupling had indeed been achieved, the desired compound had not be obtained however. Instead, we observed formation of the phenanthrene product, phenanthrene-2,3,6,7-tetrol **161** in 24% yield following purification (Scheme 77).

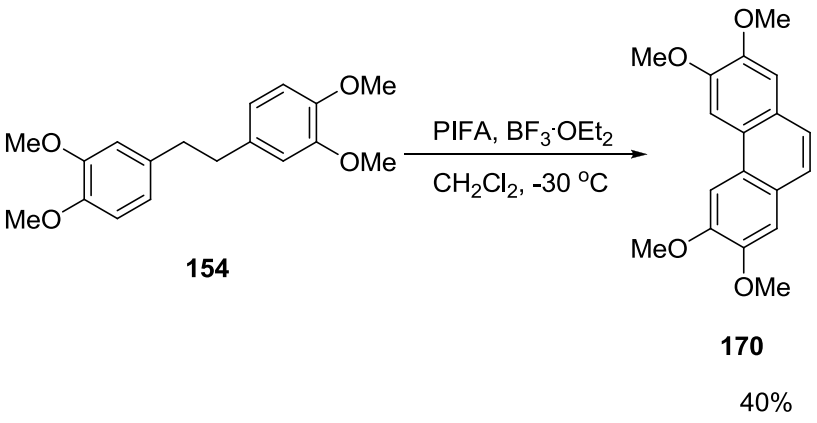


Scheme 77

This oxidative coupling-aromatisation outcome for tetrol **153** has been previously reported in the literature and 9,10-dihydrophenanthrene-2,3,6,7-tetrol has not been isolated under oxidising conditions. [101,113]

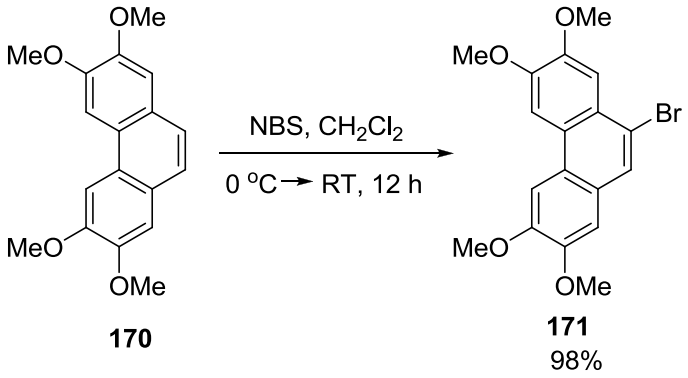
*2.4.2.2 Oxidative coupling of tetramethoxy compound **154***

We then attempted oxidative coupling of methoxybenzene **154** using 1.5 equivalents of PIFA and 1 equivalent of $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at -40 ^oC. This procedure has been previously reported in the aryl coupling of similar substrates,[114] however when trying to form a six-membered ring, aromatisation was once again reported (Scheme 78).[101] This agrees with the results of our reaction, since we observed the formation of 2,3,6,7-tetramethoxyphenanthrene **170** with complete aromatisation in 40% yield.



Scheme 78

At this stage, bromination on the fully aromatic compound was not attempted as there is literature precedent[115] of bromination on the least aromatic, alkene-like bond taking place upon treatment with NBS (Scheme 79).



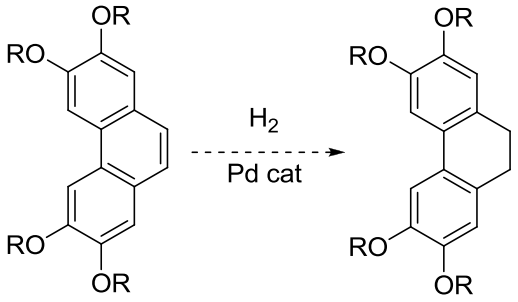
170 **171** 98%

Scheme 79[115]

It was therefore reasoned, that since that bond is the one which brominates first in **171**, it is the one with the most alkene character and as a result, it could possibly be selectively hydrogenated to yield the desired compound.

2.5 Hydrogenation

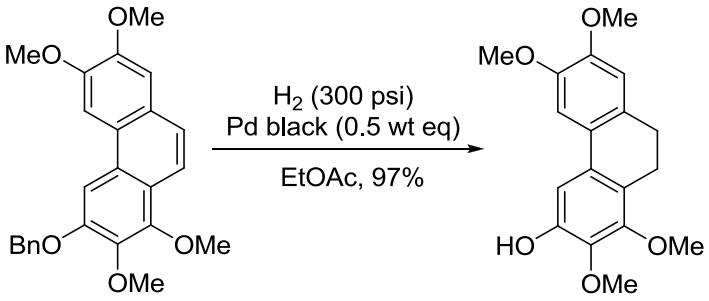
*2.5.1 Attempts to de-aromatise phenanthrenes **161** and **170***



R = H (**161**) or Me (**170**)

Scheme 80

Accordingly, hydrogenation of tetrol **161** and separately tetramethoxy compound **170** in methanol, using 5 mol % Pd/C catalyst under 1 atmosphere of hydrogen gas was attempted. The reaction was monitored by ^{1}H NMR spectroscopy. However no product was observed, even after a week of vigorous stirring at room temperature and further increased catalyst loading. A literature search revealed that similar systems required forcing conditions in order to proceed e.g. 300 psi pressure of hydrogen gas and 0.5wt equivalents of Pd black catalyst (Scheme 81).[116]



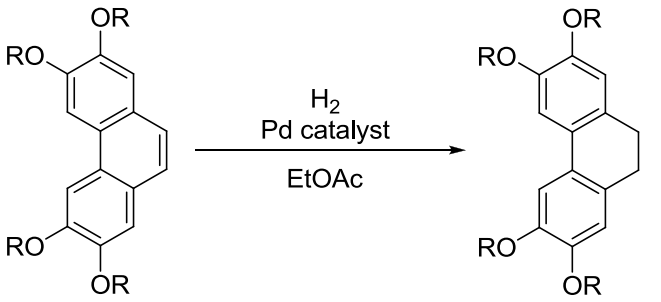
172 **173**

Scheme 81:[116] Dearomatisation *via* hydrogenation

At that stage it became obvious that hydrogenation conditions at 1 atmosphere of hydrogen gas would not succeed in reducing the aromatic bond in **161** or **170**. More forcing conditions

such as higher pressures, temperature and more active catalyst needed be employed. For that reason, the same experimentation was carried out at GSK Tonbridge where the use of high pressures and temperatures was feasible.

Attempted hydrogenation was performed on both phenanthrene-2,3,6,7-tetrol **161** and 2,3,6,7-tetramethoxyphenanthrene **170**. The different reaction conditions attempted are shown below (Table 19). All reactions were carried out in EtOAc at 0.028M concentration.



161 : R = H
170 : R = Me

174 : R = H
175 : R = Me

Entry	Starting Material	Catalyst	Loading (% wt)	Temperature (^{o}C)	Pressure (bar)	Time	Outcome
1	**161**	5% Pd/C	5	RT	5	30 min	**161** recovered
2	**161**	5% Pd/C	5	RT	5	30 min	**161** recovered
3	**161**	5% Pd/C	5	RT	10	1 hr 30 min	**161** recovered
4	**161**	5% Pd/C	50	RT	10	1 hr 30 min	**161** recovered
5	**161**	5% Pd/C	50	RT	10	1 hr 30 min	**161** recovered
6	**161**	5% Pd/C	50	RT	10	1 hr 30 min	**161** recovered
7	**161**	5% Pd/C	100	RT	10	2 hr	**161** recovered
8	**161**	5% Pd/C	100	RT	10	2 hr	**161** recovered
9	**161**	5% Pd/C	100	75	10	2 hr	**161** recovered
10	**161**	5% Pd/C	100	75	15	2 hr	**161** recovered
11	**161**	5% Pd/C	100	75	15	12 hr	**161** recovered
12	**161**	10% Pd/C	100	75	15	24 hr	**161** recovered
13	**161**	10% Pd/C	100	75	15	2 days	**161** recovered
14	**161**	10% Pd/C	100	75	15	2 days	**161** recovered
15	**161**	Pd black	100	75	15	2 hr	**174**[c]
16	**170**	5% Pd/C	5	RT	5	30 min	**170** recovered
17	**170**	5% Pd/C	100	RT	5	30 min	**170** recovered
18	**170**	5% Pd/C	100	75	15	2 hr	**170** recovered
19	**170**	10% Pd/C	100	75	15	24 hr	**170** recovered
20	**170**	Pd black	100	75	15	24 hr	**170** recovered

Table 19

These reactions were monitored originally by ^{1}H NMR and then, once the retention times of the starting material and product were established, by HPLC. All reactions yielded starting material with the exception of entry 15, where 100 mol % of Pd black catalyst was used at 15 bar and 75 ^{o}C. The reaction reached completion to the desired product **174** within 2 hours. Upon completion, the catalyst was carefully filtered off under a blanket of nitrogen gas, to avoid it catching fire, and the solvent was evaporated. However, in the time it took to perform this work-up procedure the product (**174**) re-aromatised back to the starting material. This comes as no surprise, as the starting material is by far more thermodynamically stable. It is however unfortunate, as no clean ^{1}H NMR spectrum of the desired product could be obtained and evidently this route could no longer be followed.

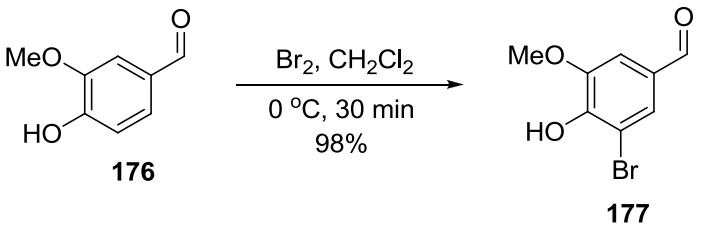
2.6 Redesigning the route: Bromine-incorporation in the first step.

From our findings so far it was established that bromine incorporation could not be achieved after the Wittig reaction, as the methylene group directs at the 6- position with 100% regiocontrol. Neither could bromine not be incorporated following oxidative coupling, since these dihydrophenanthrenes oxidise in air (Section 2.4.1).

For these reasons it was decided to investigate early bromine incorporation as means to our natural product. When designing the new route we chose to use the same method of constructing the carbon backbone. The fundamental difference would be the incorporation of bromine in the first step of the synthesis rather than later on.

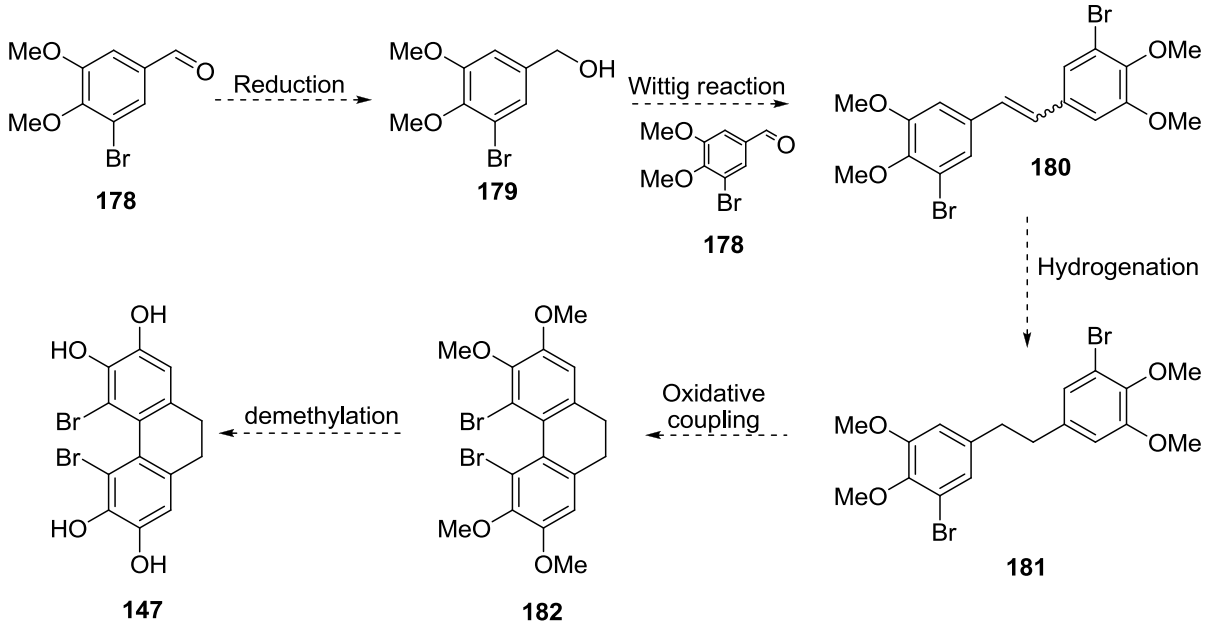
Earlier research showed that the tertiary carbocation formed during electrophilic bromination of tetrol **153**, dominates the position of substitution. So the next logical step would be to have a group at that position which will destabilise the carbocation and hence not favour its formation; this way, the substitution will be directed at the desired position.

In the literature,[117] 4-hydroxy-3-methoxybenzaldehyde **176** is brominated at the 5- position with 100% regiocontrol using molecular bromine (Scheme 82).



Scheme 82[117]

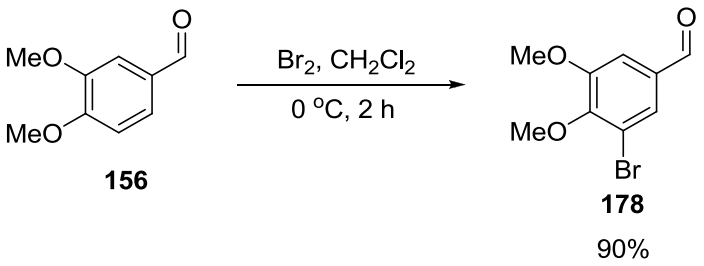
It is believed that this preferred position of substitution is not only due to the directing effects of the hydroxyl group (which will form a keto-intermediate) but rather due to the destabilising ability of the aldehyde group which directs at that position whose formation does not involve a tertiary carbocation. For this reason, it was speculated that bromination of 3,4-dimethoxybenzaldehyde **156** will yield 3-bromo-4,5-dimethoxybenzaldehyde **158** (Scheme 33), where the bromine will be at the desired position. This substrate is not only valuable to the synthesis because of the directing ability of the aldehyde, but also because the presence of an aldehyde will allow for the continuation of the synthesis following the same route as previously; Wittig reaction, hydrogenation, oxidative coupling and finally demethylation to obtain (±)-polysiphenol (Scheme 83).



Scheme 83: Retrosynthesis involving early bromide incorporation

2.6.1 Early bromide incorporation

Accordingly, 3,4-dimethoxybenzaldehyde (**156**) was dissolved in CH_2Cl_2, cooled to 0 ^oC and to that a solution of molecular bromine in CH_2Cl_2 (1 equivalent) was added. The reaction was stirred at 0 ^oC for 2 hours and following evaporation of the solvent and recrystallisation from CH_2Cl_2 and petroleum ether, the desired product, 3-bromo-4,5-dimethoxybenzaldehyde (**178**) was obtained as a white solid in 90% yield (Scheme 84).

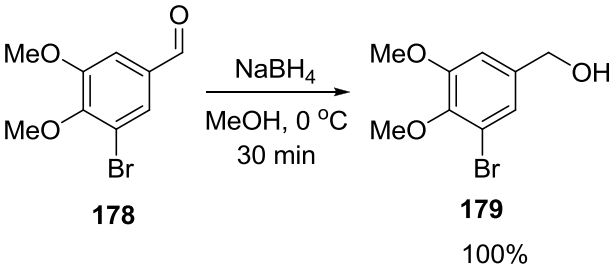


Scheme 84

The identity of the product was established by comparing its ^1H and ^{13}C NMR to that of the commercially available compound. 5-Bromo-3,4-dimethoxybenzaldehyde **176** is available for purchase from Sigma Aldrich and this meant that our sequence to the natural product was shortened by one step. However, we have still proved that bromination of the aldehyde directs at the desired position and this constitutes the first example of this reaction.

With the bromine at the correct position, the synthesis was at the stage where the previous, optimised procedure could be followed. The use of the one-pot Wittig reaction once again would be implemented in hope that bromine-incorporation would not change the reactivity.

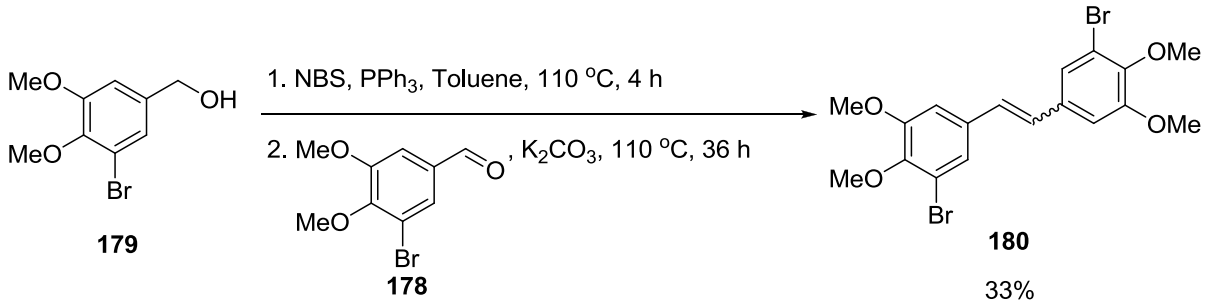
5-Bromo-3,4-dimethoxybenzaldehyde **178** was used as the starting material and a simple $NaBH_4$ reduction in methanol at 0 ^oC gave alcohol **179** in 100% yield as a colourless oil (Scheme 85).



Scheme 85

*2.6.2 One-pot Wittig reaction. From bromobenzene **179** to bromostilbene **180***

Alcohol **179** was used without further purification and was submitted to the one-pot Wittig reaction. As previously described, 6-bromo-3,4-dimethoxybenzaldehyde **178** as the coupling partner, the desired product, 1,1'-(*E)*-ethene-1,2-diylbis(5-bromo-3,4-dimethoxybenzene) (**180**) was obtained following recrystallisation from IPA (33% yield) (Scheme 86). Due to the conjugated nature of the alkene double bond, the ^{1}H NMR alkene shows as a singlet at δ_{H} 6.91 ppm rather than the standard alkene region (5-6 ppm). The aromatic protons are distinguished as they appear as doublets, with a coupling constant of 2.1 Hz, indicative of *meta*- coupling.

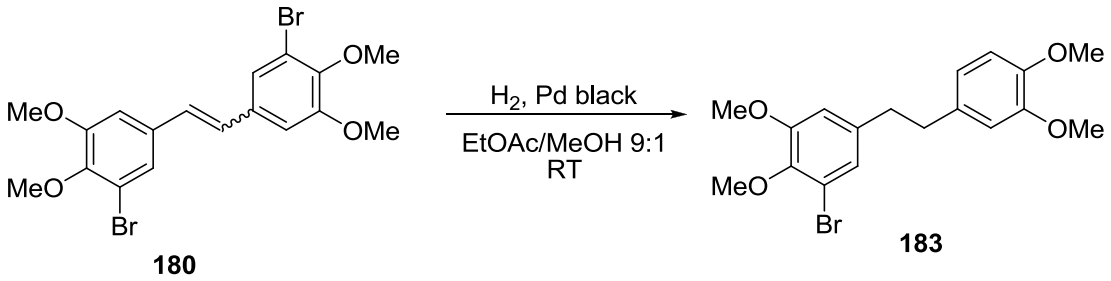


Scheme 86

*2.6.3 Hydrogenation. From alkene **180** to alkane **181***

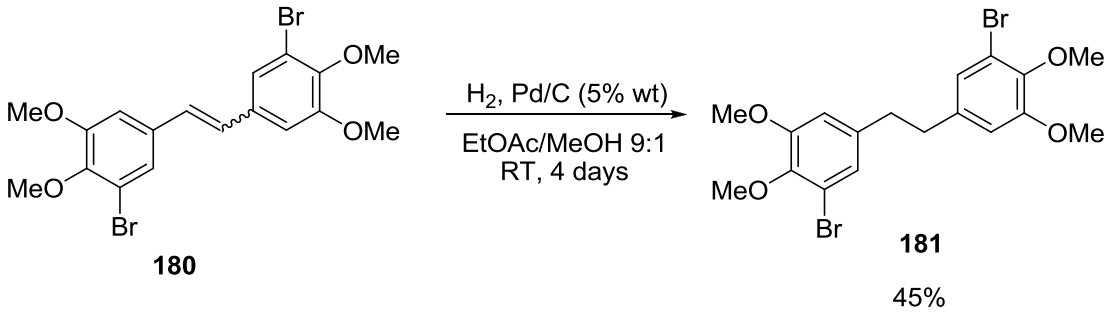
With alkene **180** in hand and the bromines installed at the correct position, we then proceeded to reduce the alkene double bond by means of Pd-catalyzed hydrogenation. The same protocol as before was followed and alkene **180** was dissolved in a 1:9 MeOH / EtOAc mixture and Pd/C (5% wt) was added. The reaction mixture was put under a nitrogen atmosphere and then purged with hydrogen gas. Hydrogenation was carried out at room

temperature with vigorous stirring and was monitored by ^{1}H-NMR. However, transformation of this substrate was very slow and also showed some signs of decomposition of the starting material and product by de-bromination as indicated by the presence of additional aromatic peaks in the ^{1}H NMR spectrum. Efforts to improve the rate and selectivity of the reaction by means of increasing the pressure or by using a more active catalyst such as Pd black were unsuccessful and only resulted in the de-bromination of one aromatic ring to give the mono-brominated dimethoxybenzene **183** (Scheme 87).



Scheme 87

Finally, it was found that the best conditions for hydrogenation of alkene **180** were the use of Pd/C (5% wt) at room temperature with monitoring by ^{1}H-NMR; the reaction reached completion in 4 days. However de-bromination products could still be observed (~20% as observed by ^{1}H-NMR) but following purification by recrystallisation from IPA, 1,1'-ethane-1,2-diylbis(5-bromo-3,4-dimethoxybenzene) (**181**) was obtained pure as white crystals in 45% yield (Scheme 88).



Scheme 88

*2.6.4 Oxidative coupling of **181** to phenanthrene **182***

The next step in the proposed synthesis was the oxidative coupling. Upon exposure to PIFA, 1,1'-ethane-1,2-diylbis(5-bromo-3,4-dimethoxybenzene) (**181**) has the choice of two ways to cyclise, but we speculated that the preferred conformational orientation of the methoxy groups (observed in the crystal structure, Figure 7) would prevent it from cyclising the undesired way due to a steric clash (Figure 8).

It was also predicted that with the bromine atoms in place, aromatisation would be avoided as free rotation about the biaryl C-C bond is prevented and the molecule is unable to become planar. However, means of selectively producing one enantiomer over the other without the use of a chiral auxiliary could not be established, and hence it was expected that the product would be necessarily racemic.

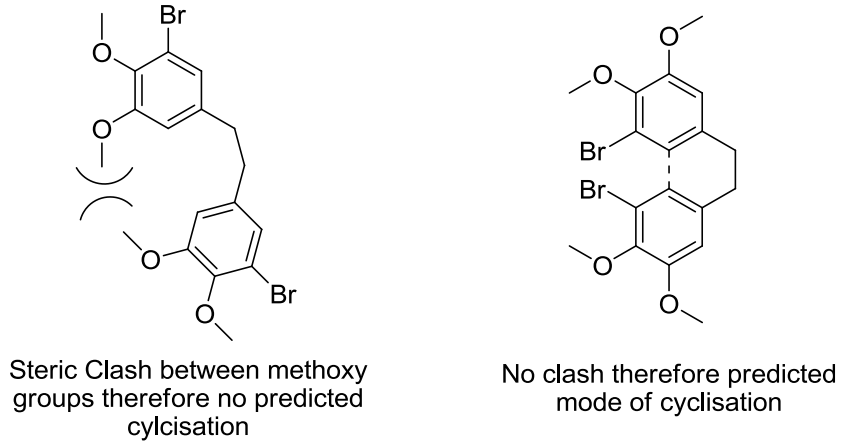
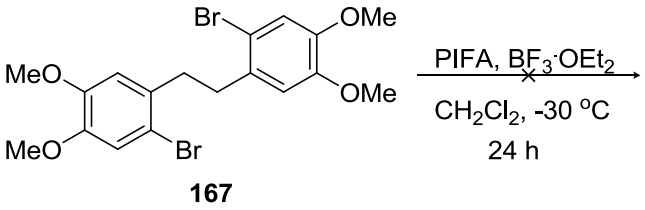


Figure 8: Steric clash suppressing aromatisation to the phenanthrene

To test the former idea, oxidative coupling of bromomethoxybenzene **167** – with the bromines incorrectly positioned-was subjected to cyclisation using PIFA and $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at -30 ^oC for 24 hours, only to yield starting material. This result suggests that the 2-position is perhaps blocked to coupling by the orientation of the methoxy group and comes as good news, verifying that once the bromine atoms are placed at the desired position (5-position), the mode of cyclisation should be the one to furnish (±) –polysiphenol (Figure 9).



167

Scheme 89

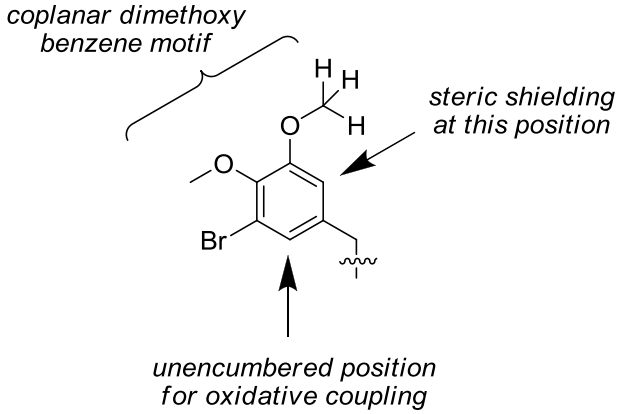
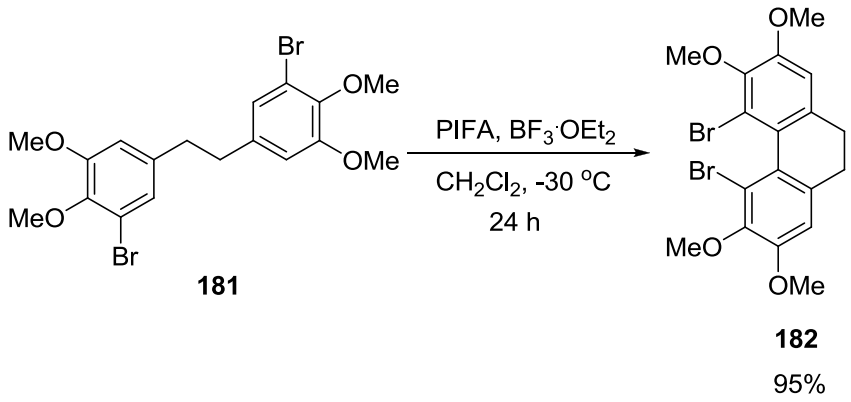


Figure 9

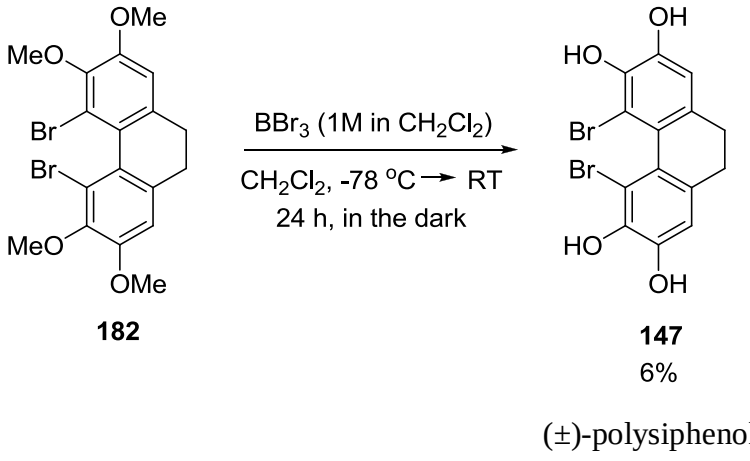
1,1'-Ethane-1,2-diylbis(5-bromo-3,4-dimethoxybenzene) (**181**) was subjected to the oxidative coupling conditions: PIFA and $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at -30 ^oC for 24 hours and following evaporation of the solvent and recrystallisation from IPA, it was pleasing to obtain exclusive formation of the product, 4,5-dibromo-2,3,6,7-tetramethoxy-9,10-dihydrophenanthrene (**182**), as off-white crystals in 95% yield (Scheme 38). This was the most challenging step and it was gratifying to observe that the oxidative coupling proceeded with such high selectivity and in such high yield. The identity of **182** was verified by comparing the ^1H NMR data of the product with that of the starting material **181** where a complete change in the aromatic pattern was observed: the two doublets at δ_H 6.95 ppm and δ_H 6.57 ppm (due to *meta*- coupling) had now been transformed into a singlet at δ_H 6.84 ppm, and this served as proof of the oxidative coupling albeit not confirming the regiochemistry, final proof of which awaited global deprotection. Noteworthy is the fact that compound **182** lacks the propensity to aromatise due to the existence of the bromine groups at the 6-position, restricting rotation and preventing the molecule from being planar.



Scheme 90

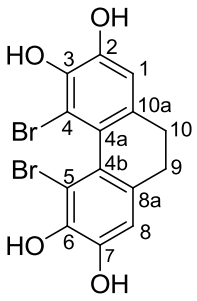
*2.6.5 Deprotection of **182** to (±)-polysiphenol **147***

With 4,5-dibromo-2,3,6,7-tetramethoxy-9,10-dihydrophenanthrene (**182**) in hand, it was now time for the final step, the demethylation. For this, the starting material was dissolved in CH_2Cl_2, cooled to -78 °C and BBr_3 (1M in CH_2Cl_2) was slowly added taking care to avoid exposure of the solution with light. The reaction was allowed to reach room temperature and stirred a further 24 hours. The reaction was monitored by ^1H NMR and comparison of the new product signals with those in the literature revealed exclusive formation of the natural product. Upon completion and aqueous work-up the crude mixture was subjected to preparative TLC followed by flash chromatography to obtain the natural product, (±)-polysiphenol **147**, as a green oil (0.009 g, 6%) (Scheme 91). It is suspected that the desired product decomposes on silica and this accounts for the low yield as well as its appearance.



Scheme 91: Methoxy-deprotection; the last step to the synthesis of (±)-polysiphenol

The identity of the product was confirmed by comparing its ^{1}H and ^{13}C NMR spectra to that of the natural product data for **147** in the literature and by MS and HRMS. In the ^{1}H NMR spectrum the aromatic protons resonate as a singlet at δ_H 6.85 ppm and the two alcohol groups as singlets at δ_H 5.59 and δ_H 5.49 ppm. The benzylic protons appear as multiplets at δ_H 2.64-2.49 ppm, as due to restricted rotation there is differentiation between pseudoaxial and pseudoequatorial protons. In the ^{13}C NMR spectrum, aromatic carbons resonate between 143 and δ_C 113 ppm, the ones at higher ppm being those bearing the hydroxyl groups. The bromine-bearing carbon is observed at δ_C 135.59 ppm and finally the benzylic resonances are seen at δ_C 31.20 ppm. The HRMS for $C_{14}H_8O_4Br_2$ is calculated at $(M)^+$ 399.8927 and found 399.8934. A comparison with the literature values[118] are tabulated below (Table 20).



147

Position	δ_H (mult) found[a]	δ_H (mult) lit[a118]	δ_C (mult) found[a]	δ_C (mult) lit[a118]
1, 8	6.85 (s)	6.84 (s)	113.5	113.5
2, 7			143.2	143.2
3, 6			139.3	139.2
4, 5			110.2	110.1
4a, 4b			127.1	127.0
9, 10	ax 2.49 (m) eq 2.64 (m)	ax 2.50 (m) eq 2.62 (m)	31.2	31.2
8a, 10a			135.6	135.6

a. $CDCl_3$ as solvent

Table 20

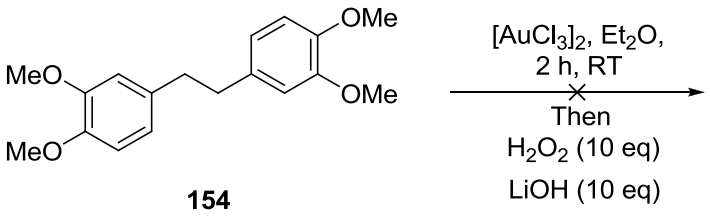
2.7 Attempts to utilise the Au-mediated biaryl coupling in the synthesis of (±)-polysiphenol

It was believed that previous studies on Au-mediated biaryl coupling could also be utilised to construct the aryl-aryl bond of polysiphenol.

The Au-biaryl coupling was simultaneously attempted along with the other couplings and knowledge from previous work was used when choosing the substrates. When carrying out the biaryl coupling, it was observed that alcohol moieties interfered with the Au centre and resulted in blocking of the $AuCl_3$ reagent by coordination of the hydroxyl on the Au centre. Hence using 1,1'-ethane-1,2-diyldibenzene-3,4-diol **153** as a substrate was avoided and instead 1,1'-ethane-1,2-diylbis(3,4-dimethoxybenzene) **154** was used**,** as it was believed that the reaction would be comparable to the Au-coupling of anisole which proceeded without any problem.

Tetramethoxy compound **154** was found to be soluble in diethyl ether so was selected as a test substrate using the optimised reaction conditions from the biaryl coupling studies to carry out the Au-mediated homocoupling.

$AuCl_3$ was loaded in a round-bottomed flask under an atmosphere of nitrogen (glovebox) and then dry diethyl ether was added, much in the same fashion as all our previous Au chemistry. Only half the amount of the solvent was used for this purpose as the other half was used to dissolve tetramethoxy compound **154** and add it to the $AuCl_3$/diethyl ether mixture in the round-bottomed flask. Once addition was complete, the same protocol as the one used in all previous studies on Au chemistry was used. The reaction was stirred for 2 hours at room temperature after which, LiOH/ H_2O_2 were added. After stirring at room temperature for a further 5 minutes, the reaction was quenched with water and extracted using diethyl ether. The organic layer was washed with water and dried over magnesium sulphate and the solvent was evaporated to yield an off-white solid. This was submitted for mass spectrometry and ^1H NMR both of which confirmed the presence of 1,1'-ethane-1,2-diylbis(3,4-dimethoxybenzene) **154** with no sign of any product (Scheme 92).

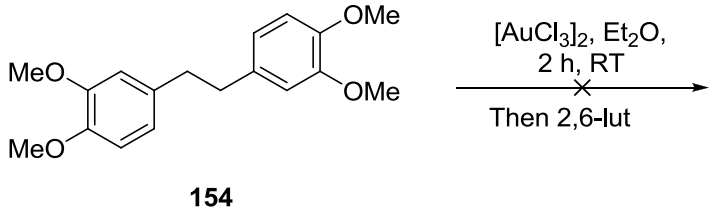


154

Scheme 92

Having observed that the reaction only returned starting material, the reaction was repeated and the crude mixture was subjected to HPLC which unfortunately showed only the presence of starting material. This could mean one of two things. That either the $AuCl_3$ is not adding to the aromatic ring or that once it's added, it cannot cyclise and hence is subject to protodeauration upon addition of LiOH/ H_2O_2. Previous experience with Au-mediated biaryl coupling suggests that the electrophilic substitution of Au on the aryl is an equilibrium reaction so the most probable scenario is the one of protodeauration.

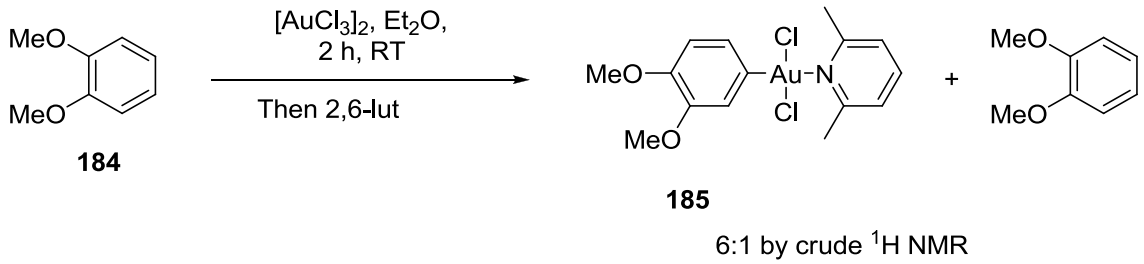
To test the theory the experiment was carried out once more but instead of adding LiOH/ H_2O_2 after 2 hours, 2,6-lutidine was added in order to isolate the 2,6-lutidine adduct. HPLC analysis of the crude mixture only showed starting material and 2,6-lutidine and this was further confirmed by ^{1}H NMR after aqueous work-up (Scheme 93).



154

Scheme 93

These discouraging results pointed to the direction that the di-methoxy aromatic is presumably too hindered and very readily protodeaurated. To test this theory, the reaction was attempted on 1,2-dimethoxybenzene (**184**) using the exact same conditions as before and isolating the intermediate with 2,6-lutidine. To our great satisfaction, ^{1}H NMR of the crude reaction mixture showed the presence of the desired gold complex **185** and some starting material in a 6:1 ratio (Scheme 94). The crude mixture was not further purified.



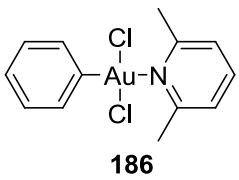
Scheme 94

Previous findings suggest that the auration reaction is an equilibrium, where the equilibrium lies between electrophilic substitution and protodeauration of the aryl ring (Scheme 95). By removing the HCl generated in the reaction, the equilibrium is forced to the right hand side and the desired products are obtained. The successful auration of 1,2-dimethoxybenzene (**184**) suggests that protodeauration is not the problem but quite possibly the problem lies in the initial auration step.

Scheme 95

The next step was to attempt the reaction using 3,4-dimethoxytoluene **187** to establish whether the extra methyl group activates the ring excessively, whether it sterically hinders substitution or whether it was an undesired effect of the pattern of substitution.

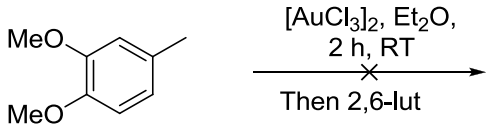
When subjecting 3,4-dimethoxytoluene **187** to the reaction conditions and following addition of 2,6-lutidine, HPLC analysis was carried out on the crude mixture. Prior to carrying out HPLC analysis on the crude mixture, the phenylgold-lutidine adduct **186** (Figure 4) was placed on the HPLC column to verify that Au adducts can be detected by HPLC and this was indeed the case.



186

Figure 4

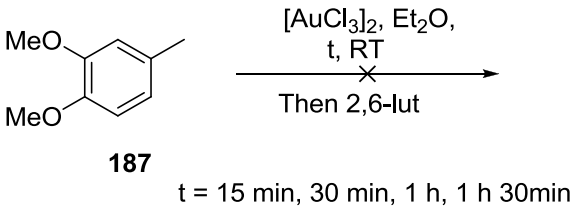
Analysis revealed signs of both starting material and 2,6-lutidine but unfortunately no signs of the desired Au complex. Further confirmation came from ^{1}H NMR following aqueous work-up (Scheme 96). This confirmed that the substrate was rather too sterically hindered for auration.



187

Scheme 96

The final step into the investigation was to carry out the reaction with 3,4-dimethoxytoluene **187** by varying the reaction time with $AuCl_3$ to examine whether the substrate is so activated that once the $AuCl_3$ adds onto the aromatic ring it experiences deprotoauration since we established that the electrophilic substitution reaction is an equilibrium. We carried out the reaction at different reaction times (15 and 30 minutes, 1 hour and 1 hour and 30 minutes). Unfortunately, all the reactions yielded the same results, starting material and 2,6-lutidine and none of the desired complex (Scheme 97).



187

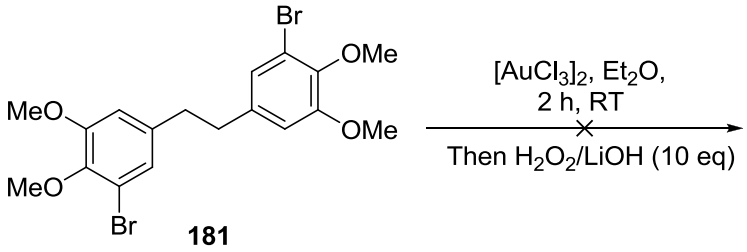
t = 15 min, 30 min, 1 h, 1 h 30min

Scheme 97

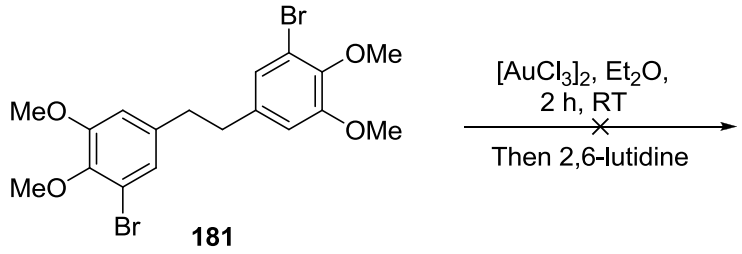
From the findings it was concluded that 1,1'-ethane-1,2-diylbis(3,4-dimethoxybenzene) (**154**) does not undergo electrophilic auration and it was decided to focus on other means of biaryl coupling, hence abandoning this route.

For completion purposes coupling of the brominated substrate, 1,1'-ethane-1,2-diylbis(5-bromo-3,4-dimethoxybenzene) (**181**) was also attempted. Given the previous findings, it was not expected to react and this was confirmed, as only starting material was returned both in the case of reacting with 10 equivalents of H_2O_2/LiOH (Scheme 98) and when attempting to

isolate the intermediate with 2,6-lutidine (Scheme 99). At this point Gold(III)-mediated biaryl coupling as means for this particular transformation was abandoned.



Scheme 98



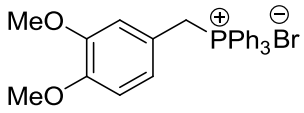
Scheme 99

3. CONCLUSION

Overall, we have successfully synthesised (±)-polysiphenol *via* a five-step route, in an overall yield of 1%. This, to the best of our knowledge, is the first total synthesis of (±)-polysiphenol (**10**).[111] The low overall yield is attributed to the final methoxy deprotection step which needs to be further optimised as this was not carried out due to time restrictions. We have examined electrophilic bromination on two different groups of substrates and rationalised our results. Furthermore, we have developed a telescopic one-pot Wittig reaction from benzylic alcohols to styrenes and optimised the steps, as well as examined hydrogenation of phenanthrenes. Finally, we have also synthesised 1,1'-ethane-1,2-diylbis(2,5,6-tribromobenzene-3,4-diol) (**28**), another natural product of the Rhodomelaceae family currently patented as a food preservative, *via* a four-step route. We envisage that our route can also be applied to the synthesis of other natural products in the family of Rhodomelaceae, by making slight modifications to the starting materials.

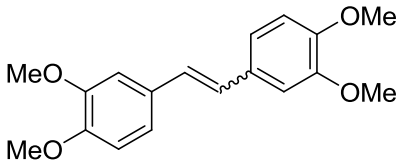
4. EXPERIMENTAL

3.1 (3,4-Dimethoxybenzyl)triphenylphosphonium bromide (160)[102]



Alcohol **159** (5 g, 30 mmol) was dissolved in CH_2CH_2 (200 mL) at room temperature and 1.1 equivalents of NBS (5.8 g, 33 mmol) was added, followed by 2 equivalents of PPh_3 (15.7 g, 60 mmol). The reaction was stirred at room temperature for 16 hours. The solvent was removed *in vacuo* to obtain a crude white solid which was further purified by recrystallisation (EtOAC, 150 mL) to yield ylide **160** as a white solid (12.3 g, 67%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.52, 3.79 (2s, 6H), 5.30 (s, 2H), 6.59–6.64 (m, 3H), 6.86 (t, 1H), 7.60–7.65, 7.72–7.78 (2m, 15H).

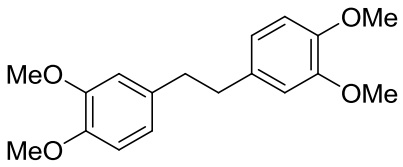
1,1'-Ethene-1,2-diylbis(3,4-dimethoxybenzene) (155)[106]



To a stirred solution of alcohol **159** (25 g, 149 mmol) in toluene at room temperature was added PPh_3 (78 g, 298 mmol). After vigorous stirring, NBS (29 g, 163.5 mmol) was added and the reaction mixture was heated under reflux for 2 hours. The reaction was monitored by HPLC and upon completion, the reaction mixture was cooled to room temperature, aldehyde **156** (24.8 g, 149 mmol) added, followed by potassium carbonate (134 g, 968.5 mmol). Heating under reflux was resumed for a further 4 hours, and the reaction was monitored by HPLC. Upon completion, the reaction was allowed to reach room temperature and the solvent was evaporated under reduced pressure. The crude solid was dissolved in TBME (500 mL), washed with water (3 x 500 mL) and brine (1 x 500 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated. The crude solid (90 g) was purified by recrystallisation (IPA, 260 mL) to give to give 1,1'-ethene-1,2-diylbis(3,4-dimethoxybenzene) **155** (16.6 g, 37%) as white crystal needles; m.p. 152-153 ^{o}C lit.[106] 153-154 ^{o}C; ***cis*-isomer**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72-6.85 (m, 6H), 6.47 (s, 2H), 3.86 (s, 6H), 3.68 (s, 6H) ; ***trans*-isomer**:

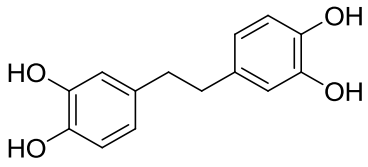
^{1}H-NMR (400 MHz, $CDCl_3$) δ6.78-7.06 (m, 8H), 3.95 (s, 6H), 3.91 (s, 6H); MS (ES) *m/z* 300 (M^+).

3.2 1,1'-Ethane-1,2-diylbis(3,4-dimethoxybenzene) (154)[106]



To a stirred solution of stilbene **155** (16.6 g, 55.3 mmol) in NMP (250 mL) was added Pd/C (0.83 g, 0.5 w/w). Hydrogenation was carried out at room temperature at 50 psi pressure of hydrogen gas for 20 minutes. Upon completion of the reaction, the solvent was evaporated, the resulting solid dissolved in TBME (200 mL) and washed with water (3 x 500mL). The organic was separated, dried ($MgSO_4$) and solvent evaporated. The crude solid was purified by recrystallisation from IPA (100 mL) to yield 1,1'-ethane-1,2-diylbis(3,4-dimethoxybenzene) **154** (13.7g, 82%) as white crystal needles; m.p. 108-110 ^{o}C lit.[106] 108-109 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ6.78 (δ, 2H), 6.71 (d, 2H), 6.66 (s, 2H), 3.86 (s, 6H), 3.84 (s, 6H), 2.85 (s, 4H); MS (ES) *m/z* 302 (M^+).

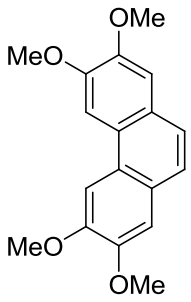
3.3 1,1'-Ethane-1,2-diyldibenzene-3,4-diol (153)[107]



To a stirred solution of methoxybenzene **154** (0.10 g, 0.33 mmol) in CH_2Cl_2 (5 mL) under N_2 at -78 ^{0}C was added a solution of BBr_3 (1M in CH_2Cl_2, 1.35 mL, 1.35 mmol) dropwise over a period of 30 minutes avoiding exposure of the reaction mixture to light. Following addition, the reaction was allowed to reach room temperature and stirred for a further 3 hours. It was then quenched with MeOH (5 mL) and solvent evaporated. The resulting solid was dissolved in TBME (10 mL) and washed with water (3 x 10 mL) and brine (2 x 10 mL). The organic extracts were combined, ($MgSO_4$) and evaporated to give 1,1'-ethane-1,2-diyldibenzene-3,4-

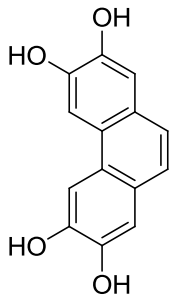
diol **153** (0.080 g, 100%) as an off-white solid; m.p. 159-160 ^{o}C lit.[107] 160-161 ^{o}C; ^{1}H NMR (400 MHz, *d*-MeOH) δ 6.63 (d, 2H), 6.58 (d, 2H), 6.45 (dd, 2H), 4.92 (s, 4H), 2.66 (s, 4H); MS (ES) *m/z* 246 (M^{+}).

3.4 2,3,6,7-Tetramethoxyphenanthrene (170)[101]



To a stirred solution of methoxybenzene **154** (1.0 g, 3.31 mmol) in dry CH_2Cl_2 (50 mL) at -30 ^{0}C was added PIFA (1.84 g, 6.62 mmol) followed by $BF_3{\cdot}OEt_2$ (0.56 mL, 4.63 mmol) and the reaction was stirred at -30 ^{0}C for 24 hours. Upon completion, the solution was filtered through a plug of silica and the solvent evaporated. The resulting crude solid was recrystallised from a 3:1 mixture of IPA (9 mL) and EtOAc (11 mL) to yield 2,3,6,7-tetramethoxyphenanthrene **170** (0.38 g, 40%) as white crystal needles; m.p. 178-180 ^{o}C lit.[101] 178-180 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 2H), 7.59 (s, 2H), 7.25 (s, 2H), 4.16 (s, 6H), 4.07 (s, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 149.2, 148.8, 126.4, 124.3, 108.4, 102.8, 56.1, 55.9. MS (ES) *m/z* 298 (M^{+}).

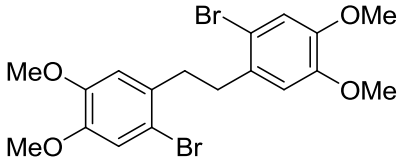
3.5 Phenanthrene-2,3,6,7-tetrol (161)[119]



To a stirred solution of tetramethoxyphenanthrene **170** (0.100 g, 0.33 mmol) in CH_2Cl_2 (5 mL) under N_2 at -78 ^{0}C was added BBr_3 (1M in CH_2Cl_2, 1.35 mL, 1.35 mmol) slowly over a

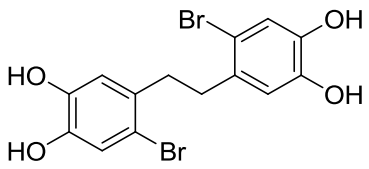
period of 30 minutes avoiding exposure of the reaction mixture to light. Following addition, the reaction was allowed to reach room temperature and stirred for a further 2 days. It was poured into a 2M NaOH (100 mL) solution at 0 ^{0}C. The aqueous layer was extracted with CH_2Cl_2 and the organic extracts combined and washed with water (3 x 25 mL) and brine (1 x 25 mL), dried ($MgSO_4$) and evaporated to furnish phenanthrene-2,3,6,7-tetrol **161** (0.085 g, 100%) as a white solid; m.p 182-183 ^{o}C; ^{1}H NMR (400 MHz, *d*-MeOH) δ 7.76 (d, 2H), 7.29 (d, 2H), 7.10 (d, 2H); ^{13}C NMR (400 MHz, *d*-MeOH) δ 145.7, 144.9, 126.0, 124.4, 122.9, 111.4, 106.1; MS (ES) *m/z* 242 (M^+).

3.6 1,1'-Ethane-1,2-diylbis(6-bromo-3,4-dimethoxybenzene) (167)[81]



To a stirred solution of methoxybenzene **154** (0.50 g, mmol) in 1,2-DCE at room temperature under N_2 were added TMG (1 drop, catalytic) and NBS (0.88 g, mmol). The reaction mixture was heated under reflux for 4 days. Upon completion the reaction mixture was allowed to reach room temperature and the solvent evaporated. The residue was taken up in CH_2Cl_2 (50 mL) and washed with water (3 x 50 mL) and saturated aqueous $Na_2S_2O_4$ solution (2 x 50 mL), organic extracts combined dried ($MgSO_4$) and passed through a pad of silica. The resulting product (0.66 g, 86%) was recrystallised from EtOAc (12 mL), MeOH (6 mL) and Petroleum Spirit 40-60 (12 mL) to give 1,1'-ethane-1,2-diylbis(6-bromo-3,4-dimethoxybenzene) **167** (0.64g, 83%) as white crystalline needles; m.p. 158-160 ^{o}C lit.[81] 157-159 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (s, 2H), 6.63 (s, 2H), 3.88 (s, 6H), 3.82 (s, 6H), 2.97 (s, 4H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 148.3, 148.0, 132.5, 115.5, 114.2, 113.4, 56.2, 56.1, 36.2; MS (CI) *m/z* 478 $(M + NH_4)^+$; HRMS (CI+, NH_3) *m/z* calcd for $C_{18}H_{24}NO_4{}^{79}Br_2$ $(M + NH_4)^+$ 476.0072, found 476.0078.

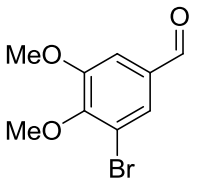
3.7 1,1'-Ethane-1,2-diylbis(6-bromobenzene-3,4-diol) (164)[120]



To a stirred solution of bromomethoxybenzene **167** (0.10 g, 0.217 mmol) in CH_2Cl_2 (2 mL) under N_2 at -78 ^oC was added BBr_3 (1M in CH_2Cl_2, 0.87 mL, 0.87 mmol) slowly over a period of 30 minutes avoiding exposure of the reaction mixture to light. Following addition, the reaction was allowed to reach room temperature and was stirred for a further 24 hours. The solvent was evaporated, the residue dissolved in EtOAc and washed with water (3 x 10 mL) and brine (2 x 10 mL). The organic layer was dried ($MgSO_4$) and the solvent evaporated to yield product **164** (0.08 g, 93%) as a white solid; m.p. 205-207 ^oC lit.[120] 205-26 ^oC; ^1H NMR (400 MHz, d-DMSO) δ 9.23 (s, 2H), 9.12 (s, 2H), 6.90 (s, 2H), 6.68 (s, 2H), 2.67 (s, 4H); ^{13}C NMR (400 MHz, d-DMSO) δ 144.7, 131.4, 118.7, 116.7, 111.9, 35.9;

Alternatively, bromotetrol **164** was prepared by dissolving tetrol **153** (0.80 g, 0.33 mmol) in a solution of bromine (4 equiv.) in acetic acid (300 mL). Following addition and vigorous stirring at room temperature for 4 hours, the mixture was decolourised and a white solid was formed. The acetic acid was removed in vacuo and the crude product was submitted for characterisation with no further purification.

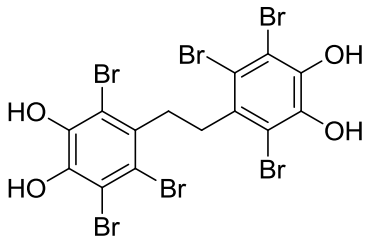
3,4-Dimethoxy-5-bromobenzaldehyde (178)[121]



Dimethoxybenzaldehyde **156** (0.2 g, 1.2 mmol) was dissolved in CH_2Cl_2 (10 mL), cooled to 0 ^oC and to that a solution of molecular bromine in CH_2Cl_2 (1 equivalent) was added. The reaction was stirred at 0 ^oC for 2 hours and following evaporation of the solvent and recrystallisation from CH_2Cl_2 and petroleum ether, the desired product, 3-bromo-4,5-

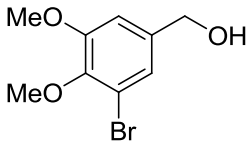
dimethoxybenzaldehyde (**178**) was obtained as a white solid (0.25 g, 90%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.84 (s, 1H), 7.66 (d, 1H), 7.40 (d, 1H), 3.96 (s, 3H), 3.94 (s, 3H);

3.8 1,1'-Ethane-1,2-diylbis(2,5,6-tribromobenzene-3,4-diol) (165)[68]



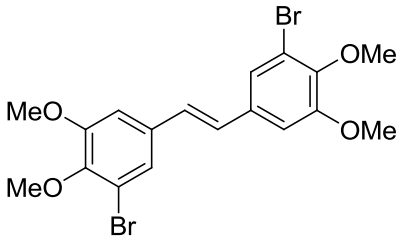
To a stirred solution of dihydrostilbene **153** (0.10 g, 0.041 mmol) in acetic acid (3 mL) at room temperature was added bromine (0.042 mL, 0.82 mmol). The reaction was stirred for 18 hours resulting in a white solid in a yellow solution. The acetic acid was evaporated *in vacuo* to give 1,1'-ethane-1,2-diylbis(2,5,6-tribromobenzene-3,4-diol) **165** (0.19 g, 66%) as a white solid; m.p. 229-231 ^{o}C lit.[68] 230-232 ^{o}C; ^{13}C NMR (400 MHz, *d*-DMSO) δ144.1, 144.0, 131.5, 117.1, 114.4, 114.3, 36.8; MS (EI) *m/z* 720 $(M+ H)^{+}$; HRMS (EI) *m/z* calcd for $C_{14}H_8O_4{}^{79}Br_6$ $(M)^{+}$ 713.5523, found 713.5522.

3.9 5-Bromo-3,4-dimethoxybenzylalcohol (179)[117]



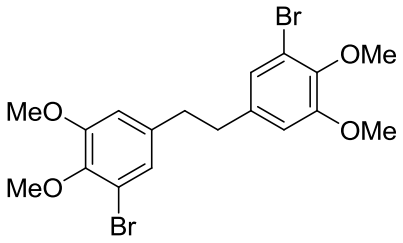
To a stirred solution of benzaldehyde **178** (0.50 g, 2.04 mmol, 1.0 equiv) in MeOH (50 mL) at 0 °C was added $NaBH_4$ (0.15 g, 4.09 mmol, 2.0 equiv). After 30 min of stirring at 0 °C, the reaction was quenched by slow addition of water (25 mL), poured into water (50 mL), and extracted with EtOAc (3 × 50 mL). The combined organic layers were then washed with water (50 mL) and brine (50 mL), dried ($MgSO_4$), and concentrated to afford 5-bromo-3,4-dimethoxybenzylalcohol **178** (0.49 g, 99% yield) as a colourless oil which was carried forward without further purification; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (1H, s), 6.72 (1H, s), 4.45 (2H, s), 3.78 (3H, s), 3.74 (3H, s), 2.94 (1H, br s).

3.10 1,1'-(*E*)-Ethene-1,2-diylbis(5-bromo-3,4-dimethoxybenzene) (180)[122]



To a stirred solution of alcohol **179** (0.50 g, 2.03 mmol) in toluene at room temperature was added PPh_3 (1.06 g, 4.04 mmol). The reaction was then heated under reflux to dissolve the PPh_3 and then NBS (0.40 g, 2.27 mmol) was added slowly. Heating under reflux was continued for a further 4 hours. The reaction mixture was then cooled to room temperature, the aldehyde (0.50 g, 2.06 mmol) was added followed by K_2CO_3 (1.68 g, 13.4 mmol). Heating was continued for 36 hours, the reaction was then cooled down to room temperature, the solvent evaporated and the resulting crude solid was dissolved in EtOAc (250 mL) and washed with water (3 x 200 mL) and brine (200 mL). The aqueous layer was washed with EtOAc and the organic layers were combined, dried ($MgSO_4$) and evaporated. The crude product was then recrystallised from IPA (50 mL) to yield 1,1'-(*E*)-ethene-1,2-diylbis(5-bromo-3,4-dimethoxybenzene) **180** (0.31 g, 33%) as white crystals; m.p. 193-194 ^oC lit.[122] 194-196 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 7.32 (d, 2H), 6.99 (d, 2H), 6.91 (s, 2H), 3.95 (s, 6H), 3.91 (s, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 153.8, 146.6, 134.2, 127.6, 123.0, 118.1, 109.6, 60.8, 56.1; MS (CI) *m/z* 476 $(M + NH_4)^+$; HRMS (CI+, NH_3) *m/z* calcd for $C_{18}H_{22}NO_4{}^{79}Br_2$ $(M + NH_4)^+$ 473.9916, found 473.9916.

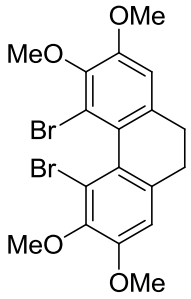
3.11 1,1'-Ethane-1,2-diylbis(5-bromo-3,4-dimethoxybenzene) (181)[123]



To a stirred solution of stilbene **180** (0.45 g, 0.98 mmol) in a 1:9 MeOH / EtOAc mixture (30 mL) was added Pd/C (0.02 g, 5% w/w). The reaction mixture was put under a nitrogen

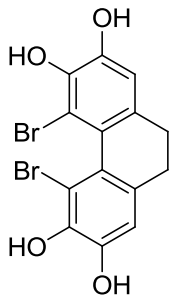
atmosphere and then purged with hydrogen gas. Hydrogenation was carried out at room temperature with vigorous stirring for 4 days and was monitored by ^{1}H-NMR. Upon completion, the reaction was passed through a pad of celite and the solvent evaporated. The resulting crude solid was purified by recrystallisation from IPA (10 mL) to yield 1,1'-ethane-1,2-diylbis(5-bromo-3,4-dimethoxybenzene) **181** (0.22 g, 45%) as white crystals; m.p. 92-94 ^{o}C lit.[123] 92-95 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ6.95 (d, 2H), 6.57 (d, 2H), 3.83 (s, 6H), 3.81 (s, 6H), 2.80 (s, 4H); ^{13}C NMR (400 MHz, $CDCl_3$) δ153.43, 144.62, 138.39, 124.42, 117.42, 112.20, 60.60, 56.06, 37.34; MS (CI) *m/z* 478 $(M + NH_4)^+$; HRMS (CI+, NH_3) *m/z* calcd for $C_{18}H_{24}NO_4{}^{79}Br_2$ $(M + NH_4)^+$ 476.0056, found 476.0062.

3.12 4,5-Dibromo-2,3,6,7-tetramethoxy-9,10-dihydrophenanthrene (182)



To a stirred solution of bromomethoxybenzene **181** (0.20 g, 0.51 mmol) in dry CH_2Cl_2 (5 mL) at -40 ^{0}C was added PIFA (0.24 g, 0.56 mmol) followed by $BF_3{\cdot}OEt_2$ (1 drop, catalytic) and the reaction was stirred at -30 ^{0}C for a period of 24 hours. Upon completion, the solvent was evaporated and the resulting crude solid was recrystallised from IPA (10 mL) to yield 4,5-dibromo-2,3,6,7-tetramethoxy-9,10-dihydrophenanthrene **182** (0.20 g, 95%) as off-white crystals; m.p. 208-210 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ6.84 (s, 2H), 3.94 (s, 6H), 3.92 (s, 6H), 2.75-2.57 (m, 4H); ^{13}C NMR (400 MHz, $CDCl_3$) δ152.0, 145.6, 137.9, 128.7, 119.1, 110.2, 60.7, 56.1, 31.5; MS (CI) *m/z* 476 $(M + NH_4)^+$; HRMS (CI+, NH_3) *m/z* calcd for $C_{18}H_{22}NO_4{}^{79}Br_2$ $(M + NH_4)^+$ 473.9929, found 473.9931.

3.13 4,5-Dibromo-9,10-dihydrophenanthrene-2,3,6,7-tetrol (147) ((±)-Polysiphenol)[111]



To a stirred solution of tetramethoxyphenanthrene **182** (0.20 g, 0.51 mmol) in CH_2Cl_2 (6 mL) under N_2 at -78 ^oC was added BBr_3 (1M in CH_2Cl_2, 2.03 mL, 2.03 mmol) slowly over a period of 30 minutes avoiding exposure of the reaction mixture to light. Following addition, the reaction was allowed to reach room temperature and stirred for a further 24 hours. The solvent was then evaporated, the residue dissolved in EtOAc and washed with water (3 x 10 mL) and brine (2 x 10 mL). The organic layer was dried ($MgSO_4$) and the solvent evaporated. The crude mixture was purified firstly by preparative TLC and then by flash chromatography (5% MeOH in CH_2Cl_2) to yield 4,5-dibromo-9,10-dihydrophenanthrene-2,3,6,7-tetrol **147** [(±)-Polysiphenol] (0.009 g, 6%) as a green oil. ^1H NMR (500 MHz, $CDCl_3$): δ 6.85 (s, 2H), 5.59 (s, 2H), 5.49 (s, 2H), 2.64-2.49 (m, 4H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 143.2, 139.3, 135.6, 127.1, 113.5, 110.2, 31.2; MS (EI) *m/z* 402 $(M+ H)^+$; HRMS (EI) *m/z* calcd for $C_{14}H_8O_4{}^{79}Br_2$ $(M)^+$ 399.8927, found 399.8934.

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